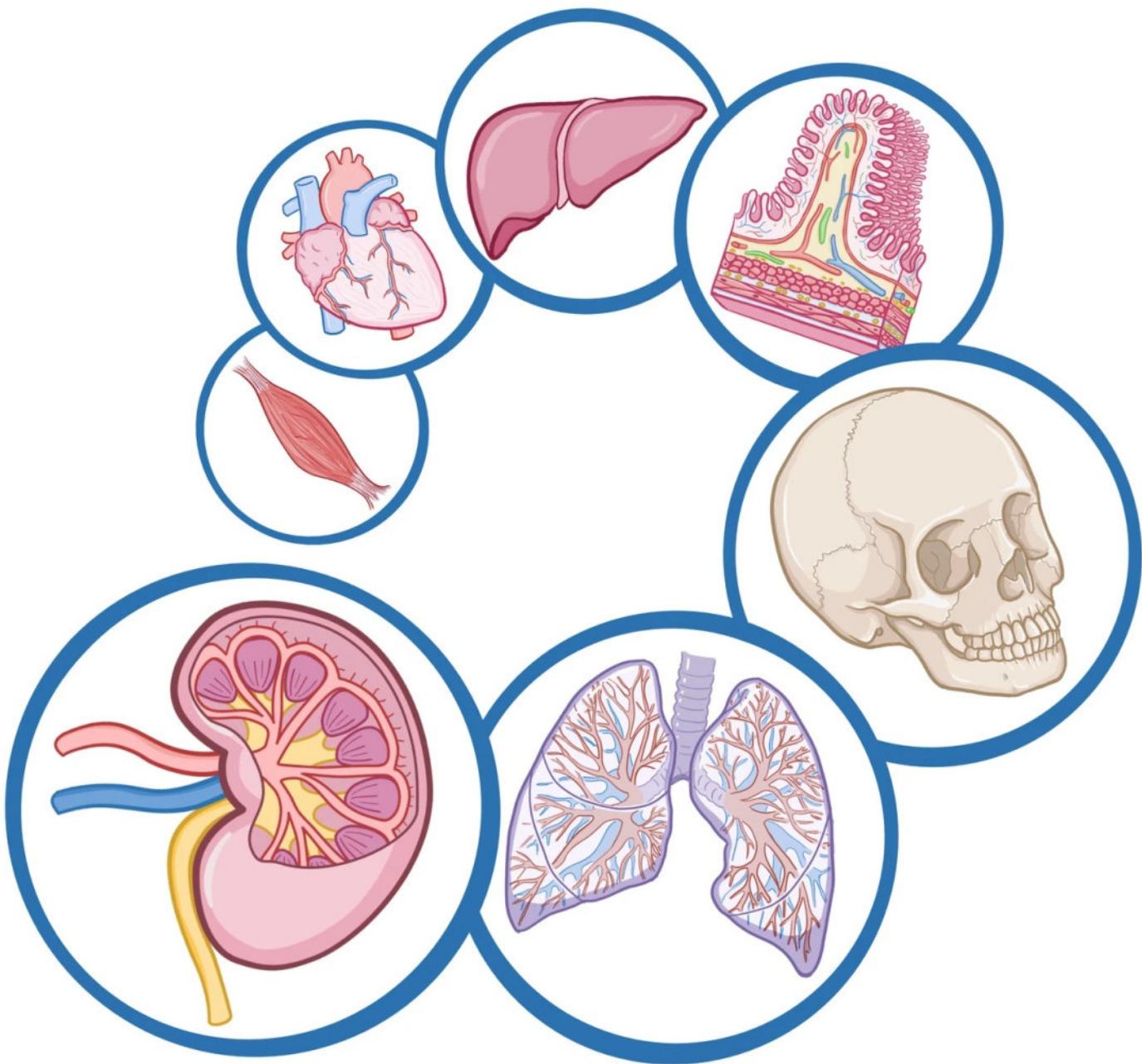


# PHYSIOLOGY



HIGH-YIELD  
NOTES

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# NOTES

## CARBOHYDRATE METABOLISM

# CITRIC ACID CYCLE (KREBS CYCLE)

[osms.it/citric-acid-cycle](https://osms.it/citric-acid-cycle)

- Generates energy in the form of GTP, NADH, and FADH<sub>2</sub>
- Occurs **in mitochondria**
- Starts with acetyl-CoA → CO<sub>2</sub>

### Process

- Acetyl-CoA + oxaloacetate (via citrate synthase) → citrate + CoA
- Citrate (via aconitase) → isocitrate
- Isocitrate + NAD<sup>+</sup> (via isocitrate dehydrogenase) → α-ketoglutarate + NADH + CO<sub>2</sub>
  - Rate-limiting step
- α-ketoglutarate + NAD<sup>+</sup> + CoA-SH (α-ketoglutarate dehydrogenase) → succinyl-CoA + NADH + CO<sub>2</sub>
  - Requires five cofactors: thiamine, lipoic acid, CoA, FAD<sup>+</sup>, NAD<sup>+</sup>
  - See mnemonic
- Succinyl-CoA + phosphate + GDP (via succinate thiokinase) → succinate + GTP
- Succinate + FAD<sup>+</sup> (via succinate dehydrogenase) → fumarate + FADH<sub>2</sub>
- Fumarate + H<sub>2</sub>O (via fumarase) → malate
- Malate + NAD<sup>+</sup> (via malate dehydrogenase) → oxaloacetate + NADH
  - Oxaloacetate then enters next cycle
- Generates one GTP molecule, three NADH molecules, one FADH<sub>2</sub> molecule



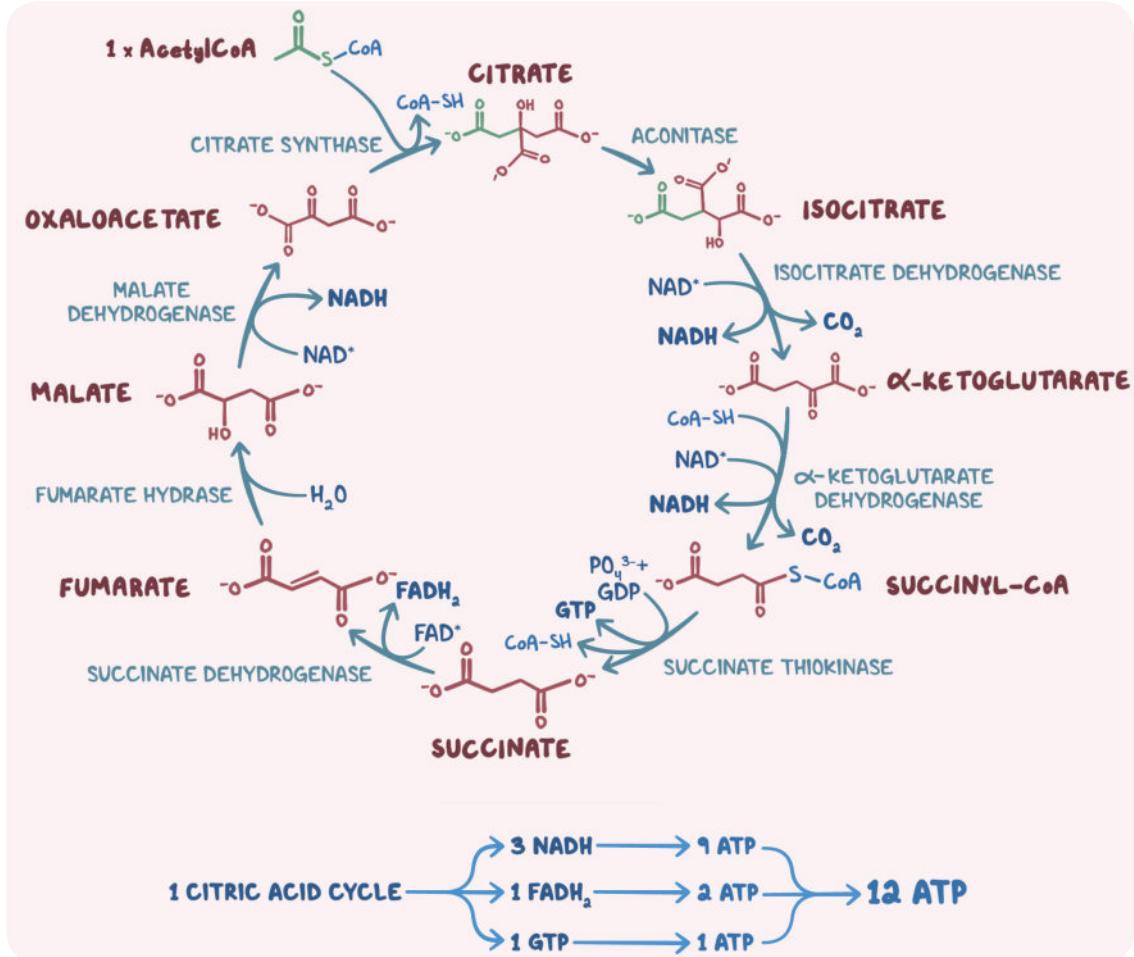
**MNEMONIC: T-rex Loves and Cares For Nachos**

**Five required cofactors**

**T**hiamine  
**L**ipoic **a**cid  
**C**o**A**  
**F**AD<sup>+</sup>  
**N**AD<sup>+</sup>



**Figure 1.1** Mnemonic for the five cofactors required by α-ketoglutarate dehydrogenase.



**Figure 1.2** The citric acid (Krebs) cycle. Each acetyl-CoA molecule generates 12 ATP.

## ELECTRON TRANSPORT CHAIN & OXIDATIVE PHOSPHORYLATION

[osms.it/etc-and-oxidative-phosphorylation](http://osms.it/etc-and-oxidative-phosphorylation)

### Oxidative phosphorylation

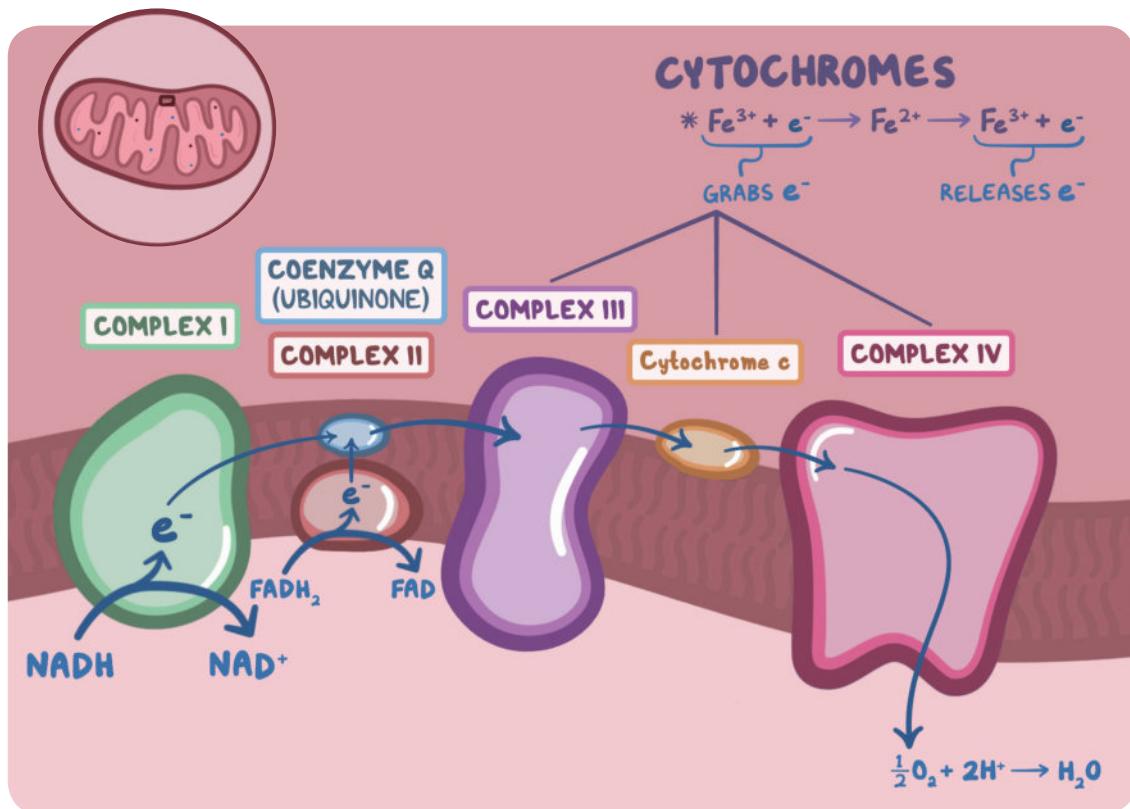
- Generates energy as ATP
- Occurs in inner mitochondrial membrane

### Electron transport chain

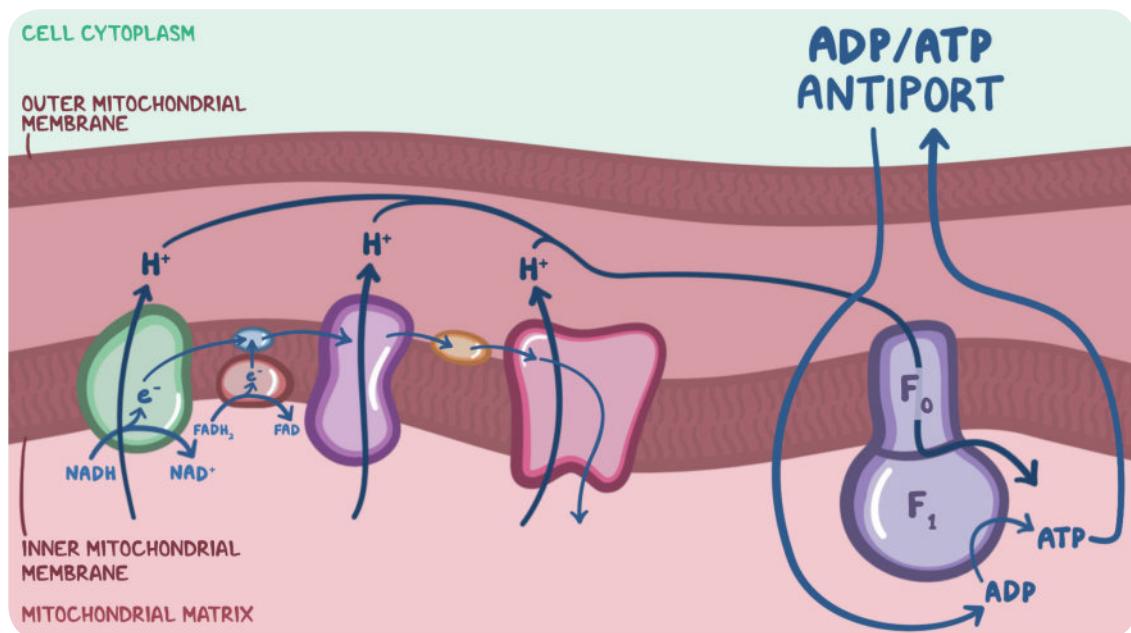
- Series of proteins, lipids, metals that facilitates electron movement → proton gradient used to create ATP
- Starts with electron donors NADH, FADH<sub>2</sub>
  - NADH from cytoplasm comes through malate-aspartate shuttle

- FADH<sub>2</sub> from cytoplasm comes through glycerol-3-phosphate shuttle
- NADH donates electron to complex I (contains flavin mononucleotide, iron-sulfur centers) → NAD<sup>+</sup>
- FADH<sub>2</sub> donates electron to complex II (i.e. succinate dehydrogenase) → FAD
- Electrons from either complex flow into coenzyme Q (ubiquinone)
- Coenzyme Q passes electrons to cytochromes (proteins with heme)

- groups —  $\text{Fe}^{3+} + \text{e}^- \leftrightarrow \text{Fe}^{2+}$ ): complex III (cytochromes b and c1) → cytochrome c → complex IV (cytochrome oxidase: cytochromes a, a3) → oxygen
- Movement of electrons → electrical current → complexes I, III, IV use this energy to pump protons across inner mitochondrial membrane
  - Protons can move back into mitochondria through  $\text{F}_0 \rightarrow$  proton gradient forms, powering  $\text{F}_1: \text{ADP} \rightarrow \text{ATP}$ 
    - Collectively called complex V
  - An ADP/ATP antiport pumps ATP into cytoplasm of the cell, supplies complex V with new ADP



**Figure 1.3** The flow of electrons through the electron transport chain, which takes place in the inner mitochondrial membrane.



**Figure 1.4** Oxidative phosphorylation. The passing of electrons along the electron transport chain generates an electrical current, which provides the energy that allows complexes I, III, and IV to pump protons into the space between the inner and outer mitochondrial membranes. This creates a gradient across the inner mitochondrial membrane. The protons use proton channel  $F_0$  to flow down the gradient, back into the mitochondrial matrix.  $F_0$  is attached to enzyme  $F_1$ , an ATP synthase, which uses the proton gradient to phosphorylate  $ADP \rightarrow ATP$ .

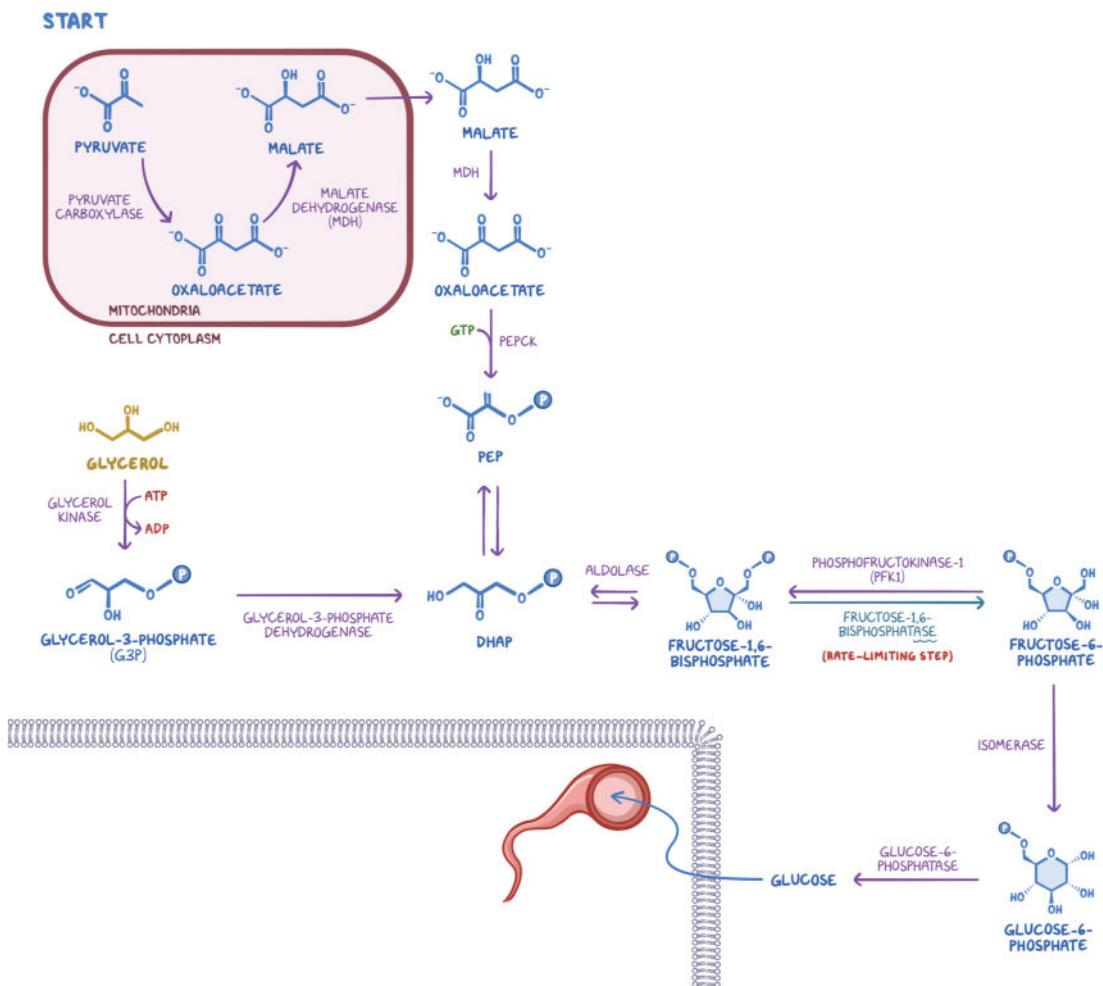
## GLUCONEOGENESIS

[osms.it/gluconeogenesis](http://osms.it/gluconeogenesis)

- Synthesis of glucose from non-carbohydrate substrates
    - E.g. amino acids, lactate, glycerol
  - Occurs primarily in liver cells; also in epithelial cells of kidney, intestine
    - Inside cytoplasm, mitochondria, endoplasmic reticulum
  - Starts with glycogenolysis after glucose depletion
- Process**
- Like backwards glycolysis, with three exceptions
  - Obtaining pyruvate
    - Lactate (via lactate dehydrogenase)  $\rightarrow$  pyruvate
    - Amino acids (not leucine, lysine); e.g. alanine (via alanine transaminase)  $\rightarrow$  pyruvate
- Pyruvate
  - Obtaining ATP, glycerol
    - Triacylglyceride breakdown  $\rightarrow$  fatty acids and glycerol  $\rightarrow$  acetyl CoA + ATP ( $\beta$ -oxidation)
  - Pyruvate (via pyruvate carboxylase)  $\rightarrow$  oxaloacetate
  - Oxaloacetate (malate dehydrogenase)  $\rightarrow$  malate
  - Malate leaves mitochondria; malate (via malate dehydrogenase)  $\rightarrow$  oxaloacetate
  - Oxaloacetate (via PEPCK)  $\rightarrow$  phosphoenolpyruvate (PEP)
  - PEP undergoes reversed glycolysis reactions until dihydroacetone-phosphate (DHAP)
    - Alternatively, glycerol (via glycerol kinase)  $\rightarrow$  glycerol-3-phosphate;

- glycerol-3-phosphate (via glycerol-3-phosphate dehydrogenase) → DHAP
- DHAP (via aldolase) → fructose-1,6-bisphosphate
  - Fructose-1,6-bisphosphatase → fructose-6-phosphate
    - Rate-limiting step

- Fructose-6-phosphate (via isomerase) → glucose-6-phosphate
- Glucose-6-phosphate (via glucose-6-phosphatase) → glucose



**Figure 1.5** The process of gluconeogenesis.

# GLYCOGEN METABOLISM

[osms.it/glycogen-metabolism](http://osms.it/glycogen-metabolism)

- Polymer of glucose molecules linked by glycosidic bonds
- Stores energy in skeletal muscle, liver

## Glycogen synthesis

- Glucose + phosphate (via hexokinase) → glucose-6 phosphate
- Glucose-6 phosphate (via phosphoglucomutase) → glucose-1-phosphate + energy (UTP)
- Glucose-1-phosphate + UTP (via UDP-glucose pyrophosphorylase) → UDP-glucose
- UDP-glucose added (via glycogen synthase) to glycogen branch/glycogenin (→ alpha-1,4-glycosidic bond)
- Branching enzyme cuts off part of glucose chain, creates branch (→ alpha-1,6-glycosidic bond)

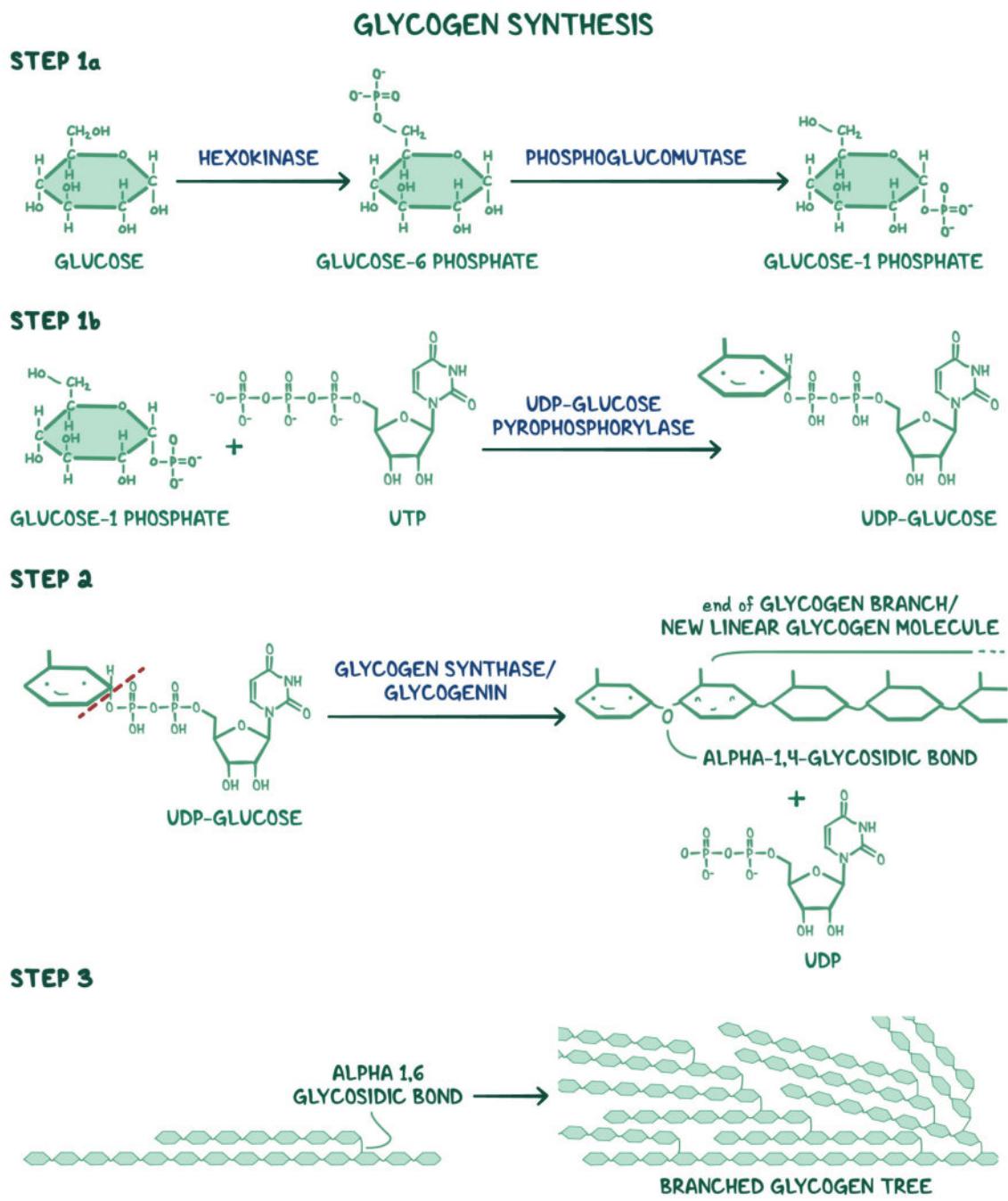
## Glycogen breakdown, AKA glycogenolysis

- Glucagon → liver breakdown of glycogen
- Epinephrine → skeletal muscle breakdown of glycogen
- Glycogen phosphorylase cleaves alpha-1,4 bonds on branches; catalyzes phosphate transfer to glucose residue → one glucose-1-phosphate is released at a time
  - Repeats until branch is only 4 glucose units long
- Debranching enzyme: 4-alpha-glucanotransferase moves 3 glucose units off branch, onto main chain; alpha-1,6-glucosidase cleaves last remaining glucose

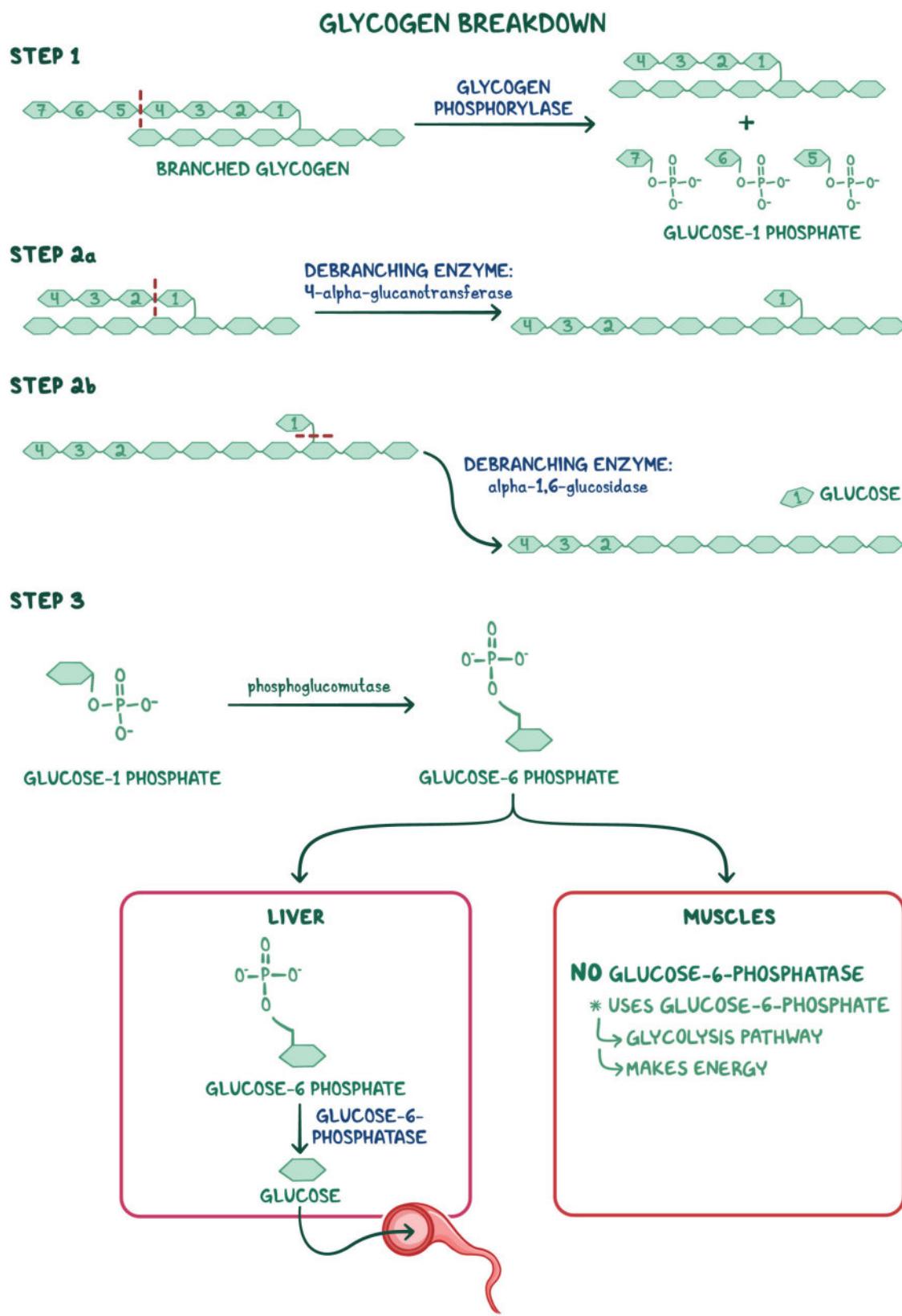
- Cleaved glucose-1-phosphate (via phosphoglucomutase) → glucose-6-phosphate
  - With glucose-6-phosphate
- In liver cells, glucose-6-phosphatase removes phosphate → free glucose into blood
- In skeletal muscle, glucose-6-phosphate → glycolysis pathway

## Regulation

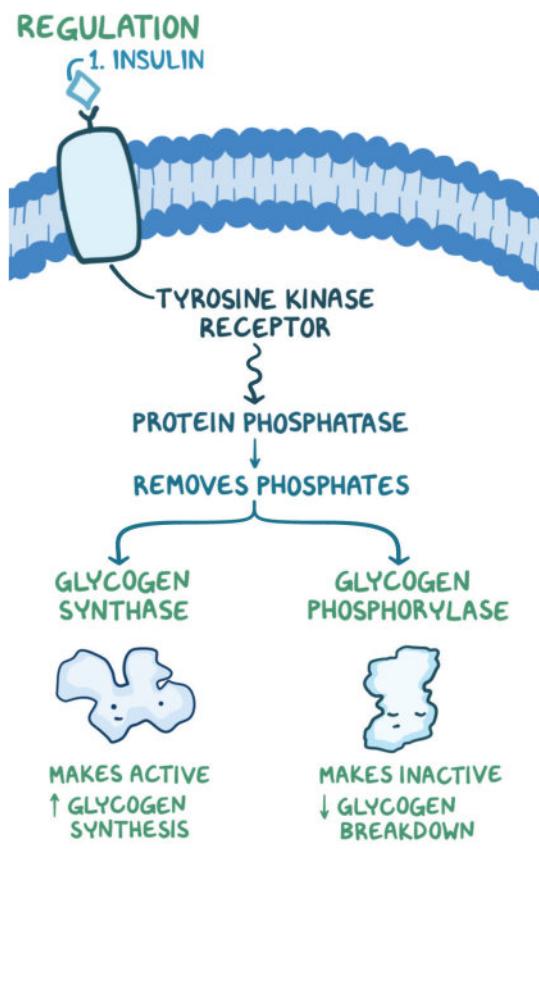
- Principles
  - Glycogen synthase: active without phosphate
  - Glycogen phosphorylase: active with phosphate
- Hormones
  - Insulin: binds to membrane tyrosine kinase receptors → protein phosphatase removes phosphates → glycogen synthase activates, glycogen phosphorylase deactivates
  - Glucagon: binds to membrane G-protein coupled receptors (in liver) → ATP (adenylyl cyclase) → cAMP → kinase A → adds phosphates → glycogen phosphorylase activates, glycogen synthase deactivates



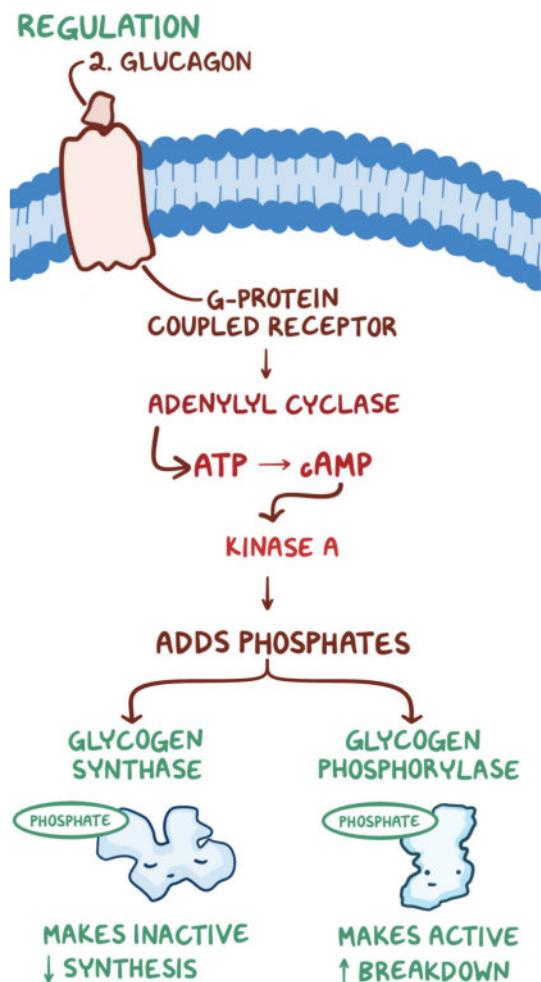
**Figure 1.6** The process of glycogen synthesis.



**Figure 1.7** Glycogen breakdown. The process is completed differently in the liver and skeletal muscles due to the respective presence and absence of glucose-6-phosphatase in each.



**Figure 1.8** The role of insulin in the regulation of glycogen levels.



**Figure 1.9** The role of glucagon in the regulation of glycogen levels.

## GLYCOLYSIS

[osms.it/glycolysis](http://osms.it/glycolysis)

- Energy-producing breakdown of glucose into pyruvate
- Occurs in **cytoplasm** of all cells

### PROCESS

- Glucose transporter (GLUT) carries glucose into cell
- Kinases (hexokinase, glucokinase) phosphorylate glucose → conformational change, i.e. glucose can't diffuse out) →

- glucose-6-phosphate
  - Uses one ATP molecule
- Glucose-6-phosphate (via phosphoglucoisomerase) → fructose-6-phosphate
- Fructose-6-phosphate (via **phosphofructokinase-1**) → fructose-1,6-bisphosphate
  - **Rate-limiting step**
  - Uses one ATP molecule

### Enzyme activation

- Fructose-6-phosphate (via phosphofructokinase-2) → fructose-2,6-bisphosphate
  - Up-regulated by insulin; down-regulated by glucagon
  - Fructose-2,6-bisphosphate activates phosphofructokinase-1
- Fructose-1,6-bisphosphate (via aldolase)  
→ glyceraldehyde 3-phosphate (G3P) + dihydroacetone-phosphate (DHAP)
  - DHAP (via isomerase) → G3P → 2x G3P molecules per glucose
- G3P (via G3P-dehydrogenase) → 1,3-diphosphoglycerate (1,3-BPG); H<sup>+</sup> + NAD<sup>+</sup> → NADH (x2)
  - 2x NADH enter electron transport chain
- 1,3-BPG + ADP (via phosphoglycerate kinase) → 3-phosphoglycerate + ATP (x2)
  - Creates two ATP molecules
- 3-phosphoglycerate (via mutase) → 2-phosphoglycerate (x2)
- 2-phosphoglycerate (via enolase) → phosphoenolpyruvate (PEP) + H<sub>2</sub>O (x2)
- PEP + ADP (via pyruvate kinase) → pyruvate + ATP (x2)
  - Creates two ATP molecules
  - Up-regulated by fructose-1,6-bisphosphate (feed-forward regulation)
  - Down-regulated by ATP, alanine
- In total, process generates two ATP molecules
- In cells with oxygen, pyruvate enters citric acid cycle, electron transport chain to make more ATP
  - 30–32 in total

# PENTOSE PHOSPHATE PATHWAY

[osms.it/pentose-phosphate-pathway](http://osms.it/pentose-phosphate-pathway)

- Synthesis of ribose, NADPH from unused glucose
- Occurs in cytoplasm of all cells

### Irreversible oxidative phase

- Glucose-6-phosphate + NADP<sup>+</sup> (via glucose-6-phosphate dehydrogenase) → 6-phosphogluconate + NADPH
  - Rate-limiting step
- 6-phosphogluconate + NADP<sup>+</sup> (6-phosphogluconate dehydrogenase) → ribulose-5-phosphate + NADPH + CO<sub>2</sub>

### Reversible non-oxidative phase

- Two options:
  - Ribulose-5-phosphate (via isomerase) → ribose-5-phosphate
  - Ribulose-5-phosphate (via epimerase) → xylulose-5-phosphate

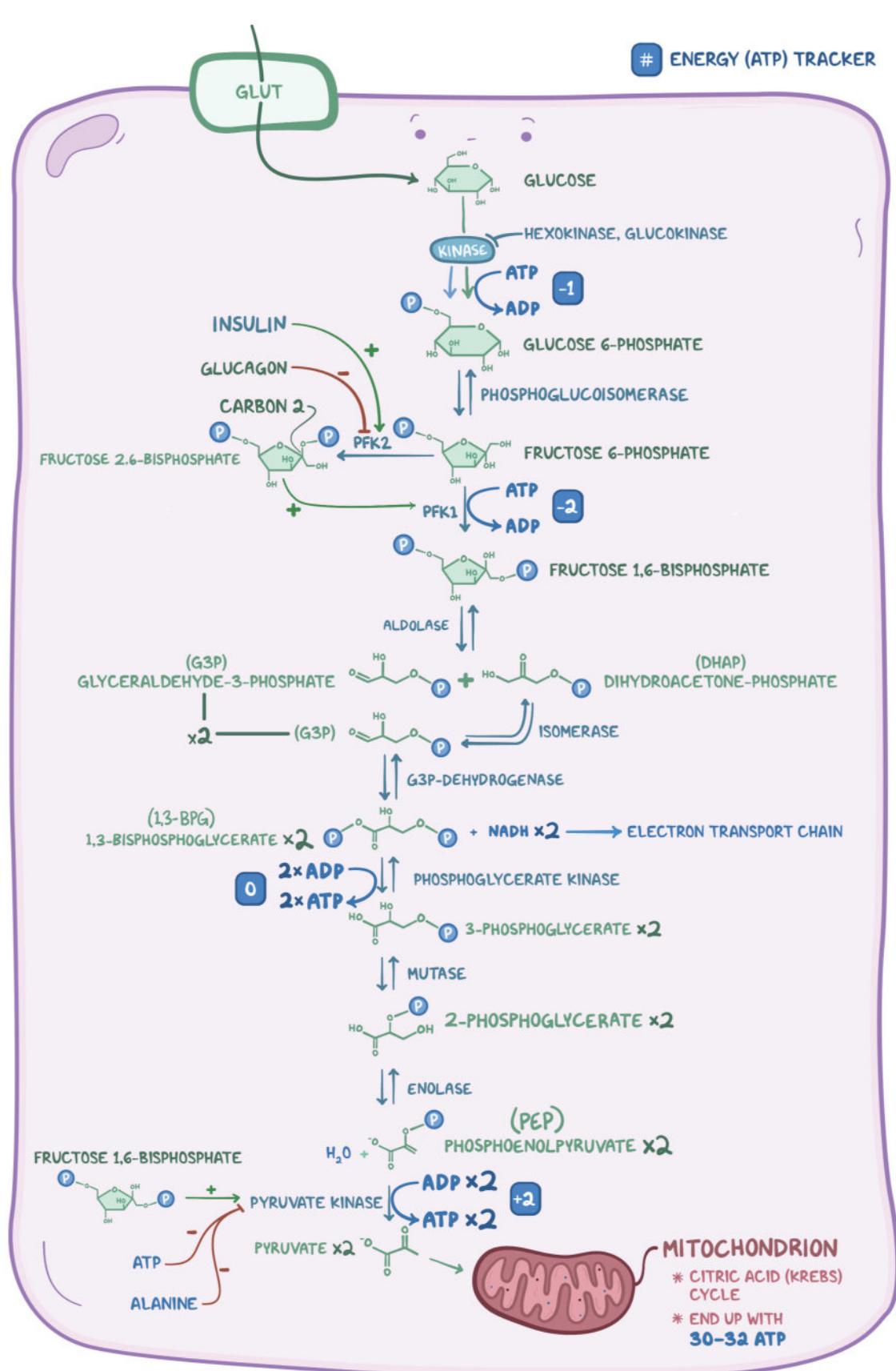
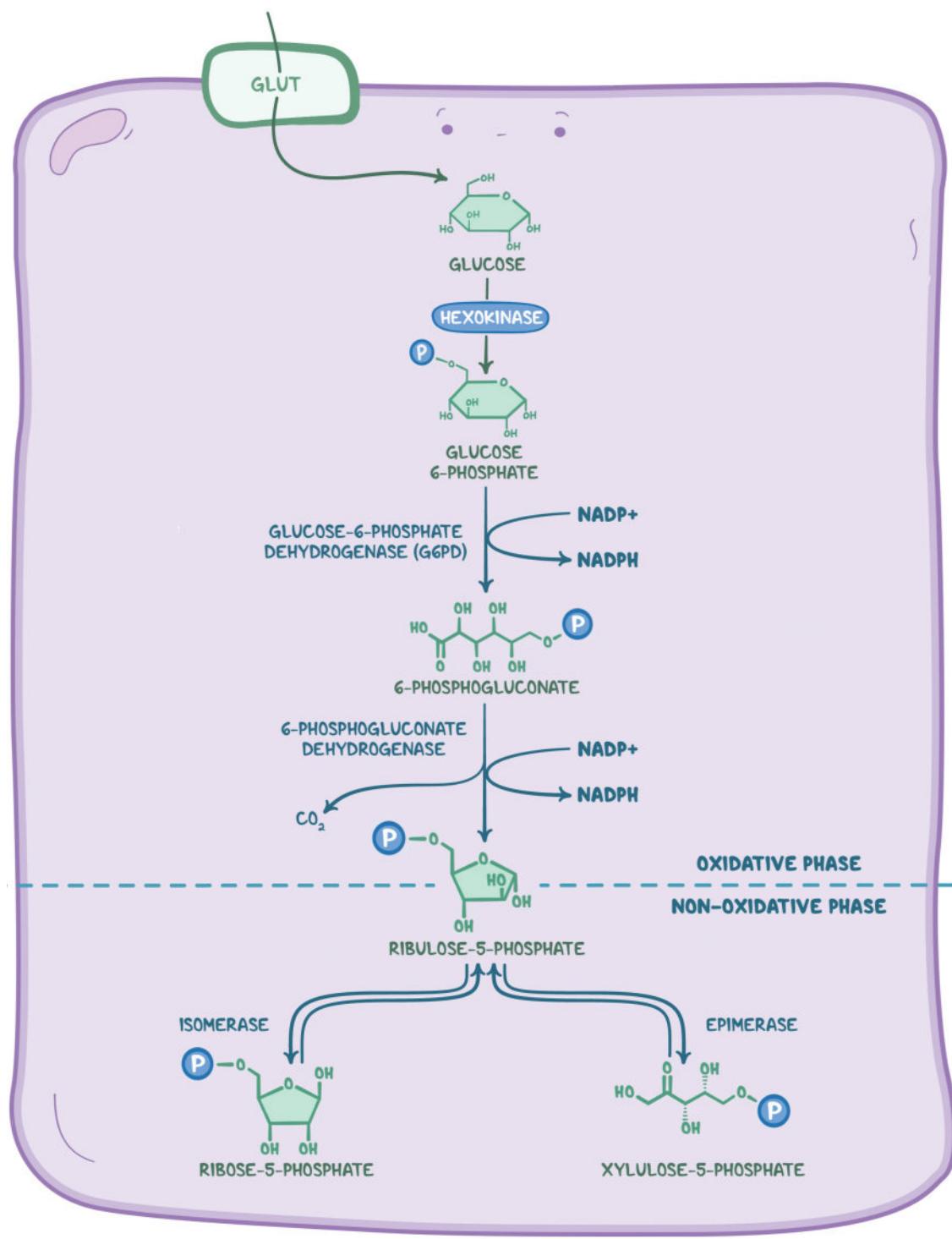


Figure 1.10 Glycolysis.



**Figure 1.11** Pentose phosphate pathway.



# NOTES

## FAT & CHOLESTEROL METABOLISM

# CHOLESTEROL METABOLISM

[osms.it/cholesterol-metabolism](http://osms.it/cholesterol-metabolism)

- Cholesterol insoluble in water → moves through blood stream with lipoproteins
- Cholesterol used in cell membrane for flexibility, durability
  - At ↓ temperature, cholesterol squeezed between phospholipid molecules, keeps membrane fluid
  - At ↑ temperature, cholesterol pulls phospholipid molecules together
- Cholesterol used by adrenal glands, gonads; makes steroid hormones
  - Adrenal glands form corticosteroids (e.g. cortisol, aldosterone); testes (testosterone); ovaries (estradiol, progesterone)

## CHOLESTEROL SYNTHESIS

- Mevalonate pathway; occurs in smooth endoplasmic reticulum

### Pathway

- Two acetyl-CoA molecules joined by acetyl-CoA acyltransferase → acetoacetyl-CoA, CoA
- HMG-CoA synthase combines acetoacetyl-CoA, acetyl-CoA → 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), CoA
- HMG-CoA reductase reduces HMG-CoA into mevalonate, removes CoA-SH, water
  - Rate limiting cholesterol synthesis step
- Mevalonate-5-kinase uses ATP to phosphorylate mevalonate → mevalonate-5-phosphate
- Phosphomevalonate kinase uses ATP to phosphorylate mevalonate-5-phosphate → mevalonate pyrophosphate
- Mevalonate pyrophosphate decarboxylase removes carboxyl group → isopentenyl pyrophosphate

- Geranyl transferase condenses three isopentenyl pyrophosphate molecules → farnesyl pyrophosphate
- Squalene synthase condenses two farnesyl pyrophosphate molecules → squalene
- Oxidosqualene cyclase converts squalene into lanosterol (cyclization)
- Lanosterol converted into 7-dehydrocholesterol, eventually cholesterol

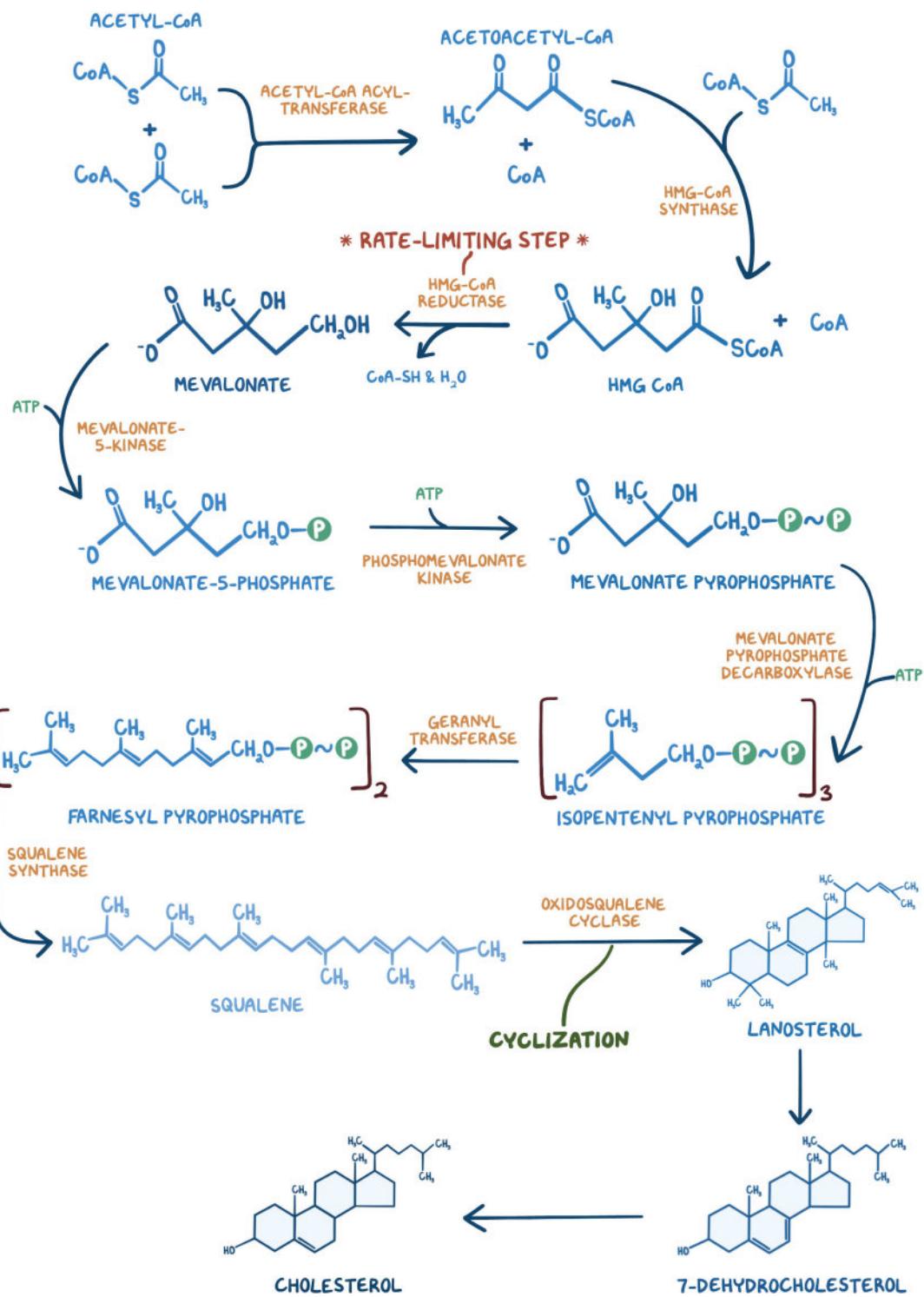
### Cholesterol synthesis regulation

- SREBP, INSIG1, SCAP (collection of proteins)
  - ↓ cholesterol → INSIG1 falls off of SCAP-SREBP → SREBP cleaving → binds sterol regulatory element → ↑ HMG-CoA reductase gene expression

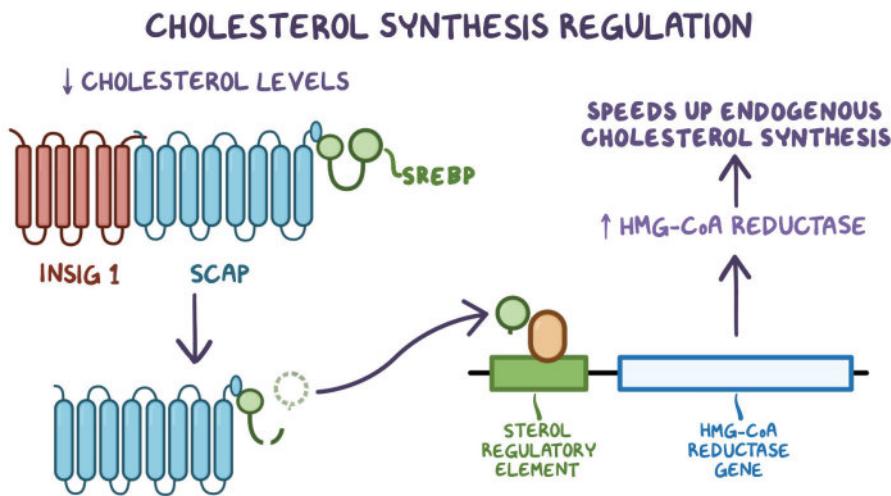
## CHOLESTEROL USE & STORAGE

- Majority of cholesterol used by liver, ends up as bile acids
- Include cholic acids, chenodeoxycholic acids
  - Conjugation with taurine forms taurocholic acid, taurochenodeoxycholic acid respectively
  - Conjugation with glycine forms glycocholic acid, glycochenodeoxycholic acid respectively
- Stored in gallbladder
- Released into intestines after meals, aids fat digestion
- Most reabsorbed by intestine; some eliminated through feces
  - Enterohepatic circulation: reabsorbed bile acids enter portal bloodstream, return to liver cells

## CHOLESTEROL SYNTHESIS      MEVALONATE PATHWAY



**Figure 2.1** Cholesterol synthesis via the mevalonate pathway.



**Figure 2.2** Cholesterol synthesis regulation.

## FATTY ACID SYNTHESIS

[osms.it/fatty-acid-synthesis](http://osms.it/fatty-acid-synthesis)

- Fatty acids: simplest lipid form
  - Long carbon, hydrogen chain atoms
  - Classification: short, medium, long, very long chain fatty acids
- Short, medium chain fatty acids
  - Primarily obtained from diet
- Long, very long chain fatty acids
  - Synthesized by liver, fat cells
- **Synthesis:** combine acetyl-CoA molecules into palmitoyl-CoA
  - 16 carbon chain fatty acid; precursor to longer chain fatty acids

### BEFORE FATTY ACID SYNTHESIS

- Acetyl-CoA must be obtained
- In response to insulin, cells take in glucose
  - Consumed as carbohydrates
- In cell, glycolysis breaks glucose down into pyruvate molecules
- Mitochondria convert pyruvate into acetyl-CoA using pyruvate dehydrogenase
- Typically, acetyl-CoA combines with oxaloacetate, enters citric acid cycle → forms citrate → forms electron carriers (join electron transport chain in oxidative

phosphorylation) → creates adenosine triphosphate (ATP)

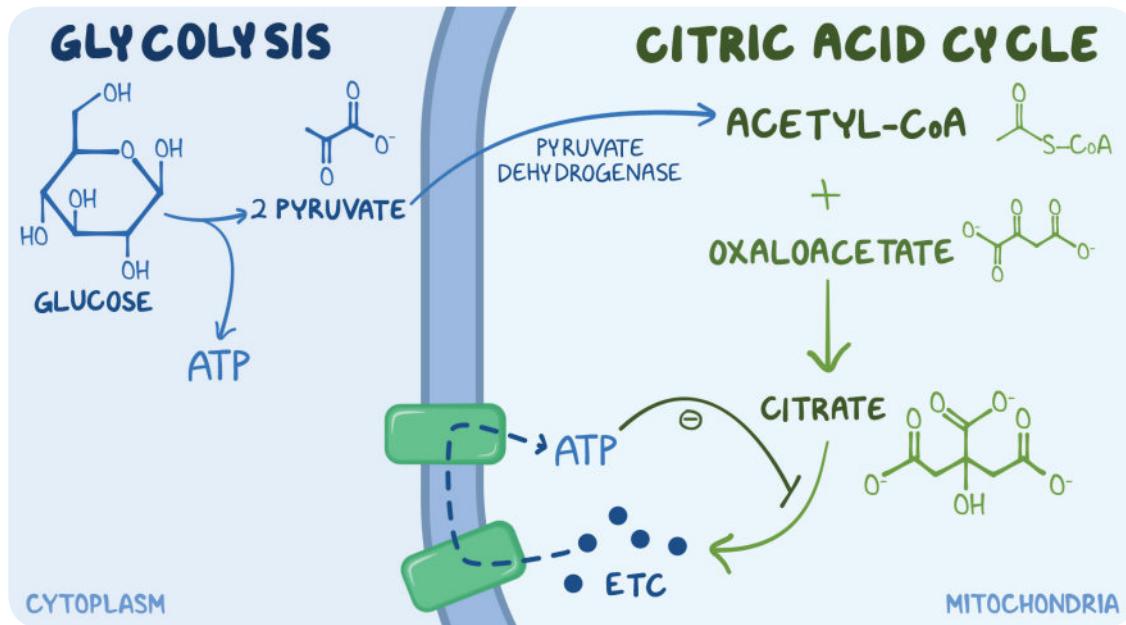
### FATTY ACID SYNTHESIS

- ATP inhibits enzymes needed for citric acid cycle
  - Allows additional acetyl-CoA to be funneled toward pathways involving fatty acid synthesis

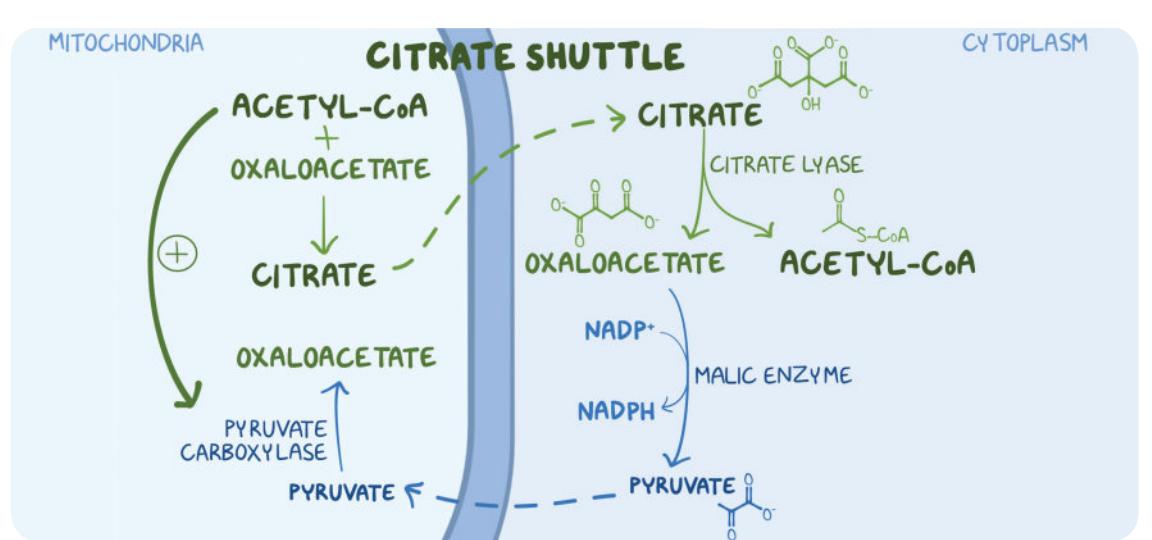
#### Stages

- Acetyl-CoA combines with oxaloacetate → forms citrate → crosses mitochondrial membrane into cytoplasm
- In cytoplasm, citrate lyase cleaves citrate into acetyl-CoA, oxaloacetate
  - Malic enzyme converts oxaloacetate into pyruvate ( $\text{NADP}^+ \rightarrow \text{NADPH}$  in process), which can cross back into membrane
  - Then converted back into oxaloacetate by pyruvate carboxylase
- Acetyl-CoA carboxylase adds carboxyl group to acetyl-CoA → forms malonyl-CoA
  - Rate limiting fatty acid synthesis step
  - Requires ATP, biotin, carbon dioxide (A-

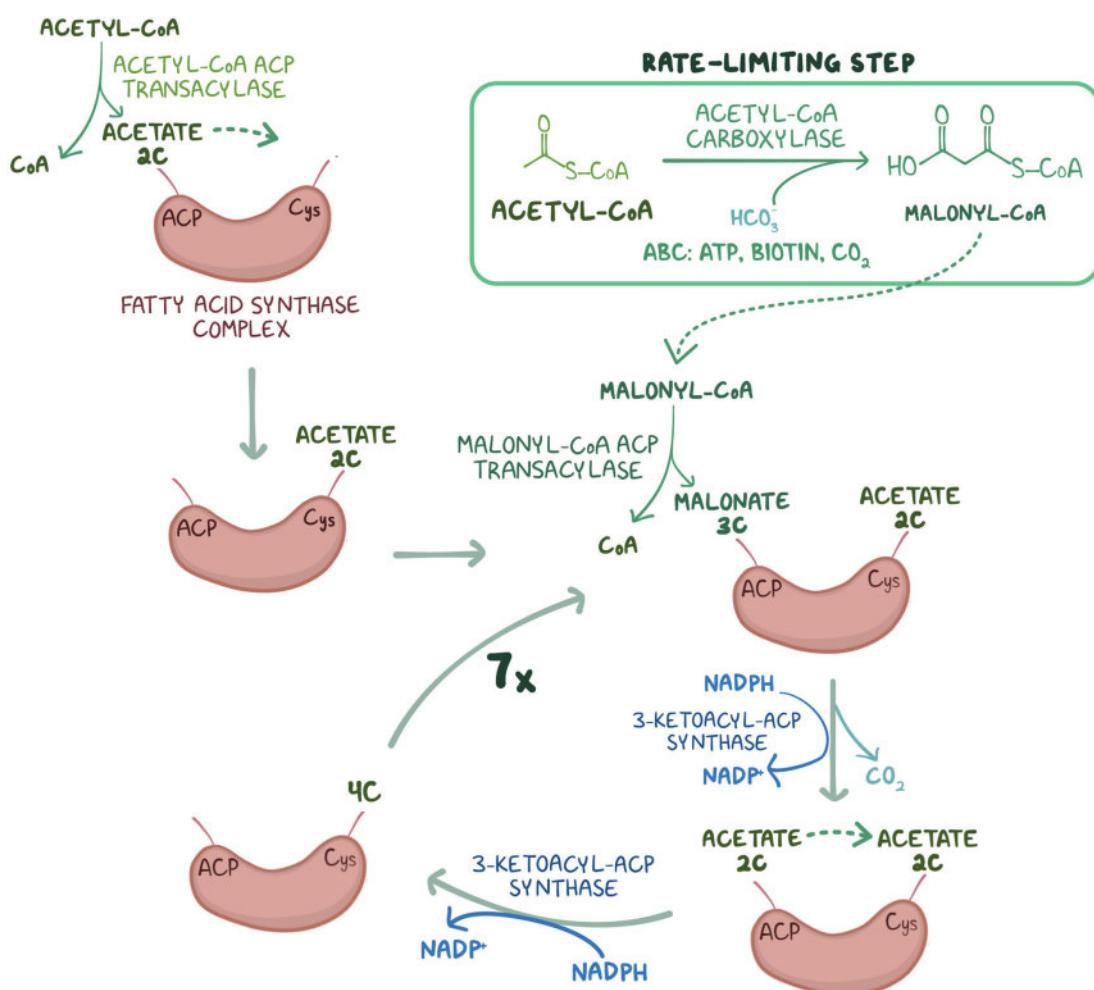
- B-C) as cofactors
- Acetyl-CoA carboxylase: tightly regulated (hormonal, allosteric regulation); hormonal regulation uses insulin, glucagon to remove/add phosphate group on acetyl-CoA carboxylase; insulin ↑ activity/vice versa; allosteric regulation uses citrate, fatty acids to ↑/↓ acetyl-CoA carboxylase activity by allosteric binding
- Multiple enzymes form fatty acid synthase complex (acyl carrier protein (ACP) on one end, cysteine amino acid on other)
- Acetyl-CoA ACP transacylase removes CoA group from acetyl-CoA, attaching resulting acetate to ACP → moves to cysteine residue
- Malonyl-CoA ACP transacylase removes CoA group from malonyl-CoA, attaching resulting malonate to ACP
- 3-ketoacyl-ACP synthase cuts off carbon (was added to malonate earlier), released as CO<sub>2</sub> (leaving behind acetate) → condenses it with acetate on cysteine residue → forms four carbon chain (using one NADPH molecule for each process)
- Malonyl-CoA added across seven cycles forming 16 carbon chain fatty acid polymer
  - Each cycle uses one acetyl-CoA (converted into malonyl-CoA), two NADPH molecules
- In total, eight acetyl-CoA molecules (including initial molecule) used along with 14 NADPH molecules



**Figure 2.3** Acetyl-CoA is produced by mitochondria using pyruvate molecules (made during glycolysis). ATP inhibits citric acid cycle enzymes so that acetyl-CoA can be used in fatty acid synthesis pathways.



**Figure 2.4** The citrate shuttle transports acetyl-CoA out of the mitochondria by combining it with oxaloacetate to form citrate. Once citrate is in the cytoplasm, it is converted back to oxaloacetate and acetyl-CoA, allowing acetyl-CoA to be used in fatty acid synthesis.



**Figure 2.5** Fatty acid synthesis. Malonyl-CoA added across seven cycles → 16 carbon chain fatty acid polymer called palmitoyl-CoA.

# FATTY ACID OXIDATION

[osms.it/fatty-acid-oxidation](https://osms.it/fatty-acid-oxidation)

- AKA  $\beta$ -oxidation
- Fatty acids broken down to produce energy
- Takes place in mitochondria of heart, skeletal muscles, liver cells

## OXIDATION PREPARATION

- Triglycerides (three fatty acids attached to glycerol) in adipocytes → broken down by hormone sensitive lipase
  - ↓ blood glucose → ↑ glucagon → ↑ hormone sensitive lipase → ↑ fatty acid breakdown
- Fatty acids leave fat cells → enter bloodstream
- Albumin in blood binds to fatty acids → carries them to target cells
- Fatty acid dissociates from albumin → diffuses into cell
- Fatty acyl-CoA synthetase adds CoA to end of fatty acid (→ fatty acyl-CoA), using up two ATP molecules
- Fatty acyl-CoA cannot cross cell membrane, carnitine shuttle used
  - Carnitine acyltransferase 1 (outer membrane) replaces CoA on fatty acid with carnitine (→ fatty acyl-carnitine)
  - Fatty acyl-carnitine, CoA cross inner mitochondrial membrane
  - Carnitine acyltransferase 2 (inner membrane) replaces carnitine on fatty acid with CoA (→ fatty acyl-CoA)

## OXIDATION PROCESS

- Occurs on  $\alpha$ ,  $\beta$  carbon atoms of fatty acyl-CoA
  - Acyl-CoA dehydrogenase moves one hydrogen from each carbon to nearby flavin adenine dinucleotide molecule (FAD) → FADH<sub>2</sub>, enoyl-CoA
  - Enoyl-CoA hydratase transfers hydroxyl group to  $\beta$  carbon →  $\beta$ -hydroxyacyl-CoA
  - $\beta$ -hydroxyacyl-CoA dehydrogenase removes two hydrogens from  $\beta$  carbon

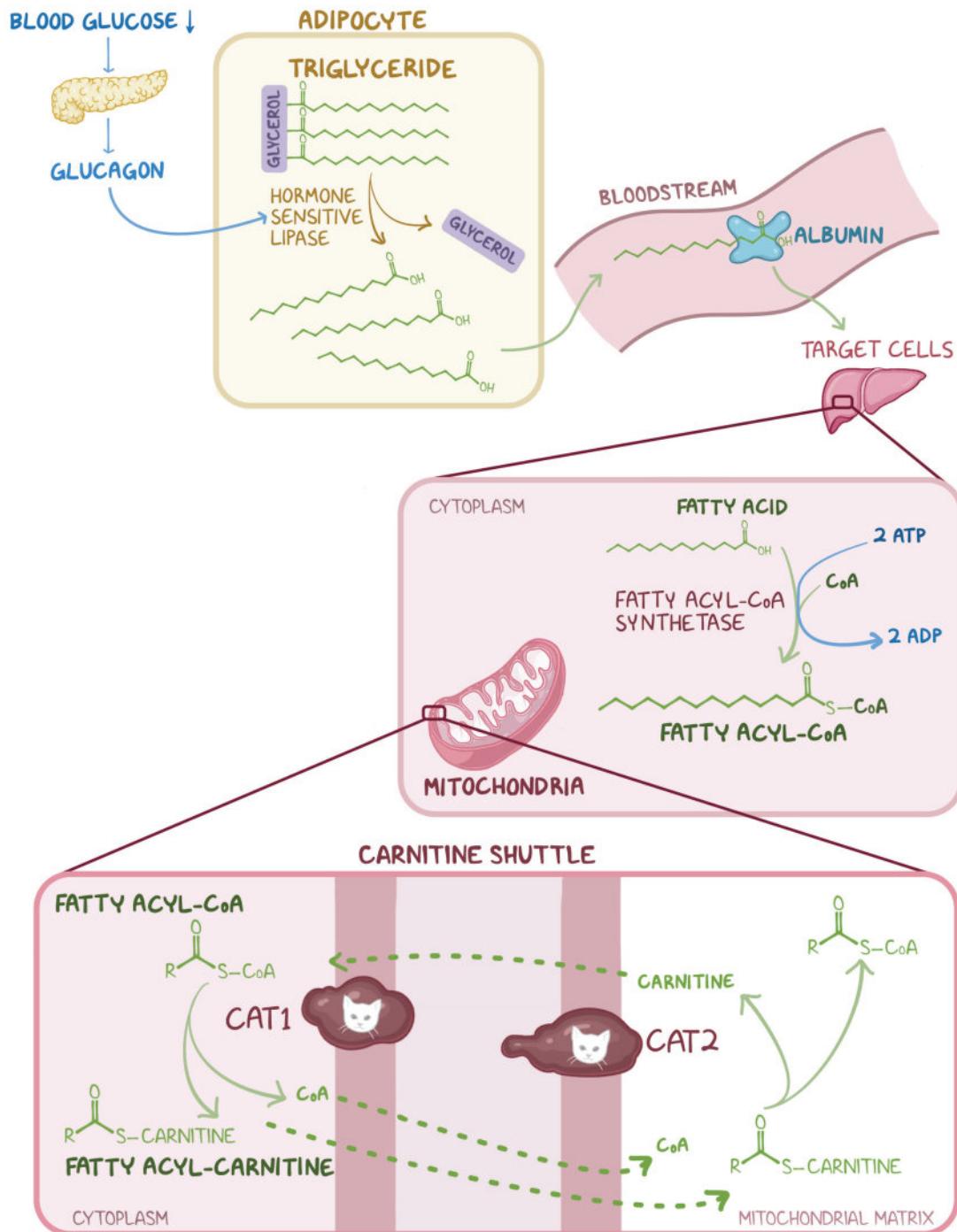
transferring one to nicotinamide adenine dinucleotide (NAD) → NADH,  $\beta$ -ketoacyl-CoA

- $\beta$ -ketothiolase cleaves off two carbon atoms → acetyl-CoA, fatty acyl-CoA molecule (two carbons shorter—which can be further oxidized)

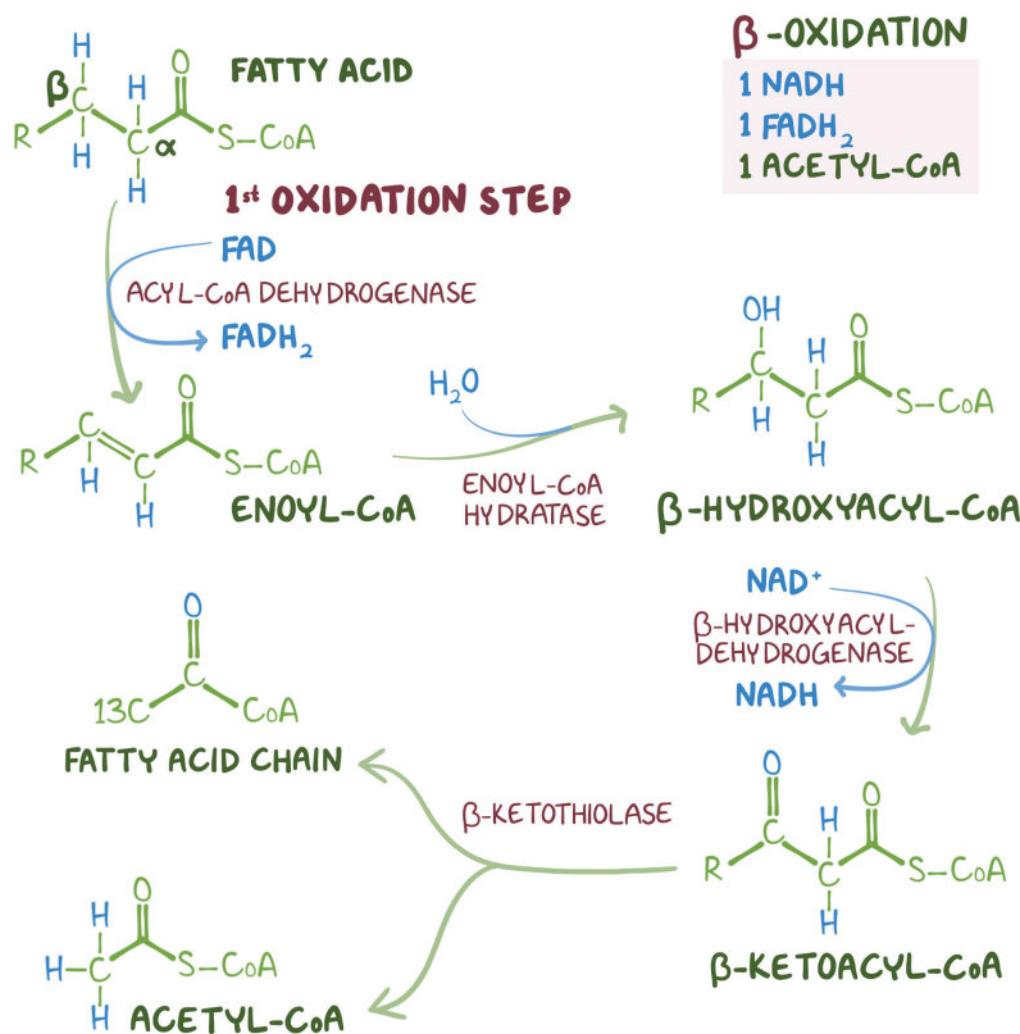
## OXIDATION CYCLE

- One oxidation cycle: 1 NADH, 1 FADH<sub>2</sub>, 1 acetyl-CoA
- Fatty acids with even number of carbon atoms
  - Oxidation repeats until just acetyl-CoA remains
- Fatty acids with odd number of carbon atoms
  - Oxidation repeats until three carbon propionyl-CoA is left; propionyl-CoA is broken down differently
- Propionyl-CoA carboxylase
  - Adds carboxyl group to propionyl-CoA → methylmalonyl-CoA
  - Cofactors required: ATP, biotin, carbon dioxide (A-B-C)
- Methylmalonyl-CoA mutase
  - Rearranges carbon atoms on methylmalonyl-CoA → succinyl-CoA
  - Cofactor required: Vitamin B<sub>12</sub>
- Succinyl-CoA
  - Can enter citric acid cycle/used for heme synthesis
- Very long fatty acids (22 carbons atom/longer)
  - Peroxisomes may be needed
  - Peroxisomal oxidation uses different enzymes until fatty acid is smaller than 22 carbon atoms
- NADH, FADH<sub>2</sub>
  - Can enter electron transport chain
  - Creates ATP → approximately three + two ATP molecules

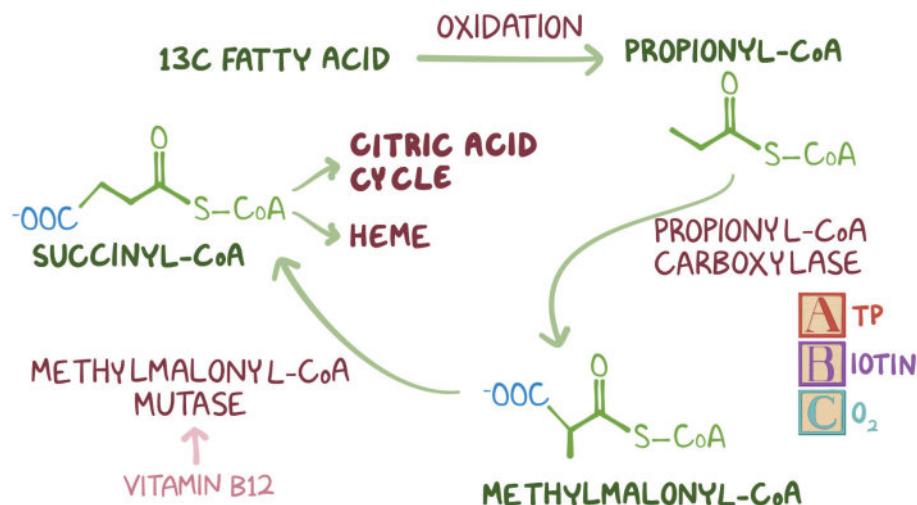
- Acetyl-CoA
  - Can enter citric acid cycle
  - Creates more NADH, FADH<sub>2</sub> → approximate total of 12 ATP molecules



**Figure 2.6** Oxidation preparation requires the use of two ATP molecules and results in fatty acyl-CoA being present in the mitochondrial matrix.



**Figure 2.7** Oxidation preparation requires the use of two ATP molecules and results in fatty acyl-CoA being present in the mitochondrial matrix.



**Figure 2.8** Fatty acid oxidation when the fatty acid has an odd number of carbon atoms.

# KETONE BODY METABOLISM

[osms.it/ketone-body-metabolism](https://osms.it/ketone-body-metabolism)

## KETONE BODIES

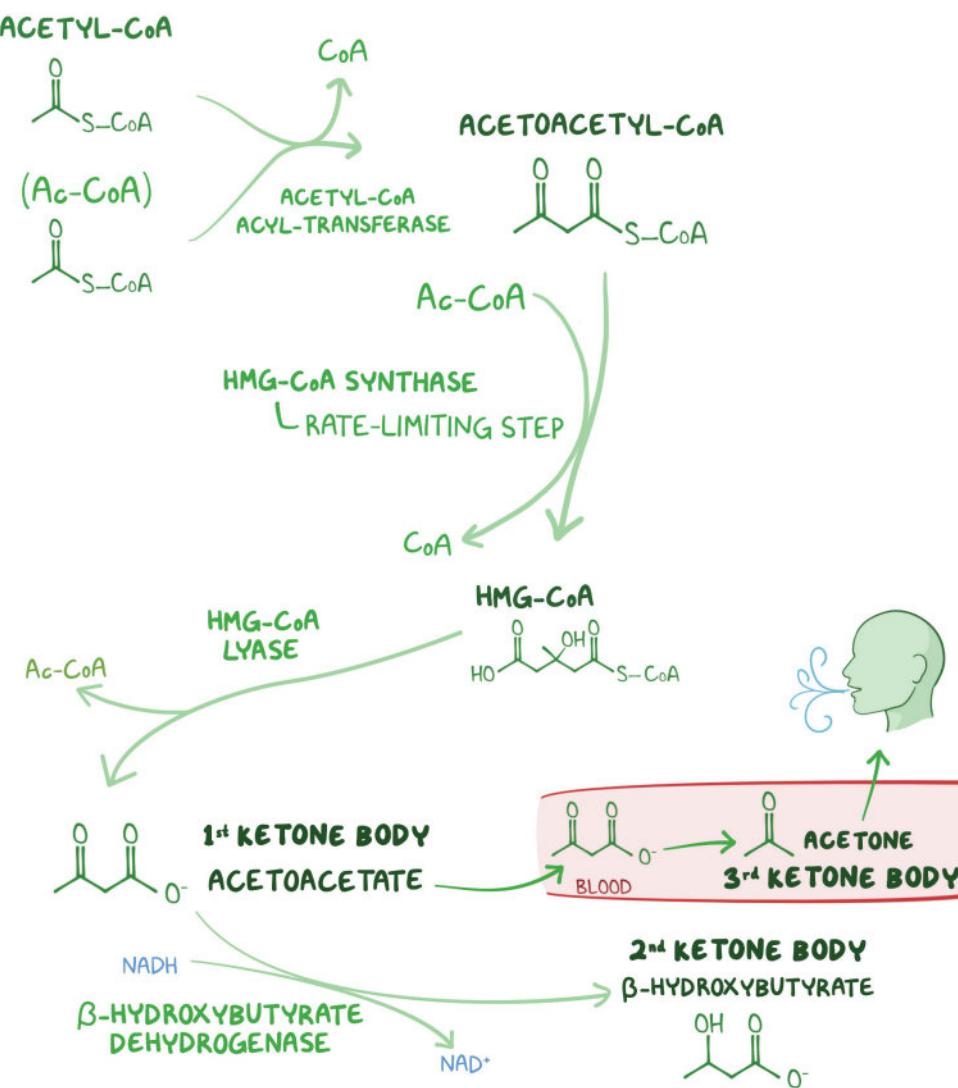
- Acetoacetate,  $\beta$ -hydroxybutyrate, acetone (all contain ketone C=O group)
- Produced by liver mitochondria using acetyl-CoA
  - During physiological states such as fasting, carbohydrate-restrictive diets (e.g Atkins, ketogenic diet), intense exercise, pathological states such as Type 1 diabetes mellitus, alcoholism (lack of glucose to power cells)
- Released into bloodstream → picked up by majority of cells → re-converted into acetyl-CoA → enter mitochondria, produce ATP

## KETONE BODY BREAKDOWN

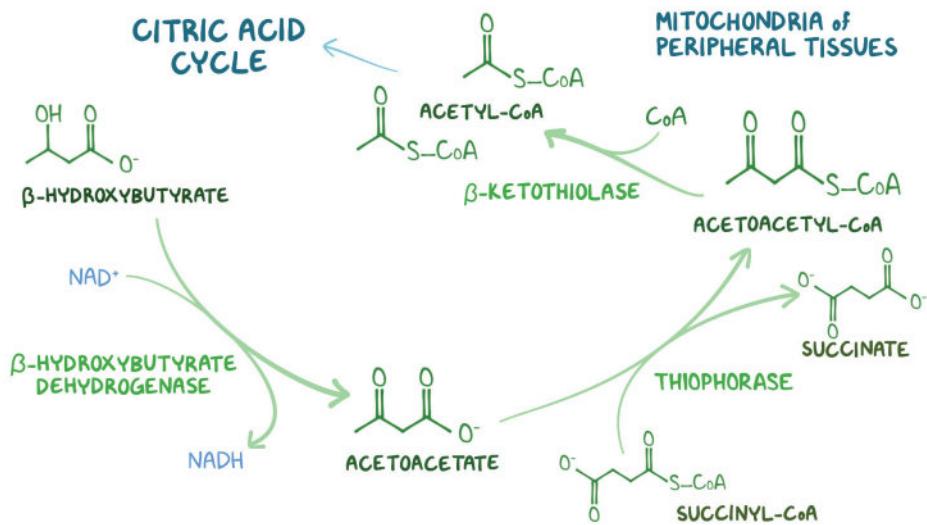
- $\beta$ -hydroxybutyrate, acetoacetate in blood diffuses into peripheral tissue mitochondria
  - $\beta$ -hydroxybutyrate dehydrogenase converts  $\beta$ -hydroxybutyrate back into acetoacetate
- Thiophorase can add CoA from succinyl-CoA to acetoacetate → form acetoacetyl-CoA, succinate
- $\beta$ -ketothiolase cleaves acetoacetyl-CoA with CoA → forms two acetyl-CoA molecules
  - Can enter citric acid cycle to make ATP

## KETONE BODY SYNTHESIS

- Two acetyl-CoA molecules are joined (acetyl-CoA acyltransferase) → acetoacetyl-CoA + CoA
- HMG-CoA synthase
  - Acetoacetyl-CoA + acetyl-CoA → 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) + CoA (rate-limiting ketone body synthesis step)
- HMG-CoA lyase removes acetyl-CoA from HMG-CoA → acetoacetate
- Remaining ketone bodies formed
  - $\beta$ -hydroxybutyrate dehydrogenase adds hydrogen from NADPH to acetoacetate →  $\beta$ -hydroxybutyrate
  - Acetoacetate in blood spontaneously loses a carbon → acetone (exhaled through lungs)



**Figure 2.9** Ketone body synthesis.



**Figure 2.10** Ketone body breakdown.



# NOTES

## NUCLEIC ACID METABOLISM

### NUCLEOTIDE METABOLISM

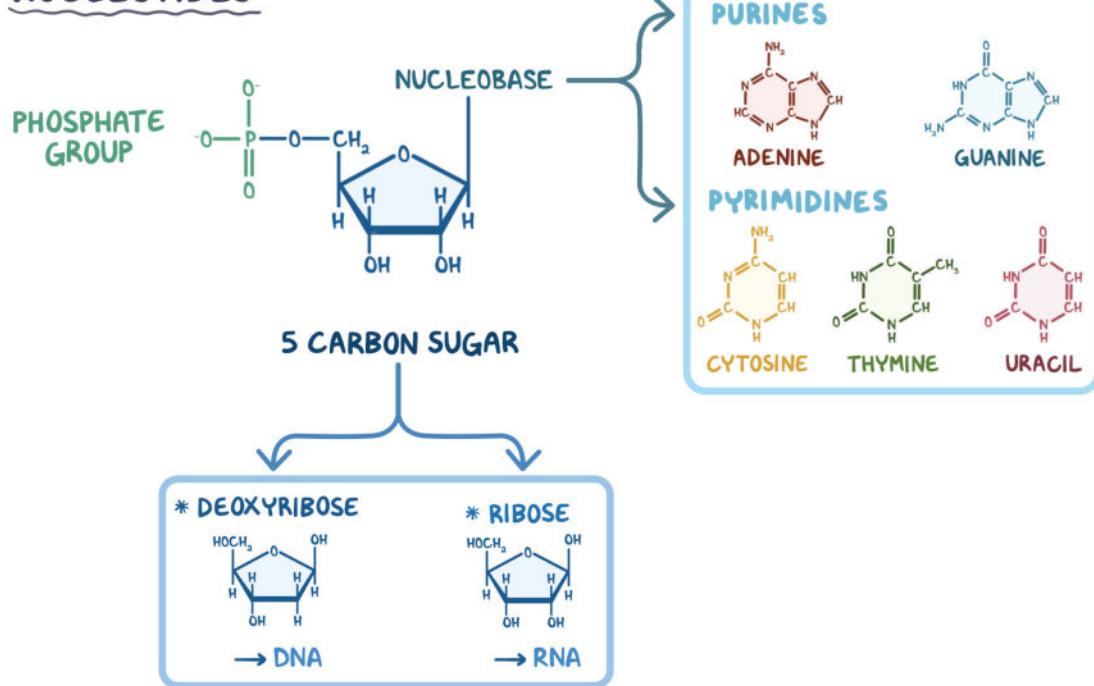
[osms.it/nucleotide-metabolism](https://osms.it/nucleotide-metabolism)

#### Nucleotides

- Building blocks of DNA, RNA
- Consist of 5 carbon sugar, phosphate group, nitrogenous base/nucleobase
  - 5 carbon sugar: deoxyribose ( $\rightarrow$  DNA) or ribose ( $\rightarrow$  RNA)
  - Nucleobase: pyrimidine (cytosine, thymine for DNA, uracil for RNA) or purine (adenine, guanine)
  - Sugar + nucleobase = nucleoside

- RNA nucleosides (resulting nucleotide)
  - Adenine + ribose = adenosine (monophosphate  $\rightarrow$  AMP)
  - Guanine + ribose = guanosine (monophosphate  $\rightarrow$  GMP)
  - Cytosine + ribose = cytidine (monophosphate  $\rightarrow$  CMP)
  - Uracil + ribose = uridine (monophosphate  $\rightarrow$  UMP)

#### NUCLEOTIDES



**Figure 3.1** Nucleotide components: a phosphate group, a sugar (deoxyribose or ribose), and a nucleobase (adenine, guanine, cytosine, thymine, and uracil).

- DNA nucleosides (resulting nucleotide)
  - Adenine + deoxyribose = deoxyadenosine (monophosphate → dAMP)
  - Guanine + deoxyribose = deoxyguanosine (monophosphate → dGMP)
  - Cytosine + deoxyribose = deoxycytidine (monophosphate → dCMP)
  - Thymine + deoxyribose = deoxythymidine (monophosphate → dTMP)

#### De novo nucleotide synthesis

- RNA nucleotides start with ribose-5-phosphate
  - Then for pyrimidine nucleotides (UMP and CMP)
  - Then for purine nucleotides (AMP and GMP)

- DNA nucleotides start with diphosphates of RNA nucleotides
  - Ribonucleotide diphosphate reductase reduces ribose to deoxyribose
  - Molecules then lose phosphate groups → dCMP, dUMP, dAMP, dGMP
  - Thymidylate synthetase converts dUMP into dTMP

#### Nucleotide breakdown

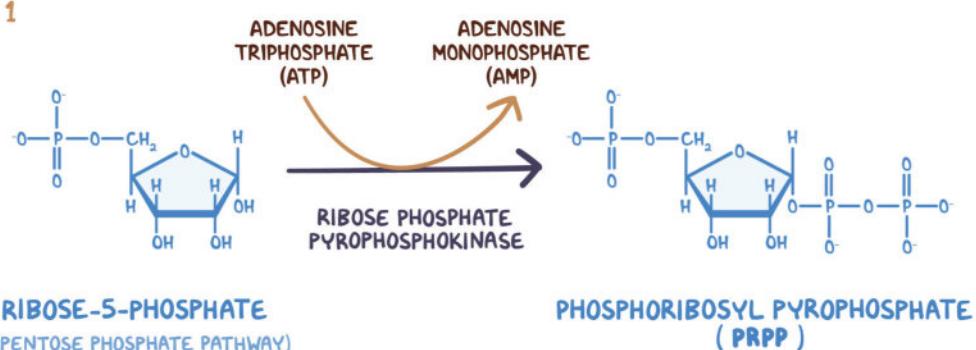
- Pyrimidine rings C,T,U broken down into  $\text{CO}_2$  +  $\text{NH}_3$ , excreted through exhalation/urine
- Purine rings G,A degraded into uric acid, excreted through urine

#### Salvage pathway

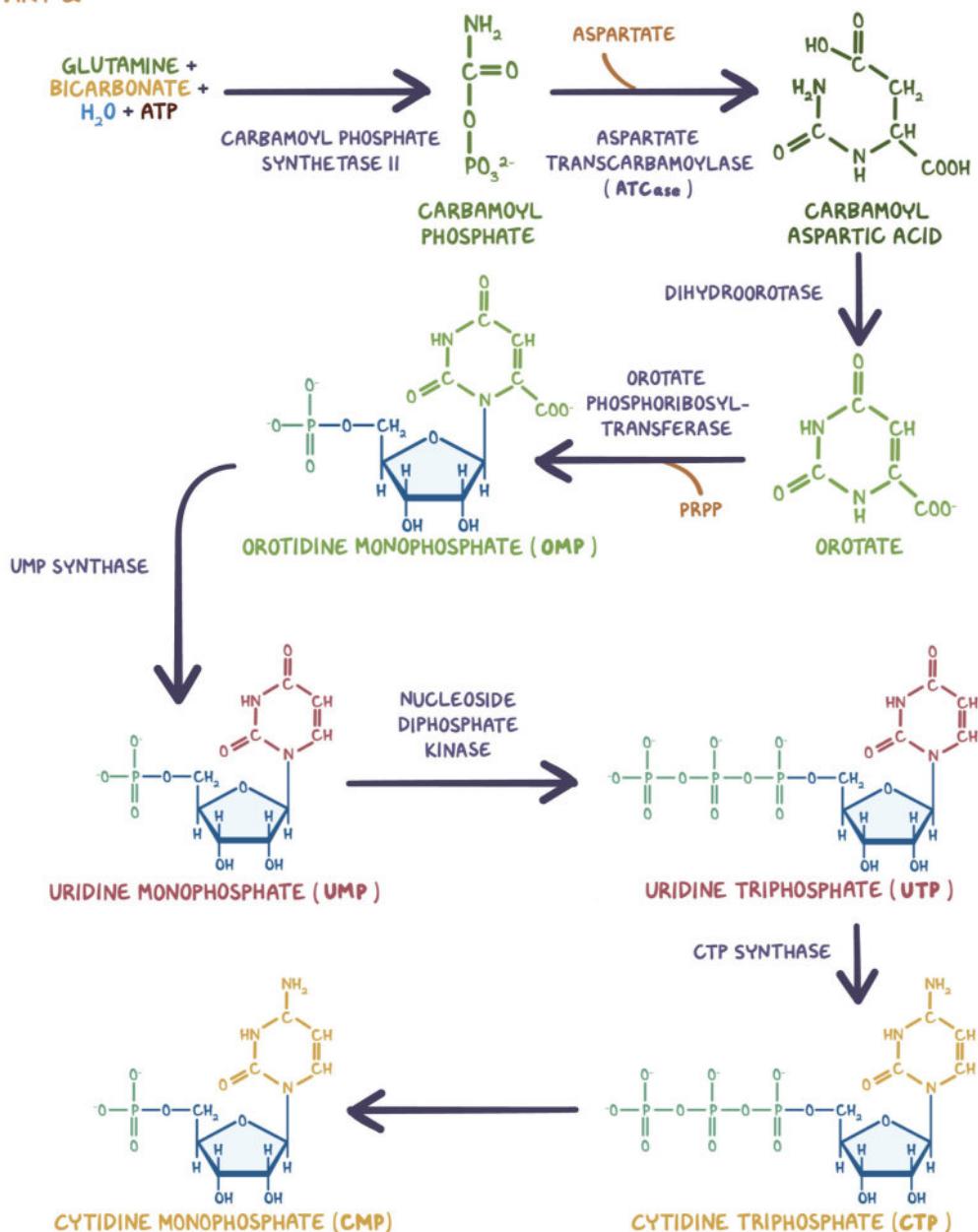
- Guanine, hypoxanthine from purine breakdown can be restored into GMP, AMP

## DE NOVO SYNTHESIS of PYRIMIDINES (RNA)

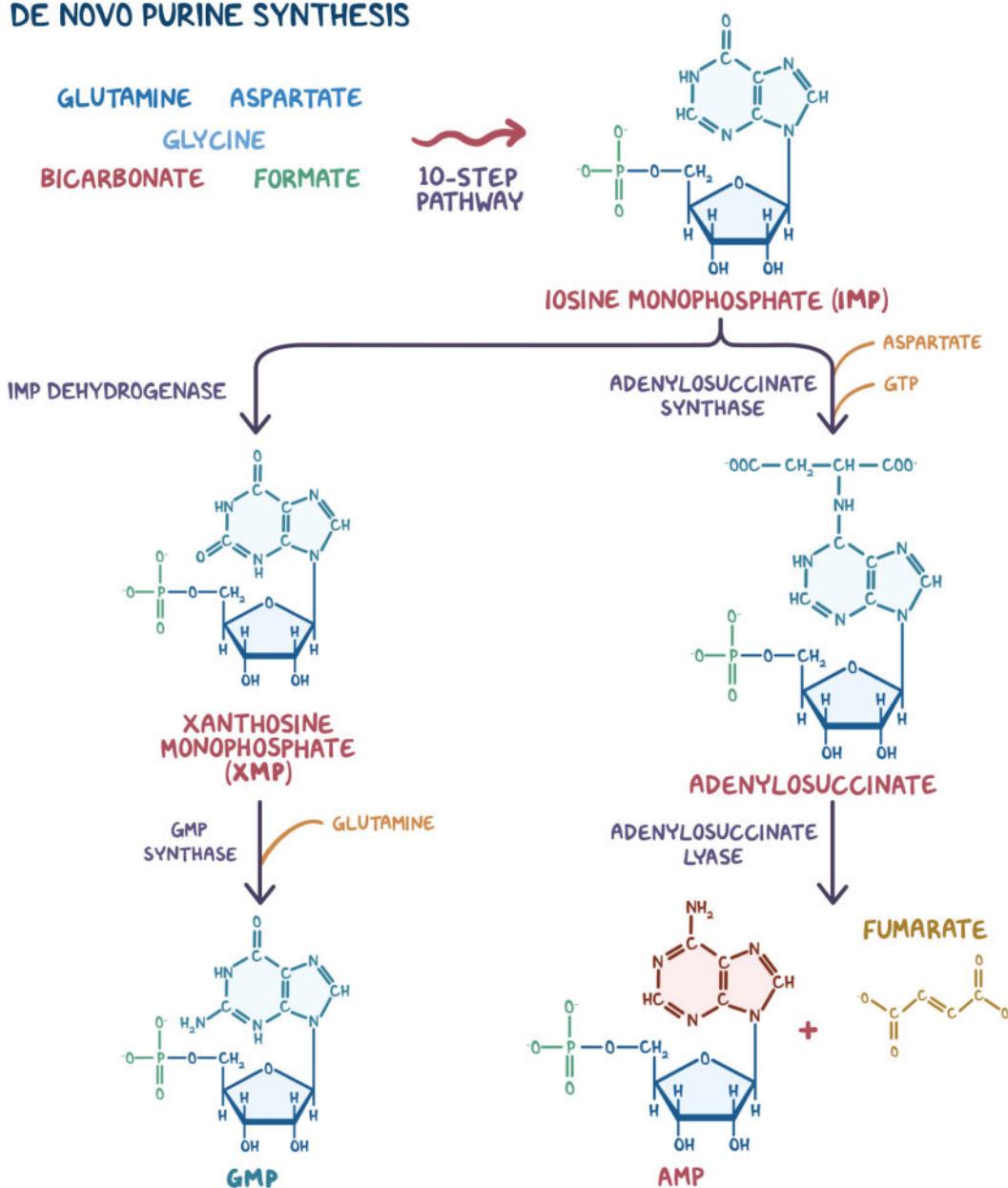
## PART 1



## PART 2

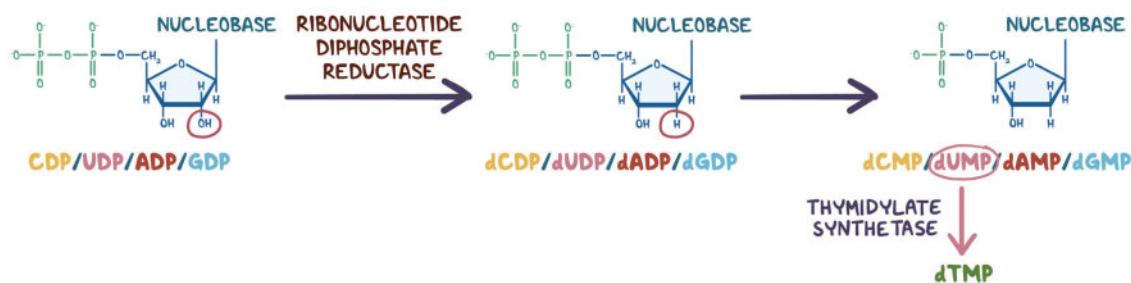
**Figure 3.2** De novo synthesis of RNA pyrimidines. CTP naturally loses phosphate groups → CMP.

## DE NOVO PURINE SYNTHESIS



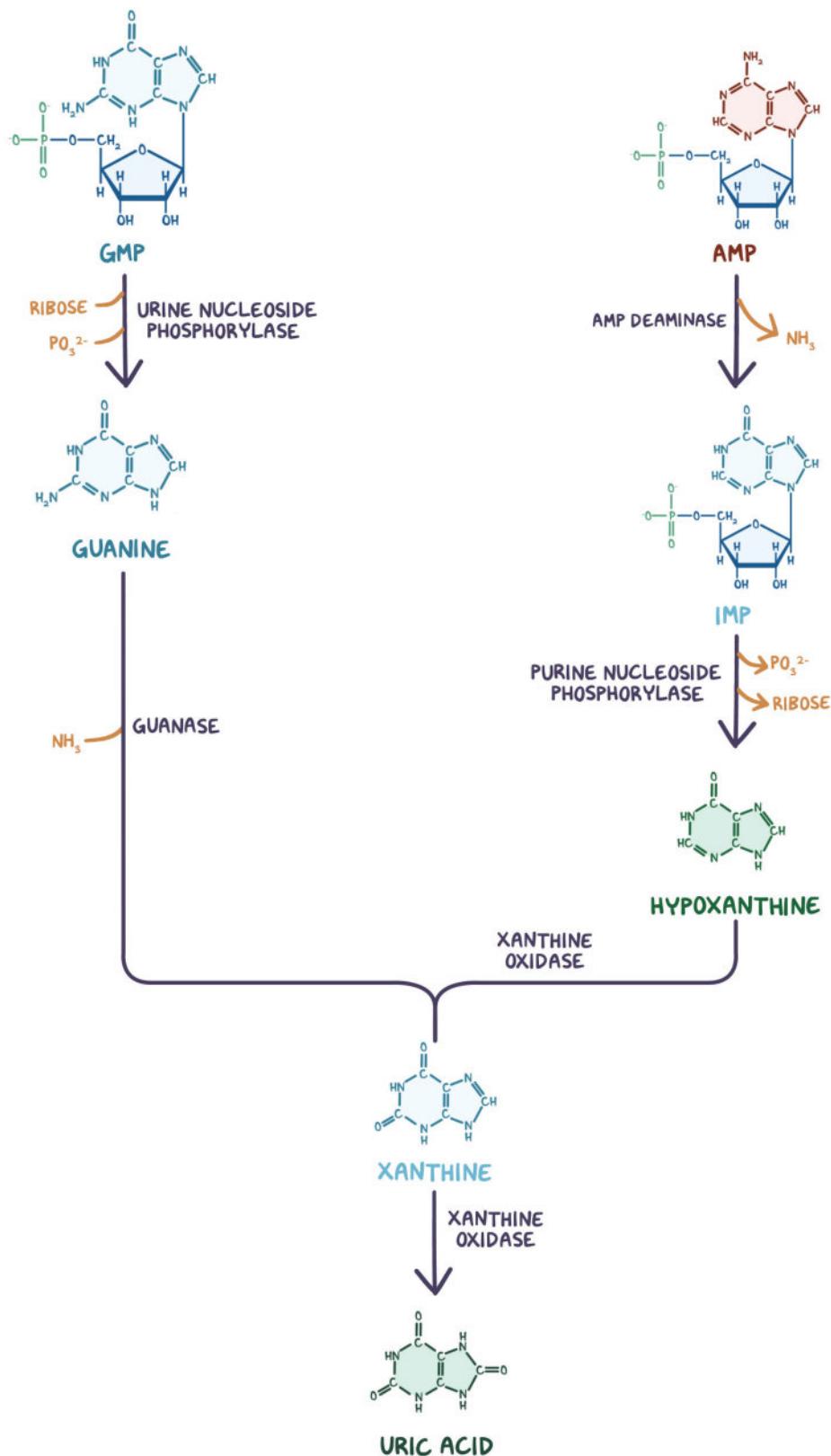
**Figure 3.3** De novo synthesis of RNA purines from precursor Iosine Monophosphate (IMP).

## DNA NUCLEOTIDE SYNTHESIS

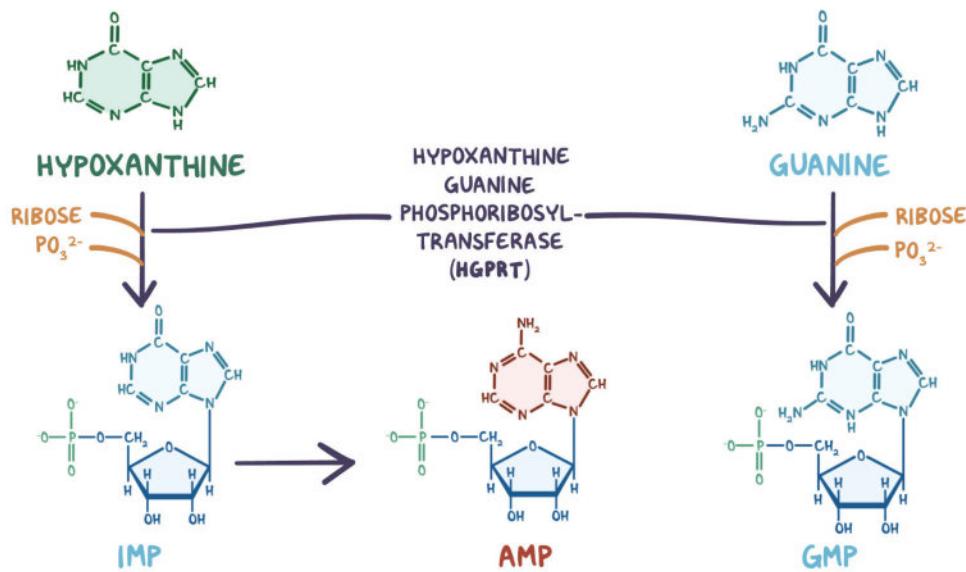


**Figure 3.4** DNA nucleotide synthesis from diphosphates of RNA nucleotides.

## PURINE BREAKDOWN

**Figure 3.5** Breakdown of purines into uric acid.

## SALVAGE PATHWAY



**Figure 3.6** Salvage pathways that restore AMP and GMP.



# NOTES

## PROTEIN METABOLISM

# AMINO ACIDS & PROTEIN FOLDING

[osms.it/amino-acids-protein-folding](https://osms.it/amino-acids-protein-folding)

## AMINO ACIDS

ALANINE (ALA)	(brown)
ARGININE (ARG)	(orange)
ASPARAGINE (ASN)	(light blue)
ASPARTIC ACID (ASP)	(green)
CYSTEINE (CYS)	(yellow)
GLUTAMIC ACID (GLU)	(teal)
GLUTAMINE (GLN)	(orange)
GLYCINE (GLY)	(light blue)
HISTIDINE (HIS)	(pink)
ISOLEUCINE (ILE)	(brown)

LEUCINE (LEU)	(orange)
LYSINE (LYS)	(blue)
METHIONINE (MET)	(green)
PHENYLALANINE (PHE)	(orange)
PROLINE (PRO)	(light blue)
SERINE (SER)	(brown)
THREONINE (THR)	(green)
TRYPTOPHAN (TRP)	(purple)
TYROSINE (TYR)	(orange)
VALINE (VAL)	(brown)

5 = DISPENSABLE  
~ made in QUANTITY

6 = CONDITIONALLY ESSENTIAL  
~ made MOST of the TIME (NOT ALWAYS)

9 = ESSENTIAL  
~ cannot make OURSELVES  
~ OBTAINED from our DIET

Figure 4.1 The 20 amino acids used by humans.

- Amino acids: organic compounds with  $-\text{NH}_2$ ,  $-\text{COOH}$  groups
- Side chain gives specific properties
  - Hydrophilic: polar side chains → acidic (e.g. carboxyl); basic (e.g. amine)
  - Hydrophobic: non-polar side chains → alkyl, aromatic
- Molecular charge depends on pH
  - Low pH: + amine, 0 carboxyl
  - High pH: - carboxyl, 0 amine
  - Neutral: + amine, - carboxyl → zwitterion
- Zwitterion: compound with both positive, negative charges
  - Occurs in each amino acid at specific pH (AKA pI/isolectric point)

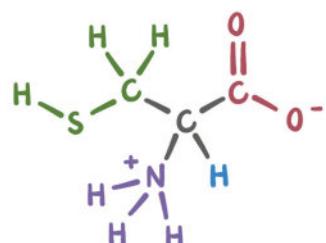
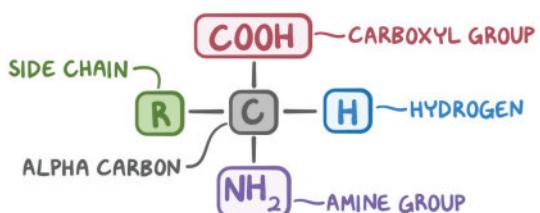
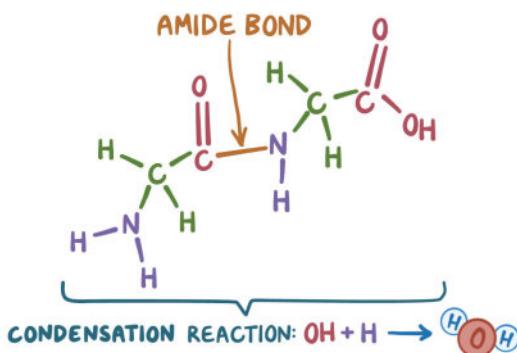
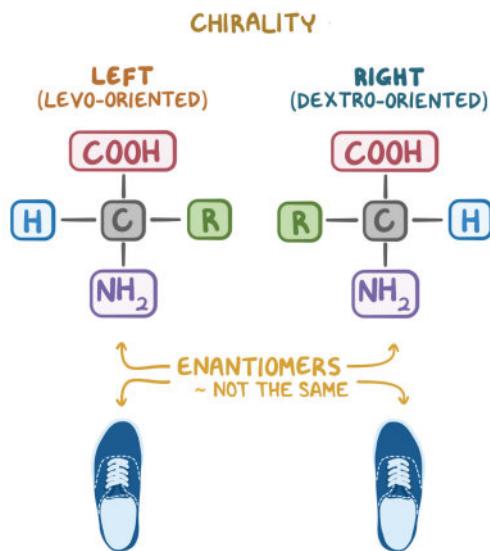


Figure 4.2 Amino acid structure.

- Proteins: amino acid chains connected by peptide bonds
  - Peptide bond: amide bond formed between amino acids by condensation of  $\text{-NH}_2$  with  $\text{-COOH} \rightarrow$  releases  $\text{H}_2\text{O}$
  - Resonance: electrons shared across bond  $\rightarrow$  partial double-bond character  $\rightarrow$  improved strength
- Amino acids: chiral molecules
  - Enantiomers/mirror images are distinct
  - Proteins only made of L-amino acids
- Protein production occurs in ribosomes



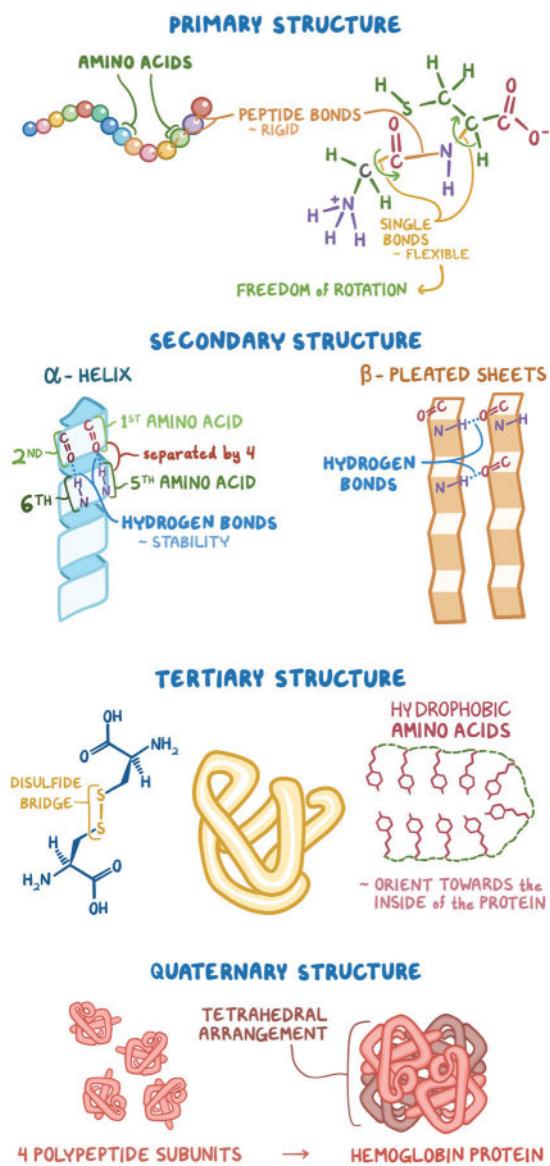
**Figure 4.3** Amide (peptide) bonds form between amino acids through a condensation reaction.



**Figure 4.4** Enantiomers are two forms that look like mirror images but are not interchangeable, like a left and right shoe. Proteins are only made out of levo-oriented amino acids.

### Primary, secondary, tertiary, quaternary protein structures

- Primary: linear amino acid sequence connected by peptide bonds
- Secondary:  $\alpha$ -helix,  $\beta$ -pleated sheet
- Tertiary: overall shape, including secondary structures, with other features (e.g. disulfide bridge, hydrophobic bonds)
- Quaternary: final level; combination of multiple amino acid chains (e.g. hemoglobin)

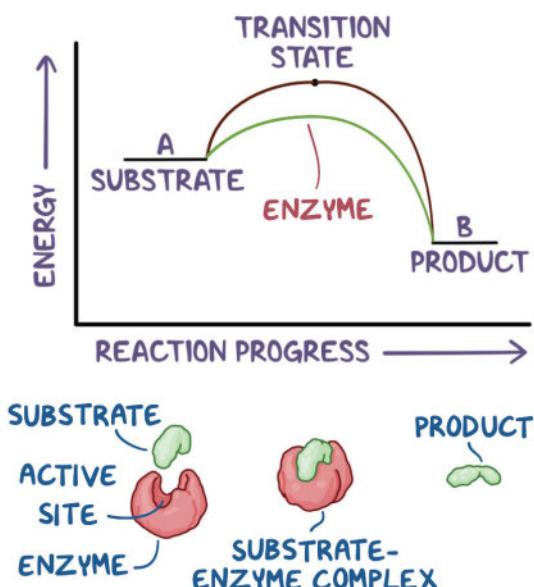


**Figure 4.5** The four levels of structure for proteins.

# ENZYME FUNCTION

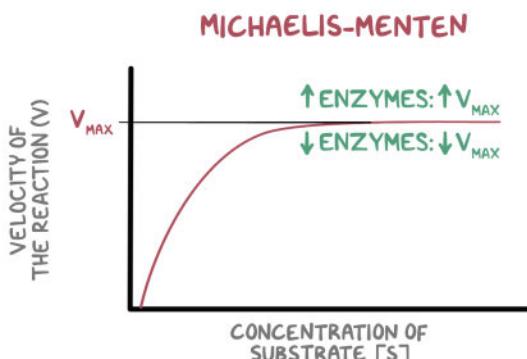
[osms.it/enzyme-function](https://osms.it/enzyme-function)

- Enzymes: biochemical reaction catalysts
- Substrates bind to active site → enzyme-substrate complex
- Not used up in reactions
- Highly specific (e.g. amylase in saliva → large carbohydrate breakdown)



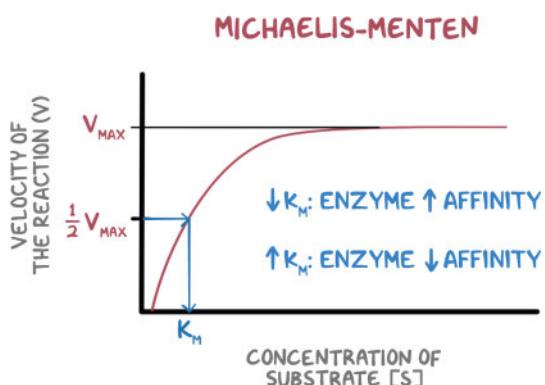
**Figure 4.6** Transition state: intermediate step in reaction with high energy. Enzymes speed up reactions by binding substrate (enzyme-substrate complex), which stabilizes the transition state and decreases the amount of extra energy required for the reaction to proceed.

- Enzyme kinetics: catalysis rate
- $V_{max}$ : maximum reaction velocity with fixed enzyme quantity
  - ↑ substrate → ↑ velocity, until all enzymes bind
  - ↑ enzymes → ↑  $V_{max}$
  - ↓ enzymes → ↓  $V_{max}$
  - Non-competitive inhibition (inhibitory molecule binds to active allosteric site → prevents substrate binding) → ↓  $V_{max}$



**Figure 4.7** Michaelis–Menten graph: used to visualize enzyme kinetics. With a fixed amount of enzyme, the reaction velocity ↑ as substrate is added, until the active sites on all of the enzymes become saturated. At this point, the reaction speed plateaus →  $V_{max}$ .

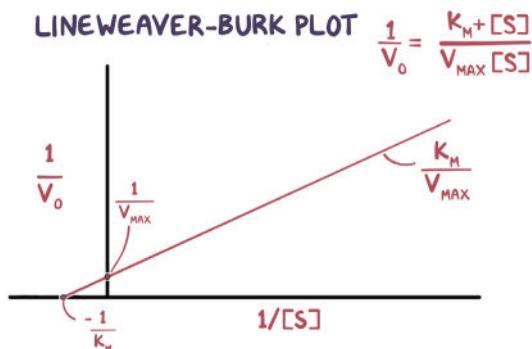
- $K_m$ : substrate concentration when reaction velocity is half of maximum
  - ↑ enzyme affinity (e.g. activator molecules) → ↓  $K_m$
  - ↓ enzyme affinity (e.g. competitive inhibition) → ↑  $K_m$



**Figure 4.8**  $K_m$  is found using a Michaelis–Menten diagram by identifying  $\frac{1}{2} V_{max}$  on the y-axis, then finding the corresponding substrate concentration value on the x-axis.

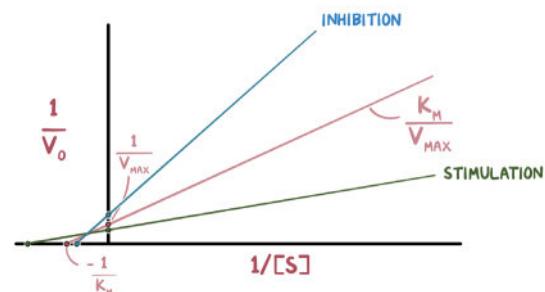
- Lineweaver–Burk plot
  - Based on Michaelis–Menten equation

$$V_0 = \frac{V_{\max}[S]}{K_m + [S]} \rightarrow \frac{1}{V_0} = \frac{K_m + [S]}{V_{\max}[S]}$$



**Figure 4.9** The Lineweaver–Burk plot shows  $K_m$  and  $V_{\max}$  as functions of the x, y intercepts.

### LINEWEAVER-BURK PLOT



**Figure 4.10** Processes that  $\uparrow V_{\max} \downarrow 1/V_{\max}$  → the line slopes lower on the graph than the control. Processes that  $\downarrow V_{\max} \uparrow 1/V_{\max}$  → the line slopes higher on the graph than the control.

## AMINO ACID METABOLISM

[osms.it/amino-acid-metabolism](https://osms.it/amino-acid-metabolism)

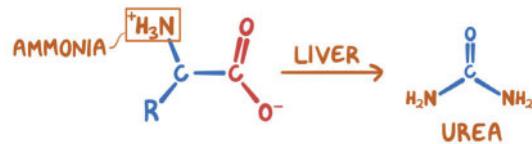
- Dietary protein broken down into amino acids → used to synthesize other proteins
  - Excess amino acids used for energy/ stored as fat/glycogen
- Portal vein delivers absorbed amino acids (and other nutrients) to liver after uptake by small intestine → liver synthesizes needed proteins (e.g. albumin, immunoglobulins), non-essential amino acids
- Amino acids delivered to cells throughout body via blood → enter cell by facilitated/ active transport → used for protein synthesis (e.g. hormones, enzymes)
- Ammonia ( $\text{NH}_4^+$ ): toxic metabolic by-product from amino acid catabolism → converted to urea (liver) → eliminated (kidneys)

### Transamination

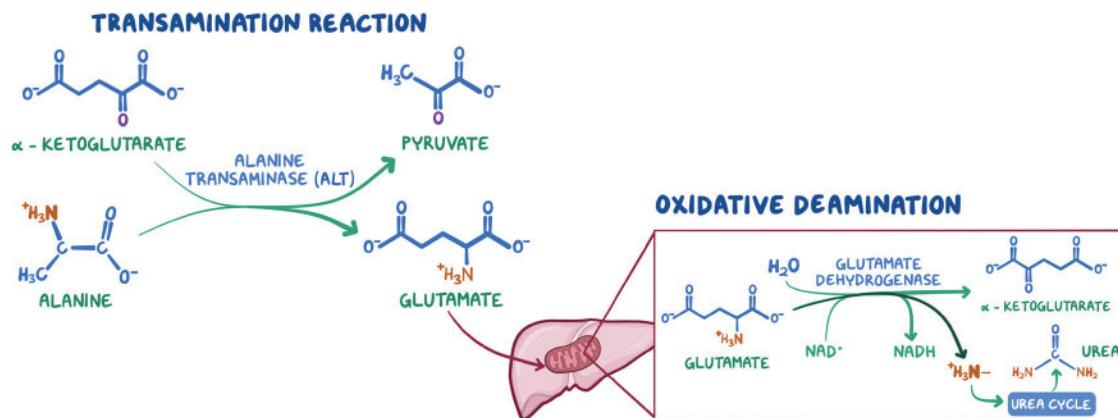
- Reversible reaction
  - Transfers nitrogen-containing amine group to another molecule
- Amino group transferred (via aminotransferase + vitamin  $B_6$  cofactor)  $\rightleftharpoons$  alpha ketoglutarate (acceptor molecule) → alpha-keto acid + glutamate
  - Glutamate oxidatively deaminated in liver mitochondria → ammonia byproduct converted to urea (via urea cycle) → eliminated (kidneys)

### Deamination

- Nitrogen-containing amine group removal (via deaminase) → amino acid utilized for energy
- Produces ammonia → converted to urea → renal excretion



**Figure 4.11** Ammonia → urea in the liver.



**Figure 4.12** Example of a transamination reaction with amino acid alanine. ALT switches the amino group on alanine with the oxygen group on  $\alpha$ -ketoglutarate, resulting in ketoacid pyruvate and amino acid glutamate, which has the amino group. Glutamate is the only amino acid that doesn't have to transfer its amine group to another molecule. It undergoes oxidative deamination, a process that removes hydrogens and an amino group.

