Boards & Beyond: 
Endocrinology Slides

Color slides for USMLE Step 1 preparation
from the Boards and Beyond Website

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Boards & Beyond provides a virtual medical school curriculum used by students around the globe to supplement their education and prepare for board exams such as USMLE Step 1.

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Thyroid Gland

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

Thyroid Embryology
- Forms from floor of pharynx (epithelial cells)

24-28 Day Old Embryo

Foramen Cecum
- 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

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

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

Thyroid Hormones
- Contain the element iodine
- Iodized salt
  - Table salt (NaCl) mixed with small minute amount of iodine
  - Done in many countries to prevent iodine deficiency
  - Added to salt in US in 1924

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

- **Iodine** = I (chemical element, atomic number 53)
- **Iodide** = iodine 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 I₂ (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

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"

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

Eyes of the follicular cell:

- Thyroid Peroxidase (TPO)
- Organification of iodide into MIT/DIT
- Coupling of MIT/DIT into T3/T4
- 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

TBG - T4 → T4

Radioactive Iodine

- \(^{131}\)I is an isotope of iodine
- Has 53 protons like elemental iodine
- Extra neutrons
- Emits radiation (β-decay)
- Exposure to 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

Amiodarone

- Mimics T4
  - Inhibits 5'-deiodinase
  - \(\text{T3} \rightarrow \text{TSH}\) from pituitary gland
  - TSH rises after start of therapy then normalizes

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

Radionuclide Iodine

- \(^{131}\)I is an isotope of iodine
- Has 53 protons like elemental iodine
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- Emits radiation (β-decay)
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TBG - T4 → T4
Thyroid Hormone

CNS and Bone effects

- 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

Effects of Thyroid Hormone

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

Effect of Thyroid Hormone

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
- Hypothyroid patients: weight loss

Metabolic Effects

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

Hyperthyroid patients:

- ↑ cholesterol
- Hyperglycemia

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

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**Thyroid Hormone Regulation**

- Serum T4/T3 level sensed by hypothalamus
- Releases thyroid releasing hormone (TRH)

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**Thyroid Panel**

- Four standard measurements to assess thyroid

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<tr>
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<th>Normal Value</th>
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<tr>
<td>TSH</td>
<td>0.4 to 5.0 mU/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>
</tr>
<tr>
<td>Free T4</td>
<td>0.01-0.03 nmol/L</td>
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</table>

Note: 
- T4 > T3
- Total T4 > Free T4 (most bound to TBG)

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**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

---

**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
**Thyroid Disorders**

### Hyperthyroid
- Thyroid gland overactive
- Leads to weight loss
- Increased metabolic rate
- Tremors
- Thyroid enlargement
- Thyrotoxicosis

### Hypothyroid
- Thyroid gland underactive
- Leads to weight gain
- Decreased metabolic rate
- Constipation
- Dry skin
- Bradycardia

### Hyperlipidemia
- Classic feature of hypothyroidism
- Increased total cholesterol
- Increased LDL cholesterol
- Primary mechanism: Decreased LDL receptor density
  - T₃ upregulates LDL receptor gene activation

### Myxedema
- Non-pitting edema of the skin from hypothyroidism
- Hyaluronic acid deposits in dermis
- Draws water out → swelling
- Usually facial/peri orbital swelling
- Pretibial myxedema
  - Special form of myxedema over shin
  - Seen in Graves' disease (hyperthyroidism)
- Myxedema coma = coma from hypothyroidism

### Thyroid Disorders
- Jason Ryan, MD, MPH
**Goiter**
- Enlarged thyroid
- High TSH, inability to produce T3/T4
- Thyroid stimulating antibodies (Graves')

**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)

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

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

**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

**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

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)

Reverse T3

- 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

Hyperthyroidism

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

Lab Findings

- 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

- Best initial test is TSH
Graves' Disease

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

Graves' Disease

- Exophthalmos (bulging eyes)
  - Proptosis (protrusion of eye) and pretibial 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
**Thionamides**
- Methimazole: teratogen
  - Associated with congenital malformations
  - Especially 1st trimester
  - PTU often used during early pregnancy

**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

**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

**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)

**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)

Iodine

- Deficiency
  • Hypothyroidism
  • Goiter

- Excess
  • Hypothyroidism
  • Wolff-Chaikoff

- Load
  • Hyperthyroidism

Hypothyroidism
- Iodine deficiency
- Iodine excess
- Congenital hypothyroidism
- Amiodarone
- Thyroiditis
  • Hashimoto’s (#1 cause when dietary iodine is sufficient)
  • Subacute
  • Riedel’s

Iodine Deficiency
- “Endemic goiter”
  • Goiter in region with widespread iodine deficiency
  • Common in mountainous areas (iodine depleted by run-off)
  • Constant elevation of TSH → enlarged thyroid

Iodine Excess
- Excessive iodide in diet could lead to hyperthyroidism
  • Thyroid protects itself via Wolff-Chaikoff Effect
  • Organification inhibited by ↑ iodide
    • Less synthesis of MIT/DIT
    • Chronic, high iodine intake → goiter/hypothyroidism

Amiodarone
- Two types of hyperthyroidism
  • Type I
    • Occurs in patients with pre-existing thyroid disease
      • Graves’ or Multi-nodular goiter
      • Amiodarone provides iodine → excess hormone production
  • Type II
    • Destructive thyroiditis
      • Excess release T4/T3 (no ↑ hormone synthesis)
      • Direct toxic effect of drug
      • Can occur in patients without pre-existing thyroid illness

