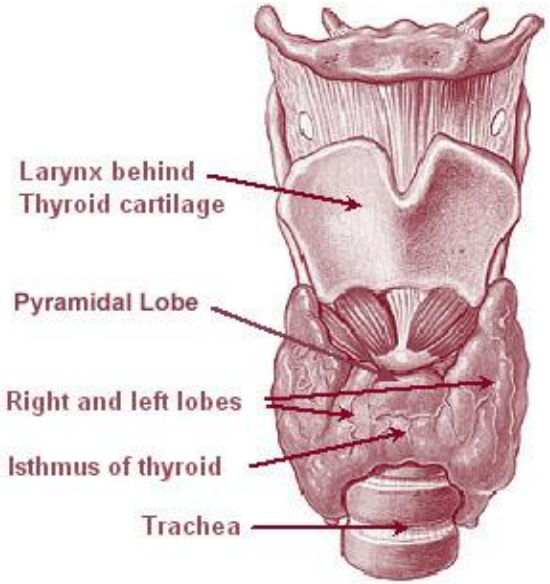
Thyroid Gland

Jason Ryan, MD, MPH

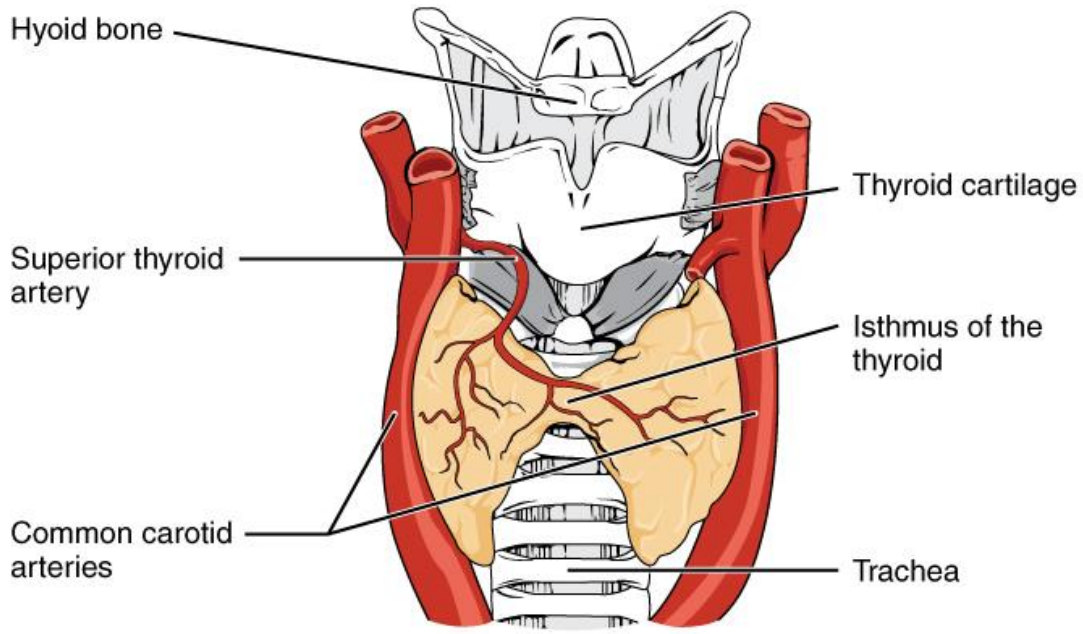
Thyroid Anatomy

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



Thyroid Anatomy

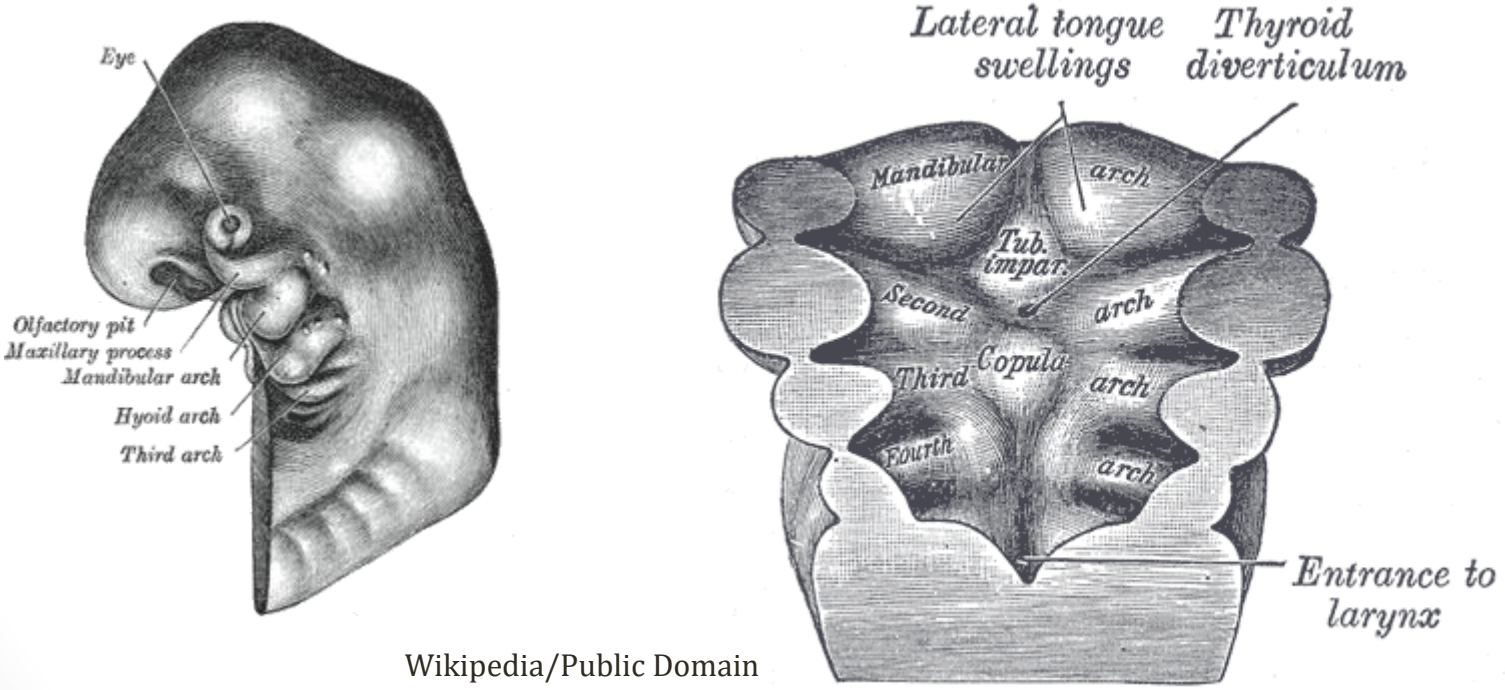
- Blood supply: superior and inferior thyroid arteries
- Superior thyroid: 1st branch external carotid artery
- Inferior thyroid: Thyrocervical trunk (off subclavian)



Thyroid Embryology

- Forms from floor of pharynx (epithelial cells)

24-28 Day Old Embryo



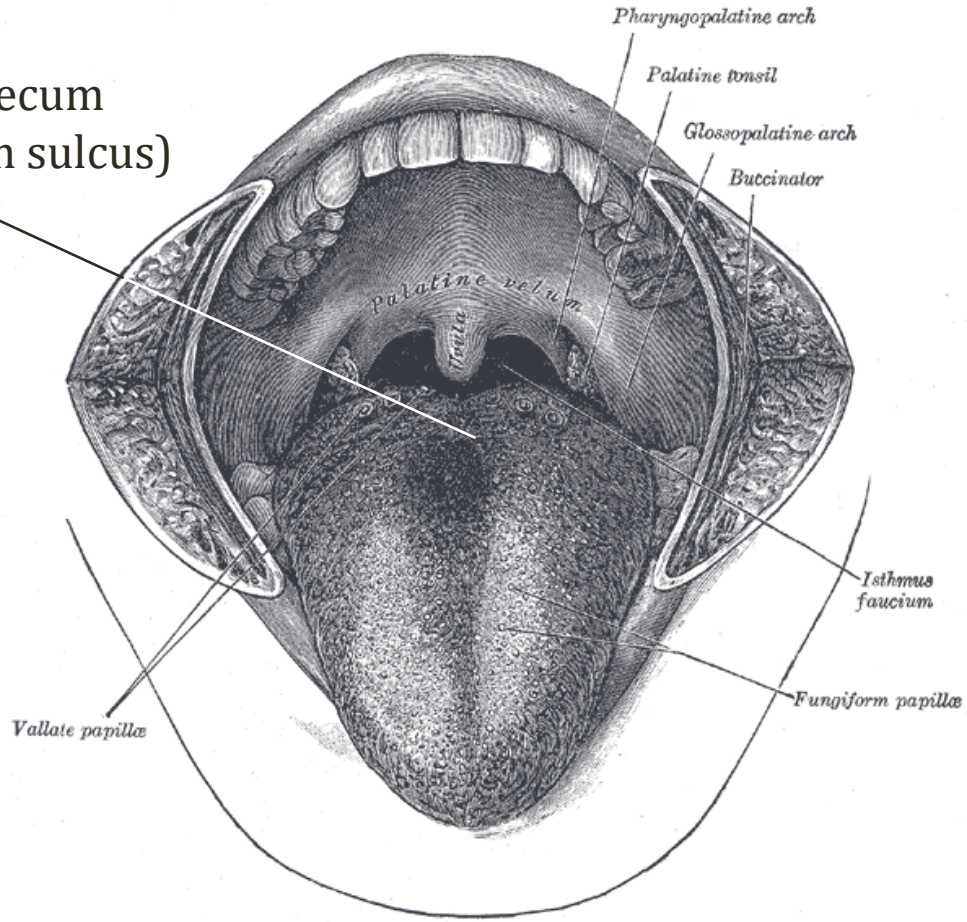
Wikipedia/Public Domain

Thyroid Embryology

- 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

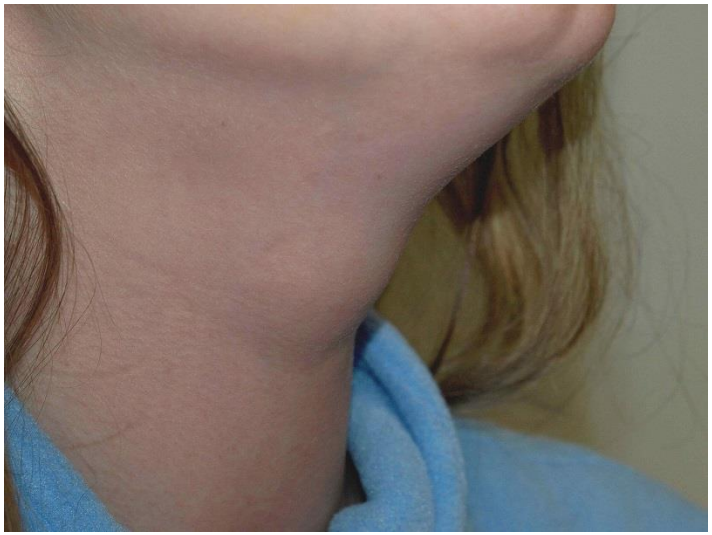
Foramen Cecum

Foramen Cecum
(end of median sulcus)



Thyroglossal Duct Cyst

- Persistent remnant of thyroglossal duct
- **Midline neck mass**; usually painless
- Usually discovered in childhood
- Classically, move up with swallowing or tongue protrusion
- May contain thyroid cells



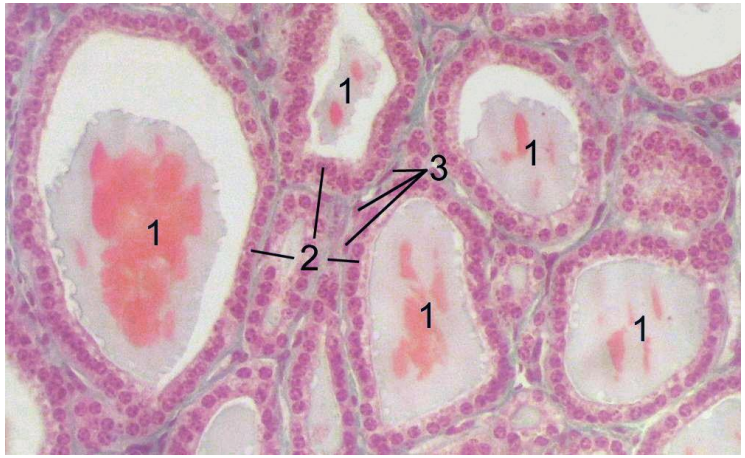
Klaus D. Peter, Gummersbach, Germany

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



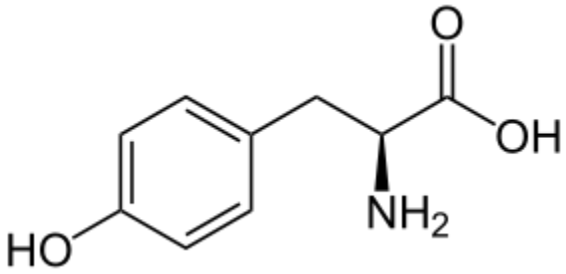
Uwe Gille/Wikipedia

Thyroid Hormones

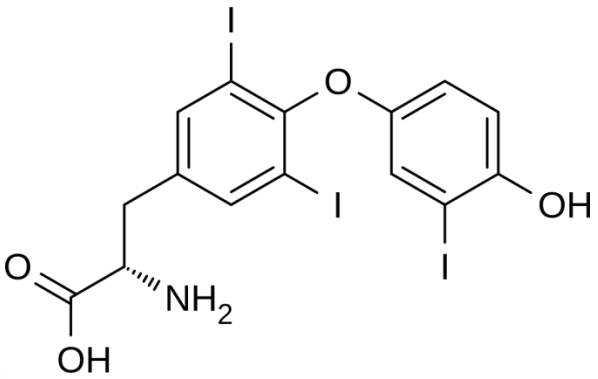
- Contain the element **iodine**
- **Iodized salt**
  - Table salt (NaCl) mixed with small minute amount of iodine
  - Done in many countries to prevent iodine deficiency
  - Added to salt in US in 1924

Thyroid Hormones

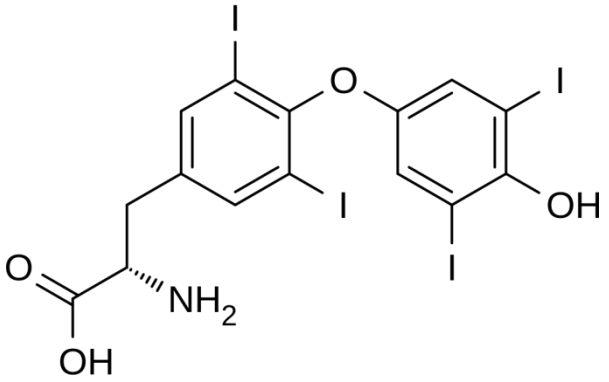
- Two hormones: T3 and T4
- Synthesized from tyrosine and iodine



Tyrosine



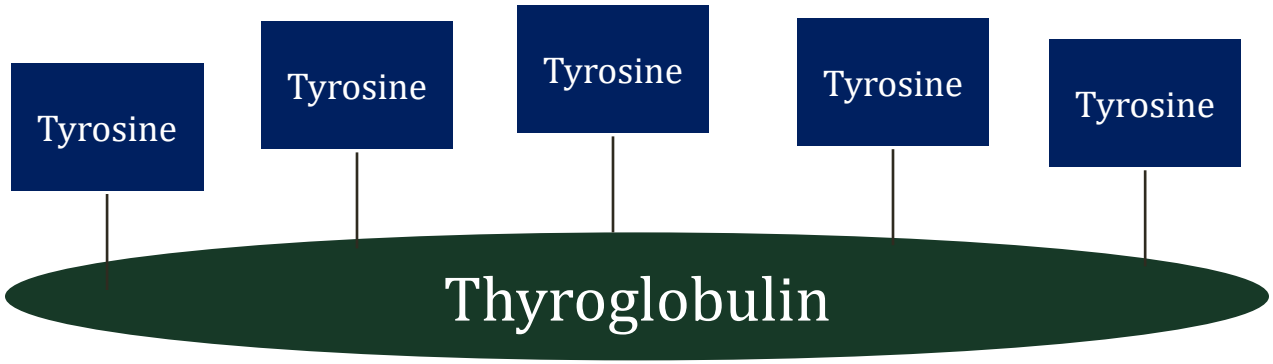
Triiodothyronine ($\mathbf{T_3}$)



Thyroxine ($\mathbf{T_4}$)

Thyroglobulin

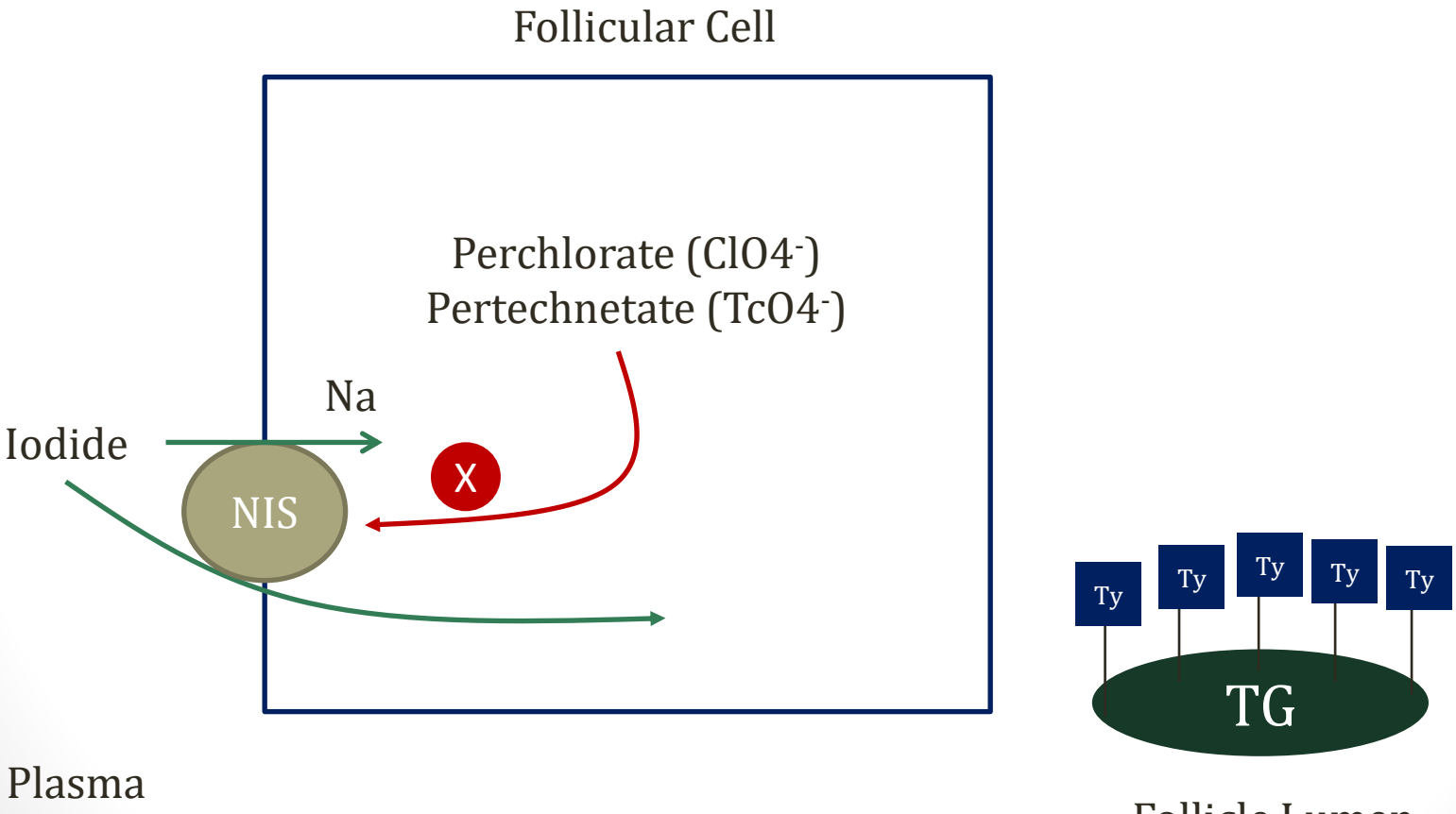
- Large protein
- Produced by thyroid follicular cells
- Contains numerous tyrosine molecules

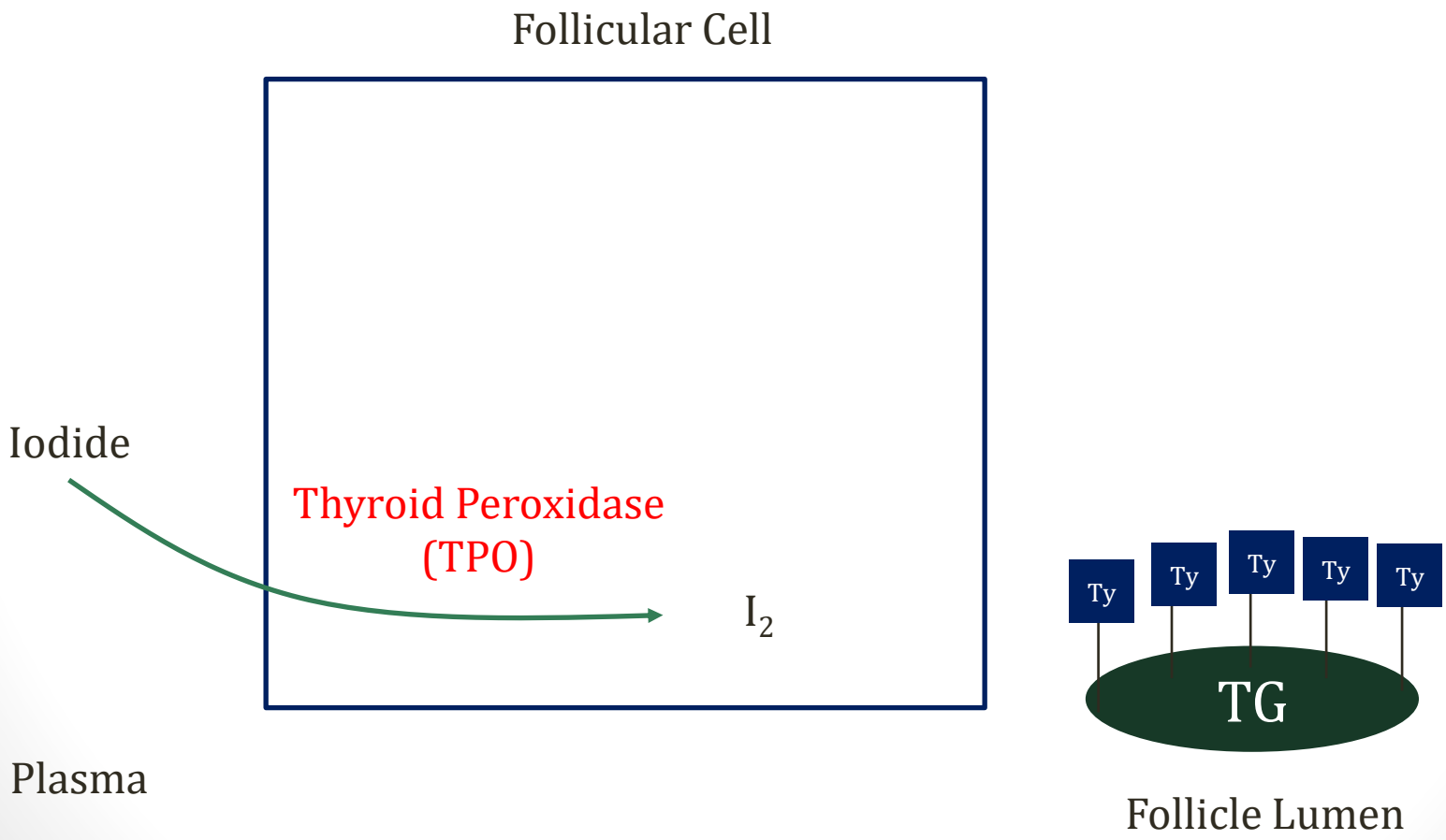


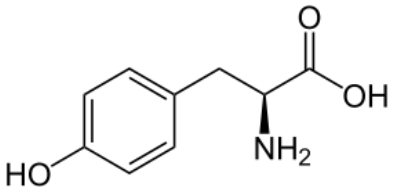
Iodine

- **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 I_2 (undergo "**oxidation**")
  - Added to organic/carbon structures ("**organification**")

NIS
Na-Iodine Symporter





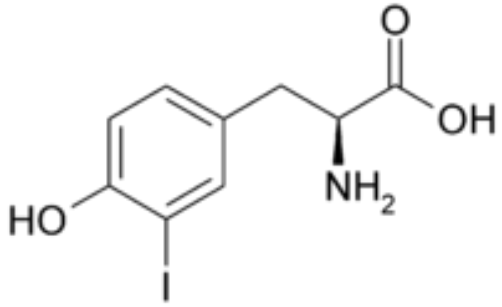


Tyrosine

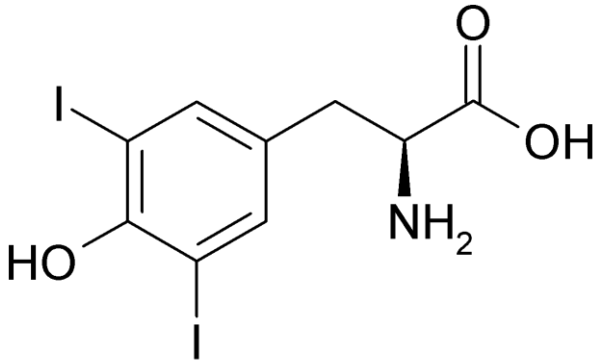
+

Iodine (I_2)

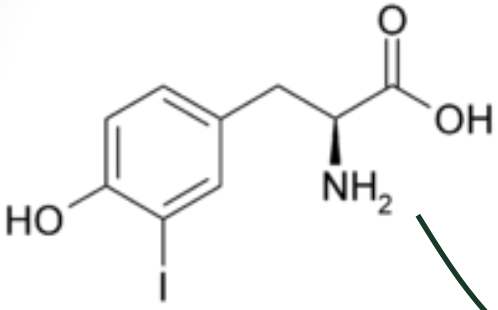
Thyroid Peroxidase (TPO)



Monoiodotyrosine (MIT)

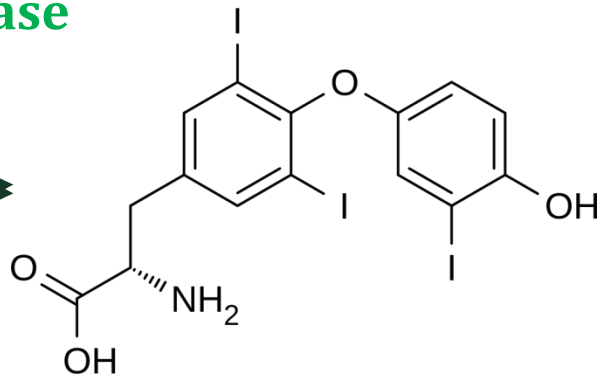


Diiodotyrosine (DIT)

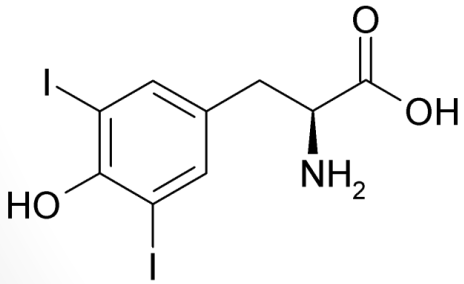


Monoiodotyrosine
(MIT)

Thyroid Peroxidase (TPO)



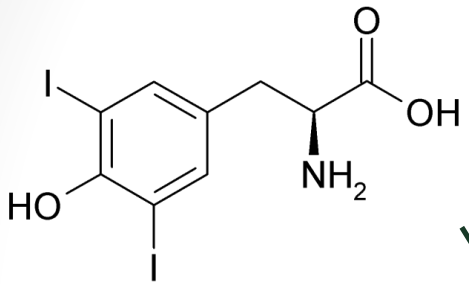
Triiodothyronine ($\mathbf{T_3}$)



Diiodotyrosine
(DIT)

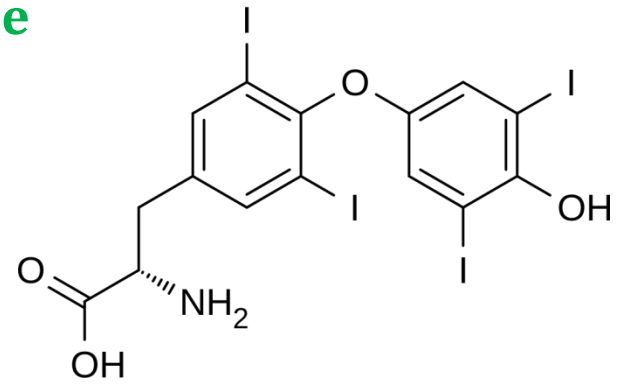
Hormone Synthesis

Coupling Reactions

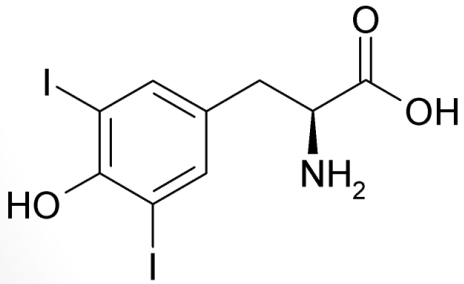


Diiodotyrosine (DIT)

Thyroid Peroxidase (TPO)



Thyroxine ($\mathbf{T_4}$)



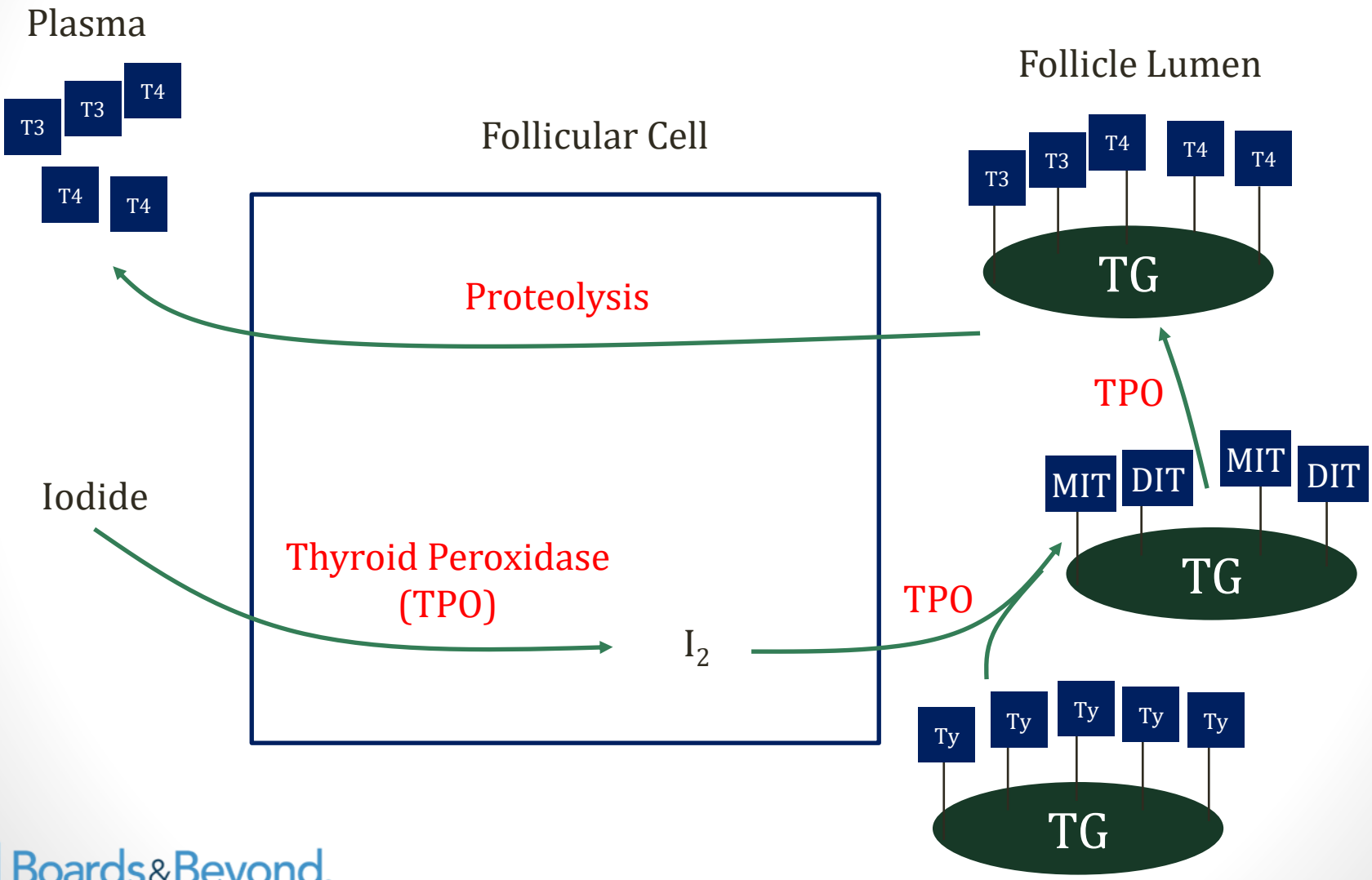
Diiodotyrosine (DIT)

TPO

Thyroid Peroxidase

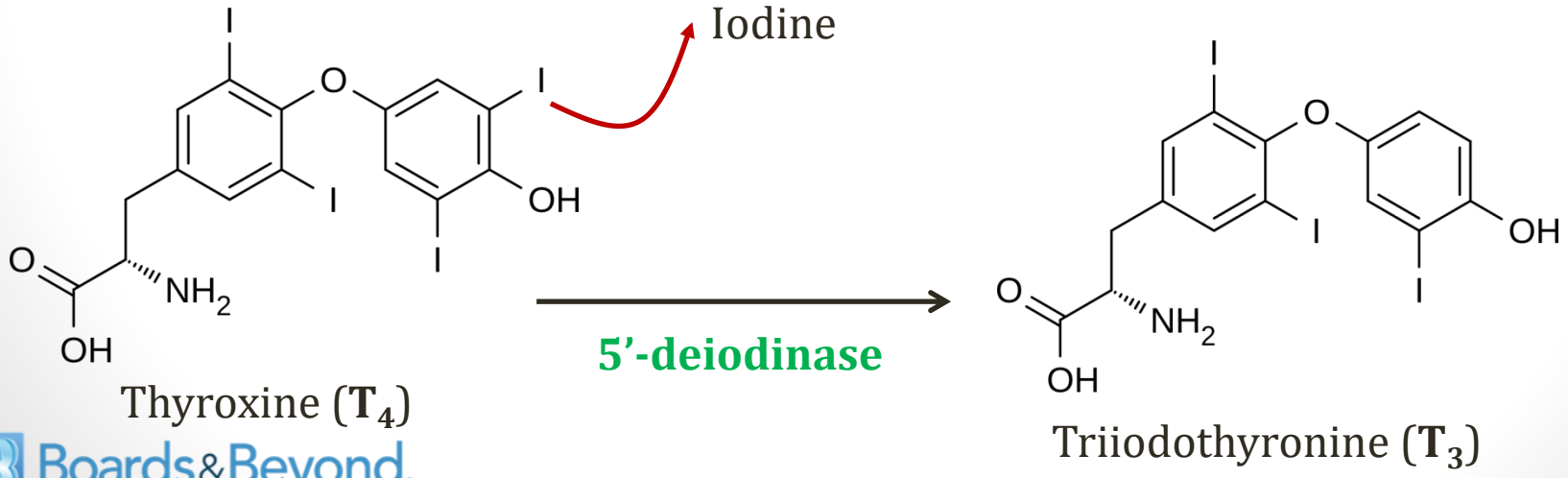
- Multifunctional enzyme
- Catalyzes:
  - Oxidation of iodide
  - Organification of iodine into MIT/DIT
  - Coupling of MIT/DIT into T3/T4
- TPO antibodies common in autoimmune thyroid disease

Hormone Synthesis



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**



Thyroxine ($\mathbf{T_4}$)

Triiodothyronine ($\mathbf{T_3}$)

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

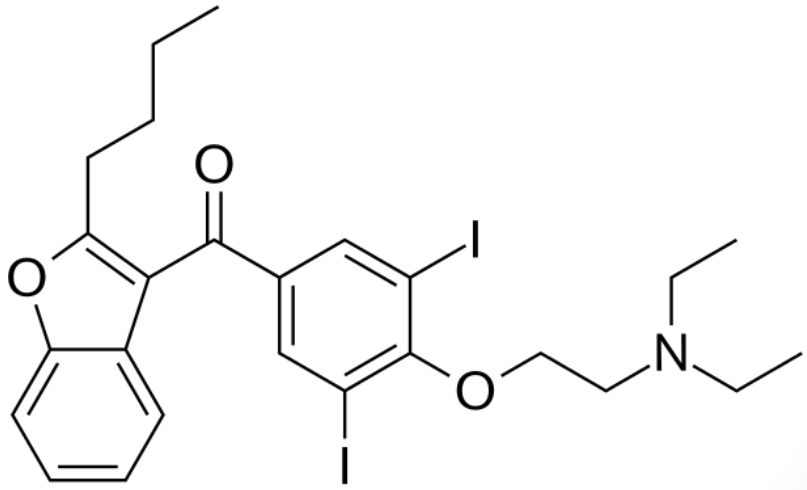
PTU and Methimazole are both "thioamides"

Wolff-Chaikoff Effect

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

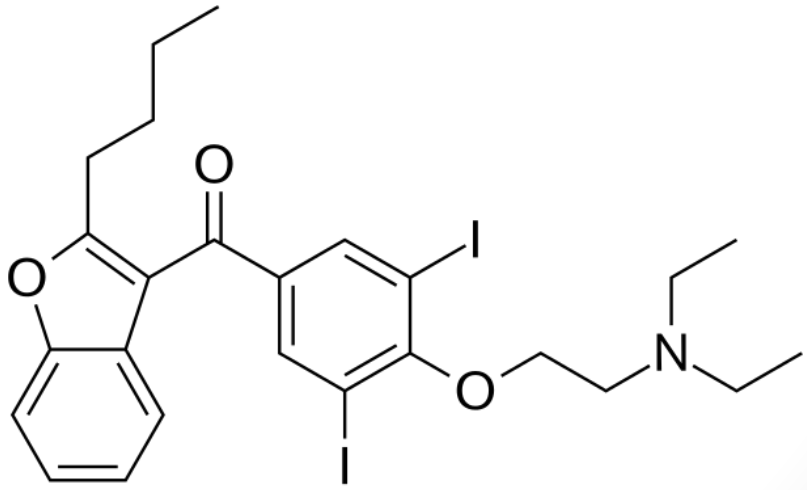
Amiodarone

- Class III antiarrhythmic drug
- Commonly used in atrial fibrillation
- Contains iodine
- Can cause **hypothyroidism** via excess iodine
  - Wolff-Chaikoff Effect



Amiodarone

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



Radioactive Iodine

- I^{131} is an isotope of iodine
  - Has 53 protons like elemental iodine
  - Extra neutrons
- Emits radiation (β-decay)
- Exposure → radioactive iodine in thyroid gland
  - Competes with elemental iodine for uptake
  - Will concentrate in thyroid gland
- Small dose: Used for imaging (I^{123})
- Large dose: Destroys thyroid tissue
  - Used as therapy for hyperthyroidism

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

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

TBG

Thyroxine-Binding Globulin

Rise in TBG

↓

More bound T4

↓

Less free T4

↓

↑TSH

↓

↑Total T4

↓

↑ Free T4 (back to normal)

↓

↓TSH (back to normal)

Thyroid Hormone Receptor

- Family of nuclear receptors
- Hormone-activated transcription factors
- Modulate gene expression

Effects of Thyroid Hormone

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

Thyroid Hormone

Metabolic Effects

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

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
- Hyperthyroid patients: **weight loss**

McDonough AA, et al. **Thyroid hormone coordinately regulates Na+-K+-ATPase alpha- and beta-subunit mRNA levels in kidney.** Am J Physiol. 1988 Feb;254(2 Pt 1):C323-9.

Thyroid Hormone

Cardiac Effects

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

Thyroid Hormone

CNS and Bone effects

- TH required for normal bone growth/CNS maturation
- Childhood hypothyroidism → **cretinism**
  - Stunted growth
  - Mental retardation
- Causes
  - Iodine deficiency (3rd world)
  - Thyroid dysgenesis
  - Inborn errors of hormone synthesis (dyshormonogenesis)
  - TPO most common

Thyroid Hormone

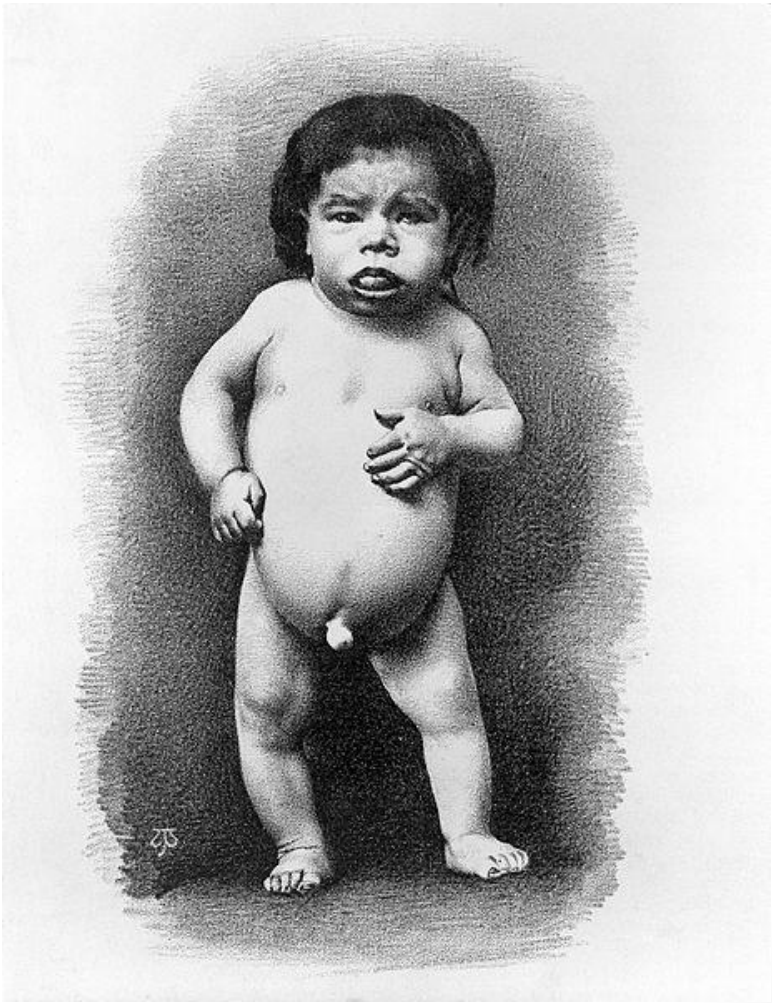
CNS and Bone effects

- Most common **treatable** cause of mental retardation
- Most babies appear normal
  - Maternal T3/T4 crosses placenta
- Newborn screening programs
  - Measure T4 or TSH from heel-stick blood specimens

Thyroid Hormone

CNS and Bone effects

- Mental retardation
- Coarse facial features
- Short stature
- Umbilical hernia
- Enlarged tongue



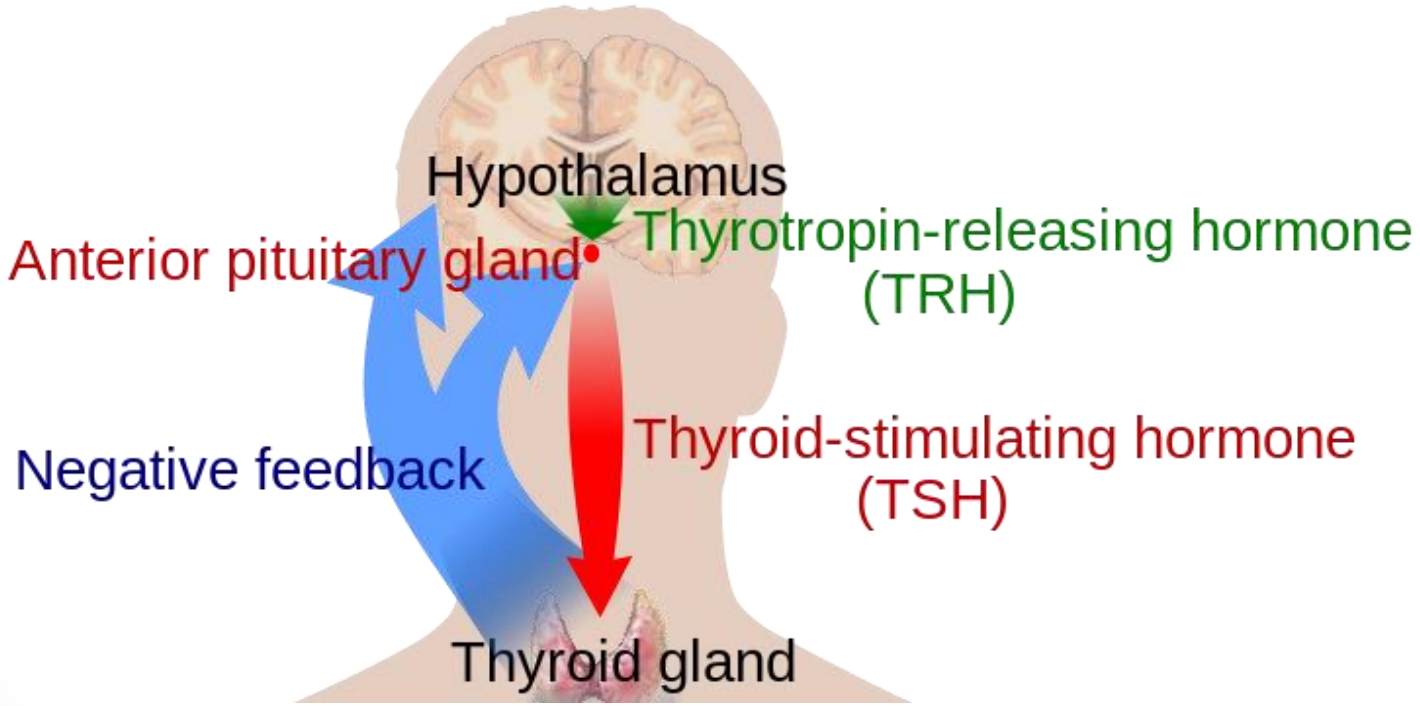
Wellcome Images/Wikipedia

Thyroid Hormone Regulation

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

Thyroid Hormone Regulation

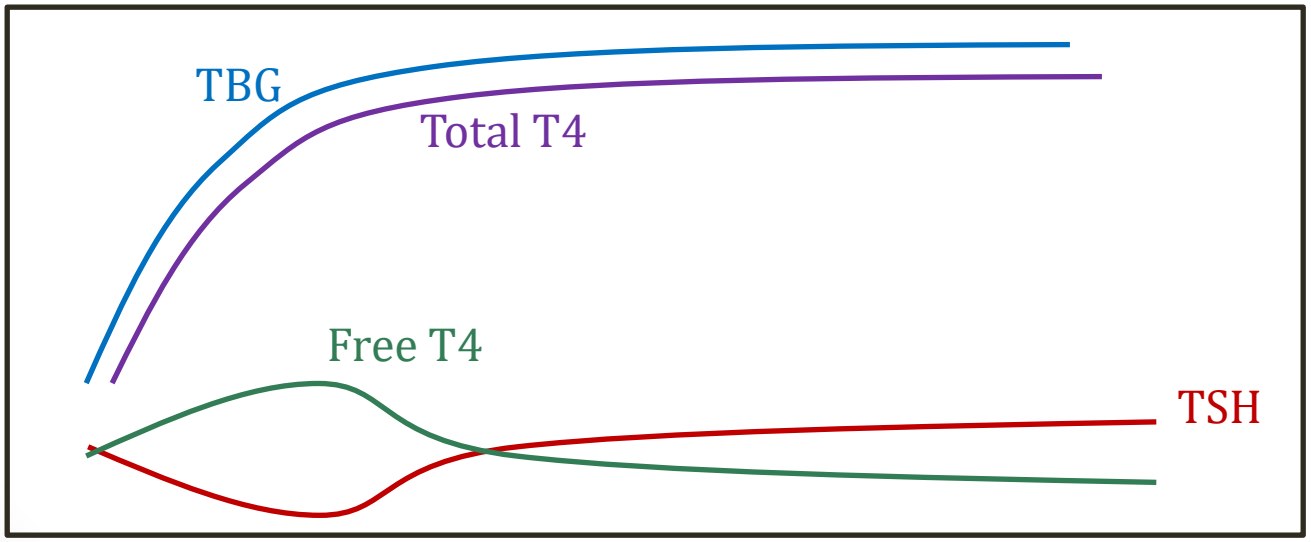
- Serum T4/T3 level sensed by hypothalamus
- Releases thyroid releasing hormone (TRH)



Mikael Häggström/Wikipedia

Pregnancy

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



Thyroid Panel

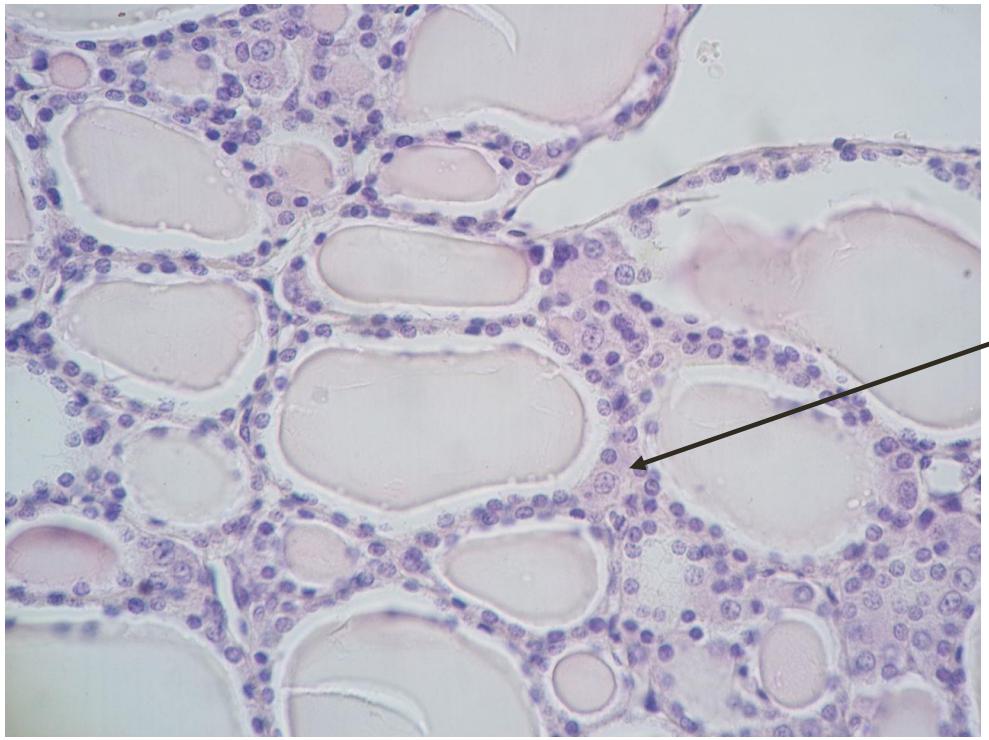
- Four standard measurements to assess thyroid

Test	Normal Value
TSH	0.4 to 5.0 mU/L
Total T4	60 to 145 nmol/L
Total T3	1.1 to 3 nmol/L
Free T4	0.01-0.03nmol/L

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

Calcitonin

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



Andrea Mazza/Wikipedia

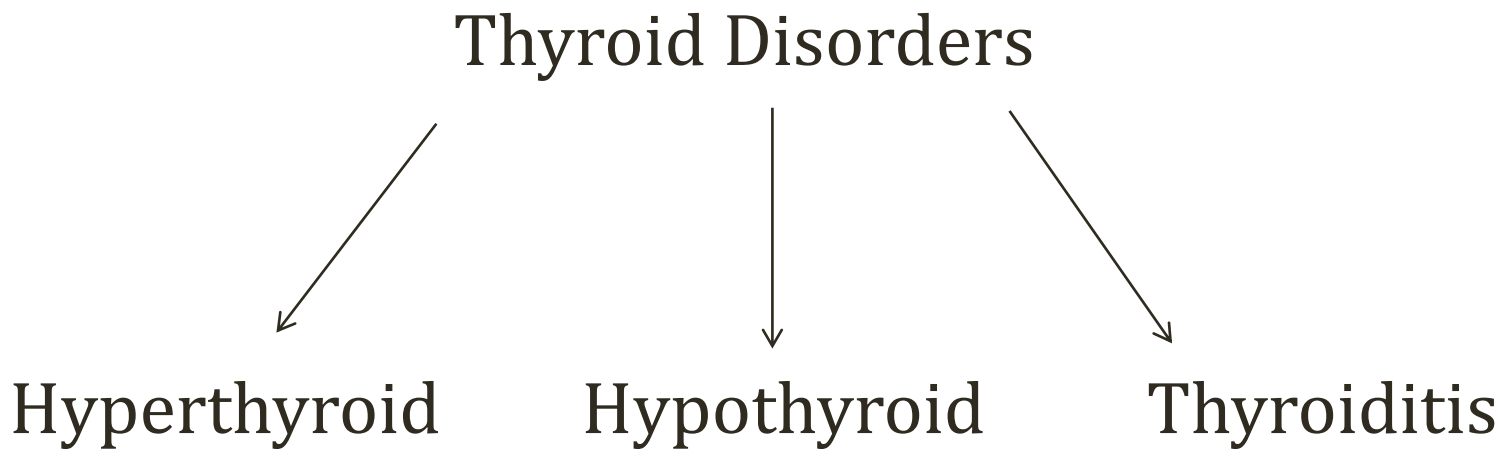
Calcitonin

- 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

Jason Ryan, MD, MPH

Thyroid Disorders



Hypothyroidism

- Metabolism **SLOWS DOWN**
- Lethargy, fatigue
- Weakness; dyspnea on exertion
- Cold intolerance
- Weight gain with loss of appetite
- Constipation
- Hyporeflexia
- Dry, cool skin
- Coarse, brittle hair
- Bradycardia

Hyperlipidemia

- Classic feature of hypothyroidism
- ↑ total cholesterol
- ↑ LDL cholesterol
- Primary mechanism: **↓ LDL receptor density**
  - T_3 upregulates LDL receptor gene activation

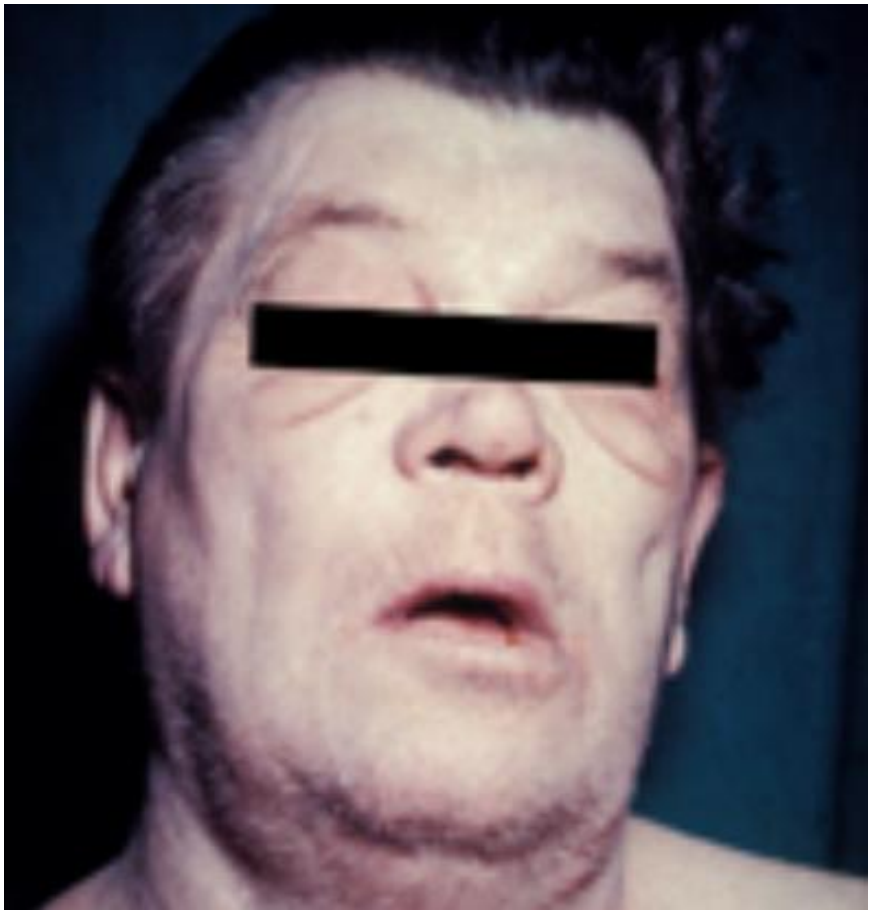
Myxedema

Thyroid dermopathy

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

Myxedema

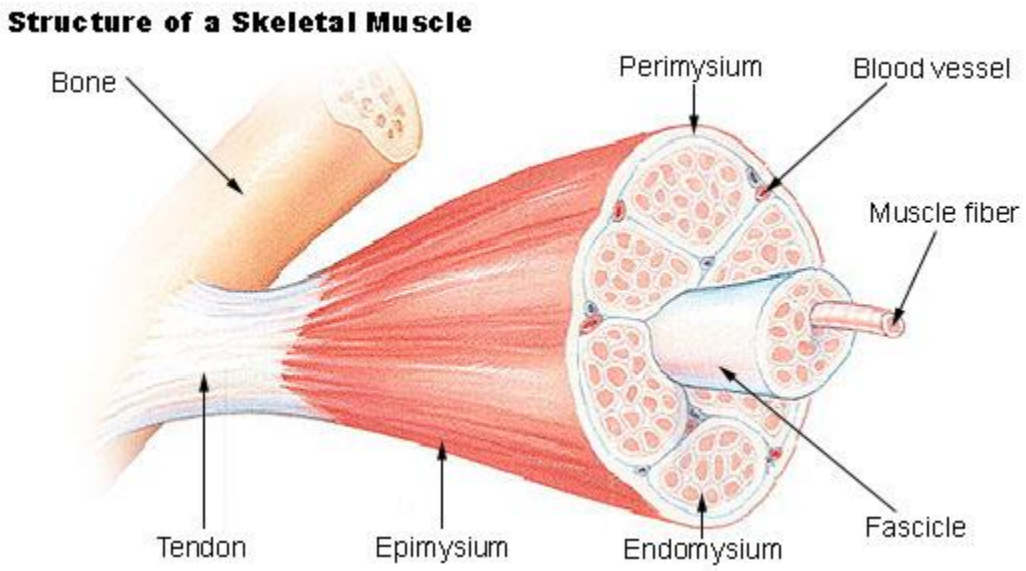
Thyroid dermopathy



Herbert L. Fred, MD and Hendrik A. van Dijk

Hypothyroid Myopathy

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



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Hyponatremia

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

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**

Hyperthyroidism

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

Thyroid Storm

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

Goiter

- Enlarged thyroid
- High TSH, inability to produce T3/T4
- Thyroid stimulating antibodies (Grave's)