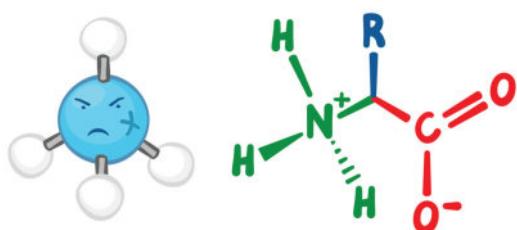
## NITROGEN & THE UREA CYCLE

[osms.it/nitrogen-and-urea-cycle](https://osms.it/nitrogen-and-urea-cycle)

- Ammonia ( $\text{NH}_3$ ): toxic protein catabolism byproduct; detoxification by liver (forming non-toxic urea)

- Glutamine synthetase:  $\text{NH}_3 + \text{glutamate} \rightarrow \text{glutamine}$
- Glutamine transported through blood
- Glutaminase: glutamine  $\rightarrow \text{NH}_3 + \text{glutamate}$
- In liver mitochondria

### AMMONIA



**Figure 4.13** Ammonia is composed of a nitrogen-containing amino group, an acidic carboxyl group, and a side chain.

- $\text{NH}_3$  reaches liver in two ways, sometimes as glutamate

### Glucose-alanine cycle

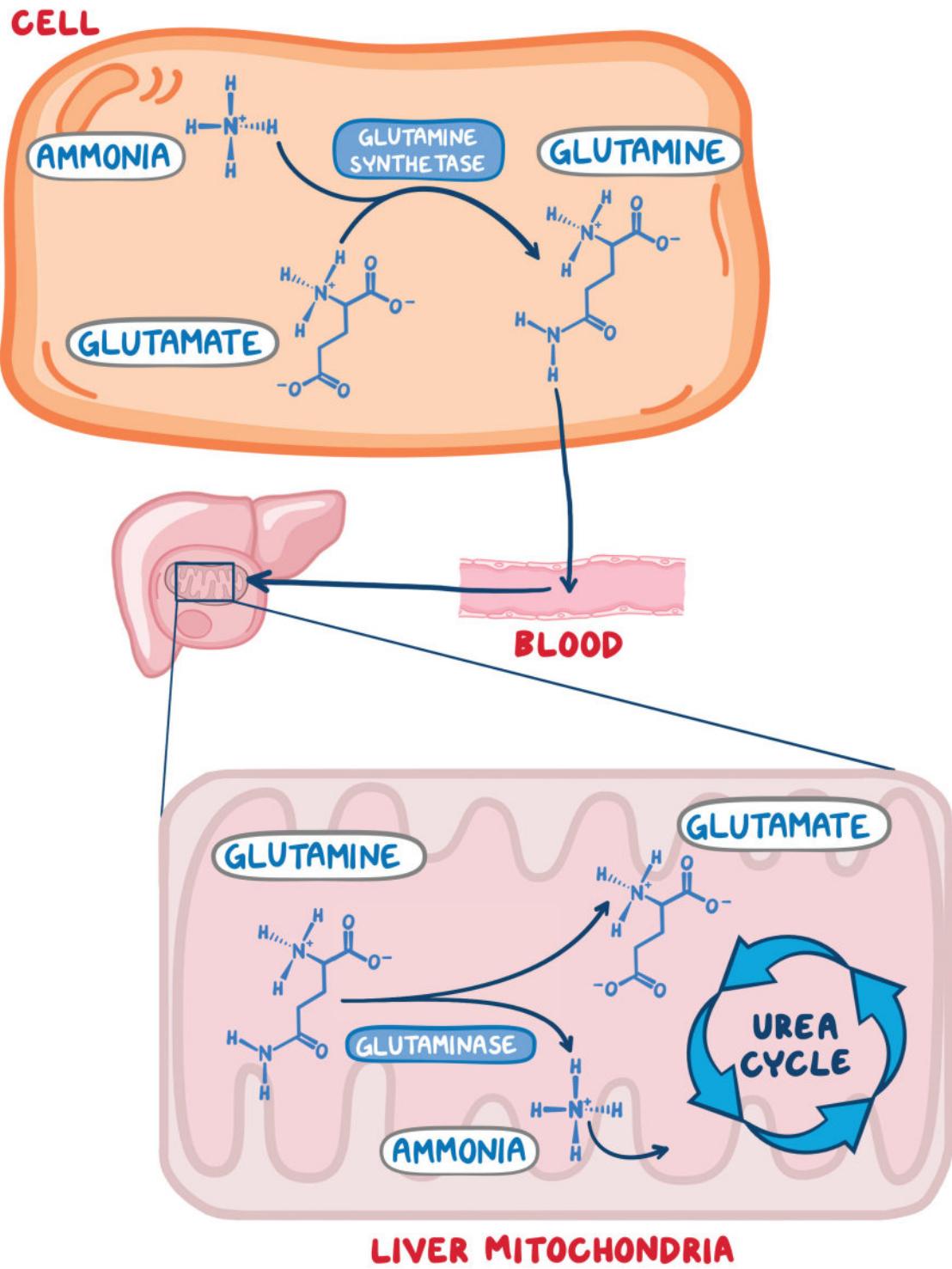
- Only from muscle
- Glutamate dehydrogenase:  $\text{NH}_3 + \text{alpha-ketoglutarate} \rightarrow \text{glutamate}$
- Alanine transaminase: glutamate  $\rightarrow \text{alpha-ketoglutarate} + \text{alanine}$
- Alanine transported through blood
- Alanine transaminase:  $\text{alpha-ketoglutarate} + \text{alanine} \rightarrow \text{glutamate} + \text{pyruvate}$

### Glutamate- $\text{NH}_3$ conversion: two ways

- Glutamate dehydrogenase:  $\text{glutamate} \rightarrow \text{NH}_3 + \text{alpha-ketoglutarate}$ 
  - Free  $\text{NH}_3$  enters urea cycle
- Aspartate transaminase:  $\text{glutamate} + \text{oxaloacetate} \rightarrow \text{aspartate} + \text{alpha-ketoglutarate}$ 
  - Aspartate carries  $\text{NH}_3$  into urea cycle

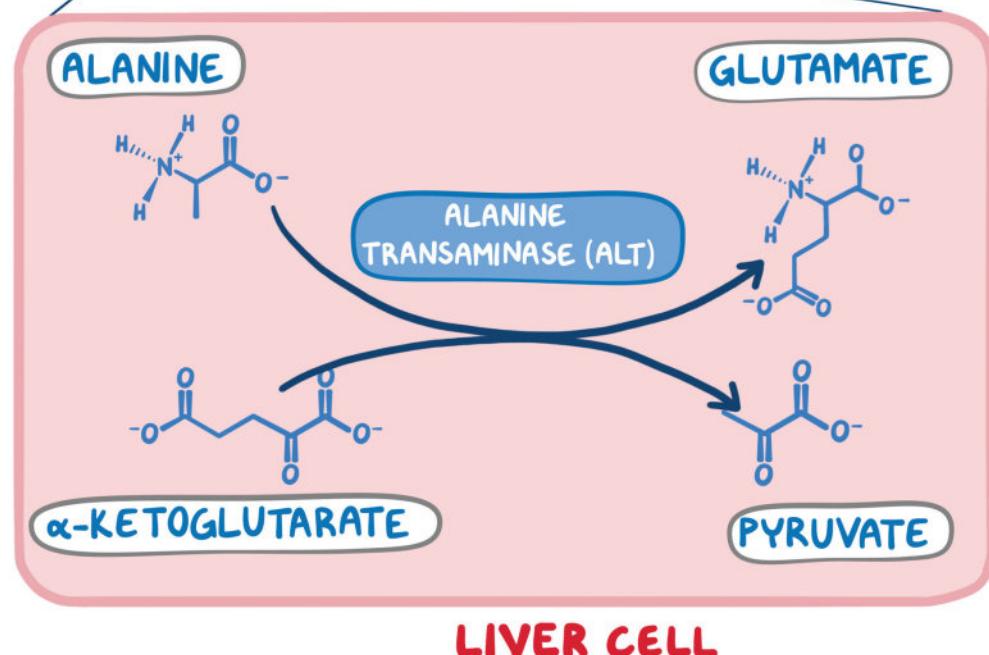
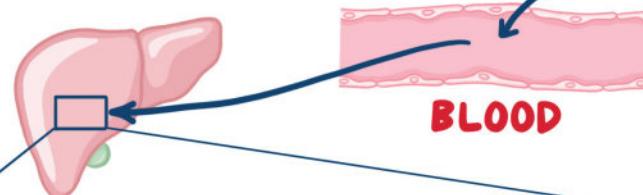
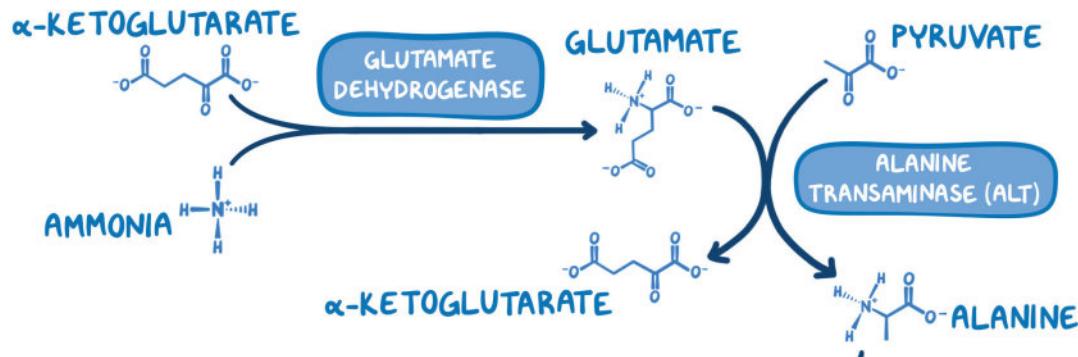
### Glutamine synthetase system

- From all tissues

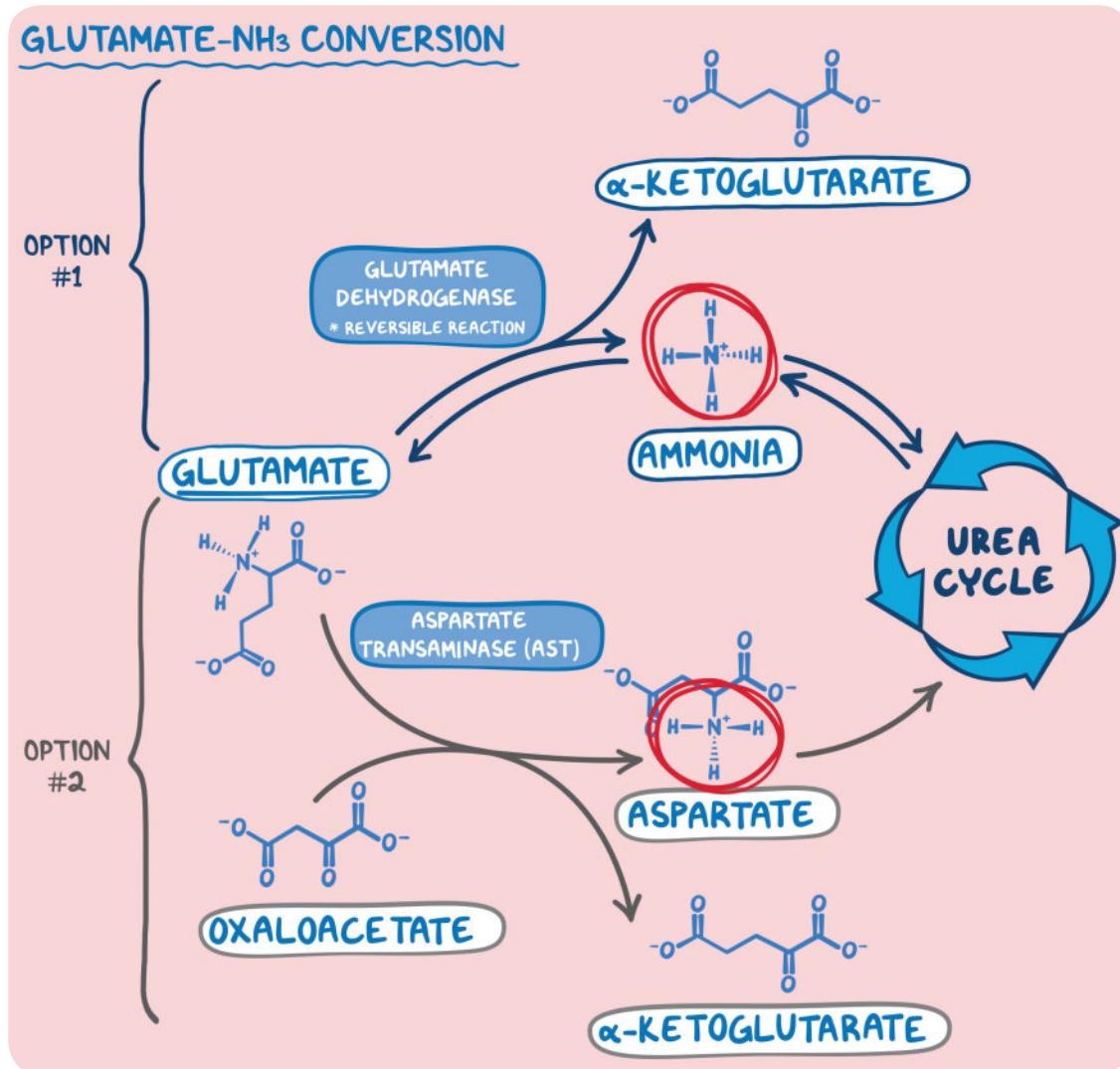


**Figure 4.14** The glutamine synthetase system of ammonia reaching the liver.

## SKELETAL MUSCLE CELL



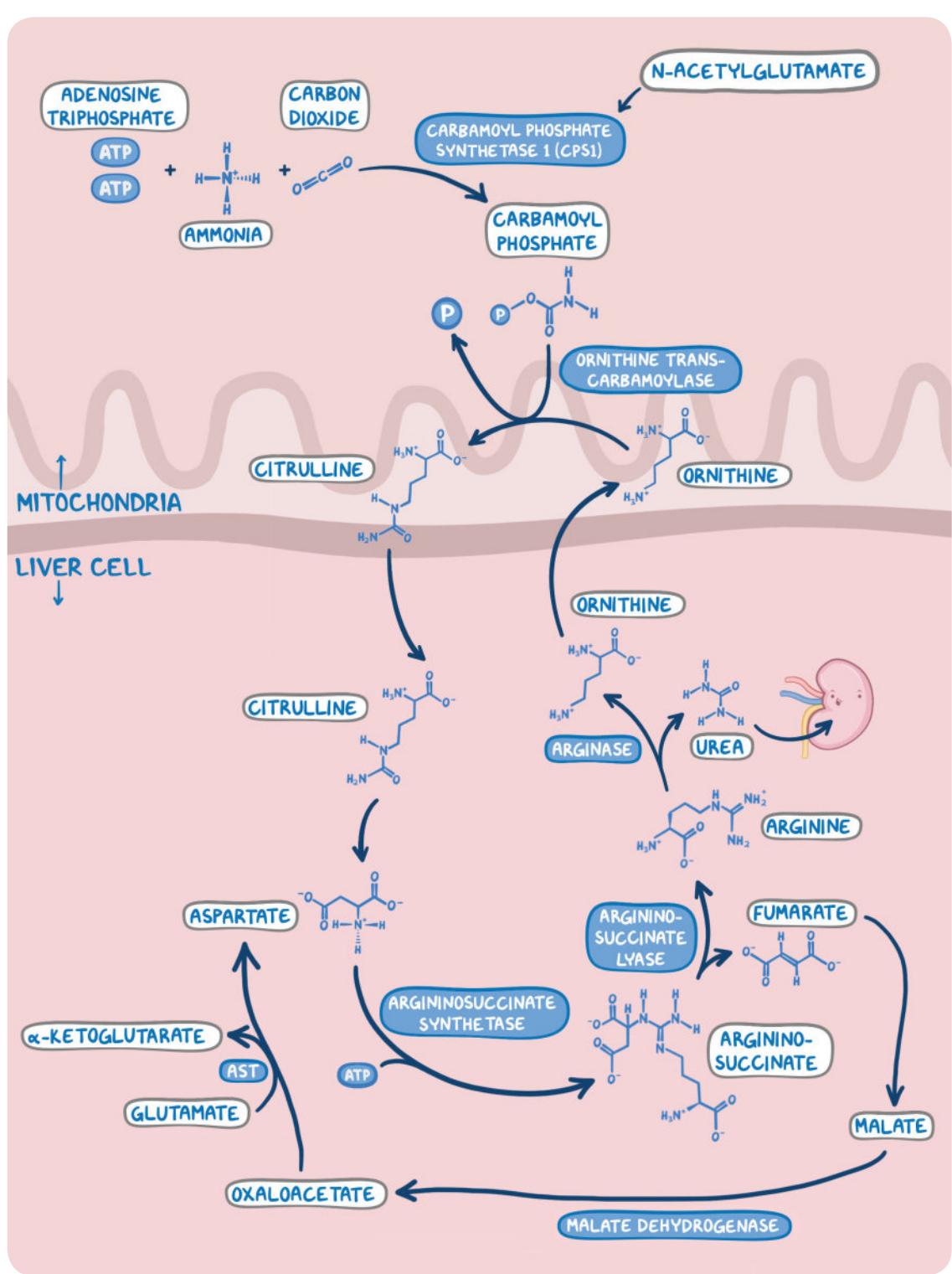
**Figure 4.15** The glucose-alanine cycle of ammonia reaching the liver.



**Figure 4.16** Once glutamate is in a liver cell, there are two possible outcomes for it that depend on which enzyme it encounters (glutamate dehydrogenase or AST). In Option #1, ammonia enters the urea cycle; in Option #2, the ammonia group is carried into the urea cycle as part of the amino acid aspartate.

#### Urea cycle

- Starts in liver cells' mitochondria
- Carbamoyl phosphate synthetase 1 (CPS1)
  - NH<sub>3</sub> + CO<sub>2</sub> + 2ATP → carbamoyl phosphate
  - N-acetylglutamate → ↑ CPS1 affinity for ammonia (by allosteric binding)
- Ornithine transcarbamylase: ornithine + carbamoyl phosphate → citrulline + phosphate
- Citrulline moves to cytoplasm
- Argininosuccinate synthetase: citrulline + aspartate + ATP → argininosuccinate
- Argininosuccinate lyase: argininosuccinate → fumarate + arginine
  - Fumarate → malate; malate → oxaloacetate (by malate dehydrogenase); oxaloacetate + glutamate → aspartate + α-ketoglutarate (by aspartate transaminase) → aspartate can enter next cycle
  - Arginine → urea + ornithine (by arginase) → ornithine can enter next cycle
- Resulting urea then enters blood, excreted by kidneys



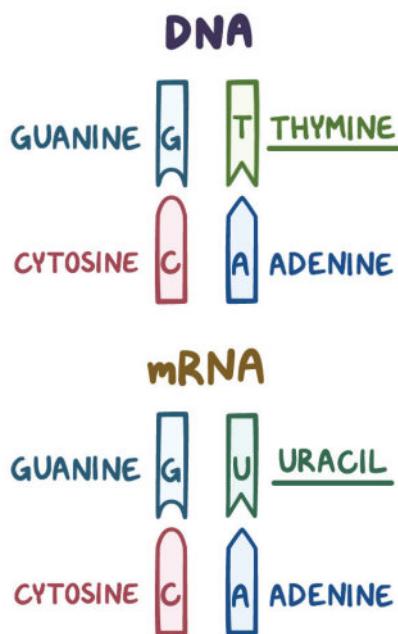
**Figure 4.17** Illustration of the urea cycle, starting with the synthesis of carbamoyl phosphate from ATP, ammonia, and carbon dioxide, with the help of enzyme CPS1.

# PROTEIN STRUCTURE & SYNTHESIS

[osms.it/protein-structure-and-synthesis](https://osms.it/protein-structure-and-synthesis)

- Proteins: functional structures composed of amino acids; synthesized within cells
- Genes, housed within DNA, provide blueprint for protein synthesis
- Codon: nucleotide triplet containing sequence of three nucleotide bases (A, G, T, C)
  - Codes for specific amino acid
  - 64 codons code for 20 amino acids; > one codon for most amino acids (UUU, UGC code cysteine)
  - One “start” codon; three “stop” codons

## NUCLEOBASES



**Figure 4.18** The four nucleobases used in DNA are guanine, cytosine, thymine, and adenine. In mRNA, uracil (U) is used rather than thymine.

## TRANSCRIPTION

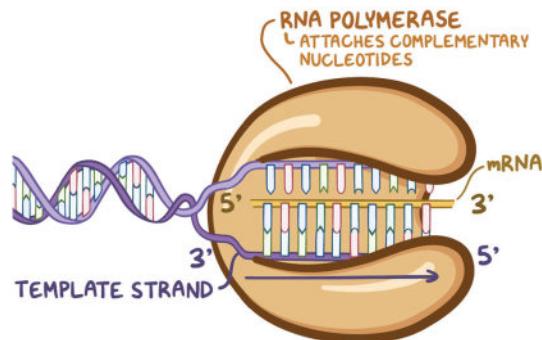
- Messenger RNA (mRNA) transcribes code from DNA
- Begins at promoter
  - Base sequence establishes transcription starting point

## Initiation

- RNA polymerase separates DNA helix at promoter site

## Elongation

- RNA polymerase unwinds, rewinds DNA → matches RNA nucleotides with DNA bases → links them together



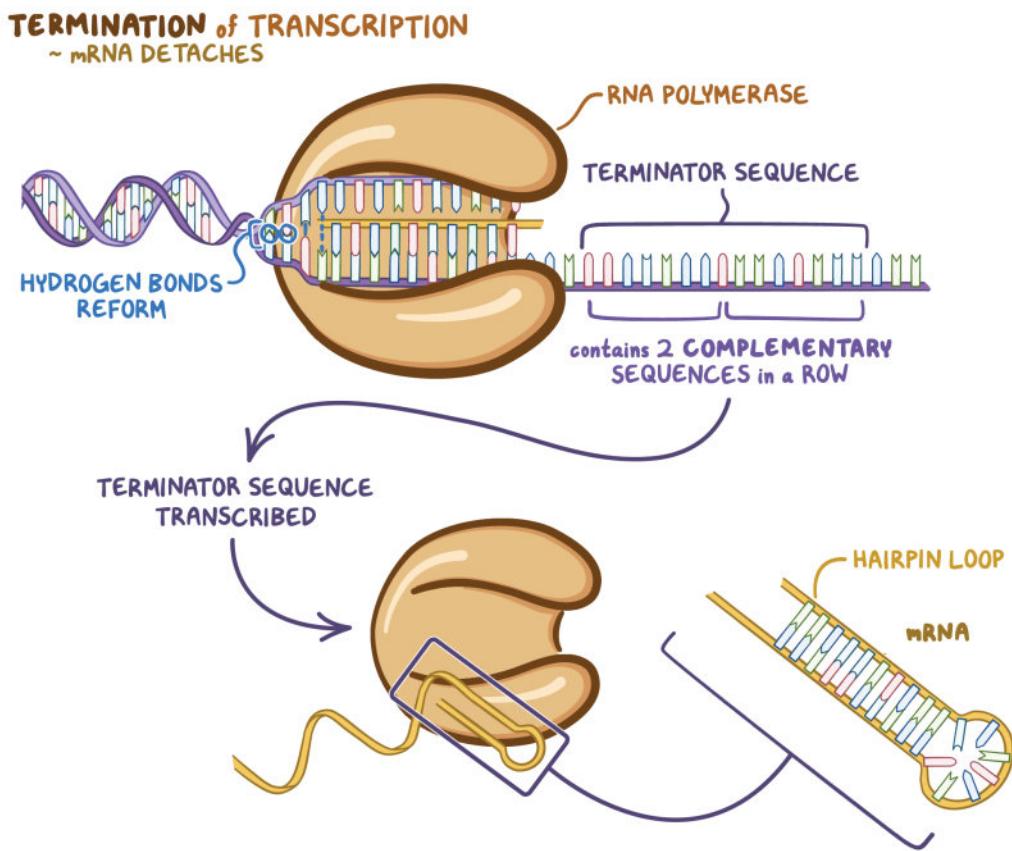
**Figure 4.19** Elongation: RNA polymerase attaches complementary mRNA nucleotides to the unzipped DNA template strand to build an mRNA molecule.

## Termination

- Ends at termination signal; base sequence establishes transcription end point

## Pre-mRNA formed

- Contains non-coding areas (introns)
  - Spliceosomes snip out introns → functional mRNA
  - mRNA complex proteins added → guide mRNA out of nucleus



**Figure 4.20** Termination: when the two complementary sequences in the terminator sequence get transcribed into mRNA, they bond with each other, creating a hairpin loop that causes the RNA polymerase to detach from the DNA strand.

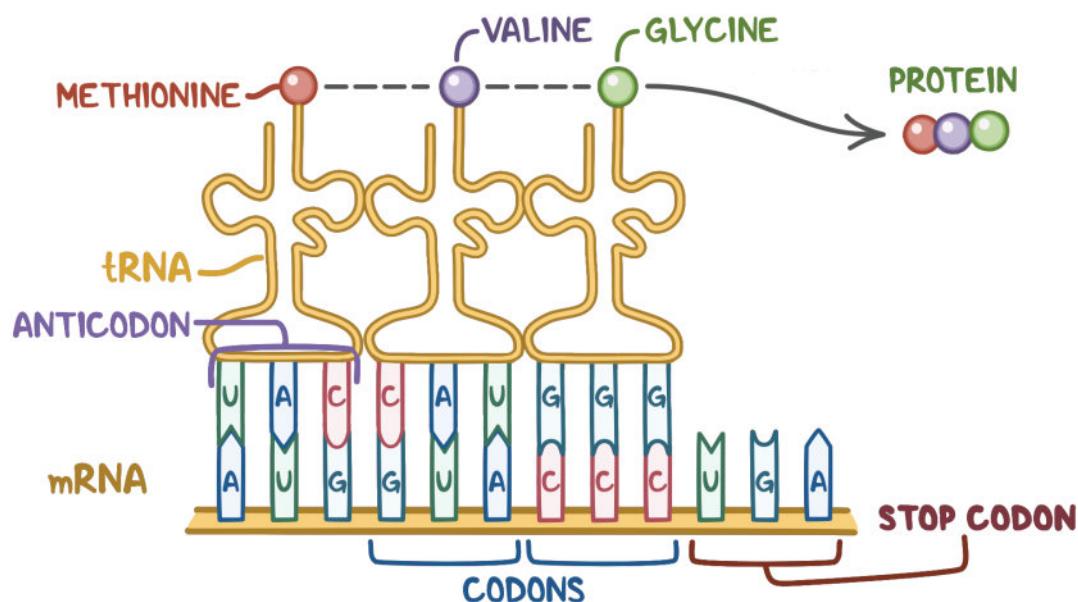
## TRANSLATION

- Base sequence contained in mRNA translated into assembled polypeptide

### Three RNA types required

- mRNA: carries coded message out of nucleus to ribosome in cytoplasm
- Ribosomal RNA (rRNA): “workbench” for protein synthesis
- Transfer RNA (tRNA): brings amino acids to workbench assembly site at ribosome
  - Folded into “cloverleaf” shape
  - Acceptor stem: attaches to amino acid
  - Anticodon: complementary to mRNA codon (tRNA binds with mRNA through complementary base pairing)

## TRANSLATION



**Figure 4.21** Translation: as ribosomes line tRNA molecules up with their complementary codons, the amino acids held by the tRNA bind with each other to form a protein, which is a chain of amino acids. The process is terminated at a stop codon.



# NOTES

## INTRODUCTORY BIOSTATISTICS

# INTRODUCTION TO BIOSTATISTICS

[osms.it/intro-biostatistics](http://osms.it/intro-biostatistics)

- Statistics: process of collecting, organizing, analyzing data set variables
- Biostatistics: focus on data related to living things
- Descriptive statistics: summarizes, describes population information
- Inferential statistics: examines relationships between two/more variables → applies results of sample population to target population

## POPULATION & SAMPLE

### Population

- Group (people, specimens, events) with defined criteria (e.g. October–March emergency room visits)
- Parameter: numerical population description (e.g. range, mean, standard deviation)
  - $\mu$  = population mean
  - $\sigma$  = population standard deviation

### Sample

- Subset drawn from population (e.g. influenza-related October–March emergency room visits)
- Represents population → inferences can be made about population
- Statistic: numerical sample description (e.g. range, mean, standard deviation)
- $\bar{X}$  = sample mean
- SD = sample standard deviation
- Sampling error: sample does not accurately reflect population
  - Usually due to wide variation within sample
  - ↑ sample size helps avoid sampling error

- Selection bias: sample does not accurately reflect population
  - Occurs when precautions to obtain representative sample are not used
  - Randomization helps eliminate bias

### Case (data point)

- Single observation (e.g. one individual visiting emergency room for influenza symptoms)

## TYPES OF HYPOTHESES

### Null hypothesis ( $H_0$ )

- States that there is no relationship between variables
- Any observed relationship due to chance (e.g. no relationship between body mass index (BMI), hypertension)

### Alternative hypothesis (research hypothesis)

- States expected relationship between variables (e.g. relationship between BMI, hypertension)

### Hypothesis testing

- Statistical methods used to determine relationship strength between variables, how much of observed relationship is due to chance, significance of observations
- Statistical significance: relationship between variables is caused by something other than chance
- Usually defined by a p-value of  $< 0.05$  (5%); "p" stands for "probability"
  - Type 1 error: probability of incorrectly rejecting null hypothesis (i.e. concluding significant relationship between

- variables when there is not)
- Type 2 error: incorrectly accepting null hypothesis (i.e. concluding there is no significant relationship between variables, missing present association)
- Clinical significance: practical importance of study results that may not be statistically significant

## RELIABILITY & VALIDITY

- Measurement characteristics used to collect data

### Validity: accuracy

- Instrument actually measures variable (concept, construct) it is supposed to measure (e.g. urine dipstick accurately detects proteinuria)
- Valid instrument must be reliable

### Reliability: repeatability

- Instrument consistently yields same results with repeated measurements (e.g. urine dipstick reliably detects proteinuria with each measurement)
- Reliable instrument may/may not be valid

## TYPES OF VARIABLES

- Variable: defined characteristic being studied; can assume different values
- Independent variable: manipulated (treatment) variable
- Dependent variable: outcome variable; influenced by independent variable

- What is effect of X (independent variable) on Y (dependent variable); how is X related to Y?
- E.g. what is the effect of lipid-lowering drug (X) on individual's cholesterol level (Y)?

## GRAPHIC DESCRIPTION OF DATA

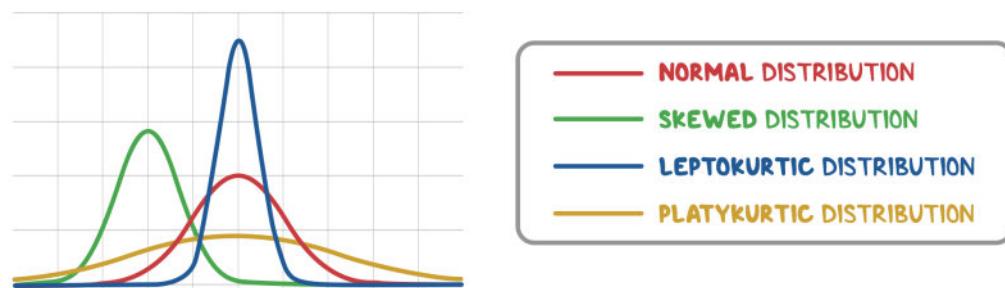
- When values are plotted on graph → variety of frequency distributions (curves) result
- Properties of distributions: central tendency, dispersion

### Normal (Gaussian) curve

- Symmetrical distribution of scores around mean
  - Forms classic bell shape
  - Values lie within two standard deviations of mean
  - Most natural phenomena show this type of distribution
  - Parametric tests utilized in research

### Non-Gaussian curve

- Asymmetrical distribution of scores around mean
  - Skewed (negatively/positively) curve
  - Kurtotic (flat/peaked) curve  
(leptokurtic—thin, positive kurtosis;  
platykurtic—flat negative kurtosis)
  - Nonparametric tests utilized in research



**Figure 5.1** Visualization of normal (red), skewed (green) and kurtotic (blue and yellow) distributions.

# MEAN, MEDIAN, MODE

[osms.it/mean-median-mode](http://osms.it/mean-median-mode)

- Central tendency measures
- More curve symmetry → more alike mean, median, mode

## Mean ( $\bar{X}$ )

- Central value calculated by adding each value in data set → dividing by total number of data points
- Expressed as formula: total sum of individual data points  $X_1, X_2, \dots, X_n$ , divided by n (number of data points)

$$\bar{X} = \frac{(X_1 + X_2 + \dots + X_n)}{n}$$

$$\frac{17+19+20+20+61+61+62}{7} = \frac{260}{7} = 37.14$$

- Can be influenced by an extreme value (outlier) → skewed data

## Median

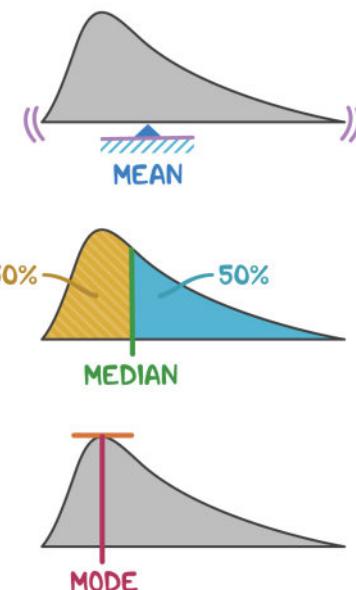
- Calculates central value when possible outliers present
- Divides set of data into two halves
  - Half of values > median, half < median
- Most commonly used expression of central tendency
- Arrange data in order of magnitude → find midpoint

17 19 20 20 61 61 62 100

- Odd number of values → one “middle” number
- Even number of values → two middle-values values (20, 61)
  - Calculate median by averaging two values:  $(20+61)/2 = 40.5$

## Mode

- Central value appearing most often in data sequence
  - Bimodal (two modal), trimodal (three modes), amodal
- 17 19 20 20 61 61 62 100
  - Bimodal dataset with two mode values of 20, 61
- Not affected by outliers



**Figure 5.2** Mean, median, and mode in a skewed curve.

# PROBABILITY

[osms.it/probability](http://osms.it/probability)

- Relative likelihood that event will/will not occur
  - To calculate chance that event/outcome will occur → divide number of times event happened by number of times event could have happened
    - E.g. event A is rolling a die and getting a three
    - Since a die has six sides, there are six possible numbers, so the probability (P) of rolling a three is  $1/6$ , or 0.167 (16.7%)

$$P(A) = \frac{1}{6} = 0.167 = 16.7\%$$

**Figure 5.3** Probability of rolling a three on a six-sided die.

## RULES

## Rule 1

- Probability of event A can range anywhere from 0% to 100%
    - $0 \leq P(A) \leq 1$

## Rule 2

- Sum of probabilities of all possible outcomes = 1

$$P(\text{ } \square) + P(\text{ } \square) = 1$$

$$0.167 + 0.167 + 0.167 + 0.167 + 0.167 + 0.167 = 1$$

**Figure 5.4** Visualization of Rule 2.

## Rule 3 (complement rule)

- Probability that event will not occur = 1 minus probability that it does occur
    - $P = 1 - P(A)$

$$\begin{aligned}
 P(\text{ } & \text{ } \square \text{ } \square \text{ } \square \text{ } \square \text{ } \square) \\
 = 1 - P(\text{ } & \text{ } \square \text{ } \square) \\
 = 1 - 0.167 \\
 = 0.833
 \end{aligned}$$

**Figure 5.5** Probability of not rolling a three =  $1 - P(\text{rolling a three})$ .

## Rule 4

- Probability of two disjoint (mutually exclusive) events = the sum of the first event plus the second event
    - $P(A \text{ or } B) = P(A) + P(B)$

## Rule 5

- Probability for two not disjoint (not mutually exclusive) events = sum of the probability of event A and the probability of event B, minus the probability of event A and B together

$$\square P(A \text{ or } B) = P(A) + P(B) - P(A \text{ and } B)$$

## Rule 6

- Probability of two independent events = probability of the first event multiplied by the probability of the second event

$$\square P(A \text{ and } B) = P(A) \times P(B)$$

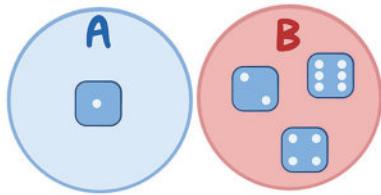
## Rule 7

- Conditional probability (probability of event A, given what happens in event B) = probability of event A and event B divided by probability of event B

## Rule 8

- Probability of events A, B = probability of event A multiplied by conditional probability of event B given event A occurred

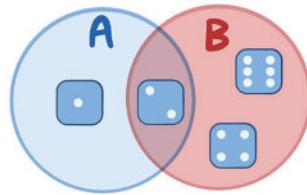
\* DISJOINT or MUTUALLY EXCLUSIVE



EVENT A : ROLLING < 2

EVENT B : ROLLING an EVEN No.

\* NOT DISJOINT or NOT MUTUALLY EXCLUSIVE



EVENT A : ROLLING ≤ 2

EVENT B : ROLLING an EVEN No.

ROLL a 2

**Figure 5.6** A visualization of the difference between mutually exclusive and not mutually exclusive events.

$$P(A \text{ given } B) = \frac{P(A \cap B)}{P(B)}$$

DIE 1 + DIE 2 = 7  
DIE 1 or DIE 2

	2	3	4	5	6	7
2						
3						
4						
5						
6						
7						

$$P(A) = \frac{6}{36} = 0.167$$

$$P(B) = \frac{11}{36} = 0.33$$

**Figure 5.7** Rule 7, conditional probability: determining P(A) and P(B) when event A depends on event B. In this case, we are finding the probability that the roll of two dice adds up to seven (event A) given that the first die is either a five or a six (event B). Once P(A) and P(B) are known, they are used to solve for P(A given B).

# RANGE, VARIANCE, & STANDARD DEVIATION

[osms.it/range-variance-standard-deviation](http://osms.it/range-variance-standard-deviation)

- Measures distribution of variables

## Range

- Difference between highest, lowest value
- E.g. Range of individuals' cholesterol levels
  - 130, 150, 152, 158, 165, 289, 354
  - Range 354 - 130 = 224mg/dL
- E.g. individual weight (in kg)
  - 10 + 45 + 50 + 55 + 90
  - Range = 90 - 10 = 80

## Variance

- Sum of squared deviations from mean, divided by number of distributions

$$\sigma^2 = \frac{\sum(x-\bar{x})^2}{n}$$

- E.g. variance of individual weight (in kg)
  - $(10 - 50)^2 + (45 - 50)^2 + (50 - 50)^2 + (55 - 50)^2 + (90 - 50)^2 / (5) = 650 \text{ kg}^2$

## Standard deviation (SD)

- Square root of variance –

$$\sigma = \sqrt{\frac{\sum(x-\bar{x})^2}{n}}$$

- E.g. SD of individual weight:  $\sqrt{650} = 25.5\text{kg}$

- In Gaussian curve
  - 68 - 95 - 99 rule: 68% of data points lie within 1 SD from mean; 95% lie within 2 SD, 99% lie within 3 SD
- Z-score = number of SD data point is away from mean
  - Data point minus the population mean, divided by the population standard deviation

$$\frac{x - \mu}{\sigma}$$

- E.g. blood glucose population mean = 90g/dL, SD = 20g/dL, data point = 130g/dL ( $130 - 90 / 20 = 2$ )

- Coefficient of variation (CV) = SD/mean; also expressed as percentage, obtained by multiplying the CV by 100

# TYPES OF DATA

[osms.it/types-of-data](http://osms.it/types-of-data)

- Determining type of data to be collected helps establish which sort of distributions can logically be used to describe variable

## Nominal data

- Can assume one of a limited number of possible values (e.g. ABO blood types)
  - No meaningful rank order; no median, mean, standard deviation; mode used for analysis
  - Includes dichotomous variables (e.g. normal, abnormal)

## Ordinal data

- Ordered in meaningful way (e.g. systolic murmur ranking from 1–6)
  - Follows order, but quantitative differences not clear (do not indicate degree of difference between observations)
  - Median, mode can be used; mean usually not suitable to describe sample/population

## Discrete data

- Measured in whole numbers (no decimal values)
  - E.g. number of pregnancies

## Continuous data

- Can take on infinite number of value (e.g. weight, height, blood glucose)
  - Mean, median, mode, standard deviation can be calculated

## Interval data

- Indicates meaningful quantitative difference between two values; values can be placed in clear, logical order
  - E.g. temperature on Celsius/Fahrenheit scale; difference between 90° and 60° measured as 30°
  - Arbitrary zero point
  - Mean, median, mode, standard deviation can be calculated

## Ratio data

- Has absolute, meaningful zero point
- Can use multiplication, addition, subtraction to calculate ratios
- Mean, median, mode using ratio data

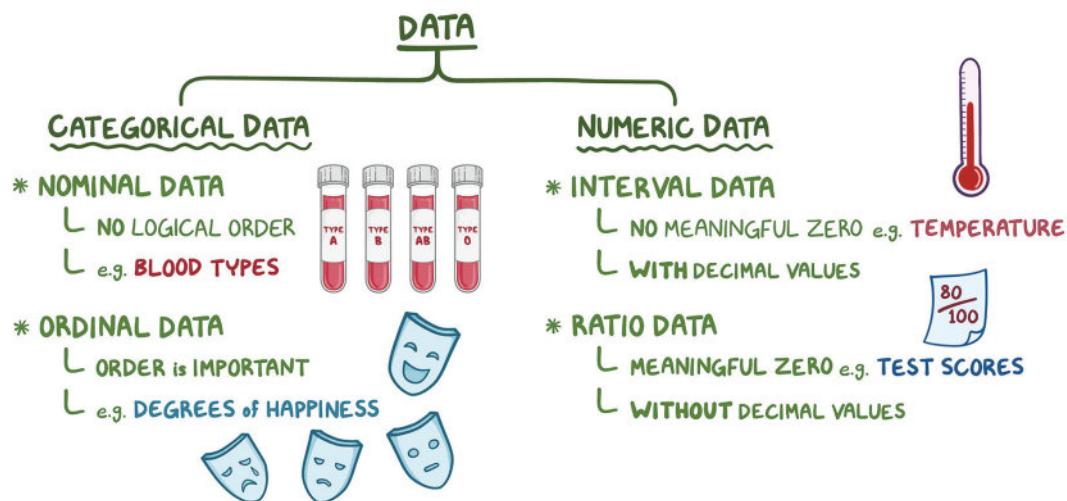


Figure 5.8 Types of data.



# NOTES CAUSATION & VALIDITY

## CAUSALITY

[osms.it/causality](http://osms.it/causality)

- Consequential relationship between two events (e.g. A caused B)
  - Contrast with correlation: association between two events
- Consequential relationship may be direct/indirect
  - Direct: event caused direct consequence which → effect ( $A \rightarrow B$ )
  - Indirect: initial event → another event → final effect ( $A \rightarrow x \rightarrow y \rightarrow B$ )
- Correlation is not equal to causation
  - Two correlated events may seem to have consequential relationship; sometimes due to random chance/external factors/confounding (noncausal) variables

- Example: the longer you smoke, the higher your risk of developing lung cancer

### Biologic coherence

- Causal mechanism for effect agrees with current knowledge
  - Example: factually known that cigarettes contain carcinogenic agents

### Biologic plausibility

- Proposed mechanism of effect makes sense according to current knowledge
  - Example: because we know cigarettes contain carcinogenic agents, it makes sense that cigarette-smoke exposure → higher probability of developing lung cancer

### Consistency with other knowledge

- Association has been shown repeatedly
  - Example: it has been repeatedly proven that smoking confers higher risk of developing lung cancer

### Specificity

- Chances that effect is due to other causes
  - Example: can there be another explanation for developing lung cancer besides exposure to cigarette smoke?

### Experimental evidence

- When you remove cause, effect disappears
  - Example: if you stop smoking, your risk of developing lung cancer decreases

### Analogy

- Similar events have been proven to cause similar effects
  - Example: smoking other substances has

been known to cause lung pathology

## CAUSAL RELATIONSHIP TYPES

### Necessary and sufficient

- Presence of A required, present in adequate amounts to cause B
  - Example: autosomal dominant mutation with complete penetrance both necessary, sufficient for disease to develop

### Necessary but not sufficient

- Presence of A required, not present in adequate amounts to cause B
  - Example: heat required to cause burn, however, low heat will not cause burn; it is necessary but not sufficient

### Not necessary but sufficient

- Presence of A not required, but is enough to cause B
  - Example: gunshot to head sufficient to cause death, however, not necessary, as there are many other causes of death

### Not necessary and not sufficient

- Presence of A not needed nor enough to cause B
  - Example: urinary infection not necessary nor sufficient to cause pelvic inflammatory disease; urinary infection can be present without pelvic inflammatory disease, individual can have pelvic inflammatory disease without having urinary tract infection

# BIAS

[osms.it/bias](http://osms.it/bias)

- Error in one step of study design/conduction/analysis → results interpretation that is different from truth
  - Many types of biases, no common classification

- Results of one group will be inherently different to other group's results
  - Example: blood glucose levels of groups measured by different machines; one gave accurate results, other reported inaccurate results

## SELECTION BIAS

- Errors made when choosing/following population to be studied
  - Can occur at different stages of study
  - Most commonly occurs when chosen sample is not representative of population

### Non-differential misclassification

- Measurement error likely to have occurred in both groups
  - Results among two groups will not differ greatly
  - Example: machine used to determine blood glucose levels for both groups was inaccurate

## MEASUREMENT BIAS

- AKA information bias
- Errors made when measuring data/results of interest
  - Most commonly results in results misclassification which can be differential/non-differential

## OTHER BIAS TYPES

- Information gathering, management can → other bias types
- AKA information bias

### Procedure bias

- People allocated to different groups not treated identically
  - Usually due to lack of blinding

### Differential misclassification

- Error in measurement more likely to occur in one group than another

- Example: people in one group spend more time in hospital than other group

### Recall bias

- Awareness of event/effect influences individual's recall of cause
  - Most common in retrospective studies
  - Example: after a person with cancer knows that radiation exposure is a cancer development risk factor, the person may place more emphasis on exposure to radiation than someone without cancer

### Lead-time bias

- Early diagnosis extends follow-up period, making it seem as if event being studied took longer to progress
  - Example: early cervical cancer detection may make it seem as if cancer is less aggressive because of more time spent living with diagnosis

### Observer-expectancy bias

- When belief in intervention's effectiveness interferes with reported treatment outcome
  - Example: researcher's belief in drug efficacy may interfere with reported results

## CONFOUNDING

[osms.it/confounding](https://osms.it/confounding)

- Occurs when external event is related to possible cause, outcome of interest but is not on causal pathway
- Example: study exploring relationship between exercising, overall health, we know that

- Exercising known to improve overall health
- Exercising associated with healthy lifestyle, but is not result of healthy lifestyle

## INTERACTION

[osms.it/interaction](https://osms.it/interaction)

- Combination of two/more factors changes disease incidence compared to influence they would have had individually
  - Describes way multiple factors interact to produce event

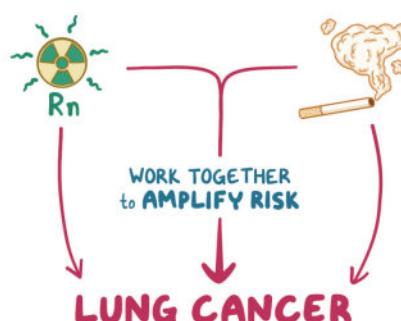
### Synergism

- Refers to potentiation effect multiple factors may have on one another
- Example:  $2 + 2 = 5$

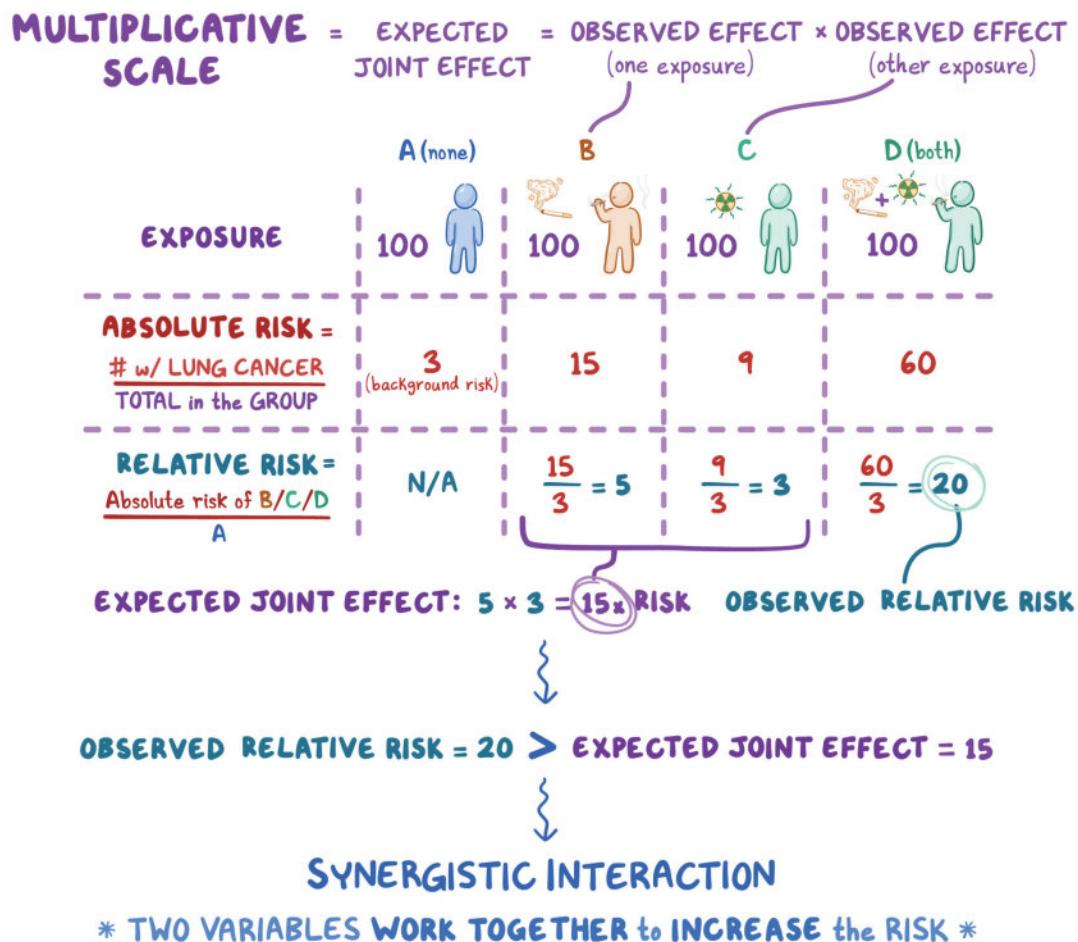
### Antagonism

- Refers to inhibition effect multiple factors may have on one another
- Example:  $2 + 2 = 3$

### e.g. of BIOLOGICAL INTERACTION



**Figure 6.1** Biological interaction is when two exposures, like radon gas and cigarette toxins, work together to influence an outcome, like lung cancer.



**Figure 6.2** A graph representing data collected from four groups with 100 people per group: those with no exposure to radon or cigarette toxins (A), those with exposure to only cigarette toxins (B), those with exposure to only radon (C), and those with exposure to both radon and cigarette toxins (D). The multiplicative scale was used to calculate the expected joint effect of radon and cigarette toxins based on their independent effects (columns B and C). These two exposures are said to have a synergistic interaction because observed relative risk > expected joint effect. If observed relative risk had been < expected joint effect, the interaction would have been antagonistic.



# NOTES COMMUNITY HEALTH

## DYNAMICS OF OUTBREAKS

- Outbreak: sudden increase in disease occurrence in a specific time, place, population (e.g. outbreaks of foodborne-related norovirus acute gastroenteritis)

- Infective outbreaks depend on causative pathogen characteristics (such as mode of transmission)

# MODES OF INFECTIOUS DISEASE TRANSMISSION

[osms.it/transmission](http://osms.it/transmission)

## TRANSMISSION

- The passing of a pathogen-causing communicable disease from an infected host to another individual/group

## MODES OF TRANSMISSION

- Depends on responsible organism's characteristics

### Direct

- Interpersonal contact → infected individuals spread disease
  - One-to-one (e.g. venereal infection with sexual intercourse)
  - One-to-multiple (e.g. influenza with a violent sneeze in a crowded environment)

### Indirect

- Common vehicle (e.g. contaminated air, water/food supply, needle-sharing)
- Vectors (e.g. mosquito/tick)

# OUTBREAK INVESTIGATIONS

[osms.it/outbreak-investigations](http://osms.it/outbreak-investigations)

## CHARACTERISTICS OF AN OUTBREAK

- Explosive: in epidemic curve, there is a fast, abrupt rise in number of cases, followed by fast, abrupt fall
- Indirect transmission: infection limited to individuals who share common exposure

- Direct transmission: often impossible to associate new cases to primary case (first symptomatic case occurring in defined setting)

## STEPS TO INVESTIGATE AN OUTBREAK

### Validate outbreak's existence in a population

- Define number of cases (numerator)
- Define the extent of the population susceptible to disease (denominator)
- Determine whether number of observed cases is more than expected number of cases
- Calculate the attack rate: proportion of an initially disease-free population that develops disease
  - Proportion is used because the individuals in the numerator (those who have the disease) are included in the denominator (the total population)

### Investigate cases by looking for interactions of time, person, place

- Are there interactions between variables?

### Develop hypotheses

- Consider existing knowledge about the disease, findings from current investigation

### Test hypotheses

- Analyze data (e.g. case-control study, laboratory tests such as chemical/immunological fingerprinting)

### Recommend measures for disease control, prevention

- E.g. remove infection source, establish environmental controls (interrupt disease transmission), improve sanitation, immunize susceptible individuals

# DISEASE SURVEILLANCE

[osms.it/disease-surveillance](http://osms.it/disease-surveillance)

- Essential public health tool, aimed at predicting, observing, minimizing outbreaks
- Based on systematic collection, analysis, interpretation of epidemiologic data
- Monitored parameters examples
  - Changes in disease incidence/mortality
  - Changes in quantity of risk factors for a disease in environment
  - Completeness of vaccination coverage
  - Prevalence of drug-resistant organisms

## MODALITIES OF SURVEILLANCE

### Passive

- Using existing data on reportable diseases such as anthrax, cholera, gonorrhea
- Pros
  - Comparatively inexpensive, easy to develop
  - Areas that require urgent intervention are quickly identified by international comparisons
- Cons
  - Surveillance is not the primary

responsibility of case-reporting individuals

- Local outbreaks may be missed

### Active

- Implementing surveillance program (e.g. field visits to clinics, hospitals, communities)
- Pros
  - Reporting more accurate; individuals recruited specifically for surveillance program
  - Local outbreaks are more likely to be identified
- Cons
  - More expensive to develop, maintain

## DIFFICULTIES

- Obtaining reliable data in low-income countries → underreporting risk
  - Areas may be difficult to reach
  - Communication with central authorities can be challenging
  - Resources such as diagnostic laboratories not always available

# VACCINATION & HERD IMMUNITY

[osms.it/vaccination-herd-immunity](https://osms.it/vaccination-herd-immunity)

## HERD IMMUNITY BASICS

- Herd immunity: phenomenon in which entire population is indirectly protected against disease when critical percentage of members are immune
  - Immunity can be innate/acquired through vaccination/by naturally recovering from infection
  - The higher the proportion of immune people in a population, the less likely the encounter between a susceptible person and an infected one → chain of infection is disrupted

### Conditions

- Host is a single species
- Transmission of the organism must be spread by direct contact
- No reservoir outside the human host
- Infections must induce solid immunity

## HERD IMMUNITY & COMMUNITY HEALTH

- The critical percentage of immune individuals needed to achieve herd immunity varies according to disease contagiousness (e.g. 94% in measles [highly communicable] → increased number of individuals need to be immune)
- Because of herd immunity, vaccination programs do not necessitate yield 100% immunization rates, yet can achieve highly effective protection by immunizing critical percentage of a population
- Herd immunity is important for public health because individuals who cannot develop immunity or cannot be vaccinated depend on herd immunity (e.g. newborn infants, individuals with immunodeficiency due to HIV/AIDS, cancer, cancer treatments)



# NOTES

## EPIDEMIOLOGY MEASURES

### DIRECT STANDARDIZATION

[osms.it/direct-standardization](https://osms.it/direct-standardization)

#### STANDARDIZATION

- Methods used to compare health event rates of two/more populations (e.g. mortality rates) by standardizing characteristics responsible for inter-population differences
- E.g. remove confounding variables (age) when comparing two groups' crude mortality rate (CMR) to get age-adjusted mortality rate
  - CMR: number of people who died in one group, divided by the group population (100,000 or 1,000)

#### DIRECT STANDARDIZATION

- Compares differences in health events among two/more populations by calculating age-adjusted rate

- Used when event distribution in each age group within population is known
- Process for calculating direct standardization for age-adjusted mortality rate
  - Choose reference (standard) population (e.g. separate population such as a national-level population)
  - Multiply other population of interest's age-specific mortality rates to number of people in each age group of reference population
  - Add up number of expected deaths from all age groups
  - Calculate age-adjusted mortality rate
  - Compare two age-adjusted mortality rates

### INDIRECT STANDARDIZATION

[osms.it/indirect-standardization](https://osms.it/indirect-standardization)

- Used when number of events/mortality rates in each age group within population is not known
- Process for calculating indirect standardization for age-adjusted mortality rate
  - Choose reference population with known mortality rates

- Multiply other population of interest's age-specific mortality rates to number of people in each age group of reference population
- Add up number of expected deaths from all age groups
- Calculate standardized mortality ratio (SMR)



AGE	n° of PEOPLE	DEATHS	MORTALITY RATE
> 40	18,000	18	0.001
< 40	5,000	50	0.01
TOTAL	23,000	68	

AGE	n° of PEOPLE	DEATHS	MORTALITY RATE
> 40	3,000	7	0.0024
< 40	23,000	115	0.005
TOTAL	26,000	122	

## STEP 1: CHOOSING a REFERENCE ( or STANDARD ) POPULATION

### STEP 2:

$$\text{CITY 2 MORTALITY RATE} \times \frac{\text{CITY 1 n° of PEOPLE in EACH AGE GROUP}}{\text{CITY 1 n° of PEOPLE in EACH AGE GROUP}} = \text{EXPECTED n° of DEATHS in CITY 2 with the SAME AGE DISTRIBUTION as CITY 1}$$

↓

$$\begin{aligned} > 40 &\rightarrow 0.0024 \times 18,000 = 43 \text{ EXPECTED DEATHS} \\ < 40 &\rightarrow 0.005 \times 5,000 = 25 \text{ EXPECTED DEATHS} \end{aligned} \quad \left. \right\} 68$$

AGE - ADJUSTED MORTALITY RATE:

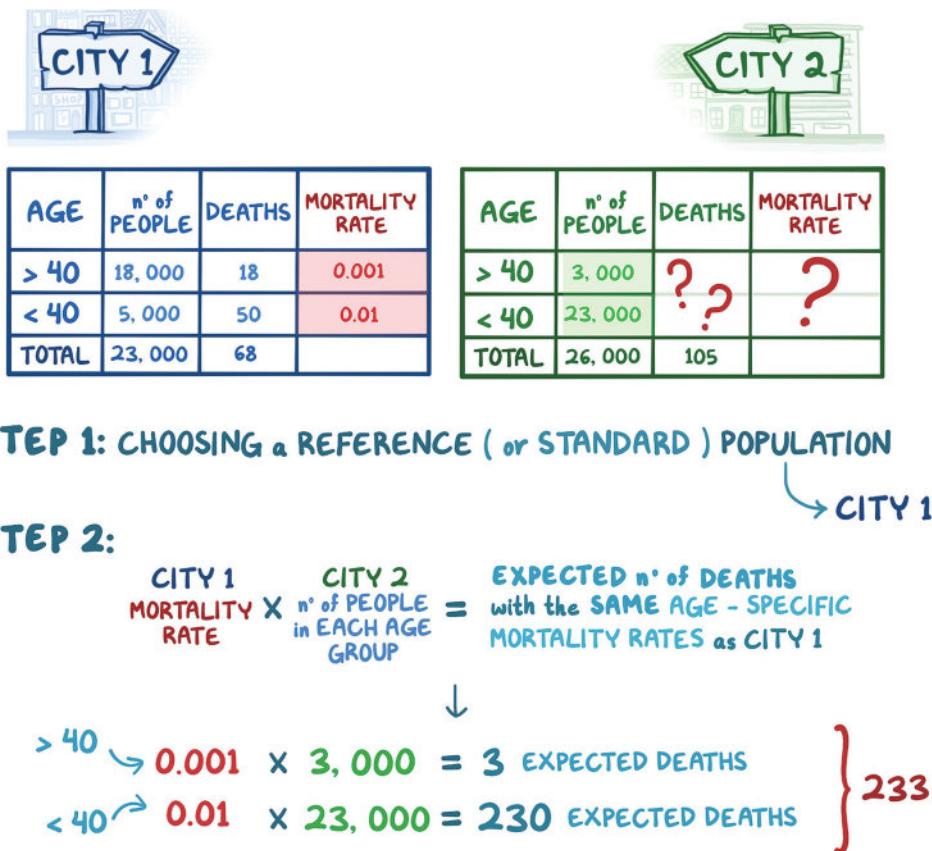
$$\frac{68}{23,000} = 0.003$$

MORTALITY RATIO:

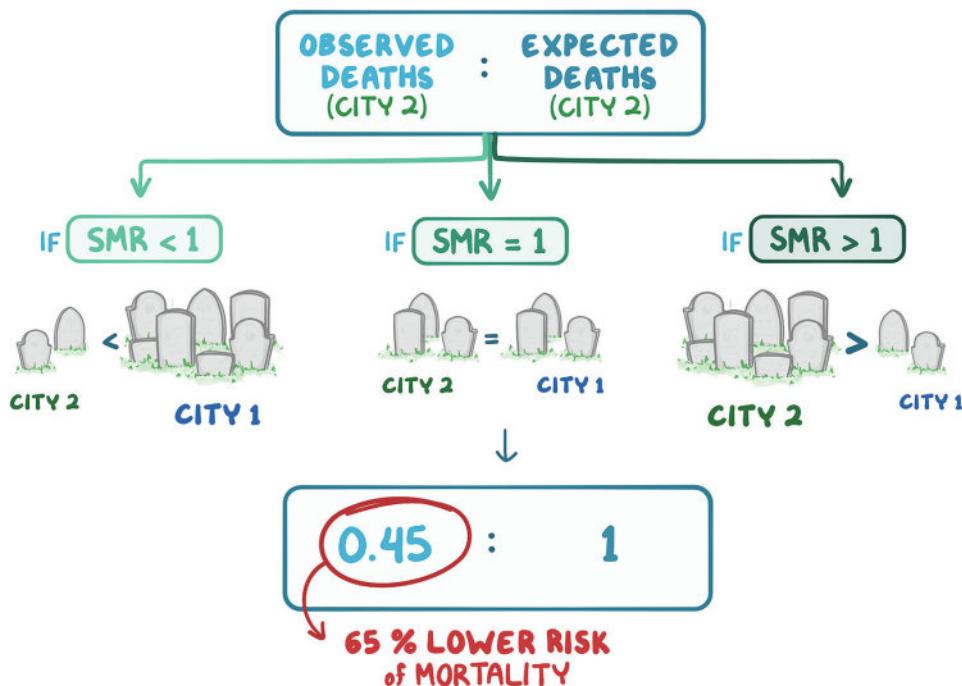
$$1 : 1$$

AFTER USING DIRECT STANDARDIZATION

**Figure 8.1** Using direct standardization to find the age-adjusted mortality rate for City 2, using City 1 as the reference population.



**STEP 3: CALCULATE the STANDARDIZED MORTALITY RATIO (SMR)**



**Figure 8.2** Using indirect standardization to find the standardized mortality ratio for City 2, using City 1 as the reference population.

# INCIDENCE & PREVALENCE

[osms.it/incidence-prevalence](https://osms.it/incidence-prevalence)

- Measures number of people who have disease
- Reported as population percentage/ratio (e.g. cases per 1000)

## Incidence

- Number of new disease cases in population over time period (usually one year)
  - Affected by preventive measures (vaccination, diagnostic techniques)

## Prevalence

- Number of total (old, new) disease cases in population in particular time point (point prevalence)
  - Shows disease commonness in group of people
  - Affected by cure rate, survival rate, death rate, recurrence

## Relationship between incidence and prevalence

- New disease cases (incidence) added to amount of disease present in population (baseline prevalence) → ↑ prevalence
- ↑ death rate, cure rate → ↓ prevalence (↓ total disease cases)
- If incidence > death/cure rate → net ↑ prevalence; if incidence < death/cure rate → net ↓ prevalence

$$\text{prev ALence} = \frac{\text{ALL cases}}{\text{population at risk}}$$

$$\text{iNcidence} = \frac{\text{New cases}}{\text{population at risk}}$$

# MEASURES OF RISK

[osms.it/measures-of-risk](https://osms.it/measures-of-risk)

- Probability that event will occur (e.g. disease development risk)

- Smokers are 10 times more likely to develop bladder cancer

## Absolute risk

- Disease incidence in population who have been exposed to specific risk factor
  - E.g. 1 out of 50 (2%) diabetics will develop cardiovascular disease (CVD)

$$\text{Absolute risk} = \frac{\# \text{ of events in a group}}{\# \text{ of individuals in that group}}$$

$$\text{Relative risk} = \frac{\text{Probability of event in exposed population}}{\text{Probability of event in unexposed population}}$$

## Relative risk (RR)

- Compares disease development probability between exposed group, unexposed group
  - E.g. smokers' bladder cancer incidence (30%), non-smokers' bladder cancer incidence (3%)
  - RR = 0.3/0.03 = 10

## Absolute risk reduction (ARR)

- AKA risk difference
- Outcomes comparison (change in risk)
  - Between population that has received treatment for a disease, population that has not received treatment
- ARR = risk (untreated) - risk (treated)
  - E.g. 4% bladder cancer occurrence in group that receives particular drug, 20% in group that does not receive drug
  - ARR = 0.2 - 0.04 = 0.16 or 16%
  - For every 100 individuals receiving drug, 16 bad outcomes would be avoided

### Number needed to treat

- Determines how many individuals should be treated with medication to prevent one person from developing bladder cancer
  - Number needed to treat:  $1/0.16 = 6.25$
  - About six people should be treated

$$\# \text{ needed to treat} = \frac{1}{\text{Absolute risk reduction}}$$

## ODDS RATIO

[osms.it/odds-ratio](https://osms.it/odds-ratio)

- Measures association between exposure (e.g. risk factor, health characteristic), outcome (e.g. disease, mortality)
  - E.g. Which group is at higher risk of experiencing an adverse outcome? Does an intervention change risk degree for a group?
- Used in case-control studies: case group with identified outcome, control group without identified outcome
- Calculated using 2X2 frequency table
  - Divide odds of disease in exposed individuals by odds of disease in unexposed individuals

$$OR = \frac{40/20}{60/80} = \frac{2}{0.75} = 2.66$$

- OR = 1 → exposure does not affect odds of outcome
- OR > 1 → exposure associated with higher odds of outcome
- OR < 1 → exposure associated with lower odds of outcome

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

2 x 2 FREQUENCY TABLE			
		+ (DISEASE)	- (NO DISEASE)
+ (EXPOSED)	a:	# of exposed individuals (smokers) w/bladder cancer = 40	b: # of exposed individuals (smokers) w/o bladder cancer = 60
	c:	# of unexposed cases w/bladder cancer = 20	d: # of unexposed cases w/o bladder cancer = 80

# ATTRIBUTABLE RISK (AR)

[osms.it/attributable-risk](http://osms.it/attributable-risk)

- AKA risk difference/excess risk
- Measures difference in disease risk between exposed population, unexposed population
  - Often used in cohort studies

## AR for exposed individuals

$$AR = \frac{A}{A+B} - \frac{C}{C+D}$$

$$AR = \frac{40}{100} - \frac{20}{100} = 0.4 - 0.2 = \frac{20}{100}$$

$$\frac{AR}{\text{incidence in exposed}} \times 100$$

$$\frac{20}{40} \times 100 = 50\%$$

- 50% of bladder cancer incidence → attributable to smoking in exposed population

## AR for population (PAR)

PAR = incidence in population - incidence in unexposed

$$PAR = \frac{60}{200} - \frac{20}{100} = 0.3 - 0.2 = \frac{10}{100}$$

$$\frac{10}{20} \times 100 = 50\%$$

		2 x 2 FREQUENCY TABLE		TOTALS
		+ (DISEASE)	- (NO DISEASE)	
+ (EXPOSED)	+	a: # of exposed individuals (smokers) w/bladder cancer = 40	b: # of exposed individuals (smokers) w/o bladder cancer = 60	100
	-	c: # of unexposed cases w/bladder cancer = 20	d: # of unexposed cases w/o bladder cancer = 80	100
		60	140	200

# MORTALITY RATES & CASE-FATALITY

[osms.it/mortality\\_rates\\_case-fatality](http://osms.it/mortality_rates_case-fatality)

- Mortality rate: death incidence in population over period of time

## Annual mortality rate

- Mortality rate from all causes (crude death rate)
  - Calculated by taking total number of

deaths from all causes in one year divided by total number of people at risk in population at mid-year

- Annual mortality = total number of deaths (850) ÷ total number of people at risk in population at mid-year (500,000) = 0.0017

- Percent:  $0.0017 \times 100 = 0.17\%$
- Per 100,000:  $0.0017 \times 100,000 = 170$   
(170 death per 100,000 people during year)

#### Population-specific mortality rate

- Mortality rate for specific sub-population (e.g. biologically-female individuals; cancer-related deaths, neonatal mortality)
  - E.g. neonatal mortality rate = number of deaths among children < 28 days old (during given time interval) ÷ number of live births (during same time interval) × 1,000

#### Case-fatality rate

- Percent of people that die within certain period of time post-diagnosis
  - Calculated by dividing number of post-diagnosis deaths by total number of diagnosed individuals, multiplied by 100
- Measures disease severity

$$\text{Case mortality rate from disease A} = \frac{40}{250} = 0.16 = 16\%$$

## DALY & QALY

osms.it/DALY-QALY

- Disease burden measurement: impact of health problem on individual/population

#### Disability-Adjusted Life Years (DALY)

- Determines disease burden according to years of life, or to compare specific intervention's effect (e.g. new medication reducing diabetes risk)
  - Morbidity, mortality combined into single metric
- DALY: years of lost life due to premature death (YLL) + years lived disability (YLD)
  - YLL: number of deaths (N) × standard life expectancy at age of death in years (L)
  - YLD: number of incident cases (I) × disability weight (DW) × average duration of disability in years (L)
  - DW: reflects disease severity on 0 (perfect health) to 1 (dead) scale

#### Quality-Adjusted Life Years (QALY)

- Determines disease burden according to quality of years of life, relative value of interventions (e.g. cost-utility analysis); guides healthcare-resource prioritization
- Measures years of life with illness/disability (considered less than year of healthy life)
- QALY = number of years lived × utility weight
  - One healthy year of life = 1 QALY (1 year of life × 1 utility weight)
  - One year of life lived in situation with illness/disability (e.g. chronic pain) = 1 year × 0.5 (utility weight) = 0.5 QALYs
  - Death: assigned value of 0 QALYs



# NOTES

## NON-PARAMETRIC TESTS

### NON-PARAMETRIC TESTS

- For data that is assumed to not be distributed normally

- For nominal/ordinal level variables

## CHI-SQUARED TEST

[osms.it/chi-squared\\_test](http://osms.it/chi-squared_test)

- Chi-square ( $\chi^2$ ) goodness-of-fit test
- Test compares categorical variables
  - Assesses for significant association
- Examines whether collected data is significantly different than theoretical model
  - How “good is the fit” between data, what is expected
- Null hypothesis: no significant difference between theorized/expected, observed ratios
  - $\chi^2 = \text{sum of } [(observed - expected)^2 / expected]$
- Use  $\chi^2$  table to find critical  $\chi^2$ 
  - Adjusted for degrees of freedom [ $n - 1$ ], at selected p-value
- Accept null hypothesis if  $\chi^2 <$  critical  $\chi^2$

### CHI-SQUARE TEST OF INDEPENDENCE

- For analysis of contingency tables (or crosstabs tables)
- Investigates whether two/more categorical variables are statistically significant
- Used for multiple variables
- Degrees of freedom = (# of rows – 1) × (# of columns – 1)
- Requires > 5 data points in all cells of table; whole numbers
- Higher  $\chi^2$  results in lower p-value

## FISHER'S EXACT TEST

[osms.it/Fisher\\_exact\\_test](http://osms.it/Fisher_exact_test)

- Variant of chi-square test
  - Used with small sample size
- Used to determine exact probability of association between two categorical variables (i.e. significance of association [contingency] between classifications)
- Use for 2 × 2 contingency tables (< 5 in a cell)
  - p-values calculated exactly
  - $p < 0.05$ , unlikely to be random association

# KAPLAN-MEIER SURVIVAL ANALYSIS

[osms.it/Kaplan-Meier\\_survival\\_analysis](http://osms.it/Kaplan-Meier_survival_analysis)

- Estimates survival from lifetime data; measures fraction of survivors over treatment time; simplest method of computing survival over time
  - Plot of percent survival versus time; generated from status at last observation, time to event
  - Large sample size → approaches population effect
- Accounts for censored data; withdrawn from study, lost to follow-up; alive at last follow-up (i.e. right-censoring—data above a certain value, but otherwise unknown)
- Limited capacity to estimate survival adjusted for covariates

# KAPPA COEFFICIENT

[osms.it/kappa-coefficient](http://osms.it/kappa-coefficient)

- AKA Cohen's kappa coefficient
- Measure of inter-rater agreement
- Compares ability of different raters to classify categorical variables
- Interobserver agreement: accounts for agreement that occurs by chance, when raters measure same thing, using same observation method
- Calculated from observed, expected frequencies from diagonal of contingency table
- If kappa = 1
  - Agreement is perfect
- If kappa = 0
  - Agreement is no better than if agreement happened by chance
- Example for interpreting agreement based on kappa coefficient
  - None:  $< 0$
  - Fair: 0.20–0.40
  - Moderate: 0.40–0.60
  - Good: 0.60–0.80
  - Very good: 0.80–1.00

# MANN-WHITNEY U TEST

[osms.it/Mann-Whitney\\_u\\_test](http://osms.it/Mann-Whitney_u_test)

- Nonparametric test equivalent to unpaired t-test
- Compares differences between two unpaired groups that are not normally distributed
- Uses number ranks rather than raw data
- Provides p-value indicating whether or not groups are significantly different from each other ( $p < 0.05$ ; unlikely to happen by chance)

# SPEARMAN'S RANK CORRELATION COEFFICIENT

[osms.it/Spearmans-rank-correlation-coefficient](http://osms.it/Spearmans-rank-correlation-coefficient)

- Spearman's rho ( $\rho$ )
- Non-parametric equivalent of Pearson's correlation coefficient
- Measure strength, direction of monotonic association between two ranked variables
  - Monotonic association means variables increase together (i.e. as value of one variable increases value of other variable increases also/as value of one variable increases, other variable value will decrease)
  - Does not have to be linear, but must be entirely increasing/entirely decreasing (may include plateaus)
  - Use for continuous/discrete ordinal, interval, ratio variables
- Sign indicates direction of association
  - x and y increasing → +ve  $\rho$ ; x and y decreasing → -ve  $\rho$
- $\rho$  increases as correlation approaches perfect monotone relationship between variables
- Two formulas
  - One for when there are no tied ranks
  - One for tied ranks
- Use critical values ( $r_s$ ) from Spearman's rank coefficient tables to determine significance of r (Spearman's coefficient of sample)



# NOTES

## PARAMETRIC TESTS

### PARAMETRIC TESTS

- ANOVA, t-tests
- Use for following data
  - Randomly selected samples

- Independent observations
- Population standard deviations (SDs) are same
- Data distributed normally/approximately normally

## ANOVA

[osms.it/one-way\\_ANOVA](http://osms.it/one-way_ANOVA)

[osms.it/two-way\\_ANOVA](http://osms.it/two-way_ANOVA)

[osms.it/repeated-measures\\_ANOVA](http://osms.it/repeated-measures_ANOVA)

- AKA analysis of variance
- Determines differences between > two samples
  - Measures differences among means
- F-ratio (F statistic)
  - $F = \frac{\text{variance between groups}}{\text{variance within each group}}$
- Computer program calculates p-value from F; use F to accept/reject null hypothesis
  - F approx. = 1; p large; accept null hypothesis
  - F large → p small (alpha set at 0.05 significant → reject null hypothesis)
- Assumptions
  - Samples drawn randomly; sample groups have homogeneity of variance (i.e. from same population; interval, ratio data)

### 1-way ANOVA

- Between groups design
- One independent variable
  - May have multiple levels (e.g. drug A effect vs. drug B vs. placebo on specified outcome)

### Factorial ANOVAs

- Factorial designs
- Two-way, three-way, four-way ANOVA, more (two, three, four, etc. independent variables)

### Single-factor repeated measures ANOVA

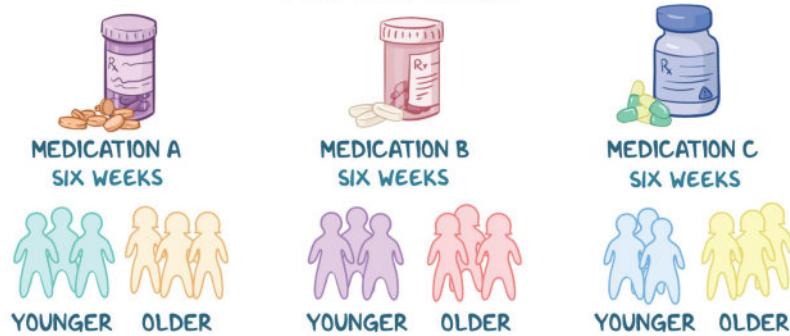
- ANOVAs involving repeated measures/within groups/subjects
- One independent variable with multiple levels tested within one subject group (e.g. drug A vs. drug B vs. placebo tested within same individuals at different times)
  - ↓ variation effect between sample groups

## LOWERING SYSTOLIC BLOOD PRESSURE

### ONE-WAY ANOVA



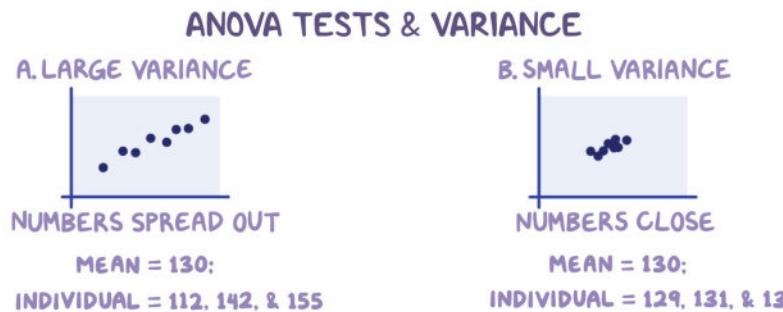
### TWO-WAY ANOVA



### REPEATED MEASURES ANOVA



**Figure 10.1** Examples demonstrating a one-way, two-way, and repeated measures ANOVA. The one-way ANOVA has one independent variable (medication type) with multiple levels (medications A, B, and C). The two-way ANOVA looks at two independent variables (medication type and age category) that each have multiple groups (medications A, B, and C; younger and older). The repeated measures ANOVA follows the same group of people over a period of time to measure the effects of the same medication over time. In this case, the independent variable is time, divided into three groups (one month, three months, and six months), and the dependent variable is systolic blood pressure.

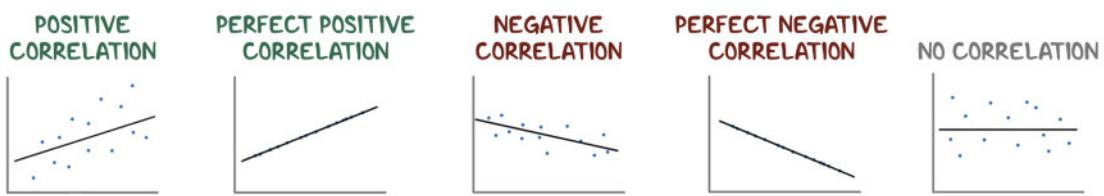


**Figure 10.2** All ANOVA tests assume that the groups have equal variance. A large variance means that the numbers are very spread out from the mean; a small variance means that the numbers are very close to the mean. Variances between groups are considered unequal when the variance of one group is greater than twice the variance of the other group.

## CORRELATION

[osms.it/correlation](http://osms.it/correlation)

- Investigates relationships between variables; determines strength, type (positive/negative) relationship
- Correlation coefficient:  $r (-1 > r < +1)$ 
  - Perfect positive correlation:  $r = +1$
  - Perfect negative correlation:  $r = -1$
  - No correlation:  $r = 0$
  - Strong correlation:  $r > 0.5 < -0.5$
  - Weak correlation:  $0 < r < 0.5$ , or  $0 > r > -0.5$
- Pearson product-moment coefficient: interval/ratio data; calculates linear relationship degree between two variables
- Confidence interval (CI): population based on correlation coefficient
  - Indicates range within population correlation coefficient lies
- P-value for correlation coefficient based on null hypothesis
  - I.e. if true ( $p > 0.05$ ), no correlation between variables
- Coefficient of determination:  $r^2$  or  $R^2$  ( $0 < R^2 < 1$ )
  - Fraction of variation of variable of interest (x axis) due to another variable of interest (y axis)
  - Remaining proportion due to natural variability
  - Low  $R^2$  may indicate poor linear relationship, may be strong nonlinear relationship
- Eta-squared ( $\eta^2$ ): analogous to  $R^2$  for ANOVA
- Correlation  $\neq$  causation, consider
  - How strong is association?
  - Does effect always follow cause?
  - Is there a dose response?
  - Relationship biologically plausible, coherent?
  - Consistent finding?
  - Other factors involved?
  - Good experimental evidence?
  - Analogous examples?



**Figure 10.3** Scatterplots are used to plot measurements, with one measured variable on each axis. Each data point represents one individual. A trend line is drawn to best represent the collection of data points on the plot, with roughly half the points above the line and the other half below the line. A perfect positive or negative correlation means that the trend line passes through every single data point.

## HYPOTHESIS TESTING

[osms.it/hypothesis-testing](https://osms.it/hypothesis-testing)

- Calculating sample size required to test hypothesis
- Equations used for calculating power can also be used to calculate sample size for a predefined alpha (0.05)
- Requires knowledge of
  - Clinically important effect size (larger sample size needed to detect smaller effects)
  - Surrogate endpoint use rather than direct outcome
- Desired power; alpha (if not 0.05); confidence interval
- Statistical tests to be used
- Data lost to follow-up
- Test group SD; population of interest expected frequency within test group
- Statistician's advice
  - Optimize sample size, avoid underpowered studies, enable valid data interpretation

## LINEAR REGRESSION

[osms.it/linear-regression](https://osms.it/linear-regression)

- Simple linear regression: assumes linear relationship; slope  $\neq 0$ ; data points close to line
- Examine weight of two variables' (x, y) effects; predict effects of x on y
- Fit best straight line to x, y plot of data
  - Equation:  $y = bx + a$  (x and y are independent variables; b = slope of line (regression coefficient); a = intercept )
- 95% CI for slope range; larger sample  $\rightarrow$  narrower CI; if range does not include zero  $\rightarrow$  real correlation suggested
- p-value for null hypothesis
  - No linear correlation (i.e. slope = 0; p < 0.05  $\rightarrow$  real correlation suggested)

## OTHER REGRESSION ANALYSES

- Multiple linear regression
  - Examines effects of more than one variable on y
- Multiple nonlinear regression
  - Examines correlations among nonlinear data, more than one independent variable

- Logistic regression
  - Predicts likelihood of categorical event in presence of multiple independent variables

# LOGISTIC REGRESSION

[osms.it/logistic-regression](http://osms.it/logistic-regression)

- Predictive analysis: describes relationship between binary dependent variable (i.e. takes one of two values), multiple independent variables
- Assumptions
  - Dichotomous outcome (e.g. yes/no; present/absent; dead/alive)
  - No outliers: assess using z scores
  - No intercorrelations: assess using correlation matrix
- May use logit (assumes log distribution of event's probability)/probit (model assumes normal distribution)
- Rule of 10: stable values if based on minimum of 10 observations per independent variable
- Regression coefficients: indicate contribution of individual independent variables; odds ratios
- Tests to assess significance of independent variable
  - Likelihood ratio test; Wald test
- Bayesian inference: prior (known) distributions for regression coefficients; conjugate prior; automatic software (e.g. OpenBUGS, JAGS to simulate priors)

# TYPE I & TYPE II ERRORS

[osms.it/type-i-and-type-ii-errors](http://osms.it/type-i-and-type-ii-errors)

## POWER

- Refers to test probability correctly rejecting false null hypothesis
- Power:  $(1 - \beta)$ 
  - Likelihood that statistically non-significant result is correct (i.e. not false negative—type II error)
- Medical research
  - Power typically set at 0.80
- Increasing power
  - $\downarrow$  type II error chance;  $\uparrow$  type I error chance
- Power increases when  $\uparrow$  sample size,  $\downarrow$  SD,  $\uparrow$  effect size

## EFFECT SIZE

- Relationship strength between variables
- Statistical significance does not necessarily indicate clinical significance
- Random variation (SD) may  $\downarrow$  differences between outcomes of interest between hypothesis' test groups
- $$ES = \frac{\bar{X}_1 - \bar{X}_2}{SD}$$
  - ES is effect size
  - $X_1$  is the mean for Group 1
  - $X_2$  is the mean for Group 2
  - SD is the standard deviation from either group

- Adjust for variation in test groups with Cohen's d (assumes each group's SD is same)
  - Cohen's d = (mean 1 – mean 2)/SD
  - 0.2 = small effect size
  - 0.5 = medium effect size
  - $\geq 0.8$  = large effect size

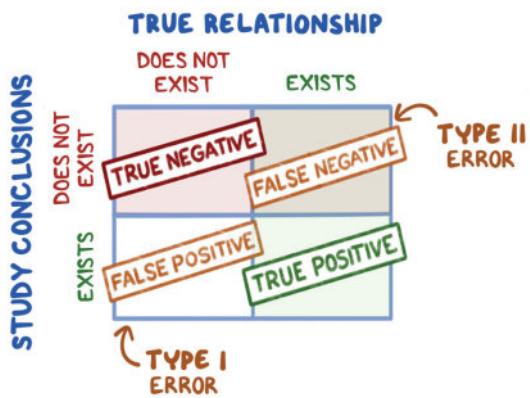
## SAMPLE SIZE

- Smaller sample size
  - ↑ sampling error chance
  - Lower power
  - ↑ type II error chance (false negative)

## BAYESIAN THINKING

- Relates p-value to context
  - Can involve complex mathematics
- Measures event probability given incomplete information
- Joint distribution between given information (usually probability density), experimental results

## RELATIONSHIP BETWEEN MEDICATION & BLOOD PRESSURE



**Figure 10.4** A Type I error occurs when no true relationship exists between two variables, but the study concludes there is one; a type II error occurs when there is a true relationship between two variables, but the study concludes there is no relationship.



# NOTES

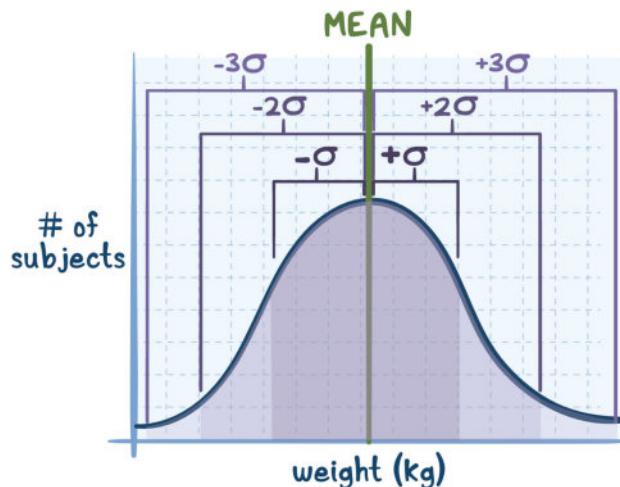
## STATISTICAL PROBABILITY DISTRIBUTIONS

### NORMAL DISTRIBUTION & Z-SCORES

[osms.it/normal-distributions-z\\_scores](http://osms.it/normal-distributions-z_scores)

#### NORMAL DISTRIBUTION

- Data grouped around central value, no left/right bias, in “bell curve” shape
- Probability distribution for normal random variable  $x$
- $f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-(\frac{1}{2})[(x-\mu)/\sigma]^2}$
- $\mu$  = mean of normal random variable  $x$
- $\sigma$  = standard deviation
- $\pi = 3.1416 \dots$
- $e = 2.71828 \dots$
- Normal distribution:  $\mu = 0, \sigma = 1$



#### Z-SCORES

- Standardized score
- Uses data set mean, standard deviation to determine measurement location
  - Represents deviation from mean
- Expressed in standard deviations
- Sample z-score for measurement  $x$
- $$z = \frac{x - \bar{u}}{\sigma}$$
- $\mu$  = population mean
- $\sigma$  = standard deviation

#### BELL CURVE

1 standard deviation:  
68% =  $+/- \sigma$

2 standard deviations:  
95% =  $+/- 2\sigma$

3 standard deviations:  
99% =  $+/- 3\sigma$

# STANDARD ERROR OF THE MEAN

[osms.it/standard-error-of-mean](https://osms.it/standard-error-of-mean)

- AKA SEM, standard deviation

- $$\sigma_{\bar{x}} = \frac{\sigma}{\sqrt{n}}$$

- $\sigma$  = standard deviation
- n = sample size

# PAIRED T-TESTS

[osms.it/paired-t-test](https://osms.it/paired-t-test)

- Statistical hypothesis test (parametric)
- Determines if two groups are statistically different (compares two groups' means)
- Groups can occur naturally (e.g. smokers compared to non-smokers)/groups can be created experimentally (e.g. control group compared to treatment group)
- $t = \frac{\text{difference between means}}{\text{variance/sample size}}$
- $= \frac{\text{sample mean} - \text{population mean}}{\text{sample standard error of the mean}}$

- $$\frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

- $\bar{x}_1$  = mean of sample 1
- $\bar{x}_2$  = mean of sample 2
- $n_1$  = sample size of sample 1
- $n_2$  = sample size of sample 2

- $s_1^2 = \frac{\sum (x_1 - \bar{x}_1)^2}{n_1 - 1}$
- $s_2^2 = \frac{\sum (x_2 - \bar{x}_2)^2}{n_2 - 1}$

# ONE-TAILED & TWO-TAILED TESTS

[osms.it/one-tailed-two-tailed-tests](https://osms.it/one-tailed-two-tailed-tests)

- Tails: ends of probability curve
- Alternative (research) hypothesis proposes groups under investigation are different in some way/relationship between them exists

## ONE-TAILED TESTS

- Alternative hypothesis is directional (i.e. specifies direction of difference/relationship)
  - Extreme values of one of distribution tails are of interest given difference type/expected relationship (solid theoretical

basis required for one-tailed test)

- Alternative hypothesis predicts relationship between groups either positive/negative (e.g. Group A will score higher on particular test than Group B)

## TWO-TAILED TESTS

- Alternative hypothesis is non-directional (i.e. non-specified direction of difference/relationship)
  - Extreme values on either tail of sampling distribution support null hypothesis rejection (e.g. Group A scores will be different than Group B)



## NOTES STUDY DESIGN

### SAMPLING

[osms.it/sampling](http://osms.it/sampling)

- Selection of individuals for study from specific population
- Aims to represent, estimate characteristics of that population

### PLACEBO EFFECT & MASKING

[osms.it/placebo-effect-and-masking](http://osms.it/placebo-effect-and-masking)

#### WHAT IS THE PLACEBO EFFECT?

- Refers to situation where study participant's belief in treatment brings about positive effect
  - E.g. individuals given placebo drug tend to report improvements even when treatment has no real effect
- Placebos can be affected by study participant's psychological responses to context in which treatment is taking place
- Placebo can be drug/pharmacologically inactive substance indistinguishable from an active treatment/can be based on any expectation the person may have about

intervention under study

- Useful in studying rate of side effects, reactions to drug

#### WHAT IS MASKING?

- Subjects and/or investigators are unaware of treatment assignment
  - Single blind: subjects are unaware of treatment assignment
  - Double blind: subjects, investigators are unaware of treatment assignment
  - Triple blind: treatment administrator unaware of treatment assignment

### CASE-CONTROL STUDY

[osms.it/case-control\\_study](http://osms.it/case-control_study)

- Study that determines potential risk factors in individuals with condition
- May rely on individual recall, past medical history, autopsy
- Example: Percentage of people who gave

birth to child with condition A who had previously taken drug B during pregnancy

- All children either do or do not have condition A
- We assess whether they did/did not

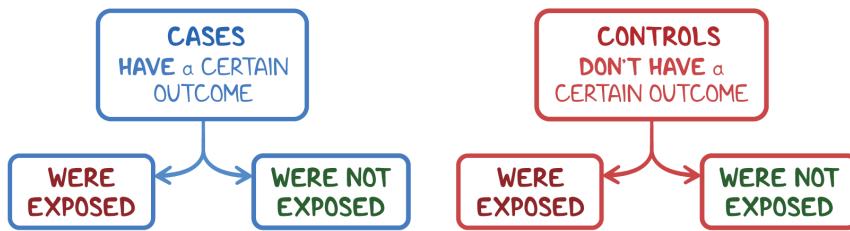
take drug B during pregnancy

### Pros

- More easily examines rare diseases than prospective studies; less expensive and time-consuming
- Individuals not exposed to possible risk factors
- Past medical history used to determine potential multiple risk factors

### Cons

- Potential problems matching cases and controls
  - E.g. study may be influenced by characteristics not being studied (confounding variables)
- Potentially biased (relies on individual recall)
  - E.g. study candidates may emphasize potential risk factors rather than controls



**Figure 12.1** Case-control study design.

# COHORT STUDY

[osms.it/cohort-study](http://osms.it/cohort-study)

- Measures disease within group of individuals (cohort) over period of time
- Focuses on disease development
- Two types: prospective cohort, retrospective cohort

- Useful information on risk
- Matching decreases influence of confounding variables

### Cons

- Expensive, time-consuming
- Follow-up with people over time can be difficult; subjects may be lost

## PROSPECTIVE COHORT STUDY

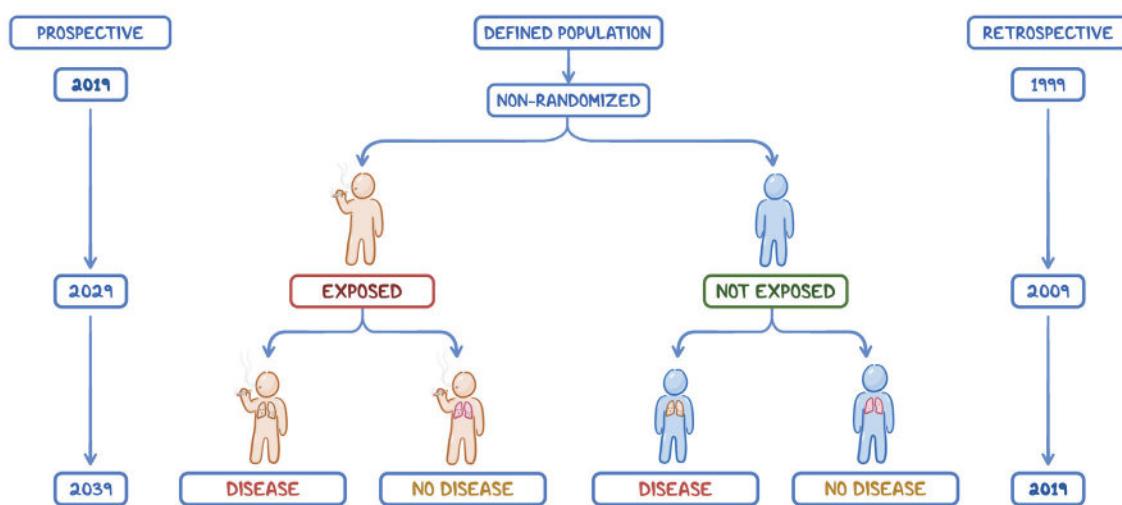
- AKA longitudinal, concurrent cohort study
- Results not known until after intervention
- Used to follow up on people who received treatment/were exposed to risk factors
- Laboratory tests often used as surrogate markers – for example, increase in hemoglobin immediately after blood transfusion assumed to mean that transfusion was effective
- Example: RSV rates of premature birth cohorts

## RETROSPECTIVE COHORT (HISTORICAL COHORT, NONCONCURRENT PROSPECTIVE) STUDY

- Same prospective cohort study design but uses past data to determine future time frame; study and obtention of results faster
- Use pre-existing population to decrease study duration
- Can be conducted relatively quickly, inexpensively
  - E.g. mortality rates according to duration of smoking

### Pros

- Easier to conduct than randomized controlled studies



**Figure 12.2** Design of prospective and retrospective cohort studies with hypothetical time frames. Exposed = smokers, not exposed = non-smokers, disease = lung cancer.

## CROSS-SECTIONAL STUDY

[osms.it/cross-sectional\\_study](http://osms.it/cross-sectional_study)

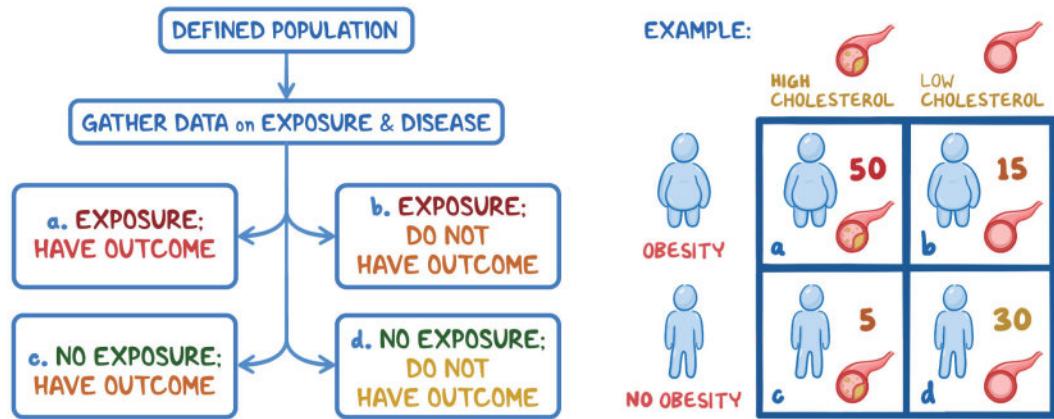
- Study that observes a group of people at one point in time
- Examines relationship between an exposure (variable), disease being investigated
- Example: the relationship between endometrial cancer, hormone replacement therapy (HRT)

### Pros

- Less time-consuming, expensive than longitudinal studies, as individual follow-up not necessary
- Good for establishing overall association between exposure and disease
- Can establish disease prevalence (number of individuals with particular disease in their lifetime)

### Cons

- Establishes disease prevalence but not incidence (percentage of individuals who may develop a particular disease within a year)
- Does not establish temporal relationship between exposure and disease
- Potentially biased if surveys used
- Retrospective studies: data quality may be compromised due to poor recall//“recall bias,” where people are more likely to recall certain events



**Figure 12.3** Design of a cross-sectional (prevalence) study. Example: obesity is the exposure, and high cholesterol is the outcome.

## ECOLOGIC STUDY

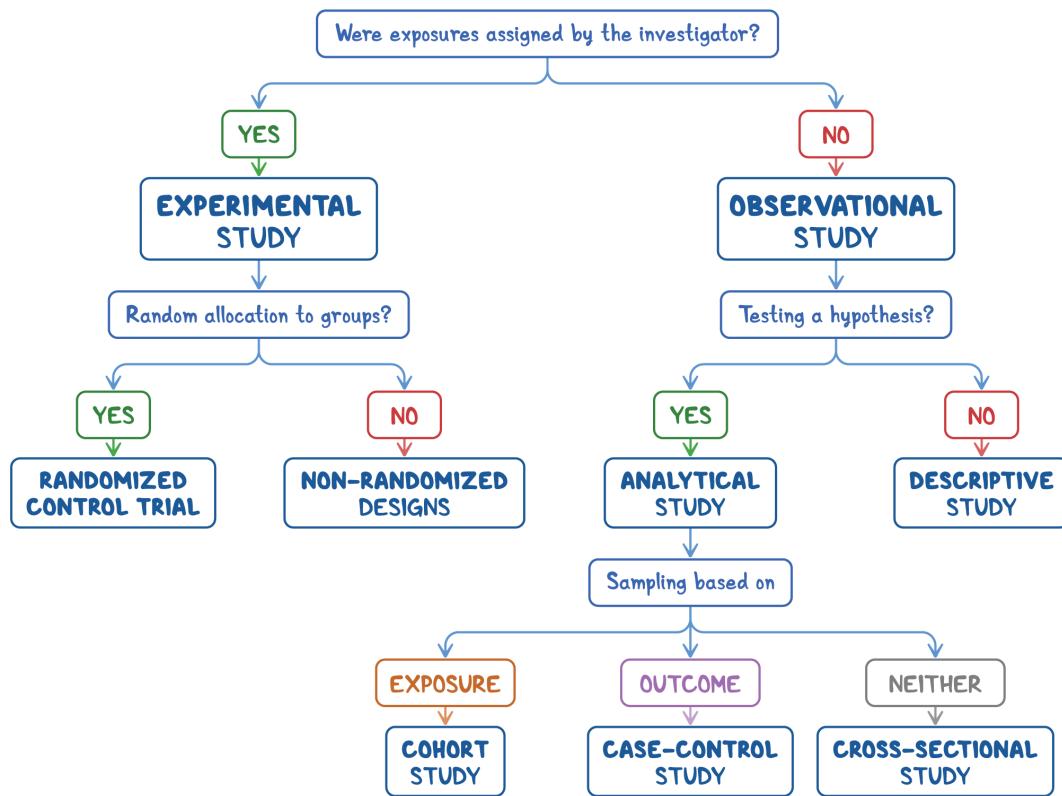
[osms.it/ecologic-study](http://osms.it/ecologic-study)

- Observes at least one variable
  - Exposure/outcome
- Measured at group level
- At least one comparison group, disease occurrence compared between groups
- Often used to make large-scale comparisons
- Examples
  - Rate of cancer occurrence in one population
  - Average sunlight exposure at different geographical locations
  - Comparing per capita dietary fat consumption, cardiovascular disease mortality
  - Disease occurrence compared between groups

# RANDOMIZED CONTROL TRIAL (RCT)

[osms.it/randomized-control-trial](http://osms.it/randomized-control-trial)

- Examines effectiveness of intervention (e.g. medications, treatment protocols)
- Three features: randomization, control, manipulation
- Considered gold standard of experimental research, identifying cause-and-effect relationships
- Study participants randomly assigned either experimental group or control group
- Example: Effects of drug A versus drug B on hypercholesterolemia in individuals with type 2 diabetes mellitus



**Figure 12.4** A summary flowchart of the different types of study designs.



# NOTES TESTING

## SENSITIVITY (SN) & SPECIFICITY (SF)

[osms.it/sensitivity-specificity](https://osms.it/sensitivity-specificity)

- Validity measure; concerned with how close test's result is to truth (i.e. did test/instrument measure what it is intended to measure?)
  - No perfect test → some miscalculation degree inevitable (i.e. healthy individual tests positive for disease → false positive; sick individual tests negative → false negative)
  - Sn, Sp: complementary test characteristic measures must be used together

### SENSITIVITY

- Population proportion who test positive for disease, have disease
- AKA **true positive rate**
- Highly sensitive test with positive result identifies people who are truly diseased (true positives), some healthy people (false positives)
- **Sensitivity:** proportion containing all truly positive, false positives
- Can assume two things
  - Test with high sensitivity is negative, individual must be healthy → rule out disease
  - Test with high sensitivity is positive, individual may/may not have disease (ensure lack of false positive; further testing required)
  - High sensitivity negative test → useful for ruling-out disease

### SPECIFICITY

- Population proportion tests negative for disease, free of disease
  - AKA **true negative rate**
- Highly specific test with negative result
- Identifies all people who are truly free of disease (true negatives), some sick people (false negatives)
- **Specificity:** proportion containing all truly negative, false negatives; two things assumed
  - Test with high specificity positive → confirm disease
  - Test with high specificity negative → individual may/may not have disease (ensure not false negative; further testing required)
- Positive test with high specificity → useful disease confirmation

### CUTOFF POINT

- For continuous variables: sensitivity, specificity may overlap → midpoint usually sought (avoids misclassification)
- Cutoff point needed to distinguish between normal/healthy, abnormal/unhealthy results

### High cutoff point

- **Highly specific:** **low false positives**
  - Everyone categorized as abnormal has disease
- **Poorly sensible:** **high false negatives**
  - Not everyone categorized as normal is free of disease

- I.e. previous hypertension definition stated 140/90mmHg as cutoff point
  - Highly specific: everyone categorized as abnormal has disease
  - Poorly sensitive: not everyone categorized as normal is free of disease

### Low cutoff point

- Poorly specific: high false positives
  - Not everyone categorized as abnormal has disease
- Highly sensitive: low false negatives
  - Everyone categorized as normal is free of disease
- I.e. new hypertension definition states 120/80mmHg as cutoff point
  - Poorly specific: not everyone categorized as abnormal has diseases
  - Highly sensitive: everyone categorized as normal is free of disease

### Cutoff point determined by test's purpose

- Screening test
  - Needs to detect all possible diseased → low cutoff point → highly sensitive → low false negatives
- Confirmatory test
  - Need to be sure of disease presence → high cutoff point → highly specific → low false positives

## SEQUENTIAL & SIMULTANEOUS TESTING

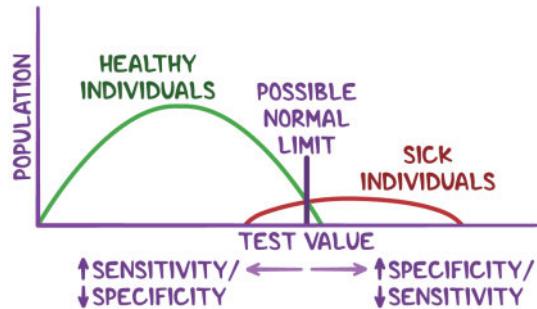
### Sequential testing

- AKA two-stage testing
- Consecutive tests performed with different characteristics → obtain more specific results
  - Perform first test → positive → perform second test → positive → disease likely present
  - Perform first test → negative → disease not likely present
- Similar to “double checking” results
- First test often easier/cheaper/less invasive than second test
- Sensitivity, specificity calculations must include both tests' characteristics
- Net sensitivity: proportion of true cases that test positive on both first, second test

- First test sensitivity x second test sensitivity
- Net specificity: proportion of healthy people that test negative on either first, second test
  - $(\text{First test specificity} + \text{second test specificity}) - (\text{first test specificity} * \text{second test specificity})$

### Simultaneous testing

- Two tests with different characteristics performed at same time → more sensitive results
  - Simultaneous testing: three groups of people
  - People detected only by Test A
  - People detected only by Test B
  - People detected by both Test A and Test B
  - Pools all possibly relevant information → more sensitive results
- Sensitivity, specificity calculations must include both tests' characteristics
- Net sensitivity: proportion of true cases that test positive on either test A or B
  - $(\text{Test A sensitivity} + \text{Test B sensitivity}) - (\text{Test A sensitivity} * \text{Test B sensitivity})$
- Net specificity: proportion of healthy people that test negative on both tests A and B
  - $\text{Test A specificity} * \text{Test B specificity}$



**Figure 13.1** Illustration showing how sensitivity and specificity are affected by moving the cut-off point.

## SENSITIVITY & SPECIFICITY

		DISEASE		TESTING TOTAL	MEASURES
TEST	POSITIVE	PRESENT	ABSENT		
POSITIVE	True positives (TP)	False positives (FP)		Total positive test (TP + FP)	Positive Predictive Value (PPV) = $\frac{\text{true positives}}{\text{total positives}}$
NEGATIVE	False negatives (FN)	True negatives (TN)		Total negative test (FN + TN)	Negative Predictive Value (NPV) = $\frac{\text{true negatives}}{\text{total negatives}}$
TOTAL DISEASE	Total disease (TP + FN)	Total no disease (FP + TN)		Total population (TP + FP + TN + FN)	Muscles, liver
MEASURES	Sensitivity = $\frac{\text{true positives}}{\text{total disease}}$	Specificity = $\frac{\text{true negatives}}{\text{total no disease}}$		Prevalence = $\frac{\text{Total disease}}{\text{total population}}$	

## POSITIVE & NEGATIVE PREDICTIVE VALUE

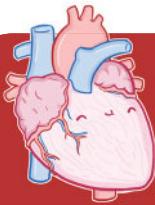
[osms.it/positive-negative-predictive-value](https://osms.it/positive-negative-predictive-value)

- PPV: probability that if test is positive, person has disease
  - Divide true positives, total positive test number
- NPV: probability that if test is negative, person is free of disease
  - Divide true negatives, total negative test number
- Both measures directly influenced by prevalence, test specificity
  - High prevalence: more likely that person has disease → ↑ PPV
  - Low prevalence: less likely that person has disease → ↑ NPV
  - Low prevalence: need a good test in confirming disease (high specificity) → ↑ PPV

# TEST PRECISION & ACCURACY

[osms.it/test-precision-accuracy](https://osms.it/test-precision-accuracy)

- Both concerned with how likely test to be reproduced → return results close to truth
  - Neither measuring devices nor people perfect → affects test precision, accuracy
- **Test precision:** how repeatable test results are over time, regardless of result accuracy
  - **High precision test:** consistently deliver similar results, regardless of whether true/not
- **Test accuracy:** how true test results are, regardless of test repeatability
  - **High accuracy test:** gives correct results; cannot always be reproduced
- Comparing test precision, accuracy
  - Oximeter consistently (precisely) reports true  $pO_2$  (accurately)
  - Oximeter consistently (precisely) reports  $pO_2$  20% lower than truth (not accurate)
  - Oximeter inconsistently (not precise) reports true  $pO_2$  (accurate)
  - Oximeter inconsistently (not precise) reports  $pO_2$  20% lower than truth (not accurate)



# NOTES

## CARDIOVASCULAR ANATOMY & PHYSIOLOGY

# CARDIOVASCULAR ANATOMY & PHYSIOLOGY

[osms.it/cardiovascular-anatomy-physiology](https://osms.it/cardiovascular-anatomy-physiology)

## CARDIOVASCULAR SYSTEM

- Cardia-, cardi-, cardio-
  - Heart, which pumps blood
- Vascular: blood vessels (carry blood to body, return it to heart)
- Delivers oxygen, nutrients to organs, tissues
- Removes waste (carbon dioxide, other cellular respiration by-products) from organs, tissues

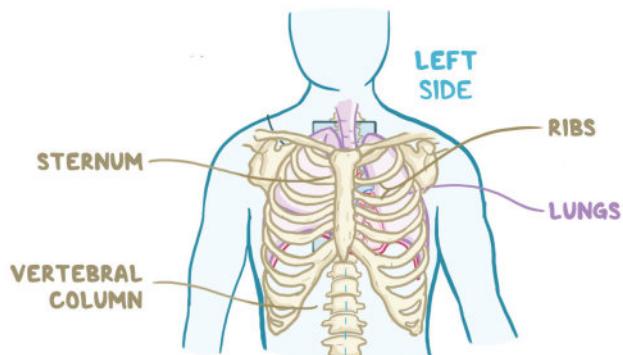
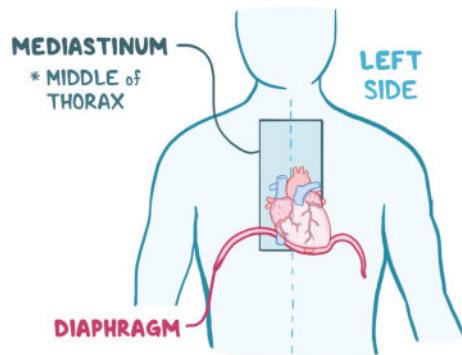
## MORPHOLOGY

- Size: about size of person's fist (correlated with person's size)
- Shape: blunt cone-shaped
- Position: slightly shifted to left side
- Location
  - Lies in mediastinum in thoracic cavity

- Sits on top of diaphragm (main breathing muscle)
- Behind sternum (breast bone)
- In front of vertebral column
- Between lungs
- Enclosed, protected by ribs
- Right, left sides separated by muscular septum

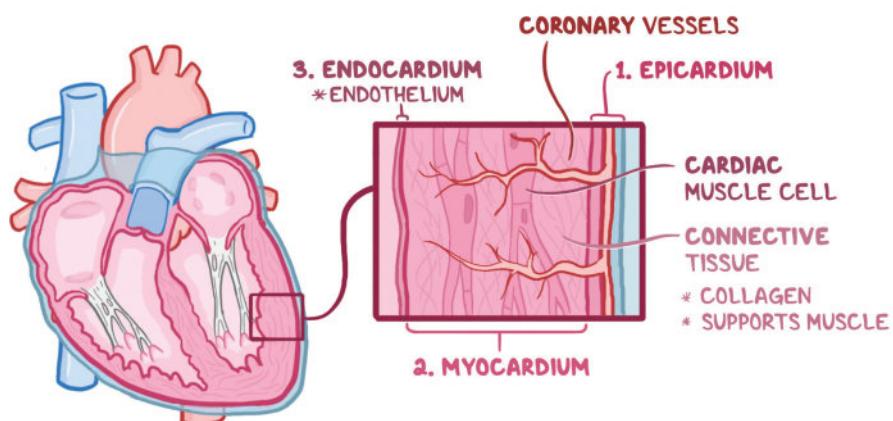
## Heart wall layers

- Epicardium: covers surface of heart, great vessels (AKA visceral pericardium)
- Myocardium: muscular middle layer
  - Cardiac muscle cells: striated branching cells with many mitochondria, intercalated disks for synchronous contraction
  - Cardiac myocytes: striated, branching cells with fibrous cardiac skeleton

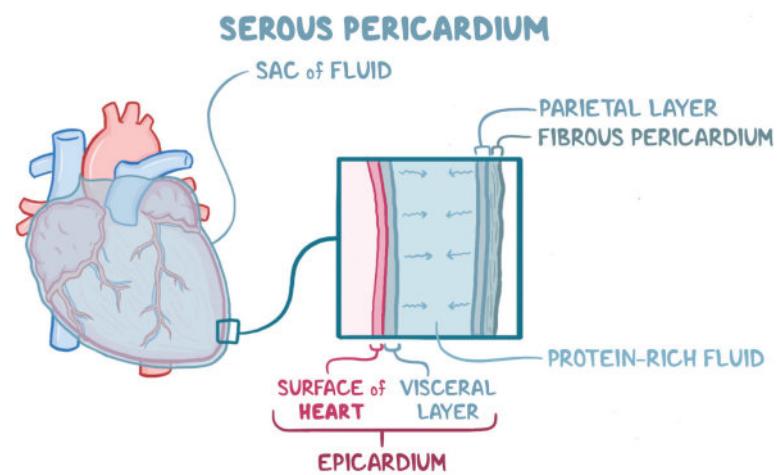


**Figure 14.1** Heart location relative to other thoracic structures.

- (supports muscle tissue, crisscrossing connective tissue collagen fibers); coronary vessels (lie on outside of heart, penetrate into myocardium to bring blood to that layer)
- **Endocardium:** innermost layer
    - Made of thin epithelial layer, underlying connective tissue
    - Lines heart chamber, valve
  - **Pericardium:** double-layered sac surrounding heart
    - **Fibrous pericardium:** outer layer; tough fibrous connective tissue anchors heart within mediastinum
- Serous pericardium: simple squamous epithelium layer
- Parietal pericardium: lines fibrous pericardium
- **Visceral pericardium (epicardium):** covers outer surface of heart
- Cells of parietal, visceral pericardium secrete protein-rich fluid (pericardial fluid) → fills space between layers (lubricant for heart, prevents friction)



**Figure 14.2** Heart wall layers, from superficial to deep.



**Figure 14.3** Layers of the pericardium (the double-layered sac surrounding the heart.)

### Atrioventricular valves

- Separate atria from ventricles
- Tricuspid valve
  - Three cusps with chordae tendinae (tether valve to papillary muscle)
  - Prevents blood backflow into right atrium (right ventricle contracts → papillary muscles contract, keep chordae tendinae taut)
- Bicuspid / mitral valve
  - Two cusps: anterior, posterior leaflet
  - Both have chordae tendinae tethered to papillary muscles in left ventricle
  - Prevents blood backflow back into left atrium

### Semilunar valves

- Located where two major arteries leave ventricles
- Pulmonary valve
  - Three half-moon shaped cusps
  - Prevents blood backflow into right ventricle
- Aortic valve
  - Three cusps
  - Prevents blood backflow into left ventricle

### Blood flow physiology

- Deoxygenated blood enters right side of heart via superior, inferior vena cava (veins)
- Coronary sinus (tiny right atrium opening) collects blood from coronary vessels → right atrium → tricuspid valve → right

- ventricle → pulmonary valve → pulmonary trunk → pulmonary arteries → pulmonary arterioles → pulmonary capillaries → alveoli
- Blood collects oxygen from alveoli, removes carbon dioxide
- Oxygenated blood travels through pulmonary venules → pulmonary veins → left atrium → bicuspid/mitral valve → left ventricle → aortic valve → aorta → organs, tissues
- Deoxygenated blood returns to heart

### SYSTEMIC VS. PULMONARY CIRCULATION

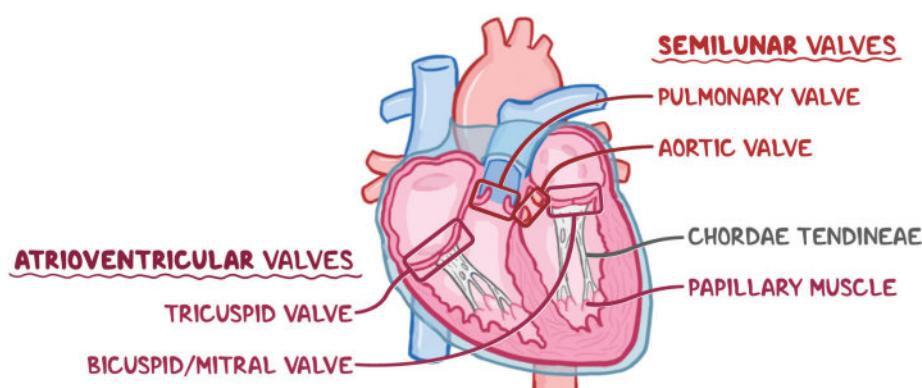
- Pulmonary, systemic circulation both pump same amount of blood

#### Pulmonary circulation

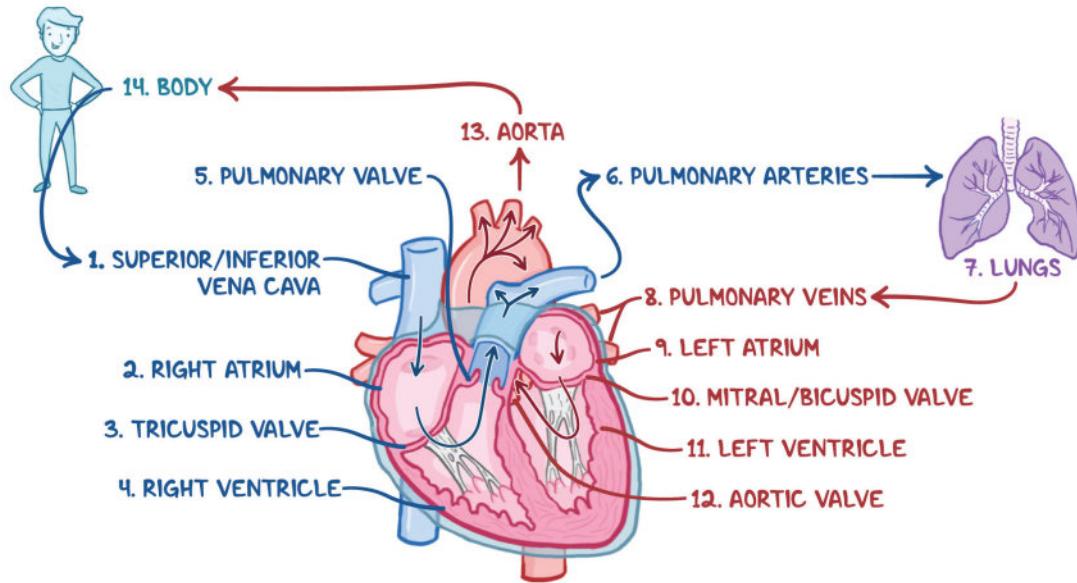
- Low pressure system
- Right side of heart pumps deoxygenated blood through pulmonary circulation to collect oxygen
  - Right atrium → right ventricle → pulmonary arteries → lungs

#### Systemic circulation

- High pressure system
- Left side of heart pumps oxygenated blood to systemic circulation
  - Pulmonary veins → left atrium → left ventricle → aorta → body
  - Left ventricle three times thicker than right ventricle ( $\uparrow$  systemic circulation resistance)



**Figure 14.4** The four heart valves. The chordae tendinae and papillary muscles attached to the atrioventricular valves prevent blood backflow into the atria.



**Figure 14.5** Blood flow physiology starting with the superior and inferior vena cavae bringing deoxygenated blood from the body to the right atrium of the heart.

## VENTRICULAR SYSTOLE VS. DIASTOLE

### Systole

- Ventricular contraction/atrial relaxation
- Occurs during S1 sound
  - Aortic, pulmonic valves open → blood pushed into aorta, pulmonary arteries
- Systolic blood pressure
  - Arterial pressure when ventricles squeeze out blood under high pressure
  - Peripheral pulse felt

### Diastole

- Ventricular relaxation/atrial contraction
- Occurs during S2 sound
  - Tricuspid, mitral valves open → blood fills ventricles
- Diastolic blood pressure
  - Ventricles fill with more blood (lower pressure)

## BLOOD DISTRIBUTION

- Average adult: 5L/1.32gal total blood volume (not cardiac output)
- 10% of total volume (approx. 500ml/0.13gal) in pulmonary arteries, capillaries, pulmonic circulatory veins
- 5% of total volume (250ml/0.07gal) in one

of four heart chambers

- 15% (750ml/0.2gal) in systemic arteries
  - 15% to brain
  - 5% nourishes heart
  - 25% to kidneys
  - 25% to GI organs
  - 25% to skeletal muscles
  - 5% to skin
- 5% (250ml/0.07gal) in systemic capillaries
- 65% (3.25L/0.86gal) in systemic veins
- Numbers can change (e.g. exercise)

## BLOOD FLOW TERMINOLOGY

### Preload

- Amount of blood in left ventricle before contraction
- Determined by filling pressure (end diastolic pressure)
- “Volume work” of heart

### Afterload

- Resistance (load) left ventricle needs to push against to eject blood during contraction
- “Tension work” of heart
- Components include
  - Amount of blood in systemic circulation

- Degree of arterial vessel wall constriction (for left side of heart, main afterload source is systemic arterial resistance; for right side of heart, main afterload source is pulmonary arterial pressure)

### Stroke volume (SV)

- Blood volume (in liters) pumped by heart per contraction
- Determined by amount of blood filling ventricle, compliance of ventricular myocardium

### Cardiac output (CO)

- Blood volume pumped by heart per minute (L/min)
- $CO = SV * \text{heart rate}$
- Example
  - $SV = 70\text{mL}$  ejected per contraction
  - $HR = 70\text{bpm}$
  - $CO = 70 * 70 = 4900\text{mL/min} = 4.9\text{L/min}$

### Venous return

- Blood-flow from veins back to atria

### Ejection fraction (EF)

- Percentage of blood leaving heart during each contraction
- $EF = (\text{stroke volume} / \text{end diastolic volume}) * 100$

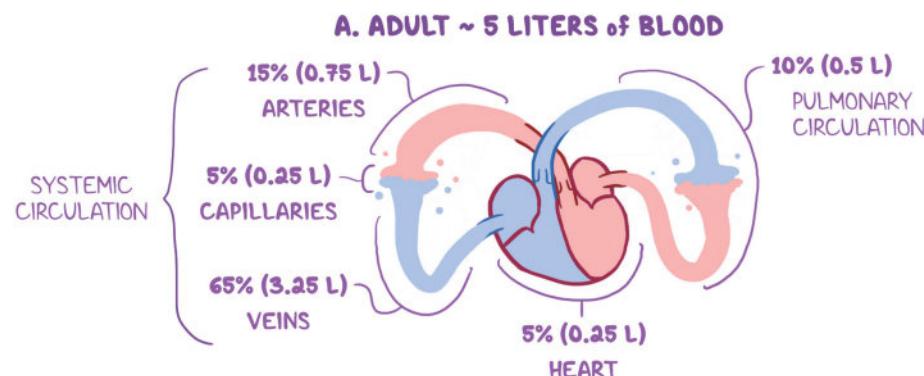
### Frank-Starling Mechanism

- Ventricular contraction strength related to amount of ventricular myocardial stretch
- Maximum contraction force achieved when myocardial actin, myosin fibers are stretched about 2–2.5 times normal resting length

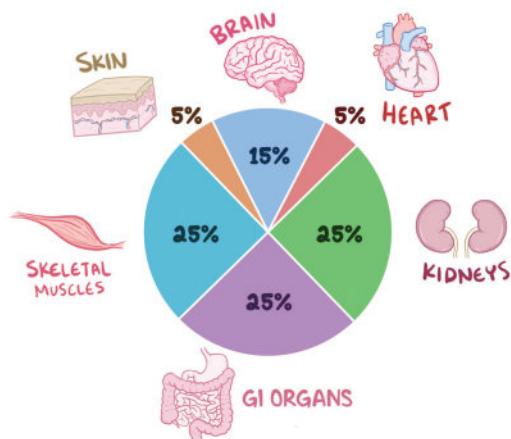
## BLOOD VESSEL LAYERS ("TUNICS")

### Tunica intima (interna)

- Innermost layer



### B. SYSTEMIC ARTERIAL BLOOD DISTRIBUTION



**Figure 14.6** A: Total blood volume distribution in an average adult. B: Systemic arterial blood distribution.

- Endothelial cells create slick surface for smooth blood flow
- Receives nutrients from blood in lumen
- Only one cell thick
  - Larger vessels may have subendothelial basement membrane layer (supports endothelial cells)

#### Tunica media

- Middle layer
- Mostly made of smooth muscle cells, elastin protein sheets
- Receives nutrients from blood in lumen

#### Tunica externa

- Outermost layer
- Made of loosely woven fibers of collagen, elastic
  - Protects, reinforces blood vessel; anchors it in place
- Vaso vasorum ("vessels of the vessels")
  - Tunica externa blood vessels are very large, need own blood supply

## ARTERIES

#### Key features

- High pressure, thicker than veins, no valves

#### Types

- "Elastic" arteries (conducting arteries)
  - Lots of elastin in tunica externa, media
  - Stretchy; allows arteries to expand, recoil during systole, diastole
  - Absorbs pressure
  - Largest arteries closest to heart (aorta, main branches of aorta, pulmonary arteries) have most elastic in walls
- Muscular arteries (distributing arteries)
  - Carry blood to organs, distant body parts
  - Thick muscular layer
- Arterioles (smallest arteries)
  - Artery branches when they reach organs, tissues
  - Major systemic vascular resistance regulators
  - Bulky tunica media (thick smooth muscle layer)
  - Regulate blood flow to organs, tissues
  - Contract (vasoconstriction) in response to hormones/autonomic nervous system, ↓ blood/↑ systemic resistance
  - Vasodilate (relax) ↑ blood flow to organs/tissues, ↓ systemic resistance
  - Ability to contract/dilate provides thermoregulation

## VEINS

#### Key features

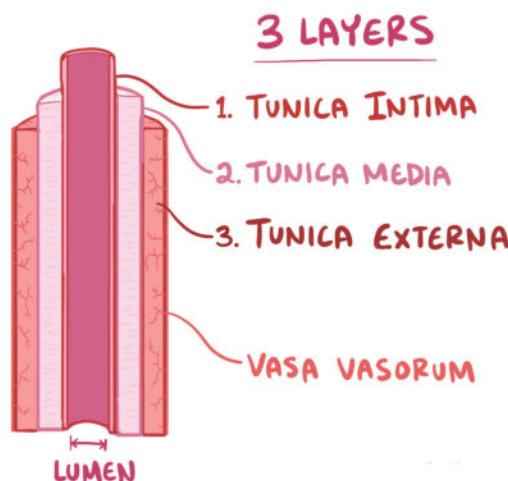
- Low pressure
- Cannot tolerate high pressure but are distensible → adapts to different volumes, pressures
- Have valves (folds in tunica interna) to resist gravity, keep blood flowing unidirectionally heart

#### Types

- Venules: small veins that connect to capillaries

## CAPILLARIES

- Only one cell thick (flat endothelial cells)
- Oxygen, carbon dioxide, nutrients, metabolic waste easily exchanged between tissues; circulation through capillary wall by diffusion



**Figure 14.7** The three layers, or "tunics," of a blood vessel.

- Fluid moves out of vessel, into interstitial space (space between blood vessels, cells)
  - Water-soluble substances (ions) cross capillary wall through clefts, between endothelial cells, through large pores in fenestrated capillary walls
  - Lipid-soluble molecules (oxygen, carbon dioxide) dissolve, diffuse across endothelial cell membranes

### BULK FLOW

- Passive water, nutrient movement across capillary wall down concentration gradient

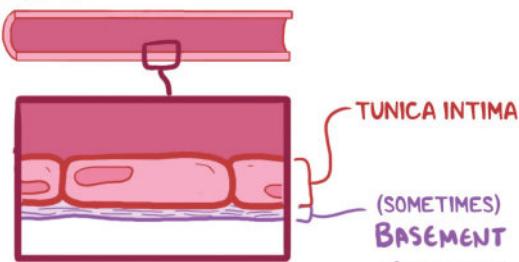
### LARGEST ARTERIES



### ARTERIOLE



### CAPILLARY



### META ARTERIOLE



### VENULE

### Key features

- Moves large amounts of water, substances in same direction through fenestrated capillaries
- Material movement
- Faster transport method
- Regulates blood, interstitial volume
- Filtration, reabsorption
- Continuous fluid mixing between plasma, interstitial fluid

### Types

- Filtration: bulk flow when moving from blood to interstitium
- Reabsorption: bulk flow when moving from interstitium to blood

### Other characteristics

- Kidney: major site of bulk flow where waste products are filtered out, nutrients reabsorbed
- Fluid filters out of capillaries into interstitial space (net filtration) at arteriolar end, reabsorbed (net reabsorption) at venous end
  - Hydrostatic interstitial fluid pressure draws fluid into capillary
  - Hydrostatic capillary pressure pushes fluid out of capillary
  - Colloid interstitial fluid pressure pushes fluid out of capillary
  - Colloid capillary pressure draws fluid into capillary

### MICROCIRCULATION

- Microcirculation: arterioles + capillaries + venules
- Arteriole blood flow through capillary bed, to venule (nutrient, waste, fluid exchange)
  - Capillary beds composed of vascular shunt (vessel connects arteriole, venule to capillaries), actual capillaries
  - Terminal arteriole → metarteriole → thoroughfare channel → postcapillary venule
  - Precapillary sphincter: valve regulates blood flow into capillary
  - Various chemicals, hormones, vasomotor nerve fibers regulate amount of blood entering capillary bed

**Figure 14.8** Key features of different blood vessel types.

# LYMPHATIC ANATOMY & PHYSIOLOGY

[osms.it/lymphatic-anatomy-physiology](https://osms.it/lymphatic-anatomy-physiology)

## LYMPHATIC SYSTEM

### Function

- Fluid balance
  - Returns leaked interstitial fluid, plasma proteins to blood, heart via lymphatic vessels
  - Lymph: name of interstitial fluid when in lymph vessels
  - Lymphedema: lymph dysfunctional/absent (lymph node removal in cancer)  
→ edema forms
- Immunity
- Fat absorption

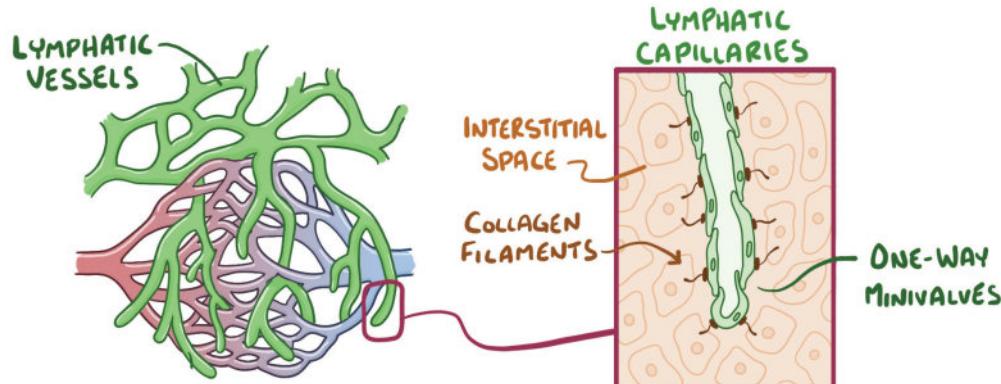
### Lymphatic capillaries

- Collect interstitial fluid leaked by capillaries
- Found in all tissues (except bone, teeth, marrow)
  - Microscopic dead-ended vessels unlike blood capillaries, helps fluid remain inside
  - Usually found next to blood capillaries
- Lymph moves via breathing, muscle contractions, arterial pulsation in tight tissues

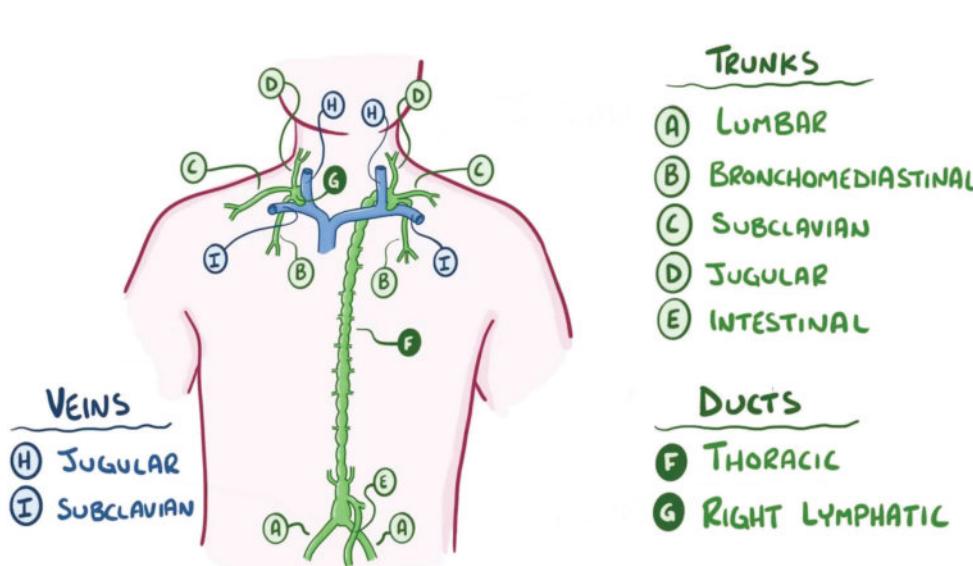
- Carries particles away from inflammation sites/injury towards bloodstream, stopping first through lymph nodes that filter out harmful substances
- Overlapping endothelial cells create valves; prevent backflow, infectious spread
- **Lacteals:** specialized lymphatic capillaries found in small intestine villi
  - Carry absorbed fats into blood
  - Chyle: fat-containing lymph

### Larger lymphatics

- Capillaries → collecting vessels → trunks → ducts → angle of jugular, subclavian veins; right lymphatic duct empties into right angle, thoracic into left
- Collecting vessels have more valves, more anastomoses than veins
  - Superficial collecting vessels follow veins
  - Deep collecting vessels follow arteries
- Lymphatic trunks
  - Paired: lumbar, bronchomediastinal, subclavian, jugular
  - Singular: intestinal



**Figure 14.9** Lymphatic vessels collect interstitial fluid (which is then called lymph) and return it to the veins. Lymphatic capillaries have minivalves that open when pressure in the interstitial space is higher than in the capillary and shut when pressure in the interstitial space is lower.