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

Amiodarone

Congenital Hypothyroidism

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

Thyroid Hormone

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

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
  - Done for Graves’ or malignancy
- 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

Always check TSH before starting amiodarone

Amiodarone

Hypothyroidism

Wolff-Chaikoff Hypothyroidism

↓T4→T3

Hyperthyroidism

Iodine Load Thyroiditis

Hyperthyroidism

↓T4→T3

Iodine Excess

Inhibits 5’-diodinase

Wellcome Images/Wikipedia
Hashimoto's Thyroiditis
Chronic Autoimmune Thyroiditis
- Most common cause of hypothyroidism (non-diet)
- Lymphocytes infiltrate thyroid gland
  - Autoimmune disorder (T-cell attack thyroid; B cell activation)
  - HLA-DR3, HLA-DR5 and others

Hashimoto's Thyroiditis
Chronic Autoimmune Thyroiditis
- 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

Hashimoto's Thyroiditis
Chronic Autoimmune Thyroiditis
- Antibodies produced
- Anti - TPO
- Anti - thyroglobulin
- Histology:
  - Massive lymphocytic infiltrate (germinal centers)
  - Hurthle cells (enlarged eosinophilic follicular cells)

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

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

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)
Thyroid Cancer

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

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

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

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

Thyroid Cancer
- Papillary
- Follicular
- Medullary
- Anaplastic
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

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

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

Follicular Carcinoma
- Possible \textit{hematogenous} metastasis
- Treatment:
  - Thyroidectomy
  - I\textsubscript{131} to ablate any remaining tissue or metastasis

Anaplastic Carcinoma
- Undifferentiated Carcinoma
  - Occurs in \textit{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
**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 system
- Increase Na+/Water resorption
- Promote K+/H+ excretion

**Collecting Duct**
- Lumen (Urine)
- Principal Cell
- Na+ Interstitium/Blood
- Aldosterone
- Aldosterone
- H2O
- ATP
- H+ Intercalated Cell
- Aldosterone
- H+
### 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)

### 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

### 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

### Cortisol
- Hormone Effects
  - Maintains **blood pressure**
  - Effects on vascular smooth muscle
  - Increases vascular sensitivity (α1) to norepi/epi
  - ↓NO mediated vasodilation
  - ↑ cortisol: hypertension (Cushing’s disease)
  - ↓ cortisol: hypotension (adrenal insufficiency)
Cortisol

Hormone Effects

- Suppresses immune system
- Sequester lymphocytes in spleen/nodes
- Reduce T and B cell levels in plasma
- Block neutrophil migration
  - ↑ peripheral neutrophil count
- Mast cells: blocks histamine release
  - ↓ eosinophil counts
- Basis for steroids as immunosuppressive drug therapy

Corticosteroid Drugs

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

Cortisol

Effects

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

Cortisol

Effects

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

Cortisol

Effects

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

Zona Glomerulosa

Zona Glomerulosa
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

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

Low Cortisol

Signs/Symptoms

- Hypoglycemia
- Nausea/vomiting

CAH

Congenital Adrenal Hyperplasia

- All result in low cortisol
- Stimulates ACTH release
- Can cause ↑ production of other hormones
  - Mineralocorticoids
  - Androgens

1 Cortisol → ACTH → Adrenal Hyperplasia → ↑ Non-cortisol hormone synthesis

CAH

Cholesterol → Aldosterone → Cortisol → Androgens

CAH

Congenital Adrenal Hyperplasia

Jason Ryan, MD, MPH

Matthew Colo/Wikipedia
21-α Hydroxylase Deficiency

- **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)
  - Excess androgens
    - Female (XX): Ambiguous genitalia
    - Male (XY): Precocious (early) puberty
  - Androgen deficiency
    - Female (XX): Normal genitalia
    - Male (XY): Female or ambiguous genitalia

Ambiguous Genitalia

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

Aldosterone

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

ACTH Effects

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

Proopiomelanocortin

- ACTH
  - MSH
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 form: 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

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
</tr>
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</table>
| Classic, Salt-losing | Nausea/Vomiting
|                   | Volume depletion
|                   | Hypertension
|                   | Hypokalemia
| Milder Forms      | Females: Ambiguous genitalia
|                   | Males: Precocious puberty |

21-α Hydroxylase Deficiency

Cholesterol
Aldosterone
Cortisol
Androgens

↑ ACTH

17-α Hydroxylase Deficiency

Cholesterol
Aldosterone
Cortisol
Androgens

↑ ACTH
**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**
- Males (XY):
  - Female or ambiguous external genitalia
  - Absent uterus/fallopian tubes (Sertoli cells → MIH)
  - Undescended testes
- Females (XX):
  - Normal at birth
  - Primary amenorrhea at puberty
  - Theca cells lack of androgens → ↓ estradiol
  - Often diagnosed at puberty
  - XX female fails to develop
  - XY phenotypic female or male fails to develop
  - Hypertension, low K+ identified

**17-β Hydroxysteroid Dehydrogenase Deficiency**
- ↑ ACTH
- Cholesterol
- Aldosterone
- Cortisol
- Androgens

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

**3-β Hydroxysteroid Dehydrogenase Deficiency**
- Low cortisol
- Excess mineralocorticoids: HTN, ↓K+
- Low androgens
- CYP17A1: adrenal gland and gonads