Wikipedia/Public Domain

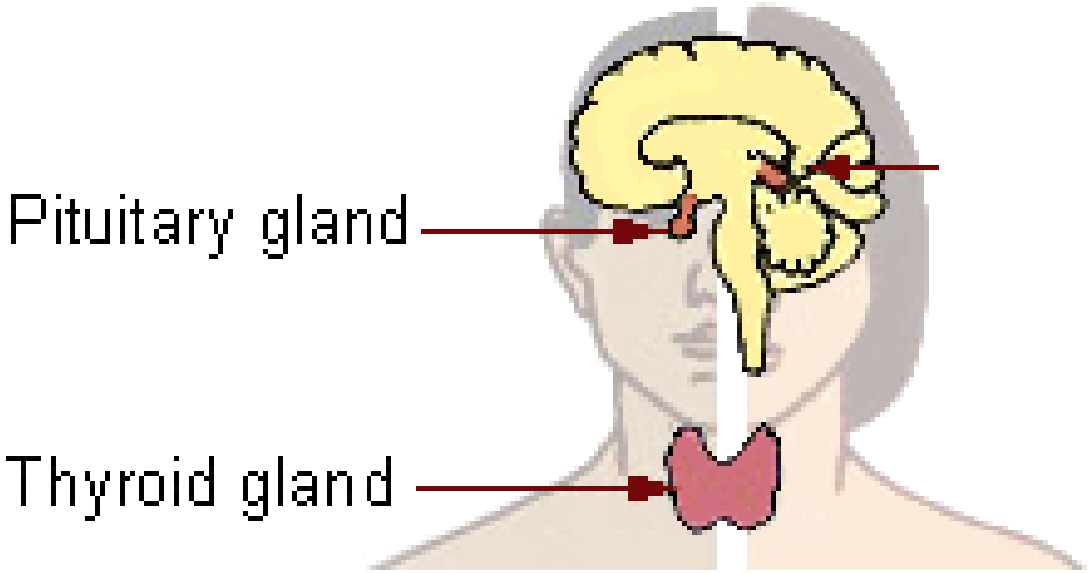
Lab Findings

- Best initial test is **TSH**

TSH

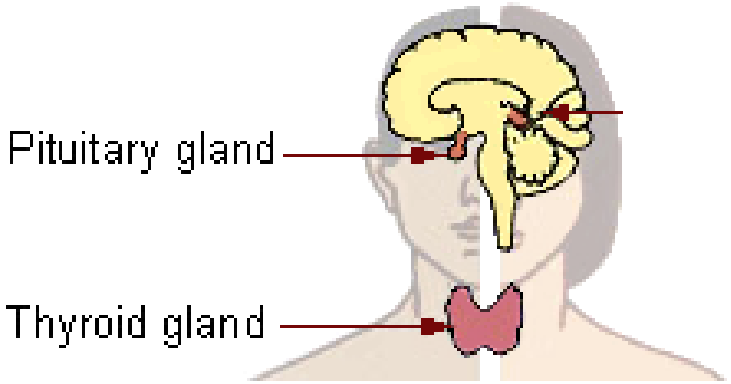
Lab Findings

- 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



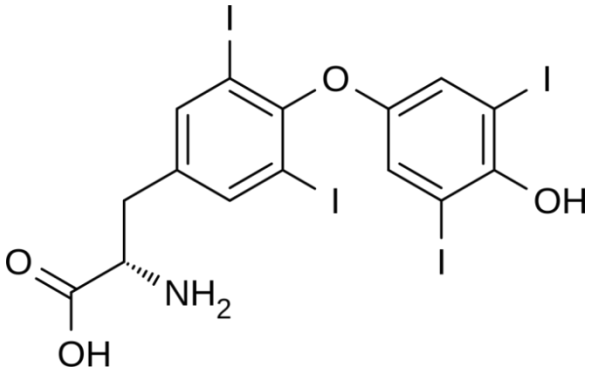
Lab Findings

- 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)

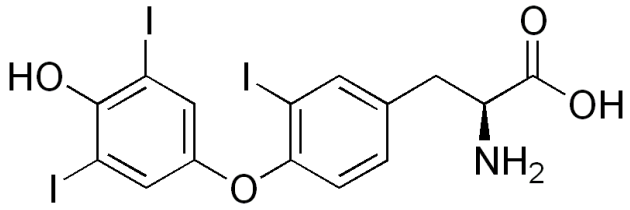


Reverse T3

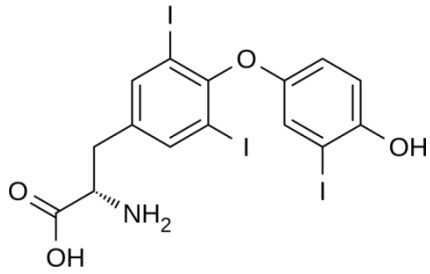
- Isomer of T3 also derived from T4



Thyroxine ($\mathbf{T_4}$)



Reverse T3



Triiodothyronine ($\mathbf{T_3}$)

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

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

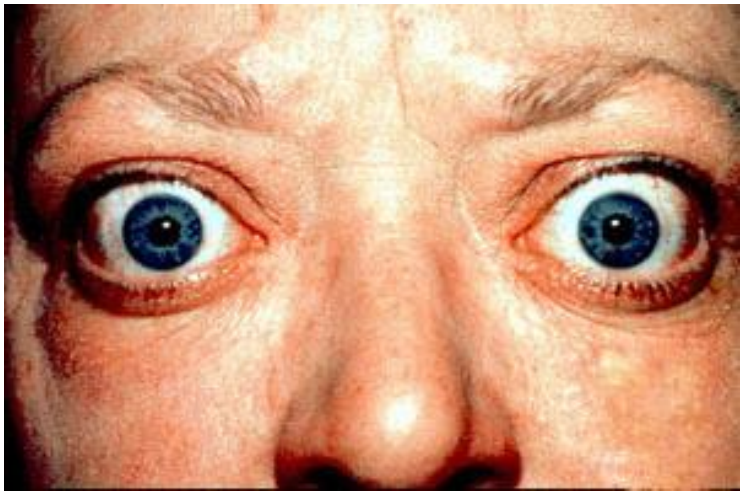
Grave's Disease

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

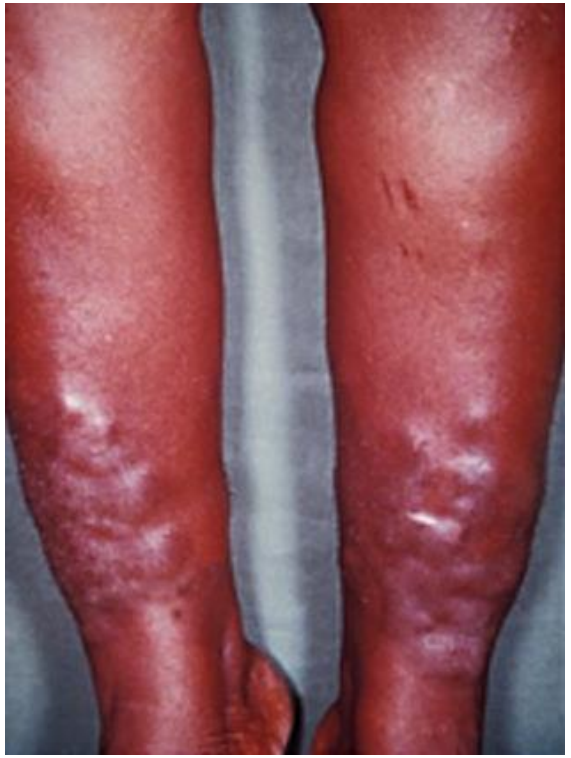
Grave's Disease

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

Grave's Disease



Jonathan Trobe, M.D./Wikipedia



Herbert L. Fred, MD and Hendrik A. van Dijk

Grave's 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

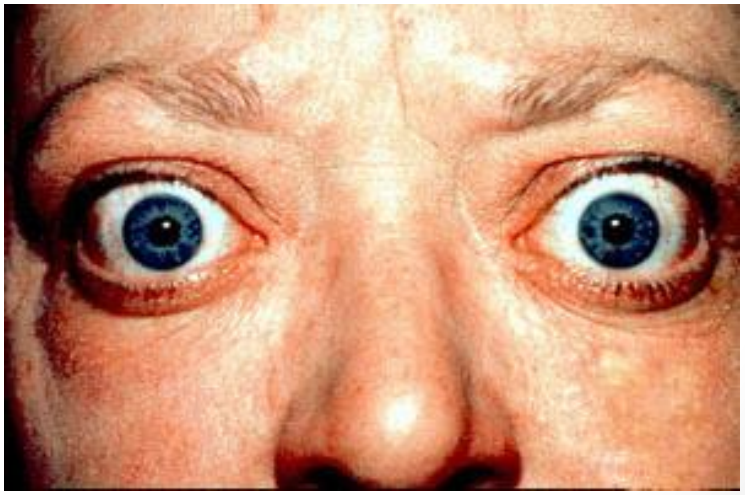
Thyroid Storm

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

Grave's 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



Jonathan Trobe, M.D./Wikipedia

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

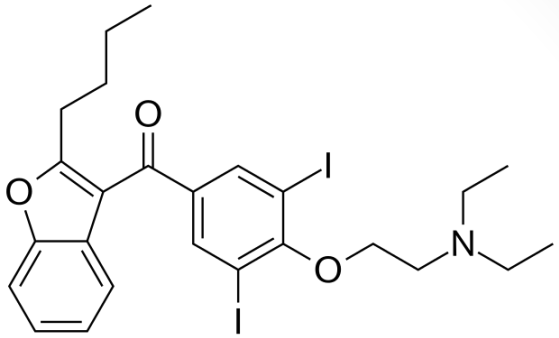
Radioactive Iodine Uptake

- 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**
  - Introduction of iodine → hyperthyroidism
- Often occurs in patients with **toxic adenomas**
  - Drugs administered with high iodine content
  - Expectorants (potassium iodide)
  - CT contrast dye
  - Amiodarone

Amiodarone



- Two types of hyperthyroidism
- Type I
  - Occurs in patients with **pre-existing thyroid disease**
  - Grave's 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**

Hypothyroidism

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

Iodine Deficiency

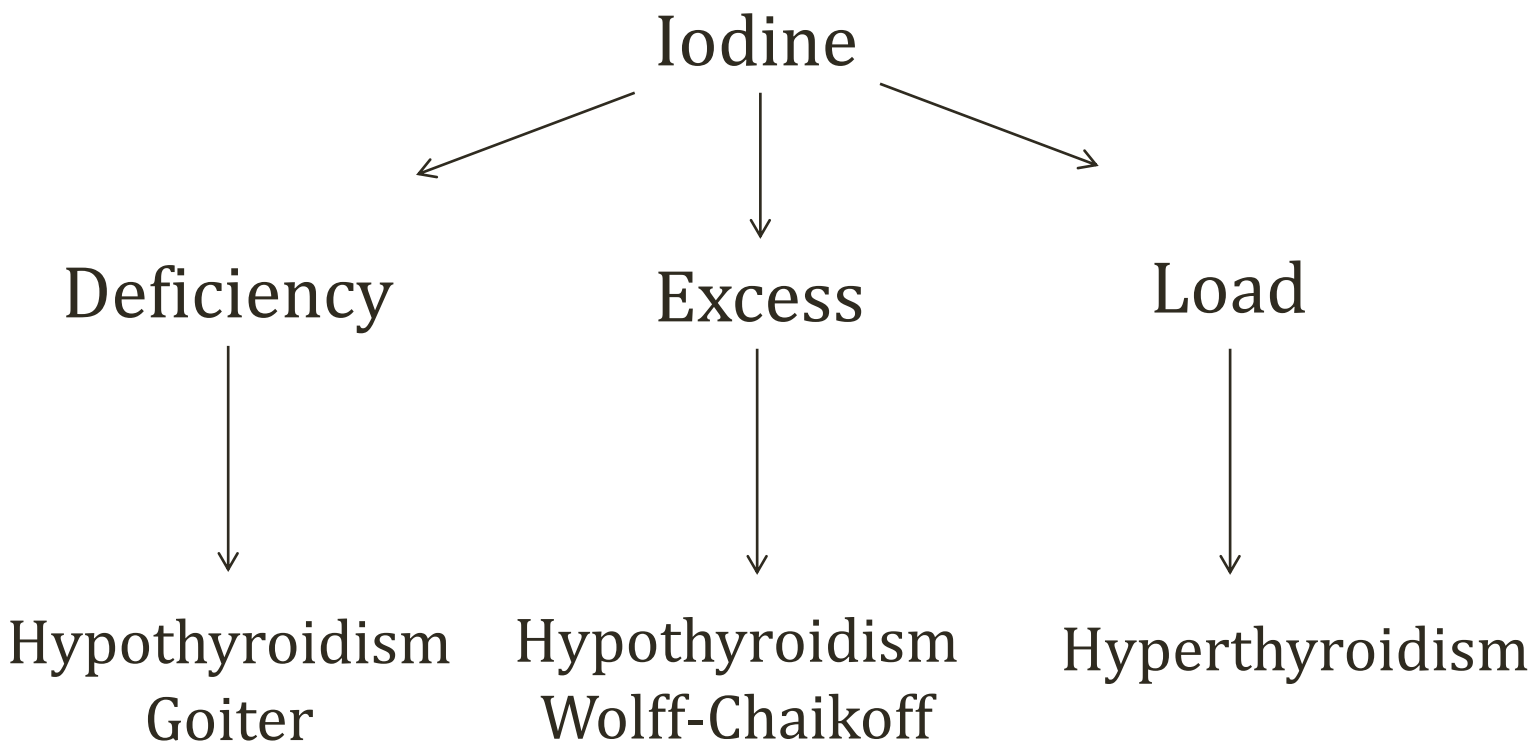
- "Endemic goiter"
  - Goiter in region with widespread iodine deficiency
  - Common in mountainous areas (iodine depleted by run-off)
- Constant elevation of TSH → enlarged thyroid

Wellcome Images

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

Iodine



Goitrogens

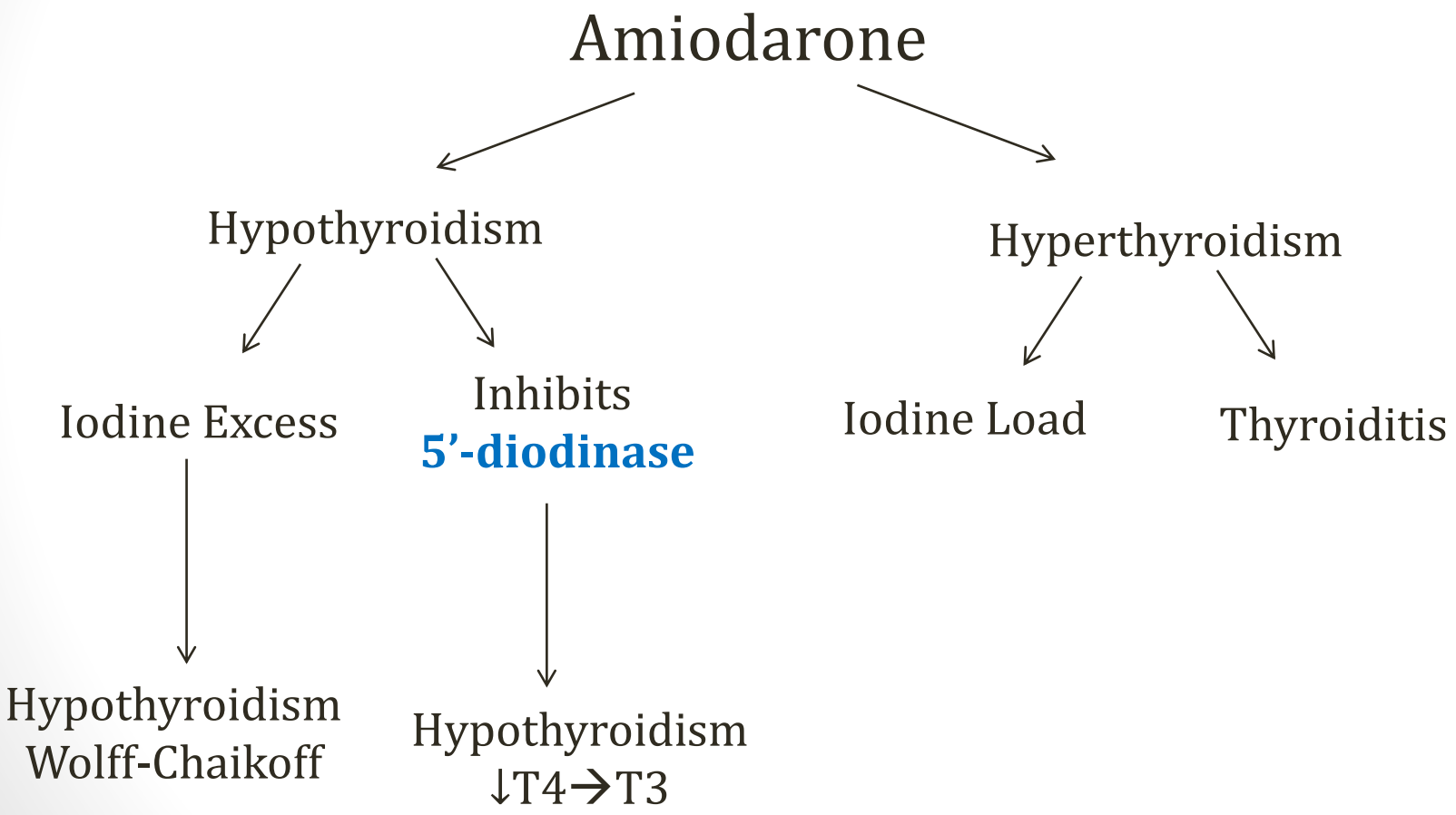
- Substances that inhibit thyroid hormone production
- Most common is iodine
- **Lithium** (inhibits release of thyroid hormone)
- Certain foods (cassava and millet)

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

Always check TSH before starting amiodarone



Congenital Hypothyroidism

- TH required for normal bone growth/CNS maturation
- Childhood hypothyroidism → **cretinism**
  - Stunted growth
  - Mental retardation
- Causes
  - Iodine deficiency (3rd world)
  - Thyroid dysgenesis
  - Inborn errors of hormone synthesis (dyshormonogenesis)
  - TPO most common

Thyroid Hormone

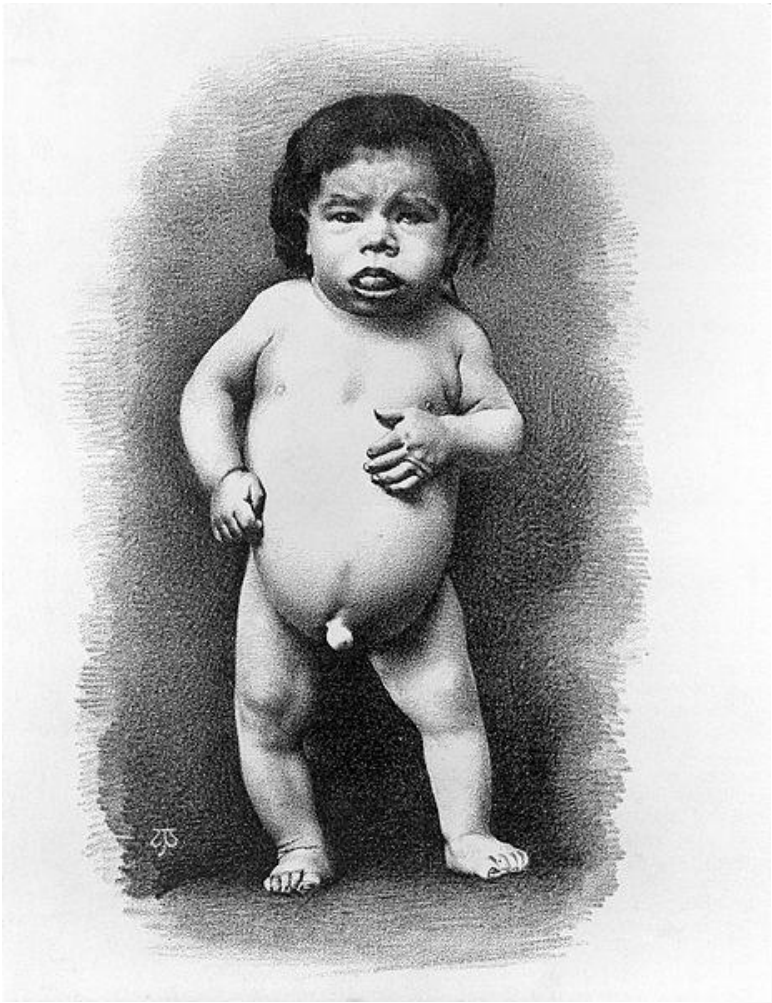
CNS and Bone effects

- Most common **treatable** cause of mental retardation
- Newborn screening programs
  - Measure T4 or TSH from heel-stick blood specimens

Thyroid Hormone

CNS and Bone effects

- Mental retardation
- Coarse facial features
- Short stature
- Umbilical hernia
- Enlarged tongue



Wellcome Images/Wikipedia

Iatrogenic Hypothyroidism

- Thyroid surgery
  - Often done for Grave's or malignancy
- Radioiodine therapy
  - I^{131} administered orally as solution or capsule
  - Beta-emissions → tissue damage
  - Ablation of thyroid function over weeks
  - Done for Grave's or malignancy
- Neck radiation
  - Hodgkin's lymphoma
  - Head and neck cancer

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

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 Grave's without eye/skin findings
  - Serum thyroid stimulating immunoglobulins not elevated
- Followed sometimes by hypothyroidism
  - Can look like Hashimoto's
- Usually self-limited (weeks)

Thyroid Cancer

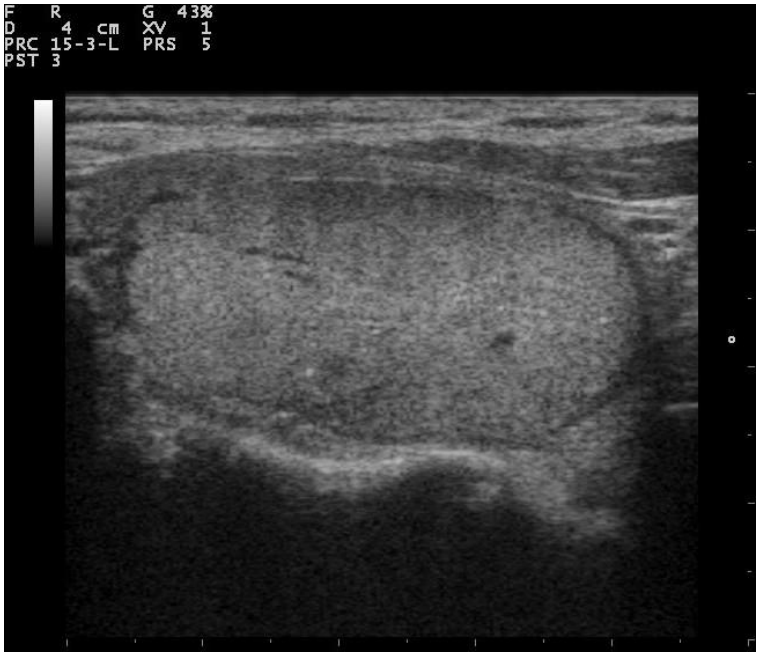
Jason Ryan, MD, MPH

General Principles

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

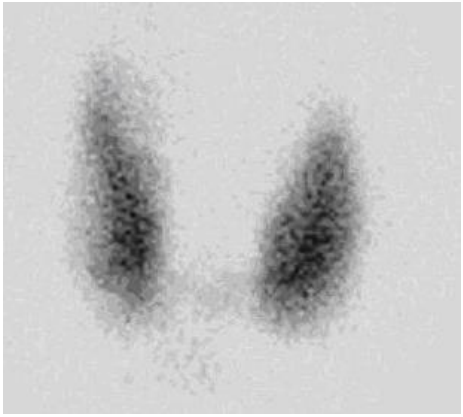
Thyroid Imaging

- **Ultrasound**
  - Some characteristics suggest cancer
  - Borders, vascularity, calcifications



Nevit Dilmen/Wikipedia

Radioactive Iodine Uptake



Myohan /Wikipedia

- Small oral dose I^{131} given to patient
- Scintillation camera → image of thyroid
- Normal: diffuse, even uptake
- Diffuse high uptake: Grave's
- 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

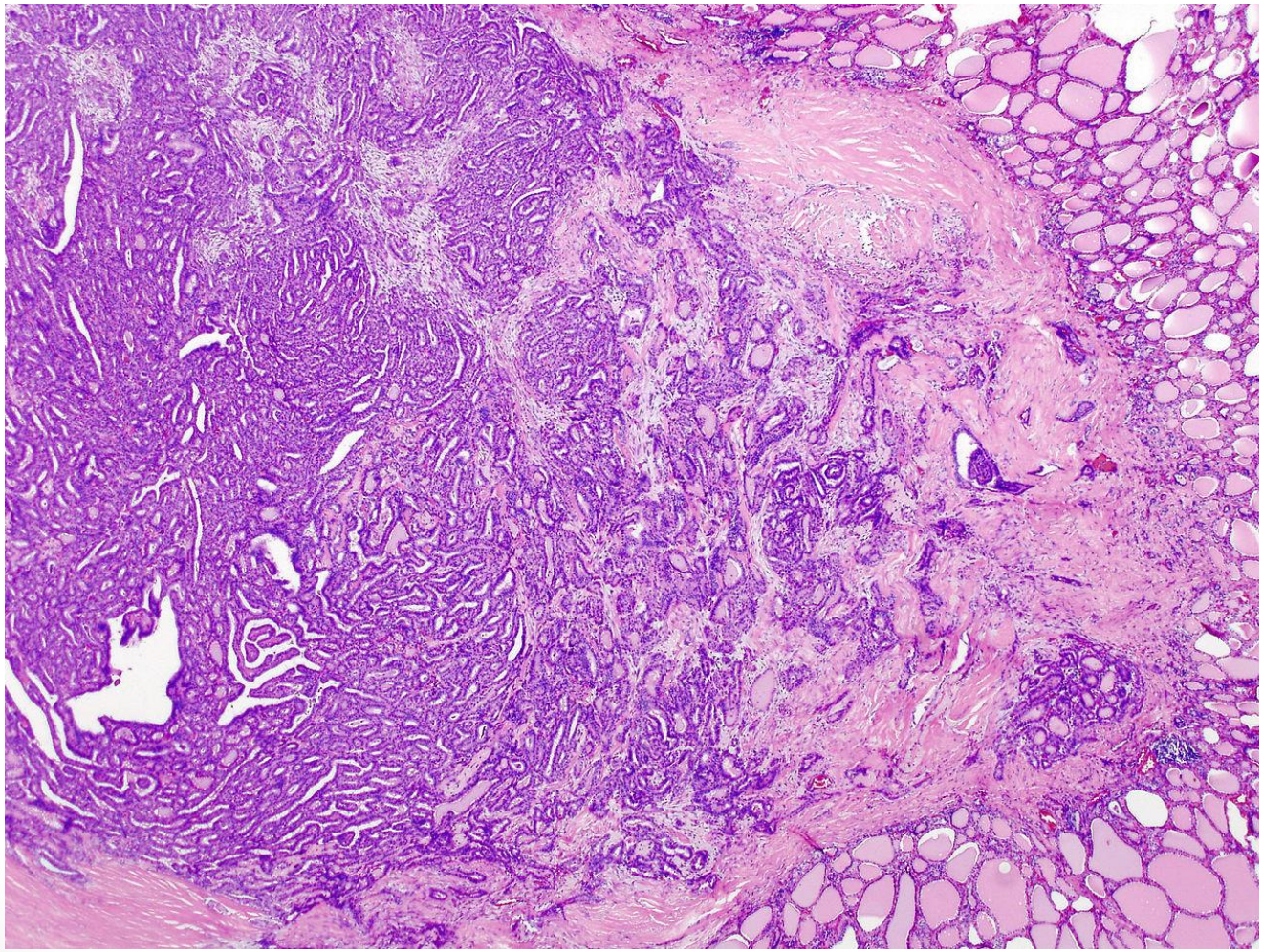
Thyroid Cancer

- 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

Papillary Carcinoma



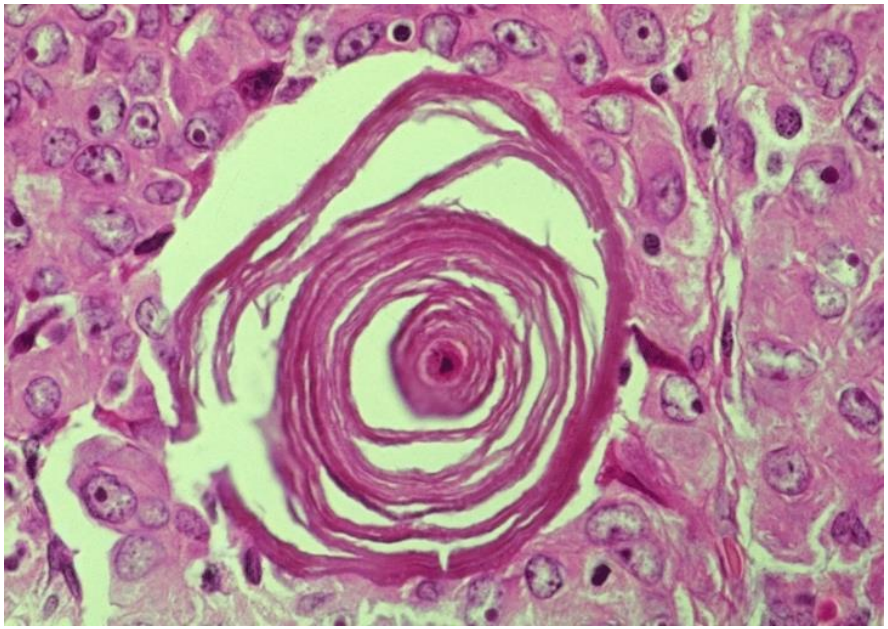
KGH/Wikipedia

Papillary Carcinoma

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

Psammoma Bodies

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



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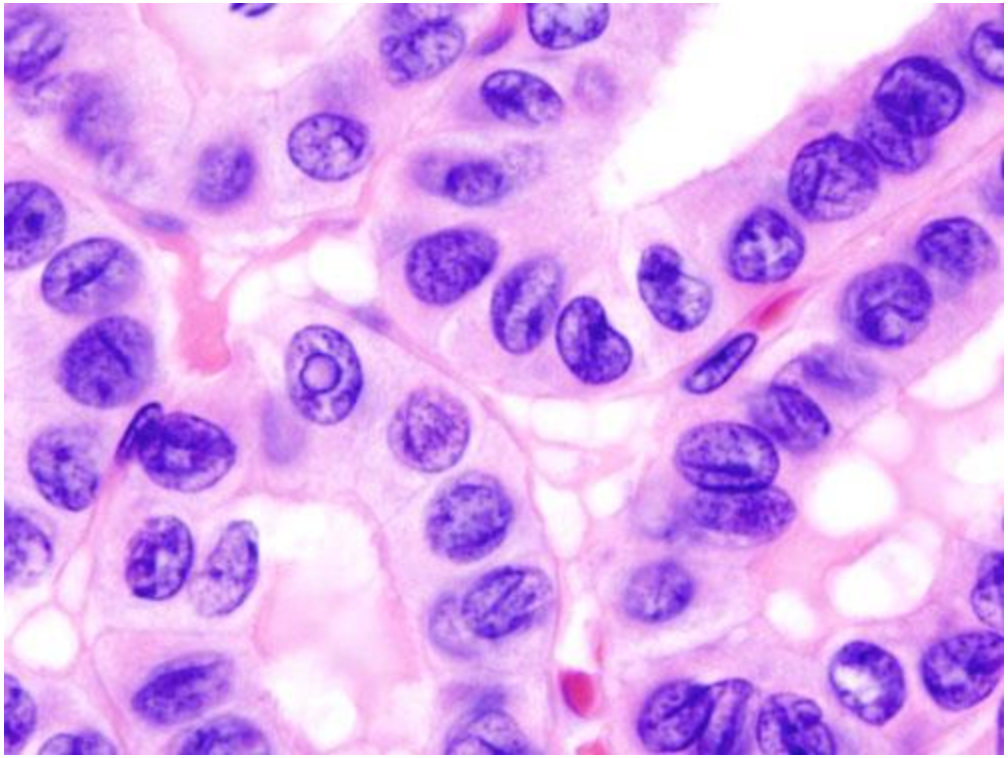
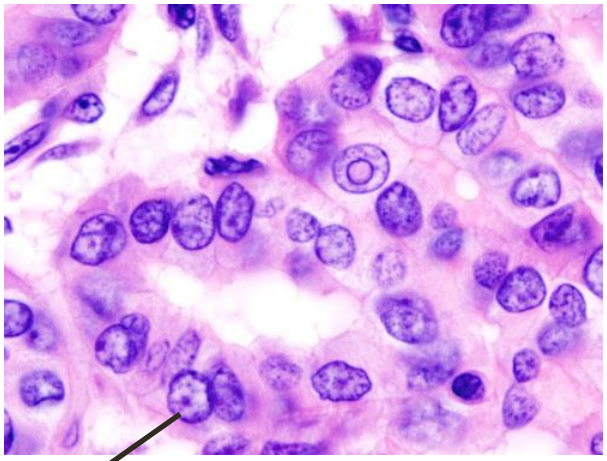
Nuclear Grooves



KGH/Wikipedia

Orphan Annie's Eyes

- Empty-appearing nuclei



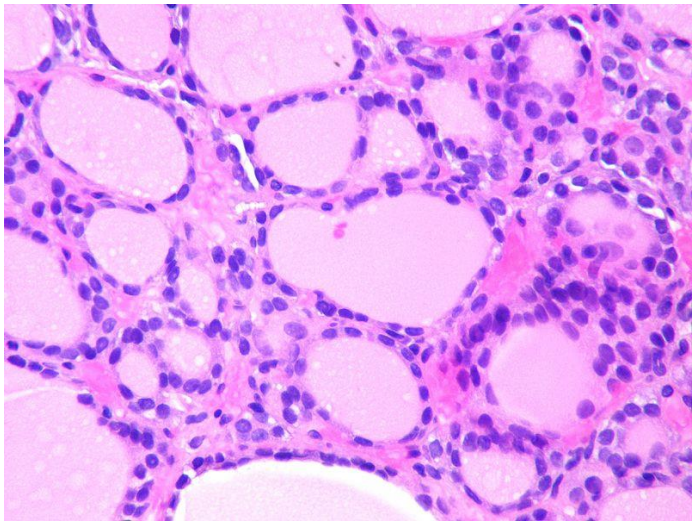
KGH/Wikipedia

White clearing

William Creswell/Flikr

Follicular Carcinoma

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



Yale Rosen/Wikipedia

Follicular Carcinoma

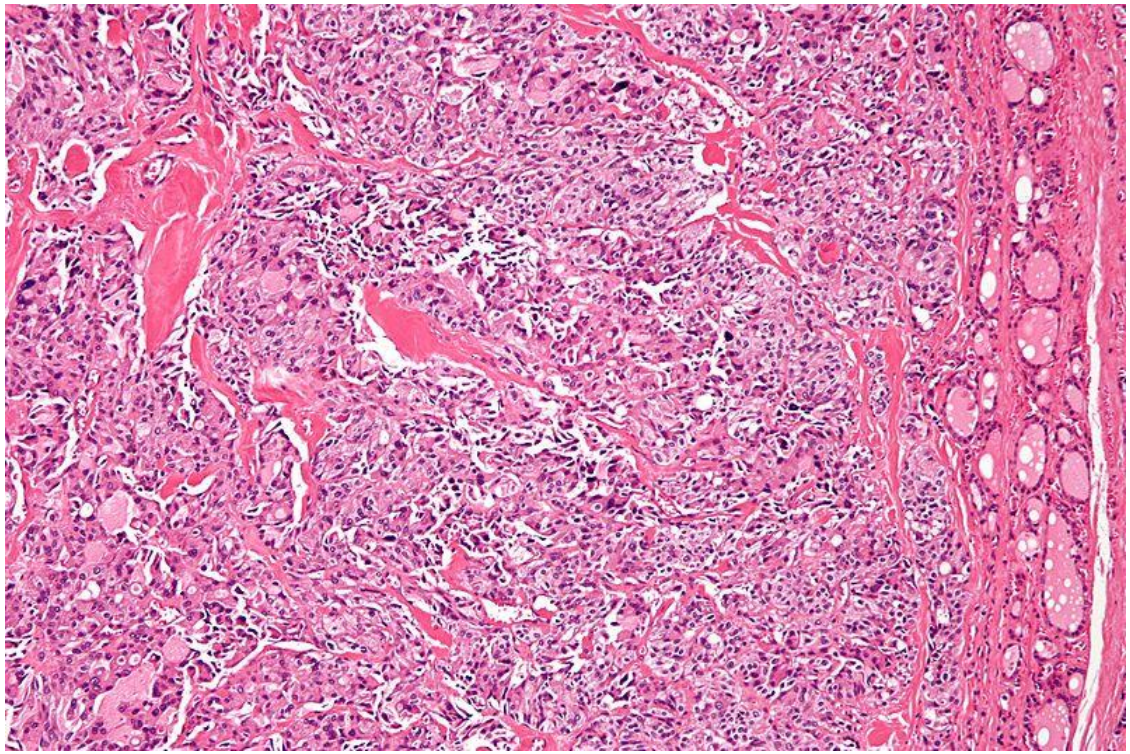
- Possible **hematogenous** metastasis
- Treatment:
  - Thyroidectomy
  - I^{131} to ablate any remaining tissue or metastasis

Medullary Carcinoma

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

Medullary Carcinoma

Malignant cells/Amyloid “stroma”



Nephron/Wikipedia

MEN Syndromes

Multiple Endocrine Neoplasia

- 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**

Anaplastic Carcinoma

Undifferentiated Carcinoma

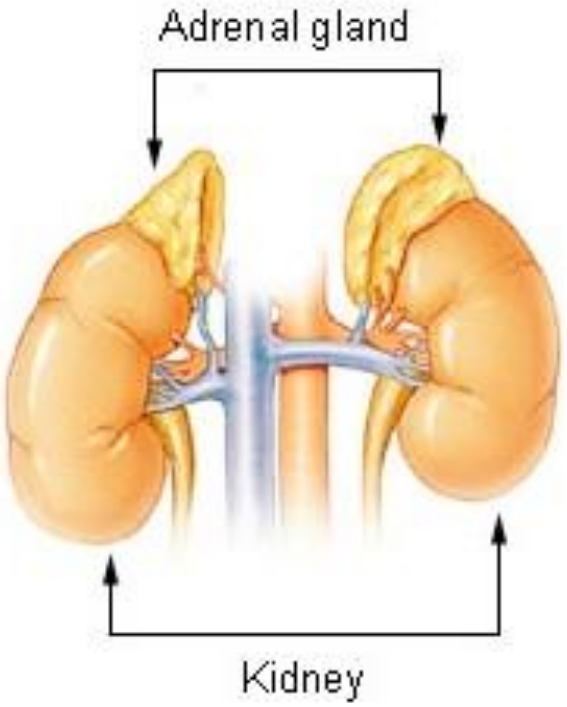
- Occurs in **elderly**
- Highly malignant - invades local tissues
  - Dysphagia (esophagus)
  - Hoarseness (recurrent laryngeal nerve)
  - Dyspnea (trachea)
  - Don't confuse with Riedel's ("rock hard" thyroid/young pt)
- Poor prognosis
- Pathology: Undifferentiated cells
  - No papilla, follicles,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

Adrenal Glands

Jason Ryan, MD, MPH

Adrenal Glands

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



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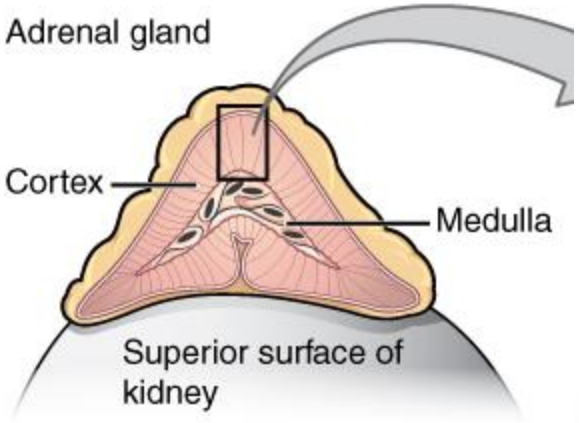
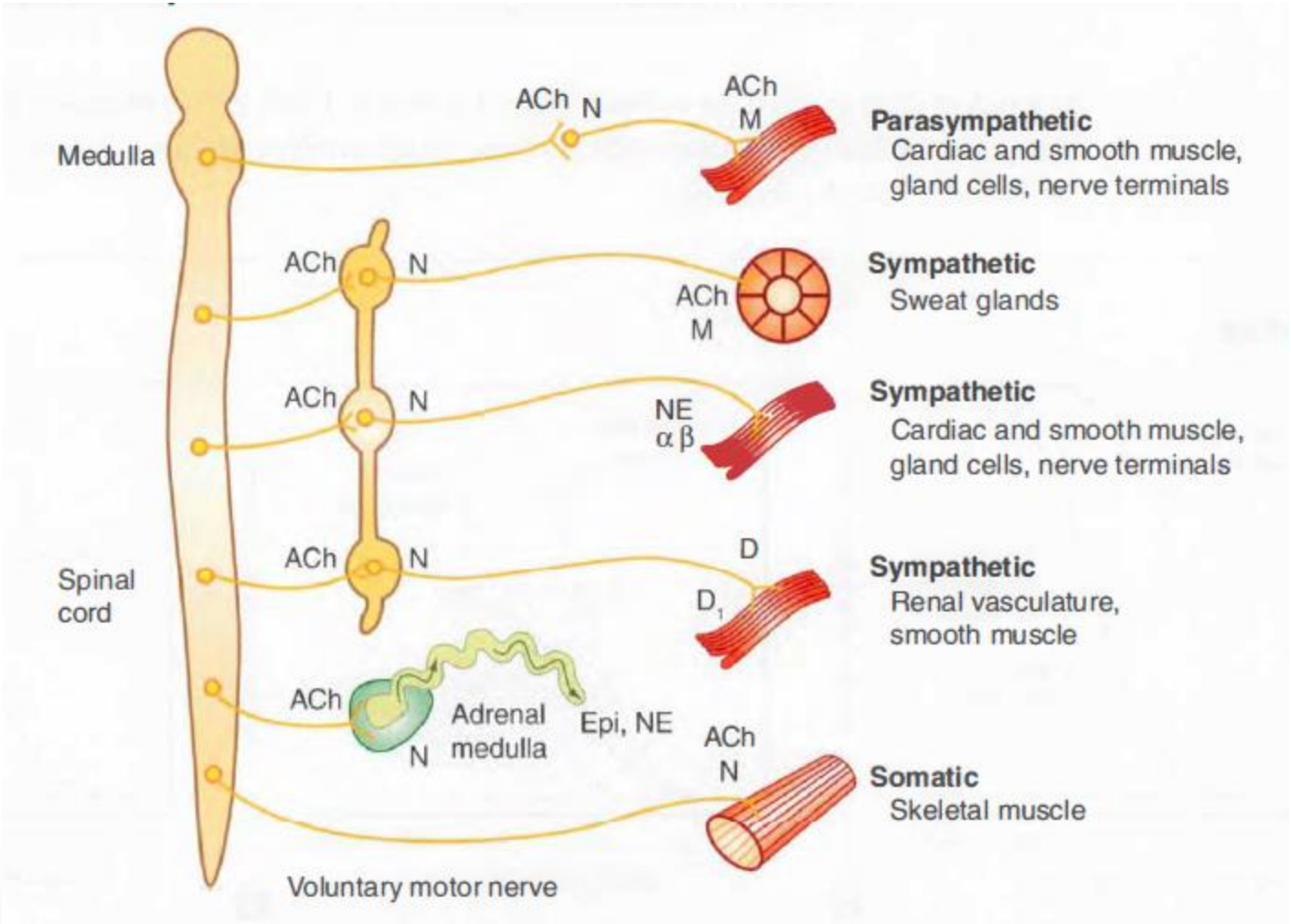
Cortex and Medulla

- 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



OpenStax College/Wikipedia

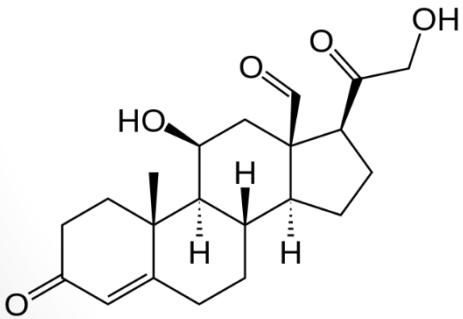
Signal Transmission



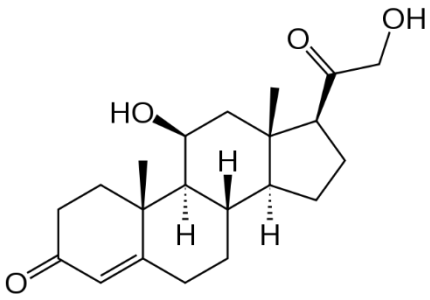
Use with permission, Katzung BG, Basic and Clinical Pharmacology, 10th ed. New York, McGraw Hill, 2007

Mineralocorticoids

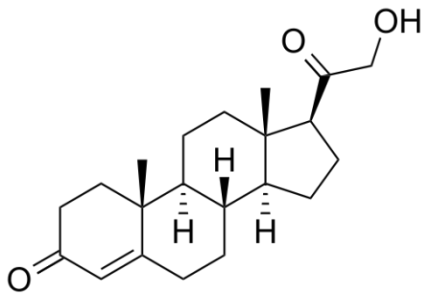
- Most important is **aldosterone**
- Key effects on kidney function
- Release controlled by RAA system
  - **Renin-angiotensin-aldosterone**
- Increase Na^+/Water resorption
- Promote K^+/H^+ excretion



Aldosterone

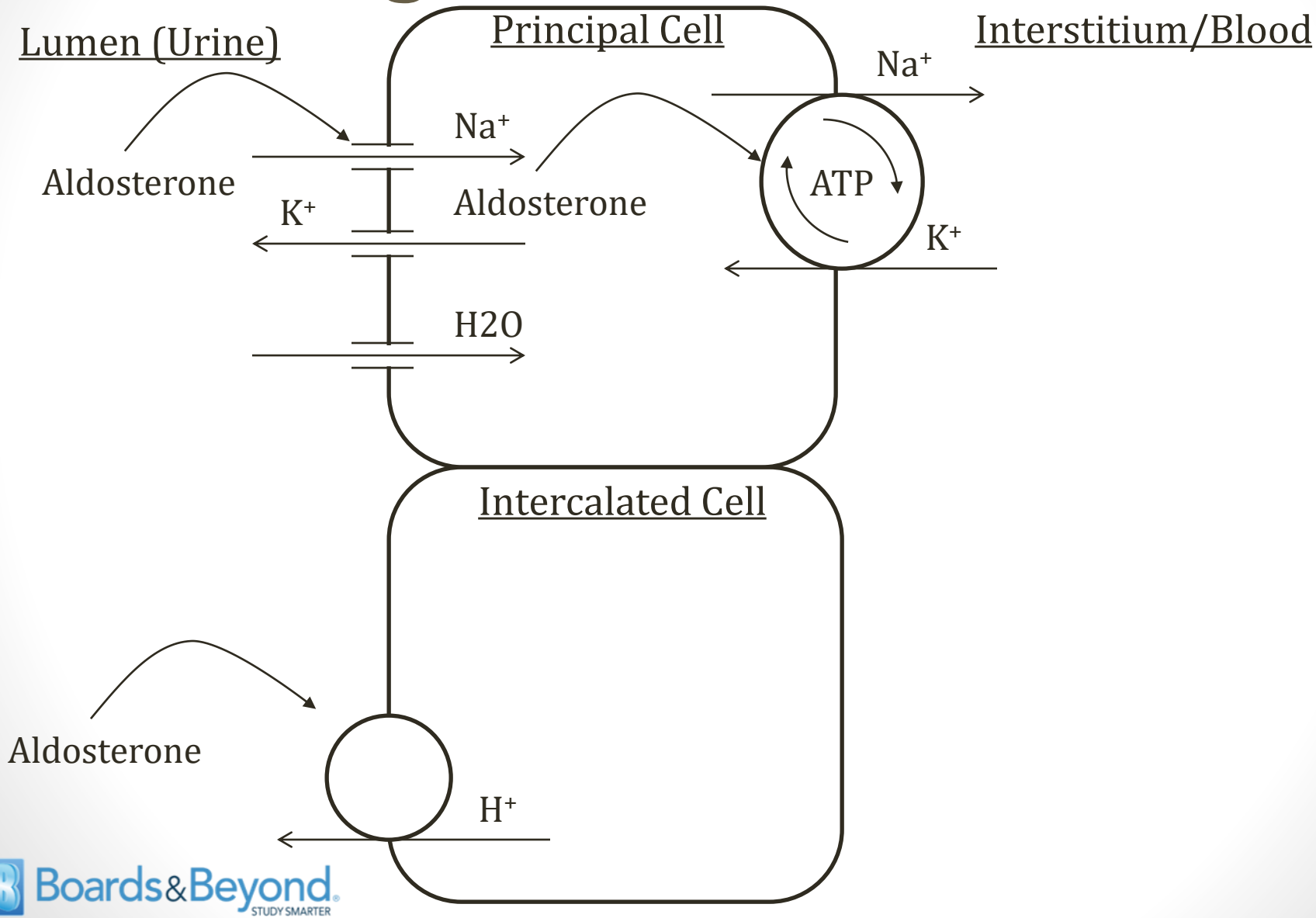


Corticosterone



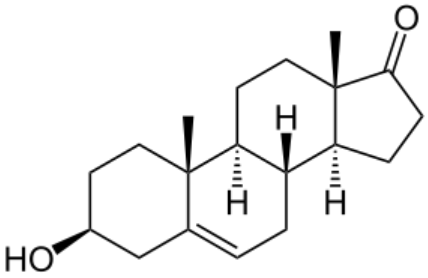
11-deoxycorticosterone

Collecting Duct

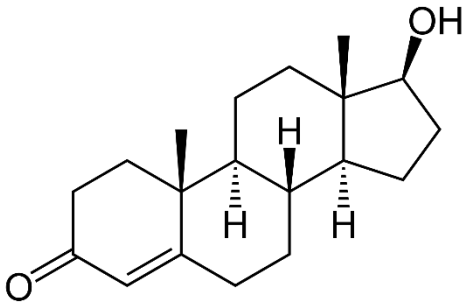


Adrenal Androgens

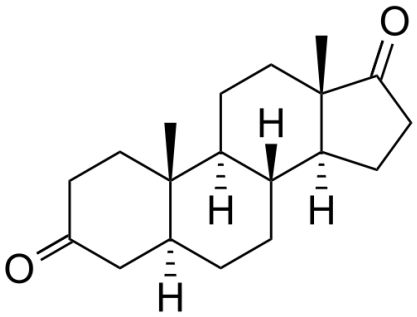
- Small contribution to androgen production in males
- ~50% androgens for females
- Clinical relevance: **congenital adrenal hyperplasia**
  - Over/underproduction → abnormal sexual development
- Production stimulated by ACTH (like cortisol)



Dehydroepiandrosterone (DHEA)

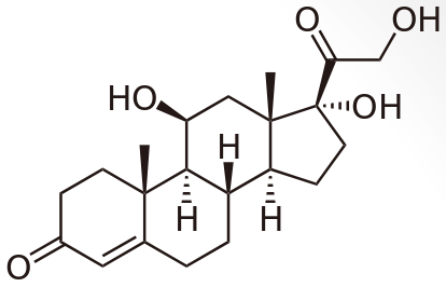


Testosterone



Androstenedione

Cortisol

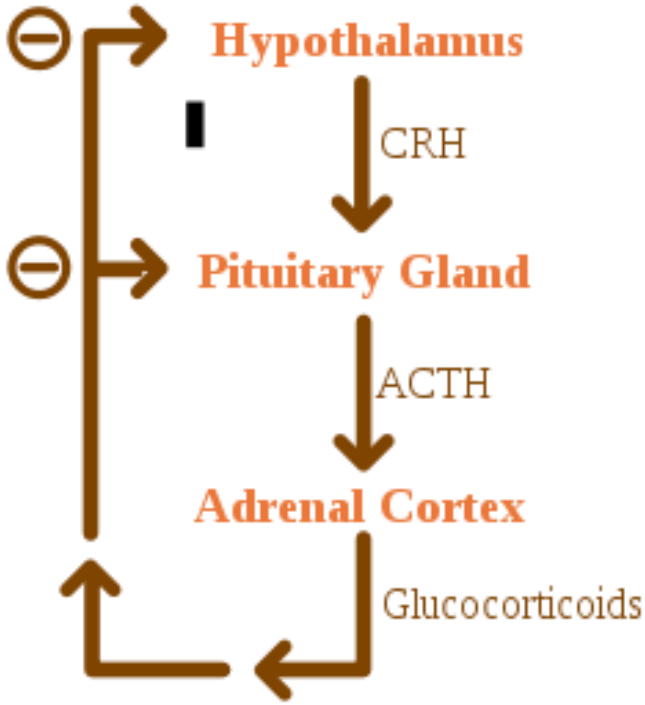


Cortisol

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

Pituitary-Adrenal Axis

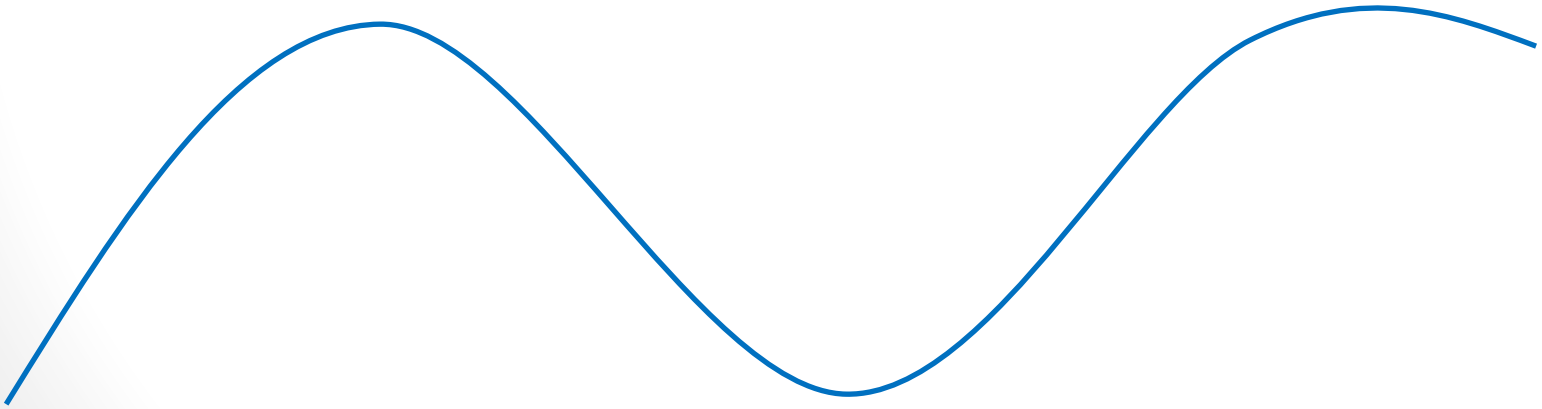
- Controls **cortisol secretion**
- Hypothalamus: CRH
  - Corticotropin releasing hormone
  - Paraventricular nucleus (PVN)
- Anterior pituitary: ACTH
  - Adrenocorticotropic hormone
  - Acts on adrenal gland
  - cAMP/PKA 2nd messenger
- Adrenal: Cortisol



