**Hormones-Receptors:**

**Learning Objectives:**
1. Define the properties of hormone-receptor interactions, 
2. Choose a $K_D$ for a hormone receptor interaction and calculate the free hormone concentrations needed to achieve 10 or 90% receptor occupancy, 
3. Identify the major classes of receptors and the features that distinguish them, 
4. Review the G-protein cycle and the effectors that various $\alpha$-subunits modify, 
5. Give examples of the types of signaling processes that modulate cell function following hormone binding, 
6. Describe the mechanism of action of steroid (and thyroid) hormones, 
7. Indicate the common structural and functional properties of receptors for these hormones, 
8. Describe three mechanisms by which cells can reduce their sensitivity to hormones.

### Properties of Hormone-Receptor Interactions:

- **Highly Specific** (circulating hormone concentration $= 10^{-7}$ to $10^{-12} M$)
- **Usually a simple, bimolecular, reversible reaction** ($H + R \rightleftharpoons HR$)
- **Saturable** (normal enzyme binding curve):
  - Maximum hormone binding capacity due to finite numbers of receptors in cells or on their surfaces, there is a maximum hormone binding capacity and $:.$ a maximum biological response.
  - Maximal biological response may equal the percentage of receptors occupied with hormone OR when only a fraction of the receptors are occupied (these spare receptors $\uparrow$ sensitivity of a cell to a given level of hormone)

### CHEMICAL CLASS | HORMONE | MAJOR SOURCE
--- | --- | ---
**Amines** | Dopamine | CNS
 | Norepinephrine | CNS, adrenal medulla
 | Epinephrine | Adrenal medulla
 | Melatonin | Pineal
**Iodothyronines** | Thyroxine ($T_4$) | Thyroid
 | Triiodothyronine | Peripheral tissues (thyroid)
**Small Peptides** | Vasopressin (ADH) | Posterior pituitary
 | Oxytocin | Posterior pituitary
 | Atrial Natriuretic Peptide | Heart
 | Melanocyte Stimulating H. (MSH) | Pars intermedia
 | Angiotensin II | Blood (from precursor)
 | Thyrotropin Releasing H. (TRH) | Hypothalamus, CNS
 | Gonadotropin Releasing H. (GnRH) | Hypothalamus, CNS
 | Growth H. Releasing H. (GHRH) | Hypothalamus, CNS
 | Corticotropin Releasing H. (CRH) | Hypothalamus, CNS
 | Somatostatin | Hypothal., pancreas, gut, other
**Proteins** | Insulin | $\beta$-cells in pancreas
 | Glucagon | $\alpha$-cells in pancreas
 | Growth Hormone (GH) | Anterior pituitary
 | Prolactin (Prl) | Anterior pituitary
 | Parathyroid Hormone (PTH) | Parathyroid glands
 | $\beta$-lipotropin and enkephalin | Pituitary, CNS
 | Calcitonin | C-cells thyroid
 | Adrenocorticotropic H. (ACTH) | Anterior pituitary
 | Secretin | GI tract, CNS
 | Cholecystokinin (CCK) | GI tract, CNS
 | Gastrin | GI tract, CNS
 | Gastric Inhibitory Peptide (GIP) | GI tract
**Glycoproteins** | Follicle Stimulating H. (FSH) | Anterior pituitary
 | Luteinizing H. (LH) | Anterior pituitary
 | Chorionic Gonadotropin (hCG) | Placenta
 | Thyroid Stimulating H. (TSH) | Anterior pituitary
**Steroids** | Estrogens | Ovary, placenta
 | Progesterone | Corpus luteum, placenta
 | Testosterone (T) | Leydig cells in testis
 | Dihydrotestosterone | T sensitive tissues
 | Glucocorticoids | Adrenal cortex
 | Aldosterone | Adrenal cortex
 | Vitamin D metabolites | Skin $\rightarrow$ liver $\rightarrow$ kidney

**CHEMICAL CLASS**

**Hormone**

**MAJOR SOURCE**
• **High Affinity:** Hormone-receptor complexes must form in the presence of very low circulating hormone levels. The equilibrium association constant ($K_A$) must be very high.
  - Given that circulating hormone concentration = $10^{-7} - 10^{-12}M$, the $K_A$ must be $\sim 10^{5} - 10^{12}M^{-1}$ (normally $10^{10}M^{-1}$).
  - Hormone-receptor interactions are often defined by equilibrium dissociation constant ($K_D$ = $1/K_A$)
    - If $K_D$ is $10^{-10}M$ and $[H]$ is also $10^{-10}M$, $[R]/[HR] = 1 := [R] = [HR]$. When $[H] = K_D$, half of the receptors are bound to hormone and half are free.
    - A ten-fold increase in the free hormone concentration above the $K_D$ results in receptor occupancy of roughly 90%. A free hormone concentration that is $1/10^8$ the $K_D$ would result in close to 10% occupancy.

**Binding Occurs in Responsive Tissue:**

**Mechanisms of Hormone Action:**

- **Peptide, Glycoprotein, and Amino Acid Derivative Hormone Receptors:** Peptide hormones and amines are too polar to passively diffuse through lipoprotein membranes and too large to pass through membrane pores. The response is initiated at the outer surface of target cells by binding to glycoprotein receptors anchored within the plasma membrane.
  - **G-Protein Coupled Receptors (7-transmembrane domains):** coupled to membrane associated G-proteins → modulation of effectors ($G_\alpha$=cAMP, $G_\beta\gamma$=ion channels, $G_\gamma$=PLC, $G_\delta$=cGMP).
    - Heterotrimeric G-proteins are comprised of three subunits, $\alpha$, $\beta$ and $\gamma$.
    - The $\alpha$-subunit ($G_\alpha$) is a GTPase (cleaves GTP→ GDP and P.). Products of hydrolysis dissociate very slowly from the $\alpha$-subunit of the heterotrimer in unstimulated cells. $G_\alpha$ is predominately binds GDP in the absence of hormone.
    - In the presence of hormone, the occupied receptor interacts with the G-protein → release of bound GDP, and replacement by GTP → $G_\alpha$ dissociation from the hormone-receptor complex and $\beta\gamma$. $G_\alpha$ interacts with a downstream effector. When GTP is hydrolyzed, $G_\alpha$-GDP dissociates from the effector, activity stops, and $G_\alpha$ reassociates with $\beta\gamma$.

**G-protein Coupling to Adenylate Cyclase ($G_\alpha$):**

- $G_\alpha$-GTP activates adenylate cyclase; $G_\alpha$-GDP does not.
- Activated adenylate cyclase → cAMP → Protein Kinase A (PKA) activation (dissociation of regulatory and catalytic subunits) → phosphorylation of regulatory protein targets.
  - phosphorylation of lipase in epinephrine-stimulated adipocytes → triglyceride hydrolysis.
  - phosphorylation of glycogen synthetase in epinephrine-stimulated liver cells → inhibition of glycogen synthesis.
  - phosphorylation of CREB in nuclei (cyclic AMP response element binding protein) → transcription regulation of nearby genes.

**G-protein Coupling to Phospholipase C ($G_\alpha$):**

- $G_\alpha$ → activation of phospholipase C → cleavage of PIP$_2$ to the intracellular mediators diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP$_3$). IP$_3$ releases Ca$^{2+}$ from vesicular storage sites. DAG associates with and activates protein kinase C (PKC) in the presence of Ca$^{2+}$.
  - PIP$_2$ can also be phosphorylated by PI$_3$-Kinase → phosphatidylinositol 3,4,5-trisphosphate (PIP$_3$) → activation of protein kinases (PDKs) → phosphorylation (activation) of Akt → phosphorylation of target proteins (including transcription factors).

- **Kinase Receptors (single membrane-spanning domains):**
  - **Tyrosine Kinase Receptors:** (insulin, epidermal growth factor, and platelet derived growth factor)
    - Signal transduction requires dimerization of the agonist-receptor complexes and trans-autophosphorylation → phosphorylation of downstream substrates.
  - **Serine/Threonine Kinase Receptors:** (Mullerian inhibitory substance and inhibit)
    - Ligand binding → dimerization and phosphorylation of cytoplasmic substrates (Smads) → translocation to the nucleus → interaction with gene regulatory proteins
  - **Guanylate Cyclase Receptors:** (ANP)
    - Binding of ANP to its receptor → ↑ cytoplasmic levels of cGMP → ↑PKG
  - **Cytokine Receptor Family:** (GH, Prolactin, EPO, other growth factors)
    - Family lacks intrinsic enzymatic activity (no internal kinase domain). They associate with soluble cytoplasmic tyrosine kinases (JAKs) after ligand binding and dimerization. JAKs interact with and are activated by the cytoplasmic domains of the dimerized receptor → phosphorylation of STATs (Signal Transducers and Activators of Transcription) → regulation of transcription of specific genes.
Inhibition of G-Proteins:
Uncoupling of receptor from G-protein occurs in the β-adrenergic system in which phosphorylation of the cytoplasmic domains of the receptor reduces its affinity for G-protein. Phosphorylation is mediated by β-adrenergic receptor kinase, or β-ARK, which associates with free βγ at the membrane and is positioned to phosphorylate the receptor. A cytoplasmic component, β-arrestin, then binds to the phosphorylated receptor and blocks its interaction with G-protein. The higher the hormone concentration, the greater the concentration of βγ in the membrane, and the greater is the potential for desensitization. Phosphorylation of the β receptor by βARK blocks its ability to bind to G-proteins.

- Internalization of hormone-receptor complexes (Receptor Mediated Endocytosis): Hormone-receptor complexes cluster in regions of the membrane called clathrin-coated pits that invaginate and pinch off from the membrane to form coated vesicles. Adaptins, also found in the coat, recognize cytoplasmic domains of the receptors and to trap them within the coated pit. Receptors that are not degraded can be recycled to the cell surface.

- Steroid, Thyroid, Vitamin A, and Vitamin D Receptors:
  - Lipid soluble ligands passively diffuse across cell membranes where they bind to receptors that are located in the cytoplasm or the nucleus of a target cell and form hormone/receptor complexes that bind to DNA. With steroid hormones, DNA binding is preceded by displacement of associated heat shock-like proteins (stabilizing proteins that prevent receptors from interacting with DNA when the ligand is absent). All hormone/receptor complexes dimerize and translocate to the nucleus where they interact with DNA at palindromic hormone response element (HRE) sites → initiation or suppression of transcription of nearby genes under HRE control.
    - Thyroid hormone, Vitamin D, and Vitamin A derivatives associate with hormone response elements even in the absence of hormone.
    - Receptors have three structural domains: (1) a C-terminal hormone binding region, (2) a central, highly conserved DNA binding domain, and (3) a variable N-terminal domain that participates in recruitment of transcription factors.

Regulation of Intracellular Responses: depends on hormone availability and sensitivity of cells to a given hormone
- Factors Influencing Availability of Hormone:
  - Secretion Rate
  - Uptake and Degradation Rate
  - Binding/Plasma Carrier Protein Equilibrium (transport steroids and thyroid hormones).
  - Positive- and Negative-feedback loops
- Factors Influencing Cellular Sensitivity to Hormone:
  - Negative Cooperativity: increasing receptor occupancy decreases the affinity of remaining receptors for hormone
    - Modulates hormone action by providing high cell sensitivity (receptor affinity) at low hormone concentrations and low sensitivity at high hormone concentrations.
  - Down Regulation: exposure to high concentrations of hormone → decrease the number of surface membrane receptors (receptor-mediated endocytosis)

Hormone Inactivation:
- Peptide Hormones: inactivated by proteases on the cell surfaces of target tissues or internalized and transported to lysozymes for degradation
- Steroid Hormones: inactivated in liver where enzymes in the smooth ER convert them to polar derivatives that are filtered but not reabsorbed by the kidney.

Testicular Feminization Syndrome: Failure to synthesize a functional androgen receptor → testis of an XY individual produces testosterone, but target tissues that depend on testosterone for differentiation (vas deferens, seminal vesicles, seminiferous tubules, etc) fail to develop. Dihydrotestosterone (required for differentiation of the prostate and formation of male external genitalia), is also ineffective because it uses the same receptor → birth of a baby that looks like and is raised as a female. At puberty, the pituitary ↑ production of luteinizing hormone (LH) → stimulation of testis to produce more testosterone. The normal regulatory feedback loop (elevated levels of testosterone inhibit further secretion of LH) is inoperative in the absence of a functional testosterone receptor → ↑ testosterone ↑ to abnormally high levels yet secondary male sex characteristics fail to develop. The individual develops a female phenotype because of aromatase-mediated conversion of testosterone to estrogen in peripheral tissues. Testicular Feminization is detected at puberty when menstruation does not occur.

A decrease in response of a cell with β-receptors to a given level of epinephrine could result from ↓ number off- receptors, ↓ affinity of epinephrine and the β-receptor, ↑ amount of arrestin bound to β-receptor, or ↓ cytoplasmic concentration of protein kinase A
Learning Objectives: (1) Describe the structure of the hypothalamus and pituitary and their vascularization, (2) Explain the functional relationship between the hypothalamus and the posterior pituitary, (3) List the major stimuli for the release of anti-diuretic hormone and oxytocin, (4) Explain the functional relationship between the hypothalamus and the anterior pituitary, (5) List the target tissues and major actions of the anterior pituitary hormones, (6) Explain what controls prolactin secretion, (7) List the hypothalamic releasing factors and their targets, (8) Explain the concept of negative- and positive-feedback controls, (9) Describe the major classes of endocrine disorders at the level of the hypothalamus, anterior pituitary and target tissues.

Overview of the Hypothalamic-Pituitary Axis:
• Nervous system: rapidly responding system regulating activities of muscle and secretory cells by means of nerve impulses and neurotransmitters.
• Endocrine system: slower responding system influencing all cells by means of hormones.
  o Hypothalamus: mass of approximately 10g
  o Pituitary Gland: mass of approximately 500mg
    • Posterior Pituitary (neurohypophysis): stores and secretes two hormones that were synthesized in hypothalamus: oxytocin and ADH.
      o Develops from neuroectoderm of the floor of the brain (hypothalamic)
      o Consists of pars nervosa, infundibulum (connecting stalk to the brain), and median eminence (connects the infundibulum to the brain).
    • Anterior Pituitary (adenohypophysis): secretes ACTH, TSH, LH, FSH, GH, and Prolactin.
      o Develops from ectoderm of the roof of the mouth (no connection remains in adults).

Functional Relationship Between the Hypothalamus and the Pituitary:

Posterior Pituitary: Axons with cell bodies in the hypothalamus terminate in a capillary plexus supplied by the inferior hypophyseal artery. Peptide hormones synthesized in these cell bodies travel as neurosecretory granules that are stored in nerve terminals lying in the posterior pituitary and are released into peripheral circulation by nerve impulses transmitted to the posterior pituitary by the hypothalamus. A single cell performs hormone synthesis, storage, and release.

Anterior Pituitary: A collection of endocrine cells regulated by blood-borne stimuli from neural tissue of hypothalamus. Cell bodies of a given hypothalamic neuron synthesizes releasing or inhibiting hormones that are stored in the median eminence near the capillary plexus of the superior hypophyseal artery. Stimulation releasing or inhibiting hormones enter capillary plexus travel down Long Portal Veins to exit from the secondary capillary plexus and reach specific adenohypophyseal endocrine target cells ↑ or ↓ output of tropic hormones peripheral circulation.

Posterior Pituitary Hormones: both hormones are small peptides (9aa), synthesized from pre-pro-hormones with an associated neurophysin region.
• ADH/Arginine Vasopressin: conserves body water and regulates tonicity.
  o Target Cells: renal tubular cells responsible for reabsorbing free water.
    • Water deprivation → ADH secretion ↓ water clearance and ↑ conservation of water.
    • Water load → ↓ ADH secretion and ↑ water clearance.
      • Δ in osmolality is sensed by specialized osmoreceptor neurons with connections to ADH nerve cells.
  o Lack of ADH secretion → diabetes insipidus.
• Oxytocin: ejects milk from lactating mammary glands in the breast via contraction of myoepithelial cells (in response to afferent suckling stimulation) and enhances contraction of smooth muscle of the uterus during parturition (in response to dilation of the cervix).
Anterior Pituitary Hormones:

- **Growth Hormone:** Most abundant pituitary hormone (~40-50% of pituitary cells). Basal plasma basal levels are <5 ng/ml.
  - Growth promoting actions of GH on muscle and the skeleton are insulin-like. GH's long term effects on carbohydrate metabolism and lipolytic effects are opposite to those of insulin.
    - Induces liver and other tissues to secrete Insulin-like Growth Factor I (IGF-I) (somatomedins) - (MW 8000). IGF-I circulates bound to a protein complex (MW 120,000).
    - Prolactin and insulin may stimulate somatmedin release from liver.
  - GH does not regulate a secondary endocrine organ, but GH receptors exist in the adrenal cortex.
  - Release is stimulated by Growth Hormone Releasing Hormone (GHRH – 40-44AA) and is inhibited by Somatostatin.

Since GH is secreted in a pulsatile fashion, measurements of GH at any time point may be meaningless. Provocative tests are usually used to measure GH (administration of an agent known to provoke GH output). If there is a defect in GH synthesis or release, there will be no rise in GH levels after stimulation (e.g. measuring plasma GH levels 20-40 min following strenuous exercise or 60-120 min following administration of arginine. Administration of insulin can also be used to induce brief hypoglycemia, another strong stimulator of GH secretion). Thyroid hormone and cortisol also affect growth at the tissue level. Tests of these hormonal levels are therefore also warranted.

- **Prolactin:** 198AA polypeptide → breast development and milk production (and infertility in excess amounts via inhibition of GnRH) ($t^{1/2} = 20$ minutes)
  - Dopamine tonically inhibits secretion. Stress, exercise, suckling, pregnancy, and estrogen → ↑ secretion. Basal level ↑ with sleep (NO circadian rhythm).
  - Induces synthesis of casein and lactalbumin in mammary glands.
  - Does not regulate a secondary endocrine gland, but receptors for exist in the adrenal cortex.
    - Excess prolactin secretion → galactorrhea (milk discharge from the nipple) and inhibition of GnRH secretion.
  - Prolactin is constitutively released (secretion also ↑ by Thyrotropin Releasing Hormone) and secretion is tonically inhibited by Dopamine :. secretion is ↑ when the vascular connection between the anterior pituitary and the hypothalamus is interrupted.