**Figure 14.10** Lymphatic system structures and their locations in the body.

- Ducts
  - Upper right lymphatic drains right arm; right thorax; right side of head, neck
  - Thoracic duct drains into cisterna chyli (a dilation created to gather all lymph drained from body area that's not covered by upper right lymphatic duct)

### LYMPHOID CELLS

- Lymphocytes: T subtype activate immune response; B subtype → plasma cells, produce antibodies
- Macrophages: important in T cell activation, phagocytosis
- Dendrocytes: return to nodes from inflammation sites to present antigens
- Reticular cells: similar to fibroblasts; create mesh to contain other immune cells

### LYMPHOID TISSUES

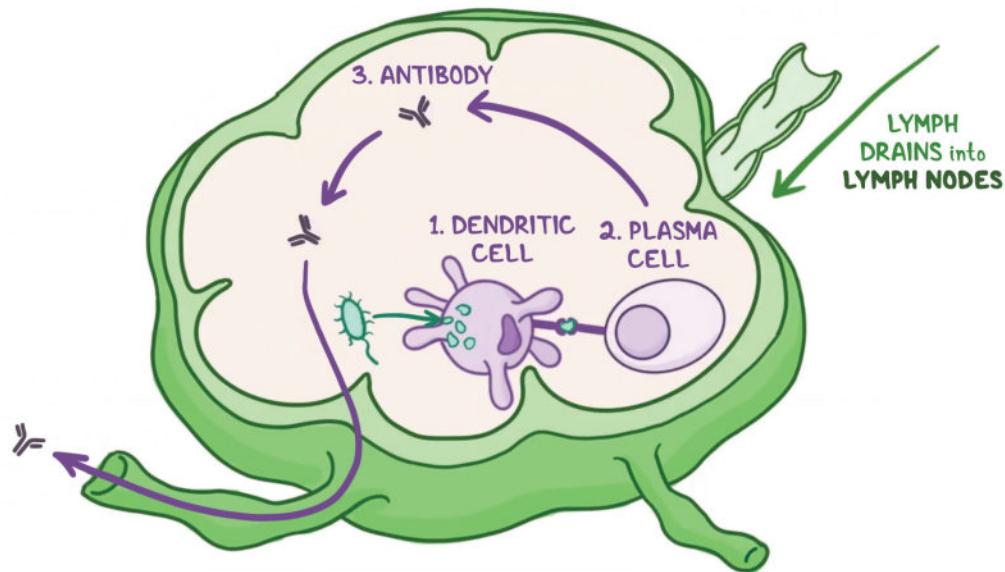
- Reticular connective tissue
- Composition: macrophage-embedded reticular fibers
- Loose
  - Diffuse lymphoid tissue
  - Venules enter, filters blood
  - Found in all organs
- Dense
  - Follicles/nodules
  - Mostly contain germinal centers

- Found in larger organs (lymph nodes)/ individually (mucosa)

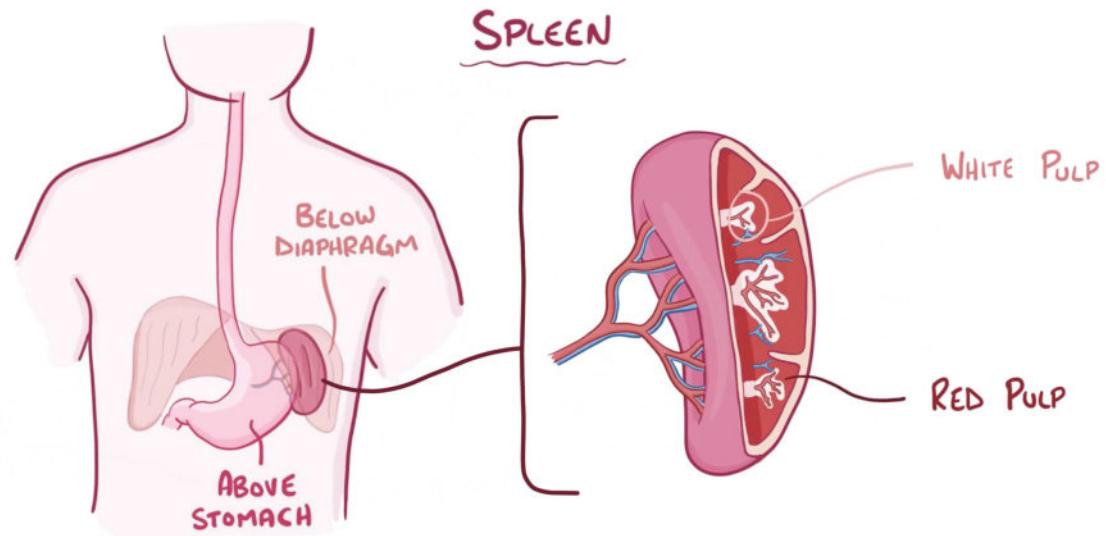
### LYMPHOID ORGANS

#### Spleen

- Largest lymphoid tissue in body
- Located below left side of diaphragm
- Blood supplied by splenic artery; blood leaves spleen via splenic vein
  - Capsules with projections into organ, form splenic trabeculae
- Function
  - Macrophages remove foreign particles, pathogens from blood
  - Red blood cell turnover
  - Compound storage (e.g. iron)
  - Platelet/monocyte storage
  - Blood reservoir: stores about 300ML/0.08gal
  - Fetal erythrocyte production
- Histology
  - White pulp: lymphocyte, macrophage islands that surround central arteries
  - Red pulp: composed mostly of red blood cells, macrophages; macrophages remove old red blood cells, platelets; splenic cords (reticular tissues running between venous sinusoids)



**Figure 14.11** In lymph nodes, dendritic cells present pieces of pathogens they come across to B cells. If a dendritic cell presents something foreign to a B cell, the B cell turns into a plasma cell and starts secreting antibodies, which flow into the lymph and exit the lymph node.



**Figure 14.12** Spleen location, histology.

### Lymph nodes

- Hundreds scattered throughout body, often grouped along lymphatic vessels
  - Superficial, deep
  - Many found in inguinal, axillary, cervical regions
- Function
  - Lymph filtration, immune system activation
- Kidney-shaped formations
  - Built like tiny spleens, 1–25cm/0.4–9.8in long
  - Covered by capsule with trabeculae, extend inward; trabeculae divide nodes sectionally
- Cortex
  - Subcapsular sinus, lymphoid follicle, germinal center

- Medulla
  - Medullary cord, medullary sinus
- Lymph flows through afferent lymphatic vessels → enters node through hilum → subcapsular sinus → cortex → medullary sinus → exiting via efferent lymphatic vessels in hilum
  - Fewer efferent vessels than afferent vessels, slows traffic down → allows node to filter lymphatic fluid
- Swollen painful nodes indicate inflammation, painless nodes may indicate cancer

### Thymus

- Located between sternum, aorta in mediastinum
- Two lobes, many lobules composed of cortex, medulla
  - Cortex: T lymphocyte maturation site (immature T lymphocytes move from bone marrow to thymus for maturation)
  - Medulla: contains some mature T lymphocytes, macrophages, cell-clusters called thymic corpuscles (corpuscles contain special T lymphocytes thought to be involved in preventing autoimmune disease)
- Lymphocyte production site in fetal life
  - Active in neonatal, early life; atrophies with age

### Bone marrow

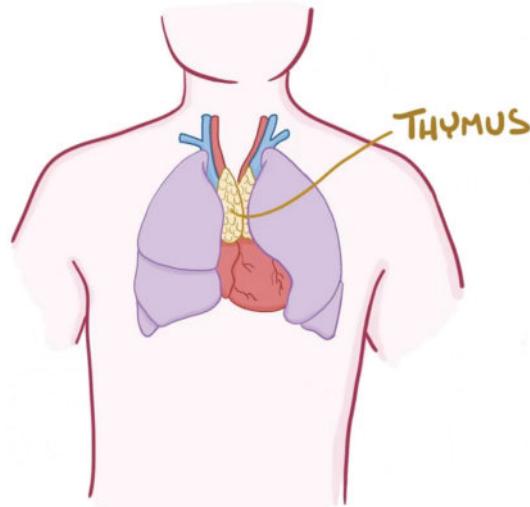
- B cells: made, mature in bone marrow
- T cells: made in bone marrow, mature in thymus

### Mucosa-associated lymphoid tissue (MALT)

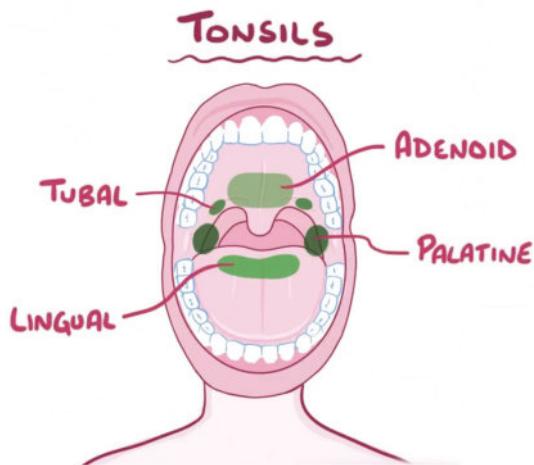
- Lymphoid tissue that is associated with mucosal membranes
- Tonsils: lymphoid-tissue ring around pharynx
  - Have crypts (epithelial invaginations) which trap bacteria
  - Palatine: paired tonsils on each side of pharynx (largest tonsils, most often inflamed)
  - Lingual: near base of tongue
  - Pharyngeal: near nasal cavity (called adenoid when inflamed)
  - Tubal: near Eustachian tube
- Peyer's patches: small bowel MALT

### Appendix

- Worm-like large bowel extension
- Contains numerous lymphoid follicles
- Fights intestinal infections



**Figure 14.13** Thymus location.



**Figure 14.14** Tubal, pharyngeal (adenoid), palatine, and lingual tonsils create a lymphoid-tissue ring around pharynx.

# NORMAL HEART SOUNDS

[osms.it/normal-heart-sounds](http://osms.it/normal-heart-sounds)

## HEART SOUNDS

### Causes

- Opening / closing cardiac valves
- Blood movement: into chambers, through pathological constrictions, through pathological openings

## WHERE ARE THEY HEARD?

- By auscultating specific points individual sounds can be isolated
  - These points are not directly above their respective valves, but are where valve sounds are best heard; however, they generally map a representation of different heart chambers
- Knowing normal heart size, auscultation locations allows for enlarged (diseased) heart detection

### Optimal auscultation sites

- Aortic valve sounds: 2<sup>nd</sup> intercostal, right sternal margin
- Pulmonary valve sounds: 2<sup>nd</sup> intercostal space, left sternal margin
- Tricuspid valve sounds: 4/5<sup>th</sup> intercostal, left sternal margin
- Mitral valve sounds: 5<sup>th</sup> intercostal space, midclavicular line (apex)

## NORMAL HEART SOUNDS

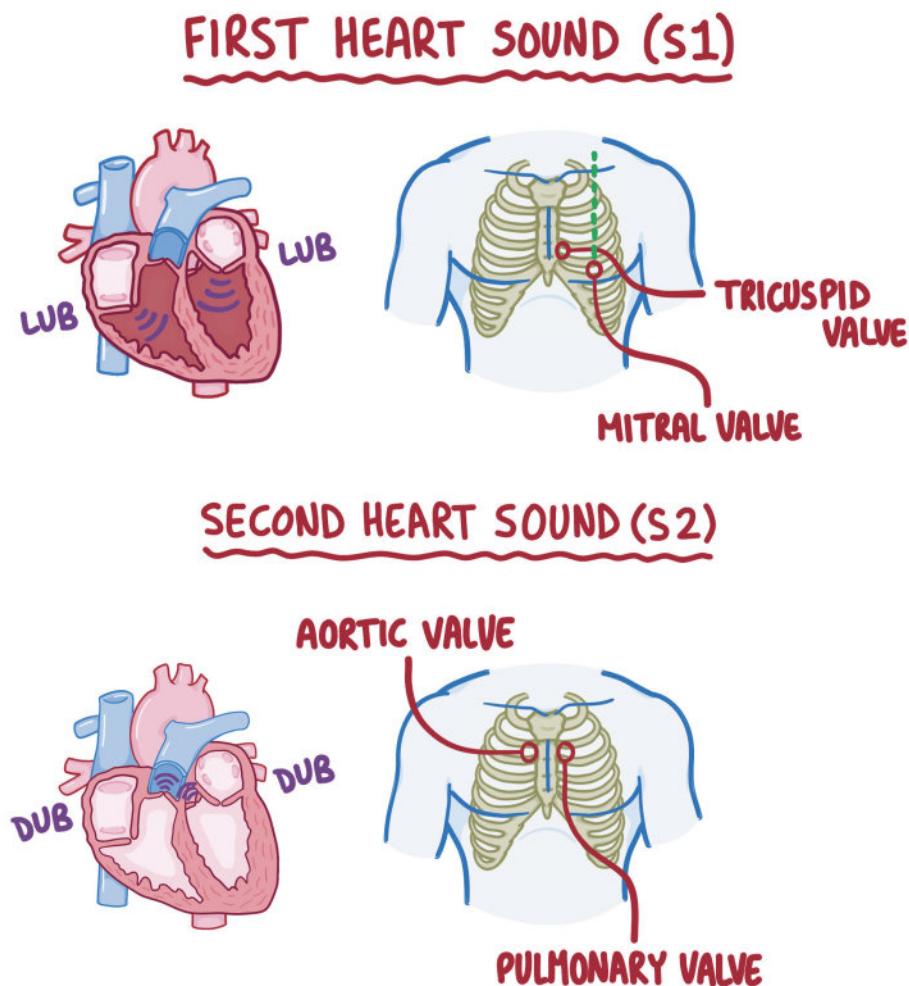
- Two sounds for each beat
  - Lub (S1), dub (S2)
- Factors affecting intensity
  - Intervening tissue, fluid presence, quantity
  - Mitral valve closure speed (mitral valve contraction strength)

### S1 heart sound

- “Lub”: low-pitched sound
- Marks beginning of systole/end of diastole
- Early ventricular contraction (systole) → ventricular pressure rises above atrial pressure → atrioventricular valves close → S1
- S1: mitral, tricuspid closure
  - Intensity predominantly determined by mitral valve component, loudest at apex
- S1 (lub) louder, more resonant than S2 (dub)
- S1 displays negligible variation during breathing

### S2 heart sound

- “Dub”: higher-pitched sound
- Marks end of systole/beginning of diastole
- S2: semilunar valves (aortic, pulmonic) snap shut at beginning of ventricular relaxation (diastole) → short, sharp sound
- Best heard at Erb's point, 3rd intercostal space on left, medial to midclavicular line
- Splits on expiration
  - During expiration S2 split into earlier aortic component; later, softer pulmonic component (A2 P2). Lower intrathoracic pressure during inspiration → ↑ right ventricular preload → ↑ right ventricular systole duration → delays P2
  - ↓ left ventricular preload during inspiration → shorter ventricular systole, earlier A2
  - A2, P2 splitting during inspiration usually about 40ms
  - A2, P2 intensity roughly proportional to respective systemic, pulmonary circulation pressures
  - P2 best heard over pulmonic area



**Figure 14.15** Valves that close to produce S1 and S2 sounds and optimal auscultation sites.

## ABNORMAL HEART SOUNDS

[osms.it/abnormal-heart-sounds](http://osms.it/abnormal-heart-sounds)

### ABNORMAL S1

#### Loud S1

- As left ventricle fills, pressure increases
- As left atrium empties, pressure increases as it empties against increasingly pressure-loaded ventricle; as atrium approaches empty, pressure begins to decrease
- Differential diagnosis: short PR interval, mild mitral stenosis, hyperdynamic states
- Short PR interval (< 120ms)
  - Normally atrioventricular valve leaflets

drift towards each other before onset of systole

- Shorter PR interval → less time to drift closure → wider closure distance → louder S1
- Short PR interval → incomplete ventricular emptying → higher ventricular filling pressure → ventricular pressure crosses critical atrioventricular valve closing threshold while atrial pressures are still high → load snap

- Mild mitral stenosis
  - Significant force required to close stenotic mitral valve → large atrioventricular pressure gradient required
  - Slam shut with increased force, producing loud sound
- Hyperdynamic states
  - Shortened diastole → large amount of ongoing flow across valve during systole → leaflets wide apart, pressure remains high
  - Results in forceful atrioventricular valve closure

### Soft S1

- Differential diagnosis: long PR intervals, severe mitral stenosis, left bundle branch block, chronic obstructive pulmonary disease (COPD), obesity, pericardial effusion
- Long PR intervals (> 200ms)
  - Atrium empties fully → low pressure → low ventricular pressure required to close atrioventricular valves → valves close when ventricle is in early acceleration phase (low pressures) → soft sound
- Severe mitral stenosis
  - Leaflets too stiff, fixed to change position

### Variable S1

- Auscultatory alternans
  - When observed with severe left ventricular dysfunction, correlate of pulsus alternans
- Differential diagnosis: atrioventricular dissociation, atrial fibrillation, large pericardial effusion, severe left ventricular dysfunction

### Split S1

- S1 usually a single sound
  - Near-simultaneous mitral, tricuspid valve closures; soft intensity of tricuspid valve closure
- Splitting usually from tricuspid valve closure being delayed relative to mitral valve closure
- Differential diagnosis: right bundle branch block, left-sided preexcitation, idioventricular rhythm arising from left

ventricle

## ABNORMAL S2

### Split S2

- Physiological S2 splitting
  - Expiration: S1 A2P2 (no split)
  - Inspiration: S1 A2....P2 (40ms split)
- Wide split
  - Detection: splitting during expiration
  - Expiration: S1 A2..P2 (slight split)
  - Inspiration: S1 A2.....P2 (wide split)
  - Differential diagnosis: right bundle branch block, left ventricle preexcitation, pulmonary hypertension, massive pulmonary embolism, severe mitral regurgitation, constrictive pericarditis
- Fixed split
  - Splitting during both expiration, inspiration; does not lengthen during inspiration
  - Expiration: S1 A2..P2 (slight split)
  - Inspiration: S1 A2..P2 (slight split)
  - Differential diagnosis: atrial septal defect, severe right ventricular failure
- Reversed split
  - Split during expiration, but not inspiration
  - Expiration: S1 P2....A2 (moderate split)
  - Inspiration: S1 P2A2
  - Differential diagnosis: left bundle branch block, right ventricle preexcitation, aortic stenosis/AR

### Abnormal single S2 variants

- Loud P2
  - Expiration: S1 A2P2
  - Inspiration: S1 A2....P2!
  - Diagnosis: pulmonary hypertension
- Left ventricular outflow obstruction
  - Absent A2
  - Expiration: S1 P2
  - Inspiration: S1 P2
  - Diagnosis: severe aortic valve disease
- Fused A2/P2
  - Expiration: S1 A2P2
  - Inspiration: S1 A2P2
  - Differential diagnosis: ventricular septal defect with Eisenmenger's syndrome, single ventricle

## ADDED HEART SOUNDS

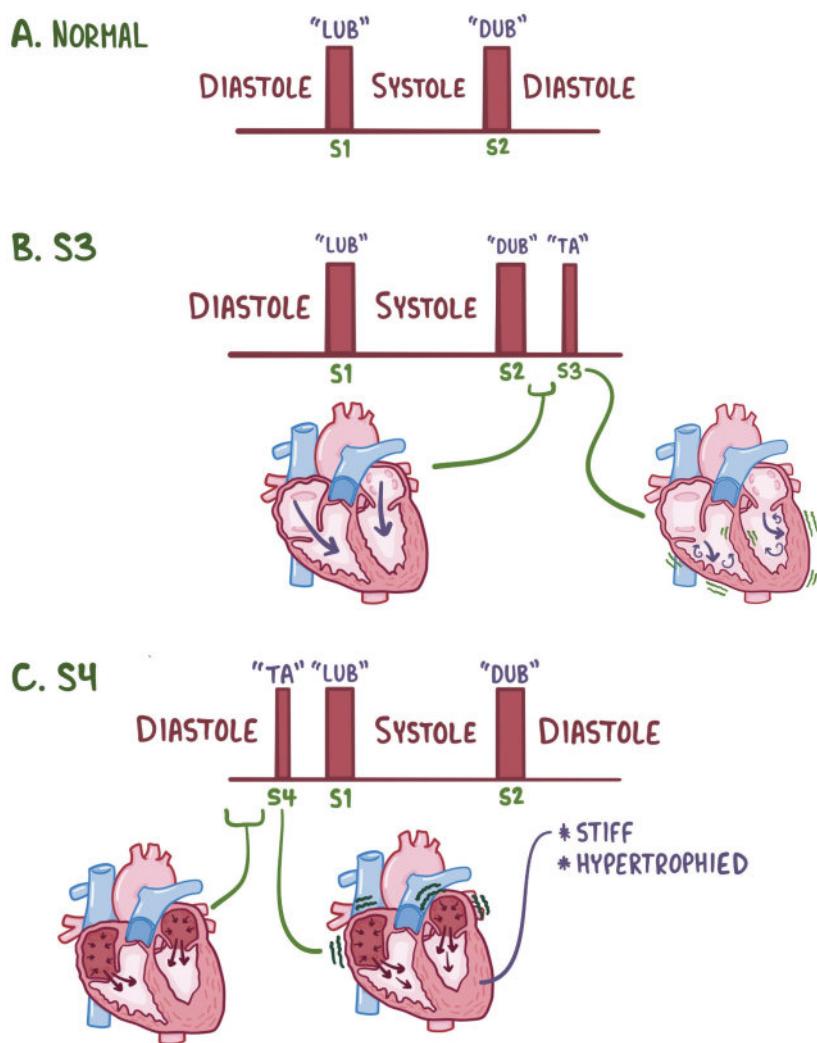
### S3 heart sound

- S3 (ventricular gallop)
  - Low-pitched early diastolic sound
  - Best heard in mitral/apex region
  - Left lateral decubitus position
- Associated with volume overload conditions
- Early diastolic sound, produced in rapid filling phase → excessive volume filling ventricle in short period → rapid filling → chordae tendineae tensing → S3 sound
- Children/adolescents: may be normal
- Middle aged/elderly person: usually pathological
  - Over 40 years old: indicative of left ventricular failure

- Auscultatory summary: S1... S2.S3... S1

### S4 heart sound

- S4 (atrial gallop): low pitched late diastolic (pre-systolic) sound, best heard in mitral/apex region, left lateral decubitus position
- Associated with hypertension, left ventricular hypertrophy, ischaemic cardiomyopathy
- Pressure overload: thought to be caused by atrial contraction into stiff / non-compliant ventricle
- Chronic heart contraction effort against increased pressure → hypertrophy → stiff ventricle (concentric hypertrophy)
- Always pathological
- Auscultatory summary: S4.S1...S2...S4.S1



**Figure 14.16** Linear representation of A: normal (S1, S2), B: S3, and C: S4 heart sounds.

### Summation gallop

- Superimposition of atrial, ventricular gallops during tachycardia
- Heart rate ↑ → diastole shortens more than systole → S3, S4 brought closer together until they merge

## HEART MURMURS

### Key features

- Blood flow silent when laminar, uninterrupted
- Turbulent flow may generate abnormal sounds (AKA “heart murmurs”)
- Murmurs can be auscultated with stethoscope

### Causes

- May be normal in young children, some elderly individuals
- ↓ blood viscosity (e.g. anaemia)
- ↓ diameter of vessel, valve, orifice (e.g. valvular stenosis, coarctation of aorta, ventricular septal defect)
- ↑ blood velocity through normal structures (e.g. hyperdynamic states—sepsis, hyperthyroid)
- Regurgitation across incompetent valve (e.g. valvular regurgitation)

### Describing heart murmurs

- Specific language used to describe murmurs in diagnostic workup
- **Timing:** refers to timing relative to cardiac cycle
  - Systolic “flow murmurs”: aortic, pulmonic stenosis; mitral, tricuspid regurgitation; ventricular septal defect; aortic outflow tract obstruction
  - Diastolic: aortic, pulmonic regurgitation; mitral, tricuspid stenosis
  - Continuous murmurs are least common, generally seen in children with congenital heart disease (e.g. patent ductus arteriosus, cervical venous hum)
  - Occasionally may have two related murmurs, one systolic, one diastolic; gives impression of continuous murmur (e.g. concurrent aortic stenosis, aortic regurgitation)

### Location

- Location on chest wall where murmur is best heard

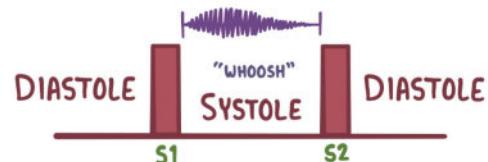
### Radiation

- Location where murmur is audible despite not lying directly over heart
- Generally radiate in same direction as turbulent blood is flowing
- Aortic stenosis: carotid arteries
- Tricuspid regurgitation: anterior right thorax
- Mitral regurgitation: left axilla

### Shape

- How sound intensity changes from onset to completion
- Shape determined by pattern of pressure gradient driving turbulent flow, loudest segment occurring at time of greatest gradient (moment of highest velocity)
- Three basic shapes: crescendo-decrescendo, uniform (holosystolic when occurring during systole), decrescendo
- Crescendo-decrescendo, uniform generally systolic; decrescendo murmurs generally diastolic

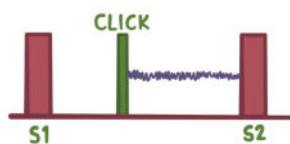
### CRESCEDO - DECRESCENDO MURMUR



### DECRESCEDO MURMUR



### UNIFORM MURMUR



**Figure 14.17** Three basic heart murmur shapes: crescendo-decrescendo, decrescendo, uniform/holosystolic.

- Pitch
  - High pressure gradients → high pitched murmurs (e.g. mitral regurgitation, ventricular septal defect)
  - Large volume of blood-flow across low pressure gradients → low pitched murmurs (e.g. mitral stenosis)
  - If both high pressure, high flow (severe aortic stenosis), both high, low pitches are produced simultaneously → subjectively unpleasant/"harsh" sounding murmur
- Intensity
  - Murmur loudness graded on scale from I–VI
  - Dependent on blood velocity generating murmur; acoustic properties of intervening tissue; hearing; examiner experience; stethoscope used, ambient noise presence
  - I: barely audible
  - II: faint, but certainly present
  - III: easily, immediately heard
  - IV: associated with thrill (palpable vibration over involved heart valve)
  - V: heard with only edge of stethoscope touching chest wall
  - VI: heard without stethoscope (or without it making direct contact with chest wall)
- Quality
  - Subjective, attempt to describe timbre, depends on how many different base frequencies of sound are generated, relative amplitude of various harmonics
  - Mitral regurgitation: blowing/musical
  - Mitral stenosis: rumbling
  - Aortic stenosis: harsh
  - Aortic regurgitation: blowing
  - Still's murmur (benign childhood): musical
  - Patent ductus arteriosus: machine-like

### Diagnostic maneuvers (dynamic auscultation)

- Some maneuvers may elicit characteristic intensity/timing changes (changes in hemodynamics during maneuvers)
- **Dynamic auscultation:** listening for subtle changes during physical maneuvers
- Inspiration
  - ↓ intrathoracic pressure → ↑ pulmonary venous return to right heart → ↑ right heart stroke volume → right sided murmurs → ↑ intensity
  - Dilation of pulmonary vascular system → ↓ pulmonary venous return to left side of heart → ↓ left heart stroke volume → left side murmurs → ↓ intensity
- Expiration
  - ↑ intrathoracic pressure → ↓ venous return to right heart → ↓ right ventricle stroke volume → ↓ intensity of right sided murmurs
  - ↑ pulmonary venous return to left side → ↑ left ventricle stroke volume → left sided murmur → ↑ intensity
- Valsalva maneuver
  - Forceful exhalation against closed glottis
  - ↓ venous return to heart → ↓ left ventricular volume → ↓ cardiac output
  - Murmurs of hypertrophic obstructive cardiomyopathy, occasionally mitral valve prolapse → ↑ intensity
  - All other systolic murmurs → ↓ intensity
- Isometric handgrip
  - Squeeze two objects (such as rolled towels) with both hands
  - Do not simultaneously Valsalva
  - If unconscious, simulate by transient arterial occlusion (BP cuffs applied to both upper arms, inflated to 20–40mmHg above systolic blood pressure for 20 seconds)
    - ↑ venous return, ↑ sympathetic tone → ↑ heart rate, systemic venous return → ↑ cardiac output → murmurs from mitral regurgitation, aortic regurgitation, ventricular septal defect → ↑ intensity
    - Murmur from hypertrophic obstructive cardiomyopathy → ↓ intensity
    - Murmur from aortic stenosis → most commonly unchanged
- Leg elevation
  - Lying supine, both legs raised 45°
  - ↑ venous return → ↑ left ventricular volume
  - Murmur from hypertrophic obstructive cardiomyopathy → ↓ intensity
  - Murmurs from aortic stenosis, mitral regurgitation may → ↑ intensity

- Müller's maneuver
  - Nares closed, forcibly suck on incentive spirometer/air-filled syringe for 10 seconds (conceptual opposite of Valsalva)
  - ↓ venous return → ↓ left ventricular volume → ↓ systemic venous resistance murmur from hypertrophic obstructive myopathy → ↑ intensity
  - Murmur from aortic stenosis may → ↓ intensity
- Squatting to standing
  - Abruptly stand up after 30 seconds of squatting
  - ↓ venous return → ↓ left ventricular volume
  - Murmur from hypertrophic obstructive cardiomyopathy → ↑ intensity
  - Murmur from aortic stenosis may → ↓ intensity
- Standing to squatting
  - From standing upright, squat down
  - If unable to squat, examiner can passively bend knees up towards abdomen to mimic maneuver
  - ↑ venous return → ↑ left ventricular volume
  - Murmur from hypertrophic obstructive cardiomyopathy → ↓ intensity
  - Murmur from aortic stenosis may → ↑ intensity
  - Murmur from aortic regurgitation → ↑ intensity

### Systolic murmurs

- Aortic stenosis
  - Aortic valve auscultation site: 2nd intercostal, right sternal margin
  - S1, closing of mitral valve, during systole → heart contracts against closed stenotic aortic valve → pressure must rise during systole to force open stenotic aortic valve → valve pops open → produces ejection click
  - Followed by ↑ flow as heart contracts more forcefully to empty left ventricle → murmur intensity ↑ as flow across partially open valve ↑
  - Chamber begins to empty → pressure, flow diminish → ↓ murmur intensity
  - Radiates to neck/carotids (murmur occurs in aorta, these are its first branches)
  - Auscultatory summary: S1. Ejection click. Crescendo-decrescendo murmur. S2
- Pulmonic stenosis
  - Pulmonary valve auscultation site: 2nd intercostal space, left sternal margin
  - S1, closing of tricuspid valve, during systole
  - Heart contracts against closed pulmonic valve → pressure builds during systole, forcing open stenotic pulmonic valve → valve pops open → ejection click
  - Flow rate increases as heart contracts more forcefully to empty right ventricle → murmur gets louder as flow across partially open valve increases → chamber empties → pressure, flow diminishing → ↓ murmur intensity
  - Radiates to neck/carotids, back
  - Auscultatory summary: S1. Ejection click. Crescendo-decrescendo murmur. S2
- Mitral regurgitation
  - Mitral valve auscultation site: 5<sup>th</sup> intercostal space, midclavicular line/apex
  - Holo-/pansystolic murmur (occurs for systole duration)
  - Normal S1 as mitral valve closes → in mitral regurgitation, valve cannot completely close → pressure builds in left ventricle (with closed aortic valve) → blood forced back through partially closed mitral valve → murmur occurs along with S1 as long as pressures remain high enough
  - Aortic valve will open to redirect majority of blood → left ventricle continues contracting → continuously raised pressures → blood continuously flowing through partially closed mitral valve (whole of systole)
  - As heart continues to contract, pressure ↑, but atrium becomes more compliant. Even though blood-flow across partially closed valve may ↑, pressure in atrium does not significantly increase
  - Left ventricle pressure notably higher than left atrium → sound does not

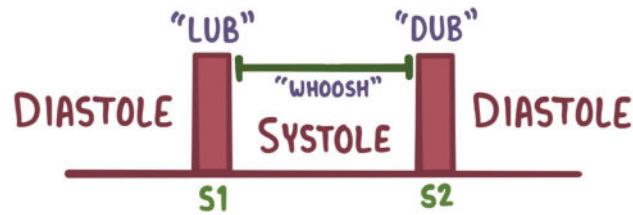
- change throughout murmur
- Referred to as “flat” murmur because intensity does not change
- Radiates to axilla due to direction of regurgitant jet
- **Auscultatory summary:** S1. Flat murmur. S2
- Tricuspid regurgitation
  - **Tricuspid valve auscultation site:** 4/5th intercostal, left sternal margin
  - Holo-/pansystolic murmur
  - Normal S1 occurs due to tricuspid valve closure → pulmonic valve closed, pressure rises in right ventricle
  - In tricuspid regurgitation, valve cannot completely close → pressure builds in right ventricle → blood forced back out through partially closed tricuspid valve → murmur is continuous as long as pressures remain high enough
  - Pulmonic valve opens to redirect blood → left ventricle maintains contraction (thus raises pressure) → blood continues flowing through partially closed tricuspid valve (through whole systole)
  - Atrium becomes more compliant as it fills → atrium pressure does not significantly increase
  - Right ventricle pressure notably higher than that of right atrium → murmur sound does not change throughout murmur
  - Referred to as “flat” murmur (intensity does not change)
  - **Auscultatory summary:** S1. flat murmur. S2
- Mitral valve prolapse
  - **Mitral valve auscultation site:** 5<sup>th</sup> intercostal space, midclavicular line/apex
  - Mitral valve billows into left atrium → clicking sound (unlike aortic stenosis, not associated with ejection of blood, non-ejection click, mid-late systolic)
  - Ventricle contracts → mitral valve closure → S1 → pressure rises → mitral valve accelerates into left atrium → stops abruptly (chordae tendineae restraint) → rapid tensing → click
  - Often associated with mitral regurgitation → after click murmur of

- mitral regurgitation may follow
- **Auscultatory summary:** S1. Mid systolic click with late systolic murmur. S2

### Diastolic murmurs

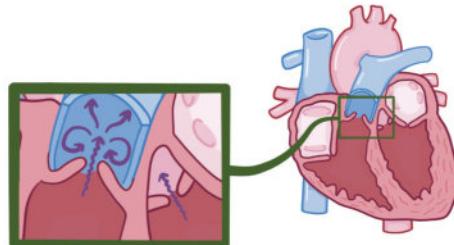
- Aortic regurgitation
  - **Aortic regurgitation auscultation site:** left parasternal border
  - Blood flows back through incompletely closed aortic valve
  - Occurs between S2, S1
  - S2, aortic valve closure → mitral valve opens, heart in diastole → blood enters left ventricle through regurgitant valve, through normal filling via mitral valve
  - Initially, low pressure in ventricle (compared to systemic blood pressure forcing blood through regurgitant valve) → ventricle fills → as pressure mounts, less flow through regurgitant valve → decrescendo murmur
  - Early diastolic decrescendo murmur
  - **Auscultatory summary:** S1. S2. Early diastolic decrescendo murmur. S1
- Pulmonic regurgitation
  - **Pulmonic regurgitation auscultation site:** upper left parasternal border
  - Blood flows back through incompletely closed pulmonic valve
  - Occurs between S2, S1
  - S2 aortic valve closure → tricuspid valve opens, heart in diastole → incomplete pulmonic valve closure → right ventricle fills via incompletely closed pulmonic valve as well as tricuspid valve
  - Initially → low ventricle pressure allows for high flow through regurgitant valve → pressure rises, ↓ flow through regurgitant valve → decrescendo murmur
  - Early diastolic decrescendo murmur
  - **Auscultatory summary:** S1. S2. Early diastolic decrescendo murmur. S1
- Mitral stenosis
  - **Mitral valve auscultation site:** 5<sup>th</sup> intercostal space, midclavicular line/apex
  - Mitral valve can't open efficiently
  - S2 → aortic valve closure → milliseconds later, mitral valve should open (fill ventricle during diastole), only small opening occurs

## SYSTOLIC MURMURS

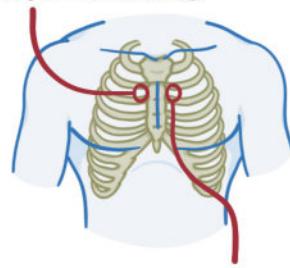


### STENOSIS

↳ AORTIC or PULMONIC VALVE



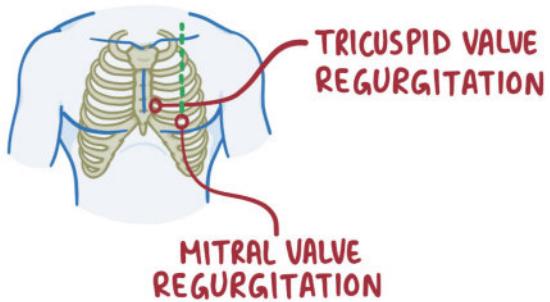
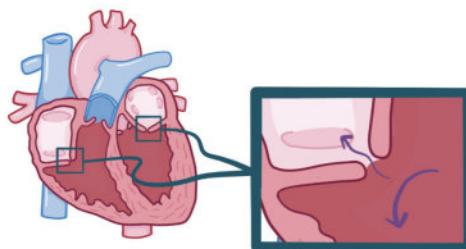
### AORTIC VALVE STENOSIS



### PULMONARY VALVE STENOSIS

### REGURGITATION

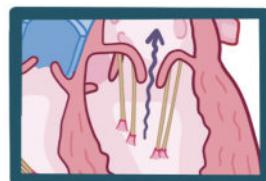
↳ MITRAL or TRICUSPID VALVE



### MITRAL VALVE PROLAPSE

~ if SEVERE ENOUGH ~~~

MITRAL REGURGITATION



### VENTRAL SEPTAL DEFECT

\* HOLOSYSTOLIC MURMUR

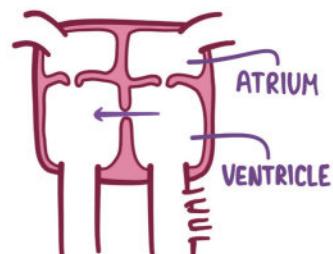
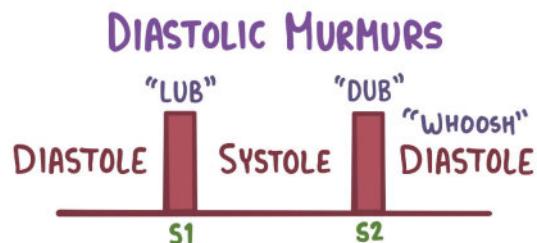


Figure 14.18 Causes of systolic murmurs.

- Beginning of diastole, highest flow of blood comes from left atrium to left ventricle (rapid filling), fills more blood at beginning of diastole (beginning due to highest pressure difference) → most intense phase of murmur
- Aortic valve closure → mitral valve opens, due to stenotic leaflets, they can only open slightly → chordae tendineae snap as limit is reached (similar to ejection snap) → opening snap from stenotic leaflets shooting open (milliseconds after S2) → highest intensity of murmur thereafter → murmur diminishes as pressure equalises
- End of diastole atrium contracts to force remaining blood into left ventricle → atrial kick sound (presystolic accentuation at end of murmur)
- **Auscultatory summary:** S1. S2. Opening snap. Decrescendo mid diastolic rumble. Atrial kick. S1
- Tricuspid stenosis
  - **Tricuspid valve auscultation site:** 4/5<sup>th</sup> intercostal space, left sternal margin
  - Tricuspid valve can't open efficiently
  - S2 → pulmonic valve closure → milliseconds later, tricuspid valve should open (fill ventricle during diastole), only small opening occurs
  - Beginning of diastole, high flow of blood comes from right atrium to right ventricle (rapid filling), fills more blood at beginning of diastole (due to highest pressure difference) → most intense murmur phase
  - Pulmonic valve closure → tricuspid valve opens (due to stenotic leaflets, they can only open slightly) → chordae tendineae snap as limit is reached (similar to ejection snap) → opening snap from stenotic leaflets shooting open (milliseconds after S2) → highest murmur intensity thereafter → murmur diminishes as pressures equalise
  - End of diastole atrium contracts to force remaining blood into left ventricle → atrial kick sound (presystolic accentuation at end of murmur)
  - **Auscultatory summary:** S1. S2. Opening snap. Decrescendo mid diastolic rumble. Atrial kick. S1



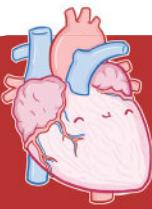
**Figure 14.19** Diastolic murmurs are heard as a “whoosh” after S2.

### Murmur Identification

- Detect murmur?
  - Yes/no
- Identify phase?
  - **Systolic/diastolic:** S1 -systole- S2 -diastole- S1 (in tachycardia, feel pulse → tapping → ejection phase, therefore S1)
- Which valves normally open/which valves normally closed
  - Systole, aortic and pulmonic, open (mitral and tricuspid, closed)
  - If systolic murmur, either open valves stenotic/closed valves regurgitant (1/4 choice)
  - Diastole, mitral and tricuspid, open (aortic and pulmonic, closed) (1/4 choice)
- To choose between four resultant options auscultate over respective areas, employ maneuvers as required

### MISCELLANEOUS HEART SOUNDS

- Mechanical valve clicks
  - Distinctly audible, harsh, metallic sound
- Pericardial knock
  - Sound occasionally heard in constrictive pericarditis; similar in acoustics, timing to S3
- Tumor plop
  - Rare low-pitched early diastolic sound, occasionally heard in atrial myxoma presence
  - Occurs when relatively mobile tumour moves in front of mitral valve during diastole → functional mitral stenosis along with low pitched diastolic rumbling murmur



# NOTES

## BLOOD PRESSURE REGULATION

### REGULATION OF ARTERIAL PRESSURE

- Must be maintained at a constant level of ~100mmHg
- Changes in blood pressure activate baroreceptors and/or chemoreceptors (fast response) and renin-angiotensin-aldosterone system (slow response), causing a series of events that eventually bring blood pressure back to normal (discussed later)
- Central mechanisms regulating blood pressure are cardiac output, peripheral resistance, and blood volume

### Cardiac output and peripheral resistance relate to blood pressure

- $P_a = \text{cardiac output} \times \text{TPR}$ 
  - $P_a$  = mean arterial pressure
  - Cardiac output = cardiac output (mL/min)
  - TPR = total peripheral resistance (mmHg/mL/min)
- Mean arterial pressure varies directly with cardiac output and total peripheral pressure, can be changed by altering one or both
- Blood pressure varies directly with blood volume because cardiac output depends on blood volume
  - Cardiac output is equal to stroke volume (ml/min) times heart rate (beats/min)
  - Normal is 5–5.5L/min
- $P_a$  is regulated by two mechanisms
  - Baroreceptor reflex: neurally mediated (short-term, fast response)
  - Renin-angiotensin-aldosterone system: hormonally mediated (long-term, slow response)

### MEASURING BLOOD PRESSURE

- Auscultatory method: an indirect method of measuring pressure by listening to Korotkoff sounds in the brachial artery

using a sphygmomanometer

1. Wrap blood pressure cuff around upper arm just above elbow
2. Rapidly inflate cuff until pressure in it exceeds systolic pressure (up to around 180mmHg) to stop blood flow
3. Press lightly with the stethoscope bell over the brachial artery just below edge of cuff
4. Reduce cuff pressure slowly and listen with stethoscope for sounds in the brachial artery while simultaneously observing the mercury gauge
  - The first tapping sound (Korotkoff sound) represents systolic pressure
  - When the tapping sound disappears, it represents diastolic pressure

### HOMEOSTATIC IMBALANCES IN BLOOD PRESSURE

#### Normal blood pressure in adults

- Affected by age, weight, sex and race
- Systolic pressure: 90–120mmHg
- Diastolic pressure: 60–80mmHg

#### Hypertension

- Chronically elevated blood pressure
  - Systolic pressure: > 140mmHg
  - Diastolic pressure: > 90mmHg

#### Hypotension

- Low blood pressure
  - Systolic pressure: <90mmHg
  - Diastolic pressure: <60mmHg
- Often normal variation
- Acute hypotension
  - Can be a sign of circulatory shock
- Orthostatic hypotension
  - Temporary drop in blood pressure caused by rapidly standing up from a sitting or lying position
  - Common in the elderly
- Chronic hypotension
  - Often a sign of an underlying condition

# BARORECEPTORS

[osms.it/baroreceptors](http://osms.it/baroreceptors)

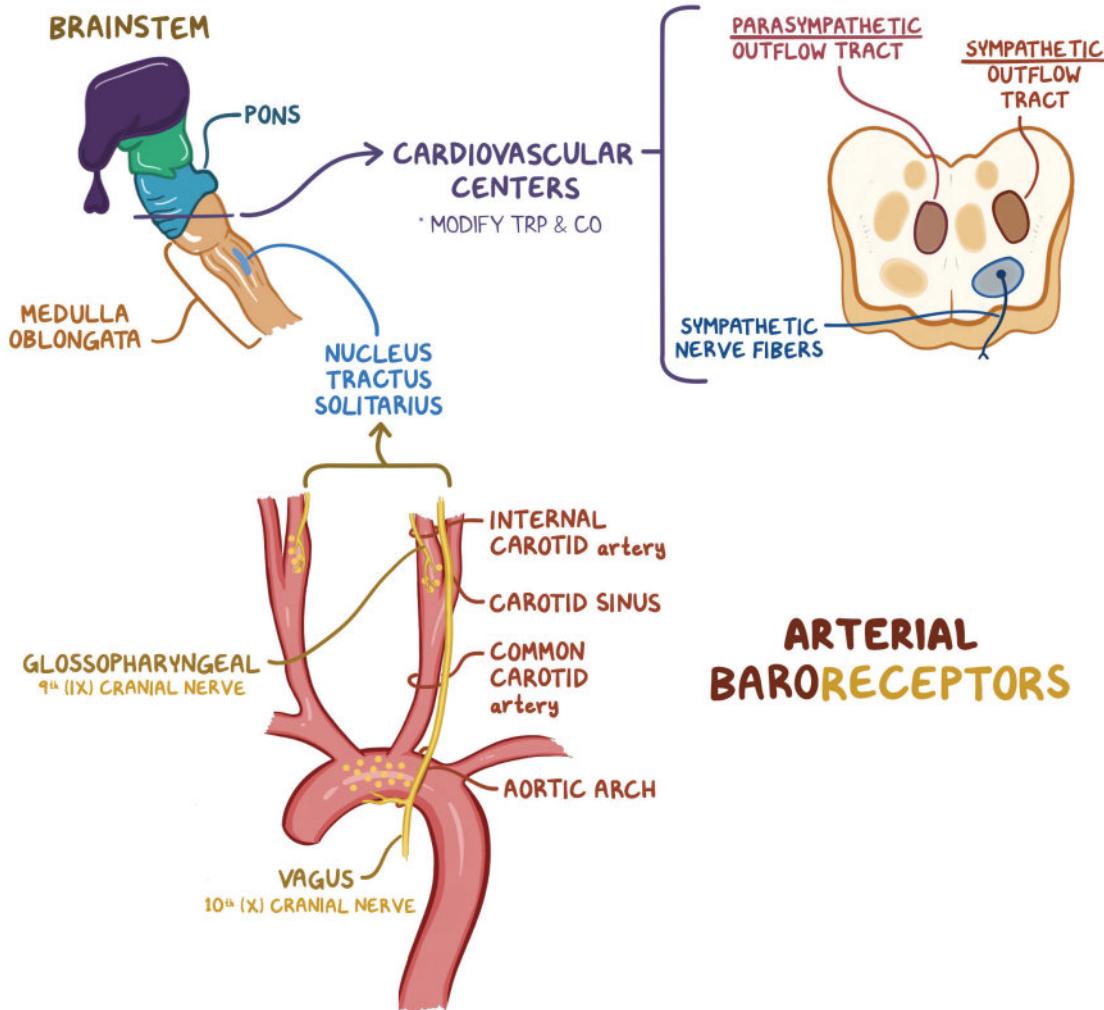
## BARORECEPTOR REFLEX

- Short term, fast neural response to change in blood pressure
- Alters peripheral resistance and cardiac output
- Mediated by baroreceptor cells
  - Specialized nerve endings called mechanoreceptors, located in aortic arch and carotid sinus; sensitive to pressure or stretching
  - Most sensitive to rapid pressure changes
- **Carotid sinus baroreceptors:** responsive to both decreases and increases in pressure
- **Aortic arch baroreceptors:** predominantly responsive to increases in pressure
- Change in blood pressure activates reflex arc
  - Baroreceptors → afferent neurons → brain stem centers → processing information and generating response → efferent neurons → changes in the heart and blood vessels
  - Increase of blood pressure → stretching of baroreceptors → depolarizing receptor potential (higher rate action potential)
  - Decrease of blood pressure → decreased stretch of baroreceptors → hyperpolarizing potential (lower rate action potential)
- Sensitivity can be altered as a result of some diseases
- **Chronic hypertension:** result is adaptation of baroreceptors
  - Baroreceptors are adjusted to monitor pressure changes at higher setpoint
- **Atherosclerosis:** carotid sinus syndrome
  - Baroreceptors are more sensitive; even light pressure on the carotid sinus can cause extreme bradycardia

## INTEGRATED FUNCTION OF BARORECEPTORS

### Response to increased $P_a$

- ↑ firing rate: carotid sinus nerve (glossopharyngeal nerve, CN IX), aortic arch nerve afferent fibers (vagus nerve, CN X)
- Glossopharyngeal, vagus nerve fibers synapse in nucleus tractus solitarius of medulla, (transmits blood pressure information)
- Nucleus tractus solitarius governs coordinated response series; returns  $P_a$  down to normal levels
  - ↑ parasympathetic outflow to heart
  - ↓ sympathetic outflow to heart, blood vessels
- Decrease in sympathetic activity
  - Complements increase in parasympathetic activity → decrease in heart rate
  - Decrease in cardiac contractility
  - Decreased heart rate + decreased cardiac contractility → decrease in cardiac output → decrease of  $P_a$  ( $P_a = \text{cardiac output} \times \text{TPR}$ )
  - Arteriolar vasodilation → decrease in TPR → decrease of  $P_a$  ( $P_a = \text{cardiac output} \times \text{TPR}$ )
  - Vasodilation of veins → increased compliance of veins → increased unstressed volume → decreased stressed volume → reduction in  $P_a$
- Once  $P_a$  reduced back to the set-point pressure (i.e., 100 mmHg), activity of the baroreceptors and the cardiovascular brainstem centers return to baseline level



**Figure 15.1** Locations of arterial baroreceptors and pathways that transmit their signals.

### CARDIOPULMONARY (LOW PRESSURE) BARORECEPTORS

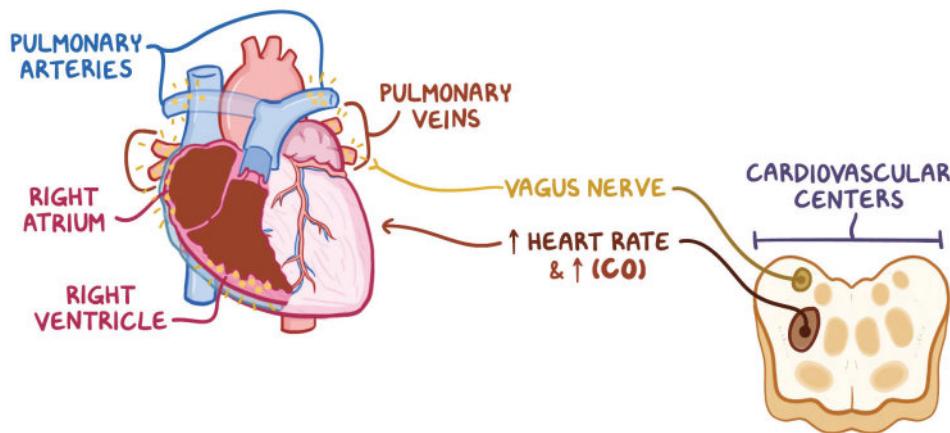
- Located in the vena cava, pulmonary arteries and atria
- These baroreceptors are volume receptors - they detect changes in blood volume
- Increased blood volume and subsequent increases in venous and atrial pressure are detected by cardiopulmonary baroreceptors which generates several responses

#### Cardiopulmonary baroreceptors responses

- Secretion of atrial natriuretic peptide (ANP), a polypeptide hormone secreted by the myocytes in the atrial wall

- ANP causes generalized vasodilation
- This vasodilatation in the kidney increases glomerular filtration rate which results in increased  $\text{Na}^{+}$  and  $\text{H}_2\text{O}$  filtration and excretion → decreased blood volume
- Decreased secretion in ADH
  - Decreased water reabsorption in the collecting ducts → decreased blood volume
- Increase of heart rate (Bainbridge reflex)
  - Increased cardiac output → increased renal perfusion → increased  $\text{Na}^{+}$  and  $\text{H}_2\text{O}$  excretion

## CARDIOPULMONARY BARORECEPTORS



**Figure 15.2** Locations of cardiopulmonary baroreceptors and pathway that transmits their signals.

## CHEMORECEPTORS

[osms.it/chemoreceptors](https://osms.it/chemoreceptors)

### CHEMORECEPTOR REFLEX

- Blood pressure regulation pathway that involves chemoreceptors for  $O_2$  in the aortic and carotid bodies
- Central and peripheral chemoreceptors

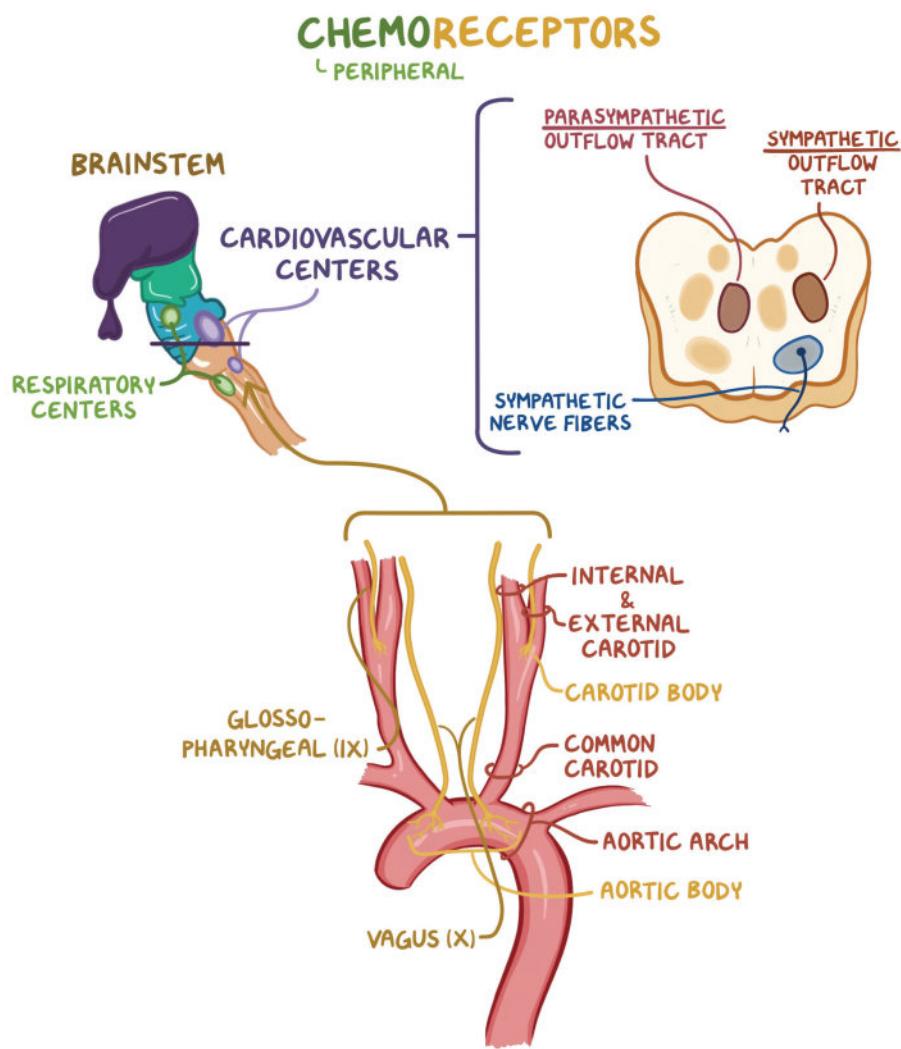
### PERIPHERAL CHEMORECEPTORS

- Located in carotid bodies (near common carotid artery bifurcation, in aortic bodies along aortic arch)
- Very sensitive partial pressure of  $O_2$  decreases
  - Also sensitive to partial pressure of  $CO_2$  increases ( $pCO_2$ ), pH decreases
- Reflex arc
  - Decreased  $pO_2$  → chemoreceptors (afferent neurons) increase firing of action potential (hyperpolarization potential) → efferent neurons → increased sympathetic outflow → arterial vasoconstriction in skeletal muscle, renal and splanchnic circulation → increased total peripheral pressure
- These chemoreceptors are also involved in control of breathing

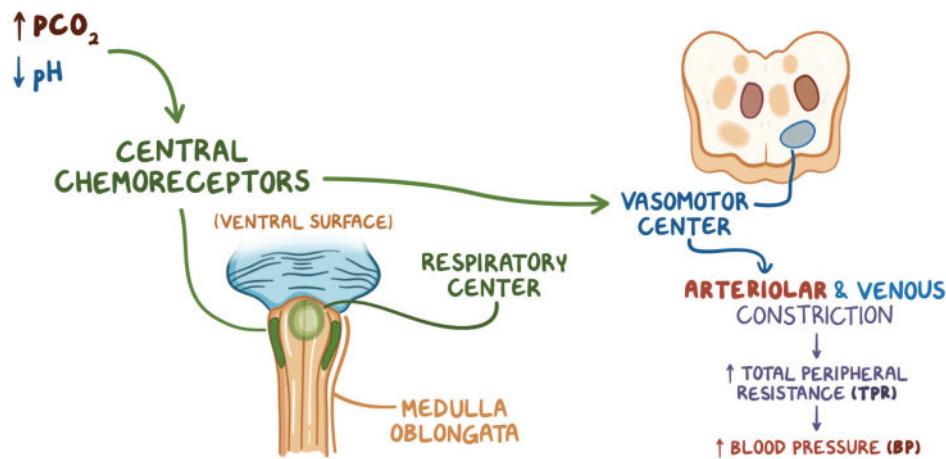
- Decrease of  $pO_2$  causes an increase in ventilation which decreases the parasympathetic outflow to heart → ↑ heart rate → ↑ cardiac output

### CENTRAL CHEMORECEPTORS

- Located in the medulla
- Most sensitive:  $CO_2$ , pH
- Less sensitive:  $O_2$
- Reflex arc
  - Decrease in brain blood flow → increased  $pCO_2$ , decreased pH → chemoreceptors (afferent neurons) increase firing of action potential (hyperpolarization potential) → efferent neurons → increased sympathetic outflow → arterial vasoconstriction in skeletal muscle, renal and splanchnic circulation → increased total peripheral pressure



**Figure 15.3** Locations of peripheral chemoreceptors and locations in the brainstem to which they transmit their signals.



**Figure 15.4** Central chemoreceptors are located in the medulla of the brainstem and are most sensitive to changes in  $\text{CO}_2$  and pH levels.

# RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM

[osms.it/renin-angiotensin\\_aldosterone\\_system](https://osms.it/renin-angiotensin_aldosterone_system)

- Hormonally mediated, slow regulation of blood pressure
- Regulates  $P_a$  by regulating blood volume

## Direct renal mechanism

- Increase of  $P_a$  causes increased filtration rate in the tubules
- In this situation, the kidney cannot reabsorb filtrate fast enough → more fluid leaves the body in urine → blood volume and blood pressure drops

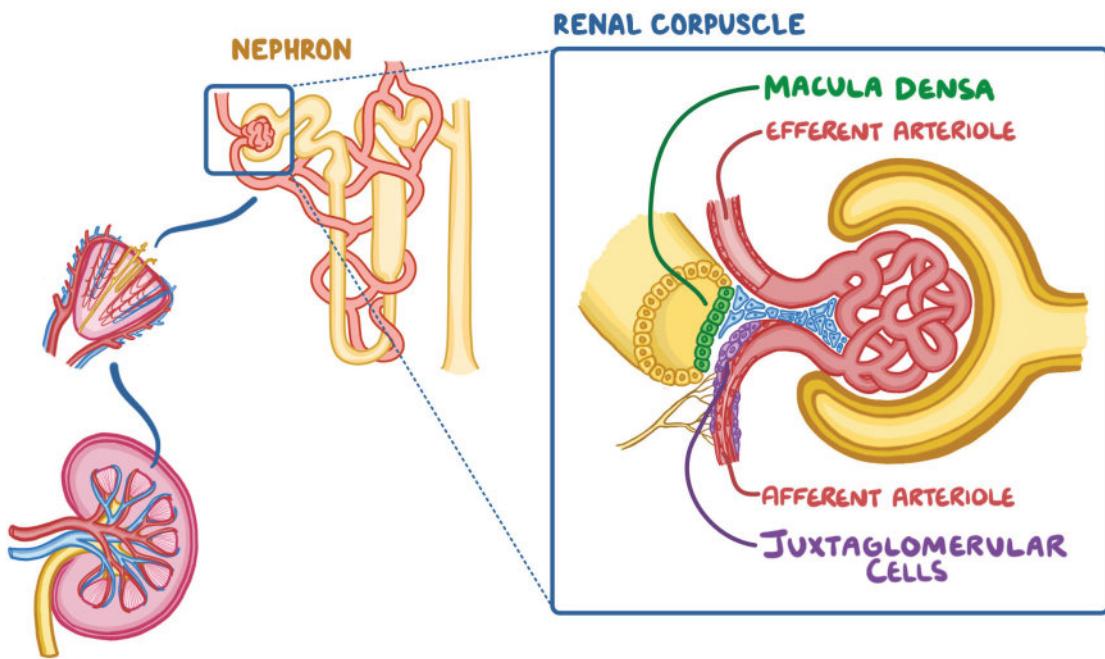
## Indirect renal mechanism

- Renin-angiotensin aldosterone system
- Decrease of  $P_a$  and/or decrease of  $Na^+$  concentration causes decrease in kidney perfusion which in turn causes a series of events
- Cells of the macula densa sense the change in blood volume/osmolarity and in turn stimulate renin production
  - Renin is an enzyme secreted by juxtaglomerular cells of the juxtaglomerular apparatus of the nephron
  - Renal sympathetic nerves and beta-1 agonists also cause renin production
- Renin converts angiotensinogen to angiotensin I
- Angiotensin-converting enzyme (ACE) in the lungs and kidneys converts angiotensin I to angiotensin II

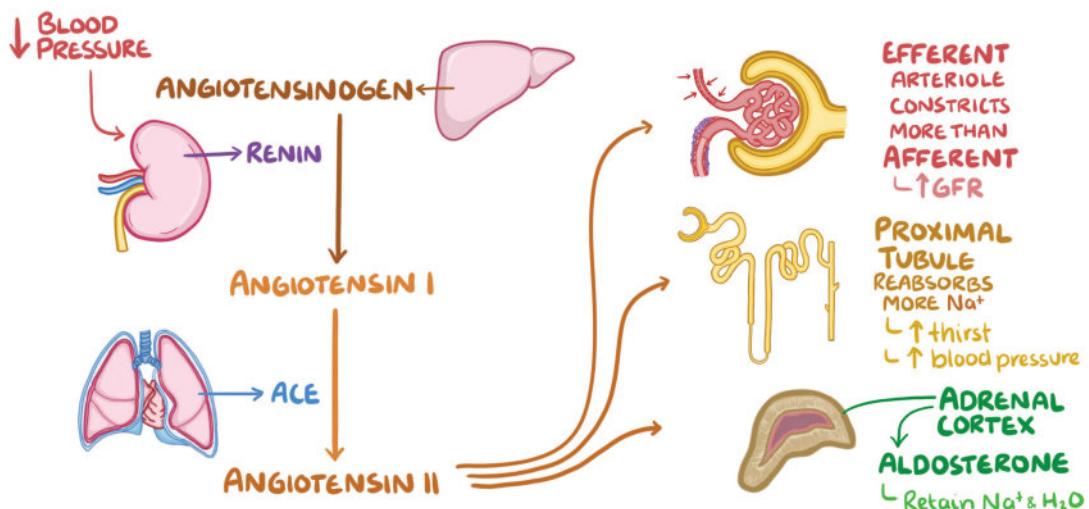
- Stimulates the synthesis and secretion of aldosterone in the glomerulosa cells of the adrenal gland
- Aldosterone causes  $Na^+$  reabsorption to increase in principal cells of renal distal tubule, collecting duct
  - Increased  $Na^+$  concentration → increased osmolarity → increased ECF and blood volume
- Angiotensin II
  - Stimulates  $Na^+$ -  $H^+$  exchange → increased  $Na^+$  reabsorption
  - Stimulates antidiuretic hormone (ADH) secretion
  - Acts on hypothalamus (stimulates thirst, water intake)
  - Causes vasoconstriction of the arterioles → increased total peripheral resistance (TPR)

## Antidiuretic hormone (ADH)

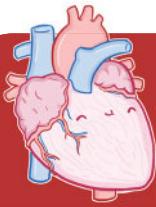
- Hormone produced in **hypothalamus**, secreted by **pituitary** gland's posterior lobe
- Stimulated by low blood volume, increase of serum osmolarity and angiotensin II
- Receptors for ADH
  - **V1 receptors:** vasoconstriction of arterioles
  - **V2 receptors:** increase water reabsorption by principal cells of the renal collecting duct



**Figure 15.5** Macula densa cells are chemoreceptors located in the distal convoluted tubule. When they sense a ↓ in  $P_a$  and/or  $\text{Na}^+$ ,  $\text{Cl}^-$ ; they stimulate renin production by nearby juxtaglomerular cells. Renin initiates angiotensin II activation, which acts in multiple areas to increase blood pressure.



**Figure 15.6** RAAS system summary.



# NOTES CARDIAC CYCLE

## MEASURING CARDIAC OUTPUT - FICK PRINCIPLE

[osms.it/Fick-principle](http://osms.it/Fick-principle)

- Model used to measure cardiac output (CO)
  - Output of left, right ventricles equal during normal cardiac function
- Steady state: rate of  $O_2$  consumption = amount of  $O_2$  leaving lungs via pulmonary vein - amount of  $O_2$  returning via pulmonary arteries  $\times$  CO
- Pulmonary blood flow of right heart = CO of left heart: used to calculate CO

Cardiac Output =

$$\frac{O_2 \text{ consumption}}{[O_2] \text{ pulmonary vein} - [O_2] \text{ pulmonary artery}}$$

- $250 \text{ mL/minute} = \text{total } O_2 \text{ consumption}$  ( $70 \text{ kg}$ , biologically-male individual); pulmonary venous  $O_2$  content =  $0.20/\text{mL}$ ; pulmonary arterial  $O_2$  content =  $0.15/\text{mL}$

$$\text{Cardiac Output} = \frac{250 \text{ mL/min}}{0.20 \text{ mL} - 0.15 \text{ mL}} = 5000 \text{ mL/min}$$

- Also measures blood flow to individual organs
  - Renal blood flow = renal  $O_2$  consumption / renal arterial  $O_2$  - renal venous  $O_2$

## CARDIAC & VASCULAR FUNCTION CURVES

[osms.it/cardiac-and-vascular-function-curves](http://osms.it/cardiac-and-vascular-function-curves)

- Curves depicting functional connections between vascular system, right atrial pressure, and CO

### CARDIAC FUNCTION CURVE (CO CURVE)

- Plot of relationship between left ventricle (LV) CO, right atrial (RA) pressure
- Based on Frank-Starling relationship describing CO dependence on preload
  - Preload (determined by RA pressure),

independent variable; CO, dependent variable

- $\uparrow$  venous return  $\rightarrow \uparrow$  RA pressure  $\rightarrow \uparrow$  LV end-diastolic volume (EDV)/preload, myocardial fiber stretch  $\rightarrow \uparrow$  CO
- LV CO (L/min) = LV venous return/preload (RA pressure in mmHg)
- Relationship remains intact with steady state of venous return
- RA pressure 4mmHg  $\rightarrow$  curve levels off at maximum 9L/min

## VASCULAR FUNCTION CURVE

- Plot of relationship between venous return, RA pressure
- Independent of Frank-Starling relationship
  - Venous return independent variable; RA pressure dependent variable
  - Venous return, RA pressure: inverse relationship
- ↑ RA pressure → ↓ pressure gradient between systemic arteries, RA → ↓ venous return to RA; CO

## Mean systemic pressure (MSP)

- Pressure equal throughout vasculature
- Influenced by blood volume, distribution

## Total peripheral resistance (TPR)

- Primarily determined by pressure in arterioles; determines slope of curve
- ↓ TPR (↓ arteriolar resistance) → ↑ flow from arterial to venous circulation → ↑ venous return → clockwise rotation of curve
- ↑ TPR (↑ arteriolar resistance) → ↓ flow from arterial to venous circulation → ↓ venous return → counterclockwise rotation of curve

# ALTERING CARDIAC & VASCULAR FUNCTION CURVES

[osms.it/altering-cardiac-vascular-function-curves](http://osms.it/altering-cardiac-vascular-function-curves)

- Curves combined → changes in CO visualized, cardiovascular parameters altered
- Curves can be displaced by changes in blood volume, inotropy, TPR

## INOTROPIC AGENTS

- Alters cardiac curve
- Positive inotropic agents (e.g. digoxin) at any level of RA pressure
  - ↑ contractility, stroke volume (SV), CO → (1) cardiac curve shifts upward, (2) vascular function curve not affected, (3) x-intercept (steady state) shifts upward, to left
- Negative inotropic agents (e.g. beta-blockers)
  - Opposite effect

## BLOOD VOLUME

- Alters vascular curve
- ↑ circulating volume (e.g. blood transfusion)
  - ↑ MSP → (1) curves intersect at ↑ CO, RA pressure, (2) parallel shift of x-intercept (steady state), vascular curve

to right, (3) no change in TPR

- ↓ circulating volume (e.g. hemorrhage)
  - Opposite effect
- Changes in venous compliance are similar to blood volume changes
  - ↓ venous compliance → changes similar to ↑ circulating volume
  - ↑ venous compliance → changes similar to ↓ circulating volume

## TOTAL PERIPHERAL RESISTANCE

- Alters both curves due to changes in afterload (cardiac curve), venous return (vascular curve)
- ↑ TPR → ↑ arterial pressure → ↑ afterload → ↓ CO → (1) downward shift of cardiac curve, (2) counterclockwise rotation of vascular curve, (3) ↓ venous return, (4) RA pressure unchanged, ↓/↑ (depending on cardiac, venous curve alteration), (5) curves intersect at altered steady state
- ↓ TPR (arteriolar dilation)
  - Opposite effect

# PRESSURE-VOLUME LOOPS

[osms.it/pressure-volume\\_loops](https://osms.it/pressure-volume_loops)

- Graphs represent pressure, volume changes in LV during one heartbeat (one cardiac cycle/"stroke work")
- Pressure in left ventricle on y axis, volume of left ventricle on x axis

## FOUR PHASES

### Ventricular filling during diastole

- At end of this phase:
  - Mitral valve closed
  - Left ventricle filled (EDV); relaxed, distended
  - EDV = 140mL

### Isovolumic contraction

- Systole begins (ventricular contraction)
- No changes to ventricular volume (mitral, aortic valve closed)
- Pressure builds

### Ventricular ejection

- Pressure in left ventricle > aortic pressure → aortic valve opens → blood ejected

### Isovolumic relaxation

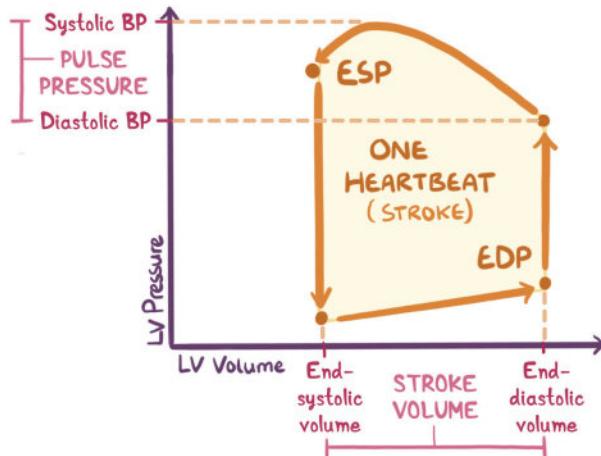
- Ventricle starts relaxing → aortic pressure > LV pressure → aortic valve closes
- End of systole
- ESV = 70mL

## STROKE VOLUME (SV)

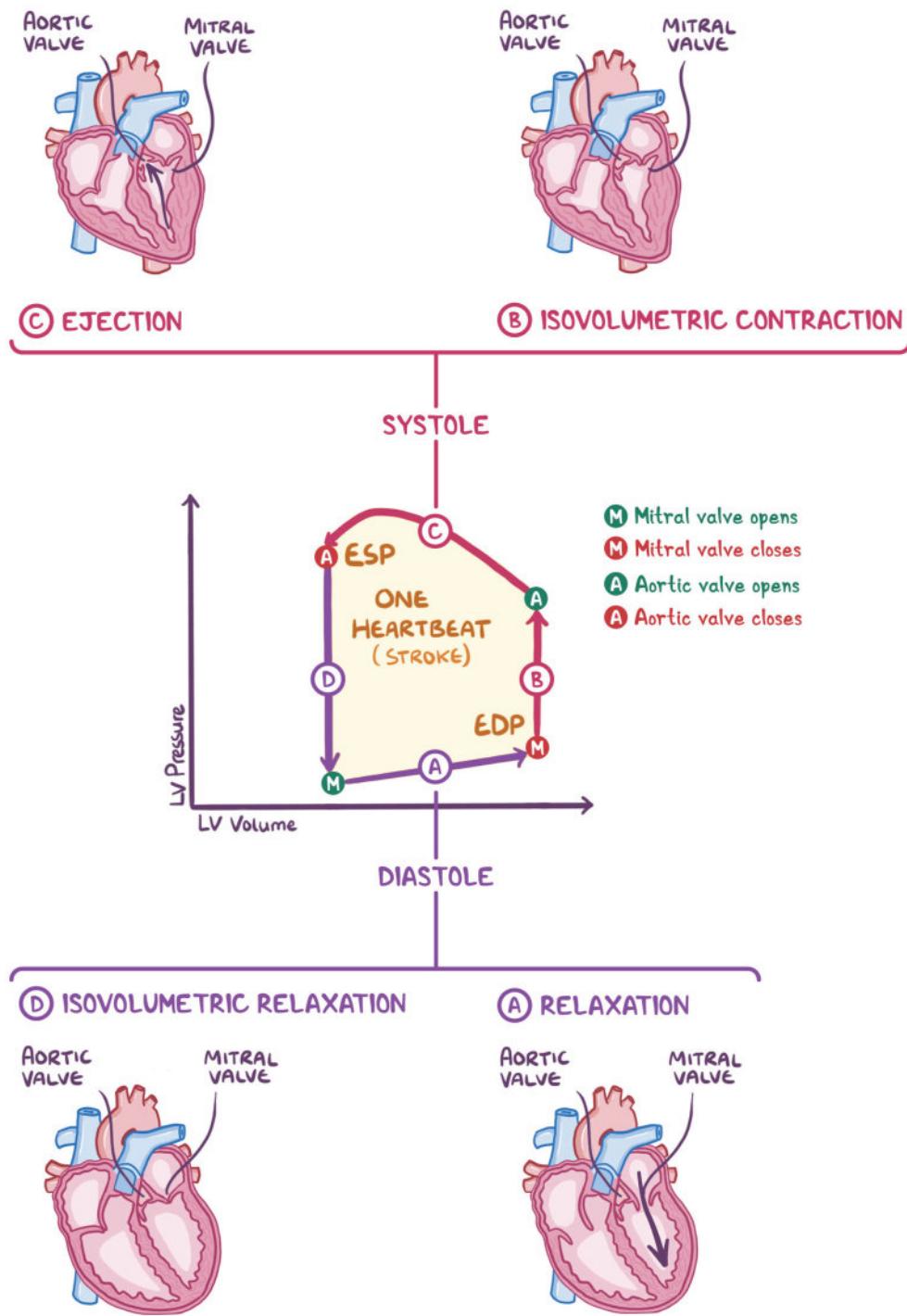
- STROKE VOLUME (SV)
- Amount of blood pumped by ventricles in one contraction
- SV = EDV - ESV

## STROKE WORK (SW)

- Work of ventricles to eject a volume of blood (i.e. to eject SV)
- Represented by area inside of loop



**Figure 16.1** Measurements that can be obtained from the pressure-volume loop graph. Pulse pressure is measured in mmHg and reflects the throbbing pulsation felt in an artery during systole. Pulse pressure = systolic blood pressure - diastolic blood pressure. Stroke volume is measured in mL and is blood volume ejected by left ventricle during every heartbeat. Stroke volume = end-diastolic volume - end systolic volume.



**Figure 16.2** The four phases of the pressure-volume loop and the condition of the heart during each phase.

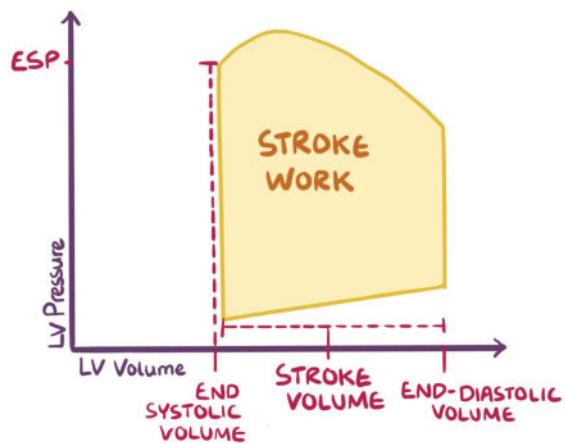
# CHANGES IN PRESSURE-VOLUME LOOPS

[osms.it/changes\\_in\\_pressure-volume\\_loops](https://osms.it/changes_in_pressure-volume_loops)

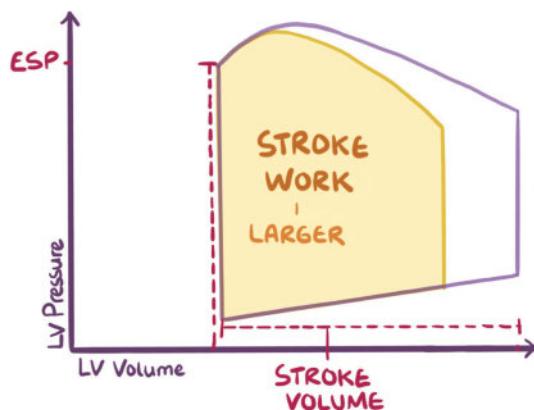
- Cardiac parameters change → volume-pressure loops change
- ↑ preload ( $\uparrow$  EDV) → ↑ strength of contraction → ↑ stroke volume → larger loop
- ↑ afterload → ↑ ventricular pressure during isovolumetric contraction → ↑ less blood leaves ventricle → ↑ end-systolic volume

- (ESV) → ↓ SV → loop narrower, taller (smaller SV, higher pressure; stroke work remains relatively stable)
- ↑ contractility → blood under ↑ pressure → longer ejection phase → left ventricular pressure = aortic pressure → ↑ SV, stroke work, ↓ ejection fraction (EF), EDV → loop widens

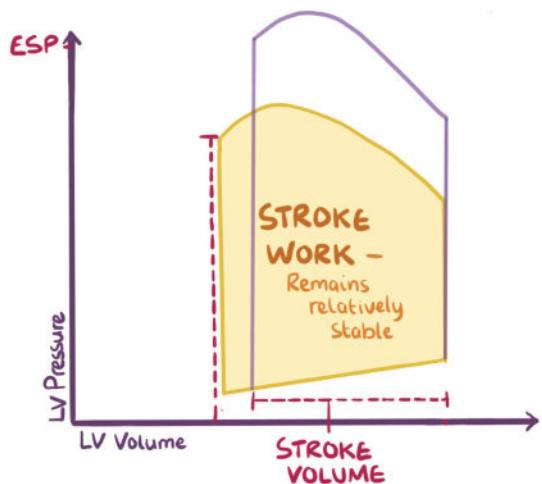
A. NORMAL PRESSURE-VOLUME LOOP



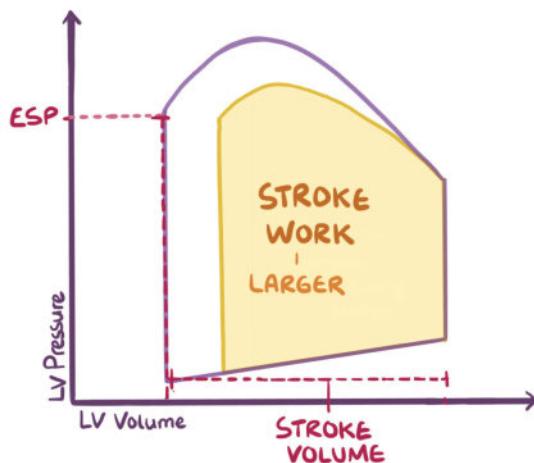
B. INCREASED PRELOAD



C. INCREASED AFTERLOAD



D. INCREASED CONTRACTILITY



**Figure 16.3** Changes in stroke work as a result of increased preload (B), afterload (C), and contractility (D) represented on pressure-volume loop graphs.

# CARDIAC WORK

[osms.it/cardiac-work](http://osms.it/cardiac-work)

- Work heart performs as blood moves from venous to arterial circulation during cardiac cycle

## PHASES OF CARDIAC WORK

### Atrial systole

- Begins when atria, ventricles in diastole
- Atrioventricular (AV) valves open → passive ventricular filling
- Atrial depolarization → atria contract (atrial kick during systole) → completes ventricular filling (EDV)
- Venous pulse: "a" wave ( $\uparrow$  atrial pressure)
- ECG
  - P wave, PR interval

### Isovolumetric ventricular contraction

- Ventricular contraction begins (ventricular systole) → ventricular pressure  $>$  atrial pressure → AV valves close (S1); semilunar valves closed
- ECG
  - QRS complex

### Rapid ventricular ejection

- Ventricular systole continues → left ventricular pressure  $>$  aortic pressure → aortic valve forced open → blood ejected (SV) (blood also ejected into pulmonary vasculature via pulmonic valve)
- $\uparrow$  aortic pressure
- Atrial filling begins
- ECG
  - ST segment

### Reduced ventricular ejection

- $\downarrow$  ventricular ejection velocity
- $\uparrow$  atrial pressure
- Ventricular repolarization begins
- ECG
  - T wave

### Isovolumetric ventricular relaxation

- Ventricles relaxed (ventricular diastole);

ventricular pressure  $<$  aortic pressure → **aortic valve closes** (S2); causes dicrotic notch on aortic pressure curve

- All valves closed
- Ventricular volume
  - Constant
- Complete ventricular repolarization
- ECG
  - T wave ends

### Rapid ventricular filling

- Ventricular diastole continues → ventricular pressure  $<$  atrial pressure → AV valves open
- Passive ventricular filling (ventricles relaxed, compliant)
- S3 (normal in children) produced by rapid filling

### Reduced ventricular filling (diastasis)

- Ventricular diastole continues; ventricles relaxed
- **Mitral valve** open
- Changes in heart rate (HR) alter length of diastasis

## TYPES OF CARDIAC WORK

### Internal work

- Pressure work: within the ventricle to prepare for ejection
- Quantified by multiplying isovolumic contraction time by ventricular wall stress
- Accounts for 90% of cardiac work

### External work

- Volume work: ejecting blood against arterial resistance; product of pressure developed during ejection, SV
- Represented by area contained in pressure-volume loop
- Accounts for 10% of cardiac work

### Myocardial oxygen consumption

- Pressure work  $>$  volume work

- Aortic stenosis → ↑↑ pressure work → ↑↑ oxygen consumption, ↓ CO
- Strenuous exercise → ↑ volume work → ↑ oxygen consumption, ↑ CO

#### **LV and right ventricle (RV)**

- Volume work: CO LV = RV CO

- Pressure work: LV (aortic pressure 100mmHg) > RV (pulmonary pressure 15mmHg)
  - ↑ systemic pressure (e.g. hypertension) → ↑ LV pressure work → ventricular wall hypertrophy
  - Law of Laplace for sphere (e.g. heart): **thickness of heart wall increases → greater pressure produced**

# CARDIAC PRELOAD

[osms.it/cardiac-preload](http://osms.it/cardiac-preload)

- **EDV:** volume load created by blood entering **ventricles** at end of diastole before contraction
- Establishes sarcomere length, **ventricular stretch as ventricles fill** (length-tension relationship)

## **FACTORS AFFECTING PRELOAD**

### **Venous pressure**

- Includes blood volume, rate of venous return to RA
- ↑ **blood volume**, venous return → ↑ preload

### **Ventricular compliance**

- **Flexibility:** ability to yield when pressure applied
- Compliant, "stretchy" ventricles → ↑ preload
- Noncompliant, stiff ventricles → ↓ preload

### **Atrial contraction**

- Early ventricular diastole → ventricles relaxed, passively fill with blood from atria via open AV valves → late ventricular diastole atrial systole (atrial kick) → additional blood into ventricles
- Accounts for 20% of ventricular preload

### **Resistance from valves**

- Stenotic mitral, tricuspid valves create inflow resistance → ↓ filling → ↓ preload
- Stenotic pulmonic, aortic valves create outflow resistance → ↓ emptying → ↑ preload

### **HR**

- Normal heart rate allows adequate time for ventricles to fill
- Tachyarrhythmias → ↓ filling time → ↓ preload

# CARDIAC AFTERLOAD

[osms.it/cardiac-afterload](http://osms.it/cardiac-afterload)

- Amount of resistance ventricles must overcome during systole
- Establishes degree, speed of sarcomere shortening, ventricular wall stress (force-velocity relationship)
- ↑ afterload → ↓ velocity of sarcomere shortening
- ↓ afterload → ↑ velocity of sarcomere shortening

## FACTORS AFFECTING AFTERLOAD

### LV

- Systemic vascular resistance (SVR)
- Aortic pressure

### RV

- Pulmonary pressure

### Resistance from valves

- Stenotic pulmonic, aortic valves create outflow resistance → ↑ afterload

# LAW OF LAPLACE

[osms.it/law-of-Laplace](http://osms.it/law-of-Laplace)

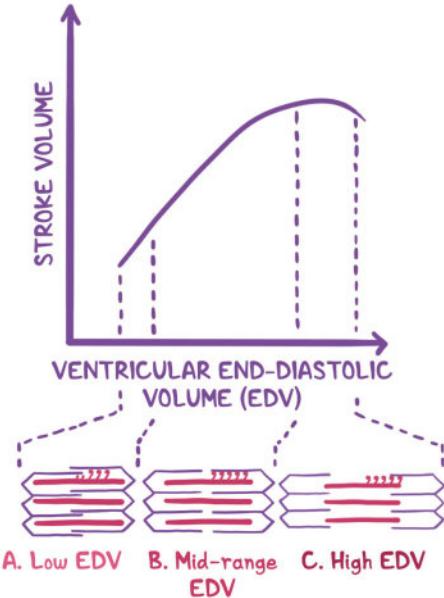
- Describes pressure-volume relationships of spheres
- Blood vessels
  - > radius of artery = > pressure on arterial wall
- Heart
  - **Wall tension** produced by myocardial fibers when ejecting blood **depends on thickness** of sphere (heart wall)
- **Laplace's formula:** **tension** on myocardial fibers in **heart wall** = **pressure** within ventricle × **volume** in ventricle (radius) / **wall thickness**

- $T = \frac{P \times r}{h}$ 
  - T = wall tension
  - P = pressure
  - r = radius of ventricle
  - h = ventricular wall thickness
- Dilation of heart muscle increases tension that must be developed within heart wall to eject same amount of blood per beat
- Myocytes of dilated left ventricle have greater load (tension)
  - Must produce greater tension to overcome aortic pressure, eject blood → ↓ CO

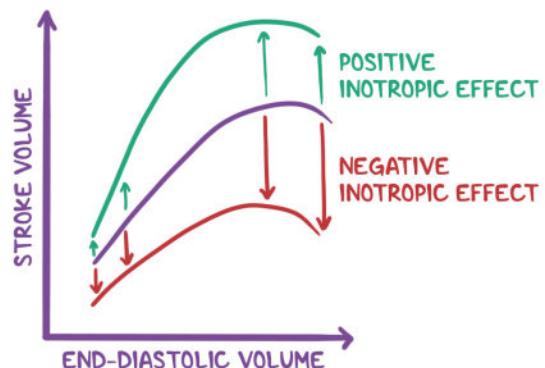
# FRANK–STARLING RELATIONSHIP

[osms.it/Frank-Starling\\_relationship](https://osms.it/Frank-Starling_relationship)

- Loading ventricle with blood during diastole, stretching cardiac muscle → force of contraction during systole
- Length-tension relationship
  - Amount of tension (force of muscle contraction during systole) → depends on resting length of sarcomere → depends on amount of blood that fills ventricles during diastole (EDV)
  - Length of sarcomere determines amount of overlap between actin, myosin filaments, amount of myosin heads that bind to actin at cross-bridge formation
  - Low EDV → ↓ sarcomere stretching → ↓ myosin heads bind to actin → weak contraction during systole → ↓ SV
  - Too much sarcomere stretching prevents optimal overlap between actin, myosin → ↓ force of contraction → ↓ SV
- Allows intrinsic control of heart = venous return with SV
- Extrinsic control through sympathetic stimulation, hormones (e.g. epinephrine), medications (e.g. digoxin) → ↑ contractility (positive inotropy), SV
- Negative inotropic agents (e.g. beta-blockers) → ↓ contractility → ↓ SV



**Figure 16.4** Graphical representation of the Frank–Starling relationship and sarcomere length at low, mid-range, and high EDVs. A mid-range EDV (B), where the volume of blood returning to the ventricles is increasing but is not too large (C), allows for best myosin–actin binding → ↑ strength of contractions → ↑ stroke volume.



**Figure 16.5** Graphical representation of positive and negative inotropic effects on the Frank–Starling relationship.

# STROKE VOLUME, EJECTION FRACTION, & CARDIAC OUTPUT

[osms.it/stroke-volume-ejection-fraction-cardiac-output](http://osms.it/stroke-volume-ejection-fraction-cardiac-output)

## SV

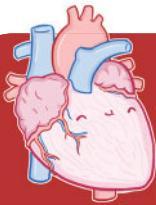
- Volume of blood (mL) ejected from ventricle with each contraction
- Calculated as difference between volume of blood before ejection/EDV, after ejection (ESV)
- $EDV (120mL) - ESV (50mL) = 70mL$
- SV affected by **preload, afterload, inotropy**

## EF

- Fraction of EDV ejected with each contraction
- $SV (70)/EDV (120) = 58\% (EF)$
- Average = 50–65%

## CO

- Volume of blood ejected by ventricles per minute
- $SV (120) \times HR (70) = 4900mL/min$



# NOTES

## CARDIAC

### ELECTROPHYSIOLOGY

## ACTION POTENTIALS IN PACEMAKER CELLS

[osms.it/pacemaker-cell-action-potentials](https://osms.it/pacemaker-cell-action-potentials)

### Pacemaker cells

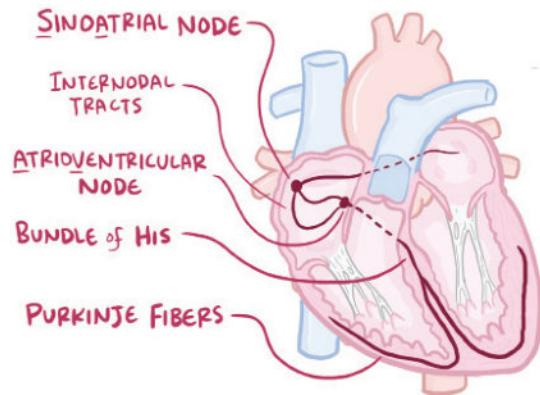
- Groups of cardiac muscle cells with ability to spontaneously create action potential (automaticity) and comprise intrinsic conduction system
- Directly influenced by sympathetic and parasympathetic nervous systems
- Comprise about 1% of heart cells
- Differ in speed of spontaneous depolarization
- Cells with fastest rate of depolarization at any given time determine heart rhythm
  - Remaining/slower cells called latent pacemakers

### SA node

- Primary pacemaker cells located in wall of right atrium
- Rate: 60–100 bpm
  - Usually determines normal heart rhythm

### Latent pacemaker cells

- AV node
  - Located at base of right atrium, near septum
  - Rate: 40–60 bpm
- Bundle of His
  - Divides into right and left bundle branches, travels through septum between ventricles
  - Rate: 20–40 bpm
- Purkinje fibers
  - Spread throughout ventricles
  - Rate: 20–40 bpm



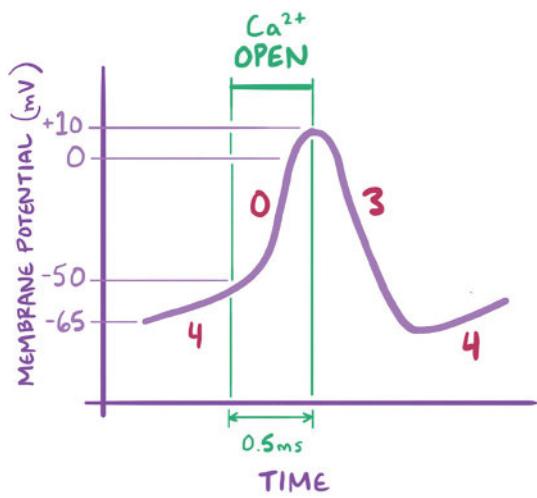
**Figure 17.1** Locations of pacemaker cells within the heart.

### Action potentials in pacemaker cells

- Rapid electrical changes across membrane of pacemaker cells
- Conducted to rest of heart

### Action potential phases

- Phase 4: sodium moves into cell through funny channels (open in response to hyperpolarization); slowly depolarizes cell until threshold potential met
  - Responsible for instability of resting membrane potential
- Phase 0: strong inward calcium current; responsible for rapid depolarization
- Phase 3: strong potassium current moves out of cell; responsible for repolarization
  - Phases 1, 2 absent in pacemaker cells  
→ no plateau



**Figure 17.2** Graph depicting the action potential of a pacemaker cell.

## ACTION POTENTIALS IN MYOCYTES

[osms.it/myocyte-action-potentials](http://osms.it/myocyte-action-potentials)

### Myocytes

- Receive signal from pacemaker cells causing them to contract
- Able to depolarize, spread action potentials
- Action potential phases:
  - Phase 0 (depolarization phase): rapid influx of sodium into cell (inward current); responsible for rapid depolarization
  - Phase 1: sodium current stops, potassium slowly flows out of cell; depolarization stops, re-polarization starts
  - Phase 2: calcium current moves into cell, balances potassium current moving out of cell; charge balance between inside, outside of cell creates plateau

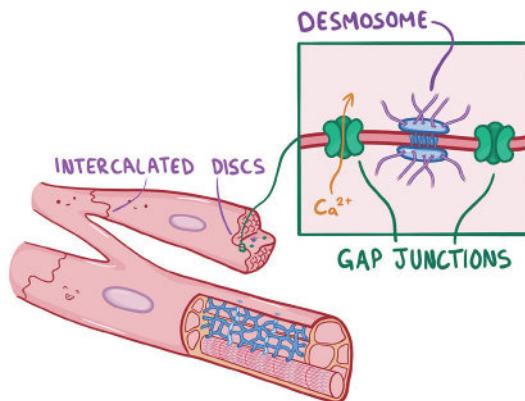
- Phase 3: calcium current moving into cell stops; potassium current moving out of cell continues; repolarization continues
- Phase 4: potassium current moving out of cell approaches equilibrium between inside, outside of cell; sodium, calcium current moving into cell balance outward potassium current; resting membrane potential achieved

# ELECTRICAL CONDUCTION IN THE HEART

[osms.it/heart-electrical-conduction](https://osms.it/heart-electrical-conduction)

- Transmission of electrical signals across heart cells leads to rhythmic myocardial contraction
- Intercalated discs connect cells and allow myocardium to act as syncytium
  - Contain **desmosomes** (holds cells together) and **gap junctions** (areas of low resistance to electrical flow)
- **Cardiac action potential:** sequential flow of electrons across ion channels in cardiac cell membranes, resulting in electrical activation of myocardial cells
  - **Depolarization:** cation movement into cell, producing positive cell charge relative to outside
  - **Polarization:** anion movement into cell, producing negative cell charge relative to outside
- **Pathway of electrical conduction**
  - Sinoatrial node (SA node) → atrial internodal fibers → atrioventricular node (AV node) → bundle of His → Purkinje fibers → ventricular myocytes

- These structures responsible for electrical conduction, spontaneous depolarization; do not generate contractile force



**Figure 17.3** Desmosomes and gap junctions present at intercalated discs allow the myocardium to act as a syncytium.

# CARDIAC CONDUCTION VELOCITY

[osms.it/cardiac-conduction-velocity](https://osms.it/cardiac-conduction-velocity)

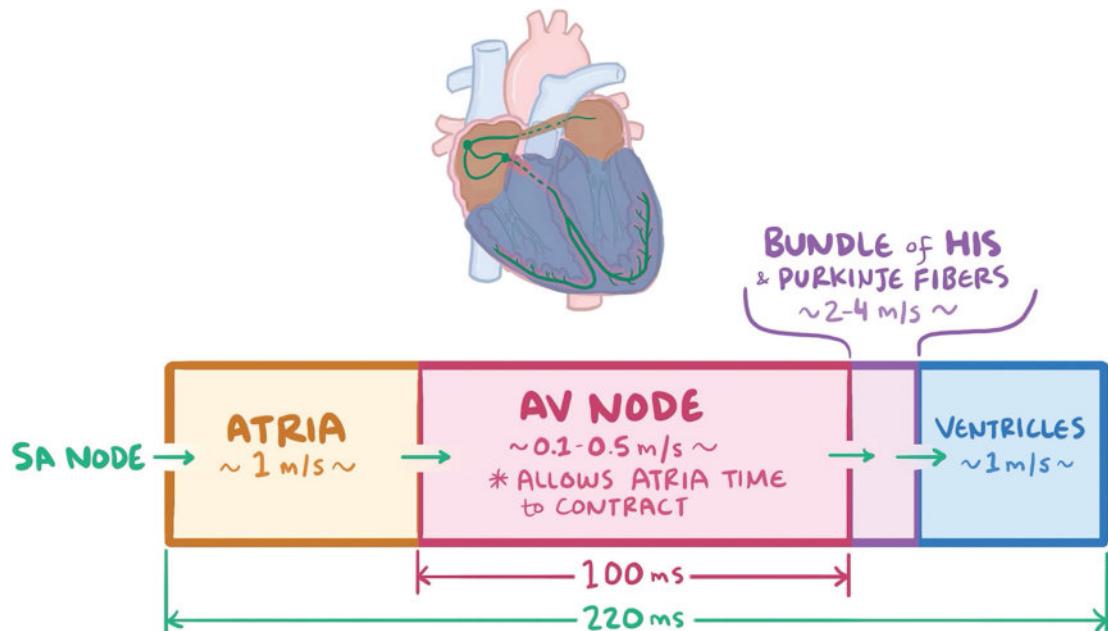
- Speed at which depolarization wave spreads among myocardial cells
  - Measured in meters per second (m/s)
- Each myocardial structure has a different conduction speed related to its purpose
  - Slowest: AV node
  - Fastest: Purkinje fibers
- **AV delay:** slow conduction through AV node ensures adequate ventricular filling
  - Speed: 0.01–0.05m/s
  - Blood flows from atria to ventricles

- Rapid conduction through Purkinje fibers ensures adequate blood ejection
  - Speed: 2–4m/s

## Velocity depends on two factors

- **Amount of ions** going into cell during action potential
  - More ions → faster depolarization → faster spread
  - Fewer ions → slower depolarization → slower spread

- Interconnectedness of myocardial conduction cells
  - More gap junctions → more interconnected cells → less resistance to ion flow between cells
  - Fewer gap junctions → fewer interconnected cells → increased resistance to ion flow between cells



**Figure 17.4** Conduction speeds of different myocardial structures.

## EXCITABILITY & REFRACTORY PERIODS

[osms.it/excitability-refractory-periods](http://osms.it/excitability-refractory-periods)

### Refractory period

- Time in which myocardial cell cannot be depolarized
- **Absolute refractory period:** no stimulus, no matter its size, can depolarize cell
  - Phases 0, 1; part of phase 2
- **Effective refractory period:** large stimulus can generate action potential
  - However, too weak to be conducted
- **Relative refractory period:** large stimulus can generate action potential
  - Big enough to be conducted

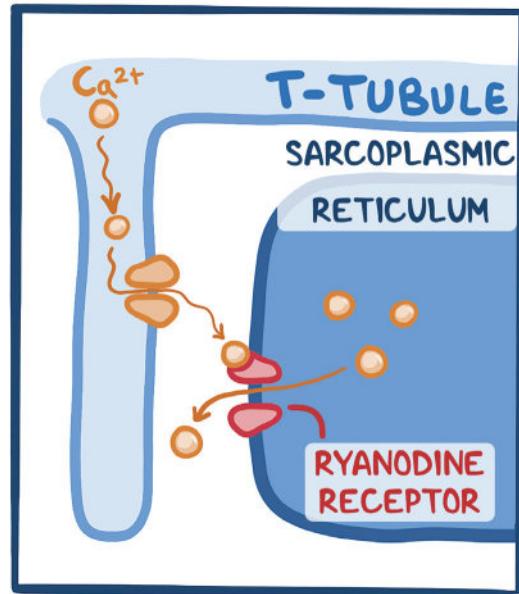
### Excitability

- Ability of myocardial cells to depolarize in response to incoming depolarizing current
- **Supranormal period:** < normal stimulus may produce action potential large enough to be conducted
  - Resting membrane potential has not yet been achieved
  - Membrane potential closer to threshold than normal, refractory periods over

# CARDIAC EXCITATION-CONTRACTION COUPLING

[osms.it/cardiac\\_excitation-contraction\\_coupling](https://osms.it/cardiac_excitation-contraction_coupling)

- Plateau in action potential of myocyte membrane allows influx of calcium, stimulating muscle contraction
  - Calcium enters cell via L-type voltage gated channels
  - Higher intracellular  $\text{Ca}^{2+}$  triggers release of more  $\text{Ca}^{2+}$  from sarcoplasmic reticulum through ryanodine receptors (AKA calcium-induced release)
  - Released  $\text{Ca}^{2+}$  attaches to troponin C  
→ tropomyosin moves → actin-myosin cross bridges → contraction
- Cross bridges last as long as  $\text{Ca}^{2+}$  occupies troponin
  - Tension is proportional to intracellular  $\text{Ca}^{2+}$  concentration
- Intracellular  $\text{Ca}^{2+}$  removed by two mechanisms that induce relaxation, keep  $\text{Ca}^{2+}$  from damaging cell contents
  - $\text{Ca}^{2+}$  ATPase uses ATP energy,  $\text{Na}^+$ / $\text{Ca}^{2+}$  ATP exchanger uses  $\text{Na}^+$  inward current to remove  $\text{Ca}^{2+}$  from cell through sarcolemmal membrane, remove  $\text{Na}^+$  through  $\text{Na}^+/\text{K}^+$  ATPase
  - $\text{Ca}^{2+}$  ATPase removes  $\text{Ca}^{2+}$  into sarcoplasmic reticulum; calsequestrin binds  $\text{Ca}^{2+}$ , keeping it inside



**Figure 17.5** Depolarization of a cardiomyocyte by calcium-induced calcium release.

# CARDIAC LENGTH TENSION

[osms.it/cardiac-length-tension](https://osms.it/cardiac-length-tension)

- Degree filament overlap correlates to tension
  - $L_{max} = 2.2 \mu\text{m}$  is maximal tension
  - In shorter/longer cells, tension will be decreased
- $\uparrow L \rightarrow \uparrow \text{Ca}^{2+}$  sensitivity of troponin C  $\rightarrow \uparrow \text{Ca}^{2+}$  release from sarcoplasmic reticulum
- Can extend to ventricle length/tension relationship curve
  - Cardiac muscle < elastic than skeletal; only ascending curve demonstrates its contraction
- $\uparrow$  resting tension: small changes produce  $\uparrow$  tension
- Frank–Starling basis;  $\uparrow$  fiber length  $\rightarrow$  stronger contraction
  - Preload = LV end-diastolic volume (L), if  $\uparrow$  means ventricular fiber length  $\uparrow$
  - Afterload = aortic pressure; if preload  $\uparrow$   $\rightarrow$  afterload tension and pressure  $\uparrow$

# CARDIAC CONTRACTILITY

[osms.it/cardiac-contractility](https://osms.it/cardiac-contractility)

- Positive inotropes:  $\uparrow$  force of myocardial contraction
- Negative inotropes:  $\downarrow$  force of myocardial contraction
- Proportional to  $\text{Ca}^{2+}$  concentration
  - Proportional to  $\text{Ca}^{2+}$  released
  - Depends on storage, current size
- faster, systole shorter; Frank–Starling effective
  - $\text{Na}^+/\text{K}^+$  ATPase phosphorylation; increases relaxation due to secondary channel activations
  - Troponin I phosphorylation;  $\text{Ca}^{2+}$  binds less troponin C  $\rightarrow$  effect on excitation contraction coupling, prolongs filling, higher ejection fraction

## WHAT AFFECTS INOTROPISM? – AUTONOMIC NERVOUS SYSTEM

### Sympathetic

- Positive inotropic effects:  $\uparrow$  contractility
- Causes faster relaxation, faster refill, increased heart rate (HR)
- Increased tension development rate
  - $\beta_1$  receptor is  $G_s$  coupled, activates adenylyl cyclase  $\rightarrow$  cAMP produced
  - pKA activated  $\rightarrow$  phosphorylation  $\rightarrow$  sarcolemmal  $\text{Ca}^{2+}$  channel activity  $\rightarrow$   $\uparrow$  contraction
  - Phospholamban phosphorylation; stops sarcoplasmic  $\text{Ca}^{2+}$  ATPase inhibition, decreasing time of IC  $\text{Ca}^{2+}$ , making HR

faster, systole shorter; Frank–Starling effective

- $\text{Na}^+/\text{K}^+$  ATPase phosphorylation; increases relaxation due to secondary channel activations
- Troponin I phosphorylation;  $\text{Ca}^{2+}$  binds less troponin C  $\rightarrow$  effect on excitation contraction coupling, prolongs filling, higher ejection fraction

### Parasympathetic

- Negative inotropic effects:  $\downarrow$  contractility on atria via muscarinic receptors
- Acidosis also has negative inotropic effect  $\rightarrow$   $\downarrow$  contractility
- $G_k$  (type of  $G_i$ ), adenylyl cyclase couple, resulting in
  - Decreased  $\text{Ca}^{2+}$  plateau current
  - ACh increases  $I_{\text{KACH}}$
  - $\rightarrow$   $\downarrow$  action potential duration  $\rightarrow$   $\downarrow$   $\text{Ca}^{2+}$  current  $\rightarrow$   $\downarrow$  AP width
- Phosphodiesterase metabolises cAMP, inhibit phosphodiesterase, increase contractility IP3 stimulates Ca release in SR, increases force of contraction

### Heart rate (HR)

- HR increases contractility
- Diastole affected more than systole
- Ca can't be removed as quickly as it accumulates → new equilibrium
  - ↑ action potentials/time: increased total trigger  $\text{Ca}^{2+}$ , increased inward current
  - ↑  $\text{Ca}^{2+}$  influx → ↑ stores; phospholamban phosphorylated, thus inhibited
- Positive staircase effect/Bowditch staircase/Treppe phenomenon
  - On first, beat still no extra  $\text{Ca}^{2+}$
  - Afterward,  $\text{Ca}^{2+}$  accumulates until max  $\text{Ca}^{2+}$  storage achieved
- Postextrasystolic potentiation
  - Same effect as positive staircase
  - Extrasystole < powerful, but creates one more chance for calcium entry
  - Because the voltage channels are open more, postextrasystolic beat has higher tension than extrasystolic

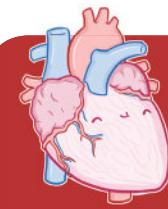
### WHAT AFFECTS INOTROPISM? – DRUGS

#### Cardiac glycosides

- Digoxin, digitoxin, ouabain; congestive heart failure treatment
  - Inhibit  $\text{Na}^+/\text{K}^+$  ATPase; + inotropic, ↑ intracellular  $\text{Na}^+$  changes  $\text{Na}/\text{Ca} \rightarrow$  decreases exchange → **intracellular calcium increases** → increases tension
  - Nifedipine also acts on  $\text{Ca}^{2+}$  by blocking ryanodine receptors

#### Beta adrenergics

- Isoproterenol, norepinephrine, epinephrine, dopamine, dobutamine
  - ↑ cAMP → ↑ contractility



# NOTES

## ELECTROCARDIOGRAPHY(ECG)

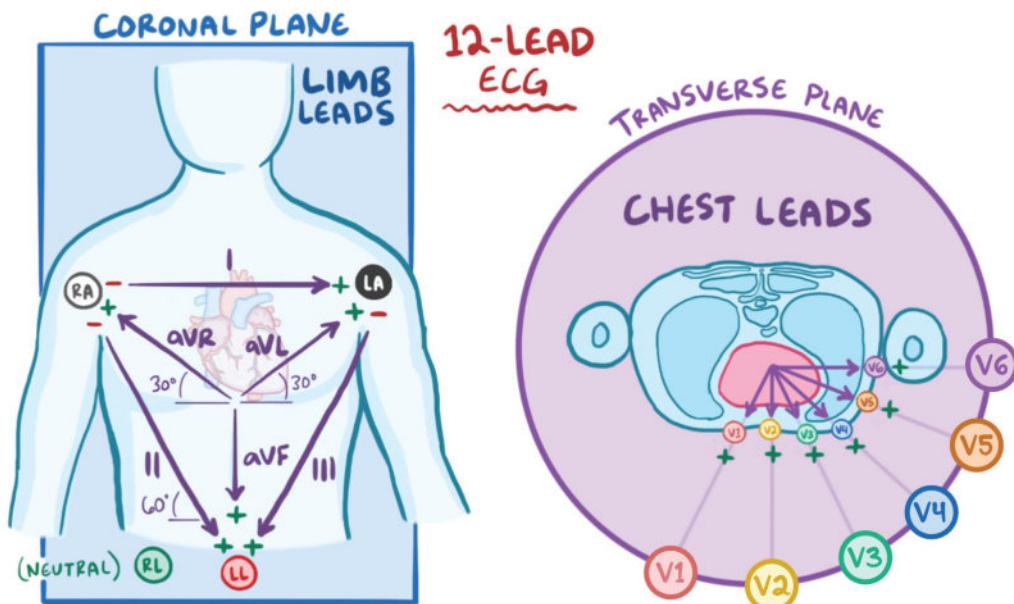
## ECG BASICS

[osms.it/ECG-basics](http://osms.it/ECG-basics)

- ECG traces provide information on heart's electrical activity, rate, rhythm
  - Depolarization waves moving towards electrode → positive deflection
  - Depolarization waves moving away from electrode → negative deflection
- 12 lead ECG (EKG) records heart electrical activity during heartbeat
  - Six limb leads (I, II, III, AVR, AVL, AVF)
  - Six chest leads (V1–V6)
- P wave: atrial depolarization
  - PR interval: beginning of atrial contraction to beginning of ventricular contraction (time for impulse to reach ventricles from sinus node)
- PR segment: end of P wave to beginning of QRS complex; signifies AV nodal delay
- QRS complex: ventricular depolarization
- T wave: ventricular repolarization
- QT interval: time from start of Q wave to end of T wave; represents time taken for ventricular depolarization, repolarization
- U wave: sometimes seen after T wave (not shown), represents purkinje fiber repolarization

### RECORDING ECGs

- Recorded on 1mm graph paper (10mm = 1mV)



**Figure 18.1** Lead placement in the coronal and transverse plane.

- x-axis = time (1mm = 0.04s)
- y-axis = voltage (10mm = 1mV)
- Limb leads: I, II, III, AVR, AVL, AVF
  - Bipolar leads: I, II, III
  - Unipolar leads: AVR, AVL, AVF (augmented voltage for right arm, left arm, left foot)
  - Lateral leads: I, aVL, V5, V6
  - Inferior leads: II, III, AVF
  - Six limb leads provide six viewpoints of cardiac activity, in frontal plane
- Electrodes placed on shoulders, abdomen to record limb leads
- Chest leads (precordial): V1 –V6
  - Septal leads: V1,V2
  - Lateral leads: V5,V6
  - Anterior leads: V3,V4
  - Six chest leads provide six viewpoints of cardiac activity, in horizontal plane

## ECG NORMAL SINUS RHYTHM

[osms.it/ECG-normal-sinus-rhythm](http://osms.it/ECG-normal-sinus-rhythm)

- P waves precede QRS complexes in 1:1 relationship
- SA node (sinus node), dominant centre of automaticity
  - Normal sinus rhythm 50–90bpm
- Constant RR interval
- Predictable recurring wave pattern (P-waves, QRS, T waves)
- P waves
  - Upright in leads I, II, AVF
  - Amplitude < 2.5mm in limb leads
  - Sinus arrhythmia: can be normal if sinus rate varies with respiratory cycle, relatively mild/abnormal if sinus rate varies unpredictably, very dramatic

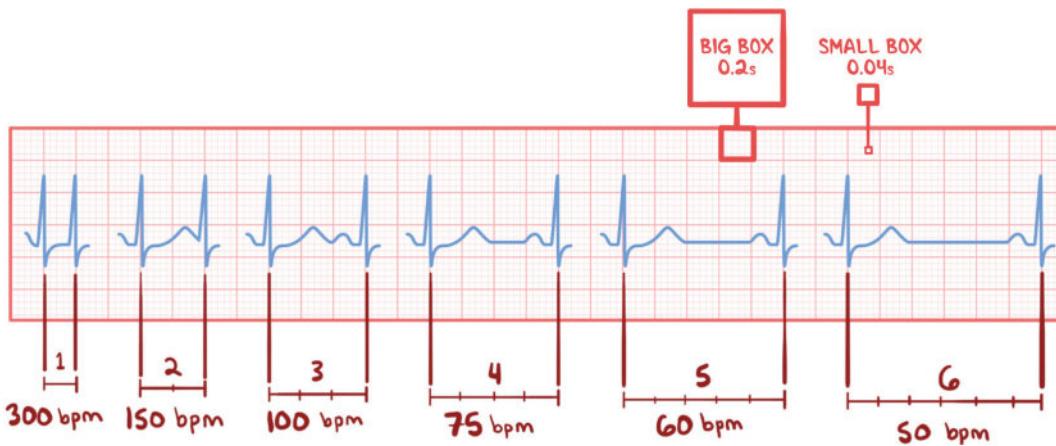
## ECG RATE & RHYTHM

[osms.it/ECG-rate-rhythm](http://osms.it/ECG-rate-rhythm)

### RATE DETERMINATION

- Box method: measure R-R interval by large boxes
  - ECG grid: thick lines 5mm apart (0.20s); thin lines 1mm (0.04s)
  - Locate R wave peak on thick line as “start”
  - Label blocks (thick lines): 300; 150; 100; 75; 60; 50
  - Locate next R wave peak to estimate heart rate
- Fast heart rates: use fine division within boxes for more accurate estimates
- Slow heart rates: use 2.5s marks at top of trace paper

- Locate R wave peak on large block line as “start”
- Count subsequent number of complete R waves in 10s strip (total strip)
- To calculate heart rate
  - Count number of QRS complexes across entire recording, multiply by six for heart rate; used to estimate heart rate during irregular rhythms



**Figure 18.2** The Box method measures distance between R-R intervals to calculate the heart rate.

## ECG INTERVALS

[osms.it/ECG-intervals](http://osms.it/ECG-intervals)

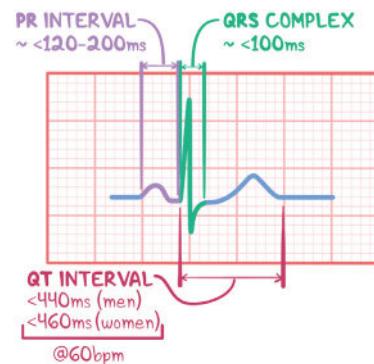
### PR INTERVAL & SEGMENT

- Normal interval 0.12–0.20s
  - Measure duration(s) from start of P to start of Q
- Normal segment: usually isoelectric, may be displaced

- QTc interval corrected for heart rate; 0.35–0.44s for normal heart rate (60–100bpm)
- Long QTc (> 500ms) → prone to rapid, potentially fatal ventricular rhythm

### QRS INTERVAL

- Normal QRS: <0.10–0.12s (slight variation between references)
  - Measured from start of Q to end of S
- QRS amplitude (voltage): wide range of normal limits
  - Low voltage: < 5mm limb leads, < 10mm chest leads
  - Increased voltage can indicate left ventricular hypertrophy, right ventricular hypertrophy, may be normal
  - Narrow (< 0.12s) / wide (> 0.12s)



**Figure 18.3** An ECG interval includes a segment and one or more waves and should be completed within a specific amount of time to be considered healthy.

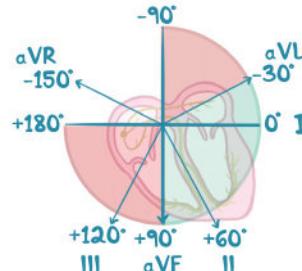
### QT INTERVAL

- Normal QT < 50% RR interval, only for normal heart rates
- Measure QT from start of Q to end of T
- Measure RR interval as time between R-R

# ECG AXIS

[osms.it/ECG-axis](http://osms.it/ECG-axis)

- Mean direction (vector) of ventricular depolarization wavefront
  - Mean QRS vector normally downward from AV node through stronger left ventricle
- Normal axis range -30° to +90° of frontal plane
- Limb leads indicate vector deviation in frontal plane
  - Divided into four quadrants



**Figure 18.4** The green shows a normal range. The red bottom left quadrant would indicate right ventricular hypertrophy while the top right would indicate left ventricular hypertrophy.

# ECG TRANSITION

[osms.it/ECG-transition](http://osms.it/ECG-transition)

- Chest leads provide information on vector rotation in horizontal plane
  - **Normal:** gradual transition of QRS through leads V1–V6
  - QRS complex switches from predominantly negative to positive either between V2, V3 or between V3, V4

## R WAVE PROGRESSION

- **Early:** tall R wave in V1, V2
- **Delayed R:** transition point between V4, V5/between V5, V6
  - R amplitude > S; no progression through V5, V6
- **Reverse:** decreasing amplitude

## ASSESSMENT FOR NORMAL REGULAR RHYTHM

- Is there a P before every QRS complex?
- Is there a QRS after every P?
- Are the P waves normal?

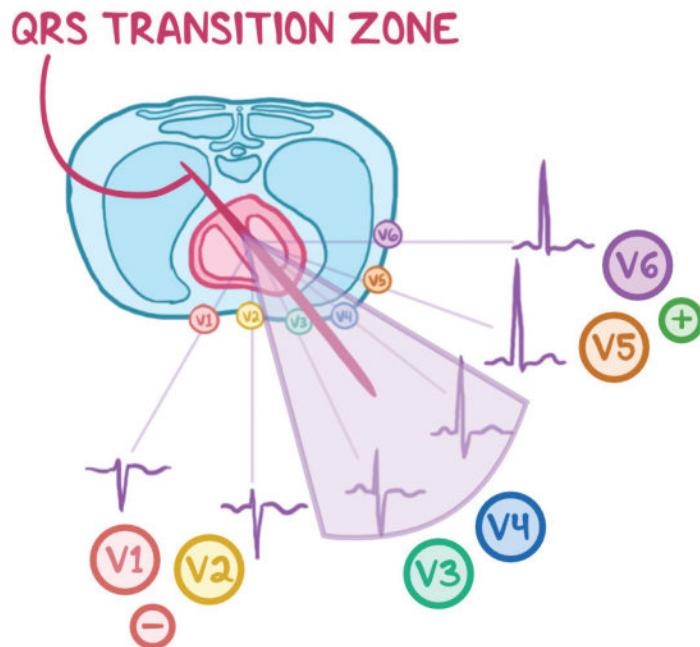
## ABNORMAL RATES & RHYTHMS

- Conventionally defined, sinus bradycardia <60bpm
  - True normal adult resting heart rate is 50–90bpm
- Sinus tachycardia > 100bpm
- If SA node fails, other latent ectopic pacemakers capable of automaticity
  - Atria, AV junction, His bundle, bundle branches can set heart rate
  - Each foci has unique rate (atrial foci 60–80bpm; junctional foci 40–60bpm; ventricular foci 20–40bpm)
  - **Overdrive suppression:** mechanism by which only foci/node with highest firing frequency rate conducts impulses, suppresses other pacemaker sites

## Heart blocks

- **Sinus block**
  - SA node temporarily ceases to conduct impulse; usually resumes, may cause escape rhythm

- AV block
  - First degree: prolonged PR interval > 0.2s
  - Second degree: some P waves conducted to ventricles, followed by QRS complex while some not
  - Third degree: atria, ventricles beat asynchronously with no conduction through AV node (complete dissociation between P, QRS complexes)
  
- **Bundle branch blocks**
- Left bundle branch block (LBBB)
  - Activation of left ventricle delayed causing left ventricle to contract later than right ventricle
  - Broad QRS < 120ms
  - Secondary R wave (R') in leads V1-3
  - Slurred S wave in lateral leads (I, aVL, V5-6)
  - Secondary repolarization abnormalities in right precordial leads (ST depression, T wave inversions)
- Right bundle branch block (RBBB)
  - Activation of right ventricle delayed causing right ventricle to contract later than left ventricle
  
- Left anterior fascicular block
  - Impulses conducted to left ventricle via left posterior fascicle
  - Left axis deviation
  - Increased R wave peak time in aVL
  - Small Q waves, tall R waves in leads 1, aVL
  - Small R waves, deep S waves in leads II, III, aVF
  - Increased QRS voltage in limb leads
  - Prolonged R wave peak time in aVL > 45ms
- Left posterior fascicular block
  - Impulses conducted to left ventricle via left anterior fascicle
  - Right axis deviation
  - Increased R wave peak time in aVF
  - Small R waves with deep S waves in leads I, aVL
  - Small Q waves with tall R waves in leads II, III, aVF
  - Increased QRS voltage in limb leads



**Figure 18.5** The QRS transition zone usually occurs in the V3 and V4 lead. V1 and V2 are mostly positive while V5 and V6 are mostly negative.