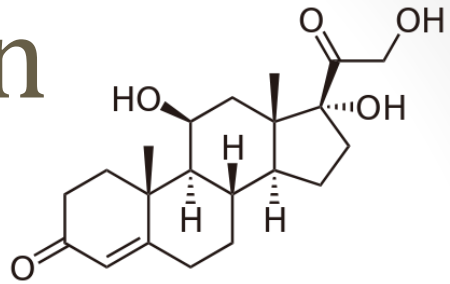
Drosenbach/Wikipedia

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 Binding Globulin

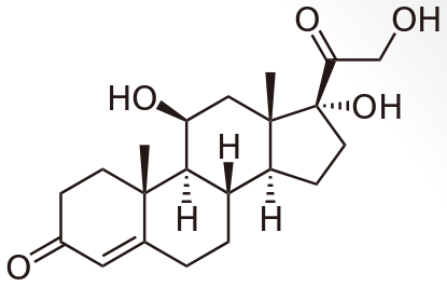


Cortisol

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

Cortisol

Hormone Effects

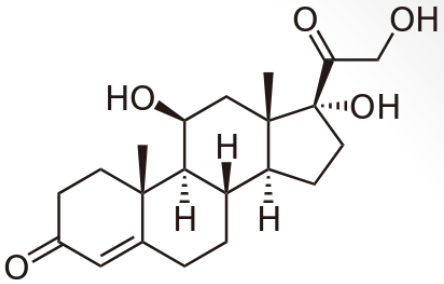


Cortisol

- 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

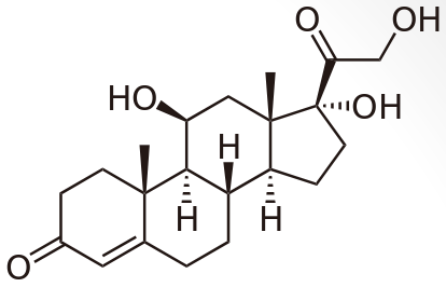
Hormone Effects



Cortisol

- 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

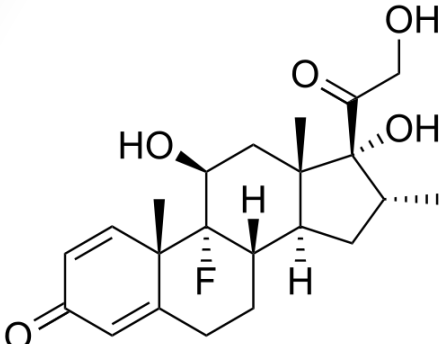
Cortisol



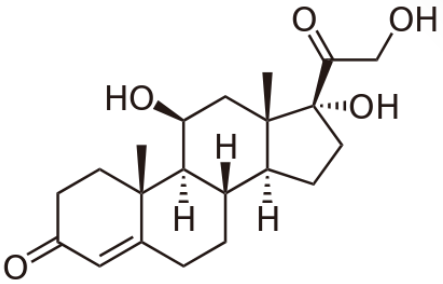
Cortisol

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

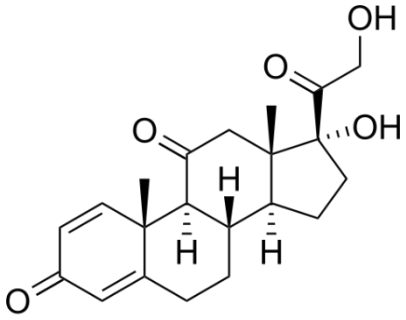
Corticosteroid Drugs



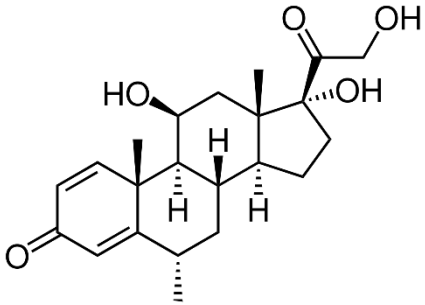
Dexamethasone



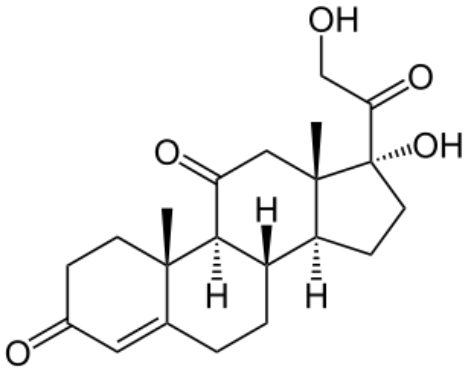
Cortisol



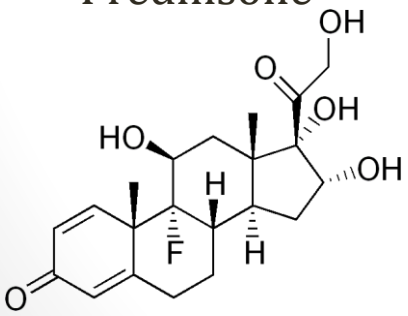
Prednisone



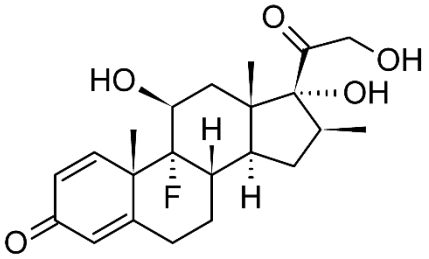
Methylprednisolone



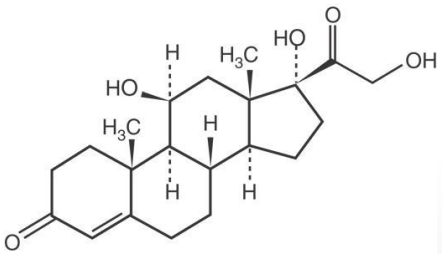
Cortisone



Triamcinolone



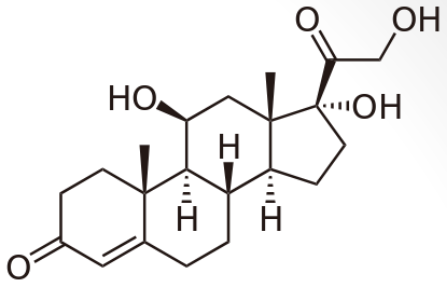
Betamethasone



Hydrocortisone

Cortisol

Effects

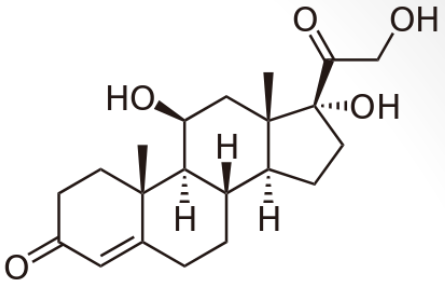


Cortisol

- 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

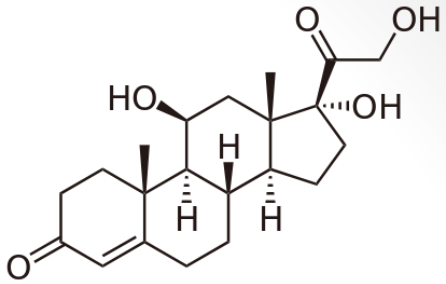


Cortisol

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

Cortisol

Effects

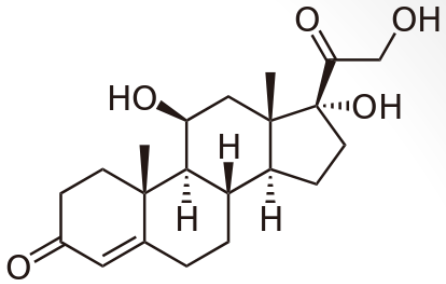


Cortisol

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

Cortisol

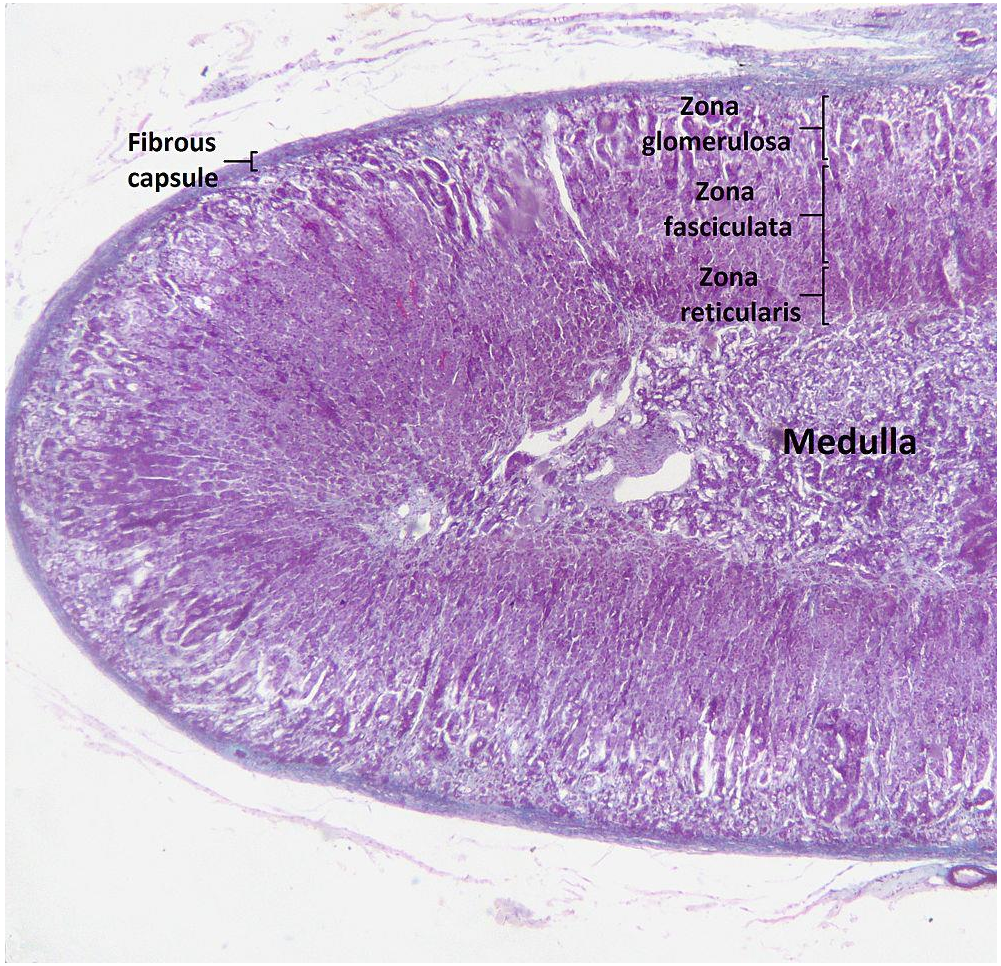
Effects



Cortisol

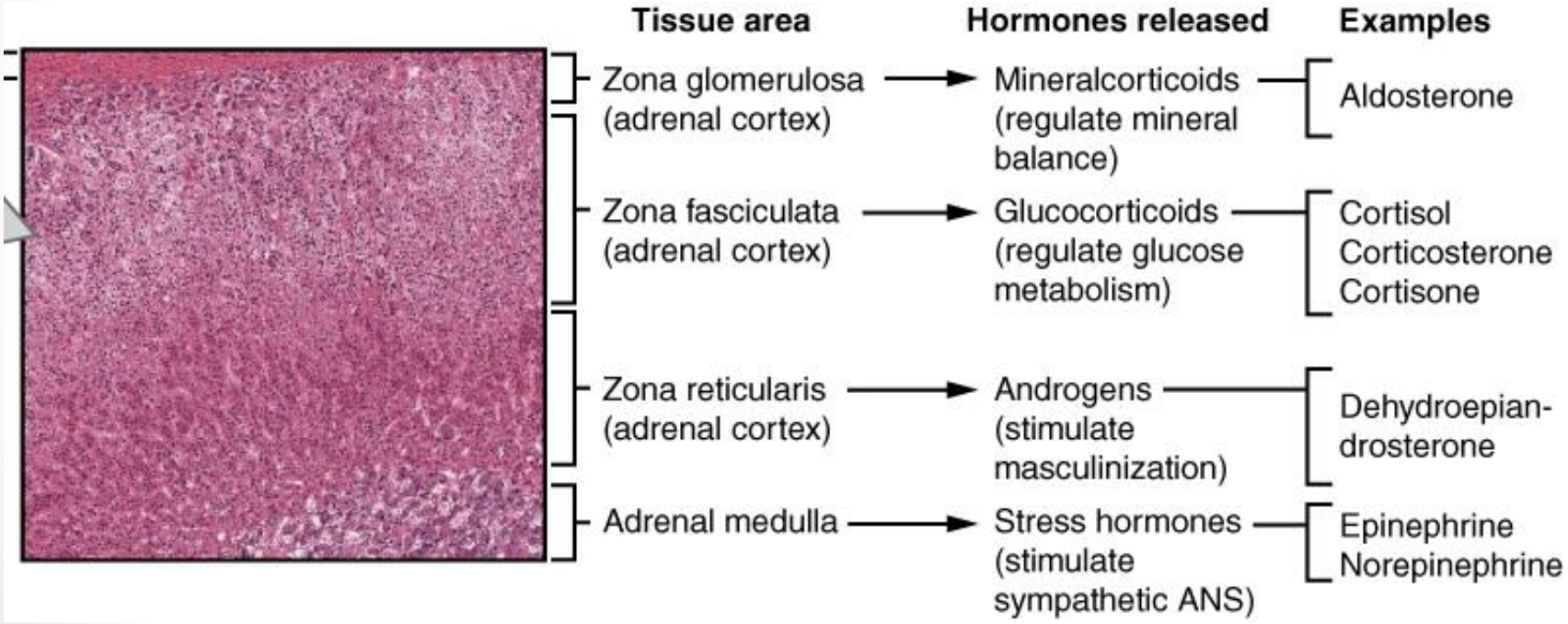
- Muscle atrophy
- Skin effects
  - Blunted epidermal cell division in skin
  - ↓ collagen, inhibition of fibroblasts
  - Net effects: **Thin skin, easy bruising, striae**
- Bones: Inhibits osteoblasts
  - Steroids → osteopenia and osteoporosis

Zones of the Adrenal Glands

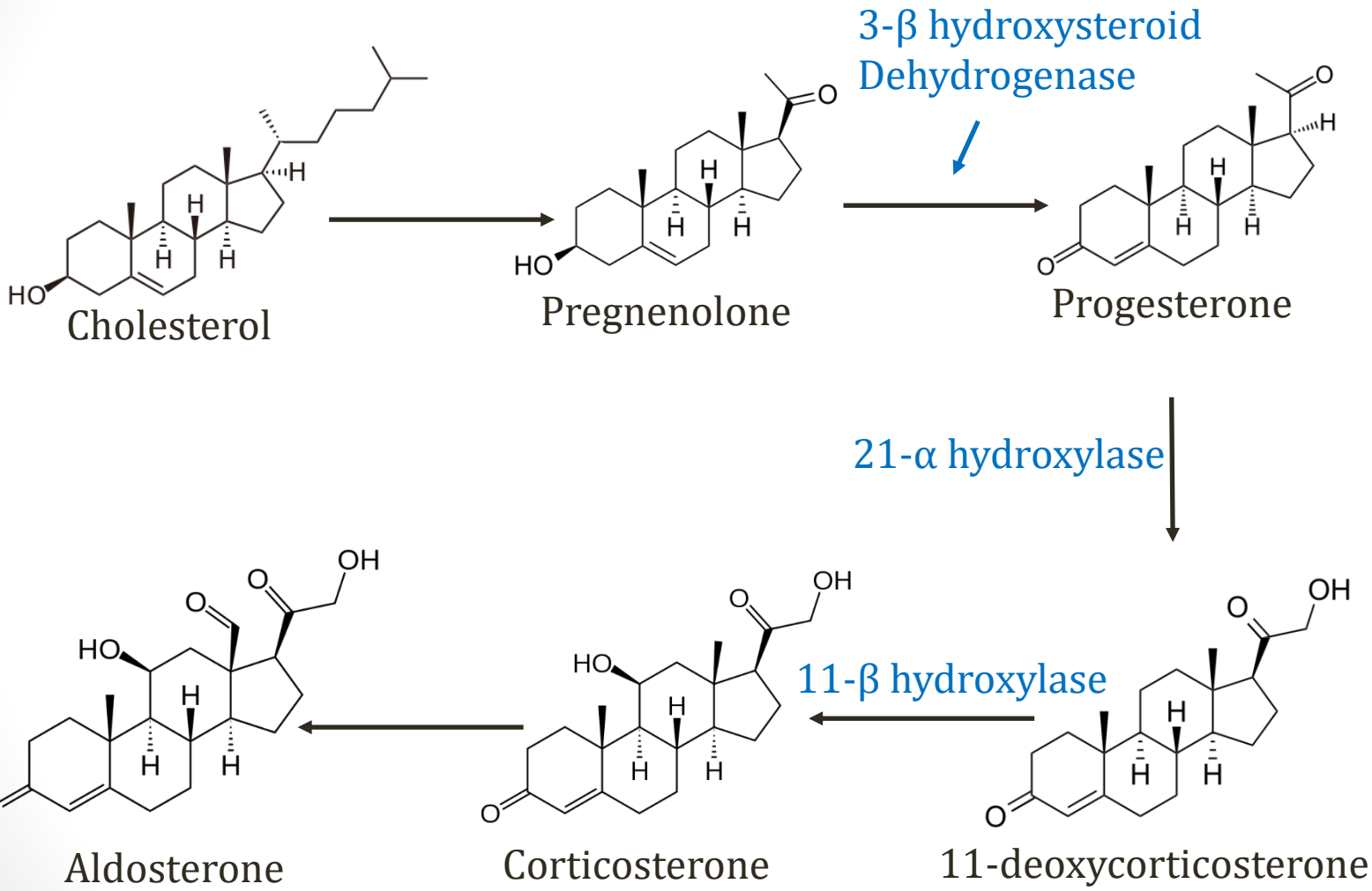


Jpogi/Wikipedia /Public Domain

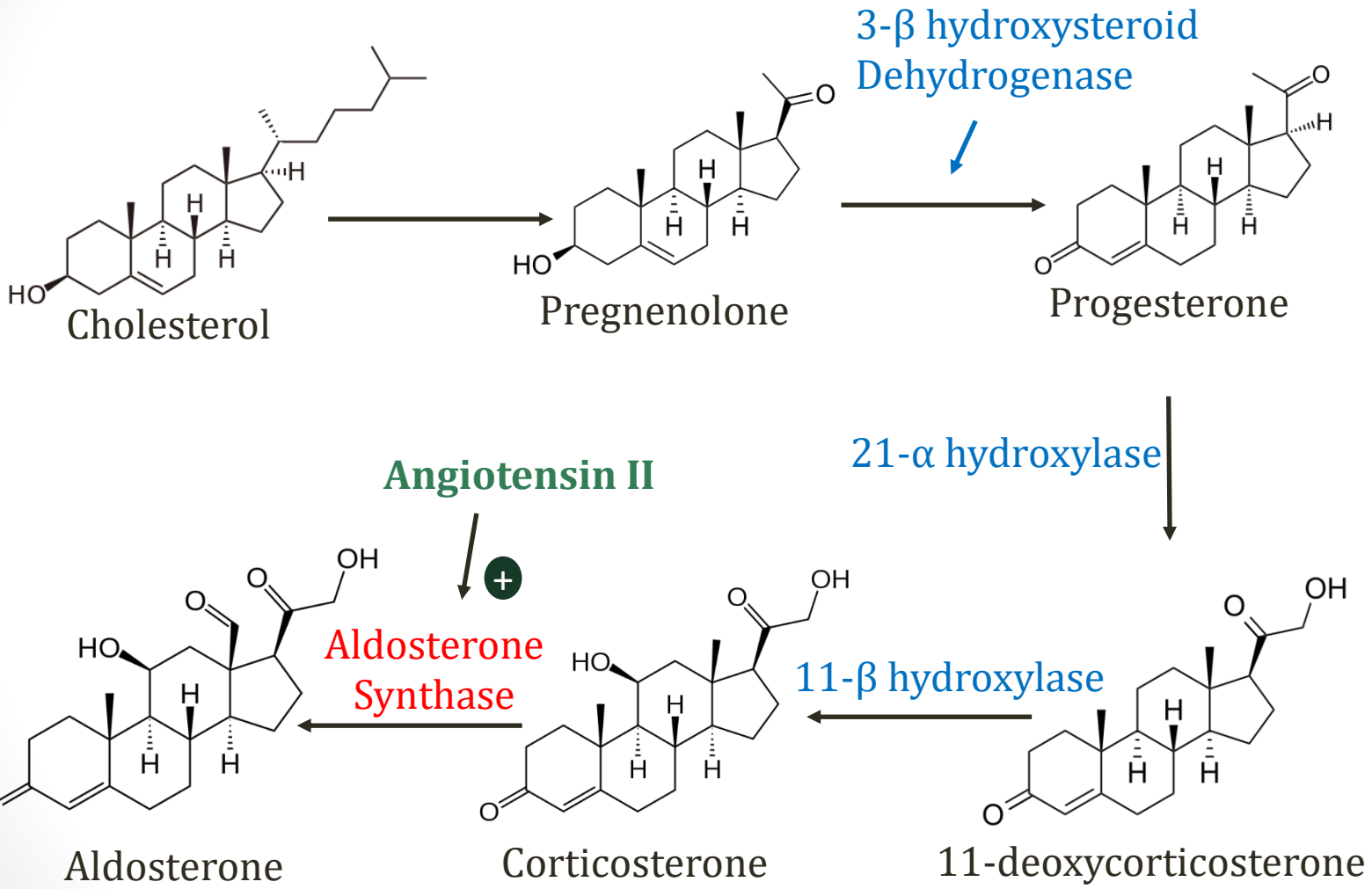
Zones of the Adrenal Glands



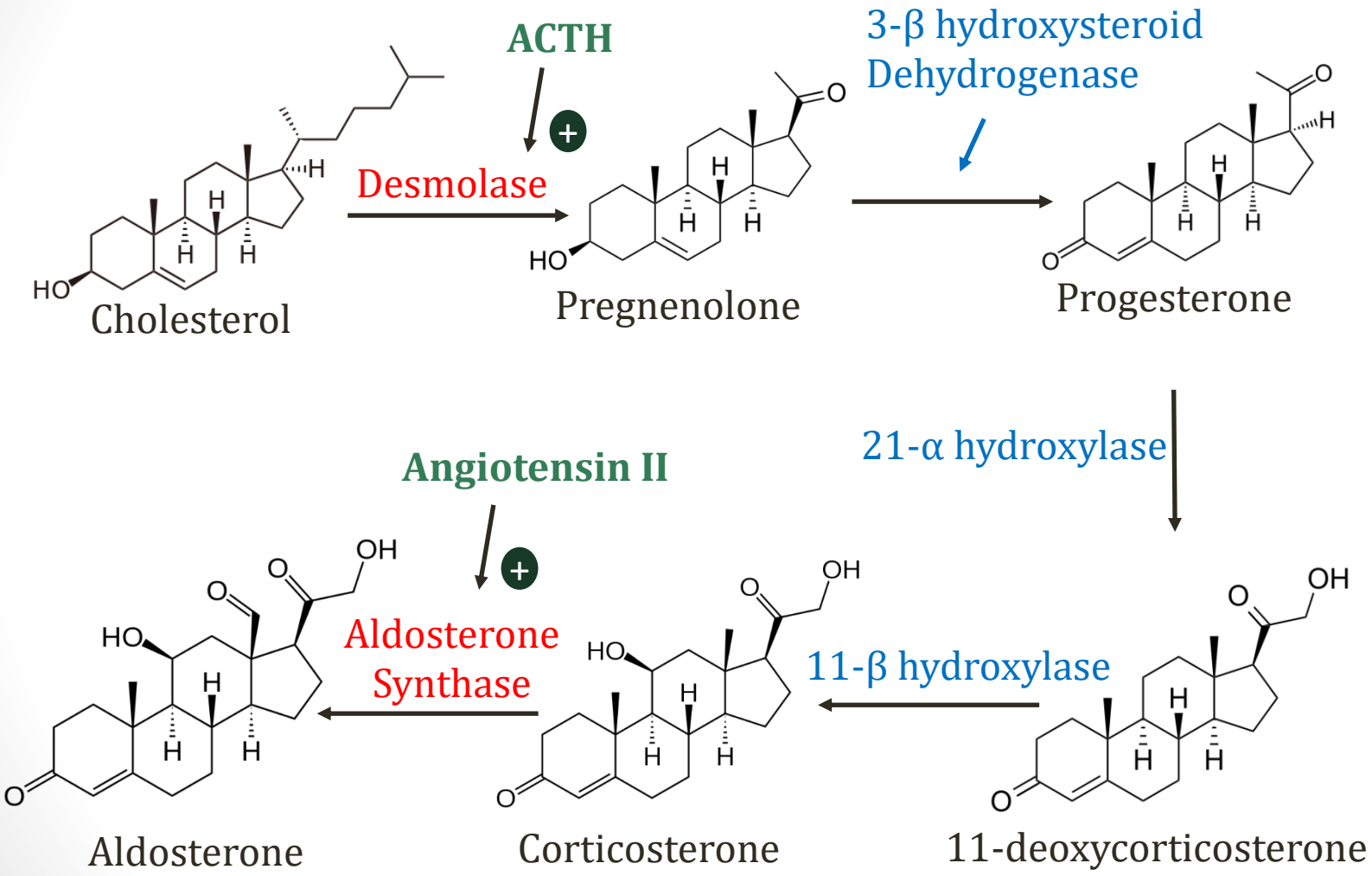
Zona Glomerulosa

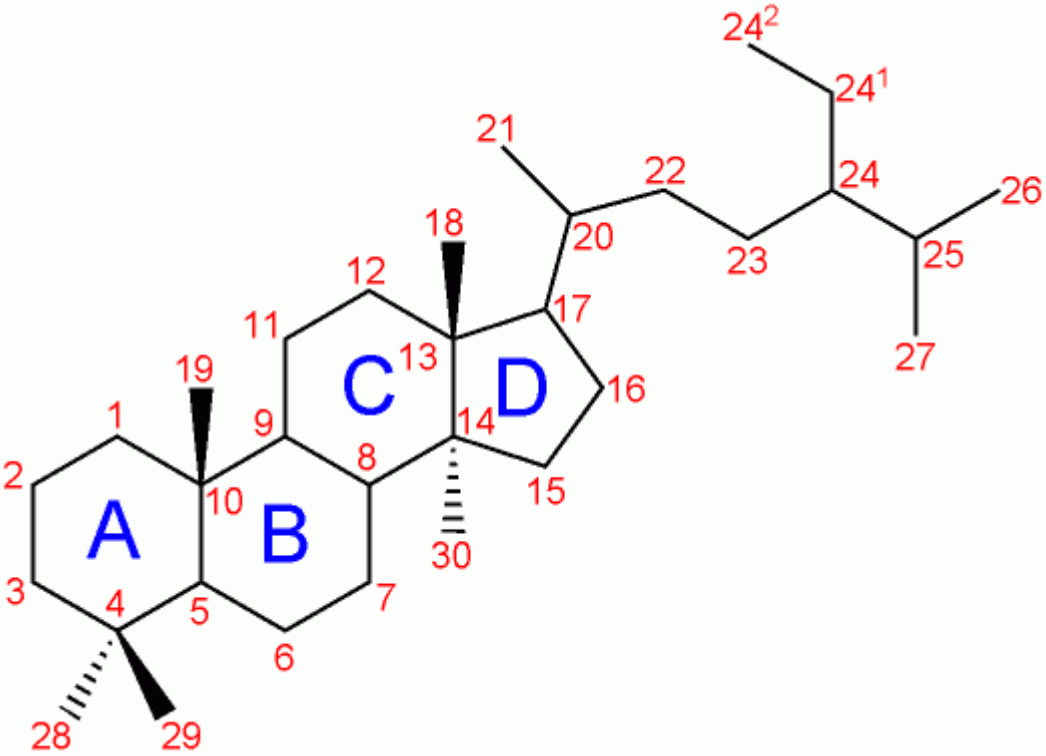


Zona Glomerulosa



Zona Glomerulosa





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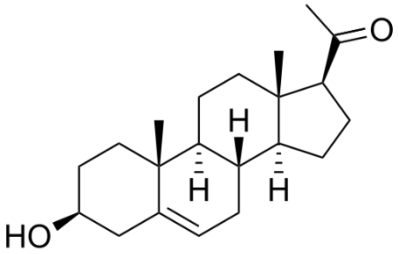
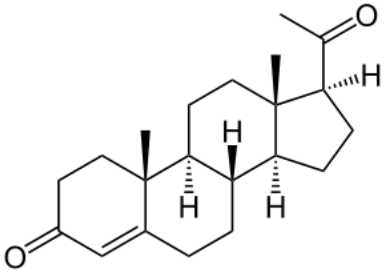


Pregnenolone

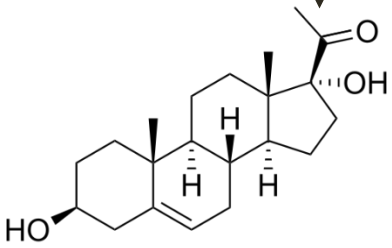


Progesterone

Zona Glomerulosa

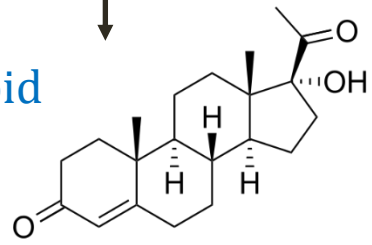
Zona Fasciculata

17-α hydroxylase



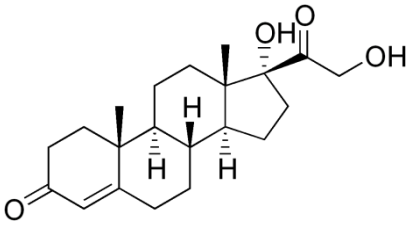
17-Hydroxypregnenolone

3-β hydroxysteroid Dehydrogenase



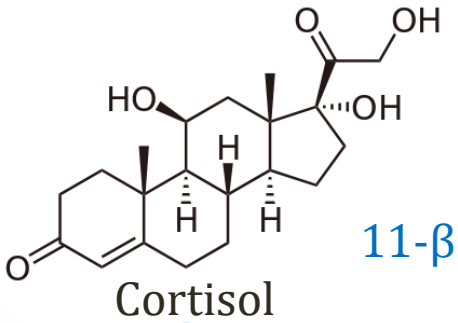
17-Hydroxyprogesterone

21-α hydroxylase

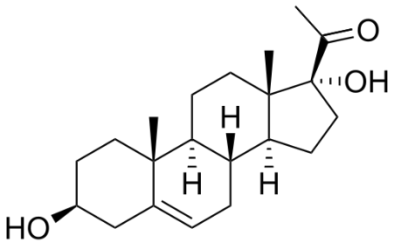


11-Deoxycortisol

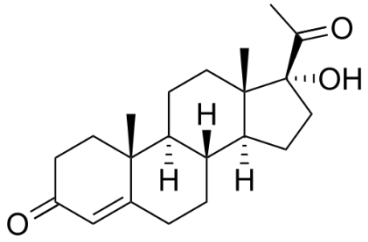
11-β hydroxylase



Cortisol



17-Hydroxypregnenolone



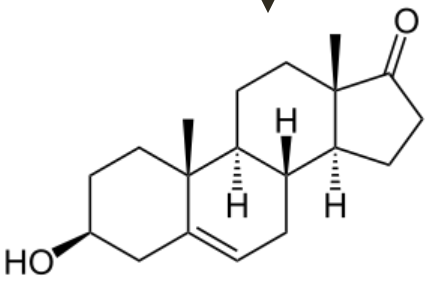
17-Hydroxyprogesterone

Zona Fasciculata

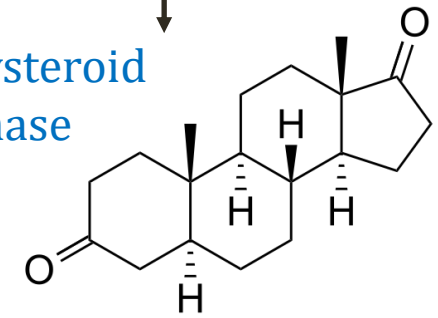
Zona Reticularis

17, 20 lyase

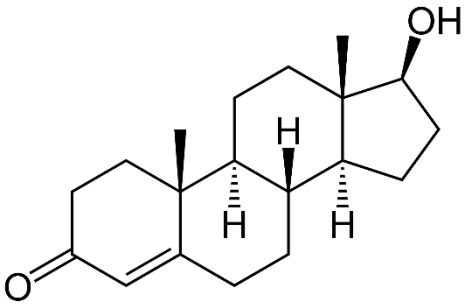
3-β hydroxysteroid Dehydrogenase



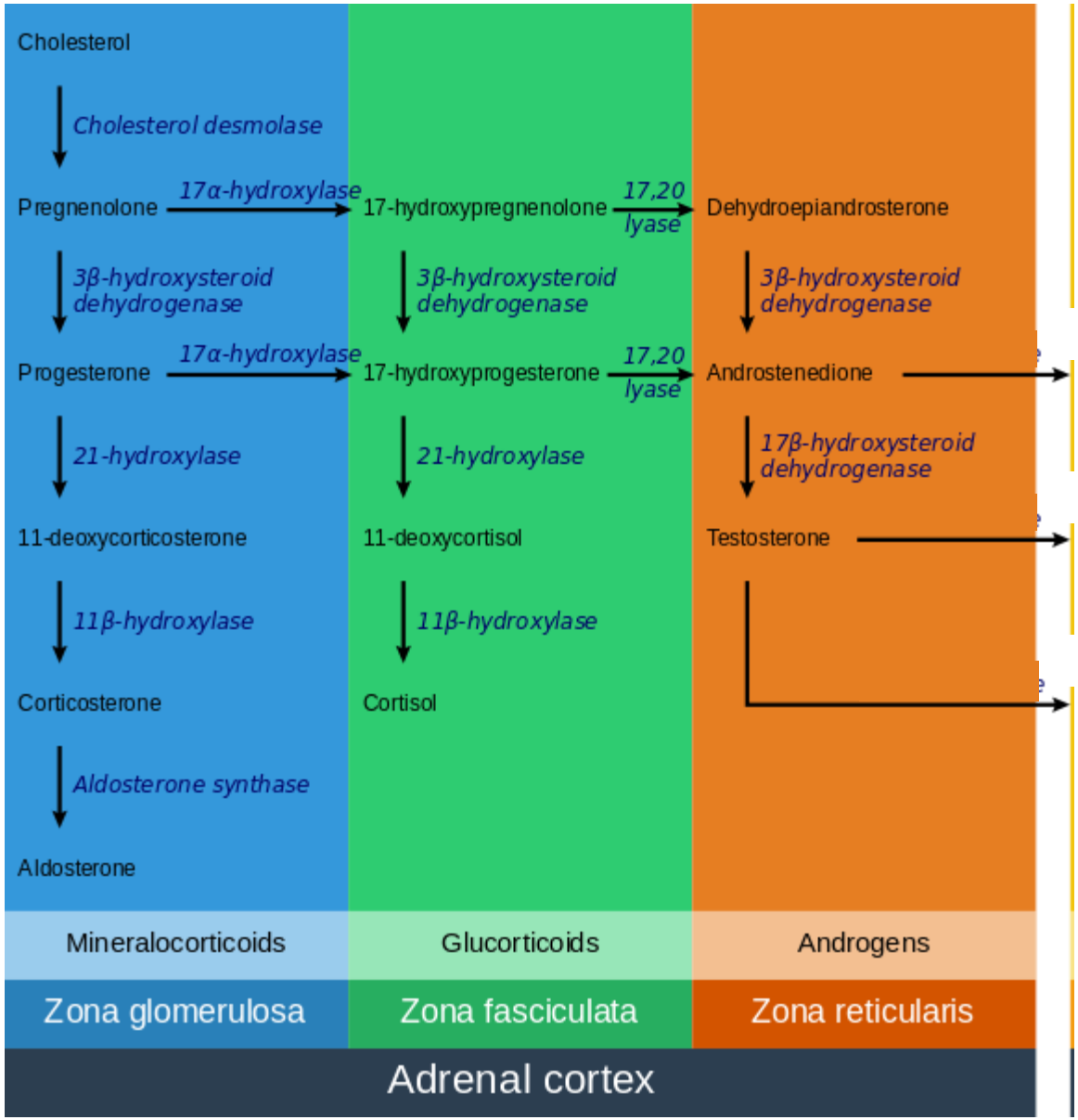
Dehydroepiandrosterone (DHEA)



Androstenedione

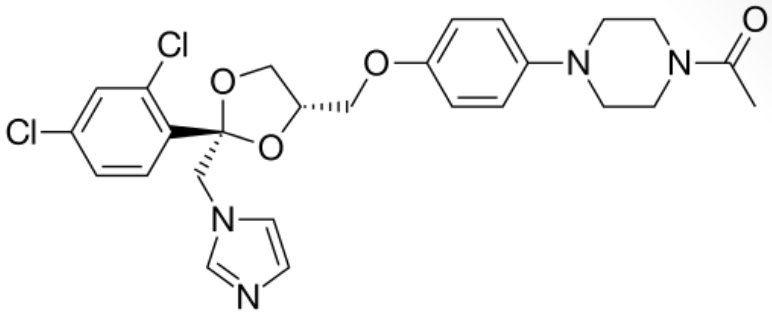


Testosterone



Matthew Colo/Wikipedia

Ketoconazole



- Antifungal
- Blocks ergosterol synthesis in fungi
- Potent inhibitor of 17,20 lyase
  - ↓ androstenedione/testosterone
  - Key side effect: **gynecomastia**
- Also inhibits 17-alpha hydroxylase, desmolase
  - **Blocks cortisol synthesis**
  - Can be used to treat Cushing's syndrome

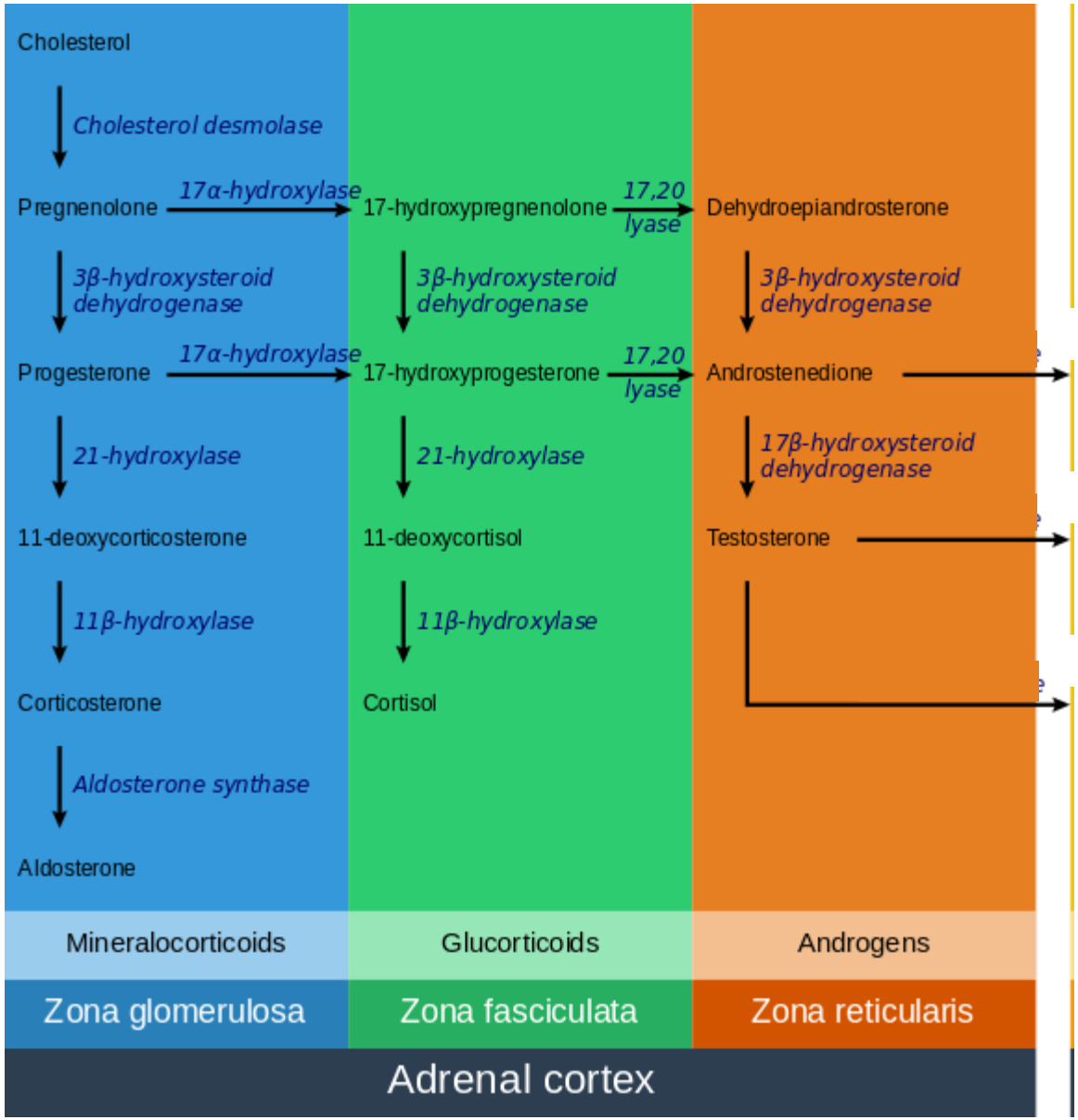
Congenital Adrenal Hyperplasia

Jason Ryan, MD, MPH

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



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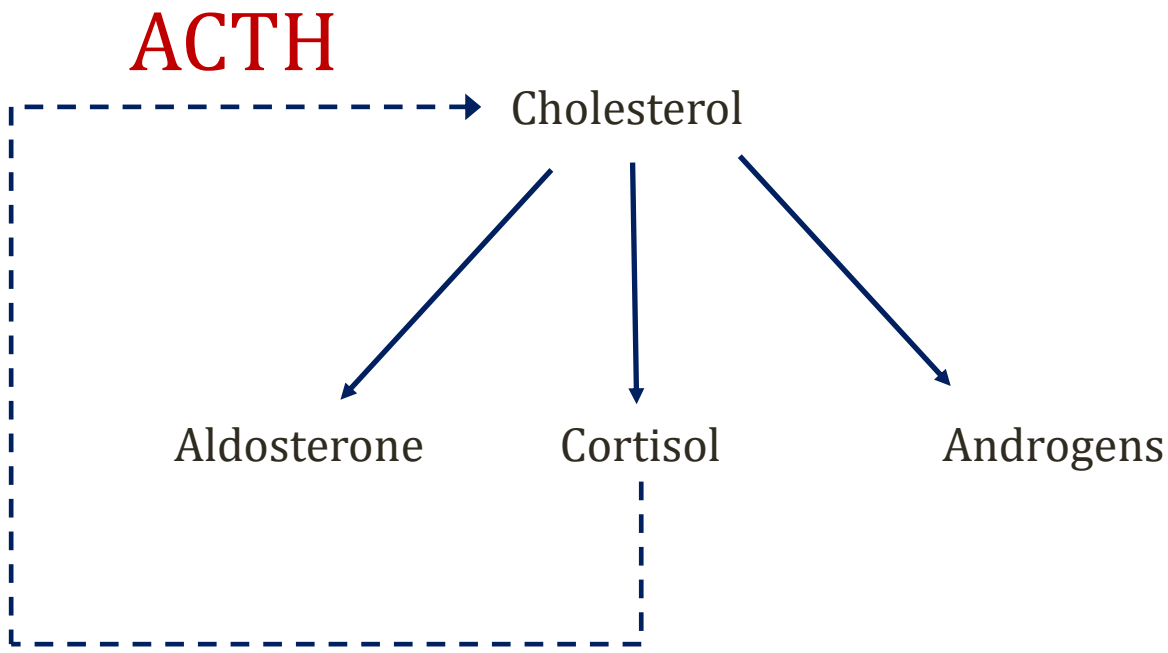
CAH

Congenital Adrenal Hyperplasia



CAH

Congenital Adrenal Hyperplasia

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

↓ Cortisol → ↑ACTH → **Adrenal Hyperplasia** → ↑ Non-cortisol hormone synthesis

Low Cortisol

Signs/Symptoms

- Hypoglycemia
- Nausea/vomiting

Aldosterone

Signs/Symptoms

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

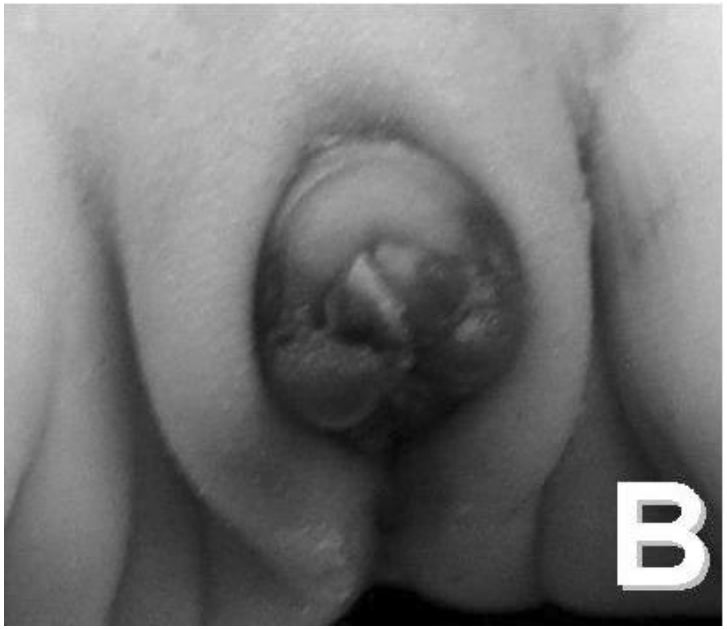
Androgens

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

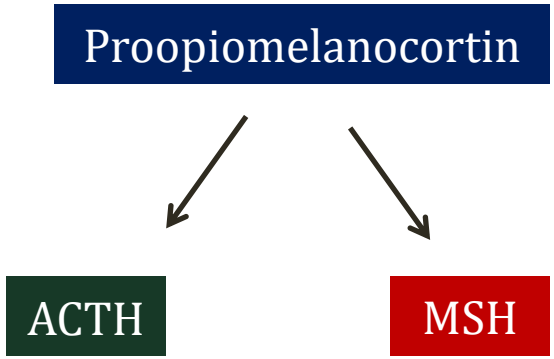
- Females (XX) with excess androgen exposure
- Males (XY) with deficient androgen exposure



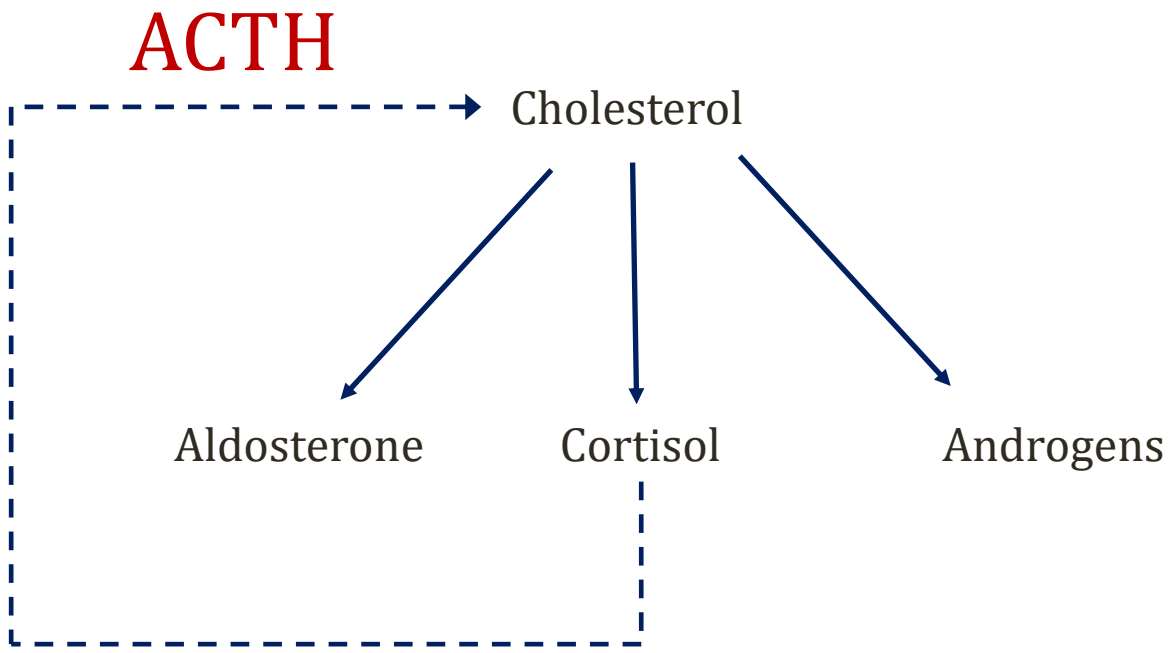
Diabetic fetopathy associated with bilateral adrenal hyperplasia and ambiguous genitalia: a case report. *Journal of Medical Case Reports*. 2008; **2** : 251. doi:10.1186/1752-1947-2-251

ACTH Effects

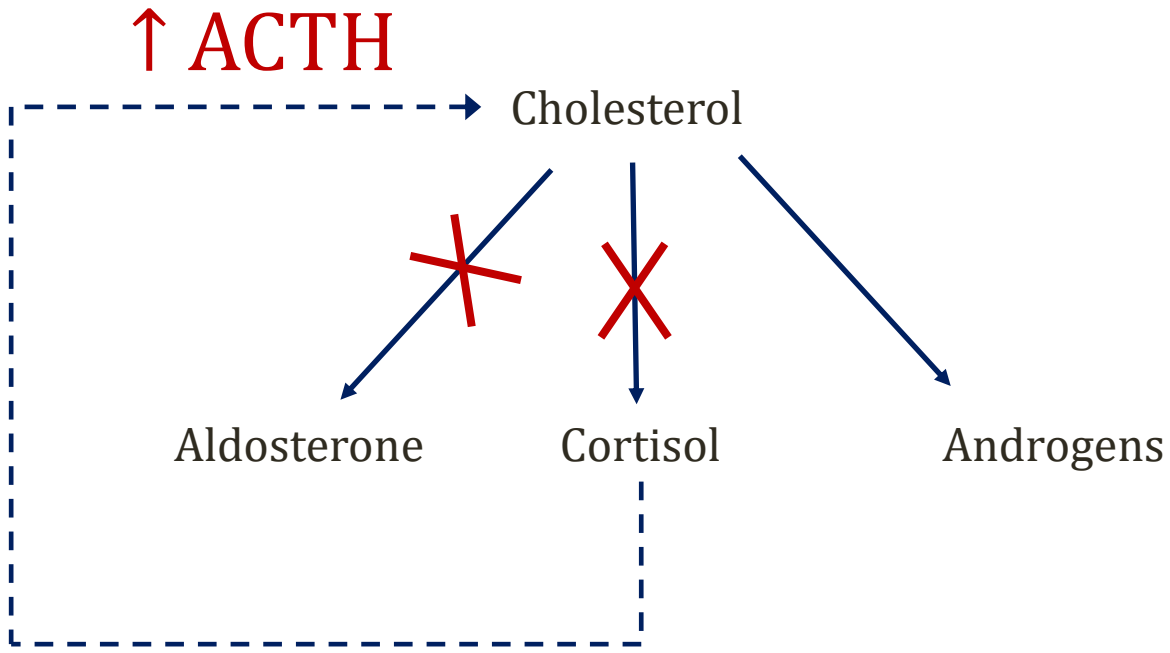
- High ACTH can case **skin hyperpigmentation**
- Melanocyte stimulating hormone (MSH)
  - Common precursor protein in pituitary with ACTH
- ↑ melanin synthesis



21-α Hydroxylase Deficiency



21-α Hydroxylase Deficiency



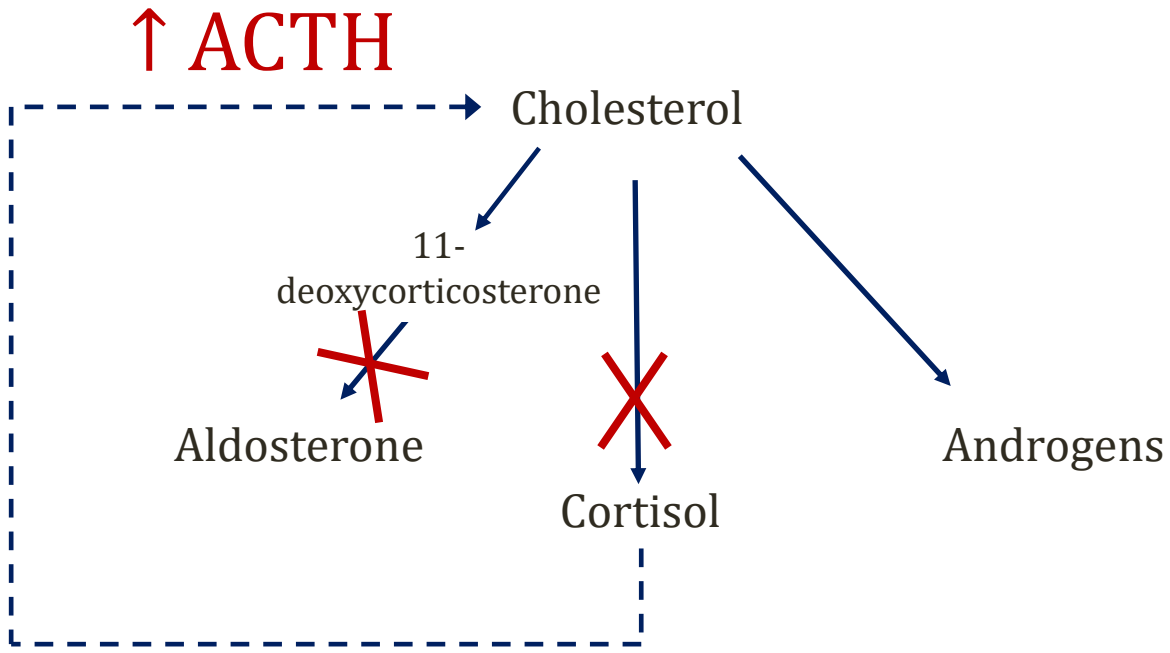
21-α Hydroxylase Deficiency

- Classic cause of CAH (90% of CAH)
- Low cortisol symptoms
- Low mineralocorticoid symptoms
- Excess androgen symptoms
  - Girls (XX): **ambiguous genitalia**
  - Boys (XY): precocious puberty (early onset)
- Variable symptoms based on enzyme levels
  - Classic form: 0 to 2% normal enzyme activity
  - Non-classic forms: 20-50% normal enzyme activity

21-α Hydroxylase Deficiency

Type	Clinical Features
Classic, Salt-losing	Nausea/Vomiting Volume depletion Hyperkalemia 7 to 14 days
Milder Forms	Females: Ambiguous genitalia Males: Precocious puberty

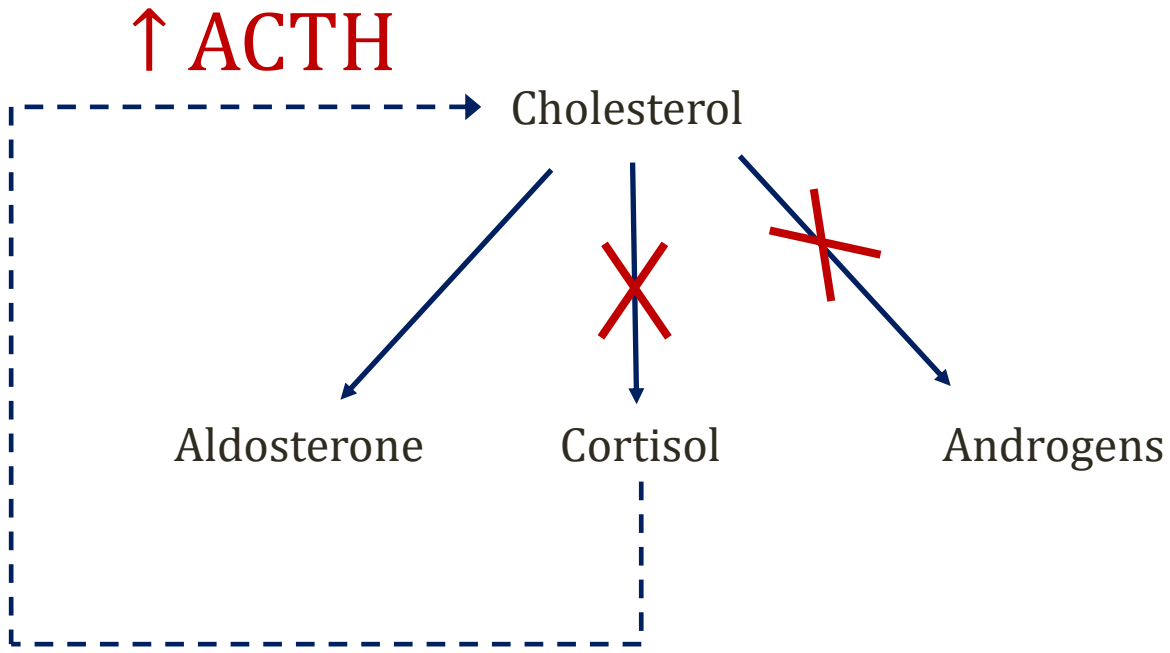
11-β Hydroxylase Deficiency



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



17-α Hydroxylase Deficiency

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

17-α Hydroxylase Deficiency

- Low cortisol
- Excess mineralocorticoids: HTN, $\downarrow K^+$
- Low androgens
  - CYP17A1 : adrenal gland and gonads

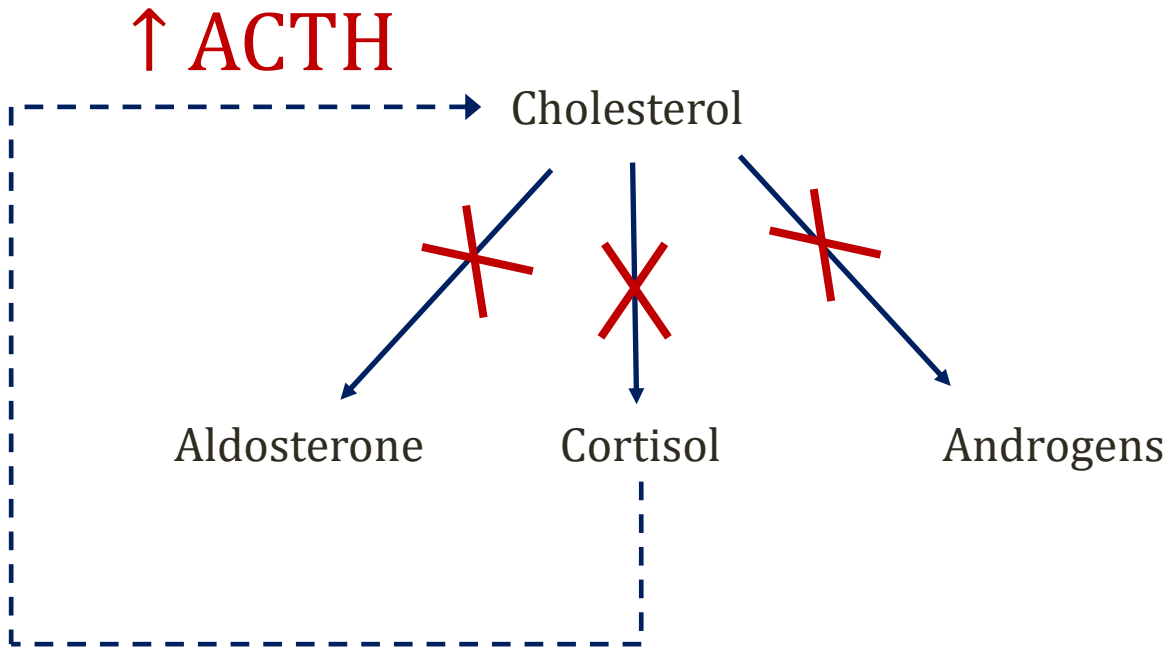
17-α Hydroxylase Deficiency

- Males (XY):
  - Female or ambiguous external genitalia
  - Absent uterus/fallopian tubes (Sertoli cells → MIH)
  - Undescended testes

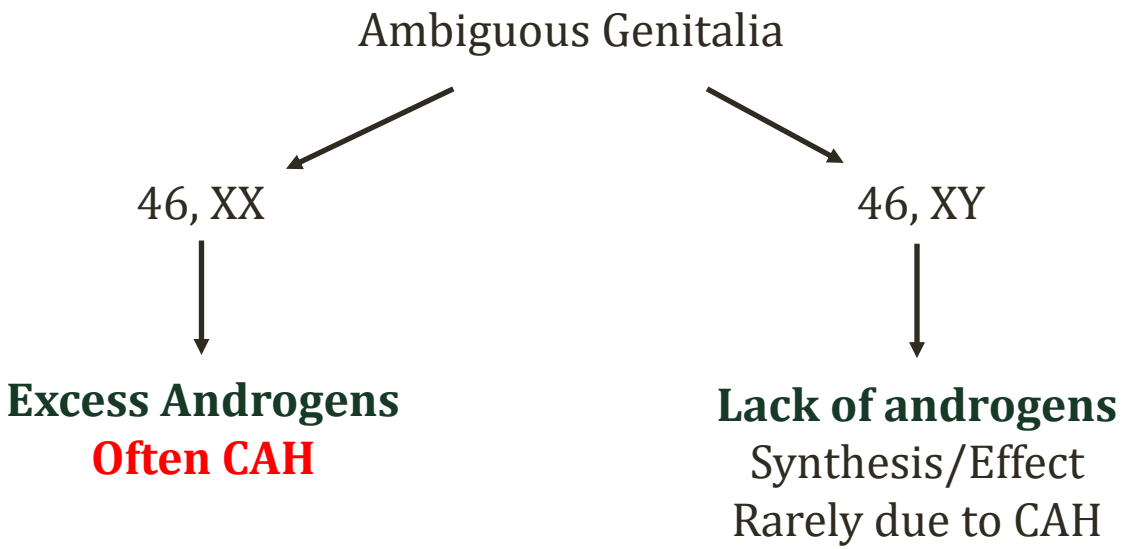
17-α Hydroxylase Deficiency

- 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

3-β Hydroxysteroid Dehydrogenase Deficiency



Disorders of Sex Development



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)

Adrenal Disorders

Jason Ryan, MD, MPH

Adrenal Disorders

- Excess cortisol
- Insufficient cortisol
- Excess mineralocorticoids
- Tumors

Cushing's Syndrome

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

Cushing's Syndrome

Excess Cortisol Effects

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

Cushing's Syndrome

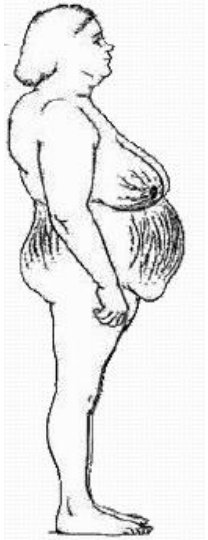
Excess Cortisol Effects

- Cortisol alters GnRH release → ↓ FSH,LH
- Menstrual irregularities in women
  - Abnormal cycles (80%)
  - Oligomenorrhea (~30%)
  - Amenorrhea (~30%)
- Hirsutism of face in women
- Males: Erectile dysfunction

Cushing's Syndrome

Excess Cortisol Effects

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



SherryC1234

Homini/Flikr

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

Wikipedia/Public Domain

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

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

- **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

Cushing's Syndrome

Diagnosis

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

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

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

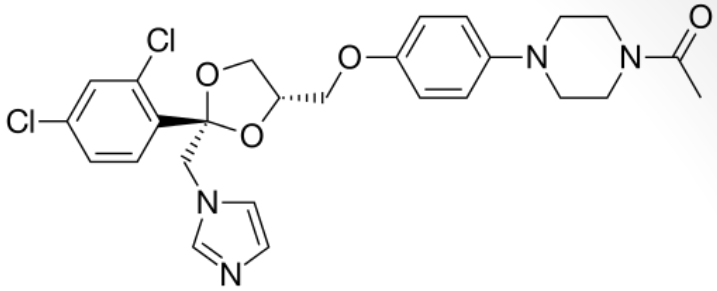
	Low Dose	High Dose
Normal	↓	↓
Pituitary Adenoma	--	↓
ACTH Tumor	--	--

Cushing's Syndrome

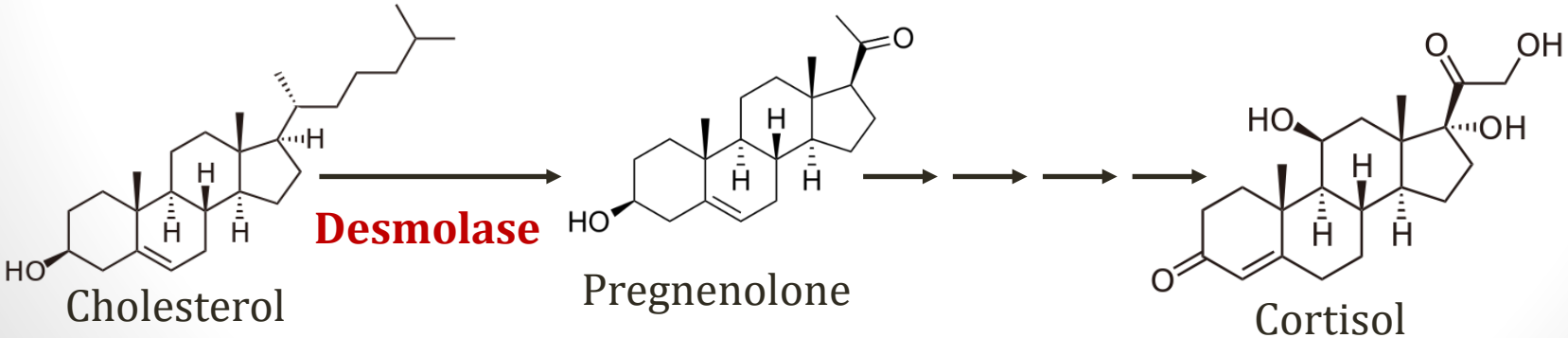
Treatment

- **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

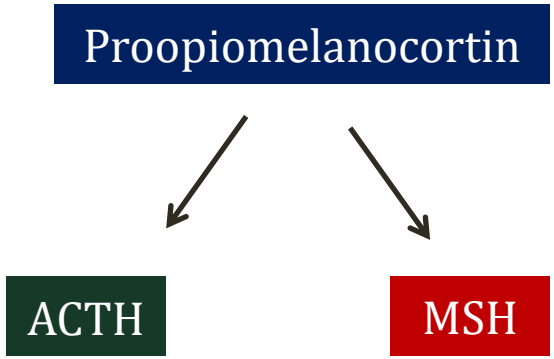
Adrenal Insufficiency

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 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



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 is palmar creases
- Classic scenario:
  - GI symptoms (nausea, pain)
  - Darkening skin