- **Pro-opiomelanocortin:** stimulates cortisol release by adrenal cortex (ACTH) and melanin synthesis (β-lipotropin)
  - 31,000 MW glycoprotein pro-hormone that is cleaved into β-lipotropin (C-terminus), which contains γ-lipotropin, β-MSH, β-endorphin, γ-endorphin, α-endorphin, and enkephalin. N-terminus has no known function (contains γ-MSH, a possible modulator of mineralocorticoid synthesis).
    - ACTH (39AA): Corticotropin releasing hormone (CRH – 41AA) and ADH ↑ ACTH synthesis and secretion on a circadian rhythm. Hypoglycemia, stress, pyrogen and low glucocorticoid levels ↑ ACTH release. The most important pigmentary hormone.
    - β-lipotropin (91AA): induces pigmentation and may affect adrenal steroid secretion

- **FSH, LH, and TSH:** all share similar α subunits (differ by degree of glycosylation) and β subunits confer specificity.
  - hCG (human chorionic gonadotropin) is a placental glycoprotein hormone with biologic activity indistinguishable from that of LH.
    - $t^{1/2}$ of FSH, LH, and TSH = 30 min – 2 hrs.
    - $t^{1/2}$ hCG = 24-30 hours.
    - Individual subunits are devoid of biologic activity and $t^{1/2} = 10-30$ min.
  - Release of LH and FSH is stimulated by Gonadotropin Releasing Hormone (GnRH), found in the medial hypothalamic nuclei. Response to GnRH is modulated by the sex steroids. High, steady levels (as opposed to cyclical levels) of GnRH block gonadal steroidogenesis
    - GnRH acts via phospholipase C (PLC).
  - Release of TSH and prolactin are stimulated by the triptide Thyrotropin Releasing Hormone (TRH) via phospholipase C.
    - TRH-induced TSH response decreases with age in men but not in women. TRH can be formed in the hypothalamus as well as other locations (CNS)
Feedback Control Mechanisms:

<table>
<thead>
<tr>
<th>Hormone</th>
<th>MW (AA)</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Hormone (GH)</td>
<td>21,700</td>
<td>Hepatocyte. Stimulates somatomedin synthesis. May directly affect lipid, carbohydrate and AA metabolism.</td>
</tr>
<tr>
<td>Prolactin (PRL, hPr)</td>
<td>22,500</td>
<td>Stimulates mammary ductal epithelium to synthesize alpha lactalbumin. Needs supporting hormones: cortisol, progesterone, estrogen, insulin.</td>
</tr>
<tr>
<td>Adrenocorticotropic (ACTH)</td>
<td>4,500</td>
<td>Stimulates adrenal steroidogenesis. Derived from pro-opiomelanocortin (POMC)</td>
</tr>
<tr>
<td>β-Lipotropin (β-LPH)</td>
<td>9,500</td>
<td>Stimulates melanocytes to synthesize melanin. Derived from POMC.</td>
</tr>
<tr>
<td>Thyrotropin (TSH)</td>
<td>30,000</td>
<td>Stimulates thyroid cells to trap iodide and to synthesize and secrete thyroid hormones.</td>
</tr>
<tr>
<td>Luteinizing Hormone (LH)</td>
<td>30,000</td>
<td>Stimulates cells of the theca interna, corpus luteum, and the Leydig cells to synthesize sex steroid hormones.</td>
</tr>
<tr>
<td>Follicle Stimulating Hormone</td>
<td>30,000</td>
<td>Stimulates proliferation of granulosa cells in the ovary; binds to Sertoli cells in the seminiferous tubules to induce spermatogenesis and stimulates androgen binding protein (ABP) synthesis.</td>
</tr>
</tbody>
</table>

Endocrine Disorders:

- **Hyposecretion**:
  - **Primary**: endocrine target gland secretes too little hormone due to abnormal function (e.g. ↓ cortisol secretion by adrenal gland because of the genetic absence of a steroid-forming enzyme, or ↓ secretion of thyroid hormones by thyroid gland due to lack of iodine).
  - **Secondary**: endocrine target gland is normal but its tropic hormone (pituitary) is abnormally low (e.g. hyposecretion of thyroid hormone due to ↓ TSH secretion by pituitary).

- **Hypersecretion**:
  - **Primary**: A dysfunctional gland secretes excess hormone (e.g. a tumor of the source gland)
  - **Secondary**: Excessive stimulation by a tropic hormone.
• **Hyporesponsiveness:** the target cells do not respond to the third hormone. In hyporesponsiveness the plasma hormone concentration is normal or elevated, but the response to administered hormone is low.
  - Lack or deficiency of receptors for the hormone: e.g. type II diabetes (insulin is produced but few insulin receptors exist).
  - Post-receptor defect in target cells: Normal activated receptor is unable to cause downstream signal transduction
  - Lack of metabolic activation of a hormone: e.g. normal secretion of testosterone (T) and normal T receptors and dihydrotestosterone (DHT), but lack of enzyme (5α-reductase) that converts T → DHT (results in a lack of virilization of the urogenital sinus and the external genitalia during embryogenesis - **congenital 5α-reductase deficiency**).

**Overview:** Complex process driven by growth hormone (absolutely required). Other (permissive) contributors include: thyroid hormones, androgens, estrogens, glucocorticoids, insulin, parental height, nutrition, and psychological stress.

**Learning Objectives:** (1) Describe the effects of growth hormone and its relationship to insulin-like growth factors, (2) Explain the control of growth hormone secretion, (3) Describe the effects of other hormones on growth.

**Growth Hormone:** attainment of adult height is absolutely dependent on GH.

- GH acts by stimulating mitosis of target tissues, including:
  - promotion of bone lengthening by maturation of mitosis of chondrocytes (lay down new cartilage)
  - stimulation of gluconeogenesis (↑ hepatic glucose output and ↓ glucose uptake – anti-insulin)
  - stimulation of lipolysis (↑ fat metabolism)
  - promotion of protein synthesis (↑ amino acid uptake) → tissue enlargement.

**Somatomedin Mechanisms:**
- GH mediates polypeptides IGF-I and –II, and somatomedin C synthesis and local release by the liver (primary source) and other tissues .: Plasma [IGF-I] reflects availability of GH and/or rate of growth.
  - e.g. rapidly-growing children have higher than average concentrations of IGF-I, whereas slow-growing children have lower values.
  - IGF-I regulates GH secretion by negative feedback.
- Children or adults who are resistant to GH (receptor defect) have low concentrations of IGF-I despite high concentrations of GH (growth is restored to nearly normal rates following daily administration of IGF-I).
  - IGF-I is the most important mediator of the actions of GH. IGF-II is more involved during fetal development (along with insulin)
    - IGF-I stimulates cell division in cartilage and many other tissues
    - IGF-I acts locally in an autocrine/paracrine manner to stimulate cell division and bone growth (: IGF-I in the circulation plays only a minor role in stimulating growth). IGF-I and II are present in blood at high concentrations throughout life and circulate tightly bound to IGF binding proteins.
      - t1/2 IGF-I = 15 hours.

**Regulation of GH Secretion:** GH is secreted in episodic bursts (largest secretion in early hours of sleep) .: the most meaningful diagnostic evaluation is to obtain a 24-hour integrated concentration of GH in blood

- Males secrete most GH during sleep (deep slow wave period)
- Females secrete more GH during the day (more frequent and higher amplitude pulses)

**Thyroid Hormones:** Growth is stunted in children with thyroid hormone deficiency (due to ↓ GH synthesis and ↓ GHRH receptors on somatotropes). Treatment of hypothyroid children with thyroid hormones results in rapid growth and maturation of bone. Thyroid hormones have little growth-promoting effect in the absence of GH.

**Insulin:** The primary growth-promoting hormone during fetal development (insulin activates IGF-I receptors). Insulin is required to maintain normal growth during postnatal life (permissive), but insulin cannot sustain normal growth in the absence of GH.
**Gonadal Hormones (Pubertal Growth Spurt & pituitary sensitivity to GnRH):** Beginning of sexual maturation and dramatic acceleration of growth occur together (growth curves are similar in boys and girls, but girls begin earlier in life). The growth spurt is due to sex steroids (produced in the gonads and the adrenals).

- **Estrogens** (not androgens) are responsible for the aforementioned processes…
  - Aromatase-deficient children do not experience pubertal growth (but have ↑ levels of androgens). Estrogen increases in the plasma of both girls and boys early in puberty.
  - Most of ↑ height stimulated by estrogen (or androgens) at puberty is due to ↑ secretion of GH and ↓ IGF-1.
    - Short stature of Pygmies is due to a genetic inability to produce IGF-1 (normal GH and IGF-1 levels before puberty, but have no IGF-1 ↑ during puberty and ↓ no pubertal growth spurt.
- **Glucocorticoids:** required for synthesis of GH and normal growth. Excess glucocorticoids → ↓ GH secretion (glucocorticoids also antagonize the effects of GH).

**Genetics and Target Height:** Mid-parental height is a mean of individual parental heights. 2.5 inches are added to predict male percentile value and 2.5 inches are subtracted to predict female percentile value. This gives a target height. Two SDs (~4 inches) are plotted above and below (target height is ~ 50th percentile for a given family).

**Extremes of GH Secretion:**
- Hypersecretion (pituitary tumor) in children → gigantism
- Hypersecretion (pituitary tumor) in adults → acromegaly (disfiguring bone thickening – bone cannot grow longitudinally once epiphyseal plates have closed – enlargement of hands and feet, protrusion of lower jaw, and ↑ body hair).
- Hyposecretion in children → stunted growth
  - Normal secretion and malnutrition in children → stunted growth

**Combined Pituitary Hormone Deficiency (CPHD):** deficits in formation of the somatotropes and gonadotropes. Can arise from range of causes such as tumor, surgery, trauma, or genetic defects (in one of several transcription factors responsible for anterior pituitary development) → selective combinations of deficits in hormone output from the pituitary depending on the cell types affected. [Failure of gonadotropes may → ↓ Testosterone levels → ↓ LH and FSH were low (Even after injection of GnRH, the patient will show prepubertal levels of LH and FSH) ↓. Testosterone and GH can be provided pharmacologically, bypassing the pituitary deficit.]

**Acromegaly:** (↑ IGF-1, ↑ glucose after meals, ↓ TSH) Symptoms: retro-orbital headache, diplopia (double vision), enlargement of hands, feet, nose, lips, tongue, and jaw, ↓ libido, beard growth, and pubic/axillary growth (due to ↓ FSH/LH and ↓ T), slow DTRs, fatigue and cold intolerance (↓ TSH). Blood Values: plasma cortisol ↓ (↓ ACTH), plasma growth hormone ↑, serum thyroxine ↓, serum testosterone ↓
- Post-pubertal GH hyperfunctional state commonly caused by a tumor (adenoma of anterior pituitary in adults who’s growth begins after epiphyseal plates are closed). If such a tumor arose before puberty → extended long bone growth → gigantism. ↑ GH → flat bones thicken and tissues grow. Slow progress ↓ often missed or misdiagnosed in early stages. Glucose tolerance test is diagnostic (In a normal individual, there is almost complete cessation of any GH secretion under ↑ blood glucose, whereas in an acromegalic, plasma GH levels remain elevated). Adrenal, thyroid, and reproductive hormone systems are compromised by a tumor impinging on pituitary cells. GH → ↑ blood sugar (counter-insulin effect) → glucose intolerance (if chronically high GH secretion). Body tries to compensate by ↑ insulin production → hyperinsulinemia → insulin resistance and clinical diabetes in some cases. Treatment: transphenoidal surgery to remove the adenoma. Or treatment with somatostatin analogs to shrink the tumor before surgery. Radiation therapy can be used if the surgical tumor removal is incomplete and if medications are ineffective.

**Diabetes Insipidus:** - production of large amounts of hypotonic urine due to ↓ ADH production. Urine osmolality is very low (few electrolytes). Plasma Na⁺ concentration ↑ (excessive water loss → hyperosmotic plasma with hyponatremia. Prolonged flow can continue to sweep out sodium, even at low concentration → hyponatremia. Excessive water loss → ↓ total body water → ↓ blood pressure (postural hypotension) → tachycardia (baroreceptors sense ↓ BP and respond by ↑ heart rate). Hyperosmotic plasma and ECF → ↑ thirst and drinking (polydypsia). 5% dextrose (isosmotic) is used to replace lost water (hyposmotic fluids would lyse cells).
Dextrose is metabolized (leaves water behind without ↑ electrolytes). ADH can also be administered IV or trans-nasally → normal water retention.

**Adrenal**

**Learning Objectives:** (1) Describe location, structure and organization of adrenal gland, (2) Indicate how the general structure of cortical hormones dictates their physical characteristics, and how these dictate many (3) functional characteristics, (4) Describe the synthesis, transportation and mode of action of the cortical hormones, (5) Compare the regulation, transportation and effects of glucocorticoids, mineralocorticoids and adrenal androgens, (6) Relate the functions of mineralocorticoids and glucocorticoids to the symptoms and signs of excesses and deficits in these hormones, (7) Describe the synthesis and metabolism of adrenal catecholamines, (8) Describe regulation of secretion, transportation and modes of action of catecholamines.

**Overview and Development:**

- **Pair of glands (5g each)**
- **Morphologically and embryologically distinct outer adrenal cortex (90% of adrenal mass) producing steroid hormones and inner adrenal medulla producing Epi and NE**
- **Richly vascularized with arterial blood flow to both the cortex and medulla. Blood flowing from the cortex drains into medullary capillary sinusoids . blood supply to medulla is rich in cortical hormones.**
- **Loss of the adrenal cortex by disease or surgery results in death within 1-2 weeks without replacement treatment. Every organ system is affected but the most likely cause of death is circulatory collapse resulting from sodium depletion (if caloric intake is limited, death may result from hypoglycemia.)**

**Adrenal Cortex:**

- **Fetal Adrenal Gland:** significantly larger than adult adrenal with a fetal zone (steroidogenic area – producing DHEA). After birth, the fetal zone disappears and leads to the definitive cortex.
- **Adrenal Medulla:** Neuroectoderm in origin and is innervated by the paravertebral sympathetic ganglia → splanchnic nerves. Medulla stores 5-6mgs of Epi and NE in secretory granules (chromaffin cells). **Survival without the adrenal medulla is possible as long as the rest of the sympathetic system is functional.**
- **Adrenal Cortex:** produces adrenocortical hormones (glucocorticoids – Cortisol - and mineralocorticoids – Aldosterone)
  - **Zona Glomerulosa:** produces aldosterone (contains A-II and ACTH receptors)
  - **Zona Fasciculata:** produces cortisol
  - **Zona Reticularis:** produces cortisol and androgens (dehydroepiandosterone and androstenedione)

**Adrenocorticoids:**

- **Overview:**
  - All adrenal cortical hormones derive from cholesterol (∴ all have similar hormonal structures - hydrophobic, require carrier proteins, enter cells by diffusely crossing the plasma membrane – and relatively minor differences provide specificity).
  - The specific product of a given cell depends on the enzymes within that cell and its responsiveness to different stimuli.
  - The rate-limiting step in synthesis is the first, from **cholesterol to pregnenolone,** which is common to all members of this class of hormone.

This step is regulated by stimulatory factors that promote production of **Steroid Acute Regulatory Protein (StAR),** which stimulates the transport of cholesterol from the cytosol into the mitochondria where it can be acted on by the first enzyme in the initial common pathway to yield pregnenolone.

- Mineralocorticoid activity is predominantly associated with aldosterone and glucocorticoid activity with cortisol, high levels of each will produce the alternate effect.
  - Cortisol has 10x the glucocorticoid effect of aldosterone.
  - Cortisol has 0.25% of the mineralocorticoid effect of aldosterone.
  - Cortisol readily binds mineralocorticoid receptor proteins, but **type II 11β-hydroxysteroid dehydrogenase (which converts cortisol to cortisone) is found in mineralocorticoid sensitive tissues.
- Action of Steroid Hormones:

Free steroid hormones enter cells by passive diffusion and bind cytoplasmic receptor proteins. Dimerization occurs, heat-shock stabilization proteins dissociate and binding to SREs occurs. In the cytosol, mineralocorticoids bind preferentially to type I receptors (kidney, colon, sweat and salivary glands) and glucocorticoids bind preferentially to type II receptors (various tissues).

Regulation of Cortisol and Adrenal Androgen Production by ACTH:

- ACTH is derived from proopiomelanocortin (POMC) in the pituitary.
- In the absence of ACTH, the zona fasciculata and zona reticularis atrophy (ACTH binds to specific receptors in all three layers of the adrenal cortex).
  - In the zona glomerulosa, ACTH has a minor role in influencing production of aldosterone (prime regulator is angiotensin II).
- Circulating levels of ACTH are the controlling factor for cortisol and androgens (via an ↑ cAMP → production of StAR protein → entry of cholesterol into mitochondria → conversion of cholesterol to pregnenolone). Stimulation by ACTH leads to ↑ steroid hormone secretion within 1-2 minutes, peaking in ~15 minutes.
  - Production of ACTH is controlled by corticotrophin releasing hormone (CRH) from the hypothalamus.
    - Secretion of CRH by the hypothalamus and ↓ ACTH by the pituitary follows a circadian rhythm (peak rate of ACTH secretion in early AM) and a steady decline through to PM.
    - Cortisol secretion parallels Δ ACTH.
      - Circadian rhythm is the result of Δ in sensitivity of the CRH secreting cells to cortisol
        - Low sensitivity to cortisol in the morning hours → less negative feedback ↓: higher rates of CRH secretion ↓: higher basal ACTH production ↓: ↑ cortisol secretion). ↑ sensitivity during the course of the day → ↓ CRH, ↓ ACTH and ↓ cortisol levels.
      - Stressful stimuli → ↑ CRH secretion over-riding the diurnal rhythm. Chronic stress leads to establishment of a new steady state production of ACTH and cortisol.

- Function of Cortisol: The Stress Hormone - permissive maintenance of vital functions during periods of prolonged stress and containment of the inflammatory response.
  - ↑ Cortisol leads to:  

<table>
<thead>
<tr>
<th>Class</th>
<th>Steroid</th>
<th>Secretion Rate</th>
<th>Plasma Conc.</th>
<th>% Bound</th>
<th>t½</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoid</td>
<td>Cortisol</td>
<td>20mg/day</td>
<td>40-180ng/ml</td>
<td>~95%</td>
<td>90 min</td>
</tr>
<tr>
<td>Mineralocorticoid</td>
<td>Aldo.</td>
<td>0.25mg/day</td>
<td>0.25ng/ml</td>
<td>40% - albumin 20% - CBG</td>
<td>30 min</td>
</tr>
<tr>
<td>Androgen</td>
<td>DHEA</td>
<td>10-20mg/day</td>
<td>2-8ng/ml</td>
<td>~98% (sulfonated and bound to albumin)</td>
<td>20-30min</td>
</tr>
<tr>
<td></td>
<td>DHEA-S</td>
<td>N/A</td>
<td>400-1200ng/ml</td>
<td>~90%</td>
<td>10-20 hours</td>
</tr>
<tr>
<td></td>
<td>Andro.</td>
<td>2-3mg/day</td>
<td>1-2ng/ml</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

In 21-hydroxylase deficiency, cortisol and aldosterone are not made negative feedback loops are broken down and androgens accumulate from continued synthesis of pregnenolone and other progesterone precursors. In males this has little effect. In females, masculinizing effects are seen (Congential Adrenal Hyperplasia) – salt wasting is also seen as Na⁺ uptake is severely limited.
- **↑ Blood Glucose** (by mechanisms which oppose insulin).
- **↑ Catabolism** (by facilitating breakdown of protein from muscle and connective tissue to free amino acids for gluconeogenesis. Also stimulates production of gluconeogenic enzymes in liver).
- **↓ Glucose Use** (by inhibiting glucose transport into cells (but not in the brain)).
- **↓ Protein Synthesis** (by reducing rates of protein synthesis everywhere except in liver → ↑ plasma amino acid levels)
- **↑ Breakdown of Peripheral Fat** to liberate fatty acids and glycerol for gluconeogenesis.
- **↑ central fat deposition** (trunk and face)
- **CNS:**
  - Feedback inhibition of CRH and ACTH production
  - Initial euphoria followed by depression
- **↓ bone mass** → early osteoporosis
- **Immune Function:** contains inflammatory response
  - stabilizes lysosomal membranes (prevents release of degradative enzymes)
  - ↓ capillary permeability (↓ edema)
  - ↓ phagocyte activity
  - ↓ synthesis of IL-1
  - ↓ production of eicosanoids
  - ↓ release of histamine from mast cells in the lung

**↓ Cortisol leads to:**
- **CNS:**
  - Taste and smell are accentuated
- **Cardiovascular:**
  - Widespread vasodilation and ↓ blood pressure – cortisol is required to maintain sensitivity to epinephrine and norepinephrine
- **Renal:** in absence of cortisol, patient cannot produce hypotonic urine ∴ cannot eliminate free H₂O (↓GFR) → H₂O intoxication as ADH secretion is not suppressed by hyposmolality in the absence of cortisol.
  - Permissive role in maturation of many fetal organ systems, intestinal enzymes and pulmonary surfactant.

- **Pharmacological Administration of Glucocorticoids:** prolonged administration of pharmacological glucocorticoids → feedback inhibition of ACTH → atrophy of dependent adrenal cells (zona fasciculata and zona reticularis) → ↓ ability to generate cortisol. Withdrawal from treatment must ∴ be gradual to permit recovery of the patient's own cortisol generating system.

- **Elimination of cortisol from the body:**
  - Filtered in the glomerulus → urine.
  - Cortisol is also enzymically reduced in the liver→ tetrahydrocortisol and conjugated with glucuronic acid (filtered at the kidney and excreted in the urine as glucuronide metabolites).

**Adrenal Androgens:** Produced in large quantities in fetus and are important for fetal development. Adrenal androgen production ↑ during prepubertal period (adrenarche) and contributes to puberty.