**CAH Screening**
- Some states screen with newborn blood testing
- Measure level of 17-Hydroxyprogesterone
  - Elevated level in 21-α hydroxylase deficiency (most common)
CAH Treatment

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

- Hypertension
- Hyperglycemia
- Diabetes (insulin resistance)
- Immune suppression
  - Risk of infections, especially opportunistic

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

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
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 → adrenal hyperplasia → ↑cortisol

Cushing’s Syndrome
Causes
• Special note: skin hyperpigmentation
  • Can occur in ACTH-dependent Cushing's syndrome
  • Caused by ↑ ACTH not cortisol
  • ↑ ACTH → ↑ MSH

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Cushing's Syndrome
Diagnosis
• Measuring plasma cortisol difficult
  • Circadian rhythm → high levels in AM
  • Most cortisol bound to CBG
  • CBG levels can affect serum measurement

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Cushing’s Syndrome
Diagnosis
• 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)

Cushing’s Syndrome
Diagnosis
• Measuring plasma cortisol difficult
  • Circadian rhythm → high levels in AM
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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

ACTH-Dependent Causes (High ACTH) | ACTH-Independent Causes (Low ACTH)
--- | ---
Cushing's disease | Steroid therapy
Ectopic ACTH | Adrenal adenoma

Cushing's Syndrome

Diagnosis

- Step 1: Establish Cushing's syndrome
- Step 2: Establish cause
- Key test is serum ACTH level

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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

Adrenal Insufficiency

- Insufficient cortisol production
- **Primary** adrenal insufficiency (Addison's disease)
  - Failure of adrenal gland
  - Cortisol and aldosterone will be low
  - ACTH will be high
- **Secondary** adrenal insufficiency
  - Failure of pituitary ACTH release
  - Only cortisol will be low

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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Cushing's Syndrome

Diagnosis

- Step 1: Establish Cushing's syndrome
- Step 2: Establish cause
- Key test is serum ACTH level

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**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

**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

**Adrenal Crisis**

- Acute adrenal insufficiency
- Abrupt loss of cortisol and aldosterone
- Main manifestation is shock
- Hypoglycemia
- Other symptoms: nausea, vomiting, fatigue, confusion
  - Infection, surgery, trauma in patient with adrenal insufficiency
  - Patients on chronic steroids
  - "Stress dose steroids" for prevention

**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
• 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

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

2o Adrenal Insufficiency
• No skin findings
• ACTH is not elevated
• No hyperkalemia
• Aldosterone not effected

2o 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

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2o Adrenal Insufficiency
Important Points
• No skin findings
• ACTH is not elevated
• No hyperkalemia
• Aldosterone not effected
Primary Aldosteronism

**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

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

**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

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

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
  - Secrete 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
  • Older test: 24 hour collection of VMA
• Serum catecholamine levels not routinely used
  • Levels fluctuate
  • Some metabolism intratumoral
  • Breakdown products of catecholamines measured
    • Usually via 24 hour urine collection

Clinical presentation
• Classically episodic symptoms
  • Hypertension
  • Headaches
  • Palpitations
  • Sweating
  • Pallor (pale skin)
**Adrenal Adenomas**
- Often discovered on abdominal imaging
- "Adrenal incidentaloma"
- Concern for malignancy and/or functioning adenoma

**MIBG**
- Chemical analog of norepinephrine
- Diagnosis of pheochromocytoma & neuroblastoma
- Concentrated in sympathetic tissues
- Labeled with radioactive iodine (I$^{131}$)
- 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)
    - Rapid eye movements, rhythmic jerking, ataxia
    - Half of OMA patients have a neuroblastoma
- 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

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

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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 Release

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

Insulin
- Protein hormone
- Synthesized by beta cells
- Synthesized as preproinsulin
  - Made by ribosomes of rough endoplasmic reticulum
- Preproinsulin cleaved to proinsulin
  - Transported 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

GLUT-2 and Glucokinase
Both in liver/pancreas

Endocrine Pancreas
Jason Ryan, MD, MPH
**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**

- Ty Ty P P

**PIK3 Pathway**

Phosphatidylinositol 3-kinase Pathway

- Catalyzes many intracellular processes
  - Glycogen formation
  - Fatty acid synthesis
  - GLUT-4 glucose transporter

**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

**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
Insulin Dependent Organs
• Muscle and fat
  • Use GLUT-4 for glucose uptake
  • Depend on insulin (no insulin = no GLUT-4)

Insulin Effects
• Fatty acid synthesis
  • Activates acetyl-CoA carboxylase
  • Inhibits hormone sensitive lipase
• 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

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 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 Effects
• Glucose uptake (skeletal muscle, adipose tissue)
  • Glycogen synthesis
    • Activates glycogen synthase
    • Inhibits glycogen phosphorylase
    • Inhibits gluconeogenesis
    • ↑ Fructose-2,6-bisphosphate levels
    • Inhibit Fructose 1,6 bisphosphatase 1

Insulin Dependent Organs
• Muscle and fat
  • Use GLUT-4 for glucose uptake
  • Depend on insulin (no insulin = no GLUT-4)
**Glucagon Receptor**
- G-protein receptor
- Activates adenylyl cyclase
- Increases cAMP
- Activates protein kinase A (PKA)

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

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

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

**Insulin**
- 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

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**Hypoglycemia**
- Uconscous 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 adenyl cyclase
  - Different site from beta-adrenergic agents
  - Raises cAMP →↑ 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