Wikipedia/Public Domain

Adrenal Crisis

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

Addison's Disease

Common Causes

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

Metastasis from Lung Cancer

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

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

Xishan01/Wikipedia

2º Adrenal Insufficiency

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

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

2º Adrenal Insufficiency

Important Points

- No skin findings
  - ACTH is not elevated
- No hyperkalemia
  - Aldosterone not effected

Adrenal Insufficiency

Diagnostic Tests

- 8 AM serum cortisol
  - Levels should be highest at this time
  - Low level indicates disease
- Serum ACTH
  - High ACTH with low cortisol = primary disease
  - Low ACTH with low cortisol = secondary disease

Adrenal Insufficiency

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

Primary Aldosteronism

Mineralocorticoid Excess

- **Hypertension**, classically at a young age
- **Hypokalemia**
  - Weakness, muscle cramps
  - Unreliable finding → many cases with normal K^+
- **Metabolic alkalosis**

Primary Aldosteronism

Most common causes

- Bilateral idiopathic hyperaldosteronism (~60%)
- Aldosterone-producing adenoma (~30%)
  - Sometimes called Conn's syndrome

Primary Aldosteronism

Diagnosis

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

Primary Aldosteronism

Diagnosis

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

Primary Aldosteronism

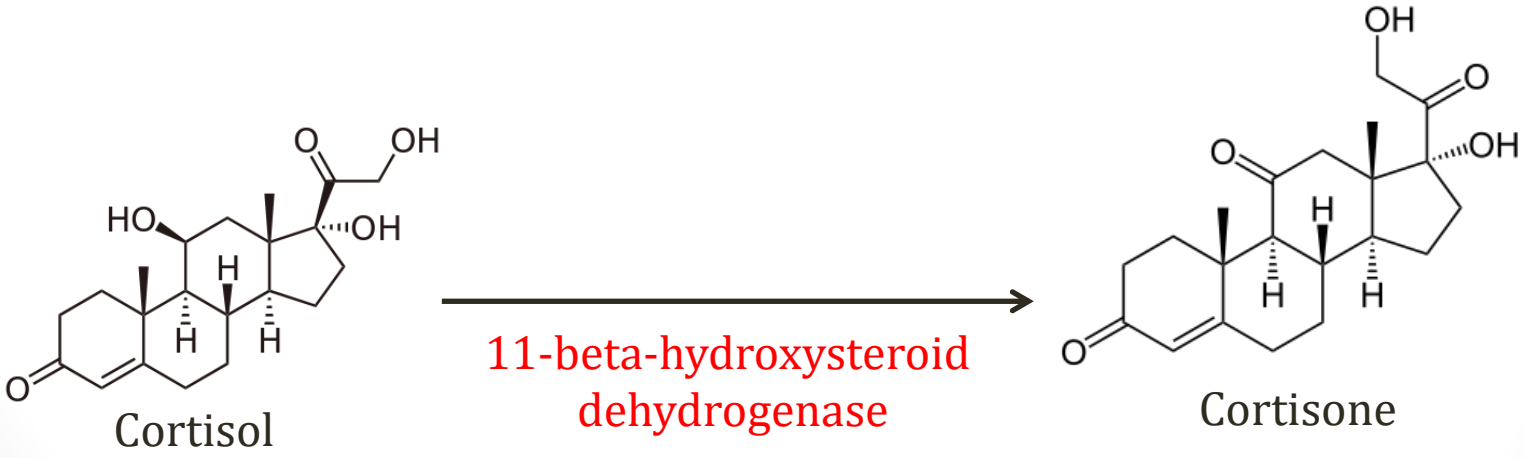
Treatment

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

Licorice

Pikaluk/Flikr

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



Cortisol

Cortisone

Pheochromocytoma

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

Pheochromocytoma

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

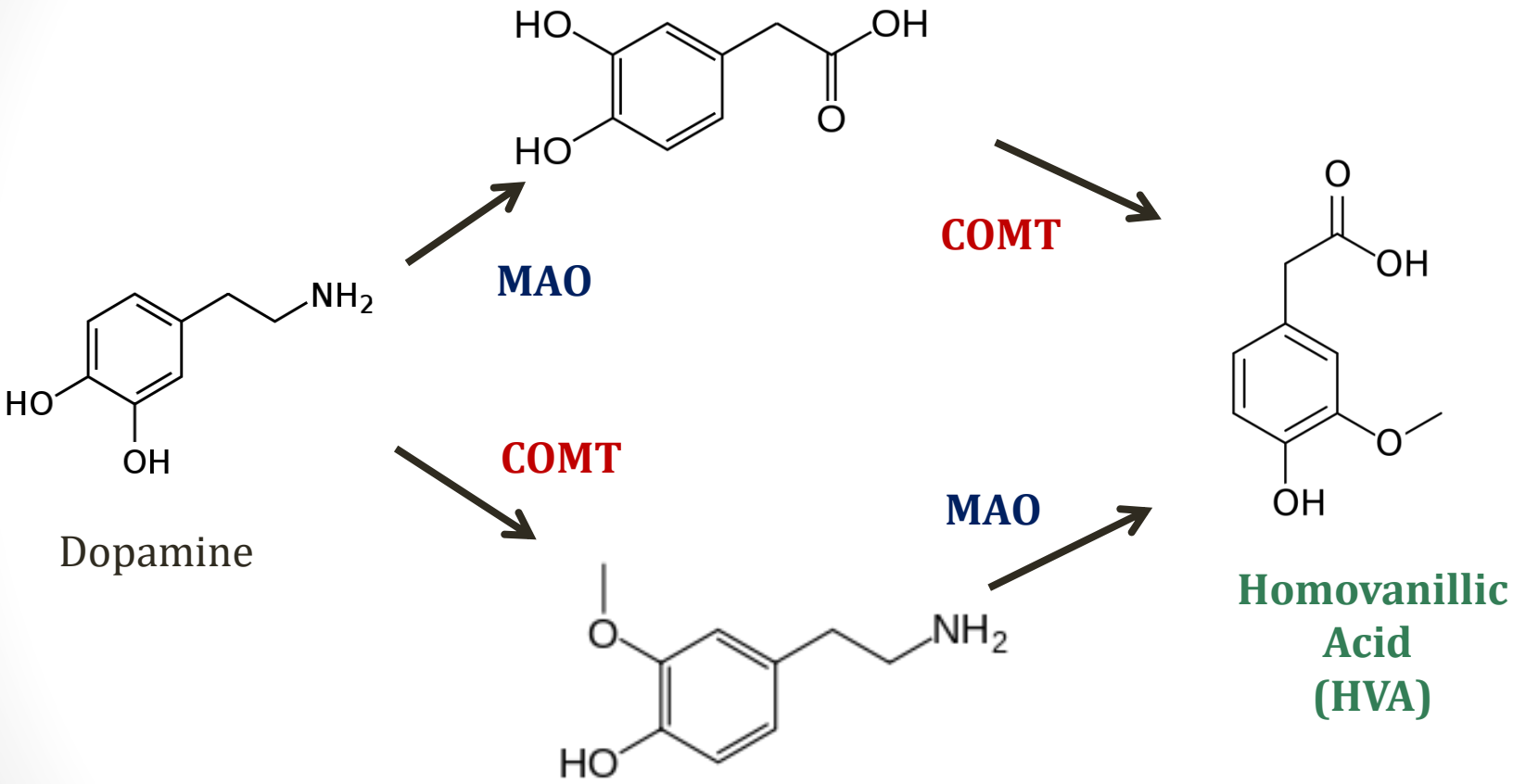
Pheochromocytoma

Diagnosis

- Serum catecholamine levels not routinely used
  - Levels fluctuate
  - Some metabolism intratumoral
- Breakdown products of catecholamines measured
  - Usually via 24 hour urine collection

Pheochromocytoma

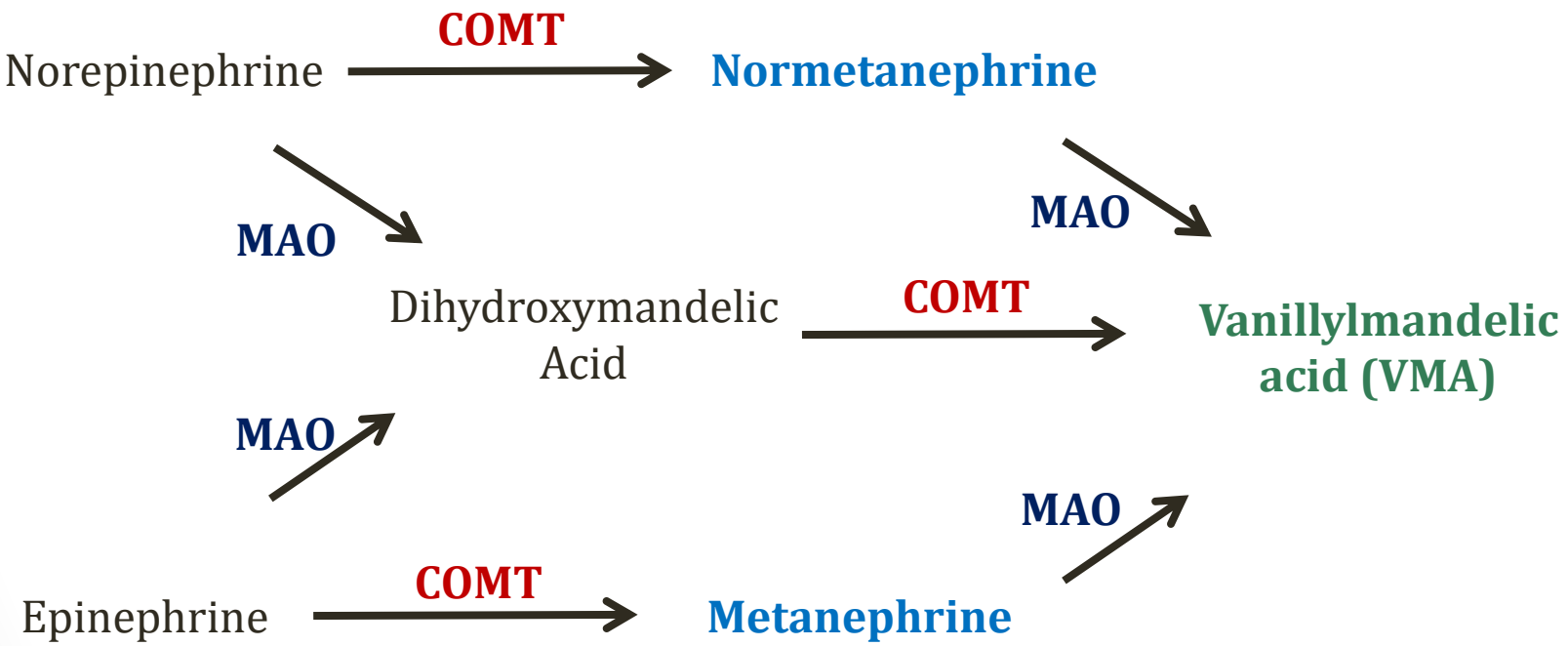
Diagnosis



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

Pheochromocytoma

Diagnosis



Pheochromocytoma

Diagnosis

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

Pheochromocytoma

Treatment

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

Paraganglioma

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

Neuroblastoma

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

Neuroblastoma

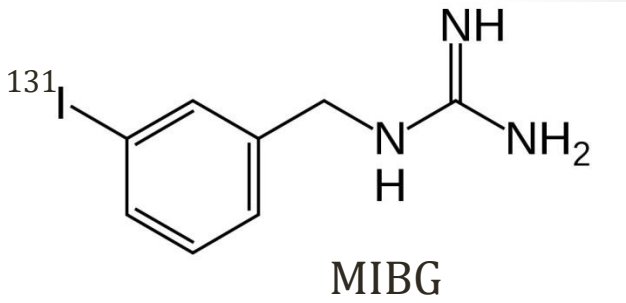
- Symptoms related to tumor mass effect
  - Commonly present as abdominal pain
- Can synthesize catecholamines
  - Rarely cause symptoms like pheochromocytoma
  - **Urinary HVA/VMA levels** used for diagnosis
- Rare feature: Opsoclonus-myoclonus-ataxia (OMA)
  - Rare paraneoplastic syndrome
  - Rapid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

Neuroblastoma

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

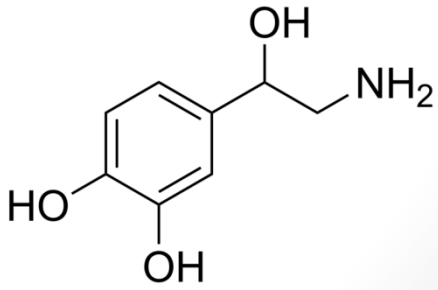
MIBG

Metaiodobenzylguanidine



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
  - Simultaneous administration of **potassium iodide**
  - Non-radioactive iodine
  - Will be taken up by thyroid instead



Norepinephrine

Adrenal Adenomas

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

Adrenal Adenomas

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

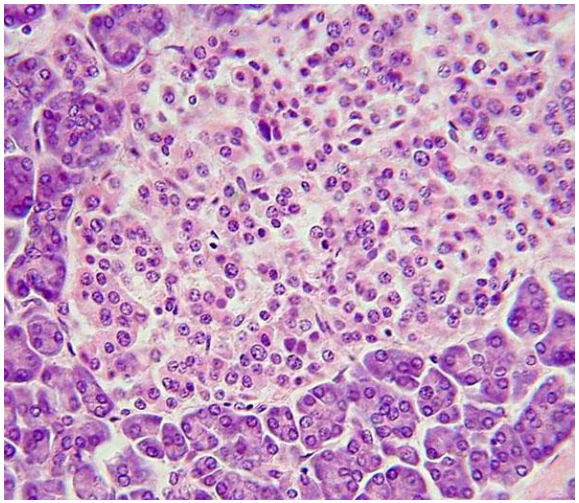
Endocrine Pancreas

Jason Ryan, MD, MPH

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



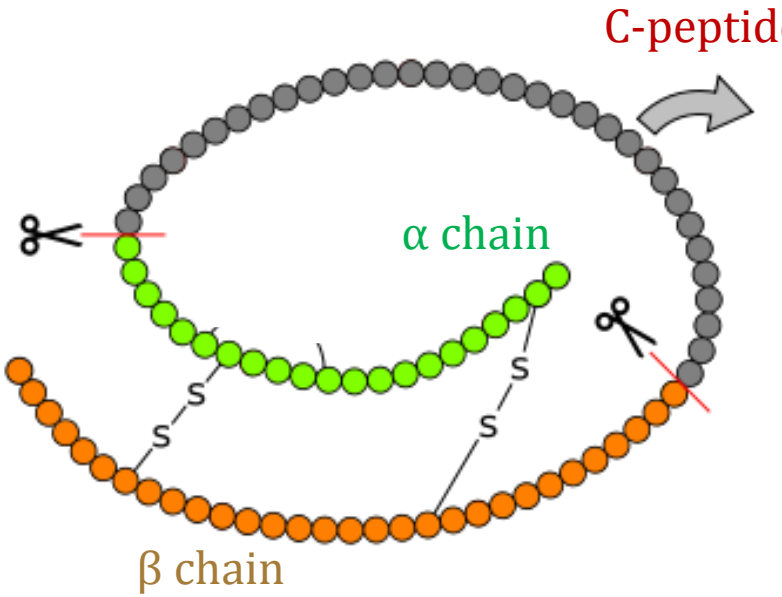
Polarlys/Wikipedia

Insulin

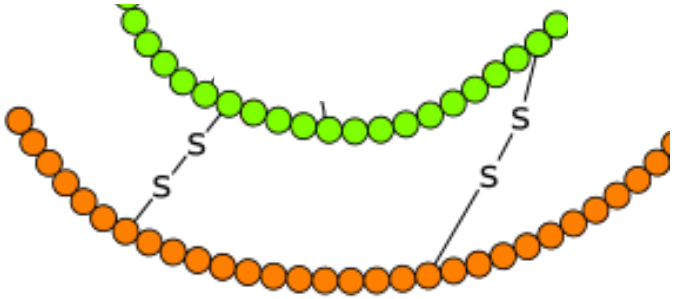
- Protein hormone
- Synthesized by **beta cells**
- Synthesized as preproinsulin
  - Made by ribosomes of rough endoplasmic reticulum
- Preproinsulin cleaved to proinsulin
  - Transported to Golgi apparatus
- Packaged into secretory granules
  - Proinsulin cleaved to insulin and C-peptide in granules

Insulin Structure

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

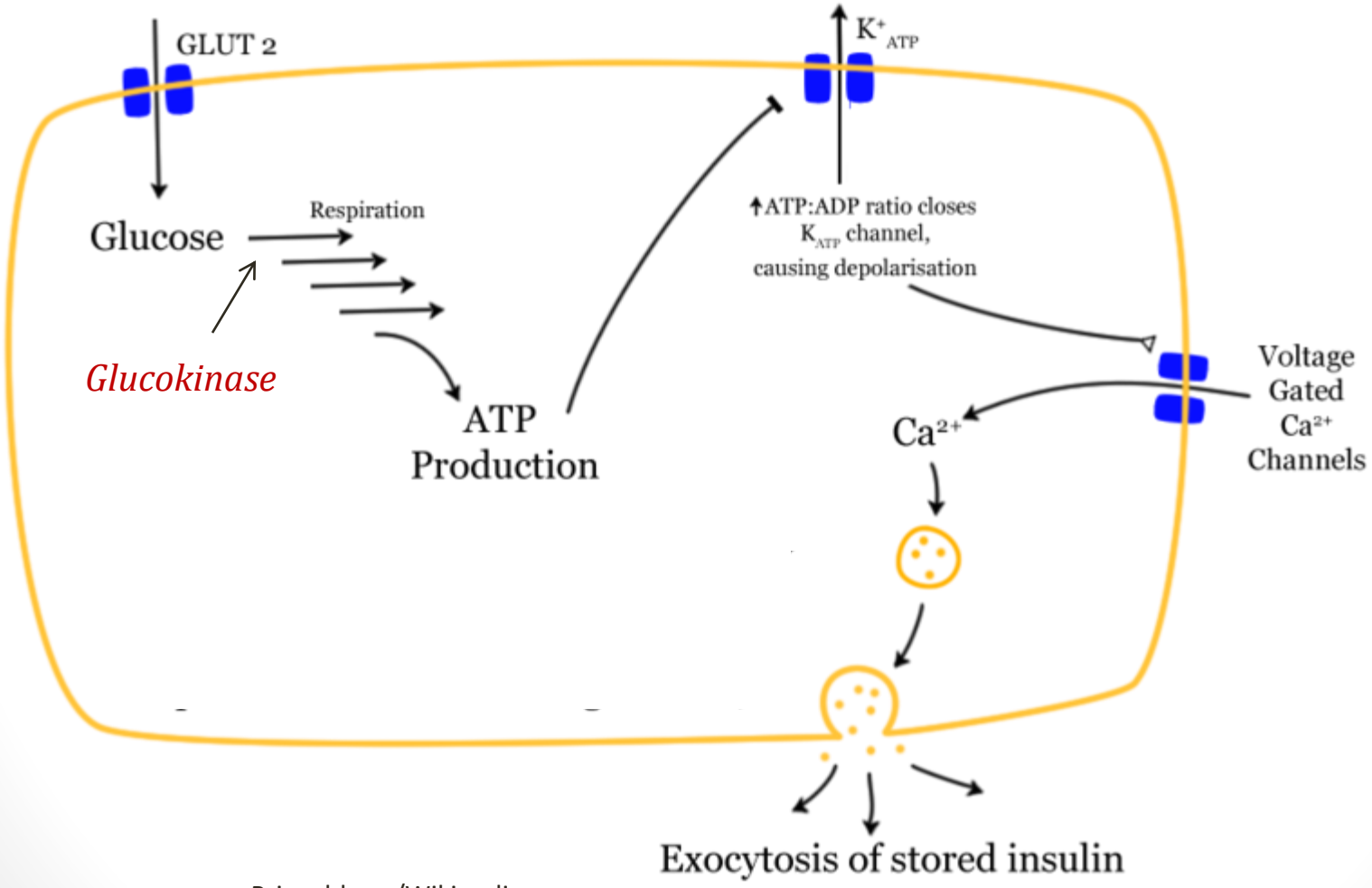


Zapyon/Wikipedia



Insulin Release

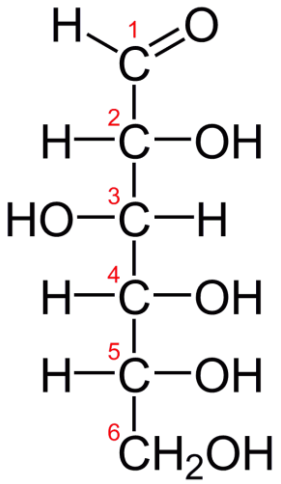
GLUT-2 and Glucokinase
Both in liver/pancreas



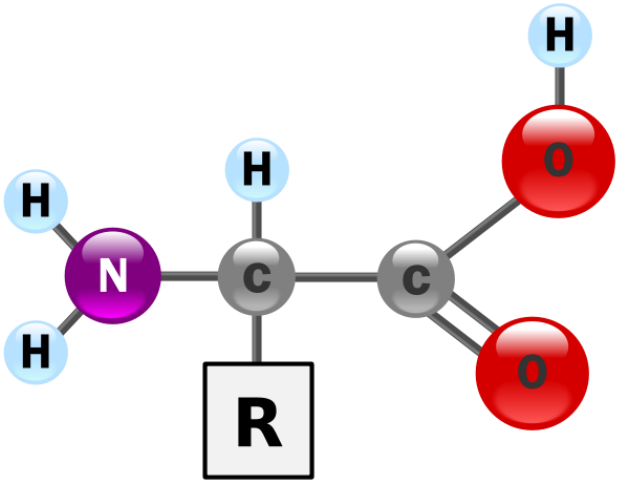
Prisonblues /Wikipedia

Insulin Release

- Produced in response to: **glucose**, **amino acids**



Glucose



Amino Acid

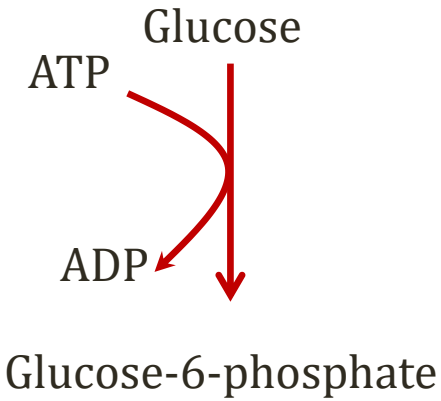
Wikipedia/Public Domain

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

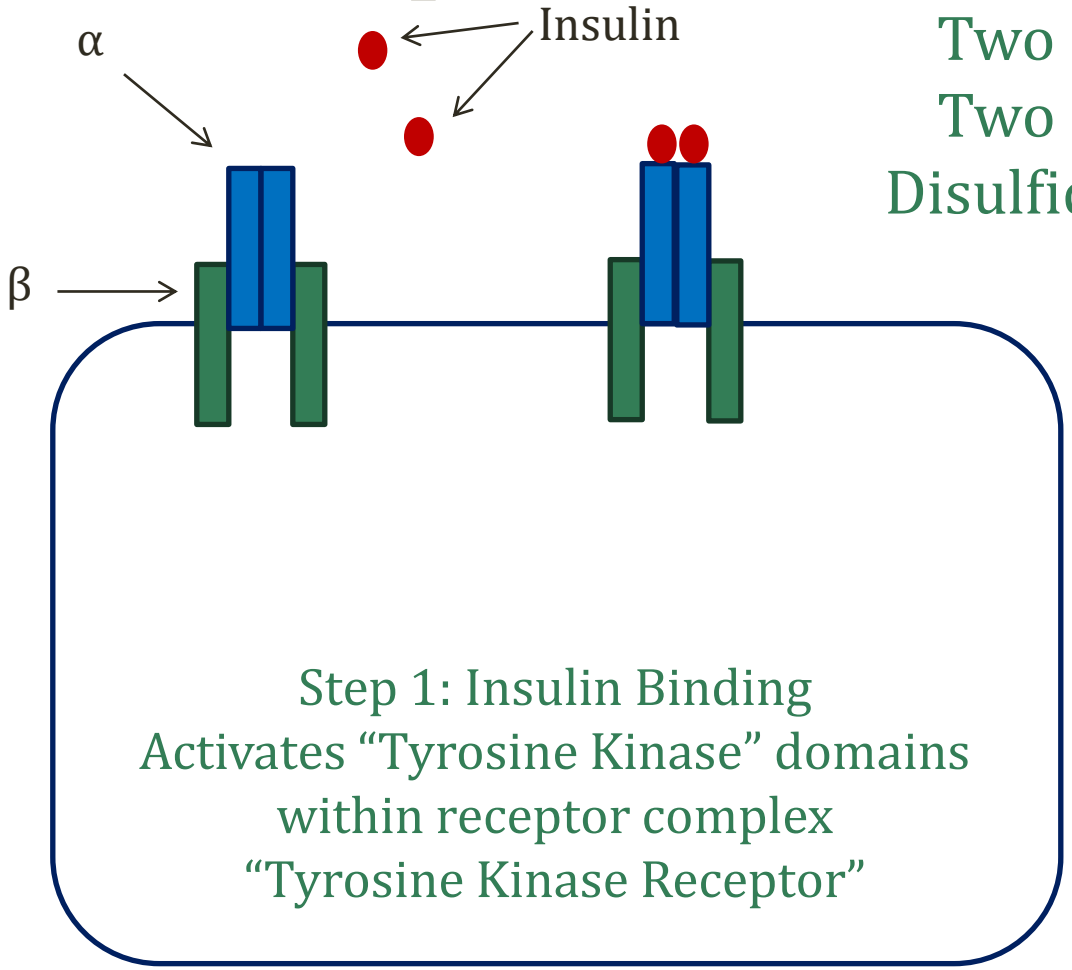
- **Bidirectional** glucose transporter
- Found in liver, kidney, beta cells
  - Liver, kidney: Gluconeogenesis
  - Beta cells: Glucose in/out based on plasma levels
- Also found in intestine, other tissues

Insulin Release

Key Points

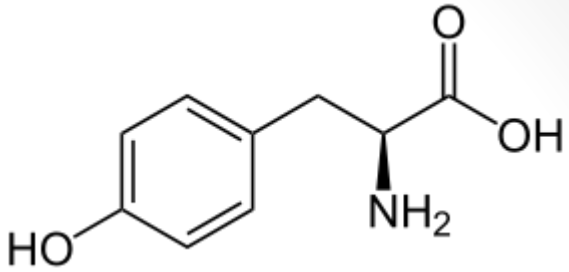
- Glucose into beta cells via GLUT-2
- Glucose → G-6P via glucokinase
- ATP produced → Closure of K^+ channels
- Depolarization
- Voltage-gated calcium channels open
- Calcium → insulin release from vesicles

Insulin Receptor

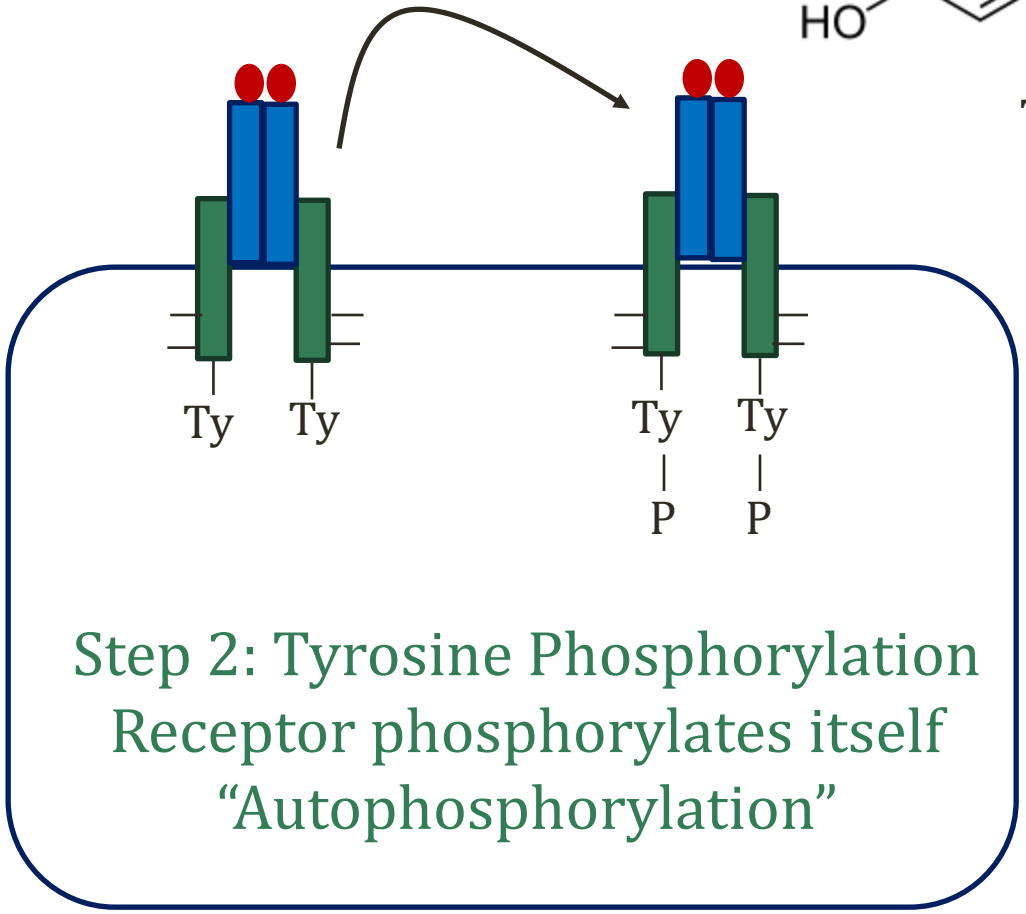


Tetramer
Two α units
Two β units
Disulfide bonds

Insulin Receptor

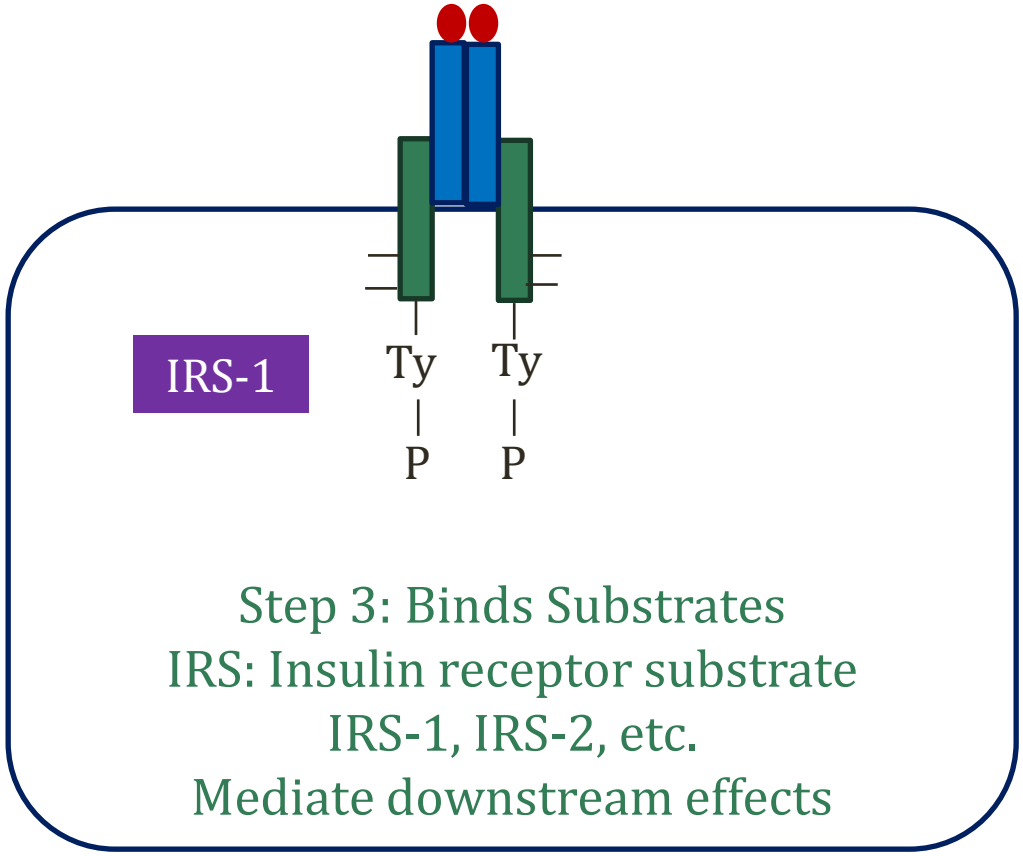


Tyrosine



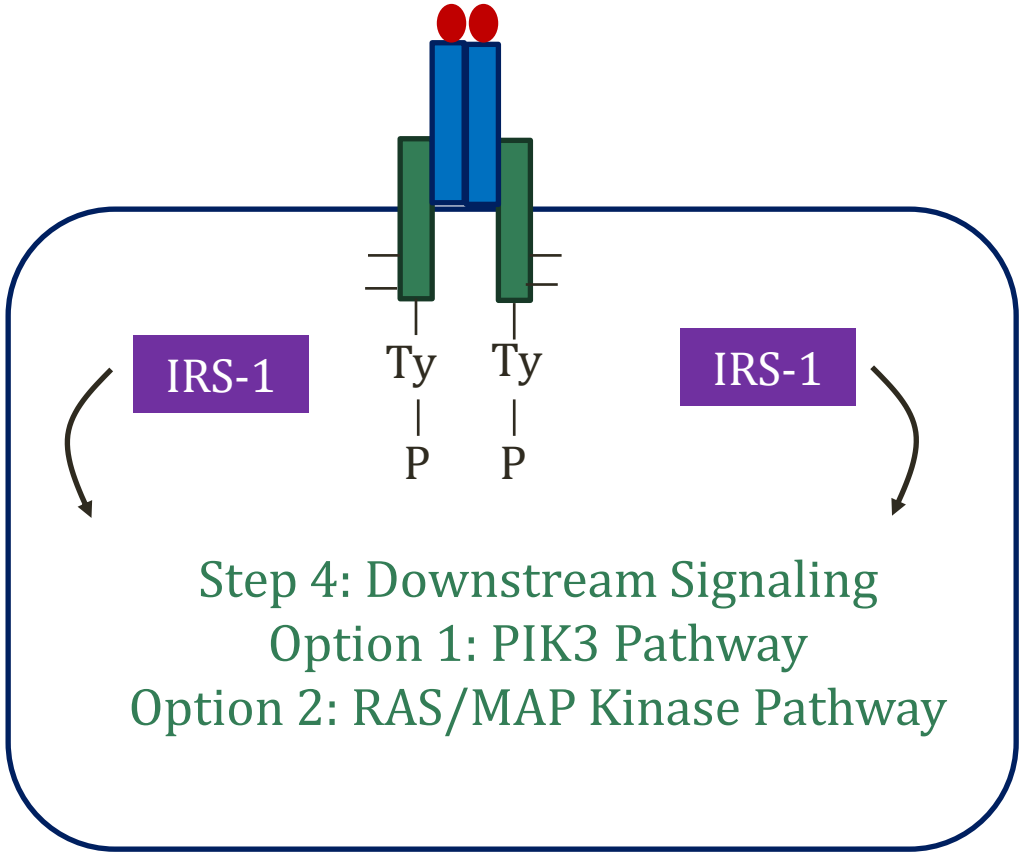
Step 2: Tyrosine Phosphorylation
Receptor phosphorylates itself
"Autophosphorylation"

Insulin Receptor



Step 3: Binds Substrates
IRS: Insulin receptor substrate
IRS-1, IRS-2, etc.
Mediate downstream effects

Insulin Receptor

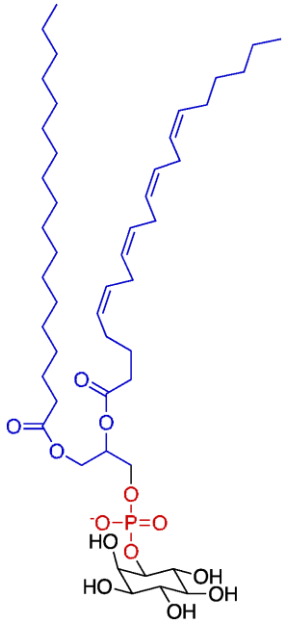


Step 4: Downstream Signaling
Option 1: PIK3 Pathway
Option 2: RAS/MAP Kinase Pathway

PIK3 Pathway

Phosphatidylinositol 3–kinase Pathway

- Intracellular lipid kinases
- Phosphorylate 3'-hydroxyl group of phospholipids
  - Forms PIP_3 from PIP_2

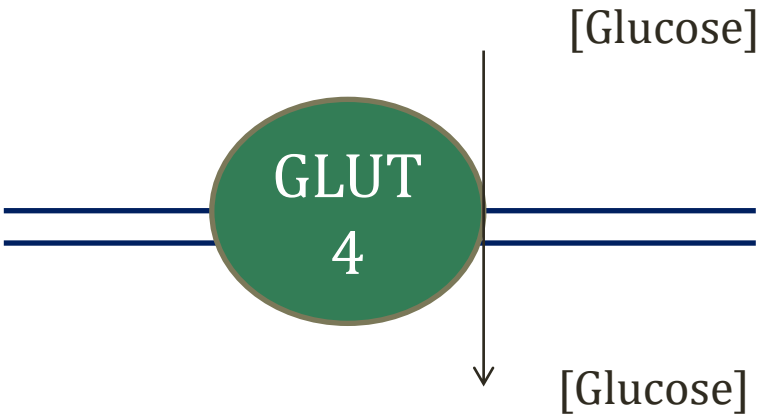


Phosphatidylinositol

PIK3 Pathway

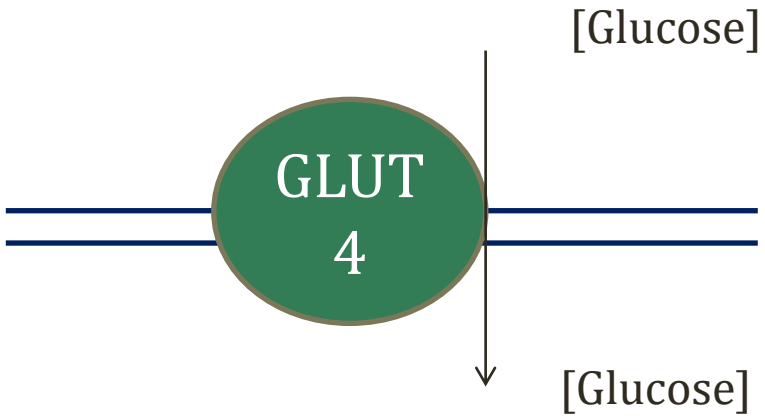
Phosphatidylinositol 3–kinase Pathway

- 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**

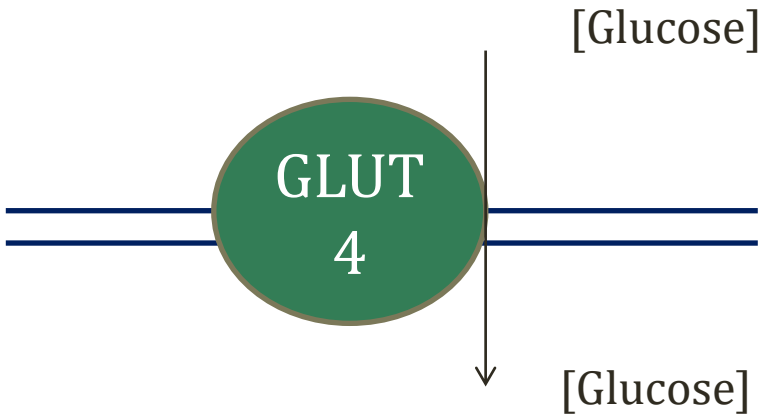
Insulin Receptor

Key Points

- Tetramer of α/β subunits with disulfide bridges
  - α: extracellular
  - β: transmembrane
- Insulin binding → **tyrosine kinase** activity
- Autophosphorylation of tyrosine residues
- PIK3 Pathway → **GLUT-4 glucose transporter**
- RAS/MAP Kinase Pathway: growth/gene transcription

Insulin Dependent Organs

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



Insulin Independent Organs

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

Insulin Effects

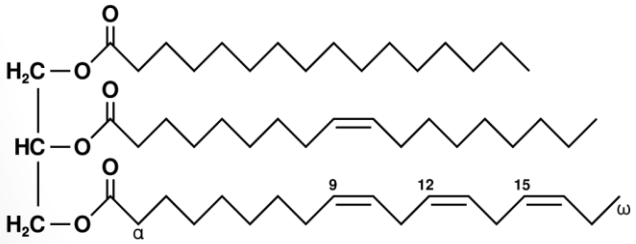
- Glucose uptake (skeletal muscle, adipose tissue)
- **Glycogen synthesis**
  - Activates glycogen synthase
  - Inhibits glycogen phosphorylase
- **Inhibits gluconeogenesis**
  - ↑ Fructose-2,6-bisphosphate levels
  - Inhibit Fructose 1,6 bisphosphatase 1

Insulin Effects

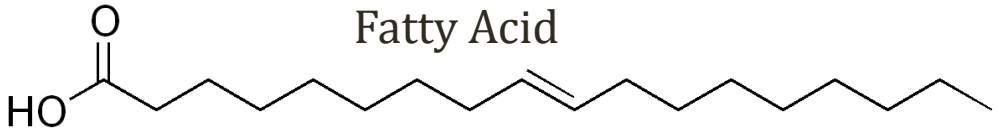
- **Fatty acid synthesis**
  - Activates acetyl-CoA carboxylase
  - Inhibits hormone sensitive lipase
- **Protein synthesis**
  - Stimulates entry of amino acids into cells → protein synthesis
  - Important for muscle growth
- Key side effect insulin therapy: weight gain

Hormone Sensitive Lipase

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

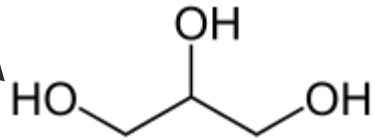


Triacylglycerol



Fatty Acid

Hormone Sensitive Lipase



Glycerol

Liver

Insulin Effects

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

Glucagon

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

Glucagon

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

Glucagon

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

Glucagon Receptor

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

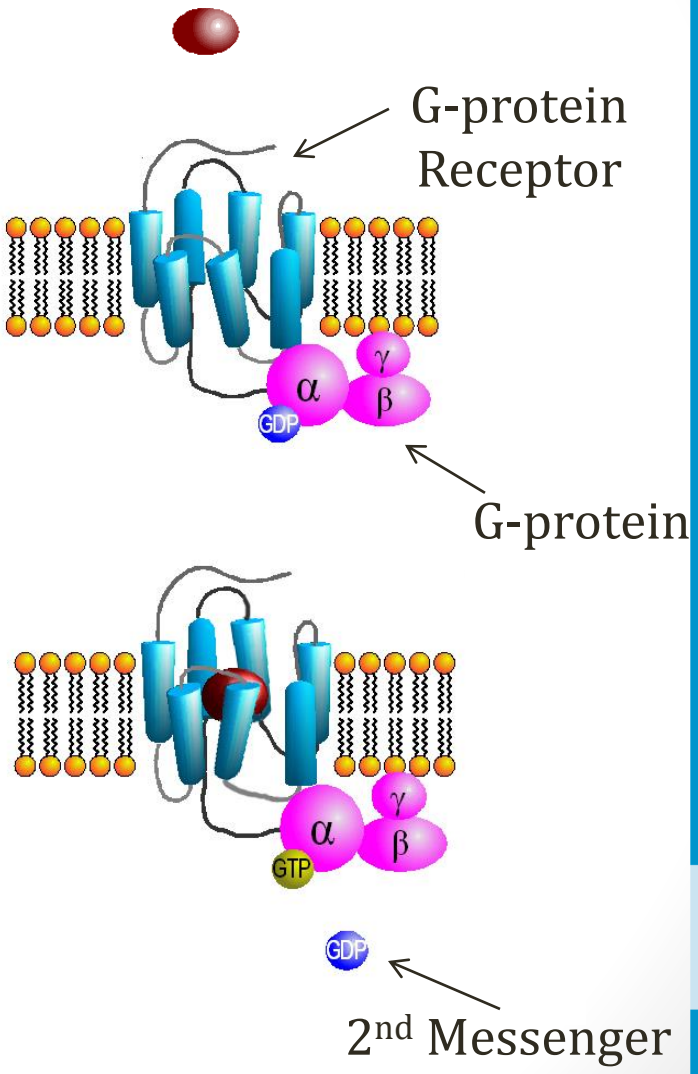


Image: "Activation cycle of G-proteins by G-protein-coupled receptors" by Sven Jähnich

Glucagon Receptor

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

Watanabe M, et al. Histologic distribution of insulin and glucagon receptors. Brazilian Journal of Medical and Biological Research (1998) 31: 243-256

Hypoglycemia

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

Beta Blocker Overdose

- Causes bradycardia and hypotension
- Drug of choice: **Glucagon**
  - Activates **adenylyl cyclase**
  - Different site from beta-adrenergic agents
  - Raises cAMP → ↑ 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

	Exogenous Insulin	Insulinoma	Oral Hypoglycemics
Insulin	+	+	+
C-peptide	--	+	+
Hypoglycemic Agent Screen	--	--	+

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

Glucagonoma

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

Glucagonoma

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

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

Diabetes

Jason Ryan, MD, MPH

Diabetes

- Chronic disorder of **elevated blood glucose levels**
- Caused by:
  - Insufficient insulin
  - Insufficient response to insulin ("insulin resistance")
  - Both

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

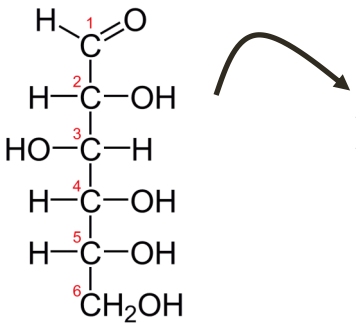
Diabetes Diagnosis

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

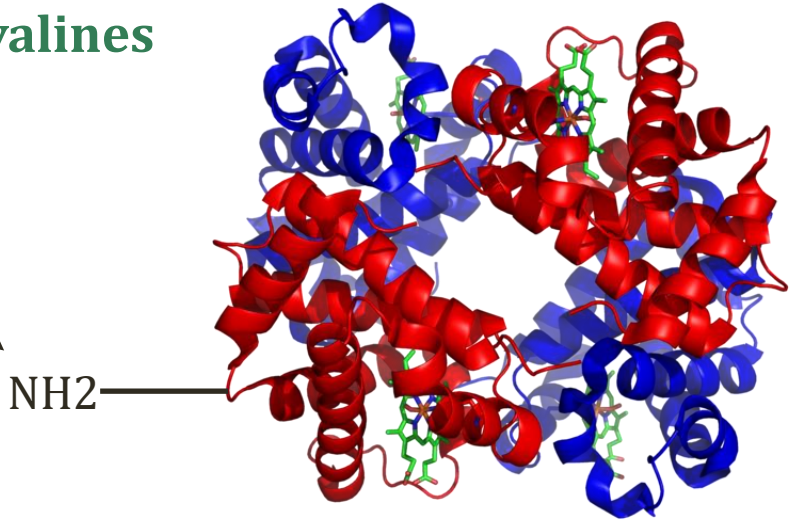
State	Fasting plasma glucose
Normal	<100mgl/dl
Pre-diabetes	100 to 125mg/dl
Diabetes	>=126mg/dl

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**



Glucose



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

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

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

Type 1 Diabetes

Wikipedia/Public Domain

- 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**

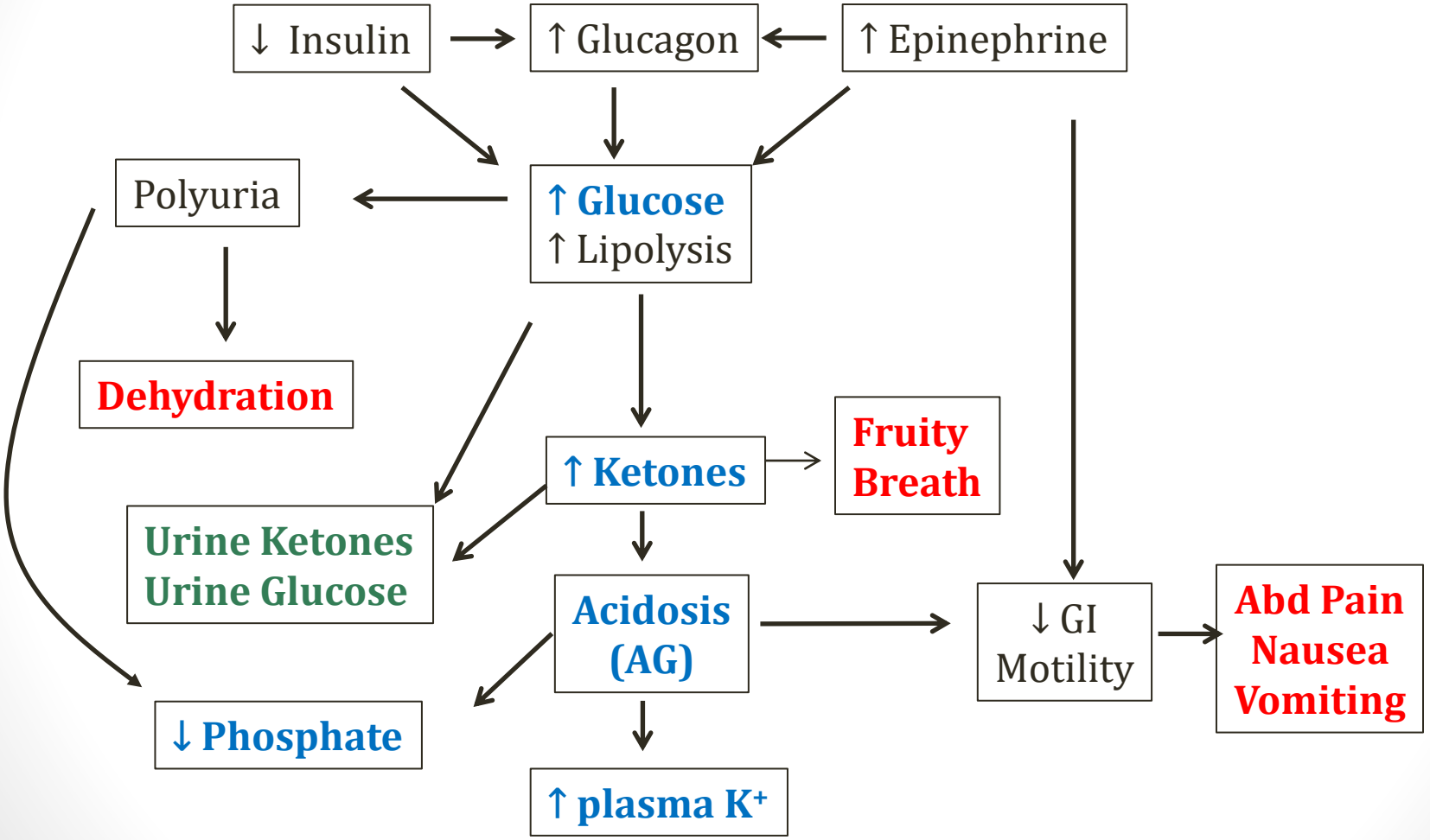
Diabetic Ketoacidosis

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**

Diabetic Ketoacidosis

DKA



Diabetic Ketoacidosis

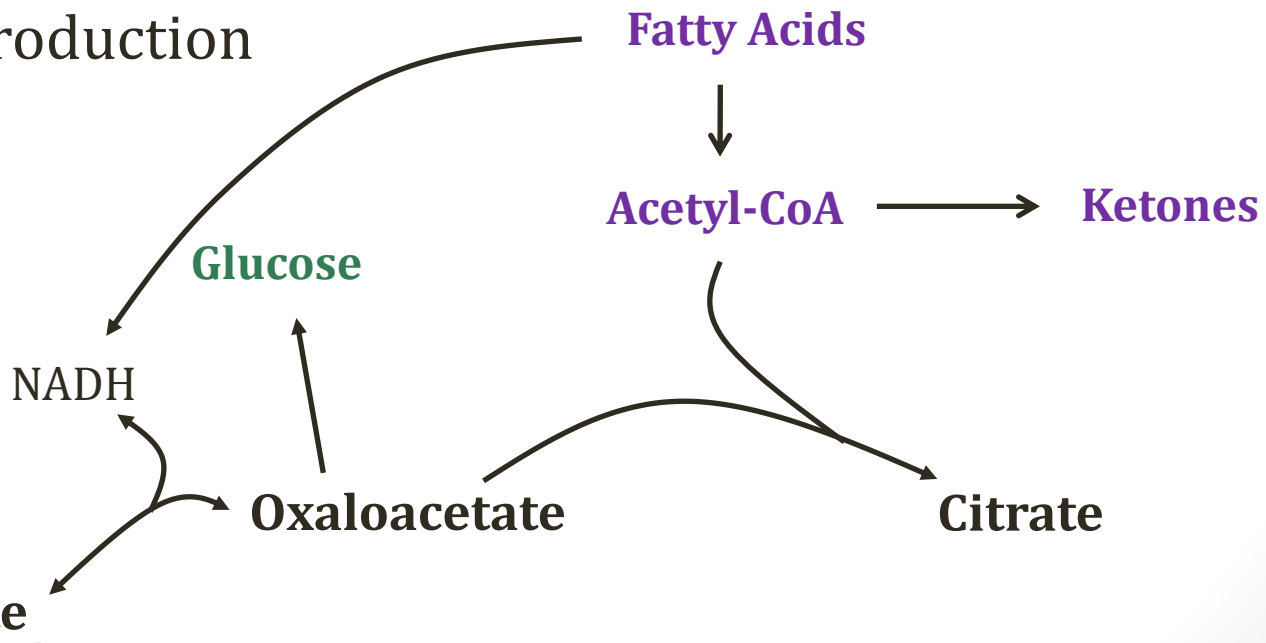
Clinical Presentation

- 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

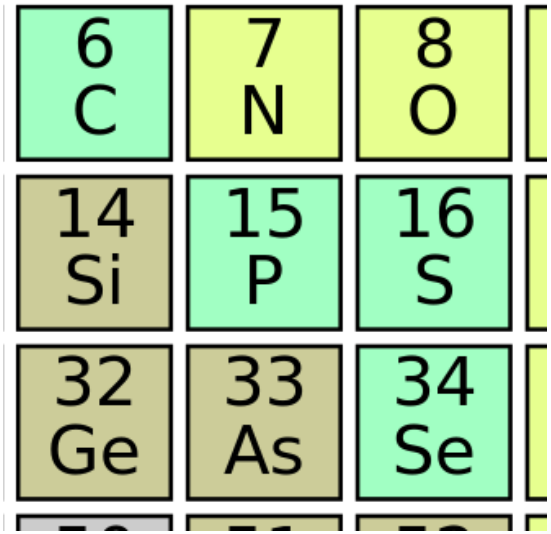
DKA

- Low insulin/high epinephrine
- High fatty acid utilization
- Oxaloacetate depleted → TCA cycle stalls
- ↑ acetyl-CoA
- Ketone production



Phosphate

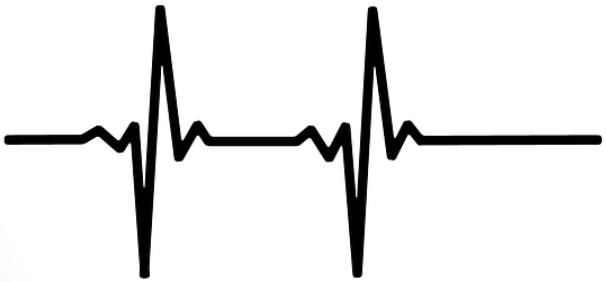
- Risk of **hypophosphatemia**
  - Acidosis → shifts phosphate to extracellular fluid
  - Phosphaturia caused by osmotic diuresis
- Loss of ATP
  - Muscle weakness (respiratory failure)
  - Heart failure (↓ contractility)



Diabetic Ketoacidosis

Clinical Presentation

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



Pixabay/Public Domain

_DJ_/Wikipedia

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

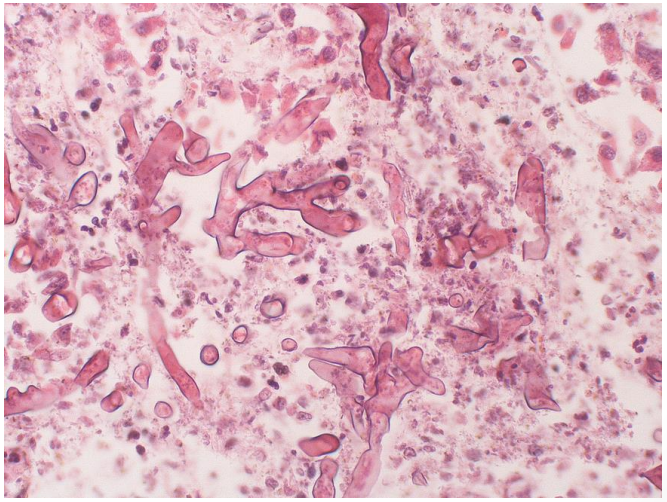
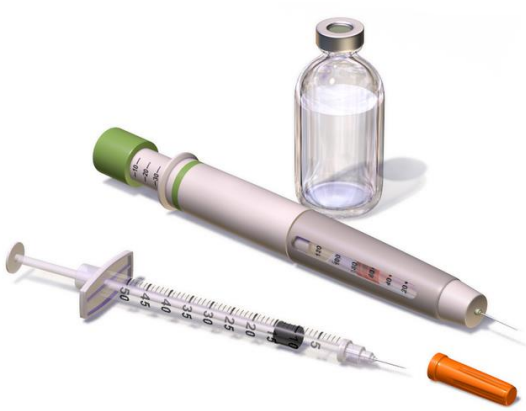


Image courtesy of Yale Rose/Flickr

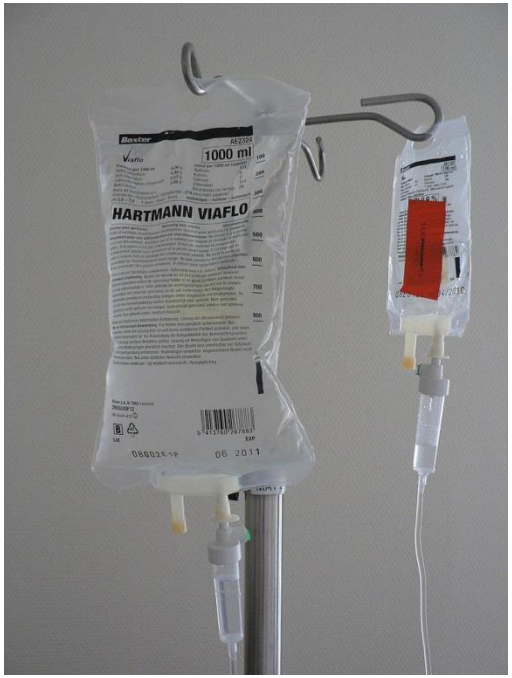
Diabetic Ketoacidosis

Treatment

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



BruceBlaus/Wikipedia



Harmid/Wikipedia

Diabetic Ketoacidosis

Treatment

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

Type 2 Diabetes

- **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

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

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

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Type 2 Diabetes

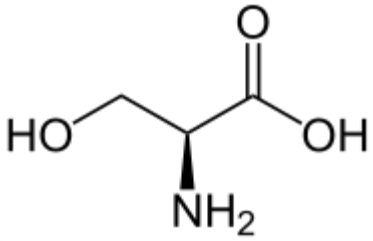
Risk Factors

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

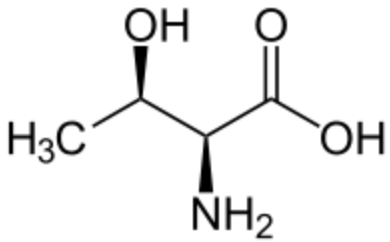
Type 2 Diabetes

Insulin Resistance Mechanism

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



Serine



Threonine

Type 2 Diabetes

Histology

- Classic finding is **amyloid** in pancreatic islets
- **Amylin** peptide normally made by beta cells
  - Precise function not known
  - Packaged and secreted with insulin
  - Pramlintide: amylin analog used for diabetes treatment
- 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 osmolarity** → CNS dysfunction

HHS

Hyperglycemic Hyperosmolar Syndrome

- Polyuria, polydipsia
- Dehydration
- **Mental status changes**
  - Confusion
  - Coma
- Treatment similar to DKA (insulin, IVF)