- **Females:** adrenals are major source of androgens
  - after conversion into testosterone (source of 50% of testosterone in women) in the periphery (aromatase)→ stimulation of axillary and pubic hair growth.
  - Androstenedione is converted in the periphery to estrogen (the major source of this hormone in post-menopausal women)
    - DHEA levels may have an influence on libido in women.
  - **Males:** DHEA is insignificant (source of 5% of testosterone) in comparison to testosterone (produced in the testes ~ 95%), and dihydrotestosterone (produced from testosterone in the testes and peripherally).
  - **Levels of DHEA production are close to those of cortisol in young adults and ↓ with age.**
    - Adrenal androgen production is under the control of ACTH (no negative feedback loop).
    - Free DHEA-S in plasma is filtered in the kidney and excreted in the urine (in the sulfated form).

**Aldosterone:** primary function of aldosterone is to ↑ Na⁺ reabsorption in the distal nephron and ↑ K⁺ excretion
- production is under the control of A-II, plasma K⁺ and ACTH
  - A-II is produced in response to ↑ renin, which cleaves circulating angiotensinogen to produce A-I (which is converted into A-II by converting enzyme in the lung). Renin release ↑ by ↓ perfusion pressure at the afferent arterioles or by sympathetic stimulation via the renal nerve.
- Angiotensin II stimulates production of aldosterone by the cells of the zona glomerulosa via a receptor-mediated \( \uparrow \) in inositol 1,4,5 triphosphate (IP\(_3\)) \( \rightarrow \) \( \uparrow \) STAR protein \( \rightarrow \) entry of cholesterol into the mitochondria \( \rightarrow \) conversion of cholesterol to pregnenolone \( \rightarrow \) synthetic pathway.
  - Aldosterone levels are \( \uparrow \) by elevated estrogen (pregnancy), following an estrogen-stimulated \( \uparrow \) in hepatic synthesis of angiotensinogen.

**Adrenal Medulla: Catecholamines**
- Medullary cells are modified postganglionic neurons (chromaffin cells).
  - Innervation is via splanchnic nerves (paravertebral sympathetic ganglion)
- Chromaffin granules contain stored catecholamines (5 epinephrine : 1 norepinephrine). ATP is present in a ratio of 1 ATP : 4 catecholamines. Enkephalin, \( \beta \)-endorphin and precursors are present in small amounts
- **Biosynthesis of Catecholamines:**
  - Tyrosine \( \rightarrow \) DOPA \( \rightarrow \) Dopamine \( \rightarrow \) Norepinephrine \( \rightarrow \) Epinephrine (via PMNT - phenylethanolamine-N-methyltransferase). PMNT conversion of NE \( \rightarrow \) E is partly induced by cortisol.
  - Chromaffin granules are secreted in response to sympathetic cholinergic stimulation (binding of acetylcholine to the chromaffin cells \( \rightarrow \) \( \uparrow \) intracellular calcium levels \( \rightarrow \) exocytosis).
    - 50% of catecholamines are free in solution and 50% are loosely associated with albumin.
    - Rapidly cleared from the circulation \( t^{1/2} = 10-15 \) seconds). \(~90\%\) is cleared on a single pass through microvasculature.
      - Catecholamines taken up by neurons are repackaged for reuse or are degraded monoamine oxidase (MAO).
      - Catecholamines are also inactivated enzymically by MAO and catecholamine-O-methyl transferase.
  - Products of degradation are coupled with sulfate or glucuronic acid and excreted in the urine (Vanillyl Mandelic Acid, Metenephrine, or Normetanephrine).
    - All Epinephrine in circulation is adrenal in origin.
    - Much of circulating NE arises by diffusion from sympathetic synapses elsewhere in the body.
- **Function of Catecholamines:**
  - E and NE are equally effective in stimulating \( \beta 1 \) receptors.
  - NE is a potent \( \alpha \) agonist and has little effect on \( \beta 2 \) receptors.
  - E is an even more powerful \( \alpha \) agonist in many organs and is a powerful \( \beta 2 \) agonist.

**Prednisone:** a pure glucocorticoid that has little mineralocorticoid effect (even at the high concentrations used pharmaceutically). Glucocorticoid potency is 4x that of cortisol. Circulating prednisone (acts as cortisol) \( \rightarrow \) negative feedback \( \downarrow \) release of CRH and ACTH \( \rightarrow \) effect of long-term treatment removal of trophic stimulation (ACTH) on growth and maintenance of the zona reticularis and zona fasciculate (atrophy). After one year there is little remaining endogenous glucocorticoid function. Prednisone treatment \( \rightarrow \) symptoms associated with Cushing’s syndrome (manifestations of excess glucocorticoid activity from any cause): development of a “moon face,” “buffalo hump,” and truncal obesity (all from central fat deposition), easy bruising (loss of connective tissue supporting the microvasculature), immune function \( \downarrow \), blood glucose \( \uparrow \) (may \( \rightarrow \) diabetes mellitus), blood pressure \( \uparrow \) (due to \( \uparrow \) cardiovascular responsiveness to catecholamines), \( \downarrow \) renal calcium reabsorption and GI uptake of calcium \( \rightarrow \) \( \downarrow \) plasma calcium \( \rightarrow \) \( \uparrow \) PTH \( \rightarrow \) osteoporosis susceptibility. GI secretions are promoted by glucocorticoids (excess may \( \rightarrow \) GI ulcers), initial euphoria (followed by long term depression), sleep disturbances, and impaired memory. Rapid removal of treatment \( \rightarrow \) little or no circulating glucocorticoid (endogenous machinery is atrophied and non-functional) \( \rightarrow \) life-threatening adrenal insufficiency (with a high susceptibility to hypoglycemia if caloric intake is restricted) \( \rightarrow \) removal from glucocorticoid treatment must be staggered to allow normal function to return in response to stimulation from rising ACTH levels as the exogenous glucocorticoid is reduced (can take months).

**Addison’s Disease (1° hyposecretion):** the adrenal gland is being destroyed by a recurrence of an earlier infection with tuberculosis \( \rightarrow \) inability to produce aldosterone \( \rightarrow \) \( \uparrow \) renal Na\(^+\) loss, hypovolumia, hypotension, and tachycardia, cortisol, and adrenal androgens. Renin, AIJ, and ACTH are all \( \uparrow \). \( \uparrow \) ACTH can have MSH (melanocyte stimulating hormone) effects \( \rightarrow \) hyperpigmentation; \( \downarrow \) cortisol and aldosterone \( \rightarrow \) \( \uparrow \) ADH levels (because of hypovolemia and \( \uparrow \) CRH) \( \rightarrow \) sodium loss disproportionately more than water \( \rightarrow \) \( \downarrow \) free water clearance \( \rightarrow \) hyponatremia and hyperkalemia \( \rightarrow \) \( \downarrow \) GFR (\( \uparrow \) creatinine; BUN \( \uparrow \) with \( \downarrow \) GFR, but \( \downarrow \) in response to \( \downarrow \) protein breakdown (due to \( \downarrow \) cortisol). May \( \rightarrow \) hyperpigmentation, \( \uparrow \) BUN, \( \uparrow \) A-II, \( \downarrow \) \( C_{H_2O} \)

**Cushing’s Disease (2° Cortisol Hypersecretion):** an ACTH secreting pituitary adenoma \( \rightarrow \) symptoms of hypercortisolemia and androgen excess. A 24-hour urine free cortisol measurement \( \rightarrow \) \( \uparrow \) circulating cortisol (indicative of Cushing’s syndrome). Hypercortisolism can result from a cortisol secreting tumor in the adrenal (but would lead to depressed ACTH - primary hypercortisolism) \( \rightarrow \) ACTH secreting tumors (secondary hypersecretion of cortisol) are most commonly (80-90%) non-cancerous adenomas in the pituitary, (5x more frequently in women). Tumors outside the pituitary (often lung cancer) can lead to ectopic ACTH production (3x more common in men).
Ingest more calories than are necessary for our metabolic needs. Extra calories are stored in the form of fat, carbohydrate, or protein.

**Dexamethasone suppression test:** Administration of dexamethasone (synthetic glucocorticoid) normally ↓ endogenous cortisol production (negative feedback), by ↓ ACTH production. In people with an ACTH secreting tumor, a low dose of Dex will have little effect. **CRH stimulation test:** Administration of CRH can also be used to distinguish pituitary from ectopic tumors. CRH increases ACTH secretion from a pituitary tumor (∴ ↑ cortisol to even higher levels) but ectopic tumors do not have CRH receptors. Do not respond to CRH. ACTH is measured directly in plasma by radioimmunoassay, or by provocative tests (CRH stimulation). **Inferior Petrosal Sinus Sampling:** If the tumor is in the pituitary the blood in the sinus will be enriched in ACTH compared to blood from the forearm, especially after CRH administration. For an ectopic tumor the ACTH will usually be the same at both sites.

**11β Hydroxysteroid Dehydrogenase–II Deficiency - Hyperaldosteronism:** ↓ renin and ↓ aldosterone. Cortisol:cortisone is ~ 50:1 (normally 1:1) ➝ **Apparent Mineralocorticoid Excess (AME)** as cortisol is not converted to cortison (gives the symptoms of hyperaldosteronism: ↑ Aldosterone hypersecretion – Conn’s Disease - ↑ Na⁺, ↓ K⁺, ↑ TBW, alkalosis) without elevated aldosterone and with normal cortisol levels. Similar symptoms can be generated by ingestion of large amounts of liquorice (contains glycyrrhetinic acid, an inhibitor of 11βOHSD). Treatment with dexamethasone therefore dramatically reduces the adrenal production of cortisol and hence reduces the inappropriate mineralocorticoid effects. Spironolactone (an inhibitor of the mineralocorticoid receptor) dampens responsiveness to excess cortisol-related mineralocorticoid activity.

**Pheochromocytoma:** ➝ ↑ BP, ↑ HR, and anxiety. Primarily hypersecretion of NE and not E (smaller E-NE ratio).

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**Pancreas and Metabolism**

**Lecture Objectives:** (1) List the body's fuels and fuel stores, (2) Describe the status of fuel utilization/storage in brain, muscle, liver and adipose tissue in the fed state, postabsorptive (interprandial), during starvation, exercise and diabetes, (3) Describe the organization, the cell types and the products of the endocrine pancreas, (4) Describe proinsulin and its relationship to insulin, (5) List the factors regulating the secretion of insulin and describe the cellular mechanism controlling its release in response to increase glucose, (6) List the factors regulating the secretion of glucagon. Describe glucagon's mechanisms and sites of action, (7) Describe the receptor and initial post-receptor mechanisms of insulin in target cells, (8) List functions of insulin, (9) Describe the mechanism by which insulin promotes glucose uptake in responsive tissues.

**Overview:** Metabolic processes require a constant expenditure of energy, but our intake of food is intermittent. During meals, we ingest more calories than are necessary for our metabolic needs. Extra calories are stored in the form of fat, carbohydrate, or protein.

- **Energy Reservoirs:**
  - Largest and most efficient energy reservoir is fat (8 kcal/g vs. 1 kcal/g for glycogen).
    - **Fat** is stored in adipose tissue as triglyceride (broken down to free fatty acids and glycerol when needed – glycerol is converted to glucose by the liver). Muscle, liver, and some other organs also possess small stores of triglyceride for local fuel needs. Lipid is used for fuel storage due to its ability to concentrate calories in small volumes.
  - **Glucose** is stored in liver and other tissues as glycogen (also used for triglyceride synthesis by the liver and adipose tissue). Between meals and during a fast, hepatic glycogen is degraded and glucose is released into circulation.
    - Most other tissues do not possess the enzymatic apparatus to form free glucose from glycogen. Peripheral glycogen is used for local needs.
  - Synthesis of protein from amino acids occurs in all tissues (most active following a meal). There is no real storage form of protein, yet during a fast, there is breakdown of protein in most tissues often ➝ gluconeogenesis. **Humans cannot lose more than 25-30% of protein without dying** (protein is needed for neurotransmitter function).
Regulation of Energy Metabolism: Anabolism (fuel deposition) and Catabolism (fuel mobilization) are regulated by insulin, glucagon, and somatostatin.

- **Insulin**: produced by β-cells in Islets of Langerhans (pancreas). Secretion is modulated by Δ [glucose] and/or [amino acids] in circulation, by neural factors and by GLIP-1 and GIP.

**Tissue Fuel Utilization:**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Kcal/day</th>
<th>Fuel Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>500</td>
<td>Glucose (+ Ketone Bodies if necessary)</td>
</tr>
<tr>
<td>Muscle</td>
<td>800</td>
<td>FFA, Glucose, AAs</td>
</tr>
<tr>
<td>Liver</td>
<td>300</td>
<td>FFA, Glucose, AAs</td>
</tr>
<tr>
<td>Other Tissues</td>
<td>400</td>
<td>Variable</td>
</tr>
<tr>
<td>Total</td>
<td>2,000</td>
<td></td>
</tr>
</tbody>
</table>

- The brain uses glucose as its only fuel source (except during prolonged starvation → Ketone Body use - acetoacetate + β hydroxybutyrate).
- **Brain consumes ~120 g/day of glucose (~25% of the body's total caloric expenditure).**
- Muscle comprises 40% of body mass and accounts for 25-40% of fuel consumption at rest (may ↑ up to 90% of total oxygen consumption during exercise). Muscle uses fatty acids as well as glucose as a fuel.
- **Glucose is the major fuel of muscle following a carbohydrate meal, and fatty acids and ketone bodies are used during periods of caloric deprivation.**

**Fuel Status in Organs Under Various Physiological States:**

- **The Fed State (↑ insulin):**
  - **Carbohydrate Meal:**
    - **Processes in Muscle:**
      - Glucose Uptake
      - Glycogen Formation
      - Amino Acid Uptake
      - Protein Synthesis
      - ↓ Protein Degradation
    - **Processes in Adipose Tissue:**
      - Glucose Uptake
      - Fat (triglyceride synthesis)
      - Fat Uptake from Lipoprotein
      - ↓ Lipolysis
    - **Processes in Liver:**
      - Glucose Uptake
      - ↑ Glycogen Synthase Activity → glycogen formed
      - Lipid Synthesis
      - ↓ Glycogenolysis and Gluconeogenesis
      - Glucagon Maintains Normoglycemia During a Protein Meal

- **Protein Meal:** Amino acids in the protein meal stimulate insulin and glucagon production. Glucagon prevents insulin from driving down blood glucose after a purely protein meal, where there is no carbohydrate intake.

- **The Post-Absorptive/Interprandial State [3-12 hours] (diminished insulin):**
  - Use of Stored Fuels.
  - Circulating Glucose Derived from Glycogenolysis and to some extent, Gluconeogenesis.
  - ↓ Use of Glucose by Adipose Tissue and Muscle.
  - Free Fatty Acids are a Major Fuel of Peripheral Tissue.
• **Brief Starvation [12 hours-3 days]** (low insulin):
  - Liver – gluconeogenesis → ketone body formation.
  - Adipose Tissue – lipolysis → free fatty acid release.
  - Muscle – amino acid release → ketone bodies and fatty acids are major fuels.
  - Brain – continued use of glucose.

• **Diabetes (no insulin):**
  - **Total lack of insulin (Type I diabetes)**
    - Catabolism of Fat, Carbohydrates, and Protein.
    - Hyperglycemia and Ketoadidosis
      - Excess Glucose is made from Excess AA Release.
      - Excess FFA release → Excess Ketone Bodies → Ketoadidosis.
    - Symptoms of Diabetes.
  - **Lesser degrees of insulin insufficiency or insulin resistance (Type II diabetes)**
    - Primarily disordered glucose metabolism.
    - Glucose tolerance test can show degree of insulin resistance.

  - **Glucose Tolerance Testing:** measures rise in blood glucose and recovery following an oral 75g dose of glucose.

• **Exercise:**
  - ↑ use of fuel by contracting muscle
  - Principal fuels are glucose and FFAs from circulation, and glycogen and triglycerides from muscle.

  - Accelerated repletion of muscle glycogen occurs during recovery

<table>
<thead>
<tr>
<th>At Rest</th>
<th>Light Work</th>
<th>Heavy Work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle</td>
<td>0.30</td>
<td>2.05</td>
</tr>
<tr>
<td>Abdominal Organs</td>
<td>0.25</td>
<td>0.24</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>Brain</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Skin</td>
<td>0.02</td>
<td>0.06</td>
</tr>
<tr>
<td>Heart</td>
<td>0.11</td>
<td>0.23</td>
</tr>
<tr>
<td>Other</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Sum</td>
<td>1.00</td>
<td>3.00</td>
</tr>
</tbody>
</table>

*Increased oxygen consumption during exercise is mainly to meet muscle needs.*

At rest & during moderate exercise, muscle uses FFAs as major fuel (conserving glucose for use in brain). As exercise intensity rises, muscle becomes increasingly dependent on carbohydrate as a fuel for recruited glucose-dependent fibers, and FFA use ↓.

*During exercise, glycogenolysis and gluconeogenesis ↑, FFA release from adipose tissue ↑ (↑ lipolysis), insulin ↓, glucagon ↑ (later), catecholamines ↑, catabolism ↑.*

*During recovery, muscle has FFAs available for fuel (liberated in response to exercise) → ↓ use of glucose for oxidation → storage as glycogen. Muscle has enhanced sensitivity to insulin → promotion of glucose uptake and glycogen formation.*

### Endocrine Pancreas:

- **Diabetes = the three Ps (polyphagia, polydipsia, polyuria)**
- **Type I Diabetes:** Insulin dependent diabetes. Age of onset is < 35 years. Prevalence is 0.5 %. Insulin secretion is diminished or absent. Patients are ketosis prone. Atherosclerosis is ++++. Eye, kidney, or nerve complication are ++++
- **Type II Diabetes:** Non-insulin dependent diabetes (NIDDM). Age of onset is > 35 years. Prevalence is 5.0 %. Insulin secretion is moderately diminished or increased (delayed). Patients are NOT ketosis prone. Atherosclerosis is +++++. Eye, kidney, or nerve complication are ++. **Type II diabetes is more common in the obese and the elderly: the likelihood of developing this form of diabetes doubles with every 20% increase in weight and 10-year increase in age.**

### A common cause of Type II diabetes in obese individuals is down regulation of insulin receptors.
Islets of Langerhans:
- β-cell - produces insulin
- α-cell - produces glucagon
- δ-cell - releases somatostatin (inhibits release of both insulin and glucagon)
- PP cell - releases pancreatic polypeptide (function is unknown) – not co-released with insulin

- Insulin: 6000MW. 52AA in two chains (A and B), linked by disulfide bridges.
- Formed as result of cleavage pre-proinsulin (101 AA) → pro-insulin (84 AA) with A- and B-chains linked by a 33 AA connecting peptide (C-peptide), which is proteolytically cleaved in the B cell and it is released into the circulation together with insulin in a 1:1 ratio (C-peptide has no known function – but is used to measure endogenous insulin secretion).
  - Exogenous insulin was formerly obtained from cows and pigs, and is now synthesized via recombinant DNA methodology (recombinant human insulin is less antigenic it allows supply to keep pace with the ↑ therapeutic demand).
  - **Insulin Secretion:**
    - Stimuli: Glucose, Amino Acids, Fatty Acids, Catecholamines (β-adrenergic), Acetylcholine, Intestinal Peptides (GIP, GLIP), Sulfonylureas (glyburide, glipizide, tolbutamide)
    - Inhibitors: Catecholamines (α-adrenergic), Somatostatin, Serotonin, Prostaglandin E.
  - the net catecholamine effect is inhibition as hypoglycemia → ↑ activity → ↑ glucagon

- Insulin Action:
  - Biological Effects of Insulin:
    - Transport: Glucose, Ions, Amino Acids (seconds)
    - Metabolism: CHO, Lipid, Protein (seconds-minutes)
    - Genetic: Growth, Proliferation, Enzymes – induction and repression (hours-days)
      - Tyrosine trans-auto-phosphorylation → insulin receptor substrate (IRS-1 and -2) activation → activation of downstream targets (including PI3K, Grb-SOS, and SHPTP).
      - Muscle and adipose tissue contain a special class of glucose transporters (GLUT-4), which are upregulated by insulin.
  - Glucagon: 29AA peptide.
    - Stimuli: ↓ blood glucose, ↑ free amino acids (especially Alanine and Arginine), and sympathetic stimulation.
    - Inhibitors: ↑ blood glucose, somatostatin, and insulin.
      - Mechanism of Action:
        - Primarily acts in liver (~90% of glucagon is cleared from blood into liver in one pass).
          - No direct effect on glucose uptake by muscle.
        - Acts via $G_c (cAMP)$ → glycogenolysis and gluconeogenesis → ↑ glucose release.
          - Also ↑ β-oxidation of Fatty Acids and inhibits glycogen synthase activity

† extracellular glucose → ↑ glucose inside β-cell (via insulin-insensitive GLUT-2 channels) → ↑ ATP/ADP ratio → closes an ATP-sensitive membrane potassium channel → membrane depolarization → opening of voltage-sensitive calcium channels → calcium ions enters the cell → exocytosis of insulin containing secretory granules.
**Potassium Uptake:** Insulin ↑ movement of potassium into cells (especially in liver and muscle) via ↑ activity of Na^+\text{-}K^+ ATPase. This can → loss of body potassium in Type I diabetics (when insulin levels are very low)

**Glucose Metabolism**

**Learning Objectives:**
1. Describe the role of the liver in glucose homeostasis,
2. Describe glycogenesis and glycogenolysis and hormonal regulation in liver and muscle,
3. Describe gluconeogenesis in liver (and kidney) and its hormonal regulation,
4. List and rank in terms of relative importance the substrates for gluconeogenesis,
5. Identify the sources of gluconeogenic precursors and the mechanisms regulating their availability,
6. Identify the sources of circulating glucose, the sites of utilization and the hormonal mechanisms regulating usage and production during phases of starvation from postprandial to 40 days.