**Insulinoma**
- Diagnosis: fasting insulin level
- Also elevated
  - C-peptide
  - Proinsulin
- Need to exclude exogenous insulin administration

**Fasting Hypoglycemia**
- Differential diagnosis
  - Exogenous insulin
  - Oral hypoglycemics (sulfonylureas →↑ insulin)
  - Insulinoma

<table>
<thead>
<tr>
<th>Differential Diagnosis</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>
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<tr>
<td>C-peptide</td>
<td>-</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)
Glucagonoma

- **Weight loss**
  - Liver gluconeogenesis
  - Consumption of proteins/amino acids

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

Glucagonoma

- **Necrolytic migratory erythema**
  - Red, blistering rash
  - Itchy, painful
  - Fluctuates in severity
  - **Genitals, buttocks, groin**
  - Key clinical scenario: new diabetes and rash

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**
- **Necrolytic migratory erythema**
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- **Weight loss**
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- **Consumption of proteins/amino acids**
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 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)

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 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>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;100mg/dl</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>100 to 125mg/dl</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&gt;=126mg/dl</td>
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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

- Autoimmune disorder
- Type IV hypersensitivity reaction
- T-cell mediated destruction of beta cells
- Inflammation of islets
- Lymphocytes on biopsy ("Insulitis")
- Decreased number of beta cells
- Loss of insulin
- Associated with HLA-DR3 and HLA-DR4
- Autoantibodies may be present
  - Islet-cell antibodies
  - Insulin antibodies

Glucose Tolerance Test

- Oral glucose load administered
- Plasma glucose measured 1-3 hours later
- High glucose indicates diabetes
- Often used to screen for gestational diabetes
  - Some insulin resistance normal in pregnancy
  - Need to study response to glucose load for diagnosis

Hemoglobin A1C

- Reflects average glucose over past 3 months
  - Normal < 5.7%
  - Pre-diabetes: 5.7 to 6.4%
  - Diabetes: >=6.5%
- Sometimes used for diagnosis
- Important for monitoring therapy
  - Higher value = worse control of blood sugar

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

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

Diabetic Ketoacidosis

DKA

- Low insulin / high epinephrine
- High fatty acid utilization
- Oxaloacetate depleted \( \rightarrow \) TCA cycle stalls
- \( \text{Acetyl-CoA} \)
- Ketone production

Phosphate

- Risk of hypophosphatemia
  - Acidosis \( \rightarrow \) 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

Treatment

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

Image courtesy of Yale Rose / Flickr

Image courtesy of *Han Z* / *Wikipedia*

Image courtesy of *Wikipedia*
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

Type 2 Diabetes

Risk Factors

- Insulin resistance
  - Muscle, adipose tissue, liver
  - Reduced response to insulin → hyperglycemia
  - Pancreas responds with ↑ insulin
  - Eventually pancreas can fail → ↓ insulin

Type 2 Diabetes

Risk Factors

- Family history
  - Strong genetic component (more than type I)
  - Any first degree relative with T2DM: ↑ 2-3x risk

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

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Diabetic Complications

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

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
  - Amylin peptide normally made by beta cells
    - Precise function not known
    - Packaged and secreted with insulin
    - Pramlintide: amylin analog used for diabetes treatment
  - Accumulates in islets in patients with type 2 diabetes

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 osmolality → CNS dysfunction

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
**Non-enzymatic Glycation**

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

**Atherosclerosis**

Diabetic Macroangiopathy

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

**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

**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
**Glomerular Basement Membranes**
- AGEs → diffuse *basement 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*

**Polyol Pathway**
- Little activity at physiologic glucose levels
- Chronic hyperglycemia can lead to ↑ sorbitol
- Sorbitol is osmotic agent
- Draws in fluid → *osmotic damage*
- Likely involved in many diabetic complications
  - Cataracts
  - Neuropathy

**Sorbitol Accumulation**

**Glomerulosclerosis**
- Diffuse *glomerulosclerosis*
  - Deposits of proteins (collagen IV)
  - Diffusely on basement membranes of glomeruli capillary loops
  - Mesangial cell proliferation
  - Also occurs with aging and hypertension
  - If severe → 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

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**Cataracts**
- Sorbitol accumulates in *lens*
- ↑ osmolarity
- Fluid into lens
- Opacification over time
Diabetes Complications

- Non-enzymatic Glycation
- Sorbitol Accumulation

Non-enzymatic Glycation
- Atherosclerosis
- Diabetic Kidney Disease
- Retinopathy
- Neuropathy

Sorbitol Accumulation
- Cataracts

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

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

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"

Neuropathy

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

Diabetic Foot Disease

- Neuropathy + ischemia can lead to:
  - Ulcers
  - Infection
  - Amputation
  - Made worse by poor wound healing from PVD
  - Prevention: Regular foot exams
  - Ulcer treatment:
    - Wound management
    - Sometimes antibiotics
    - Hyperbaric oxygen chamber

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### Type 1 versus Type 2

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<th>Type 2</th>
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<tbody>
<tr>
<td>Pathophysiology</td>
<td>Loss of insulin</td>
<td>Insulin Resistance</td>
</tr>
<tr>
<td>Insulin</td>
<td>Low</td>
<td>High then low</td>
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<tr>
<td>Biopsy</td>
<td>InsulinLv</td>
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<tr>
<td>Age</td>
<td>Children</td>
<td>Adults</td>
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<tr>
<td>Genetic Predisposition</td>
<td>Weaker</td>
<td>Stronger</td>
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<tr>
<td>Complications</td>
<td>DKA</td>
<td>HRS</td>
</tr>
</tbody>
</table>
**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
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