# ECG CARDIAC HYPERTROPHY & ENLARGEMENT

[osms.it/ECG-cardiac-hypertrophy-enlargement](http://osms.it/ECG-cardiac-hypertrophy-enlargement)

## ATRIAL DILATION/ENLARGEMENT

- Biphasic P waves > one small box in lead V1
- Initial component of wave larger
  - Right atrial enlargement
- Terminal component of wave larger
  - Left atrial enlargement
- Amplitude of P wave in any limb lead > 2.5mm
  - Probable right atrial enlargement

- Sum of S wave depth in V1 + R wave height in either V5/V6 > 35mm
- Possible left axis deviation
- Left ventricular 'strain pattern'
  - Downsloping ST segments, T wave inversions in lateral leads

## RIGHT VENTRICULAR HYPERTROPHY

- V1–V6 all consisting of small r waves, deep S waves (no R wave transition)
- Tall R wave in V1 that progressively shortens across to V6 (reverse R wave transition)
- Possible right axis deviation



## LEFT VENTRICULAR HYPERTROPHY

- Deep S wave in lead V1
- Tall R wave in V5 and/or V6

**Figure 18.6** Hypertrophy is an enlargement of the muscle wall while an increase in volume is known as dilation.

## CHARACTERISTICS of CARDIAC HYPERTROPHY

	LEFT	RIGHT
ATRIAL ENLARGEMENT	V1: Biphasic P, II: Double-Humped	II & V1: Big P
VENTRICULAR ENLARGEMENT	V1: Big R; V5: Big S	V1: Huge S; V5 & V6: Huge R

# ECG MYOCARDIAL INFARCTION & ISCHEMIA

[osms.it/ECG-cardiac-infarction-ischemia](http://osms.it/ECG-cardiac-infarction-ischemia)

## MYOCARDIAL INFARCTION

- Complete/partial blockage in coronary artery causing myocardial damage
- ST elevation MIs (STEMIs): **complete artery blockage**
  - ST elevation present on ECG; emergency
- Non-ST elevation MIs (NSTEMIs): **partial artery blockage**
  - ST elevations not present on ECG
  - Less emergent than STEMI

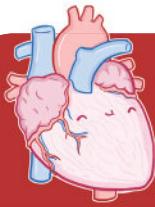
## ISCHEMIA

- **Inverted T waves**; slight to deep; most pronounced in chest leads
- **Angina**: transient T wave inversion; may occur without infarction
- Inverted T wave in any leads V2–V6 are abnormal
  - Suggest ischemia, variety of other pathologies
- **Acute or recent infarction**: elevated ST segment (slight to extensive)
  - One of the earliest ECG signs of infarction
  - Returns to baseline over time
- **Restricted coronary blood flow**: flat depressed ST segment
  - Suggests subendocardial infarction; any ST depression

## NECROSIS

- Pathologic Q wave;  $> 0.04\text{s}$ , amplitude  $< \frac{1}{3}$  -  $\frac{1}{4}\text{mm}$  the R wave height
  - Non-pathological q waves  $< 0.04\text{s}$  considered normal
- Ignore AVR lead; record leads with Q (pathological), q (physiological) waves; ST depression/elevation; inverted T waves
- Anterior left ventricular infarction (q in V5, V6)
  - Chest leads anterior location; Q waves in leads V1, V2, V3 /V4
- Posterior infarction
  - Large R in leads V1, V2; possible Q in V6
  - **Mirror test**: invert, examine reflection for vQ, ST elevation in leads V1, V2
- **Lateral infarction**: Q in leads I, AVL
- **Inferior infarction**: Q in leads II, III, AVF

ECG CHARACTERISTICS of COMMON ARRHYTHMIAS		
	ISCHEMIA	INFARCTION
<b>SUBENDOCARDIAL</b>	Stable angina; ST Depressions	Unstable angina; NSTEMI; ST Depresssions; T wave Inversion
<b>TRANSMURAL</b>	Unstable angina; NSTEMI; ST Depresssions; T wave Inversion	STEMI; T wave inversions; Hyperacute T waves; ST elevation; Pathologic Q waves



# NOTES HEMODYNAMICS

## BLOOD PRESSURE, BLOOD FLOW, & RESISTANCE

[osms.it/blood-pressure-blood-flow-resistance](https://osms.it/blood-pressure-blood-flow-resistance)

### PRESSURE (P)

- Force over area → blood pressure is force of blood over blood vessel surface area

### BLOOD FLOW (Q)

- Volume ( $\text{cm}^3$ ) blood flow through vessel over period of seconds (s)
- E.g.  $Q = 83\text{cm}^3/\text{s}$

### Determined by two factors

- $\Delta P$  = Pressure gradient (mmHg); difference in pressure between two blood vessel ends
- $R$  = Resistance (mmHg/mL per min)
  - $Q = \Delta P/R$
- $Q$  directly proportional to pressure gradient
  - Increased pressure gradient → increased blood flow
- $Q$  inversely proportional to resistance
  - Increased resistance → decreased blood flow

### BLOOD FLOW VELOCITY (v)

- Major mechanism for changing blood flow is changing resistance
- Blood flow velocity ( $v$ ) is distance (cm) traveled in certain amount of time (s)

- Using the equation for area ( $A$ ) of a circle,  $(d/2)^2 \times \pi$ , we get  $(2/2)^2 \times \pi = 3.14\text{cm}^2$
- Since cardiac output = blood flow → convert L/min to  $\text{cm}^3/\text{s} \rightarrow 1000\text{cm}^3$  in a L, 60 seconds in a minute, multiplying those equals  $83\text{cm}^3/\text{sec}$
- Rearranging formula, velocity equals flow rate divided by area, equals about  $26\text{cm/s}$ , about  $1\text{km/hr}$

### TOTAL PERIPHERAL RESISTANCE (TPR)

- Resistance of entire systemic vasculature
  - Can be measured by substituting cardiac output for flow ( $Q$ ), pressure difference between aorta, vena cava for  $\Delta P$
- Resistance within an organ
  - Can be measured by substituting organ blood flow for flow ( $Q$ ), pressure difference in pressure between organ artery, vein for  $\Delta P$

# PRESSES IN THE CARDIOVASCULAR SYSTEM

[osms.it/cardiovascular-system-pressures](http://osms.it/cardiovascular-system-pressures)

- Blood pressure highest in large arteries (e.g. brachial artery), about 120/80mmHg

## SYSTOLIC BLOOD PRESSURE

- First/top number
- Pressure in aorta caused by ventricular contraction
- During systole, heart contracts → transfers kinetic energy (140mmHg) to blood → aortic elastic walls stretched, where some kinetic energy stored as elastic energy of walls (form of potential energy) → blood pressure drops to 120mmHg (systolic pressure)

## DIASTOLIC BLOOD PRESSURE

- Second/bottom number
- Pressure caused by recoil of arteries during diastole
- During diastole, heart relaxes, aortic valves close → kinetic energy drops to 50mmHg → potential energy of stretched aortic walls adds to kinetic energy again when walls recoil → pressure rises to 60mmHg (diastolic pressure) → allows blood to move forward
- Pulse pressure: difference between systolic, diastolic pressure

## Mean arterial pressure (MAP/P<sub>a</sub>)

- Average blood pressure during cardiac cycle including systolic, diastolic blood pressure
- MAP, pulse pressure decline with distance from heart

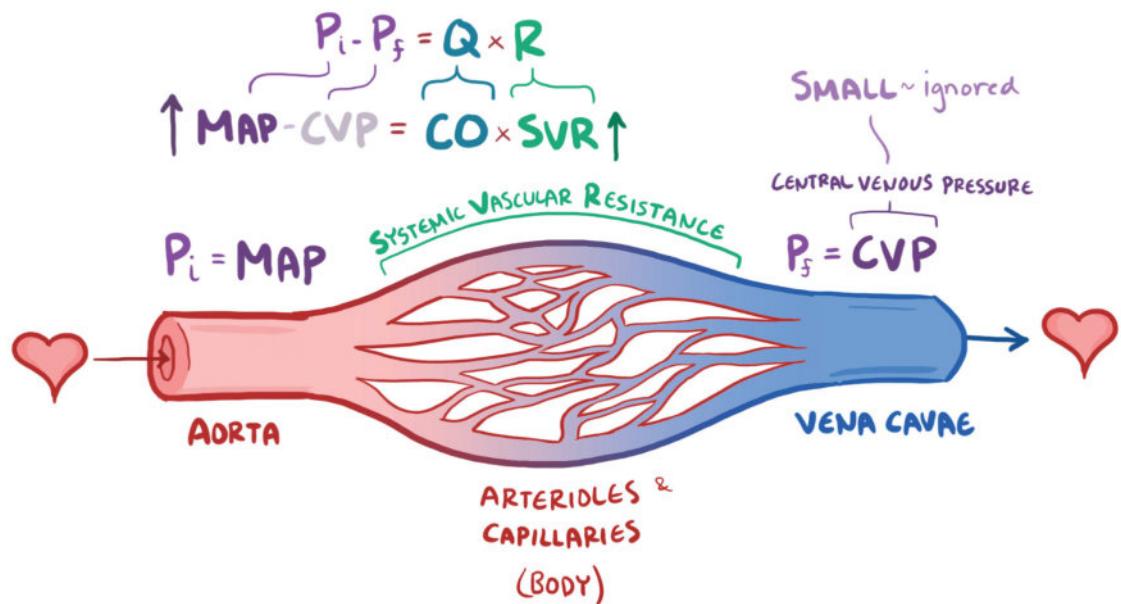
## MAP measured in two ways

- Diastole lasts longer than systole, therefore MAP is equal to one third systolic pressure plus two thirds diastolic pressure
  - $\text{MAP} = \frac{1}{3} \text{ systolic pressure} + \frac{2}{3} \text{ diastolic pressure}$

- For person with normal blood pressure of 120/80mmHg
  - $\text{MAP} = \frac{1}{3} 120 + \frac{2}{3} 80 = 93\text{mmHg}$
- Diastole lasts longer than systole; roughly equal to diastolic pressure plus one-third pulse pressure

$$\text{MAP} = \text{Diastolic pressure} + \frac{\text{pulse pressure}}{3}$$

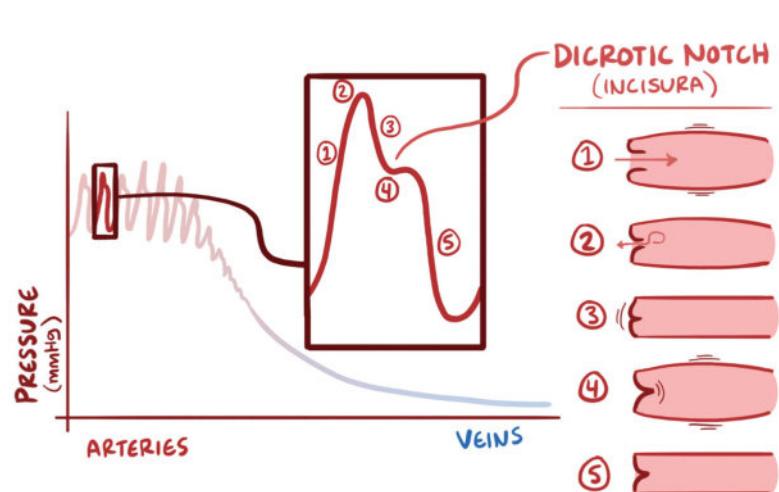
- For person with normal blood pressure of 120/80mmHg
 
$$\text{MAP} = 80\text{mmHg} + \frac{120\text{mmHg}}{3} = 93\text{mmHg}$$
- MAP demonstrated using relationship of blood flow, blood pressure, resistance, applying the following equation
  - $Q = \Delta P/R \rightarrow P_i - P_f = Q \times R$ 
    - $P_i$  = mean arterial pressure (MAP)
    - $P_f$  = central venous pressure (CVP)
    - $Q$  = blood flow, equals cardiac output (CO)
    - $R$  = resistance; combined resistance of all of blood vessels of systemic circulation equals systemic vascular resistance (SVR)
- Applying this equals the following
  - $\text{MAP} - \text{CVP} = \text{CO} \times \text{SVR}$
- CVP is a small number, usually ignored; equation simplified
  - $\text{MAP} = \text{CO} \times \text{SVR}$
- Based on this relationship → increased resistance will cause increased blood pressure



**Figure 19.1** Visualization of MAP equation components.

## PRESSURE GRADIENT

- Pressure gradient pressure difference between two ends of blood vessel
  - Gradient from aorta to arteriole ends
- Pressures in different parts of cardiovascular system not equal, keeps blood moving
- Blood flow generated by heart pumping action, moves along pressure gradient from high pressure areas (arteries) to low pressure areas (veins)
- Fluctuations on arterial side
  1. Blood ejected into aorta → pressure rises
  2. Small amount of blood backflows into ventricles
  3. Valves close → pressure drops
  4. Dicrotic notch/incisura pressure drop followed by small pressure increase as a result of valve recoiling
  5. Aorta settles, heart relaxes → pressure drops
- Pulse pressure lower in aorta than in large arteries → because pressure from blood travels faster than blood itself; pressure waves bounce off branch points in arteries which increases pressure even more
- Systolic pressure higher in large arteries than aorta, blood keeps moving forward
- Diastolic pressure is lower than in large arteries → mean arterial pressure mostly affected by diastolic pressure → mean arterial pressure is higher in aorta → driving force for blood flow
  - For example: aortic systolic pressure is 115mmHg; diastolic pressure is 85mmHg → Mean arterial pressure is 95mmHg; large artery systolic pressure is 120mmHg; diastolic pressure is 80mmHg → mean arterial pressure is 93mmHg



**Figure 19.2** The five stages of fluctuation in arterial pulse pressure.

## SYSTEMIC CIRCULATION

- Mean pressure in aorta results from two factors
  - Blood volume (cardiac output)
  - Compliance (low compliance → high pressure)
- Pressure remains high in large arteries because of high elastic recoil

### Small arteries

- Pressure decreases; biggest pressure drop is in arterioles (30mmHg)
  - Occurs because arterioles develop high resistance to flow

### Capillaries

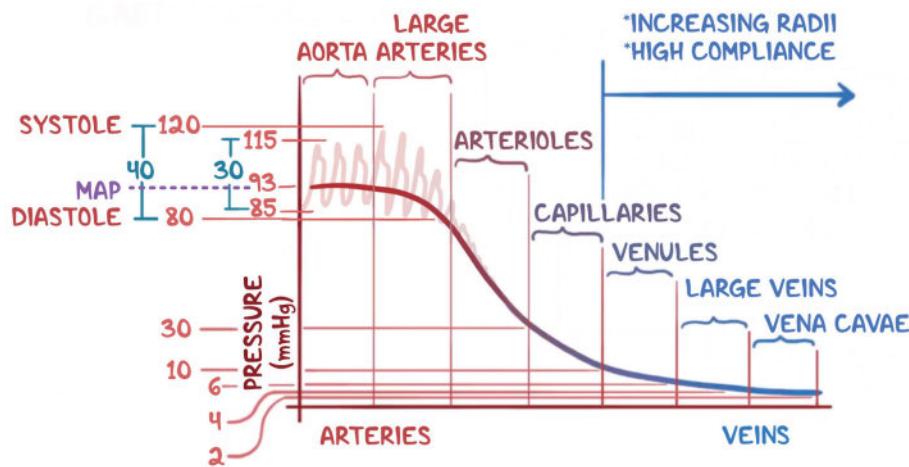
- Pressure drops from 30mmHg to 10mmHg
- Two causes for pressure drop
  - Fluid filtration in capillaries
  - Increase frictional resistance
- Pressure drop is less than in arterioles
  - Many capillaries running in parallel → reduces total resistance (total resistance for vessels in parallel is less than resistance in any individual vessel)

### Veins

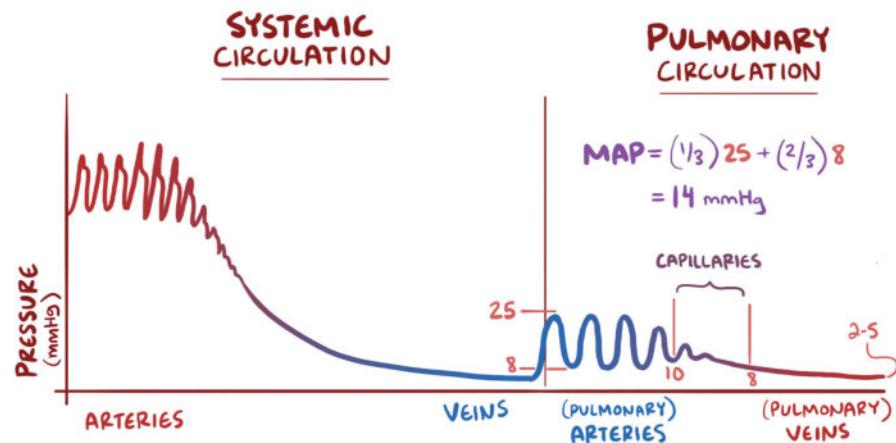
- Systolic pressure drops even further → 4mmHg in vena cava, 2mmHg in right atrium
  - Venous pressure too low to promote venous return to heart
- Factors that facilitate venous return
  - **Muscular pump:** as muscles contract, relax they compress surrounding veins, force blood towards heart
  - **Respiratory pump:** during inhalation, abdominal pressure increases, forces blood in local veins forward
  - **Sympathetic vasoconstriction:** as smooth muscle in veins contracts, blood pushed towards heart

## PULMONARY CIRCULATION

- Right ventricle → lungs → left atrium
- **Pulmonary arteries:** systolic pressure 25mmHg; diastolic pressure 8mmHg
  - Mean arterial pressure →  $25 \left(\frac{1}{3}\right) + 8 \left(\frac{2}{3}\right) = 14\text{mmHg}$
- **Capillaries:** pressure drops to 10mmHg
- **Pulmonary vein:** pressure drops to 8mmHg
- **Left atrium:** pressure drops to 2–5mmHg



**Figure 19.3** Visualizing pressures throughout the systemic cardiovascular system.



**Figure 19.4** Visualizing pressures in the pulmonary circulation.

# RESISTANCE TO BLOOD FLOW

[osms.it/resistance-to-blood-flow](http://osms.it/resistance-to-blood-flow)

## RESISTANCE

- Opposition to flow → amount friction as blood passes through blood vessels
- Determined by
  - Blood viscosity
  - Total length blood vessels
  - Diameter blood vessels

## Poiseuille Equation

- Describes relationship between resistance, blood vessel diameter, blood viscosity

$$R = \frac{8\eta l}{\pi r^4}$$

- R = resistance
- $\eta$  = blood viscosity
- l = length of blood vessel
- $r^4$  = radius (diameter) blood vessel raised to fourth power

## Points expressed by Poiseuille equation

- Resistance to blood flow is directly proportional to blood viscosity, blood vessel length
- Resistance to flow is inversely proportional to radius to fourth power ( $r^4$ ) → when radius decreases, resistance increases by fourth power → e.g. radius decreases by one half, resistance increases 16-fold

## SERIES & PARALLEL RESISTANCE

- Resistance also depends on blood vessel arrangement → series/parallel

### Series resistance

- Sequential flow from one vessel to next
- Illustrated by arrangement of blood vessels within an organ
- Major artery → smaller arteries → arterioles → capillaries → venules → veins
- Total resistance of system arranged in series** is equal to sum of individual resistances

$$R_{total} = R_{arteries} + R_{arterioles} + R_{capillaries} + R_{venules} + R_{veins}$$

- Blood flow at each part of system is identical but pressure decreases progressively (greatest decrease in arterioles)

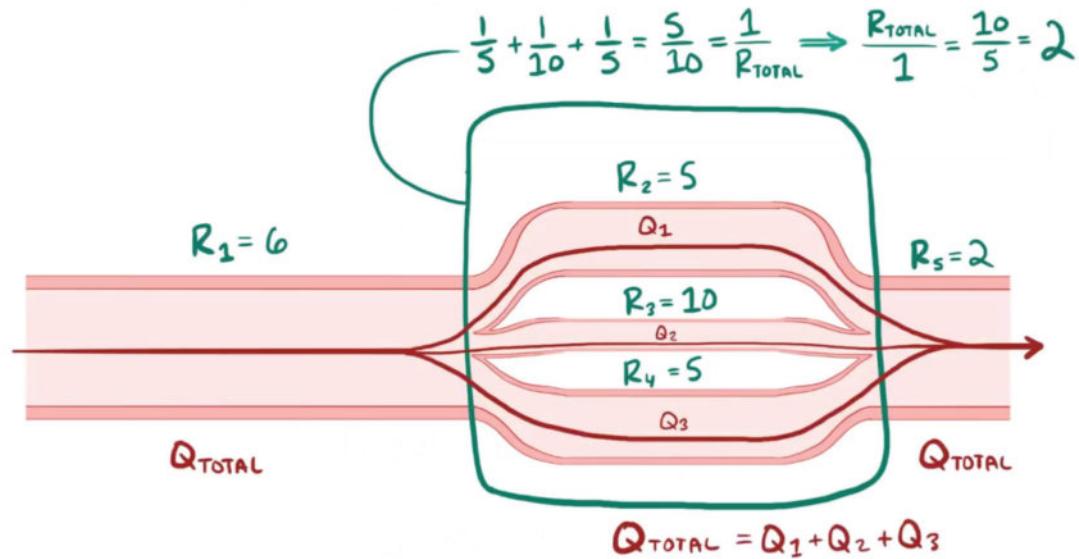
### Parallel resistance

- Simultaneous flow through each parallel vessel
- Illustrated by arrangement of arteries branching off aorta
- Cardiac output → aorta → branching → cerebral, coronary, renal system etc. → capillaries → venules → veins → vena cava → right atrium
- Total resistance** less than any individual resistance

$$\frac{1}{R_{total}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4} + \frac{1}{R_5} + \dots$$

- Numbered subscripts represent cerebral, renal, coronary, other systems
- Blood flow in each system is only small portion of total blood flow → no pressure lost in major arteries (remains same as in aorta)

$$R_{\text{TOTAL}} = 6 + 2 + 2 = 10 \frac{\text{mmHg} \cdot \text{min}}{\text{Liter}}$$



**Figure 19.5** Calculating the total resistance for this system involves finding the total parallel resistance first and then adding  $R_1$ ,  $R_{\text{Parallel}}$ , and  $R_5$ . The total blood flow in series,  $Q$ , is equal across all parts of the system. Individual vessels in the parallel system have different  $Q$ 's, since the blood flow is split between each of the vessels, but they add up to  $Q_{\text{Total}}$ .

# LAMINAR FLOW & REYNOLDS NUMBER

[osms.it/laminar-flow-and-Reynolds-number](https://osms.it/laminar-flow-and-Reynolds-number)

## LAMINAR FLOW

- Smooth blood flow through blood vessels  
→ blood velocity highest in center, lowest towards blood vessel walls → zero at walls

## TURBULENT FLOW

- Laminar flow disrupted; blood flows axially, radially → kinetic energy wasted → more energy needed to drive blood

## Reynolds Number

- Determines whether flow likely to be laminar/turbulent

$$N_R = \frac{\rho d v}{\eta}$$

- $N_R$  = Reynolds number
- $\rho$  = blood density
- $d$  = blood vessel diameter
- $v$  = blood flow velocity
- $\eta$  = blood viscosity
- As viscosity decreases (e.g. anemia), Reynolds number increases
- As velocity increases (e.g. increased cardiac output), Reynolds number increases

- Since velocity depends on diameter

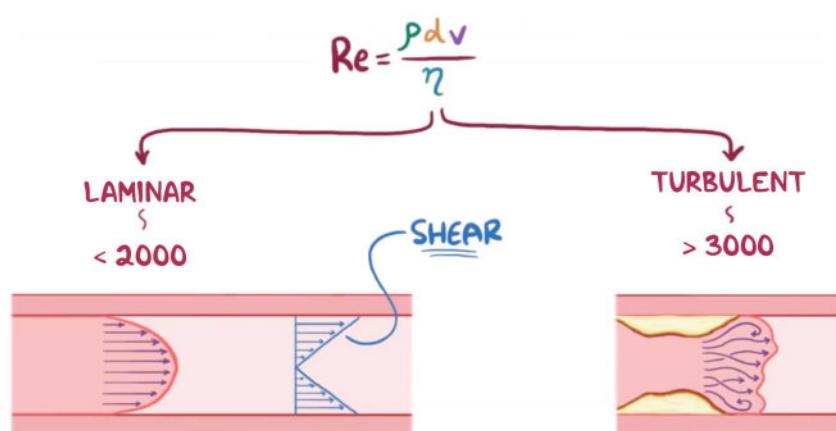
- $v = 4Q / \pi d^2$
- Decrease in diameter (e.g. thrombus, atherosclerotic plaque) → velocity increases → Reynolds number increases

- Values of Reynolds number

- If  $< 2000$  → laminar flow
- If  $> 2000$  → increased likelihood of turbulent flow
- If  $> 3000$  → turbulent flow

## SHEAR

- Friction between blood, vessel walls
- Highest at vessel wall, lowest in center → difference in blood flow velocity
- Difference in velocity is parabolic → moving away from walls velocity increases quickly, near middle change in velocity low
- Shear inhibits red blood cell aggregation, lowers viscosity



**Figure 19.6** Reynolds number is a way to predict whether a fluid is going to be laminar (smooth) or turbulent. Differences in velocity across a blood vessel cause shear.

# COMPLIANCE OF BLOOD VESSELS

[osms.it/compliance-of-blood-vessels](http://osms.it/compliance-of-blood-vessels)

## COMPLIANCE (C)

- AKA capacitance/distensibility: ability of blood vessels to distend, hold an amount of blood with pressure changes
- $C = V / P$ 
  - C = compliance of blood vessel (mL/mmHg)
  - V = volume of blood (mL)
  - P = pressure (mmHg)
- High volume, low pressure → high compliance (veins); low volume, high pressure → low compliance (arteries)
- Arteriosclerosis → low compliance → low ability to hold an amount of blood at same pressure → blood backs up in veins
  - Arteries also become less compliant with age
  - If compliance decreases in veins (venoconstriction) → volume decreases (shift from veins to arteries)

## ELASTANCE (E)

- Inverse of compliance
  - Blood vessel ability to recoil back after distension
- $E = P / V$ 
  - E = elastance of blood vessel (mmHg/mL)
  - P = pressure (mmHg)
  - V = volume of blood (mL)

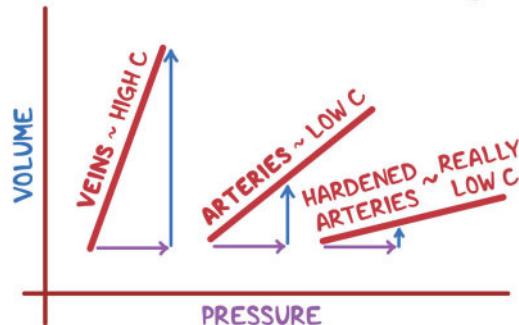
### During systole

- Heart contracts → transfers kinetic energy (140mmHg) to blood → stretches aortic elastic wall, where some kinetic energy stored as elastic energy of walls (form of potential energy) → blood pressure drops to 120mmHg (systolic pressure)

### During diastole

- Heart relaxes, aortic valves close → kinetic energy drops to 50mmHg → potential energy of stretched aortic walls adds to kinetic energy again when walls recoil → pressure rises to 60mmHg (diastolic pressure) → allows blood to move forward during diastole
- Pulse pressure: 120mmHg - 60mmHg = 60mmHg
- Elastance buffers, dampens pulse pressure → Windkessel effect
- Without elastic properties, blood pressure would be 140/50mmHg with pulse pressure 90mmHg

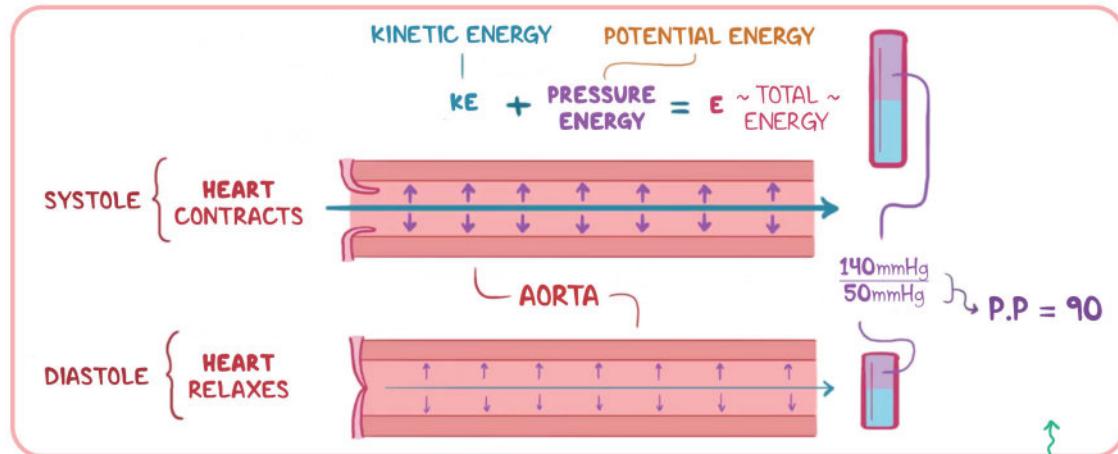
$$\text{COMPLIANCE} \sim C = \frac{V \text{ (mL)}}{P \text{ (mmHg)}}$$



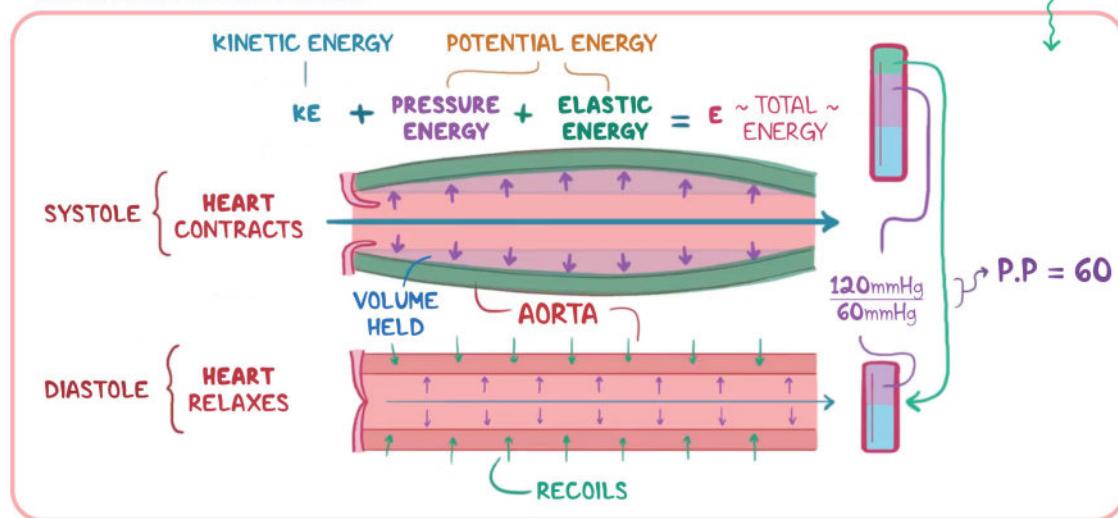
**Figure 19.7** The same pressure will expand the volumes of vessels differently depending on their compliance.

## WINDKESSEL EFFECT

### WITHOUT ELASTIC ARTERIES



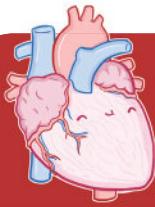
### WITH ELASTIC ARTERIES



**Figure 19.8** Windkessel effect: elastance dampens pulse pressure by lowering systolic pressure and increasing diastolic pressure.

**Systole:** aorta's walls stretch with high pressure contractions and store some energy as elastic energy. Since the total energy is the same as it would be without elastic arteries, there must be less kinetic energy and pressure energy to make room for the elastic energy → lower systolic blood pressure.

**Diastole:** elastic walls recoil, releasing the stored elastic energy and converting it to pressure energy and kinetic energy → more pressure energy.



# NOTES

## NORMAL VARIATIONS

- Physiological adaptations within cardiovascular system in response to changes such as hemorrhage, exercise, postural changes

# CARDIOVASCULAR CHANGES DURING EXERCISE

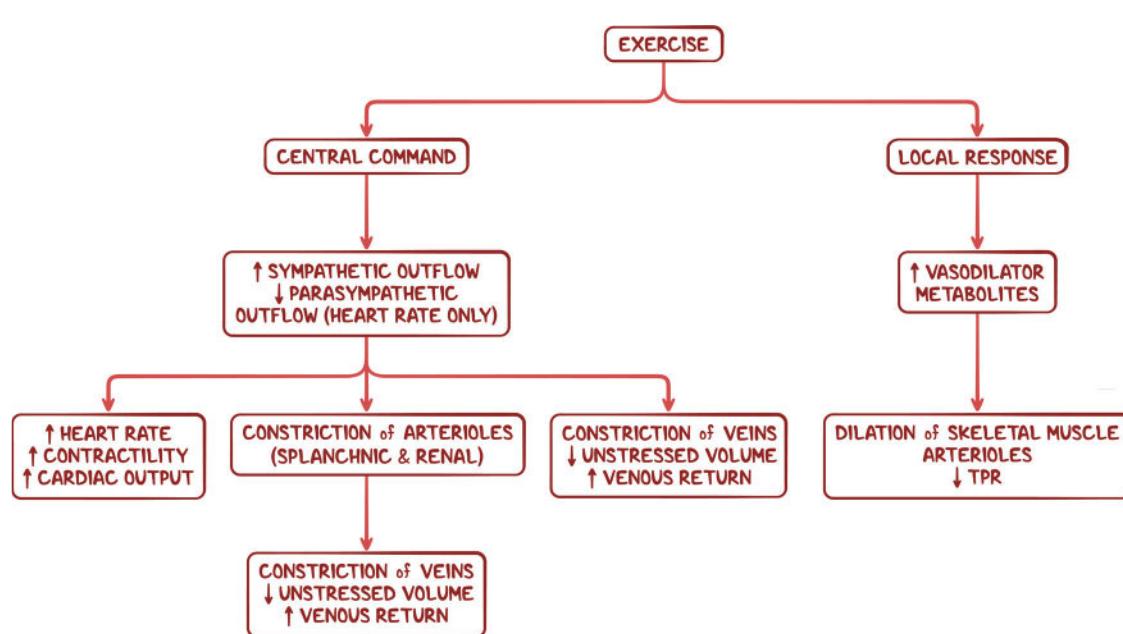
[osms.it/cardiovascular-changes-exercise](https://osms.it/cardiovascular-changes-exercise)

- Involves central nervous system (CNS), local mechanisms
  - CNS responses: changes in autonomic nervous system (ANS) due to inputs from cerebral motor cortex
  - Local responses: exercise causes ↑ blood flow, O<sub>2</sub> delivery to skeletal muscles
- Exercise results in ↑ sympathetic (β1 receptors), ↓ parasympathetic activity to heart → ↑ cardiac output due to ↑ heart rate + ↑ stroke volume
- Muscle changes also occur
  - ↑ metabolites (lactate, potassium, adenosine) are produced → metabolites stimulate local vasodilation → ↑ blood flow → ↓ overall total peripheral resistance (TPR)

### OVERALL RESPONSE TO EXERCISE

- Central command: ↑ cardiac output (CO), vasoconstriction in some vascular beds (excludes exercising skeletal muscle, cerebral, coronary circulations)
  - ↑ CO → ↑ heart rate, contractility
  - ↑ contractility → ↑ stroke volume → ↑ pulse pressure
  - ↑ CO due to ↑ venous return (sympathetic vein constriction, squeezing action of skeletal muscle on veins)

CV RESPONSES TO EXERCISE OVERVIEW	
	RESPONSE
HEART RATE	↑↑
STROKE VOLUME	↑
PULSE PRESSURE	↑ (increased stroke volume)
CARDIAC OUTPUT	↑↑
VENOUS RETURN	↑
MEAN ARTERIAL PRESSURE	↑ (slight)
TPR	↓↓
ARTERIOVENOUS O <sub>2</sub> DIFFERENCE	↑↑ (increased tissue O <sub>2</sub> composition)

**Figure 20.1** Flowchart showing cardiovascular response to exercise.

## CARDIOVASCULAR CHANGES DURING HEMORRHAGE

[osms.it/cardiovascular-changes-hemorrhage](https://osms.it/cardiovascular-changes-hemorrhage)

- Blood loss → ↓ arterial pressure → compensatory responses to restore arterial pressure
  - Response mediated by baroreceptor reflex, renin-angiotensin-aldosterone system (RAAS), vascular actions

### Decrease in arterial pressure

- Hemorrhage → ↓ total blood volume → ↓ venous return to heart, ↓ right atrial pressure → ↓ cardiac output → ↓  $P_a$  as a product of cardiac output, TPR

### Return of arterial pressure

- Baroreceptors in carotid sinus detect ↓  $P_a$  → relay information to medulla via carotid sinus nerve → ↑ sympathetic outflow to heart, blood vessels; ↓ parasympathetic outflow to heart → ↑ heart rate, ↑ contractility, ↑ TPR, constriction of veins
- ↓ mean arterial pressure → ↓ perfusion to kidney → response via RAAS

- Kidney secretes renin from renal juxtaglomerular cells → ↑ angiotensin I production → converted to angiotensin II (causes arteriolar vasoconstriction, stimulates aldosterone secretion)
- Capillary changes favor fluid reabsorption
  - ↑ sympathetic outflow to blood vessels, angiotensin II → arteriolar vasoconstriction → ↓ capillary hydrostatic pressure ( $P_c$ ) → restricts filtration out of capillaries, favors absorption

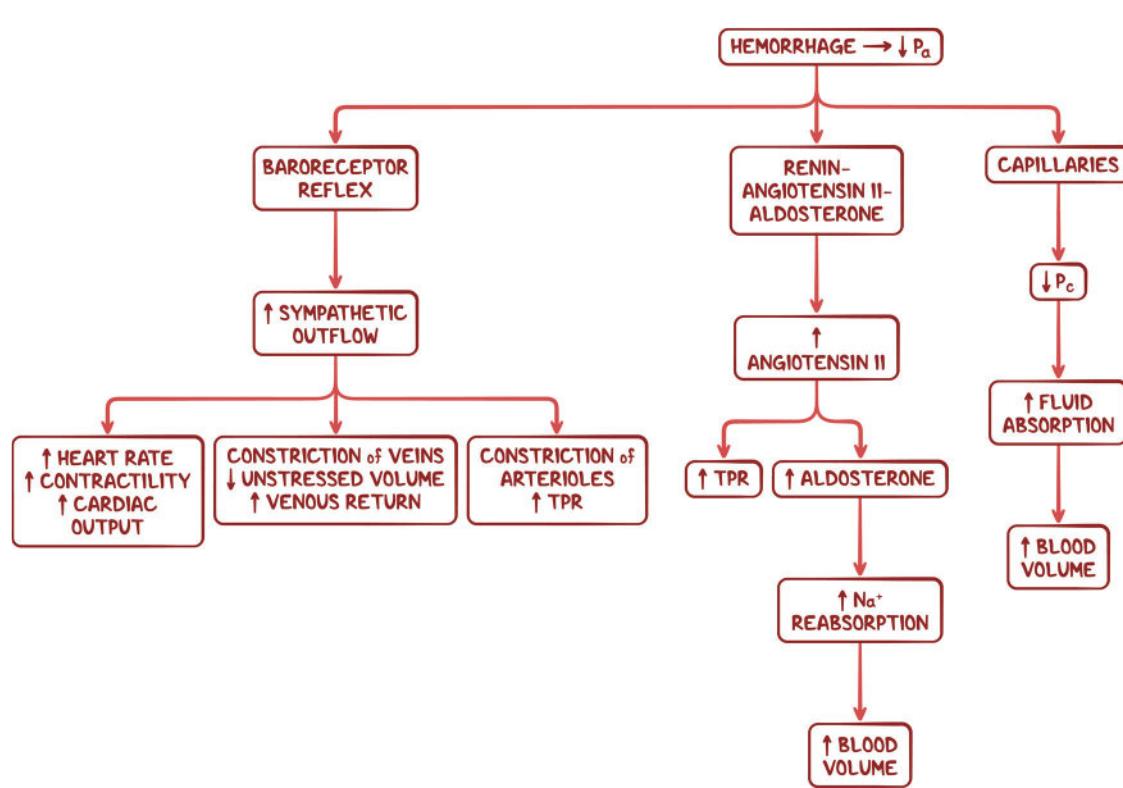
### OTHER RESPONSES IN HEMORRHAGE

- Hypoxemia (↓ arterial  $P_{O_2}$ ): carotid, aortic bodies chemoreceptors sense ↓  $P_{O_2}$  → ↑ sympathetic outflow to blood vessels → ↑ vasoconstriction, TPR,  $P_a$
- Cerebral ischemia: local ↑  $P_{CO_2}$

- ↓ blood volume → ↓ return of blood to heart
- detection by atria volume receptors
- ADH secretion to maintain adequate blood pressure → water reabsorption by renal collecting ducts → arteriolar vasoconstriction

## CV RESPONSES TO HEMORRHAGE OVERVIEW

	RESPONSE
CAROTID SINUS NERVE FINDING RATE	↓
HEART RATE	↑
CONTRACTILITY	↑
CARDIAC OUTPUT	↑
UNSTRESSED VOLUME	↓ (produces increased venous return)
TPR	↑
RENIN	↑
ANGIOTENSIN II	↑
ALDOSTERONE	↑
CIRCULATING EPINEPHRINE	↑ (secreted from adrenal medulla)
ANTIDIURETIC HORMONE (ADH)	↑ (stimulated by decreased blood volume)



**Figure 20.2** Flowchart showing cardiovascular responses to hemorrhage.

## CARDIOVASCULAR CHANGES DURING POSTURAL CHANGE

[osms.it/cardiovascular-changes-postural](http://osms.it/cardiovascular-changes-postural)

- Standing up quickly → lightheadedness, sometimes fainting (due to delayed constriction of lower extremity blood vessels → orthostatic hypotension)
  - ↓ in systolic blood pressure > 20mmHg/ diastolic blood pressure > 10mmHg within three minutes of standing
- Initiating event: pooling of blood in extremities
  - Moving from supine to standing position: blood pools in veins of lower extremities → ↓ venous return to heart, ↓ cardiac output → ↓ mean arterial pressure
  - Venous pooling → ↑ hydrostatic pressure in leg veins → ↑ fluid filtration

into interstitial fluid, ↓ intravascular volume

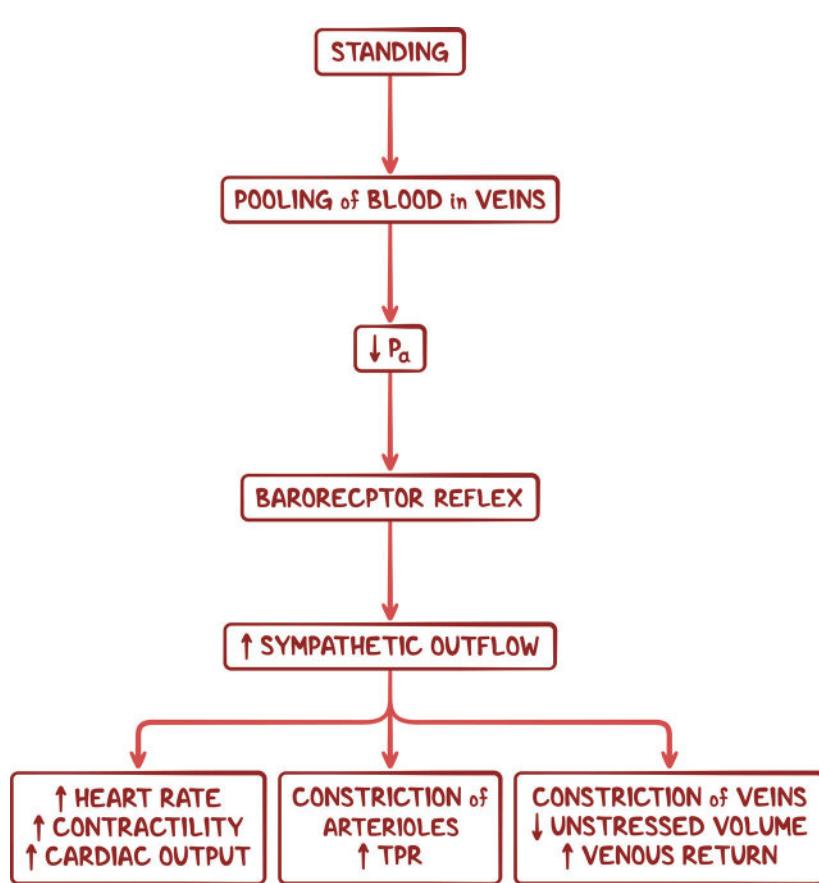
- Severe ↓ blood pressure → syncope

### Response of baroreceptor reflex

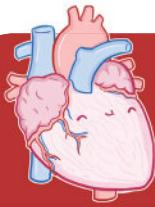
- Responsible for homeostatic blood pressure maintenance
- Carotid sinus baroreceptors detect ↓  $P_a$  → sends information to medullary vasomotor center → inactivates medulla vagal neurons, activates sympathetic neurons → ↑ sympathetic outflow to heart, blood vessels, ↓ parasympathetic outflow to heart to normalize  $P_a$
- ↑ systemic vascular resistance, cardiac output act in negative feedback mechanism to maintain  $P_a$

## CV RESPONSE TO STANDING

	INITIAL RESPONSE	COMPENSATORY RESPONSE
MEAN ARTERIAL PRESSURE	↓	↑ (toward normal)
HEART RATE	—	↑
STROKE VOLUME	↓ (decreased venous return)	↑ (toward normal)
CARDIAC OUTPUT	↓ (decreased stroke volume)	↑ (toward normal)
TPR	—	↑
CENTRAL VENOUS PRESSURE	↓ (pooling of blood in lower extremities)	↑ (toward normal)



**Figure 20.3** Flowchart showing cardiovascular response to postural change.



# NOTES

## SPECIFIC CIRCULATIONS

### CEREBRAL CIRCULATION

[osms.it/cerebral-circulation](http://osms.it/cerebral-circulation)

- Cerebral circulation: managed almost entirely by local (intrinsic) control (autoregulation; active, reactive hyperemia)
  - $\uparrow pCO_2$  ( $\uparrow H^+$ ,  $\downarrow pH$ )  $\rightarrow$  arteriolar vasodilation  $\rightarrow$   $\uparrow$  blood flow  $\rightarrow$   $CO_2$  removal (most vasoactive metabolites too big to cross blood-brain barrier  $\rightarrow$  do not affect cerebral tissue)
  - Hyperventilation works by same mechanism  $\rightarrow$   $\downarrow pCO_2$   $\rightarrow$  vasoconstriction (used to reduce swelling in situations of cerebral edema)

#### CEREBRAL BLOOD SUPPLY SEGMENTATION

- Cerebral blood supply separated into anterior, posterior segments
- Anterior, posterior circulatory segments join via arterial posterior communicating arteries, form circle of Willis
  - Back-up circulation in case of blood vessel occlusion

#### Anterior segment

- Supplied by internal carotid arteries
- Enter skull in carotid canal, branch out
  - Ophthalmic arteries: supply eyes, orbits, forehead, nose
  - Anterior cerebral artery: medial part of frontal, parietal lobes; anastomoses with counterpart via anterior communicating artery (part of circle of Willis)
  - Middle cerebral artery: supplies lateral sides of temporal, parietal, frontal lobes

#### Posterior segment

- Supplied by vertebral arteries
- Enter skull through foramen magnum, branch out
  - Right, left vertebral arteries fuse in skull  $\rightarrow$  basilar artery which supplies brainstem, cerebellum, pons
  - Posterior cerebral arteries: supply occipital lobes, inferior parts of temporal lobes

# CORONARY CIRCULATION

[osms.it/coronary-circulation](http://osms.it/coronary-circulation)

- Coronary arteries: blood vessels delivering oxygenated blood to heart (myocardium)
- Cardiac veins: blood vessels retrieving deoxygenated blood from heart

## CORONARY ARTERIES

- Two coronary arteries emerge from base of aorta, surround heart in coronary sulcus

### Left coronary artery

- Two branches; supplies left atrium, left ventricle, interventricular septum
  - Circumflex artery: supplies left atrium, posterior wall of left ventricle
  - Anterior interventricular artery: supplies interventricular septum, anterior walls of ventricles

### Right coronary artery

- Two branches; supplies right atrium, right ventricle, part of left ventricle, electrical conduction system
  - Right marginal artery: supplies lateral right side of heart, superficial parts of ventricle
  - Posterior interventricular artery: supplies interventricular septum, posterior walls of ventricles

## CORONARY CIRCULATION CONTROL

- Coronary circulation managed primarily by local (intrinsic) control, secondarily by sympathetic nervous system
  - ↑ oxygen demand → ↑ blood flow
- Active hyperemia via local (intrinsic) control triggers
  - Hypoxia → build-up of metabolites ADP, AMP → degraded to adenosine (potent vasodilator) → binds to coronary vascular smooth muscle → ↓ calcium influx into cells → vasodilation → ↑ blood flow, oxygen delivery
- Other intrinsic control of vascular tone provided by endothelial factors
  - Endothelium-derived nitric oxide: relaxes arterial smooth muscle
  - Prostacyclin: vasodilator
  - Endothelium-derived hyperpolarizing factor (EDHF): vasodilator
  - Endothelin 1: vasoconstrictor
- Reactive hyperemia
  - Brief arterial occlusion period during systole → ↓ blood flow → ↑ O<sub>2</sub> debt → vasodilation during diastole → ↑ blood flow → O<sub>2</sub> demands are met

# CONTROL OF BLOOD FLOW CIRCULATION

[osms.it/blood-flow](http://osms.it/blood-flow)

- Blood flow regulation
  - Intrinsic (local): humoral, myogenic control
  - Extrinsic (systemic): hormonal, neural

## LOCAL (INTRINSIC) BLOOD FLOW CONTROL

### Mechanisms

- Humoral: mediated by vasoactive substances
  - Histamine, nitric oxide (arteriole dilation)
  - Endothelin, serotonin
- Autoregulation: maintains constant blood flow via direct control of arterial resistance
  - Present in organs such as kidneys, brain, heart, skeletal muscle (e.g. ↓ coronary artery pressure → compensatory arteriole vasodilation → ↓ vessel resistance → constant blood flow)
- Active hyperemia: ↑ blood flow directed to organ/tissue associated with ↑ metabolic activity (e.g. ↑ blood flow in active skeletal muscle)
- Reactive hyperemia: temporary ↑ blood flow following ischemia (↓ blood flow) in organ (e.g. arterial occlusion → ↓ blood flow → ↑ O<sub>2</sub> debt → vasodilation, ↑ blood flow)
- Myogenic hypothesis for autoregulation
  - Focus on arteriolar resistance: vascular smooth muscle contracts upon stretching (↑ wall tension) and vice versa
  - ↑ blood flow → arteriole stretching → contraction → ↑ resistance → constant blood flow
  - ↓ blood flow → ↓ arteriole stretching → relaxation → ↓ resistance → constant blood flow
  - Explained by law of Laplace: ↑ pressure (P) + ↓ radius (r) → tension (T) remains constant ( $T=P \times r$ )

- Metabolic hypothesis for autoregulation, active, reactive hyperemia
  - O<sub>2</sub> distribution changes in response to O<sub>2</sub> consumption via altering arteriolar resistance
    - ↑ metabolism → ↑ vasodilating metabolites (CO<sub>2</sub>, H<sup>+</sup>, K<sup>+</sup>, lactate, adenosine) → arteriole vasodilation → ↓ resistance → ↑ blood flow, O<sub>2</sub> distribution
  - Certain tissues more susceptible to certain metabolites (coronary circulation—PO<sub>2</sub>, adenosine; cerebral circulation—PCO<sub>2</sub>)

## NEURAL & HORMONAL (EXTRINSIC) CONTROL

- Neural: sympathetic nervous system acts on vascular smooth muscle
  - $\alpha_1$ : vasoconstriction → skin, intestines
  - $\beta_2$ : vasodilation → lungs, skeletal muscles
- Hormonal: vasopressin released from anterior pituitary → vasoconstriction

# MICROCIRCULATION & STARLING FORCES

[osms.it/microcirculation-starling-forces](https://osms.it/microcirculation-starling-forces)

- Microcirculation: vascular network involving capillaries, lymphatic vessels

## Capillaries

- Vessels: thin walls lined with endothelial cells
- Arterioles → metarterioles → capillaries → venules → veins
  - Metarterioles end in precapillary sphincters → smooth muscle ring controls blood flow/capillary exchange rate by constricting/relaxing
  - Capillary blood flow regulated by intrinsic (local), extrinsic (systemic) control

## CAPILLARY EXCHANGE

- Capillaries: exchange sites for nutrients, waste, fluids between interstitial, vascular space
  - Afferent blood: capillaries → interstitial space → tissue
  - Efferent blood: tissue → interstitial space → capillaries

## Capillary exchange types

- Simple diffusion: substance exchange through lipid bilayer/between capillary wall's epithelial cells
  - Depends on driving force (partial pressure gradient), available diffusion area
  - Driving force: substances move across their own partial pressure gradient (towards ↓ concentration area)
  - Lipid soluble substances ( $O_2$ ,  $CO_2$ ) pass through lipid bilayer
  - Water soluble substances (ions, glucose, amino acids) pass between endothelial cells through fluid-filled intercellular clefts/fenestrations

- Vesicular transport: large molecule exchange (proteins) via pinocytic vesicles (caveolae)
  - In some tissues (kidney, intestine) proteins pass through capillary fenestrations
- Osmosis: if capillary wall has aqueous pores, pressure gradient across membrane, driven by Starling forces

## STARLING FORCES

- Capillary filtration/absorption depend on Starling forces: hydrostatic, colloid osmotic (oncotic) pressure
  - Filtration: fluid movement from capillaries → interstitium
  - Absorption: fluid movement from interstitium → capillaries

## Hydrostatic pressure

- Pressure exerted by fluid against capillary wall
- Capillary hydrostatic pressure ( $P_c$ )
  - Favors filtration: tends to move fluid out of capillaries
  - Blood pressure ↓ throughout capillary beds → arterial (37mmHg) > venous (17mmHg) pressure
- Interstitial fluid hydrostatic pressure ( $P_i$ )
  - Opposes filtration: pressure exerted outside capillary wall
  - Tends to move fluid into capillary
  - Contains very little fluid →  $P_i$  considered zero, slightly positive/slightly negative (1mmHg)

## Colloid osmotic pressure (oncotic pressure)

- Pressure gradient: large non-diffusible molecules (e.g. plasma proteins)
- Capillary oncotic pressure ( $\pi_c$ ) (25mmHg): created by plasma proteins (primarily albumin; reflection coefficient = 1.0); opposes filtration

- **Interstitial oncotic pressure ( $\pi_i$ )**  
(0mmHg): contains very little protein; favors filtration

### Flow direction

- **Arterial end** of capillary
  - Blood pressure's outward driving force > inwardly directed oncotic pressure force  
→ **fluid moves out** of vessel
- **Venous end** of capillary
  - Oncotic pressure inward driving force > outwardly directed hydrostatic pressure  
→ **fluid moves into** vessel
- Most fluid leaving capillary at arterial end reenters capillary before leaving venous end
- Fluid remaining in interstitial space recovered by lymphatic vessels
- Fluid movement through capillary wall is dependent on Starling force

### Starling equation

- $J_v = K_f [(P_c - P_i) - (\pi_c - \pi_i)]$ 
  - $J_v$  = fluid movement (mL/min)
  - $K_f$  = hydraulic conductance (wall to water permeability; depends on tissue, wall structure—e.g. fenestrated, non-fenestrated)

### LYMPH

- Lymphatic capillaries drain excess fluid + some proteins from interstitial space into venous system
  - Lymphatic capillaries → lymphatic vessels → thoracic duct/right lymphatic duct → subclavian vein
  - One way valves → unidirectional flow

### Edema

- Abnormal **buildup** of fluid in interstitial space
- Causes
  - Imbalance of Starling forces
  - ↑ hydrostatic **capillary pressure** (↑ volume—e.g. heart failure; obstruction; e.g. thrombosis)
  - ↓ oncotic capillary pressure (↓ **plasma protein** —e.g. liver failure, malnourishment, nephrotic syndrome)
  - ↑ **capillary permeability** (burns/inflammation)
  - **Impaired drainage** (immobility; lack of irradiated lymphatic nodes; parasitic infections of lymphatic nodes—e.g. filariasis)



# NOTES

## BODY TEMPERATURE REGULATION (THERMOREGULATION)

### NORMAL BODY TEMPERATURE

- $37 \pm 0.5^\circ\text{C}$  ( $98.6 \pm 0.9^\circ\text{F}$ )
- Hypothalamic thermoregulatory center acts as a thermostat
  - Sets temperature set-point
- Thermoreceptors
  - Peripheral (in skin) → sense surface temperature
  - Central (in the body core—e.g. hypothalamus itself) → sense core temperature
- Temperature variations activate thermoreceptors → thermoreceptors inform hypothalamus → hypothalamus activates heat regulation mechanisms → temperature returns to baseline
- Body region variations
  - Core: higher temperature, more stable
  - Skin: lower temperature, more variable
- Core temperature varies with throughout the day
  - Lower during sleep
  - Higher when awake

### BODY TEMPERATURE MAINTENANCE

- Body temperature maintained by balancing heat-generation, heat loss

#### Heat generation

- Activation of sympathetic nervous system
  - Vasoconstriction of skin arterioles → blood bypasses skin → ↓ heat loss
  - Adrenal glands release catecholamines (epinephrine, norepinephrine) → increased metabolic rate → ↑ heat

production

- Piloerection (goosebumps) → heat trapping
- Thyroid hormones released from hypothalamus → ↑ metabolic rate → ↑ heat production
- Non-shivering thermogenesis using brown adipose tissue
  - Activation of primary motor center for shivering in the posterior hypothalamus → skeletal muscle contraction → shivering → ↑ heat production
  - Behavioral changes (adding garments, tightening the arms across the chest, moving around)

#### Heat dissipation

- Inhibition of sympathetic activity in skin blood vessels → blood goes to skin → ↑ heat loss
- Activation of sympathetic cholinergic fibers innervating sweat glands → ↑ sweating → ↑ heat loss
- Behavioral changes (removing garments, reducing movements, fanning air over body)

#### Fever

- Body temperature elevation due to change in hypothalamic set-point
- Pyrogens act on hypothalamus → hypothalamus releases prostaglandins → hypothalamic set-point temperature increases → heat-generating mechanisms kicks in → body temperature rises and reaches new baseline temperature
  - Aspirin reduces fever by inhibiting prostaglandins production

- Benefits of fever
  - Inhibit bacterial growth by making growing conditions less favorable
  - Increase efficiency of immune cells

## HYPERTHERMIA

- Elevation of body temperature without change in hypothalamic set-point
- Normal mechanisms of thermoregulation are overwhelmed by various factors
  - Excessive environmental temperature
  - Impaired ability to dissipate heat
  - Excessive heat production

### Heat exhaustion

- Excessive sweating → significant water and electrolyte loss → ↓ blood volume → ↓ arterial pressure

### Heat stroke

- Hyperthermia > 40°C/105.1°F
- Potentially fatal
- Causes
  - High environmental temperature
  - Periods of intense physical activity
- Risk factors
  - Susceptible individuals: infants, children (higher metabolic rate; ineffective sweating; physical, psychological limitations); elderly (pre-existing conditions; physical, psychological limitations)
  - Medications: ones that inhibit heat-dissipating mechanisms (beta blockers, diuretics)

### Malignant hyperthermia

- Genetic alteration of ryanodine receptor 1 (RYR1) in the muscle cells
- Normally: cell depolarization → RYR1 activation → calcium release from sarcoplasmic reticulum into cytoplasm → muscle contraction
- In malignant hyperthermia: cell depolarization → RYR1 hyperactivation → excessive calcium release → **inappropriate muscle contraction**, ↑ metabolic rate → excessive heat production
- Triggered by drugs
  - Anesthetic gas: Isoflurane, Sevoflurane, Desflurane

- Depolarizing muscle relaxants: Succinylcholine, Decamethonium
- Potentially fatal
- Treatment
  - Dantrolene (skeletal muscle relaxant)

## HYPOTHERMIA

- Abnormally low temperature
  - Diagnosis: core temperature < 35°C/95°F
- Compensatory mechanisms responding to cold stress are overwhelmed
- ↓ core body temperature → ↓↓ metabolic rate → myocardial irritability, cold diuresis (↓ renal blood flow, water resorption)
  - Progressive oliguria as ↓ core temperature → ↓ intravascular volume, ↑ hematocrit, central nervous system depression

### Risk factors

- Prolonged cold exposure
  - E.g. inadequate clothing/shelter, cold water immersion
- Impaired thermoregulation
  - E.g. hypothalamic dysfunction, metabolic derangement
- ↑ heat loss
  - Multisystem trauma, shock, spinal cord transection
- Iatrogenic
  - Cold IV fluid administration, inadequate operating room warming
- ↑ risk populations
  - Older adults (↓ physiologic reserve, ↓ sensory perception, chronic medical conditions)
  - Children (↑ body surface area to body mass ratio, ↓ glycogen stores, young infants unable to use shivering thermogenesis)

### Complications

- Cardiac arrhythmias, myocardial infarction, pulmonary edema, pulmonary embolism, lactic acidosis, disseminated intravascular coagulation (DIC), coma, death

### Signs & symptoms

- Mild hypothermia
  - Core temperature 32–35°C/90–95°F

- Shivering, tachypnea, tachycardia, confusion
- Moderate hypothermia
  - Core temperature 28–32°C/82–90°F
  - ↓ shivering and muscle rigidity, hypoventilation, bradycardia, ↓ cardiac output, lethargy, arrhythmias, loss of pupillary reflexes
- Severe hypothermia
  - Core temperature < 28°C/82°F
  - Apnea, ↓ cardiac activity → ventricular arrhythmias → asystole, coma, loss of ocular reflexes, ↓↓ metabolic rate

#### Rewarming treatment

- Warmed blankets/forced warm-air system; heated, humidified oxygen; warmed crystalloid IV fluid; pleural, peritoneal lavage using warm saline solution; vasopressors
- Extracorporeal blood rewarming
  - Venovenous rewarming, hemodialysis, continuous arteriovenous rewarming (CAVR), cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO)



# NOTES

## CELLULAR STRUCTURES & PROCESSES

# CELLULAR STRUCTURE & FUNCTION

[osms.it/cellular-structure-and-function](https://osms.it/cellular-structure-and-function)

## CELL STRUCTURE BASICS

- Basic structural, biological, functional unit that comprise organism
- Smallest self-replicating life-form
- Over 200 types in human body
- Cells → tissue → organ → organ systems → organism

## Basic constituents

- Plasma membrane
- Cytoplasm
  - Fluid suspension
  - Composition: cytosol, organelles

## CYTOSOL

- Intracellular fluid
  - Composition: water; dissolved/ suspended organic, inorganic chemicals; macromolecules; pigments; organelles
- Site of most cellular activity

## ORGANELLES

- Specialized cellular subunits carry out essential functions

## Ribosomes

- Composition: rRNA, ribosomal proteins
- Can exist freely in cytoplasm/bound to endoplasmic reticulum (forms rough endoplasmic reticulum)
- Turns mRNA into protein via translation
- Organized into two subunits (40s, 60s)
  - Small subunit: binding sites for mRNA, tRNA

- Larger subunit: has ribozyme to catalyze peptide bond formation (for bonds between amino acids)

## Endoplasmic reticulum

- Membrane-enclosed organelle
- Appearance: stack of membranous, flattened disks (cisterns)
- Rough endoplasmic reticulum (RER)
  - Contains bound ribosomes on surface
  - Site of packaging, folding of proteins designated for secretion, lysosomal degradation, plasma membrane insertion; proteins packed into vesicles, sent to Golgi apparatus for further modification
  - RER cisterna continuous with nuclear envelope
- Smooth endoplasmic reticulum (SER)
  - No ribosomes
  - Site of lipid, steroid synthesis,  $\text{Ca}^{2+}$  ions storage (muscles), glycogen metabolism, detoxification (liver)

## Golgi apparatus (complex)

- Membrane-enclosed organelle
- Appearance: collection of fused, flattened sacs (cisterns) with associated vesicles, vacuoles
- Two sides
  - Cis side: receives proteins from RER (entry)
  - Trans side: opposite side, releases vesicles towards plasma membrane (exit)

- Post-translational modification site (e.g. phosphorylation, glycosylation, sulfonation) of proteins, lipids, hormones → sorted, packaged into secretory vesicles → secreted out of cell/lysosomal fusion/plasma membrane insertion

### Mitochondria

- Double membrane-enclosed organelle; synthesizes ATP for cell via aerobic respiration
  - Outer smooth membrane: encloses whole organelle
  - Inner membrane: forms folds, caverns called cristae (contain proteins needed for aerobic respiration); encloses mitochondrial matrix (contains mitochondrial DNA, ribosomes)
- Intermembrane space: space between inner, outer membrane
- In cytoplasm glucose undergoes glycolysis, glucose cleaved into pyruvate
  - Pyruvate enters mitochondria → citric acid cycle (Krebs cycle), electron transport chain (require oxygen)

- In glucose absence, mitochondria can use fatty acids as fuel via beta oxidation (only medium sized fatty acids used; longer ones chopped by peroxisome)
- Mitochondria number: correlates with cell activity/energy requirements

### Nucleus

- Large, membrane-enclosed organelle present in all cells except mature erythrocytes
- Contains genetic material (DNA, tightly packed into chromatin); coordinates cellular activities
- Most cells contain one nucleus; some cells have more (e.g. skeletal muscle cells, osteoclasts, hepatocytes)
- Usually spherical, may take on other shapes
  - Lobulated (e.g. polymorphonuclear leukocytes)
  - Elongated (e.g. columnar epithelium)

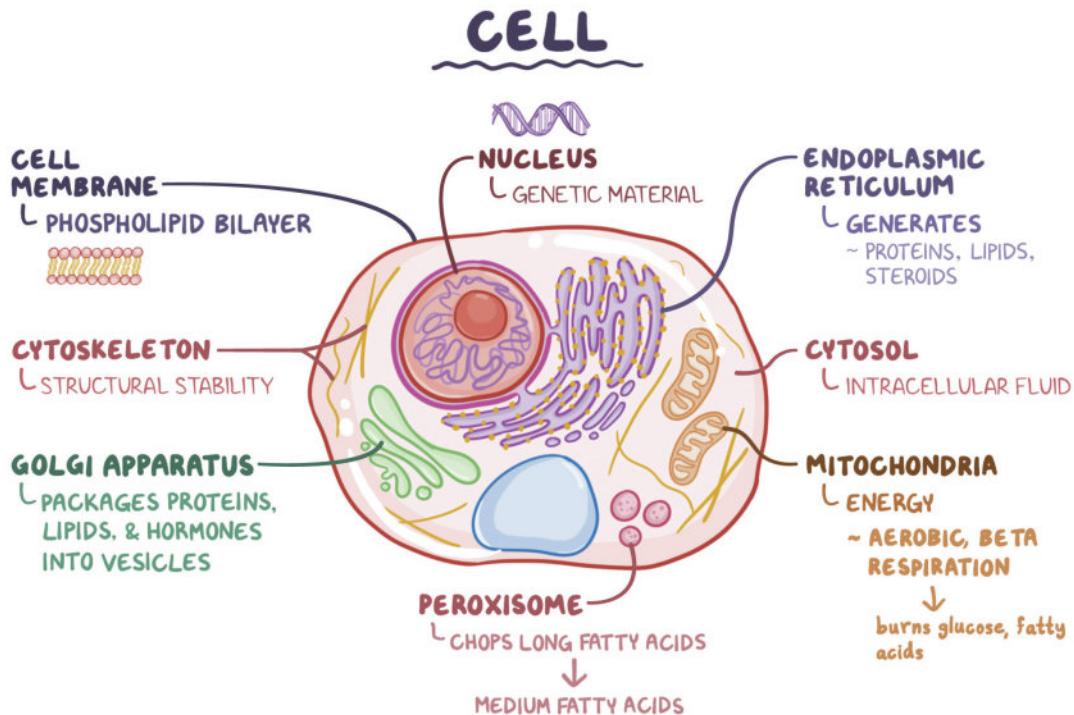


Figure 23.1 Cellular structures and their functions.

# CELL MEMBRANE

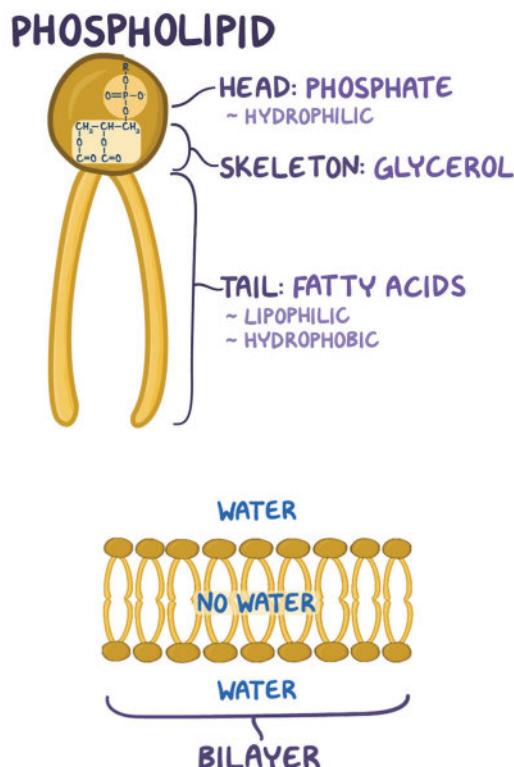
[osms.it/cell-membrane](https://osms.it/cell-membrane)

- Semipermeable membrane made from phospholipid bilayer; surrounds cell cytoplasm

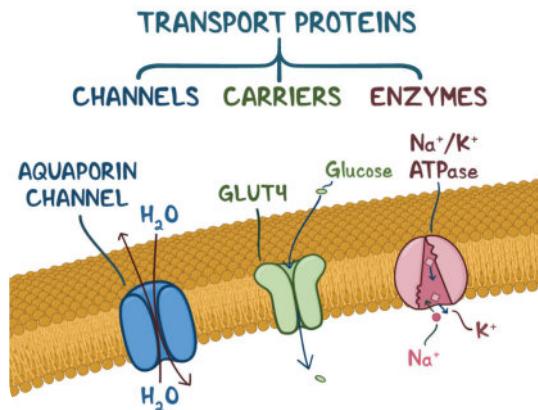
## Phospholipid bilayer

- Two-layered polar phospholipid molecules comprising two parts
  - Negatively charged phosphate "head" (hydrophilic; oriented outwards)
  - Fatty acid "tail" (hydrophobic; oriented inwards)

- Semipermeable
  - Allows passage of certain molecules through membrane ( $O_2$ ,  $CO_2$ , etc.)
  - Denies passage of others (large molecules such as proteins, glucose)
- Certain molecule transportation (ions,  $H_2O$ ) allowed through embedded membrane proteins (ion channels, pumps)



**Figure 23.2** Phospholipid parts and their arrangement in a cell membrane.



**Figure 23.3** Transport proteins move molecules that can't freely diffuse across the cell membrane. Channels form a tunnel through which water and ions flow. Carriers have a binding site for a specific molecule and gates at both ends that open sequentially. Enzymes, or ATPases, actively pump ions in/out of the cell against their concentration gradients.

# SELECTIVE PERMEABILITY OF THE CELL MEMBRANE

[osms.it/cell-membrane-selective-permeability](https://osms.it/cell-membrane-selective-permeability)

- Cell membrane controls which molecules enter, leave
  - Passive transport: no energy required
  - Active transport: energy required → adenosine triphosphate (ATP)

## PASSIVE TRANSPORT

### Simple diffusion

- Random molecular motion
- Small, nonpolar molecules move from ↑ concentration → ↓ concentration

### Fick's law

- Three factors affect diffusive flux
- Concentration gradient
  - Larger differences in solute concentration on each side of membrane → ↑ driving force → ↑ net diffusion
  - Equal concentrations → no net diffusion (e.g. CO<sub>2</sub>, O<sub>2</sub> movement between alveoli, blood)
- Membrane surface area
  - ↑ surface area available for diffusion → ↑ diffusion rate; vice versa (e.g. microvilli in small intestines amplify surface area → ↑ nutrient, water absorption)
- Distance separating each side of membrane (e.g. thickness)
  - ↑ distance molecules must travel → ↓ net diffusion; vice versa (e.g. pulmonary edema → ↑ distance between compartments → ↓ net diffusion)

### Facilitated diffusion

- Uses transport proteins (e.g. channels, carrier proteins)
- Allows larger/polar molecules to move across membrane

### Channels

- Non-specific; open to allow water, small polar molecules through (e.g. voltage-gated calcium channel)

### Carrier proteins

- Very specific, only allow certain molecules to bind (e.g. glucose transporter protein GLUT4)

## ACTIVE TRANSPORT

### Primary

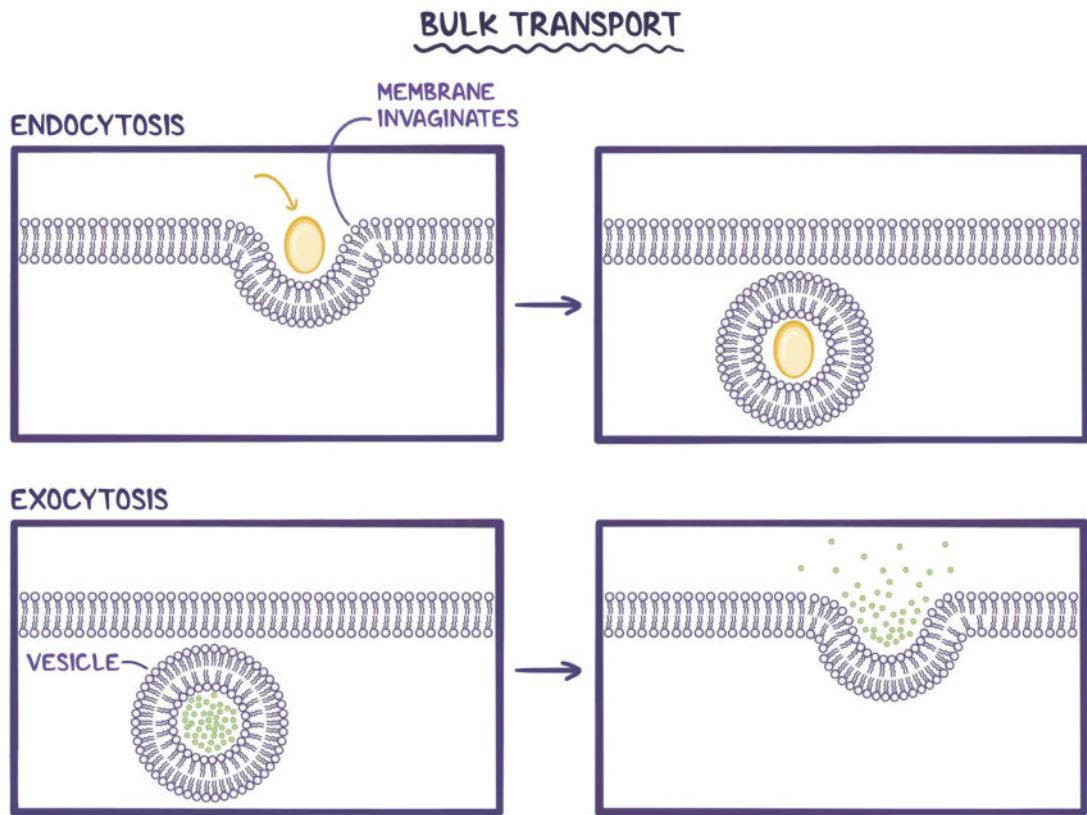
- Uses ATP
  - Enzymes called ATPases use ATP as fuel; (e.g. Na<sup>+</sup>-K<sup>+</sup> ATPase, Ca<sup>2+</sup> ATPase, H<sup>+</sup>-K<sup>+</sup> ATPase)
  - May create concentration/electrochemical gradients

### Secondary

- Uses existing electrochemical gradients
  - One solute, normally Na<sup>+</sup>, moves with concentration gradient through transporter → supplies energy transporter needs to → another solute against concentration gradient in same/opposite direction as Na<sup>+</sup> (e.g. sodium-glucose SGLT1 transporter)

### Bulk transport

- AKA vesicular transport
- Endocytosis
  - Cell membrane invaginates, pulling something in from outside (e.g. pathogen phagocytosis)
- Exocytosis
  - Vesicle inside cell pushes something out (e.g. hormone secretion)



**Figure 23.4** Endocytosis and exocytosis.

## EXTRACELLULAR MATRIX

[osms.it/extracellular-matrix](https://osms.it/extracellular-matrix)

- Environment surrounding cells
- Varies between tissues (epithelial, connective, muscular, and nervous)

### THREE MAJOR MOLECULES

#### Adhesive proteins

- Adhere cells together (communication with extracellular fluid)
  - E.g. integrins, cadherins

#### Structural proteins

- Give tissues tensile, compressive strength
- Collagen
  - Resists tension, can stretch

- Starts as procollagen → cleaved into tropocollagen → arranged into collagen fibrils

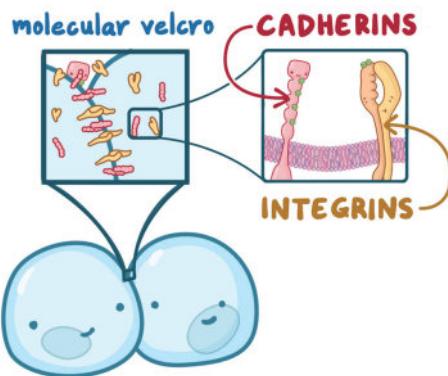
- Four types: type I (bone, skin, tendon), type II (cartilage), type III (reticulin, blood vessels), type IV (basement membrane)

- Elastin
  - Elastic, returns tissue to original shape
- Keratin
  - Tough, found in hair, nails

#### Proteoglycans

- Fill space between cells, hydrate, cushion cells
  - Consists of protein core with sugar chains

## ADHESIVE PROTEINS



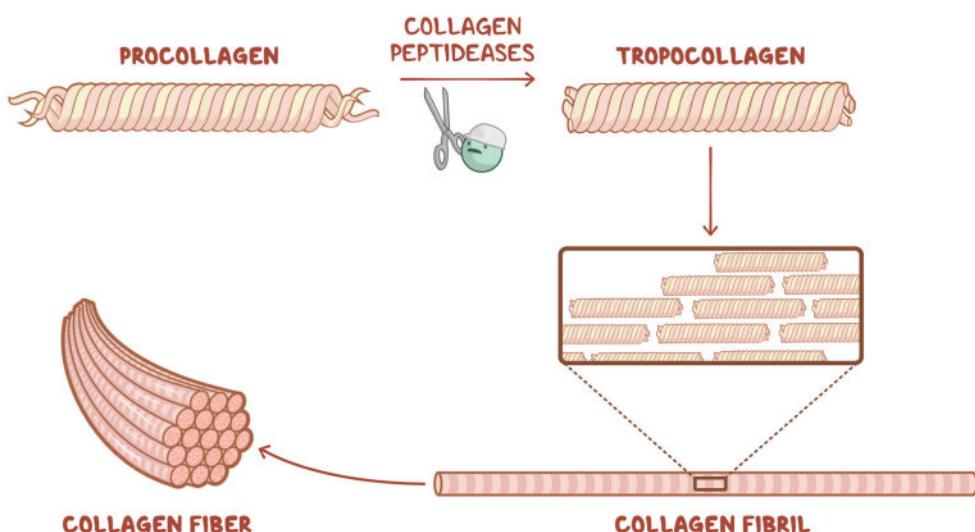
**Figure 23.5** Cadherins and integrins are both adhesive proteins which hold cells together.

## STRUCTURAL/FIBROUS PROTEINS



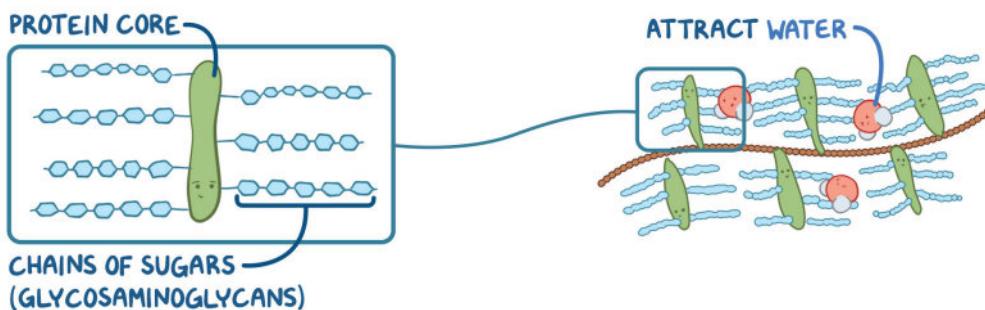
**Figure 23.6** The three kinds of structural proteins in the extracellular matrix and their functions.

## COLLAGEN



**Figure 23.7** Collagen production steps.

## PROTEOGLYCANS



**Figure 23.8** Structure of proteoglycans, which hydrate and cushion cells.

# CELL-CELL JUNCTIONS

[osms.it/cell-cell\\_junctions](https://osms.it/cell-cell_junctions)

- Protein structures that physically connect cells
- Improve cellular communication, tissue structure; allow transport of some substances between cells, create impermeable barrier for others
- Only found between immobile cells; abundant in epithelial tissue (e.g. in skin)

## THREE JUNCTION TYPES

### Tight junctions

- E.g. in gastrointestinal tract/brain
- Seal adjacent-cell plasma membranes, especially near apical surface; prevent passage of water, small proteins, bacteria
  - Formed by claudins, occludins embedded in cellular plasma membranes
  - In “leaky” epithelia, tight junctions may allow certain molecules to pass (e.g. K<sup>+</sup>, Na<sup>+</sup>, Cl<sup>-</sup> in kidney’s proximal tubules—due to ion pores)

### Adherens junctions

- E.g. in skin
- Anchor cells together, provide strength; consist of three major components
  - **Actin filaments**: provide cellular shape
  - **Protein plaques**: anchor membrane, bind to actin filaments
  - **Cadherins**: attach to protein plaques, connect to cadherins on other cells

### Gap junctions

- E.g. in heart
- Connect adjacent cells, allow rapid communication; formed by connexins → create tubular structure (allows charged particles to pass)
  - **In cardiac myocytes**: gap junctions create coordinated heart contractions
  - **In infected cells**: gap junctions send cytokines to neighboring cells, triggering apoptosis, preventing infectious spread (“bystander effect”)

## CELL-CELL JUNCTIONS

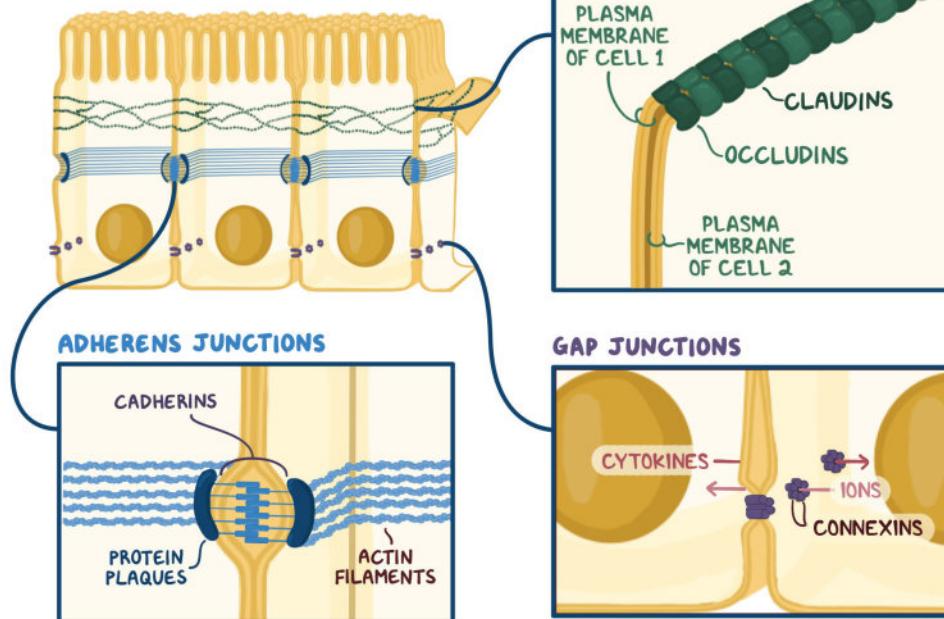


Figure 23.9 The three types of cell junctions.

# ENDOCYTOSIS & EXOCYTOSIS

[osms.it/endocytosis-and-exocytosis](https://osms.it/endocytosis-and-exocytosis)

- Transports material in/out of cell
- Requires adenosine triphosphate (ATP) for energy

## ENDOCYTOSIS

- Cells engulf extracellular material

## PHAGOCYTOSIS

- AKA cell eating
- Used by white blood cells (e.g. macrophages, neutrophils)

### Process

- Cell extends arm-like projects (AKA pseudopods) around target
- Cell membrane slowly engulfs target, invaginates to form vesicle
- Vesicle separates from cell membrane to form phagosome
- Phagosome fuses with lysosome, target is digested
- Debris released by exocytosis

## PINOCYTOSIS

- AKA cell drinking
- Used by most cells to take in extracellular fluid; non-specific

### Process

- Cell membrane invaginates around extracellular fluid
- Edges of invagination come together to form vesicle
- Motor proteins use ATP to carry vesicle into cytosol

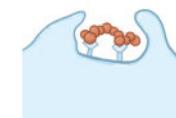
## RECEPTOR-MEDIATED ENDOCYTOSIS

- Used by cells to take in specific molecules (e.g. iron, cholesterol)

### Process

- Clathrin-covered pits/coated pits with receptors bind certain molecules

- Edges of pit come together, clathrin proteins link up
- Vesicle pinches off; clathrin detaches, returns to cell membrane
- Vesicle merges with endosome to separate receptors into second vesicle



PHAGOCYTOSIS



PINOCYTOSIS



RECEPTOR-MEDIATED ENDOCYTOSIS

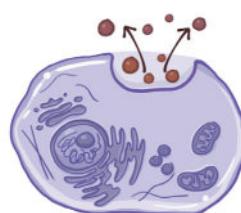
**Figure 23.10** The three types of endocytosis.

## EXOCYTOSIS

- Cells expel material into extracellular space (e.g. neurotransmitters, hormones)
- Last phagocytosis step

### Process

- Golgi apparatus creates vesicle from various proteins, lipids, hormones
- Motor proteins use ATP to carry vesicle along cytoskeleton
- Vesicle is pressed against cell membrane until rupture → spills contents into extracellular space



**Figure 23.11** Exocytosis: expulsion of material into extracellular space.

# OSMOSIS

osms.it/osmosis

- Passive water-flow across selectively permeable (semipermeable) cellular membrane; primarily determined by solute concentration differences (osmotic pressure)

## Factors affecting water movement across membrane

- Molecules (e.g. water molecules, ions) tend to move around (kinetic energy) + movement is disordered, random (entropy)  
→ larger solutes tend to block openings in semipermeable membrane
- If solute ions positively charged, they attract slightly negatively charged oxygen atom in water molecule; if solute ions are negatively charged, they attract slightly positively charged hydrogen atoms in water molecule  
→ water molecules partially attached to ion  
→ movement through membrane impeded
- Water molecules tend to move from hypotonic side (more water/less solutes) to hypertonic side (less water/more solutes)

## SELECTIVELY-PERMEABLE MEMBRANE

- Allows small molecules (e.g. water) across, but not larger molecules/ions

## Isotonic solution

- Side A = side B
- If solute concentration is same on each side of membrane → net water movement across membrane is zero (equilibrium)

## Hypertonic/hypotonic solution

- Side A > side B or side B > side A
- If solute concentration is greater on one side (hypertonic) → net water migration across membrane is from hypotonic side toward hypertonic side

## CELLULAR EFFECT

- Red blood cell in hypertonic solution → net movement of water molecules out of cell → cell shrinks (crenation)
- Red blood cell in hypotonic solution → net movement of water molecules into cell → cell swells, may burst (lyses)

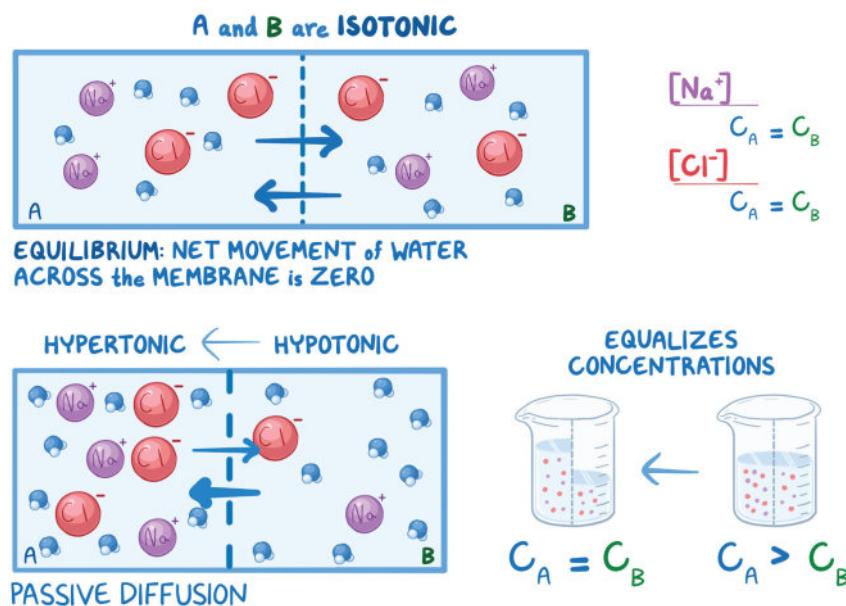


Figure 23.12 Net water molecule movement between isotonic, hyper/hypotonic solutions.

# RESTING MEMBRANE POTENTIAL

[osms.it/resting-membrane-potential](https://osms.it/resting-membrane-potential)

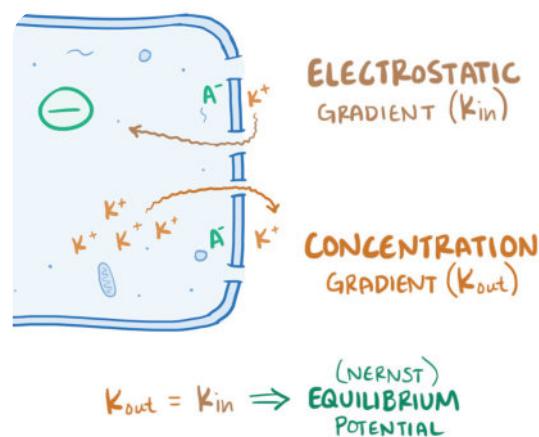
- Electric potential across cell membrane
  - Given by weighted (based on membrane permeability) sum of equilibrium potentials for all ions
- High concentrations of  $\text{Na}^+$ ,  $\text{Cl}^-$ ,  $\text{Ca}^{2+}$  outside cell; high concentrations of  $\text{K}^+$ ,  $\text{A}^-$  (various anions) inside cell → concentration gradients are established
  - Sodium-potassium pump uses ATP to move two K ions into cell, three Na ions out
  - Potassium concentration = 150mMol/L inside cell, 5mMol/L outside
- Concentration gradients establish electrostatic gradients
  - Concentration gradient pushes potassium out through potassium leak channels, inward rectifier channels
  - Anions remain in cell → negative charge builds up → potassium is pulled back into cell
- Equilibrium (Nernst) potential: electrostatic gradient equal to concentration gradient (-92mV for potassium)
- Nernst equation: equilibrium potential for an ion
  - Single charge:  $V_m = 61.5 \times \log\left(\frac{[\text{ION}]_{\text{out}}}{[\text{ION}]_{\text{in}}}\right)$

$$V_m = 30.75 \times \log\left(\frac{[\text{ION}]_{\text{out}}}{[\text{ION}]_{\text{in}}}\right)$$

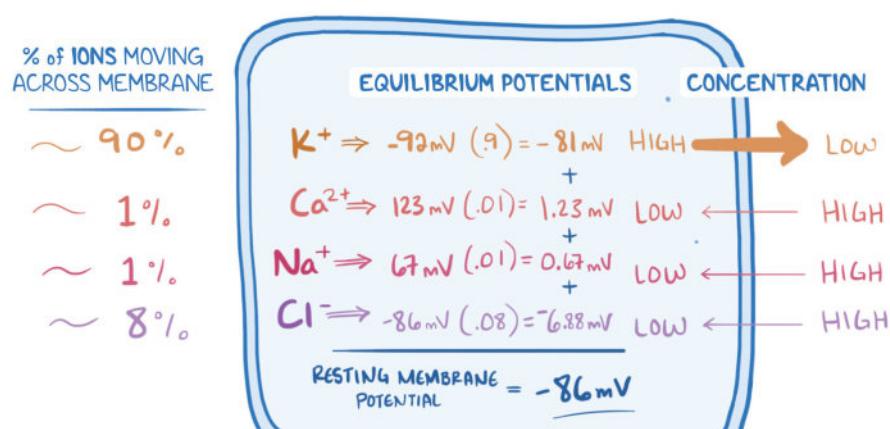
▫ Double charge:

▫ Value is flipped for negative ions

- Resting membrane potential is sum of equilibrium potentials of major ions multiplied by their membrane permeabilities



**Figure 23.13** Equilibrium potential = electric potential for attracting  $\text{K}^+$  back into the cell that's needed to balance the concentration gradient pushing  $\text{K}^+$  out of the cell.



**Figure 23.14** The resting membrane potential is closest to the equilibrium potential of the most permeable ion ( $\text{K}^+$ ). Change in permeability → change in resting membrane potential.

# CELL SIGNALING PATHWAYS

[osms.it/cell-signaling-pathways](http://osms.it/cell-signaling-pathways)

## INTRACELLULAR SIGNAL CLASSIFICATION

- Classified according to distance between signaling, target cells
  - Autocrine: cell signals nearby cells of same type, including itself (e.g. monocytes secrete interleukin-1  $\beta$ )
  - Paracrine: cell signals nearby cells of different type (e.g. ECL cells secrete histamine → signals D cells to secrete somatostatin)
  - Endocrine: cell signals distant cells (e.g. pituitary gland secretes TSH → signals thyroid gland)
- Signalling molecules (ligands) bind to receptors; can be hydrophobic/hydrophilic
  - Hydrophobic: can't float in extracellular space → brought to target cells by hydrophilic carrier proteins; can diffuse over cell membranes → bind to receptors inside cell
  - Hydrophilic: can float in extracellular space → reach target cells themselves; can't diffuse over cell membranes → bind to cell surface (transmembrane) receptors

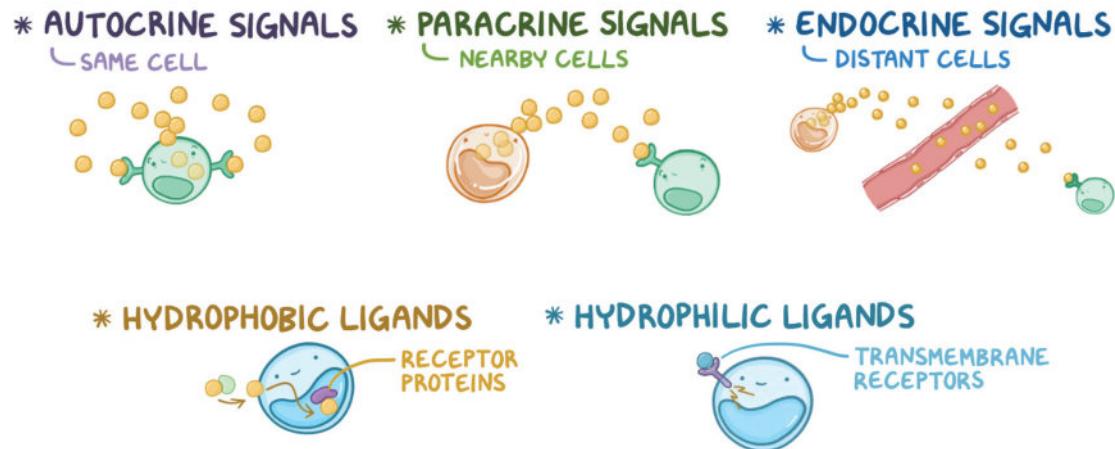
## Cell signalling pathway stages

1. Reception: ligand binds to receptor
2. Transduction: receptor changes activating intracellular molecules
3. Response: signal triggers a response in the target cell

## MAJOR TRANSMEMBRANE RECEPTOR CLASSES

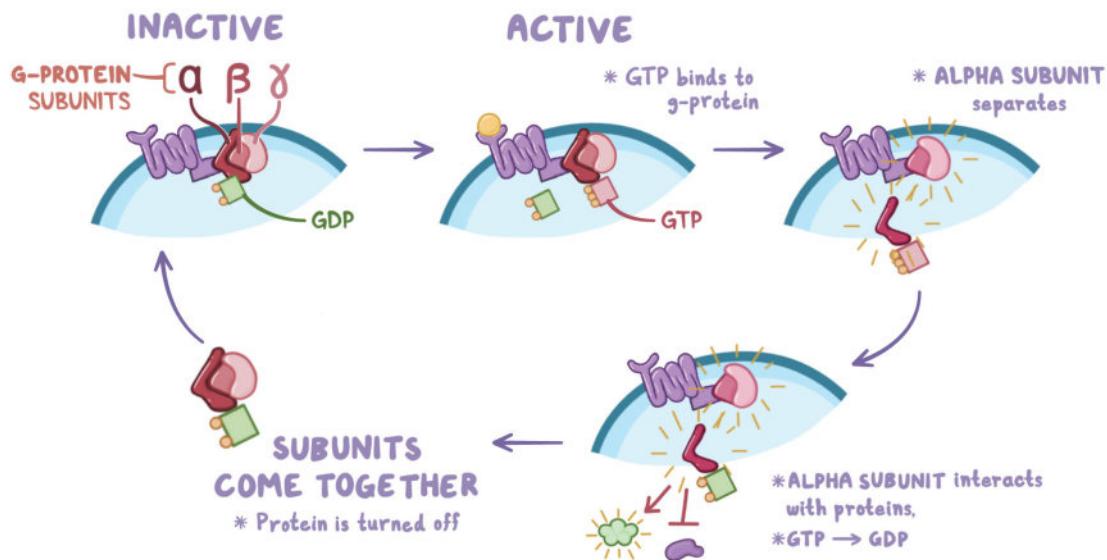
### G protein-coupled receptors

- Seven-pass transmembrane receptors
- Activate guanine nucleotide-binding (G) proteins inside cell
  - G proteins have three subunits: alpha, beta, gamma
  - Alpha binds guanosine diphosphate (GDP) when inactive
  - When ligand binds, alpha releases GDP, binds guanosine triphosphate (GTP) instead → alpha separates from beta, gamma → alpha interacts with proteins turning GTP back into GDP → reattaches



**Figure 23.15** Autocrine, paracrine, and endocrine signals refer to signal distance from its target cell. Hydrophobic and hydrophilic ligands refer to the affinity of the ligand for water.

## I. G-PROTEIN COUPLED RECEPTORS



**Figure 23.16** Mechanism of action of G-protein coupled receptors.

- Three types of G protein with different pathways
  - $G_q$ : activates phospholipase C in cell membrane → phospholipase C cleaves phosphatidylinositol 4,5-bisphosphate into inositol trisphosphate, diacylglycerol → inositol trisphosphate opens calcium channels in endoplasmic reticulum (calcium flows to cytoplasm, changing electrical charge distribution in cell → cell depolarization); diacylglycerol binds to protein kinase C which phosphorylates target proteins
  - $G_s$ : stimulates adenylate cyclase → adenylate cyclase removes phosphate from adenosine triphosphate (ATP) creating cyclic adenosine monophosphate (cAMP) → cAMP binds to regulatory subunit of protein kinase A → catalytic subunit of protein kinase A phosphorylates target proteins
  - $G_i$ : inhibits adenylate cyclase → negative feedback on  $G_s$

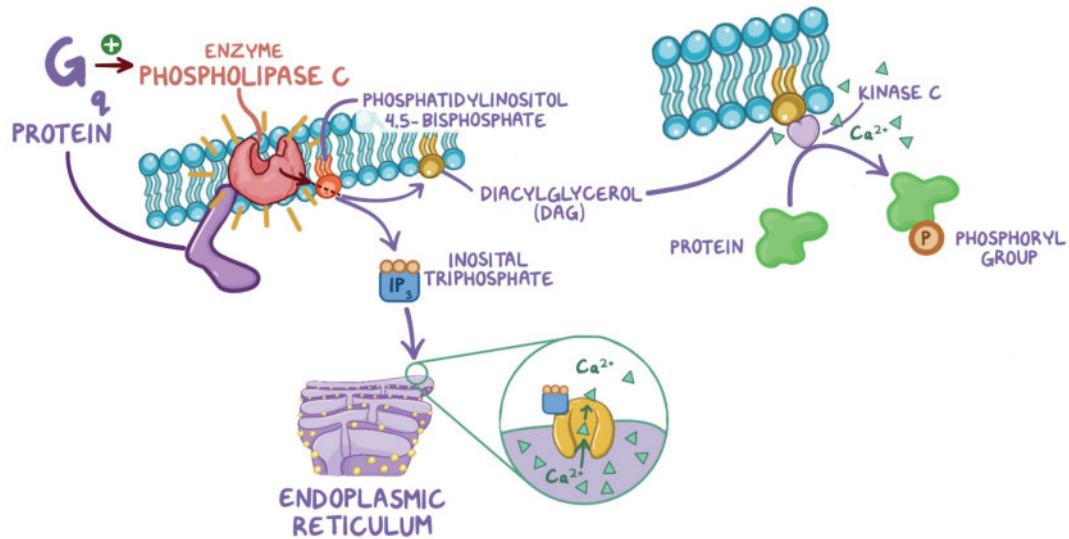
### Enzyme-coupled receptors

- Single-pass transmembrane receptors
- Trigger enzymatic activity inside cell when specific ligands bind

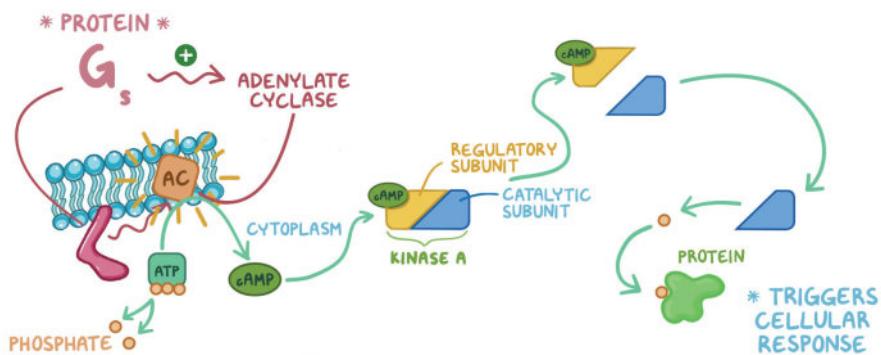
- Composition: extracellular, ligand-binding domain; intracellular, enzymatic domain
- Three main enzyme-coupled receptor types
  - Receptor tyrosine kinases: when ligand binds, these phosphorylate their own tyrosine residues → conformational change creates binding site for other signalling proteins
  - Tyrosine kinase associated receptors: when ligand binds, these phosphorylate various proteins to relay signal to tyrosine kinases inside cell
  - Receptor serine/threonine kinases: when ligand binds, type II receptors of this kind phosphorylate type I receptors, which in turn phosphorylate various proteins to relay signal to serine/threonine kinase domain inside cell

### Ion channel receptors

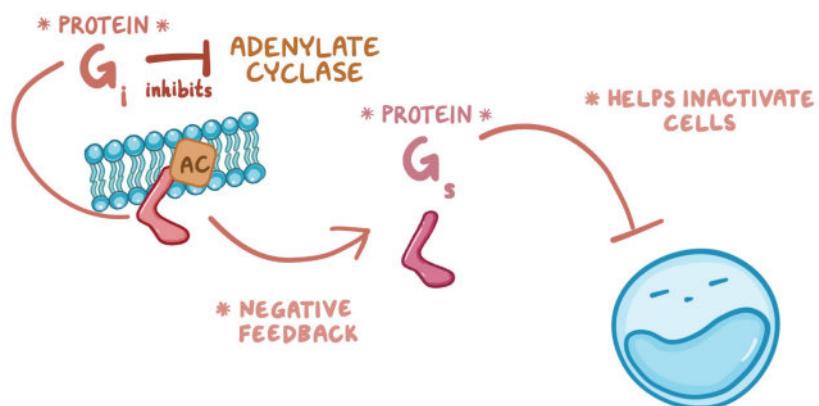
- Ion channels which open when specific ligands bind
- Allow ions (e.g. chloride, calcium, sodium, potassium) to flow through
- Resulting shift in electric charge distribution triggers response



**Figure 23.17** G<sub>q</sub> pathway.



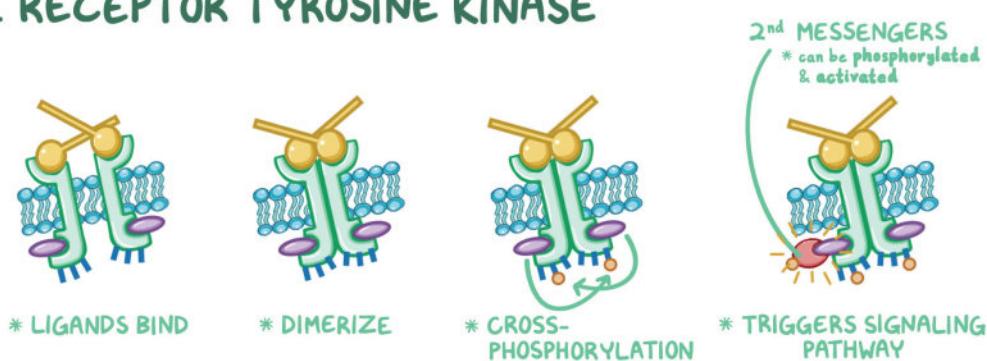
**Figure 23.18** G<sub>s</sub> pathway.



**Figure 23.19** G<sub>i</sub> pathway.

## II. ENZYME-COUPLED RECEPTORS

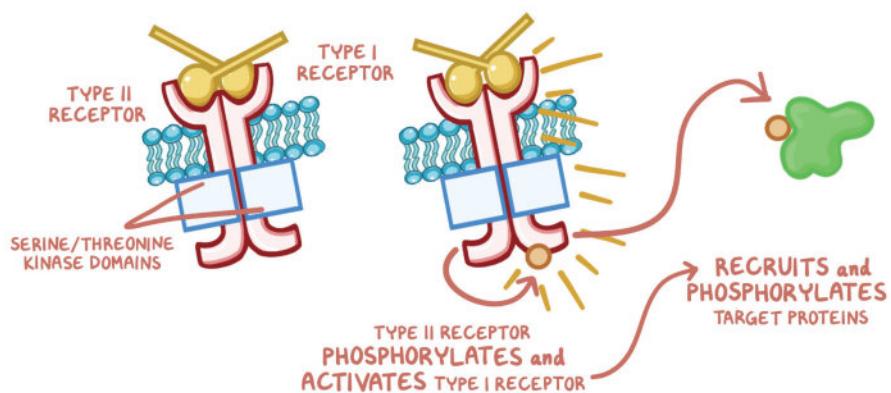
### 1. RECEPTOR TYROSINE KINASE



### 2. TYROSINE KINASE ASSOCIATED RECEPTORS

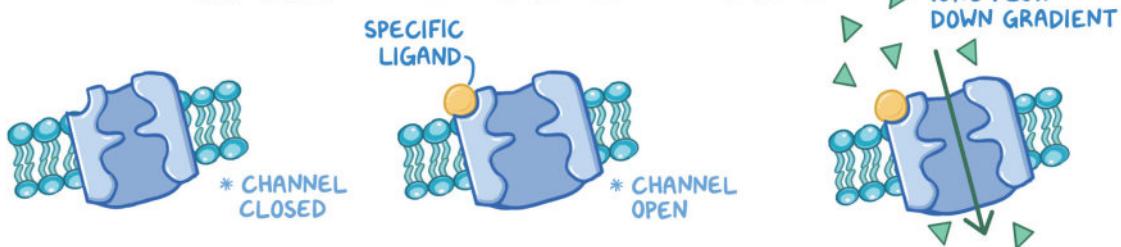


### 3. RECEPTOR SERINE/THREONINE KINASE



**Figure 23.20** Types of enzyme-coupled receptors and their pathways.

## III. ION CHANNEL RECEPTORS



**Figure 23.21** Mechanism of action for ion channel receptors.

## HORMONAL MECHANISMS

- All cells receive, process outside signals via specific proteins (receptors)
  - Ligand (signalling molecule—e.g. hormone) binds to receptor → physiological response
- Target tissue sensitivity to hormone effect controlled by receptor quantity/affinity
  - ↑ receptor quantity → ↑ maximal response
  - ↑ receptor affinity → ↑ response likelihood

▪ Second messengers: intracellular signalling molecules released by cells → triggers physiological changes in response to hormone/ligand–receptor interaction

- **Include:** cyclic AMP (cAMP), cyclic GMP (cGMP), inositol trisphosphate (IP<sub>3</sub>), diacylglycerol (DAG), Ca<sup>2+</sup>

- **Involved in cellular processes:** proliferation, differentiation, migration, survival, apoptosis

## G PROTEINS

- Membrane-bound proteins: act as molecular switches, couple hormone receptors to effector enzymes
- Heterotrimeric proteins → three subunits → alpha ( $\alpha$ ), beta ( $\beta$ ), gamma ( $\gamma$ )
- Can be stimulatory (Gs)/inhibitory (Gi)
  - Activity determined by  $\alpha$  subunit ( $\alpha s/\alpha i$ ), that contains GTPase activity

### Binding

- $\alpha$  subunit binds guanosine diphosphate (GDP)/triphosphate (GTP)
  - GDP binding → inactive state
  - GTP binding → active state → coupling
  - Guanosine nucleotide-releasing factors (GRFs) facilitate GDP dissociation
  - GTPase-activating factors (GAPs) facilitate GTP hydrolysis
- GRFs, GAPs relative activity
  - ↑ G protein activation rate
- Final signal transduction occurs via cyclic adenosine monophosphate (cAMP) signal pathway/phosphatidylinositol signal pathway

## ADENYLYL CYCLASE MECHANISM

- Hormones acting via cAMP mechanism: adrenocorticotrophic hormone, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, antidiuretic hormone (V2 receptor), human chorionic gonadotropin, melanocyte-stimulating hormone, corticotropin-releasing hormone, calcitonin, parathyroid hormone, glucagon
- Hormone binds to receptor coupled to Gs/Gi protein → adenylyl cyclase activation/inhibition → intracellular cAMP ↑/↓
- Stimulatory receptor events
  - Hormone binds to receptor →

## SECOND MESSENGER SYSTEMS

- Primary extracellular signalling molecules often hydrophilic → cannot cross cell membrane → second messenger system carries, amplifies signal across cell membrane

- conformational change in  $\alpha_s$  subunit  $\rightarrow$   $\alpha_s$  subunit releases GDP  $\rightarrow$  replacement by GTP  $\rightarrow$   $\alpha_s$  subunit detaches from Gs protein
- $\square$   $\alpha_s$  subunit-GTP complex migrates within cellular membrane  $\rightarrow$  binds  $\rightarrow$  activates adenylyl cyclase
  - $\square$  Activated adenylyl cyclase catalyzes adenosine triphosphate (ATP)  $\rightarrow$  ↑ cAMP (second messenger)
  - $\square$  Intrinsic GTPase activity in G protein  $\rightarrow$  GTP converts  $\rightarrow$  GDP  $\rightarrow$   $\alpha_s$  subunit inactive again
  - cAMP acts as second messenger  $\rightarrow$  hormonal signal amplification  $\rightarrow$  final physiological reaction
  - Intracellular cAMP  $\rightarrow$  protein kinase A activation  $\rightarrow$  intracellular protein phosphorylation  $\rightarrow$  physiological response
  - Phosphodiesterase degrades intracellular cAMP  $\rightarrow$  5' adenosine monophosphate (inactive metabolite)  $\rightarrow$  hormonal response cessation

## PHOSPHOLIPASE C MECHANISM

- Hormones acting via phospholipase C mechanism: gonadotropin-releasing hormone, thyrotropin-releasing hormone, growth hormone-releasing hormone, angiotensin II, antidiuretic hormone (V1 receptor), oxytocin
- Receptor Gq phospholipase C complex: embedded in cell membrane
- In neutral state (no bound hormone)  $\alpha_q$  subunit binds GDP  $\rightarrow$  inactive Gq protein
- Hormone binding  $\rightarrow$  GDP release from  $\alpha_q$  subunit  $\rightarrow$  GTP binding  $\rightarrow$   $\alpha_q$  subunit detaches from Gq protein
  - $\square$   $\alpha_q$ -GTP complex migrates within cell membrane  $\rightarrow$  activates phospholipase C  $\rightarrow$  DAG, IP3 released from phosphatidylinositol 4,5-diphosphate (PIP2)
  - $\square$  IP3  $\rightarrow$   $\text{Ca}^{2+}$  intracellular stores released (from endoplasmic/sarcoplasmic reticulum)
  - $\square$  DAG, IP3  $\rightarrow$  activate protein kinase C  $\rightarrow$  protein phosphorylation  $\rightarrow$  physiological response

## STEROID HORMONE MECHANISM

- Hormones acting via steroid hormone mechanism: glucocorticoids, estrogens, progesterone, testosterone, aldosterone, 1,25-dihydroxycholecalciferol, thyroid hormone
- No cell membrane-mediated transduction step
  - $\square$  Steroid hormone diffuses across cell membrane  $\rightarrow$  binds to cytosolic (or nuclear) receptor proteins (monomeric phosphoproteins)  $\rightarrow$  DNA transcription, protein synthesis initiated
- Receptor proteins
  - $\square$  Part of intracellular receptor gene superfamily
  - $\square$  Each receptor protein has six domains (A–F)
  - $\square$  Steroid hormone binds E domain near C terminus (central C domain binds to DNA via zinc fingers)
- Steroid-receptor protein complex  $\rightarrow$  conformational change in receptor protein  $\rightarrow$  activation  $\rightarrow$  enters nucleus
- Hormone-receptor complex combines with similar hormone-receptor complex (dimerization)
- New complex binds at C-domain via zinc fingers to specific DNA sequences (steroid-responsive elements), located in target genes' 5' region
- DNA-bound active hormone-receptor complex acts as transcription factor for specific genes  $\rightarrow$  messenger RNA (mRNA) transcription
- mRNA leaves nucleus  $\rightarrow$  translated into new protein with physiological action specific to original hormone

## TYROSINE KINASE MECHANISM

- Hormones acting via tyrosine kinase mechanism: insulin, insulin-like growth factor 1, growth hormone, prolactin
- Primary mechanism: tyrosine kinases phosphorylates protein tyrosine residues
- Two main categories
  - $\square$  Receptor tyrosine kinases  $\rightarrow$  intrinsic kinase activity within receptor

- Tyrosine kinase-associated receptors → no intrinsic kinase activity, associated noncovalently with proteins without kinase activity

### Receptor tyrosine kinases (RTKs)

- Three structural domains
  - **Extracellular binding domain:** binds hormone
  - **Hydrophobic transmembrane domain:** membrane anchor
  - **Intracellular domain:** tyrosine kinase activity
- Hormone binding → activation
  - Activation → phosphorylates itself, other proteins
- Monomer-type RTKs
  - E.g. epidermal growth factor receptors, nerve growth factor
  - Hormone binding to extracellular domain → receptor dimerization → intrinsic tyrosine kinase activation → tyrosine moieties phosphorylation of itself, other proteins → physiological response
- Dimer-type RTKs
  - E.g. insulin, insulin-like growth factor receptors
  - Hormone binding → intrinsic tyrosine kinase activation → tyrosine moieties phosphorylation of itself, other proteins → physiological response

### Tyrosine kinase-associated receptors

- E.g. growth hormone
- Three structural domains
  - **Extracellular binding domain:** binds hormone
  - **Hydrophobic transmembrane domain:** membrane anchor
  - **Intracellular domain:** no tyrosine kinase activity; non-covalently associated with tyrosine kinase (e.g. Janus kinase family)
- Hormone binds to extracellular domain → receptor dimerization → associated protein's tyrosine kinase activated → tyrosine moieties phosphorylation of associated protein, hormone receptor, other proteins

## GUANYLYL CYCLASE MECHANISM

- Hormones acting via guanylyl cyclase mechanism include: atrial natriuretic peptide, nitric oxide (NO)
- Extracellular receptor domain binds ligand; intracellular domain has guanylyl cyclase activity
- Ligand binding → guanylyl cyclase activation → GTP to cGMP conversion
- cGMP activates cGMP-dependent kinase → protein phosphorylation (proteins responsible for physiological response)

### Intracellular forms (e.g. NO receptor)

- Cytosolic guanylyl cyclase mediates signal conversion
- NO synthase cleaves arginine (in vascular endothelial cells) → citrulline, NO
- NO diffuses from endothelial cells into adjacent vascular smooth muscle → binds, activates soluble (cytosolic) guanylyl cyclase → GTP conversion → cGMP → smooth muscle relaxation

## SERINE/THREONINE KINASE MECHANISM

- Involved in cell proliferation regulation, apoptosis, cell differentiation, embryonic development
- G protein-linked receptors → adenylyl cyclase, phospholipase C-linked mechanism
- Hormone binding → protein kinase activation → serine, threonine moieties phosphorylation → physiological response
  - $\text{Ca}^{2+}$ -calmodulin-dependent protein kinase (CaMK), mitogen-activated protein kinases (MAPKs) phosphorylate serine, threonine in subsequent reaction cascade

# CYTOSKELETON & INTRACELLULAR MOTILITY

[osms.it/cytoskeleton-and-intracellular-motility](https://osms.it/cytoskeleton-and-intracellular-motility)

- Non-membrane-bound organelles comprising complex protein filament network
- Provide structural stability, shape, organization, intracytoplasmic motility, cell motility

## TYPES

### Microfilaments

- **Actin filaments:** approx. 7nm
- Dynamic structures made of actin monomers
  - Arranged in long twisting chain
- Form network just below cell membrane
- Functions
  - **Muscle contraction:** slide closer together, further apart
  - **Diapedesis:** create pseudopodia for white blood cells (like neutrophils)
  - **Cell division:** allows cell to pinch-off, divide into two cells during mitosis
  - **Microvilli function**
  - Mechanical cell membrane support

### Microtubules

- Approx. 25nm
- Dynamic structures made of alternating proteins
  - $\alpha$ - and  $\beta$ -tubulins; polymerize to form microtubules
- Stretch across cell
- Functions
  - **Intracellular transport** (e.g. vesicle movement, melanin transport within pigmented cells)
  - Structural integrity
  - Cell division (form mitotic spindle)
  - Cilia, flagella structural components

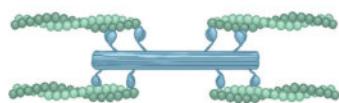
### Intermediate filaments

- Approx. 8–10nm
- Static structures made of various fibrous proteins (e.g. keratin, desmin, vimentin) depending on cell type
- Rope-like structure; forms branching network
- Functions
  - Organelle, cell-cell anchoring
  - Play key role in providing structural integrity, cell shape

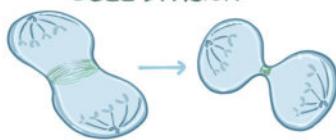
# CYTOSKELETON

## ACTIN FILAMENTS

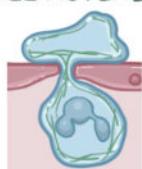
MUSCLE CONTRACTION



CELL DIVISION



CELL MOVEMENT



## INTERMEDIATE FILAMENTS

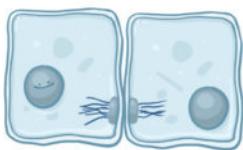


STRENGTH to CELL STRUCTURE

FASTEN ORGANELLES



ANCHOR CELLS to CELLS



ANCHOR CELLS to ENVIRONMENT



## MICROTUBULES

OVERALL SHAPE



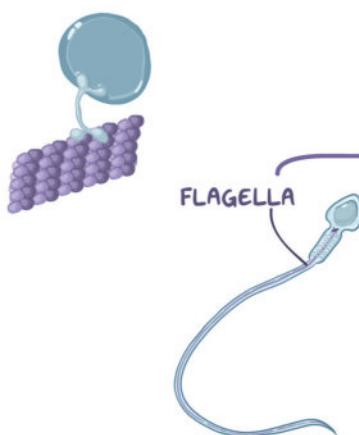
PROTOFILAMENTS



x13 →



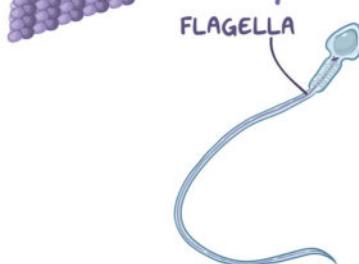
TRANSPORTATION of VESICLES



CENTRIOLES

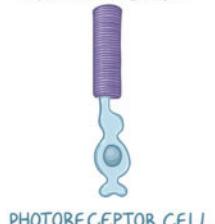


FLAGELLA



CILIA

NON-MOTILE/ PRIMARY CILIA



MOTILE/ SECONDARY CILIA

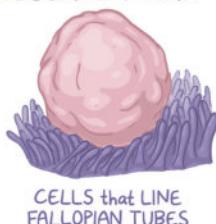


Figure 23.22 Cytoskeleton components and their functions.

# NUCLEAR STRUCTURE

[osms.it/nuclear-structure](https://osms.it/nuclear-structure)

## NUCLEAR ENVELOPE

- Encloses, separates nucleus from cytoplasm
- Composed of selectively permeable membrane phospholipid bilayer

### Nuclear pores

- Form where membranes fuse together at various intervals
- Each pore lined with nuclear pore complex (nucleoporin) to facilitate communication between nucleus, cytoplasm
- Allow bidirectional macromolecule movement

### Outer membrane

- Anchoring proteins that hold nucleus in place within cytoplasm
- Continuous with RER

### Inner membrane

- Covered by nuclear lamina
- Thin filamentous protein network, creates web within nucleus; provide support for chromatin

## NUCLEOLUS

- Dense non-membrane-bound structure; some cells have more than one nucleolus
- Contains rDNA → transcribed into rRNA
- Assembles ribosomal subunits

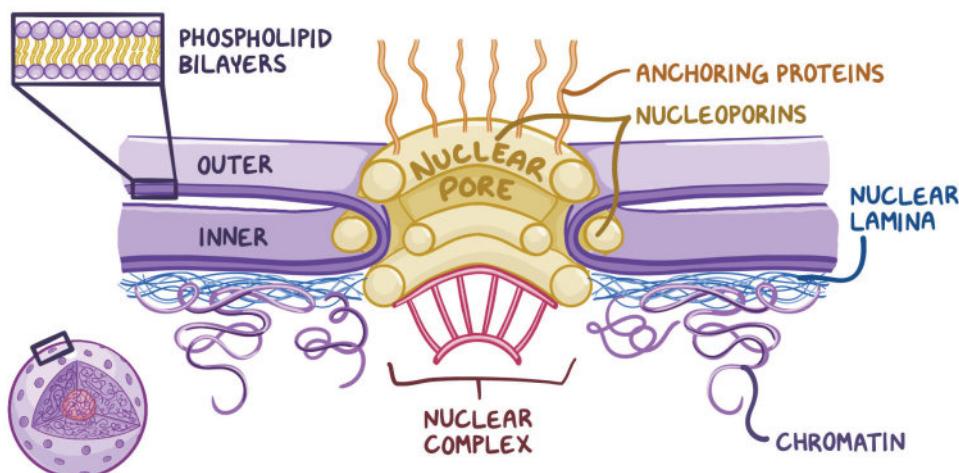
## NUCLEOPLASM

- Protoplasmic material
  - Composed of complex water, molecule, ion mixture
- Contains nucleolus, chromatin

## CHROMATIN

- Helical fiber
  - Composed of 46 DNA molecules wrapped around proteins (histones)
- Histones help regulate DNA, gene expression
- Chromosomes become visible as chromatin fibers become tightly coiled during cellular division

## NUCLEAR ENVELOPE



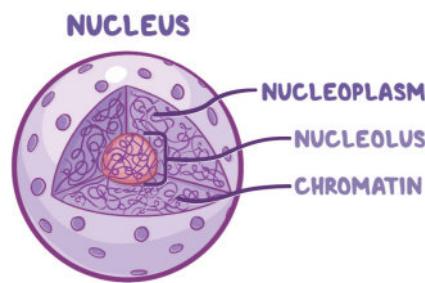
**Figure 23.23** Nuclear envelope components.

### Nucleosome

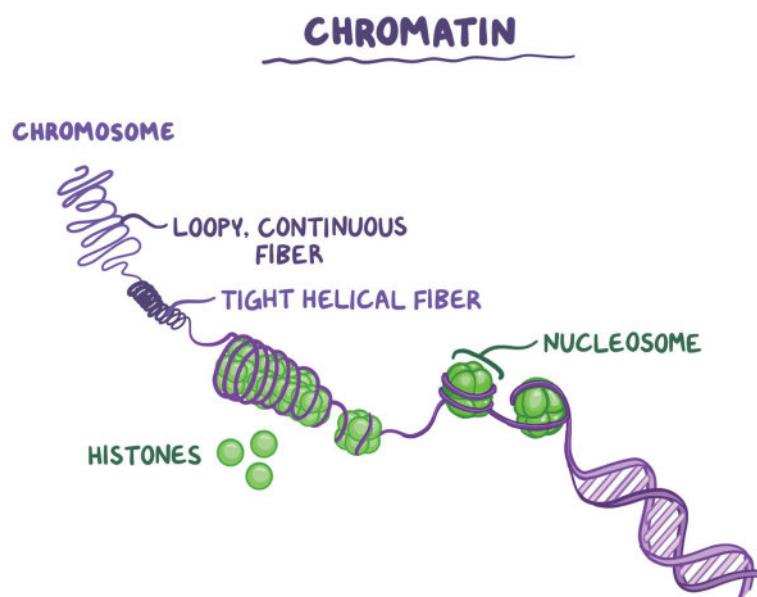
- Eight histones packed together in four stacks of two; DNA wraps around them twice
- Strung on strand of DNA-like “beads on string”

### Two chromatin types

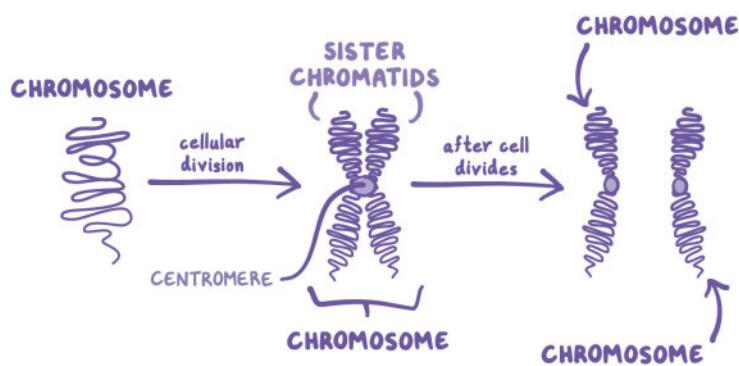
- Euchromatin: loosely packed DNA, actively being transcribed into RNA
- Heterochromatin: densely packed DNA, inactive (not being transcribed)



**Figure 23.24** The nucleoplasm contains the nucleolus and chromatin.



**Figure 23.25** In the nucleus, DNA wraps around collections of histone proteins to form nucleosomes.



**Figure 23.26** During cell division, chromosomes make an exact copy of themselves. The two are connected at the centromere. Each copy is called a sister chromatid. During cell division, the sister chromatids separate so that there is one copy of their genetic material in each daughter cell.



# NOTES CELLULAR PATHOLOGY

## NECROSIS & APOPTOSIS

[osms.it/necrosis-and-apoptosis](http://osms.it/necrosis-and-apoptosis)

- Two main ways by which cells die

### NECROSIS

- Cell death by injury/disease
  - External triggers (e.g. infection, temperature)
  - Internal triggers (e.g. ischemia)

#### Coagulative necrosis

- Occurs in hypoxic tissue
- Structural proteins bend out of shape
- Lysosomal proteins become ineffective at removing affected proteins
- Cell dies, some structure remains

#### Gangrenous necrosis

- Also occurs in hypoxic tissue
- **Dry gangrene:** tissue dries up
- **Wet gangrene:** if infection, liquefactive necrosis also occurs

#### Liquefactive necrosis

- Hydrolytic enzymes digest dead cells into creamy substance

#### Caseous necrosis

- Occurs in fungal/mycobacterial infections
- Cell disintegrate (not fully) → cottage cheese consistency

#### Fat necrosis

- Occurs in response to fatty organ trauma
- Adipose cell membranes ruptured
- Fatty acids combine with calcium, causing dystrophic calcifications
- Can occur in pancreas as result of inflammation (AKA **pancreatitis**)

### Fibrinoid necrosis

- Occurs in malignant hypertension/vasculitis
- Fibrin/inflammation damages blood vessel walls

### Also includes oncosis

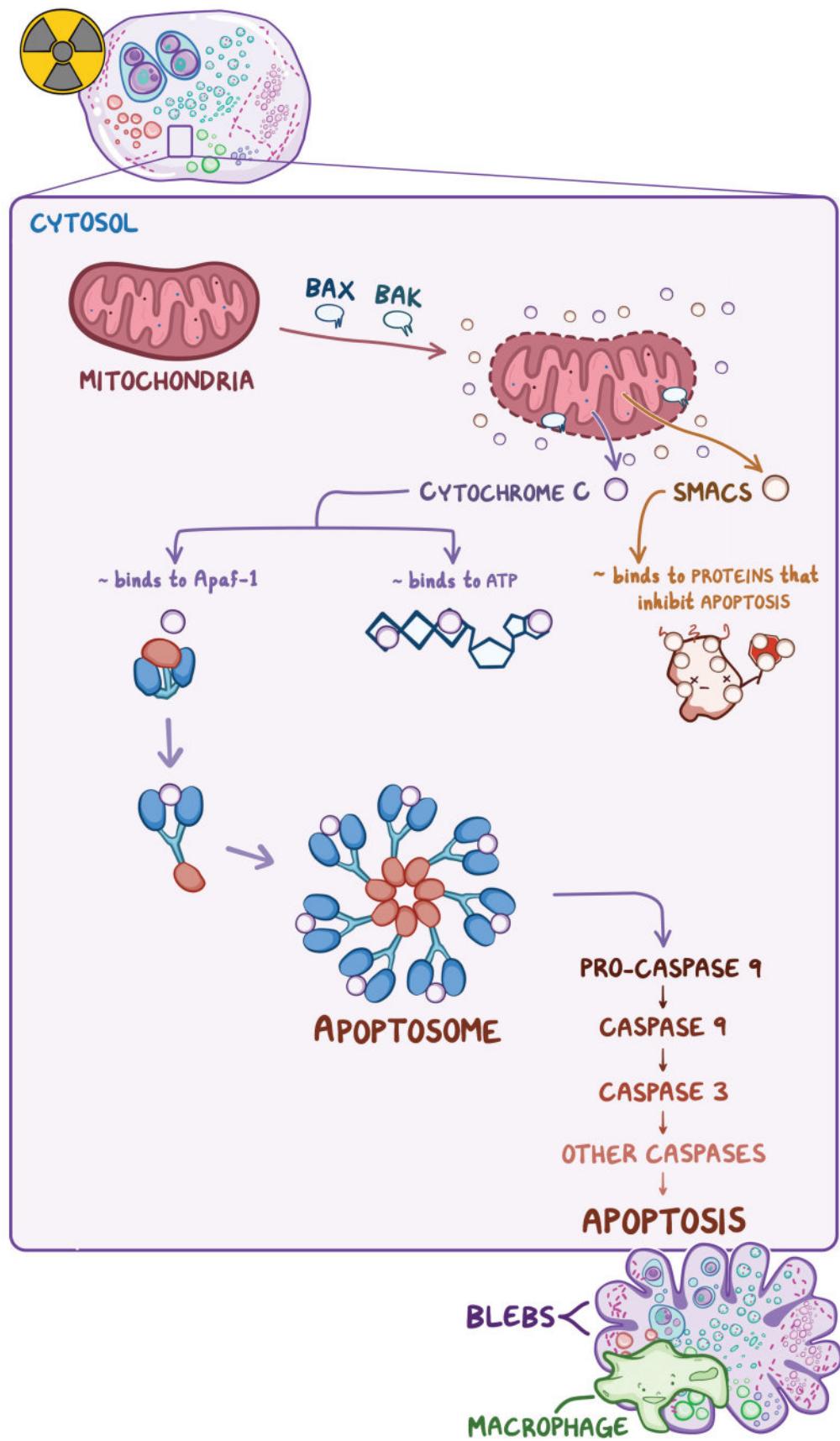
- Toxins/ischemia damage mitochondria
- ATP can no longer be synthesized (e.g. ionic pumps)
- Sodium, water flow into cell → swelling
- Cell bursts, triggers inflammatory process

### APOPTOSIS

- Programmed cell death
- Based on caspase cascade
  - Pro-caspases cleaved into caspases, activating caspase 3
  - Caspase 3 causes activation of cascade of caspase proteins
  - Cleaves various integral proteins, degrading cellular components (e.g. nucleus, organelles, cytoskeleton)
  - Cell loses structure, resulting in blebs, which break off, undergo phagocytosis

### Intrinsic/mitochondrial pathway

- Induced by stress (e.g. radiation)
- Process
  - Intracellular proteins BAX, BAK pierce mitochondrial membrane
  - This allows SMACS, cytochrome C to flow out of mitochondria
  - SMACS binds to proteins that otherwise inhibit apoptosis
  - Cytochrome C binds to ATP, APAF-1, forming apoptosome
  - Pro-caspase 9 cleaves into caspase 9, activating caspase 3



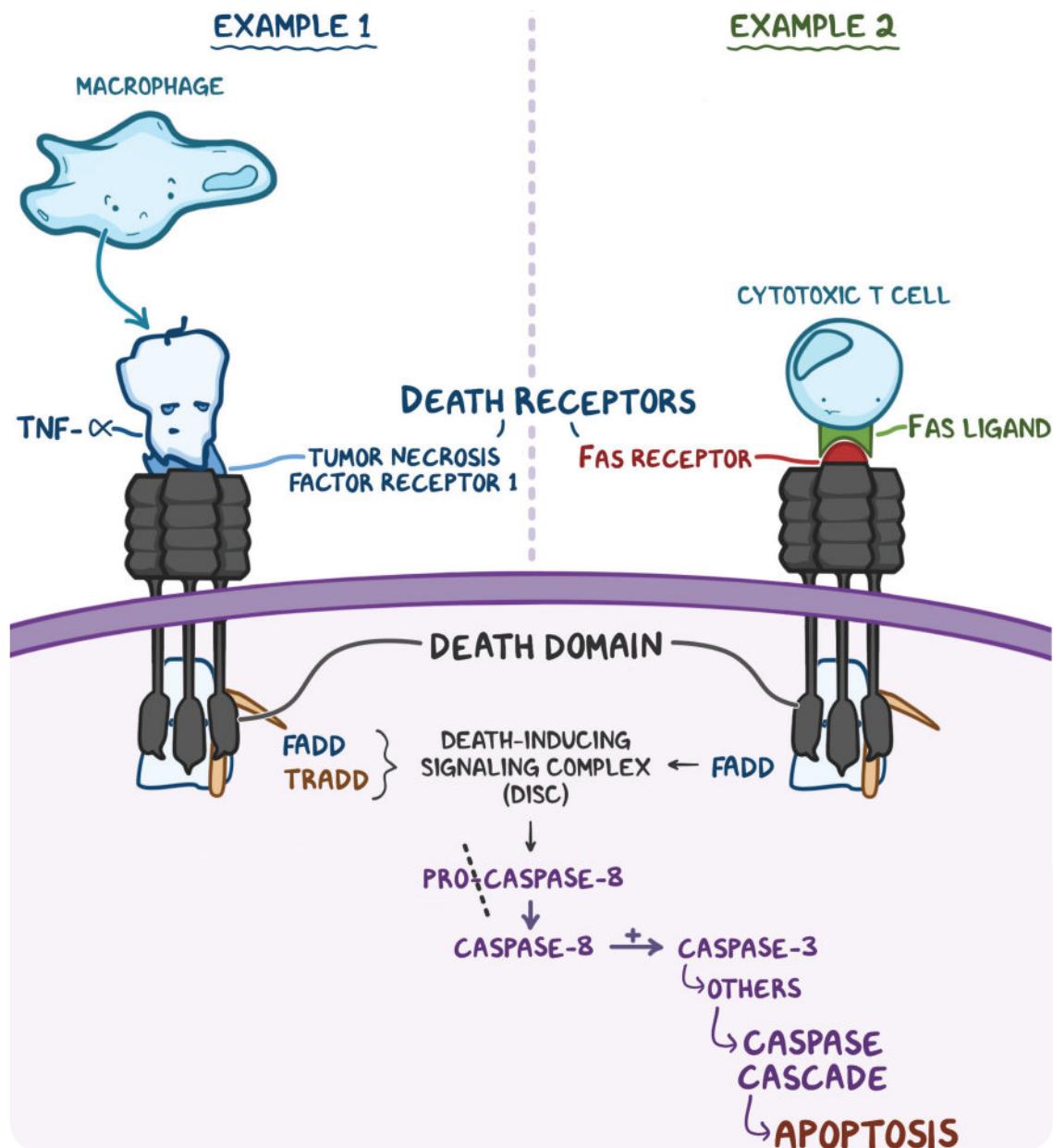
**Figure 24.1** The intrinsic/mitochondrial apoptosis pathway.

**Extrinsic/death receptor pathway**

- Process
  - External cell initiates apoptosis by releasing various signaling proteins
  - Signaling proteins bind to death receptors on cell membrane
  - Cytosolic end of protein dives deep into

cell (AKA death domain)

- Death domain changes shape, binds various proteins to form internal signalling complex
- Pro-caspase 8 cleaves into caspase 8, activating caspase 3



**Figure 24.2** Two examples of the extrinsic/death receptor pathway. In example 1, a macrophage recognizes an old cell, a pathogenic cell, or a cell that has completed its task. It releases TNF- $\alpha$ , which binds to the death receptor tumor necrosis factor receptor 1. In example 2, when a cytotoxic T cell detects that a cell is expressing foreign antigens, the T cell expresses FAS ligand on its membrane. FAS ligand binds to the death receptor called FAS receptor. In both cases, the death domain binds other proteins to form DISC and the caspase cascade leads to apoptosis.