**Overview:** Glucose is primary fuel of brain ⇢ its concentration is very highly regulated (plasma [glucose] is ~ 70-120 mg/dl (4-6mM) (Table 1), yet peripheral rates of glucose utilization vary ~100-fold. **Approximately 100g glucose is stored in the liver (as glycogen)**

**Glucose Homeostasis and the Liver:** 50-70% of a glucose meal is taken up by the liver for deposition. The liver is the major supplier of glucose to other tissues when it is no longer derived from the food we eat via gluconeogenesis or glycogenolysis. The liver functions as such because it contains glucose-6-phosphatase (catalyzes conversion of glucose-6-phosphate → free glucose). Other tissues lack glucose-6-phosphatase in significant amounts and do not release free glucose into the circulation.

- **Glycogen Metabolism:**
  - Synthesis of glycogen in liver is stimulated by insulin and ↑ plasma [glucose].
  - Glycogenolysis is stimulated by ↑ concentrations of glucagon (cAMP mechanism) and catecholamines (epinephrine, norepinephrine).
    - Insulin ↓ glycogenolysis by both glucagon and catecholamines.
    - *Liver glycogen is a short-lived but readily-mobilized source of glucose. After an overnight fast, ~100 g of glycogen is found in the liver (enough to supply the needs of brain (120 g/day) for less than a day).*

<table>
<thead>
<tr>
<th>State</th>
<th>Insulin (µU/ml)</th>
<th>Glucagon (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fed</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>Postabsorptive (12 hours)</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>Starved (3 days)</td>
<td>8</td>
<td>150</td>
</tr>
<tr>
<td>Starved (24 days)</td>
<td>7</td>
<td>150</td>
</tr>
<tr>
<td>Severe Diabetes</td>
<td>&lt;5</td>
<td>500</td>
</tr>
</tbody>
</table>

**Glucose Utilization (g/day)**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>12-hour fast</th>
<th>8-day fast</th>
<th>Marathon Run</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>120</td>
<td>45</td>
<td>120</td>
</tr>
<tr>
<td>Muscle</td>
<td>30</td>
<td>↓↓↓↓</td>
<td>500</td>
</tr>
</tbody>
</table>

**Amino acids and glucose have ↓↓ variability. Hypoglycemia is the most common presentation of Type-I diabetes. Gestational diabetes (hyperglycemia → ↓ infant mortality)**

**Stages of Glucose Digestion:**
- **Phase I (absorptive) – 3-4 hours post-glucose digestion:**
  - Blood glucose is derived principally from exogenous carbohydrates. Concentrations of insulin and glucose ↑ and glucagon is ↓. Glucose in excess of the fuel needs of liver and peripheral tissues is stored as glycogen (in liver and muscle), or is converted to lipid.
  - Liver is a net user of glucose and both glycogenolysis and gluconeogenesis are suppressed.
- **Phase II (post absorptive) – 4-12 hours post-glucose digestion:** insulin, glucose and glucagon return to basal levels and liver produces glucose (from stored glycogen).
  - Major user of glucose at this time is the brain.
  - Tissues which derive energy from anaerobic glycolysis (RBCs/WBCs, renal medulla) use glucose.
  - Muscle and adipose tissue ↓ glucose use.
- **Phase III (fast) – 12 hours – several days:**
After overnight fast, ~75% of glucose released by liver is derived from glycogen. The 100g of glycogen in the liver of post-absorptive person is adequate to meet fuel needs of peripheral tissues (about 180 g/day) for ~12 hours. gluconeogenesis replaces glycogen as the major source of glucose.

Gluconeogenesis is enhanced due to ↓ insulin and ↑ glucagon. Release of gluconeogenic precursors from peripheral tissues ↑ (result of lack of insulin).

Late Phase IV and Phase V (starvation) - ~one week: rate of gluconeogenesis ↓ due to ↑ use of fatty acids and ketone bodies (sparing gluconeogenic precursors, and especially the protein of muscle).

Gluconeogenesis: Long-lived but less flexible source of glucose than glycogen. Sole source of glucose in blood after 24-36 hours of fasting or after several hours of exercise. Gluconeogenic substrates are amino acids, lactate, pyruvate and glycerol (arise predominantly in peripheral tissues, and their rate of release into the circulation is a determinant of gluconeogenic rate).

Hepatic Phase: Not a simple reversal of the glycolytic pathway (due to several irreversible steps).

- Stimulated by glucagon and catecholamines (E and NE).
- Inhibited by insulin.
  - Glucocorticoids play a permissive role (if lacking, the ability of glucagon and catecholamines to stimulate gluconeogenesis is lost).

Peripheral Phase:
- Lactate: originates from breakdown of muscle glycogen, and the anaerobic glycolytic RBCs and renal medullary cells.
  - The Cori Cycle:

Amino Acids: originate from the degradation of proteins in muscle and other tissues.

- Protein broken down during starvation is derived from liver and other tissue in the early stages but over the longer period it is principally from muscle (up to 1/3 of body protein can be lost before death occurs).
  - Amino acid release from muscle is modulated by insulin (insulin stimulates synthesis of muscle proteins and inhibits their degradation). Glucagon does not affect amino acid release from muscle. Glucocorticoids (inhibit protein synthesis) enhance amino acid release. In prolonged
starvation and certain disease states, the release of amino acids from peripheral tissues is rate-limiting for gluconeogenesis.

- Alanine and glutamine account for 50% of the amino acid released from muscle, even though they comprise less than 15% of muscle protein because they can be formed from multiple substances by the muscle cell
  - Alanine arises from amination of pyruvate (allows for transfer of nitrogen from muscle to liver)
  - Glutamine is formed from deaminated carbon skeletons of amino acids
    - utilized primarily by the gut and by the kidney and is not a major gluconeogenic substrate for liver.
- During brief periods of starvation, renal contribution to gluconeogenesis is ~10% of that of the liver (via glutamine). During prolonged starvation and other states in which the kidney has to cope with a large acid load (e.g., metabolic acidosis), renal gluconeogenesis is accelerated. The major gluconeogenic substrate for the kidney is glutamine, which also is its major source of free NH$_3$.

- Glycerol: originates from hydrolysis of adipose tissue triglycerides.

### Hypoglycemia
Children and pregnant women are particularly susceptible to hypoglycemia during fasting. In children, the brain is large compared to protein stores available, relative to an adult. Pregnant women are especially susceptible since glucose is being used for the brains of both mother and fetus.

### Exercise-Induced Hyper/Hypoglycemia in Patients with Diabetes:

- **Normal individual:** ↓ insulin and ↑ counter-regulatory hormones during exercise → ↑ release of glucose from liver to match ↑ glucose use by exercising muscle (∴ blood glucose is constant).
- **Moderate insulin deficiency:** glucose is released from liver, but ↓ insulin level → ↓ uptake by muscle → ↑ blood glucose (can lead to severe hyperglycemia).
- **Diabetic (injection of insulin before exercising):** glucose output from the liver does not ↑, but the glucose uptake by the exercising muscle is high → hypoglycemia.

### Insulin-Glucose Interrelationships in the Diabetic during Exercise

<table>
<thead>
<tr>
<th>Status of Plasma Insulin</th>
<th>Hepatic Glucose Production</th>
<th>Muscle Glucose Utilization</th>
<th>Blood Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or slightly diminished</td>
<td>↑</td>
<td>↑</td>
<td>→</td>
</tr>
<tr>
<td>Markedly diminished</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Increased</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

### Lipid Metabolism

**Learning Objectives:**
1. Identify the lipid fuels, their sites of storage and production,
2. Describe hormonal regulation of lipid anabolism and catabolism,
3. Describe the control mechanism and hormonal regulation which dictates whether fatty acids are broken down in mitochondria or incorporated into triglycerides in muscle and liver,
4. Describe the processes and hormonal influences leading to ketone body formation in liver,
5. Describe the utilization of lipid fuels in prolonged starvation (>3 days),
6. Describe the utilization of lipid fuels in diabetic ketoacidosis.

**Overview:**
- Triglyceride (in adipose tissue) is the major caloric reservoir in humans.
  - 70-kg man has ~15 kg of adipose tissue (130,000 kcal) - sufficient to provide total body fuel needs for 60 days.
  - Triglyceride stores are broken down to provide energy during starvation and exercise.
Principal lipid fuels are free fatty acids (FFA) and the ketone bodies (acetoacetate and β-hydroxybutyrate).

Free Fatty Acid Metabolism: FFAs are found in the plasma bound to albumin (without albumin, hemolytic anemia would occur). They can be used by all tissues except the brain and obligate glycolyzers (RBCs, renal medulla), and the principal users are the liver and skeletal muscle. FFAs are the major source of fuel during early starvation and exercise.

- **Anabolism (storage) of Triglycerides:**
  - Triglycerides from circulatory chylomicra are broken down via lipoprotein lipase (found in capillary endothelia). Lipoprotein lipase is activated by insulin and → liberation of FFAs and glycerol.
  - FFAs are taken up by adipose tissue → re-esterification to triglyceride
  - Glycerol → gluconeogenesis

- **Catabolism (breakdown) of Triglycerides:**
  - Majority of FFAs in circulation derive from hydrolysis of triglycerides (lipolysis).
  - For each molecule of triglyceride degraded, three FFAs and one glycerol are liberated.
  - Factors effecting lipolysis (primary stimulus is “hormone-sensitive catabolic lipase,” a hormone stimulated by catecholamines and inhibited by insulin):
    - Stimuli: cAMP, Catecholamines, Glucocorticoids, Thyroid hormone, Growth hormone, Theophyllin, Caffeine
    - Inhibitors: Insulin, Prostaglandins, Adrenergic inhibitors (blockers), Nicotinic acid.

- Most FFA taken up by muscle cells is oxidized in the TCA cycle (2/3).
- The rate of oxidation is a function of FFA concentration in the circulation and their ability to enter the mitochondria.
  - Long-chain fatty acids cannot penetrate the inner mitochondrial membrane unless they are first bound to carnitine (allows interaction with carnitine palmitiyl transferase - CPT1).
  - This is the rate-limiting step in the metabolism of fatty acids once they enter the cell.
  - Activity of CPT1 is modulated by changes in the concentration of its inhibitor, malonyl CoA.
    - Malonyl CoA levels are ↑ by insulin and glucose → inhibition of fatty acid oxidation and ↑ synthesis of triglycerides.
    - If insulin/glucose ↓, malonyl CoA ↓, and CPT1↓ → movement of FFAs into mitochondria → oxidation.

<table>
<thead>
<tr>
<th>State</th>
<th>[Malonyl CoA]</th>
<th>Rate of FFA oxidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fed (inactive)</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Starved</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Exercise</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

- **Liver Use of FFAs:**
  - Can use FFA as major source of fuel during starvation.
  - A major portion of liver FFA use is for synthesis of triglycerides and ketone bodies.
    - Fed State: insulin ↑ and glucagon ↓ → ↑ malonyl CoA → triglyceride formation.
    - Diabetes and the Starved State: insulin ↓ and glucagon ↑ → ↓ malonyl CoA → FFA oxidation and ketone body formation.
Ketone Body Formation: Acetoacetate and β-hydroxybutyrate are derived from the partial breakdown of fatty acids in liver (only). Ketone body formation is high during starvation when plasma insulin is diminished and levels of glucagon and FFA are high. Ketone bodies are used in the brain, muscle, and all oxidative tissues except the liver.

- Ketone bodies enter mitochondria freely and carnitine is not required for their metabolism.
- After three to four days of starvation, ketone bodies are the principal fuel of skeletal muscle; and during prolonged starvation, they are the principal fuel of brain.
- In severe diabetes, the production of ketone bodies ↑ and the ability of some tissues (muscle) to use them ↓ (providing safety store for the brain).
- Insulin provides primary regulation of ketoacid metabolism

Prolonged Starvation (> 3 days):

- Plasma [acetoacetate] and [β-hydroxybutyrate] ↑ (replace glucose as primary fuel for brain). Hepatic gluconeogenesis ↓ (due to ↓ release of amino acids from muscle): brain is supplied with fuels derived from expendable fat rather than vital protein stores (loss of one-third of protein → death)
- ↓ basal metabolic rate, ↑ reabsorption of ketone bodies by the kidney, ↓ ketone body usage by muscle (FFA becomes fuel to help avoid the liver wastefully performing beta-oxidation of free fatty acids (it has plenty of ATP) to make ketones: conserving ketones for use by the brain.

Diabetic Ketoacidosis:

- Normal Individual: ↑ plasma ketone bodies during starvation occurs gradually (not associated with hyperglycemia because insulin is still present and mild acidosis occurs because ↑ renal NH₃ production enables clearance of H⁺)
- Severe Diabetes: failure to take insulin (or infection impairs effect of insulin injection) → rapid ketoacidosis (with hyperglycemia, dehydration due to osmotic diuresis, and levels of ketone bodies equal to or higher than those seen during prolonged starvation). Acidosis occurs because of the rapidity of ketoacid synthesis.
- In the absence of insulin, muscle does not take up ketone bodies as well as during fasting (as it is preferentially using the large amounts of FFAs available).
- Diabetic Ketoacidosis is primarily only found in Type I diabetics (type II diabetics have enough insulin to prevent malonyl CoA levels from dropping too low: preventing excess ketogenesis).

Glucose Intolerance: This is a state of reduced ability to restore euglycemia after a glucose load (for a diabetic - a state in which the fasting plasma glucose level is less than 140 mg per deciliter and the 30-, 60-, or 90-minute plasma glucose concentration following a glucose tolerance test exceeds 200 mg per deciliter). Normal blood values for a 75-gram oral glucose tolerance test: Fasting: 60 to 100 mg/dL, 1 hour: less than 200 mg/dL, 2 hours: less than 140 mg/dL. Between 140-200 mg/dL is considered impaired glucose tolerance or pre-diabetes (↑ risk for developing diabetes). Greater than 200 mg/dL is diagnostic of diabetes mellitus

Risk Factors for Diabetes: Family history, low activity level, poor diet, excess body weight (especially around the waist), age greater than 45 years, high blood pressure, high blood levels of triglycerides, impaired glucose tolerance, diabetes during a previous pregnancy (or a baby weighing more than 9 pounds), certain ethnicities (African-Americans, Hispanic-Americans, and Native Americans all have high rates of diabetes). Exercise and dieting can often relieve glucose resistance and can maintain this state for a long time. This may delay the onset of type II diabetes for many years

Hemoglobin A1C: a glycosylated form of hemoglobin. Glycosylation occurs at a rate dependent on the circulating glucose levels and is irreversible (persists for the life of the hemoglobin – 120 days). HbA1C: serves to monitor long-term glucose levels. Normal value = 5%. Controlled diabetic = ~7.5%.
**Long-Term Consequences of Diabetes:** neuropathy (sensory or autonomic), retinopathy (blindness), nephropathy (kidney failure) - consequences of hyperglycemia that results in increased formation of sorbitol in Schwann cells, and by abnormal glycation of proteins. One in two diabetics sufferer die from premature heart disease and ~ 30% of total deaths caused by heart failure are diabetes-related. Diabetics are twice as likely to stroke. 2/3 of amputees, 40% of new dialysis patients, and 30% of those registering as blind are diabetic.

**Interventions:** Bleeding in eye – laser surgery, Peripheral loss of sensation – avoid any tight clothing or shoes that might lead to an unperceived loss of circulation. Nephropathy – dialysis or transplant. Reduce cardiovascular risk - keep down LDLs (statins), aspirin, ↓ blood pressure (β-blockers)

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**Acute Presentation of Diabetic Ketoacidosis:** ↑ urination, ↑ thirst, confused, volume depleted, stuporous (ketoacidosis, hyperglycemia and associated hyperosmolarity), and has a fruity odor in her breath (ketones). Blood glucose and ketones are ↑ (absence of insulin). ↑ ketones → acidosis → ↑ respiratory frequency → protons enter cells in exchange for potassium. Glucose exceeds Tm glucose → ↓ volume → ↓ BP → ↑ renin → ↑ aldosterone. Treatment: insulin (correct hyperglycemia and hyperketonemia), IV fluids, balance electrolytes (prevent potassium deficiency - hypokalemia) and pH. Treat any associated bacterial infection.

Primary low insulin → ↑ blood glucose, glucosuria, osmotic diuresis, reduced plasma volume, sympathetic stimulation, increased catecholamines, and ketoacidosis. Stress (from the diabetic ketoacidosis) → ↑ cortisol and epinephrine (GH ↑ under stress but ↑ glucose will tend inhibit GH release). Insulin is a required cofactor in the production of IGF-1 and so, despite any possible elevation in GH, IGF-1 remains ↓. Plasma glucagon ↑ (even with ↑ glucose – because it is not inhibited by insulin). ↑ counter-insulin hormones → ↑ lipolysis → ↑ ketogenesis → ↑ gluconeogenesis → further ↑ ketogenesis → ↑ plasma glucose.

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**Hypoglycemia:** Frequently confused and irritable in the morning before breakfast. Syncope. Reactive Hypoglycemia: 2-3 hours after meals (more common). Caused by excessive insulin reaction, defective counter-regulatory response to normal insulin action, and especially, imbalance in food intake and administration of exogenous insulin. Fasting Hypoglycemia: >3-5 hours after meals. Caused by insulinomas (over-secrete insulin regardless of metabolic state) or deficiency of counter-insulin hormones (glucagon and cortisol). Symptoms of hypoglycemia are adrenergic (activation of sympathetic nervous system → sweating, faintness, weakness, palpitation, tremor, hunger, and nervousness) or neuroglycopenic (CNS symptoms such as headache, confusion, visual disturbances, motor weakness, gait disturbances, and marked personality changes). CNS disturbances may → loss of consciousness, convulsions, and coma. A common side-effect of insulin therapy in Type I diabetics.

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**Thyroid**

**Learning Objectives:** (1) Describe the hypothalamic-pituitary-thyroid axis, regulation of thyroid hormone metabolism and secretion, and interaction with other hormone axes, (2) Describe the molecular processes underlying thyroid hormone biosynthesis in thyroid follicular cells, (3) Describe the status and transport of thyroid hormones in the circulation, (4) Describe thyroid hormone entry into peripheral cells and intracellular metabolism and bioactivity, including interactions with nuclear receptors, (5) List the functional differences between T₃, T₄, and rT₃, (6) Describe the physiological effects of thyroid hormone at the cellular and organ levels and on basal metabolism, (7) Describe the role of thyroid hormone, and its interplay with other endocrine systems, in growth and development, (8) Describe the maternal-fetal interactions in maintaining thyroid hormone levels, (9) Describe the symptoms and signs of thyroid hormone excess and deficiency.