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

Insulin

- **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**

NPH Insulin

- *Neutral Protamine Hagedorn*
  - Regular insulin combined with **neutral protamine**
  - Slows absorption
  - Peak: 4–8 hours
  - Duration: 12–16 hours
**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

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 ↑

Hemoglobin A1C
- Used to monitor therapy
- Too high = ↑ complications
- Too low = Risk of hypoglycemia
- Goal of ≤7.0% often used in many patients

Oral/SQ Antidiabetic Agents
- Biguanides (Metformin)
- Sulfonylureas/Meglitinides
- Glitazones
- Glucosidase Inhibitors
- Amylin Analogs
- GIP-1 Analogs
- DPP-4 Inhibitors
- SGLT2 inhibitors

Biguanides
- **Metformin**
  - Oral therapy
  - Exact mechanism unknown
  - Primary effect: ↓ hepatic glucose production
    - Inhibits gluconeogenesis
Biguanides
Metformin
• Most common adverse effect is GI upset
  • Nausea, abdominal pain
  • Can cause a metallic taste in the mouth
• 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
• Other effects
  • Reduced glucose absorption from GI tract
  • Direct stimulation of glycolysis in tissues → ↑ glucose uptake
  • Reduced glucagon levels
  • Leads to ↑ insulin effect (insulin sensitivity)
    • Insulin levels fall slightly on therapy

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

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 → lactic acidosis
  • Can be life threatening
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
• 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”)

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

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

Sulfonylureas Adverse Effects
• Can also cause weight gain
• More insulin release
• Insulin causes weight gain

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Wikipedia/Public Domain
Sulfonylureas Adverse Effects
• Can also cause weight gain
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• Insulin causes weight gain
Glucosidase Inhibitors
Acarbose, Miglitol, Voglibose
- Competitive inhibitors of intestinal $\alpha$-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

Thiazolidinediones (TZDs)
Pioglitazone, Rosiglitazone
- Oral therapy
- Decreases insulin resistance

Thiazolidinediones
Potential mechanisms
- GLUT-4
  - Glucose transporter
  - Transcription upregulated
- Adiponectin
  - Adipocyte secretory protein
  - $\uparrow$ insulin sensitivity via several mechanisms
  - Signaling may lead to improved glucose levels
- Antagonism of TNF alpha insulin resistance
  - TNF-$\alpha$ 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
(TZDs)
Pioglitazone, Rosiglitazone
- Act on PPAR-$\gamma$ 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-$\alpha$
Lower triglycerides

Thiazolidinediones
Adverse Effects
- Edema
  - Occurs in ~5% patients
  - Due to PPAR-$\gamma$ effects in nephron $\rightarrow$ $\uparrow$ Na retention
  - Risk of pulmonary edema
  - Not used in patients with advanced heart failure

Thiazolidinediones
Oral therapy
- Decreases insulin resistance
**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  
  - Secreted after meals  
  - Stimulates insulin release (similar to GIP)  
  - Also blunts glucagon release, slows gastric emptying  
  - Oral glucose metabolized faster than IV glucose

---

**Amylin Analogs**  
Pramlintide  
- **GIV 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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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

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

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

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Canagliflozin, Dapagliflozin
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Reproductive Hormones

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

Reproductive Hormones
- Estrogens and androgens
- Development and function of sex organs
- Secondary sexual characteristics (puberty)

Estrogens
- Potency: Estradiol > Estrone > Estriol

Androgens
- Potency: DHT > Testosterone > others

Reproductive Hormones
- Steroid hormones (from cholesterol)
- Poorly soluble in plasma
- Carried by sex hormone binding globulins (SHBGs)
  - Smaller amount by albumin
  - Cross lipid bilayer of cells
  - Bind to intracellular receptors

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

A > E
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

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

Cirrhosis
• ↑ estrogen effects
  • Gynecomastia
  • Spider nevi
  • Palmar erythema
  • Testicular atrophy
  • Impotence
• Altered metabolism/excretion → ↑ estrogen
• ↑ SHBG → ↑ estrogen effects
• Clinical features of Testosterone/Luteinizing

Reproductive Hormones
• Hypothalamus: GnRH
• Pituitary:
  • Follicle stimulating hormone
  • Luteinizing Hormone
• Testes/Ovaries
  • Androgens/Estrogens

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

SHBG
Sex Hormone Binding Globulins

<table>
<thead>
<tr>
<th>Causes</th>
<th>↑ Estrogens</th>
<th>↑ Androgens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormones</td>
<td>Hypothyroidism</td>
<td>Nephrotic Syndrome</td>
</tr>
<tr>
<td>Clinical Effects</td>
<td>Gynecomastia (men)</td>
<td>Hirsuitism (women)</td>
</tr>
</tbody>
</table>

SHBG
Sex Hormone Binding Globulins

Low SHBG
Bound
Free
Bound
Free

High SHBG

Gynecomastia
Spider nevi
Palmar erythema
Testicular atrophy
Impotence
### 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

**Uses**
- Continuous
  - Suppression of LH/FSH release
  - Endometriosis
  - Uterine fibroids (leiomyomata)
  - Prostate cancer
  - Precocious puberty