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

Madhero88/Dermnet.com

Diabetic Complications

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

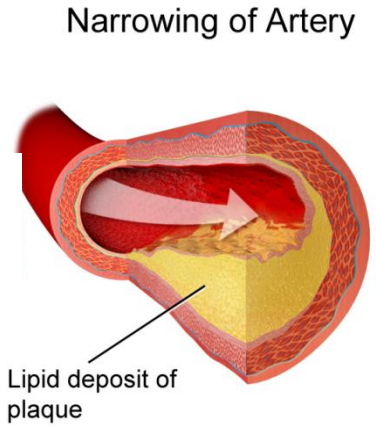
Non-enzymatic Glycation

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

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



BruceBlaus/Wikipedia

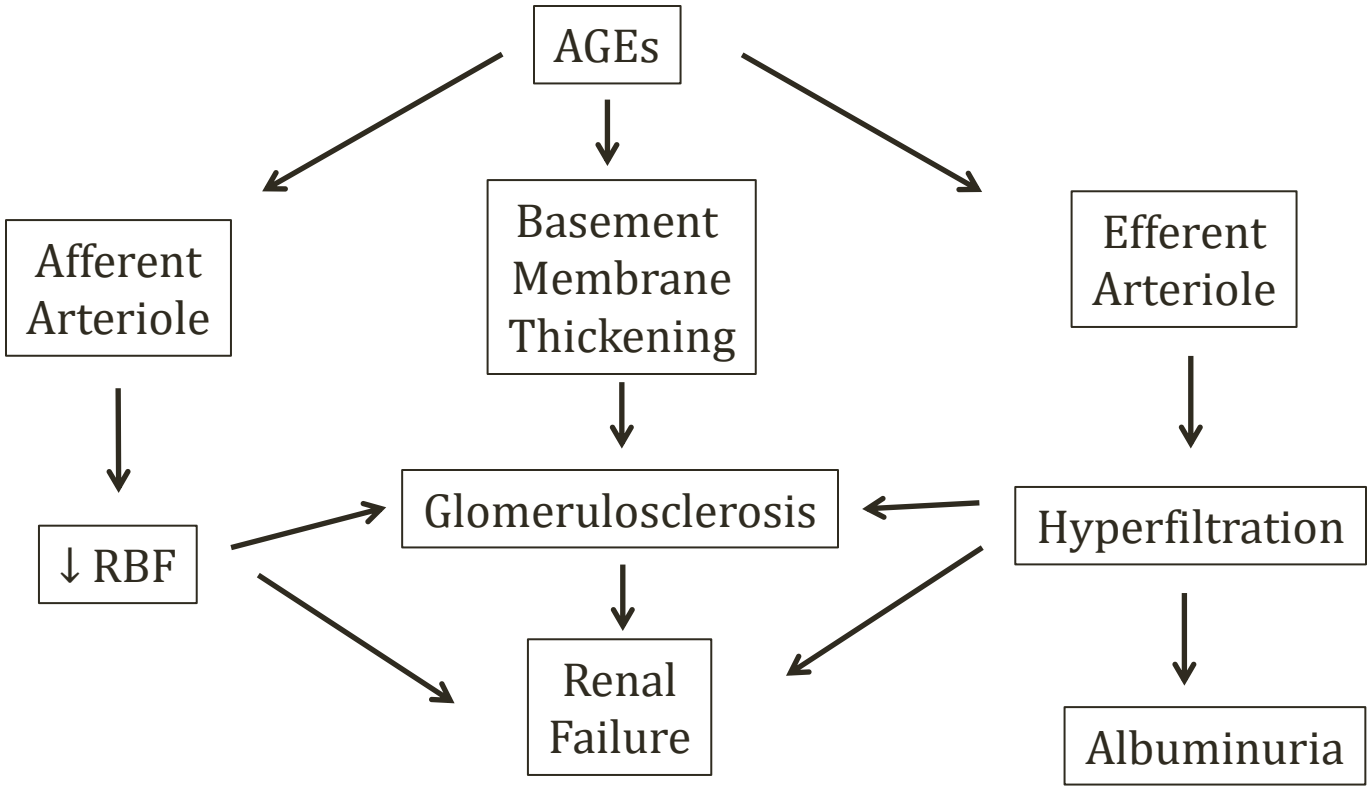
Diabetic Kidney Disease

Diabetic Microangiopathy

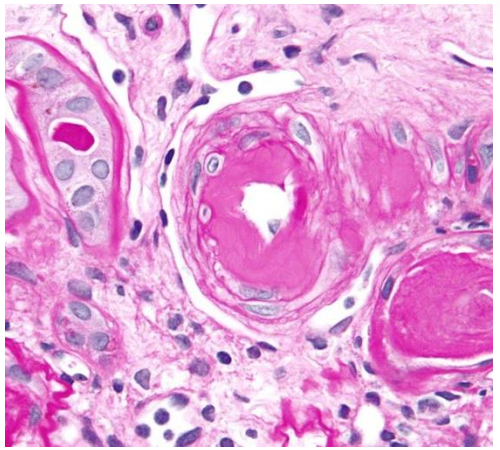
- AGEs → damage to **glomerulus** and **arterioles**
- Leads to **end stage kidney disease** in many diabetics

Diabetic Kidney Disease

Diabetic Microangiopathy



Renal Arterioles



Nephron/Wikipedia

- 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

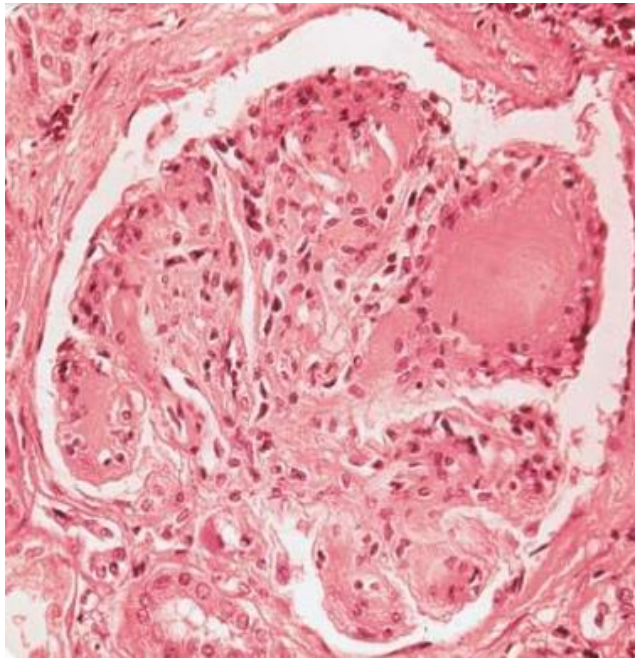
- AGEs → diffuse **basement membrane thickening**
- Visible on electron microscopy
- Can lead to mesangial proliferation in glomeruli
- End result is glomerulosclerosis

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

Kimmelstiel-Wilson Nodules

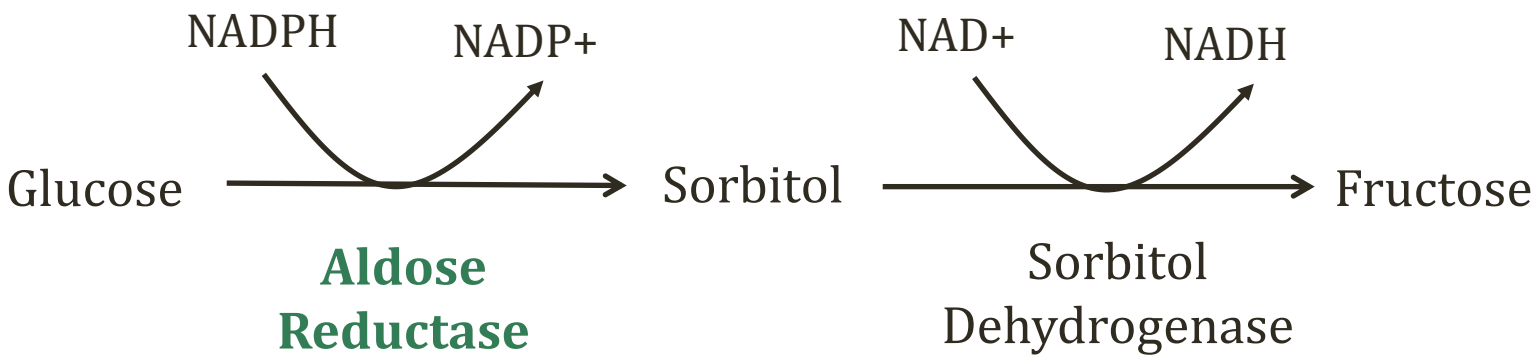
- Hallmark of nodular sclerosis of diabetes
- Pathognomonic of diabetic kidney disease



bilalbanday

Sorbitol Accumulation

Polyol Pathway

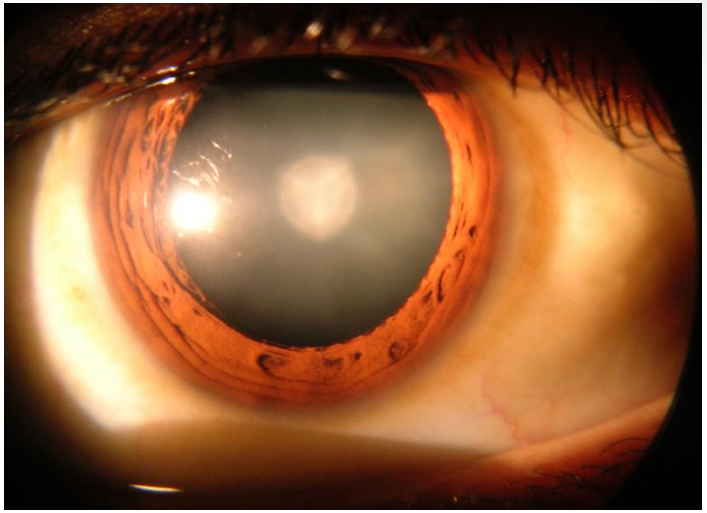


Polyol Pathway

- 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

Cataracts

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



Rakesh Ahuja, MD/Wikipedia

Neuropathy

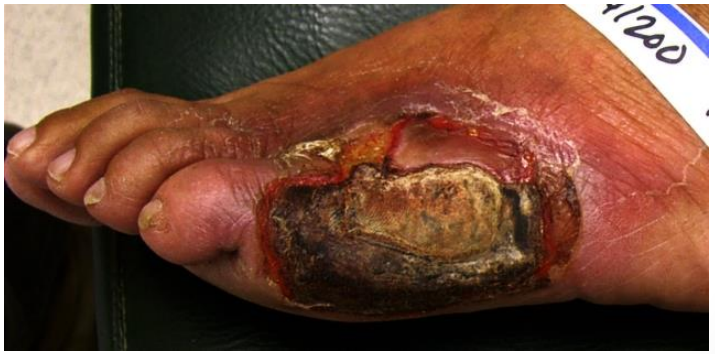
- **Sorbitol** can accumulate in **Schwann cells**
  - Myelinating cells of peripheral nerves
  - Osmotic damage → neuropathy

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 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



DrGnu/Wikipedia

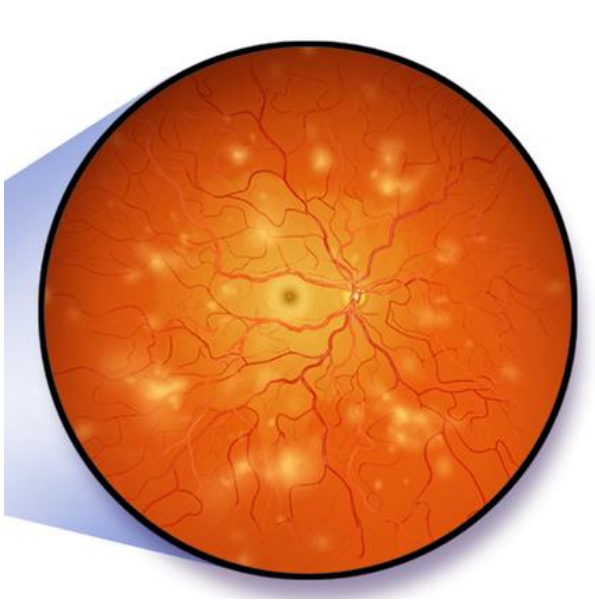
Diabetic Retinopathy

- 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

Diabetic Retinopathy

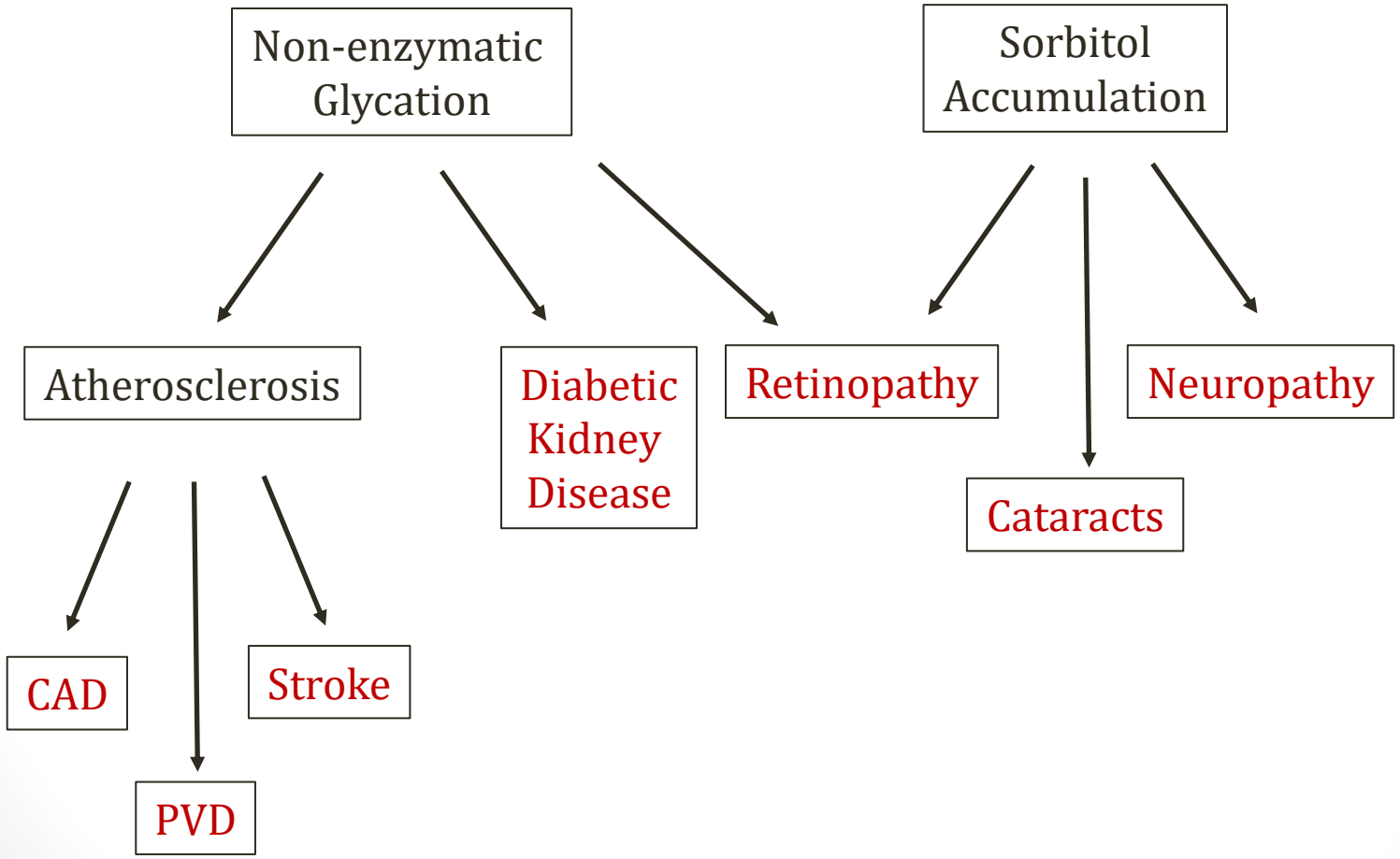
Findings

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



"Blausen gallery 2014"
Wikiversity Journal of Medicine.

Diabetes Complications



Type 1 versus Type 2

	Type 1	Type 2
Pathophysiology	Loss of insulin	Insulin Resistance
Insulin	Low	High then low
Biopsy	Insulitis	Amyloid
Age	Children	Adults
Genetic Predisposition	Weaker	Stronger
Complications	DKA	HHS

Insulin

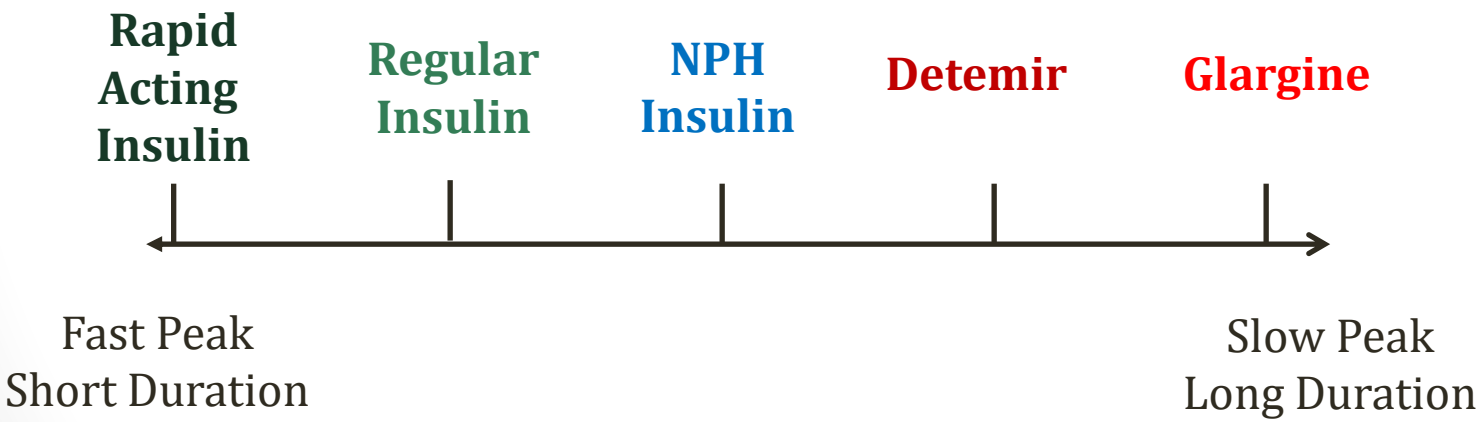
Jason Ryan, MD, MPH

Type 1 and Type 2

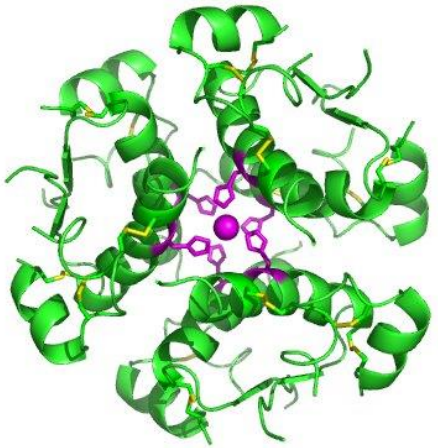
- Type 1 diabetes treated mainly with **insulin**
- Type 2 diabetes: **oral or SQ drugs +/- insulin**
  - Initial stages: Oral and/or SQ drugs
  - Advanced disease: Insulin

Insulin

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



Insulin Hexamers



Isaac Yonemoto /Wikipedia

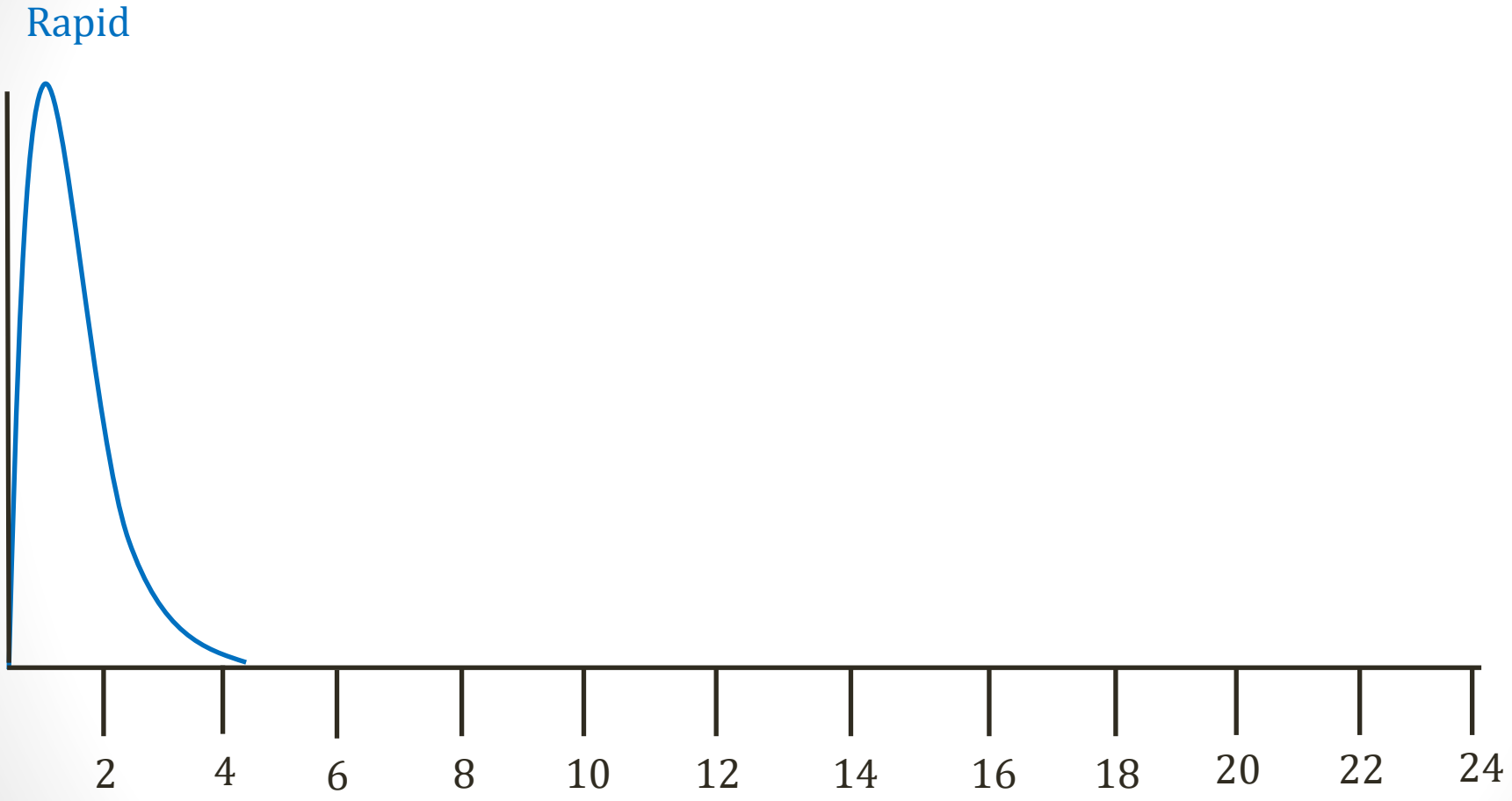
- Insulin forms **hexamers** in the body
  - Six insulin molecules linked
  - Stable structure
- Insulin usually administered **subcutaneously**
- Activity related to speed of absorption
- Insulin hexamers → slower onset of action
- Insulin monomers → faster onset of action

Rapid Acting Insulin

Lispro, Aspart, and Glulisine

- 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**

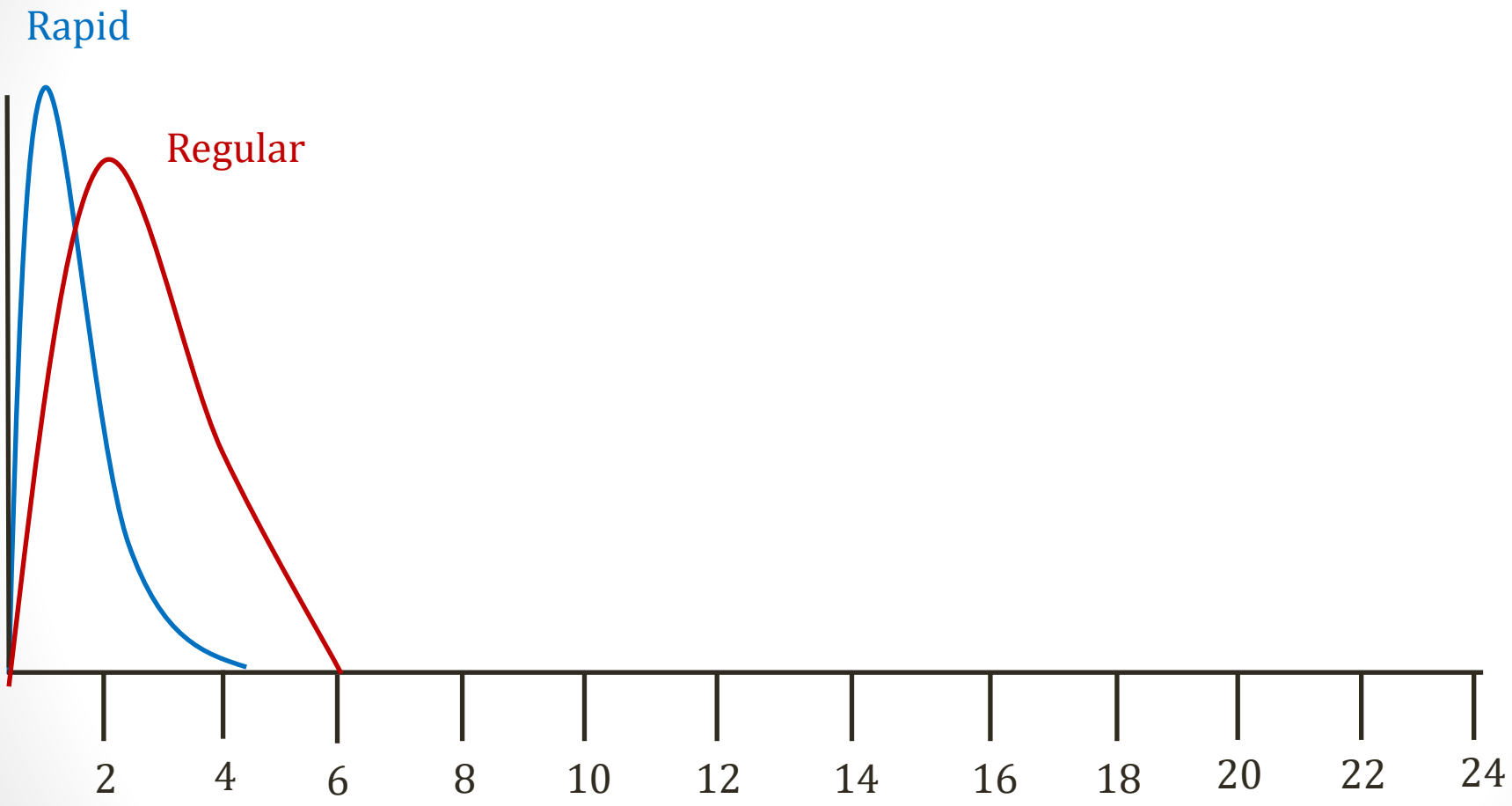
Insulin



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

Insulin



Regular Insulin

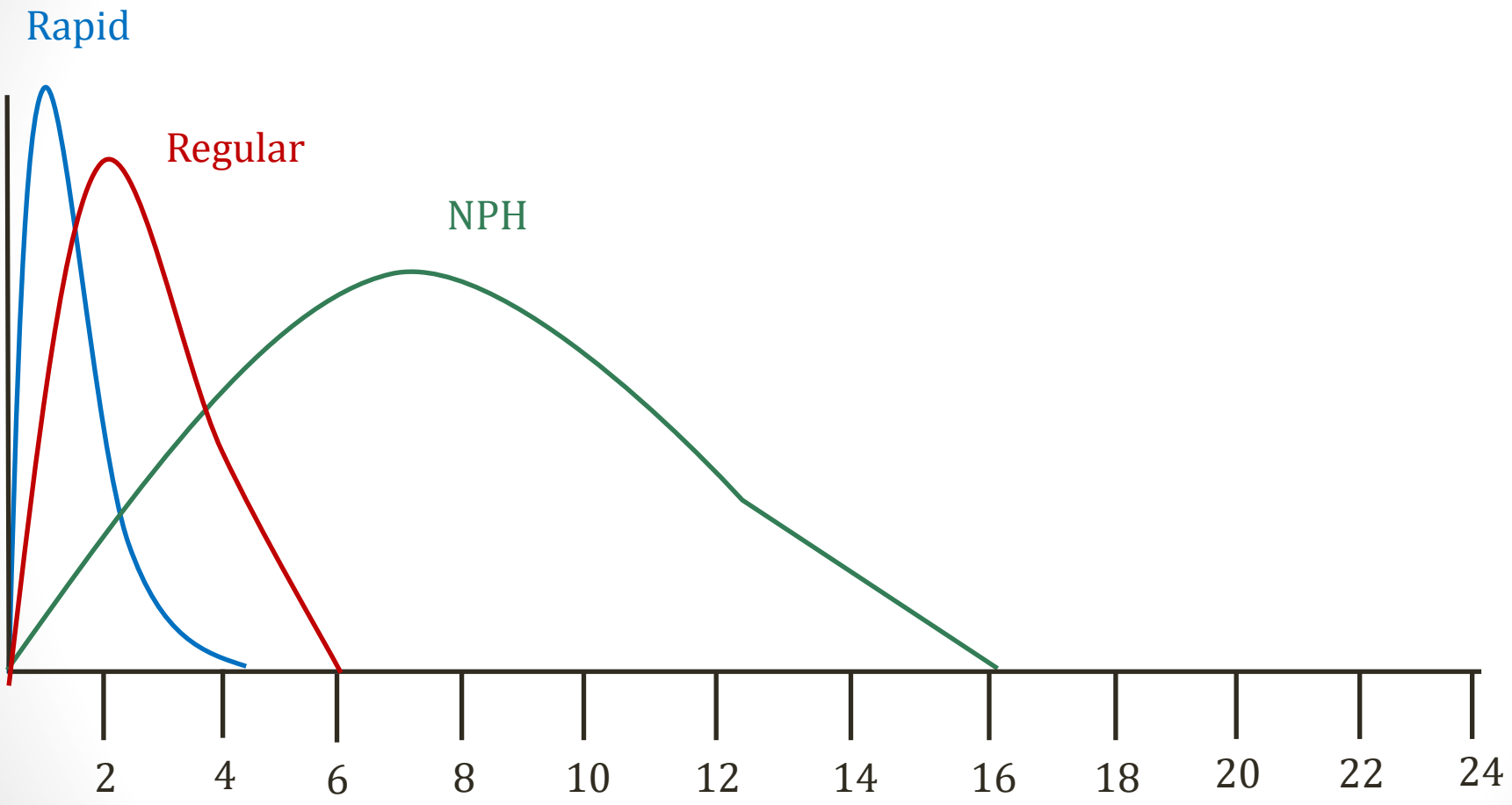
- Commonly used in hospitalized patients
  - Blood sugar elevations common with infection/surgery
  - Sliding scale dose given based on finger stick blood sugar
  - "Regular insulin sliding scale"
- Only type of insulin that is given IV
- IV regular insulin used in **DKA/HHS**
- Used to treat **hyperkalemia**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

NPH Insulin

Neutral Protamine Hagedorn

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

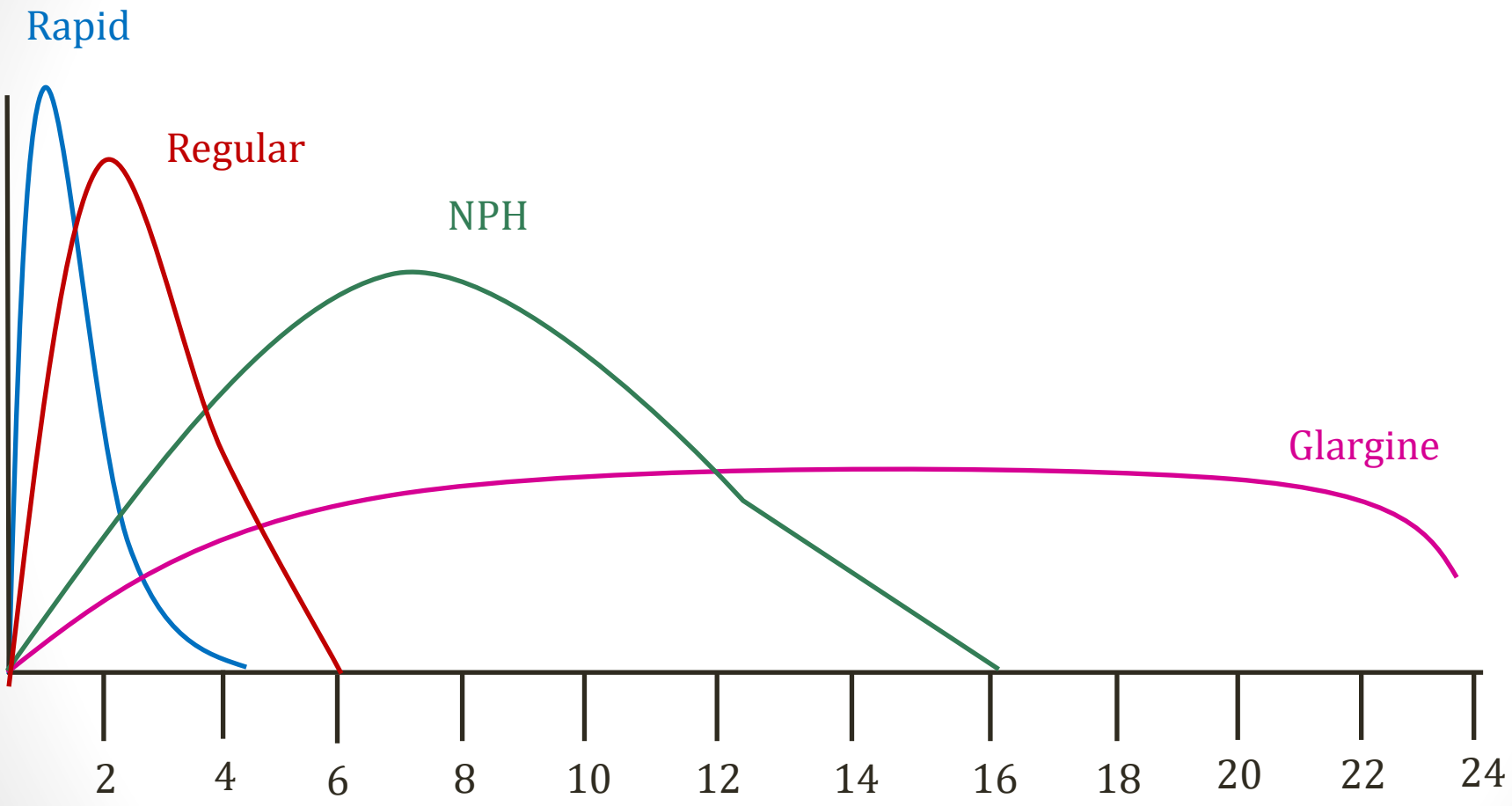
Insulin



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**

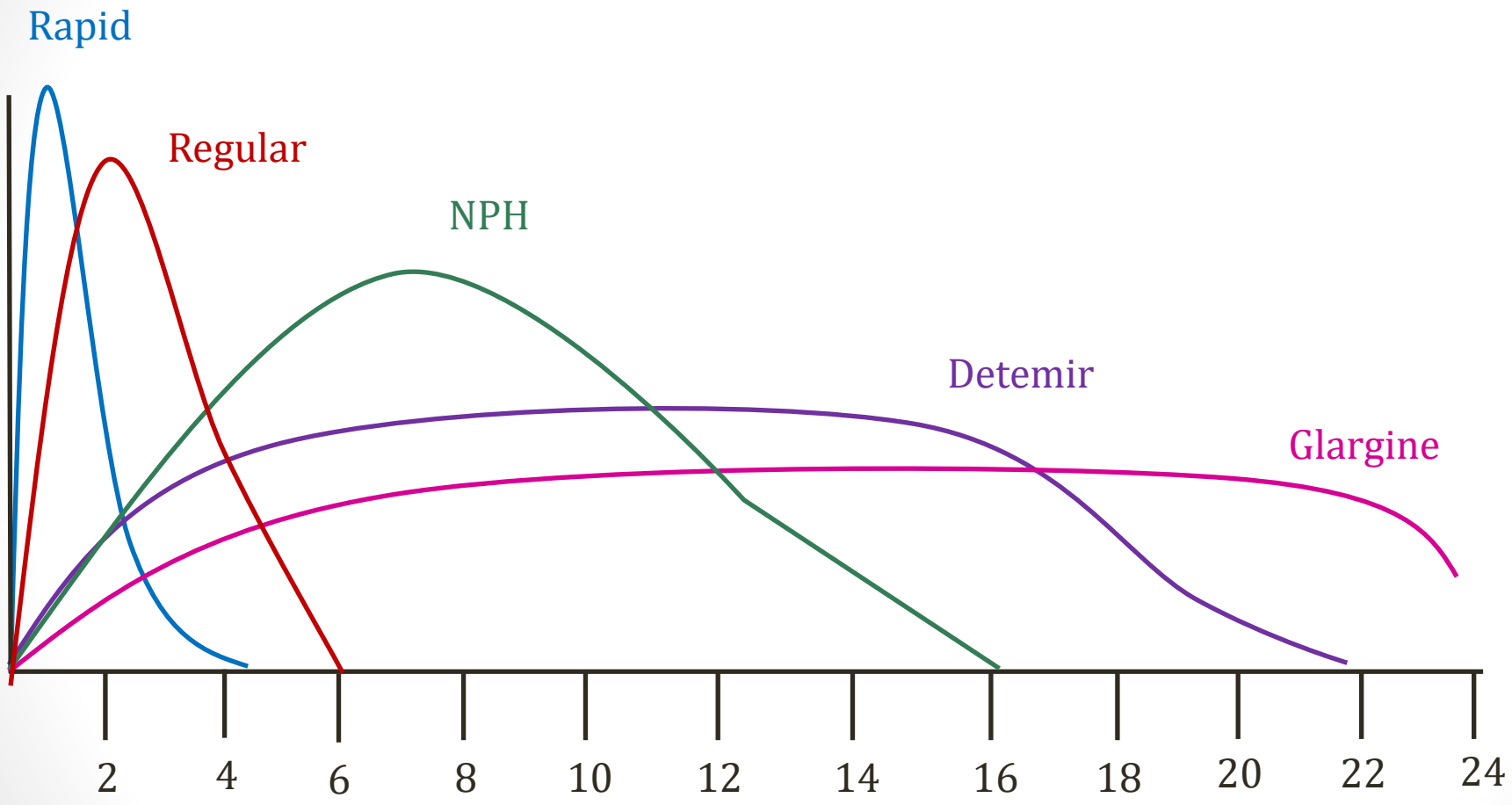
Insulin



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



Insulin

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

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

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

Weight Gain

- Occurs in most patients on insulin
- Insulin promotes **fatty acid and protein synthesis**

Wikipedia/Public Domain

Treatment of Diabetes

Jason Ryan, MD, MPH

Type 1 and Type 2

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

Hemoglobin A1C

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

Lifestyle Modifications

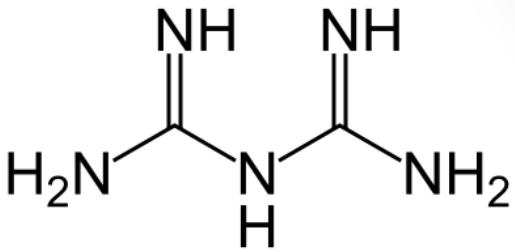
- Newly diagnosed type 2 diabetes
- **Weight loss, exercise** improve glucose levels
- First line treatment usually **lifestyle modification**
  - Usually a 3-6 month trial if initial A1c not markedly ↑

Oral/SQ Antidiabetic Agents

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

Biguanides

Metformin



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

Biguanides

Metformin

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

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

- 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

- Most common adverse effect is **GI upset**
  - Nausea, abdominal pain
  - Can cause a metallic taste in the mouth

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

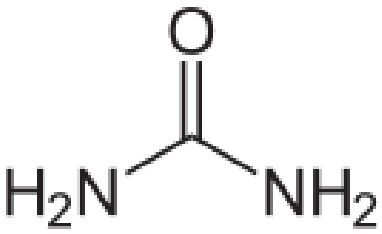
Metformin

Lactic Acidosis

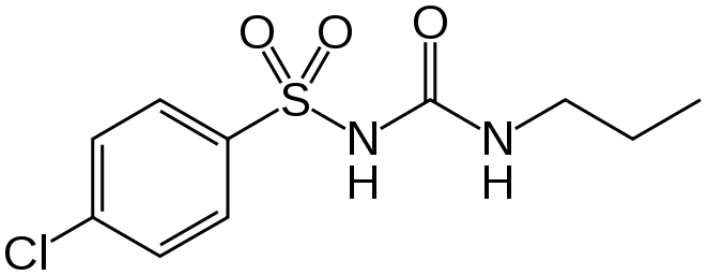
- Almost always occurs associated with:
  - **Renal insufficiency**
  - Liver disease or alcohol abuse
  - Acute heart failure
  - Hypoxia
  - Serious acute illness
- Metformin not used in patients with low GFR
- Often “held” when patients acutely ill
- Also held during IV contrast tests

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")



Urea



Sulfonylurea

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

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

Sulfonylureas

Adverse Effects

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

Wikipedia/Public Domain

Sulfonylureas

Adverse Effects

- Chlorpropamide
  - **Flushing** with alcohol consumption
    - Inhibits acetaldehyde dehydrogenase (disulfiram)
  - **Hyponatremia** (↑ADH activity)

Meglitinides

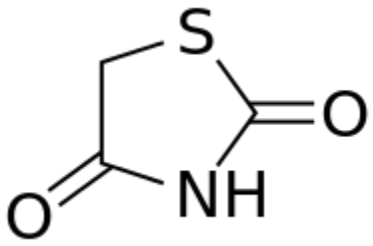
Repaglinide, Nateglinide

- 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**

Thiazolidinediones (TZDs)

Pioglitazone, Rosiglitazone

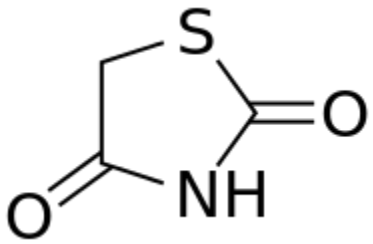
- Oral therapy
- **Decreases insulin resistance**



Thiazolidinediones (TZDs)

Pioglitazone, Rosiglitazone

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



NOTE: Fibrates activate PPAR-α
Lower triglycerides

Thiazolidinediones

Potential mechanisms

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

Thiazolidinediones

Adverse Effects

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

Thiazolidinediones

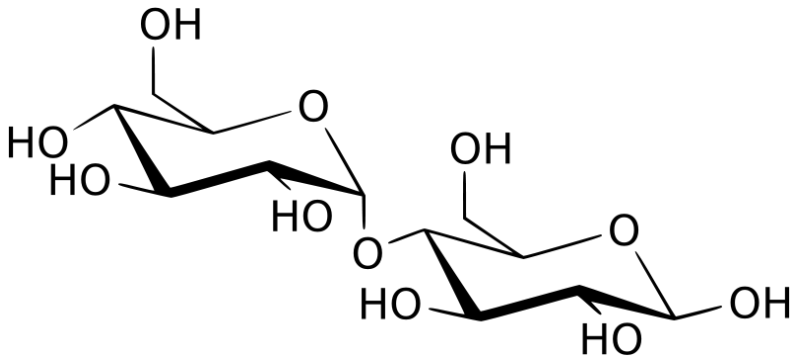
Adverse Effects

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

Glucosidase Inhibitors

Acarbose, Miglitol, Voglibose

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



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

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

Amylin Analogs

Pramlintide

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

Incretins

- Hormones that **↑ insulin secretion**
- GIP (glucose-dependent insulinotropic peptide)
  - Produced by K cells of small intestine
- **GLP-1 (glucagon-like peptide-1)**
  - Produced by L-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

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

DPP-4 Inhibitors

Sitagliptin, Linagliptin

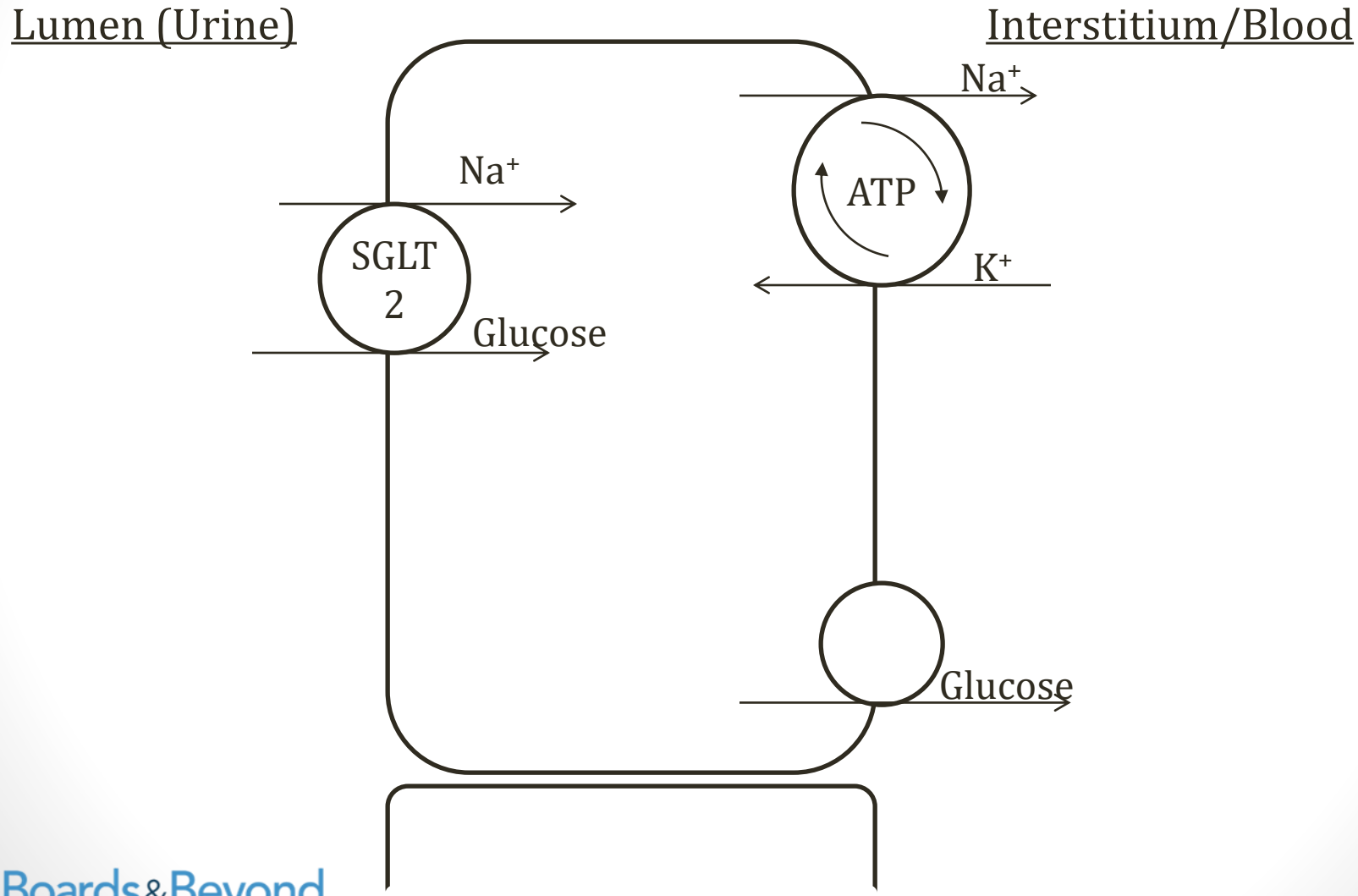
- DPP-4: Dipeptidyl peptidase 4
  - Enzyme expressed on many cells
  - Inhibits release of GIP and GLP-1
- Inhibition → ↑ GLP-1
- Oral drugs, once a day
- Side effects: **Infections**
  - Reports of urinary and respiratory infections

SGLT2 Inhibitors

Canagliflozin, Dapagliflozin

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

Proximal Tubule



SGLT2 Inhibitors

Canagliflozin, Dapagliflozin

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

Diabetes Therapy

Helpful Tips

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

Reproductive Hormones

Jason Ryan, MD, MPH

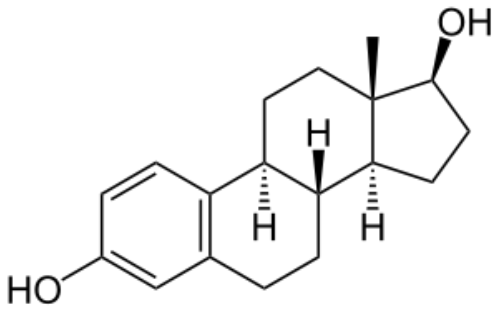
Reproductive Hormones

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

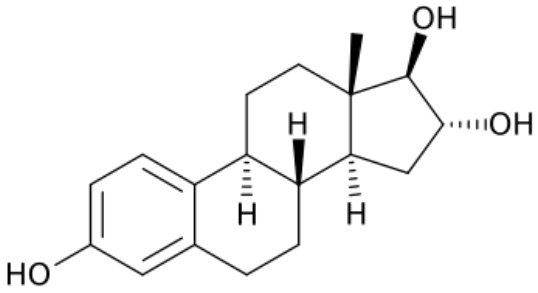
Estrogens

Potency

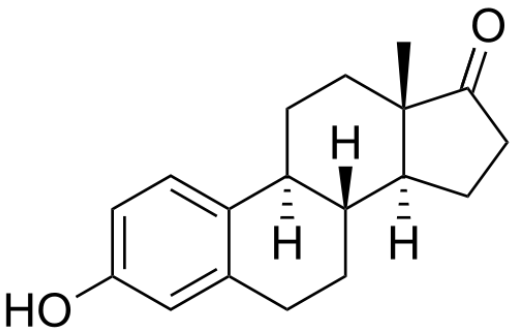
Estradiol> Estrone > Estriol



Estradiol
(17β-estradiol)



Estriol

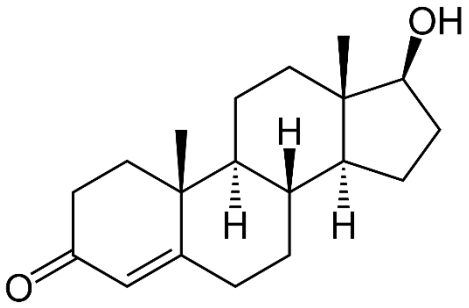


Estrone

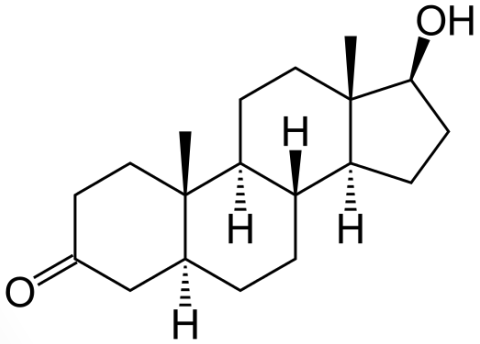
Androgens

Potency

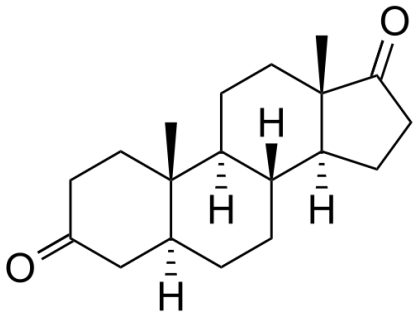
DHT > Testosterone > others



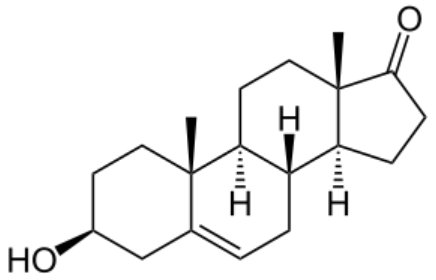
Testosterone



Dihydrotestosterone (DHT)



Androstenedione



Dehydroepiandrosterone (DHEA)

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

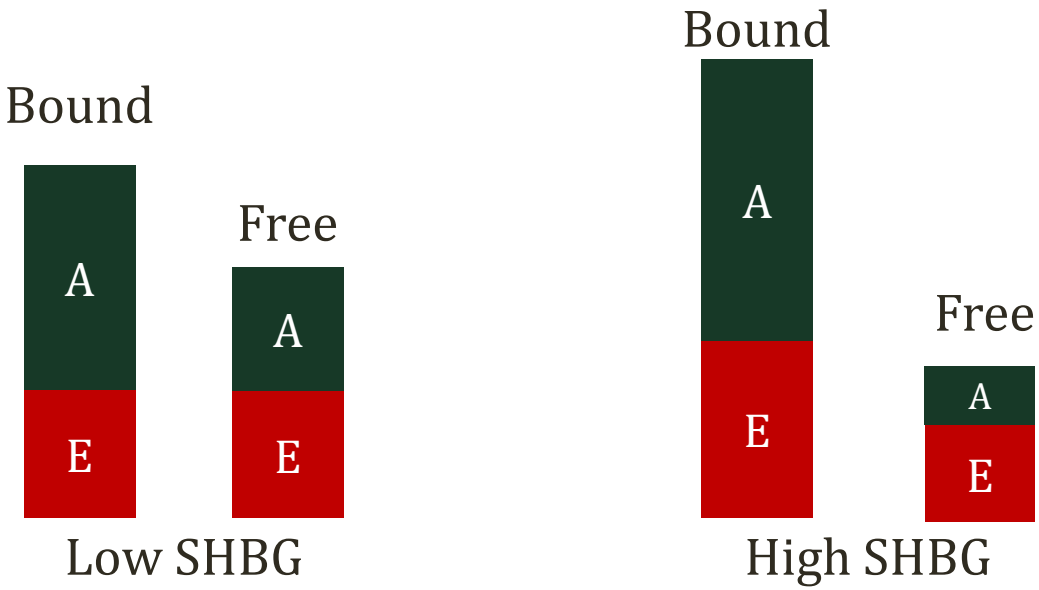
Sex Hormone Binding Globulins

- Glycoproteins
- Produced by the **liver**
- Binds androgens more than estrogens

A > E

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

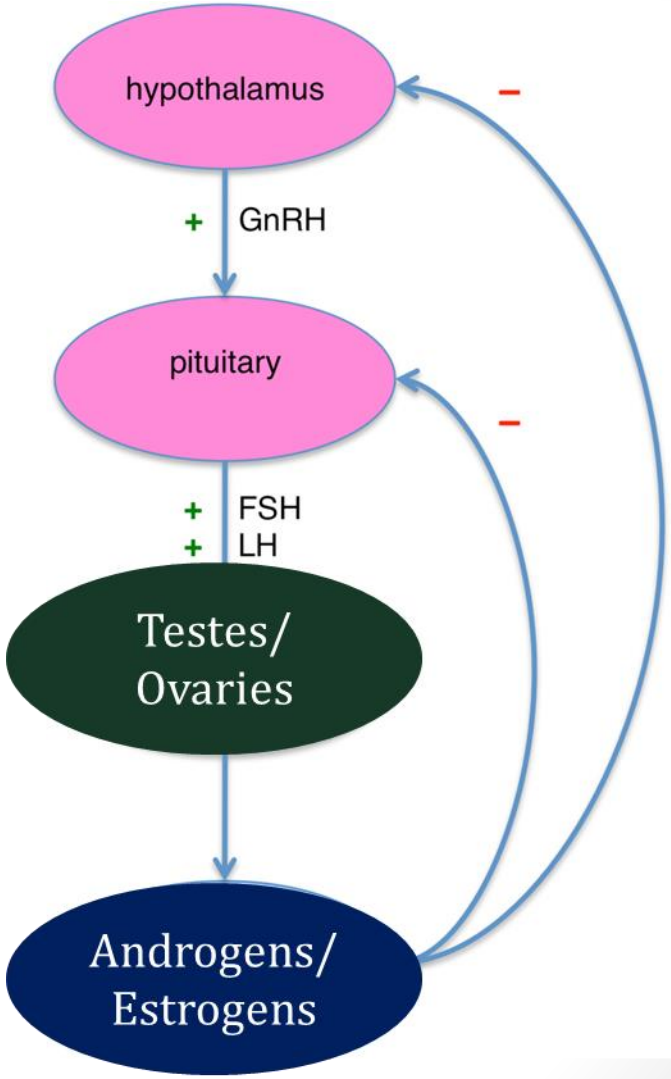
	↑ SHBG	↓SHBG
Causes	Estrogens Hyperthyroidism	Androgens Hypothyroidism Nephrotic Syndrome
Hormones	↑ Estrogen effects	↑ Androgen effects
Clinical Effects	Gynecomastia (men)	Hirsutism (women)

Cirrhosis

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

Reproductive Hormones

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



Acracia/Wikipedia

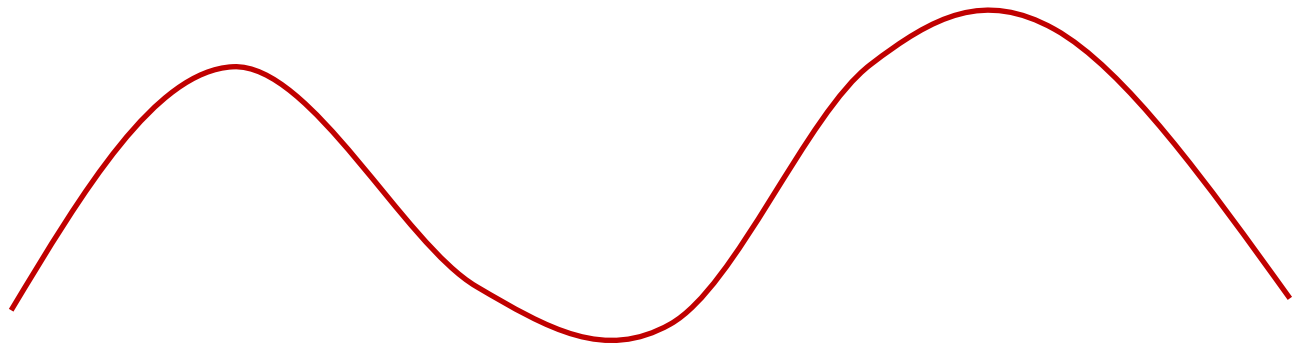
Puberty

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

GNRH

Gonadotropin-releasing hormone

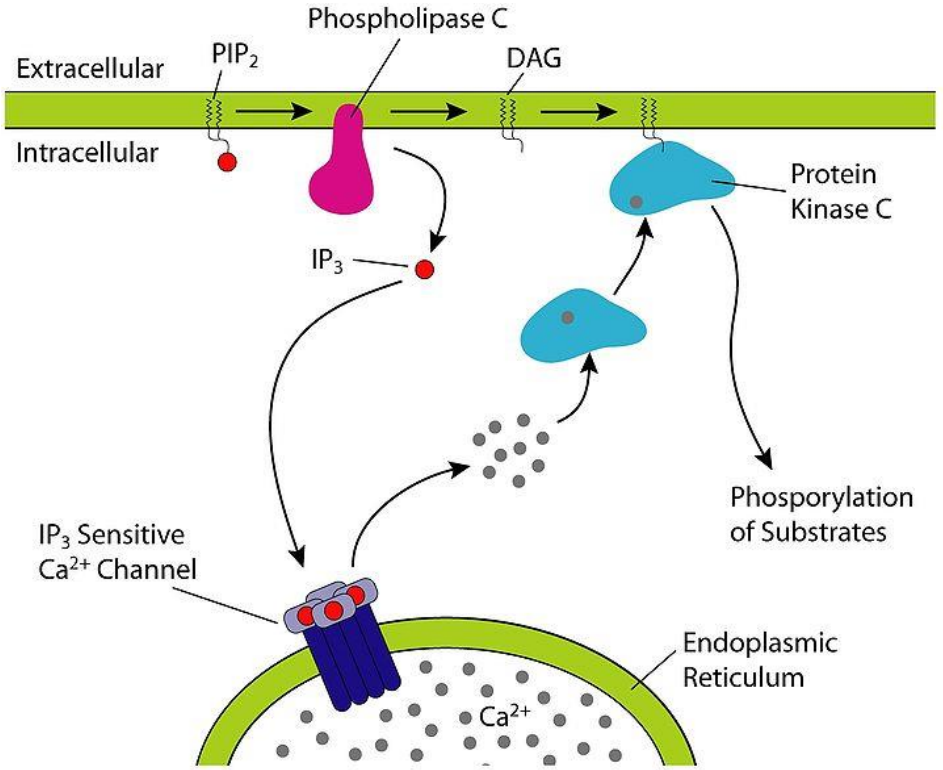
- Peptide produced by hypothalamus
- Released in pulses ("pulsatile")
  - Frequency and amplitude of pulses varies
  - Changes effect release of LH/FSH from pituitary