**Overview:** Thyroid hormone mediates physiologic processes of nearly all organ systems in a gain control manner (amplification or diminution of physiological processes). Thyroid hormone also effects fetal and juvenile growth and development (disfunction results from hyper- or hypothyroid conditions). The thyroid gland is a <30g, bilobed (separated by an isthmus), and highly vascularized structure located in the anterior neck (cannot be palpated during a normal exam). Goiters form due to dietary iodine deficiency (excess TRH/TSH), over-stimulation of the gland by thyroid stimulating hormone (TSH or thyrotropin), among others.

**Thyroid Hormone:**

- **Biosynthesis:** Synthesized from two tyrosine molecules (two coupled tyrosine rings = thyroine)
  - Structural Variants:
    - T₃ (3′,4′-triiodothyronine): lacks one iodine on its outer ring. The active form.
    - T₄ (thyroxine; 3′,5′,3,4-tetraiodothyronine): fully iodinated. The major secretory product.
    - rT₃ (reverse T₃): lacks one iodine on its inner ring. Physiologically inert.
      - **Biosynthesis** occurs only in the thyroid gland (only tissue that possesses the biosynthetic machinery to perform the unique steps involved in thyroid hormonogenesis).
      - T₃ and rT₃ can be produced from T₄ in peripheral tissues via deiodinases (selenium-containing enzymes)
        - Most of the circulating pool of T₃ (80%) is produced from T₄ by extrathyroidal deiodinase activity (particularly by the liver), rather than biosynthesis as T₃ (20%). In contrast, ALL T₄ is produced by the thyroid.
The Iodide Pump: Basolateral iodide (I\(^{-}\)) uptake from blood into thyroid follicular cell requires energy (goes against the I\(^{-}\) gradient). I\(^{-}\) uptake occurs via the Na\(^+\)/I\(^{-}\) symporter (NIS) (energy is provided by the basolateral Na\(^+\)/K\(^+\) ATPase).

Thyroglobulin Synthesis and Secretion: Thyroglobulin is synthesized and glycosylated in follicular cells secreted into the lumen by exocytosis (thyroglobulin contains tyrosine residues → thyroid hormones).

Iodine Oxidation*: I\(^{-}\) apical efflux into colloid is via pendrin (Cl\(^-\)/I\(^{-}\) transporter). Iodide (I\(^{-}\)) is oxidized to iodine (I\(_{\mathrm{o}}\)) by TPO and H\(_{2}\)O\(_{2}\).

Tyrosine Iodination (organification)*: Oxidized iodine (I\(_{\mathrm{o}}\)) atoms are covalently attached to tyrosine rings in thyroglobulin via TPO. 1-2 iodine atoms is incorporated into each tyrosine ring [→ monoiodotyrosine (MIT) or diiodotyrosine (DIT)]. Iodination is inefficient (~20% of the available tyrosines in thyroglobulin undergo organification).

Hypothalamic-Pituitary-Thyroid Axis:

- **Hypothalamus:** Thyrotropin-releasing hormone (TRH – a tripeptide) is synthesized and secreted by cells in the median eminence and arcuate nucleus. TRH is carried via the hypophyseal portal system to the anterior pituitary (adenohypophysis) where it stimulates synthesis and secretion of the TSH.
  - **Neurogenic input causes pulsatile secretion of TRH. α-adrenergic catecholamines and ADH are stimulatory, and α-adrenergic blockers are inhibitory.**
    - TRH is secreted as a large pre-pro-hormone and TRH sequences are released by peptidases. The most important regulator of TRH production is the long-loop negative feedback exerted by physiologic plasma levels of T\(_4\) and T\(_3\). Inactivation of TRH is rapid via action of a hormonally regulated TRH-degrading ectoenzyme.
    - *Exogenous TRH can promote secretion of GH and prolactin as well as TSH.
    - *Endogenous TRH is not a physiologic releasing factor for GH or prolactin, (except during pregnancy).*

- **Pituitary:** Anterior pituitary cells (thyrotropes) synthesize and secrete thyroid stimulating hormone (TSH), a glycoprotein sharing similar α-subunits with LH, FSH, and hCG (differ in levels of glycosylation). Specificity is conferred by the β-subunit.
  - TSH is stored in secretory granules in the thyrotrope and secreted into the systemic circulation as a result of TRH signaling (DAG/IP\(_3\) mechanism).
  - **In a negative feedback loop, T\(_3\) decreases TRH receptors at the thyrotope membrane ⋄ TSH synthesis and secretion is controlled by levels of free (unbound) T\(_3\)/T\(_4\).**
    - T\(_3\) and not T\(_4\) produces negative feedback effects (⋄ deiodinases convert T\(_4\) to T\(_3\) in the pituitary). Binding of the intrapituitary T\(_3\) to nuclear receptors suppresses the expression of both TSH subunits, thus inhibiting TSH production. TRH antagonizes this negative control by promoting the expression of both TSH subunits and stimulating TSH synthesis and secretion. TSH secretion is pulsatile but exhibits a circadian rhythm consistent with circadian changes in responsiveness to TRH [TSH levels are higher at night compared to daytime levels].
    - Pituitary TSH secretion is also inhibited by dopamine, somatostatin, and glucocorticoids (inhibit synthesis of TRH), ↓ responsiveness of thyrotrope to TRH, and ↓ plasma T\(_3\) levels by ↓ deiodinase activity ⋄ **Thyroid Storm is treated with glucocorticoids.**

Thyroid Hormone – Biosynthesis and Secretion: Thyroid gland tissue is composed of many follicles with a central glycoprotein core (colloid – stores thyroid hormones) surrounded by a cuboidal epithelium of cells (thyroid follicular cells). Follicular cells are functionally asymmetric, with distinct basolateral and apical membranes. A rich capillary bed perfuses the follicles near the basolateral surface. Thyroid follicular cells manufacture thyroid hormones and thyroglobulin (MW 600,000).

1. **The Iodide Pump:** Basolateral iodide (I\(^{-}\)) uptake from blood into thyroid follicular cell requires energy (goes against the I\(^{-}\) gradient). I\(^{-}\) uptake occurs via the Na\(^+\)/I\(^{-}\) symporter (NIS) (energy is provided by the basolateral Na\(^+\)/K\(^+\) ATPase).
2. **Thyroglobulin Synthesis and Secretion:** Thyroglobulin is synthesized and glycosylated in follicular cells secreted into the lumen by exocytosis (thyroglobulin contains tyrosine residues → thyroid hormones).
3. **Iodine Oxidation:** I\(^{-}\) apical efflux into colloid is via pendrin (Cl\(^-\)/I\(^{-}\) transporter). Iodide (I\(^{-}\)) is oxidized to iodine (I\(_{\mathrm{o}}\)) by TPO and H\(_{2}\)O\(_{2}\).
4. **Tyrosine Iodination (organification):** Oxidized iodine (I\(_{\mathrm{o}}\)) atoms are covalently attached to tyrosine rings in thyroglobulin via TPO. 1-2 iodine atoms is incorporated into each tyrosine ring [→ monoiodotyrosine (MIT) or diiodotyrosine (DIT)]. Iodination is inefficient (~20% of the available tyrosines in thyroglobulin undergo organification).

- The body adjusts its metabolic rate downward by shunting T\(_4\) to reverse T\(_3\) rather than to T\(_3\) during times of stress, illness and caloric deprivation as a protective mechanism.
(5) **Coupling and Storage**: Two iodinated tyrosine rings (still attached to thyroglobulin) are coupled by TPO \(\rightarrow\) precursor (storage) form of thyroid hormones (coupling of two DIT units \(\rightarrow\) T4 and coupling of MIT and DIT \(\rightarrow\) T3). Formation of T3 occurs with less frequency. The coupling reaction is inefficient (~20% of iodinated tyrosines undergo coupling - each TG molecule produces only 0.5 molecules of T4).

(6) **Colloid Reabsorption and Lysozomal Proteolysis**: When thyroid hormones are needed, colloid is pinched off and endocytozed into the follicular cell. The endocytoetic vesicles containing organified thyroglobulin fuse with intracellular lysosomes, and the thyroglobulin undergoes proteolysis \(\rightarrow\) release of mature T4, T3, and the constituent amino acids of thyroglobulin (MIT and DIT) into the cytosol of the follicular cell.

(7) **Secretion and Recycling**: T4 and T3 enter the bloodstream by simple diffusion across the basolateral membrane. DIT and MIT are deiodinated (by cytosolic thyroid deiodinase) in the thyroid follicular cell.

**Regulation of Iodide Uptake by the Thyroid Gland:**

- **Wolff-Chaikoff Effect**:
  - *Inhibition of thyroglobulin organification in response to acute iodine excess*
    - A transient effect, lasting from 26-50 hrs
    - The inhibition wears off when the thyroid gland has adapted to the higher iodide levels and resumes near-normal hormone synthesis.
    - Ability to escape from the acute Wolff-Chaikoff effect may occur as a result of down-regulation of thyroid Na\(^+\)/I\(^-\) symporter (NIS) production (\(\downarrow\)amount of iodide transported into the thyroid follicle regardless of the high serum iodide levels \(\downarrow\) returning biosynthesis to normal levels and releasing Wolff-Chaikoff inhibition).
  - In some conditions (e.g. hyperthyroidism due to Graves' disease), the abnormally functioning thyroid gland may exhibit an unusual sensitivity to iodide. \(\downarrow\) lower levels of iodide excess will trigger Wolff-Chaikoff inhibition of hormone synthesis without inducing the subsequent escape-from-inhibition response (\(\downarrow\) treatment with ICl provides dramatic recovery).
  - The escape mechanism from the Wolff-Chaikoff effect does not exist in the fetus. If the mother ingests \(\uparrow\) ICl, her response will be normal, but the fetus will quickly become hypothyroid.

**Secretion and Transport of Thyroid Hormones**: T4 and T3 are secreted from the thyroid gland at rates of 80-100 \(\mu\)gm/day and 5\(\mu\)gm/day respectively.

- Majority of circulating T4 and T3 molecules are bound.
  - 70% to thyroxine binding globulin (high affinity)
  - 15-20% to albumin (low affinity)
  - 10-15% to transthyretin (low affinity).
  - The tiny free (unbound) fraction of T4 and T3 enter cells and determines to a large extent the metabolic rate of many tissues.
  - Transport proteins act as a reservoir for buffering circulating levels of thyroid hormone
  - Transthyretin and albumin are responsible for the delivery of thyroid hormones to cells (rapid dissociation).
  - T4 binds more tightly to transport proteins than does T3
    - \(T4 - t^{1/2} = 7\) days. Extracellular pool is large.
    - \(T3 - t^{1/2} = 1\) day. Extracellular pool is small.

**Thyroid Hormone Action**: Thyroid hormones are transported into target cells by plasma membrane carriers - this is the rate-limiting step for further thyroid hormone metabolism inside target cells.

- Intracellularly, thyroid hormones bind non-histone protein nuclear receptors and with Thyroid Hormone Response Elements (TRE) \(\rightarrow\) regulates translation of various downstream targets.
- The response of various tissues to thyroid hormones vary and are proportional to the amount of nuclear thyroid hormone receptors present in the specific tissue (liver responds with large changes in protein synthesis and enzyme patterns, while the spleen and testis, are not influenced by thyroid hormones; myocardial tissue responds to thyroid hormones by increasing the number of adrenergic receptors and by increased activity of actomyosin ATPase.

- *Oxidation, iodination, and coupling (steps 3-5) all take place within the lumen (on the outer apical membrane surface) and are catalyzed by thyroid peroxidase (TPO). Hydrogen peroxide (H\(_2\)O\(_2\)) serves as a mediator (H\(_2\)O\(_2\) is generated by NADPH oxidase).
  - Compartmentalization of H\(_2\)O\(_2\) into the lumen prevents organization (introduction of iodine into protein by covalent modification) from spontaneously occurring within the follicular cell despite local high levels of iodide.
  - **Colloid normally stores a 2-3 month’s supply of organified TG and thus serves as a storage depot for both thyroid hormone and iodine.**
  - Thiocyanate (SCN\(^-\)) and Perchlorate (ClO\(_4\)\(^-\)) competitively inhibit NIS uptake of iodide (blocking active transport of I\(^-\)).
  - The rate limiting step in thyroid hormone synthesis is iodide transport from the blood into follicular cells.

- *Propylthiouracil blocks thyroglobulin iodination.*
Thyroid Hormone Physiological Function: Stimulates both anabolic and catabolic pathways of metabolism and supports a normal balance between them. Regulates body weight and basal metabolism as well as oxygen requirements.

- thyroid hormone action on protein expression and activity
- metabolic increase due to increased body temperature
- catecholamine-dependent up-regulation of β-adrenergic receptors and changes in expression of G-proteins.
  - Regulates oxidative metabolism (↑ basal metabolic rate and ↑ O2 consumption), ↑ rates of anabolic and catabolic processes, ↑ growth and development, ↑ systemic function.
  - Enhanced metabolic activity increases the body’s demand for oxygen consumption → ↑ cardiac output, ↑ respiratory drive, and ↑ production of red blood cells (↑ EPO), ↑ appetite, ↑ GI motility, and ↑ intestinal absorption.
- **Heart:**
  - **Cardiac Hypertrophy:** ↑ cardiac proteins and myocytes, ↓ collagen in non-myocytes.
  - **Contractility:** ↑ speed and force of systolic contraction, ↑ speed of diastolic relaxation.
  - **Electrical Activity:** ↑ rate of impulses, ↑ speed of conduction.
- **Skeletal Muscle:**
  - ↑ O2 consumption, ↑ blood flow, ↑ protein synthesis, and ↑ contractility
- **Bones:**
  - Lack of development without T3
- **Renal and Liver:**
  - ↑ blood flow, ↑ clearance rates, ↑ vasoactive mediation sensitivity, ↑ protein synthesis
- **Growth, Brain, and CNS:**
  - critical for normal fetal and neonatal development, regulates growth and function genes, effects mood and condition, ↑ GH and IGF secretion and ↑ tissue responsiveness.

<table>
<thead>
<tr>
<th>Target system</th>
<th>Physiological Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic adrenergic system</td>
<td>↑ β-adrenergic receptor activity</td>
</tr>
<tr>
<td></td>
<td>↑ β-receptors in heart, liver, muscle, adipocytes</td>
</tr>
<tr>
<td>Energy expenditure</td>
<td>↑ Na+/K+-ATPase expression</td>
</tr>
<tr>
<td></td>
<td>↑ thermogenesis, heat dissipation</td>
</tr>
<tr>
<td></td>
<td>↑ adaptation to cold climate</td>
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<tr>
<td>Oxygen consumption</td>
<td>↑ number mitochondria in most tissues</td>
</tr>
<tr>
<td>(mainly secondary to effects e.g. Na+/K+-ATPase activity)</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>↑ contractility (positive inotropic effect)</td>
</tr>
<tr>
<td></td>
<td>↑ sarcoplasmic Ca2+-ATPase expression</td>
</tr>
<tr>
<td></td>
<td>↑ activity and number of β-adrenergic receptors</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>↑ protein catabolism and glycogenolysis</td>
</tr>
<tr>
<td></td>
<td>Muscle fiber type switch from slow to fast</td>
</tr>
<tr>
<td>GI tract</td>
<td>maintains normal gut motility</td>
</tr>
<tr>
<td></td>
<td>↑ glucose absorption</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>↑ cholesterol synthesis</td>
</tr>
<tr>
<td></td>
<td>↑ LDL clearance (by ↑ hepatic LDL receptors)</td>
</tr>
<tr>
<td>Skeletal effects</td>
<td>promotes bone maturation, advances bone age</td>
</tr>
<tr>
<td></td>
<td>promotes bone growth (permissive for IGF-1 and maintains normal GH gene expression)</td>
</tr>
<tr>
<td></td>
<td>↑ bone turnover in adults</td>
</tr>
<tr>
<td>Plasma hormones</td>
<td>maintains normal half-lives of hormones and drugs</td>
</tr>
<tr>
<td>Brain/nervous system</td>
<td>maintenance of normal mental/emotional function and normal reflexes, including respiration</td>
</tr>
</tbody>
</table>
Maternal-Fetal Considerations: The thyroid gland forms at 2-4 weeks of gestation. TSH appears in the pituitary and iodide concentration begins in the follicular cells at 11-12 weeks. The hypothalamic-pituitary-thyroid axis is functioning by week 20. Thyroid hormone in fetal plasma during the first half of gestation is derived from the mother.

- During pregnancy, the maternal thyroid gland ↑ production of thyroid hormone (this would lead to hyperthyroidism if not for the concomitant ↑ thyroxine binding globulin (TBG) levels).
  - hCG stimulates T3/T4 secretion and inhibits TSH

- Thyroid hormone is required for normal brain development (up to 2-3 years of age). Untreated hypothyroidism during this time of development → severe and irreversible mental retardation (cretinism). Untreated hypothyroidism may impair brain function in adults, it is reversible with T4 treatment.
- Immature fetal thyroid lacks an escape mechanism from Wolff-Chaikoff inhibition ∴ chronic fetal exposure to excess iodine can lead to prolonged inhibition, causing hypothyroidism in utero.

Clinical Correlations:
- Thyroid dysfunction is most common in females (incidence of autoimmune disease is higher in women).
  - Graves’ and Hashimoto’s diseases are the most common causes of primary hyperthyroidism and hypothyroidism, respectively.
  - Post-partum thyroiditis (PPT) occurs in women during the first year following parturition (U.S. prevalence ~9% of parturient women).

<table>
<thead>
<tr>
<th>Hyperthyroidism (thyrotoxicosis) – “tired from the neck-down”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervousness</td>
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<tr>
<td>Heat intolerance</td>
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<tr>
<td>Palpitations</td>
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<tr>
<td>Muscle weakness</td>
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<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>↑ appetite</td>
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<tr>
<td>Moist, warm skin</td>
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</tbody>
</table>

Endocrine Emergency – Thyroid Storm

<table>
<thead>
<tr>
<th>Hypothyroidism – “tired from the neck-up”</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Basal metabolic rate</td>
</tr>
<tr>
<td>Weakness, fatigue, lethargy</td>
</tr>
<tr>
<td>Somnolence</td>
</tr>
<tr>
<td>Mental slowness</td>
</tr>
<tr>
<td>Goiter</td>
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<tr>
<td>Amenorrhea</td>
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<td>Δ ECG</td>
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</tbody>
</table>

Endocrine Emergency – Myxedema Coma

Resistance to Thyroid Hormone:
- Dominant Inherited Condition: condition of impaired tissue responsiveness to thyroid hormone (mutation in TH receptor gene is most common)
- Generalized RTH: hypo- or euthyroid state due to compensatory ↑ in TH secretion.
- Pituitary RTH: hyperthyroid condition resulting from impaired negative thyroid hormone feedback at pituitary.

Risk Factors for Thyroid Disease: family history (thyroid nodules), autoimmune (type I diabetes, Addison’s, Lupus, rheumatoid arthritis), type II diabetes, female > 30 years old, pregnancy, recent childbirth (~6 months post-partum), older age (9-16% of age 60+ have mild hypothyroid)
- Anti-peroxidase antibodies represent one of the major anti-thyroid antibodies (others include antibodies against thyroglobulin, TSH receptor, and Na/I co-transporter). Peroxidase and thyroglobulin are normally contained in the colloid space.