- 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

### 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

### GNRH

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

### GnRH

- Gonadotropin-releasing hormone
- Gq protein system with IP3 second messenger
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---

Eak435s /Wikipedia
Pituitary Hormones
• All have a cAMP second messenger system
  • α-subunit
  • β-subunit

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
Male Reproductive Hormones

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

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

Dihydrotestosterone (DHT)
- Testosterone converted to DHT in peripheral tissues
- Enzymes: 5-α reductase
- Many testosterone effects mediated by DHT
- DHT: ↑ potency
  - Binds androgen receptor > testosterone
  - More stable

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

**Males**

1. Development of testes requires Y chromosome
2. SRY gene produces testis determining factor
3. All males (XY) born with testes
4. "Chromosomal sex" determined by XX/XY
5. Internal/external genitalia requires hormones

**Fetus**

- Derived from mesonephric ducts
- Seminal vesicles, epididymis, vas deferens
- Requires testosterone
- External genitalia
  - Derived from urogenital sinus
  - Penis, scrotum (also prostate, bladder)
  - Requires DHT

**Testosterone Effects**

**Males**

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

**Testosterone Effects**

**Fetus**

- Internal genitalia
  - Derived from mesonephric ducts
  - Seminal vesicles, epididymis, vas deferens
  - Requires testosterone

**5-α Reductase Deficiency**

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

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**Males**

- Different effects on different growth stages
  - Fetus
  - Puberty
  - Adult
**Testosterone Effects**

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

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

**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 genitilia seen +/- hypospadias
  - Sometimes diagnosed at birth due to ambiguous genitalia

**5-α Reductase Deficiency**

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

**Testosterone Effects**

**Adults**
- Prostate growth
  - Finasteride $\rightarrow$ Decrease DHT $\rightarrow$ Treatment of BPH
- Testosterone therapy $\rightarrow$ BPH
- May effect lipids
  - Exogenous testosterone $\rightarrow$ Decrease HDL/Increase 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

**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

**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

**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

- Secrete inhibin B: Inhibits FSH
- Form blood-testis barrier
- Tight junctions between adjacent Sertoli cells
- Isolates sperm
- Protection from autoimmune attack
- 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
- Eplerenone
- Alternative to spironolactone
- Does not cause gynecomastia
- Can be used in heart failure

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Disorders of Sex Development

**Ambiguous Genitalia**
- 46, XX
- 46, XY
- Mullerian Structures
  - YES
  - Often CAH
- CAH
  - Lack of androgens
  - CAIS
  - ↓ DHT

**Abnormal Puberty**
- 46, XX
- 46, XY
- Mullerian Structures
  - YES
  - CAH
  - CAIS

**Complete Androgen Insensitivity Syndrome (CAIS)**
- 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

**Male Development**
- Y Chromosome → testes → Sertoli cells
- Mesonephric (Wolffian) ducts: male structures
- 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**
- 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
  - 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

**Disorders of Sex Development**
- Ambiguous Genitalia
- Abnormal Puberty
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

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 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

Bilateral Undescended Testes

Varicocele
• Dilatation of pampiniform plexus of spermatic veins

Cryptorchidism

Cryptorchidism Complications

Cryptorchidism Treatment
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

- 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
**Female Reproductive Hormones**

**Estrogens**
- Potency: Estradiol > Estrone > Estriol
  - Estradiol (17β-estradiol)
  - Estrone
  - Estriol

**Hormone Synthesis**
- **Theca cells**
  - Convert cholesterol into androstenedione
  - Stimulated by LH (via cAMP 2nd messenger)
- **Granulosa cells**
  - Convert androstenedione into estradiol
  - Stimulated 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
  - Antrum (fluid)
  - Granulosa Cells
  - Oocyte
  - Theca Cells

**Female Reproductive System**
Progesterone Effects

- Many effects oppose estrogen
  - Decreases expression estrogen receptors
  - Many effects favorable to pregnancy

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
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

- Estrogen levels fall at menopause
  - Ovarian estrogen production stops
  - Continued lower-level estrogen from adipose tissue
  - Endometriosis and fibroids improve
- Unopposed estrogen levels higher after menopause
  - Continued estrogen from adipose tissue
  - No progesterone to oppose estrogen effects
  - Endometrial exposure to unopposed estrogen
  - Especially in obese women
  - Increased risk of endometrial carcinoma

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

Oral Contraceptives

- Estrogen levels high during reproductive years
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  - Endometriosis
  - Uterine fibroids

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

Contraindications

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

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

- 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

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)

Combination OCPs

Contraindications

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

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
- Antrum (fluid)
- Granulosa Cells
- Oocyte
- Theca Cells

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

Menstruation
• Progesterone levels fall
• Vasoconstriction of spiral arteries
• Apoptosis of endometrial cells occurs
• Collapse and desquamation of endometrium

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

Menstrual and Uterine Cycles

Uterine Cycle
Secretory Phase
• 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
Proliferative Phase
• Menstruation followed by endometrial proliferation
• Stimulated by estrogen
• Endometrial thickness increases (>10x)
• Growth of glands, stroma, blood vessels

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Uterine Cycle
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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

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  - 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 estrogen 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

- 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

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

Menopause

- 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

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

HRT

- Benefits:
  - Relieves hot flashes
  - Improves bone density
- Possible risks:
  - ↑ risk of DVT/Stroke/MI
  - ↑ risk of breast cancer
PCOS