GNRH

Gonadotropin-releasing hormone

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



Eak435s /Wikipedia

Leuprolide

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

Leuprolide

- 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

Uses

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

Leuprolide

Uses

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

Kallmann Syndrome

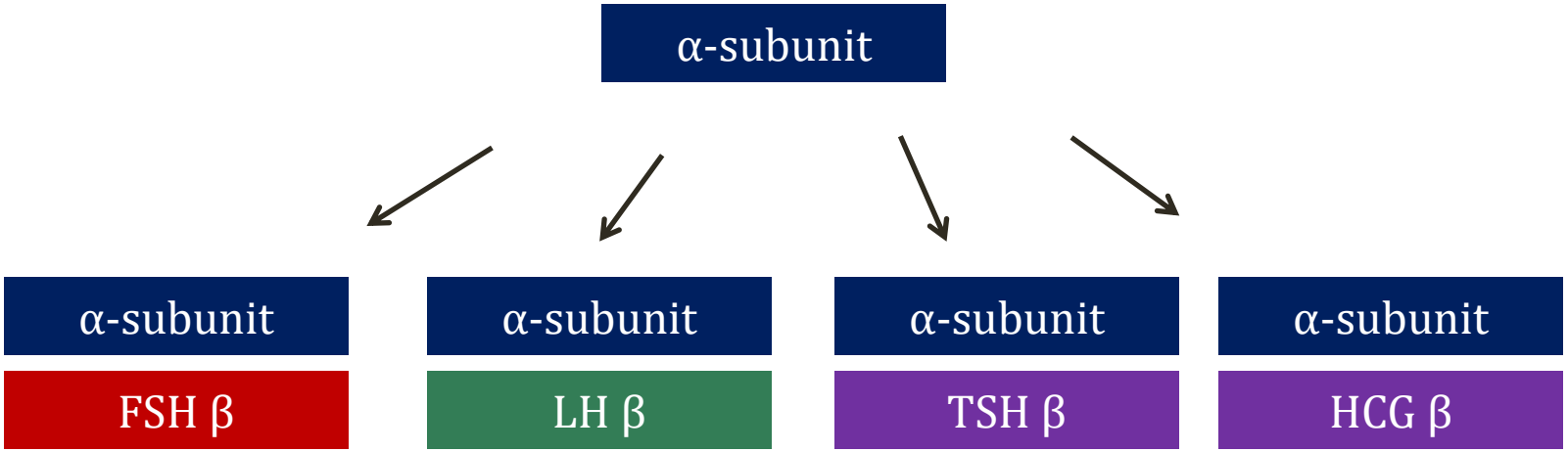
- **Absence of GnRH** secretion from hypothalamus
- Impaired migration of GnRH neurons from origin in **olfactory bulb** to hypothalamus
- Almost always occurs in males (5:1 ratio)
- Key features: hypogonadism and **anosmia**
- **Low GnRH/FSH/LH/Testosterone**
- Delayed puberty
- Small testes

Pituitary Reproductive Hormones

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

Pituitary Hormones

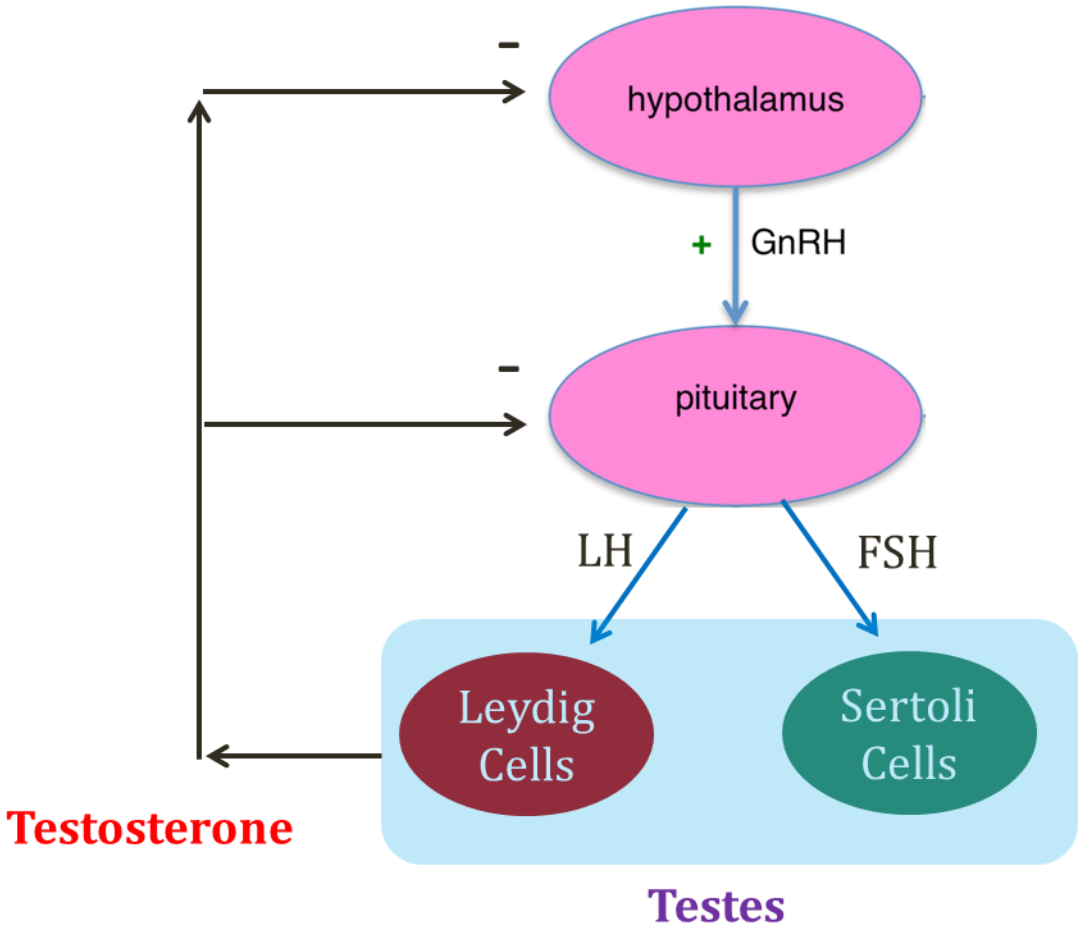
- All have a **cAMP second messenger system**



Male Reproductive Hormones

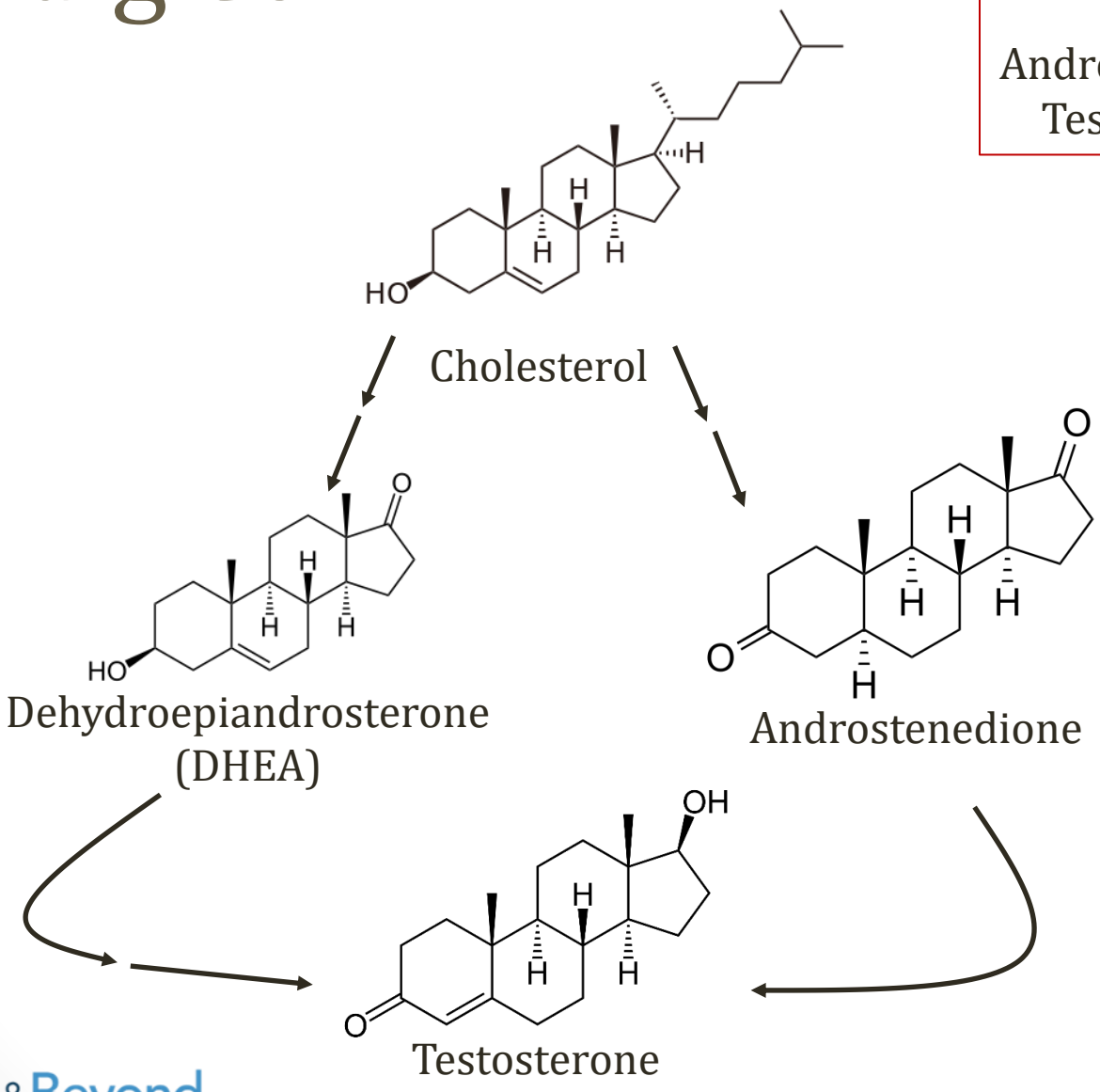
Jason Ryan, MD, MPH

Male Reproductive System



Leydig Cell

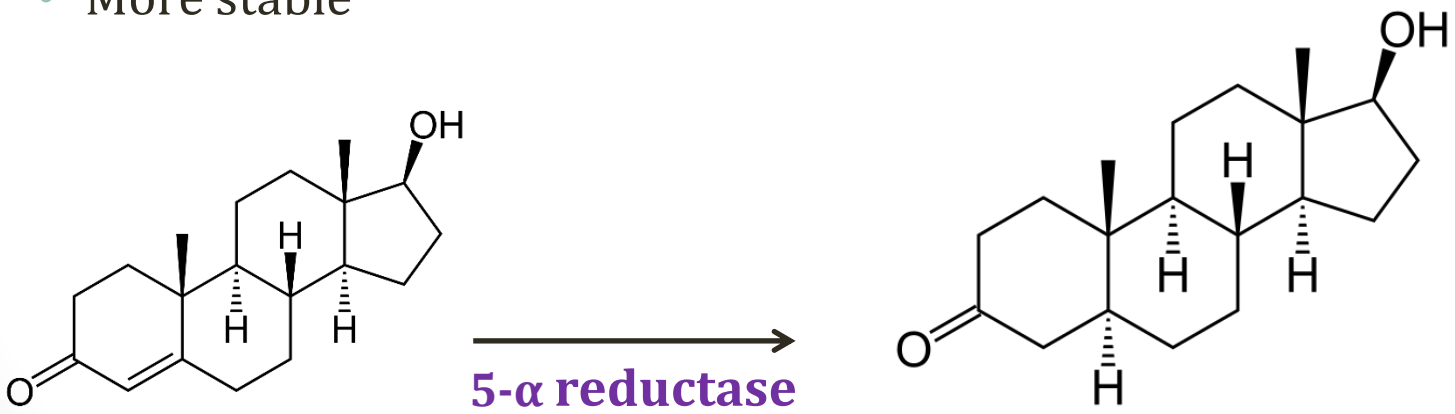
Adrenal Cortex
DHEA
Androstenedione
Testosterone



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

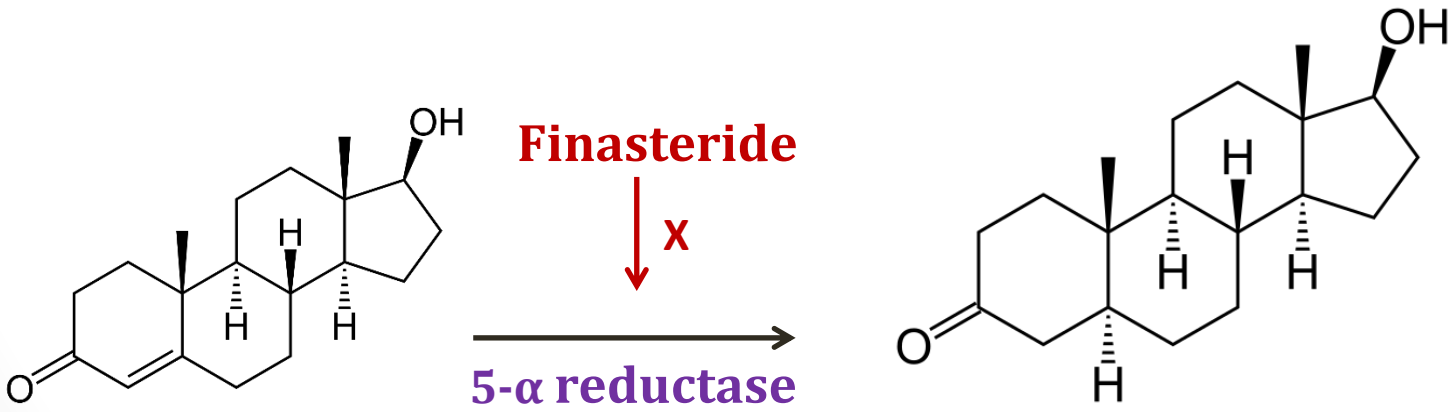


Testosterone

Dihydrotestosterone (DHT)

Finasteride

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

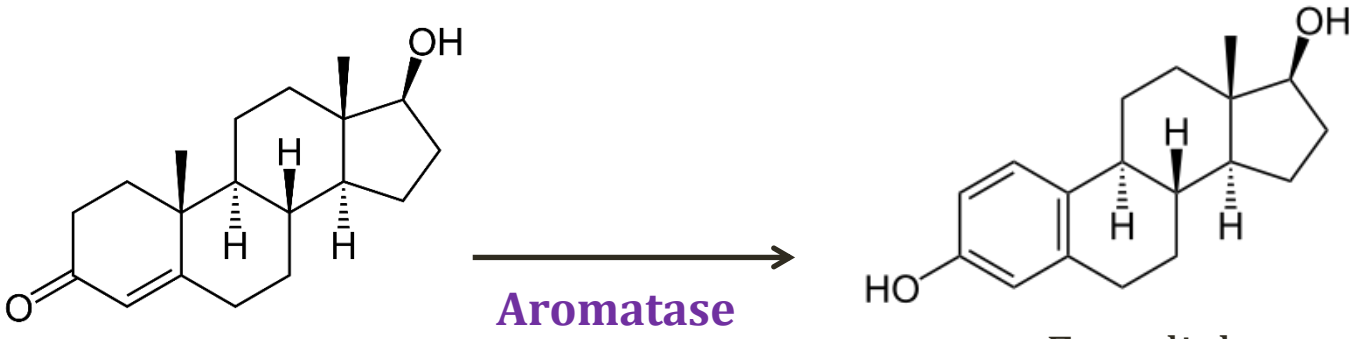


Testosterone

Dihydrotestosterone (DHT)

Estradiol

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

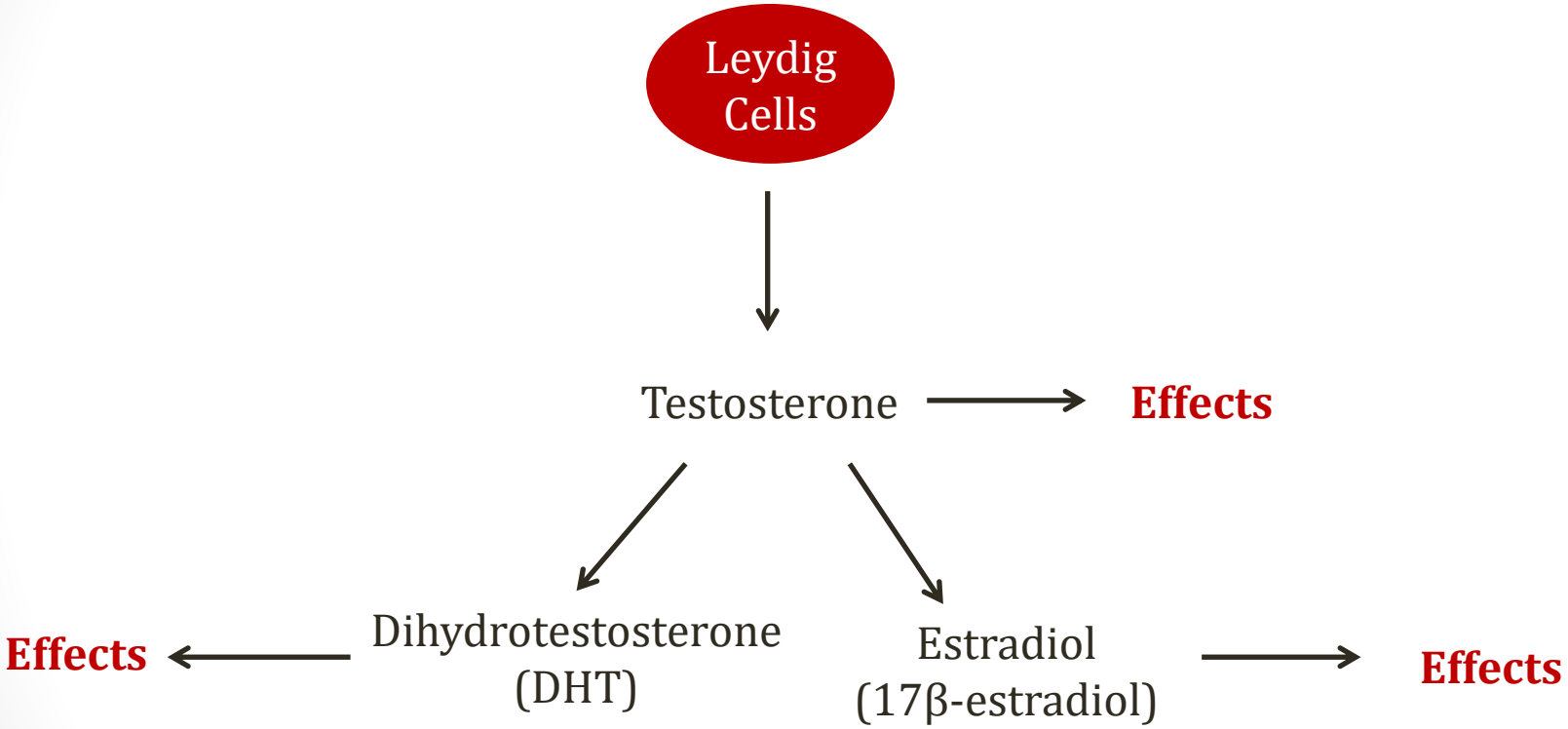


Testosterone

Estradiol
(17β-estradiol)

Testosterone Effects

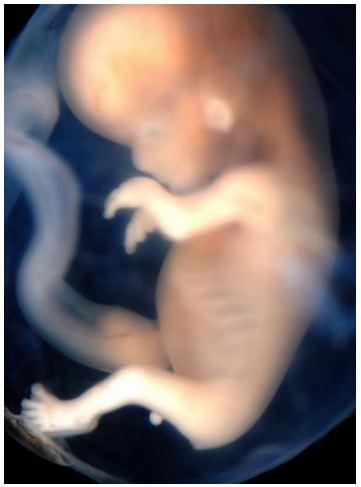
Males



Testosterone Effects

Males

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



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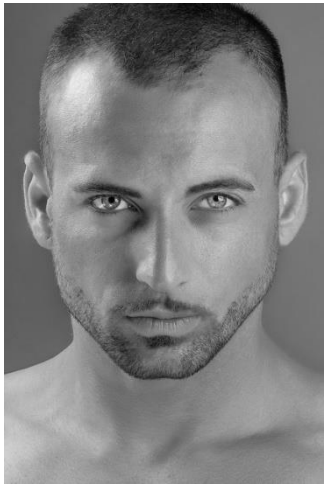

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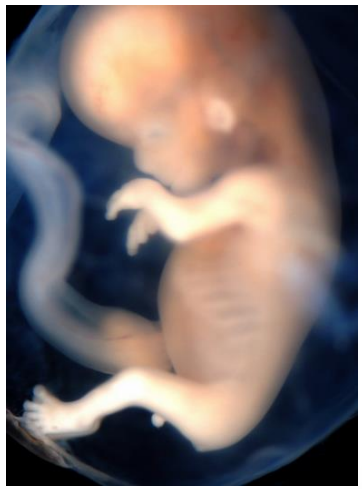
Testosterone Effects

Fetus

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



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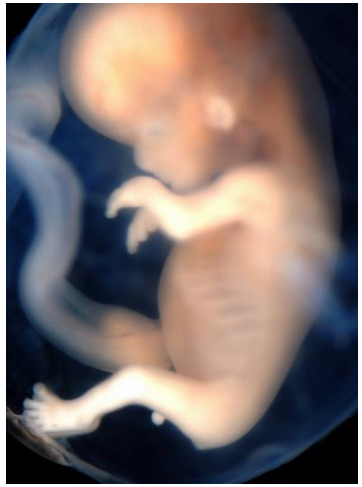
Testosterone Effects

Fetus

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



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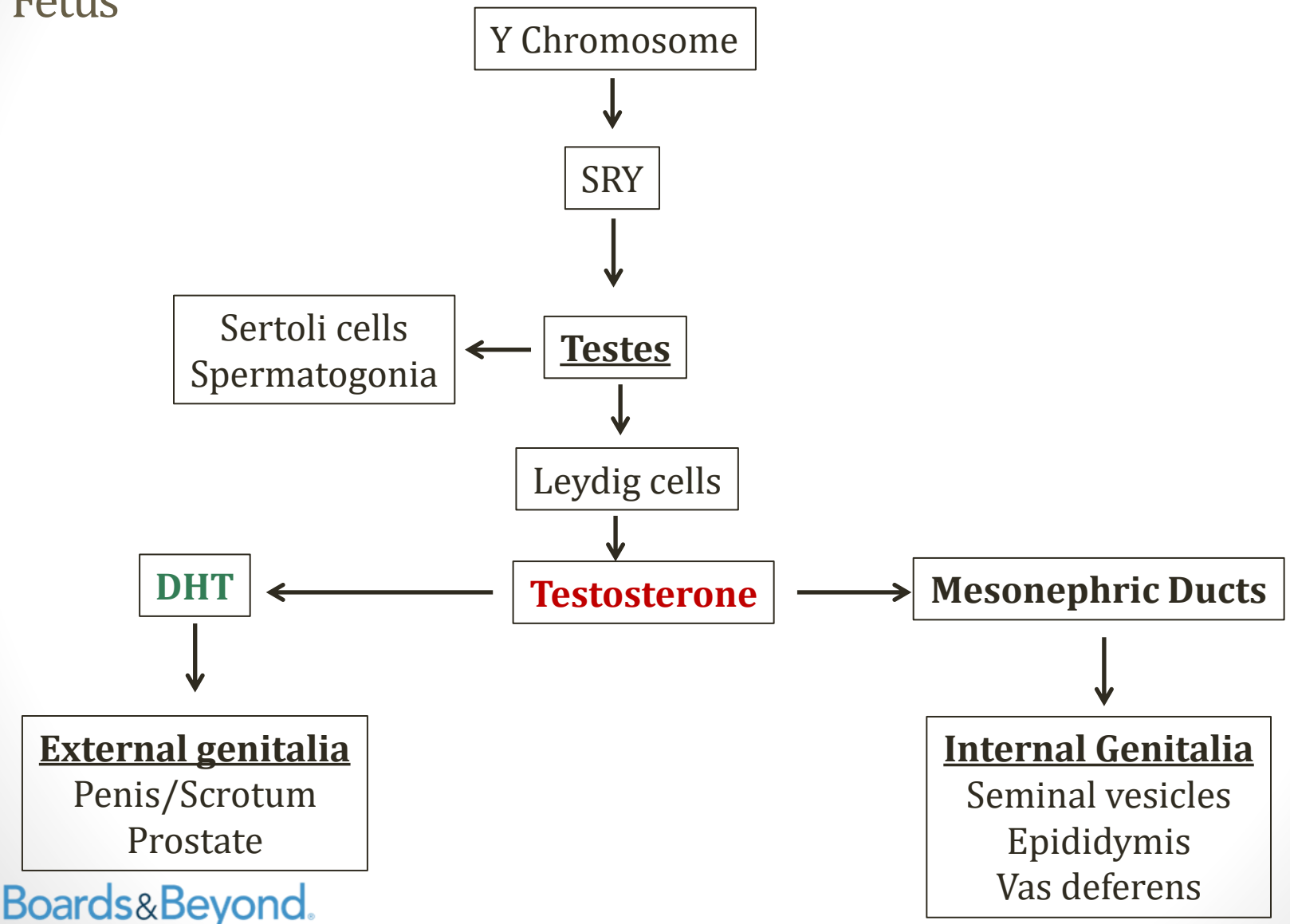
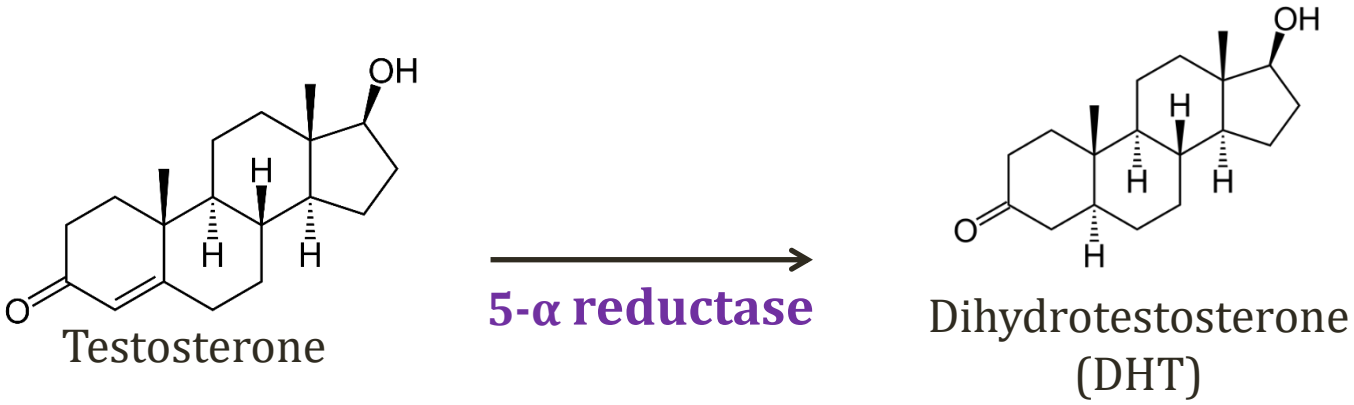
Testosterone Effects

Fetus



5-α Reductase Deficiency

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



5-α Reductase Deficiency

- **Normal internal genitalia**
  - Normal epididymis, vas deferens, seminal vesicles
  - Empty into a blind-ending vagina
- External genitalia predominately female
  - **Absent external male genitalia**
  - Range of female genitalia seen +/- hypospadius
  - 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

Dtesh71/Public Domain

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

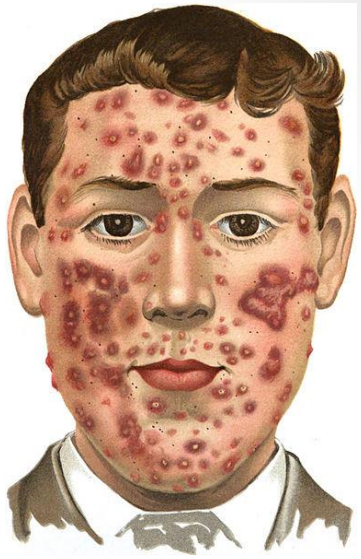
Testosterone Effects

Puberty

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

Acne

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



Wikipedia/Public Domain

Testosterone Effects

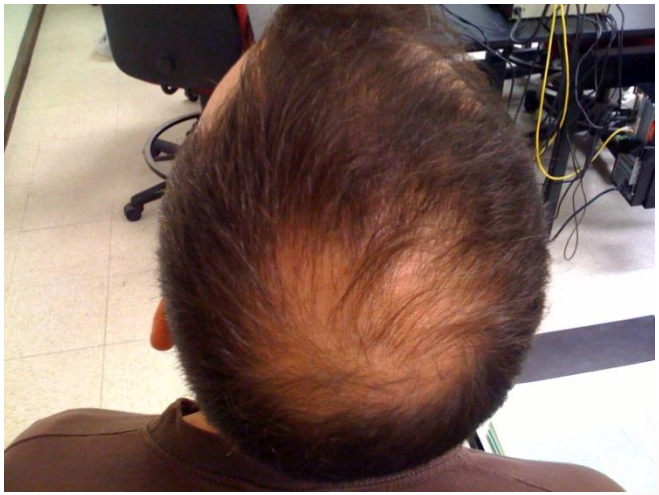
Adults

- Prostate growth
  - Finasteride → ↓DHT → Treatment of BPH
  - Testosterone therapy → BPH
- May effect lipids
  - Exogenous testosterone → ↓ HDL/↑ LDL
- Male pattern balding

Androgenic Alopecia

"Male Pattern Balding"

- 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



Welshsk/Wikipedia

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

Testosterone Therapy

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

Spermatogenesis

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

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)
  - Azoospermia
  - Gynecomastia

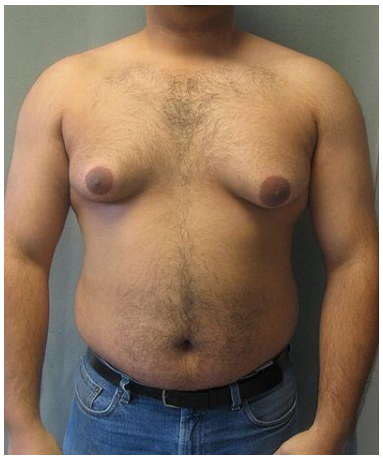
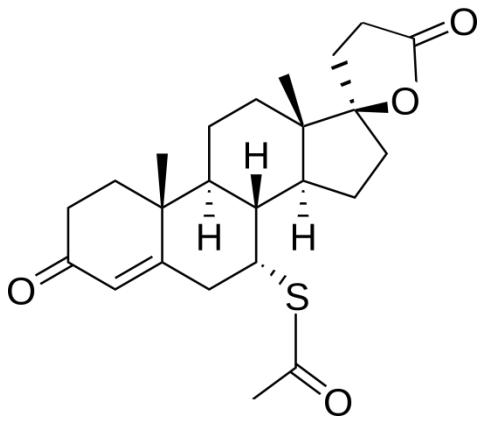


Image courtesy Dr. Mordcai Blau/Wikipedia

Spironolactone

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**

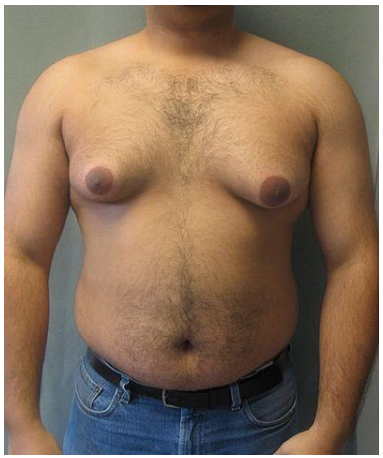
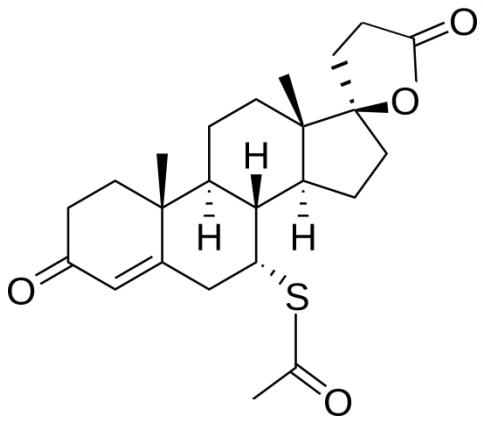


Image courtesy Dr. Mordcai Blau/Wikipedia

Spironolactone

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

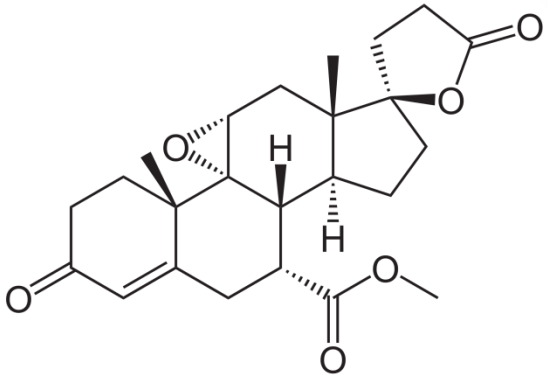
Spironolactone



Spironolactone

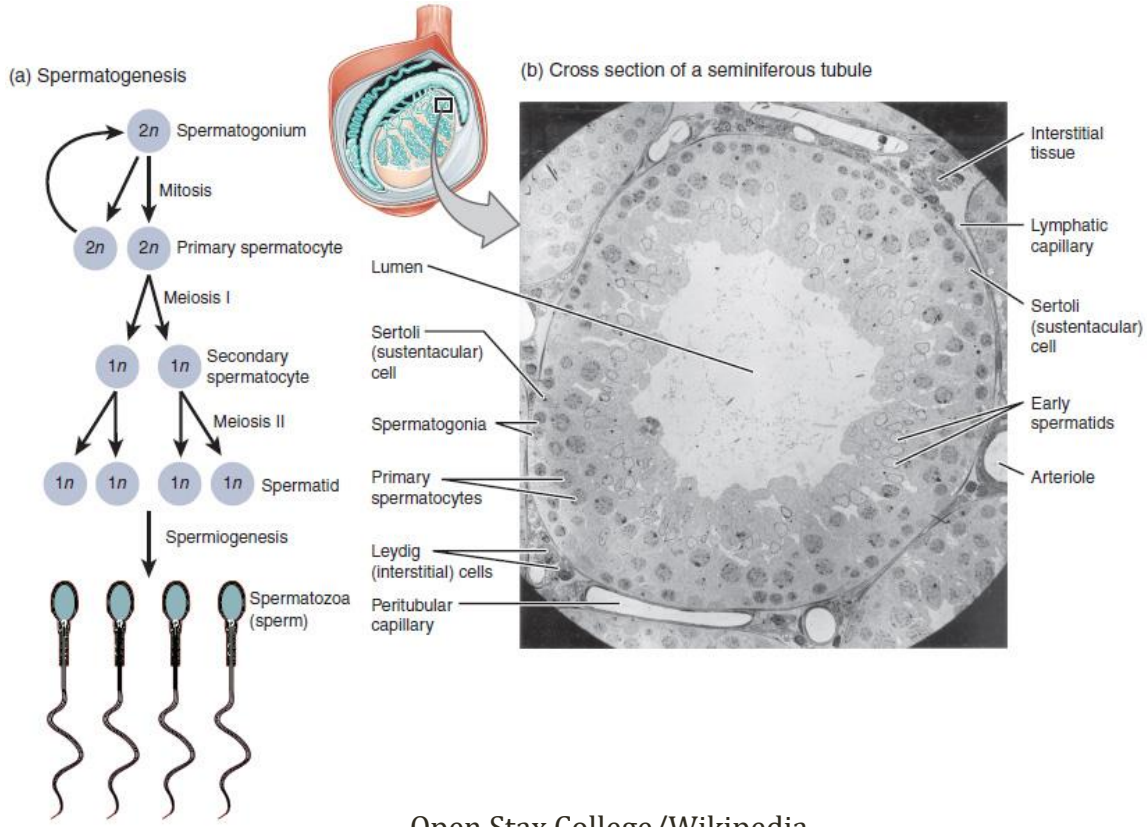
- **Eplerenone**
  - Alternative to spironolactone
  - Does not cause gynecomastia
  - Can be used in heart failure

Eplerenone



Sertoli Cells

- Support and nourish developing spermatozoa
- Regulate spermatogenesis



Open Stax College/Wikipedia

Sertoli Cells

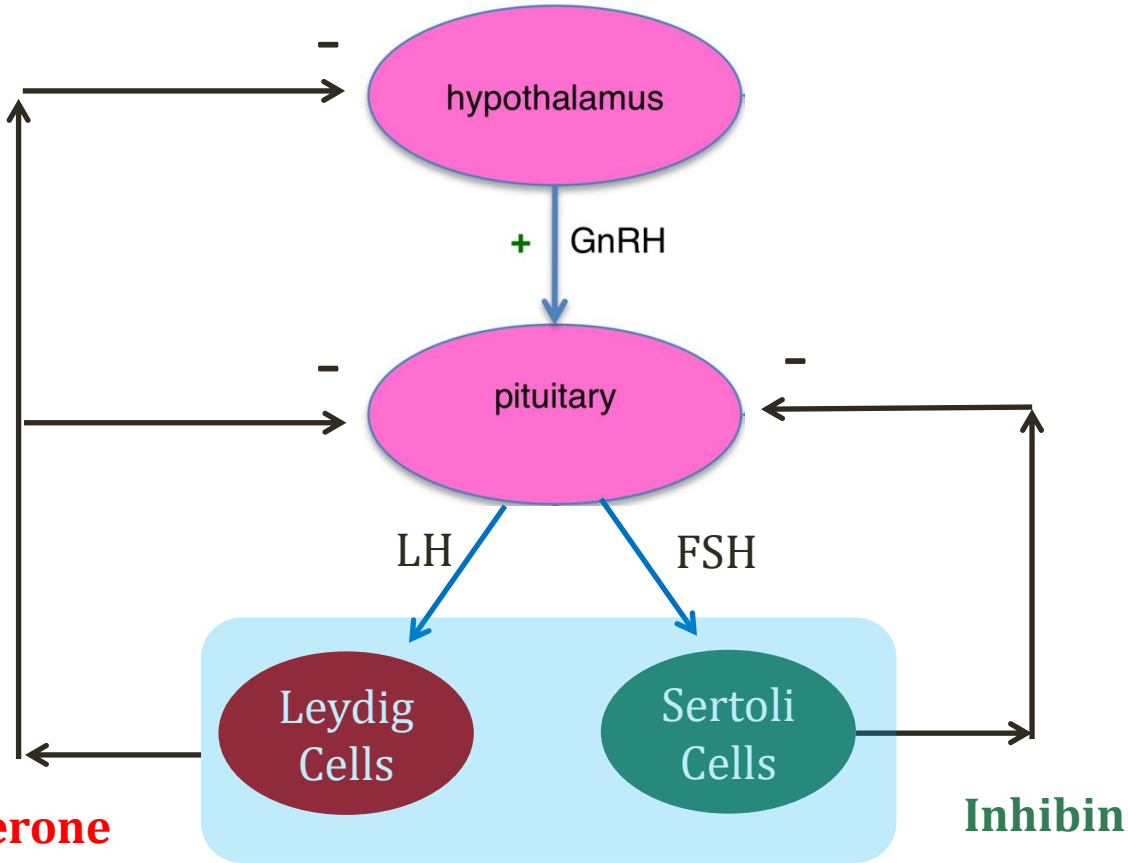
- Stimulated by FSH
- Supported by Leydig cell testosterone (paracrine)
- Need **FSH and LH** for normal spermatogenesis

Sertoli Cells

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

Sertoli Cells

- Secrete **inhibin B**: Inhibits FSH



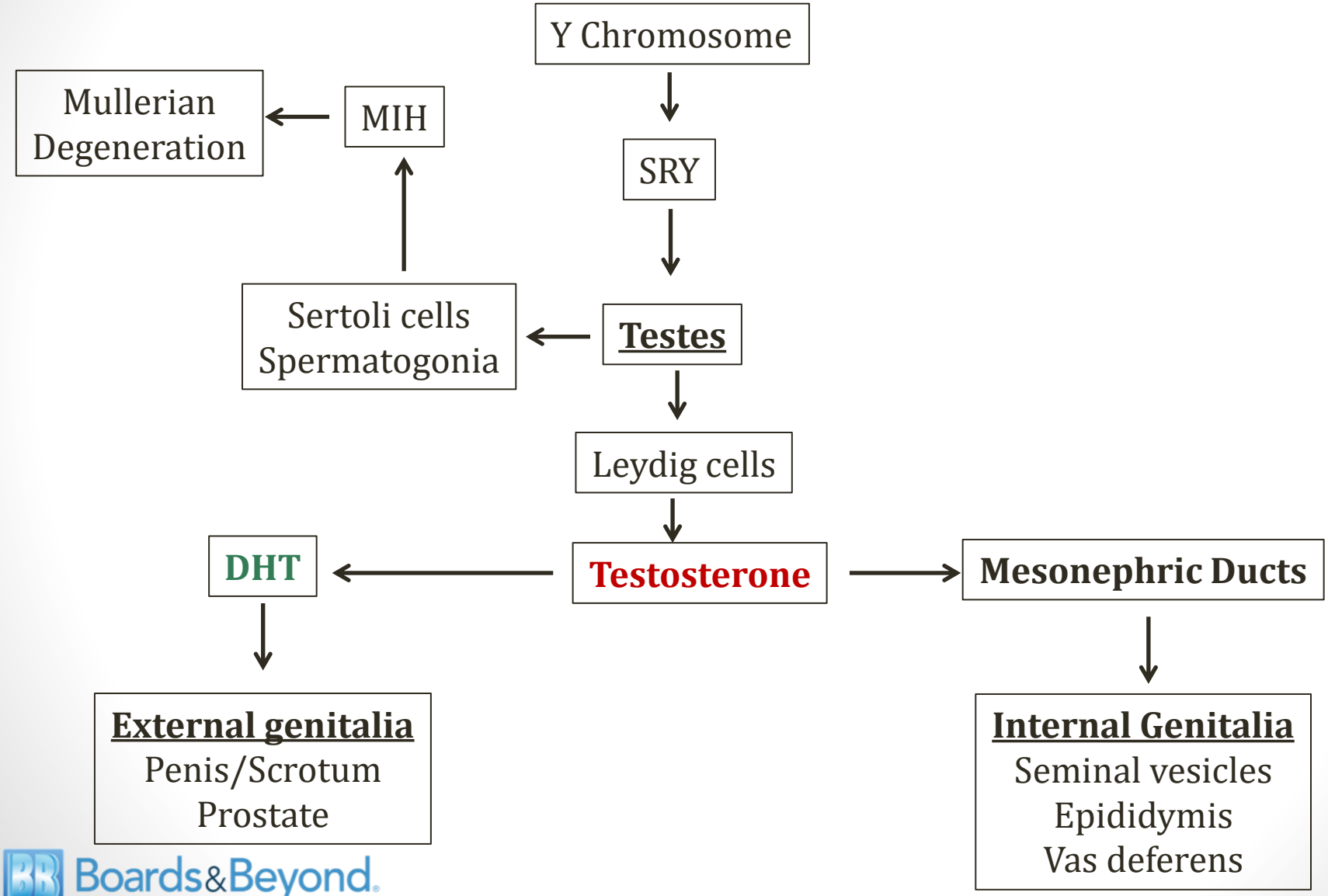
Sertoli Cells

- 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

Male Development



CAIS

Complete Androgen Insensitivity Syndrome

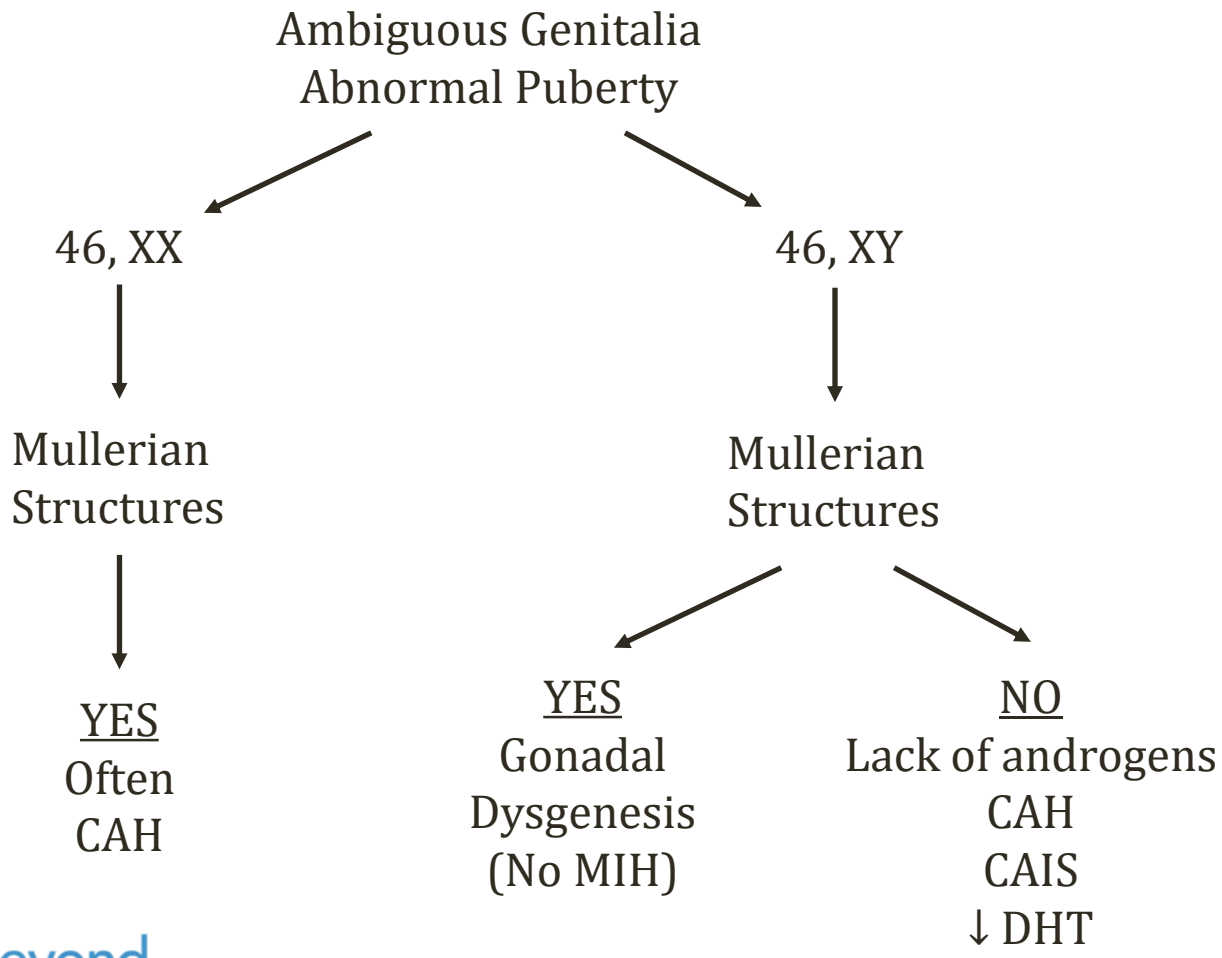
- Mutation of androgen receptor in males (XY)
- No ovaries; testes form in utero (SRY gene)
- No cellular response to androgens
  - No internal or external male genital development
- Sertoli cells (testes) present → MIH
  - Degeneration of mullerian structures
  - Absent uterus, fallopian tubes

CAIS

Complete Androgen Insensitivity Syndrome

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

Disorders of Sex Development



Temperature Effects

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

Cryptorchidism

- “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

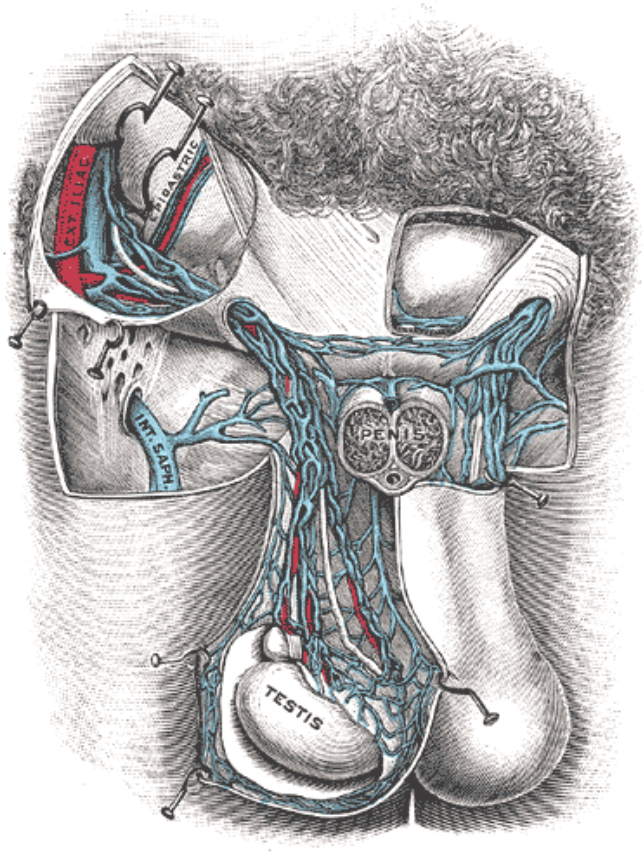
- Testes may descend on their own
  - Usually occurs by 6 months of age
- Orchiopexy
  - Surgical placement of the testis in scrotum
  - Sperm counts usually become normal
  - Done after 6 months of age

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

Varicocele

- Dilatation of **pampiniform plexus** of spermatic veins



Wikipedia/Public Domain

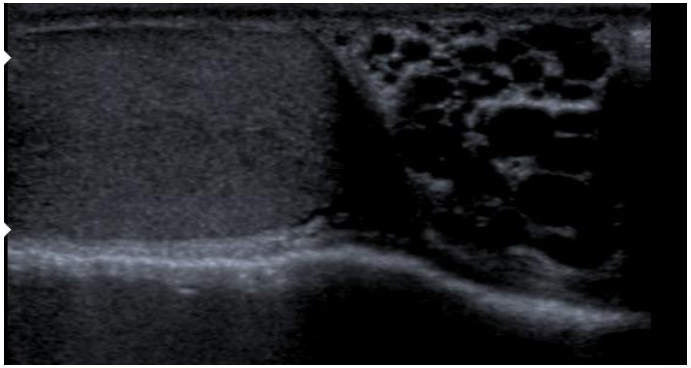
Varicocele

- 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

Fisch12/Wikipedia



Schomynv /Wikipedia

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

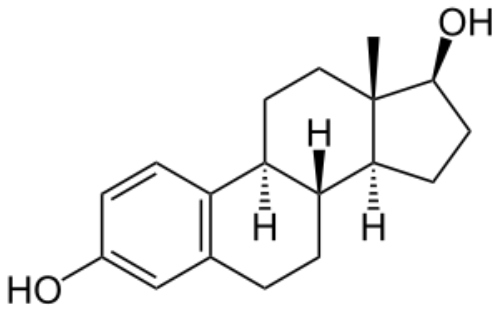
Female Reproductive Hormones

Jason Ryan, MD, MPH

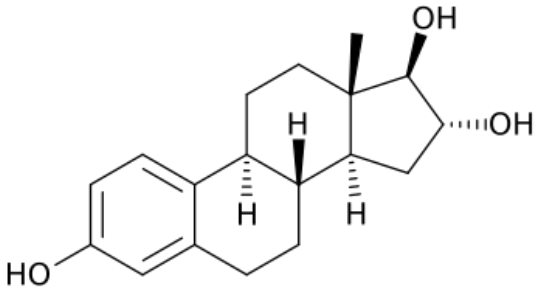
Estrogens

Potency

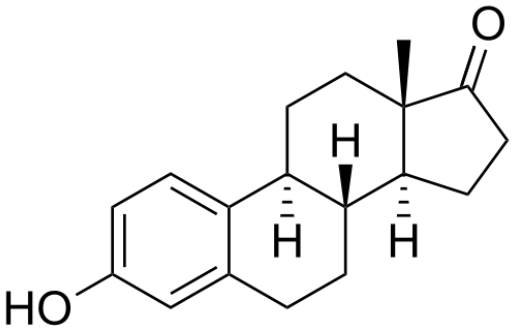
Estradiol> Estrone > Estriol



Estradiol
(17β-estradiol)



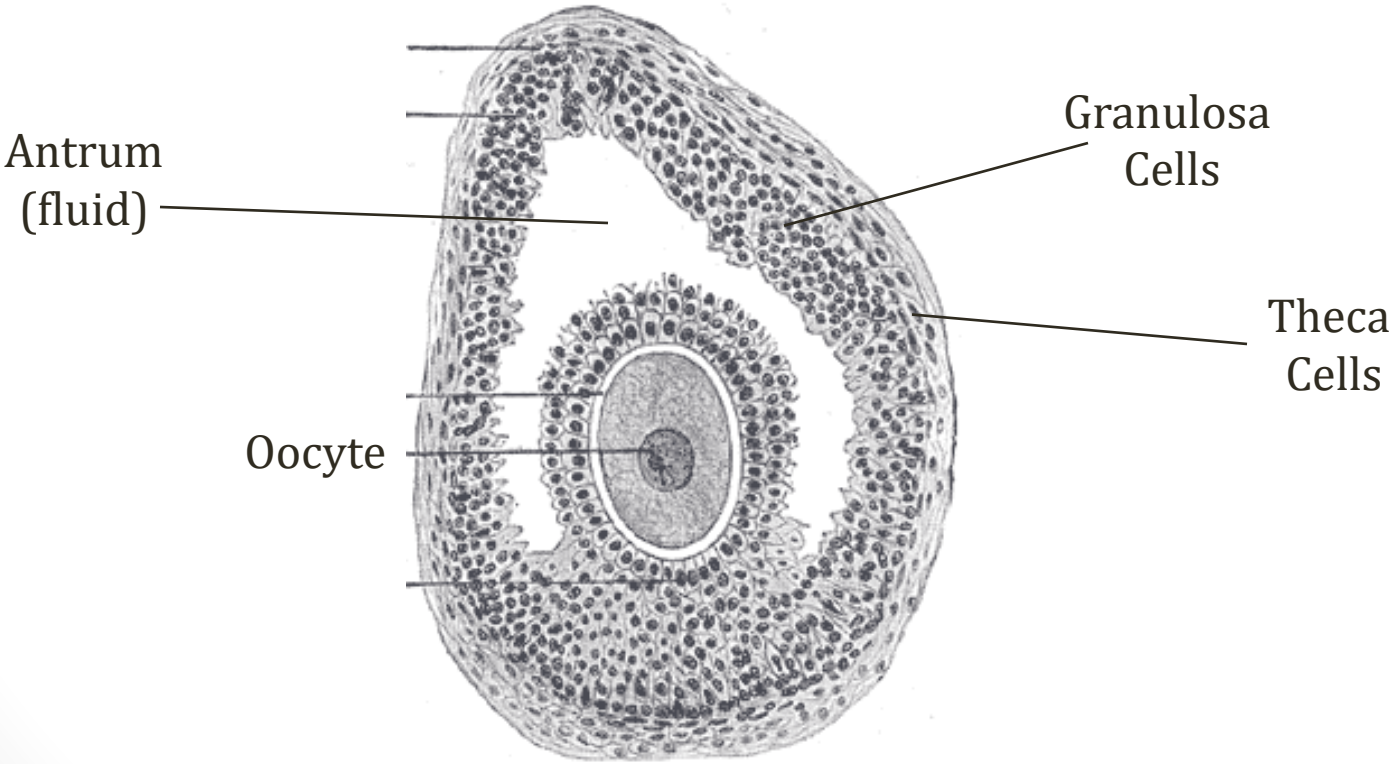
Estriol



Estrone

Ovarian Follicle

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



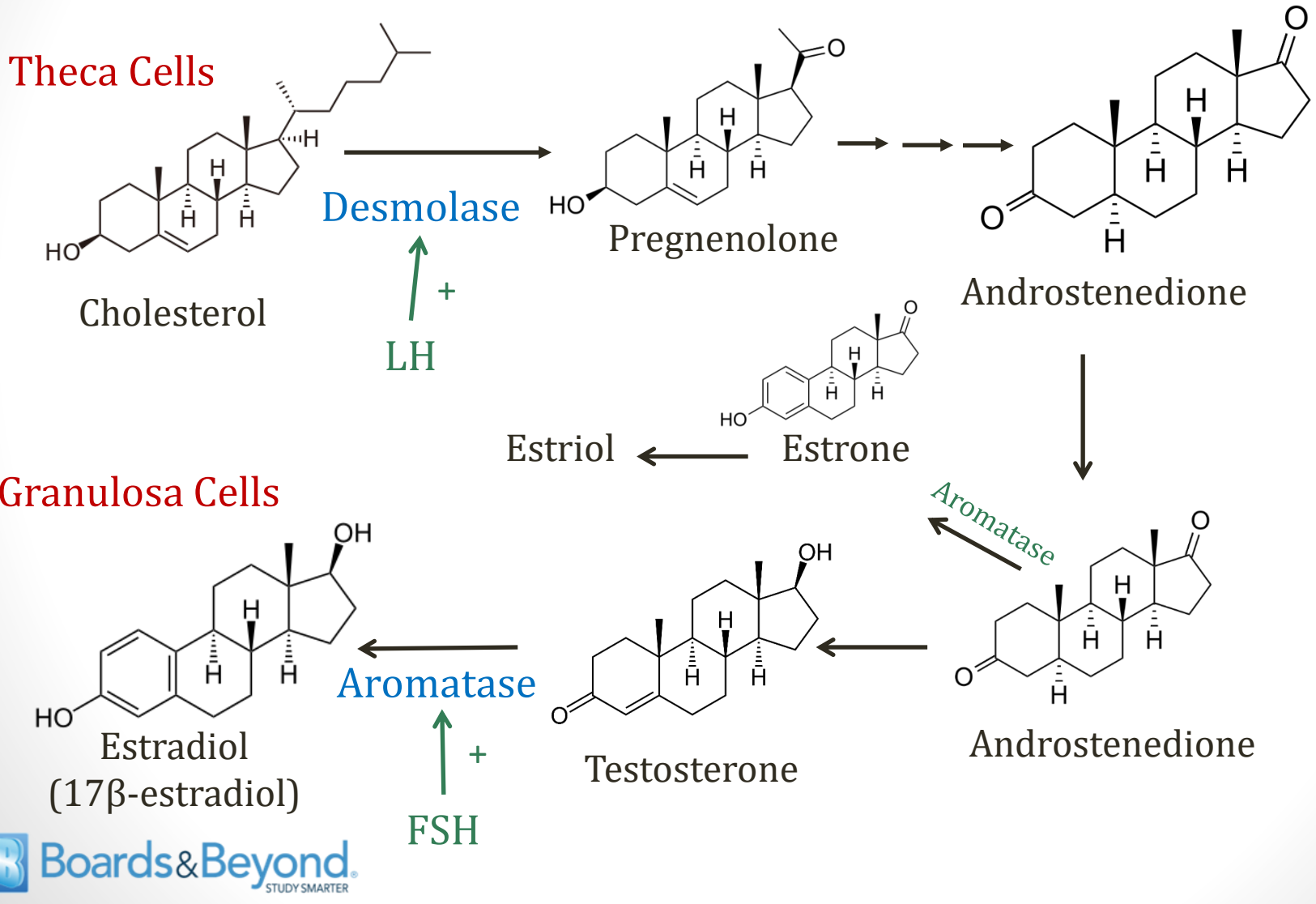
Hormone Synthesis

Estrogens

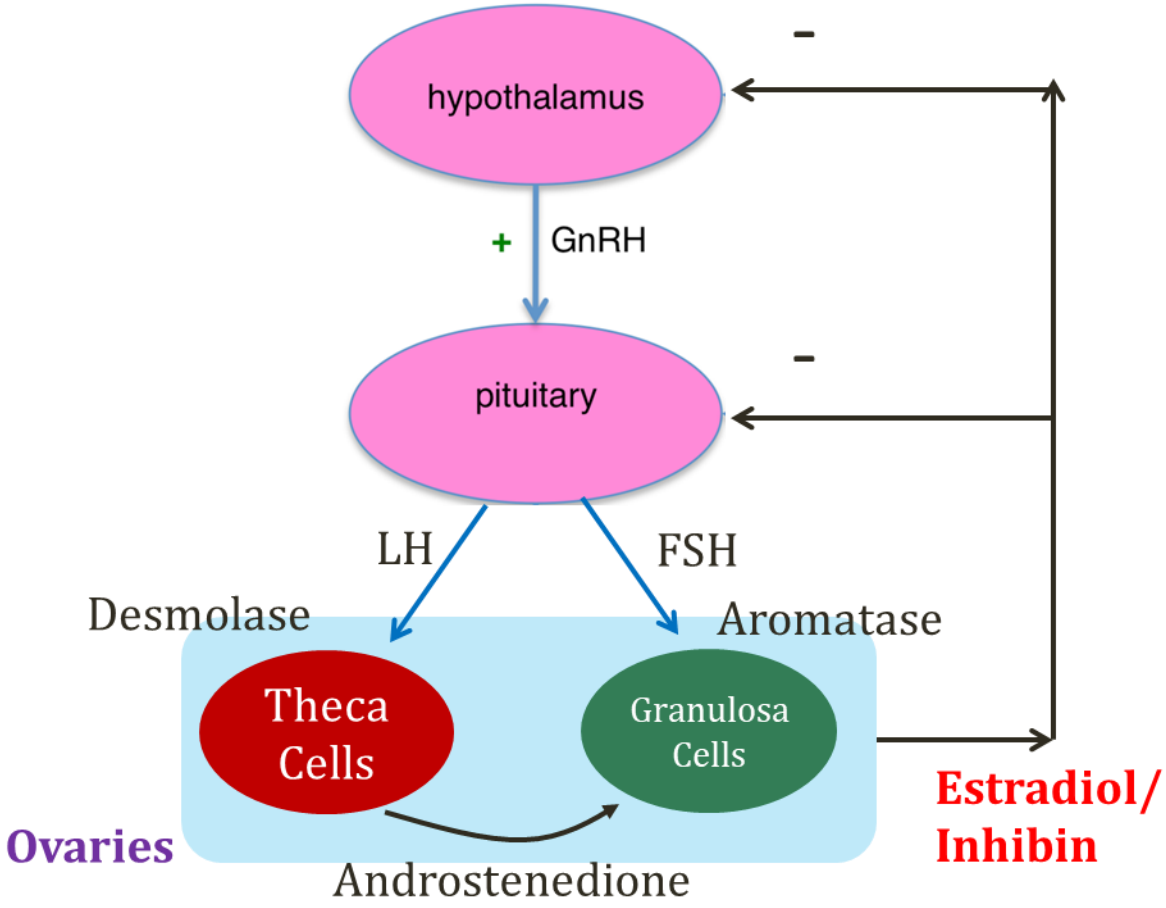
- **Theca cells**
  - Convert cholesterol into androstenedione
  - Stimulated by LH (via cAMP 2nd messenger)
- **Granulosa cells**
  - Convert androstenedione into estradiol
  - Stimulated by FSH (via cAMP 2nd messenger)
  - Also produce inhibin → suppresses FSH