# ONCOGENES & TUMOR SUPPRESSOR GENES

[osms.it/oncogenes-tumor-suppressor-genes](http://osms.it/oncogenes-tumor-suppressor-genes)

- Code for proteins involved in progression of cell cycle
  - Positive regulation: oncogenes stimulate cell growth, division
  - Negative regulation: tumor suppressor genes stop cell cycle progression, promote apoptosis

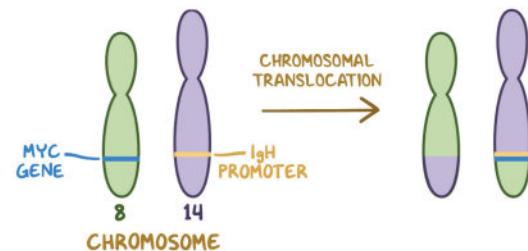
## Proto-oncogenes

- Code for growth factors, growth factor receptors (e.g. receptor tyrosine kinase)
- Signal transduction proteins (e.g. RAS GTPase), transcription factors (e.g. MYC), apoptosis inhibitors (e.g. BCL-2)
- Active when cell needs to grow, divide
- Translocations, amplifications, point mutations turn proto-oncogenes into oncogenes
  - Overexpression
  - E.g. in Burkitt lymphoma, MYC moved from chromosome 8 to near IgH promoter on chromosome 14  
→ overexpression of cyclins, cyclin-dependent kinases
  - E.g. in chronic myeloid leukemia with Philadelphia chromosome

## Tumor suppressor genes

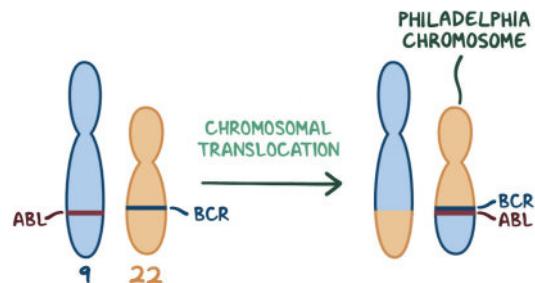
- Code for various tumor suppressors, other protein inhibitors
- Active throughout cell cycle
- Various mutations cause uncontrolled cell growth, division

## BURKITT LYMPHOMA



**Figure 24.3** Burkitt lymphoma can occur due to translocation between portions of chromosomes 8 and 14, resulting in overexpression of proto-oncogene MYC.

## PHILADELPHIA CHROMOSOME



**Figure 24.4** When a translocation occurs between the long arms of chromosomes 9 and 22, the resulting chromosome 22 with part of chromosome 9 is called the Philadelphia chromosome. It contains fusion gene BCR-ABL, whose protein BCR-ABL has tyrosine kinase activity (on/off switch for cell division). Since it's always on, myeloid cells keep dividing → leukemia.

# HYPERPLASIA & HYPERTROPHY

[osms.it/hyperplasia-hypertrophy](https://osms.it/hyperplasia-hypertrophy)

- Two ways by which cells adapt to stress
- Often happen together in tissues with stem cells

## HYPERPLASIA

- Organ/tissue cells ↑ in number
- Only happens in organs with stem cells that can differentiate, mature

### Types

- Compensatory hyperplasia: in organs that regenerate (e.g. skin)
- Hormonal hyperplasia: in organs regulated by hormones (e.g. endocrine)

### Causes

- Physiological processes: e.g. pregnancy → enlargement of breast

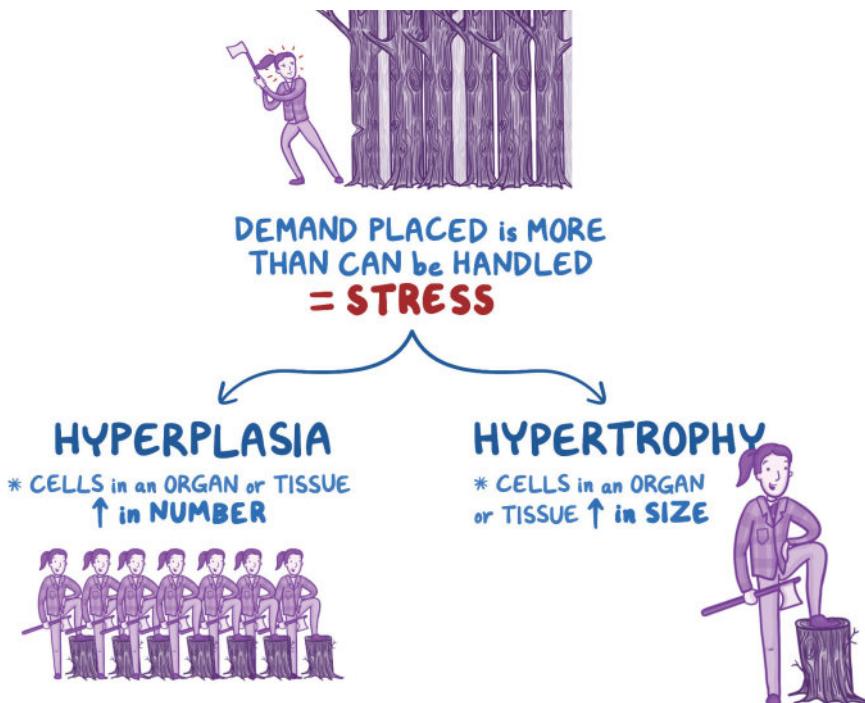
- Pathological processes: e.g. excessive hormonal stimulation → excessive endometrial growth
- Sometimes associated with cancer: cells mutate → dysplasia

## HYPERTROPHY

- Organ/tissue cells ↑ in size

### Causes

- Physiological processes: e.g. ↑ functional demand → muscle cells produce more myofilaments
- Pathological processes: e.g. hypertension → cardiac myocytes produce more myofilaments



**Figure 24.5** An analogy to describe the difference between hyperplasia and hypertrophy. When the workload is bigger than one lumberjack can handle, she gets stressed. Hyperplasia is like hiring more lumberjacks to help; hypertrophy is like the one lumberjack getting bigger and tougher so she can cut down more trees on her own.

# METAPLASIA & DYSPLASIA

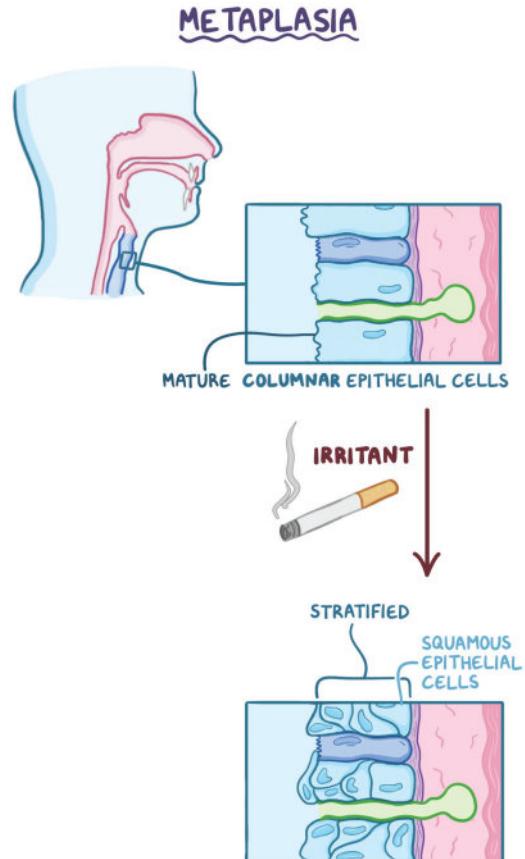
[osms.it/metaplasia-and-dysplasia](http://osms.it/metaplasia-and-dysplasia)

## METAPLASIA

- Mature differentiated cell transforms into new mature cell type
- Often caused by environmental stressor
  - E.g. tobacco smoke: pseudostratified columnar epithelial cells in airways → stratified squamous epithelium
- Reversible if stimulus reverted

## DYSPLASIA

- Tissue develops large number of immature cells
- Precancerous state
- Four pathological changes to cell
  - Anisocytosis (AKA unequal cells)
  - Poikilocytosis (AKA abnormally-shaped cells)
  - Hyperchromatism (AKA excessive pigmentation)
  - Increases number of mitotic figures (AKA more mitosis)



**Figure 24.6** Example of metaplasia caused by exposure to tobacco smoke.

# ATROPHY, APLASIA, & HYPOPLASIA

[osms.it/atrophy-aplasia-hypoplasia](http://osms.it/atrophy-aplasia-hypoplasia)

- Three ways by which cellular, bodily growth fails/reverts

## ATROPHY

- Cell/organ/tissue size reduction
- Causes include disuse, denervation, ischemia, nutrient starvation, interruption of endocrine signals

- May be associated with ↓ cell number (e.g. apoptosis)
  - E.g. orthopedic casting of an extremity
- May be associated with ↓ cell size
  - Loss of nerve/hormonal supply
  - Ubiquitin proteasome pathway: proteasome destroys polyubiquitinated filaments/vacuoles destroy ubiquitin-

tagged organelles (e.g. muscle atrophy)

## APLASIA

- Failure of organ/tissue to form properly
- Growth fails during embryogenesis with no precursor cells

## HYPOPLASIA

- Reduced size/abnormal shape of organ/tissue
- Growth fails during embryogenesis in some precursor cells

# FREE RADICALS & CELLULAR INJURY

[osms.it/free-radicals-and-cellular-injury](http://osms.it/free-radicals-and-cellular-injury)

## FREE RADICAL

- Chemical species with unpaired electron in outer orbit
  - Physiologic causes: e.g. oxidative phosphorylation, enzyme activity
  - Pathologic causes: e.g. ionizing radiation, inflammation, metal interactions, drugs/chemicals)
- May result in cellular injury

## FREE RADICAL CELLULAR INJURY MECHANISMS

### Lipid peroxidation

- Free radicals "steal" electron from lipids on cell membrane
- Damages cell membrane, entire cell

### Protein oxidation

- Free radicals oxidize proteins, including DNA, inside cell
  - DNA oxidation → mutations → cancer

## DEFENSE AGAINST FREE RADICALS

### Antioxidants

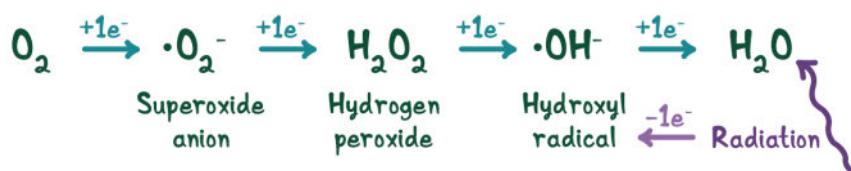
- E.g. vitamins A, C, E
- Eliminate free radicals by donating electrons

### Metal carrier proteins

- E.g. transferrin for iron, ceruloplasmin for copper
- Bind, carry metals to prevent free radical production

### Enzymes

- Eliminate various free radical species
  - Superoxide dismutase → superoxide
  - Catalase → hydrogen peroxide
  - Glutathione peroxidase → hydroxyl radical



**Figure 24.7** Oxygen is an example of a molecule that can become a free radical.

# ISCHEMIA

[osms.it/ischemia](https://osms.it/ischemia)

- Reduction in blood flow to organ/tissue → oxygen shortage
  - Caused by blockage/compression of blood vessel

## Arterial ischemia

- ↓ arterial blood flow → ↓ oxygen received
- E.g. **atherosclerosis**: plaque blocks arteries to heart → ischemic heart disease

## Venous ischemia

- ↓ venous blood flow → ↓ drainage → ↓ blood flow → ↓ oxygen received
- E.g. **Budd–Chiari syndrome**: clot blocks hepatic vein → liver ischemia → edema/hepatomegaly

## Outcomes

- Sometimes, congestion → ↑↑ pressure → fluid forced out/edema
- ↓↓ oxygen → cell death (e.g. tissue necrosis, infarction)
  - **Ischemic penumbra**: ischemic but still viable tissue
  - **Collateralization**: growth of collateral vessels to serve ischemic tissue
- **Time to reperfusion**: time taken to re-establish perfusion before cells die
  - Short → cells survive → reversible
  - Long → cells die → irreversible

# INFLAMMATION

[osms.it/inflammation](https://osms.it/inflammation)

- Immune response described by four key signs:
  - **Calor**: heat
  - **Dolor**: pain
  - **Rubor**: redness
  - **Tumor**: swelling
- May also involve “functio laesa” (AKA loss of function)
- Triggered by external, internal factors
- External
  - Non-microbial: allergens, irritants, toxic compounds
  - Microbial: virulence factors, pathogen associated molecular patterns (PAMPs)
- Internal
  - Damage associated molecular patterns (DAMPs)

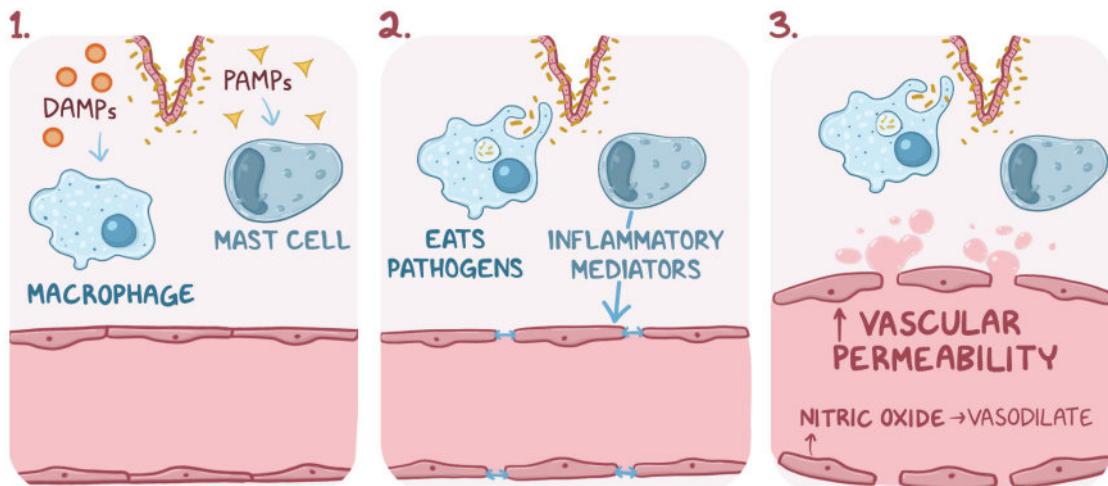
## Example process

- PAMPs, DAMPs recognized by pattern recognition receptors (PRRs) on immune

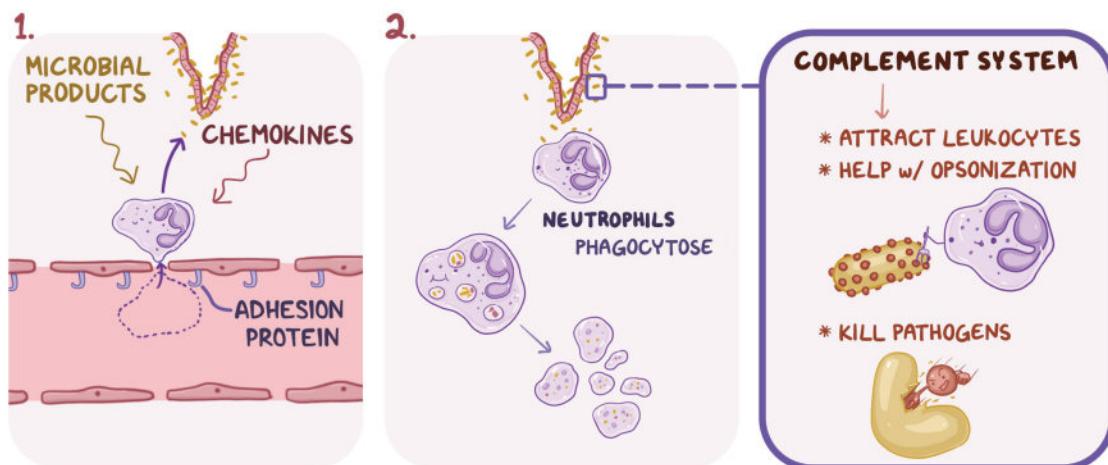
cells

- Activate cells, sparking inflammatory response
- Mast cells contain granules with inflammatory mediators
  - E.g. histamine, serotonin, cytokines, and eicosanoids
- → separate endothelial cells on nearby capillaries
- Macrophages eat any invading pathogens
- Cytokines cause capillaries to enlarge, ↑ vascular permeability
- Endothelial cells release nitric oxide for vasodilation, ↑ vascular permeability
- Leukocytes, especially neutrophils, attracted through capillaries by chemokines, microbial products; squeeze through membrane
  - AKA extravasation
- Leukocyte follows gradient of inflammatory mediators

- Neutrophils phagocytose pathogens immediately before destroying themselves
- Antibodies bound to pathogens activate complement system
  - Aids in opsonization, kills pathogens by lysis
- Dendritic cells phagocytose pathogens, present antigens to T lymphocytes, activating adaptive immune system
- Ends with tissue repair



**Figure 24.8** 1: DAMPs and PAMPs activate immune cells. 2: Macrophages phagocytose pathogens at the site of inflammation. Mast cells release inflammatory mediators that widen the distance between adjacent endothelial cells. 3: Endothelial cells release nitric oxide → ↑ vasodilation, vascular permeability.



**Figure 24.9** 1: Neutrophils are the first leukocytes recruited during the acute inflammatory process. They squeeze through the gap between endothelial cells (extravasation) and follow the gradient of inflammatory mediators to the site of inflammation. 2: Neutrophils quickly phagocytose pathogens. While this is happening, complement proteins are activated by the presence of pathogens and help with opsonization (they bind to microbes so leukocytes can more easily eat them). Some can also kill pathogens by forming a channel in their membranes.



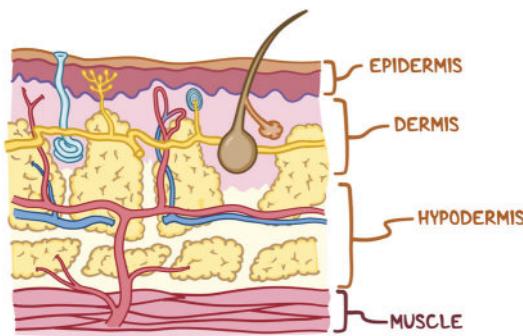
# NOTES

## SKIN STRUCTURES

# SKIN ANATOMY & PHYSIOLOGY

[osms.it/skin-anatomy-and-physiology](http://osms.it/skin-anatomy-and-physiology)

- Skin is body's largest organ
  - Seven percent of total body weight
- Comprises integumentary system, appendages (hair, nails, oil, sweat glands)
  - Protects body (infection, abrasion, dehydration, etc)
  - Regulates body temperature
  - Detects pain, sensation, pressure
  - Essential for vitamin D production
- Three layer division
  - Epidermis, dermis, hypodermis



**Figure 25.1** The three layers of the skin, from superficial to deep, include: the epidermis, dermis, and hypodermis.

### EPIDERMIS

- Epidermis
  - Stratified squamous epithelium
  - Thin outermost layer
- Multiple layers of developing keratinocytes (contain keratin)
  - Make, secrete glycolipids; prevent water seeping into/out of body

### Stratum basale

- Innermost layer: single columnar stem cell layer; dividing, producing keratinocytes
  - Keratinocytes contain cholesterol precursors activated by UVB light → vitamin D (regulates calcium absorption)
- Also contains melanocytes (secrete melanin, giving skin its color)
  - UVB light stimulates melanin secretion → placed into melanosomes, moved up by keratinocytes → scatters UVB light → natural sunscreen (prevents skin cancer from excessive UVB light)

### Stratum spinosum

- Second layer: comprises 8–10 keratinocyte cell layers which can no longer divide
  - Proteins on keratinocytes help them adhere together
  - Dendritic cells seek out invading microbes

### Stratum granulosum

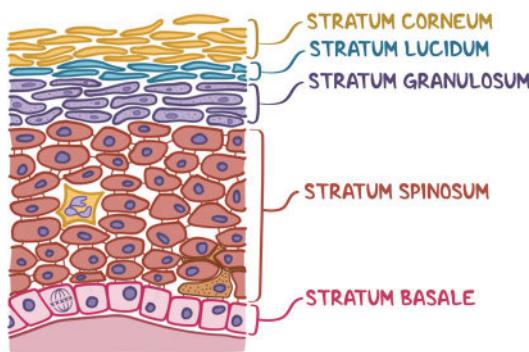
- Third layer: comprises 3–5 keratinocyte cell layers undergoing keratinization (flatten out, die) → epidermal skin barrier formed
  - Keratohyalin granules in keratinocytes contain keratin precursors which aggregate, cross-link → keratin bundles
  - Lamellar granules in keratinocytes contain glycolipids (secreted to cell surface, glues cells together)

### Stratum lucidum

- Fourth layer: comprises 2–3 dead keratinocyte cell layers that have secreted most of their lamellar granules
  - Only found in thick skin (e.g. palms, soles of feet)

### Stratum corneum

- Uppermost layer: comprises 20–30 dead keratinocyte cell layers glued together with glycolipids
  - Dead keratinocytes secrete defensins to fight pathogens
  - Cells from stratum lucidum push up → cells from this layer shed → skin flakes/dandruff



**Figure 25.2** The five layers of the epidermis. Stratum basale is the deepest layer and stratum corneum is the most superficial.

## DERMIS

- Dermis
  - Central layer
  - Two layer division (papillary layer; deeper, thicker reticular layer)

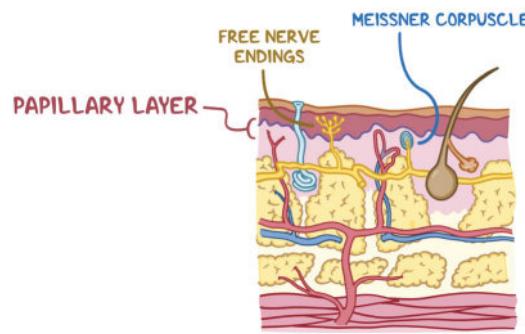
### Papillary layer

- Fibroblasts (producing collagen) arranged in papillae
- Contains blood vessels, macrophages, nerve endings (e.g. Meissner's corpuscles for fine touch, free nerve endings for pain)
- Responsible for fingerprints ( $\uparrow$  gripping, sensing abilities)

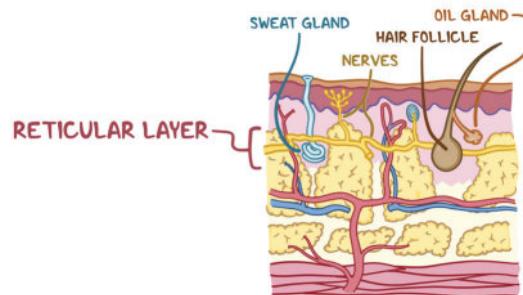
### Reticular layer

- Fibroblasts (produces elastin for flexibility)
- Contains oil, sweat glands; lymphatic, blood vessels; hair follicles; macrophages; nerves (e.g. Pacinian corpuscle for pressure, vibration)
- Collagen packed tightly →  $\uparrow$  support
- Regulates temperature with blood vessels, sweat glands

- Blood vessels dilate when hot (blood moves closer to surface → allows heat loss)/contract when cold (blood moves away from surface → prevents heat loss)
- Sweat glands  $\uparrow$  secretion when hot ( $\uparrow$  heat to evaporate sweat)/ $\downarrow$  when cold ( $\downarrow$  heat to evaporate sweat)



**Figure 25.3** The papillary layer of the dermis contains multiple types of nerve endings.



**Figure 25.4** Contents of the reticular layer of the dermis.

## HYPODERMIS

- Hypodermis (subcutaneous tissue) inner layer
  - Contains adipocytes (store fat), fibroblasts, macrophages, blood vessels, nerves, lymphatics
  - Insulates deeper tissues; provides padding; anchors skin to underlying muscle with connective tissue (e.g. collagen)

# HAIR, SKIN, & NAILS

[osms.it/hair-skin-and-nails](https://osms.it/hair-skin-and-nails)

- Skin appendages include hair, nails, skin glands (oil/sebaceous, sweat/sudoriferous)
  - Regulate body temperature; environmental protection
  - Originate in dermis
- Hair, nails comprised of long, filamentous protein (keratin)
  - Keratin: produced by keratinocytes during keratinization (cells rapidly replicate, die)
  - Soft keratin (produced by skin); hard keratin (produced by hair, nails)

## HAIR

- Includes vellus hairs (short, thin); terminal hairs (more visible, growth starts at puberty)
- Found everywhere
  - Exceptions: palms, soles of feet, lips
- Hair strands sit in follicle; epidermal tissue dips into dermis
  - Associated with sebaceous glands,

- arrector pili muscles, apocrine glands, nerve receptors
- Composition: shaft, root, bulb
  - Hair matrix: active hair growth site, found inside bulb; contains keratinocytes, melanocytes; blood supplied by papilla
- Keratinocytes die, flatten out → hard keratin fills up cell → gradually get pushed up follicle forming hair
  - Hair growth: includes growth, resting phases
  - Keratinocytes in bulb replicate set number of times → follicle eventually stops producing hair/produce vellus hairs instead (genetically determined) → baldness
- Melanocytes produce melanin (protein pigments that give hair color)
  - Melanocytes move melanin into melanosomes → taken up by keratinocytes

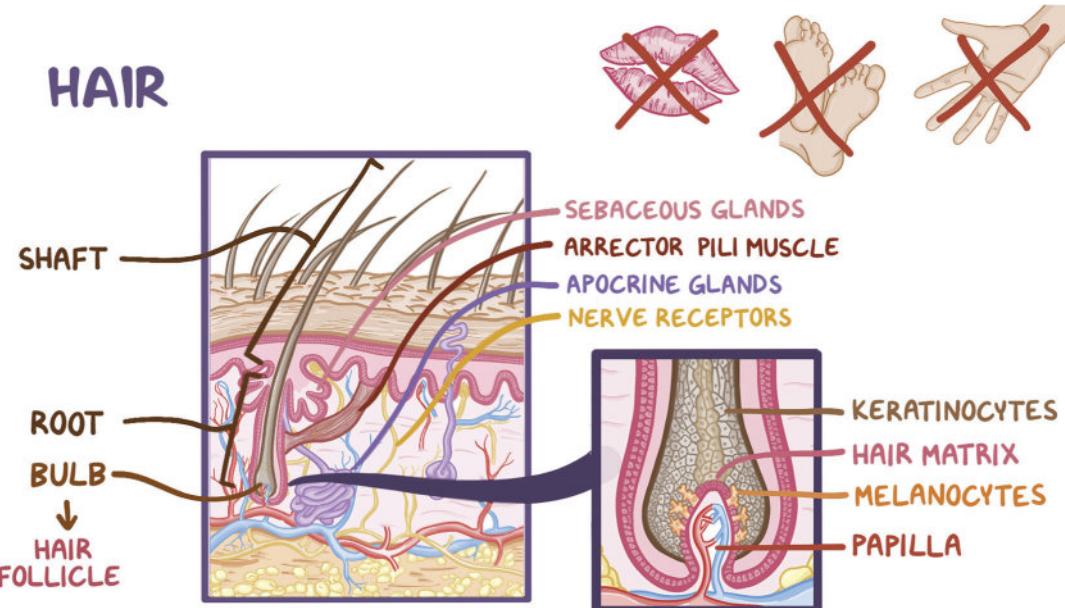


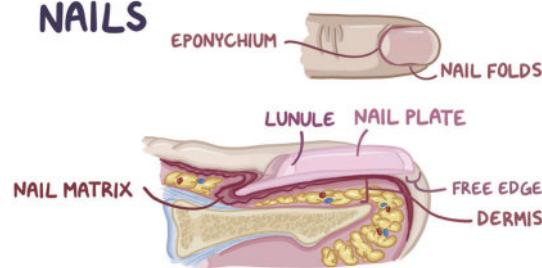
Figure 25.5 Composition of hair and associated structures.

- ↑ age → ↓ melanin → faded, white hair
- Nerve receptors around bulb stimulated when hair shaft moves
- Arrector pili muscle contracts, pulls hair (e.g. cold weather/frightened) → goosebumps

## NAILS

- Grow from proximal to distal fingertips/toes
  - Surrounded on either side by nail folds
  - Closed off proximally by eponychium → forms cuticle (dead skin keratinocytes that cover junction between nail, skin)
- Nail matrix composition: lunula, nail plate
  - Lunula: white, crescent-shaped part of nail near eponychium
  - Free edge: nail plate portion hanging over skin
- Modified keratinocytes in matrix form plate by keratinization (similar to hair)
- Nails grow continually through life (unlike hair)

## NAILS



**Figure 25.6** Superior view and cross section of a finger illustrating components of the nail.

## SEBACEOUS GLANDS

- Secrete sebum (softens hair shaft, prevents moisture-loss, deters pathogens) onto hair follicles/through pores → skin surface
- During puberty: ↑ androgen hormones → ↑ sebum production → blocks pores, plugs hair follicles → enclosures allow infection development (e.g. acne, folliculitis)

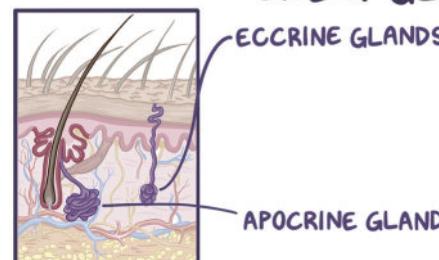
## SUDORIFEROUS GLANDS

- AKA sweat glands
- Eccrine (merocrine) glands
  - Found everywhere
  - Exceptions: lips, ear canal, clitoris, glans of penis
- Coil-shaped structure; in dermis; duct opens into pore on skin surface
- Sweat: hypotonic (mostly water, electrolytes); dermidin (destroys bacteria); cools body (evaporation)
- Sympathetic nervous system activation during ↑ cardiovascular activity, fight-or-flight response, fear/anxiety

## Apocrine glands

- Found in armpits, genitals
  - Become active during puberty
- Similar to eccrine glands
  - Bigger, fewer; produce secretions with ↑ lipids, proteins
  - Secretions metabolized by bacteria → body odor
- Several modified apocrine gland types
  - Ceruminous glands: in ear; produce cerumen; protects eardrum (with ear canal hairs)
  - Mammary glands: in breasts; produce milk

## SWEAT GLANDS



**Figure 25.7** The two types of sweat glands (sudoriferous glands).

# WOUND HEALING

[osms.it/wound-healing](https://osms.it/wound-healing)

- Damaged tissue repair process
  - Acute wounds heal quickly (days–weeks)
  - Chronic wounds heal slowly (months)

## Regenerative tissue capacity

- Classification: labile, stable, permanent
- **Labile tissues** (e.g. skin, connective tissue, intestines)
  - **Heal well:** stem cells constantly divide → rapid, effective healing
- **Stable tissues** (e.g. liver, endocrine glands, proximal kidney tubules)
  - **Heal slowly:** mature differentiated cells divide/regenerate by hyperplasia
- **Permanent tissues** (e.g. skeletal muscle, cartilage, neurons)
  - **Heal poorly:** lack of stem cells, no hyperplasia → replaced by scar tissue (fibrosis) → function loss

## Open wounds

- Open wounds healed by primary, secondary, tertiary intention
- Primary intention (most surgical wounds)
  - Wound edges fuse (e.g. stitching/gluing) → stem cells (e.g. epidermis) approximate, regenerate damaged tissue (minimal scarring)
- Secondary intention
  - Wound edges too far apart (e.g. pressure ulcers, tooth extraction, severe burns) → stem cells do not approximate → wound replaced by connective tissue growing from base upwards (slower healing; more scar tissue)
- Tertiary intention (delayed closure)
  - Wound cleaned, debrided → purposefully left open (↓ bacterial contamination likelihood) → closed by primary intention/left open for secondary intention

## Penetrating trauma wound healing

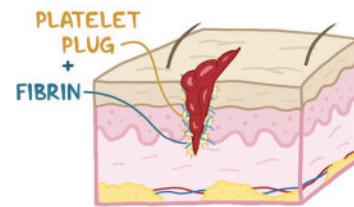
- Penetrating trauma wound healing steps (e.g. cutting finger → damaged epidermis, dermis, interstitial space)
- Hemostasis (first step)
  - Blood vessels constrict → platelets adhere to site → forms platelet plug → fibrin mesh reinforces platelet plug → forms **blood clot**
- Inflammation (second step)
  - Damaged cells release chemokines, cytokines → **neutrophils, macrophages** recruited; **blood vessels dilate** → **immune cells clear debris**, digest dead/damaged cells, destroy microbes → blood clot, dead macrophages combine, form scab
- Epithelialization/migration (third step)
  - **Basal cells** (epidermal stem cells) proliferate, replace lost/damaged cells → **rejuvenated epidermal layer** (approx. 48 hours)
- Fibroplasia (fourth step)
  - **Fibroblasts** in dermis proliferate, secrete **collagen** (assemble → form collagen fibrils → collaged bundles) → blood vessel growth stimulated (**angiogenesis**); fibroblasts also produce glycoproteins, sugars → **create granulation tissue** in dermal layer
- Maturation (fifth step)
  - **Collagen cross-linking:** covalent bonds form between collagen bundles, improving tensile strength
  - **Collagen remodeling:** fibroblasts degrade subpar collagen
  - **Contraction:** myofibroblasts produce contractile proteins, pulling wound's edges together
  - **Repigmentation:** melanocytes proliferating, restoring color to damaged skin

### Chronic wounds

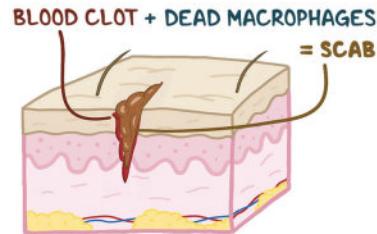
- Healing prevention factors → chronic wounds
  - Narrowed capillaries: prolonged compression/disease (e.g. diabetes, atherosclerosis) → ↓ blood flow → damaged tissue cannot be reached by immune cells, insufficient oxygen/nutrients → tissue necrosis
  - Infection: pathogens compete for oxygen; cause ongoing damage, inflammation
  - Edema: disrupts fibroblast activity, collagen deposition, collage cross linking

### WOUND HEALING

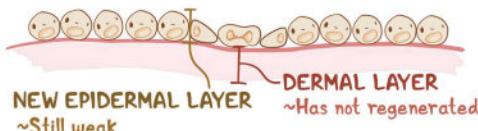
#### FIRST STEP



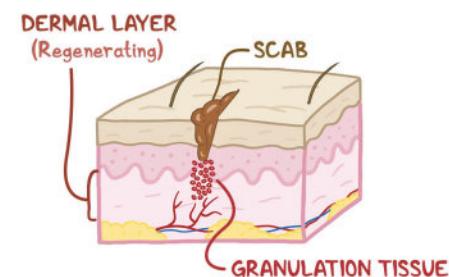
#### SECOND STEP



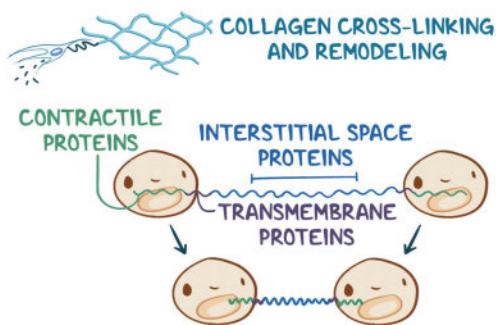
#### THIRD STEP



#### FOURTH STEP



#### FIFTH STEP



**Figure 25.8** The five steps of penetrating trauma wound healing.



## NOTES EARLY WEEKS

# HUMAN DEVELOPMENT DAYS 1–4

[osms.it/human\\_development\\_days\\_1-4](https://osms.it/human_development_days_1-4)

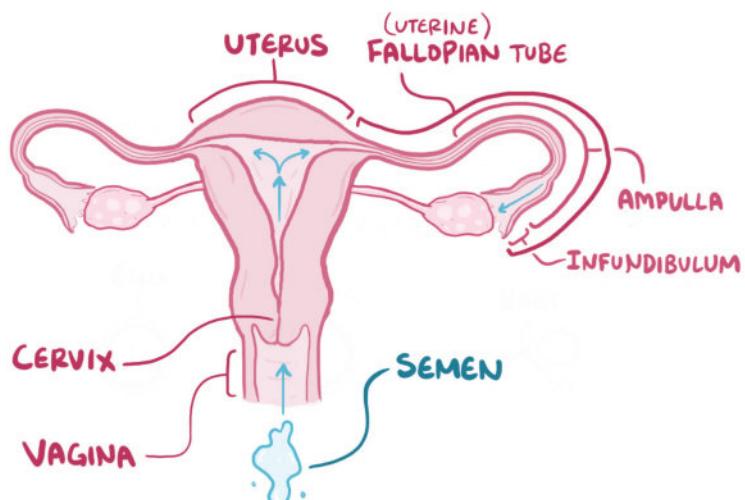
### FERTILIZATION

- Oocyte, spermatozoa fuse → zygote
  - Oocyte viable 12–24 hours after ovulation; sperm cells retain fertilizing power 24–48 hours after ejaculation
  - Coitus must occur no more than two days before/24 hours after ovulation for fertilization
- Ejaculation → 200 million spermatozoa enter vaginal canal → alkaline seminal fluid neutralizes acidic vaginal fluid
- Only 1% enter cervix → travel through uterus → **ampullary region** of uterine tube (**most likely place for fertilization**)
- Cervix → oviduct
  - 30 minutes to 6 day journey

- Ovulation → spermatozoa driven by chemoattractants (produced by cumulus cells of oocytes) to ampulla of uterine tube

### Two required processes

- **Capacitation:** epithelial interactions between sperm, uterine wall
  - Glycoprotein coat, seminal plasma proteins covering acrosomal region removed → easier enzyme release → acrosomal reaction
- **Acrosomal reaction:** after binding to zona pellucida
  - Release of enzymes (e.g. acrosin, hyaluronidase) needed to penetrate zona pellucida



**Figure 26.1** Sperm pathway through the uterus.

## PHASES OF FERTILIZATION

### Phase I: penetration of corona radiata

- Capacitated spermatozoa allowed to pass through corona radiata

### Phase II: penetration of zona pellucida, sperm binding

- Zona pellucida: glycoprotein layer surrounding oocyte; AKA “jelly coat”
  - Facilitates binding of sperm cell, induces acrosomal reaction mediated by ligand zona pellucida sperm-binding protein 3 (ZP3)
- Approx. 500 spermatozoa arrive at this layer
- Sperm-binding initiates release of acrosin (hydrolytic enzyme) → sperm cell penetrates zona pellucida → sperm makes contact with oocyte → cortical reaction (release of lysosomal enzymes from cortical granules of oocyte) → cortical granules initiate zona reaction, prevent further sperm penetration (polyspermy) by forming protective hyaline layer, inactivate receptor sites on zona pellucida
  - Cortical reaction also activates oocyte to prepare for second meiotic division

### Phase III: fusion of oocyte, sperm cell

- Interactions between integrins, ligands → adhesion of sperm, oocyte
  - Fusion of sperm, egg plasma membranes
- Secondary oocyte completes meiosis II → forms female pronucleus, second polar body
- Head, tail of spermatozoa enters oocyte → travels to female pronucleus (containing 23 chromosomes) using tail, energy generated by mitochondria
- Tail, mitochondria detach → sperm nucleus becomes male pronucleus
- Male, female pronuclei move toward each other → merge into single nucleus → cell becomes diploid (zygote contains maternal, paternal genetic information)
- Preparation for mitotic division

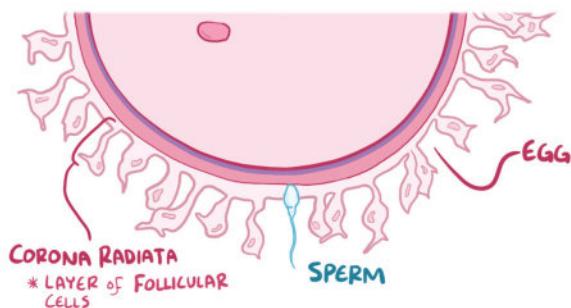
## ZYGOTE TO BLASTOCYST IMPLANTATION

### Cleavage

- Series of fast mitotic divisions of zygote → increase number of cells, decrease size
- 36 hours after fertilization → first cleavage division → two cells (blastomeres)
  - Second division → four blastomeres; third division → eight blastomeres; etc.
- After third cleavage, blastomeres form compact ball of cells connected by tight junctions (compaction)
- Three days after fertilization, cells of compacted embryo divide again → mulberry-shaped 16-cell **morula** (composed of two zones: inner, outer cell mass)
- Four to **five days after fertilization**, embryo consists of approx. 100 cells
- Fluid accumulates within internal cavity (blastocoel) → **blastocyst**
- **Blastocyst**: fluid-filled hollow cell, two zones
  - **Trophoblast**: single layer of large flattened cells, stemming from morula's outer cell mass; gives rise to placenta
  - **Embryoblast**: 20–30 pluripotent cells located on one side, stemming from inner cell mass; gives rise to embryo

## PHASES of FERTILIZATION

### PHASE I



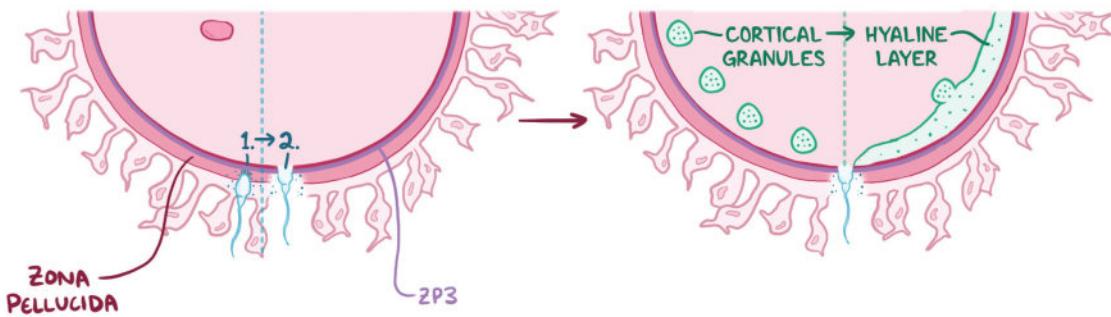
### PHASE II

#### ACROSOMAL REACTION

1. RELEASES ACROGIN
2. SPERM & EGG FUSE

#### CORTICAL REACTION

- \* GRANULES FUSE with CELL MEMBRANE



### PHASE III

#### MEIOSIS II

SECOND POLAR BODY  
\* APOPTOSIS

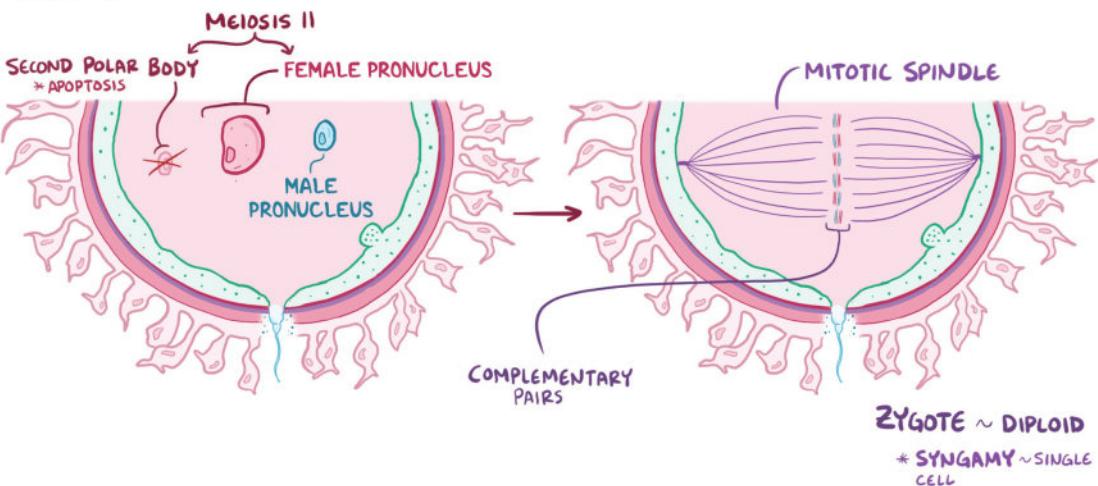
FEMALE PRONUCLEUS

MALE PRONUCLEUS

COMPLEMENTARY PAIRS

MITOTIC SPINDLE

ZYGOTE ~ DIPLOID  
\* SYNGAMY ~ SINGLE CELL

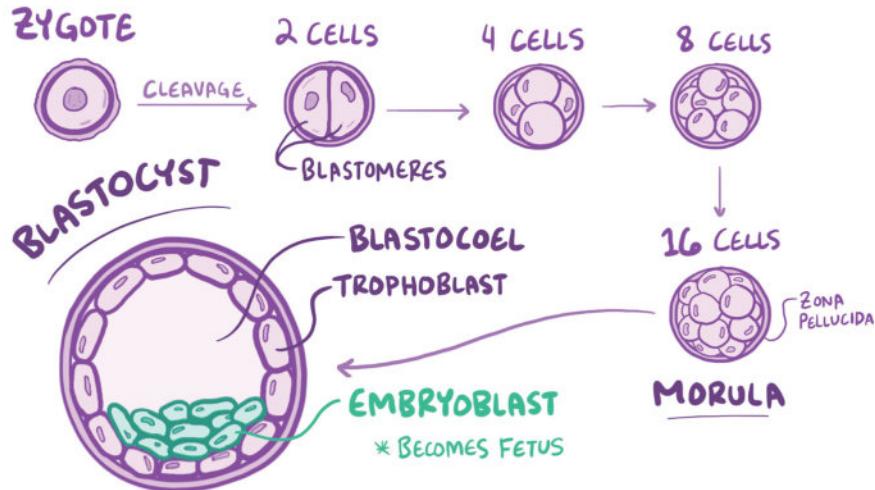


**Figure 26.2** Phases of fertilization.

Phase I: sperm penetrates corona radiata.

Phase II: penetration of zona pellucida, sperm binding.

Phase III: fusion of sperm, oocyte; pronuclei fuse to form diploid zygote cell.



**Figure 26.3** Process of going from zygote to blastocyst.

## HUMAN DEVELOPMENT DAYS 4–7

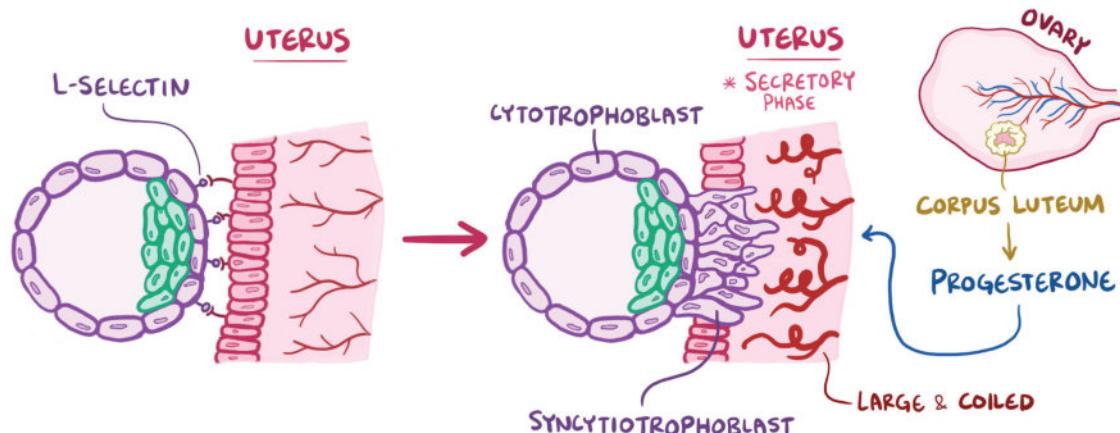
[osms.it/human\\_development\\_days\\_4-7](https://osms.it/human_development_days_4-7)

### DAY 7

#### Implantation

- Trophoblast binds to uterine wall with L-selectin, integrin receptors
  - Penetrates between epithelial cells

- Uterus at implantation in secretory phase
  - High progesterone released from corpus luteum develops endometrium for implantation
  - Blastocyst implants into decidua basalis, along superior posterior wall of uterus



**Figure 26.4** Implantation, syncytiotrophoblast proliferation, and development of spiral arteries under the influence of progesterone secreted by the corpus luteum.

# HUMAN DEVELOPMENT WEEK 2

[osms.it/human-development-week-2](https://osms.it/human-development-week-2)

## DAY 8

### Trophoblast

- Proliferates, forms two layers
- **Cytotrophoblast** (cellular trophoblast): inner layer of mononucleated cells
  - Produces primary chorionic villi, protrudes into syncytiotrophoblast
- **Syncytiotrophoblast**: outer multinucleated mass of cells (without distinct cell boundaries)
  - Invades decidua basalis with finger-like processes; makes enzymes that erode uterine cells; blastocyst burrows into decidua basalis surrounded by pool of blood leaked from degraded blood vessels
  - Human chorionic gonadotropin (**hCG**) maintains viability of corpus luteum → secretes estrogen, progesterone until week eight (**hCG**: basis for pregnancy tests)

### Embryoblast

- Differentiates into two layers, forms flat disc
- **Hypoblast**: small cuboidal cells adjacent to blastocyst → yolk sac
- **Epiblast**: columnar cells
  - Cavity forms inside → amniotic cavity
  - Lined with amnioblasts

## DAY 9

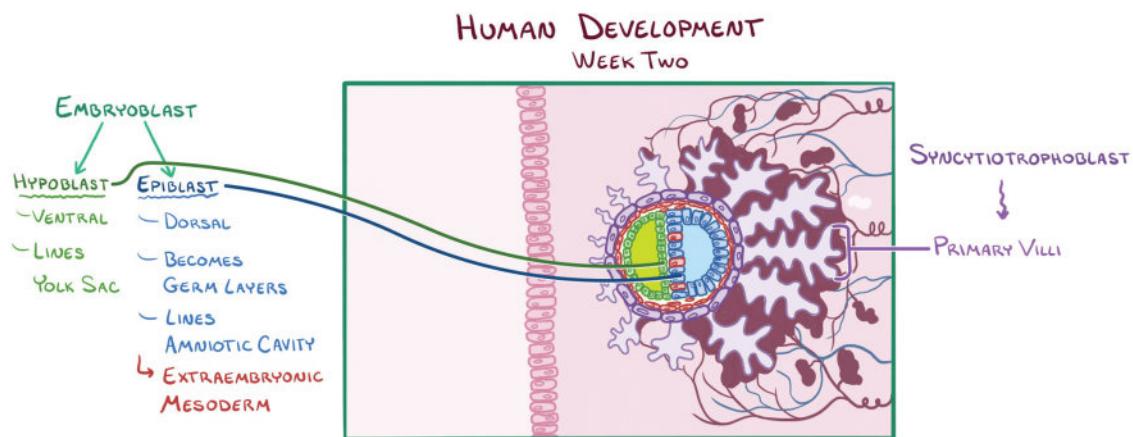
- Lacunar stage of trophoblast development
  - Vacuoles appear in syncytium → vacuoles fuse → form large empty spaces (lacunae)
- At abembryonic pole, flattened cells (from hypoblast) form exocoelomic (Hauser) membrane → line inner surface of cytotrophoblast
  - Hauser membrane, hypoblast line exocoelomic cavity (primitive yolk sac)

## DAY 12

- Progesterone levels continue to rise → decidua undergoes decidual reaction
  - Decidual cells enlarge, become coated in sugar-rich fluid (helps sustain embryo)
  - Blastocyst embeds in endometrial stroma
  - Lacunae form within syncytiotrophoblast (erodes endometrial sinusoids)
  - Lacunae fuse with sinusoids → fill with maternal blood → uteroplacental circulation established

## DAY 13

- Secondary yolk sac forms within exocoelomic cavity
- **Hypoblast cells**: differentiate into extraembryonic mesoderm cells outside embryo
  - Mesoderm cells: line inside of cytotrophoblast, syncytiotrophoblast; line chorionic cavity
- **Epiblast**: gives rise to embryo's germ layers (endoderm, mesoderm, ectoderm)
- **Amniotic cavity** develops above bilaminar disk, becomes lined with epiblast cells



**Figure 26.5** Summary of the growth that occurs during the second week of development.

## HUMAN DEVELOPMENT WEEK 3

[osms.it/human-development-week-3](https://osms.it/human-development-week-3)

### DAY 14

- Syncytiotrophoblast cells form little protrusions called primary villi
- Villi form around fetus; lacunae form between villi
- Arteries, veins merge within lacunae → form large pool of blood (junctional zone)
- Villi submerged within junctional zone

### Gastrulation

- Major event, establishes three germ layers
- Begins with formation of primitive groove (narrow depression into center of epiblast layer)
  - Starts at caudal end, grows towards cranial end → cranial-caudal axis
  - Groove forms on dorsal side of embryo → dorsal-ventral axis
  - Two sides of groove: left, right side of body (bilateral symmetry)
- Primitive node forms at cephalic end of primitive groove
  - Contains primitive pit, surrounded by slightly elevated area of ectoderm
- Primitive groove, node, pit → form **primitive streak**
- **Epiblast cells** migrate towards primitive groove → move to bottom, slide under

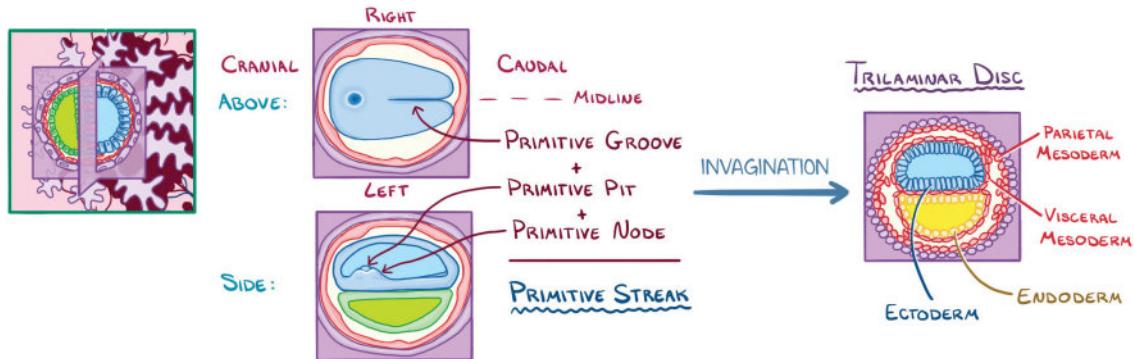
### (invagination)

- After invagination, cells differentiate into three new layers of embryonic disc (**trilaminar disc**)
- Cells of trilaminar disc multipotent (ability to differentiate into many tissues, organs)
  - Some epiblast cells displace ventral hypoblast layer, form **endoderm**
  - Invaginated epiblast cells between newly formed endoderm, epiblast → **mesoderm** layer
  - Rest of epiblast forms **ectoderm** layer

### DAY 15

- Two areas of ectoderm layer (cranial, caudal region) push ventrally, fuse with endoderm (exclude mesoderm layer) → form two bilaminar regions in otherwise trilaminar disc
  - Cranial bilaminar region develops into oropharyngeal membrane → disintegrates in fourth week to form mouth opening
  - Caudal bilaminar region develops into cloacal membrane → disintegrates in seventh week to form anal opening, genitourinary tracts

## GASTROULATION / DAY 14



**Figure 26.6** Day 14: formation of the primitive streak and trilaminar disc.

### DAY 17

- Group of mesoderm cells form solid rod (**notochord**)
  - Notochord: transient embryonic structure (**nucleus pulposus**) of intervertebral disc: remnant in adult life)
  - Solid structure → helps influence how embryo folds
  - Secretes protein called **Sonic Hedgehog** (SHH) → guides tissue differentiation

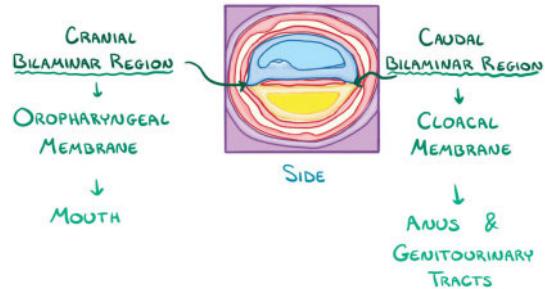
### DAY 20

- Mesoderm cells around notochord differentiate into three specialized types of cells
  - Paraxial mesoderm, intermediate mesoderm, lateral plate mesoderm; make different tissues, organs
- Notochord starts process called **neurulation** → stimulates cells of **ectoderm** to form **neural plate**
- Neural plate folds, forms neural groove with edges called **neural folds**
- Neural plate continues to grow, neural folds come together, pinch off from surface of ectoderm to form neural tube between ectoderm, mesoderm
- Trophoblast continues to develop: **vasculogenesis**
  - Primary villi: made up of cytotrophoblastic core covered by syncytial layer
  - Secondary villi: form when extraembryonic somatic mesoderm cells

penetrate primary villi → grow toward decidua

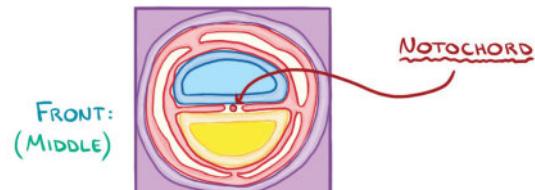
- Tertiary villi: form when mesodermal cells differentiate into small blood vessels → form villus capillary system → fetal contribution to placenta

### DAY 15



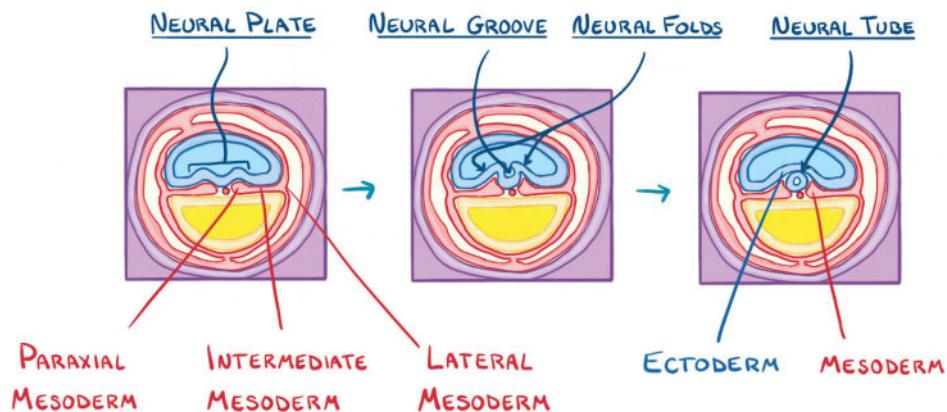
**Figure 26.7** Day 15: bilaminar regions of trilaminar disc.

### DAY 17

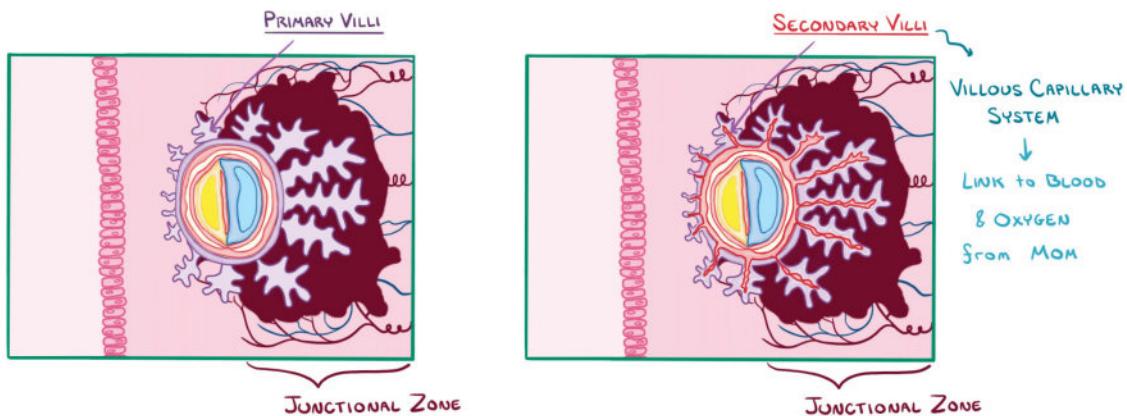


**Figure 26.8** Day 17: formation of notochord from mesoderm cells.

## NEURULATION / DAY 20



**Figure 26.9** Day 20: differentiation of mesoderm near neural plate into paraxial, intermediate, and lateral plate mesoderm; formation of neural tube in process called neurulation.



**Figure 26.10** During week 3, extraembryonic mesoderm cells migrate into the primary villi, forming secondary villi. The secondary villi differentiate into fetal vessels known as the villous capillary system, which is the fetal contribution to the placenta.



# NOTES GERM LAYERS

## ECTODERM

[osms.it/ectoderm](https://osms.it/ectoderm)

- Beginning of week 3
  - Ectoderm layer broader in cephalic region than in caudal region
- Notochord initiates neurulation, forming neural tube between mesoderm, ectoderm
- On dorsal side of neural tube as neural folds fuse, neural crest cells migrate
  - Form new cell layer between ectoderm, neural tube
  - As neural crest cells migrate throughout fetus, they give rise to tissues including peripheral nervous system (sensory ganglia, sympathetic neurons, Schwann cells), skin melanocytes, part of facial bones, adrenal gland chromaffin cells, thyroid parafollicular (C) cells
- Neural tube has an opening on each end
  - Cranial neuropore (top): closes around day 25
  - Caudal neuropore (bottom): closes around day 28
- Surface ectoderm forms ectodermal thickenings, otic, lens placodes, near cranial end of ectoderm
  - Otic placodes form otic vesicles → cochlea, inner ear
  - Lens placodes → lens, cornea of eyes
- Other ectoderm cells form sensory epithelium (e.g. lining of nose, mouth)
- Other ectoderm cells form epidermis layer of fetal skin, associated structures (e.g. hair, nail, sweat glands, pituitary gland, mammary glands)
- Ectoderm, parietal layer of mesoderm fold around with two sides meeting up in midline
  - Forms anterior body wall, everywhere except middle where yolk sac still pouches out → gut tube formed inside embryo's body (tube inside of tube)

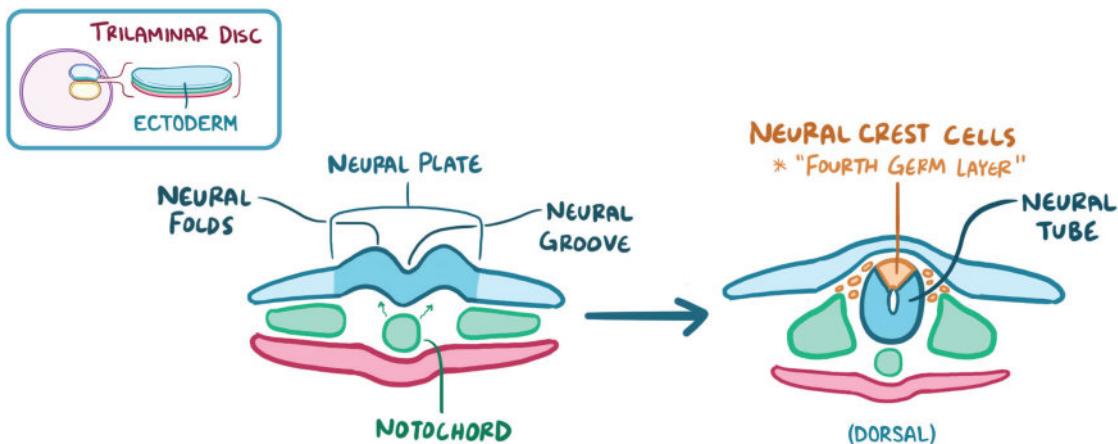
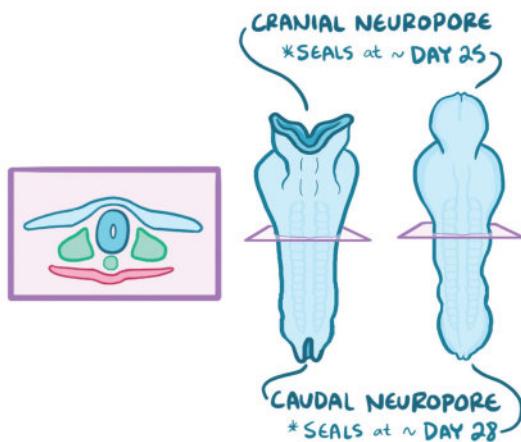
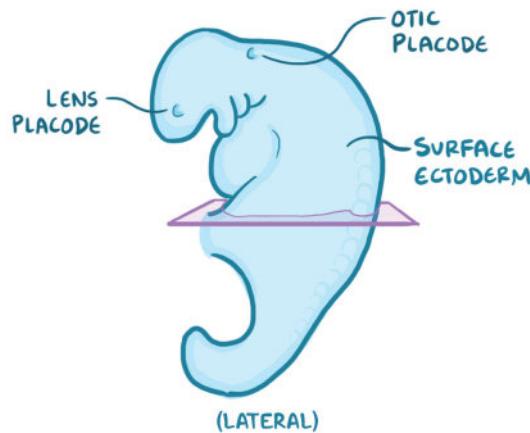


Figure 27.1 Development of neural tube and neural crest cells.



**Figure 27.2** The neural tube initially has openings at each end, called cranial and caudal neuropores. Both pores close by around day 28.

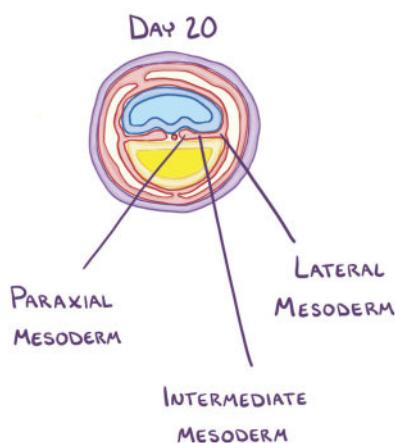


**Figure 27.3** The surface ectoderm forms thickenings—the lens and otic placodes—that become eye and ear structures, respectively.

## MESODERM

[osms.it/mesoderm](http://osms.it/mesoderm)

- Day 20
  - Mesoderm cells around notochord differentiate into three specialized types of cells that will form different tissues, organs
  - Paraxial mesoderm, intermediate mesoderm, lateral plate mesoderm



**Figure 27.4** The three types of mesoderm that develop around day 20.

### Paraxial mesoderm

- Starts to segment into paired tissue blocks called somites, one of each sitting alongside notochord, neural tube above it
  - About three somite pairs form per day in craniocaudal direction
  - By week five, there are 42–44 pairs of somites
  - Number of somites can be used to determine embryo age
- Somites divide into three regions
  - Sclerotome: gives rise to bone, cartilage
  - Myotome: gives rise to muscles
  - Dermatome: gives rise to dermis skin layer

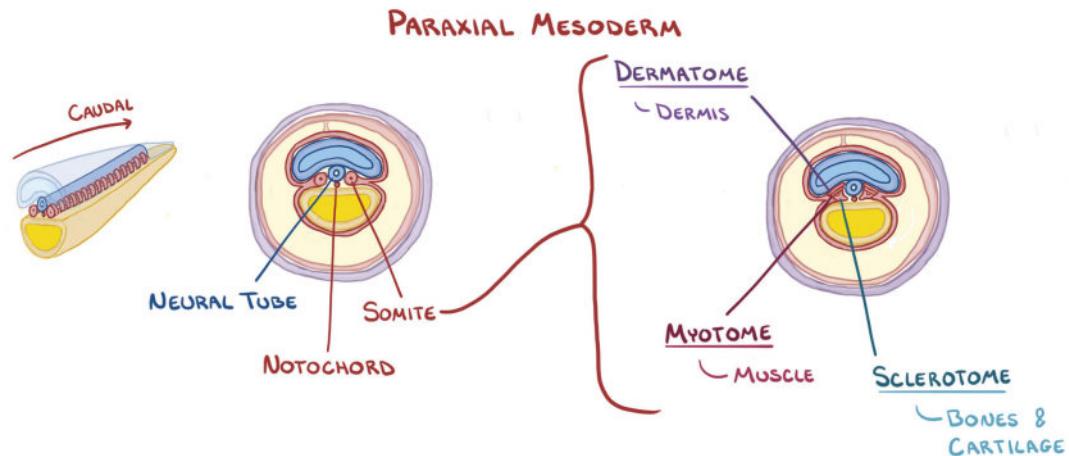
### Intermediate mesoderm

- Gives rise to urogenital structures (e.g. adrenal cortex, kidneys, ovaries, testes)

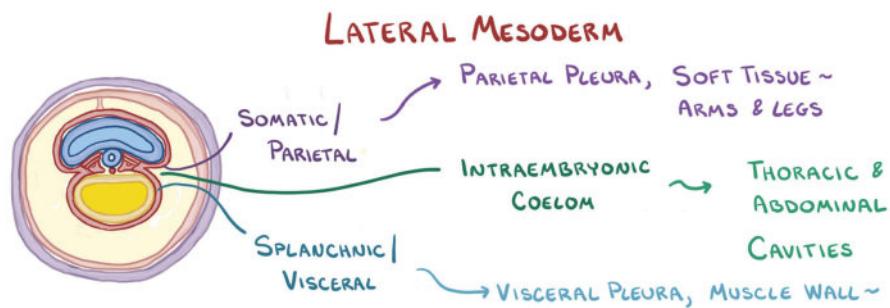
### Lateral plate mesoderm

- Gives rise to serous membranes, soft tissues of arms, legs, muscular gut wall, heart, circulatory system

- Serous membranes
  - Become visceral, parietal serous membranes
- Two layers of visceral membrane come together to form mesentery (suspends gut tube in abdominal cavity)



**Figure 27.5** The paraxial mesoderm segments into somites. The somites then divide into three regions which develop into distinct body structures.

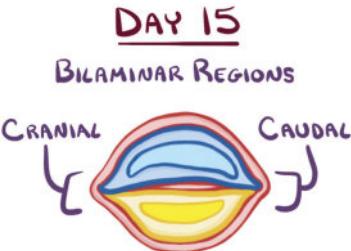


**Figure 27.6** Membranes of the lateral mesoderm and their derivatives.

## ENDODERM

[osms.it/endoderm](http://osms.it/endoderm)

- Day 15
  - Cranial, caudal ectoderm regions push ventrally, fuse with endoderm layer
  - Two bilaminar regions formed
  - Cranial bilaminar region → oropharyngeal membrane → mouth
  - Caudal bilaminar region → cloacal membrane → opening of anus, genitourinary tracts



**Figure 27.7** Cranial and caudal bilaminar regions of the embryo (lateral view).

## ▪ Week 4

- Embryo folds in two directions
- **Longitudinal plane:** cranial, caudal folds; embryo begins to curl into fetal position; folding shapes part of yolk sac into gut tube with rest remaining connected in middle via vitelline duct
- **Transversal plane:** lateral plates of mesoderm split into parietal (somatic) mesoderm layer, visceral (splanchnic) mesoderm layer; parietal mesoderm follows ectoderm, forms chest wall, abdominal body wall; visceral layer of mesoderm follows endoderm, forms gut tube
- Endoderm becomes **epithelial cell lining of gastrointestinal tract**, while mesoderm becomes muscular wall
- In addition to gastrointestinal, respiratory tract epithelium
  - Endoderm gives rise to tonsils, **thyroid, parathyroid glands, thymus**, part of **liver, gallbladder, pancreas**
  - Endoderm cells form parts of ear, epithelial lining of **urethra**, urinary bladder

**GUT TUBE STRUCTURE**

- Gut tube divided into foregut, midgut, hindgut

**Foregut**

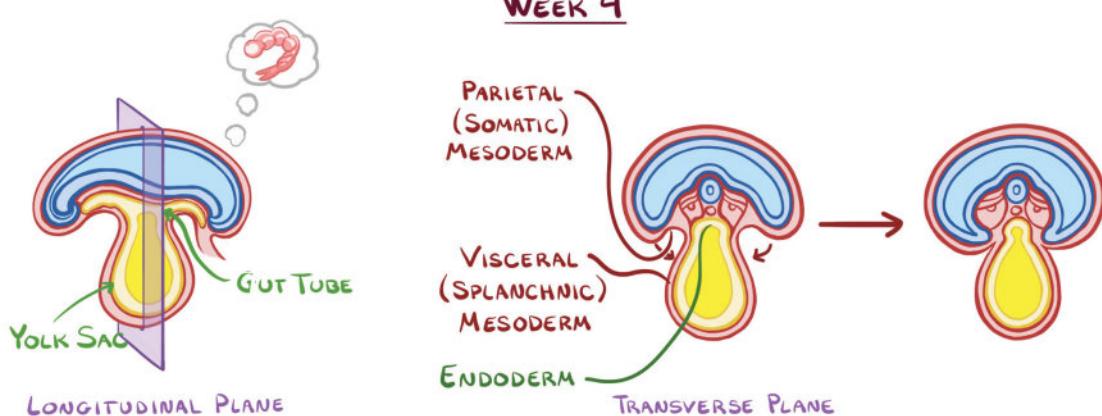
- Around week 4
  - Once oropharyngeal membrane breaks down, foregut (including pharynx) connects to primitive mouth (stomodeum)
- Around week 5
  - Foregut gives rise to trachea, lungs

**Midgut**

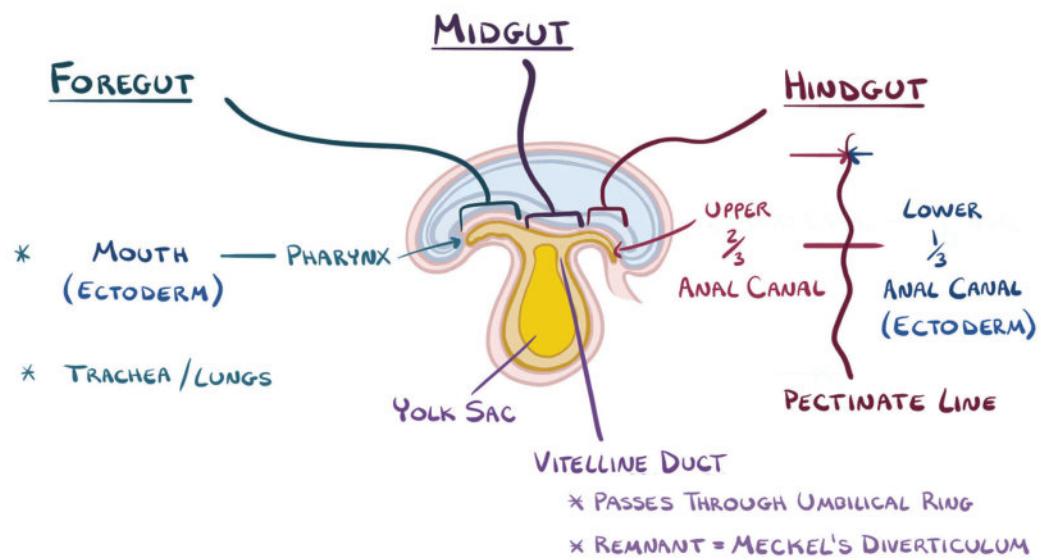
- Remains connected to yolk sac which sits outside body via vitelline duct (yolk stalk) which passes through umbilical ring
- Over time vitelline duct gets thinner, collapses; in some people it remains as Meckel's diverticulum

**Hindgut**

- Around week 7
  - Once cloacal membrane breaks down, **upper two thirds of anal canal** (derived from endoderm) meet up with lower one third of anal canal, called proctodeum (derived from ectoderm)
  - **Pectinate line:** in adults, the line **where the upper two thirds (endoderm) and lower third (ectoderm) of the anal canal meet up**



**Figure 27.8** Week 4: the embryo folds in the longitudinal and transverse planes.



**Figure 27.9** Locations and derivatives of the foregut, midgut, and hindgut (lateral view).



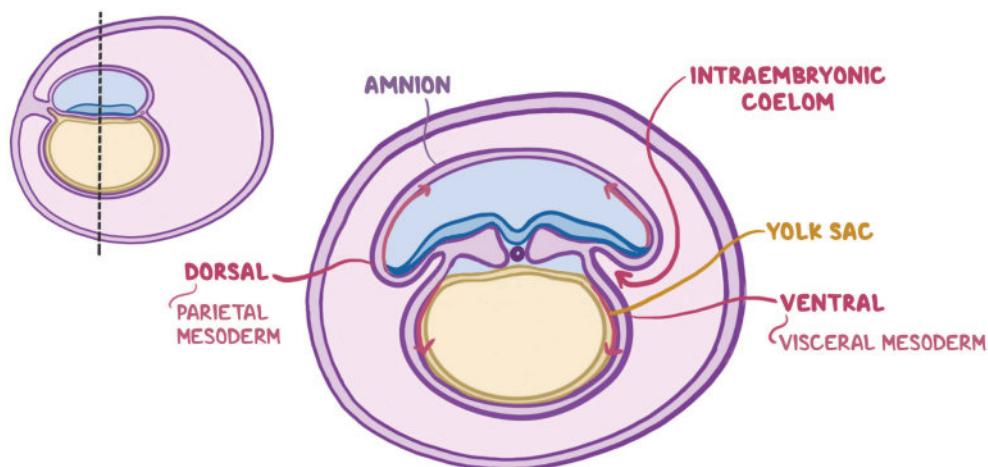
## NOTES EARLY STRUCTURES

# DEVELOPMENT OF THE DIGESTIVE SYSTEM & BODY CAVITIES

[osms.it/digestive-system-and-body-cavities-development](https://osms.it/digestive-system-and-body-cavities-development)

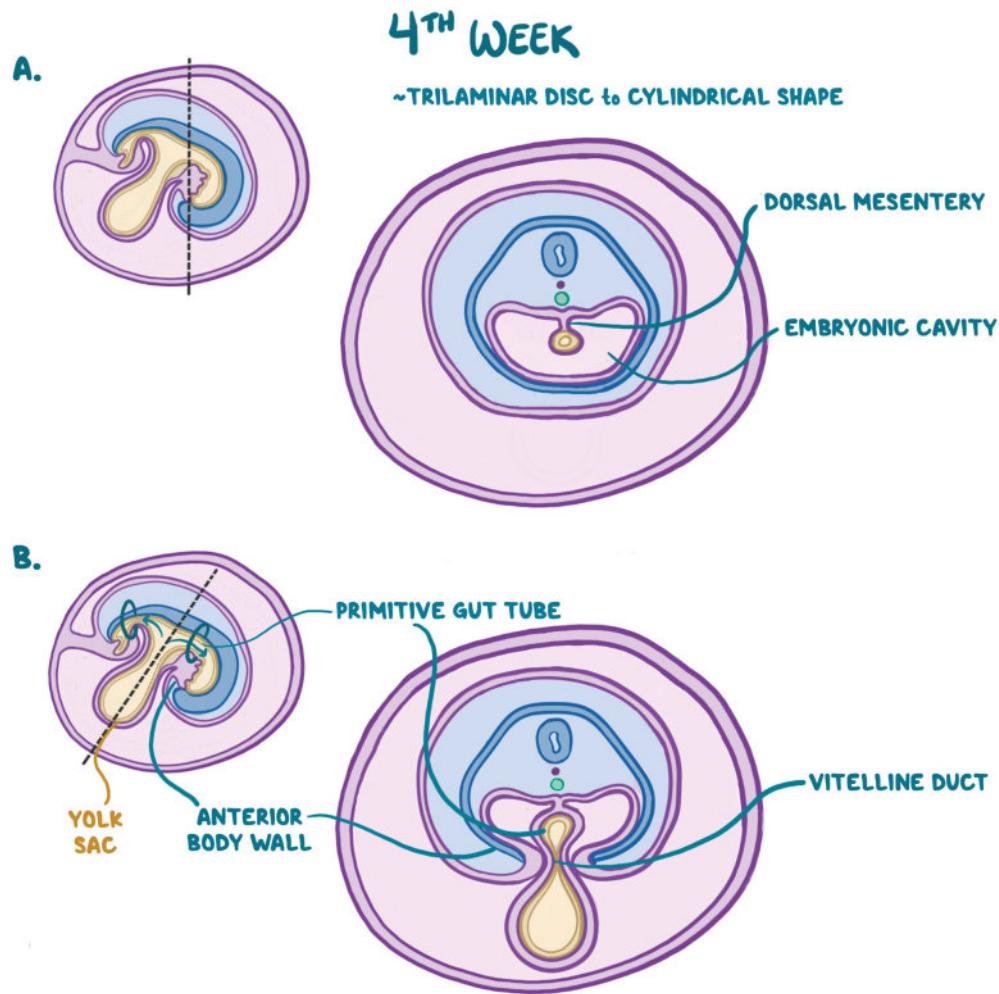
- Endoderm forms gut tube epithelium
- The rest derives from mesoderm
  - Around week 3 lateral mesoderm splits into parietal (somatic) mesoderm → adheres to ectoderm; visceral (splanchnic mesoderm) → adheres to endoderm
  - Space between the split is called intraembryonic coelom/intraembryonic cavity
  - Eventually becomes thoracic, abdominal cavity
- Parietal mesoderm → gives rise to serous membrane that lines abdominal, thoracic cavity (parietal pleural, peritoneal, pericardial membrane), soft tissues of arms, legs
- Visceral mesoderm → gives rise to serous membrane that lines various organs (visceral pleural, peritoneal, pericardial membrane), muscular wall of gut, heart, circulatory system
- Two visceral peritoneal membranes come together, form mesentery (suspends gut tube in abdominal cavity)

### DAY 19



**Figure 28.1** During week 3, lateral mesoderm splits into parietal and visceral mesoderm. They give rise to serous membranes that cover various body parts.

- During week 4 embryo begins to curl into fetal position
  - Combined visceral mesoderm, endoderm layer folds rostrally, caudally → shapes part of yolk sac forming primitive gut tube
  - The rest of yolk sac is connected in middle via vitelline duct
- Combined parietal mesoderm, ectoderm folds down with amnion forming lateral body folds
- Eventually merge, become anterior body wall of embryo



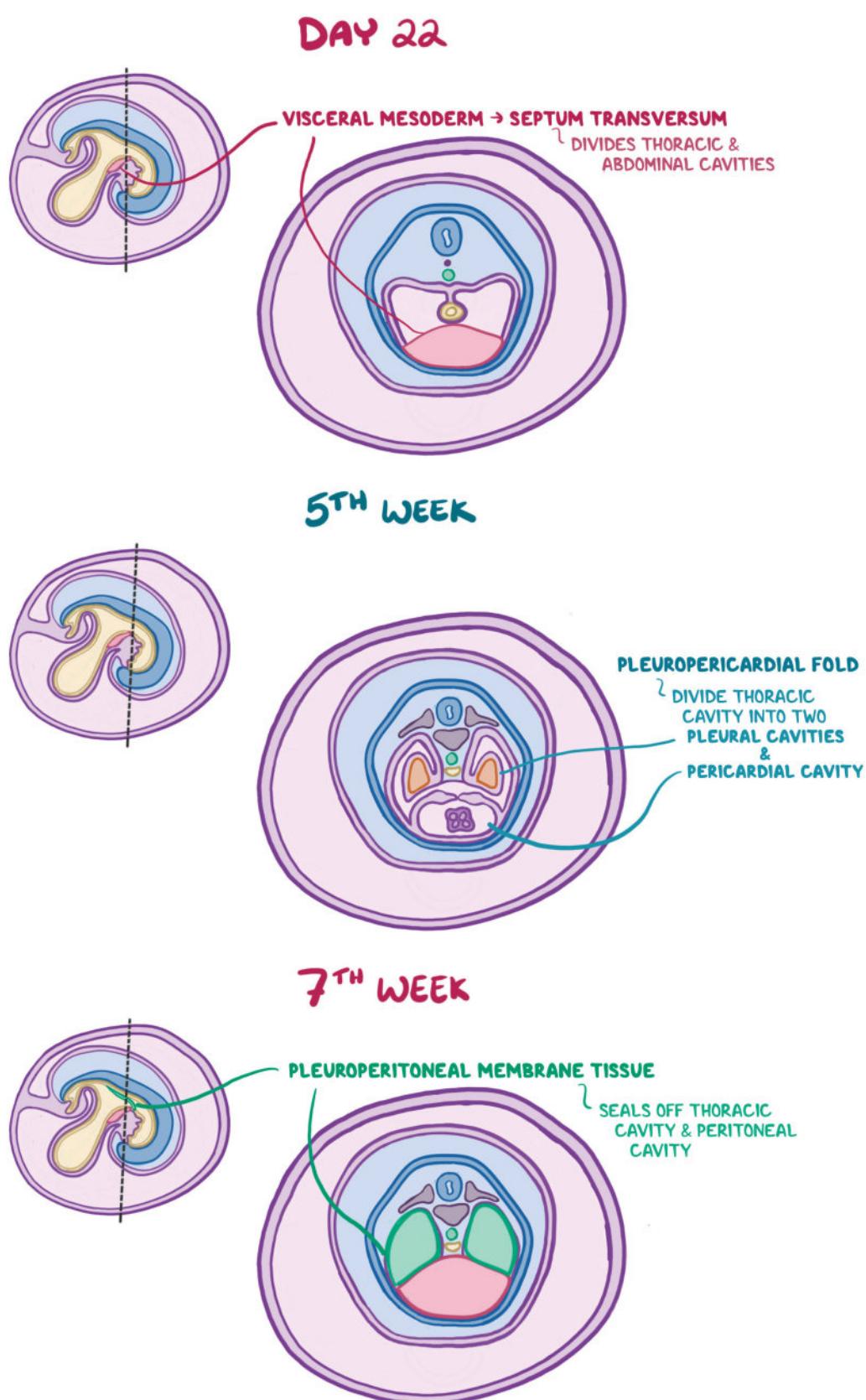
**Figure 28.2** Appearance of the embryo in week 4 in caudal (A) and mid- (B) sections.

## DEVELOPMENT OF BODY CAVITIES

- Around day 22, thick plate of visceral mesoderm called septum transversum forms just cranial to vitelline duct
  - Divides primitive body cavity into thoracic cavity, abdominal cavities
- Around week 5, two tissue flaps called the pleuroperitoneal folds, grow out of lateral body wall, fuse together
  - Divides thoracic cavity into two pleural
- In week 7, pleuroperitoneal folds extend ventrally from body wall, fuse with septum transversum
  - Forms pleuroperitoneal membrane, which seals thoracic cavity from peritoneal cavity
  - Pericardial, pleural cavities in thorax, peritoneal cavity in abdomen

cavities, one pericardial cavity

- In week 7, pleuroperitoneal folds extend ventrally from body wall, fuse with septum transversum
  - Forms pleuroperitoneal membrane, which seals thoracic cavity from peritoneal cavity
  - Pericardial, pleural cavities in thorax, peritoneal cavity in abdomen



**Figure 28.3** Development of body cavities on day 22 and during weeks 5 and 7.

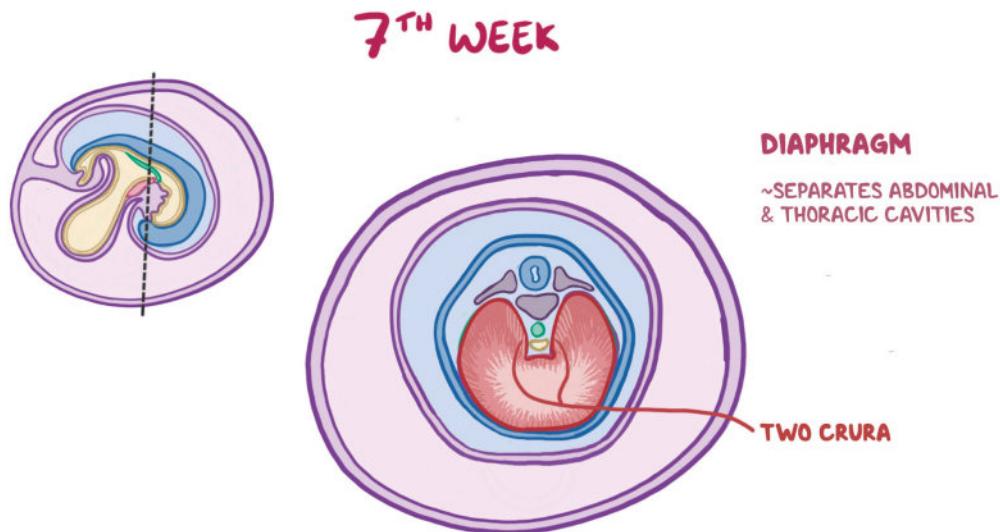
## DEVELOPMENT OF THE DIAPHRAGM

- Develops from four components
  - Septum transversum, pleuroperitoneal membranes, dorsal mesentery of esophagus, from somites at levels C3–C5
- Mesodermal cells from third, fourth, fifth

pairs of somites penetrate pleuroperitoneal membranes

- Form muscular portion of diaphragm

- Septum transversum forms tendinous portion of diaphragm
- Mesoderm of lumbar region gives rise to two crura of diaphragm

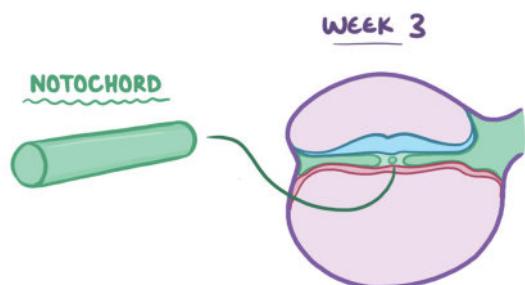


**Figure 28.4** Location of the developed diaphragm.

## THE HEDGEHOG SIGNALING PATHWAY

[osms.it/hedgehog-signaling-pathway](http://osms.it/hedgehog-signaling-pathway)

- Pathway which plays key role in **structuring general body shape**
- Mediated by **sonic hedgehog proteins** secreted by notochord → proteins diffuse through interstitial fluids
- Functions of sonic hedgehog protein
  - Binds to patched receptor on embryonic cell membrane
  - Patched receptor inhibits cell differentiation; sonic hedgehog protein inhibits patched
  - Inhibits the inhibitor → facilitates cell differentiation

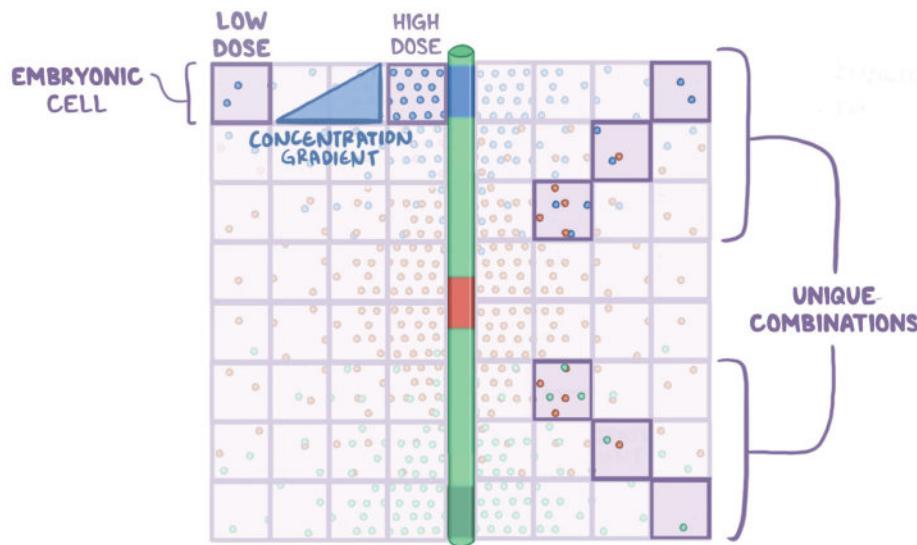


**Figure 28.5** The notochord is a solid line of mesoderm at the center of the embryo. It secretes different kinds of hedgehog proteins.

- Sonic hedgehog proteins control gene expression → gene expression depends on amount of sonic hedgehog protein reaching embryonic cells, duration of exposure
- Notochord secretes different kinds of hedgehog proteins
- Embryonic cells are exposed to different combinations of proteins that helps distinguish their position relative to each other (awareness in space), their course of differentiation

## REGULATION BY HOMEobox GENES

- Homeobox genes code for transcription factors that activate gene cascades which regulate segmentation, craniocaudal patterning
- Homeobox gene products are transcription factors called **Hox proteins**
- Homeobox genes arranged into four clusters on four different chromosomes ▫ HOXA, HOXB, HOXC, HOXD
- Genes toward 3' end of chromosomes control cranial structure development, genes toward 5' end control caudal structure development
- Highly conserved genes across vast evolutionary distances
  - Demonstrated by the fact that a fly can function perfectly well with chicken Hox protein in its place
- **Mutations** in Hox genes can result in **body parts, limbs in the wrong place** along the body e.g. extra fingers/toes



**Figure 28.6** SHH and other notochord proteins diffuse through the embryo, creating a concentration gradient that tells embryonic cells where they are located in three dimensional space. The unique combinations of proteins determine into which tissues the cells differentiate.

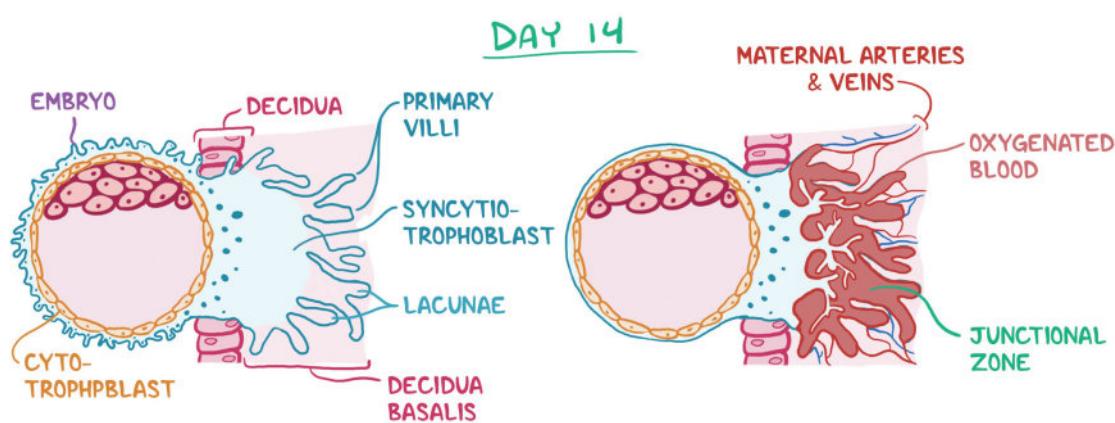
# DEVELOPMENT OF THE PLACENTA

[osms.it/placenta-development](http://osms.it/placenta-development)

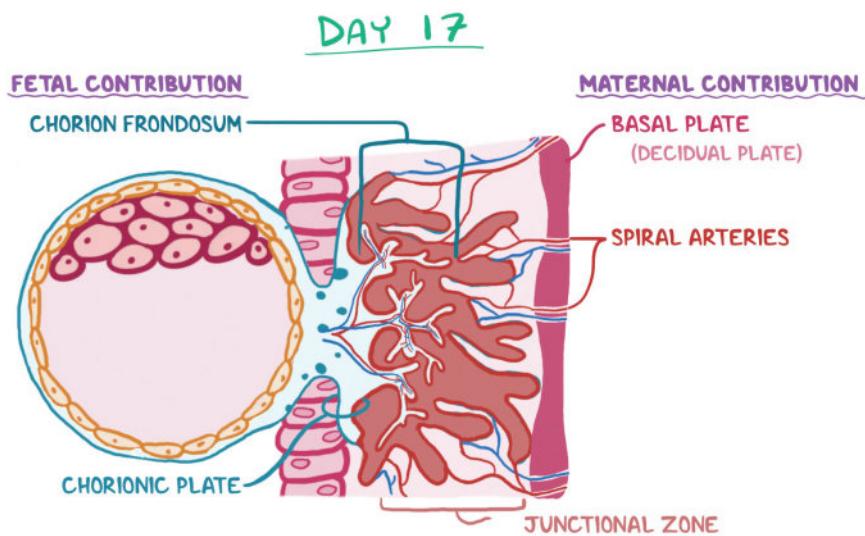
- The placenta is **co-created by fetus, mother**
  - Around day 14, **syncytiotrophoblast** cells form little protrusions called primary villi
    - Villi form all the way around fetus
  - Cells clear out from between primary villi
    - Leave behind empty spaces called lacunae
  - Maternal arteries, veins grow into decidua basalis, merge with lacunae
    - **Maternal arteries fill lacunae with oxygenated blood**
    - Maternal veins pick up deoxygenated blood
    - Junctional zone formed as arteries, veins continue to merge
  - Formation of feto-placental circulation begins on day 9
    - **Day 9, lacunar stage:** vacuoles form lacunae in syncytiotrophoblast; endometrial sinusoids start to **grow into decidua basalis**
    - **Day 12:** sinusoids merge with syncytial lacunae, filling them with blood
    - **Day 14:** cells of **cytotrophoblast** penetrate syncytiotrophoblast, form **primary villi**
    - **Day 16:** extraembryonic mesoderm cells penetrate into primary villi forming secondary villi, later differentiate into small blood vessels (tertiary villi)
  - Around day 17, feto-placental circulation established
    - Fetal mesoderm cells enter primary villi → form fetal arteries, capillaries, veins within each villi
    - Villi capillaries connect to umbilical cord blood vessels → links maternal, fetal circulation
- of decidua basalis tissue that maternal spiral arteries, veins pass through to get to junctional zone
- **Fetal contribution:** derived from chorionic plate (trophoblast, extraembryonic mesoderm)
    - **Chorionic frondosum:** numerous villi that emerge from chorionic plate
    - Junctional zone between basal plate, chorionic plate
  - Space forms around fetus called chorionic cavity
    - Contains amniotic cavity, yolk sac, embryo
    - **Chorion laeve:** chorionic cavity wall where syncytiotrophoblast villi regressed
    - Outside of chorion laeve, thin layer of decidua (decidua capsularis)
  - On ultrasound, chorionic cavity shows up as relatively large, dark space
    - Used to identify pregnancy even before fetus can be seen
  - During fourth, fifth months of development, walls called decidual septa form
    - Divide placenta into 15–20 different regions called cotyledons
  - Each cotyledon contains about 100 spiral arteries providing steady supply of oxygenated blood
  - Oxygen, glucose, molecules like immunoglobulins, hormones, certain toxins are able to move across into fetal capillaries
    - Carbon dioxide moves out of fetal capillaries, enters blood in junctional zone
  - Placenta covers about 15–30% of uterine wall at any given time during development
  - Placenta grows, thickens
    - At full term, is 20cm/7.9in across (size of frisbee)
  - During third stage of labor placenta is expelled from body as afterbirth

## PLACENTAL STRUCTURE

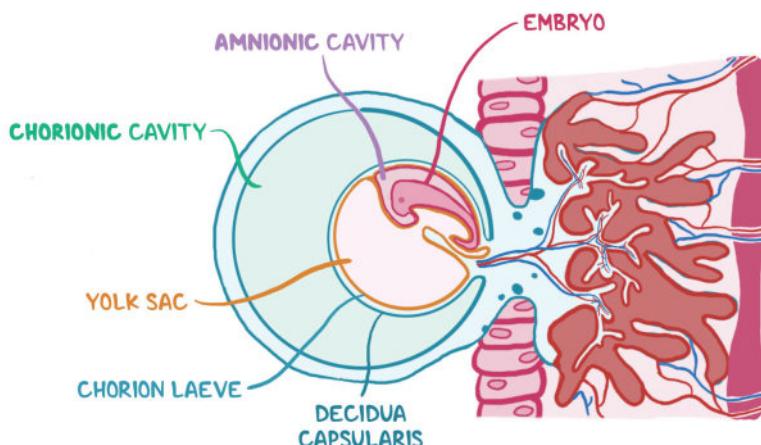
- **Maternal contribution:** derived from uterine endometrium
  - **Basal plate (decidual plate):** thick layer



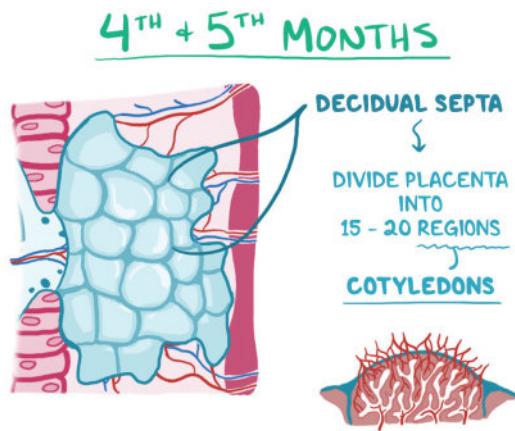
**Figure 28.7** Formation of feto-placental circulation: primary villi form. Cells clear out between primary villi, forming lacunae. Tiny maternal arteries and veins merge with lacunae, and the lacunae fill with oxygenated blood. Lacunae merge to form a single pool, the junctional zone.



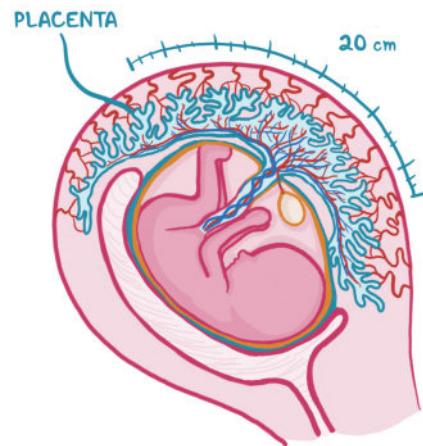
**Figure 28.8** Fetal and maternal contributions to the placenta.



**Figure 28.9** Contents of the chorionic cavity.



**Figure 28.10** Decidual septa form in months four and five that divide the placenta into regions called cotyledons.

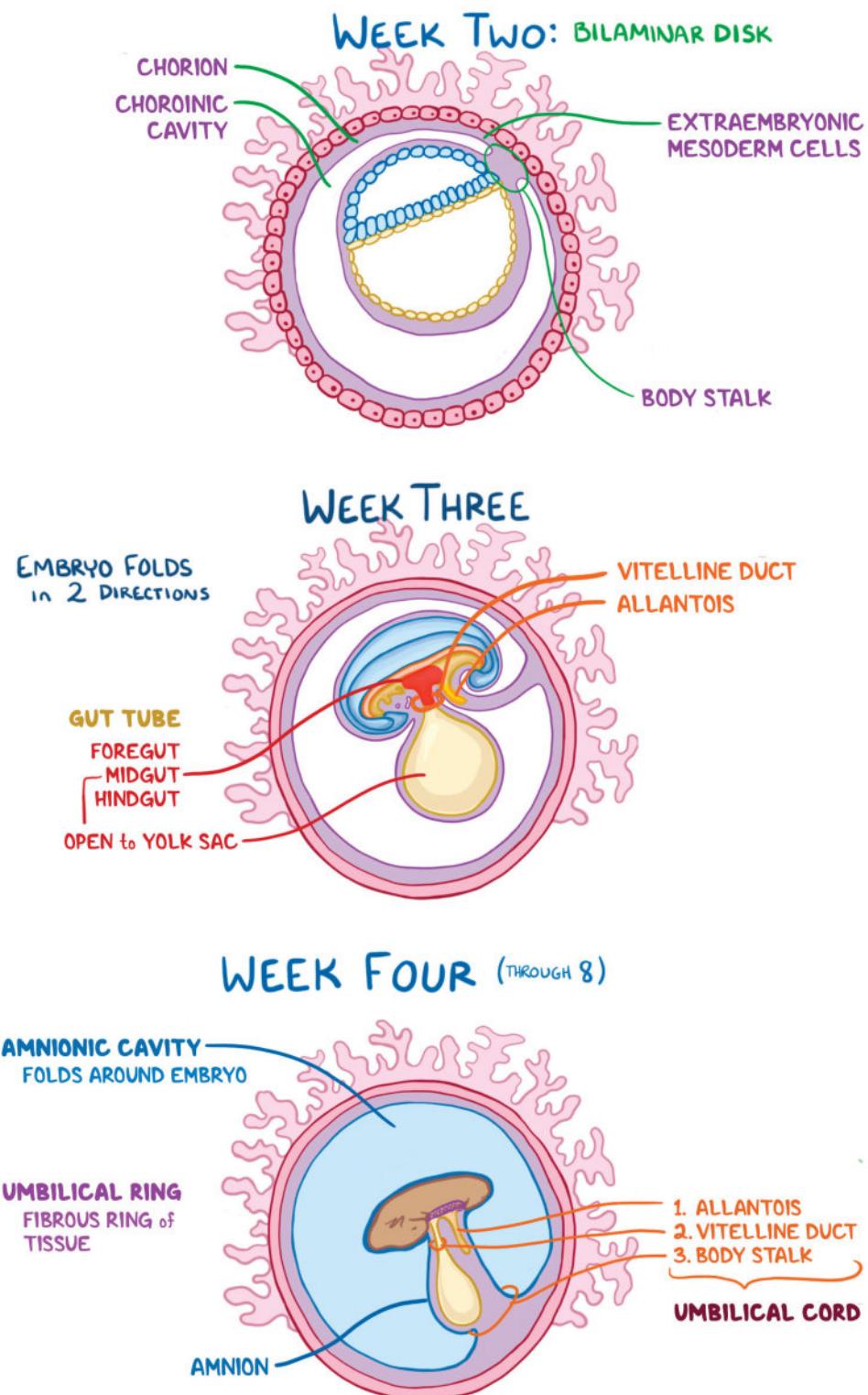


**Figure 28.11** The placenta covers approximately 15–30% of uterine wall and is about 20cm/7.9in across at full term.

## DEVELOPMENT OF THE UMBILICAL CORD

[osms.it/umbilical-cord-development](http://osms.it/umbilical-cord-development)

- Umbilical cord is a long flexible stalk containing **two arteries, one vein**; connects fetus to placenta
- Forms from three structures
  - **Body (connecting) stalk:** short band of extraembryonic mesoderm that connects embryo to chorion at week 2
  - **Vitelline duct:** open connection between yolk sac, midgut at week 3
  - **Allantois:** small hindgut outpocketing that grows into umbilical cord at week 3
- **In week 4:** amniotic cavity folds down, around embryo → body stalk, vitelline duct, allantois pushed together, form umbilical cord → emerge out of umbilical ring (fibrous tissue ring that develops on abdominal wall at location where they emerge)
- **Between weeks 4–8:** cells lining amniotic cavity produce amniotic fluid → amnion swells, takes up most of space in chorionic cavity
  - Amnion folds → covers body stalk, vitelline duct forming an outer membrane for umbilical cord
- **Around week 6:** physiological umbilical herniation
  - Due to rapid intestinal growth, part of intestine herniates through umbilical ring into umbilical cord; withdraws back into abdominal cavity by end of third month
- After umbilical cord formation, **vitelline duct, yolk sac shrink, eventually disappear**
  - If vitelline duct does not regress all the way → Meckel's diverticulum
- Allantois continues developing into bladder
  - **Remnant of allantois:** fetus → urachus; adult → median umbilical ligament
- **Final umbilical cord:** contains two umbilical arteries, one umbilical vein, **gelatinous substance called Wharton's jelly** which protects umbilical vessels
- **After birth:** umbilical vein → round ligament of liver, umbilical arteries; medial umbilical ligaments



**Figure 28.12** Formation of the umbilical cord and structures within it.



**Figure 28.13** Cross section of the umbilical cord revealing its components and their remnants.

## DEVELOPMENT OF THE FETAL MEMBRANES

[osms.it/fetal-membrane-development](http://osms.it/fetal-membrane-development)

- AKA extraembryonic membranes: tissues that form in uterus during first few weeks of development
  - Amnion, yolk sac, chorion, allantois

### AMNION

- On day 8, space appears between epiblast, cytotrophoblast → amniotic cavity
- Cells from epiblast migrate to form thin layer around amniotic cavity, separating it from cytotrophoblast → amnion

### YOLK SAC

- On day 9, hypoblast cells migrate to form thin membrane around blastocoel, forming yolk sac walls → yolk sac fills with vitelline fluid
  - Vitelline fluid provides nourishment for embryo
- Nutrients in yolk sac eventually consumed, yolk sac, vitelline duct shrink, disappear

### CHORION

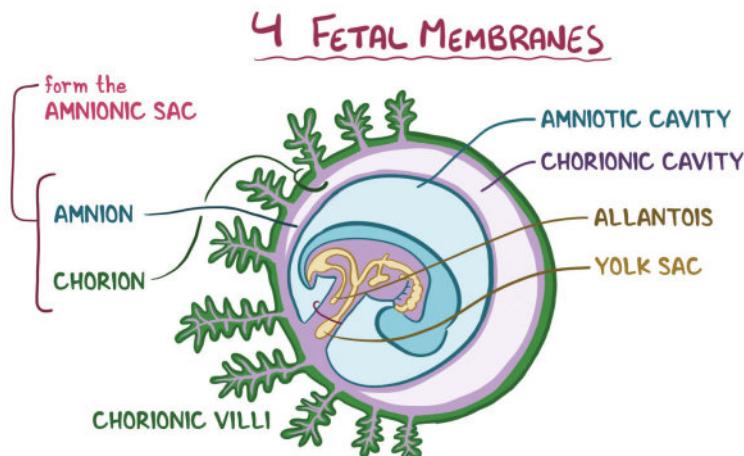
- By day 10, epiblast cells differentiate into extraembryonic mesoderm
  - Settle between amniotic cavity/yolk sac, cytotrophoblast → creating thick layer of extraembryonic mesoderm tissue between the two
  - A space forms within this layer →

extraembryonic coelom/chorionic cavity  
▫ Cavity continues to expand until there is only a thin layer of extraembryonic mesoderm lining amniotic cavity/yolk sac, cytotrophoblast

- Cavity does not form at body stalk where embryoblast remains attached to chorion
  - At this point, chorion contains extraembryonic mesoderm, cytotrophoblast, syncytiotrophoblast
- Chorion develops chorionic villi, invades endometrium, eventually helps form fetal part of placenta

### ALLANTOIS

- Develops as an outpouching of hindgut during week 3
  - Serves as canal through which urine is eliminated, before urethra develops
  - Degenerates into fibrous structure called urachus, remains attached to urinary bladder
- During week 4, allantois, vitelline duct, body stalk combine to form umbilical cord
- Between weeks 4–8, amnion secretes amniotic fluid → amniotic cavity swells, folds down around embryo → protects, insulates embryo → continues to grow → amnion, chorion fuse together, form amniotic sac



**Figure 28.14** Four fetal membranes include: amnion, chorion, allantois, yolk sac.

## DEVELOPMENT OF TWINS

[osms.it/twin-development](https://osms.it/twin-development)

### FRATERNAL (DIZYGOTIC) TWINS

- Occur at rate of about 10 per 1,000 births worldwide
- Originate from **two separate eggs** (hyperovulation) fertilized individually by **two different sperms** → zygotes have completely different genetic makeups
  - Hyperovulation may be due to an overabundance of follicle-stimulating hormone (FSH)
- Mothers of fraternal twins tend to be older (> 35 years), taller, heavier on average, with shorter, more frequent menstrual cycles → high levels of follicle-stimulating hormone

### IDENTICAL (MONOZYGOTIC) TWINS

- Occur at a rate of about 4 per 1000 births worldwide
- Originate from **single zygote that splits into two groups of cells** → zygotes have identical genetic makeup
- The split can occur at **any time during first thirteen days** of development
- Identical DNA → identical physical traits that have a strong genetic basis → sex, hair, eye color, blood type, other physical features

### IDENTICAL TWIN CATEGORIES

- Categorized by how, when division occurs → affects how identical twins share space, resources in uterus

#### Dichorionic-diamniotic

- Division occurs within **2–3 days** following fertilization
- Embryos develop completely separately from one another
- Have separate placentas, amniotic sacs

#### Monochorionic-diamniotic

- Division occurs between **3–8 days** following fertilization
- Embryos share a single placenta, separate amniotic sacs

#### Monochorionic-monoamniotic

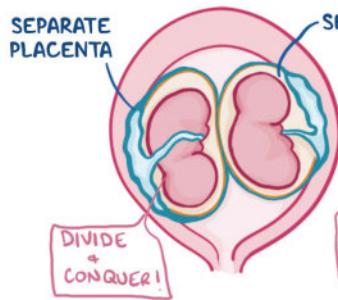
- Division occurs between **8–13 days** after fertilization
- Embryos share both placenta, amniotic sac

## IDENTICAL TWINS

IF SPLIT OCCURS:

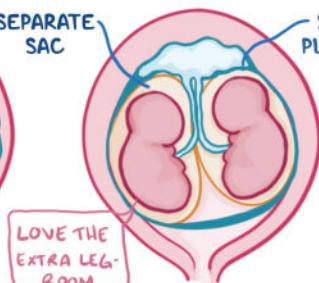
2-3 DAYS AFTER

DICHORIONIC-DIAMNIOTIC



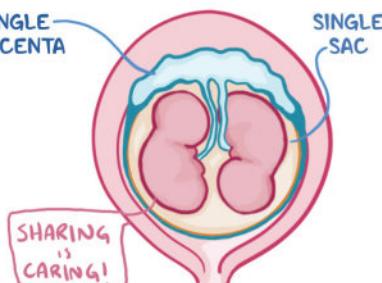
3-8 DAYS AFTER

MONOCHORIONIC-DIAMNIOTIC



8-13 DAYS AFTER

MONOCHORIONIC-MONOAMNIOTIC



**Figure 28.15** The way the womb is shared by identical twins depends on the time frame in which the zygote splits in two.



# NOTES

## BODY SYSTEM STRUCTURES

### DEVELOPMENT OF THE SKELETAL SYSTEM

[osms.it/axial-skeleton-development](https://osms.it/axial-skeleton-development)

- Follows gastrulation (AKA formation of ectoderm, mesoderm, endoderm)

#### Axial skeleton

- Skull, vertebrae, rib cage, sternum
- Derived from mesoderm
- Exception: some skull bones come from ectoderm

#### Appendicular skeleton

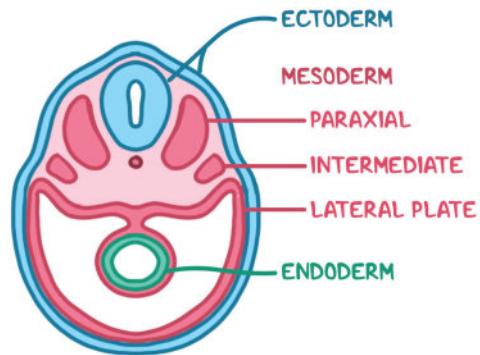
- Pelvic, shoulder girdles; bones in limbs
- Derived from mesoderm

#### Pathways of bone development

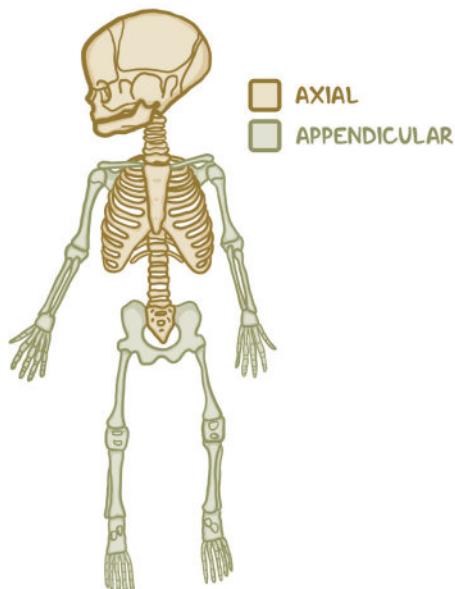
- AKA ossification
- Two pathways
  - Endochondral, intramembranous

#### Endochondral ossification

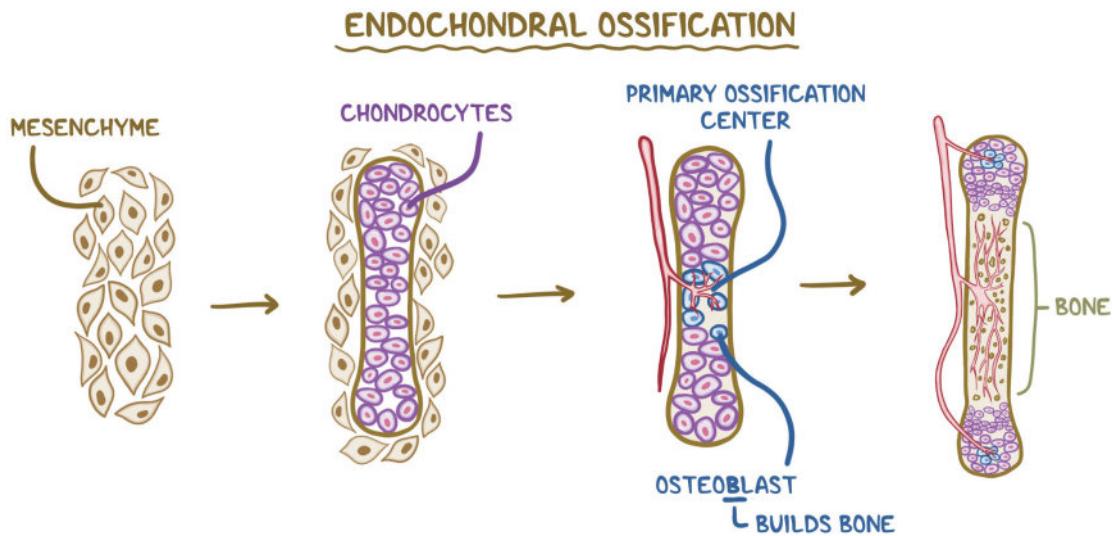
- Almost all bones
  - Exceptions: clavicles; parietal, frontal bones of skull; maxilla; mandible; nasal bone; parts of temporal, occipital bones
- Hyaline cartilage serves as bone formation model
  - Mesenchymal cells differentiate into chondrocytes, which form cartilaginous model
  - Bone develops by replacing cartilage



**Figure 29.1** Cross section through an embryo demonstrating ectoderm, mesoderm, and endoderm. Paraxial and lateral plate mesoderm give rise to bones and muscles.



**Figure 29.2** Axial and appendicular skeletons.



**Figure 29.3** Endochondral ossification: the primary ossification center is at the center of the cartilage model. Blood vessels enter the primary ossification center, bringing nutrients, osteoblasts, and osteoclasts. Osteoblasts replace chondrocytes at the primary ossification center and replace cartilage with bone. Osteoclasts start to break down the center of bone, which leads to the formation of bone marrow.

#### Intramembranous ossification

- Clavicle, flat bones (e.g. parietal bones, mandible)
- Bone develops directly on membranous sheaths
  - Mesenchymal cells differentiate into osteoblasts, secrete osteoid (AKA unmineralized matrix)
  - Osteoid calcifies after deposition of calcium phosphate

#### DEVELOPMENT OF THE SKULL

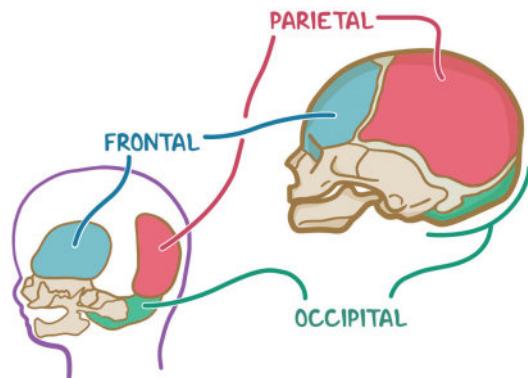
##### Neurocranium

- Encases brain
- Three parts
  - Membranous neurocranium, cartilaginous neurocranium/ chondrocranium, viscerocranium

##### Membranous neurocranium

- Comprises flat bones that cradle brain
- AKA cranial vault
- Derived from neural crest cells, paraxial mesoderm
- Ossifies via intramembranous ossification

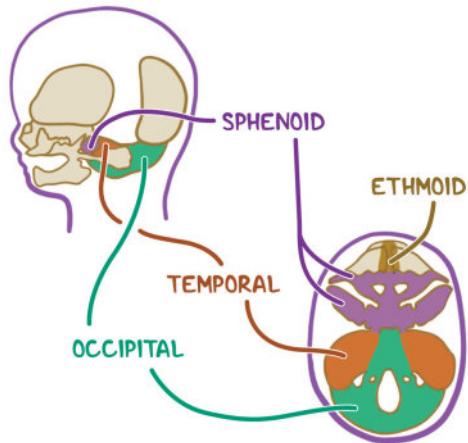
#### MEMBRANOUS NEUROCRANIUM



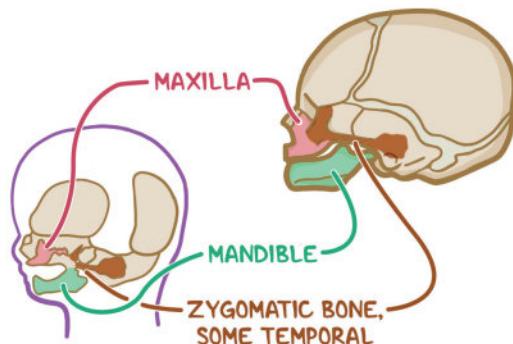
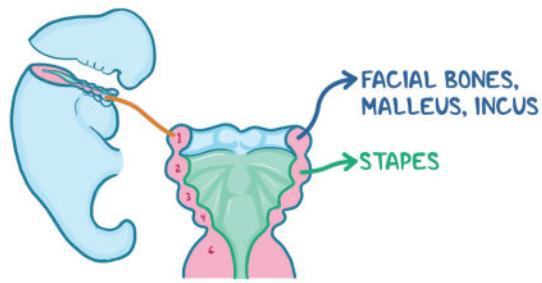
**Figure 29.4** Lateral view of membranous neurocranium. It is composed of the flat bones that form a hard, protective shell around the brain.

##### Cartilaginous neurocranium

- AKA chondrocranium
- Bones around base of skull
- Derived from neural crest cells, paraxial mesoderm; become prechordal, chordal chondrocranium, respectively
- Ossifies via endochondral ossification

**CARTILAGINOUS NEUROCRANUM**

**Figure 29.5** Lateral view (left) and superior view (right) of bones comprising cartilaginous neurocranium.

**VISCEROCRANIUM**

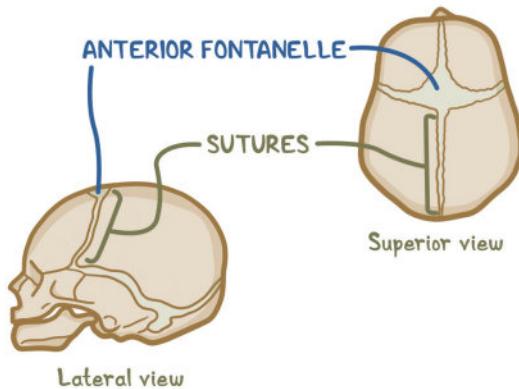
**Figure 29.6** The viscerocranum arises primarily from the first pharyngeal arch with stapes arising from the second arch. The viscerocranum is composed of the facial bones (illustrated here in a lateral view).

**Viscerocranum**

- Facial bones
- Six pharyngeal arches; facial bones arise from first arch
  - Dorsal side: maxilla, zygomatic bones, parts of temporal bone
  - Ventral side: Meckel's cartilage undergoes intramembranous ossification; becomes mandible
  - Dorsal tip of mandibular process, second pharyngeal arch → become incus, malleus, stapes

**Temporary skull structures**

- Skull bones not fully fused at birth
  - Allows molding of fetal head during passage through birth canal
  - Closes by 18 months old, allows brain growth
- Sutures: narrow gaps between bone plates filled with fibrous tissues
- Fontanelles: wide sutures where > two bones meet
  - Anterior fontanelle most prominent
  - Where two parietal, two frontal bones meet

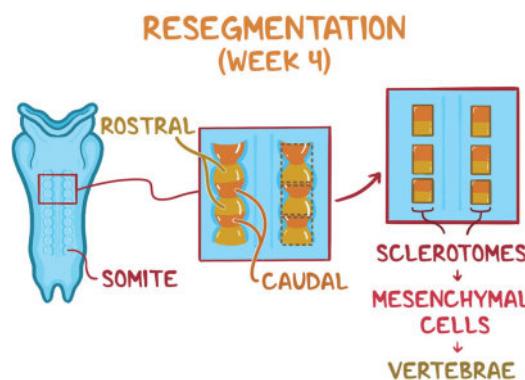


**Figure 29.7** Lateral and anterior view of the anterior fontanelle where the frontal and parietal bones meet.

## VERTEBRAE, RIBS, & STERNUM

### Spinal vertebrae

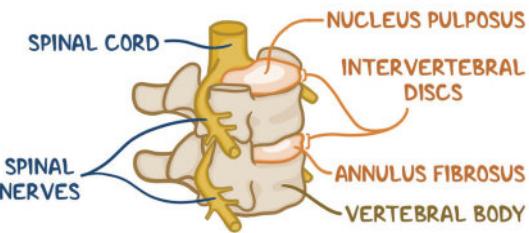
- Week 4: develop from somites
- Sclerotome portion undergoes resegmentation
  - Sclerotome cells from cephalic portion of somite fuse with caudal portion of neighboring somite
- Sclerotome cells surround notochord, spinal cord; transform into mesenchymal cells
- Mesenchymal cells form vertebrae through endochondral ossification
- Ribs then emerge from costal facets of thoracic vertebrae



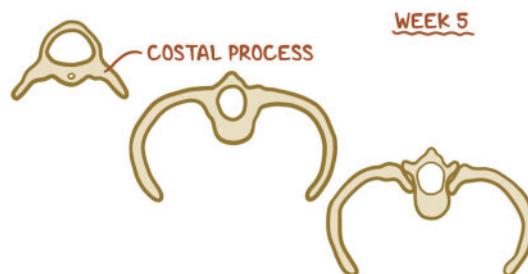
**Figure 29.8** Spinal vertebrae development occurs by resegmentation of somites.

### Intervertebral discs

- Arise from mesenchymal cells between cephalic, caudal sclerotome segment
- Notochord enlarges in area of intervertebral disc, contributing to nucleus pulposus
  - Intervertebral disk formed as nucleus pulposus surrounded by annulus fibrosus
- Myotomes bridge intervertebral discs, form vertebral muscles
- Primary spinal curves established: thoracic, sacral



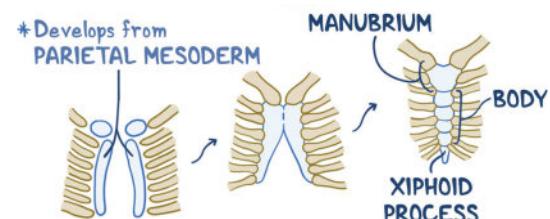
**Figure 29.9** Relationship between vertebrae, intervertebral discs, spinal cord, and spinal nerves.



**Figure 29.10** Rib development arises from costal processes of thoracic vertebrae.

### Sternum

- Arises from parietal mesoderm layer in anterior body wall
- Cartilaginous bars form on either side of midline, fuse
  - Differentiate into manubrium, main body of sternum, xiphoid process



**Figure 29.11** Sternum development arises from parietal mesoderm.

# DEVELOPMENT OF THE MUSCULAR SYSTEM

[osms.it/muscular-system-development](https://osms.it/muscular-system-development)

## KEY POINTS

- Mesoderm: becomes vast majority of muscles
- Paraxial mesoderm: becomes skeletal muscle
- Visceral/splanchnic mesoderm: becomes cardiac muscle, some smooth muscle
- Ectoderm: becomes remaining smooth muscle

## DEVELOPMENT OF SKELETAL MUSCLE

### Mesodermal cells

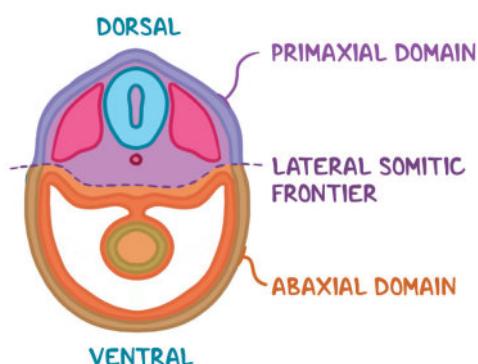
- Form myogenic cells, which undergo mitosis
- Form postmitotic myoblasts
  - Synthesize actin, myosin
- Fuse, form multinucleated myotubes
  - Myotubes synthesize actin, myosin, troponin, tropomyosin, other muscle proteins
- Proteins aggregate, **form** myofibrils (AKA **muscle fibers/cells**)

### Paraxial mesoderm

- Divides into segments, AKA somitomeres, in craniocaudal sequence
- Seven somitomeres form head, neck muscles
  - Contribute to pharyngeal arches' formation
- Remaining somitomeres form 35 pairs of somites for trunk region
- Undergo epithelialization
  - AKA form balls of epithelial cells

### Somites

- Ventral region of each somite forms sclerotome
  - AKA bone-forming cells
- Upper region of each somite forms dermatome plus two muscle-forming areas
- Cells of ventrolateral, dorsomedial lip of somites migrate ventral to dermatome, proliferate there to form dermomyotome
  - Exception: some cells of ventrolateral lip migrate into parietal mesoderm layer of lateral plate mesoderm; these contribute to abaxial domain, discussed below
- Lateral somitic frontier separates somite clusters from parietal mesoderm into two domains
  - **Primaxial domain:** consists of somites around neural tube; receives signals for differentiation from notochord, neural tube; forms shoulder, back, intercostal muscles
  - **Abaxial domain:** receives signals for differentiation from lateral plate mesoderm; forms infrahyoid, abdominal wall, limb muscles



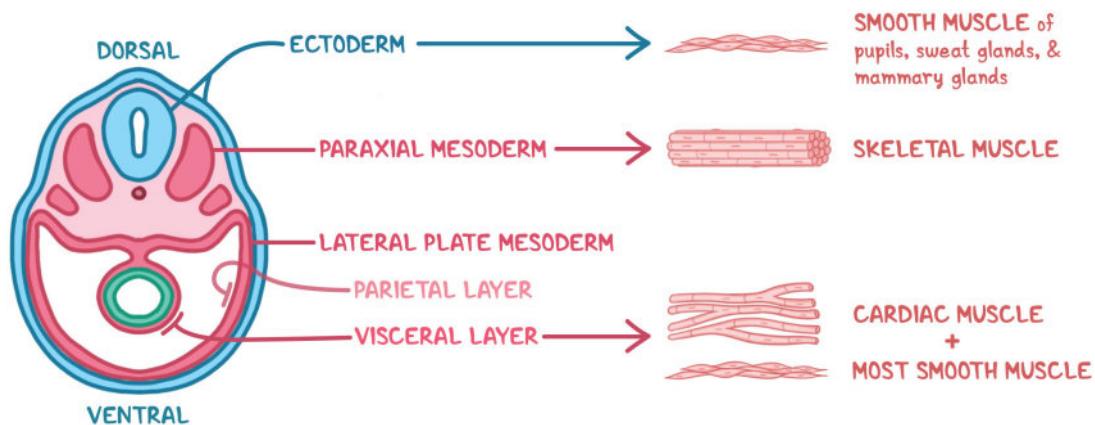
**Figure 29.12** Divisions of mesoderm created by lateral somitic frontier.