Poly cystic Ovarian Syndrome

- Common cause secondary amenorrhea
- Genetics plus diet/obesity → ↑ LH:FSH ratio
- LH drives androstenedione from theca cells
- Some androgens → estrone in adipose tissue
- Estrone → ↓ FSH → anovulation

Hyperinsulinemia

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

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
  - Suppress LH
  - Estrogen → ↑ SHBG → ↓ androgens
- Spironolactone
  - Blocks androgens
- Metformin/TZDs
  - Diabetes drugs that improves insulin resistance
  - Not routinely used unless patient develops diabetes

PCOS

Clinical features

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

Hypercetinsulinemia

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

PCOS

Genetics

- Anovulation
- Follicular Cysts
- ↑ Androstenedione (Theca cells)
- Hirsutism/Acne
- ↑ Estrone (Adipose)
- ↓ FSH
- ↓ Progesterone
- ▼ Testosterone
- Estradiol (Granulosa cells)
- ↑ LH/↓ FSH

PCOS

Growth

- Genes
- Diet/Obesity
- Hyperinsulinemia

PCOS

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**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>Mulherian Dysgenesis</td>
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</tr>
</tbody>
</table>
Pituitary Gland

Jason Ryan, MD, MPH

Anterior Pituitary Gland

Adenohypophysis

- 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>Corticotroph</td>
<td>Adrenocorticotropic hormone (ACTH)</td>
</tr>
<tr>
<td>Thyrotroph</td>
<td>Thyroid-stimulating hormone (TSH)</td>
</tr>
<tr>
<td>Gonadotroph</td>
<td>Luteinizing hormone (LH)</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
<td></td>
</tr>
<tr>
<td>Somatotroph</td>
<td>Growth hormone (GH)</td>
</tr>
<tr>
<td>Lactotroph</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

Pituitary Gland

- Connected to hypothalamus via pituitary stalk
- Connects to median eminence of hypothalamus
  - One of the circumventricular organs (CVOs)
  - Does not contain blood brain barrier

Pituitary Gland

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

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 (GRH)</td>
<td>GH/Somatostatin</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Prolactin</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>GHR/TSH</td>
</tr>
</tbody>
</table>
**Prolactin**

- Protein hormone
- Regulates milk production in mothers

---

**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

---

**Prolactin in Pregnancy**

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

---

**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 in Pregnancy**

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

---

**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

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**Prolactin in Pregnancy**

- **Prolactin**
  - Protein hormone
  - Regulates milk production in mothers

---
Dopamine Agonists

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

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>
<th>Disease</th>
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<tbody>
<tr>
<td>Lactotrophs</td>
<td>Hyperprolactinemia</td>
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<tr>
<td>Thyrotrophs</td>
<td>General hyperthyroidism</td>
</tr>
<tr>
<td>Corticotrophs</td>
<td>Cushing’s disease</td>
</tr>
<tr>
<td>Somatotrophs</td>
<td>Acromegaly/Gigantism</td>
</tr>
</tbody>
</table>

Dopamine Antagonists

- Antipsychotics: Haloperidol, Risperidone
- Antiemetics: Metoclopramide
- Blockade of D2: ↑ prolactin

- Side Effects:
  - Amenorrhea
  - Breast engorgement
  - Galactorrhea
  - Sexual dysfunction
- Can also cause Parkinsonian symptoms
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

Redacted text
**Growth Hormone**

- **Somatotropin**
  - Many stimulants and suppressors
  - Pituitary release stimulated by:
    - GHRH
    - Exercise
    - Sleep (very high just after onset of sleep)
  - Released inhibited by:
    - Glucose
    - Somatostatin (released in response to IGF-1; GH)
    - IGF-1 (direct and indirect)

**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

**Growth Hormone**

- Liver contains many growth hormone receptors
- GH → Liver → IGF-1 secreted
- Insulin-like growth factor 1/Somatotropin
- 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

**Hypopituitarism**

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

**Hypopituitarism**

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

**Hypopituitarism**

- Treatment
  - Hormone therapy
  - Corticosteroids
  - Thyroid hormone
  - Growth hormone
  - Estrogen/testosterone
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
Direct Effects
• Promotes lipolysis
  • Activates hormone sensitive lipase
  • Production of IGF-1 from liver

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

Growth Hormone
IGF-1 Effects
• Chondrocytes
  • Increased linear growth
• Muscle
  • Lean muscle mass
• Organs
  • Increased organ size

Growth Hormone
IGF-1 Effects
• Opposes Insulin
• Raises blood sugar

Growth Hormone
Bone/Muscle
Linear Growth
Lean muscle Mass

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  • GHRH level will be high
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

- Insulin resistance → ↑ insulin → diabetes
  - Diabetes in 10-15% of patients
  - Abnormal glucose tolerance in 50% of patients

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**

**Growth Hormone Excess**

**Treatment**

- **Octreotide**
  - Analog of somatostatin
  - Suppresses release of growth hormone
  - Also surgery, radiation
  - Goal: **Lower IGF-1** to within reference range
  - Bony abnormalities do not regress
  - Joint symptoms often continue

**Oxytocin**

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

- Four endocrine glands
- Formed by 3rd/4th pharyngeal pouch
- Located behind thyroid
- Secrete parathyroid hormone (PTH)
- Important for calcium, phosphate homeostasis