Hormone Synthesis

Estrogens



Female Reproductive System



Estrogen Effects

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

Estrogen Effects

Puberty

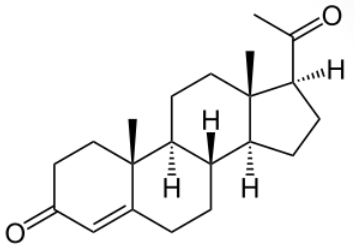
- Breast enlargement
- Pigmentation of areolas
  - Also seen in pregnancy
- Female body habitus
  - Narrow shoulders, broad hips
  - Female fat distribution in breasts and buttocks
- Note: Pubic and axillary hair from androgens

Estrogen Effects

Pituitary

- ↓ FSH secretion (negative feedback)
- ↓ LH secretion (negative feedback)
- Exception: Can trigger LH surge (positive feedback)

Progesterone



Progesterone

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

Progesterone Effects

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

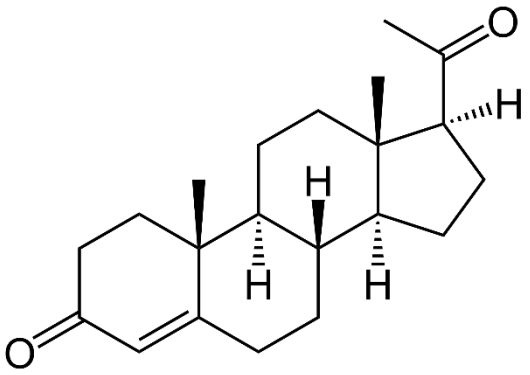
Progesterone Effects

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

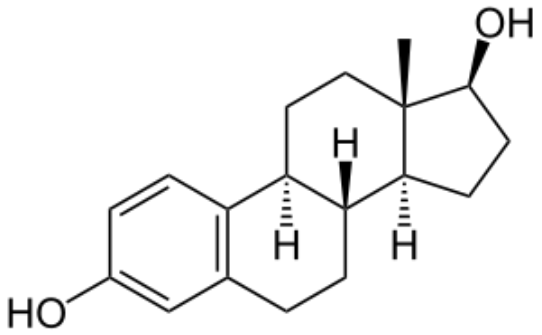
Oral Contraceptives

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

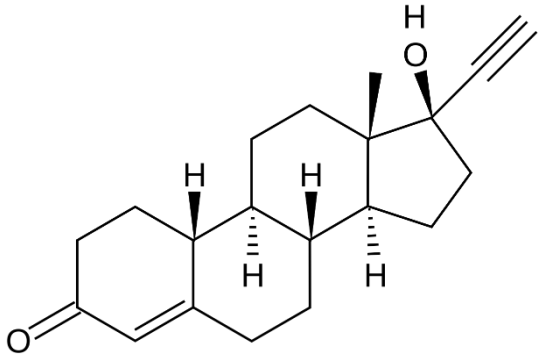
Oral Contraceptives



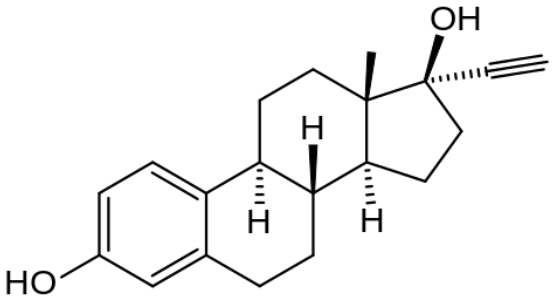
Progesterone



Estradiol



Norethisterone



Ethinyl estradiol

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

Medroxyprogesterone

Depo-Provera

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

Combination OCPs

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

Combination OCP Risks

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

Combination OCP Risks

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

Combination OCPs

Contraindications

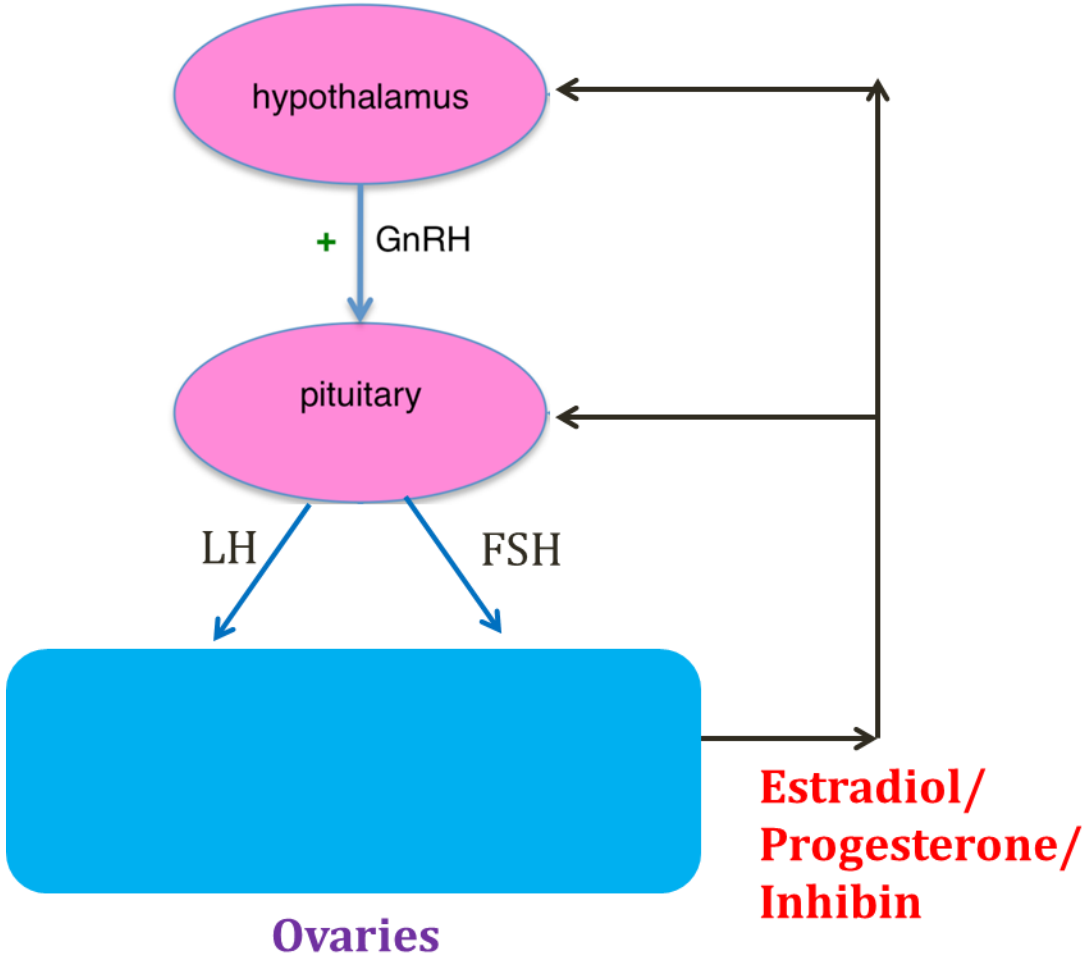
- **Smokers** >35 years of age
  - Risk of CV events
- History of DVT/PE

Pixabay/Public Domain

Menstrual Cycle

Jason Ryan, MD, MPH

Female Reproductive System



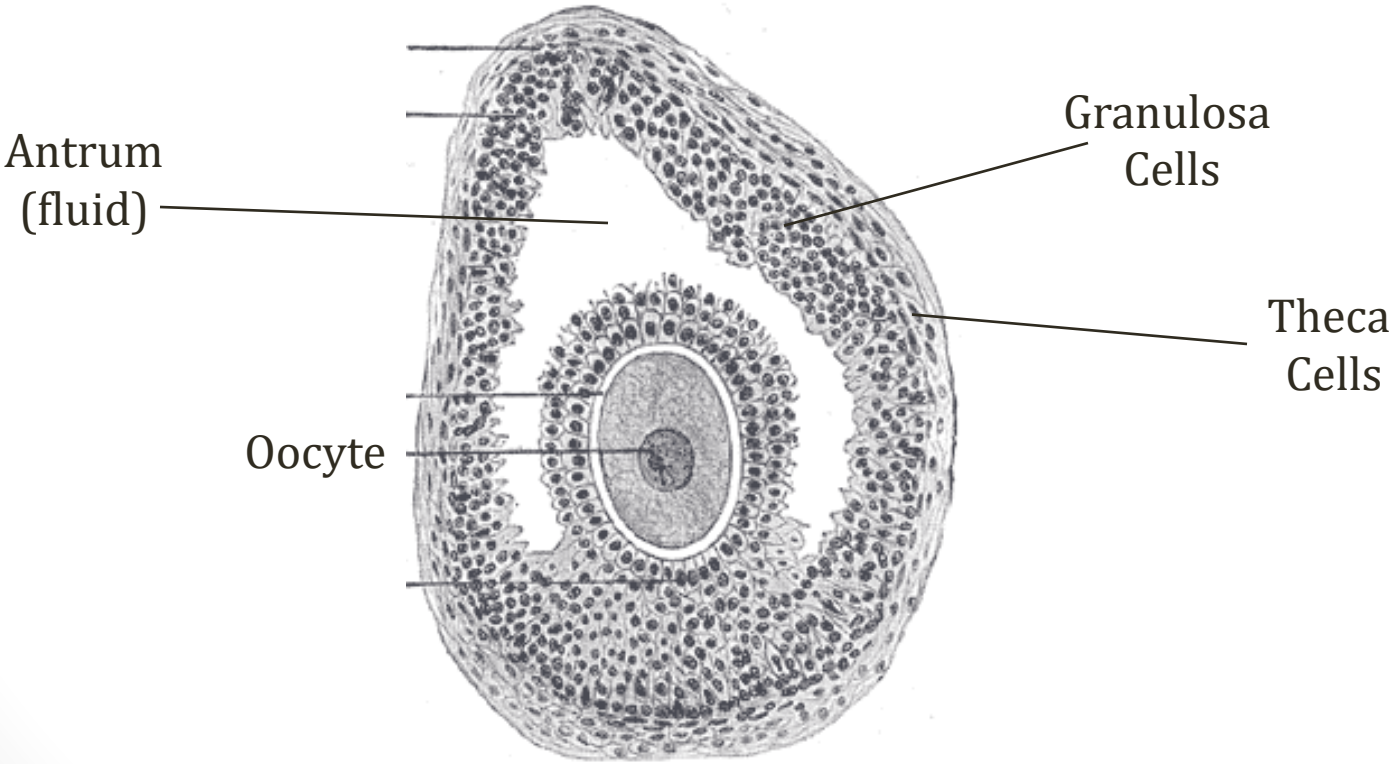
Ovaries

Basic Principles

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

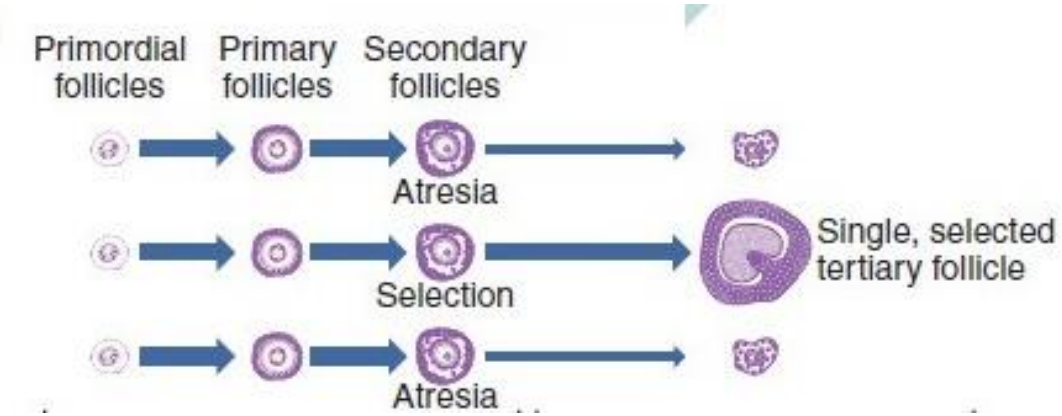
Ovarian Follicle

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



Ovarian Follicle

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



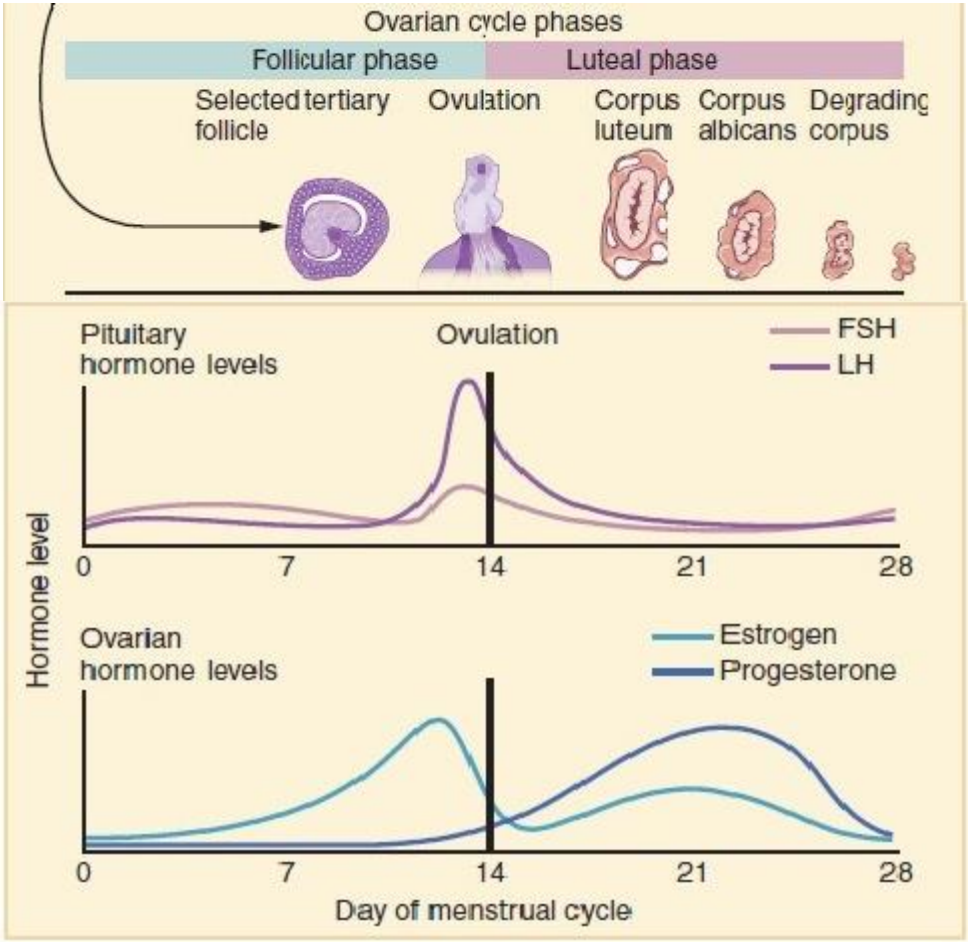
OpenStax College/Wikipedia

Menstrual Cycle

Basic Principles

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

Menstrual Cycle



OpenStax College/Wikipedia

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)

Menstrual Cycle

Ovulation

- **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

OTRS/Wikipedia

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**)

Menstrual Cycle

Luteal phase

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

Menstrual Cycle

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

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

Uterine Cycle

Proliferative Phase

- Menstruation followed by endometrial **proliferation**
- Stimulated by **estrogen**
- Endometrial thickness increases (>10x)
- Growth of glands, stroma, blood vessels

Uterine Cycle

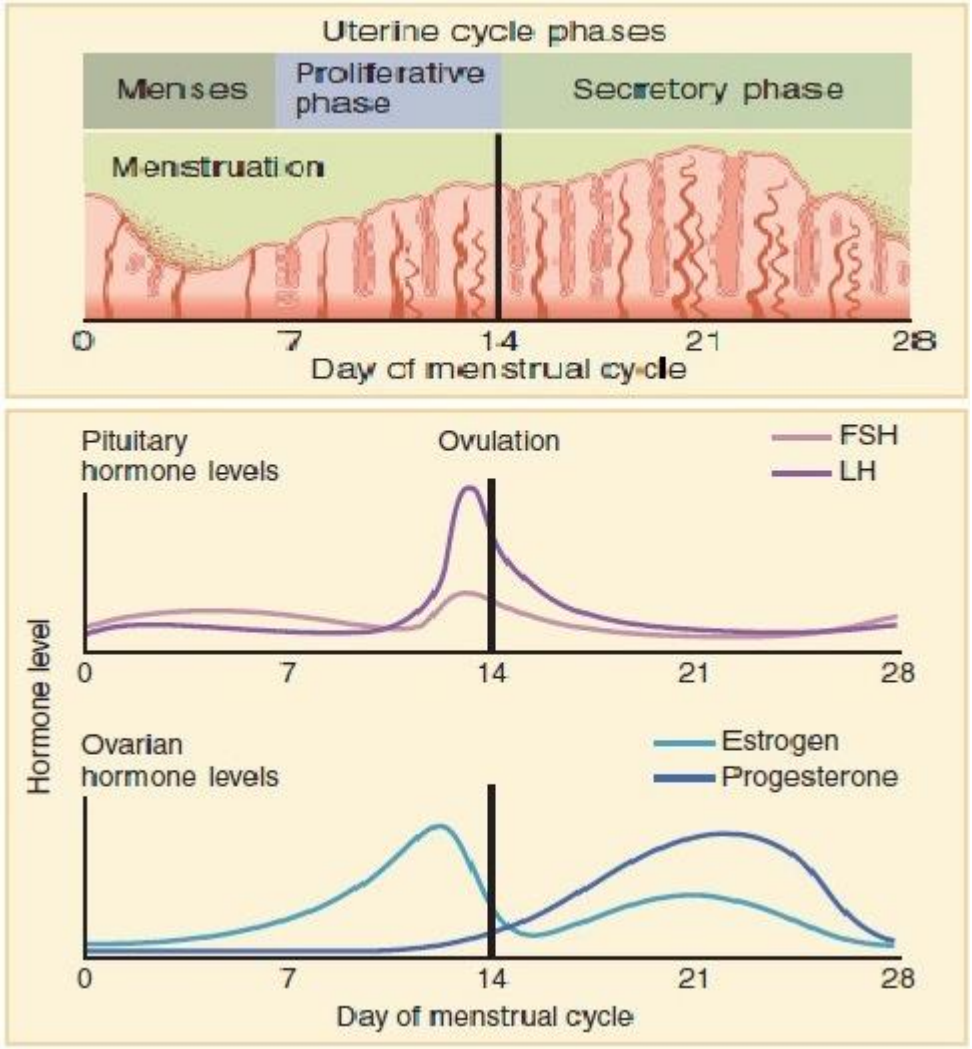
Secretory Phase

- 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

Menstruation

- Progesterone levels fall
- Vasoconstriction of spiral arteries
- **Apoptosis** of endometrial cells occurs
- Collapse and desquamation of endometrium

Menstrual and Uterine Cycles

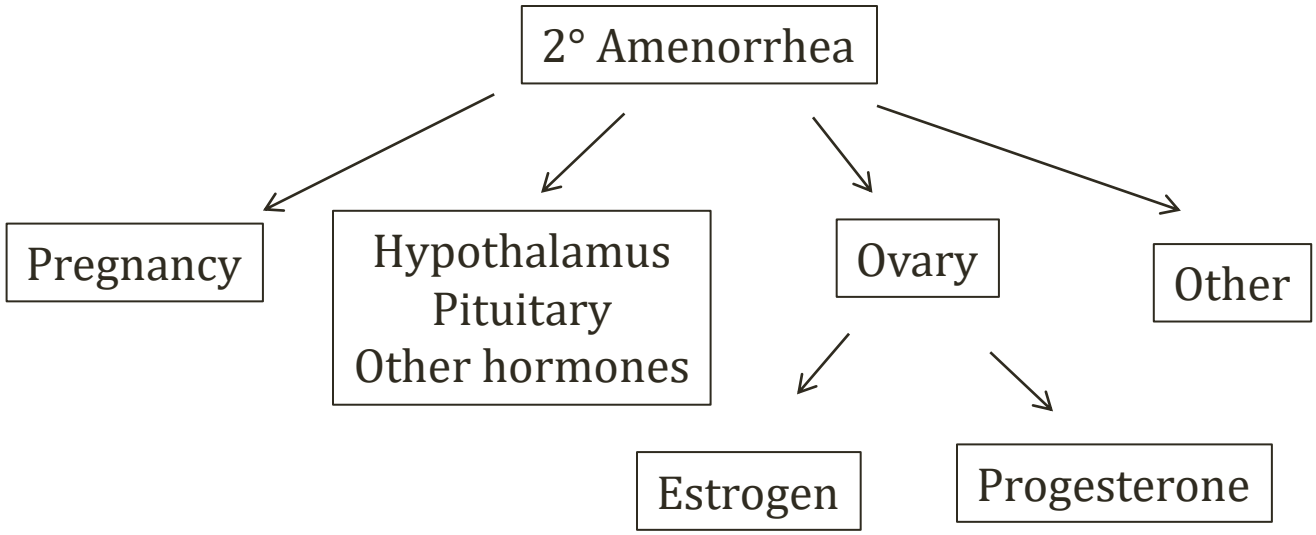


OpenStax College/Wikipedia

Amenorrhea

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

Secondary Amenorrhea



Progestin Challenge

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

Progestin Challenge

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

Mullerian Dysgenesis

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

Secondary Amenorrhea

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

Secondary Amenorrhea

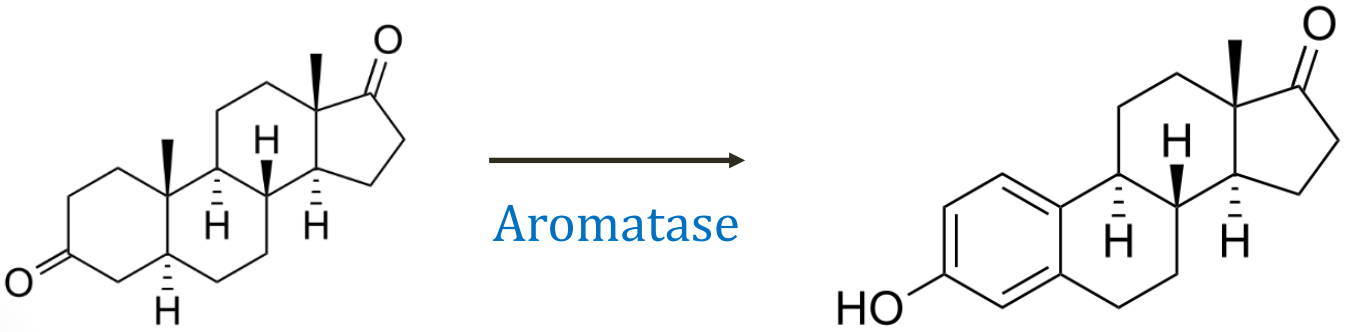
- **Low body weight**
  - "Functional hypothalamic amenorrhea"
  - Stress plus low caloric intake → ↓ GnRH/LH/FSH
  - Patients respond to pulsatile GnRH
  - Can occur in anorexia

Menopause

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

Menopause

- Loss of estradiol production from ovaries
  - Source of estrogen becomes adipose tissue
  - Aromatase coverts 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



Androstenedione

Estrone

Menopause

Symptoms

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

Menopause

Symptoms

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

HRT

Hormone Replacement Therapy

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

HRT

Hormone Replacement Therapy

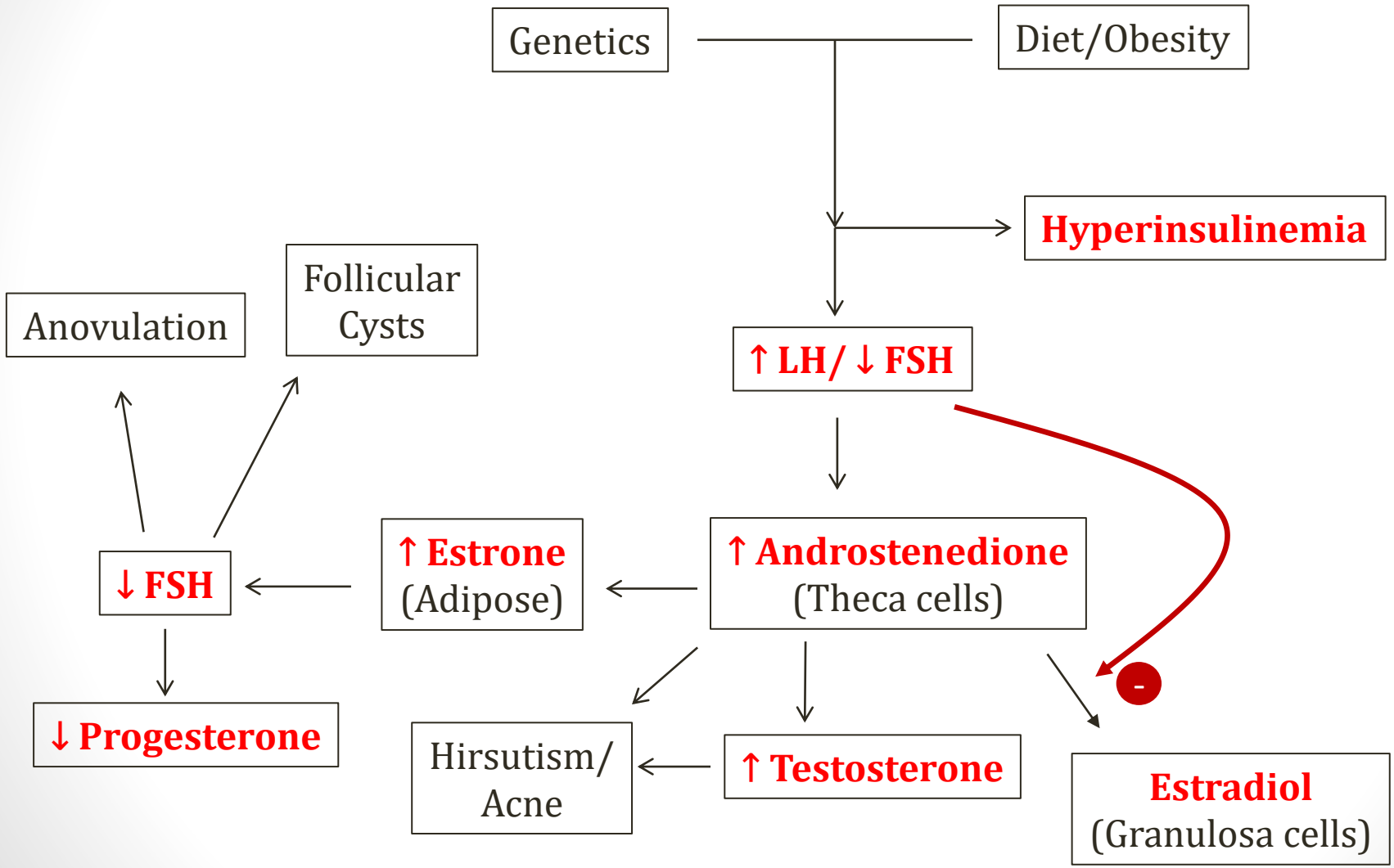
- Benefits:
  - **Relieves hot flashes**
  - Improves bone density
- Possible risks:
  - ↑ risk of DVT/Stroke/MI
  - ↑ risk of breast cancer

PCOS

Polycystic Ovarian Syndrome

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

PCOS



Hyperinsulinemia

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

PCOS

Clinical features

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

PCOS

Diagnosis

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

PCOS

Treatment

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

PCOS

Other Features

- Risk of **diabetes**
  - ~10% of women with PCOS develop DM by 40 years old
- Acanthosis Nigricans
  - Plaques of darkened skin
  - Associated with insulin resistance
  - Common in diabetes, PCOS, also gastric cancer
- Endometrial cancer
  - Unopposed estrogen (lack of progesterone)
  - ↑ risk of endometrial hyperplasia and carcinoma

Amenorrhea Workup

Rule out:
Pregnancy
Thyroid
Cushing
Prolactin
Anorexia

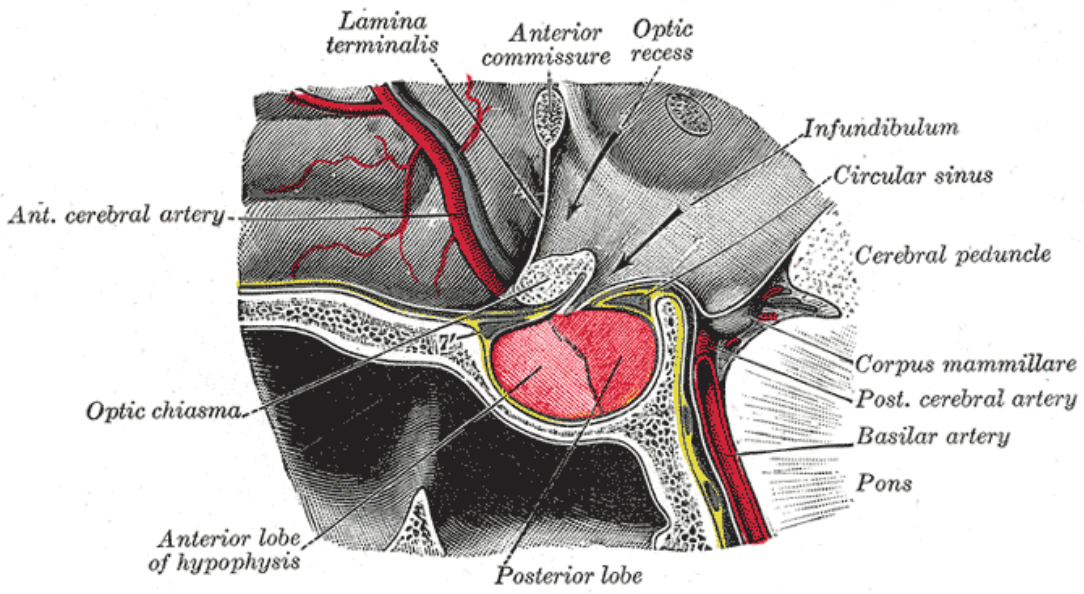
↓ FSH	↑ FSH	Normal FSH
PCOS (↑LH:FSH)	Menopause	Mullerian Dysgenesis

Pituitary Gland

Jason Ryan, MD, MPH

Pituitary Gland

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



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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

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

Anterior Pituitary Gland

Adenohypophysis

- Derived from **Rathke's pouch**
  - Outgrowth of oral cavity
- Contains five cell types that make hormones

Cell Type	Hormone
Corticotrophs	Adrenocorticotropic hormone (ACTH)
Thyrotrophs	Thyroid-stimulating hormone (TSH)
Gonadotrophs	Luteinizing hormone (LH) Follicle-stimulating hormone (FSH)
Somatotrophs	Growth hormone (GH)
Lactotrophs	Prolactin

Hypothalamic Portal System

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

Hypothalamus	Pituitary
Corticotropin-releasing hormone (CRH)	ACTH
Thyrotropin-releasing hormone (TRH)	TSH
Gonadotropin-releasing hormone (GnRH)	LH/FSH
Growth hormone–releasing hormone (GHRH)	GH
Dopamine	Prolactin
Somatostatin	GH, TSH

Prolactin

- Protein hormone
- Regulates milk production in mothers

Øyvind Holmstad/Wikipedia

Prolactin

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

Prolactin

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

Prolactin 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 in Pregnancy

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

Prolactin in Pregnancy

- Prolactin stimulates growth of mammary glands
- Milk production in pregnancy does not occur
  - **Estradiol and progesterone** block prolactin effect on milk
- After childbirth → ↓ estradiol and progesterone
  - Milk production occurs

Dopamine Agonists

Cabergoline, Bromocriptine

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

Pituitary Adenomas

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

Cell Type	Disease
Lactotrophs	Hyperprolactinemia
Thyrotrophs	Central hyperthyroidism
Corticotrophs	Cushing's disease
Somatotrophs	Acromegaly/Gigantism

Pituitary Adenomas

General Symptoms

- Headaches
- Classic cause of **bitemporal hemianopsia**
- Compression of **optic chiasm**

JFW/Wikipedia

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)

Prolactinoma

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

Dopamine Antagonists

- Antipsychotics: Haloperidol, Risperidone
- Antiemetics: Metoclopramide
- Blockade of D2: **↑ prolactin**
- Side Effects:
  - Amenorrhea
  - Breast engorgement
  - Galactorrhea
  - Sexual dysfunction
- Can also cause **Parkinsonian symptoms**

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

Craniopharyngioma

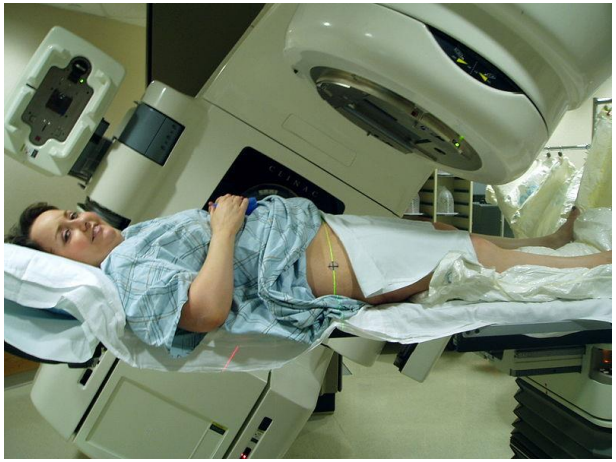
- Benign tumor
- Usually occurs in children 10-14 years old
- Symptoms from compression
  - Hypopituitarism
  - Headache, visual field defects
  - Behavioral change (frontal lobe dysfunction)
- Derived from remnants of Rathke's pouch

Empty Sella Syndrome

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

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

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)

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**

Hypopituitarism

Treatment

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

Growth Hormone

Somatotropin

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

Growth Hormone

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 JAK 2 itself and on GH receptor
- Forms binding sites for many signaling molecules
- Alters gene expression

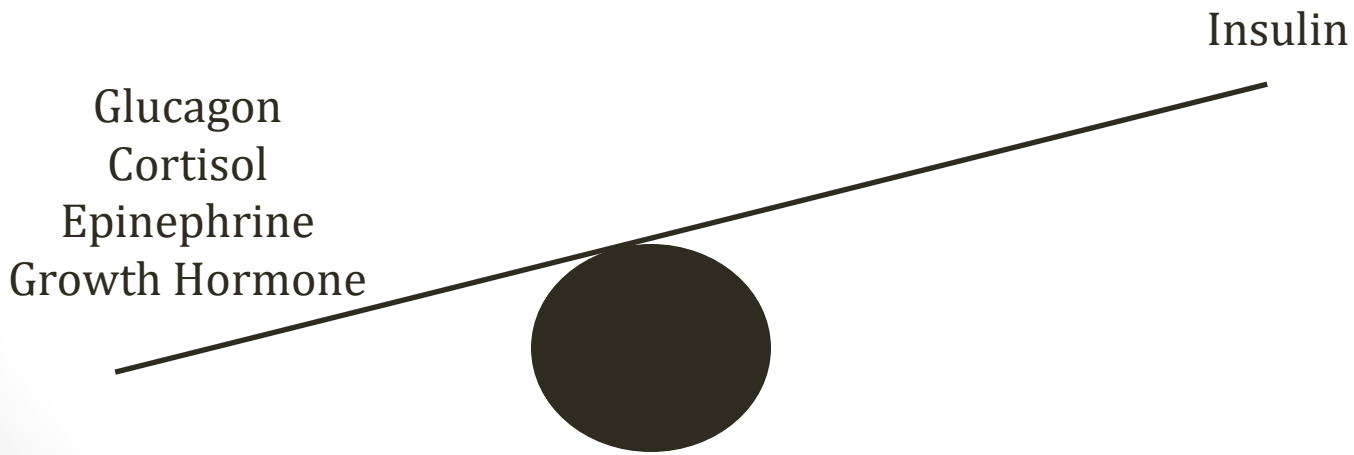
Growth Hormone

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

Growth Hormone

Direct Effects

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



Growth Hormone

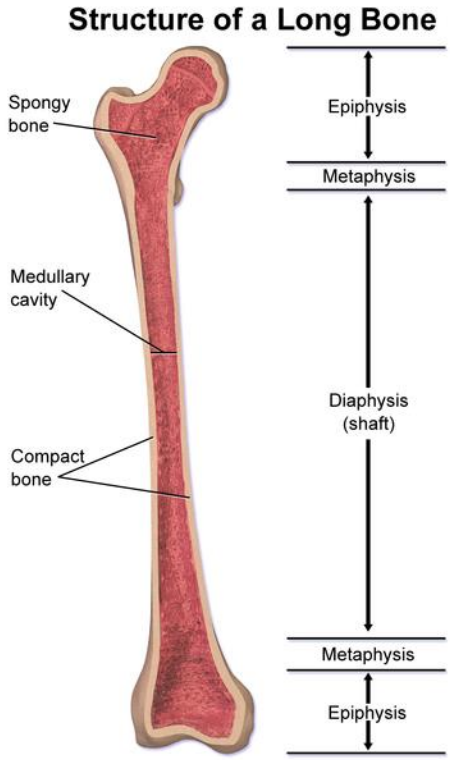
Direct Effects

- Promotes lipolysis
  - Activates hormone sensitive lipase
- Production of IGF-1 from liver

Growth Hormone

IGF-1 Effects

- **Chondrocytes**
  - Increased linear growth
- Muscle
  - Lean muscle mass
- Organs
  - Increased organ size



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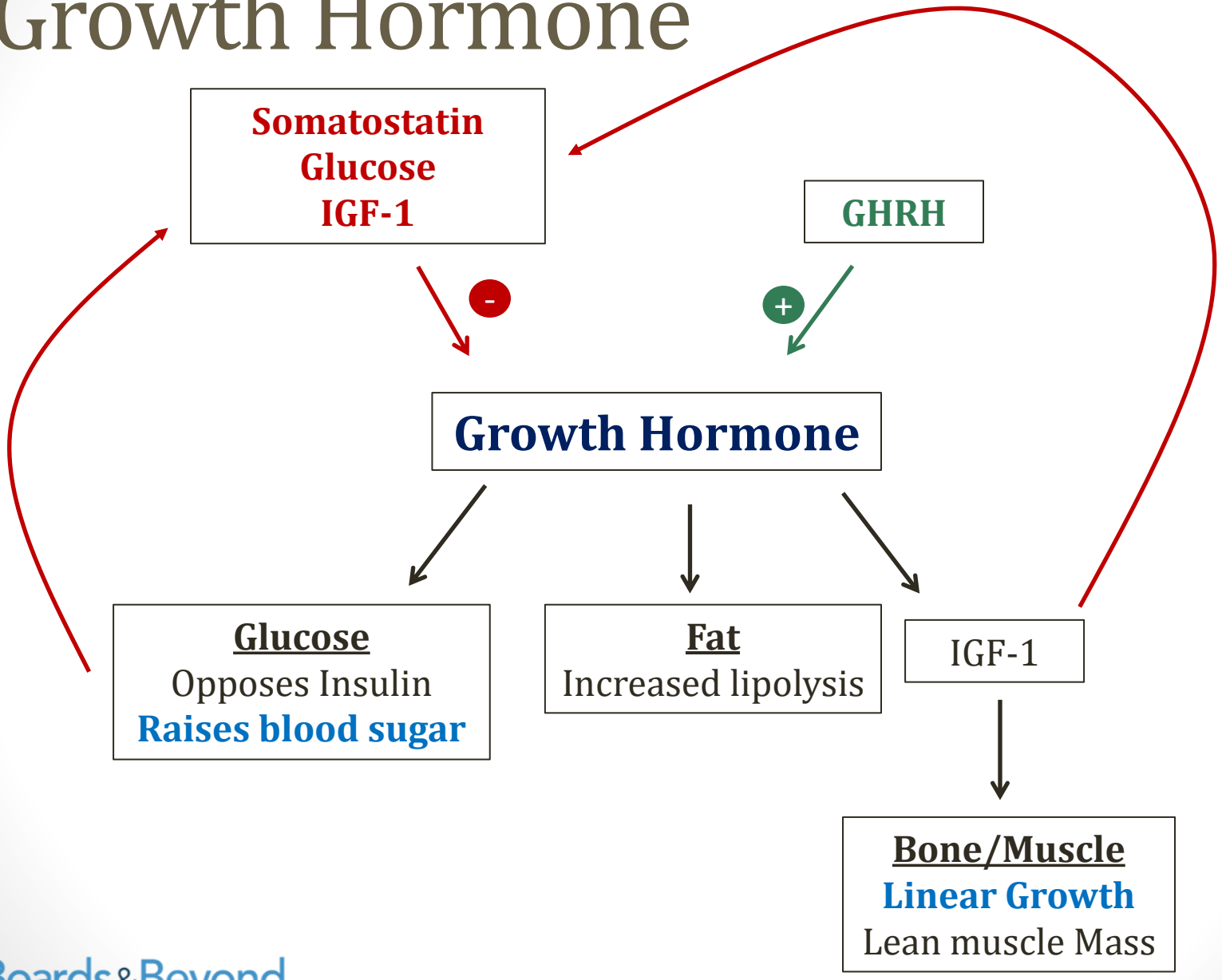
Growth Hormone



Growth Hormone Deficiency

- Children:
  - Failure to grow
- Adults
  - ↑ fat
  - ↓ lean body mass
  - Low energy

Growth Hormone Deficiency

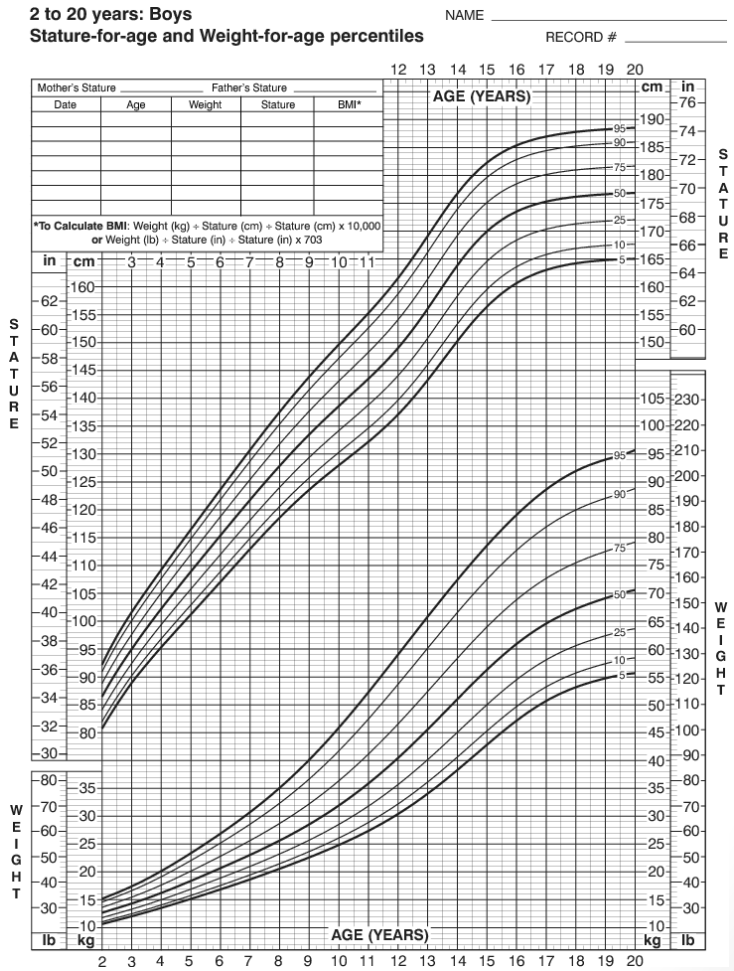
- Most commonly from pituitary tumor
  - Mass effect
  - Consequence of surgery/radiation
- Treatment: Synthetic growth hormone
- Monitoring: **Serum IGF-1 level**

Growth Hormone 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

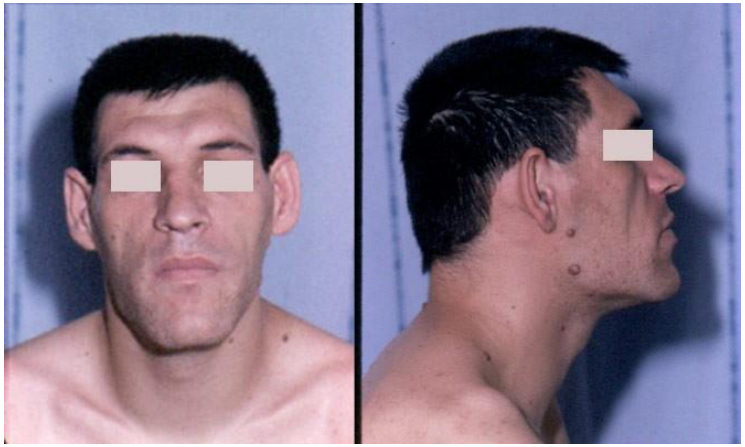
Growth Hormone Excess

- 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



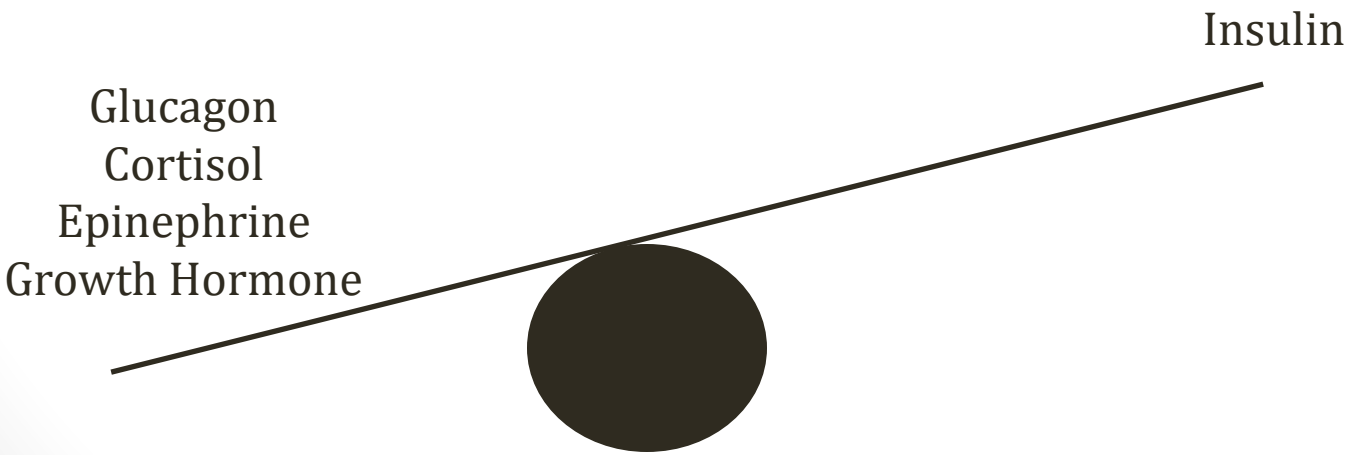
Philippe Chanson and Sylvie Salenave

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)

Growth Hormone Excess

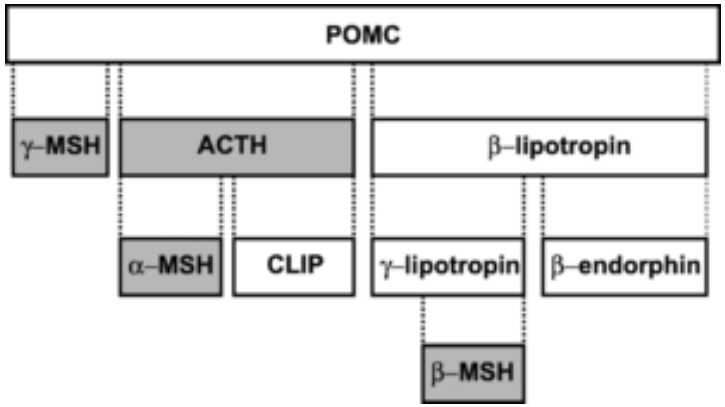
Treatment

- **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

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**



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

Oxytocin

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

Somatostatin

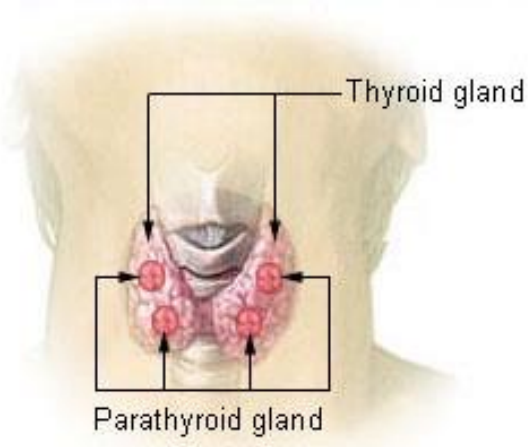
- **Inhibits** release of many hormones
- Released by D cells throughout GI tract
- Also found in **nerves** throughout entire body
- Originally discovered in hypothalamus
- Inhibits **growth hormone release**
- Used therapeutically (Octreotide) :
  - Acromegaly
  - Carcinoid syndrome
  - Glucagonoma/insulinoma
  - Upper GI bleeding (↓ splanchnic blood flow)

Parathyroid Glands

Jason Ryan, MD, MPH

Parathyroid Glands

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



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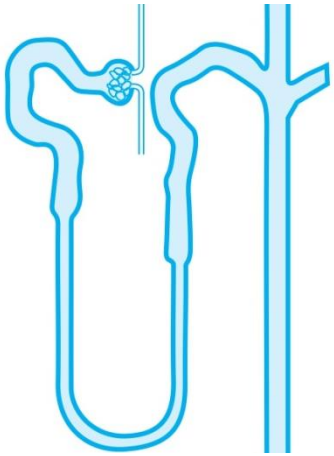
Parathyroid Hormone

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



BruceBlaus/Wikipedia

Parathyroid Hormone Effects

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

Parathyroid Hormone

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

Parathyroid Hormone

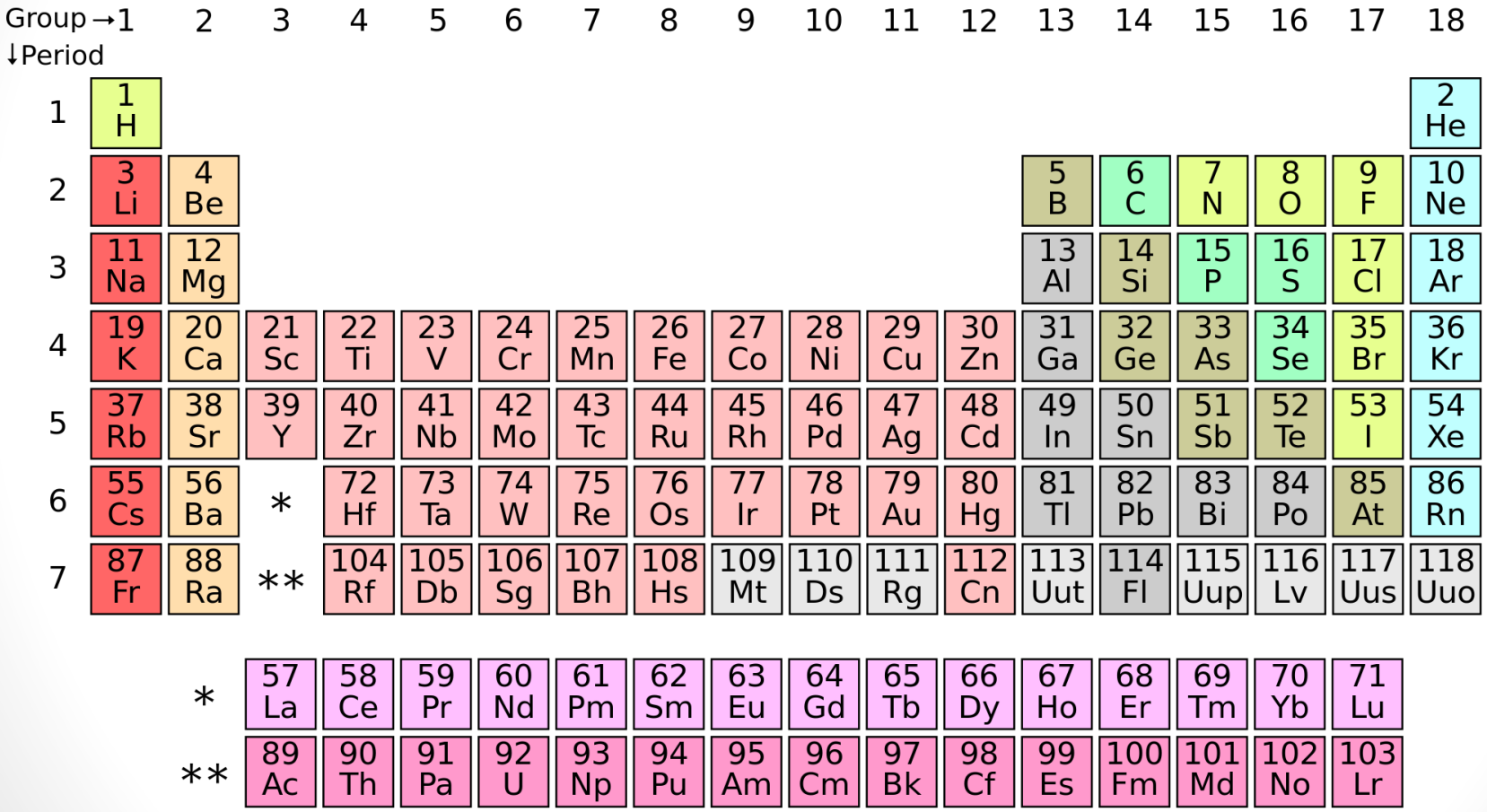
Magnesium

- High magnesium
  - ↓ PTH (same effect as calcium)
  - Magensium can activate CaSRs
- Low Mg
  - ↑ PTH release (same effect as calcium)
  - ↑ GI and renal magensium along with calcium

Parathyroid Hormone

Magnesium

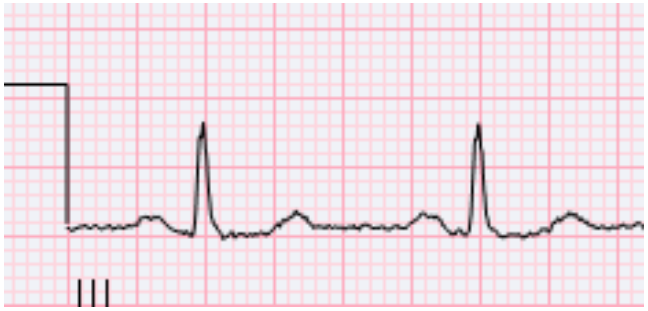
- Very low Mg → inhibits PTH release
  - Some Mg required for normal CaSR function
  - Abnormal function → suppression of PTH release
  - **Hypocalcemia often seen in severe hypomagenesemia**

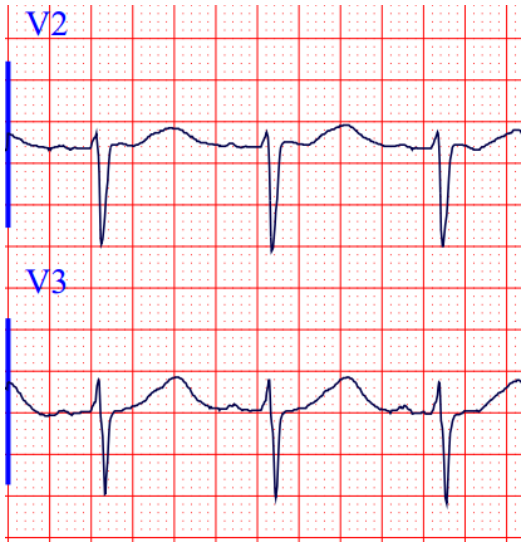


DePiep /Wikipedia

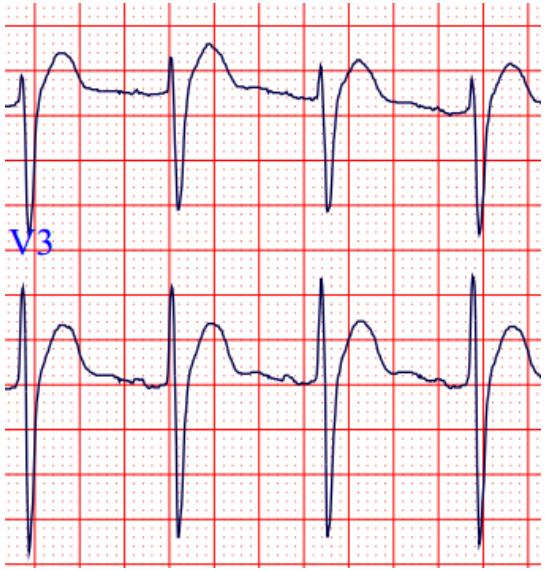
Qt Interval

Normal Qt





Prolonged Qt: ↓Mg, ↓Ca

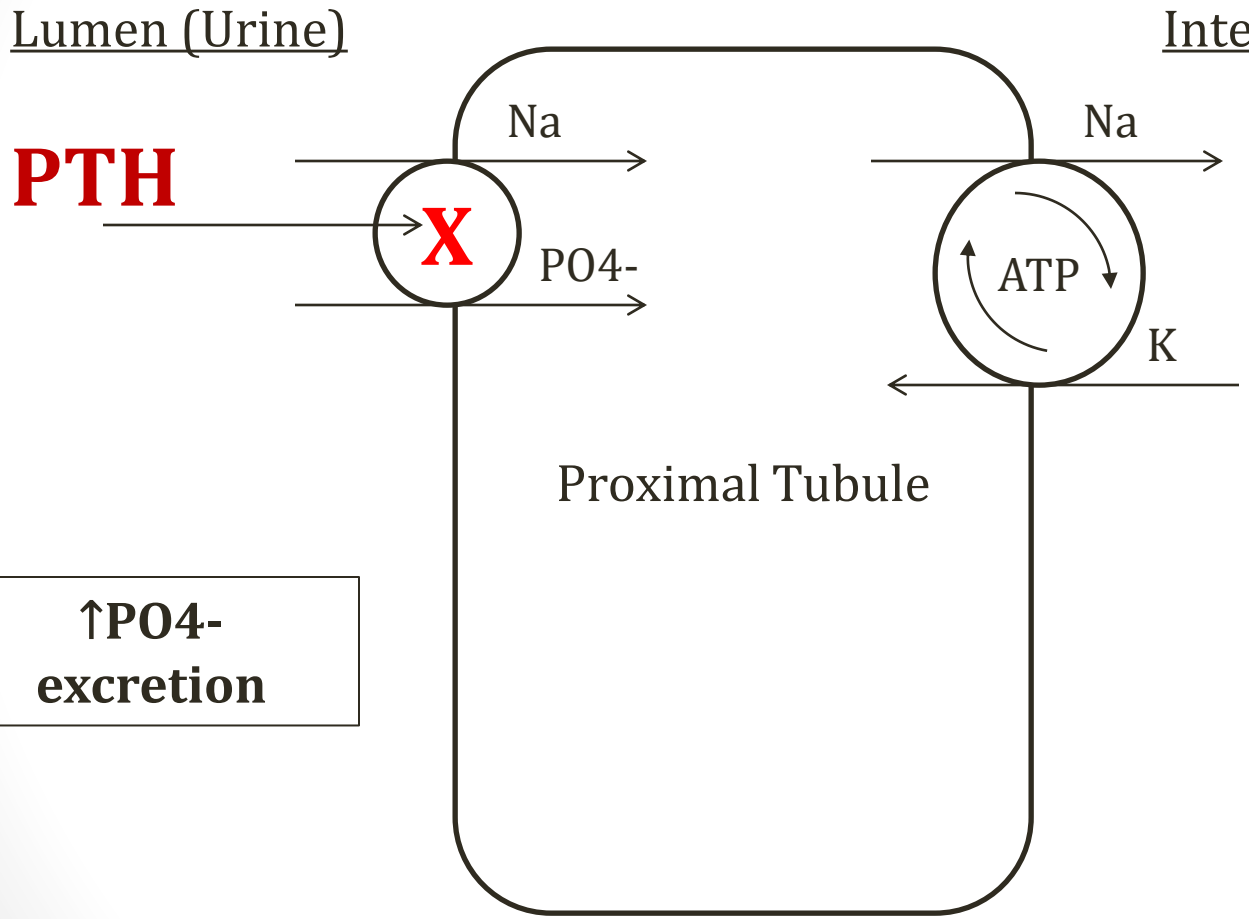


Short Qt: ↑Ca

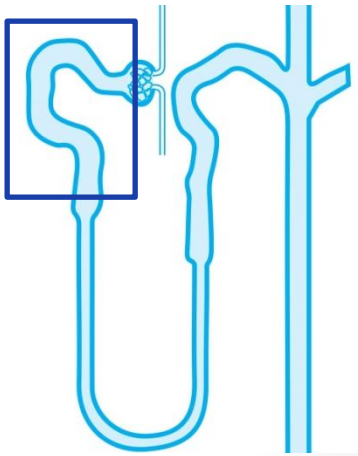
Parathyroid Hormone Effects

- Kidney:
  - ↑ Ca^{2+} resorption (DCT)
  - ↓ $P04^{3-}$ resorption (PCT)
  - ↑ 1 ,25-$(0H)_2$ vitamin D production
- GI:
  - ↑Ca2+ and $P04^{3-}$ absorption (via vitamin D)
- Bone:
  - ↑Ca2+ and $P04^{3-}$ resorption (direct and via vitamin D)