Treatment:
- Hyperthyroidism: aimed at ↓ overproduction of thyroid hormones with drugs that inhibit thyroid hormone synthesis (propylthiouracil) and/or drugs that inhibit peripheral effects of thyroid hormones (adrenergic blocking agents).
  - Surgery or radioactive iodine (I131 - destroys part of the tissue), may be used to ↓ excessive thyroid hormone production.
- Hypothyroidism: requires hormone replacement therapy (T4)
Calcium Intake and Excretion:

- Average intake of dietary calcium is 400-600 mg/day. One quart of skim milk = 1200 mg calcium.
- Minimum daily requirement (adequate intake):
  - 18-50 yo = 1000 mg/day
  - 50+yo = 1200 mg/day
- There are 900-1400 grams Ca^{2+} in the skeleton (the principal Ca^{2+} and phosphate storage site). ECF contains ~1 gram Ca^{2+}. The intestine, kidneys, and bone are constantly exchanging calcium with that in the ECF pool.
  - **Bone is the primary store for phosphate and calcium.**
  - **Plasma calcium levels are normally tightly regulated phosphate less so.**
- **Parathyroid hormone (PTH)** and the vitamin D metabolite, 1,25-dihydroxyvitamin D (1,25(OH)_{2}D) are the principal regulators of calcium balance in the body.
  - **PTH** is responsible for minute-by-minute control of calcium balance (regulates renal handling of calcium)

**Hashimoto’s Thyroiditis (primary hypothyroidism):** Presents with complaints of feeling cold and fatigued. Hashimoto’s thyroiditis is an autoimmune process that is characterized by auto-antibodies against antigens derived from thyroid gland components → generalized destruction of thyroid follicles → ↓ thyroid hormone biosynthesis and secretion. Additionally, anti-TSH receptor antibodies that bind to the TSH receptor (without activating it), block TSH stimulation of the thyroid gland. Net result is diminished production of T3 and T4 from the thyroid gland. A primary disease ↓ level of T3 produced from the pituitary is high. Progressive → loss of the thyroid gland. Treatment by supplementation with T4. More prevalent in women (10:1). ↑ TPR, ↑ cholesterol, goiter, Abs

**Hypothyroidism → Fatigue** -- ↓ energy expenditure and fuel usage, ↓ brain/nervous system activity, **Weight gain** (moderate) -- ↓ BMR and hence energy expenditure, but appetite and food intake does not drop in keeping, ↓ lipogenesis and lipolysis, ↓ lipoprotein lipase activity, ↓ number of LDL receptors, net effect ↑ plasma LDL levels. **Constipation** -- ↓ GI motility, Bradycardia -- (sympathetic adrenergic activity consequent on ↓ β-receptor number); SV and CO also ↓. ↓ **Reflexes** -- ↓ nervous system activity, ↓ nerve conduction, **Narrowed pulse pressure** reflects ↓ systolic pressure and ↑ diastolic pressure (↑ TPR), ↓ rate of cholesterol metabolism (most significantly, ↓ removal of LDL from circulation) → accumulation of cholesterol (hypercholesterolemia) → atherosclerosis.

**Grave’s Disease (thyrotoxicosis - primary hyperthyroidism):** Autoimmune hyperfunctionality of the thyroid gland (excessive stimulation of the TSH receptors). Grave’s disease is more prevalent in women than men. TSH levels are ↓ (negative feedback from ↑T₃/T₄ levels). Over-stimulation of TSH receptors occurs via anti-TSH receptor antibodies that stimulate → uncontrollable activation of the thyroid that mimics the tropic effects of TSH - ↑ size and number of follicular cells (becomes unresponsive to feedback mechanisms). ↑ vascularization of the enlarged thyroid is manifested by an audible bruit

↑ sympathetic adrenergic activity → tachycardia and palpitations activity, ↑ pulse pressure due to ↑ systolic pressure (↑ contractility) and ↓ diastolic pressure (↓ TPR), **Anxiety and Insomnia** due to over-stimulation of nervous system (↑ β-adrenergic activity), **Hyperdefecation** due to ↑ GI motility. **Prominent Stare** due to up-regulation of β-adrenergic receptors,↑ muscle tone in eye muscles, and lid retraction, **Exophthalmos** due to an autoimmune attack on retroorbital fibroblasts and adipocytes, accompanied by fibroblast proliferation and GAG (glycosaminoglycan) accumulation in the retroorbital tissues. Accumulation of GAGs and swelling of these tissues forces the eye forward, **Weight gain or loss** occurs primarily from net changes in metabolic processes. In hyperthyroidism, the net effect is to favor catabolic rather than anabolic processes → ↑ lipolysis, ↑ glycojenolysis, and ↑ protein catabolism predominate over the corresponding ↑ in biosynthetic processes .↑ basal metabolic rate and ↑ energy expenditure → weight loss, Hyperthyroidism → **Bone breakdown** (but both osteoclastic and osteoblastic activity ↑) → ↑ serum calcium → osteoporosis, Hyperthyroid → ↓ serum cholesterol levels.

**Treatment** reduces high levels of T3/T4 (agents that block iodide uptake or TPO activity). Long term treatment is to remove the overstimulated gland (ablative treatment with I^{131} or surgery). Treatment usually → hypothyroidism (treated by T₄ supplementation). Overproduction leading to thyroid storm (or prior to surgery) can be temporarily decreased by the Wolff-Chaikoff effect, which inhibits organification of thyroglobulin (escape occurs within a few days in normal patients by down-regulation of iodine uptake at the basolateral membrane). Escape often does not occur in patients with Grave’s disease.

**Parathyroid and Calcium Metabolism**

**Learning Objectives:**
- (1) Understand the role of calcium, phosphorus and magnesium metabolism on bone health.
- (2) Develop an understanding of how vitamin D and parathyroid hormone function for the regulation of calcium homeostasis.
- (3) Understand the physiologic functions of calcitonin and parathyroid hormone related peptide.
- (4) Develop an appreciation for the metabolism of vitamin D and its functions on calcium metabolism in the intestine and bone.
- (5) Understand the physiologic functions of parathyroid hormone on calcium and phosphorous metabolism.
- (6) Understand how 1,25-dihydroxyvitamin D and parathyroid hormone interact with osteoblasts to stimulate osteoclasts to mobilize calcium stores from the skeleton.

**Calcium Intake and Excretion:**

- Average intake of dietary calcium is 400-600 mg/day. One quart of skim milk = 1200 mg calcium.
- Minimum daily requirement (adequate intake):
  - 18-50 yo = 1000 mg/day
  - 50+yo = 1200 mg/d.
  - There are 900-1400 grams Ca^{2+} in the skeleton (the principal Ca^{2+} and phosphate storage site). ECF contains ~1 gram Ca^{2+}. The intestine, kidneys, and bone are constantly exchanging calcium with that in the ECF pool.
  - **Bone is the primary store for phosphate and calcium.**
  - **Plasma calcium levels are normally tightly regulated phosphate so.**
- **Parathyroid hormone (PTH)** and the vitamin D metabolite, 1,25-dihydroxyvitamin D (1,25(OH)_{2}D) are the principal regulators of calcium balance in the body.
  - **PTH** is responsible for minute-by-minute control of calcium balance (regulates renal handling of calcium)
- PTH's major role is to keep the serum calcium level from declining
  - ↑ renal reabsorption of calcium
  - ↑ bone resorption,
  - In-directly, by stimulating the production of 1,25(OH)₂D → ↑ intestinal calcium absorption).
  - 1,25(OH)₂D controls day-by-day calcium balance (regulates the amount of dietary calcium absorbed in the small intestine).
    - promotes the absorption of calcium and phosphorus from the intestine to the ECF pool
    - works along with PTH to mobilize stem cell differentiation into osteoclasts.
  - ~30% of daily Ca²⁺ intake is absorbed from the gut into the ECF, and part of the calcium in the ECF is lost through enteric secretion into the gut.
    - Net absorption of calcium is approximately the same as the amount lost per day via urinary excretion.
      - In the steady state (calcium balance), the transfer rates for calcium entering bone and that leaving it are the same.
        - Positive Calcium Balance: When calcium is deposited into the bones and there is more calcium entering the body than leaving
        - Negative Calcium Balance: When there is inadequate intake of calcium from the diet to compensate for renal and gut losses
          - Urinary calcium excretion reflects the relationship between GFR and tubular reabsorption, and net calcium absorption and bone resorption. In general, the urinary excretion of calcium does not vary widely despite considerable dietary fluctuations.

Vitamin D: essential for normal bone growth and development. The principal function is to maintain serum calcium and phosphorus in the normal range to support neuromuscular activity and most metabolic functions and also thereby permitting the passive mineralization of the collagen matrix laid down by osteoblasts resulting in normal bone mineralization. Recommended adequate intake from birth-50 years is 200 IU of vitamin D/day; 50-70 years, 400 IU a day; 70+ years, 600 IU/day. MOST IS BOUND TO PLASMA PROTEINS
- The major source of vitamin D is from casual exposure to sunlight (the precursor of cholesterol, 7-dehydrocholesterol, in the skin is converted to previtamin D → vitamin D₃ by a temperature dependent mechanism).
  - Vitamin D₃ and vitamin D₂ are rarely found naturally in foods (only oily fish). Fortified foods: milk, cereals and one brand of juice products (Minute Maid orange juice).
    - Increase in skin melanin content and use of sunscreen → ↓ production of vitamin D₃.
  - Vitamin D is fat-soluble and is absorbed into the lymphatic system (with chylomicra). Vitamin D is biologically inert. Hydroxylation (in the liver) → 25-hydroxyvitamin D (the major circulatory form).
    - 25(OH)D is hydroxylized again in the kidneys → 1,25-dihydroxyvitamin D (1,25(OH)₂D)
      - The major rate-limiting step is the enzyme required for hydroxylation in the kidneys
        - the enzyme is stimulated by ↑ PTH and by ↓ phosphate and is inhibited by ↑ FGF23.
          - negative feedback by inhibiting the 1-hydroxylase and stimulating the 24-hydroxylase
  - 1,25(OH)₂D (↑plasma calcium and phosphate): ↑ efficiency of intestinal calcium absorption and mobilizes preosteoclasts → osteoclasts (via RANKL system in the osteoblasts) → ↑ calcium reabsorption from the bone.
    - The active form has a lower affinity for the plasma binding protein and thus has a shorter half life (15 hours vs 15 days for 25(OH)D₃).
      - Production of 1,25(OH)₂D is stimulated by PTH, hypocalcemia, and hypophosphatemia.
        - PTH ↓ intracellular phosphate concentrations in the kidney → ↑ production of 1,25(OH)₂D.
  - 1,25(OH)₂D interacts with nuclear vitamin D receptor → formation of a complex with the retinoic acid receptor → activation of vitamin D responsive elements (enhance or inhibit gene expression).
  - 1,25(OH)₂D ↑ intestinal calcium absorption along SI (maximum effect in the duodenum) and ↑ phosphate absorption (maximum effect in the jejunum).
  - induce the formation of ECaC and calbindin in kidney (↑ calcium reabsorption).
    - Vitamin D receptor (VDR) is found in most tissues. 1,25(OH)₂D is a potent inhibitor of proliferation of cells that possess a VDR.

Parathyroid Hormone (PTH): single-chain, 84 AA with a free alpha-amino group on the amino-terminal residue and a carboxyl group on the other end (the amino-terminal position is essential for the biologic activity of PTH)
- Synthesis and Secretion:
  - Pre-pro-parathyroid hormone (~100 AA) is synthesized within chief cells in the parathyroid in response to plasma calcium levels → instant conversion to pro-parathyroid hormone (~90 AA) in the cell → rapid conversion to parathyroid hormone (84 AA). PTH is the stored form.
Bone Crystallization and Solubilization:

- Up to 50 residues can be removed from the C-terminus before activity is lost, but activity is lost from removal of one single N-terminal amino acid.

- Parathyroid glands monitor the blood’s ionized calcium levels (via a 7 transmembrane helical receptor - the calcium sensor).
  - Calcium ↓ → ↑ expression of PTH gene → ↑ PTH secretion.
    - Diagnostic immunoradiometric assay (IRMA) for PTH measures intact PTH (1-84).

- Functions: Principal function of PTH is to maintain a normal calcium level (PTH causes ↑ plasma calcium and ↓ plasma phosphate).
  - Hypocalcemia →
    - Bone:
      - Short-term (2-3 hours) – ↑ release of calcium from the bone fluid compartment by changing the permeability of osteocytes and other cells of the bone membrane.
      - Long-term - Induces stem cells to become osteoclasts → ↑ bone resorption.
        - ↑ RANKL (the ligand expressed on the surface of osteoblasts that binds to and activates the RANK receptor on the surface of pre-osteoclasts leading them to develop into active osteoclasts.

- Osteoprotegerin (OPG) - a form of receptor analogous to free RANK which is released from osteoblasts (and some other tissues). OPG can bind to RANKL, blocking RANK activation.

- ↑ renal calcium reabsorption and inhibits renal phosphorus reabsorption (↑ excretion).
  - Inhibition of renal phosphorus reabsorption is via cAMP mediated inhibition of a Na⁺-Phosphate co-transporter.

- ↑ renal formation of 1,25-dihydroxyvitamin D
  - → ↑ intestinal calcium absorption
  - → ↑ bone resorption

FGF23: a fibroblast growth factor that ↓ the number of Na⁺-Phosphate co-transporters in the luminal membrane → ↓ phosphate reabsorption and ↓ conversion of 25OH-D3 to the active 1,25 (OH)₂D3 form (which in turn ↓ phosphate uptake in the small intestine) by promoting formation of inactive 24,25(OH)2D3.

- FGF23 production ↑ with ↑ dietary phosphate intake and ↓ with ↓ dietary phosphate intake.
- FGF23 is produced by osteoblasts in response to ↑ 1,25 (OH)₂D3.

Magnesium: Magnesium deficiency: skeletal response (bone resorption) to PTH is inhibited → ↓ release of calcium into the blood (:. chronic magnesium deficiency → impaired secretion/ synthesis of PTH). Very high levels of magnesium also → inhibition of PTH production.

- Magnesium deficiency → impaired enzymatic activity of Na⁺-K⁺ ATPase → ↑ movement of potassium to ECF and ↑ [Na⁺]ICF
- Normal serum magnesium ~1.6-2.1 mEq/L (serum magnesium levels are often inaccurate)
  - Recommended dietary intake of magnesium is ~5 mg/kg (350 mg daily).
    - 1/3 of daily intake is absorbed by the ileum and subsequently excreted in the urine.
    - ~50%-60% of the magnesium filtered by the kidney is reabsorbed in the ascending loop of Henle.
      - Diuretics may cause ↑ magnesium loss through the urine. Twenty-four hour urinary excretion of magnesium may be increased by 25% to 50% in patients on chronic diuretic therapy.

Bone Crystallization and Solubilization:

- Crystalization or solubilization of bone mineral is determined by balancing calcium and phosphate such that they can mineralize under the appropriate conditions (pyrophosphate stabilizes this). During mineralization, osteoblasts secrete alkaline phosphatase that cleaves pyrophosphate → ↓ stabilization and ↑ phosphate → ↑ calcium phosphate crystallization.

- Osteoblasts also lay down the collagen and other proteins which form the bone matrix around which mineralization occurs. Normal bone mineralization only occurs when the calcium x phosphate product is supersaturated.

- Solubilization: Bone resorption is carried out by osteoclasts (large multinuclear cells derived from monocytic precursors). Osteoclasts secrete acids and proteases that can dissolve the mineral crystals and the protein matrix from underlying bone.

The PTH, Vitamin D, and Calcium Equilibria (regulation occurs in the kidneys, skin, liver, and intestines):

- Normal serum calcium level is ~8.8-0.2 mg/dl.
- At pH of 7.4, 1 gm of albumin binds 0.8 mg/dl of calcium (.: total serum calcium concentrations should always be evaluated with a serum albumin level).
  - The free form of calcium is responsible for all of the calcium actions in the body.
Similar disease characteristics can accompany defects in the hydroxylase to produce 1,25(OH)2D levels, Hypocalcemia/Osteomalacia, hyperparathyroidism and associated with hypercalcemia. Untreated asymptomatic. Fatigue and occasional palpitations may result from neuropathic atrophy of muscle fibers (common in Primary Hyperparathyroidism, osteoporosis.

Exercise:

GI and Growth Hormone:

Thyroid Hormone:

Parathyroid Hormone Related Peptide: 141AA peptide with 9 residues in the N-terminal region that are identical to PTH. ~50% of cancer-associated hypercalcemia is caused by PTHrP. Plays a critically important role in regulation of chondrogenesis during fetal bone development and maturation. An important paracrine signal for cellular communication to mesenchymal and epithelial tissues including breast, skin and hair follicles.

Estrogen: effects of PTH at the bone and effects of PTH at the kidney → bone breakdown and renal calcium reuptake. Following menopause (FSH, LH, and estradiol), loss of estrogen is a significant factor in increasing calcium loss and increasing the tendency to osteoporosis. The main reason why osteoporosis is more prevalent among older women is associated with the loss of estrogen effects past menopause, leading to greater rates of resorption, although lower bone density at maximum and other factors may contribute.

Glucocorticoids: Necessary for normal skeletal growth. In excess renal and GI calcium (re)uptake → hypocalcemia → secondary hyperparathyroidism. cortisol → OPG production by osteoblasts → osteoclastic activity → bone resorption → osteoporosis.

Thyroid Hormone: T3 is required for normal skeletal development. Absence of T3 → delayed ossification of cartilaginous bone growth centers. Excess T3 → bone resorption (bone metabolism). plasma calcium levels → PTH release → calcium loss in the urine → production of 1,25D3 → calcium uptake from the GI → osteoporosis.

Growth Hormone: Somatomedin (IGF-1) is mitogenic for chondrocytes and bone cells. GH deficiency GH → calcium uptake from GI and renal phosphate reabsorption.

Exercise: Load bearing exercise is necessary to maintain normal bone mass. Prolonged inactivity → negative calcium balance → hypercalcemia → PTH secretion → urinary calcium losses and reduced 1,25D3 promoted calcium uptake from the GI. Excessive exercise in women can amenorrhea (due to GnRH suppression) → depression of estrogen levels → PTH activity at bone → osteoporosis.

Primary Hyperparathyroidism (most common cause is benign adenoma): PTH, plasma Ca2+. Patients are commonly asymptomatic. Fatigue and occasional palpitations may result from neuromuscular atrophy of muscle fibers (common in hyperparathyroidism and associated with hypercalcemia). Untreated, hyperparathyroidism bone loss and osteoporosis. ~15% of hyperparathyroid cases are the result of hyperplasia which may be sporadic or associated with inherited traits.

Hypocalcemia/Osteomalacia: diffuse pain and muscular weakness; plasma phosphorus, plasma calcium, plasma 25-(OH)D levels, plasma PTH, and low urinary calcium output. Hypocalcemia with PTH levels and urinary calcium suggest calcium stores (uptake) or inadequate plasma Vitamin 25 (OH)D3 symptoms of osteomalacia (impaired bone mineralization). Similar disease characteristics can accompany defects in the hydroxylase to produce 1,25 (OH)2D3 or as a result of resistance to 1,25 D3.

o **Causes:**
  - Lack of dietary vitamin D3 and/or sunlight to facilitate endogenous production, malabsorption of dietary vitamin D3, impaired renal hydroxylation to 1,25 derivative (chronic renal disease or genetic defect in enzyme).
  - Low phosphate (since both calcium and phosphate are required for mineralization). May arise from impaired renal reuptake of phosphate caused by renal disease or genetic defect or rarely from low dietary intake.
  - Metabolic acidosis (chronic renal disease) → ↓ pH effects mechanisms influencing bone formation and resorption

o **Treatment:** Administer oral vitamin D3, calcium supplements and recommend levels of sunlight exposure.

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**Reproduction**

**Learning Objectives:**
1. Outline the hypothalamic-pituitary-gonadal axis in general terms,
2. Consider the biochemical properties of each key reproductive hormone,
3. Define sex and its determination, including examples of dysfunction,
4. Compare sexual development in males and females,
5. Review the specifics of reproductive endocrinology in the male,
6. Discuss issues of male fertility,
7. Review female reproductive anatomy and histology,
8. Describe the coupled ovarian and uterine events of the menstrual cycle,
9. Consider the roles of estrogen and progesterone throughout life,
10. Describe the molecular aspects of estrogen and progesterone receptor action,
11. Discuss hormone replacement therapy,
12. Discuss conception, contraception, and assisted reproduction,
13. Review fertilization, implantation and placenta formation,
14. Describe key maternal, placental and fetal hormones and their variation during pregnancy,
15. Consider the hormonal and neural control of parturition and lactation.