## DEVELOPMENT OF CARDIAC MUSCLE

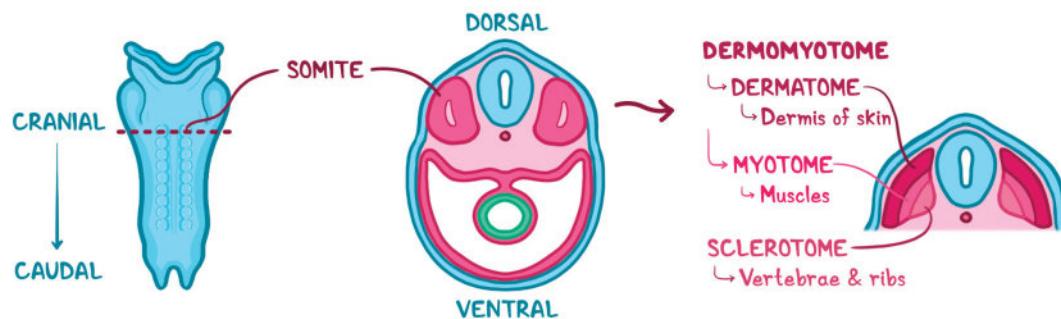
- Develops from visceral (i.e. splanchnic) mesoderm surrounding endothelial heart tube
- Myoblasts adhere via special attachments, which later become intercalated discs
- Patterning of striations forms branch-like lines
  - Unlike straighter lines of skeletal muscles

## DEVELOPMENT OF SMOOTH MUSCLE

- Paraxial mesoderm cells from first seven somite pairs form smooth muscle of head
  - Includes tongue, jaw muscles, throat muscles
- Develops in response to signals released by neural crest cells
- Visceral/splanchnic mesoderm surrounding gut tube → becomes digestive system muscles
- Ectoderm → becomes sphincter, dilator muscles of pupils, mammary glands, sweat glands
- Proepicardial cells, neural crest cells → becomes smooth muscle of aorta, arteries



**Figure 29.13** Cross section through an embryo demonstrating the origins of skeletal, cardiac, and smooth muscle.



**Figure 29.14** Different regions of the somite form different body structures. The myotome is responsible for skeletal muscle formation.

# DEVELOPMENT OF THE LIMBS

[osms.it/limb-development](http://osms.it/limb-development)

## Limb buds: overview

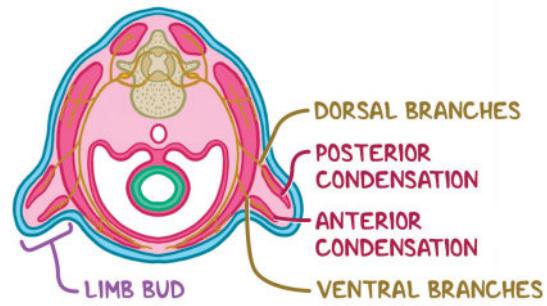
- End of week 4: limb buds visible on ventrolateral body wall
- Limb bud structure
  - Mesenchymal core: forms connective tissue, bones
  - Myotomes: form muscles
  - Ectoderm cover: forms epidermis of skin

## Connective tissue & bones

- Development determined by series of interactions between ectoderm, mesenchyme
- Ectoderm at the limb apex proliferates, forms apical ectodermal ridge (AER) → induces adjacent mesenchyme to remain undifferentiated, rapidly proliferating cells
  - AKA undifferentiated zone
- Ectoderm further influences mesenchyme
- Mesenchyme differentiates into cartilage, muscle; forms three components proximo-distally
  - Stylopod: becomes humerus/femur
  - Zeugopod: becomes radius/ulna, tibia/fibula
  - Autopod: becomes carpals, metacarpals, metatarsals
- Week 6: limb bud apexes flatten, become hand, foot plates
- Fingers, toes formed via localized apoptosis induced by AER
  - Separates hand, foot plates into five parts
- Mesenchyme underneath differentiates into chondrocytes
  - Chondrocytes form primary hyaline cartilage models of future bones
- As chondrogenesis stops, joint formation induced
  - Condensed mesenchyme differentiates into dense fibrous tissue (forms articular cartilage, synovial membrane, menisci, ligaments of joint)

## Limb muscle development

- Derived from dorsolateral cells of somites
  - AKA myotomes
  - Myotomes from C4-T2 migrate to upper limb
  - Myotomes from L2-S2 migrate to lower limb
- During migration to limbs, myotomes form two compartments
  - Anterior condensation → flexor, pronator muscles of upper limb; flexor, adductor muscles of lower limb
  - Posterior condensation → extensor, supinator muscles of upper limb; extensor, abductor muscles of lower limb
  - Ventral primary branches of spinal nerves, mesenchyme divide; form dorsal, ventral branches to these compartments
  - Week 7: limbs rotate
- Upper limb rotates 90° laterally
  - Lower limb rotates 90° medially

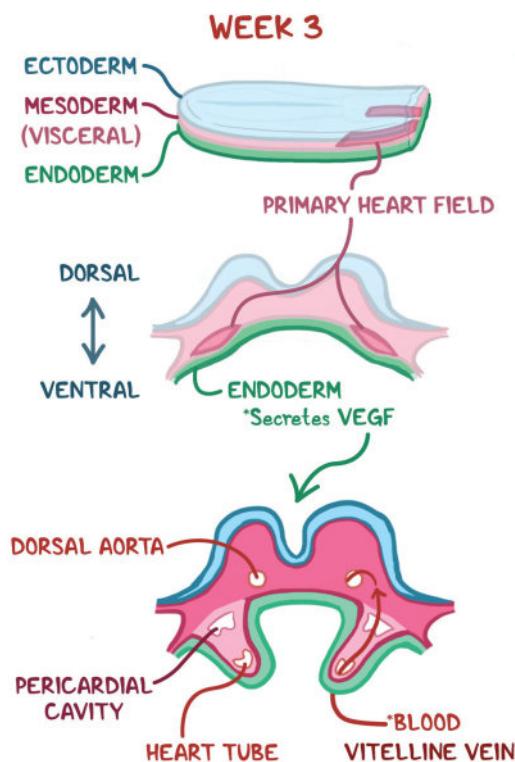


**Figure 29.15** Limb muscle development: myotomes migrate to limbs, forming anterior and posterior condensations that are innervated by ventral and dorsal branches of the spinal nerve's primary ventral branches.

# DEVELOPMENT OF THE CARDIOVASCULAR SYSTEM

[osms.it/cardiovascular-system-development](https://osms.it/cardiovascular-system-development)

- Begins during week 3
- Mesoderm cells travel through primitive streak to embryo's head, form horseshoe-shaped area with two limbs
  - AKA primary heart field
- Vascular endothelial growth factor (VEGF) signals limbs' cells to organize into two tubes
- Lateral mesoderm splits into somatic, splanchnic layers
  - Concurrently, primitive pericardial cavity forms lateral to each tube
- At inferior end, each endocardial tube connects to vitelline vein stemming from yolk sac
- Mesoderm cells also form pair of longitudinal vessels (AKA dorsal aortae)

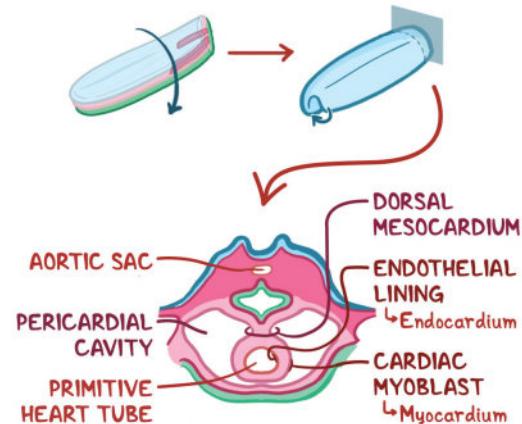


**Figure 29.16** Early development of the cardiovascular system starting in week 3.

## LATERAL FOLDING OF EMBRYO

- Embryo folds into cylindrical shape as lateral borders meet at midline
  - Two endocardial tubes fuse, forming primitive heart tube
- Left, right vitelline veins also fuse, forming sinus venosus
  - AKA inflow tract
- Aortae fuse, forming aortic sac
  - AKA outflow tract
- Primitive pericardial cavities fuse around heart tube, forming pericardial cavity
- Heart tube remains attached to pericardial cavity by sheet of mesoderm called dorsal mesocardium; heart tube now has two layers (endothelial lining, cardiac myoblasts)
- Endothelial lining forms endocardium
- Cardiac myoblasts form myocardium
  - Some myocardial cells in sinus venosus begin to produce rhythmic electrical discharge
- Mesenchymal cells of dorsal mesocardium form proepicardial organ
  - These cells proliferate, migrate over myocardium, form epicardium

## LATERAL FOLDING

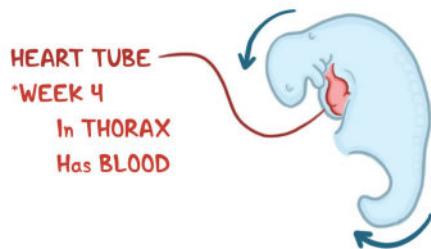


**Figure 29.17** Structures formed as a result of lateral folding of the embryo.

## CRANIOCAUDAL FOLDING OF EMBRYO

- Cylindrical embryo folds down its length, forming shrimp-like shape
  - Heart pushed toward chest
- By week 4: heart tube reaches thorax, circulating blood can be seen travelling through heart tube

## CRANIOCAUDAL FOLDING



**Figure 29.18** Craniocaudal folding of the embryo places heart tube in thorax.

## PARTITION OF THE HEART TUBE

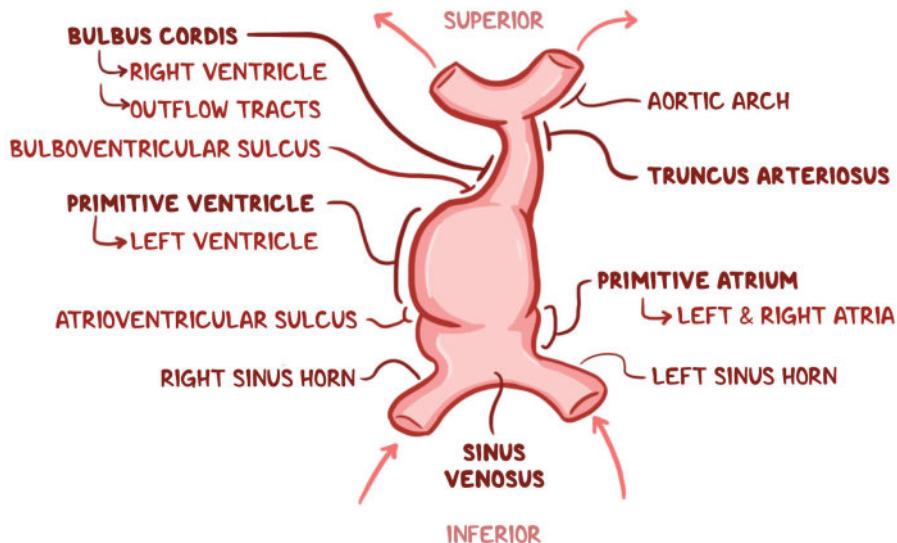
### Sections of the heart tube

- Sinus venosus: left, right sinus horn bring in blood
- Primitive atrium, primitive ventricle separated by atrioventricular sulcus

- Primitive atrium: becomes left, right atria
- Primitive ventricle: forms left ventricle
  - Separated from bulbus cordis by bulboventricular sulcus
- Bulbus cordis: forms right ventricle, outflow tracts for both ventricles
- Truncus arteriosus: at top of heart tube
  - Pumps blood through aortic sac into early version of circulatory system

## LOOPING OF THE HEART TUBE

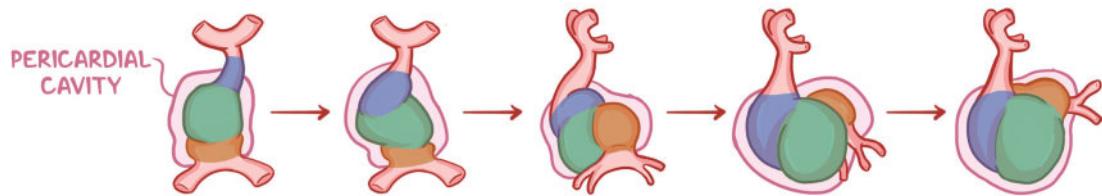
- Heart tube folds into “C” shape
- Truncus arteriosus and bulbus cordis move down, to right
  - Form top portion of “C”
- Primitive ventricle bends to right of midline, slightly to front
  - Forms middle portion of “C”
- Primitive atrium, sinus venosus
  - Form bottom of “C”
- Enlarging ventricle moves left
  - Crosses over midline again, covers primitive atrium
- Visceral pericardium attaches to outside of heart, forms epicardium



**Figure 29.19** Heart tube sections and the structures they become.

## LOOPING

BULBUS CORDIS → RIGHT VENTRICLE  
 PRIMITIVE VENTRICLE → LEFT VENTRICLE  
 PRIMITIVE ATRIUM → LEFT & RIGHT ATRIA



**Figure 29.20** During week 4, the heart tube undergoes looping: tube lengthens, walls thicken, and sections move towards appropriate locations to continue development.

## FURTHER PARTITIONING OF THE HEART

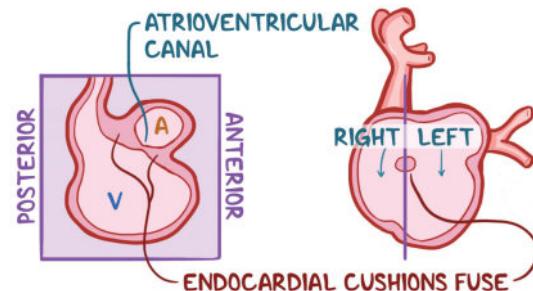
- Mesoderm proliferates on anterior, posterior walls of atrioventricular canal
  - Forms anterior, posterior endocardial cushion
  - Cushions grow towards each other, fuse
- Heart now separated into left, right atrioventricular canals
- Endocardial cells proliferate on ventricular side of each canal
  - These form leaflets of mitral, tricuspid valves
- Canals now divided into atria, ventricles

### Formation of the atria

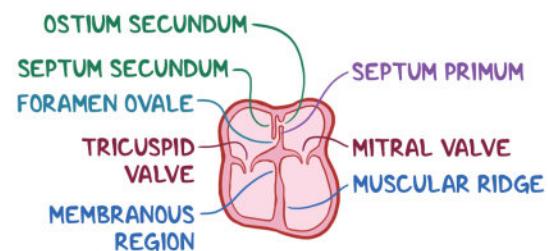
- Crescent-shaped septum primum grows downward between future left, right atria
  - Opening (AKA ostium primum) remains
- Septum primum continues to grow, fuses with endocardial cushion, closes ostium primum completely
- Ostium secundum appears in center of septum primum
- **Septum secundum** grows downward just to right of septum primum, covers ostium secundum
  - Leaves small opening (AKA foramen ovale)
- Septum secundum acts as one-way valve, allowing blood flow from left to right atrium
- After birth, closure of foramen ovale is facilitated by
  - ↓ in right atrial pressure due to occlusion of placental circulation
  - ↑ in left atrial pressure due to ↑ pulmonary venous return

### Formation of ventricles

- Muscular ridge of tissue grows upward from apex, fuses with thinner membranous region coming down from endocardial cushions
  - Forms left, right ventricles
- **End of week four:** cardiac loop starts to take shape of adult heart



**Figure 29.21** Fusion of the endocardial cushions separates the heart into right and left atrioventricular canals.

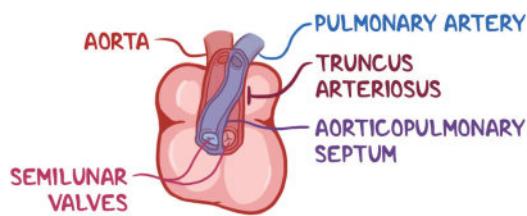


**Figure 29.22** Structures contributing to the formation of the atria and ventricles.

## DEVELOPMENT OF THE ARTERIAL SYSTEM

### Development of the aorta

- Starts with division of truncus arteriosus
- Two endocardial cushions appear on right-superior, left-inferior walls
- Cushions grow with spiraling trajectory, wrap around each other
- Form aorticopulmonary septum
  - Divides into root of aorta, pulmonary artery
  - Semilunar valves develop shortly after



**Figure 29.23** Anterior view of heart visualizing development of the aorta and pulmonary artery.

### Arteries of head & neck region, pulmonary arteries

- Come from five aortic arches
- 1<sup>st</sup> arch: maxillary artery
- 2<sup>nd</sup> arch: stapedial artery
- 3<sup>rd</sup> arch: two common carotid arteries, part of internal carotid arteries
- 4<sup>th</sup> aortic arch
  - Left 4<sup>th</sup> arch: aortic arch
  - Right 4<sup>th</sup> arch: right subclavian artery
- 6<sup>th</sup> arch: pulmonary arteries, ductus arteriosus

### Remaining arteries

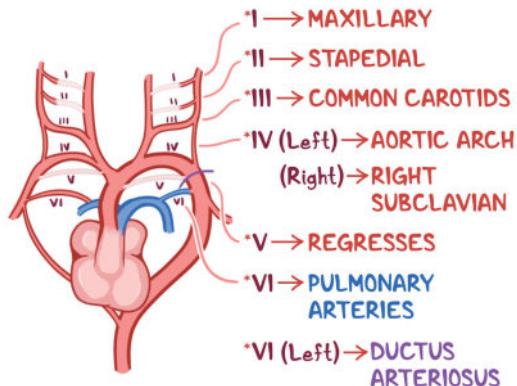
- Develop mainly from right, left dorsal aortae → fuse during lateral folding, form dorsal aorta
- Dorsal aorta sprouts posterolateral arteries; lateral arteries; ventral arteries (AKA vitelline, umbilical)

## DEVELOPMENT OF THE VENOUS SYSTEM

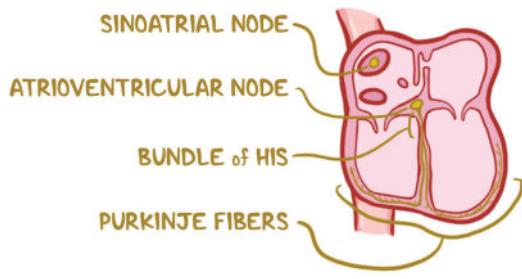
- Develops from sinus venosus
- Week 4: sinus venosus receives deoxygenated blood from sinus horns, opens in center of primitive atrium
- Each horn receives blood from vitelline/omphalomesenteric veins, umbilical veins, common cardinal veins
- Next, sinus venosus becomes asymmetric, shifts to right
  - Caused by left to right shunts
- Right sinus horn enlarges; becomes smooth-walled part of right atrium; forms openings for superior, inferior vena cavae
- Left sinus horn shrinks; persists as coronary sinus, oblique vein of left atrium

## DEVELOPMENT OF THE CONDUCTING SYSTEM

- Special group of myocardial cells in wall of sinus venosus organize, synchronize their electrical discharge, form pacemaker centers
  - Cells in wall of sinus venosus: form sinoatrial node
  - Cells in atrioventricular septum: form atrioventricular node
  - Cells in interventricular septum: form bundle of His
  - Rest of ventricular myocardium: form modified cardiac myocytes, which become Purkinje fibers



**Figure 29.24** Aortic arches and their derivatives. The arches exist from weeks four to six and sprout from aortic sac.



**Figure 29.25** The heart's conducting system.

## FETAL CIRCULATION

[osms.it/fetal-circulation](https://osms.it/fetal-circulation)

### KEY POINTS

- Placenta: low-resistance circuit, organ of gas exchange
- Fetal systemic circulation: low-resistance circuit
- Lungs: filled with fluid, hypoxic vasoconstriction
  - High-resistance circuit, no role in gas exchange
- Right side of heart pressure > left side of heart pressure
- Ductus venosus, foramen ovale, ductus arteriosus shunt blood away from fetal lungs

### Pattern of flow

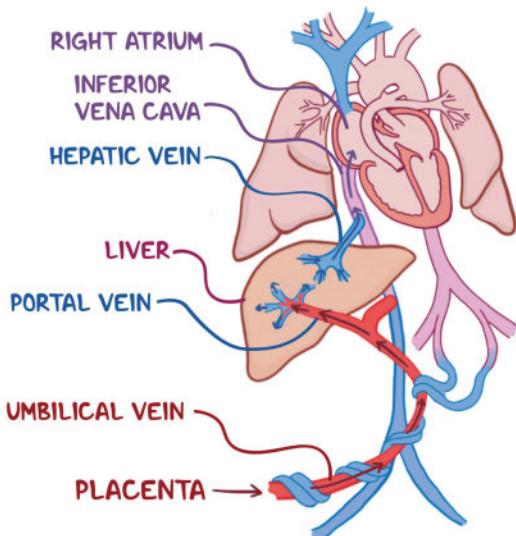
- Placenta → umbilical vein → divides into left, right umbilical vein
- Left umbilical vein → portal vein → liver → hepatic vein → inferior vena cava → right atrium
- Right umbilical vein → ductus venosus (bypasses liver) → inferior vena cava → right atrium
- Right atrium → left atrium via foramen ovale
  - Small amount of blood from right atrium enters right ventricle, pulmonary artery, lungs
- Blood shunted from pulmonary artery to aorta by small blood vessel
  - AKA ductus arteriosus
- Aorta → oxygenated blood delivered

to systemic circulation → right, left  
common iliac arteries → internal, external iliac arteries → umbilical arteries → deoxygenated blood back to placenta

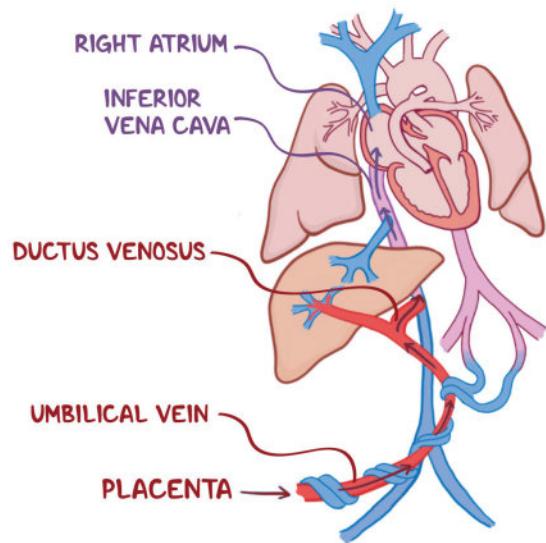
### CHANGES AT BIRTH

- Pulmonary circulatory pressure ↓ while systemic circulation ↑
  - When umbilical cord cut, low-resistance circuit removed → systemic circulation increases
  - Lung fluid replaced by air as neonate takes first breaths/cries
  - Oxygen diffuses into blood vessels surrounding alveoli, pulmonary arterioles relax, pulmonary resistance falls, blood flows into lungs
- Closing of ductus arteriosus
  - Pressure changes cause decreased blood flow through ductus arteriosus
  - Complete closure: 12–24 hours after birth
  - Physical remnant: ligamentum arteriosum
- Closing of foramen ovale
  - Pressure in right side of heart falls, seals foramen ovale
  - Physical remnant: fossa ovalis
- Umbilical vein forms round ligament of liver
- Ductus venosus forms ligamentum venosum of liver

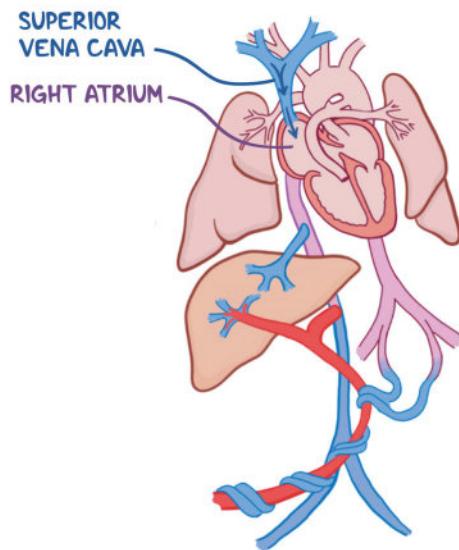
## FETAL CIRCULATION: PATHS TO RIGHT ATRIUM



1a. Left umbilical vein to portal vein



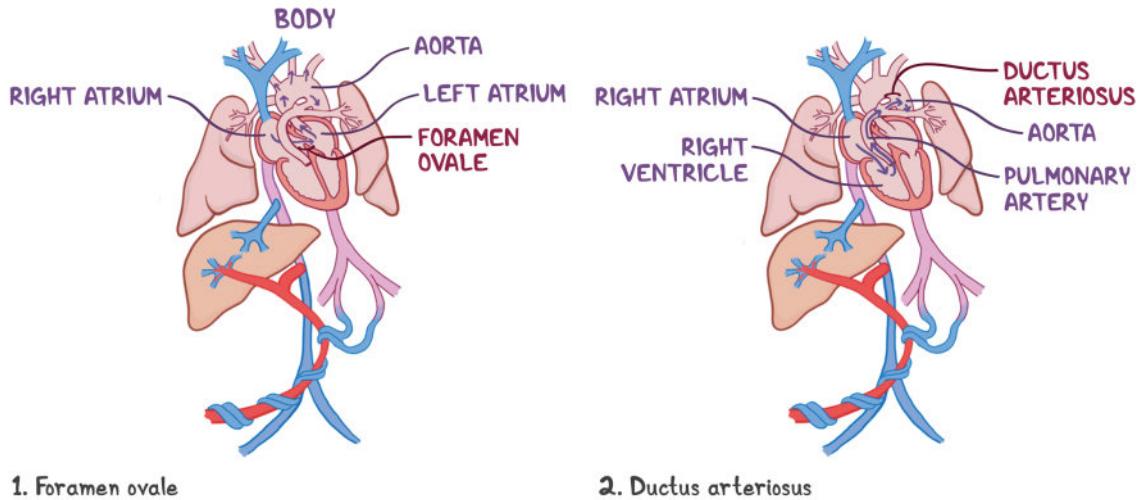
1b. Left umbilical vein to ductus venosus



2. Superior vena cava

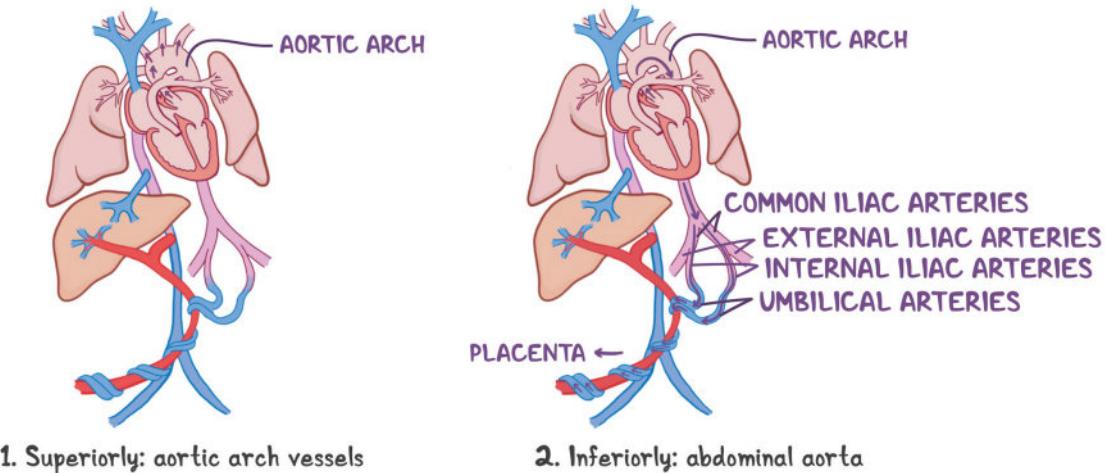
**Figure 29.26** The fetal right atrium receives blood from the inferior vena cava (via liver and ductus venosus) and the superior vena cava.

## FETAL CIRCULATION: PATHS FROM RIGHT ATRIUM TO AORTA

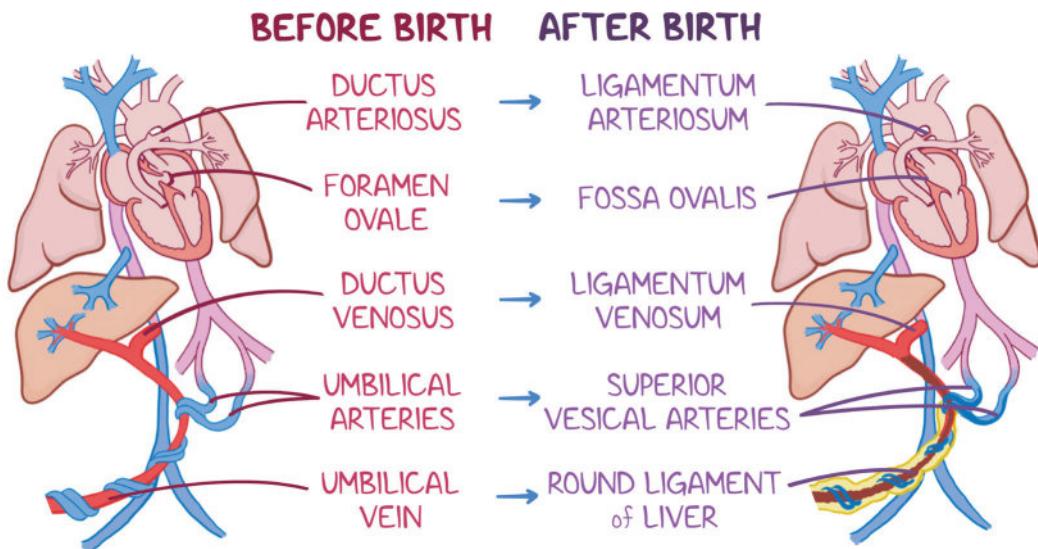


**Figure 29.27** In the fetal circulatory system, blood can travel from the right atrium to the aorta through either the foramen ovale or the ductus arteriosus. The majority of the blood takes the first path from the higher pressure right atrium to the lower pressure left atrium, bypassing the right ventricle entirely. The blood that does flow into the right ventricle is shunted from the high pressure pulmonary artery to the lower pressure aorta through the ductus arteriosus.

## FETAL CIRCULATION: PATHS AWAY FROM AORTA



**Figure 29.28** The aorta sends blood to the entire body through its various branches. The interior iliac arteries each give rise to an umbilical artery. These arteries travel alongside the umbilical vein and bring deoxygenated blood back to the placenta, where CO<sub>2</sub> is delivered and O<sub>2</sub> is picked up. This cycle repeats until birth.



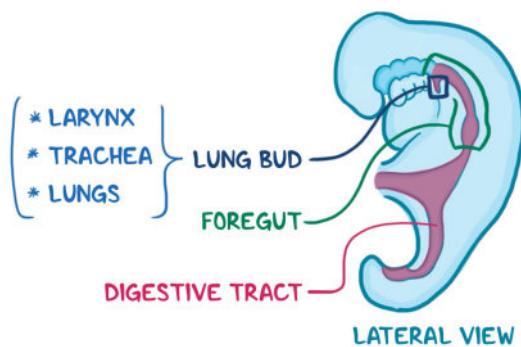
**Figure 29.29** The fetal circulatory adaptations and their physical remnants after birth. The umbilical arteries and vein are surrounded by a substance called Wharton's jelly in the umbilical cord. Once exposed to the cold air, Wharton's jelly shrinks and squeezes the umbilical blood vessels, causing them to wither. The arteries constrict and flatten, and are mostly gone within a few months; only a small portion remains and subsequently function as the superior vesical arteries, which supply blood to either side of the bladder.

## DEVELOPMENT OF THE RESPIRATORY SYSTEM

[osms.it/respiratory-system-development](https://osms.it/respiratory-system-development)

### KEY POINTS

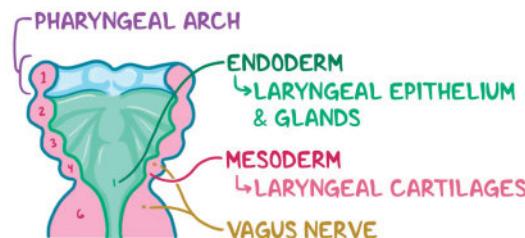
- Week 4: starts developing
  - Lung bud sprouts from foregut portion of digestive tract
- Endoderm, mesoderm: form lower respiratory tract structures
  - Larynx, trachea, lungs



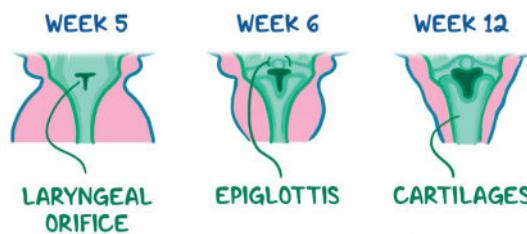
**Figure 29.30** Week 4: lung bud sprouts from foregut.

## DEVELOPMENT OF THE LARYNX

- Begins as slit between 4<sup>th</sup>, 6<sup>th</sup> pharyngeal arches
- Endoderm of arches: forms laryngeal epithelium, glands
- Mesoderm of arches: forms laryngeal muscles, cartilages
- Arches carry the laryngeal branches of vagus nerve
- Week 5: laryngeal orifice forms
  - Laryngeal epithelium turns into laryngeal ventricles, which give rise to vocal cords
- Week 6: epiglottis forms
- Week 12: laryngeal orifice has adult shape; thyroid, cricoid, arytenoid cartilages



**Figure 29.31** The endoderm and mesoderm of the pharyngeal arches contribute to larynx formation.



**Figure 29.32** Key timing and features in larynx development.

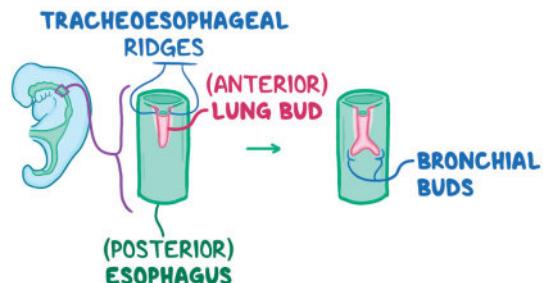
## DEVELOPMENT OF THE TRACHEA & LUNGS

- Week 4: two tracheoesophageal ridges grow towards one another, fuse into septum
- Septum divides foregut into two regions
  - Posterior: esophagus
  - Anterior: lung bud

### Composition of lung bud

- Endoderm: gives rise to epithelial, glandular structures of trachea, lungs
- Visceral mesoderm: gives rise to muscles, cartilage, connective tissue

### Lung bud bifurcates into two bronchial buds



**Figure 29.33** At the loose end, the lung bud bifurcates into two bronchial buds which give rise to the lungs.

## STAGES OF LUNG DEVELOPMENT

### Pseudoglandular stage: weeks 5–16

- Bronchial buds differentiate
  - Left and right main/primary bronchi
  - Three lobar/secondary bronchi for right lung lobes, two for left lung lobes
- Lobar/secondary bronchi: divide into 10 segmental/tertiary bronchi on right, eight on left
  - AKA lung segments
- Segmental/tertiary bronchi divide repeatedly until 15–25 terminal bronchioles formed
- Lungs now consist of simple columnar epithelium

### Canalicular stage: weeks 16–26

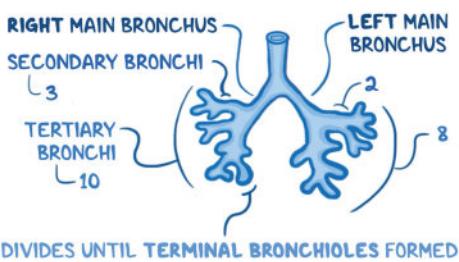
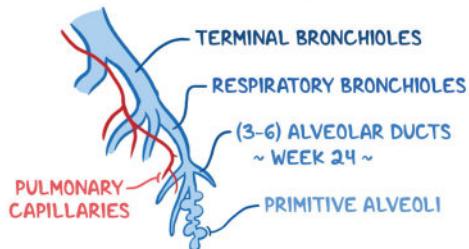
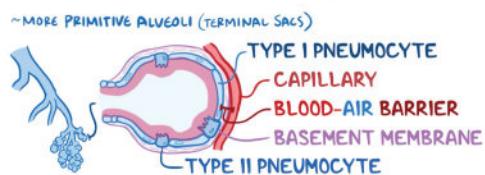
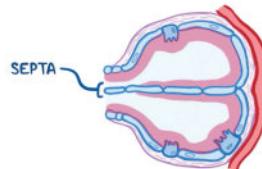
- Terminal bronchioles continue to divide, form respiratory bronchioles
- Respiratory bronchiole divides into three to six alveolar ducts
- Prominent capillary network forms
- Week 24: primitive alveoli appear closer to trachea
- Lungs now consist of simple cuboidal epithelium
  - Unsuitable for gas exchange

**Terminal sac stage: week 26–birth**

- More primitive alveoli form
- Epithelial lining of terminal sacs differentiate
- Flat cells in direct contact with endothelium of the capillaries
  - AKA type I pneumocytes, form blood-air barrier
  - Also includes basement membrane
- Pulmonary surfactant produced by large, cuboidal cells
  - AKA type II pneumocytes

**Alveolar stage: week 36–8 years old**

- Terminal sacs partitioned by secondary septae
- Number of adult alveoli increase
  - 0–70 million at birth, 300–400 at eight years old
- Number of respiratory bronchioles increases with lung size

**STAGE 1: PSEUDOGLANDULAR WEEKS 5–16****STAGE 2: CANALICULAR WEEKS 16–26****STAGE 3: TERMINAL SAC WEEK 26–BIRTH****STAGE 4: ALVEOLAR WEEK 36–8 YEARS (after birth)**

**Figure 29.34** The stages of lung development.

# DEVELOPMENT OF THE GASTROINTESTINAL SYSTEM

[osms.it/gastrointestinal-system-development](https://osms.it/gastrointestinal-system-development)

## Primitive gut tube

- Forms during week 3
- Extends from buccopharyngeal membrane to cloacal membrane
- Divided into three parts according to arterial supply
  - Foregut, midgut, hindgut

## Foregut

- Supplied by celiac trunk
- Gives rise to superior part of digestive tube
  - Pharynx to **first half of duodenum**
  - Also liver, gallbladder, pancreas

## Midgut

- Supplied by superior mesenteric artery
- Briefly, midgut communicates with yolk sac via vitelline duct

## Hindgut

- Supplied by inferior mesenteric artery

## DERIVATIVES OF THE FOREGUT

### Pharynx & esophagus

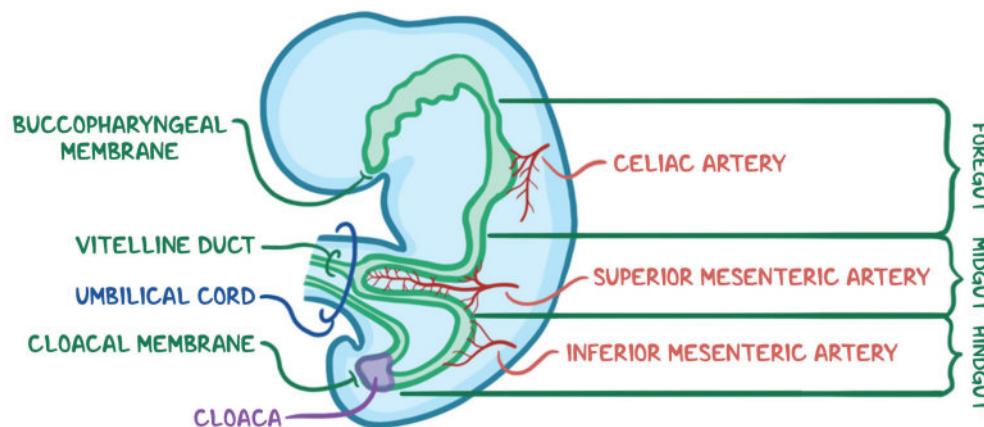
- Pharynx develops from 4<sup>th</sup>, 6<sup>th</sup> pharyngeal

arches

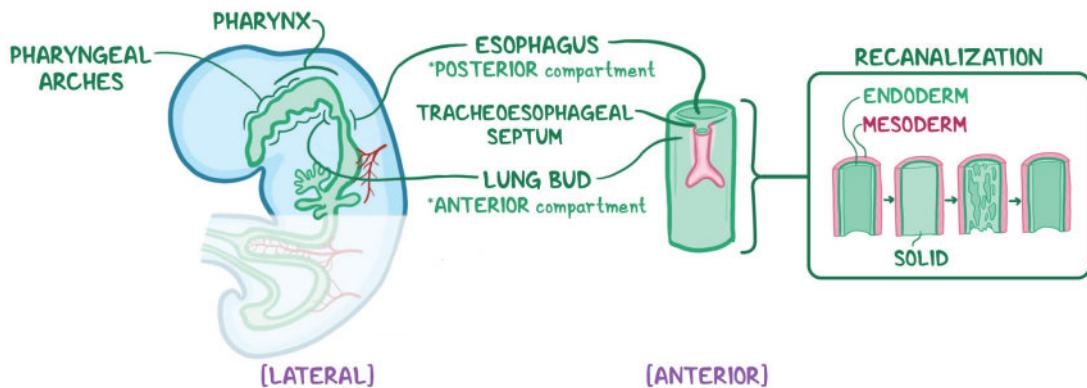
- Week 4: tracheoesophageal septum divides foregut below pharynx into two regions
  - Esophagus: posterior
  - Lung bud: anterior
- **Esophageal epithelium**, glands derived from foregut endoderm
  - Epithelium proliferates, initially fills lumen
  - By week 8: becomes hollow tube via recanalization
- Esophageal muscles, adventitia derived from surrounding mesoderm

### Stomach & duodenum

- Begin as small dilation of foregut
- Ventral mesogastrium attaches ventral border to anterior body wall
- Dorsal mesogastrium attaches dorsal border to posterior body wall
  - Dorsal border: grows faster, forms greater curvature
  - Ventral border: lesser curvature
- Stomach undergoes 90°, clockwise rotation along its length
  - Pulls dorsal, ventral mesogastria with it



**Figure 29.35** The primitive gut tube at week 3, including subdivisions and their blood supplies.



**Figure 29.36** The pharynx and esophagus are derivatives of the foregut. The tracheoesophageal septum divides the foregut into the esophagus posteriorly and the lung bud anteriorly. The esophageal endoderm (epithelium) initially proliferates and fills the lumen, but recanalization is complete by week 8.

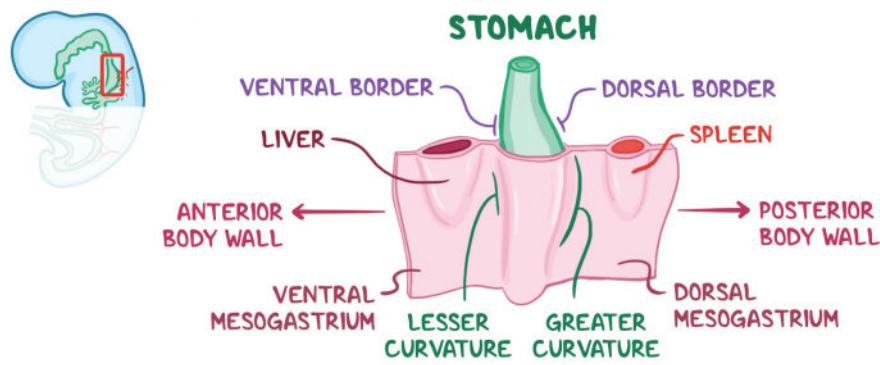
- Greater curvature moves to right side of body, lesser curvature to left
- Stomach now has anterior, posterior faces
- Ventral mesogastrium: becomes lesser omentum
- Dorsal mesogastrium: grows, bends as stomach rotates
  - Forms cavity (AKA omental bursa) between stomach, posterior body wall
- Omental bursa: communicates with peritoneal cavity through omental foramen
  - Omental bursa grows, fills with peritoneal fluid
  - Develops two projections: upper recess, lower recess
- Upper recess: extends behind developing liver
- Lower recess: extends downward over developing intestines
  - Sheets of dorsal mesogastrium that form lower recess fuse, forming greater omentum
- Stomach rotates once more on frontal plane
  - Repositions superior end of stomach
  - Forms cardiac sphincter, pylorus
  - Turns duodenum into C-shaped loop, with middle of "C" on right side
- First two sections of duodenum: derived from last part of foregut
- Tiny tissue buds on last portion of foregut grow, develop into liver, gallbladder, pancreas

#### Liver & gallbladder

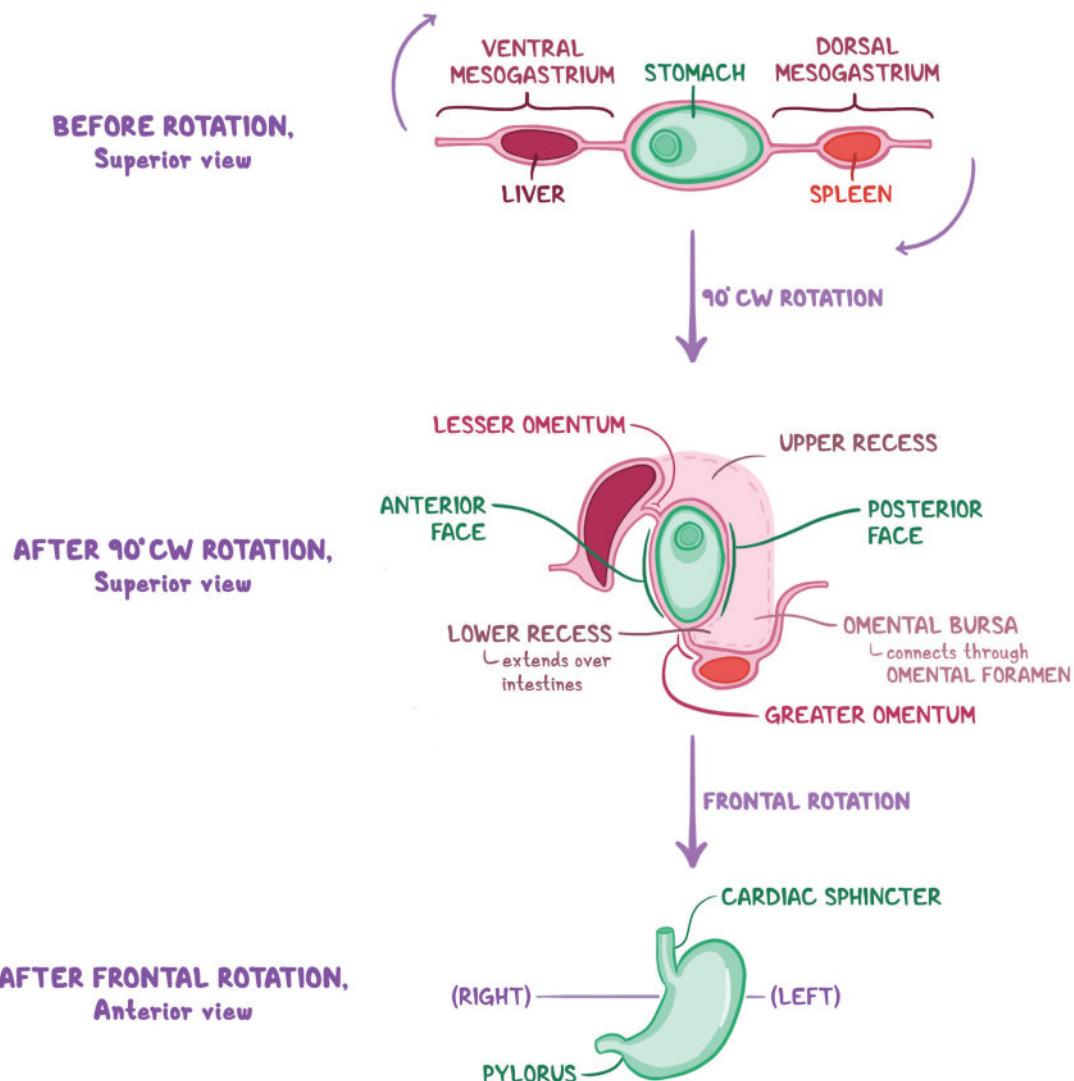
- Liver bud, AKA hepatic diverticulum, gives rise to liver, gallbladder, biliary duct system
  - Forms inside ventral mesogastrium, extends into sheet of mesoderm that separates developing heart from midgut (AKA septum transversum)
  - Contains mesoderm, endoderm
- Foregut endoderm forms hepatocytes
  - During week 12: hepatocytes start producing bile during mesoderm
  - Forms Kupffer cells, hematopoietic tissue
  - During week 6: produce red blood cells
- Liver bud divides into two parts
  - Larger, superior portion: becomes liver
  - Smaller, inferior part: becomes gallbladder

#### Pancreas

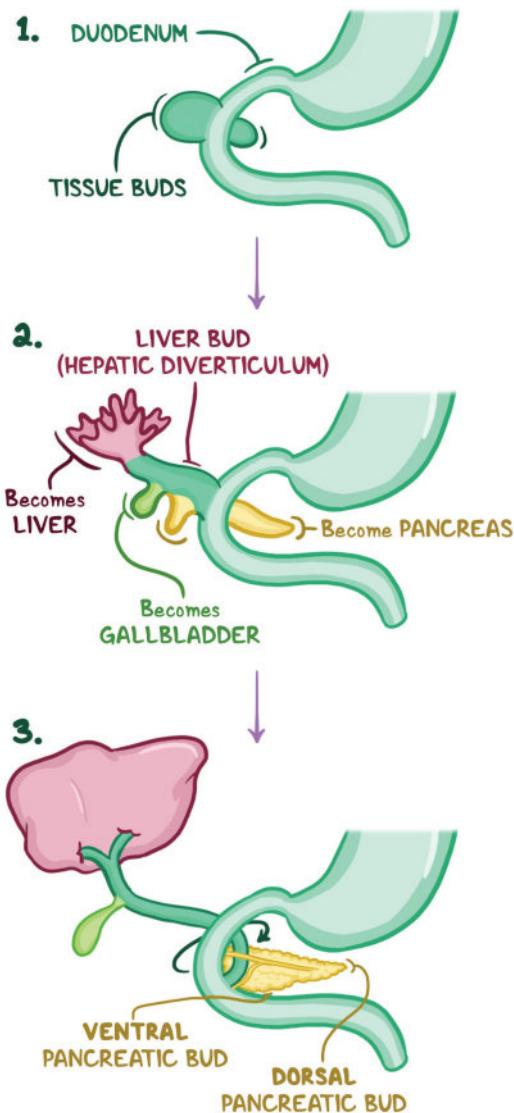
- Two pancreatic buds eventually fuse to form entire organ
  - Dorsal bud: forms tail, body, part of head
  - Ventral bud: forms most of head
- Week 10: begins secreting insulin



**Figure 29.37** Lateral view of the embryo visualizing the stomach and associated structures before any rotation has taken place. The stomach presents as small foregut dilation beneath esophagus. Starting at week 5, the liver grows between the layers of the ventral mesogastrium and the spleen grows between the layers of the dorsal mesogastrium.



**Figure 29.38** The two rotations events in the development of the stomach.



**Figure 29.39** Anterior view: the liver, gallbladder, and pancreas develop from tissue buds at the distal end of the foregut.

## DERIVATIVES OF THE MIDGUT

- Key elements
- Parts of small, large intestines derive from midgut
  - Small intestine: third, fourth sections of duodenum; jejunum; ileum
  - Large intestine: cecum, appendix, ascending colon, proximal  $\frac{2}{3}$  of transverse colon

## Physiologic gut herniation

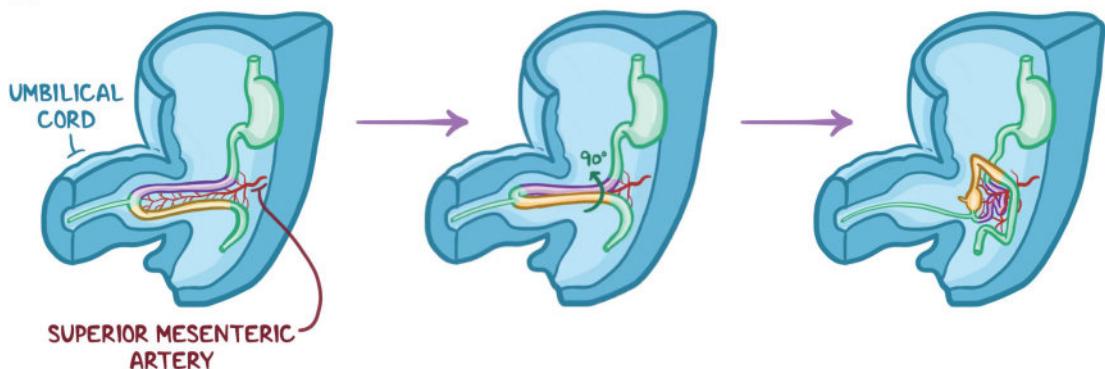
- During rapid gut tube growth, primary intestinal loop **herniates through vitelline duct, develops inside umbilical cord**
- Primary intestinal loop protrudes inside umbilical cord, superior mesenteric artery grows between loop's two limbs
  - Cranial limb: initially develops above superior mesenteric artery
  - Caudal limb: develops below superior mesenteric artery
- First, loop **rotates 90° counterclockwise around axis of superior mesenteric artery**
  - Moves cranial limb to right side of artery, inferior limb to left
- Cranial limb becomes convoluted
  - Marks future jejunal, ileal anses
- Caudal limb develops small dilation
  - Eventually becomes cecum, appendix
- Week 10: loop rotates final 180°, moves into abdominal cavity
  - Formerly caudal limb now frames developing small intestine loops, becomes ascending colon, right  $\frac{2}{3}$  of transverse colon

## DERIVATIVES OF THE HINDGUT

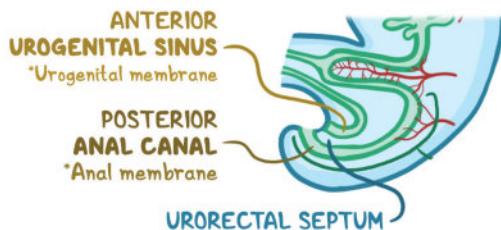
- Left  $\frac{1}{3}$  of transverse colon, descending colon, sigmoid colon, upper part of anal canal derive from hindgut
- Begins after caudal limb of midgut, extends to cloacal membrane
- Anal canal's lower portion derives from primitive anus (AKA proctodeum)
  - Proctodeum: pit of ectoderm that forms below cloacal membrane
- Week 4: Urorectal septum forms
  - Separates cloaca into anterior urogenital sinus, posterior anal canal; covered by urogenital, anal membranes, respectively
- End of week 7: separation completed
  - Anal membrane ruptures, forming continuous anal canal
  - Anal canal opens in embryo's tail-region

**PHYSIOLOGIC GUT HERNIATION**  
\* UNTIL WEEK 10 \*

■ CRANIAL LIMB  
■ CAUDAL LIMB



**Figure 29.40** The process of physiologic gut herniation.

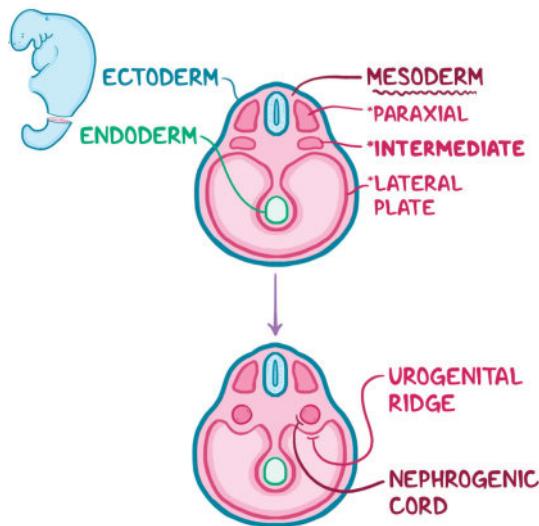


**Figure 29.41** Hindgut structures at week 7 when the anal membrane has ruptured to form a continuous anal canal.

# DEVELOPMENT OF THE RENAL SYSTEM

[osms.it/renal-system-development](https://osms.it/renal-system-development)

- Begins in week 4
- Intermediate mesoderm on each side of embryo condenses, forming cylindrical structure (AKA urogenital ridge)
- Urogenital ridge runs parallel to future spinal column; has two portions
  - Genital ridge: becomes gonads
  - Nephrogenic cord: becomes urinary structures



**Figure 29.42** Week 4: urogenital ridge formation.

- Three structures emerge from nephrogenic cord in cranio-caudal fashion
  - Pronephros, mesonephros, metanephros

## Pronephros

- Beginning of week 4:** arises in neck region
- End of week 4:** regresses
- Does not produce urine
- Consists of pronephric duct, nephrotomes
  - Pronephric duct: tube that runs length of nephrogenic cord

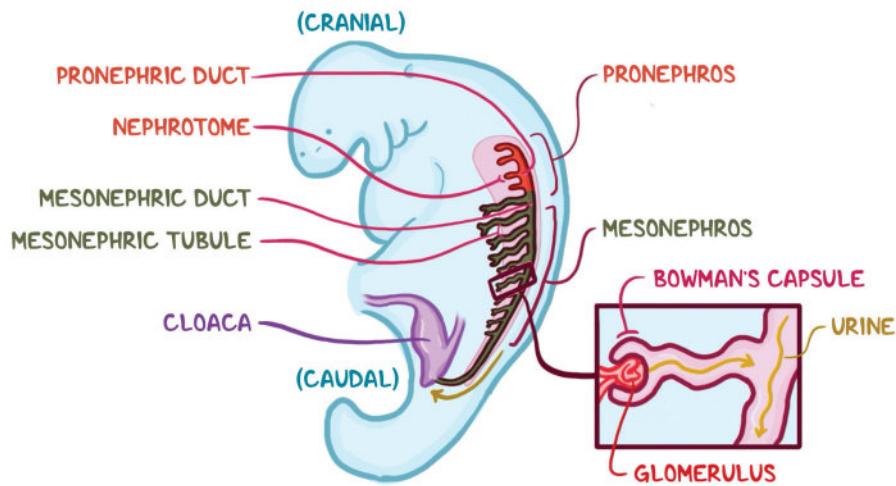
- Nephrotomes: chunks of tissue that break off nephrogenic cord

## Mesonephros

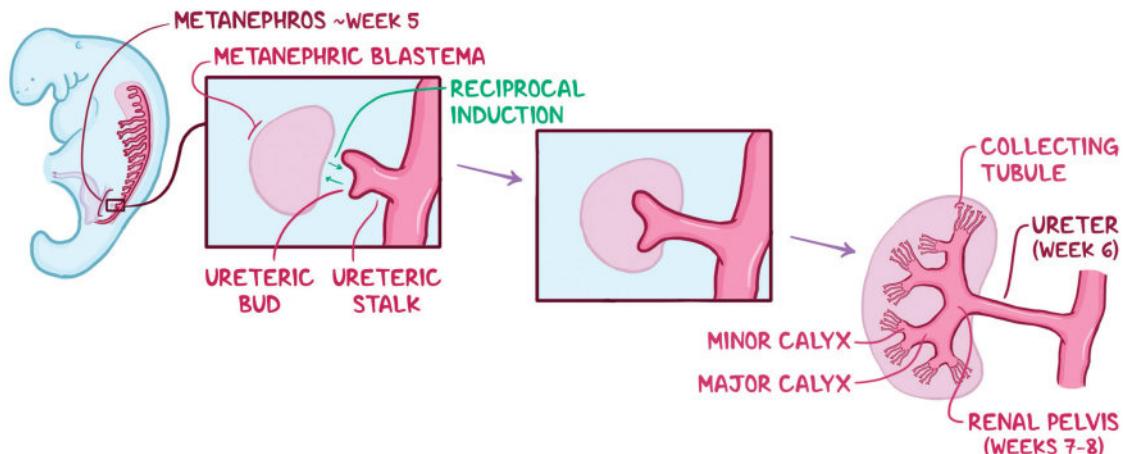
- Arises in thoracic, upper lumbar region of nephrogenic cord
- Consists of mesonephric duct, mesonephric tubules
- Mesonephric duct:** develops from pronephric duct
  - Extends pronephric duct to cloaca
- Mesonephric tubules:** hollow, S-shaped tubes
  - Connect to mesonephric duct on one end
  - On other end, form cup (AKA Bowman's capsule) around clump of capillaries (AKA glomerulus)
  - Glomerulus extracts fluid from capillaries, fluid flows down duct, becomes urine, drained through mesonephric duct into cloaca
  - After week 10, permanent kidneys take over, mesonephros regresses

## Metanephros

- Week 5:** develops in pelvic region
- Forms **permanent** kidneys
- Intermediate mesoderm near the mesonephric duct differentiates into metanephric mesoderm (AKA metanephric blastema)
- This induces **mesonephric duct** to sprout **ureteric bud**
  - Ureteric bud connected mesonephric duct via the ureteric stalk
- Ureteric bud lengthens, secretes growth factors
- This causes metanephric mesoderm to grow (AKA reciprocal induction)
- Ureteric bud grows into metanephric mesoderm
  - Metanephric mesoderm surrounds end



**Figure 29.43** Locations and components of the pronephros and mesonephros.



**Figure 29.44** Development of the kidney from the metanephros.

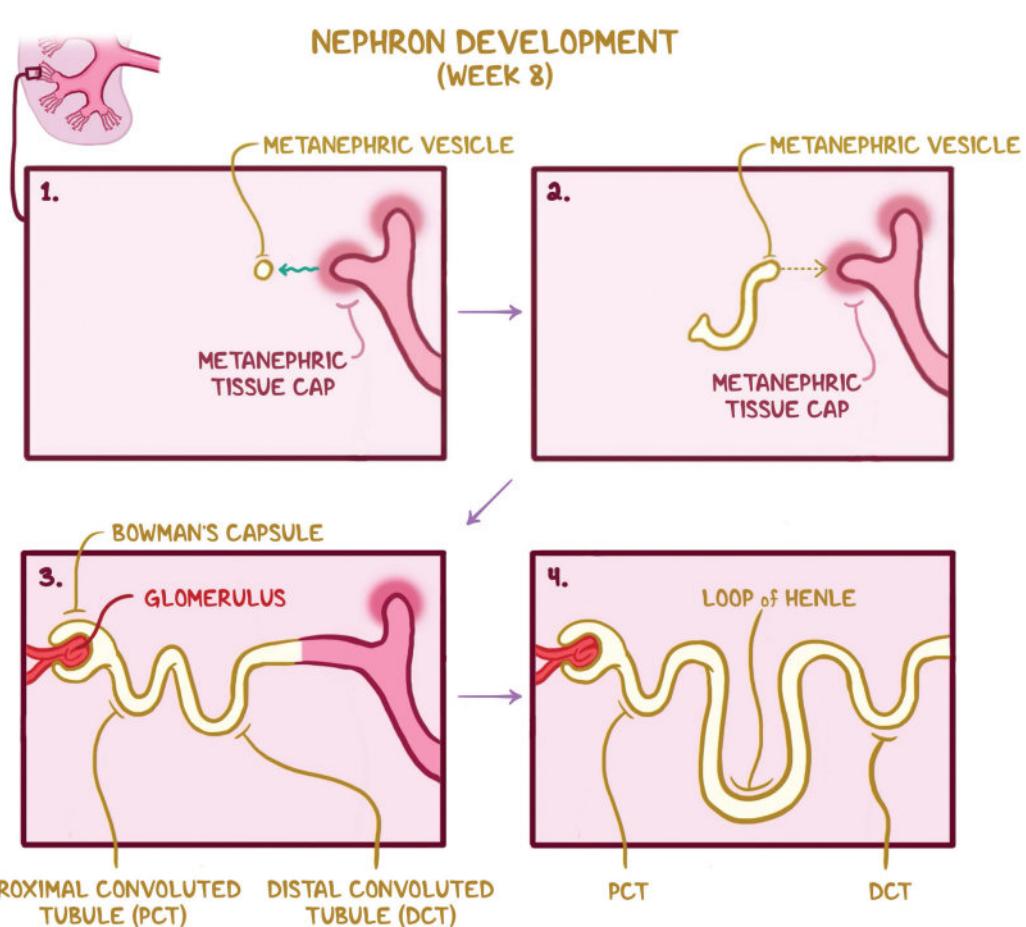
of ureteric bud, leaving just ureteric stalk uncovered

- Week 6: ureteric stalk lengthens, forms ureter
- Weeks 7–8: ureteric bud divides in half, forms renal pelvis
- Division continues: two major calyces become minor calyces, then millions of collecting tubules

#### Nephrons

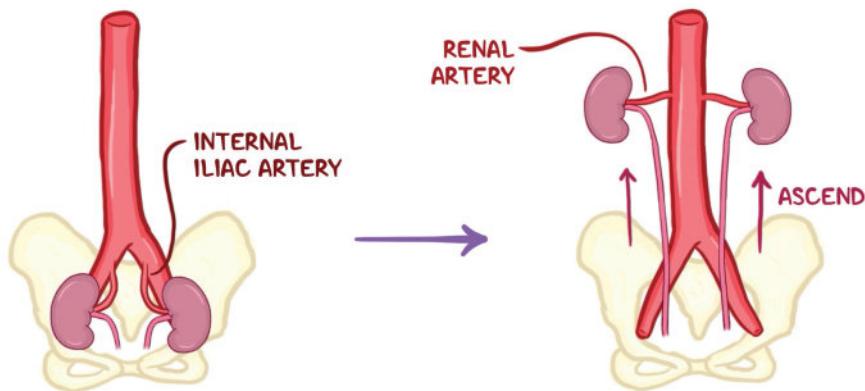
- Week 8: start forming
- Cells in collecting tubules signal adjacent metanephric mesoderm to form round cell clusters (AKA metanephric vesicles)
  - Vesicles elongate, bend into S-shaped tube

- End of tube (AKA distal convoluted tubule) connects with collecting tubules
- Other end forms proximal convoluted tubule; becomes Bowman's capsule, glomerulus
- Portion between distal, proximal convoluted tubules lengthens, forms loop of Henle
- Week 10: nephrons start producing urine
- Initially, kidneys nourished by internal iliac arteries
- As permanent kidneys develop, they move up from pelvis to reach upper abdomen
  - Renal arteries form, lower branches degenerate



**Figure 29.45** Nephron development begins at week 8.

- 1: Metanephric tissue cap signals adjacent metanephric mesoderm to form round cell clusters called metanephric vesicles.
- 2: Vesicles elongate, curve; end of tube connects with collecting duct.
- 3: Proximal and distal convoluted tubules (PCT, DCT).
- 4: Tube lengthens between PCT, DCT → loop of Henle.

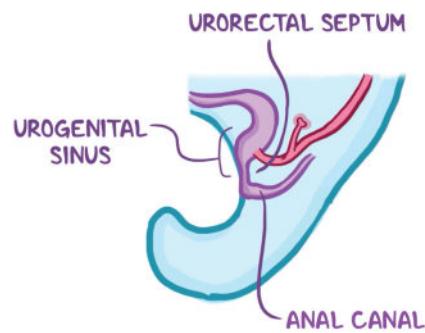


**Figure 29.46** The kidneys are originally nourished by the internal iliac arteries. As kidneys ascend, the aorta forms branches at higher and higher levels to supply them. The renal arteries develop once the kidneys have reached their final position and earlier branches degenerate.

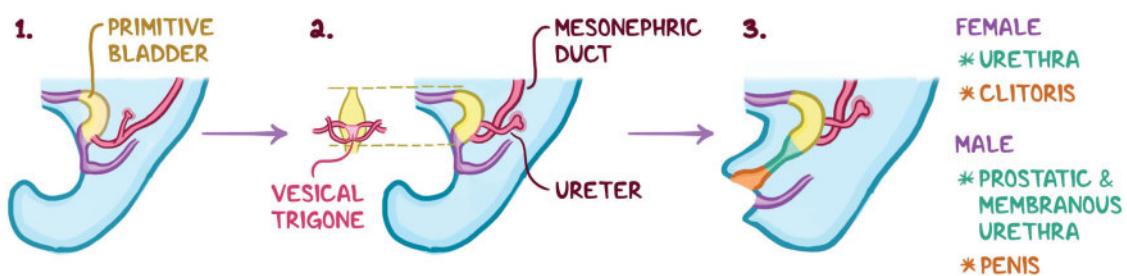
## DEVELOPMENT OF THE BLADDER & URETHRA

- Week 4: begins developing
- Wall of tissue forms in cloaca (AKA urorectal septum)
  - Splits cloaca into posterior anal canal, anterior urogenital sinus
  - Top portion of urogenital sinus forms primitive bladder
- Ureters develop from ureteric stalk, open into mesonephric ducts
  - Drain into bladder
- Weeks 5–6: mesonephric ducts get absorbed into bladder
  - Form vesical trigone (AKA smooth part of bladder)
- Middle portion of urogenital sinus forms urethra (female); prostatic, membranous parts of urethra (male)

- Bottom portion of urogenital sinus grows towards genital tubercle
  - Forms clitoris (female), penis (male)



**Figure 29.47** Week 4: the urorectal septum forms, splitting cloaca (forming urogenital sinus, anal canal).



**Figure 29.48** Development of the bladder and urethra.

- 1: Top portion of the urogenital sinus stretches out to form primitive bladder.
- 2: During weeks 5 and 6, the mesonephric ducts are absorbed into the bladder, forming the smooth part of the bladder wall called the vesical trigone.
- 3: Outcomes for the middle and bottom portions of the urogenital sinus in individuals who are genetically male and female.

# DEVELOPMENT OF THE INTEGUMENTARY SYSTEM

[osms.it/integumentary-system-development](http://osms.it/integumentary-system-development)

## DEVELOPMENT OF THE SKIN

### Epidermis

- Derived from single layer of surface ectoderm
- In second month: cells divide, forms layer of periderm (AKA epitrichium)
- Cells of periderm desquamated during second ½ of prenatal life, form vernix caseosa
- Neural crest cells invade epidermis, form melanocytes
  - Move to keratinocytes in skin, hair bulb
  - Produce skin, hair pigmentation
- Cells in basal layer proliferate, form intermediate zone
- By end of fourth month, four layers complete
  - Basal/germinative layer, spinous layer, granular layer, horny layer
- Hair, nails, glands all develop as epidermal proliferations

### Dermis

- Derived from mesenchyme from three sites
- Lateral plate mesoderm: produces dermis of limbs, body wall
- Paraxial mesoderm: produces dermis of back
- Neural crest cells: dermis of neck, face
- During third, fourth months, dermis forms many irregular papillary structures (AKA dermal papillae)
  - Project upward into epidermis
  - Contain Meissner corpuscles (AKA tactile sensory receptors)

### Hair

- Week 12: hair follicles form from cells of stratum basale
- Begins as epidermal proliferation that penetrates into dermis (AKA hair bud)

- Hair bud invaginates at terminal end, forming hair papillae
- Each hair papilla fills with mesoderm
  - Vessels, nerves develop
- Cells of hair bud's center become keratinized, forming hair shaft
- Peripheral cells form the epithelial hair sheath
- Mesenchyme surrounding hair bud forms dermal root sheath, attached arrector pili muscle
- By end of third month, first hair appears as lanugo
  - Begins to shed at term
- Sebaceous gland forms from small bud in mesoderm
  - Secretes sebum

### Nails

- By end of third month, nail fields form from thickenings at tips of digits
- Nail fields form nail root through migration
- Growth proximal, dorsal to each side of digit
- Tissue proliferates around each nail field, forming shallow depression
- Epidermis at nail roots differentiates into fingernails, toenails
  - Reaches tips by ninth month of development

### Sweat glands

- Eccrine glands
  - Forms over most of body
  - Buds arise from germinative layer
  - Buds grow into dermis
  - Terminal part coils, forms secretory part of glands
- Apocrine glands
  - Develop during puberty over hairy parts of the body
  - Arise from epidermal buds that produce

hair follicles

### Mammary glands

- Modified sweat glands
- Arise as bilateral bands of thickened epidermis (AKA mammary lines/mammary ridges)
- Week 7: these lines extend from base of forelimb to base of hindlimb
  - Most of the line disappears, except in thoracic region
- Mammary lines penetrate mesenchyme, give rise to 16–24 sprouts that form small buds
- By end of intrauterine life, sprouts are canalized, form lactiferous ducts
- Lactiferous ducts initially open into small epithelial pit
  - Shortly after birth, proliferate, transform into nipple
- At puberty, lactiferous ducts stimulated by estrogen, progesterone to form alveoli, secretory cells



# NOTES

## HEAD & NECK STRUCTURE

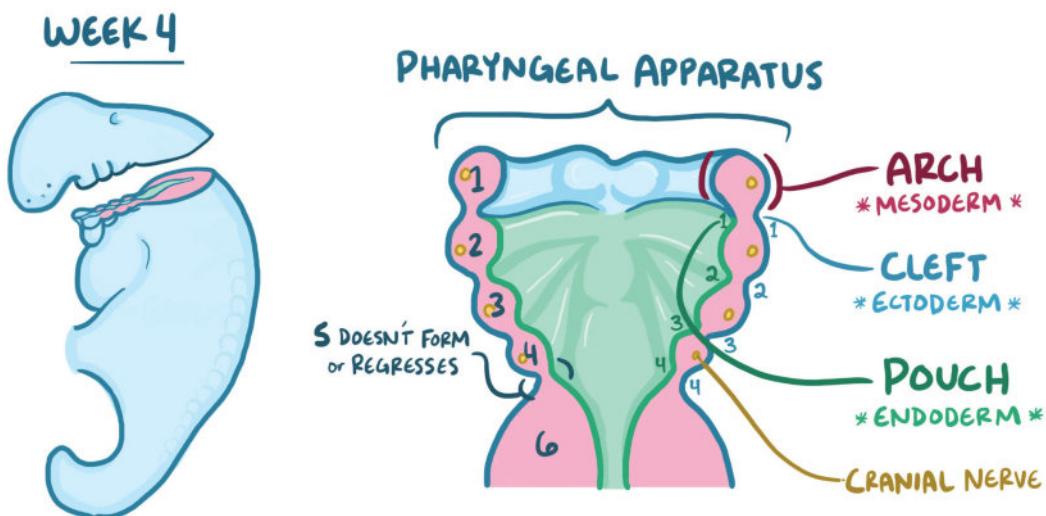
# PHARYNGEAL ARCHES, POUCHES, & CLEFTS

[osms.it/pharyngeal-arches-pouches-clefts](https://osms.it/pharyngeal-arches-pouches-clefts)

- Week 4: pharyngeal apparatus begins to form, develop into various head, neck structures
- Bars of **mesoderm** form **six** pharyngeal **arches** in craniocaudal fashion
  - Numbered from one to six
  - 5<sup>th</sup> quickly regresses, does not form any structures
- Between pharyngeal arches, **four** pharyngeal **clefts** cover each arch's external part with **ectoderm**
- **Four** pharyngeal **pouches** line each arch's internal part with **endoderm**
- Each pharyngeal arch carries its own cranial nerve

### First pharyngeal arch

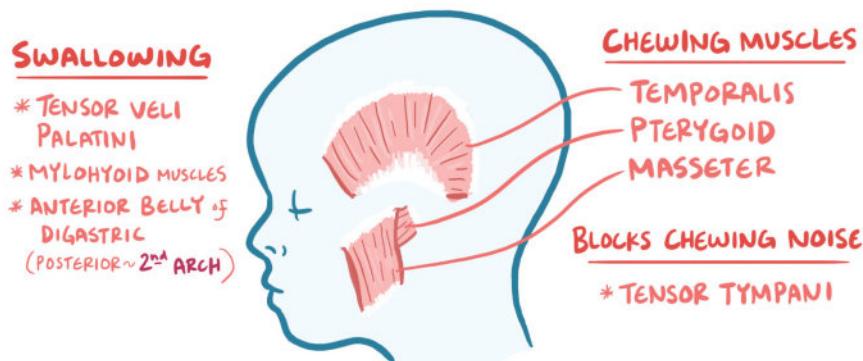
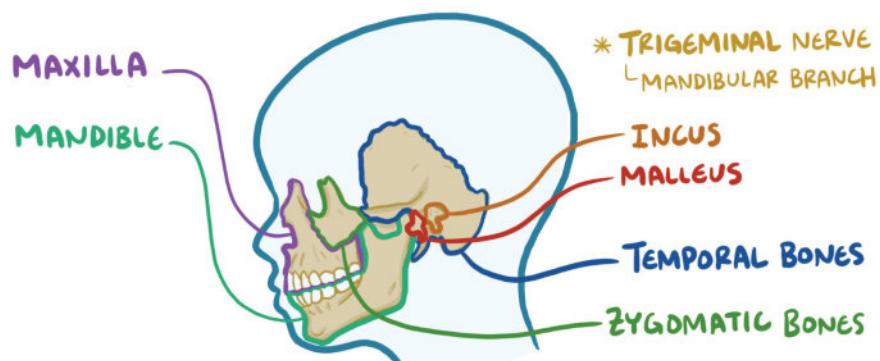
- Innervated by mandibular branch of trigeminal nerve (CN V<sub>3</sub>)
- Bones
  - Forms maxilla, mandible temporal, zygomatic bones
  - Two small portions of mandible form incus, malleus bones of middle ear
- Muscles
  - Muscles that help with chewing: temporalis, masseter, pterygoid muscles, tensor tympani muscles
  - Muscles that help with swallowing: tensor veli palatini, mylohyoid muscles, anterior belly of digastric muscle



**Figure 30.1** Locations of the pharyngeal arches, clefts, and pouches.

## 1<sup>ST</sup> PHARYNGEAL ARCH

\* EVERYTHING WE NEED to CHEW \*



**Figure 30.2** Bones and muscles originating from the first pharyngeal arch.

### Second pharyngeal arch

- Innervated by facial nerve (CN VII)
- Bones
  - Lesser horns, upper portion of hyoid bone
  - Styloid process of temporal bone
  - Stapes bone of middle ear
- Muscles
  - Stylohyoid muscle, posterior belly of digastric muscle
  - Stapedius muscle of middle ear

### Third pharyngeal arch

- Innervated by glossopharyngeal nerve (IX)
- Bones
  - Rest of hyoid bone
- Muscles
  - Stylopharyngeus muscle in throat

### Fourth pharyngeal arch

- Innervated by superior laryngeal branch vagus nerve (CN X)
- Muscles
  - Levator palatini, pharyngeal constrictors, cricothyroid muscle

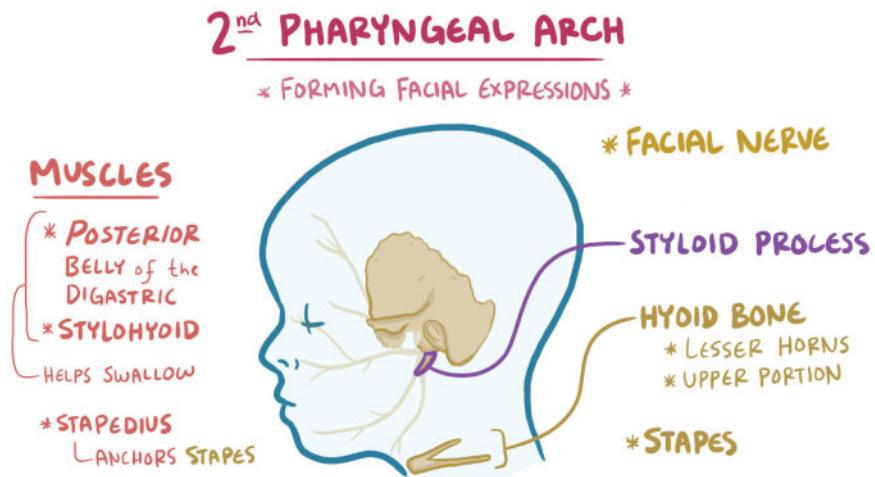
### Sixth pharyngeal arch

- Innervated by recurrent laryngeal branch of CN X
- Muscles
  - Rest of intrinsic muscles of larynx

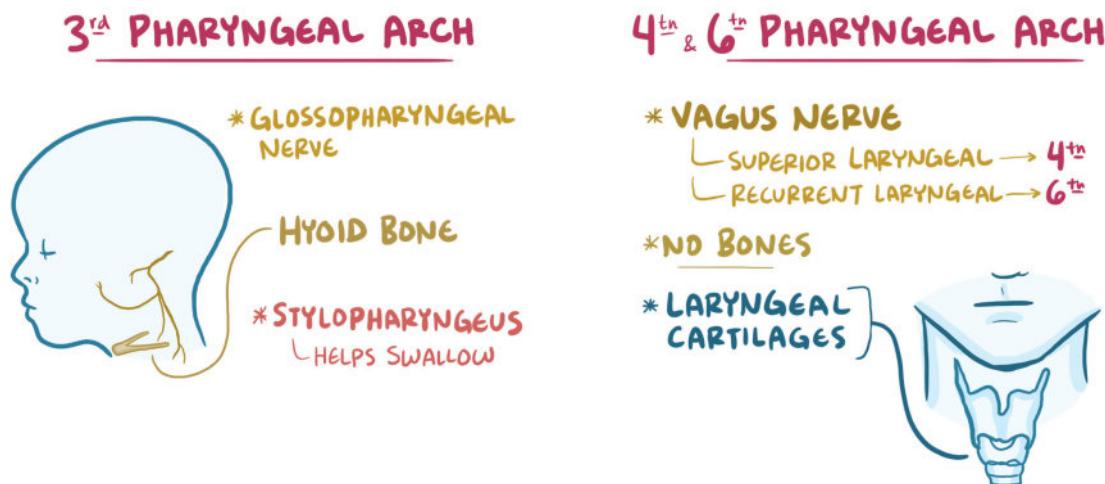
## PHARYNGEAL CLEFTS AND POUCHES

### First pharyngeal cleft, pouch

- Form ear
- **Cleft** gives rise to external auditory meatus, ear drums



**Figure 30.3** Bones and muscles originating from the second pharyngeal arch.



**Figure 30.4** Structures originating from the third, fourth, and sixth pharyngeal arches. Muscles from fourth and sixth not shown.

- Pouch gives rise to internal auditory meatus, AKA middle ear, eustachian tube

#### Second-fourth clefts

- Fade as embryo grows
  - Cells lining second pharyngeal pouch multiply, migrate to form primitive tonsils

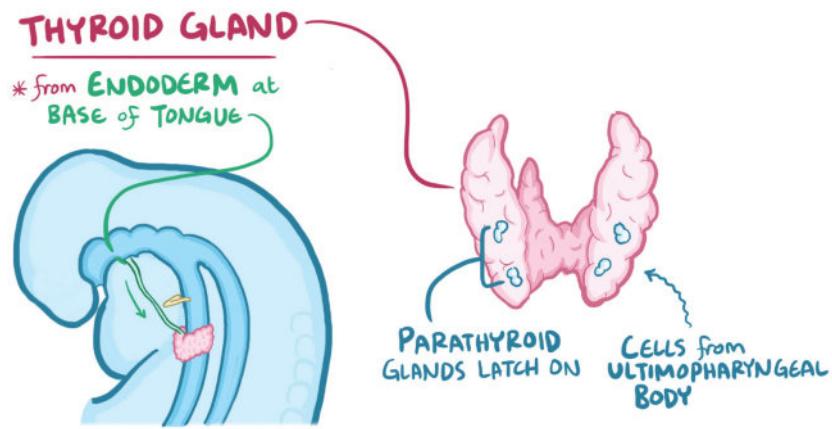
#### Third, fourth pouches

- Both divide into dorsal, ventral portions
- Dorsal portion of third pouch becomes inferior parathyroid gland
- Ventral portion becomes primitive thymus
  - Later descends down to chest

- Dorsal portion of fourth pouch becomes superior parathyroid gland
- Ventral portion becomes ultimo-pharyngeal body
  - Contains cells which differentiate into parafollicular/C-cells, migrate into thyroid

#### Thyroid and parathyroid glands

- Thyroid develops from endoderm at base of tongue independent of pharyngeal apparatus, descends down neck
- Parathyroid glands latch onto thyroid



**Figure 30.5** Thyroid develops from endoderm at base of tongue independent of pharyngeal apparatus, descends down neck. Parathyroid glands latch on as it passes by them.

## DEVELOPMENT OF TEETH

[osms.it/development-of-teeth](https://osms.it/development-of-teeth)

- Tooth development, AKA odontogenesis, involves epithelial, neural crest-derived mesenchymal interaction
- Week 6: basal layer of oral epithelium has formed C-shaped dental lamina
  - Gives rise to 10 dental buds in each jaw

### Cap stage

- Invagination of deep surface of buds → dental cap
- Each dental cap consists of:
  - Outer dental epithelium
  - Inner dental epithelium
  - Central core of stellate reticulum
- Mesenchyme forms dental papilla, which form odontoblasts
  - Produce dentin
- Remainder of dental papilla forms pulp

### Bell stage

- Dental cap grows, indentation deepens, forming bell-shaped configuration
- Inner dental epithelium cells transform into ameloblasts
  - Produce enamel deposited over dentin

- As enamel thickens, ameloblasts retreat into stellate reticulum, regress
- Also form enamel knot, which regulates early tooth development

### Root formation

- Inner and outer dental epithelial layers invade underlying mesenchyme, form epithelial root sheath
- Pulp begins to narrow as more dentin laid down
  - Forms canal containing nerves, blood vessels
- Mesenchymal cell differentiation
  - Cementoblasts produce cementum (AKA type of specialized bone)
  - Periodontal ligament gives structural integrity to tooth
- As root lengthens, it pushes crown into oral cavity
  - Deciduous teeth (AKA milk teeth) arise 6–24 months of age
- Permanent teeth buds form during third month of development, remain dormant until sixth year of life

# DEVELOPMENT OF THE BRAIN

[osms.it/development-of-the-brain](http://osms.it/development-of-the-brain)

## DEVELOPMENT OF BRAIN VESICLES

- Neural plate folds, forming neural tube
- Rostral region develops into brain
- Week 4: primary brain vesicles develop
- Week 6: vesicles develop

### Primary vesicle: forebrain/prosencephalon

- Secondary vesicles
  - Telencephalon: cerebral hemispheres, caudate, putamen, amygdaloid, claustrum, laminal terminalis, olfactory bulbs, hippocampus
  - Diencephalon: epithalamus, subthalamus, thalamus, hypothalamus, mammillary bodies, neurohypophysis, pineal gland, globus pallidus, renina, iris, ciliary body, optic nerve (CN II), optic chiasm, optic tract

### Primary vesicle: midbrain/mesencephalon

- Secondary vesicle
  - Mesencephalon

### Primary vesicle: hindbrain/rhomobencephalon

- Secondary vesicles
  - Metencephalon: pons, cerebellum
  - Myelencephalon: medulla

## DEVELOPMENT OF HINDBRAIN/RHOMBENCEPHALON

- Alar, basal plates separated by sulcus limitans

### Basal plate

- Contains three groups of motor nuclei
- General somatic efferent
  - Cranial nerves III, IV, VI (metencephalon); XII (myelencephalon)
  - Innervation: somatic striated muscle (extrinsic eye muscles, tongue)
- Special visceral efferent
  - Cranial nerves V, VII (metencephalon); IX, X (myelencephalon)

- Innervation: striated muscle of pharyngeal arches, AKA pharynx
- General visceral efferent
  - Cranial nerve III (metencephalon); IX, X (myelencephalon)
  - Innervation: parasympathetic pathway to sphincter pupillae; smooth muscles of airways, heart, salivary glands, viscera

### Alar plate neuroblasts

- Contain three groups of sensory relay nuclei
- General visceral afferent
  - Cranial nerve X (myelencephalon)
  - Innervation: viscera, AKA gastrointestinal tract
- Special afferent
  - Cranial nerves VII, IX (metencephalon, myelencephalon); VIII (metencephalon)
  - Innervates: tongue, palate, epiglottis, AKA taste; cochlea, semicircular canals, AKA balance, hearing
- General somatic afferent
  - Cranial nerves V, VII (metencephalon); IX (myelencephalon)
  - Innervation: touch, temperature, pain in head, neck

## MYELENCEPHALON

- Gives rise to medulla oblongata
  - Transitional zone between brain, spinal cord
- Alar plate sensory neuroblasts give rise to
  - Cochlear nuclei, vestibular nuclei, spinal trigeminal nucleus, solitary nucleus, dorsal column nuclei, inferior olfactory nuclei
- Basal plate motor neuroblasts give rise to
  - Nuclei of CN X, IX, XI
- Roof plate lined by ependymal cells covered by vascular mesenchyme, AKA pia mater
  - Collectively known as tela choroidea
  - Projects into ventral cavity, invaginations form choroid plexus

- Choroid plexus produces cerebrospinal fluid

## METENCEPHALON

- Develops from rostral rhombencephalon, gives rise to cerebellum, pons

### Cerebellum

- Functions as center for coordination, posture
- Neuroectoderm cells proliferate
  - In ventricular zone, form cerebellar nuclei, Purkinje cells, golgi cells
  - In external germinal layer, form basket, granule, stellate cells
  - External, internal germinal layers form astrocytes, oligodendrocytes, Bergmann cells

### Pons

- Serves as pathway for nerve fibers between spinal cord, cerebrum, cerebellum
- Base of pons contains
  - Pontine nuclei from alar plate
  - Corticobulbar, corticospinal, corticopontine fibers from cell bodies in cerebral cortex; pontocerebellar fibers
  - Alar plate sensory neuroblasts (CN V, CN II, CN III)
  - Basal plate motor neuroblasts (CN V, CN VI, CN VII)

## DEVELOPMENT OF MESENCEPHALON

- Gives rise to midbrain
- Basal plate neuroblasts give rise to motor nuclei
  - Oculomotor (III) nucleus → general somatic efferent column
  - Edinger-Westphal nucleus of oculomotor nerve (III) → general visceral efferent
  - Substantia nigra
  - Red nucleus
  - Trochlear (IV) nucleus, part of CN V migrate to metencephalon
- Alar plate sensory neuroblasts gives rise to superior, inferior colliculi
- Crus cerebri contains corticobulbar, corticospinal, corticopontine fibers

## DEVELOPMENT OF THE PROSENCEPHALON

### Diencephalon

- Develops from median portion of prosencephalon
- Consists of one roof plate, two alar plates; basal plate regresses
- Alar plates give rise to
  - Epithalamus: also develops from roof plate; gives rise to pineal body, habenular nuclei, commissure, posterior commissure, tela choroidea, third ventricle choroid plexus
  - Thalamus: gives rise to thalamic nuclei, lateral geniculate body, medial geniculate body
  - Subthalamus: gives rise to subthalamic nucleus; zona incerta; lenticular, thalamic fasciculi (AKA fields of Forel)
  - Hypothalamus: also develops from floor plate; gives rise to hypothalamic nuclei, mammillary bodies, neurohypophysis
- Optic vesicles, cups, stalks derivatives of diencephalon
  - Give rise to retina, iris, ciliary body, CN II, optic tract
- Hypophysis (AKA pituitary) develops from two different structures
- Anterior lobe/adenohypophysis
  - Develops from Rathke's pouch
  - Ectodermal diverticulum of primitive oral cavity/stomodeum
- Posterior lobe/neurohypophysis
  - Develops from the infundibulum
  - Neuroectodermal evagination of hypothalamus

### Telencephalon

- Gives rise to cerebral hemispheres, caudate, putamen, amygdaloid, claustrum, lamina terminalis, olfactory bulbs, hippocampus
- Week 5: cerebral hemispheres begin emerging as two outpocketings of prosencephalon
  - Contain cerebral cortex, white matter, lateral ventricles

### Basal ganglia

- Basal part of hemispheres grow, bulge into the lateral ventricles, giving rise to part of hemisphere wall (AKA corpus striatum)

- Expands: gives rise to caudate nucleus, putamen, amygdaloid nucleus, claustrum
- Divided by fibers of internal capsule
  - Single layer of ependymal cells form choroid plexus
  - Thickened wall of hemisphere forms hippocampus
  - Only globus pallidum arises from neuroblasts of subthalamus that migrated into the hemispheres

### Hemispheres

- Rapid, extensive growth of hemispheres creates many convolutions (AKA gyri)
  - Separated by grooves (AKA sulci) fissures
- Hemispheres develop frontal, parietal, occipital, temporal lobes, which overlie insula

### Cerebral cortex

- Develops from paleopallium/archipallium, neopallium
- Initially has neuroepithelial, mantle, marginal layers
- Neuroblasts proliferate, migrate to subpial regions to differentiate into mature neurons
  - Continues until all layers are formed
- Early formed neuroblasts have deep position in cortex, whereas later formed neuroblasts more superficially positioned
- Classified into neocortex, allocortex

- Neocortex: AKA isocortex
- Allocortex: subdivided into 2 parts
  - Archicortex: includes hippocampal formation
  - Paleocortex: includes olfactory cortex
- Telencephalon also gives rise to olfactory bulbs, tracts

### DEVELOPMENT OF COMMISSURES

- Bundles of nerve fibers connecting corresponding areas in right, left hemispheres
- Cross in midline of brain via lamina terminalis (AKA commissural plate)
- Anterior commissure
  - Appears first
  - Connects olfactory bulbs, middle, inferior temporal gyri
- Hippocampal commissure/fornix commissure
  - Appears second
  - Fibers arise in hippocampus → connect to lamina terminalis → mammillary body, hypothalamus
- Corpus callosum
  - Appears third
  - Largest commissure
  - Forms bundle in lamina terminalis, connects two homologous neocortical areas of cerebral hemispheres

# DEVELOPMENT OF CRANIAL NERVES & AUTONOMIC NERVOUS SYSTEM

[osms.it/development-cranial-nerves-ANS](http://osms.it/development-cranial-nerves-ANS)

## DEVELOPMENT OF CRANIAL NERVES

- By week 4: nuclei for all cranial nerves present
- Except olfactory (I), optic (II) nerves, all cranial nerves arise from hindbrain
- Motor nuclei derived from rhombomeres produced by neuroepithelium
  - Gives rise to motor nuclei of cranial nerves IV, V, VI, VII, IX, X, XI, XII
  - Motor neurons for these nuclei reside within brain
- Cranial nerve sensory ganglia originate from neural crest cells, ectodermal placodes

## DEVELOPMENT OF AUTONOMIC NERVOUS SYSTEM

- Comprised of efferent motor fibers
  - Innervate smooth muscle, cardiac muscle, secretory glands
  - Divided into sympathetic, parasympathetic systems

### Sympathetic nervous system

- Ganglia arise from basal plate of neural tube, neural crest cells
  - Basal plate gives rise to preganglionic sympathetic neurons in intermediolateral horns of spinal cord

- Neural crest cells give rise to postganglionic sympathetic neurons of sympathetic chain ganglia, prevertebral sympathetic ganglia, adrenal chromaffin cells
- Cell bodies of preganglionic neurons reside at T1–L2 of spinal cord
- Preaortic ganglia located at major vessel branches

### Parasympathetic nervous system

- Ganglia arise from basal plate of neural tube, neural crest cells
  - Basal plate gives rise to preganglionic parasympathetic neurons of cranial nerve nuclei—CN III (midbrain), CN VIII (pons), CN IX, X (medulla), spinal cord at S2–S4
  - Neural crest cells give rise to postganglionic parasympathetic neurons of ciliary ganglion (CN III), pterygopalatine ganglion (CN VII), submandibular ganglion (CN VII), enteric ganglion (Meissner, Auerbach, CN X), ganglia of abdominal, pelvic cavities
- Neuron cell bodies reside in brainstem, S2–S4 of spinal cord

# DEVELOPMENT OF THE SPINAL CORD

[osms.it/development-spinal-cord](https://osms.it/development-spinal-cord)

## NEURAL TUBE

- Neural plate folds in cephalocaudal manner, forming neural tube
  - Open at each end, forming cranial, caudal neuropores
- Three layers: neuroepithelial cells/ ventricular zone, mantle layer/intermediate zone, marginal layer/outermost layer

### Neuroepithelial cells

- Form thick layer of pseudostratified epithelium
  - Rapid division forms more neuroepithelial cells, produces neuroepithelium
  - Neuroepithelium gives rise to neuroblasts (AKA primitive nerve cells)

### Mantle layer

- Forms around neuroepithelial layer
- Composed of neuroblasts that migrated from neuroepithelial layer
- Gives rise to gray matter of spinal cord

### Marginal layer

- Contains neuroblast nerve fibers
- Gives rise to white matter
- Myelination → color

### Thickening of mantle layer

- Ventral, dorsal thickening occurs as more neuroblasts form
- Ventral thickening produces basal plates
  - Basal plates form ventral motor horn of spinal cord
- Dorsal thickening produces alar plates
  - Alar plates form dorsal sensory horn of spinal cord
- Sulcus limitans divides basal, alar plates
- Intermediate horn develops between motor, sensory horns
  - Located at T1-T12, L2/L3

- Contain sympathetic portion of autonomic nervous system
- Dorsal midline portion (AKA roof plate) ventral midline portion (AKA floor plate) of neural tube do not contain neuroblasts
  - Serve as crossover pathways

## CELL DIFFERENTIATION

### Development of nerve cells

- Start out as round, apolar cells
- Differentiate as primitive axons, dendrites develop
  - Bipolar neuroblast differentiates into multipolar neuroblast
  - Eventually develops into neuron

### Development of glial cells

- Glioblasts formed by neuroepithelial cells that migrate to the mantle and marginal layers
- Differentiate into glial cells
  - Protoplasmic astrocytes, fibrillar astrocytes: provide support, metabolic functions
  - Oligodendroglial cells: myelination in CNS
  - Microglia cells: phagocytic activity
- Neuroepithelial cells cease to produce neuroblasts, glioblasts
  - Differentiate into ependymal cells, which line central canal of spinal cord

## DEVELOPMENT OF SPINAL NERVES AND GANGLIA

- Week 4: development of spinal nerves begins
- Motor nerve fibers arise from cell bodies in basal plates (AKA ventral horns)
  - Form bundles (AKA ventral motor roots)
- Processes from nerve cell bodies in spinal cord ganglia

- Form bundles (AKA dorsal sensory roots)
- Spinal nerves split into rami containing both motor, sensory fibers
- Dorsal primary rami
  - Innervate dorsal axial musculature, vertebral joints, skin of back
- Ventral primary rami
  - Innervate limbs, ventral body wall
  - Form brachial, lumbosacral plexus

## MYELINATION OF THE NERVOUS SYSTEM

### Myelination in PNS

- Carried out by Schwann cells

- Originate from neural crest cells
- Each Schwann cell myelinates just one axon of peripheral nerve, wrapping around axon to form neurilemma (AKA myelin, sheath)

### Myelination in CNS

- Carried out by oligodendrocytes
  - One oligodendrocyte can myelinate ≤ 50 axons
  - Myelination of corticospinal tracts incomplete until first one-two years of postnatal life

# DEVELOPMENT OF THE EAR

[osms.it/development-of-the-ear](http://osms.it/development-of-the-ear)

- Comprised of internal, middle, outer ear

## DEVELOPMENT OF THE INTERNAL EAR

- Around day 22, otic placodes formed
- Ectoderm thickens each side of rhombencephalon
- Sides invaginate, form otic/auditory vesicles (AKA otocysts)
- Ototesticular cells of vesicles differentiate into ganglion cells for vestibulocochlear/statoacoustic ganglia
- Each vesicle divides, forming two components that will become membranous labyrinth
  - Ventral component: forms saccule, cochlear duct
  - Dorsal component: forms utricle, semicircular canals, endolymphatic duct

## DEVELOPMENT OF THE COCHLEA

- Week 6: cochlear duct forms as saccule forms tubular outgrowth
  - Cochlear duct spirally penetrates mesenchyme
  - Completes 2.5 turns by week 8

- Week 7: cochlear duct cells give rise to spiral organ of Corti
  - Cochlear duct remains connected to saccule via ductus reunions
  - Mesenchyme surrounding cochlear duct differentiates into cartilaginous shell
- Week 10: large vacuoles appear in cartilage
  - Form two perilymphatic spaces: scala vestibuli, scala tympani
  - Cochlear duct now separated from scala vestibuli by vestibular membrane, from scala tympani by basilar membrane
  - Lateral wall of cochlear duct remains attached to cartilage by spiral ligament
  - Median angle of cochlear duct connected to cartilaginous process called modiolus

## DEVELOPMENT OF ORGAN OF CORTI

- Epithelial cells of cochlear duct form two ridges
  - Inner ridge gives rise to spiral limbus
  - Outer ridge gives rise to sensory hair cells of auditory system
- Tectorial membrane covers sensory cells

while attached to spiral limbus

- Sensory cells, tectorial membrane: organ of Corti

## DEVELOPMENT OF SEMICIRCULAR CANALS

- Week 6: flattened outpouchings appear on dorsal component/utricle of otic vesicle
  - Central portion of their walls eventually disappear, semicircular canals develop
- Each canal has two ends
  - Crus ampullare: dilated end
  - Crus nonampullare: does not dilate
  - Cells in ampullae form crista ampullaris
- Maculae acusticae develop in walls of utricle, saccule
  - Maintenance of equilibrium: change in position of head, body generates impulses in sensory cells of cristae, maculae; carried by cranial nerve VIII/ vestibular fibers

## DEVELOPMENT OF THE MIDDLE EAR

- Composed of tympanic cavity, Eustachian tube/auditory tube
- Tympanic cavity develops from first pharyngeal pouch/endoderm
- Pouch expands, reaches floor of first pharyngeal cleft
  - Distal part of pouch widens, becomes primitive tympanic cavity
  - Proximal part remains narrow, becomes auditory tube

## DEVELOPMENT OF THE OSSICLES

### Malleus and incus

- Derived from cartilage of first pharyngeal arch
  - Tensor tympani muscle innervated by mandibular branch of trigeminal nerve

### Stapes

- Derived from cartilage of second arc
  - Stapedius muscle innervated by facial nerve

### Ossicles

- Appear during the first half of fetal life
- Remain embedded in mesenchyme until it dissolves in eighth month
  - Space around ossicles forms
- Endodermal epithelium of primitive tympanic cavity covers space's wall
  - Connects ossicles to cavity wall like mesentery
- During late fetal life, tympanic cavity expands dorsally to form tympanic antrum
- After birth, epithelium of tympanic cavity extends to the mastoid process
  - Forms air sacs (AKA pneumatization)
  - Mastoid air sacs communicate with tympanic antrum, tympanic cavity

## DEVELOPMENT OF THE EXTERNAL EAR

- External auditory meatus derived from dorsal portion of first pharyngeal cleft
- During third month, epithelial cells of meatus' floor proliferate, form solid epithelial plate (AKA meatal plug)
  - During seventh month meatal plug dissolves, creating definitive eardrum
  - Meatal plug persists until birth → congenital deafness
- Composition of eardrum
  - Ectodermal epithelial lining of auditory meatus
  - Endodermal epithelial lining of tympanic cavity
  - Intermediate mesoderm layer of connective tissue
- Auricle
  - Auricle develops from six mesenchymal proliferations/auricular hillocks at dorsal ends of first, second pharyngeal arches surrounding first pharyngeal cleft
  - These proliferations later fuse, form definitive auricle

# DEVELOPMENT OF THE EYE

[osms.it/development-of-the-eye](http://osms.it/development-of-the-eye)

## KEY POINTS

- Day 22: begins with formation of optic grooves on both sides of forebrain
- As neural tube closes, optic grooves form outpouchings (AKA optic vesicles)
- Optic vesicles reach surface ectoderm, induce lens formation
  - Optic vesicles invaginate, form double layered optic cups
  - Inferior surface of optic cup forms choroid fissure pathway for hyaloid artery
- Week 7: choroid fissure closes, gives rise to pupil
- Ectoderm cells elongate, form lens placode
- Lens placode invaginates, forms lens vesicle

## DEVELOPMENT OF THE RETINA

- Optic cup has two layers
  - Inner, outer layer initially separated by intraretinal space; obliterated in adult
  - Outer/pigmented layer: gives rise to pigmented layer of retina
  - Inner/neural layer: gives rise to neural layer of retina
- Posterior 4/5: pars optica retinae
- Cells bordering the intraretinal space differentiate into rods and cones
- Adjacent mantle layer: gives rise to neurons and supporting cells
  - Outer, inner nuclear layers, ganglion cell layer
- Surface fibrous layer contains nerve cell axons of deeper layers
  - Nerve fibers converge towards optic stalk
  - Optic stalk develops into optic nerve
- Anterior 1/5: pars ceca retinae
  - Pars iridica retinae: forms inner layer of iris
  - Pars ciliaris retinae: forms ciliary body

## Iris

- Three layers
- Outer, pigmented layer of optic cup
- Inner, neural layer of optic cup
- Richly vascularized connective tissue layer containing pupillary muscles
  - Sphincter, dilator pupillae develop from ectoderm of optic cup
- Pars ciliaris retinae
  - Externally covered by mesenchyme layer, forms ciliary muscle
  - Internally connected to lens by suspensory ligament/zonula

## DEVELOPMENT OF THE LENS

- Cells of optic vesicles elongate, fill lumen of vesicle with primary lens fibers
  - End of week 7: fibers reach anterior vesicle wall
  - Secondary fibers area added to central core

## DEVELOPMENT OF CHOROID, SCLERA & CORNEA

- End of week 5: loose mesenchyme surrounds eye primordium, differentiates into 2 layers
  - Inner layer: similar to pia mater, forms highly vascularized pigmented layer, AKA choroid
  - Outer layer: continuous with dura mater, forms sclera
- Anterior chamber forms on anterior aspect of the eye
  - Splits loose mesenchyme via vacuolization
  - Inner layer: iridopupillary membrane, sits in front of lens, iris
  - Outer layer: substantia propria of cornea, continuous with sclera
- Cornea now contains 3 layers
  - Epithelial layer derived from surface ectoderm

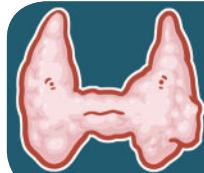
- Substantia propria
- Epithelial layer bordering anterior chamber
- Posterior chamber: space between iris, lens
- Anterior, posterior chambers filled with aqueous humor produced by ciliary process of ciliary body
  - Aqueous humor circulates from posterior into anterior chamber through pupil
  - In anterior chamber, fluid flows through canal of Schlemm (AKA scleral venous sinus) at iridocorneal angle, resorbs into bloodstream

## DEVELOPMENT OF THE VITREOUS BODY

- Mesenchyme invades inside of optic cup through choroid fissure
  - Forms hyaloid vessels, which supply lens during intrauterine life
- Invading mesenchyme also forms fibrous network between lens, retina
  - Interstitial spaces of network fill with vitreous body
- During fetal life, hyaloid vessels eventually disappear, replaced by hyaloid canal

## DEVELOPMENT OF THE OPTIC NERVE

- Develops from optic stalk, which connects optic cup to brain
- Initially, optic cup has ventral groove (AKA choroid fissure)
  - Fissure contains hyaloid vessels
  - Nerve fibers of retina line stalk's inner wall
- Week 7: choroid fissure closes
  - Narrow tunnel forms inside optic stalk
  - Nerve fibers fill tunnel, forming optic nerve
- Contents of optic nerve
  - Inner layer provides neuroglia supports optic nerve fibers
  - Hyaloid artery later transforms into central artery of retina
- Choroid: continuation of pia arachnoid, sclera continuation of dura layer of nerve



# NOTES ANATOMY & PHYSIOLOGY

## ENDOCRINE ANATOMY & PHYSIOLOGY

[osms.it/endocrine-anatomy-and-physiology](https://osms.it/endocrine-anatomy-and-physiology)

### ENDOCRINE GLANDS

- Secrete hormones directly into bloodstream (exocrine glands use ducts)
- Maintain homeostasis by controlling variables such as body temperature, fluid balance
  - Especially with negative feedback mechanisms

### HORMONES

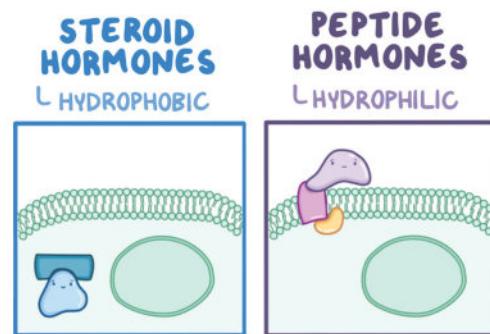
- Can be classified as steroids/non-steroids

#### Steroid hormones

- Derived from cholesterol; produced in adrenal glands, gonads (testes/ovaries)
- Hydrophobic/non-polar → travel through bloodstream with transport proteins, diffuse across target cell phospholipid membrane

#### Non-steroid hormones

- Derived from peptides/proteins or single amino acids
- Peptidic hormones are hydrophilic → bind surface receptor proteins instead of passing through target cell membrane
- Amino acid hormones derived from tyrosine; generally hydrophilic (e.g. adrenaline/epinephrine and noradrenaline/norepinephrine), apart from thyroid hormones



**Figure 31.1** Steroid hormones diffuse across the target cell membrane and bind to an intracellular receptor. Peptide hormones bind to a cell surface receptor. Both methods result in changes in gene expression.

### HORMONE SECRETION & REGULATION

#### Paracrine signaling

- Effects of hormones released by nearby cells; e.g. glucagon → activates alpha cells, inhibits beta cells

#### Sympathetic nervous system

- Epinephrine/norepinephrine alter secretion depending on adrenergic receptor type;
- e.g.  $\beta_2$ : activates beta cells

#### Parasympathetic nervous system

- Acetylcholine activates alpha cells and beta cells via M3 receptors

## GLAND LOCATIONS & FUNCTIONS

- Endocrine glands scattered throughout body

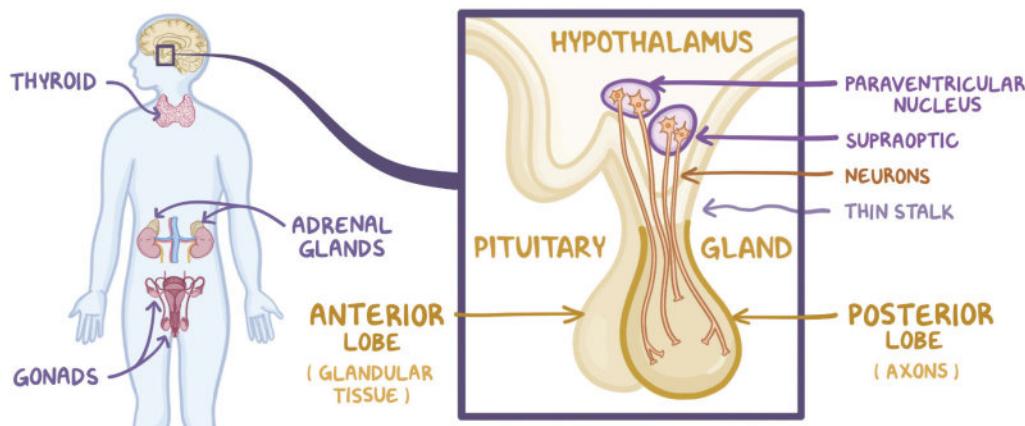
### Hypothalamus

- Located at base of brain
- Hypothalamus, brain work closely to make hormones that control other endocrine glands
- Made up of several nuclei (neuron clusters) which secrete hormones

### Pituitary gland

- Located just below brain; physically connected to hypothalamus by pituitary stalk (infundibulum)
- Made up of anterior, posterior lobe
- **Anterior pituitary:** AKA **adenohypophysis**
  - Made of glandular tissue
  - Receives stimulatory, inhibitory hormones from hypothalamus via hypothalamo-hypophyseal-portal system
- **Posterior pituitary:** AKA **neurohypophysis**
  - Made of axons from hypothalamic supraoptic, paraventricular nuclei
  - Receives hormones directly from hypothalamus
  - Instead of producing own hormones, posterior pituitary stores hormones for later release
  - Herring bodies: axon dilations which store hormones

- Hormones include antidiuretic hormone (ADH/vasopressin), oxytocin
- ADH signals: ↑ blood osmolarity, ↓ blood volume (ADH retains water from urine, constricts blood vessels → negative feedback)
- Oxytocin signals: childbirth (dilates cervix, stimulates uterine contractions), breastfeeding (contracts breast cells), social interaction, orgasm
- Stimulatory pituitary hormones
  - Thyrotropin releasing hormone (TRH): pituitary secretes thyroid-stimulating hormone (TSH) → thyroid produces thyroid hormones
  - Corticotropin releasing hormone (CRH): pituitary secretes adrenocorticotrophic hormone (ACTH) → adrenal glands produce cortisol
  - Gonadotropin releasing hormone (GnRH): pituitary secretes gonadotropins, e.g. follicle-stimulating hormone (FSH), luteinizing hormone (LH) → gonads produce gametes (sperm for testes, oocytes for ovaries), sex hormones (testosterone, estrogen, progesterone)
  - Growth hormone releasing hormone (GHRH): pituitary secretes growth hormone → growth of long bones, tissues in body
- Inhibitory pituitary hormones
  - Growth hormone inhibiting hormone (GHIH/somatostatin): pituitary secretes less/no growth hormone



**Figure 31.2** Endocrine glands' location and the relationship between the hypothalamus and the the pituitary gland's two lobes.

- Prolactin inhibiting hormone (dopamine): pituitary secretes less/no prolactin (no milk is produced whenever not breastfeeding)

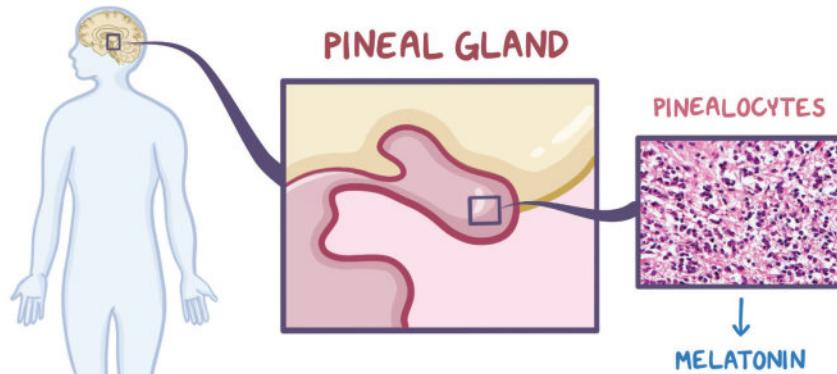
### Pineal gland

- Located behind hypothalamus, pituitary gland
- Contains pinealocytes which synthesize melatonin
  - Melatonin mostly secreted during night, regulates body's circadian rhythm (body clock)

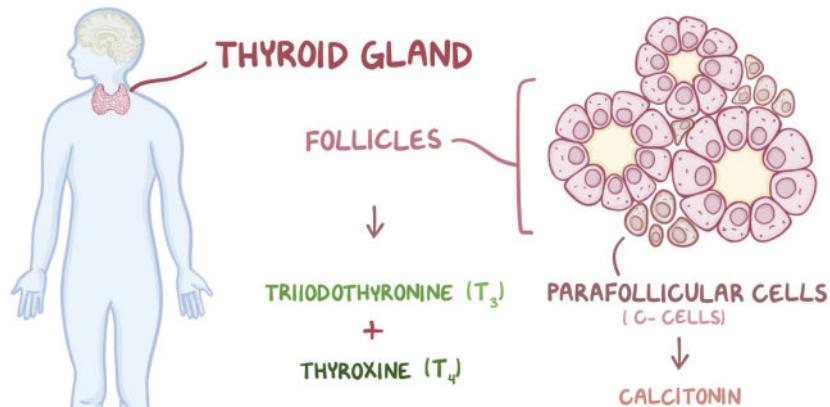
### Thyroid gland

- Located at front of neck
- Left, right lobe

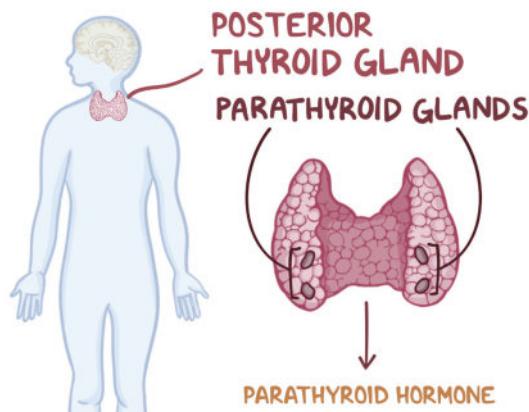
- Made of thousands of follicles which synthesize triiodothyronine ( $T_3$ ), thyroxine ( $T_4$ )
  - In the cell  $T_4 \rightarrow T_3$
  - $T_3 \rightarrow \uparrow$  basal metabolic rate
- Parafollicular cells (C-cells) between follicles secrete calcitonin
- Two parathyroid glands on back of each thyroid lobe (four in total) secrete parathyroid hormone
- Calcitonin, parathyroid hormone work similarly
  - Control calcium, phosphate, bone metabolism
- Regulated by blood calcium levels



**Figure 31.3** Pineal gland location and histological appearance of pinealocytes.



**Figure 31.4** Follicular cells of the thyroid gland synthesize  $T_3$ ,  $T_4$ ; parafollicular cells secrete calcitonin.



**Figure 31.5** The parathyroid glands are found on the back of the thyroid. They secrete parathyroid hormone.

### Adrenal glands

- Two glands situated retroperitoneally inside renal fascia, each surrounded by fibrous capsule; sit on top of kidneys
  - Connective tissue separates them from kidney, renal fascia from diaphragm
  - One of the most vascularized tissues
  - Differ in shape (right shaped as pyramid, left shaped as crescent moon)
- Outer layer (cortex) surrounding a core (medulla)
- Medulla: neuroectodermal origin; secretes catecholamines (e.g. adrenaline, noradrenaline) during “fight or flight” situations
  - ↑ blood pressure, ↑ cardiac output, ↑ bronchial dilation, ↑ glycogenolysis
- Cortex: makes up 80% of gland, mesodermal origin, secretes adrenocortical steroid hormones
  - Three zones: zona glomerulosa (makes mineralocorticoids—e.g. aldosterone), zona fasciculata (makes glucocorticoids), zona reticularis (makes sex hormone precursors)
  - Aldosterone: regulates extracellular fluid volume, potassium homeostasis; involved in renin-angiotensin-aldosterone system (RAAS); ↑ renal water and sodium reabsorption, ↑ renal potassium excretion → ↑ blood pressure
  - Cortisol: integral to stress response; also has metabolic, anti-inflammatory, immunosuppressive, vascular effects; regulated via hypothalamic-pituitary-adrenal (HPA) axis

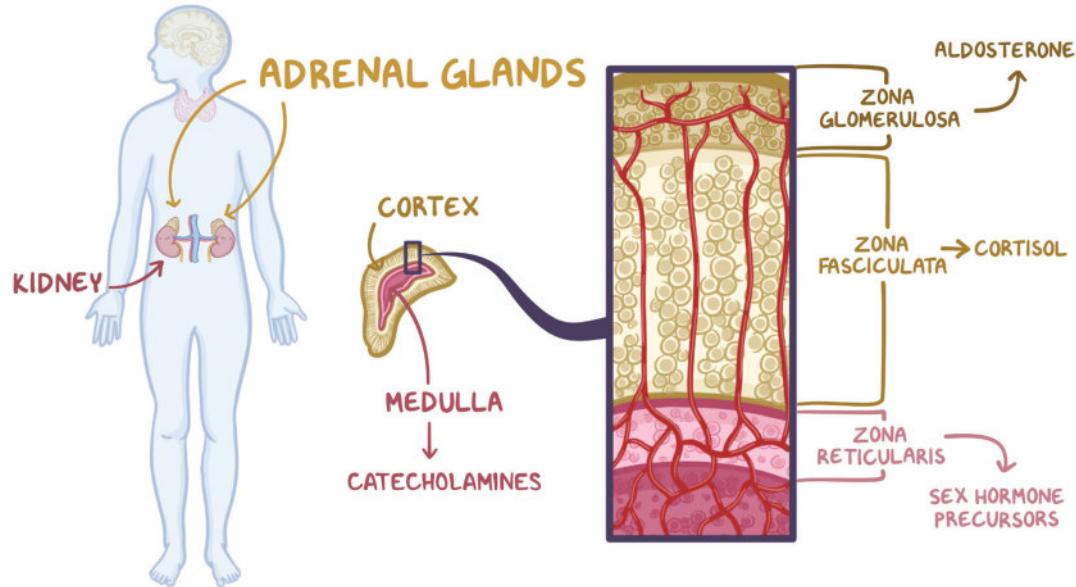
- Androgens: adrenals only source of androgens in biologically-female individuals; effects include ↑ libido, pubic hair development, sebaceous gland hypertrophy; minor role in biologically-male adults

### ENDOCRINE PANCREAS

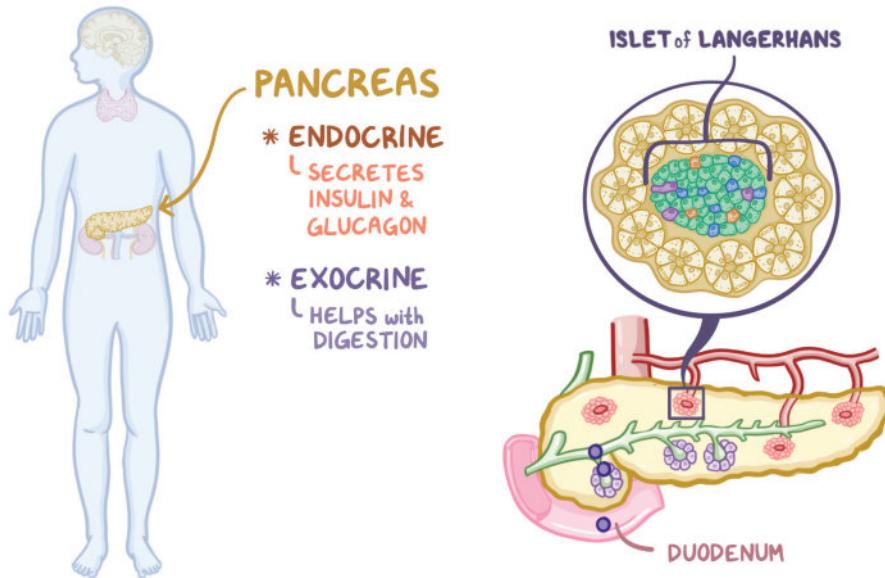
- Located behind stomach
- Three sections
  - Head, body, tail
- Has both endocrine, exocrine functions
- Contains hormone-producing cell clusters
  - Islets of Langerhans (1–2% of pancreas)
- Produce hormones secreted directly into bloodstream that regulate blood glucose

### Cell types

- Alpha ( $\alpha$ ) cells
  - 15–20% of total islet cells
  - Produce glucagon
  - ↓ blood glucose → glucagon secreted → hepatic glycogenolysis and gluconeogenesis → glucose released into bloodstream
- Beta ( $\beta$ ) cells
  - 65–80% of total islet cells
  - Produce insulin, amylin
  - ↑ blood sugar → insulin secreted → anabolic functions: promotes glucose entry into cells, ↑ glycogen synthesis, ↓ lipolysis
- Gamma ( $\gamma$ ) cells/PP cells
  - 3–5% of total islet cells
  - Produce pancreatic polypeptide
  - Secretion stimulated by meals high in protein, hypoglycemia, physical activity, fasting; inhibits pancreatic exocrine (enzymes) and endocrine (insulin) activity
- Delta ( $\delta$ ) cells
  - 3–10% of total islet cells
  - Produce somatostatin
  - Paracrine function of suppressing both insulin and glucagon
- Epsilon ( $\epsilon$ ) cells
  - < 1% of total islet cells
  - Produce ghrelin
  - Functions in appetite stimulation



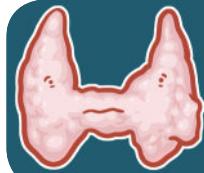
**Figure 31.6** Location of the adrenal glands and the hormones secreted by the cortex, medulla.



**Figure 31.7** The pancreas has both endocrine and exocrine functions. It has hormone-producing clusters of cells called Islets of Langerhans.

## MAJOR HORMONES AND THEIR FUNCTIONS

GLAND	HORMONE	TYPE	REGULATED BY	TARGET	FUNCTION
<b>HYPOTHALAMUS</b>	Oxytocin	Peptide	Bonding, motherhood	Uterus, mammaryes	Uterine contractions, milk ejection
	ADH	Peptide	Blood osm., volume	Kidneys	↑ water reabsorption
<b>ANTERIOR PITUITARY</b>	Growth hormone	Peptide	GHRH, GHIH	Muscles, liver	Muscle growth, bone growth (by IGF-1)
<b>THYROID</b>	T <sub>3</sub> , T <sub>4</sub>	Amine	TSH	Cells	↑ metabolism
	Calcitonin	Peptide	Calcium in blood	Bones, kidneys, etc.	↓ blood calcium levels
<b>PARATHYROID</b>	Parathyroid	Peptide	Calcium in blood	Bones, kidneys, etc.	↑ blood calcium levels
<b>ADRENAL CORTEX</b>	Cortisol	Steroid	ACTH	All tissues	↑ blood glucose, inflammatory response
	Aldosterone	Steroid	↓ blood pressure, ↑ blood potassium	Kidneys	↓ urine sodium, ↑ urine potassium
	Sex hormones	Steroid	Puberty, ongoing	Gonads	Sex characteristics
<b>ADRENAL MEDULLA</b>	Epinephrine, norepinephrine	Modified amino acid	"Fight or flight" situations	All tissues	"Fight or flight" response
<b>PANCREAS</b>	Insulin	Protein	↑ blood sugar	Liver, muscle, fat	↓ blood sugar
	Glucagon	Protein	↓ blood sugar	Liver, muscle, fat	↑ blood sugar
<b>TESTES</b>	Testosterone	Steroid	FSH, LH	Gonads	Male sex characteristics and function
<b>OVARIES</b>	High	High	FSH, LH	Gonads	Female sex characteristics and function



# NOTES

## PITUITARY HORMONES

### — GENERALLY, WHAT ARE THEY? —

- Pituitary gland: AKA hypophyseal gland/hypophysis
- Connected to hypothalamus via pituitary stalk (infundibulum) which controls pituitary secretory actions
- Consists of two embryologically, functionally different parts that secrete different hormones

#### **ANTERIOR PITUITARY (ADENOHYPOPHYSIS)**

- Connects to hypothalamus via blood vessels (hypophyseal portal system)
- Hypothalamus produces releasing hormones → pituitary secretes tropic hormones that regulate target tissues

#### **Corticotropin-releasing hormone (CRH)**

- Adrenocorticotropic hormone (ACTH) → adrenal medulla

#### **Gonadotropin-releasing hormone (GnRH)**

- Luteinizing hormone (LH), follicle-stimulating hormone (FSH) → ovaries, testes

#### **Growth hormone releasing hormone (GHRH)**

- Stimulates release of somatotropin/growth hormone (GH) → various tissues throughout body

#### **Thyrotropin-releasing hormone (TRH)**

- Thyroid-stimulating hormone → thyroid gland

#### **Prolactin (PL)**

- Acts on breasts (lactogenesis)
  - Hypothalamus inhibits prolactin production via dopamine
  - TRH, estrogen, progesterone, oxytocin stimulate prolactin

#### **POSTERIOR PITUITARY (NEUROHYPOPHYSIS)**

- Represents an extension of hypothalamus
- Does not secrete its own hormones
- Stores, releases neurohormones synthesized in hypothalamus

#### **Vasopressin/antidiuretic hormone (ADH)**

- Acts on kidney tubules, arterioles

#### **Oxytocin**

- Acts on uterus, breasts

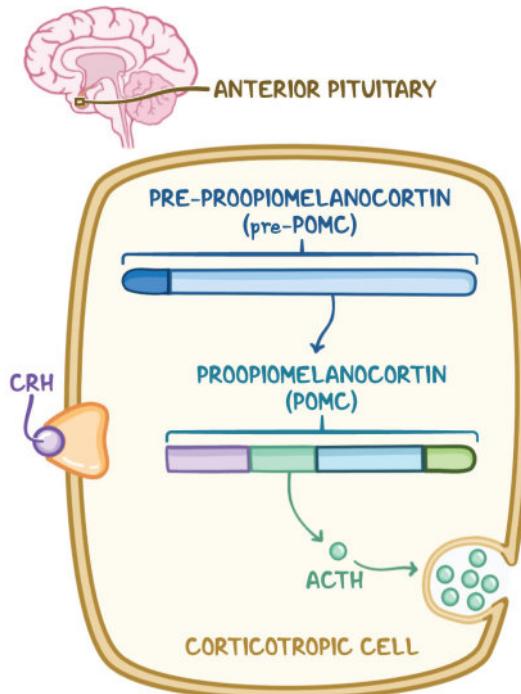
# ADRENOCORTICOTROPIC HORMONE (ACTH)

[osms.it/adrenocorticotrophic-hormone](https://osms.it/adrenocorticotrophic-hormone)

- Hormone secreted by anterior pituitary corticotropic cells
- Main action of ACTH involves stimulating adrenocortical cells of zona fasciculata of the adrenal cortex to secrete glucocorticoids (primarily cortisol)
  - Anti-inflammatory effects
  - Increases blood glucose levels
  - Increases fat and protein breakdown

## SYNTHESIS

- Pre-pro-opiomelanocortin (pre-POMC) → proopiomelanocortin (POMC) → ACTH, gamma lipotropin, beta endorphin, melanocyte-stimulating hormone



**Figure 32.1** Synthesis of ACTH in the anterior pituitary. Corticotropin releasing hormone (CRH) stimulates the cell to release ACTH.