Parathyroid Glands

Jason Ryan, MD, MPH

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Parathyroid Gland
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

Qt Interval

Normal Qt

Prolonged Qt: ↓Mg, ↓Ca

Short Qt: ↑Ca

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)

Parathyroid Hormone

Lumen (Urine)

Interstitium/Blood

PTH

10

Na

P04

Na

ATP

K

1TP04-excretion

Proximal Tubule

Vitamin D and the Kidney

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

25-OH Vitamin D

P04

PTH

1\(\alpha\)-hydroxylase

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

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

### Types of Bone

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

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

PTHrP

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Primary Hyperparathyroidism

Treatment
• 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

Osteitis Fibrosa Cystica

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

Osteitis Fibrosa Cystica

• 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

Primary Hyperparathyroidism

Symptoms
• Bones (bone pain)
  • 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

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

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Hypoparathyroidism
• Inappropriately low PTH secretion
• Not due to hypercalcemia
• Causes hypocalcemia
↓PTH    ↓Ca

FHH
Familial Hypocalciuric Hypercalcemia
• Findings:
  • Usually normal PTH
  • Mildly elevated serum calcium
  • Low urinary calcium (key finding!)
  • May looks like 1° hyperparathyroidism
  • Real world distinction from 1° disease difficult
  • Genetic testing available
  • Usually does not require treatment

Calcium-Phosphate in Renal Failure
Sick Kidneys
↓Phosphate
↓1,25-OH2 Vitamin D
↓Ca from gut
↓Ca from plasma
Hypocalcemia
↑PTH

FHH
Familial Hypocalciuric Hypercalcemia
• Rare, autosomal dominant disorder
• 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 → ↑ calcium
  • More renal resorption of calcium
  • Low urinary calcium

2° Hyperparathyroidism
• Occurs in renal failure patients
• Chronically low serum calcium → ↑ PTH
• No symptoms of hypercalcemia
• Results in renal osteodystrophy
  • Bone pain (predominant symptom)
  • Fractures (weak bones 2° chronic high PTH levels)
  • If severe, untreated can lead to osteitis fibrosa cystica

3° Hyperparathyroidism
• Consequence of chronic renal failure
• Chronically low calcium → chronically ↑ PTH
• Parathyroid becomes autonomous
• VERY high PTH levels
• Calcium may become elevated
• Often requires parathyroidectomy

↑PTH   ↓Ca

2° Hyperparathyroidism
• Occurs in renal failure patients
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↑PTH   ↓Ca
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

Causes

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

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Hypoparathyroidism

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

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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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
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

MEN 1

- 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 1

- Parathyroid adenoma
  - Occurs in 94% of patients
  - First finding in ~90% of patients
  - Will present as hyperparathyroidism
  - Often detected when asymptomatic
  - May cause recurrent kidney stones

MEN Syndromes

Jason Ryan, MD, MPH
MEN 1

- Pancreatic-duodenal neuroendocrine tumors
- Most commonly a gastrinomas
- Zollinger-Ellison syndrome: multiple peptic ulcers
- Rarely insulinomas, glucagonomas, VIPomas

MEN 2A and 2B

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

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

MEN 2A and 2B

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

Medullary Carcinoma

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

MEN 1

- Pancreatic-duodenal neuroendocrine tumors
  - Most commonly a gastrinomas
  - Zollinger-Ellison syndrome: multiple peptic ulcers
  - Rarely insulinomas, glucagonomas, VIPomas

MEN 2B

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

Mikael Häggström/Wikipedia
**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
- Germ-line 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 MEN 2 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
Signaling Pathways

Intracellular Hormones
Receptor in cytoplasm/nucleus
- Progesterone
- Estrogen
- Testosterone
- Cortisol
- Aldosterone
- Thyroid hormone

Steroid Hormones
- Estradiol
- Testosterone
- Aldosterone
- Cortisol
- Cholesterol

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

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

Hormone Effects
- Hormone
- Cell
- Effects

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

JAK/STAT
• Many cytokines
  • IFN-γ, IL-2, IL-6
  • Bone marrow
    • Erythropoietin
    • G-CSF (granulocyte-colony stimulating factor)
    • Thrombopoietin
  • Others
    • Prolactin
    • Growth hormone
**Cyclic AMP**

- Hypothalamus
  - CRH, GHRH
- **Anterior pituitary hormones**
  - FSH, LH, ACTH, TSH
- **Parathyroid gland**
  - PTH
- Others
  - Glucagon
  - ADH (V2-receptor - water)
  - Histamine (H2-receptor - stomach acid)
  - HCG
  - MSH (melanocyte stimulating hormone)

**G-Protein Linked Receptors**

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

**Pituitary Hormones**

- All have a **cAMP second messenger system**

**Cyclic GMP**

- Hormone

**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

- **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**
- Hormone
- Phospholipase C
- Inositol 1,4,5-triphosphate (IP3)

G-Protein Linked Receptors

Hypothalamus

<table>
<thead>
<tr>
<th>Hypothalamus</th>
<th>2nd Messenger</th>
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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>
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<tr>
<td>Growth hormone-releasing hormone (GHRH)</td>
<td>cAMP</td>
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</table>
### Anterior Pituitary

<table>
<thead>
<tr>
<th>Hormone</th>
<th>2nd Messenger</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>Proestrin</td>
<td>JAK/STAT</td>
</tr>
</tbody>
</table>

### Others

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