**The Hypothalamic-Pituitary-Gonadal Axis:**

- **Key Hormones:**
  - **Hypothalamic:**
    - Gonadotropin Releasing Hormone (GnRH) or Luteinizing Hormone Releasing Hormone (LHRH):
      - **10AA peptide**
        - $t_{1/2} = 4$ minutes
        - Pulsatile Release (1.5-2 hours) → release continues after menopause
      - Acts on gonadotropes of the anterior pituitary to ↑ secretion of FSH and LH (PLC mechanism)
        - Constant levels of GnRH → ↓ FSH and LH (due to down-regulation of GnRH receptors)
  - **Anterior Pituitary:**
    - Luteinizing Hormone (LH)
      - 32kD dimeric glycoprotein
      - $t_{1/2} = 20-30$ minutes
      - Acts on interstitial steroid-producing cells:
        - Leydig cells of the testis and theca cells of the ovary.
    - Follicle Stimulating Hormone (FSH)
      - 32kDa dimeric glycoprotein,
      - $t_{1/2} = 2-3$ hours
      - Acts on follicular cells:
        - Sertoli cells of the testis and granulosa cells of the ovary.
          - FSH and LH share a common α subunit with TSH and hCG, and each hormone has a distinct β subunit.
          - The α subunit is required for cooperative receptor binding, while the unique β subunit determines receptor specificity.
          - All four hormones act via adenylyl cyclase → cAMP → PKA signaling.
  - **Gonadal (steroidal sex hormones):**
    - Testosterone:
      - Produced by Leydig cells of testis.
      - Inhibits LH release by anterior pituitary and ↓ GnRH release by hypothalamus.
      - Testosterone is converted to more potent dihydrotestosterone (DHT) by $5α$-reductase-1 and -2 in target tissues (DHT binds T receptors at higher affinity).
    - Estrogens: Estrone (E1), Estradiol (E2), and Estriol (E3).
      - Androgen precursors (androstenedione and testosterone) are made by theca cells (ovarian) and converted to E1-3 in the granulosa cells (and peripheral tissues) by aromatase (FSH induced).
        - Aromatase inhibitors are effective against estrogen-dependent cancers.
      - Estriol is a fetal adrenal/liver-placental product.
      - Moderate, steady levels of estrogen acting on the hypothalamus and anterior pituitary → inhibition of LH release early in the menstrual cycle.
• **Rising levels of estrogen** → ↑ *LH release* before ovulation (by increasing the number of GnRH receptors on the gonadotropes).

  - **Progesterone:**
    - Produced by corpus luteum after ovulation and by the placenta during pregnancy.
    - Synergistic with E₂, P inhibits GnRH release.

  - **Androgen Binding Protein**.
    - 90 kDa
    - Produced by the Sertoli cells under stimulation of T and FSH and secreted into the seminiferous tubules, maintaining very high T levels around sperm maturing in the rete testis and epididymis (~200X > serum).

  ~98% of sex steroids are bound in plasma: ~2/3 of T is carried by *Gonadal Steroid Binding Globulin* (GBG), or *Sex Hormone Binding Globulin* (SHBG), and ~1/3 by albumin. The opposite ratios are true for E₂ in males. Female ratios vary within the menstrual cycle since E increases GBG synthesis. P binds to albumin and *Cortico-steroid Binding Globulin* (CBG), ~4:1.

  - **Gonadal (peptide hormones):**
    - **Inhibins** *(α and β subunits)*:
      - 32 kDa dimeric glycoproteins (18 kDa α chain and either of two 14 kDa β chains → inhibins A & B - \( \alpha\beta_A & \alpha\beta_B \)).
      - Produced by FSH-stimulated Sertoli or granulosa cells and act on the anterior pituitary to ↓ *FSH release* (negative feedback).
        - Inhibin B is produced in the male and during the follicular phase in the female
        - Inhibin A is characteristic of the luteal phase *(SECRETED BY CORPUS LUTEUM)*.
    - **Activins**:
      - Formed from two inhibin β chains
        - Either homo- \((\beta_A\beta_A & \beta_B\beta_B)\) or heterodimers \((\beta_A\beta_B)\).
      - ↑ *FSH release experimentally* but a physiologic role for this apparent positive feedback is uncertain.

  **Placental activin A** \((\beta_A\beta_A)\) and **inhibin A** \((\alpha\beta_A)\) increase dramatically before birth but their function in parturition is speculative.

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**Sex: Definition / Determination:**

- **Genetic Sex:** defined simply by the *karyotype*: 44 somatic chromosomes plus either XX (female) or XY (male).
  - **Gonadal Sex:** defined by the internal genitalia and is inherent in the genetic makeup.
Sexual Development

- Downstream action of the SRY (Sex-determining Region of Y) gene product (a transcription factor) induces testis development.
  - Both X chromosomes are required for normal ovarian development, although later only one remains active.
    - **XO** - Turner's syndrome/ovarian agenesis: streak gonads, amenorrhea, short stature, webbed neck, lacking secondary sexual characteristics
    - **YO** - lethal
    - **XXY** - Kleinfelter's syndrome/seminiferous tubule dysgenesis: male genitalia, ↑FSH, LH & E2 but ↓T, sterility, feminization, retardation.
      - Common sex chromosome disorder (>1 per 1,000).
      - An example of hypergonadotropic hypogonadism.
    - **XXX** - Triple X syndrome: nearly as frequent as Kleinfelter's but such females show no unusual abnormalities since only one X chromosome remains active.

  - **Phenotypic Sex:** defined by the genital ducts and external genitalia and by secondary sexual characteristics. In either sex, fetal steroidogenesis is supported by hCG.
    - **Male:** Sertoli cells produce Mullerian Inhibiting Hormone or Substance or Factor (MIH, MIS, MIF) a 140 kDa dimeric glycoprotein of the TGFβ superfamily of growth factors.
      - MIH causes regression of the Mullerian ducts (precursor of oviduct, uterus, vagina)
      - Leydig cells produce testosterone, supporting differentiation of the Wolffian ducts (precursor of epididymis, vas deferens, seminal vesicle, ejaculatory duct).
      - After conversion to DHT, testosterone induces the development of the prostate, urethra, penis and scrotum.
    - **Female:** (lacking MIH and testosterone)
      - Mullerian ducts develop and the Wolffian ducts regress
      - Female external genitalia appear, mainly by labial growth.

Sexual Development

- **Male:** Testosterone is synthesized at near-adult levels toward the end of the first trimester (→ differentiation of internal and external genitalia) and again at about 2 months postpartum (function unknown). T remains quite low until puberty (hypothalamic activity – initially nocturnally and then constantly) → growth of the penis, sebaceous glands, long bones, and axillary and pubic hair characterize the adolescent period. T levels reach maximum in the mid/late-20s, and fall thereafter.
- **Female:** Estrogen synthesis is seen at the end of the first trimester (gonadal development). FSH & LH are high 2-3 months post-partum (function unknown). Estrogen levels do not rise again until puberty (hypothalamic activity – initially nocturnally and then constantly) → breast development (thelarche) → development of axillary and pubic hair (pubarche) → first menstrual period (menarche). Estrogen levels peak monthly after menarche (except during pregnancy), then periods become irregular (climacteric) and cease around the fifth decade (menopause). Post-menopausal LH & FSH levels are high due to low estrogen and lack of inhibin.
- **Male AND Female:**
  - long bone growth is augmented by sex steroids (E in the female; T → E in the male)
  - high levels of sex steroids near the end of puberty → epiphyseal plate closure.
  - At 8-10 yrs, the adrenals increase their secretion of androgens (adrenarche), without significant changes in cortisol or ACTH levels → growth spurt and pubic and axillary hair growth

- **Dysfunctions:**
  - **Testicular Feminization (Androgen Insensitivity Syndrome):** XY genotype with female external genitalia due to a lack of functional androgen receptors. Y chromosome → testes → MIH and testosterone, therefore Mullerian ducts regress via MIH action but Wolffian ducts also regress since they can't respond to testosterone. Leydig cells → T but Sertoli cells can't function → no spermatogenesis. Later, without negative feedback from T, GnRH↑ → ↑LH → ↑A → ↑T → ↑E (peripheral aromatization) → breast development → female phenotype, even though T>E.
  - **5α-reductase-2 Deficiency Syndrome:** XY genotype. Begins life with a female phenotype but later reverts to a male phenotype due to non-functional 5α-reductase type 2 genes. Y chromosome → testes and internal male ducts (since T is present) but no prostate, penis, or scrotum form since conversion to DHT is required. At puberty, ↑T may promote sufficient binding to the receptor, inducing development of external male genitalia and/or the normal 5α-reductase (type I) present in the prostate and external genital tissues may suffice at very high T levels.
  - **Congenital Adrenal Hyperplasia:**
    - **Females:** masculinization, (enlargement of the clitoris and fusion of the labia before birth; increased muscular development, facial hair (hirsutism), irregular menses post-puberty).
    - **Males:** precocious puberty or supermasculinization (hypersecretion of adrenal androgens due to a defect in steroid biosynthesis). Most commonly, a 21- or 11β-hydroxylase deficiency reduces the formation of aldosterone and cortisol, resulting in accumulation of their androgen precursors.
Male Reproduction:

- **Testicular Cells:**
  - Spermatogonia *(germ cells)*: Sperm-producing stem cell line. *FSH and FH are necessary for spermatogenesis*
  - Leydig cells *(interstitial cells)*: Stimulated by LH. Synthesize and secrete T.
  - Sertoli cells *(follicular cells)*: Stimulated by FSH (and T, to produce ABP). Surround and protect developing sperm.
    - Interconnected laterally by **tight junctions**, Sertoli cells form a "blood-testis barrier," protecting developing sperm cells.
    - Contain **aromatase**: can convert T to E2.

- **Effects of Testosterone:**
  - **Fetal:**
    - Induces the Wolffian-derived duct system.
    - Induces the prostate and the urethra, penis, and scrotum via DHT.
  - **Puberty** *(anterior pituitary becomes MORE sensitive to GnRH):*
    - Induces facial, pubic and axillary hair; sebaceous glands (via DHT).
    - Sperm production, larynx development, fat and muscle distribution, promotion of bone growth during puberty but cessation of bone growth with increasing T post-puberty (T acts indirectly on bone growth by aromatase-mediated conversion to E).
  - **Adult:**
    - Sex Drive (libido in both sexes; Intrinsa® T-patch for women?)
    - Muscle growth & maintenance (T is an anabolic steroid)
    - ↑ erythropoiesis (hence higher male hematocrit)
    - ↑ male pattern baldness (via DHT)
    - ↑ cholesterol, with its negative cardiovascular consequences.

Male Fertility:

- **Oligospermia**: having less than 20 million sperm per ml ( <1/5 normal)
  - Due to ↓ GnRH (because of anabolic steroid abuse or stress), poor nutrition, and/or environmental factors (heat, toxic chemicals).
- **Physically Defective Sperm**: (e.g. double headed, short tailed). Sperm are not sufficiently motile, or not able to undergo capacitation, hyperactivation, or the acrosome reaction. *>50% defective is considered problematic.*
- **Male contraception:**
  - **Challenges**: 2-month period for sperm production and the sheer number of sperm.
  - **Future Possibilities**: GnRH or gonadotropin antagonists, testosterone analogues, progesterone, inhibitors of sperm motility or function, blockage of sperm-egg recognition.
- **Impotence** *(erectile dysfunction)*: *psychological or physiological basis.*
  - Anticholinergic drugs, nerve damage, or aging inhibit arteriolar dilation (normally occurs via the NO pathway).
  - **Viagra®** (sildenafil) is a selective inhibitor of phosphodiesterase-5 (PDE5), which hydrolyzes the signaling molecule cGMP involved in Ca²⁺ channel closure.
    - ↑[cGMP] → ↓ intracellular [Ca²⁺] → smooth muscle relaxation → erection.
- **Benign Prostatic Hyperplasia (BPH) and Male Pattern Baldness**: T must be converted to DHT for prostate growth and maintenance. inhibition of 5α-reductase-2 with Finasteride (a T analogue) is used to treat BPH (this also reverses scalp hair loss). Finasteride is used at high dose for prostatic hyperplasia *(Proscar®)* and at low dose for male pattern baldness *(Propecia®).*

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Overview of Male Hormonal Control:

Pulsatile release of **GnRH** → stimulation of gonadotropes (anterior pituitary) → secretion of LH and FSH.

**FSH** stimulates Sertoli cells to produce factors *(ABP and activins)* that support the developing sperm cells that they surround, and also to produce **inhibin-B**, *(αβB)*, which inhibits FSH release by the anterior pituitary (negative feedback).

**LH** stimulates the Leydig cells to produce testosterone. Testosterone inhibits LH release by the anterior pituitary and also inhibits GnRH release by the hypothalamus (negative feedback).

**Testosterone** is converted in non-gonadal target tissues to dihydrotestosterone *(DHT)*, by 5α-reductase-1 and -2.

**Aromatase** converts androgens to **estrogens** in peripheral tissues. In males, 80-95% of E1 and E2 are formed by peripheral aromatization, with 5-20% being testicular.
Female Reproduction:

- **Ovarian Cells:**
  - **Oogonia** *(germ cells)*: exist only during fetal life → fixed number of **primary oocytes** by birth.
  - **Theca Cells** *(interstitial cells)*: Steroidogenic counterpart of Leydig cells. Stimulated by LH to produce androstenedione.
    - Contain little aromatase and cannot effectively convert androgens to estrogens.
  - **Granulosa Cells** *(follicular cells)*: Female counterparts of Sertoli cells, surround and support developing oocytes. Stimulated by FSH → aromatase, convert theca cell androstenedione to estrogen (growth is stimulated by FSH and estradiol in the late follicular phase).

- **Hormonal Cycling:**
  
  (1) **Early Follicular:** LH and FSH ↑ as their inhibitors (progesterone, estrogen, and inhibin A ↓) The uterine lining degenerates → menstruation. ↑ FSH → new follicle development. Proliferating granulosa cells secrete inhibin B.
  
  (2) **Mid-Follicular:** ↑ inhibin B suppresses FSH release → domination of one follicle and atresia of the rest. Estrogen ↑ (due to LH-stimulated theca cell production of androgens and granulosa cell conversion to estrogen) → stimulation of growth of granulosa and theca cells.
  
  (3) **Late Follicular:** Estrogen-induced growth of the follicle → ↑↑ estrogen (+ feedback) → follicle growth. ↑ estrogen → ↑ sensitivity of anterior pituitary to GnRH → ↑ LH release (and induction of LH receptors on granulosa cells). **Estrogen levels peak**
  
  (4) **Ovulation:** ↑ LH triggers ovulation (via action on now-LH-sensitive granulosa cells → lytic enzyme and prostaglandin release). Passive co-secretion of FSH → inhibin B release. The LH surge → completion of the oocyte’s first meiotic division.
  
  (5) **Early Luteal:** The LH surge and loss of oocyte signaling to follicle → metabolic shift (↓ estrogen and inhibin B production and ↑ progesterone and inhibin A).
  
  (6) **Mid-Luteal:** CL grows under LH stimulation, and progesterone, estrogen and inhibin A ↑ maximally → inhibition of GnRH and LH (by estrogen and progesterone) and FSH (by inhibin A).

*If implantation occurs, trophoblasts of the embryo produce hCG (= LH), which maintains the corpus luteum through the first two months of pregnancy. If not...*

(7) **Late Luteal:** Lack of LH → CL degeneration → ↓ progesterone, estrogen, and inhibin A levels → release of anterior pituitary and hypothalamic inhibition.

(8) → (1) **End Cycle/Recycle:** FSH and LH ↑ → new follicle development.

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**Menstrual Cycling:**

(1) **Menstrual Phase (days 1-5):** initiation to completion of bleeding → endometrium degenerates and sloughs off → menstrual flow *(menstrual)*.

(2) **Proliferative Phase (days 5-14):** estrogen ↑ → endometrium regenerates → glandular formation → progesterone receptors appear on endometrial cells and myometrium *(which both thicken)*

(3) **Secretory Phase (days 14-28):** ↑ progesterone, mucus and fluid secretion → ↑ glycogen synthesis and ↑ vascularization and ↓ myometrial contracton → implantation. **FSH levels ↑**

- **Mid-Cycle:** estrogen causes the cervical mucus to be thin (allowing sperm movement). Progesterone → thickening and acidification of cervical mucus (preventing sperm movement and bacterial invasion).

- **End-Cycle:** ↓ estrogen and progesterone → lack of endometrial support → vasoconstriction → ↓ blood flow → ↓ prostaglandin secretion → death of tissue → myometrium rhythmically contracts → endometrial blood vessels dilate → hemorrhage through weakened capillary walls.
Timing within the menstrual cycle is ovarian, not hypothalamic, but the cycle itself cannot be initiated without GnRH stimulation of FSH release (low GnRH → amenorrhea, “hypogonadotropic hypogonadism”).
Conception, Pregnancy, and Birth:

- **During Pregnancy**: Maternal lipolysis and ketogenesis ↑, hCG replaces LH functionally (first two months), PL stimulates breast development, lactation is inhibited, and aldosterone ↑ (to expand maternal ECF).

- **Predicting Ovulation**:
  - Menstrual cycle repeats every ~28 days. LH surge, ovulation, and maximum fertility occurs at 14–15 day mid-point. Egg is viable for ~1 day and sperm is viable for ~2–4 days. There is a narrow window for conception. The cycle is not always consistent.

- **Thermogenic Effect of Progesterone**:
  - ~0.5°C in basal body temperature occurs after ovulation (persists throughout the luteal phase)

- **Vaginal Mucous**:
  - Before ovulation: thin but stringy (spinnbarkeit). Vaginal smear forms branching salt crystals (arborization/ferning)
  - After ovulation: mucous becomes highly viscous and does not form salt crystals.

- **ClearPlan® Fertility Monitors**:
  - Record daily ratio of estradiol and progesterone metabolites (averaged over several menstrual cycles).

- **Promoting Ovulation/Prime Fertilization**:
  - **Ovulation Induction**:
    - Clomiphene: (E2 antagonist) → ↑GnRH → ↑FSH
    - hMG (human menopausal gonadotropin): FSH+LH or FSH stimulation
    - Phased Protocols: administration of FSH while blocking the normal cycle with a GnRH antagonist, and terminating with a pulse of hCG (≈LH) to trigger (multiple) ovulation(s).

- **Assisted Reproductive Technologies (ART)**:
  - IVF (in vitro fertilization) and ICSI (intracytoplasmic sperm injection): multiple oocytes obtained by induction protocols, fertilized by capacitated or injected sperm, respectively.

- **Hormonal Birth Control**:
  - **Progestin**:
    - Continuous: minipill: daily oral dosage
    - Depo-Provera®: DMPA (depomedroxyprogesterone acetate): injection 4× per year
    - Norplant®: levonorgestrel implant: lasts 5 years.
      - All ↓LH, FSH & E2 to the early/mid-follicular-phase range, suppressing ovulation and also producing thick cervical mucus and a thin, atrophic endometrium.
      - All can allow irregular bleeding.
  - **Estrogen + Progestin (combination)**:
    - Oral Daily Protocol (21 days on / 7 days off or placebo)
      - Monophasic: constant E/P ratio
      - Biphasic: two different E/P ratios
      - Triphasic: three different E/P ratios.
      - Phased dosages produce more normal uterine phases, yet still suppress ovulation, sperm entry, and fertilization.
    - Cyclofem® - Injection
    - OrthoEvra® - weekly transdermal patch
    - Extended Cycle Oral - 4 periods per year (Seasonale®).
  - **Morning-After**: two doses of a progestin, 12 hours apart, within 72 hours of intercourse (Plan B®).
    - Function similarly to progestin-only contraceptive.

Fertilization and Development of Sperm: After ejaculation, sperm must undergoes:

- **Capacitation**: epididymis-derived proteins are stripped off; transmembrane proteins are rearranged; metabolism and motility increase (required for IVF).

- **Hyperactivation**: receptor-mediated calcium influx converts slow, wave-like beating to rapid, whip-like beating, triggered by proximity to the egg (paracrine signal)

- **Acrosome reaction**: sperm head binding to zona pellucida triggers exocytosis of a trypsin-like proteolytic enzyme (acrosin) from the sperm acrosome, clearing a path for the sperm head to fuse with the egg plasma membrane.
  - Of ~250 million sperm deposited in the vagina, ~100,000 reach the uterus, but several orders of magnitude fewer reach the ampulla of the oviduct.
  - Sperm can live in the female tract for 2-4 days.