## STIMULATION OF ACTH RELEASE

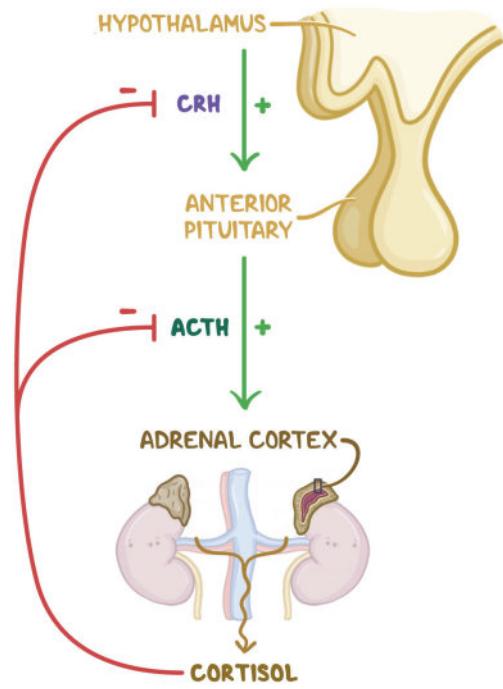
- Corticotropin releasing hormone (CRH) secreted by hypothalamus
  - Stress, low blood glucose, low glucocorticoid levels, increased sympathetic activity, normal diurnal rhythm
  - Release of ACTH demonstrates circadian rhythm affected by suprachiasmatic nucleus → low evening concentrations, high in morning

## ACTH RELEASE REGULATION

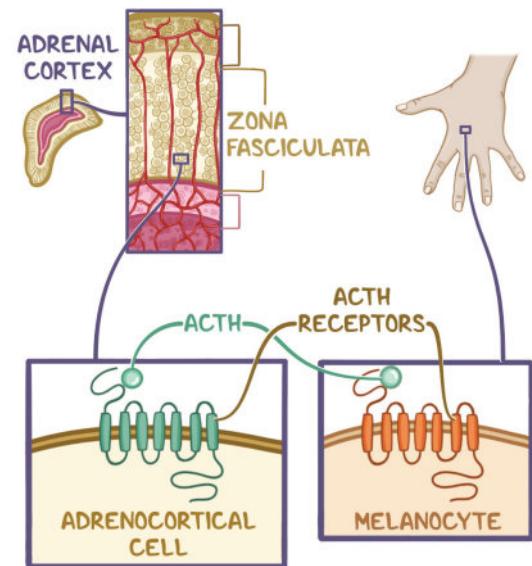
- ACTH release is regulated by hypothalamic-pituitary-adrenal axis negative feedback
  - Hypothalamus releases CRH → CRH stimulates pituitary to release ACTH → ACTH stimulates adrenal cortex to secrete cortisol → ↑ cortisol inhibits hypothalamic release of CRH → ↓ CRH decreases ACTH secretion → closed loop

## ACTH SIGNALING PATHWAY

- ACTH binds to ACTH receptor on adrenal cortex adrenocorticotrophic cells, primarily zona fasciculata; also expressed in skin, both white, brown adipocytes
- ACTH receptor is a seven-membrane-spanning G-coupled receptor
- ACTH binds to receptor → activates G<sub>s</sub> protein → α subunit released → activates adenylate cyclase → ↑ cAMP → activates protein kinase A → phosphorylation cascade → transcription factor activation → effects



**Figure 32.2** The negative feedback loop which regulates ACTH release.



**Figure 32.3** ACTH receptors are found on adrenocortical cells in the zona fasciculata of the adrenal cortex, as well as on melanocytes in the skin.

# GROWTH HORMONE (GH)

[osms.it/growth-hormone](https://osms.it/growth-hormone)

- AKA somatotropin
- Peptide hormone secreted by somatotropic cells of anterior pituitary
  - Regulates tissue growth
- Released in pulsatile manner every two hours; peaks one hour after falling asleep

## REGULATION OF SECRETION

### Induction of GH release

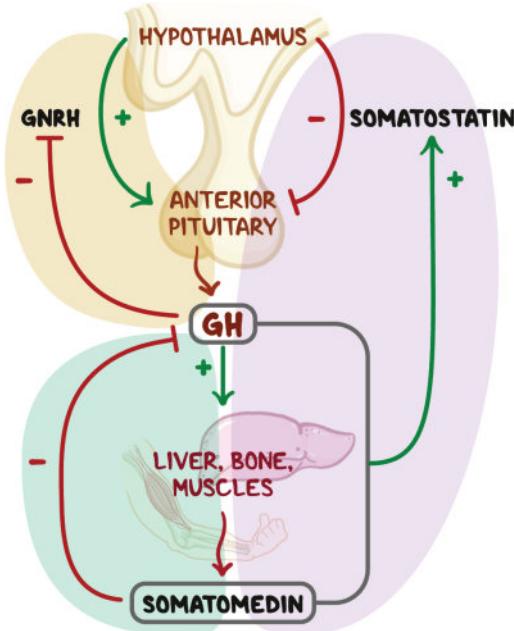
- Hypoglycemia, ↑ estrogen, testosterone (puberty), stress (e.g. trauma, fever), exercise, sleep stages III, IV

### Three negative feedback loops

- ↓ GH stimulates hypothalamus to release GHRH → ↑ GHRH stimulates pituitary to release GH → ↑ GH inhibits release of GHRH → absence of GHRH inhibits GH release → closed loop
- ↑ GH stimulates somatomedins production in the liver, bones, muscles → somatomedins inhibit GH release
- ↑ GH and somatomedins stimulate somatostatin production in hypothalamus → somatostatin inhibits GH release

## GH SIGNALING PATHWAY

- Growth hormone receptor (GHR) belongs to cytokine receptor family
- To activate intracellular signaling, GH must bind to two GH receptors → dimerization of GHR
- GH binds to receptor → conformational change → key tyrosine residue phosphorylation → activation of tyrosine kinase JAK2 → STAT5, Src family kinases, insulin receptor substrate (IRSSs) signalling molecule activation → gene transcription, effects



**Figure 32.4** The three negative feedback loops that regulate GH secretion, each highlighted in a different colour. GH and somatomedin together stimulate somatostatin production in the hypothalamus, which inhibits GH release.

## EFFECTS OF GH

- Primary effect of GH is cell metabolism stimulation, growth, division

### Direct effects

- Anti-insulin-like effects
- Carbohydrates: ↑ blood glucose levels
  - Stimulates gluconeogenesis, glycogenolysis in liver
  - Increases tissue insulin resistance
- Fats: ↑ fatty acids in blood
  - Stimulates adipose tissue lipolysis

### Indirect effect

- Insulin-like effects through insulin-like growth factors (e.g. somatomedins like IGF-1)
- Stimulates cell growth, division, and differentiation; reduces apoptosis

- Proteins: anabolic effect
  - Stimulates amino acid, protein uptake
  - Stimulates protein synthesis
  - Decreases protein breakdown
- Epiphyseal plates, cartilage
  - Stimulates bone osteoblast activity, cartilage chondrocyte activity → increased linear growth

# THYROID-STIMULATING HORMONE (TSH)

[osms.it/thyroid-hormone](http://osms.it/thyroid-hormone)

- AKA thyrotropin
- Glycoprotein hormone secreted by pituitary gland
- Main action of TSH involves stimulating thyroid gland growth, thyroid hormone synthesis, release

## STIMULATION OF TSH RELEASE

- Thyrotropin-releasing hormone (TRH) secreted by hypothalamus
  - Low  $T_3$ ,  $T_4$  blood levels
  - Decreased metabolism
  - Cold stress
  - Conditions that increase ATP demand

## REGULATION OF SECRETION

- TRH secreted by hypothalamus, stimulates pituitary thyrotropic cells to release TSH
- Thyroid hormones, specifically  $T_3$ , down-regulate TRH receptors on thyrotropic cells, inhibiting TSH secretion
- TSH release, thyroid hormone is regulated by negative feedback loop
  - Hypothalamus releases TRH → TRH stimulates pituitary to release TSH → TSH travels to thyroid follicle → stimulates thyroid hormones synthesis, secretion → thyroid hormones inhibit both TRH, TSH release → absence of TRH, TSH inhibits further thyroid hormone secretion → closed loop

## TSH SIGNALING PATHWAY

- TSH binds TSH receptor primarily found on thyroid gland follicular cells
  - Also found on adipose tissue, fibroblasts
- TSH receptor is integral membrane receptor coupled with  $G_s$  protein
- TSH binds to receptor → activates  $G_s$  protein →  $\alpha$  subunit released → activates adenylate cyclase → ↑ cAMP → activates protein kinase A → phosphorylation cascade → transcription factor activation → effects

## EFFECTS OF TSH

- TSH has two effects on the thyroid gland
  - Stimulates all the steps in thyroid hormone synthesis, secretion
  - Trophic effect: increases growth of thyroid gland

# THYROID HORMONE

[osms.it/thyroid-hormone](https://osms.it/thyroid-hormone)

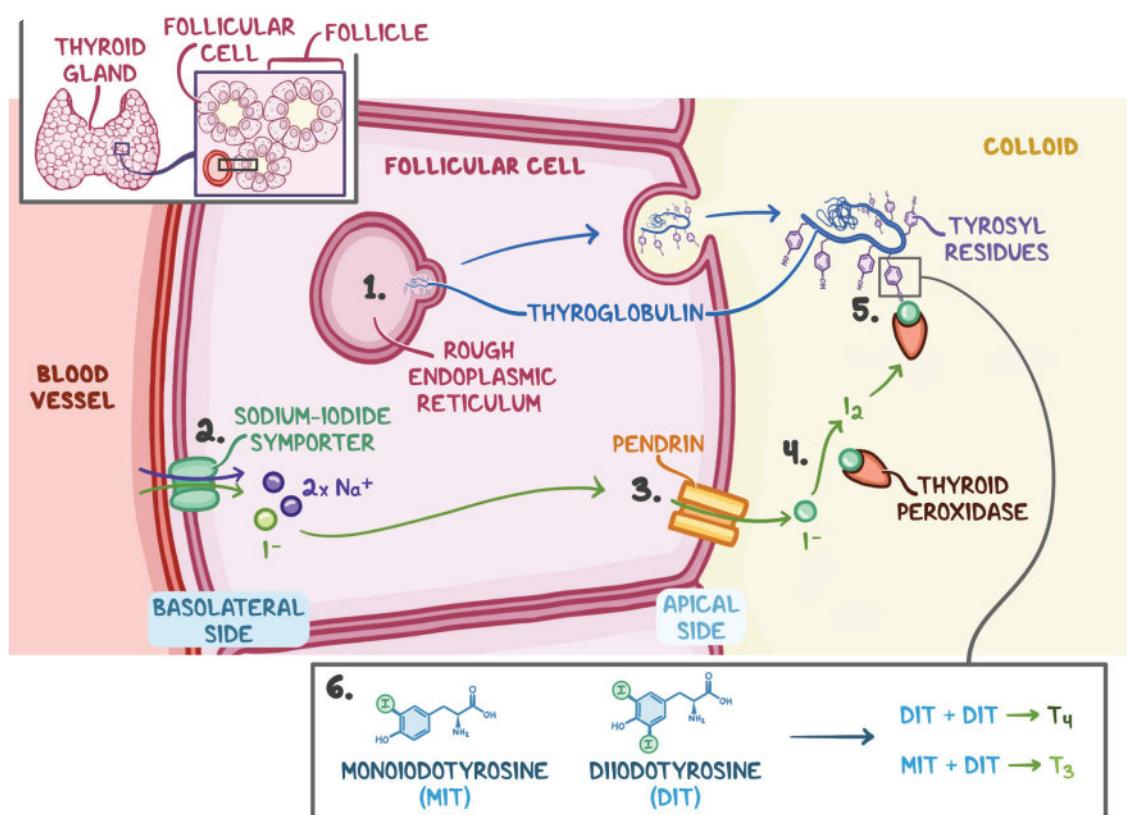
- Glycoprotein hormones  $T_3$  (triiodothyronine),  $T_4$  (tetraiodothyronine) secreted by thyroid follicular epithelial cells
- Less active form thyroid hormone ( $T_4$ ) is secreted, converted in target tissue into more active form ( $T_3$ )

## SYNTHESIS OF THYROID HORMONES

### Six steps

- Thyroglobulin (TG) synthesized in follicular cell rough endoplasmic reticulum (RER), secreted into lumen (colloid)
- Iodine from blood enters follicular cells on

- basolateral side via  $\text{Na}^+/\text{I}^-$  symport
- iodine exits cell on apical side via transporter pendrin
- Inside follicle lumen at apical side, iodine oxidized by enzyme thyroid peroxidase ( $\text{I}^- \rightarrow \text{I}_2$ )
- $\text{I}_2$  iodinates TG tyrosyl residues (organification of  $\text{I}_2$ ), catalyzed by thyroid peroxidase, forms monoiodotyrosine (MIT), diiodotyrosine (DIT)
- On TG, two DIT molecules coupled to form  $T_4$  (faster reaction); MIT coupled with DIT to form  $T_3 \rightarrow$  TG now contains  $T_3$ ,  $T_4$ , MIT, DIT residues



**Figure 32.5** Thyroid hormone synthesis overview. 1. Thyroglobulin (TG) is synthesized in rough endoplasmic reticulum, secreted into colloid. 2. Iodine enters cell from blood via  $\text{Na}^+/\text{I}^-$  symporter. 3. Iodine exits cell into colloid via pendrin. 4. Iodine is oxidized by thyroid peroxidase, become  $\text{I}_2$ . 5.  $\text{I}_2$  iodinates tyrosyl residues on TG, forming monoiodotyrosine (MIT), diiodotyrosine (DIT). 6. Two DITs combine to form  $\text{T}_4$ ; MIT combines with DIT to form  $\text{T}_3$ .

## THYROID HORMONE SECRETION AND TRANSPORT

### Thyroid hormone secretion

- Thyroid hormones stored in colloid until stimulated for secretion
  - TSH stimulation → endocytosis of iodinated TG by follicular epithelial cells → TG transportation to basal membrane → TG fuses with lysosome → TG hydrolysis,  $T_3$ ,  $T_4$ , MIT, DIT residue release →  $T_3$  (10%),  $T_4$  (90%) secreted into circulation
  - Iodide from MIT, DIT residues recycled for next synthesis

### Transport of thyroid hormones

- Once in circulation, most thyroid hormones travel bound to thyroxine-binding protein (TBP)
  - Some bound to prealbumin, albumin
- Small fraction travels unbound → physiologically active forms

### Activation of $T_4$

- 90% of secreted thyroid hormone is in less active  $T_4$  form
- $T_4$  activated in target tissue by 5'-deiodinase → removes one atom of  $I_2$  →  $T_4$  gets converted to  $T_3$

- Starvation inhibits 5'-deiodinase in target tissue, except in brain → lowers  $O_2$  consumption, basal metabolic rate (BMR)

## REGULATION OF SECRETION

### Negative feedback loop

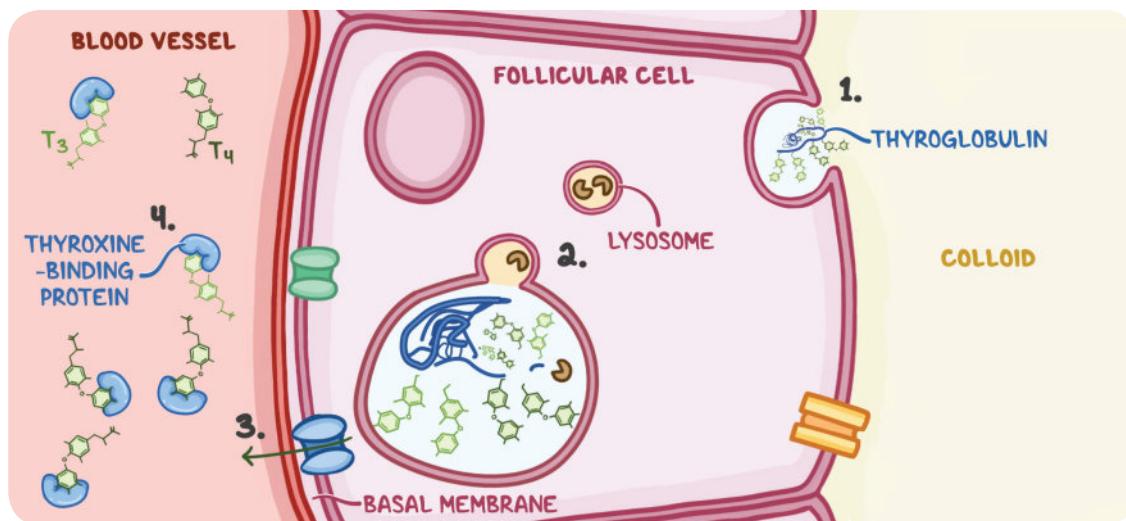
- Regulated by negative feedback loop in hypothalamic-pituitary-thyroid axis
  - Thyrotropin-releasing hormone (TRH) secreted by hypothalamus, stimulates thyrotropic cells of pituitary to release thyroid-stimulating hormone (TSH)

### Effects of TSH on thyroid gland

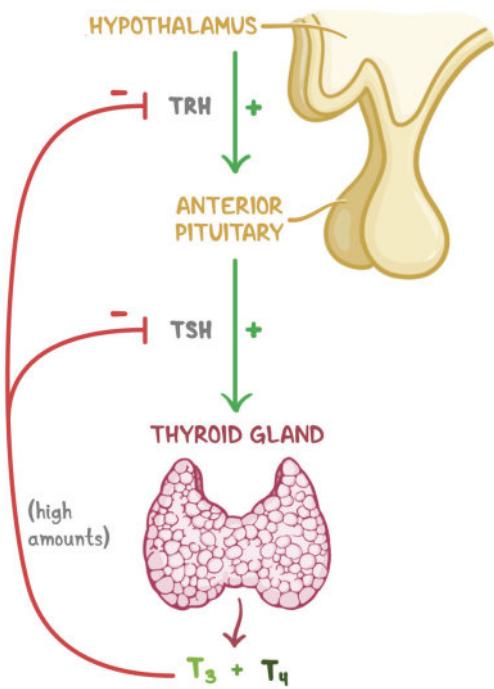
- Two effects
  - Stimulates all steps in thyroid gland synthesis, secretion
  - Trophic effect: increases thyroid gland growth

### Other regulatory factors

- Iodine deficiency
- Excessive iodine intake (Wolff-Chaikoff effect)
  - Inhibits iodine organification
- 5'-deiodinase deficiency (e.g. starvation)
- ↓ TBP synthesis (e.g. liver failure)
  - Increases unbound (active) thyroid hormones fraction



**Figure 32.6** Thyroid hormone secretion overview. 1. TG in colloid is endocytosed into follicular cell. 2. Lysosome fuses with vesicle; thyroid hormones are cleaved from TG. 3. Hormones are released into blood. 4. In blood, most thyroid hormones travel bound to a protein, thyroxine-binding protein being most common.



**Figure 32.7** The negative feedback loop which regulates thyroid hormone secretion.

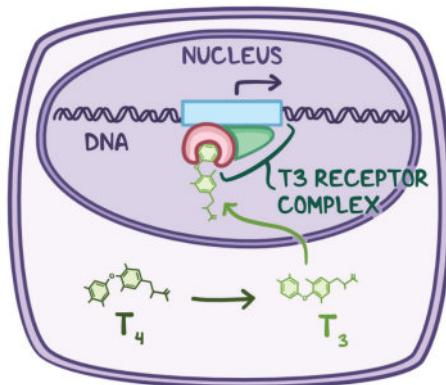
## SIGNALING PATHWAY

- Thyroid hormones act on all organ systems
- Inside target cells,  $T_4$  converts to  $T_3 \rightarrow T_3$  enters nucleus, binds nuclear receptor  $\rightarrow T_3$  receptor complex binds DNA, stimulates transcription  $\rightarrow$  translation  $\rightarrow$  protein synthesis
- $T_3$  stimulates synthesis of  $Na^+-K^+$  ATPase,  $Ca^{2+}$  ATPase, transport proteins, proteolytic, lysosomal enzymes,  $\beta 1$  adrenergic receptors, structural proteins

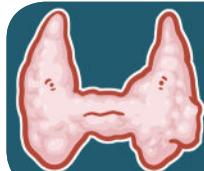
## EFFECTS OF THYROID HORMONE

- Key hormone in regulating body metabolism; also important for embryological growth
- General effect: all tissues except brain, spleen and gonads
  - $\uparrow Na^+-K^+$  ATPase  $\rightarrow \uparrow$  oxygen consumption  $\rightarrow \uparrow$  basal metabolic rate (BMR), body temperature
- Catabolic effect: metabolism of macromolecules
  - $\uparrow$  transport proteins  $\rightarrow \uparrow$  glucose absorption from GI tract

- $\uparrow$  catecholamine, glucagon, growth hormone activity  $\rightarrow \uparrow$  proteolysis, lipolysis, gluconeogenesis
- Cardiovascular system
  - $\uparrow \beta 1$  adrenergic receptors,  $Ca^{2+}$  ATPase  $\rightarrow \uparrow$  inotropic (contractility), chronotropic (heart rate) effect  $\rightarrow \uparrow$  cardiac output
- Central nervous system (CNS)
  - Gestational period  $\rightarrow$  CNS development
  - Adult period  $\rightarrow \uparrow$  brain activity, attention span, memory
- Growth
  - $\uparrow$  osteoblast, osteoclast activity  $\rightarrow \uparrow$  bone formation, maturation



**Figure 32.8** In the target cell,  $T_4$  is converted to  $T_3$ , which enters the nucleus and binds to a receptor. The receptor complex binds to DNA to stimulate transcription.



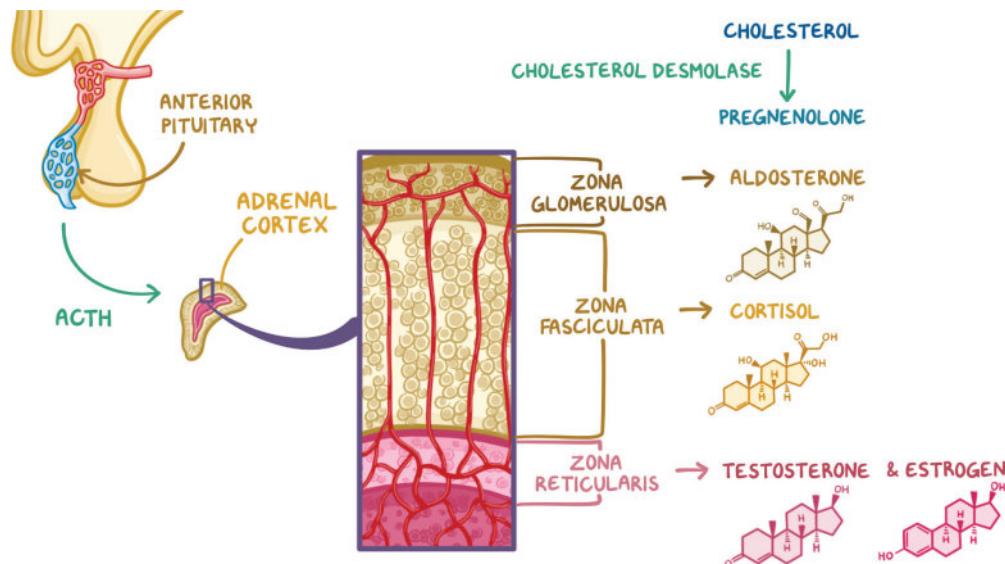
# NOTES

## ADRENAL HORMONES

# SYNTHESIS OF ADRENOCORTICAL HORMONES

[osms.it/adrenocortical-hormone-synthesis](https://osms.it/adrenocortical-hormone-synthesis)

- Synthesized from cholesterol: carbon skeleton, 21-carbon molecules; circulation supplies cholesterol which enters adrenal gland cells via endocytosis
  - Some synthesized de novo → both forms stored in cytoplasmic vesicles
- Cytochrome p450 using O<sub>2</sub>, adrenodoxin reductase, adrenodoxin transfers H<sup>+</sup> from NADPH producing energy using reduction reactions
- Different enzymes found in different layers according to which hormones synthesized
- Cholesterol desmolase found in all layers
  - Rate-limiting step; stimulated by adrenocorticotropic hormone (ACTH); converts cholesterol to pregnenolone
- Corticosteroid is common name for steroid hormones made in cortex: include mineralocorticoids, glucocorticoids



**Figure 33.1** Three zones of adrenal cortex secrete steroid hormones under control of ACTH, which is released by anterior pituitary. Adrenal cortex cells first convert cholesterol to pregnenolone using enzyme cholesterol desmolase. Pregnenolone is then converted into aldosterone in zona glomerulosa, cortisol in zona fasciculata, and testosterone and estrogen in zona reticularis.

**Mineralocorticoids**

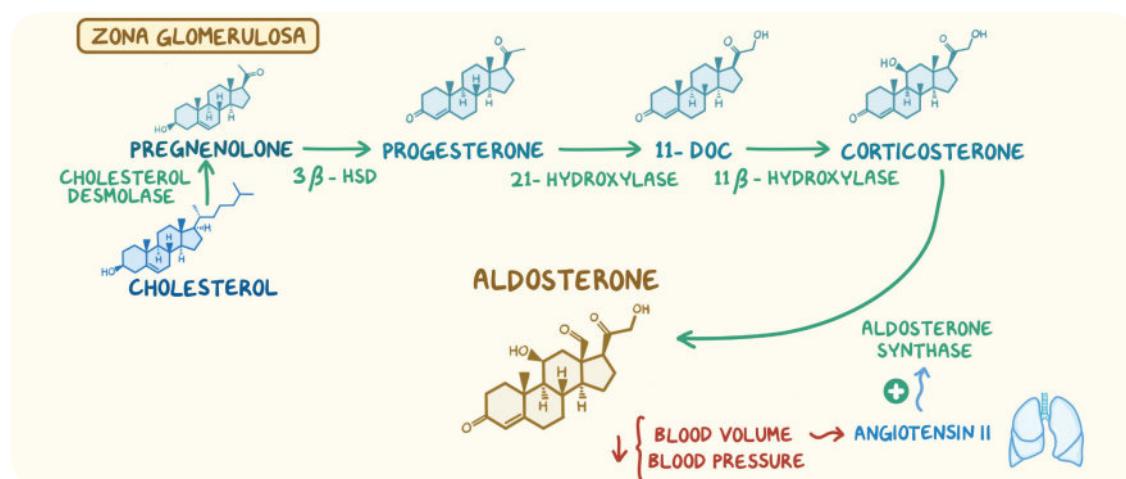
- Synthesized in zona glomerulosa
- Example: aldosterone
- Aldosterone synthase required and found only in zona glomerulosa, converts cortisone → aldosterone

**Glucocorticoids**

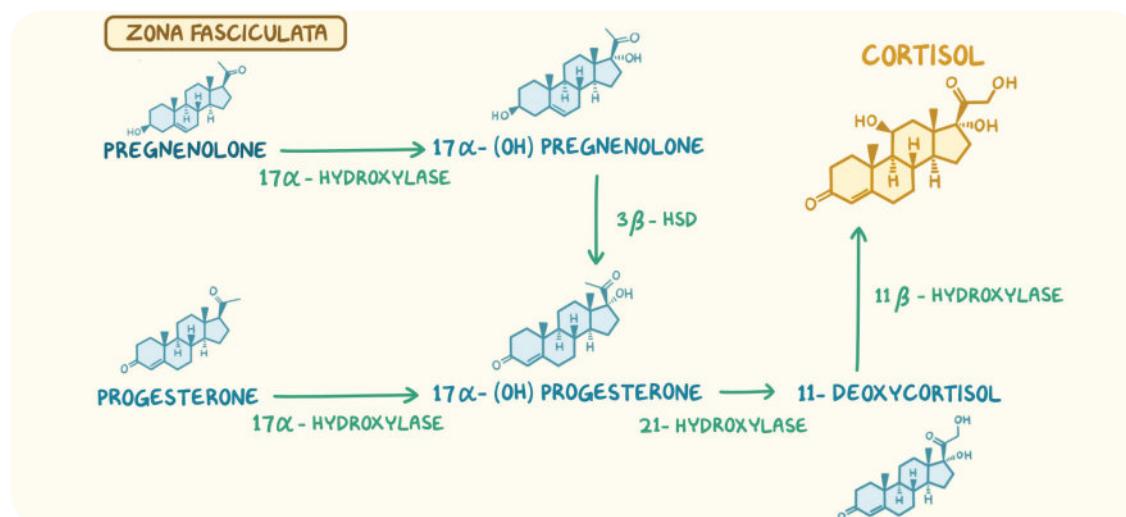
- Synthesized in zona fasciculata
- Examples: cortisol, corticosterone
- 17 $\alpha$ -hydroxylase** (if deficient corticosterone can be formed) → 3 $\beta$ -hydroxysteroid dehydrogenase → 21 $\beta$ - and 11 $\beta$ -hydroxylase

**Androgens**

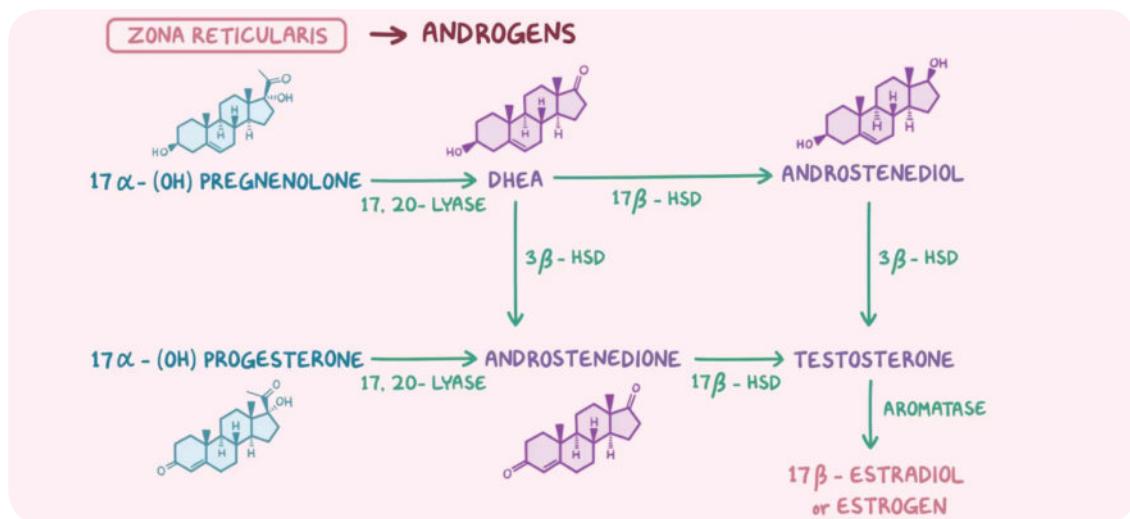
- Synthesized in zona reticularis
- Examples: dehydroepiandrosterone (DHEA), androstenedione
- 17,20-lyase responsible for conversion of glucocorticoids into androgens
- DHEA, androstenedione have a weak androgenic effect
  - Male: converted to testosterone in testes
  - Female: main source of androgens
- Low quantity of testosterone, 17 $\beta$ -estradiol



**Figure 33.2** Aldosterone synthesis in zona glomerulosa. Aldosterone synthase is stimulated by hormone angiotensin II, which is produced in lungs in response to low blood pressure, volume.



**Figure 33.3** Cortisol synthesis in zona fasciculata.



**Figure 33.4** Androgen synthesis in zona reticularis.

# CORTISOL

[osms.it/cortisol](https://osms.it/cortisol)

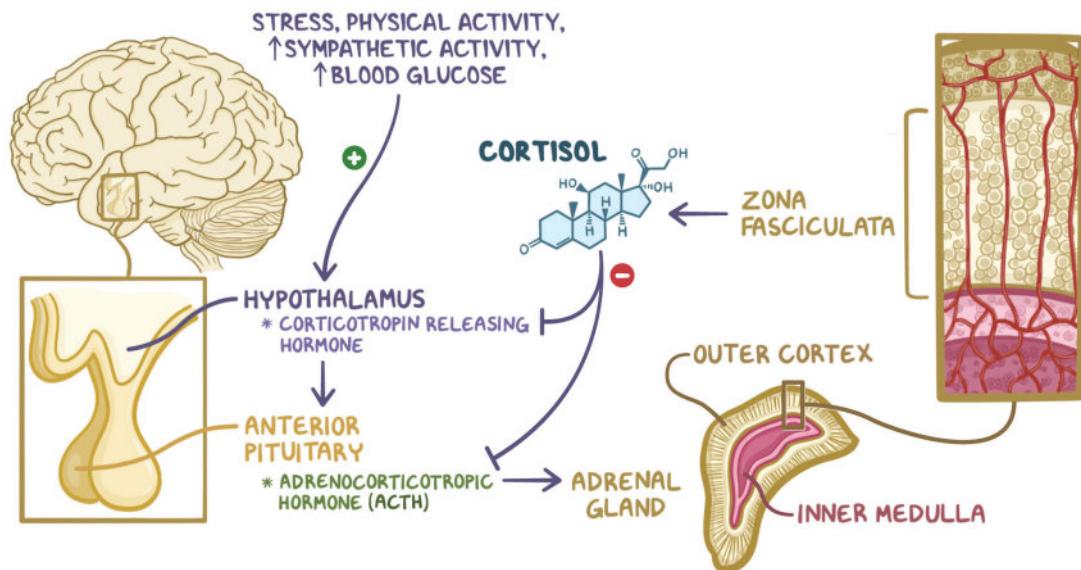
- Steroid glucocorticoid hormone secreted by adrenal cortex; has metabolic, anti-inflammatory, immunosuppressive, vascular effects
- Normal pulsatile secretion, approximately 10 surges in diurnal (daily) pattern
  - Concentration highest in morning, lowest in evening
  - Diurnal pattern:** maintained by hypothalamic suprachiasmatic nucleus; acts as central pacemaker for hypothalamic-pituitary-adrenal (HPA) axis; adrenals maintain diurnal pattern of sensitivity to ACTH

## Secretion regulation

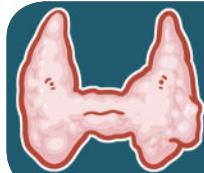
- Stress (infection, trauma, initiation of “fight or flight” response, psychological stressors), ↑ sympathetic activity, physical activity, ↓ blood glucose → hypothalamus stimulated to release corticotropin-releasing hormone (CRH) → anterior pituitary releases adrenocorticotrophic hormone (ACTH) → adrenal medulla secretes glucocorticoids (primarily cortisol) → target tissues
- Negative feedback of cortisol** to hypothalamic-pituitary axis → ↓ cortisol

## Major effects

- Metabolic:** ↑ blood glucose (considered diabetogenic hormone) by ↑ hepatic glycogenolysis, ↑ lipolysis, ↑ protein catabolism, ↓ cellular insulin sensitivity, ↑ appetite
- Immune:** ↓ intensity of immune, inflammatory responses by ↓ production of arachidonic acid metabolites (e.g. prostaglandin, thromboxane, leukotrienes), ↓ production of interleukins, interferon, tumor necrosis factor; ↓ T cell proliferation; ↓ neutrophil phagocytosis
- Vascular:** involved in normal vascular blood pressure maintenance; supports vascular smooth muscle responsiveness to catecholamine vasoconstrictive effects
- Other:** ↓ connective tissue fibroblast proliferation, ↓ bone formation, ↑ renal blood flow, ↑ erythropoietin release, alters sleep patterns



**Figure 33.5** Cortisol secretion regulation.



# NOTES PANCREATIC HORMONES

## GLUCAGON

[osms.it/glucagon](https://osms.it/glucagon)

- Peptide hormone secreted by pancreatic alpha cells
- Important for blood glucose regulation, along with insulin
- Synthesis
  - Preproglucagon → proglucagon → glucagon

### Secretion regulated mainly by glucose

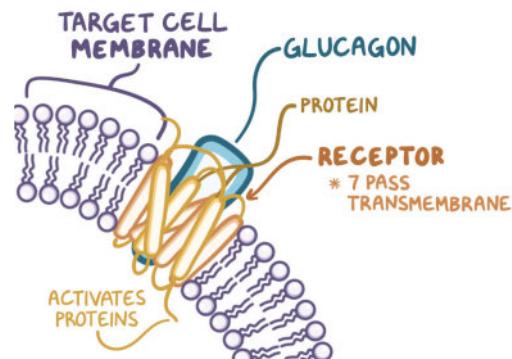
- ↓ glucose levels between meals or while sleeping → ↓ insulin → glucagon secretion stimulation → hepatic glycogenolysis, gluconeogenesis → ↑ blood glucose levels

### Other factors that regulate glucagon secretion

- Sympathetic nervous system
  - Adrenaline ( $\alpha_2$  receptors)
- Parasympathetic nervous system
  - Acetylcholine ( $M_3$  receptors)
- Alanine, arginine
  - E.g. from high protein meal
- Cholecystokinin, somatostatin
- Exercise

### GLUCAGON SIGNALING PATHWAY

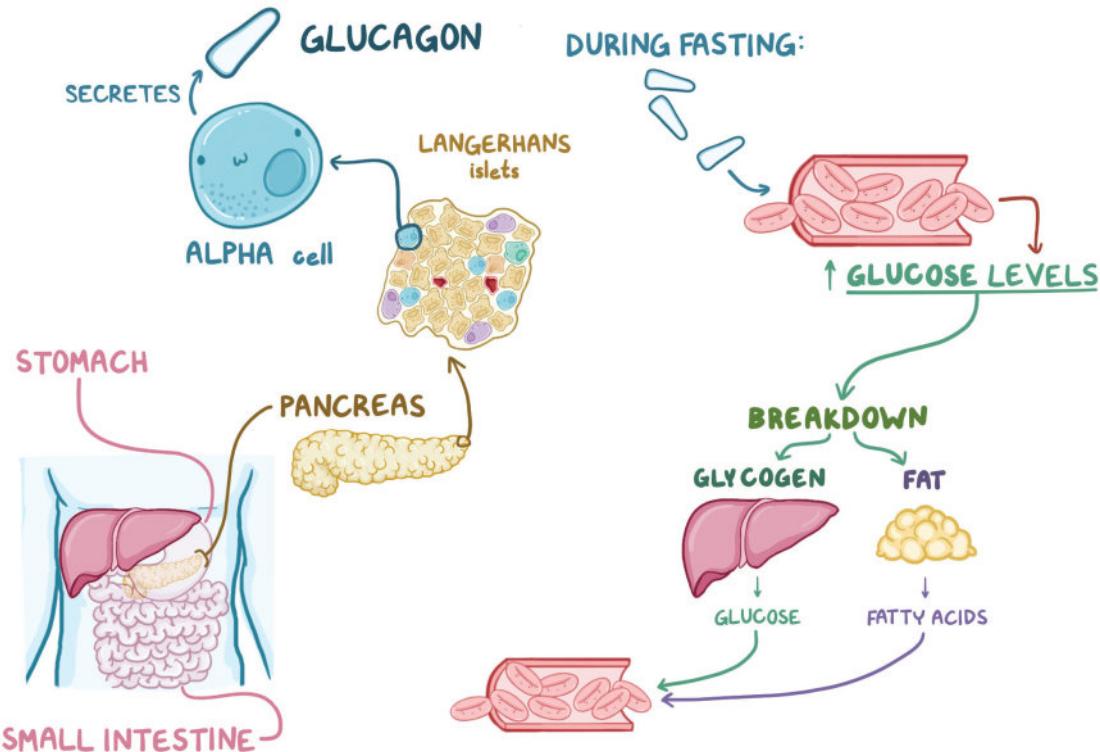
- Glucagon receptor is a heterotrimer
  - G-protein coupled receptor that contains  $\alpha$ ,  $\beta$ ,  $\gamma$  subunits
- Glucagon binds to receptor → activates  $G_s$  protein →  $\alpha$  subunit released → activates adenylate cyclase → ↑ cAMP → activates protein kinase A → phosphorylation cascade → transcription factor activation → effects



**Figure 34.1** Glucagon exerts its effects by binding to G-protein coupled receptors on the membranes of liver and adipose cells.

### EFFECTS OF GLUCAGON

- Primary action is to increase blood glucose when it falls below normal range
- Carbohydrates: ↑ blood glucose levels
  - Stimulates glycogenolysis in liver, muscle
  - Stimulates gluconeogenesis in liver, kidney
  - Inhibits hepatic glycolysis
- Fats: ↑ fatty acids, keto acid levels in blood
  - Inhibits fatty acid synthesis, oxidation in liver
  - Inhibits fat deposition in adipose tissue
  - Stimulates lipolysis
  - Stimulates keto acid production



**Figure 34.2** Glucagon is secreted by pancreatic alpha cells when glucose levels are low. It increases glucose levels in the bloodstream by inducing the breakdown of storage molecules in the liver and adipose cells.

## INSULIN

[osms.it/insulin](https://osms.it/insulin)

- Peptide hormone secreted by pancreatic beta cells
- Important for blood glucose regulation
- Consists of A and B amino acid chains connected with two disulfide (-S-S-) bonds

### SYNTHESIS

- Preproinsulin → proinsulin → insulin
- During insulin synthesis, protein called C-peptide cleaved off, secreted together with insulin in equimolar amounts within secretory vesicles → C-peptide used to measure insulin levels

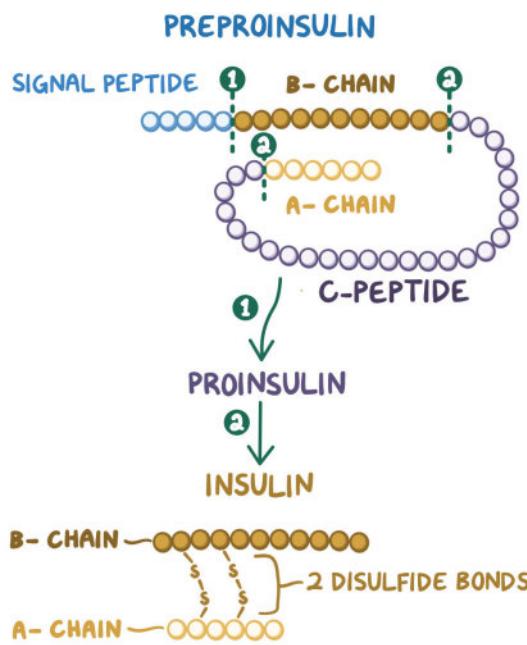
### SECRETION

#### Secretion regulated mainly by glucose

- Carbohydrates consumption → ↑ glucose → passive diffusion into beta cells through GLUT2 transporters → stimulation of insulin secretion

#### Other factors that stimulate insulin secretion

- ↑ fatty acid, amino acid levels in blood
- Parasympathetic nervous system
  - Acetylcholine ( $M_3$  receptors)
- Sympathetic nervous system
  - Adrenaline ( $\beta_2$  receptors)
- Growth hormone (GH), adrenal corticotrophic hormone (ACTH)



**Figure 34.3** Insulin synthesis.

## PHASES OF INSULIN RELEASE

- Two phases

### First phase

- Involves L-type  $\text{Ca}^{2+}$  channels
- Rapidly triggered release of preformed secretory vesicles
- Lasts 10 minutes

### Second phase

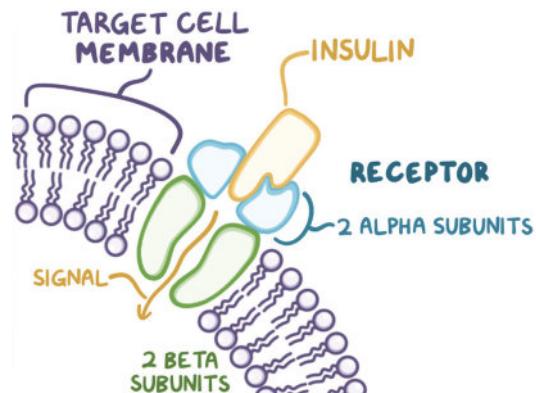
- Involves R-type  $\text{Ca}^{2+}$  channels
- Slow release of newly formed secretory vesicles
- Lasts 2–3 hours

## INSULIN SIGNALING PATHWAY

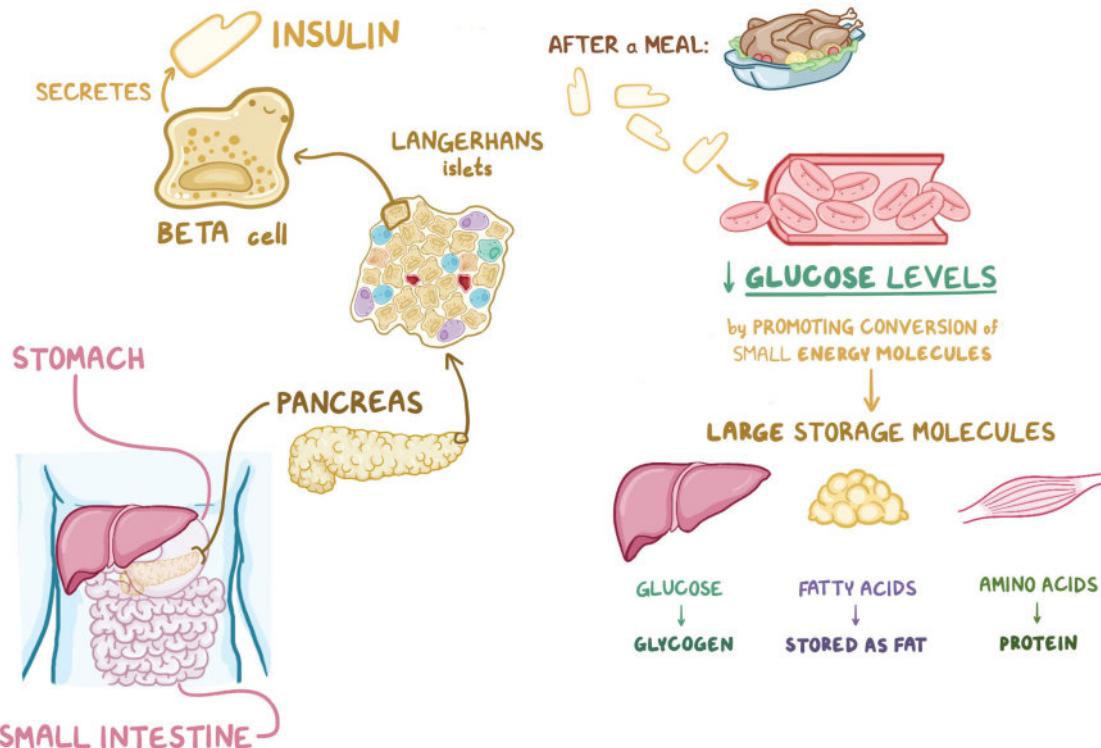
- Insulin receptor is a tetramer
  - Contains two extracellular  $\alpha$  subunits connected by disulfide bonds, two intracellular  $\beta$  subunits connected to each  $\alpha$  subunit
- Insulin binds to  $\alpha$  subunits → activates tyrosine kinase activity in  $\beta$  subunits →  $\beta$  subunit autophosphorylation → insulin receptor substrates (IRS) phosphorylation cascade → transcription factor activation → effects

## EFFECTS OF INSULIN

- The primary action of insulin is lowering blood glucose levels when above normal range
- Carbohydrates: ↓ blood glucose levels
  - Translocates GLUT4 transporters to muscle, adipose cell membranes → facilitates cell uptake of glucose
  - Activates glycogen synthesis in liver, muscles
  - Inhibits hepatic glycogenolysis, gluconeogenesis
- Fats: ↓ fatty acids, keto acid levels in blood
  - Inhibits fatty acids mobilization, oxidation
  - Stimulates fat deposition in adipose tissue
  - Inhibits lipolysis
  - Inhibits keto acid formation in liver
- Proteins: anabolic effect
  - Stimulates amino acid, protein uptake
  - Stimulates protein synthesis
  - Inhibits proteolysis
- Other: ↓  $\text{K}^+$  levels in blood
  - Increases potassium uptake
  - Stimulation of cell growth, gene expression



**Figure 34.4** Insulin exerts its effects by binding to alpha subunits of insulin receptor, which leads to signal transduction within cell.



**Figure 34.5** Insulin is secreted by pancreatic beta cells when glucose levels are high. It promotes conversion of glucose → glycogen in liver, fatty acids → fat, and amino acids → protein.

## SOMATOSTATIN

[osms.it/growth-hormone-and-somatostatin](http://osms.it/growth-hormone-and-somatostatin)

- Peptide hormone secreted by pancreatic delta cells

### Factors that regulate somatostatin secretion

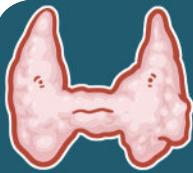
- Ingestion of glucose, fatty acids, amino acids
- Glucagon
- Sympathetic nervous system
  - $\beta$ -adrenergic agonists

### EFFECTS OF SOMATOSTATIN

- Inhibits secretion of insulin, glucagon
  - Inhibits pancreatic exocrine secretion
  - Inhibits secretion of all gastrointestinal hormones (gastrin, cholecystokinin, secretin, motilin etc.)
  - Decreases gastrointestinal motility, blood flow, gastric emptying
- Like this book? You can download more from [AfraTafreeh.com](http://AfraTafreeh.com)

### SOMATOSTATIN SIGNALING PATHWAY

- Somatostatin receptor is a G-protein coupled receptor
- Somatostatin binds to receptor → activates  $G_i$  protein → inhibits adenylate cyclase → ↓ cAMP → ↓  $Ca^{2+}$  → inhibitory effect



# NOTES

## CALCIUM & PHOSPHATE HORMONAL REGULATION

### GENERALLY, WHAT IS IT?

#### CALCIUM & PHOSPHATE HOMEOSTASIS

##### Blood calcium level regulation

- Normal total blood calcium: 8.5–10mg/dl
- Parathyroid hormone: ↑ calcium level
- Vitamin D: ↑ calcium level
- Calcitonin: ↓ calcium level

##### Extracellular calcium

- Diffusible: can cross cell membranes
  - Free-ionized calcium ( $\text{Ca}^{2+}$ ): involved in cellular processes → neuronal action

potential, muscle contraction, hormone secretion, blood coagulation

- Complexed calcium:  $\text{Ca}^{2+}$  ionically bound to other negatively-charged molecules (e.g. oxalate, phosphate → electrically-neutral molecules, do not partake in cellular processes)
- Non-diffusible: cannot cross cell membranes
  - Calcium bound to large negatively charged proteins (e.g. albumin → protein-albumin complex too large to cross cell membranes → not involved in cellular processes)

## CALCITONIN

[osms.it/calcitonin](https://osms.it/calcitonin)

#### CALCITONIN STRUCTURE

- Polypeptide hormone involved in blood calcium regulation
  - Not primary calcium regulator, even if thyroid gland removed, remaining regulatory mechanisms able to maintain calcium homeostasis
- Produced by thyroid gland's parafollicular cells (C cells)
- C cells synthesize preprocalcitonin (141 amino acid polypeptide) → successive enzymatic cleavage steps produces procalcitonin → immature calcitonin (33 amino acids) → mature calcitonin (32 amino acids) → stored/readied for release in secretory granules within C cells

#### CALCITONIN RELEASE

- Calcium-sensing receptors on C cells' surface monitor blood calcium levels → if calcium drifts above normal range → calcitonin released

#### CALCITONIN ACTION

- Lowers blood calcium level

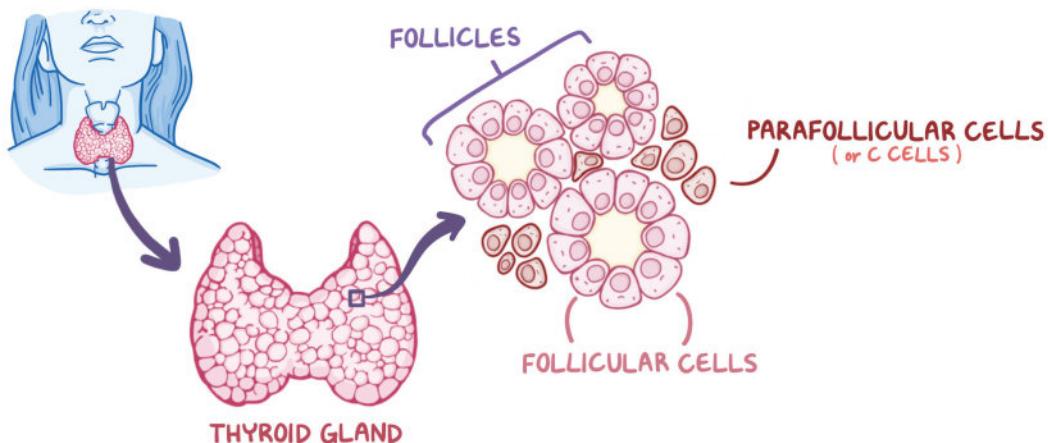
##### Bone

- ↓ bone resorption → ↓ blood calcium concentration
  - When attaching to bone matrix osteoclast membranes form multiple arms (ruffled border) → aids attachment, increases surface area → arms secrete acid → assists bone breakdown

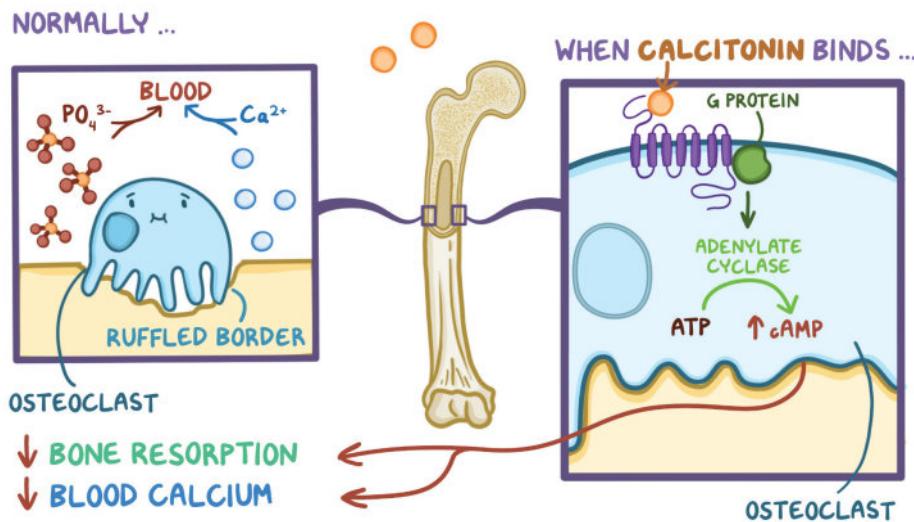
- Calcitonin binds to calcitonin receptor on basal osteoclast surface → G-protein coupled receptor activation → adenylate cyclase activation → adenosine triphosphate (ATP) converted to 3',5'-cyclic AMP (cAMP) → ↑ cAMP levels → ↓ number of osteocyte arms formed → ↓ bone resorption

### Kidneys

- ↓ calcium, phosphate reabsorption by principal cells of distal convoluted tubules



**Figure 35.1** Calcitonin is made and stored in thyroid gland's C cells.



**Figure 35.2** When calcitonin binds to its receptor on an osteoclast, it reduces number of osteoclast arms formed, decreasing bone resorption and blood calcium.

# PARATHYROID HORMONE

[osms.it/parathyroid-hormone](https://osms.it/parathyroid-hormone)

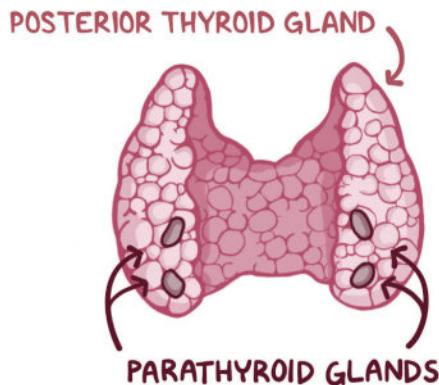
- Primary blood-calcium level regulator

## PARATHYROID GLANDS

- Hormone produced by parathyroid glands, four pea-sized glands found posterior to thyroid
  - Parathyroid gland chief cells synthesize preproparathyroid hormone (preproPTH) (115 amino acid-long protein chain → contains biologically-active parathyroid hormone segment in N-terminal 34 amino acids)
  - Within chief cell endoplasmic reticulum, protein chain cleaved by enzyme peptidase (peptidase removes “pre” segment → proPTH → transported to Golgi apparatus)
  - Final processing in Golgi apparatus (trypsin-like enzyme cleaves off six amino acid “pro” segment → functional parathyroid hormone (single chain 84 amino acid polypeptide) → packaged into secretory vesicles → eventual release)

## Ca<sup>2+</sup> CHANGES

- Ca<sup>2+</sup> level changes detected by parathyroid cell surface receptor (calcium-sensing receptor)
  - Calcium-sensing receptor is G-protein mediated receptor
  - ↑ Ca<sup>2+</sup> level → hormone release inhibition
    - Large Ca<sup>2+</sup> amounts bind to receptor → phospholipase C activation → activated enzyme splits inositol bisphosphate (PIP<sub>2</sub>) → diacylglycerol (DAG), inositol triphosphate (IP<sub>3</sub>)
    - IP<sub>3</sub> diffuses through cytoplasm to endoplasmic reticulum → binds to Ins3PR receptor on ligand-gated Ca<sup>2+</sup> channel → channel opens → calcium stored in endoplasmic reticulum released into cytoplasm → ↑ intracellular calcium → stops binding of PTH-holding granules to chief cell membrane → no PTH release
  - ↓ extracellular Ca<sup>2+</sup> levels → PTH release facilitation
    - Little/no calcium-sensing G-protein receptor activation → no inhibition of PTH granule binding → PTH release



**Figure 35.3** Location of the parathyroid glands which produce parathyroid hormone.

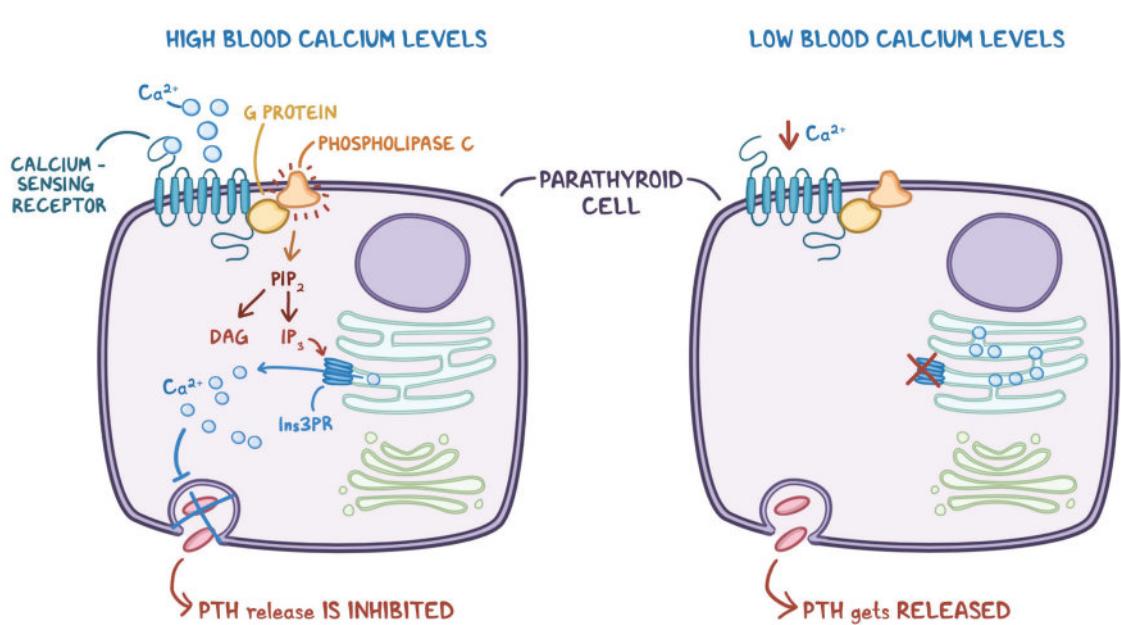
## PTH SECRETION

### Stimuli

- ↓ serum Ca<sup>2+</sup> concentration
- Mild ↓ in serum magnesium (Mg<sup>2+</sup>) concentration
- ↑ in serum phosphate → calcium phosphate complex formation → calcium receptor stimulation ↓
- Adrenaline
- Histamine

### Inhibitors

- ↑ serum Ca<sup>2+</sup> concentration
- Severe ↓ serum Mg<sup>2+</sup> concentration
- Calcitriol



**Figure 35.4** High calcium levels in blood inhibit PTH release from parathyroid cells, while low calcium levels in blood facilitate PTH release from parathyroid cells.

### Magnesium

- Involved in stimulus-secretion coupling
- Moderate  $\downarrow$  serum  $Mg^{2+}$  concentration promotes action of PTH on renal mineral resorption
- Severe hypomagnesemia (e.g. alcoholism) inhibits PTH secretion, causes PTH resistance

### EXTRACELLULAR CALCIUM INCREASE

- PTH  $\rightarrow$   $\uparrow$  extracellular calcium levels (three target organ systems)

### Bones

- PTH receptors on osteoblasts
- PTH binding  $\rightarrow$   $\uparrow$  cytokine release
  - Receptor activator of nuclear factor  $\kappa$ B ligand (RANKL)
  - Macrophage colony-stimulating factor (M-CSF)
  - Inhibits osteoprotegerin (OPG) secretion (inhibition absence  $\rightarrow$  free OPG binds to RANKL (decoy receptor)  $\rightarrow$  prevents RANK-RANKL interaction)
  - PTH-induced cytokine release permits RANK-RANKL interaction  $\rightarrow$  multiple macrophage precursors fuse  $\rightarrow$  osteoclast formation (bone breakdown)

- Bone breakdown  $\rightarrow$  release of calcium, phosphate into blood (initially forms physiologically-inactive compound)

### Kidneys

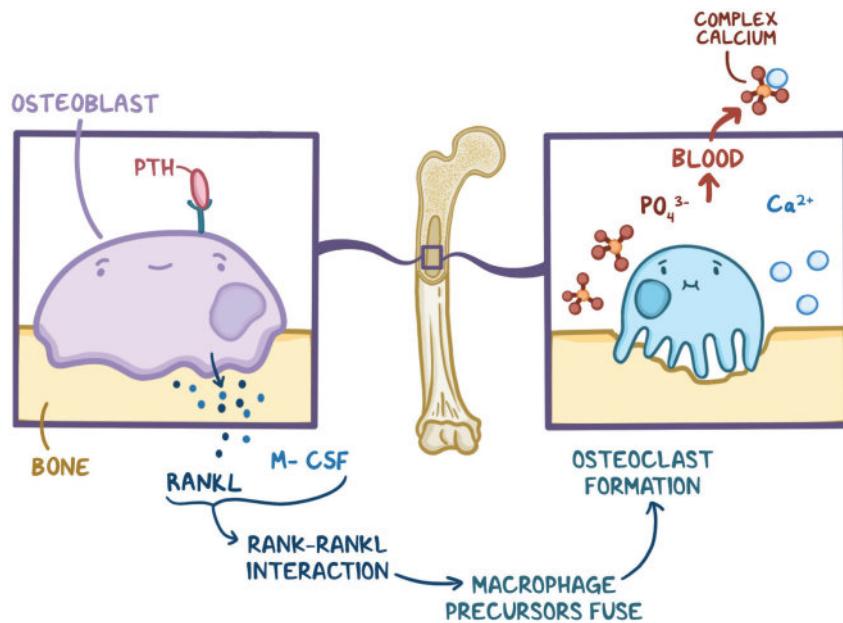
- PTH binds to receptors on cells of proximal convoluted tubules  $\rightarrow$  inhibits sodium-phosphate co-transporters on apical surface  $\rightarrow$   $\downarrow$  sodium, phosphate reabsorption  $\rightarrow$   $\uparrow$  urinary phosphate excretion
- PTH binds to receptors on principal cells of distal convoluted tubules  $\rightarrow$  sodium/calcium channel upregulation  $\rightarrow$   $\uparrow$  calcium reabsorption from urine

### Intestines

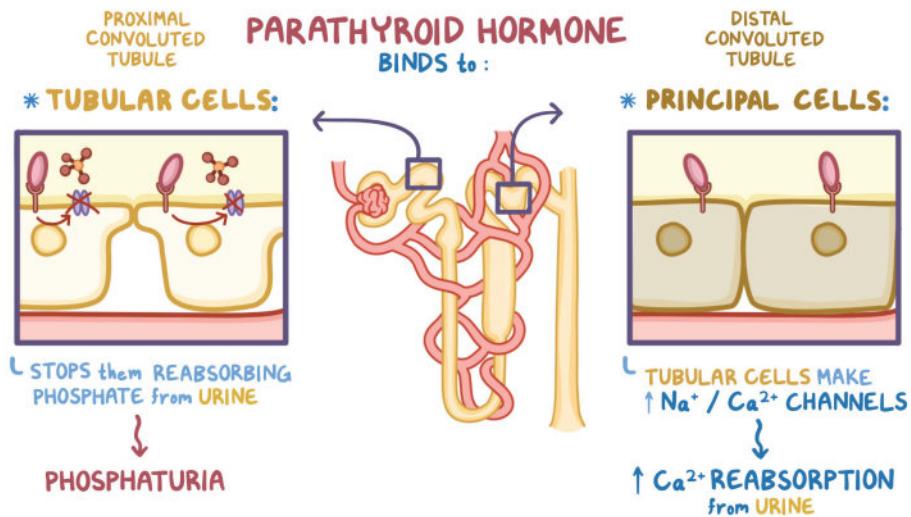
- PTH promotes vitamin D<sub>3</sub> (cholecalciferol) conversion  $\rightarrow$  active form
  - Cholecalciferol synthesized by keratinocytes in skin epidermis when exposed to UV light (also found in foods)  $\rightarrow$  cholecalciferol travels to liver, enzyme 25-hydroxylase catalyzes conversion to 25-hydroxycholecalciferol (calcidiol)
  - 25-hydroxycholecalciferol travels to kidney's proximal tubular cells  $\rightarrow$  enzyme 1-alpha-hydroxylase (upregulated by PTH) converts it to

1,25-dihydroxycholecalciferol (calcitriol),  
AKA active vitamin D

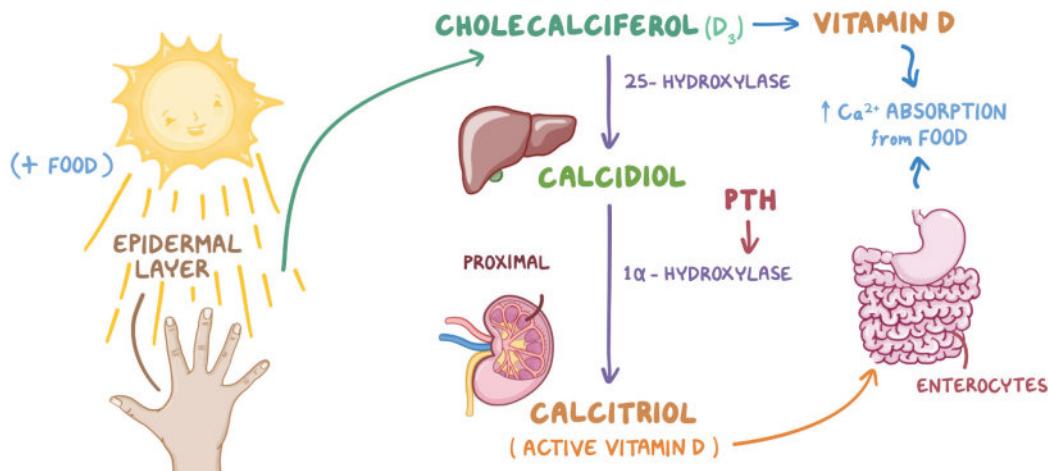
- Active vitamin D travels to gastrointestinal (GI) tract → enterocytes of small intestine → upregulates calcium channels → ↑ dietary calcium absorption



**Figure 35.5** One way PTH increases extracellular calcium levels is by stimulating osteoclast formation in bone.



**Figure 35.6** The second way PTH increases extracellular calcium levels is by ↑ urinary phosphate excretion and ↑ calcium reabsorption from urine.



**Figure 35.7** The third way PTH increases extracellular calcium levels is by helping convert cholecalciferol into vitamin D. It does so by upregulating enzyme  $1\alpha$ -hydroxylase.

## VITAMIN D

[osms.it/vitamin-D](https://osms.it/vitamin-D)

- Steroid hormone (derived from cholesterol, fat soluble) → gene transcription stimulation
  - Promotes new bone mineralization
  - ↑ serum  $\text{Ca}^{2+}$ , phosphate concentration → ↑ available substrate concentration for bone mineralization

### VITAMIN D SOURCES

#### Intestine

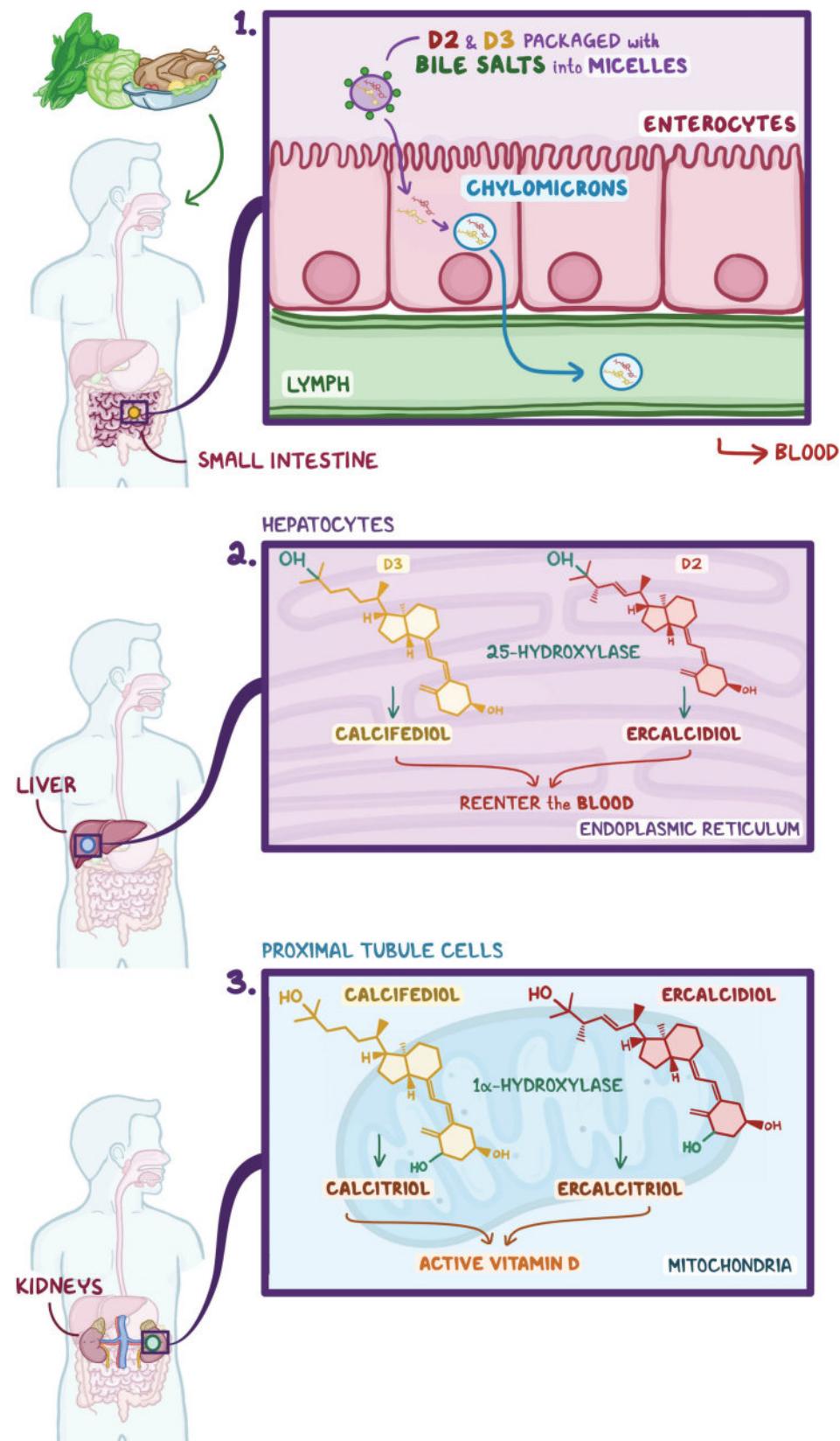
- Absorbs precursors (biologically inactive)
  - Vitamin  $D_2$  (ergocalciferol) is derived from dietary plant sources
  - Vitamin  $D_3$  (cholecalciferol) is derived from dietary animal sources

#### Skin

- Skin keratinocyte exposure (stratum basale, stratum spinosum) to UV light → vitamin  $D_3$  production
  - 7-dehydrocholesterol reacts with UVB light (wavelengths between 270–300nm) → vitamin  $D_3$

### PRECURSOR ACTIVATION

- Ergocalciferol, cholecalciferol reach small intestine lumen → packaged in small fat-soluble sacs (micelles) with aid of bile salts → diffuse through apical membrane of absorptive intestinal cells (enterocytes)
- Within enterocytes inactive vitamin D precursors integrate into lipoproteins (chylomicrons) → exit into lymphatic system → drain into blood circulation (hepatic portal vein) → bind to carrier proteins (vitamin D-binding protein/albumin) → transported to liver
- Hepatocytes contain 25-hydroxylase → hydroxyl group added to carbon 25 (C25) of ergocalciferol, cholecalciferol → **25-hydroxycholecalciferol** (calcifediol) → calcifediol (primary vitamin D circulating form) reenters blood bound to carrier proteins
  - Hepatic hydroxylation requires NADPH,  $O_2$ ,  $Mg^{2+}$  (not cytochrome P-450)
- Blood transports calcifediol to renal proximal tubules → proximal tubule cell mitochondria contain  $1\alpha$ -hydroxylase → hydroxyl added to C1 → 1,25 dihydroxycholecalciferol (calcitriol—active vitamin D form)



**Figure 35.8** Conversion of vitamins D<sub>2</sub> and D<sub>3</sub> into active vitamin D.

**Alternative pathway**

- Hydroxylation at C24 → biologically inactive 24,25-dihydroxycholecalciferol
- Pathway choice regulated by blood calcium level, parathyroid hormone
  - C1 hydroxylation occurs as response to ↓ calcium/phosphate levels
  - 1 $\alpha$ -hydroxylase activity ↑ through ↓ plasma Ca<sup>2+</sup> concentration, ↑ circulating PTH levels, ↓ plasma phosphate concentration
  - C1 phosphorylation requires NADPH, O<sub>2</sub>, Mg<sup>2+</sup>, cytochrome P-450 pathway
  - If calcium levels sufficient, inactive metabolite preferentially produced

**Kidney**

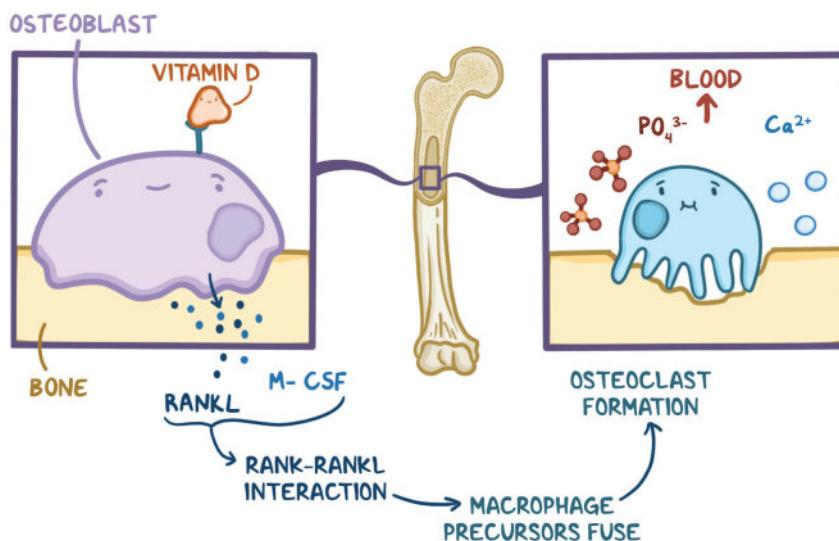
- Stimulates Ca<sup>2+</sup>, phosphate reabsorption

**Intestine**

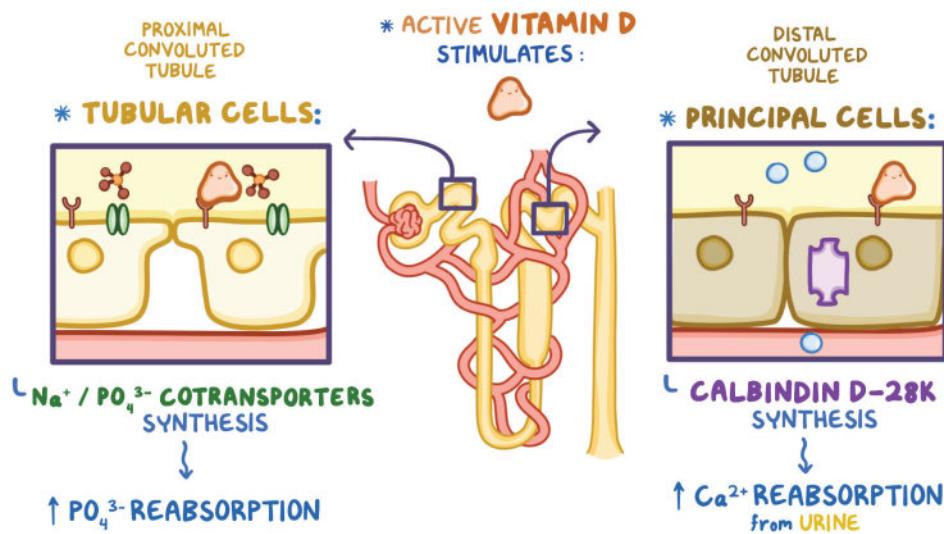
- Increases Ca<sup>2+</sup>, phosphate absorption
- Induces vitamin D-dependent Ca<sup>2+</sup> binding protein synthesis (calbindin D-28K)
  - Systolic protein → binds four Ca<sup>2+</sup> ions
- Intestinal Ca<sup>2+</sup> absorption mechanism
  - Ca<sup>2+</sup> diffusion: intestinal lumen → cell (through electrochemical gradient)
  - Inside cell: calbindin D-28K binds Ca<sup>2+</sup> → Ca<sup>2+</sup> pumped across basolateral membrane by Ca<sup>2+</sup>-ATPase

**VITAMIN D ACTIONS****Bone**

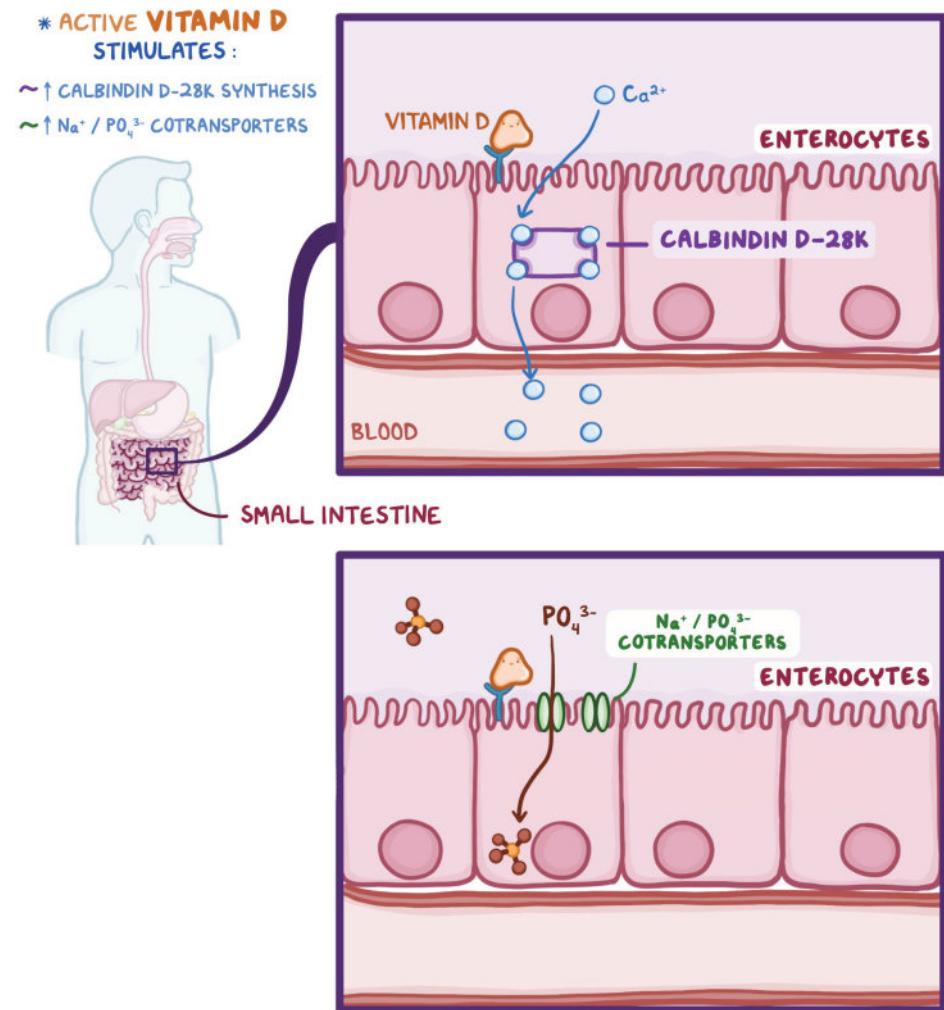
- Acts synergistically with PTH → osteoclast activity stimulation → bone resorption → old bone demineralization → ↑ Ca<sup>2+</sup>, phosphate concentration for new bone mineralization



**Figure 35.9** Vitamin D stimulates osteoclast formation, increasing blood calcium and phosphate concentrations.



**Figure 35.10** Vitamin D stimulates calcium and phosphate reabsorption in kidneys.



**Figure 35.11** Vitamin D stimulates calcium and phosphate absorption in the small intestine by increasing synthesis of calbindin D-28K and sodium/phosphate cotransporters.



# NOTES

## ANATOMY & PHYSIOLOGY

### ANATOMY

[osms.it/gastrointestinal-anatomy-physiology](http://osms.it/gastrointestinal-anatomy-physiology)

- Alimentary/GI tract: continuous muscular tube from mouth to anus
- Many digestive organs reside in abdominal, pelvic cavity; covered by mesentery

#### PERITONEUM

- Thin connective tissue composed of mesothelium, connective tissue supporting layer, simple squamous epithelium
- Lines abdominal, pelvic cavities; binds organs together, holds them in place
- Contains blood vessels, lymphatics, nerves innervating abdominal organs
  - Parietal peritoneum: lines abdominal, pelvic cavities
  - Visceral peritoneum: covers organ surfaces
  - Peritoneal cavity: potential space between parietal, visceral layers
- Intraperitoneal organs: digestive organs; keep mesentery during embryological development, remain in peritoneal cavity (e.g. stomach)
- Retroperitoneal organs: lose mesentery during embryological development, lay posterior to peritoneum (e.g. kidneys, pancreas, duodenum)
- Mesentery: double layer of parietal peritoneum on dorsal peritoneal cavity, provides routes for vessels, lymphatics, nerves to digestive organs

#### Omentum

- Visceral peritoneum layer covering stomach, intestines; contains adipose tissue, many lymph nodes
  - Expands during weight gain; "fat skin"

- Lesser omentum: double layer arises from lesser curvature of stomach, extends to liver
- Greater omentum: four layers (double sheet folds back upon itself); arises from greater curvature of stomach, covers intestines

#### GI tract layers

- Four basic tissue layers from esophagus to anus
- Serosa/adventitia
  - Outermost layer of intraperitoneal organs; also visceral peritoneum
  - Primarily composed of simple squamous epithelial cells, connective tissue
  - Secretes slippery fluid, prevents friction between viscera, digestive organs
  - Esophagus has adventitia instead of serosa
  - Retroperitoneal organs have serosa, adventitia
- Muscularis propria
  - Outer longitudinal, inner circular smooth muscle for involuntary contractions; regions of thickened circular layer forms sphincters
  - Skeletal muscle in esophagus for voluntary swallowing
  - Contains myenteric plexus (between longitudinal, circular layers of smooth muscle)
  - Myenteric plexus responsible for peristalsis, mixing
- Submucosa
  - Connective tissue that binds muscularis, provides elasticity, distensibility
  - Contains Meissner's plexus
  - Richly vascularized, innervated

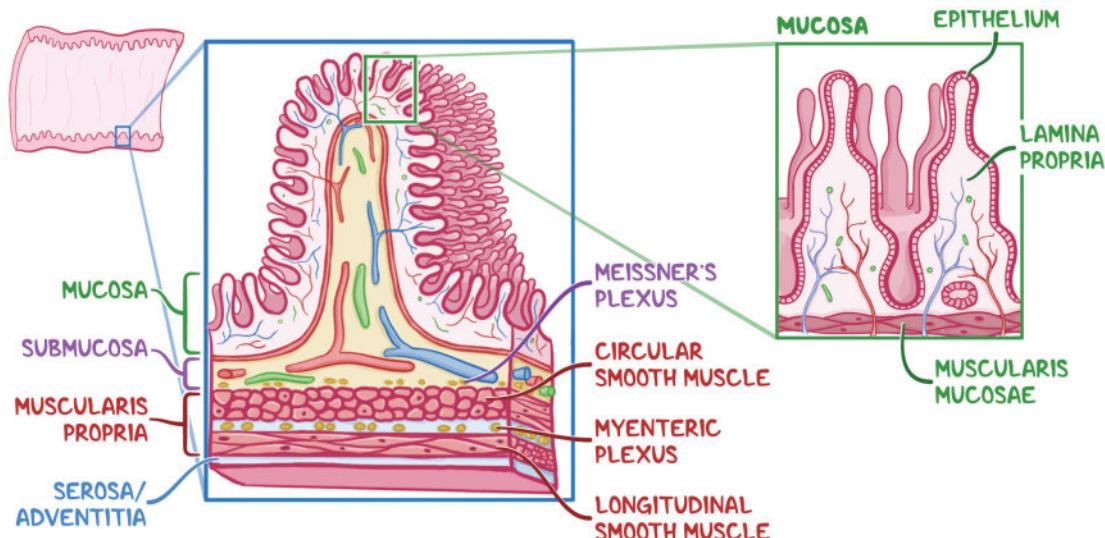
- Mucosa
  - Innermost layer composed of epithelial membrane lining entire GI tract
  - Functions:** exocrine glands secrete water, mucus, digestive enzymes, hormones; absorb digested nutrients; provides protective surface
  - Muscularis mucosae:** smooth muscle layer responsible for mucosa movement; contains folds to increase surface area
  - Lamina propria:** loose areolar connective tissue; contains blood, lymphatic vessels; contains MALT (lymphoid tissue that protects against pathogens)
  - Epithelium:** mouth, esophagus, anus composed of stratified squamous cells; rest of GI tract simple columnar with mucus secreting cells

## BLOOD CIRCULATION

- Splanchnic circulation
- Celiac trunk: supplies stomach, liver, spleen
- Superior mesenteric artery: supplies small intestine
- Inferior mesenteric artery: supplies large intestine

## INNERVATION

- Supplied by autonomic nervous system (ANS)
- Sympathetic component: thoracic splanchnic nerves → celiac plexus
- Parasympathetic component: vagus nerve
- Enteric division provides local control of GI activity; “the brain in the gut”; can function independently of ANS



**Figure 36.1** Cross section from small intestine showing the four basic tissue layers that line gastrointestinal tract: (from the outermost) serosa/adventitia, muscularis propria, submucosa, and mucosa.

# STRUCTURES

[osms.it/gastrointestinal-anatomy-physiology](http://osms.it/gastrointestinal-anatomy-physiology)

## ORAL (BUCCAL) CAVITY

### Function

- Ingestion, mechanical, chemical digestion, propulsion
- Saliva contains antibacterial properties that cleanses, protects oral cavity, teeth from infection
- Propulsion: swallowing (performed by tongue) propels food into pharynx, starts propulsion through GI tract
- Mechanical digestion: via mastication by teeth, tongue
- Chemical digestion: salivary amylase starts carbohydrate chemical breakdown

### Secretions

- Chemical digestion: salivary amylase starts carbohydrate chemical breakdown; mucin, water provide lubrication
- Lysozyme: kills some microbes
- Lingual lipase: digests some lipids

## ESOPHAGUS

- Muscular tube extending from laryngopharynx to stomach
- Esophageal hiatus: diaphragm opening where esophagus, vagus nerve pass through to abdominal cavity
- Cardiac orifice: junction of esophagus, stomach

### Function

- Propulsion/peristalsis
- Epiglottis closes larynx, routes food into esophagus
- Lower end of esophagus contains mucous cells to protect esophagus from stomach acid reflux

### Sphincters

- Upper esophageal sphincter: skeletal muscle; regulates movement from pharynx to esophagus

- Cardiac sphincter: AKA lower esophageal sphincter; smooth muscle at cardiac orifice that prevents acidic contents of stomach from moving upward into esophagus

### Histology

- Mucosa
  - Nonkeratinized stratified squamous epithelium (simple columnar epithelium near cardiac orifice)
- Mucosa, submucosa form longitudinal folds when empty
- Submucosa
  - Mucus secreting glands
- Muscularis externa
  - Superior  $\frac{1}{3}$ : skeletal muscle
  - Middle  $\frac{1}{3}$ : skeletal, smooth muscle
  - Inferior  $\frac{1}{3}$ : smooth muscle
- Adventitia instead of serosa

### Secretions

- Mucus: lubrication, protection from gastric acid

## STOMACH

- Located in upper left abdominal cavity quadrant
- Contains rugae (mucosa, submucosa) when stomach empty → expands to accommodate food

### Function

- Churning, digestion, storage
- Beginning of chemical digestion turning food into chyme to be delivered into small intestine

### Regions

- Cardia: most superior area surrounding cardiac orifice where food from esophagus enters stomach
  - Defined by Z-line of gastroesophageal junction
  - Z-line: epithelium changes from stratified squamous → simple columnar

- Fundus: area lying inferior to diaphragm, upper curvature
  - Food storage
- Body: central, largest area of the stomach
- Pylorus: connects to duodenum via pyloric sphincter
  - Controls gastric emptying, prevents backflow from duodenum into stomach

### Histology

- Muscularis contains regular GI tract layers with three-layered muscularis propria unique to stomach allowing for vigorous contractions, churning
  - Inner oblique layer
  - Middle circular layer (contains myenteric plexus)
  - Outer longitudinal layer

### Glands

- Lined with simple columnar epithelium; forms gastric pits (tube-like opening for gastric glands)
- Cardia, pylorus glands mainly secrete mucus
- Fundus, body glands secrete majority of digestive stomach secretions
- Pyloric antrum glands mainly secrete mucus, hormones (mainly gastrin)

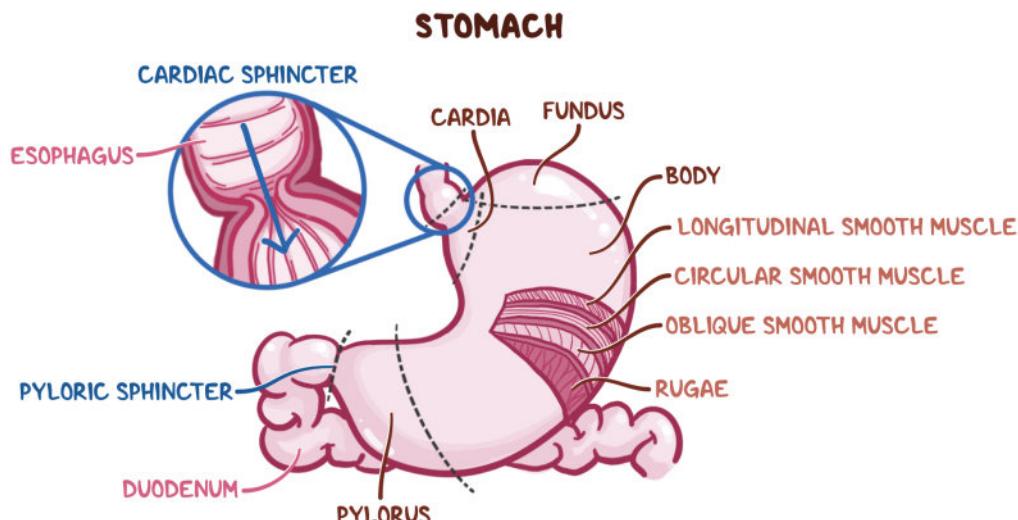
### Secretions

- Mucous cells: neck, basal regions of glands; produce mucus that protects stomach lining, lubricates food
- Parietal cells: gland apical region amongst chief cells; produce HCl, intrinsic factor
- Chief cells: gastric gland base; produce pepsinogen (protein digestion)
- Enteroendocrine cells (ECL cells): located deep in glands; secretes histamine, somatostatin, serotonin, ghrelin
- G-cells: gastrin
- D-cells: somatostatin

## SMALL INTESTINE

### Function

- Primary organ of digestion, nutrient absorption; segmentation (localized mixing area), peristalsis
- Absorption: food breakdown products absorbed
- Contains circular folds, **villi**, microvilli to maximize absorption surface area
  - Circular folds are permanent, composed of mucosa, submucosa



**Figure 36.2** Stomach anatomy.

### Innervation

- Relayed through celiac, superior mesenteric plexus
- **Sympathetic:** thoracic splanchnic
- **Parasympathetic:** vagus

### Blood supply

- Arterial: superior mesenteric artery
- Veins from small intestine → hepatic portal vein → liver

### Histology

- **Epithelium of villus:** simple columnar absorptive cells
  - Main function is absorbing nutrients
- Mucus secreting goblet cells in epithelium
- Mucosa contains pits called **intestinal crypts**
  - **Crypt cells:** secrete intestinal juice containing mucus
  - **Enterocytic cells:** within crypts, intraepithelial lymphocytes (T cells)
  - **Paneth cells:** located deep in crypts, release defensins, lysozyme to protect against pathogens

### Sections

- Duodenum
  - Mostly retroperitoneal
  - Curves around head of pancreas, receives bile from liver via bile duct, pancreatic secretions from pancreas via main pancreatic duct
  - **Ampulla of vater:** bulb-like point where bile duct, main pancreatic duct unite, deliver secretions into duodenum
  - **Major duodenal papilla:** ampulla opening into duodenum releasing bile/pancreatic secretions
  - **Hepatopancreatic sphincter:** controls bile entry, pancreatic secretions
  - Duodenal glands (Brunner's) in duodenal submucosa secrete alkaline mucus to neutralize acidic chyme
- Jejunum
  - Intraperitoneal
  - Suspended from posterior abdominal wall by mesentery
- Ileum
  - Intraperitoneal
  - Joins large intestine at ileocecal valve

- Suspended from posterior abdominal wall by mesentery
- **Peyer's patches:** lymphatic tissue sections composed predominantly of proliferating B lymphocytes, mostly located in ileal lamina propria as protection against pathogenic bacteria; B lymphocytes release IgA

### Secretions

- Brush border enzymes on microvilli complete food digestion (e.g. mucus, water, peptidases, disaccharidases)
- Pancreas, liver contribute to most small intestine digestion

## LARGE INTESTINE

- Retroperitoneal except for transverse, sigmoid parts
  - Intraperitoneal transverse, sigmoid sections anchored to posterior abdominal wall by mesocolon (mesentery)
  - Connects ileum via ileocecal valve, sphincter

### Function

- Digestion, absorption, propulsion, defecation
- **Digestion:** enteric bacteria digests remaining food
  - Bacteria also produce vitamin K, other B vitamins
- **Absorption:** absorbs mainly water, electrolytes, vitamins to concentrate, form feces
- **Propulsion:** propels feces towards rectum
- **Defecation:** stores, eliminates feces from body

### Unique features

- **Tenia coli:** three longitudinal ribbons of smooth muscle on ascending, transverse, descending, sigmoid colons that contract to produce haustra
- **Haustra:** small pouches/segments of large intestine created by tenia coli
- **Epiploic appendages:** small pouches of peritoneum filled with fat

## Regions

- Cecum → ascending colon → right colic/hepatic flexure → transverse colon → left colic/splenic flexure → descending colon → sigmoid colon → rectum → anal canal → anus
  - Cecum: pouch that lies below ileocecal valve at large/small intestine junction; beginning of large intestine
  - Appendix: pouch of lymphoid tissue (part of MALT) located in cecum, harbors bacteria to recolonize gut when needed
- Anal canal has two sphincters
  - Internal anal sphincter: involuntary, composed of smooth muscle
  - External anal sphincter: voluntary, composed of skeletal muscle

## Histology

- Muscularis mucosae consists of inner circular, outer longitudinal layers
- Large intestine mucosa: simple columnar epithelium
- Anal canal: stratified squamous epithelium
- Does not contain folds, villi, microvilli as in small intestine
- Many crypts with goblet cells

## Pectinate line

- Divides upper  $\frac{2}{3}$  from lower  $\frac{1}{3}$  of anal canal where many distinctions made
- Embryological origin
  - Above: endoderm
  - Below: ectoderm
- Epithelium
  - Above: columnar epithelium
  - Below: stratified squamous epithelium
- Innervation
  - Above: inferior hypogastric plexus
  - Below: inferior rectal nerves
- Lymph drainage
  - Above: internal iliac
  - Below: superficial inguinal lymph nodes
- Vascularization
  - Above: superior rectal artery, superior rectal vein (drains into inferior mesenteric vein → hepatic portal system)
  - Below: middle, inferior rectal arteries; middle, inferior rectal veins

## Flora

- Large intestine contains largest bacterial ecosystem in body
- Function of bacteria
  - Synthesize vitamins (vitamin K, some B vitamins)
  - Ferment indigestible carbohydrates (e.g. cellulose)
  - Metabolism/digestion of certain molecules (e.g. hyaluronic acid, mucin)
  - Live symbiotically with host
  - Present pathogens to nearby lymphoid tissue (MALT)

## Secretions

- Mucus

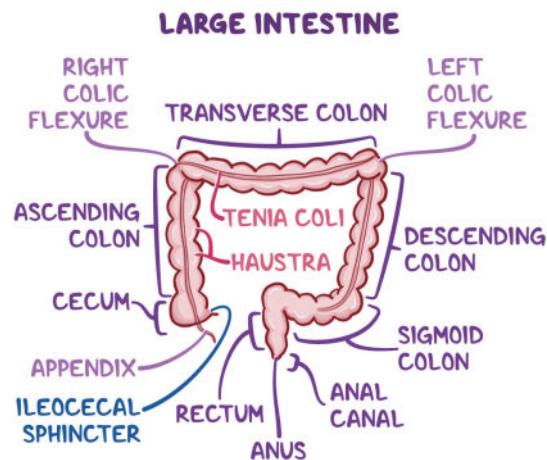
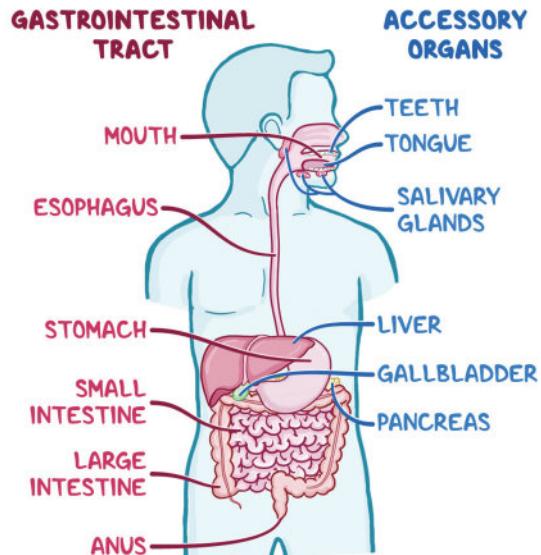


Figure 36.3 Large intestine anatomy.

## ACCESSORY ORGANS

- Gallbladder, liver, pancreas
- Liver
  - Hepatocytes produce bile which emulsifies lipid globules, aids in absorption
  - Stores glucose in form of glycogen
- Gallbladder
  - Bile storage; releases bile into small intestine in response to hormonal stimulus
- Pancreas
  - Exocrine function: acini secrete various digestive enzymes; “pancreatic juice;” e.g. secretin, cholecystokinin (CCK)
  - Endocrine function: islets produce glucagon, insulin to maintain normal glucose levels; somatostatin, pancreatic polypeptide production



**Figure 36.4** Overview of gastrointestinal tract, accessory organs structures.

## PHYSIOLOGY

[osms.it/gastrointestinal-anatomy-physiology](http://osms.it/gastrointestinal-anatomy-physiology)

### PROCESSING OF FOOD

1. Ingestion
2. Mechanical digestion
  - Carried out by teeth; increases surface area to facilitate enzymatic digestion
3. Propulsion
  - Movement, mixing of food through GI tract, starts with swallowing
4. Secretion
  - Exocrine glands secrete various digestive juices into digestive tract lumen
5. Digestion
  - Complex food broken down via enzymes
6. Absorption
  - Digested nutrients absorbed by GI mucosal cells into blood/lymph
7. Elimination
  - Indigestible substances eliminated via anus in form of feces

### GI MUSCLE PROPERTIES

- Smooth muscle of GI tract acts as syncytium
  - Muscle fibers connected by gap junctions allowing electrical signals to initiate muscle contractions from one muscle fiber to next rapidly along length of bundle
- Normal resting membrane potential of GI smooth muscles: -50mV to -60mV
- Two types of electrical waves contributing to membrane potential

#### Slow waves

- Generated, propagated by interstitial cells of Cajal (pacemaker cells)
- Slow-wave threshold: potential that must be reached by slow wave to propagate smooth muscle
- Does not cause smooth muscle contraction
- Slow-wave threshold reached → L-type calcium channels activated → calcium influx → motility initiation

- Occur at 12 cycles/minute in duodenum, decreases towards colon
- Regulated by innervation, hormones
  - Excitatory stimulants (e.g. acetylcholine, substance P), inhibitory stimulants (e.g. VIP, nitric oxide)

### Spikes

- True action potentials occurring automatically when GI smooth muscle potential becomes more positive than -40mV
- Digestive activity controls
  - Involves regulation by autonomous smooth muscle, intrinsic nerve plexuses, external nerves (ANS), GI hormones

## ENTERIC NERVOUS SYSTEM

- Intrinsic nervous system of the GI system
- Division of ANS
- Provides major nerve supply to GI tract controlling GI function, motility
  - Parasympathetic system activates digestion
  - Sympathetic system inhibits digestion
  - Also capable of self-regulation, autonomous function

### Receptors and plexus

- Chemoreceptors respond to chemicals from food in gut lumen
- Stretch receptors respond to food distending GI tract wall
- Two plexus consist of motor neurons, interneurons, sensory neurons
  - Submucosal (Meissner's) nerve plexus: innervates secretory cells → controls digestive secretions
  - Myenteric nerve plexus: innervates smooth muscle layers of muscularis → controls GI motility
- Segmentation, peristalsis mostly automatic mediated by pacemaker cells, reflex arcs

### Reflex mediation

- Short reflexes: intrinsic control (enteric nervous system)
- Long reflexes: extrinsic control outside of GI tract (e.g. CNS, autonomic nerves)

## GASTROINTESTINAL MOTILITY

### Gastric motility

- Peristaltic contractions originate in upper fundus, move to pyloric sphincter
- Moves gastric chyme forward → gastric emptying into duodenum

### Small intestinal motility

- Mix chyme, digestive enzymes, pancreatic secretions, bile → digestion
- Expose nutrients to mucosa → maximize absorption
- Advance chyme along small intestine via segmentation actions → ileocecal valve → ileocecal sphincter → large intestine

### Large intestinal motility

- Unabsorbed small intestine material → large intestine
  - Contents now feces (destined for excretion)
- Segmental contractions (cecum, proximal colon) associated with haustra (sac-like segments characteristic of large intestine) mixes contents
- Mass movements
  - Function: move contents long distances (e.g. transverse → sigmoid)
  - Occur 1–3 times daily
  - Water absorption: fecal contents → increasingly solid (hard to mobilize)
  - Final mass movements propel contents to rectum → stored until defecation
- Gastrocolic reflex
  - Stomach distension → ↑ colonic motility → ↑ mass movements
  - Afferent limb (from stomach) → parasympathetic nervous system mediates → efferent limb → CCK, gastrin production → ↑ colonic motility

- Defecation
  - Rectum 25% full → defecation urge
  - Rectum fills with feces → rectal wall distends → stretch receptors send afferent signals to spinal cord → to brain (awareness of need to defecate)
  - + afferent signals to myenteric plexus → peristaltic waves → move feces forward → internal anal sphincter relaxes → external anal sphincter

remains tonically contracted (striated skeletal muscle under voluntary control) → when appropriate, external anal sphincter relaxed voluntarily → rectal smooth muscle contracts → ↑ pressure → Valsalva maneuver (expire against closed glottis) → ↑ intra-abdominal pressure → ↑ defecation pressure → feces forced out through anal canal

## SECRETORY PRODUCTS OF THE GASTRIC MUCOSA GLANDS

	STIMULUS FOR SECRETION	SECRETORY PRODUCTS	FUNCTION
CHIEF	Gastrin Acetylcholine	Pepsinogen (converts to pepsin in presence of HCl)  Gastric lipase	Breaks down protein into peptide chains  Initiates lipolysis
D	HCl	Somatostatin (paracrine)	Modulates HCl secretion by inhibiting gastrin, histamine release
ECL	Gastrin Acetylcholine  Surges before meals (cephalic stimulation)	Histamine  Ghrelin	Primary stimulator of HCl secretion by parietal cells  Stimulates appetite Increases gastric secretion, motility
G	Partially digested protein	Gastrin	Increases secretion of HCl Relaxes ileocecal valve
MUCOUS	Mechanical stimulation by stomach contents	Mucus Bicarbonate	Protective alkaline barrier for gastric epithelium  Lubrication
PARIETAL	Gastrin (endocrine) Histamine (paracrine) Acetylcholine (neural)	HCl  Intrinsic factor	Activates pepsinogen Inactivates amylase Denatures proteins - Kills microorganisms  Binds with vitamin B12 for intestinal absorption



## NOTES GASTROINTESTINAL FUNCTION

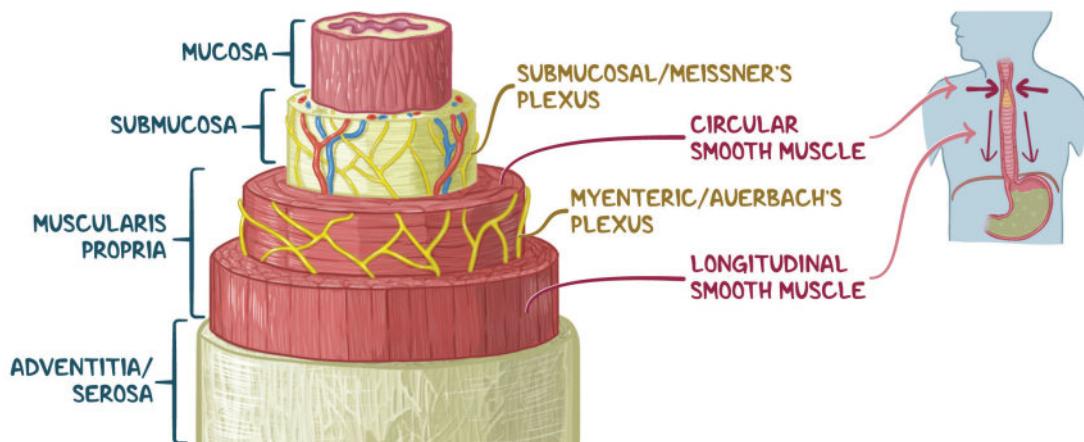
# ENTERIC NERVOUS SYSTEM

[osms.it/enteric-nervous-system-and-slow-waves](https://osms.it/enteric-nervous-system-and-slow-waves)

- Intrinsic component of gastrointestinal (GI) innervation that can function without extrinsic innervation
- Communicates with sympathetic nervous system, parasympathetics
- Ganglia located in myenteric, submucosal plexuses
  - Myenteric/Auerbach's plexus: located between longitudinal, circular smooth muscle layers; GI movement function
  - Submucosal/Meissner's plexus: located in submucosa; function in GI secretions, blood flow
- Neurons of extrinsic system release neurocrines
  - Neurochemicals consisting of neurotransmitters, neuromodulators
- Extrinsic branch of GI innervation
  - Sympathetic, parasympathetic divisions

### PARASYMPATHETIC INNERVATION

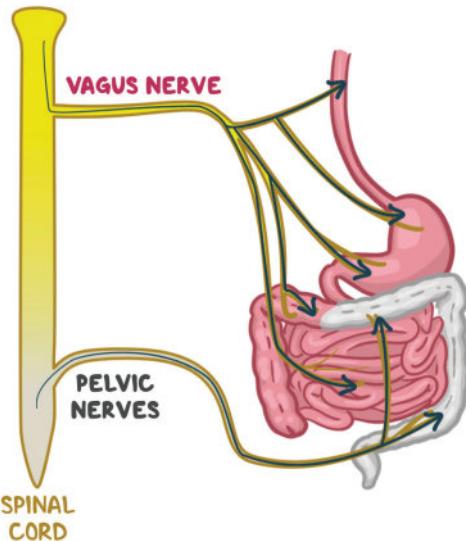
- Parasympathetic ganglia located within myenteric, submucosal plexuses
- Parasympathetic preganglionic, postganglionic neurons either cholinergic (release acetylcholine) or peptidergic (release substance P/vasoactive intestinal peptide)
- Vagus nerve innervates upper GI
  - Upper  $\frac{1}{3}$  of esophagus, stomach, small intestine, ascending, proximal transverse colon
  - Consists of 75% afferent, 25% efferent fibers
  - Vagovagal reflexes: reflexes in which both afferent, efferent limbs originate from vagus nerve



**Figure 37.1** Locations of the myenteric (Auerbach's) and submucosal (Meissner's) plexuses within the four layers of the gastrointestinal tract. The myenteric plexus is located between the circular and longitudinal smooth muscle layers, which produce different movements in the GI tract.

- Pelvic nerves innervate lower GI
  - Distal transverse colon, descending, sigmoid colon

### PARASYMPATHETIC INNERVATION



**Figure 37.2** The vagus nerve provides parasympathetic innervation from the upper esophagus to the proximal transverse colon. The pelvic nerve provides innervation from the distal transverse colon to the rectum.

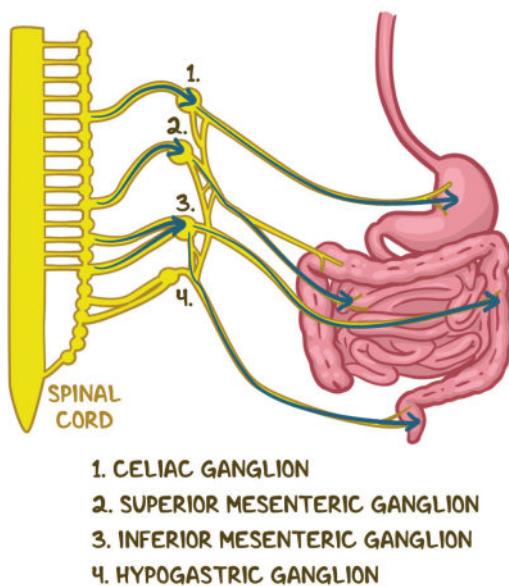
### SYMPATHETIC INNERVATION

- Sympathetic preganglionic neurons synapse in ganglia outside GI tract
  - Celiac, superior mesenteric, inferior mesenteric, hypogastric ganglia
- Sympathetic postganglionic neurons either synapse on ganglia in myenteric/submucosal plexuses or directly innervate target organs
- Sympathetic preganglionic neurons are cholinergic; sympathetic postganglionic neurons are adrenergic (release norepinephrine)

### MECHANISMS

- Slow waves
  - Duodenum: 12 waves/minute
  - Ileum: 9 waves/minute
- Migrating myoelectric complexes every 90 minutes clears any remaining chyme

### SYMPATHETIC INNERVATION



**Figure 37.3** Sympathetic preganglionic neurons synapse outside the GI tract, in the four ganglia shown above.

- Sympathetic via fibers from celiac/superior mesenteric ganglia → ↓ contractions
- Two forms of contractions; coordinated by enteric nervous system

### Innervation

- Parasympathetic via vagus nerve (CN X)
  - ↑ contractions; most nerves cholinergic, some release neurocrines (e.g. peptidergic)
- Motilin
  - Secreted by endocrinocytes in proximal small intestine, regulate contractions
- Vasoactive intestinal peptide (VIP)
  - Induces smooth muscle relaxation (e.g. sphincters); induces water secretion into pancreatic juice, bile; inhibits gastric acid secretion
- Enkephalins
  - Inhibitory modulators in myenteric, submucosal plexuses

### Segmental contractions (↓ diameter)

- Mix, expose chyme to secretions, enzymes
- Contraction → splits chyme → both orad, caudad directions → relaxation → merging of chyme → repeated

- No forward/propulsive movement along small intestine

#### **Peristaltic/longitudinal contractions ( $\downarrow$ length)**

- Move chyme down GI tract
- Contraction behind bolus → proximal portion of intestine relaxes simultaneously → chyme propelled in caudad direction
- Longitudinal, circular muscles reciprocally innervated → do not contract together; if circular muscle contracts → longitudinal muscle in same segment relaxes simultaneously

#### **Peristalsis reflex**

- Enterochromaffin-like (ECL) cells in intestinal mucosa sense food bolus → secrete serotonin (5-HT) → binds to intrinsic primary afferent neuron receptors → activates peristalsis reflex → excitatory neurotransmitters (acetylcholine, substance P, neuropeptide Y) released behind bolus → ↑ circular muscle contraction → ↓ longitudinal muscle activation → segment narrows, lengthens → in front of bolus, circular muscle inhibitory mechanisms (VIP, nitric oxide) activate, excitatory pathways in longitudinal segment activate → segment shortens, widens → chyme propelled forward in caudad direction

# GASTROINTESTINAL HORMONES

[osms.it/gastrointestinal-hormones](https://osms.it/gastrointestinal-hormones)

## SOMATOSTATIN

- Members of G protein coupled-receptor superfamily

### Function

- ↓ secretion of many other hormones (e.g. gastrin, bicarbonate, digestive enzymes)
- ↓ nutrient absorption from gut by prolonging gastric emptying time
- ↓ pancreatic secretions
- ↓ visceral blood flow

### Secretion and activation

- Central nervous system, pancreatic delta cells, enteroendocrine delta cells
- Somatostatin binds receptors → activates inhibitory G protein → inactivate adenylate cyclase → ↓ cAMP production → protein kinase not activated → ↓  $\text{Ca}^{2+}$  → inhibitory effect
- Site of action
  - Stomach, pancreas, small intestine, gallbladder, liver
- Secretory stimulants
  - Glucose, arginine, leucine, glucagon, vasoactive intestinal peptide (VIP), cholecystokinin (CCK)

## GASTRIN

### Function

- Induces gastric acid secretion

### Secretion and stimulation/inhibition

- Secreted by enteroendocrine G cells of stomach, duodenum
- Secretory stimulants
  - Presence of acidic content, partially digested food in duodenum, vagus nerve stimulation
- Inhibited by somatostatin

## MOTILIN

### Function

- Stimulates gastric, pancreatic enzyme secretion

### Secretion and stimulation/inhibition

- Secreted by enteroendocrine M cells of proximal small intestine
- Secretory stimulants
  - Duodenal alkalinization, gastric distension
- Inhibited by duodenal nutrients

## PANCREATIC PEPTIDE (PP)

### Function

- ↓ gastric emptying, slows small intestine motility

### Secretion and stimulation/inhibition

- Secreted by endocrine cells in pancreatic islets
- Secretory stimulants: intraluminal nutrients, vagal nerve activation, hypoglycemia

## PEPTIDE Y (PPY)

### Function

- Inhibits gastric acid secretion, gastric motility, slows intestinal motility
- Inhibits pancreatic exocrine secretion

### Secretion and stimulation/inhibition

- Secreted by pancreatic islet alpha cells, enteroendocrine cells
- Secretory stimulants
  - Ingestion of nutrition, bile acids, fatty acids

## SECRETIN

### Function

- ↓ acidity to improve pancreatic enzyme function
- ↑ pancreatic secretion, biliary bicarbonate, water
- Regulates pancreatic enzyme secretion
- ↓ gastric emptying, gastrin release, gastric acid secretion

### Secretion and stimulation/inhibition

- Secreted by enteroendocrine S cells in proximal small intestine
- Secretory stimulants
  - Gastric acid, bile salts, peptides, fatty acids, ethanol
- Inhibited by somatostatin

## CHOLECYSTOKININ (CCK)

### Function

- Promotes food delivery from stomach into small intestine
- Regulates nutrient-stimulated enzyme secretion
- ↑ gallbladder contraction
- ↑ enzymatic pancreatic secretion output

### Secretion and stimulation/inhibition

- Secreted by enteroendocrine I cells
- Secretory stimulants
  - Nutrition ingestion, fatty acids, amino acids

## INSULIN

### Function

- Major anabolic hormone
- ↓ blood glucose
- Promotes liver, muscle glycogen storage
- Fatty acids, triacylglycerol storage in adipose tissue
- Protein synthesis, glucagon suppression

### Secretion and stimulation/inhibition

- Secreted by beta cells of pancreatic islet cells

### Function

- Secretory stimulants
  - High blood glucose, glucose, arginine, leucine, glucagon, VIP, CCK
- Inhibited by somatostatin

## GLUCAGON

### Function

- Counteracts insulin
- ↑ blood glucose, promotes glycogenolysis, gluconeogenesis, ketogenesis
- Works mainly on liver

### Secretion and stimulation/inhibition

- Secreted by alpha cells of islet cells, L-cells of intestine
- Inhibited by somatostatin

## INCRETINS

- Includes glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP)

### Function

- ↑ insulin release from pancreatic beta-cells
- ↑ levels of cAMP in islets leading to expansion of beta-cells

## GASTRIC INHIBITORY PEPTIDE (GIP)

- AKA glucose-dependent insulinotropic peptide

### Function

- Weakly inhibits HCl production, stimulates insulin release

### Secretion and stimulation/inhibition

- Secreted by duodenal mucosa
- Secretory stimulant
  - Fatty chyme

## HISTAMINE

### Function

- Activates parietal cells to release HCl

### Secretion and stimulation/inhibition

- Secreted by stomach mucosa
- Secretory stimulant
  - Food in stomach

## SEROTONIN

### Function

- Stomach muscle contraction

### Secretion and stimulation/inhibition

- Secreted by stomach, duodenal mucosa
- Secretory stimulant
  - Food in stomach

## VASOACTIVE INTESTINAL PEPTIDE (VIP)

### Function

- Dilates intestinal capillaries
- ↑ secretions, ↓ acid secretion
- Relaxes intestinal smooth muscle
- Site of action
  - Small intestine, pancreas, stomach

### Secretion and stimulation/inhibition

- Secreted by enteric neurons/parasympathetic ganglia
- Secretory stimulant
  - Chyme, parasympathetic stimulus

## ENKEPHALINS

### Function

- Smooth muscle constriction causing ↓ fluid flow into intestines (opiates acting on enkephalin receptors ↓ fluid flow to intestines, cause constipation)
- Site of action
  - Intestine
- Secreted by
  - GI tract neurons

## GHRELIN

### Function

- Stimulate hunger
- Site of action
  - Hypothalamus lateral nucleus

### Secretion and stimulation/inhibition

- Secreted by gastric cells
- Secretory stimulant
  - Empty stomach
- Inhibited by stomach stretching when food present

## LEPTIN

### Function

- Stimulate satiety
- Site of action
  - Ventromedial nucleus of hypothalamus

### Secretion and stimulation/inhibition

- Secreted by adipocytes

# SATIETY

[osms.it/satiety](http://osms.it/satiety)

- Hypothalamus controls appetite, satiety
  - Ventral posteromedial nucleus (VPN) of hypothalamus: activates satiety
  - Lateral hypothalamic area: activates hunger, feeding

## HORMONES

### Leptin

- Stimulates satiety, decreases appetite
- Secreted by fat cells in proportion to fat amount in adipocytes

### Ghrelin

- Increases appetite, hunger
- Secreted by gastric cells before meal
- Starvation, weight loss stimulates ghrelin release

### Insulin

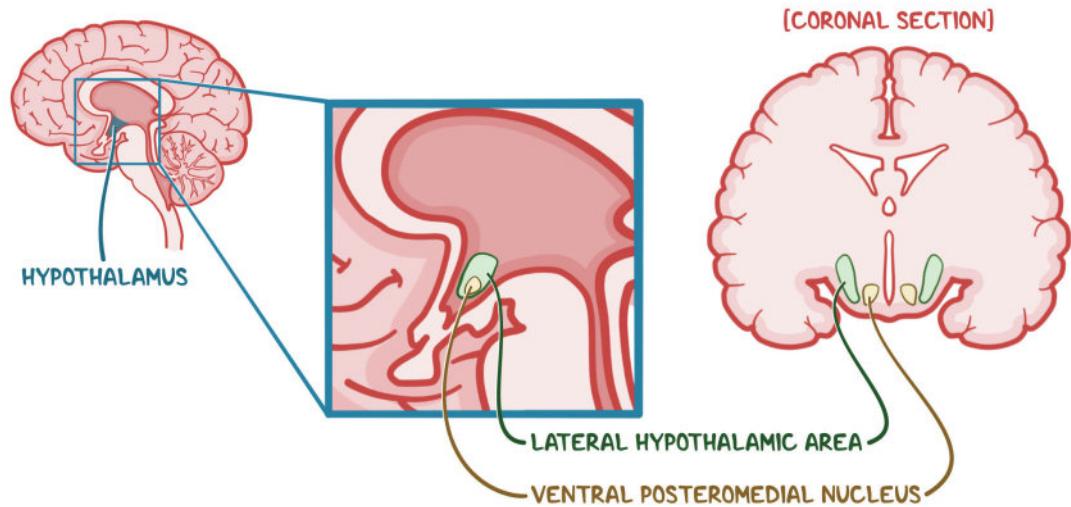
- Stimulates satiety, decreases appetite
- Fluctuates throughout day

### Peptide YY (PYY)

- Stimulates satiety, decreases appetite directly (via hypothalamus), indirectly (via inhibiting release of ghrelin)

### GLP-1

- Stimulates satiety, decreases appetite
- Secreted by intestinal L cells



**Figure 37.4** Locations of two areas in the hypothalamus that control appetite and satiety.



# NOTES

## UPPER GASTROINTESTINAL TRACT

# CHEWING & SWALLOWING

[osms.it/chewing-and-swallowing](http://osms.it/chewing-and-swallowing)

## CHEWING

- First step to process ingested food to prepare for digestion, absorption
- Three functions
  - ↓ food particle size → facilitate swallowing
  - Mix food with saliva → lubrication
  - Mix food particles with amylase → begin carbohydrate digestion
- Teeth move, masticate food into small fragments, tongue functions to taste, roll food around in oral cavity → compact into small ball (bolus)

## Oral cavity walls

- Roof: soft, hard palate
- Floor: tongue, mylohyoid muscles
- Sides: cheeks
- Front: lips, teeth

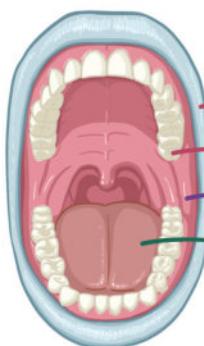
- Involuntary component of chewing
  - Mouth mechanoreceptors → sensory information to brainstem → reflex oscillatory pattern to muscles of mastication
- Voluntary component
  - Can override reflex chewing at any time

## Muscles involved with mastication

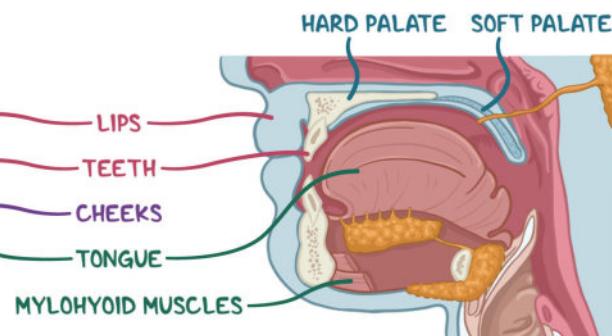
- Temporalis muscle: fan-shaped muscle on both sides of head
- Masseter muscle: connects mandible to zygomatic arch of temporal bone
- Medial pterygoid muscle: connects mandible to medial pterygoid plate
- Lateral pterygoid muscle: located at condylar process
- All muscles of mastication innervated by branches of trigeminal (CN V)

## ORAL CAVITY WALLS

- |         |
|---------|
| ■ ROOF  |
| ■ FRONT |
| ■ SIDES |
| ■ FLOOR |



[Anterior view]



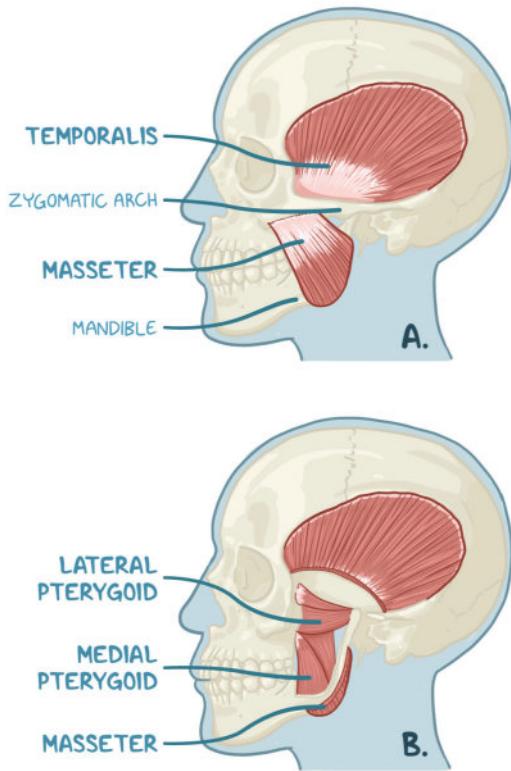
[Sagittal section]

**Figure 38.1** The structures that make up the walls of the oral cavity.

- All muscles coordinate, work together to grind, mechanically break down food
- Tongue moves from side to side to reposition food → push it between teeth to be chewed, mixed with saliva → soft, mushy bolus ready for swallowing

food in mouth) → travel via vagus and glossopharyngeal nerves → swallowing center in medulla → sends efferent, motor information via glossopharyngeal, vagus nerves → directs coordinated movement of pharyngeal striated muscle, upper esophagus

## MUSCLES of MASTICATION



**Figure 38.2** The muscles of mastication. A: The temporalis and masseter muscles are superficial to B: the lateral and medial pterygoid muscles.

## SWALLOWING

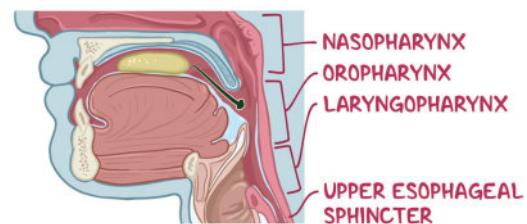
- Initiated voluntarily in mouth, involuntary thereafter
  - AKA deglutition
- Pharynx has three parts
  - Nasopharynx
  - Oropharynx
  - Throat

### Swallowing reflex

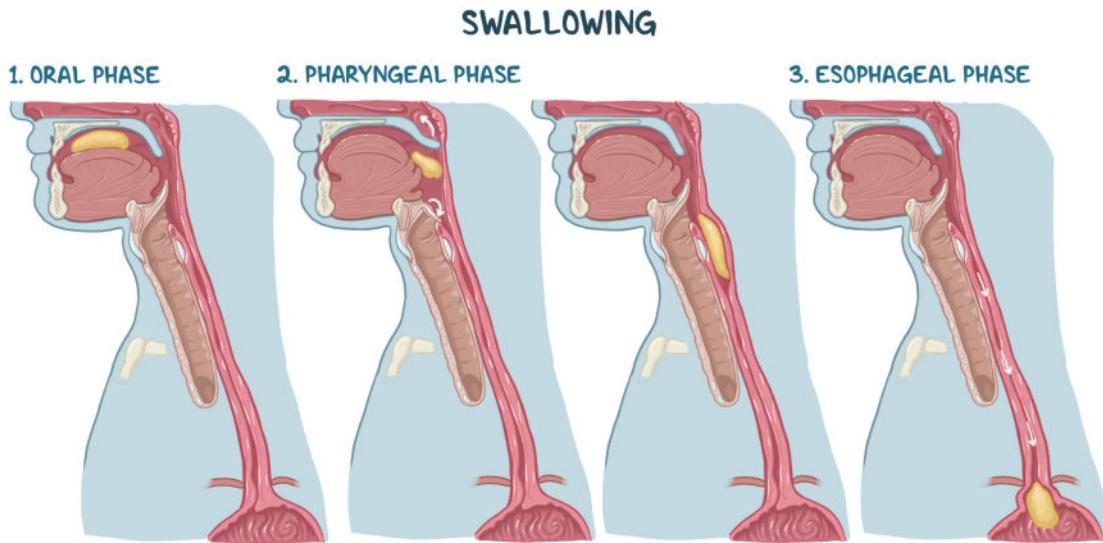
- Somatosensory receptors near pharynx → detect sensory information (e.g.

### Three phases

- Oral (voluntary)
  - Tongue presses against hard palate → forces bolus towards oropharynx → pharynx contains high density of somatosensory receptors → activation → swallowing reflex initiation in medulla
- Pharyngeal (swallowing reflex)
  - Soft palate, uvula moves upwards → creates narrow passage → prevents food reflux into nasopharynx → epiglottis closes down over laryngeal opening → larynx moves upwards against epiglottis → act as seal to prevent food entering trachea → upper esophageal sphincter relaxes → food passes from pharynx to upper esophagus → peristaltic wave initiation → food propelled through open upper esophageal sphincter
  - Breathing inhibited during this phase
- Esophageal (swallowing reflex/enteric nervous system)
  - Swallowing reflex closes upper esophageal sphincter → food cannot reflux back into pharynx → primary peristaltic wave (coordinated by swallowing reflex) → propels food along esophagus → if all food not cleared → distended esophagus → secondary peristaltic wave is initiated by enteric nervous system



**Figure 38.3** Locations of the three pharynx divisions and the upper esophageal sphincter.



**Figure 38.4** Mastication muscles. A: The temporalis and masseter muscles are superficial to B: the lateral and medial pterygoid muscles.