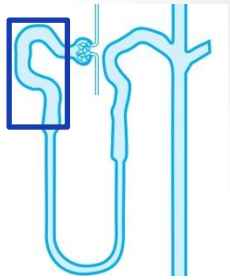
Parathyroid Hormone



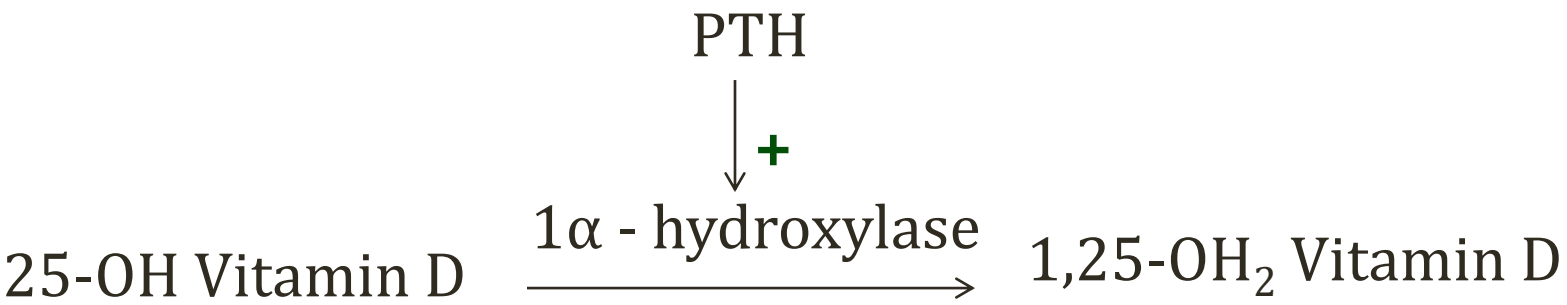
↑PO4- excretion



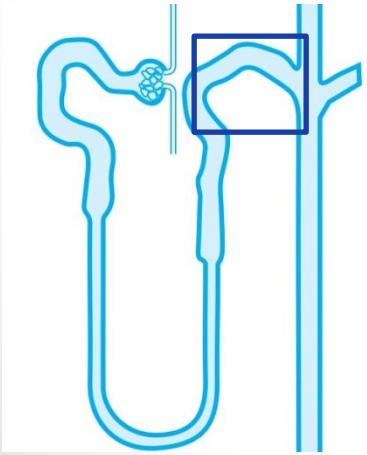
Vitamin D and the Kidney

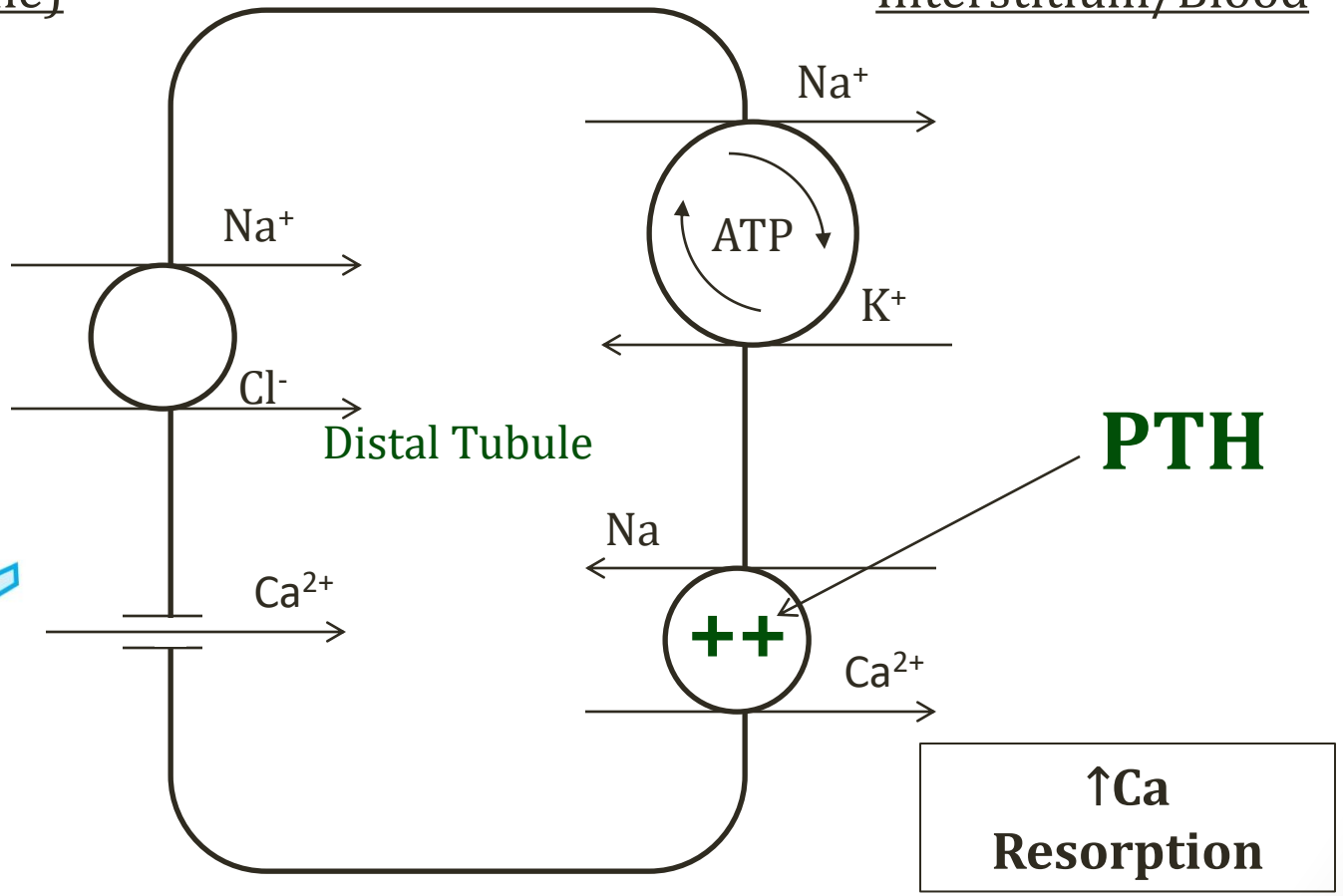


- **Proximal tubule** converts vitamin D to active form
- Can occur independent of kidney in **sarcoidosis**
  - Leads to **hypercalcemia**



Parathyroid Hormone





Parathyroid Hormone

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

Parathyroid Hormone

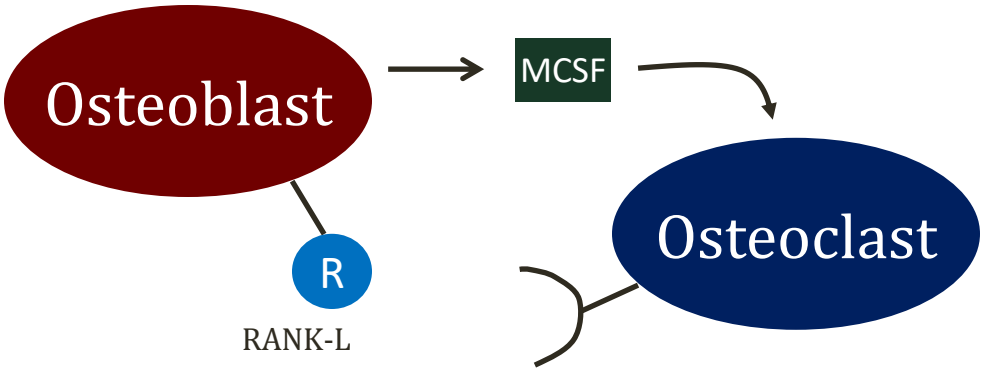
- Continuous administration of PTH
  - Bone resorption →↑ serum calcium
  - Important physiologically
- Low dose once daily bolus administration
  - Increased bone mass (bone formation)
  - **Teriparatide** used to treat osteoporosis

Parathyroid Hormone

- **Osteoblasts**
  - Bone forming cells
  - Contain PTH receptors
  - Can ↑ bone mass in response to PTH
- **Osteoclasts**
  - Bone resorbing cells
  - No PTH receptors
  - Activated indirectly by osteoblasts

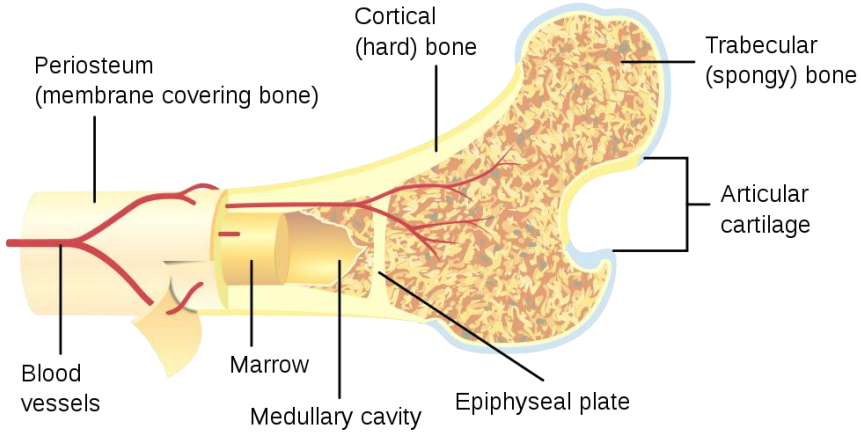
Parathyroid Hormone

- **M-CSF**
  - Macrophage colony stimulating factor
  - Secreted by osteoblasts
- **RANK-L**
  - Receptor activating nuclear factor kβ ligand
  - Expressed on surface of osteoblasts
- Both produced by osteoblasts → activate osteoclasts



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



Pbroks13/Wikipedia

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

Hyperparathyroidism

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

Primary Hyperparathyroidism

- Inappropriate secretion of PTH
- Not due to low calcium
- Commonly caused by **parathyroid adenoma**

Primary Hyperparathyroidism

- Causes **hypercalcemia**
  - ↑ renal reabsorption of Ca
  - ↑ vitamin D activation
  - ↑ bone resorption (loss of cortical bone)
- Phosphaturia

↑PTH ↑Ca

Primary Hyperparathyroidism

- Urinary calcium usually **high or normal**
- ↑ PTH → ↑ Ca urinary reabsorption → ↑ serum Ca
- ↑ serum Ca → ↑ urinary calcium

Primary Hyperparathyroidism

Symptoms

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

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

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

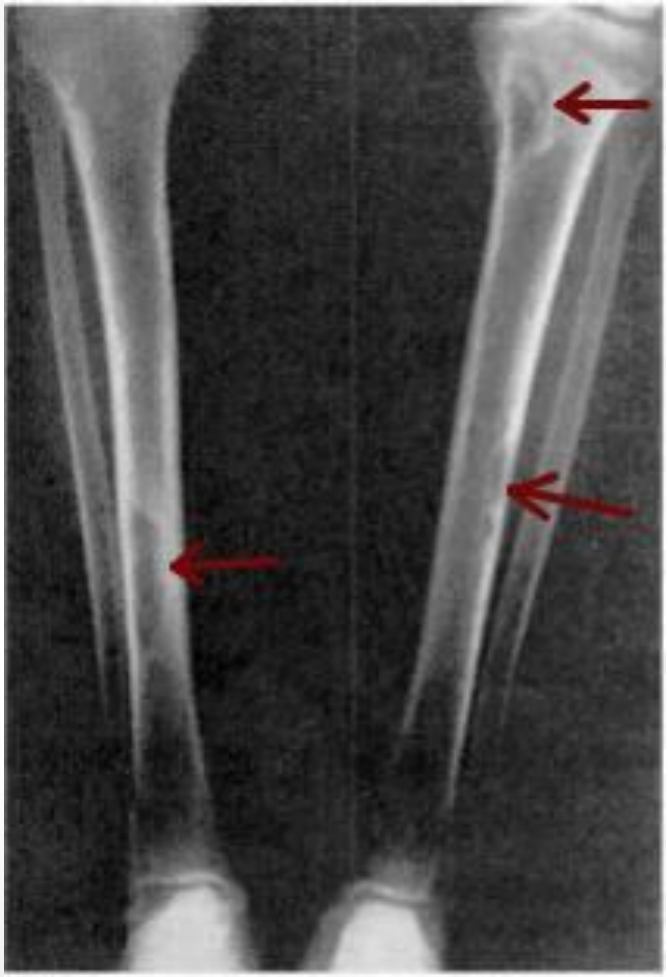
Osteitis Fibrosa Cystica

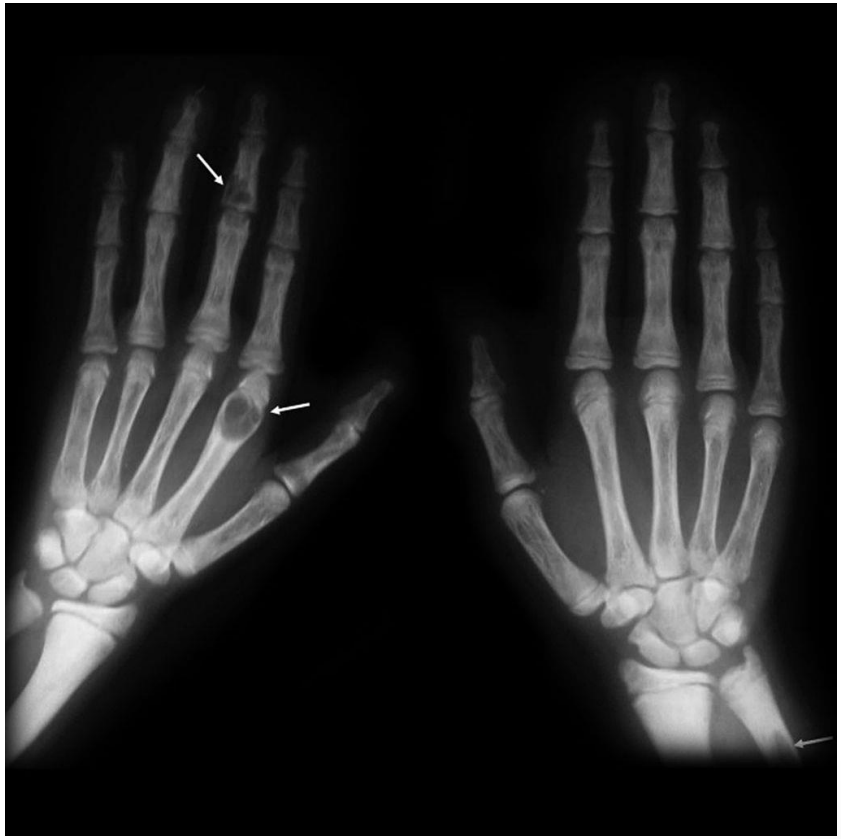
- Classic bone disease of hyperparathyroidism
- Clinical features: Bone pain and fractures

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

Osteitis Fibrosa Cystica





Frank Gaillard/Wikipedia

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

2º Hyperparathyroidism

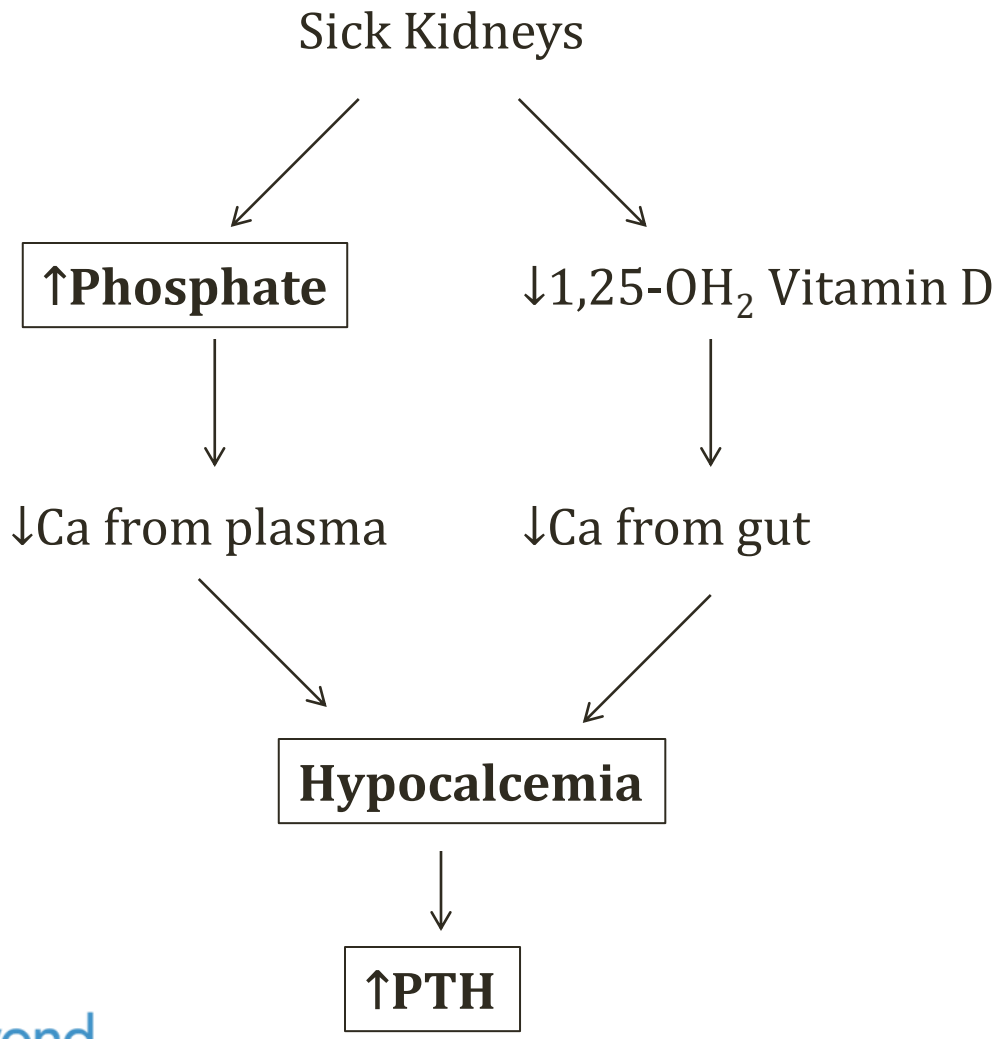
- Occurs in renal failure patients
- Chronically low serum calcium → ↑ PTH
- No symptoms of hypercalcemia
- Results in **renal osteodystrophy**
  - Bone pain (predominant symptom)
  - Fractures (weak bones 2° chronic high PTH levels)
  - If severe, untreated can lead to osteitis fibrosa cystica

↑PTH ↓Ca

3º 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

Calcium-Phosphate in Renal Failure



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

FHH

Familial Hypocalciuric Hypercalcemia

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

Hypoparathyroidism

- Inappropriately low PTH secretion
- Not due to hypercalcemia
- Causes **hypocalcemia**

↓PTH ↓Ca

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

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

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

Thymic Aplasia

DiGeorge Syndrome

- Immunodeficiency syndrome
- Failure of $3^{rd}/4^{th}$ 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

Hypoparathyroidism

Treatment

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

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

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
  - Mild mental retardation

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 – 2º hyperparathyroidism)
  - Renal losses (pseudohypoparathyroidism)

MEN Syndromes

Jason Ryan, MD, MPH

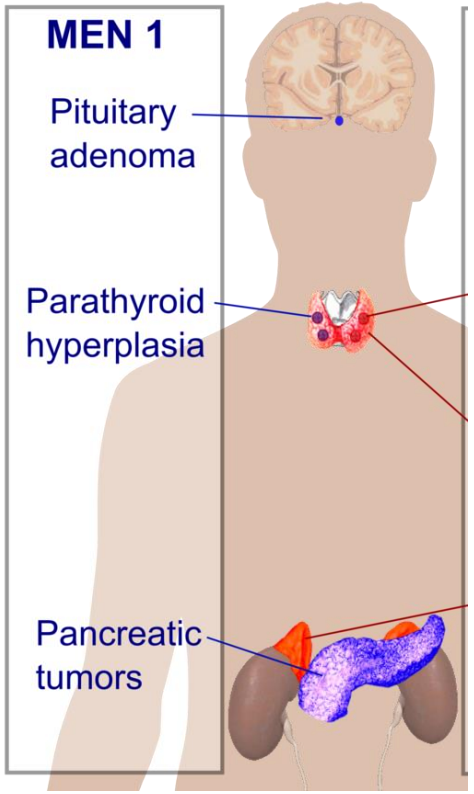
MEN Syndromes

Multiple Endocrine Neoplasia

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

MEN 1

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



Mikael Häggström/Wikipedia

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

- 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 1

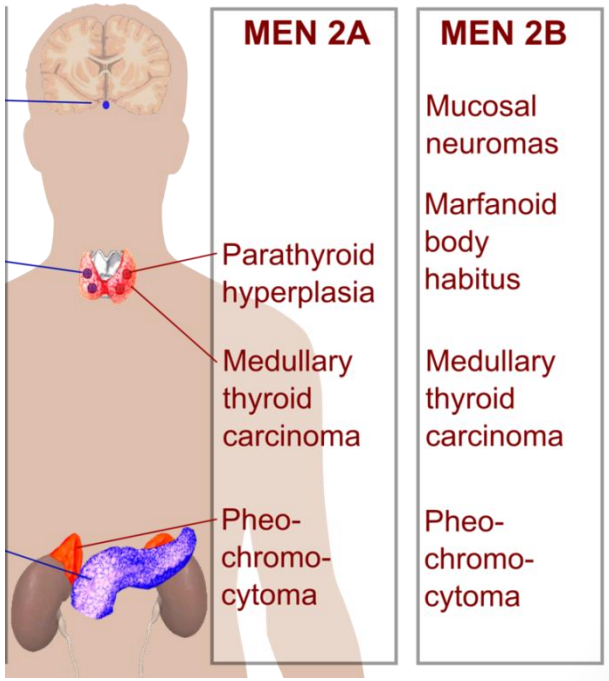
- Pituitary adenoma
  - Occurs in up to 70% of patients
  - Most commonly a prolactinoma
  - 2nd most common: GH secreting adenoma
- Pituitary adenomas not seen in other MEN syndromes
- **Pituitary disease = MEN 1**

MEN 1

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

MEN 2A and 2B

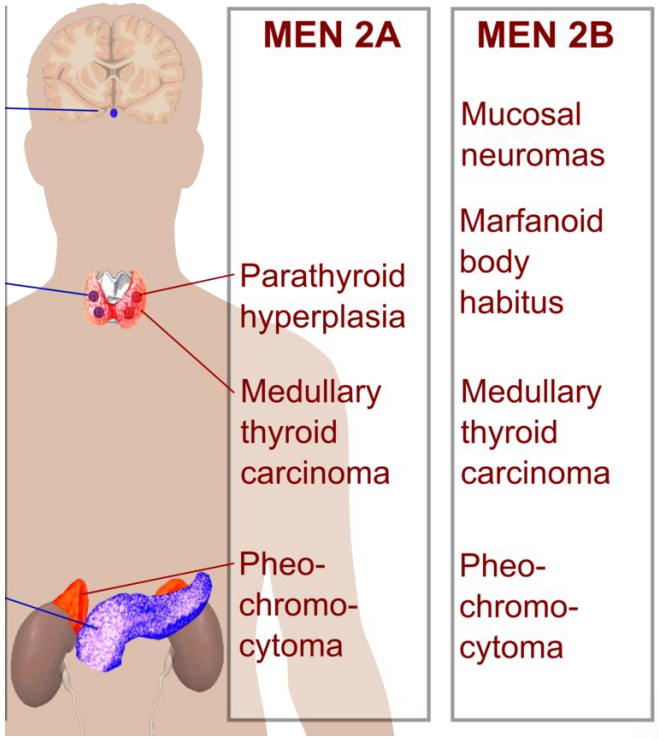
- "Medullary" tumors
  - **Medullary** thyroid carcinoma
  - Pheochromocytoma (adrenal **medulla**)



Mikael Häggström/Wikipedia

MEN 2A and 2B

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



Mikael Häggström/Wikipedia

Medullary Carcinoma

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

MEN 2A and 2B

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

MEN 2B

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

MEN 2B Neuromas

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

MEN 2B: Marfanoid

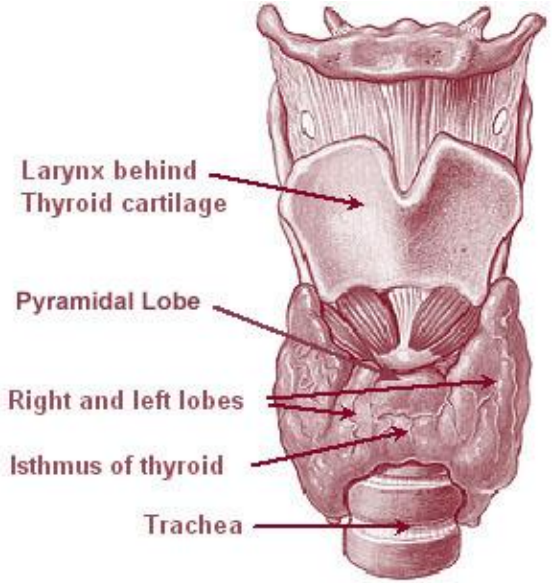
- **Tall**
- **Long wing span**
- High arched palate
- Skeletal deformations of spine:
  - Kyphoscoliosis: Curve to left/right
  - Lordosis: Curve forward
- No lens or aortic involvement (like Marfan's)

MEN 2A and 2B

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

Thyroidectomy

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



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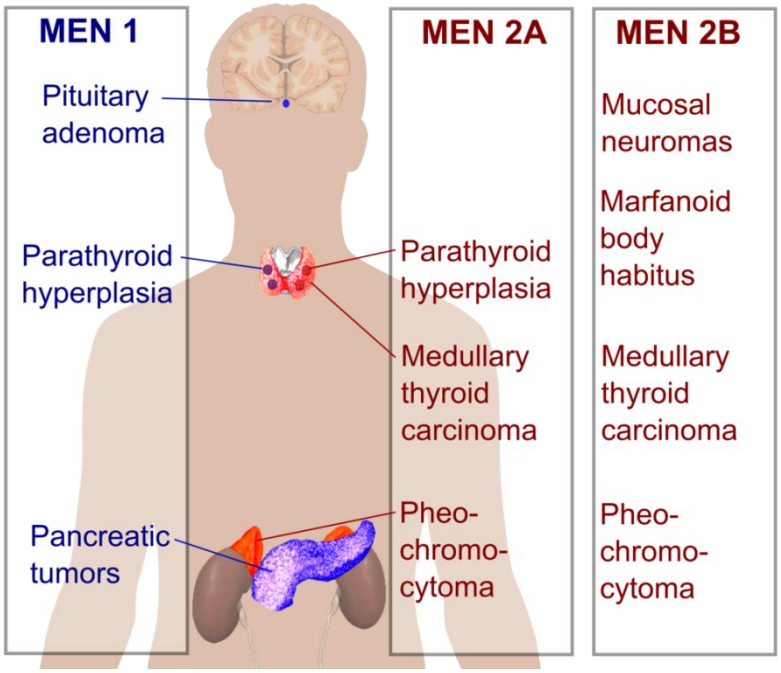
MEN Syndromes

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



Mikael Häggström/Wikipedia

Signaling Pathways

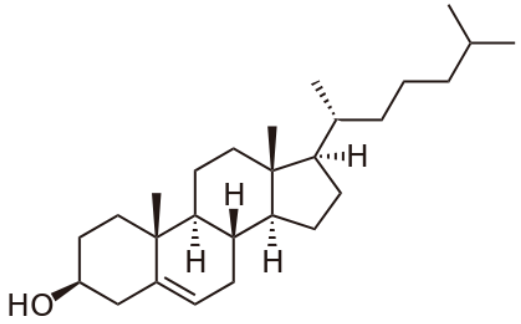
Jason Ryan, MD, MPH

Hormone Effects

Intracellular Hormones

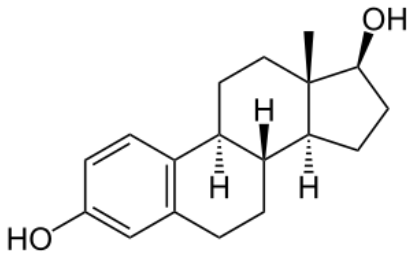
Receptor in cytoplasm/nucleus

- Progesterone
- Estrogen
- Testosterone
- Cortisol
- Aldosterone
- Thyroid hormone

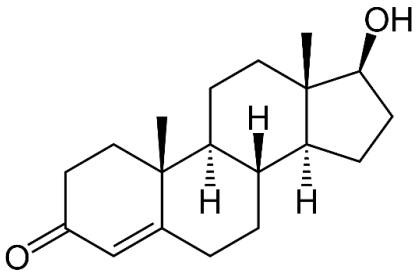


Cholesterol

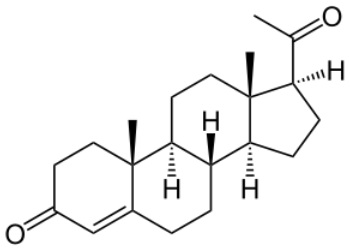
Steroid Hormones



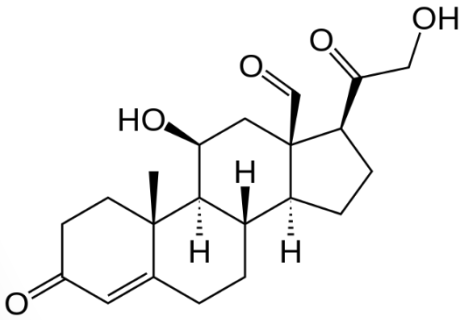
Estradiol
(17β-estradiol)



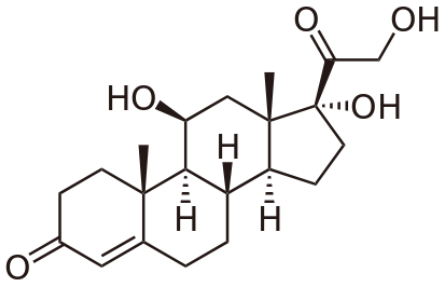
Testosterone



Progesterone



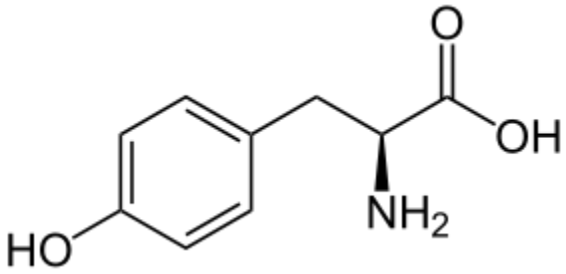
Aldosterone



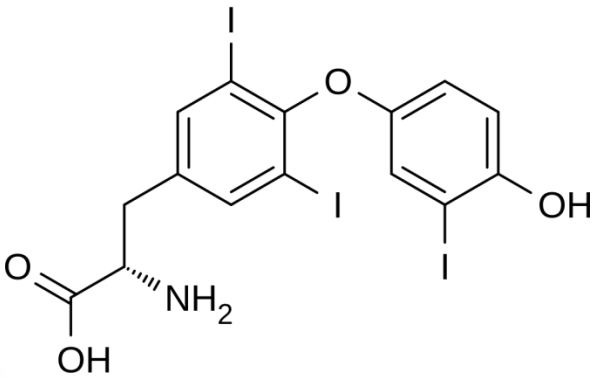
Cortisol

Thyroid Hormones

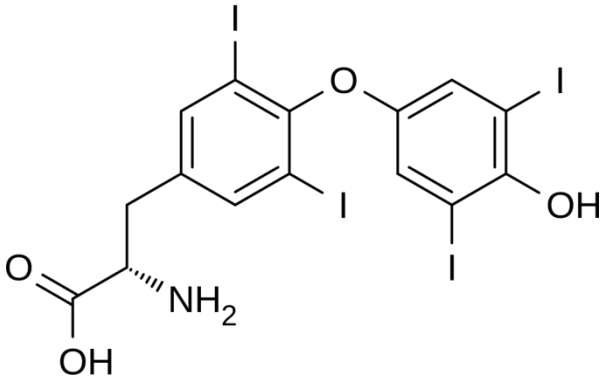
- Two hormones: T3 and T4
- Synthesized from tyrosine and iodine



Tyrosine



Triiodothyronine ($\mathbf{T_3}$)



Thyroxine ($\mathbf{T_4}$)

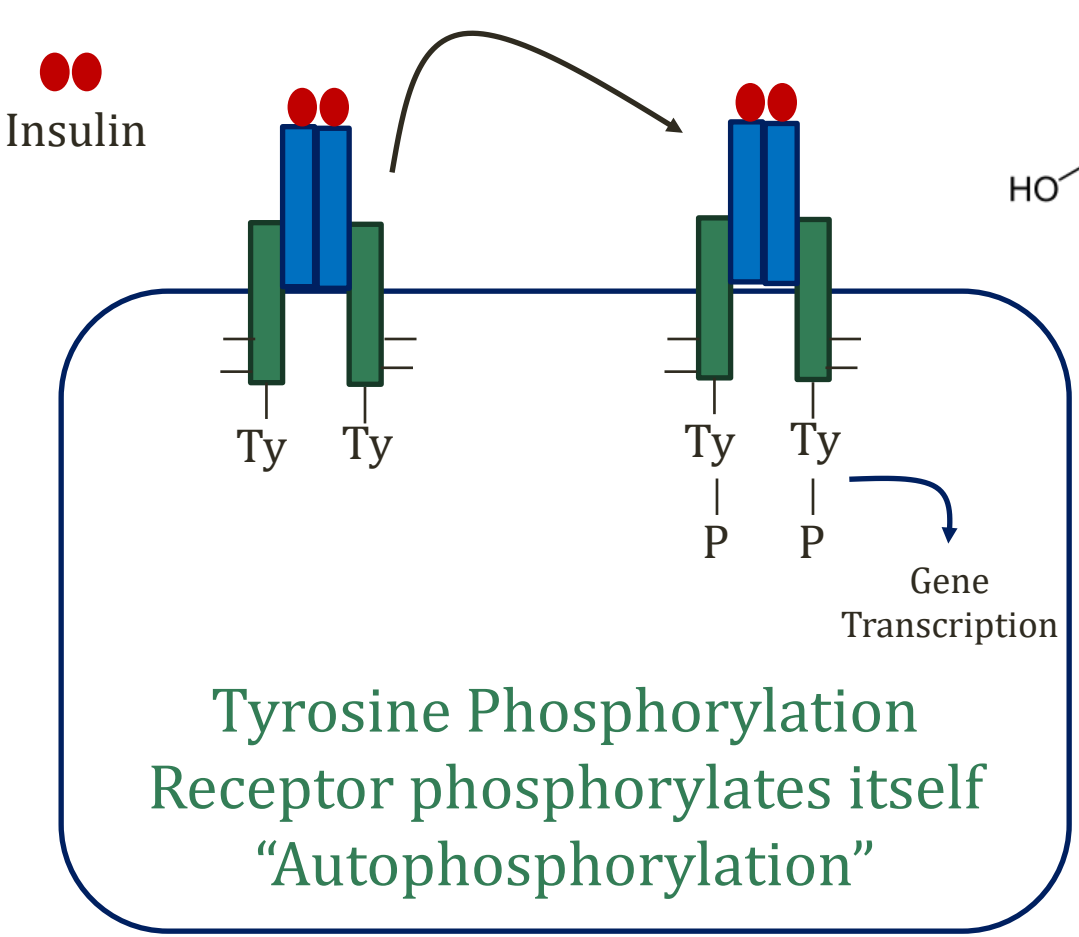
Intracellular Hormones

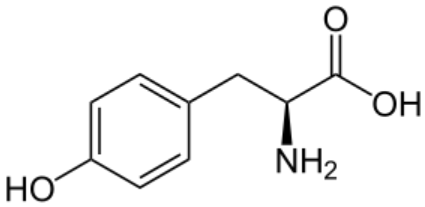
- All circulate **bound to a protein**
- Estrogen/testosterone: sex binding globulin (SBG)
- Thyroid hormone: thyroid binding globulin (TBG)
- Cortisol: corticosteroid-binding globulin (CBG)
  - Aldosterone
  - Progesterone

Extracellular Hormones

- Bind to **surface receptors**
- Use surface receptor to drive cellular changes
  - Tyrosine kinase
  - JAK/STAT
- Use **2nd messengers** to drive cellular changes
  - cAMP
  - cGMP
  - IP3

Receptor Tyrosine Kinase





Tyrosine

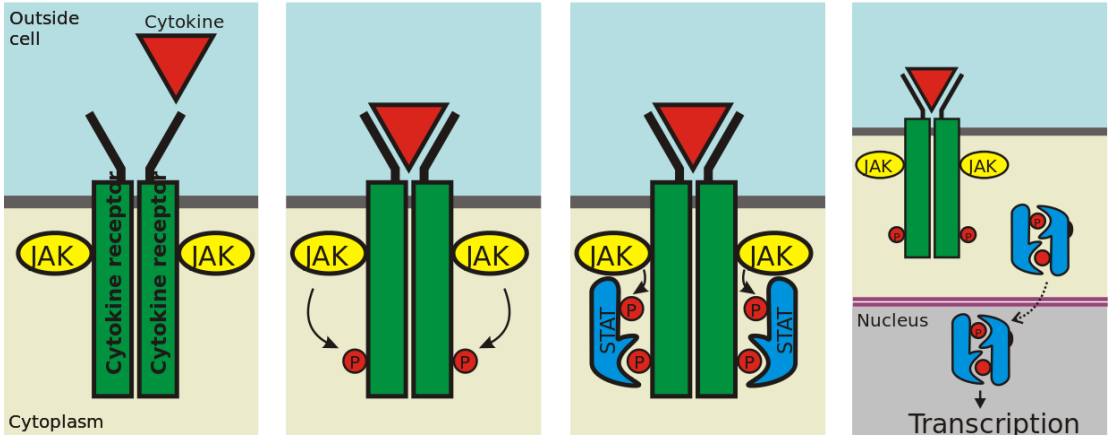
Tyrosine Phosphorylation
Receptor phosphorylates itself
"Autophosphorylation"

Receptor Tyrosine Kinase

- **Insulin**
- **Growth factors**
  - IGF-1 (insulin-like growth factor)
  - FGF (fibroblast growth factor)
  - PDGF (platelet-derived growth factor)
  - EGF (epidermal growth factor)

JAK/STAT

- Janus kinases (JAK)
  - Tyrosine kinase enzymes
- Signal Transducer and Activator of Transcription
  - STAT
  - Protein transcription factors
  - Activated by phosphorylation



Peter Znamenkiy

JAK/STAT

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

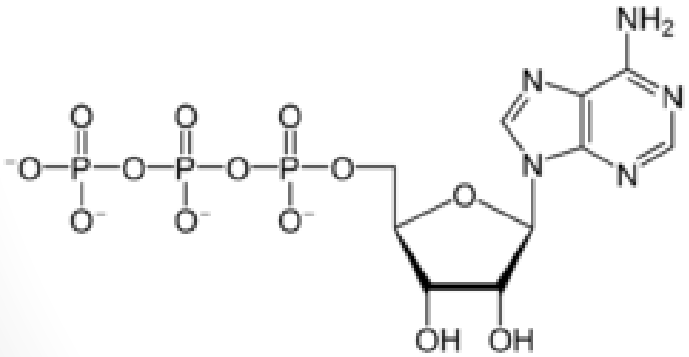
JAK2 Mutation

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

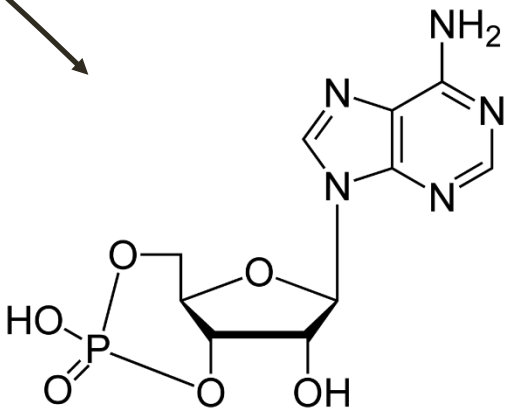
Cyclic AMP

Hormone

Adenylyl Cyclase



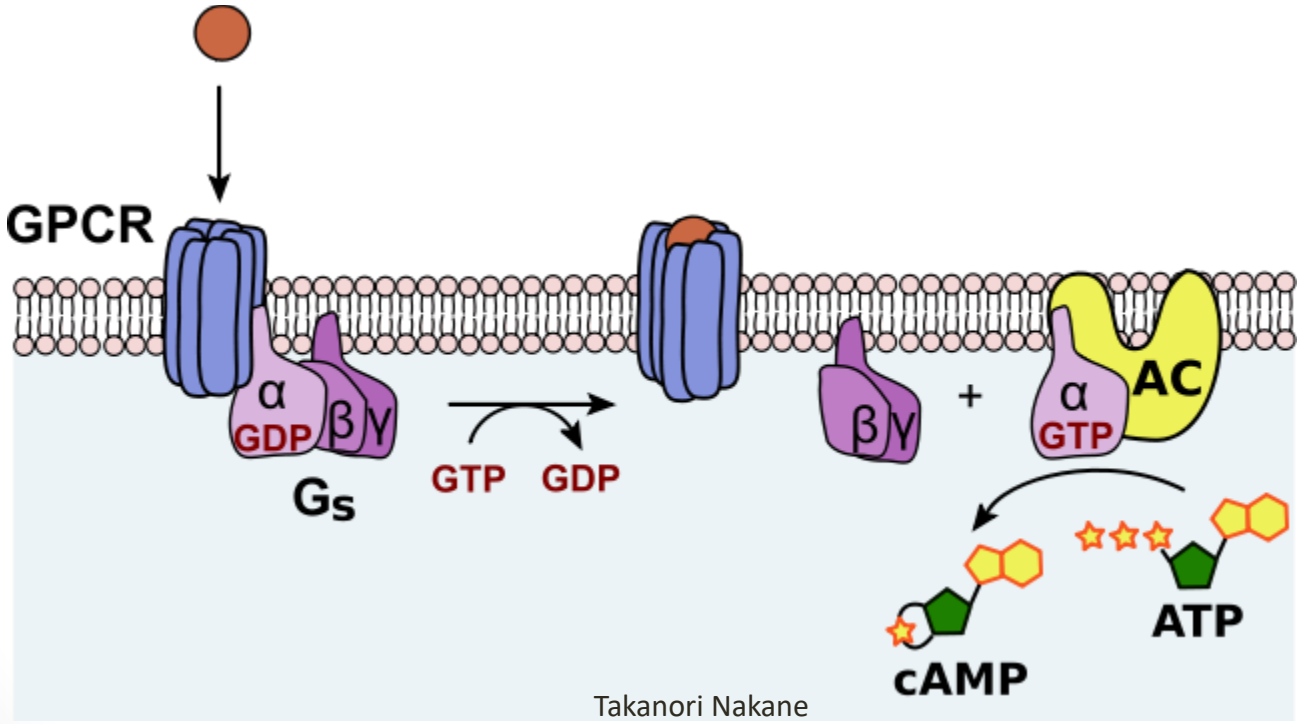
Adenosine Triphosphate



Cyclic Adenosine Monophosphate

G-Protein Linked Receptors

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



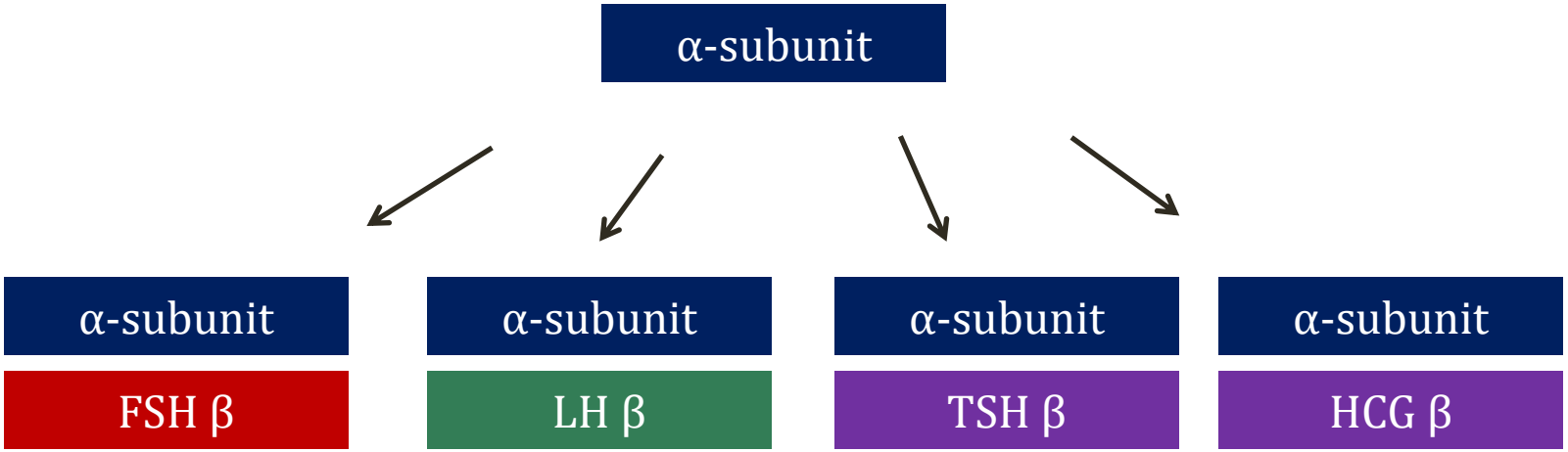
Takanori Nakane

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)

Pituitary Hormones

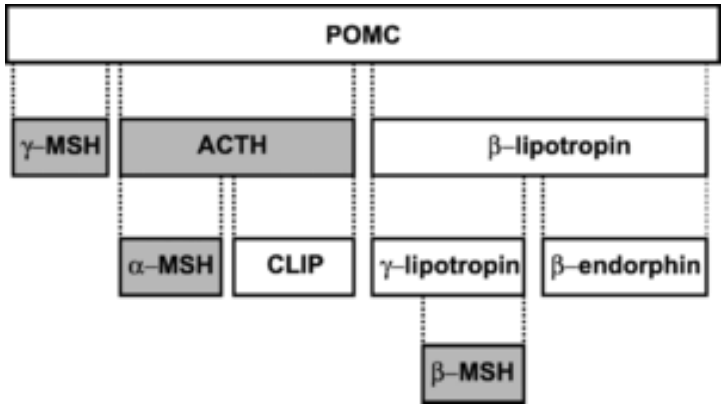
- All have a **cAMP second messenger system**



MSH

Melanocyte Stimulating Hormone

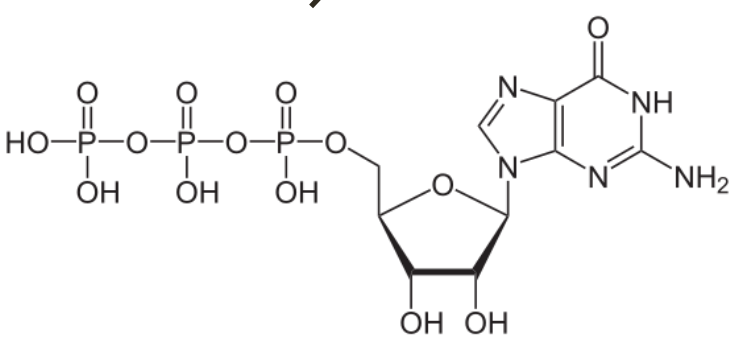
- Causes hyperpigmentation in **Cushing's disease**
- **Proopiomelanocortin**: Precursor of ACTH
- Also precursor of MSH (α/β/γ)
- MSH: Stimulates melanocytes to produce melanin



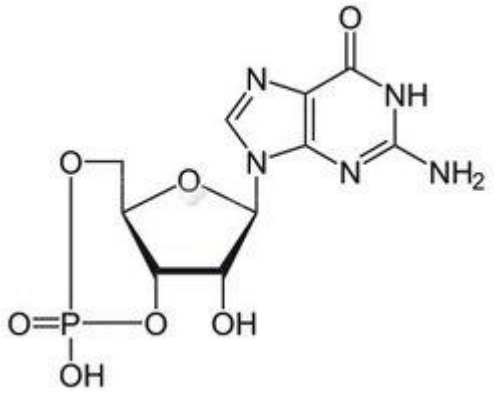
Cyclic GMP

Hormone

Guanylate Cyclase



Guanosine Triphosphate



Cyclic Guanosine Monophosphate

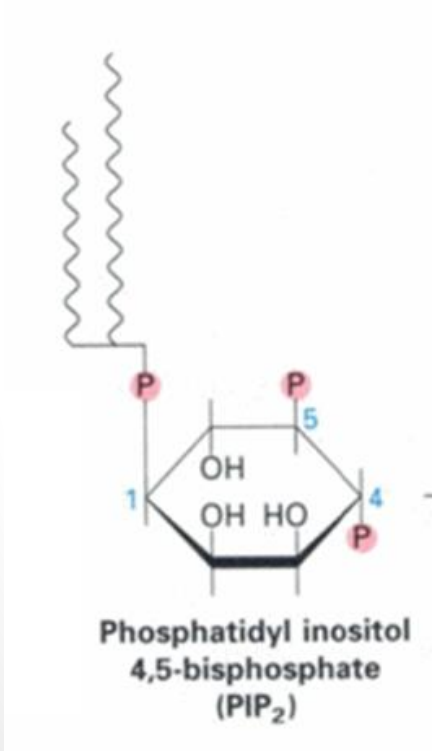
Cyclic GMP

- **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

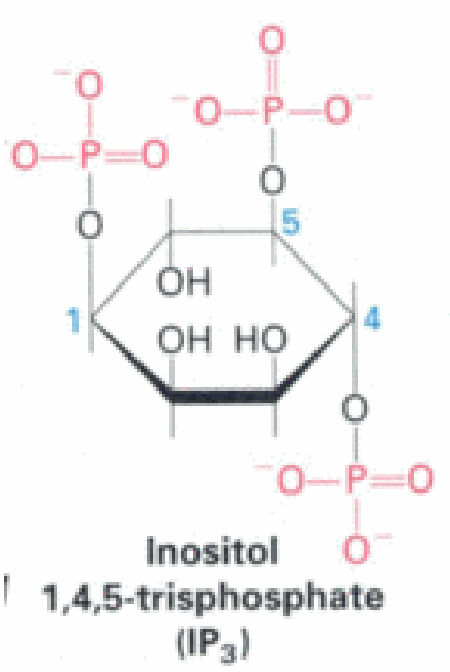
IP3

Hormone



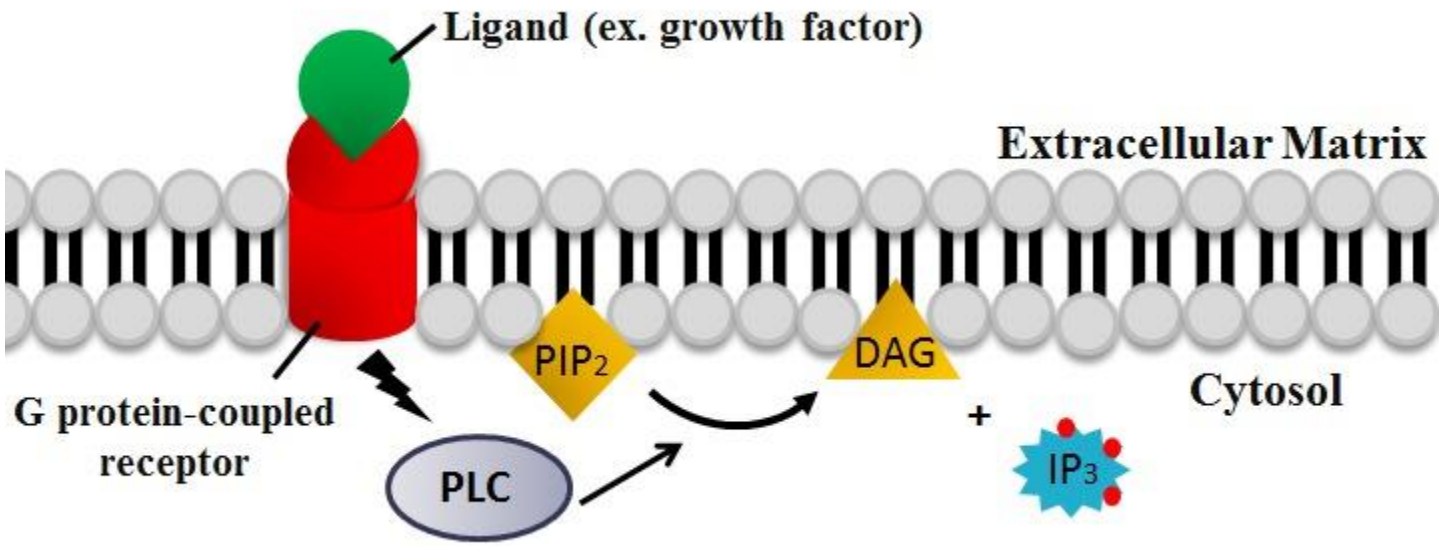
Phosphatidyl inositol
4,5-bisphosphate
(PIP_2)

Phospholipase C



Inositol
1,4,5-trisphosphate
(IP_3)

G-Protein Linked Receptors

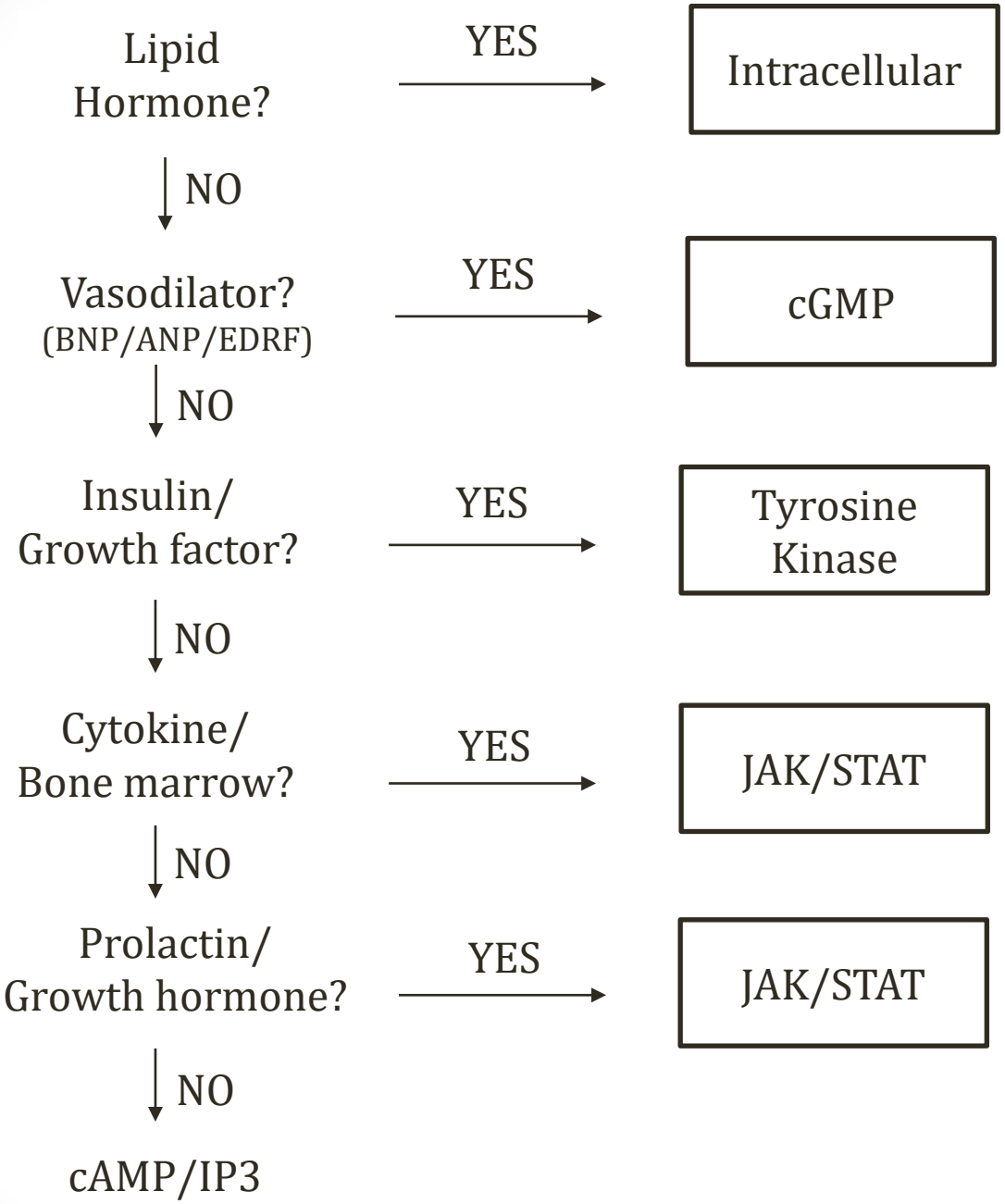


RaihaT

Inositol Triphosphate

IP3

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



Hypothalamus

Hypothalamus	2nd Messenger
Corticotropin-releasing hormone (CRH)	cAMP
Thyrotropin-releasing hormone (TRH)	IP3
Gonadotropin-releasing hormone (GnRH)	IP3
Growth hormone–releasing hormone (GHRH)	cAMP

Anterior Pituitary

Hormone	2nd Messenger
Adrenocorticotropic hormone (ACTH)	cAMP
Thyroid-stimulating hormone (TSH)	cAMP
Luteinizing hormone (LH) Follicle-stimulating hormone (FSH)	cAMP
Growth hormone (GH)	JAK/STAT
Prolactin	JAK/STAT

Others

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