Placental Hormones:

- **hCG**: produced by trophoblasts after their invasion into the endometrium (arrow). Serves as a signal from the embryo that implantation has occurred. Structurally and functionally similar
Lactation:

- Detection of hCG in the urine is the basis for home pregnancy tests.

- **Progesterone**: initially made by CL and later by placenta. Critical for maintaining uterus for implantation. Also critical for breast development, and for inhibiting uterine contractions during pregnancy. Progesterone levels rise progressively after CL degeneration (BUT efficacy of inhibition ↓ as parturition approaches).

- **RU486 (mifepristone)**: competitive inhibitor of progesterone → endometrial degradation and myometrial contraction.
  - When administered with prostaglandin (misoprostol) → expulsion of the fetus.

- **Estradiol/Estriol (E2/E3)**: cooperative products of fetal adrenal synthesis of DHEA-S → fetal liver hydroxylation to 16α-OH-DHEA-S → placental conversion to estrogens:
  - Maternal cholesterol → placenta → pregnenolone → fetal adrenal → DHEA-S
  - Fetal adrenal DHEA-S → placenta → DHEA → androstenedione → E2 and E
  - Fetal adrenal DHEA-S → fetal liver → 16α-OH-DHEA-S → placenta → 16α-OH-DHEA → E3.
    - Sulfation of DHEA eliminates any androgenic effects of high DHEA on the fetus.
    - Estrogens promote breast development and inhibit milk production before birth.
  - Levels rise at constant rates throughout pregnancy.

- **Placental Lactogen (PL) or hPL)** or Chorionic Somatomammotropin (CS): a 18.5 kDa protein (similar to GH and prolactin).
  - Facilitates breast development, maintains positive protein balance, mobilizes fats for energy, and promotes the high glucose levels required for nourishing the fetus.
  - Level rises at a near-constant rate throughout pregnancy.

Parturition and Birth:

- **30 Weeks**: rhythmic uterine contractions ↑ strength and duration.
- **8 Months**: uterine contents shift toward cervix.
- **8.5 Months**: dilation and softening of the cervix (mediated by estrogens, relaxin, and prostaglandins).
  - Progesterone causes less inhibition of contraction.
  - Uterine muscles (electrically coupled via estrogen-induced gap-junctions) are stimulated by stretch to contract coordinately.
  - Oxytocin receptors (↑ by estrogen) ↑ uterine sensitivity to oxytocin.
  - Oxytocin is released from posterior pituitary → ↑ strength and synchronicity of contractions and ↑ prostaglandin release in uterus.
  - Cervical dilation and sufficient forcible, rhythmic contractions → expulsion of fetus and placenta.

Lactation:

- **Estrogen and progesterone** (from the CL, then the placenta), **placental lactogen (PL)** and **prolactin (PRL)**, all cooperatively stimulate breast development → components required for milk synthesis, storage, and release.

- **Functions of Prolactin**:
  - **Mammogenesis** – growth and development of mammary gland
  - **Lactogenesis** – initiation of lactation
  - **Galactopoiesis** – maintenance of milk production
    - Prolactin release is inhibited by dopamine and stimulated by a Prolactin Releasing Factor (not specifically identified)
      - Estrogen stimulates synthesis and secretion of prolactin by the anterior pituitary.
  - High estrogen and progesterone inhibit milk production until birth, after which the absence of the placenta → ↓ in these hormones → ↑ milk production.
  - **The initial secretion is colostrum**, containing more protein and less fat than milk.
  - Suckling → neural input to the hypothalamus → ↓ dopamine release and ↓ PRF release.
  - ↓ dopamine and ↓ PRF → ↑ prolactin → ↑ milk synthesis in the mammary glands. Suckling also → ↑ oxytocin → myoepithelial contraction in the breast → milk ejection.
  - During nursing, neural input and ↑ prolactin ↓ GnRH release → suppressed ovulation (wet-nurse effect).
  - Hyperprolactinemia can → amenorrhea and galactorrhea.
Factors Contributing to Irregular Menses: diet issues (anorexia, bulimia), family issues (abuse or other psychosocial stressors), sexual activity, TSH/T<sub>4</sub> levels (↑TRH – reflected as ↑TSH or T<sub>4</sub> – can stimulate lactotrophs to produce excess prolactin), FSH levels, LH levels, estradiol levels, prolactin levels (high levels of prolactin, which inhibit GnRH production could cause irregular menses or stop them completely), pregnancy (hCG).

Hypothalamic Amenorrhea: athleticism, excessive dieting, anorexia, malnutrition, systemic illness, emotional trauma, rapid weight loss, or tumor (rare) → suppression of GnRH production (hypothalamic) → ↓secretion of gonadotropins and sex steroid hormones → cessation of menstruation. This amenorrhea is reversible once the stressor has been removed. Over time, hypothalamic amenorrhea may → ↑calcium loss (due to ↓estrogen) → significant risk of osteoporosis. The female athlete triad: anorexia/amenorrhea/osteoporosis.

Prolactinoma (a common, slow growing, benign pituitary tumor → hypersecretion of prolactin): Prolactin is ↑, LH/FSH are ↓, Estrogen is ↓. ↑Prolactin → ↓GnRH → ↓FSH, LH, and estradiol → disruption of menses (same as GnRH response as that during breastfeeding in the post-partum period). Galactorrhea in a prolactinoma patient occurs when sufficient prolactin secreting pituitary tissue has grown that tonic inhibition by dopamine is inadequate to prevent significant prolactin production. Treatment: management of prolactinomas with dopamine agonist drugs. An alternative cause of these symptoms is :: an exogenous dopamine antagonist. Excess TRH would also lead to overproduction of TSH, T<sub>3</sub>, T<sub>4</sub>, and prolactin and would → amenorrhea (but would also induce weight loss and other symptoms).

Polycystic Ovary Syndrome (PCOS): Infertile, hirsuitism, and irregular menses. LH is normal or ↑, FSH is usually normal and always below LH. Androstenedione is ↑, Estradiol is ↑. Follicular development does not lead to ovulation and corpus luteum formation. Instead, the hyperplastic theca interna cells of the aberrant cystic follicle produces overt androgen, which does not permit normal cycling and → amenorrhea and hirsutism. Many PCOS patients are insulin-resistant and at least 40% present with obesity.
† androgen production by theca cells → † estrogen levels (mostly from peripheral aromatase conversion of androgens) → chronic positive feedback on pituitary production of LH (as normally occurs in the late follicular phase of the menstrual cycle) → LH stimulation of theca cells → hyperproduction of androgens. Ovaries are commonly enlarged with a thickened capsule and may contain multiple unresolved follicles as cysts. Overweight PCOS patients are frequently helped by weight loss by reducing adipose tissue mass and thereby reducing the amount of peripherally-produced estrogen and/or by increasing insulin sensitivity (as in type II diabetes), which in turn reduces hyperinsulinemia and excessive androgen synthesis. Progestins are the primary therapeutic approach. Other possibilities include surgical removal of part of the ovary or anti-androgens. ↑ estrogen, Tx with progesterone, ↑ androgens, ↑ insulin-resistance.

Kallman’s Syndrome (hypogonadotropic hypogonadism): Sparse axillary hair, no beard or pubic hair, and much “baby” fat. Arm span is longer than height. Genitalia are prepubertal. Sense of smell is undeveloped. Karyotype is normal but congenital abnormalities in the anterior forebrain (mutation in cell adhesion protein – anosmin) during fetal development specifically inhibit appropriate development of tissues involved in GnRH-producing and olfactory sensory functions.

Patients are be taller than they would be without the hormonal abnormality because there is no termination of growth (normally stopped by ↑ sex steroids) and no pubertal growth spurt (often → osteoporosis).

Low testosterone levels influence behavior (less aggressive than normal adolescent males, low libido), puberty and development of secondary sexual characteristics does not occur, and the genitalia are prepubertal in appearance.

Treatment with testosterone may restore secondary sexual characteristics and libido as well as help prevent osteoporosis but cannot by itself restore fertility or change past bone growth patterns. Treatment with pulsatile GnRH or with hCG or gonadotropins is indicated in some reports to promote testicular development and possibly even fertility.

### Table of Hormones:

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Site of Production</th>
<th>Major Regulator(s)</th>
<th>Major Function(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,25-dihydroxyvitamin D₃</td>
<td>Kidneys</td>
<td>↑ by PTH, ↓Ca²⁺, and ↓phosphate</td>
<td>↑ plasma calcium and phosphate</td>
</tr>
<tr>
<td>Adrenocorticotropic Hormone (ACTH)</td>
<td>Anterior pituitary</td>
<td>↑ CRH</td>
<td>↑ androgens and cortisol</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Adrenal cortex</td>
<td>↑ A-II (maybe ↑ ACTH)</td>
<td>↑Na⁺ reabsorption, ↑K⁺ and H⁺ secretion</td>
</tr>
<tr>
<td>Atrial Natriuretic Factor (ANF, atriopeptin)</td>
<td>Heart</td>
<td>↑ Atrial Blood Pressure</td>
<td>↑ Sodium excretion → ↓BP</td>
</tr>
<tr>
<td>Calcitonin (CT)</td>
<td>Thyroid</td>
<td>Food, ↑ CCK, ↑ Secretin, ↑ Glucagon, and ↑ Gastrin</td>
<td>↓ Plasma calcium (↑ bone resorption)</td>
</tr>
<tr>
<td>Cholecystokinin (CCK)</td>
<td>Gastrointestinal tract</td>
<td>———-</td>
<td>Gastrointestinal tract; liver; pancreas; gallbladder</td>
</tr>
<tr>
<td>Chorionic Gonadotropin (CG)</td>
<td>Placenta</td>
<td>produced by trophoblasts of the embryo and secreted by CL</td>
<td>Maintains CL through ↑ two months of pregnancy</td>
</tr>
<tr>
<td>Corticotropin Releasing Hormone (CRH)</td>
<td>Hypothalamus</td>
<td>↑ by stress, ↓ by cortisol but NOT by adrenal androgens</td>
<td>↑Secretion of ACTH</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Adrenal cortex</td>
<td>↑ ACTH, stress</td>
<td>permissive maintenance of vital functions &amp; ↓ inflammatory response</td>
</tr>
<tr>
<td>Cytokines‡</td>
<td>Leukocytes, macrophages, endothelial cells, and fibroblasts</td>
<td>Varies</td>
<td>Immune defenses</td>
</tr>
<tr>
<td>Dihydrotestosterone (DHT)</td>
<td>Many target cells</td>
<td>From testosterone (via 5α-reductase)</td>
<td>Reproductive system; growth and development</td>
</tr>
<tr>
<td>DHEA (Dehydroepiandrosterone)</td>
<td>Adrenal cortex</td>
<td>From cholesterol (via pregnenolone)</td>
<td>↑ sex steroids in fetal development; influences libido in women. Other roles in adults still poorly defined.</td>
</tr>
<tr>
<td>Dopamine (DA, Prolactin-Inhibiting Hormone, PIH)</td>
<td>Hypothalamus</td>
<td>suckling → ↓ dopamine release</td>
<td>↓ secretion of prolactin and TSH</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Adrenal medulla</td>
<td>PMNT conversion of NE → E is induced by cortisol</td>
<td>Organic metabolism; cardiovascular function; response to stress</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Kidneys</td>
<td>↑ by thyroid hormone and ↑ O₂ consumption/needs</td>
<td>↑ erythrocyte production</td>
</tr>
</tbody>
</table>

*Table of Hormones:*
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Origin</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogen (E)</strong></td>
<td>Ovaries; Placenta</td>
<td>↑ by LH; ↑ or ↓ by estrogen (concentration dependent); Stimulates reproductive system; breasts; growth and development; influences gametes; ↑ prolactin; ↑ or ↓ LH (concentration dependent)</td>
</tr>
<tr>
<td><strong>Follicle-Stimulating Hormone (FSH)</strong></td>
<td>Anterior pituitary</td>
<td>Progesterone, Inhibin, and Estrogen ↓ secretion; GnRH ↑ secretion; Stimulate Gonads (↑ gamete production and ↑ sex hormone secretion)</td>
</tr>
<tr>
<td><strong>Gastrin</strong></td>
<td>Gastrointestinal tract</td>
<td>↑ by GRP and ACh (potentiated by Histamine); ↓ by GIP and secretin. Gastrointestinal tract; liver; pancreas; gallbladder</td>
</tr>
<tr>
<td><strong>Ghrelin</strong></td>
<td>Gastrointestinal tract</td>
<td>Appetite stimulant; ↑ GH secretion</td>
</tr>
<tr>
<td><strong>Glucagon</strong></td>
<td>Pancreas (α-cells)</td>
<td>↓ blood glucose, ↑ free amino acids (Ala and Arg), &amp; symp. stimulatory; ↑ blood glucose, somatostatin, &amp; insulin are inhibitory. ↑ gluconeogenesis and ↑ glycogen synthase activity</td>
</tr>
<tr>
<td><strong>Glucose-Dependent Insulinotropic Peptide (GIP)†</strong></td>
<td>Gastrointestinal tract</td>
<td>Released in response to FFAs and glucose; ↑ insulin secretion; ↓ GI motility</td>
</tr>
<tr>
<td><strong>Gonadotropin Releasing Hormone (GnRH, LHRH)</strong></td>
<td>Hypothalamus</td>
<td>↓ by E, GnRH, and Prolactin; ↑ Secretion of LH and FSH</td>
</tr>
<tr>
<td><strong>Growth Factors‡</strong></td>
<td>Multiple cell types</td>
<td>Growth and proliferation of specific cell types</td>
</tr>
<tr>
<td><strong>Growth Hormone (GH)</strong></td>
<td>Anterior pituitary</td>
<td>↑ by GHRH, stress, exercise, fasting, ↓ plasma glucose, &amp; arginine/leucine; ↓ by Somatostatin and ↑ plasma glucose; Growth, mainly via secretion of IGF-1; protein, carbohydrate, and lipid metabolism</td>
</tr>
<tr>
<td><strong>Growth Hormone Releasing Hormone (GHRH)</strong></td>
<td>Hypothalamus</td>
<td>↓ by IGF-I and GH; ↑ secretion of GH</td>
</tr>
<tr>
<td><strong>Inhibin A/B - female</strong></td>
<td>Ovaries</td>
<td>Inhibin A = luteal phase; Inhibin B = follicular phase; ↓ FSH/LH secretion</td>
</tr>
<tr>
<td><strong>Inhibin B - male</strong></td>
<td>Testes</td>
<td>Inhibin B = follicular phase; ↓ FSH/LH secretion</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>Pancreas</td>
<td>Stimuli: Glucose, AAs, FFAs, β-adrenergics, ACh, GIP, GLIP, Sulfonylureas; Inhibitors: α-adrenergics, Somatostatin, Serotonin, Prostaglandin E; ↑ glycogen synthesis and ↓ glucose uptake; growth; ↓ lipolysis and protein degradation… ↑ lipoprotein lipase activity, ↑ uptake of K⁺, ↑ uptake of AA by muscle; ↑ cell division and growth; ↓ GH secretion by negative feedback</td>
</tr>
<tr>
<td><strong>Insulin-like growth factors (IGF-I and -II)</strong></td>
<td>Liver and other cells</td>
<td>↑ by GH, T₃, Insulin (co-factor); ↑ cell division and growth; ↓ GH secretion by negative feedback</td>
</tr>
<tr>
<td><strong>Leptin</strong></td>
<td>Adipose tissue cells</td>
<td>Regulates food intake; metabolic rate</td>
</tr>
<tr>
<td><strong>β-lipotropin and β-endorphin</strong></td>
<td>Anterior pituitary</td>
<td>↑ by CRH (contained in POMC); Still poorly defined.</td>
</tr>
<tr>
<td><strong>Luteinizing Hormone (LH)</strong></td>
<td>Anterior pituitary</td>
<td>↓ by constant levels of GnRH and E, ↓ by T, progesterone, and Inhibins; ↑ by ↑ GnRH; Gonads (gamete production and sex hormone secretion)</td>
</tr>
<tr>
<td><strong>Melatonin</strong></td>
<td>Pineal</td>
<td>Sexual maturity; body rhythms</td>
</tr>
<tr>
<td><strong>Motilin</strong></td>
<td>Gastrointestinal tract</td>
<td>Sexual maturity; body rhythms</td>
</tr>
<tr>
<td>** Mullerian-Inhibiting Hormone (MIH, MIS, MIF)**</td>
<td>Testes</td>
<td>constitutive production in testes; Regression of Mullerian ducts (normal in male development)</td>
</tr>
<tr>
<td><strong>Norepinephrine</strong></td>
<td>Adrenal medulla</td>
<td>converted to E by PMNT (cortisol is cofactor); Organic metabolism; cardiovascular function; response to stress</td>
</tr>
<tr>
<td><strong>Oxytocin (OCT)</strong></td>
<td>Posterior pituitary§</td>
<td>↑ by estrogen, uterine stretch, and suckling; Milk let-down; uterine motility</td>
</tr>
<tr>
<td><strong>Parathyroid Hormone (PTH)</strong></td>
<td>Parathyroids</td>
<td>↑ by ↓ plasma Ca²⁺; ↑ Plasma calcium and ↓ plasma phosphate</td>
</tr>
<tr>
<td><strong>Placental Lactogen (PL; Chorionic Somatomammotropin: CS)</strong></td>
<td>Placenta</td>
<td>constitutive ↑ during pregnancy; Breast development; organic metabolism</td>
</tr>
<tr>
<td>Hormone</td>
<td>Primary Site</td>
<td>Action</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Ovaries; Placenta</td>
<td>see cycling during menses and pregnancy</td>
</tr>
<tr>
<td>Prolactin (PRL)</td>
<td>Anterior pituitary</td>
<td>constitutive release: ↓ by dopamine; ↑ by prolactin releasing factor, ↑ by estrogen; sucking ↑ prolactin</td>
</tr>
<tr>
<td>Relaxin</td>
<td>Ovaries</td>
<td>↑ by pregnancy</td>
</tr>
<tr>
<td>Renin (an enzyme that generates angiotensin)</td>
<td>Kidneys</td>
<td>↑ by ↓ BP or by sympathetic stimulation (afferent arteriole)</td>
</tr>
<tr>
<td>Secretin</td>
<td>Gastrointestinal tract</td>
<td>↑ plasma Ca²⁺</td>
</tr>
<tr>
<td>Somatostatin – GI</td>
<td>Pancreas</td>
<td>↑ by ↓ pH (&lt;3)</td>
</tr>
<tr>
<td>Somatostatin (SS) – CNS</td>
<td>Hypothalamus</td>
<td>——</td>
</tr>
<tr>
<td>Testosterone (T)</td>
<td>Testes</td>
<td>↑ by LH; ↑ by aromatase**; ↓ by aromatase inhibitors</td>
</tr>
<tr>
<td>Thymopoietin</td>
<td>Thymus</td>
<td>——</td>
</tr>
<tr>
<td>Thyroid-Stimulating Hormone (TSH)</td>
<td>Anterior pituitary</td>
<td>↑ by TRH; ↓ by T₃/T₄; ↓ by hCG</td>
</tr>
<tr>
<td>Thyrotropin Releasing Hormone (TRH)</td>
<td>Hypothalamus</td>
<td>↑ by α-adrenergics and ADH; ↓ by α-adrenergic blockers; ↓ by T₃; ↓ by dopamine, somatostatin, and cortisol</td>
</tr>
<tr>
<td>Thyroxine (T₄)</td>
<td>Thyroid</td>
<td>↑ by hCG; ↑ by TSH; ↓ by T₃/T₄; ↓ by iodine deficiency</td>
</tr>
<tr>
<td>Triiodothyronine(T₃)</td>
<td>Thyroid</td>
<td>↑ by hCG; ↑ by TSH; ↓ by T₃/T₄; ↓ by iodine deficiency</td>
</tr>
<tr>
<td>Vasopressin (ADH)</td>
<td>Posterior pituitary§</td>
<td>hypertonicity (↓ H₂O load) → secretion; hypotonicity (↑ H₂O load) → ↓ secretion</td>
</tr>
</tbody>
</table>

† The names and abbreviations in parentheses are synonyms. ‡ Some classifications include the cytokines under the category of growth factors. § The posterior pituitary stores and secretes these hormones; they are made in the hypothalamus. ** conversion from estrogen → testosterone is not possible