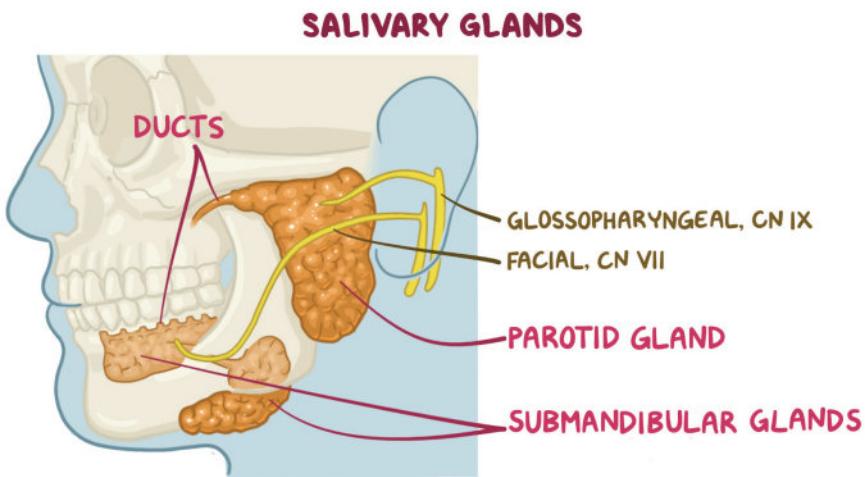
## SALIVARY SECRETION

[osms.it/salivary-secretion](https://osms.it/salivary-secretion)

### SALIVARY GLANDS

- Three major salivary glands exist outside oral cavity
  - Parotid: composed of serous cells → secrete fluid composed of ions, enzymes, water
  - Submandibular, sublingual: composed of serous, mucous cells → stringy, viscous solution of aqueous fluid, mucin glycoprotein for lubrication
- Minor salivary glands (e.g. buccal) scattered throughout oral cavity mucosa
- Each gland is **paired**; all produce saliva which are delivered to oral cavity via ducts
- **Appearance:** cluster of grapes
  - Each grape = single acinus
  - Blind end of branching duct system
- Saliva formation is two-step process
  - Acinus lined with acinar cells → produces initial saliva → passes through intercalated duct → striated duct lined with ductal cells → modify initial saliva

- myoepithelial cells stimulated neurally
- contract → saliva ejected into mouth
- Cell types
  - Acinar cells: produce initial isotonic saliva (mixture of water, ions, enzymes, mucus)
  - Ductal cells: modify electrolyte concentrations in initial saliva to produce final saliva
  - Myoepithelial cells: present in acini, intercalated ducts; contract to eject saliva into oral cavity
- Innervation of salivary glands
  - Saliva production stimulated by both parasympathetic (dominant), sympathetic activation (unique feature)
- Blood supply
  - Saliva production stimulated → unusually high blood flow
  - When corrected for organ size, blood flow is ↑ 10x more than exercising skeletal muscle



**Figure 38.5** Parotid glands sit in front of each ear. Submandibular glands sit under the mandible. Sublingual glands (not pictured) are beneath the tongue, under the mouth floor.

## SALIVA

- Produced by salivary glands; rate of 1L/daily

### Functions

- Initial digestion of starches/lipids by salivary enzymes
- Lubricating ingested food to allow movement through esophagus
- Diluting, buffering ingested foods (which may be harmful)
- Cleanses mouth
- Dissolves food chemicals so it can be tasted

### Saliva composition

- Water (97–99.5%)
- Electrolytes
- Alpha-amylase:** initial carbohydrate digestion, like potatoes/rice
- Lingual lipase:** initial lipid digestion
- Mucus
- Immunoglobulin A
- Kallikrein:** protease enzyme; cleaves high molecular weight kininogen → bradykinin → vasodilation → increased blood flow during salivary activity
- Lysozyme:** enzyme inhibiting bacterial growth, prevents tooth decay
- Defensin:** acts as local antibiotic
- pH 6.5–7.5
  - Usually maintained by  $\text{NaHCO}_3$

### Saliva formation

- Initial saliva is isotonic
  - Concentrations of  $\text{K}^+$ ,  $\text{HCO}_3^-$ ,  $\text{Na}^+$ ,  $\text{Cl}^-$  similar to plasma
- Final secreted saliva is hypotonic ( $\downarrow$  osmolarity), when compared to plasma
  - $\uparrow \text{K}^+$ ,  $\text{HCO}_3^-$ ,  $\downarrow \text{Na}^+$ ,  $\text{Cl}^-$
- Modification of saliva by ductal cells
  - Complex transport system
- Luminal membrane has three transporters
  - $\text{Na}^+ - \text{H}^+$  exchange
  - $\text{H}^+ - \text{K}^+$  exchange
  - $\text{Cl}^- - \text{HCO}_3^-$  exchange
- Basolateral membrane has two transporters
  - $\text{Na}^+ - \text{K}^+$  ATPase
  - $\text{Cl}^-$  channel
- Overall action of all transporters together
  - Absorption of  $\text{Na}^+$ ,  $\text{Cl}^- \rightarrow \downarrow \text{Na}^+$ ,  $\text{Cl}^-$  concentration in saliva
  - Secretion of  $\text{K}^+$ ,  $\text{HCO}_3^- \rightarrow \uparrow \text{K}^+$ ,  $\text{HCO}_3^-$  concentration in saliva
  - Net absorption of solute ( $\text{NaCl} > \text{KHCO}_3$ )
- Process of isotonic saliva  $\rightarrow$  hypotonic saliva
  - Ductal cells are water impermeable
  - Due to net absorption (solutes leave saliva, water does not travel with)
- Saliva tonicity depends on flow rates
  - Depends on amount of time saliva in contact with ductal cells ( $\uparrow \text{Na}^+$ ,  $\text{Cl}^-$ )

- absorption, ↑ K<sup>+</sup> secretion)
- ↑ flow rate (4mL/min): composition parallels plasma, initial saliva produced by acinar cells
- ↓ flow rate (1mL/min): most dissimilar composition to plasma
- Exception: HCO<sub>3</sub><sup>-</sup> remains constant, despite flow changes; selective parasympathetic stimulation; ↑ flow rate
  - ↑ HCO<sub>3</sub><sup>-</sup> parasympathetic stimulation
  - ↑ HCO<sub>3</sub><sup>-</sup> secretion

### Saliva secretion regulation

- Minor salivary glands continuously secreting small amounts to keep oral cavity moist
- When food enters → major glands activated → large amounts of saliva produced
- Two unique features
  - Exclusive neural control by autonomic nervous system (other gastrointestinal secretions controlled both neurally, hormonally)
  - Saliva secretion ↑ by both sympathetic + parasympathetic

- Parasympathetic innervation
  - Activity ↑ with visual stimulus of food, smell, nausea, conditional reflexes (e.g. Pavlov's salivating dog)
  - Activity ↓ with fear, sleep, dehydration
  - Chemoreceptors, mechanoreceptors in oral cavity stimulated → signal carried via facial (CN VII), glossopharyngeal (CN IX) nerves → salivatory nucleus in brain stem (medulla and pons)
  - Vinegar and citric juice → strongest chemoreceptor stimulus
  - Postganglionic neurons → release acetylcholine (ACh) → bind muscarinic receptors → ↑ IP<sub>3</sub> + intracellular Ca<sup>2+</sup> → saliva secretion
- Sympathetic innervation
  - Thoracic segments T<sub>1</sub>–T<sub>3</sub> → preganglionic nerves → synapse on superior cervical ganglion → postganglionic sympathetic neurons release norepinephrine (NE) → bind to beta-adrenergic > alpha-adrenergic receptors on acinar/ductal cells → stimulation of adenylyl cyclase → ↑ cAMP → ↑ saliva secretion

## SLOW WAVES

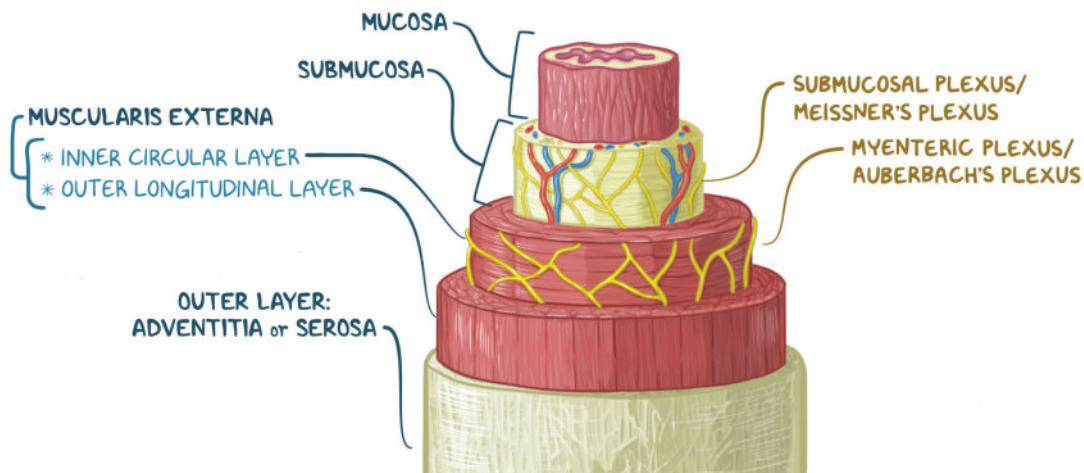
[osms.it/enteric-nervous-system-and-slow-waves](https://osms.it/enteric-nervous-system-and-slow-waves)

### ENTERIC NERVOUS SYSTEM

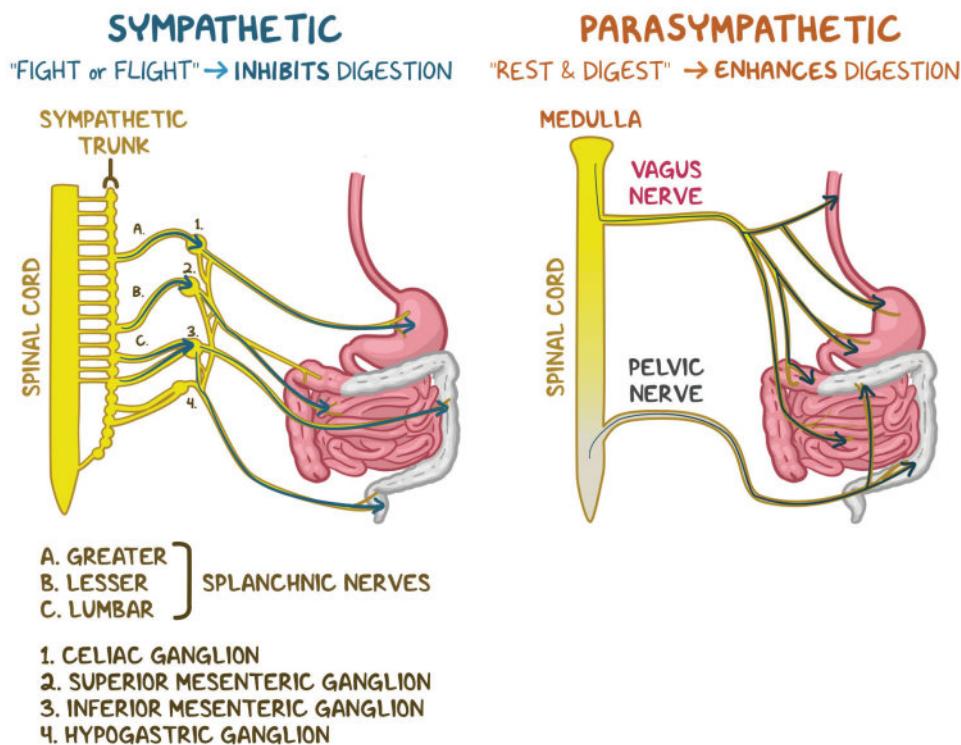
- AKA 'gut brain'
- Contains over 100 million neurons (more than spinal cord)
- Intrinsic/"in-house" nerve plexuses spread throughout GI tract like chicken wire
- Semiautonomous enteric neurons made up of two nerve plexuses (ganglia connected by unmyelinated tracts)
  - Submucosal nerve plexus → located in submucosa; innervates secretory cells; controls local digestive secretions

- Myenteric nerve plexus → located between circular, longitudinal muscle layers in muscularis externa; major controller of gastrointestinal (GI) tract motility
- Enteric nervous system connected to central nervous system (CNS) via
  - Afferent visceral fibers
  - Sympathetic, parasympathetic branches
  - Synapse with intrinsic plexus neurons

## ENTERIC NERVOUS SYSTEM



**Figure 38.6** The enteric nervous system is found within the walls of the entire gastrointestinal tract. The submucosal plexus is found in the submucosa and the myenteric plexus is found within the muscularis externa between the longitudinal and circular muscle layers.



**Figure 38.7** The gastrointestinal portions of the visceral motor system.

**Sympathetic division:** preganglionic fibers are in the lower thoracic and upper lumbar segments of the spinal cord, and they synapse in ganglia located near the spinal cord.

**Parasympathetic division:** preganglionic fibers arise from the brainstem (vagus nerve) and sacral component of the spinal cord (pelvic nerve), and synapse in a neural plexus on or very near the target organ.

## SLOW WAVES

- Unique feature of GI tract electrical activity
  - Oscillating depolarizations, repolarization of membrane potential of GI smooth muscle cells
- Depolarization → membrane potential becomes less negative → moves towards threshold → burst of action potentials (APs) occur on top of slow wave (plateau) → contraction/smooth muscle tension → membrane potential becomes more negative → moves away from threshold → repolarization → smooth muscle relaxation

## Frequency

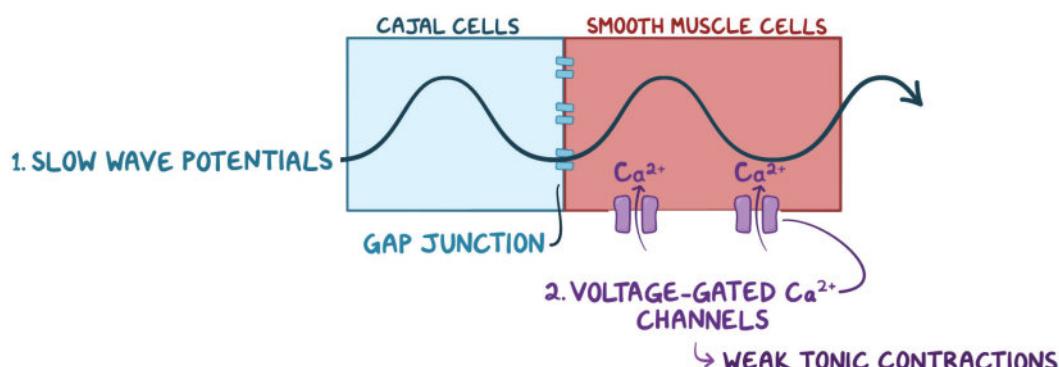
- Intrinsic rate is 3–12 slow waves/minute
- Not determined by hormonal/neural input, however can modulate amount of APs at plateau → ↑/↓ contraction strength
- Each part of GI tract has characteristic frequency
  - Stomach → slowest (3/min), duodenum → fastest (12/min)

## Mechanism

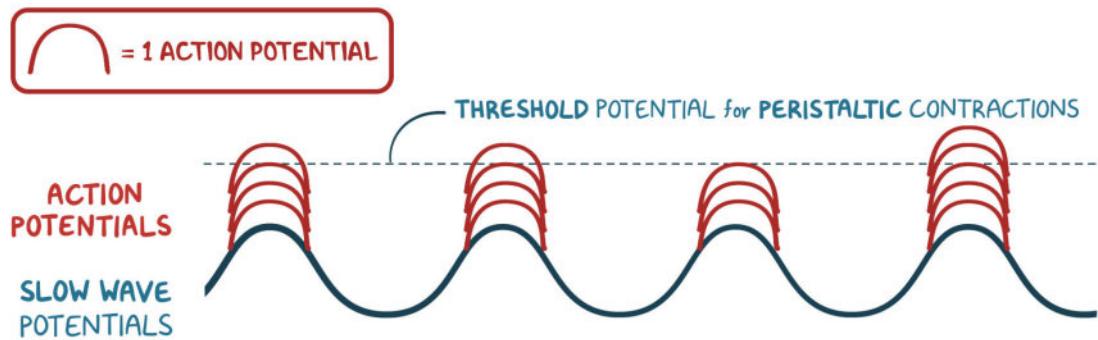
- Cyclic opening of  $\text{Ca}^{2+}$  channels →  $\text{Ca}^{2+}$  influx → depolarization
- Plateau phase maintained by continuous  $\text{Ca}^{2+}$  influx
- Opening of  $\text{K}^+$  channels →  $\text{K}^+$  outflux → repolarization

## Slow wave origin

- Myenteric plexus is network of nerves, located between longitudinal, circular layers in muscularis externa
- Interstitial cells of Cajal located in myenteric (Auerbach) plexus
  - Referred to as 'pacemaker' cells of GI tract smooth muscle
  - Cyclic, spontaneous depolarizations, repolarization occur in these cells → rapid spread to adjacent smooth muscle cells via gap junctions
- Pacemaker → frequency → AP rate → coordinated smooth muscle contraction
- Slow waves to contractions
- Subthreshold slow waves → can produce weak contraction
- Even without AP occurrence → smooth muscle not completely relaxed/tonically contracted
- Above threshold slow waves → APs occur on top of slow wave → stronger contraction → phasic contraction
- ↑↑ APs on top of slow wave → ↑↑ phasic contraction strength
- Unlike skeletal muscle, where each AP results in twitch/separate contraction, smooth muscle APs summate into one long contraction



**Figure 38.8** Slow wave origin and mechanism. Slow waves are generated by spontaneous depolarization and polarization of Cajal cells, which are attached to smooth muscle cells via gap junctions. The slow wave potentials travel through the smooth muscle cells → voltage-gated calcium channels open → weak depolarization of smooth muscle cells → weak tonic contractions that maintain the tone of the gastrointestinal tract.



**Figure 38.9** Slow wave potentials from enteric nervous system + action potentials from extrinsic nervous system → threshold potential for peristaltic contractions. Strength of contraction is determined by number of action potentials above each slow wave; rate of contraction is determined by the rate of the slow waves.

## ESOPHAGEAL MOTILITY

[osms.it/esophageal-motility](http://osms.it/esophageal-motility)

### GI MOTILITY

- Generally, GI motility refers to contraction, relaxation of GI walls, sphincters
- GI contractile tissue is all smooth muscle except
  - Pharynx
  - Upper  $\frac{1}{3}$  esophagus
  - External anal sphincter
- Smooth muscle cells connected together via gap junctions → rapid cell-to-cell transfer of action potentials → coordinated contractions

#### Two types of smooth muscle

- Circular: ↓ segment diameter
- Longitudinal: ↓ segment length
- Both contained within muscularis externa layer

#### Two types of contractions

- Phasic: periodic → relaxation
  - Located in esophagus, small intestine
- Tonic: constant level of contraction, without regular intervals of relaxation
  - Located in lower esophagus, upper stomach, ileocecal valve, internal anal sphincter

### Sphincters

- Specialized circular muscle separating adjacent GI tract regions
- Maintain positive pressure → anterograde, retrograde flow prevented
- Smooth muscle contraction → peristalsis of GI contents to sphincter → sphincter transiently lowers pressure → relaxation → passage of contents to adjacent organ
- Locations
  - Upper esophageal sphincter: pharynx-upper esophagus
  - Lower esophageal sphincter: esophagus-stomach
  - Pyloric sphincter: stomach-duodenum
  - Ileocecal sphincter: ileum-cecum
  - Internal and external sphincters: preserves fecal continence

## ESOPHAGUS

### Key features

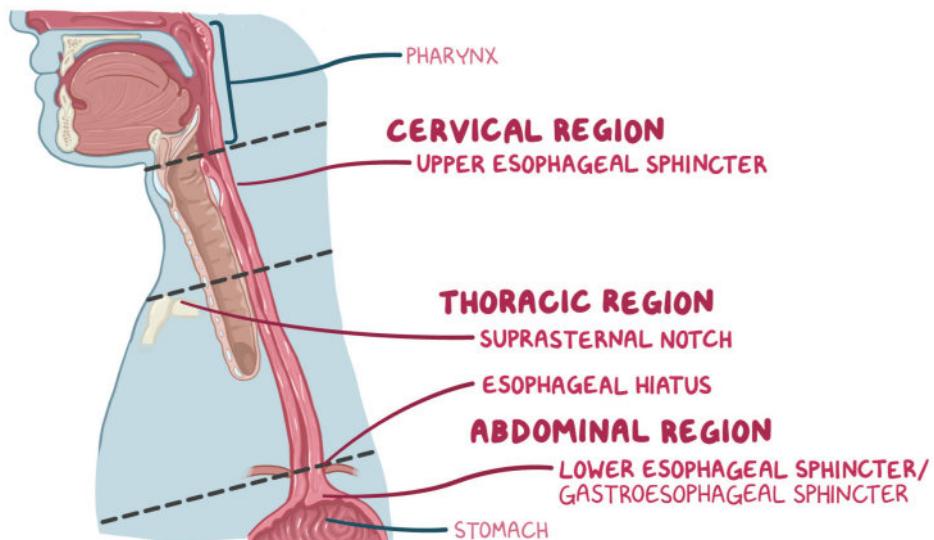
- Muscular 25cm/9.8in tube divided into three regions
- Cervical: connects with pharynx behind trachea; separated by upper esophageal sphincter

- Thoracic: suprasternal notch to esophageal hiatus in diaphragm
- Abdominal: esophageal hiatus to esophageal opening into stomach; separated by lower esophageal sphincter

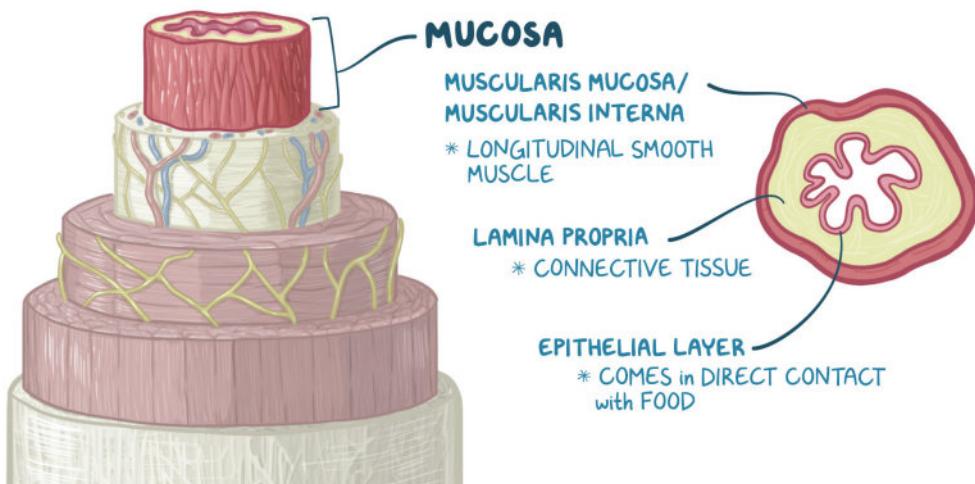
### Layers

- Adventitia
  - Thick fibrous connective tissue; outermost
- Muscularis externa
  - Outer longitudinal, inner circular muscle layers; myenteric plexus lies between

- Submucosa
  - Dense layer of connective tissue containing blood vessels, lymphatics, mucus glands secreting mucus to lumen via ducts; contains submucosal (Meissner) plexus
- Mucosa → three layers
  - Muscularis mucosa (outermost layer of longitudinal muscle)
  - Lamina propria
  - Epithelial layer



**Figure 38.10** Regions of esophagus, associated structures.



**Figure 38.11** Layers of esophageal mucosa.

### Innervation

- Intrinsic: Vagus nerve (CN X)
- Extrinsic: Myenteric plexus in muscularis externa

### Function

- Esophageal motility propels food bolus from pharynx → stomach
  - Food bolus formed in oral cavity → upper esophageal sphincter opens → bolus passes pharynx to upper esophagus → upper esophageal sphincter closes → primary peristaltic contraction → series of coordinated sequential contractions → each segment contracts → creates area of high pressure behind bolus → pushed down esophagus
  - If not all food pushed through → distension of esophageal wall → activation of mechanoreceptors in mucosal layer → afferent, sensory information to enteric nervous system and myenteric plexus → coordination of muscle contractions above site of distension + relaxation below it → secondary peristaltic wave
- Esophagus has thick muscularis externa compared to other parts of GI tract
- Primary peristaltic wave travels approximately 3cm/sec
  - Solid food takes approximately 10 seconds to travel from cervical region → stomach
  - Liquids approximately 1–2 seconds
  - Accelerated by gravity (sitting/standing > lying supine)

- Food bolus approaches lower esophageal sphincter → opening mediated by peptidergic fibers of vagus nerve, release vasoactive intestinal peptide (VIP) → lower esophageal sphincter smooth muscle relaxation → at same time, orad region of stomach relaxes (phenomenon referred to as receptive relaxation) → pressure decreases in orad stomach → food bolus propelled into stomach → lower esophageal sphincter closes immediately, returns to high pressure resting tone → prevents reflux

### Intrathoracic esophagus

- Upper, middle esophagus located in thorax, only lower esophagus located in abdomen
- Intraesophageal pressure = intrathoracic pressure which is < atmospheric pressure
- Intraesophageal pressure < intra abdominal pressure
- This pressure difference causes two problems
  - Inhibiting air from entering upper esophagus (air will travel down pressure gradient, esophagus essentially sucking air in); prevented by upper esophageal sphincter (always in closed resting state)
  - Inhibiting gastric contents from entering lower esophagus (reflux); prevented by lower esophageal sphincter (always in closed resting state)
- Conditions where intraabdominal pressure ↑↑ (e.g. pregnancy, morbid obesity) → gastroesophageal reflux

# GASTRIC MOTILITY

[osms.it/gastric-motility-and-secretions](https://osms.it/gastric-motility-and-secretions)

## STOMACH

- Anatomy differentiated based on motility, stomach can be divided into orad (proximal), caudad (distal)
  - Orad region:** fundus, proximal body; thin-walled
  - Caudad region:** distal body, antrum; thick-walled (stronger contractions to mix chyme, propel to small intestine)

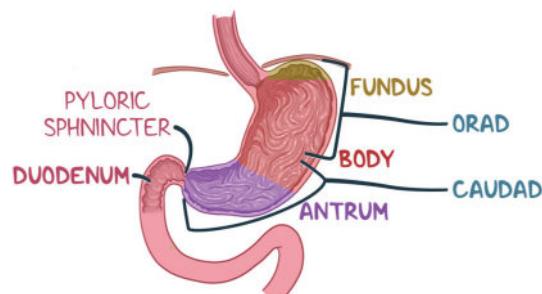


Figure 38.12 Divisions of the stomach.

## Layers

- Mucosa: innermost layer; modified → contains various glands filled with different cells → secrete components of gastric juice
- Submucosa: contains submucosal plexus → controls secretions and gastric blood flow, contains blood vessels
- Muscularis externa: modified
- Serosa: outermost layer
- Three layers of stomach muscles that involuntarily contract to produce peristalsis
  - Outer longitudinal layer
  - Middle circular layer
  - Inner oblique layer (unique to stomach)

## Innervation

- Extrinsic: autonomic nervous system
- Intrinsic: myenteric receives parasympathetic innervation (via vagus nerve), sympathetic innervation (via fibers from celiac ganglion); submucosal plexuses

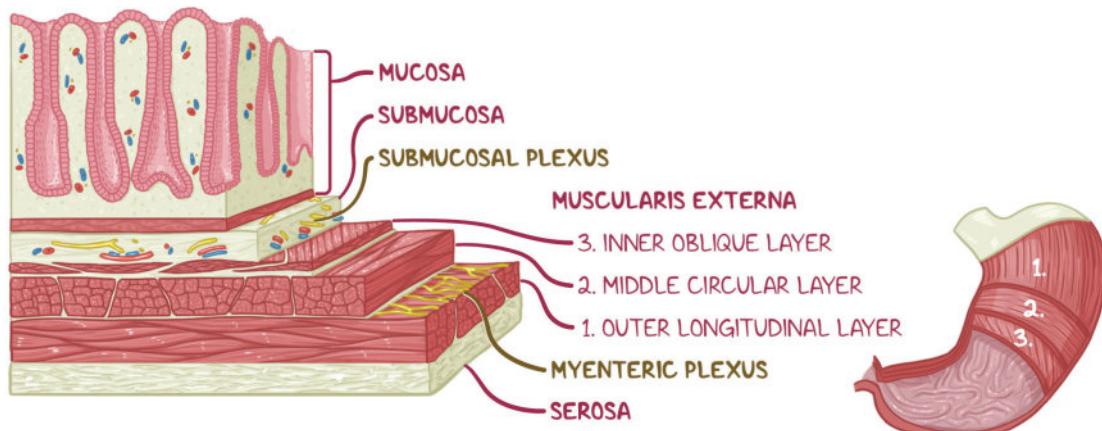


Figure 38.13 Layers of the stomach.

## COMPONENTS OF GASTRIC MOTILITY

- Three components
- Receptive relaxation
  - Relaxation of lower esophageal sphincter, orad stomach region to receive food bolus from esophagus
- Gastric contractions to break up bolus, mix with gastric secretions → initiate digestion
- Gastric emptying → propelling chyme to small intestine
  - Gastric emptying rate hormonally determined → allows adequate time for small intestine digestion/absorption
  - Liquids (faster); solids (slower)

### Receptive relaxation

- Vasovagal reflex: both afferent, efferent limbs of reflex carried within vagus nerve
  - Lower esophageal distension → relaxation, opening of lower esophageal sphincter → mechanoreceptors detect distension → send afferent sensory information to CNS through sensory neurons → CNS transmits efferent information to orad stomach smooth muscle wall → postganglionic peptidergic vagal nerve fibers release VIP → orad stomach ↓ pressure, ↑ volume → allows food bolus passage
  - Vagotomy inhibits receptive relaxation
- Stomach can accommodate up to 1.5L of food

### Gastric contractions

- Thick, muscular caudad region of stomach produces strong contractions needed to mix food with gastric secretions, digest food
- Contraction waves begin in middle stomach body → progressively ↑ strength as food approaches pylorus
- Periodically, portion of gastric contents propelled through pylorus to duodenum
  - However, most gastric contents undergo retropulsion (propelled back into stomach for further mixing)
- Majority of the chyme not initially injected through pylorus to duodenum since contraction wave closes pyloric sphincter
- Frequency of slow waves in caudad stomach; bringing membrane potential to

threshold so APs can occur

- 3–5/min → frequency of caudad stomach contraction approximately same
- Slow wave frequency not influenced by neural/hormonal input
- Frequency of APs, contraction force are influenced by neural/hormonal input
- Frequency of APs, force of contraction ↑↑ by
  - Parasympathetic stimulation
  - Gastrin
  - Motilin
- Frequency of APs, force of contraction ↓↓ by
  - Sympathetic stimulation
  - Secretin: hormone produced by duodenal S cells; regulates water homeostasis, GI tract secretions
  - Gastric inhibitory peptide (GIP): hormone secreted by intestinal K cells; inhibits gastric acid secretion, stimulates insulin secretion
- Migrating myoelectric complexes
  - Periodic gastric contractions during fasting
  - Function: clear stomach of remaining content from last meal
  - 90-minute intervals
  - Mediated by motilin

### Gastric emptying

- Emptying stomach of 1.5L postmeal can take approximately three hours
- Emptying rate closely monitored/regulated to allow ample time for stomach acid neutralization in duodenum, digestion/absorption of nutrients
- Emptying speeds
  - Liquids > solids
  - Isotonic contents > hyper/hypotonic contents
- Solid particles must be < 1mm<sup>3</sup>; retropulsion continues until this size reached
- Factors that ↑ gastric emptying time (slows gastric emptying process)
  - ↓ pH in duodenum (presence of H<sup>+</sup> ions); mediated by enteric nervous system
  - H<sup>+</sup> receptors in duodenal mucosa detect ↓ pH of intestinal contents → activate

interneurons in myenteric plexus → relay info to gastric smooth muscle → ↑ gastric emptying time/slow gastric emptying process → allows time to neutralize acid by pancreatic  $\text{HCO}_3^-$ .  
 □ ↑ fatty acids (highly fatty meal)

- The hormone cholecystokinin (CCK) secreted from duodenal I cells when fatty acids present in duodenum → slows gastric emptying (↑ gastric emptying time) → allow adequate time for fat to be digested/absorbed

## GASTRIC SECRETION

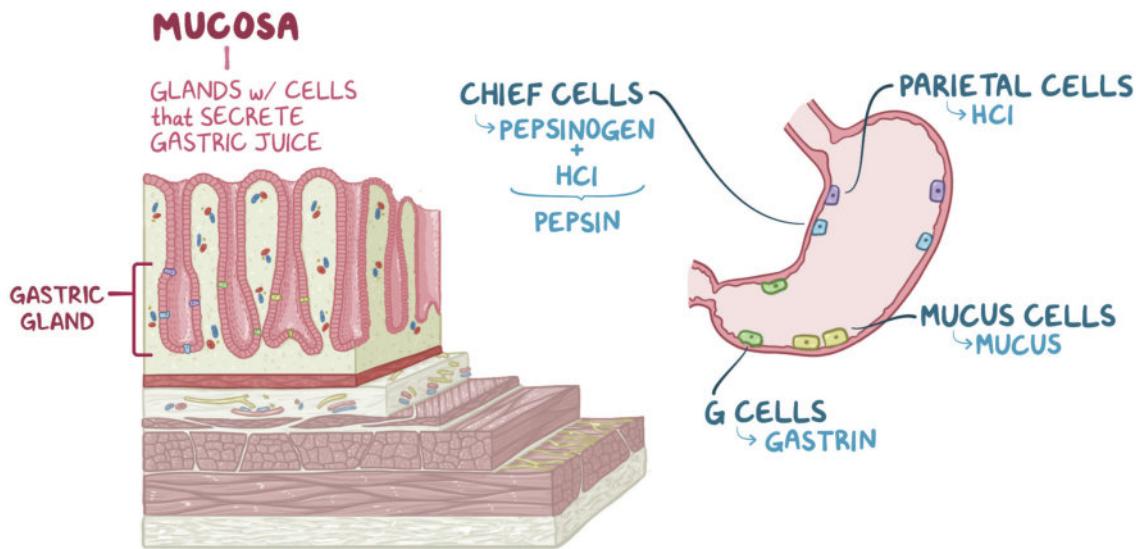
[osms.it/gastric-motility-and-secretions](http://osms.it/gastric-motility-and-secretions)

- Altogether gastric mucosa secretes fluid referred to as 'gastric juice'
- Four major components
  - HCl
  - Pepsinogen
  - Intrinsic factor (needed for vitamin  $\text{B}_{12}$  absorption in ileum)
  - Mucus (protects gastric mucosa from corrosive acids, lubricates)
- Oxytic glands
  - Found in body of stomach
  - Empty secretions via ducts into lumen of stomach
  - Opening of duct in gastric mucosa referred to as pits, lined by epithelial cells superficially

### Secretory cells

- Found in gastric glands
- Mucous neck cells
  - Scattered around neck, basally
  - Produce thin watery mucus (different from mucous cells of surface epithelium)
- Parietal (oxytic) cells
  - Found more apically; scattered around chief cells
  - Produce HCl, intrinsic factor
- Chief cells
  - Found basally
  - Produce pepsinogen (inactive form of pepsin); activated by HCl
  - Also produce lipases (15% of GI lipolysis)
- Enteroendocrine cells
  - Found deep in gland
  - Release various chemical messengers directly into lamina propria (e.g. histamine, serotonin act via paracrine mechanism, somatostatin acts via paracrine/hormone mechanism)
- G cells
  - Secrete gastrin → bloodstream → ↑ HCl secretion by parietal cells, ↑ pepsinogen secretion by chief cells + ↑ contraction of stomach muscles
- Pyloric glands found in antrum of stomach
  - Similar configuration to oxytic glands but with deeper pits
  - Mucous neck cells secrete mucus,  $\text{HCO}_3^-$ , pepsinogen → pyloric ducts
  - G cells secrete gastrin → circulation

GASTRIC CELLS OVERVIEW		
	LOCATION	SECRETION
CHIEF CELLS	Body	Pepsinogen
PARIETAL CELLS	Body	HCl + Intrinsic factor
MUCOUS CELLS	Antrum	Mucus + Pepsinogen
G CELLS	Antrum	Gastrin (to circulation)



**Figure 38.14** Location of secretory cells within gastric glands and in the stomach, as well as secretory products.

#### Mucosal barrier

- Stomach is harshest, most corrosive environment in entire GI tract
  - Due to HCl, protein-digesting enzymes
- To combat these conditions
  - Thick bicarbonate-rich mucus
  - Tight junctions joining epithelial cells together (prevents gastric juice leakage)
  - Undifferentiated stem cells → shed and replace damaged epithelial mucosal cells

#### HCl secretion and mechanism

- Parietal cells → HCl secretion → gastric content pH 1–2
- Functions to convert inactive pepsinogen (secreted by chief cells) → active pepsin → protein digestion; also functions to kill ingested bacteria
- Apical membrane of gastric gland has two transporters
  - $H^+-K^+$  ATPase:  $H^+$  secreted into stomach lumen; primary active process ( $H^+$  and  $K^+$  flow against electrochemical gradient); site of action by proton pump inhibitors (e.g. omeprazole)
  - $Cl^-$  channel:  $Cl^-$  follows  $H^+$  into lumen; passive process

- Basolateral membrane has two transporters
  - $Na^+-K^+$  ATPase
  - $Cl^-$ - $HCO_3^-$  exchanger
- Basolateral membrane cells contain carbonic anhydrase
  - $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$
  - $H^+$  then secreted with  $Cl^-$  into lumen of stomach
  - $HCO_3^-$  is absorbed into blood → 'alkaline tide' (↑ blood pH in gastric venous blood after meal)
- Overall net HCl secretion, net  $HCO_3^-$  absorption

#### HCl secretion modulation

- Gastrin (secreted into systemic circulation by gastric antral G cells)
  - Reaches parietal cells via endocrine mechanism
  - Binds to  $CCK_B$  receptors of parietal cells (affinity for gastrin = CCK)
  - Stimulates  $H^+$  secretion via  $IP_3/Ca^{2+}$  second messenger mechanism
  - Triggers for gastrin secretion: stomach distension, small peptides, amino acids in stomach, vagus nerve stimulation
  - Can indirectly stimulate  $H^+$  secretion by ↑ histamine release from endochromaffin-like (ECL) cells

- Histamine
  - Released from ECL cells in gastric mucosa
  - Paracrine diffusion mechanism to nearby parietal cells
  - Binds to  $H_2$  receptors coupled to  $G_2$  protein → stimulation of adenylyl cyclase → ↑ cAMP → activation of protein kinase A → ↑ secretion of  $H^+$  by parietal cells
  - Site of action of the  $H_2$  blockers (e.g. cimetidine)
- ACh
  - Released by vagus nerve (directly innervate parietal cells)
  - ACh directly binds to parietal cell  $M_3$  receptors → activation of phospholipase C → releases diacylglycerol (DAG) and  $IP_3$  from membrane phospholipids → ↑ intracellular  $Ca^{2+}$  →  $Ca^{2+}$  and DAG → activate protein kinases → ↑  $H^+$  secretion by parietal cells
  - Site of action of antimuscarinics (e.g. atropine); atropine does not block HCl secretion completely
  - Will block direct vagal effects on parietal cells

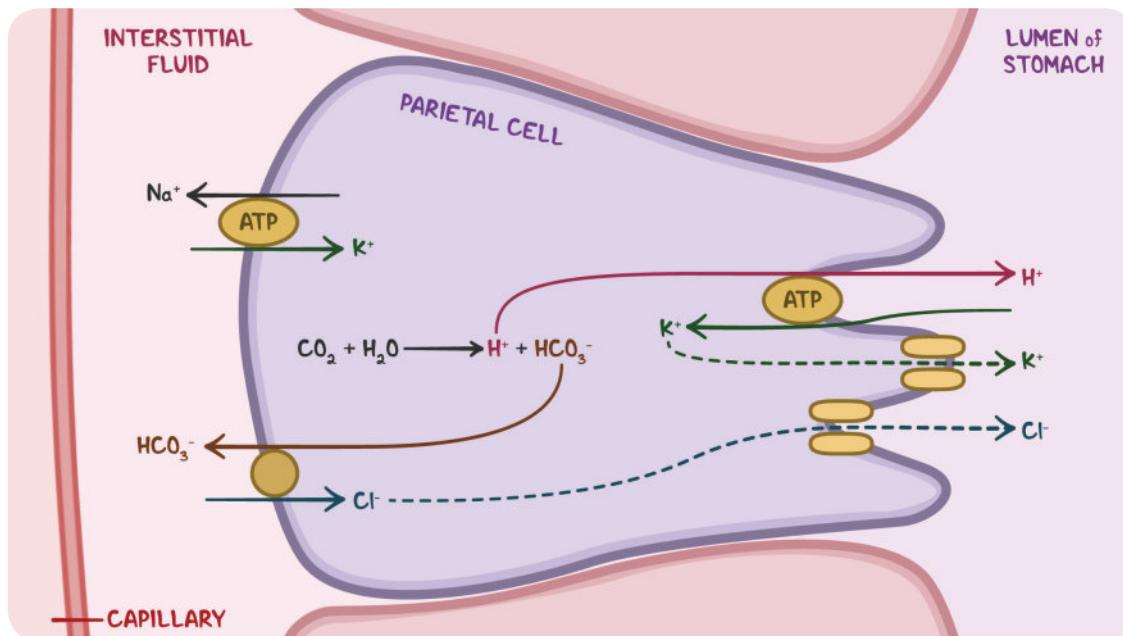
- Will not block indirect vagal effects on gastrin secretion since neurotransmitter is gastrin-releasing peptide (GRP), not ACh
- Can indirectly stimulate  $H^+$  secretion by ↑ histamine release from ECL cells
- Rate of  $H^+$  secretion is regulated by individual actions of gastrin, histamine, ACh or by the combination of them via potentiation (ability of two or more stimuli to interact together to produce a greater combined response than sum of individual effects)

#### Cephalic phase of gastric secretion

- 30% of total HCl secretion
- **Stimuli:** smell and taste of food, chewing, swallowing, conditional reflexes in anticipation of eating (ex. Pavlov's dog)
- Two physiological mechanisms
  - Direct vagal stimulation of parietal cells
  - Indirect vagal stimulation of parietal cells via gastrin

#### Gastric phase of gastric secretion

- 60% of total HCl secretion
- **Stimuli:** gastric distension, amino acid/small peptide presence



**Figure 38.15** Mechanism of HCl secretion by parietal cells in the stomach's gastric glands. Dotted lines indicate passive diffusion, whereas solid lines indicate active transport.

- Four physiological mechanisms
  - Distension → direct vagal stimulation
  - Distension → indirect vagal stimulation (via gastrin)
  - Antral distension → local gastrin release reflex
  - Amino acids/small peptides → G cells → gastrin release
- Caffeine, alcohol are also HCl secretion stimulants

#### **Intestinal phase of gastric secretion**

- 10% of total HCl secretion
- Mediated by protein digestion products

#### **Inhibition of HCl secretion**

- First major factor is ↓ pH of gastric contents
  - Gastrin secretion inhibited by low pH
  - Chyme moved to small intestine → no longer requirement of pepsinogen → pepsin
- Second major factor is somatostatin
  - Secreted by D cells in stomach
  - Inhibits H<sup>+</sup> secretion from parietal cells
  - **Direct mechanism:** somatostatin → binds to receptor on parietal cell coupled with Gi protein → ↓ adenylyl cyclase → ↓ cAMP → ↓ H<sup>+</sup> secretion
  - **Indirect mechanism:** somatostatin inhibits ECL, G cell release of histamine, gastrin, respectively
- Prostaglandins (e.g. prostaglandin E<sub>2</sub>) also inhibit histamine's stimulatory action on H<sup>+</sup> secretion via G<sub>i</sub> protein → ↓ adenylyl cyclase pathway



# NOTES

## DIGESTION & ABSORPTION

### DIGESTION & ABSORPTION

- **Digestion:** breakdown of large food molecules into monomers for absorption in gastrointestinal (GI) tract
- Chemical digestion accomplished by enzymes secreted into alimentary canal by glands

### Mechanical digestion

- Mastication
  - Mouth ingests food, begins mechanical, chemical digestion (mastication, salivation), initiates propulsion by swallowing
  - Partly voluntary, partly reflexive (e.g. stretch reflexes, pressure inputs)

### Deglutition (swallowing)

- Movement of food from mouth to stomach
- **Buccal phase:** voluntary
  - Occurs in mouth
  - Tongue pushes against hard palate forcing food bolus into oropharynx
- **Pharyngeal-esophageal phase:** involuntary
  - Controlled by brainstem swallowing center

- Cranial nerves (mainly Vagus) activate muscles of pharynx, esophagus
- Soft palate rises, closes nasopharynx, epiglottis covers larynx, upper esophageal sphincter relaxes → peristalsis moves food through pharynx, esophagus → gastroesophageal sphincter relaxes allowing food to enter

### Two absorption pathways

- **Cellular pathway:** substance crosses apical/luminal membrane to enter intestinal epithelial cell, then crosses basolateral membrane to enter into blood
- **Paracellular pathway:** move across tight junctions between intestinal epithelial cells to enter blood
- Absorptive surface maximized by villi, microvilli, folds (folds of Kerckring) in small intestine
  - Most digestion occurs in duodenum, least amount of digestion occurs in ileum (as reflected by length of villi - longest villi in duodenum, shortest in ileum)
  - **Brush border:** surface of microvilli containing digestive enzymes

# HYDRATION

[osms.it/hydration](https://osms.it/hydration)

- Total body water
  - Intracellular fluid (inside cells) + extracellular fluid (outside cells—e.g. blood, interstitium)
- Water functions
  - Bodily secretions, digestion, detoxification (urination), thermoregulation (sweating)
- Total body water balanced by intake, elimination

## Water intake

- Water ingested in fluid/food form
  - 80% → fluid; 20% → food
- Bloodstream absorption in small, large intestines

## Water loss

- Breathing; sweating; urinating, defecating

## DEHYDRATION

- Occurs when water loss > water intake
- Causes
  - Vigorous exercise, decreased oral intake, dry air, vomiting, diarrhea, excessive sweating, inability to swallow, diuretics
- Symptoms
  - Thirst, dry mouth/lips, nausea, fatigue, lightheadedness, darkened/decreased urine
- High risk groups
  - Children: lower stores of water, ↑ surface area to body mass, thirst sensors not fully developed, depend on caregivers
  - Elderly: decreased thirst sensation, medication, chronic diseases affecting kidneys

# CARBOHYDRATES & SUGARS

[osms.it/carbohydrates-and-sugars](https://osms.it/carbohydrates-and-sugars)

## DIGESTION

### Mouth

- Begins carbohydrate digestion
- Enzyme: salivary alpha amylase
  - Starts starch digestion → dextrans, maltose, maltotriose

### Stomach

- Salivary amylase inactivated
- Relatively no breakdown of starch

### Small intestine

- Majority of carbohydrate digestion
- Enzymes include
  - Pancreatic amylase: digests starch → disaccharides; hydrolyzes interior

1,4-glycosidic bonds in starch yielding disaccharides

- Intestinal brush border enzymes: digest oligosaccharides, disaccharides → lactose, maltose, sucrose → galactose, glucose, fructose; e.g. dextrinase, maltase, glucoamylase, lactase, sucrase

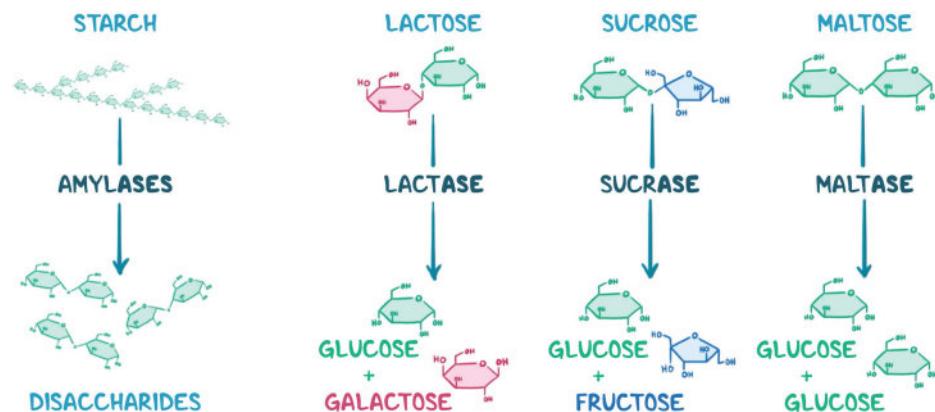
## ABSORPTION

- Primary site of absorption: small intestine

### Pathway of absorption

- Glucose, galactose: absorbed into enterocytes via sodium ion cotransport (secondary active transport) → GLUT2 transporter extrudes glucose, galactose across basolateral membrane into blood

- Sodium-glucose cotransporter (*SGLT1*): moves glucose inside enterocytes against electrochemical gradient using ATP created from sodium gradient created by sodium-potassium ATPase on the basolateral membrane
- Fructose: absorbed into enterocytes via facilitated diffusion by GLUT5 transporter
- in apical membrane → GLUT2 transporter extrudes fructose across basolateral membrane into blood; fructose absorption cannot occur against electrochemical gradient
- Monosaccharides leave epithelial cells via facilitated diffusion → enter villi capillaries → hepatic portal vein → liver



**Figure 39.1** Overview of the actions of some of the enzymes involved in carbohydrate digestion.

## PROTEINS

[osms.it/proteins](https://osms.it/proteins)

- Proteins can be absorbed in the form of amino acids, dipeptides, or tripeptides (as opposed to carbohydrates)

### DIGESTION

- Proteins → large polypeptides → smaller polypeptides/peptides → individual amino acids/dipeptides/tripeptides

### Stomach

- **Gastric pepsin** (with HCl): digests proteins → large polypeptides
  - Protein digestion starts with gastric pepsin
  - Secreted by chief cells, activated by low pH
- **Proteases** (endopeptidases, exopeptidases)
  - **Endopeptidases**: trypsin, chymotrypsin, pepsin; hydrolyze interior peptide bonds

(pepsin, trypsin, chymotrypsin)

- **Exopeptidases**: hydrolyze individual amino acids from carboxyl end (carboxypeptidases A, B)

### Small intestine

- Pancreatic, intestinal brush border enzymes continue digestion
- Pancreatic enzymes
  - **Zymogens**: trypsinogen, chymotrypsinogen, procarboxypeptidase A, B
  - **Active forms**: trypsin, chymotrypsin, carboxypeptidase
  - Enterokinase activates trypsinogen → trypsin → trypsin autocatalyzes itself, activates additional pancreatic zymogens

- Digest large polypeptides → small polypeptides/peptides
- Intestinal brush border enzymes
  - Dipeptidase, aminopeptidase, carboxypeptidase
  - Digest small polypeptides/peptides → amino acids/dipeptides/tripeptides

## ABSORPTION

- Site of absorption: small intestine

### Pathway of absorption

- Amino acids: absorbed via cotransport with sodium ions or facilitated diffusion out of epithelial cells → enter villi capillaries → hepatic portal vein → liver
  - Four separate transporters one each for neutral, acidic, basic amino acid

- Dipeptides, tripeptides: absorbed into enterocytes via cotransport with protons → broken down into amino acids/transcytosis

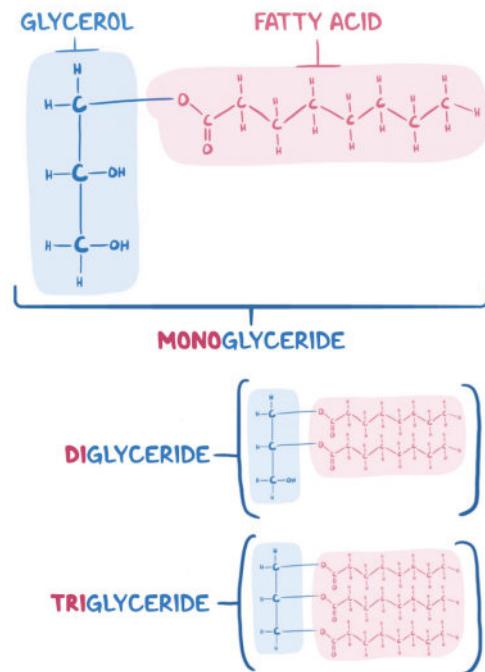
## NUCLEIC ACID DIGESTION & ABSORPTION

- Nucleic acids → pentose sugars, nitrogen-containing bases, phosphate ions
- Site of digestion: small intestine only
- Enzymes
  - Pancreatic ribonuclease, deoxyribonucleases
  - Intestinal brush border enzymes (nucleosidases, phosphatases)
- Site of absorption: small intestine
- Absorption pathway: active transport into enterocytes by membrane carriers → villi capillaries → hepatic portal vein → liver

# FATS

[osms.it/fats](http://osms.it/fats)

- Unemulsified triglycerides → monoglycerides/diglycerides, fatty acids
- Site of digestion: mouth, stomach, small intestine
- Lipid digestion begins with lingual, gastric lipases hydrolyzing triglycerides → glycerol, fatty acids
  - CCK slows gastric emptying, allowing adequate time for pancreatic enzymes to work
- Pancreatic enzymes (pancreatic lipase, cholesterol ester hydrolase, phospholipase A2), colipase finish digestion in small intestine
  - Bile salts, lysolecithin surround, emulsify dietary lipids to create large surface area for pancreatic enzymes
  - Pancreatic lipase secreted as active enzyme, hydrolyzes triglyceride → monoglyceride + 2 fatty acids
  - Colipase (secreted as inactive procolipase, activated by trypsin) binds to pancreatic lipase protecting it from being inactivated by bile salts

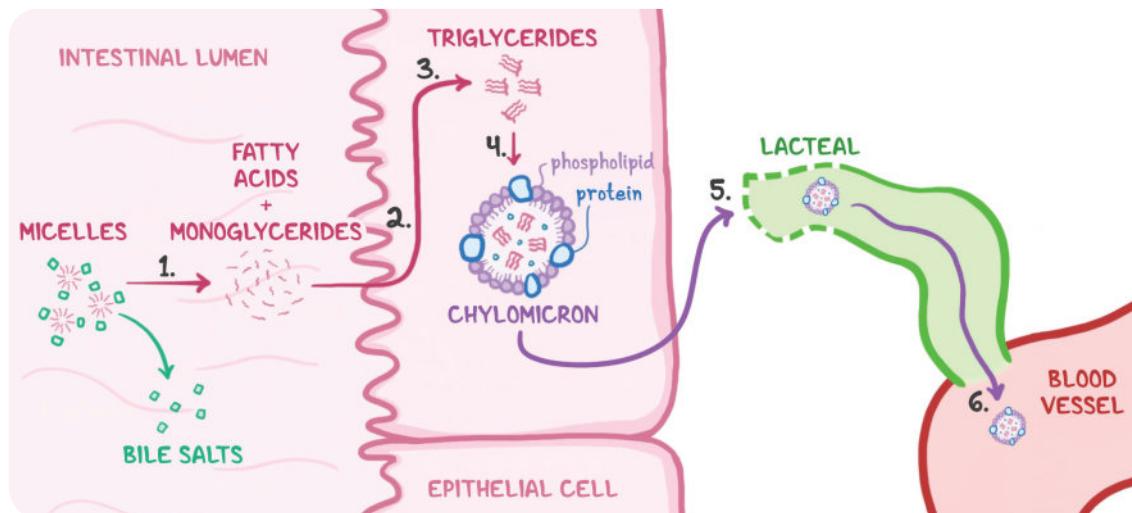


**Figure 39.2** Fats are comprised of glycerol backbone and one or more fatty acid chains. A few examples of fats shown above.

- Cholesterol ester hydrolase (secreted as active enzyme) hydrolyzes cholesterol ester → free cholesterol, fatty acids; hydrolyzes triglycerides → glycerol
- Phospholipase A2 (secreted as proenzyme, activated by trypsin) hydrolyzes phospholipids → lysolecithin, fatty acids
- **Final products of lipid digestion:** monoglycerides, cholesterol, glycerol, fatty acids, lysolecithin
  - Since products are hydrophobic (except glycerol), must be solubilized in micelles before transport to enterocyte apical membrane for absorption
  - Micelles: products of lipid digestion surrounded by bile salts
- **Site of absorption:** small intestine

### Pathway of absorption

- Fatty acids, monoglycerides absorbed via
  - Diffusion
  - Fatty acids, monoglycerides leave micelles → enter epithelial cells → triglyceride formation → chylomicrons formation (fat globules plus surface apoproteins) → chylomicrons enter lacteals → lymph in lacteal transports chylomicrons into systemic circulation
- Apoproteins are essential for absorption of chylomicrons (specifically Apo B)
- Short chain fatty acids diffuse into villi capillaries → hepatic portal vein → liver



**Figure 39.3** Overview of the fat absorption pathway.

1. Fatty acids and monoglycerides leave micelles and
2. enter epithelial cells.
3. They form triglycerides.
4. Chylomicrons containing the fats are then formed.
5. The chylomicrons enter lacteals, and
6. are transported into systemic circulation.

# VITAMINS

[osms.it/vitamins](https://osms.it/vitamins)

- With the exception of vitamin K, which is produced by intestinal bacteria, vitamins are not synthesized in body therefore must be attained by diet

## Fat soluble (Vitamins A, D, E, K)

- Location: small intestine
- Mechanism: incorporated into micelles along with products of lipid digestion, absorbed into enterocytes

## Water-soluble (B vitamins, vitamin C, biotin, folic acid, nicotinic acid, pantothenic acid)

- Location: ileum
- Mechanism: cotransport with sodium (need intrinsic factor) except vitamin B<sub>12</sub> (cobalamin)
- Vitamin B<sub>12</sub>
  - Requires intrinsic factor
    - Pathway: ingestion → stomach acidity releases B<sub>12</sub> from its food carrier proteins → free vitamin B<sub>12</sub> binds to haptocorrin (R proteins) secreted by salivary glands (protects B<sub>12</sub> from acid degradation) → pancreatic proteases degrade R proteins in duodenum → B<sub>12</sub> binds to intrinsic factors (secreted by gastric parietal cells) to protect it from pancreatic enzymes → intrinsic factor-B<sub>12</sub> complex resistant to degradation from pancreatic enzymes → absorbed in ileum

## Absorption of calcium

- Active form of vitamin D, 1,25-dihydroxycholecalciferol, required for calcium absorption
- Dietary vitamin D<sub>3</sub> (cholecalciferol) is inactive
- Cholecalciferol → 25-hydroxycholecalciferol (inactive) in liver → 1,25-dihydroxycholecalciferol in kidney by 1alpha-hydroxylase → synthesizes calbindin D-28K (vitamin D-dependent

- calcium binding protein → promotes calcium absorption from small intestine
- Decreased by: oxalic acid, tannins, magnesium, phosphorus, phytates
- Increased by: acidic conditions in intestine, vitamin D, estrogen, lactose
- Location: small intestine (primarily duodenum)
- Mechanism: vitamin D-dependent calcium binding protein

## Absorption of iron

- Location: small intestine
- Mechanism: ferric state (Fe<sup>3+</sup>) reduced → to ferrous state (Fe<sup>2+</sup>) → binds apoferritin in enterocytes → transported across basolateral membrane → binds to transferrin in blood → transferrin carries to liver

## The absorptive state: hormones

- Digested nutrients enter blood stream from intestines → blood glucose rises → stimulation of pancreatic insulin release → body cells increase glucose uptake reducing blood glucose concentration back to normal
- Hepatocytes
  - Excess glucose → glycogen for storage via glucose-6-phosphate intermediate
  - Amino acids → ketone bodies (converted to acetyl CoA if needed later)
- Myocytes
  - Excess glucose → glycogen for storage via glucose-6-phosphate intermediate
  - Amino acids → actin, myosin → muscle fibers
- Adipocytes store excess lipids increasing fat reserves

# INTESTINAL FLUID BALANCE

[osms.it/intestinal-fluid-balance](http://osms.it/intestinal-fluid-balance)

- Along with nutrient digestion, GI tract re-absorbs large amounts of fluid, electrolytes ( $\text{Na}^+$ ,  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ ,  $\text{K}^+$ )
- Small, large intestine together absorb approximately 9L/2.38 gallons daily
  - Diet  $\rightarrow$  2L/0.44 gallons; pancreatic, biliary, intestinal secretions  $\rightarrow$  7L/1.85 gallons
  - Approximately 100–200mL /0.03–0.06 gallons) excreted in feces
  - Absorptive mechanisms disrupted  $\rightarrow$  diarrhea (enormous potential body-water, electrolyte loss )

## Villi

- Line intestinal epithelial cells
  - First step: solute absorbed; second step: water follows
  - Fluid absorbed = isosmotic (water, solute absorption: parallel proportions)
  - Similar to renal proximal tubule
  - Absorptive mechanisms vary by intestinal part

## Jejunum

- Major site of  $\text{Na}^+$  absorption
  - Enters epithelial cell  $\rightarrow$   $\text{Na}^+$ -dependent coupled transporters on apical membrane ( $\text{Na}^+$ -monosaccharide cotransporters ( $\text{Na}^+$ -glucose/ $\text{Na}^+$ -galactose),  $\text{Na}^+$ -amino acid cotransporters,  $\text{Na}^+$ - $\text{H}^+$  exchanger)
  - Translocates across basolateral membrane via  $\text{Na}^+$ - $\text{K}^+$  ATPase
  - $\text{H}^+$  source (for  $\text{Na}^+$ - $\text{H}^+$  exchanger) = intracellular  $\text{CO}_2 + \text{H}_2\text{O} \rightarrow$  carbonic anhydrase converts to  $\text{H}^+$ ,  $\text{HCO}_3^- \rightarrow \text{H}^+$  secreted into lumen  $\rightarrow$  blood absorbs  $\text{HCO}_3^-$  ("alkaline tide")

## Ileum

- Same transporters as jejunum +  $\text{Cl}^-$ - $\text{HCO}_3^-$  exchanger on apical membrane
- $\text{Cl}^-$  transporter in basolateral membrane

- $\text{H}^+$  secreted into lumen +  $\text{HCO}_3^-$  secreted into lumen (via  $\text{Cl}^-$ - $\text{HCO}_3^-$  exchanger; not absorbed into blood)  $\rightarrow$   $\text{Cl}^-$ - $\text{HCO}_3^-$  exchanger,  $\text{Na}^+$ - $\text{H}^+$  exchanger  $\rightarrow$  net  $\text{NaCl}$  movement into cell  $\rightarrow$  net  $\text{NaCl}$  absorption

## Colon

- Apical membrane contains  $\text{Na}^+$ ,  $\text{K}^+$  channels
- Net  $\text{Na}^+$  absorption +  $\text{K}^+$  secretion
- Aldosterone induces  $\text{Na}^+$  channel synthesis  $\rightarrow \uparrow \text{Na}^+$  absorption, secondary to  $\text{K}^+$  secretion

## Fluid, electrolyte secretion

- Epithelial cells lining crypts of small intestine  $\rightarrow$  secrete fluid, electrolytes (mucus, lubricating fluids assisting in mixing, digestion)  $\rightarrow$  must also be absorbed more distally
- Electrolyte, fluid secretion route
  - Small intestine: paracellular route  $\rightarrow$  "leaky" tight junctions ( $\downarrow$  resistance)
  - Colon: cellular route  $\rightarrow$  "tight" tight junctions ( $\uparrow$  resistance)
- Electrolyte, fluid secretion mechanism
  - Apical membrane:  $\text{Cl}^-$  channel
  - Basolateral membrane:  $\text{Na}^+$ - $\text{K}^+$ - $2\text{Cl}^-$  cotransporter (similar to thick ascending loop of Henle)
  - $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$  ions move into cells from blood  $\rightarrow$   $\text{Cl}^-$  diffuses into lumen via  $\text{Cl}^-$  channel on apical membrane  $\rightarrow$   $\text{Na}^+$  follows  $\text{Cl}^-$  passively, paracellularly  $\rightarrow$   $\text{H}_2\text{O}$  secretion follows  $\text{NaCl}$  secretion
  - Apical  $\text{Cl}^-$  channels closed in resting state  $\rightarrow$  opens after various hormones/neurotransmitters (ACh, VIP) bind
  - Bind to basolateral receptor  $\rightarrow$  activate adenylyl cyclase  $\rightarrow$   $\uparrow$  cAMP in crypt cells  $\rightarrow$  cAMP opens  $\text{Cl}^-$  channels
  - Adenylyl cyclase can be maximally activated in cholera  $\rightarrow$  severe, life-threatening diarrhea



# NOTES LIVER, GALL BLADDER, & PANCREAS

## BILE SECRETION & ENTEROHEPATIC CIRCULATION

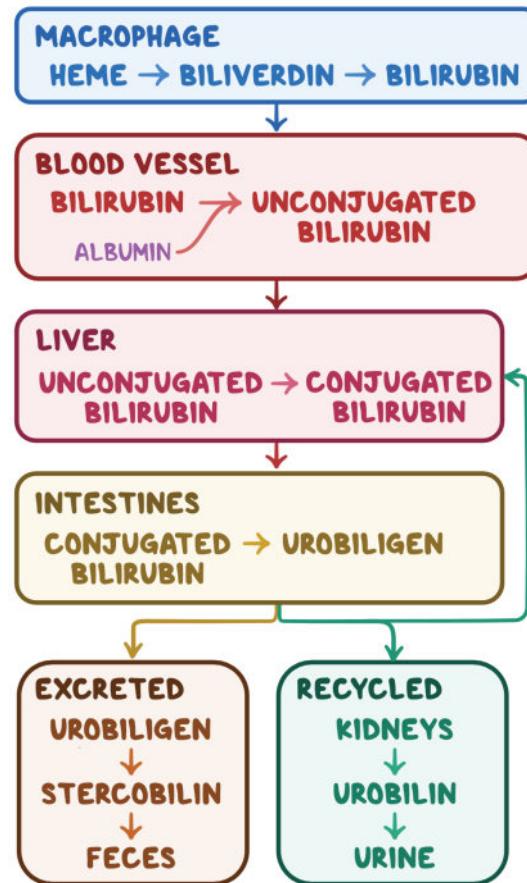
[osms.it/bile-secretion-enterohepatic-circulation](http://osms.it/bile-secretion-enterohepatic-circulation)

### SYNTHESIS OF BILE, BILIRUBIN

- Hemoglobin from old red blood cells taken up by macrophages → biliverdin → unconjugated bilirubin → released into plasma, combines with albumin → unconjugated bilirubin absorbed into hepatic cells, released from albumin → liver conjugates unconjugated bilirubin → conjugated bilirubin excreted from hepatocytes into intestines → some conjugated bilirubin converted by bacteria into urobilinogen (soluble) → some urobilinogen reabsorbed through intestinal mucosa back into blood → re-excreted by liver back into gut/excreted by kidneys into urine → urobilinogen becomes urobilin → stercobilin in feces

### RECYCLING OF BILE

- Bile transported from ileum into portal blood after digestion → portal blood delivers bile salts to liver → liver extracts bile salts from portal blood, adds to hepatic bile salt/acid pool → bile returned to gallbladder
- Some bile excreted into feces as stercobilin
- Only excreted bile needs to be replaced



**Figure 40.1** Bile synthesis to excretion/recycling pathway.

# LIVER ANATOMY & PHYSIOLOGY

[osms.it/liver-anatomy-physiology](http://osms.it/liver-anatomy-physiology)

## LIVER ANATOMY

### Functions

- Bile production, storage (e.g. glycogen), detoxification, nutrient interconversion, synthesis (e.g. albumin, clotting factors), phagocytosis (Kupffer cells)

### Location

- Located in right upper quadrant (RUQ) under diaphragm, almost entirely within rib cage
  - Largest internal organ
- Covered by visceral peritoneum
  - Except superior-most region (bare area), contacts inferior surface of diaphragm
- Falciform ligament: mesentery separates right, left lobes; suspends liver from diaphragm, anterior abdominal wall
- Round ligament/ligamentum teres: inferior to falciform ligament, remnant of fetal umbilical vein

### Four lobes

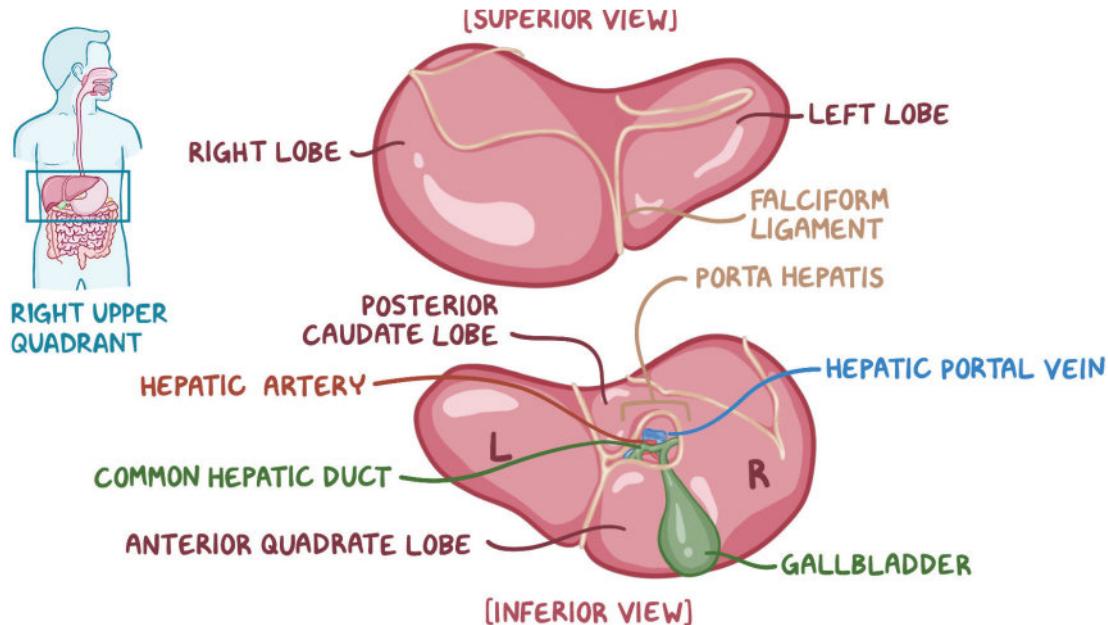
- Right lobe (largest)
- Left lobe
- Caudate lobe
- Quadrata lobe

### Blood supply

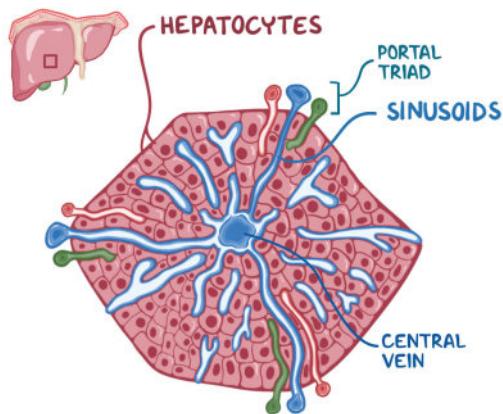
- 75% from nutrient rich, oxygen poor portal vein
- 25% from nutrient poor, oxygen rich hepatic artery
- Enterohepatic circulation gives liver first access to nutrients, toxins, medications from gut

### Liver lobule

- Functional unit of liver
  - Hexagonal liver lobule made of hepatocytes
- Each liver lobule surrounded by six portal triads on each point with lobes central vein in center



**Figure 40.2** Superior and inferior view of liver.



**Figure 40.3** Liver lobule.

- Portal triad
  - Portal venule + portal arteriole + bile duct

#### Sinusoids

- Mixing of portal vein, hepatic arterial blood
- Lined with leaky endothelial cells
- Pathway of blood flow
  - Blood from hepatic portal vein, artery → sinusoids → central vein → hepatic vein → inferior vena cava

#### Bile

- Produced by hepatocytes, excreted into bile ducts
- Composed of **bile salts**, bile pigments, cholesterol, triglycerides, phospholipids
  - Primary bile salts: cholic, chenodeoxycholic acids (cholesterol derivatives)
  - Function: emulsify fat (break into smaller pieces to maximize surface area for digestion); facilitate fat, cholesterol absorption
  - Bile salts conserved via enterohepatic circulation
  - Main bile pigment is bilirubin (waste product of hemoglobin from broken down erythrocytes), stercobilin gives feces dark color
- Bile flow
  - Parallel, opposite direction flow of blood
  - Canaliculi → bile ducts → fusion of multiple bile ducts to form common hepatic duct → fusion with cystic duct draining gallbladder → bile duct → ampulla of vater

#### Major fuels

- Glucose, fructose, galactose (after meal); fatty acids (after fasting)
  - Amino acids can also be used
  - Long-chain fatty acids: major source of fuel during prolonged fasting

#### Cell types

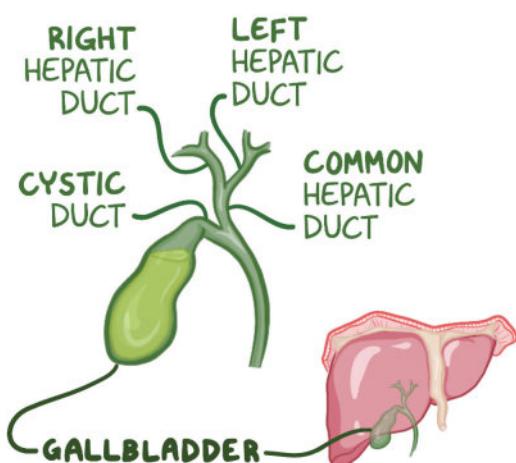
- Hepatocytes
  - Function: carry out most metabolic pathways
  - Majority cell type in liver
  - Contain large amounts of rough, smooth endoplasmic reticulum (ER), Golgi bodies, peroxisomes, mitochondria
- Endothelial cells
  - Location: sinusoidal lining
  - Function: release growth factors; secrete cytokines, endocytose ligands
  - Contain fenestrations → free diffusion of blood, nutrients between sinusoids, hepatocytes
- Kupffer cells
  - Location: sinusoidal lining
  - Function: macrophages specific to liver protect against gut-derived pathogens, release cytokines, secrete mediators of inflammatory response, remove damaged erythrocytes from circulation
- Stellate (Ito) cells
  - Location: scattered amongst hepatocytes
  - Function: primary vitamin A storage site; regulate contractility of sinusoids; control turnover of extracellular matrix, hepatic connective tissue
  - Responsible for tissue cirrhosis
- Pit cells (liver-associated lymphocytes)
  - Function: natural killer cells specific to liver

#### GALLBLADDER ANATOMY

- Muscular sac
  - Stores, concentrates bile produced by liver
- Located under inferior surface of right liver lobe
- Inner mucosa (with rugae) → allows expansion
- Smooth muscle layer → allows contraction

to occur in response to cholecystokinin (produced by duodenum) → bile released into small intestine

- Also contracts in response to vagal stimulation
- Flow of bile
  - Cystic duct → common bile duct → ampulla of vater → duodenum



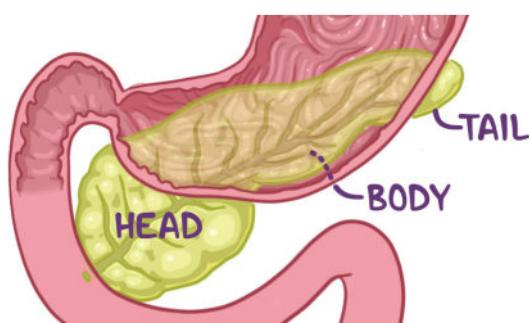
**Figure 40.4** Gallbladder.

## PANCREAS ANATOMY

- Located retroperitoneal posterior to stomach, duodenum

### Four regions

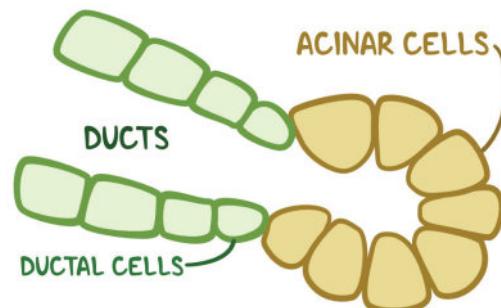
- Head: right side nestled into curve of duodenum
- Neck: thin portion between head, body
- Body: tapered left side
- Tail: ends near spleen



**Figure 40.5** Pancreatic location relative to stomach and duodenum.

## Acinar gland

- Exocrine gland
- Acinar cells
  - Contain zymogen granules full of proenzymes for digestion
- Stimulated by secretin, cholecystokinin (from duodenum), vagus nerve
- Secretes digestive enzymes into duodenum
  - Amylase, lipase, nuclease secreted as active enzymes
  - Proteases (trypsinogen, chymotrypsinogen, procarboxypeptidase) secreted in zymogen form, must be cleaved to be activated



**Figure 40.6** Acinar gland.

## Islets of Langerhans

- Endocrine gland
- Responsible for glucose homeostasis
  - Beta cells → insulin
  - Alpha cells → glucagon
  - Delta cells → somatostatin → inhibits insulin, glucagon secretion

## Ducts

- Main pancreatic duct: located centrally, fuses with bile duct to drain into duodenum
- Accessory pancreatic duct: smaller duct; empties directly into duodenum
- Ductal cells: responsible for aqueous secretions (water,  $\text{HCO}_3^-$ , sodium)
  - Secretion of bicarbonate ions neutralizes acidic chyme entering duodenum, provides optimal pH for activation of digestive enzymes

## LIVER PHYSIOLOGY

### Efficient exchange of compounds between sinusoidal blood, hepatocytes

- Fenestrated endothelial cells
- Lack of basement membrane between endothelial cells, hepatocytes
- Slow blood flow

### Biotransformation of xenobiotics

- Principal site for processing xenobiotics, toxins
- Phase I reactions: oxidation, reduction, hydroxylation, hydrolysis
  - Introduces reactive functional groups to increase compound polarity
- Phase II reactions: conjugation, sulfation, glucuronidation, methylation
- Detoxification: xenobiotic → phase I reaction → primary metabolite → phase II reaction → secondary metabolite → excretion
- Cytochrome P450 system: major xenobiotic metabolizer in body; oxidizes substrates, adds oxygen to structures
  - First pass effect for pharmaceuticals

### Regulation and maintenance of blood glucose levels

- ↑ blood glucose: → secretion of insulin by pancreas → ↑ uptake of glucose, amino acids by cells; inhibition of glycolysis, activation of glycogen synthesis, inhibition of gluconeogenesis, inhibition of glycogenolysis, inhibition of fatty acid oxidation → ↓ blood glucose
- ↓ blood glucose: ↑ breakdown of glycogen → secretion of glucagon, activation of glycolysis, inhibition of glycogen synthesis, activation of gluconeogenesis, activation of glycogenolysis, activation of fatty acid oxidation → ↑ blood glucose

### Elimination of ammonia via urea cycle

- Liver
  - Main organ responsible for eliminating ammonia via urea cycle
- Ammonia transported to liver on glutamine, alanine → converted by liver into urea for excretion in urine

### Amino acid metabolism/protein synthesis and regulation

- Liver produces plasma proteins (mainly albumin), coagulation factors, metal-binding proteins (transferrin, ceruloplasmin), lipid transporters (apoproteins), protease inhibitors (antitrypsin), glycoproteins, proteoglycans
- Can convert amino acids into glucose, fatty acids, ketone bodies
- Sugars produced by liver O-linked

### Formation of ketone bodies

- Liver
  - Only organ that can produce ketone bodies
- Cannot use ketone bodies for energy
- Ketone bodies formed when glucose levels low, high rates of fatty acid oxidation
- Ketone bodies major fuel source for central nervous system (CNS) under starvation

### Cholesterol and triacylglycerol synthesis

- Liver synthesizes very low-density lipoprotein (VLDL) to be secreted into blood
- Food plentiful → liver activates synthesis of fatty acid, triacylglycerol, cholesterol → reduces hepatic cholesterol synthesis
- Also sends excess dietary cholesterol to peripheral tissue

### Nucleotide biosynthesis

- Liver can synthesize, salvage nucleotides for use by other cells
- Salvage pathway
  - Liver converts free bases to nucleotides for secretion into circulation as needed by peripheral tissues

### Lipid metabolism

- Long-chain fatty acids
  - Liver's major fuel source during fasting
  - Triacylglycerols from adipose tissue → fatty acids bound to albumin → liver → activated via fatty Acyl-coenzyme A (acyl-CoA) synthetases → fatty-acyl-CoA → fatty-acyl-carnitine → carnitine crosses inner mitochondrial membrane → fatty-acyl-carnitine → carnitine, fatty-acyl-CoA → beta oxidation
  - Enzymes in beta oxidation, fatty-acid activation specific for length of fatty acid carbon chains

- Medium-chain-length fatty-acid oxidation
  - 4–12 carbons
  - Liver, kidney is site of oxidation
  - Activating enzyme is medium-chain-length fatty acid-activating enzyme (MMFAE)
  - Oxidation begins with medium-chain-length acyl-CoA dehydrogenase
- Very-long-chain fatty-acid oxidation
  - > 20 carbons
- Oxidized by peroxisomes to octanoyl-Coa
- Generates hydrogen peroxide instead of flavin adenine dinucleotide (FADH<sub>2</sub>), in contrast to mitochondrial beta-oxidation
- Long-chain fatty acids
  - 12–20 carbons
  - Most common type of lipid used for oxidation by liver

## PANCREATIC SECRETION

[osms.it/pancreatic-secretion](http://osms.it/pancreatic-secretion)

### FLOW RATE, COMPOSITION OF PANCREATIC JUICE

#### High flow rate

- High HCO<sub>3</sub><sup>-</sup> concentration, low Cl<sup>-</sup> concentration

#### Low flow rate

- High Cl<sup>-</sup> concentration, low HCO<sub>3</sub><sup>-</sup> concentration

### REGULATION OF BILE, PANCREATIC SECRETION

- Hormones, neural stimuli regulate secretion of bile, pancreatic juice into duodenum

#### Hormones

- Secretin
  - Released by intestinal cells in response to acidic chyme; stimulates secretion of bile, pancreatic juice
- Cholecystokinin (CCK)
  - Major stimulus for gallbladder to release bile into duodenum; stimulates secretion of enzyme-rich pancreatic juice

#### Neural stimuli

- Parasympathetic stimulation by vagus nerve stimulates secretion
  - Bile from gallbladder, pancreatic juice

#### Bile salt

- Major stimulus for more bile secretion via stimulation of secretin release

### ACTIVATION OF PANCREATIC PROTEASES

- Enteropeptidase cleaves, activates trypsinogen to trypsin → trypsin activates chymotrypsinogen into chymotrypsin, procarboxypeptidase into carboxypeptidase



# NOTES

## POPULATION GENETICS

# MENDELIAN GENETICS & PUNNETT SQUARES

[osms.it/mendelian-genetics-punnett-squares](https://osms.it/mendelian-genetics-punnett-squares)

- Genetics: science of inheritance
- Parental generation ("P") → 1<sup>st</sup> filial generation ("F1") → 2<sup>nd</sup> filial generation ("F2")
- Homozygous: male, female alleles are same
- Heterozygous: male, female alleles differ
- Phenotype: observable trait from genotype

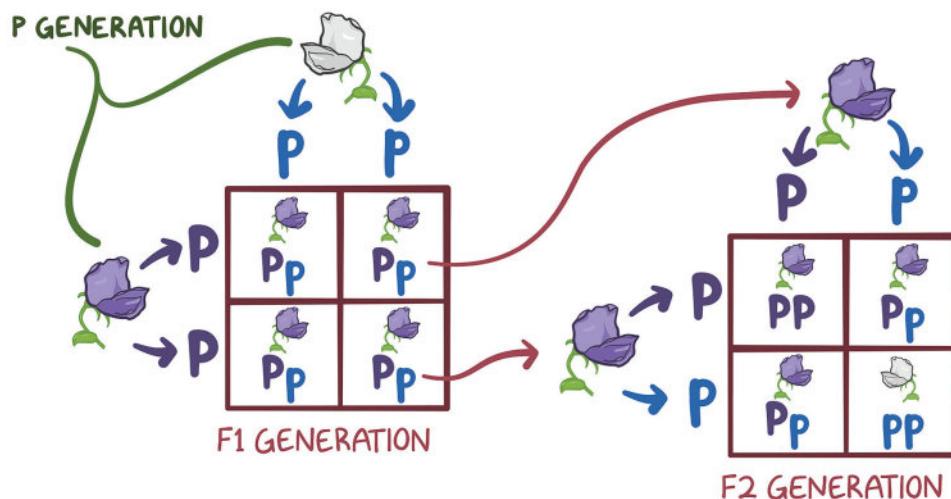
### Mendel's laws

- Law of segregation: alleles segregate, offspring acquire one allele from each parent

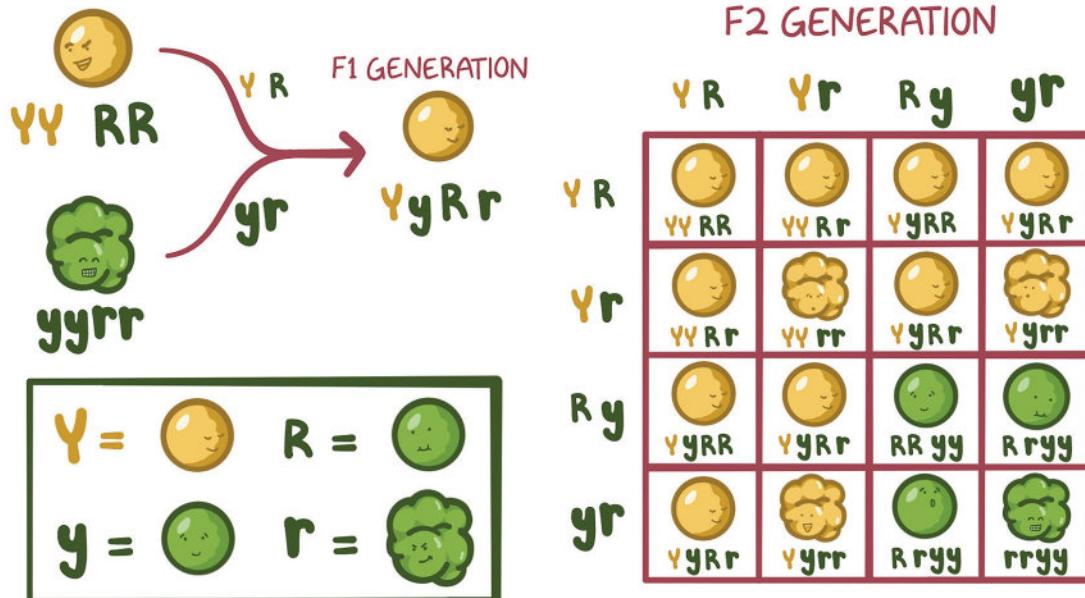
- Law of dominance: alleles can be dominant/recessive
  - Dominant traits appear when ≥ one dominant allele is present
- Law of independent assortment: separate genes assort independently
  - Genetic linkage: proximity of genes on chromosome can cause joint assortment

### Punnett square

- Table showing possible combinations of genotypes



**Figure 41.1** 2x2 Punnett squares showing the allele combinations for one gene: flower color in pea plants. The parent plants are homozygous for the flower color trait. When they are crossbred (first Punnett square), each offspring in the F1 generation gets one dominant allele (P) and one recessive allele (p). The dominant P allele masks the recessive p allele, so all the flowers appear violet. When any two of the heterozygous F1 generation plants are bred (second Punnett square), the three plants in the F2 generation with at least one P allele have a violet flower phenotype and the one plant with the homozygous pp genotype has a white flower phenotype.

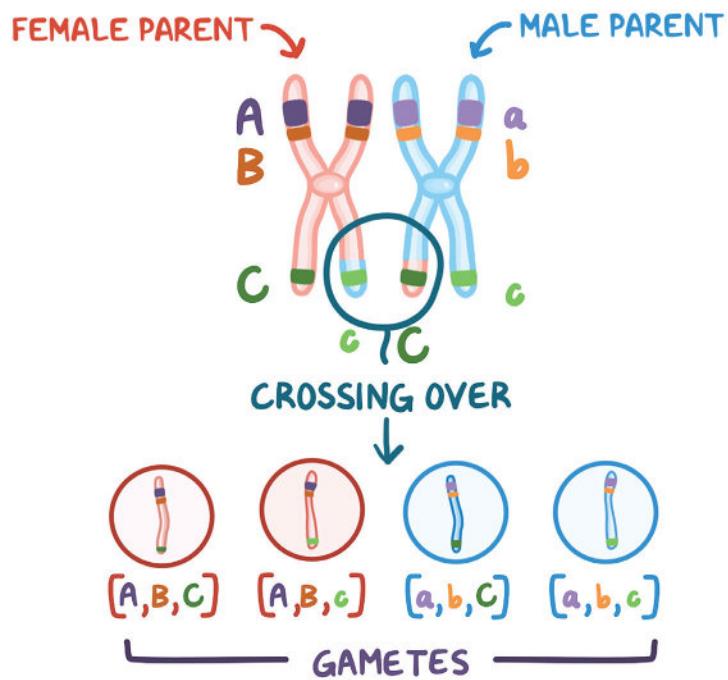


**Figure 41.2** 4x4 Punnett square showing the allele combinations for two genes: seed color (Y = yellow, y = green) and texture (R = round, r = wrinkled). One parent (P) plant is homozygous dominant (YYRR; yellow, round seeds), the second is homozygous recessive (yyrr; green, wrinkled seeds). When these plants are crossbred, all the F1 generation plants have the genotype YyRr and the phenotype of yellow, round seeds. When the F1 generation plants are bred (Punnett square), there are four possible combinations of the alleles for each parent: YR, Yr, yR, and yr. We can expect the F2 generation to have four phenotypes: yellow and round ( $\geq$  one Y and  $\geq$  one R), yellow and wrinkled ( $\geq$  one Y and two r), green and round (two y and  $\geq$  one R), green and wrinkled (yyrr). They appear in the ratio 9:3:3:1.

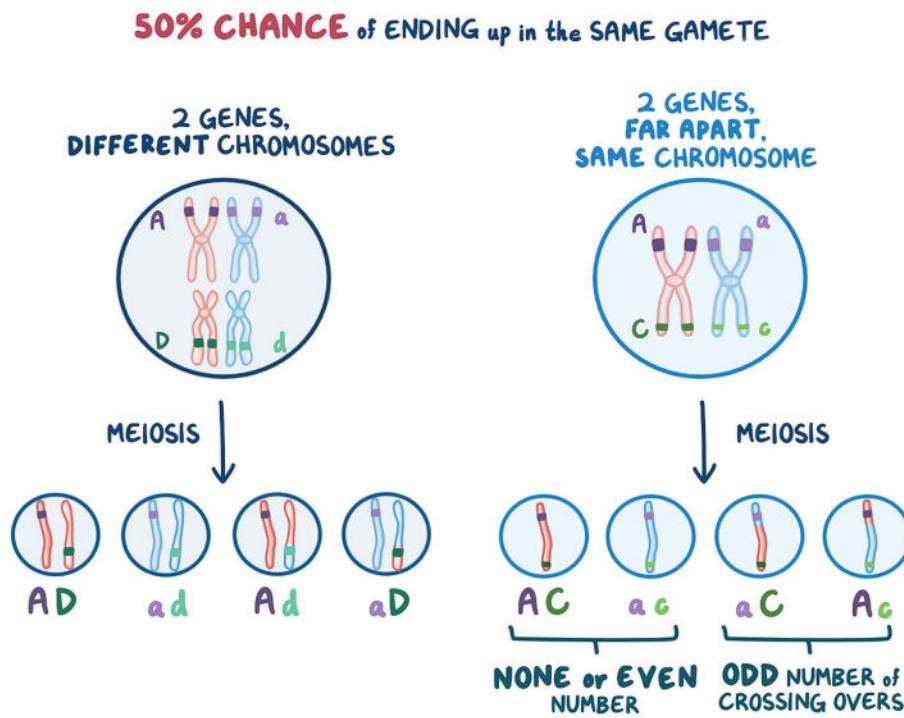
## INDEPENDENT ASSORTMENT OF GENES & LINKAGE

[osms.it/independent-assortment-and-linkage](https://osms.it/independent-assortment-and-linkage)

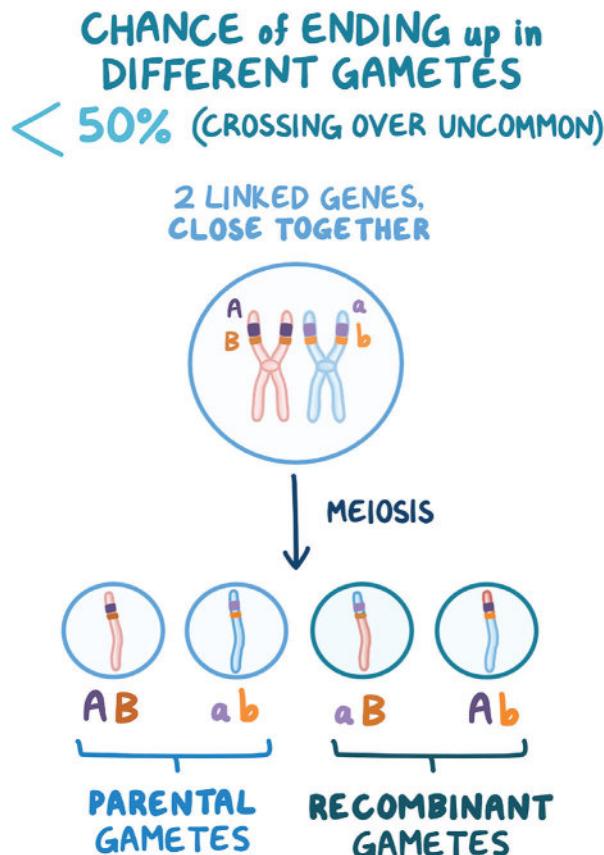
- Independent assortment: separate genes assort independently
  - Apart from in genetic linkage
  - Genetic linkage: proximity of genes on chromosome can cause joint assortment
- Crossing-over: in prophase 1 of meiosis, genes can be exchanged between adjacent chromosomes
  - Homozygous genes can occur on different gametes
  - Even repetitions of crossing-over can reverse this effect
- Linked genes have < 50% chance of occurring on different gametes
  - Parental gametes: linked genes inherited together
  - Recombinant gametes: linked genes between which crossing-over has occurred



**Figure 41.3** Red chromosome from female parent originally carried all dominant alleles for genes A, B, C; blue chromosome from male parent originally carried all recessive alleles for genes A, B, C. If crossing over occurs between the ends of the two chromosomes, dominant allele C from female parent ends up in the chromosome from male parent, vice versa.



**Figure 41.4** Any two genes on different chromosomes always have a 50% chance of going through crossing over in meiosis and showing up in the same gamete. The same is true for two genes very far apart on the same chromosome, because ending up in the same or a different gamete depends on whether there are an odd or even number of crossing overs.



**Figure 41.5** It is unlikely for a cut to occur in the small space between linked genes, which is why the chance of them crossing over and ending up in different gametes is < 50%. When linked genes are inherited together, the gametes are called “parental” because they carry same the alleles as the original chromosomes. When crossing over occurs, they are called “recombinant.”

## INHERITANCE PATTERNS

[osms.it/inheritance-patterns](https://osms.it/inheritance-patterns)

### Dominant vs. recessive inheritance patterns

- Dominant inheritance: mutation affects dominant allele → one copy causes disease
- Recessive inheritance: mutation affects recessive allele → two copies cause disease

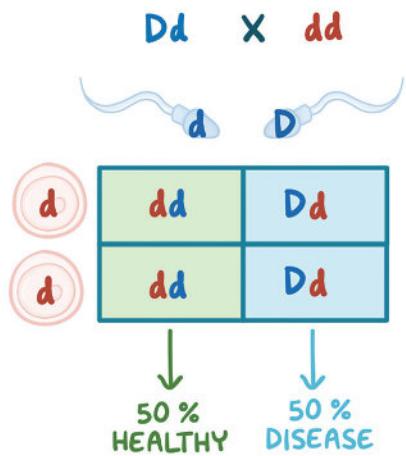
### Autosomal vs. sexual vs. mitochondrial patterns

- Autosomal inheritance: mutation affects somatic chromosome
- Sexual inheritance: mutation affects sex chromosome; X-linked/Y-linked

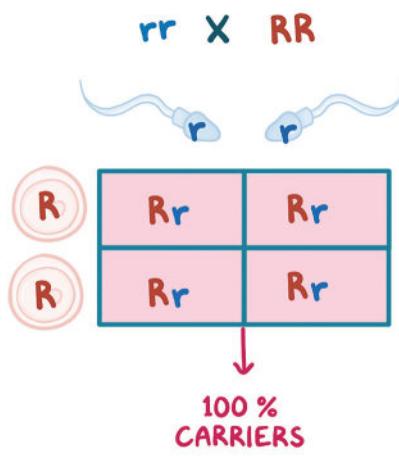
- Mitochondrial inheritance: mutation on egg's mitochondrial DNA

### Autosomal inheritance

- Autosomal dominant inheritance (e.g. Huntington's disease)
  - Dominant homozygotes (RR), heterozygotes (Rr) have disease
  - Recessive homozygotes (rr) unaffected
  - Disease too severe in homozygotes → don't reproduce

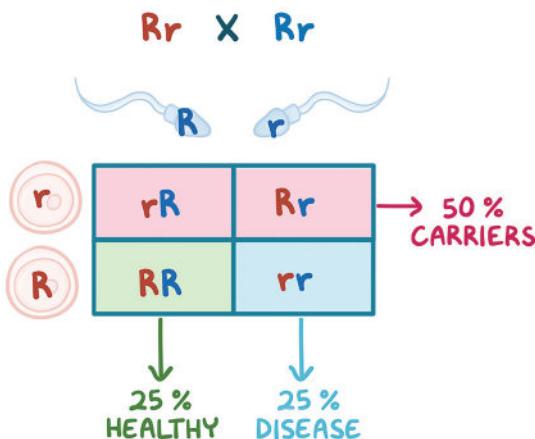


**Figure 41.6** Autosomal dominant inheritance. Punnett square demonstrating probabilities of healthy and disease genotypes in offspring when a heterozygous dominant individual ( $Dd$ ) reproduces with a healthy individual ( $dd$ ).



**Figure 41.8** Autosomal recessive inheritance. When one affected and one unaffected individual reproduce, all offspring are carriers.

- Autosomal recessive inheritance (e.g. cystic fibrosis)
  - Only recessive homozygotes have disease
  - Heterozygotes carriers
  - Tendency to skip generation
  - Children of consanguineous unions: ↑ likelihood of disease



**Figure 41.7** Autosomal recessive inheritance. Punnett square demonstrating probabilities of healthy, disease, and carrier genotypes in the offspring when two healthy carriers reproduce.

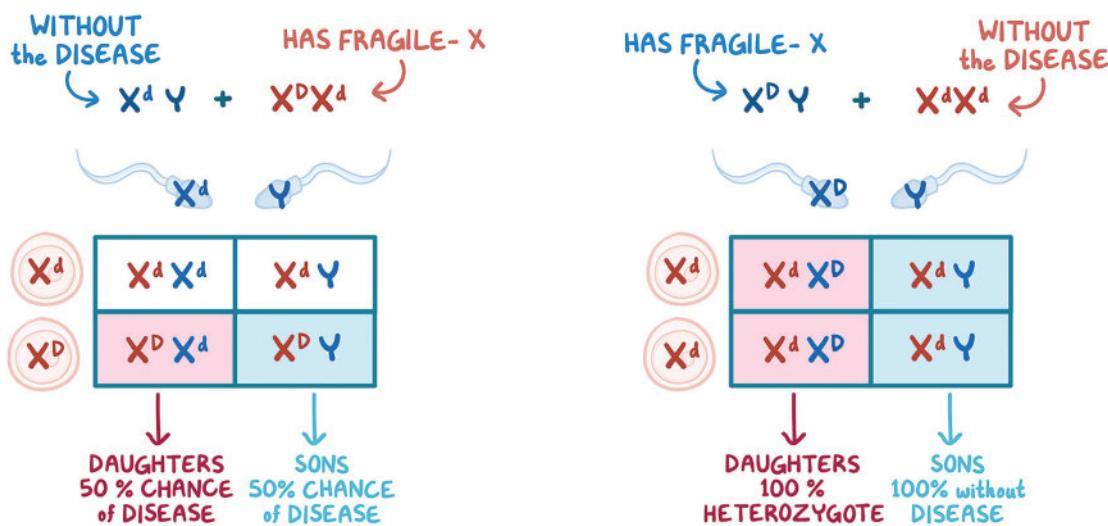
#### Sex-linked inheritance

- Males have one allele for genes on X, Y chromosomes (hemizygous)
- Females have two alleles for genes on X chromosomes (homozygous/heterozygous)
- X-linked dominant inheritance (e.g. fragile X syndrome)
  - Dominant hemizygotes, dominant homozygotes, heterozygotes have disease
  - Males reproducing with healthy females have 100% chance to pass onto female children, 0% chance to pass onto male children
  - Females reproducing with healthy males have 50% chance to pass onto children of both sexes
- X-linked recessive inheritance (e.g. hemophilia)
  - Recessive homozygotes, recessive hemizygotes have disease; heterozygotes are carriers
  - Males reproducing with healthy females have 100% chance of female children being carriers, 0% chance of passing disease onto male children
  - Heterozygous females reproducing with healthy males have 50% chance of female children being carriers, 50% chance of passing disease onto male children
- Y-linked inheritance (e.g. baldness)
  - Only male heterozygotes have disease

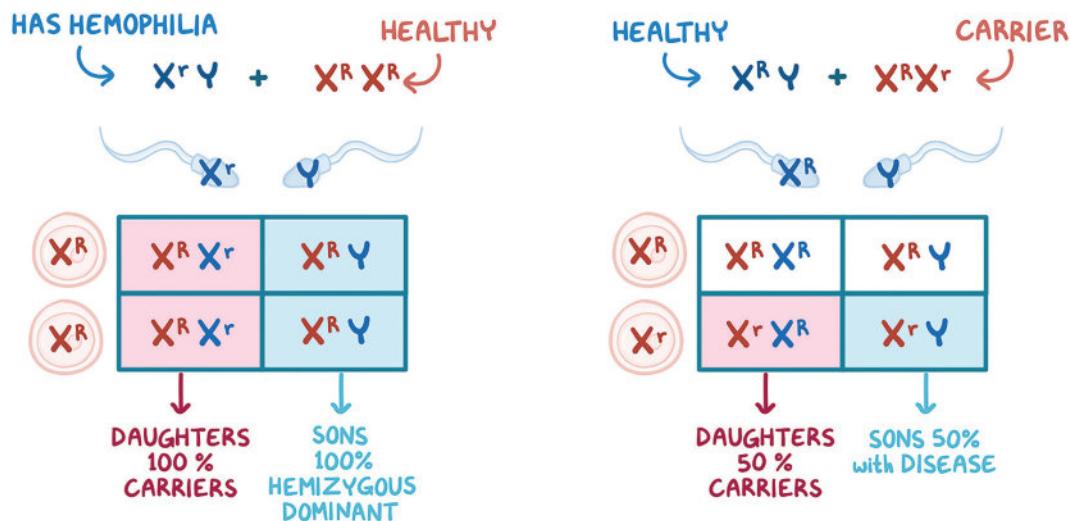
- Always passed from biologically-male parent to biologically-male child

## Mitochondrial inheritance

- Mitochondrial inheritance (e.g. DAD, AKA diabetes mellitus and deafness)
    - Males, females can develop disease
    - Only females can pass disease to offspring



**Figure 41.9** Punnett squares demonstrating the inheritance patterns for fragile X syndrome, an X-linked dominant disease, with different combinations of parental genotypes.



**Figure 41.10** Punnett squares demonstrating the inheritance patterns for hemophilia, an X-linked recessive disease, with different combinations of parental genotypes.

# EVOLUTION & NATURAL SELECTION

[osms.it/evolution-natural-selection](https://osms.it/evolution-natural-selection)

## Evolution

- Process by which populations change over time
  - Population: group of organisms within species that live in same place
  - Species: group of organisms with similar characteristics, ability to breed

## Natural selection

- Premises
  - Individuals in species have different

## traits

- Some individuals survive, reproduce
- Some traits → ↑ survival, reproduction (AKA fitness)
- → more offspring with these traits (AKA differential reproduction)
- Conclusion
  - Population slowly changes over time to favor useful traits (e.g. ↑ survival, reproduction)
- Artificial selection = selective breeding

# HARDY—WEINBERG EQUILIBRIUM

[osms.it/hardy-weinberg\\_equilibrium](https://osms.it/hardy-weinberg_equilibrium)

- Population's genetic traits remain same from one generation to next in absence of evolutionary changes (e.g. natural selection, mutation, genetic drift)
  - Natural selection causes population to favor useful traits
  - Mutation causes new traits to arise
  - Genetic drift causes trait prominence to shift by chance (AKA sampling error)

- Given probability  $p$  of dominant allele A, probability  $q$  of recessive allele a
  - $p + q = 1$
  - $\text{prob}(AA) = p^2$
  - $\text{prob}(aa) = q^2$
  - $\text{prob}(Aa) = 2pq$
- $q$  can be calculated from phenotype
  - Square root of frequency of recessive phenotype
  - → frequency of other phenotypes can be calculated

# EPIGENETICS

[osms.it/epigenetics](https://osms.it/epigenetics)

- Mechanisms to selectively activate/silence genes without modifying nucleotide sequence

## Histone modification

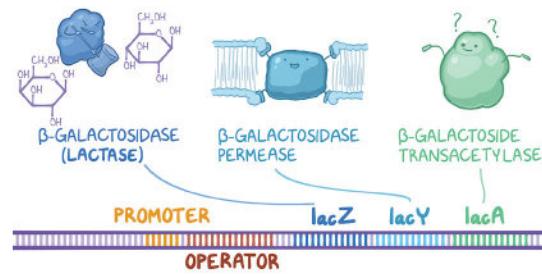
- Acetylation
  - Removes positive charge → less attraction to negative DNA phosphates → ↑ gene transcription
- Methylation
  - One methyl group → loosens histone tails → ↑ access for transcription factors → ↑ gene transcription

- 2-3 methyl groups → tightens histone tails → ↓ access for transcription factors → ↓ gene transcription
- Direct DNA modification
  - Usually occurs in long sequences of cytosine, guanine nucleotides (AKA CpG)
  - Cytosine residues undergo methylation, silencing gene expression
- Modifications occur throughout lifetime
- Affected by environmental factors (e.g. drug usage, diet, exercise)
- Changes are reversible

# LAC OPERON

[osms.it/lac-operon](https://osms.it/lac-operon)

- Collection of genes in *E. coli*, other bacteria that code for proteins required to transport, metabolize lactose
- Includes structural genes like *lacZ*, *lacY*, *lacA* as well as regulatory genes like promoter, operator
  - lacZ*: β-galactosidase (AKA lactase)
  - lacY*: β-galactosidase permease
  - lacA*: β-galactosidase transacetylase
  - Promoter: start transcription
  - Operator: prevent transcription with repressor (coded by *lacI*)
- Glucose, lactose concentrations can be used to regulate lac operon expression
  - ↑ glucose → repressor stays bound to operator, blocking RNA polymerase
  - ↑ glucose → catabolite activator protein inhibits transcription
  - ↓ glucose → repressor falls off
  - ↓ glucose → catabolite activator protein stimulates transcription

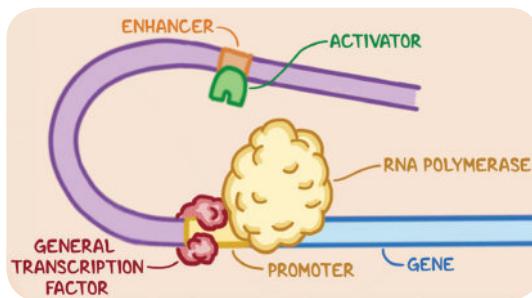


**Figure 41.11** The lac operon. β-galactosidase breaks down lactose into glucose and galactose; β-galactosidase permease allows lactose to enter the cell; β-galactosidase transacetylase's function is not clearly understood.

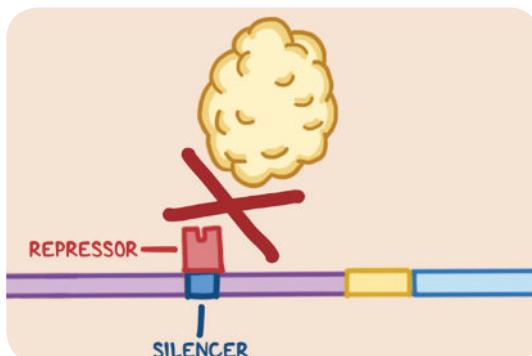
# GENE REGULATION

[osms.it/gene-regulation](http://osms.it/gene-regulation)

- Natural regulation of gene expression
- Occurs at transcription/post-transcription/translation level
- Transcriptional regulation
  - Epigenetics: chemical modifications activate/silence genes without modifying nucleotide sequence (e.g. by methylation/acetylation of histones)
  - Activators: bind to DNA enhancer → facilitate binding of general transcription factors, recruit histone acetyltransferases
  - Repressors: bind to DNA silencer → prevent RNA polymerase from binding to promoter, recruit histone deacetylases

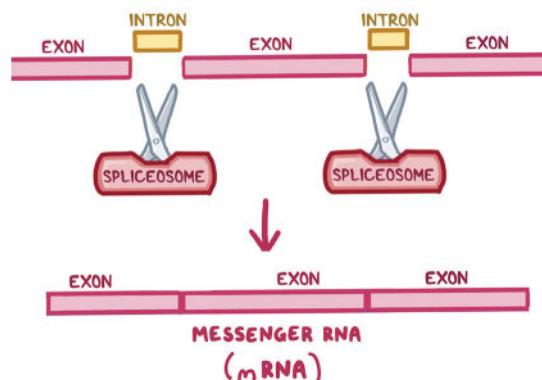


**Figure 41.12** An activator looping DNA in the nucleus.



**Figure 41.13** A repressor protein in the nucleus binding the DNA sequence called the silencer, which is on the same DNA strand as the gene.

- Post-transcriptional regulation
  - Splicing: spliceosomes remove introns (AKA non-coding sequences) from RNA → resulting mRNA codes for proteins more effectively
  - Capping: 5' end of RNA capped with protective 7-methyl-guanine → exonucleases unable to cleave off nucleotides
  - Editing: proteins convert certain nucleotides (e.g. ADAR: adenosine → inosine; CDAR: cytosine → uracil) to create sequence variation
- Translation regulation
  - Mainly occurs during initiation
  - Regulatory proteins (AKA initiation) factors must bind before ribosome can begin translation
  - Conditions like starvation, stress inhibit initiation factors to save energy



**Figure 41.14** Illustration depicting the action of spliceosomes.

# GEL ELECTROPHORESIS & GENETIC TESTING

[osms.it/gel-electrophoresis-genetic-testing](https://osms.it/gel-electrophoresis-genetic-testing)

- Method of separating, analyzing macromolecules (e.g. DNA, RNA, proteins), their fragments based on size, charge

## Apparatus

- Clear box filled with gel, often agarose
  - Small depressions (AKA "wells") at one end
  - Sample macromolecules placed separately in wells
- Power source connected to gel

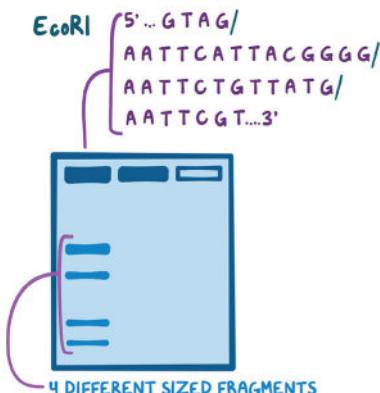
## Premise

- Current applied → macromolecule fragments move through gel
- Charge of fragments determines
  - Direction: opposites attract
  - Speed: greater magnitude → faster
- Fragment size also determines speed
  - Gel contains small pores; smaller size → faster
- Fast-moving fragments travel further over given period → production of multiple bands (one per fragment)

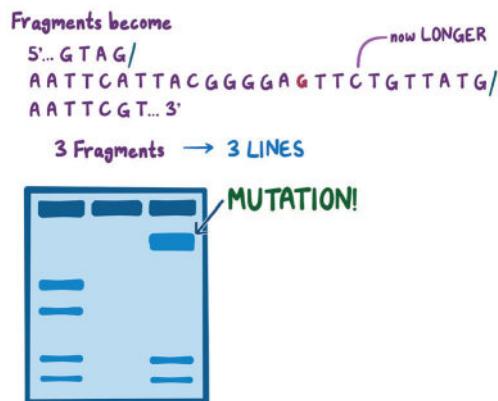
## Applications

- DNA analysis (e.g. genetic fingerprinting)
  - DNA chopped up with restriction enzymes (e.g. EcoRI cuts at GAATTC)
  - Fragments poured into wells, current applied
  - Fragments move towards positive terminal, form bands at isoelectric point
- Identifying DNA mutations
  - Mutation → restriction enzymes create different fragments → bands change
  - Smaller fragments → bands are further apart
  - More abundant fragments → bands (thicker, brighter)
- Other applications: estimation of molecule size, macromolecule separation

### NO MUTATION



### MUTATION A → G



**Figure 41.15** Identifying DNA mutations using EcoRI. A mutation in a single nucleotide from A to G in the EcoRI binding site prevents the enzyme from binding and cutting at that location. Now, in gel electrophoresis, there will be only three lines (instead of four) and one fragment will be longer, indicating that the DNA contains a mutation.

# POLYMERASE CHAIN REACTION

[osms.it/polymerase-chain-reaction](https://osms.it/polymerase-chain-reaction)

- Technique used to amplify desired DNA segment
- Based on DNA melting, enzyme-driven DNA replication
- Takes place in thermal cycler
- Four essential components
  - Template DNA: strand to be replicated
  - Nucleotides: building blocks of DNA
  - Primers: short complementary DNA strands to the 3' end of each strand
  - DNA polymerase: enzyme that synthesizes DNA from nucleotides (e.g. Taq polymerase)

## Process

- Denaturation: sample heated to 96°C/205°F → bonds between DNA strands separate, forming two template strands
- Annealing: sample cooled to 55°C/131°F → primers bind to template strands
- Extension: sample heated to 72°C/162°F → Taq polymerase synthesizes complete complementary DNA strands, starting from end of each primer

## Applications

- Cloning DNA into plasmids, replicating DNA for analysis (e.g. research and practice)



# NOTES

## TRANSCRIPTION, TRANSLATION, & REPLICATION

# DNA STRUCTURE

[osms.it/DNA-structure](https://osms.it/DNA-structure)

## DNA (DEOXYRIBONUCLEIC ACID)

- Two polynucleotide chains (double helix shape)

- Pyrimidines: cytosine (C), thymine (T) for DNA, uracil (U) for RNA
  - Mnemonic: CUT the PYE

## Nucleotides

- 5-carbon sugar, phosphate group, nitrogenous base

## Sugar

- Deoxyribose in DNA, ribose in RNA

## Nucleobases

- Purines: adenine (A), guanine (G)
  - Pure silver: purines (pure), adenine, guanine (AG)



## MNEMONIC: CUT the PYE

### Pyrimidines

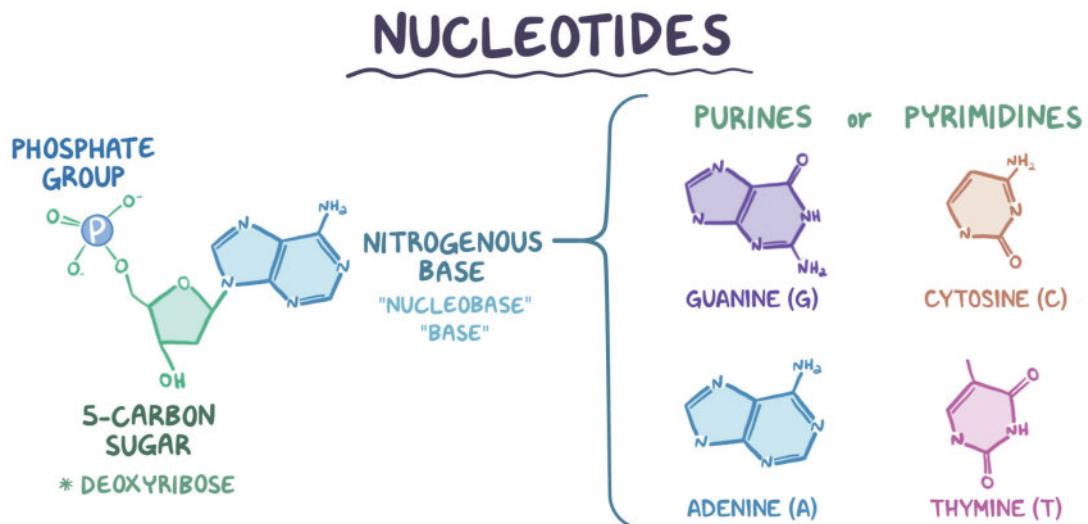
Cytosine

Uracil

Thymine

The

PYrimidinEs



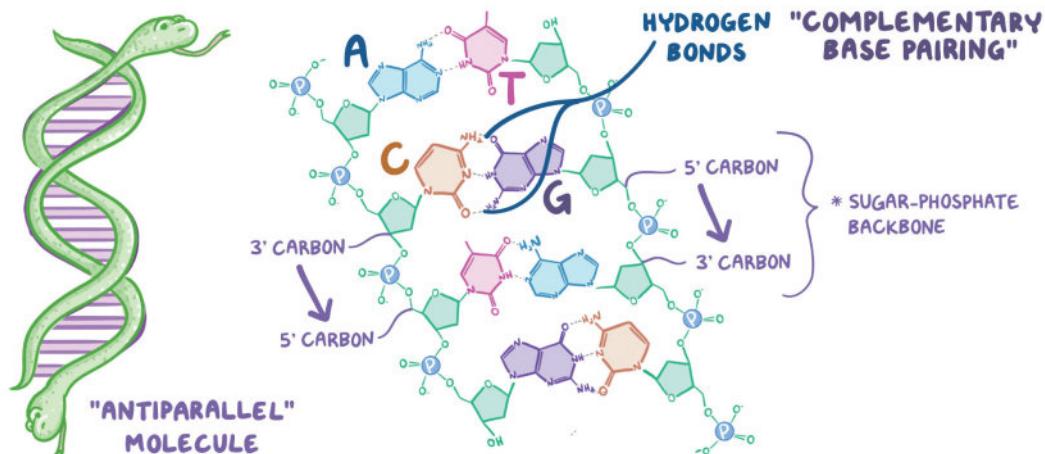
**Figure 42.1** Nucleotides consist of a phosphate group, 5-carbon sugar (deoxyribose for DNA) and a nitrogenous base. The base can be a purine, which has two rings (adenine, guanine), or a pyrimidine, which has one ring (cytosine, thymine).

## Nucleotide binding and bonding

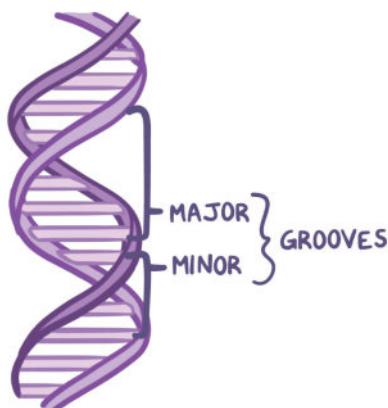
- Nucleotides bind using sugar, phosphate groups (phosphate group on 5<sup>th</sup> carbon of sugar binds covalently to 3<sup>rd</sup> carbon of sugar) → sugar-phosphate backbone
- Nucleotides form hydrogen bonds with bases on opposing strand
  - Complementary base pairing: A pairs with T/U (two hydrogen bonds), C pairs with G (three hydrogen bonds)

## DNA structure and packing

- Strands coil around each other once every 10 base pairs → major, minor grooves
- In order to be packed tightly, DNA wrapped around histones (positive charge attracts to negative charge of phosphate backbone) → nucleosomes
- Nucleosomes further packed as chromatin fibers
  - Euchromatin: loosely packed (genes frequently used)
  - Heterochromatin: densely packed (genes rarely used)



**Figure 42.2** Nucleotide binding: phosphate group on 5<sup>th</sup> carbon of sugar on one nucleotide (called 5 prime carbon) binds covalently to 3<sup>rd</sup> carbon of sugar on another nucleotide (called 3 prime carbon). This gives each DNA strand a sugar-phosphate backbone and a direction (5' to 3' and 3' to 5'). Nucleotide bonding: nucleotide bases form hydrogen bonds with the complementary base on the opposing strand, A with T (U in RNA) and C with G.



**Figure 42.3** Major and minor grooves: larger/smaller spaces between DNA strands where proteins can bind to regulate functions.



**Figure 42.4** DNA wraps around histone proteins to form nucleosomes, which pack tighter again to form chromatin fibers.

# DNA REPLICATION

[osms.it/DNA-replication](https://osms.it/DNA-replication)

- Occurs in S phase of cell cycle (before cell division)
- 46 chromosomes duplicated → each daughter cell gets genetic material
- DNA replication semiconservative → each strand of double helix template

## PROCESS

### Initiation

- Pre-replication complex seeks origin of replication, DNA helicase splits strands → replication fork
  - Single-stranded DNA binding proteins improve stability of lone strands
  - DNA topoisomerase prevents overwinding of later DNA

### Elongation

- RNA primase creates multiple RNA primers → randomly bind → DNA polymerase adds complementary nucleotides in 3', 5' direction
  - Forms single leading strand
  - Forms single lagging strand by attaching (with DNA ligase) multiple Okazaki fragments

### Termination

- DNA polymerase leaves strand at telomere (TTAGGG nucleotide sequences)
- **Hayflick limit:** maximum number of times cell's DNA can be replicated
  - Due to repeated shortening of telomeres during termination step

## DNA CLONING

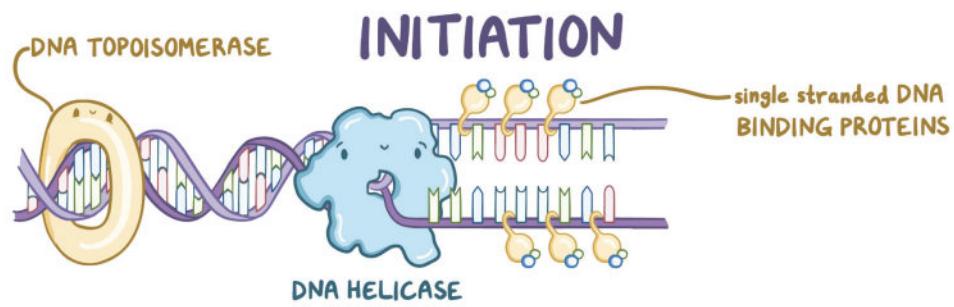
- Technique used to duplicate segment of DNA within host organism
- Uses "plasmids": genetic structures outside of chromosomes, replicate independently

### Process

- Extract desired DNA segment using specific restriction enzymes
- Paste segment into plasmid with DNA ligase → "recombinant DNA"
- Insert plasmid into host organism (e.g. *E. coli*), encouraging uptake with shock (e.g. heat)
- Identify bacteria carrying plasmid with antibiotics (plasmids given antibiotic resistance gene)
- Leave bacteria to replicate DNA segment, mass-manufacture protein(s)

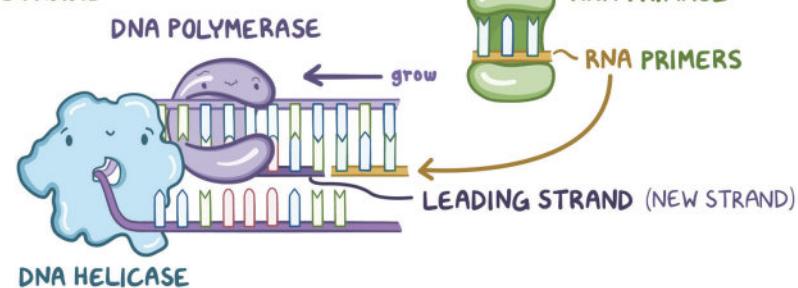
### Applications

- Producing biopharmaceuticals (e.g. insulin), gene therapy (e.g. cystic fibrosis)

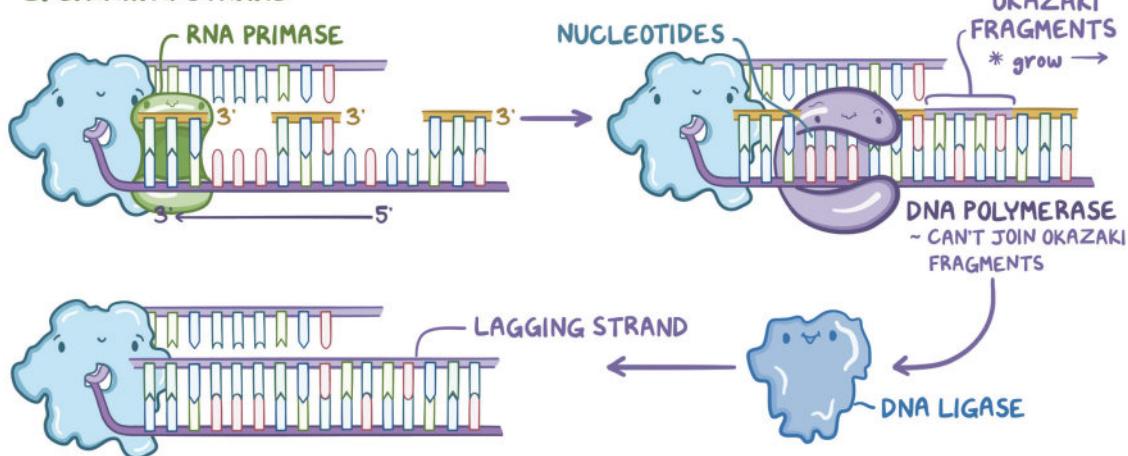


## ELONGATION

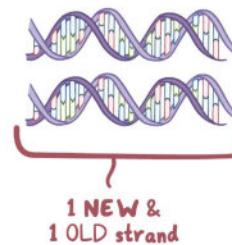
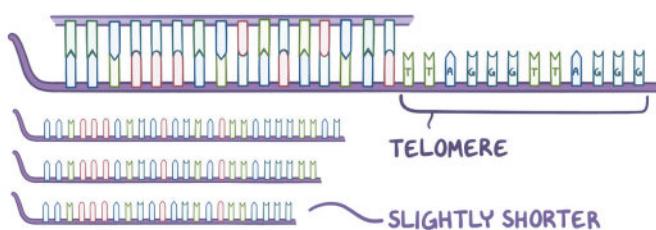
### A. LEADING STRAND



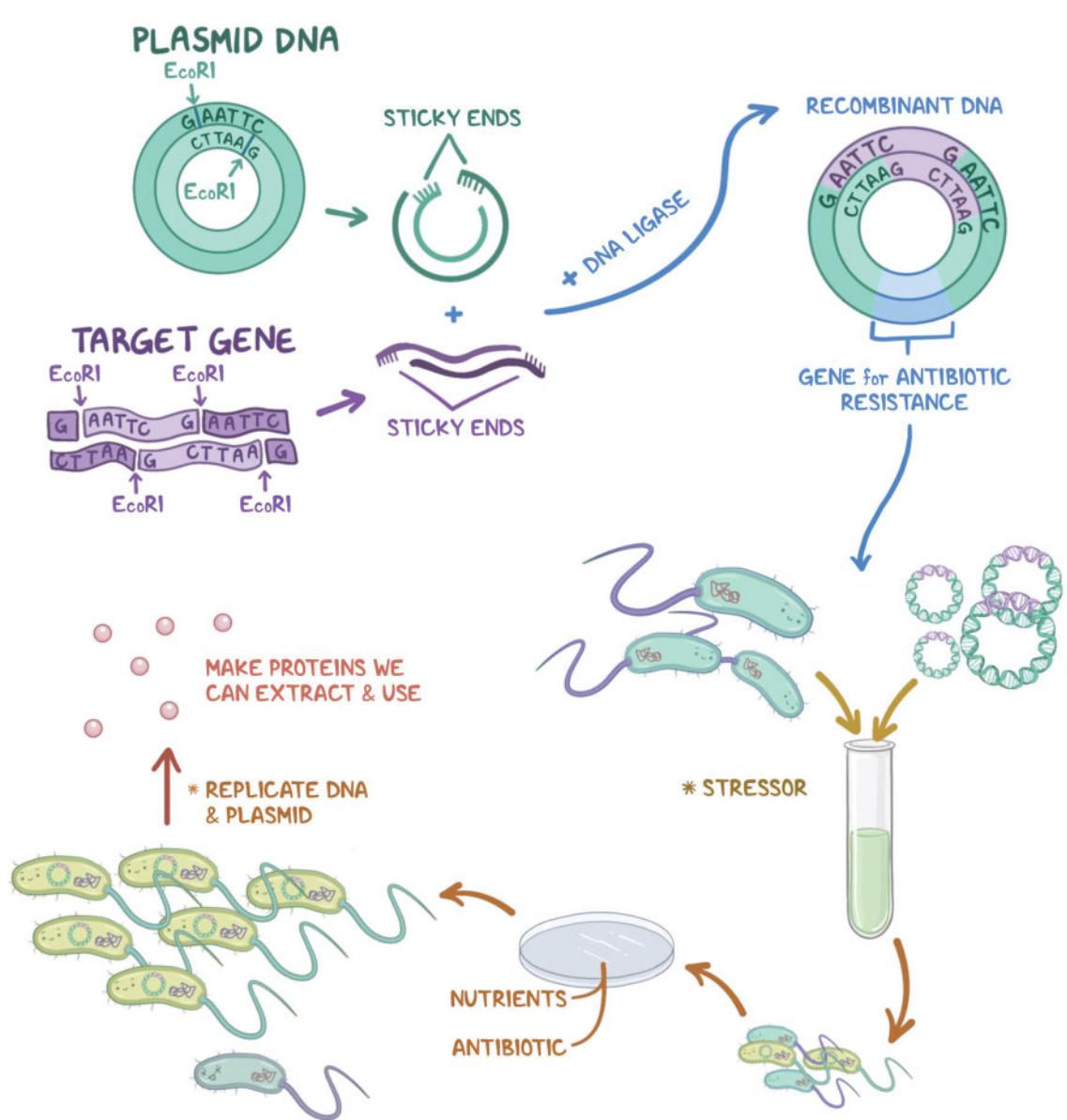
### B. LAGGING STRAND



## TERMINATION



**Figure 42.5** Three steps of DNA replication: initiation, elongation, and termination. DNA replication results in two sets of identical DNA, each containing one old strand and one new one.



**Figure 42.6** DNA cloning. Restriction enzyme (in this case, EcoRI) cleaves a known sequence surrounding a target gene and a plasmid, creating pieces with sticky ends. When DNA ligase is added, these pieces form recombinant DNA (plasmid containing target gene), as well as a gene for antibiotic resistance. A host, in this case E. coli, is combined with recombinant plasmids and subjected to a stressor so that some bacteria take up plasmid. Bacteria are allowed to replicate on plate containing antibiotic, so that only ones that have taken up plasmid can survive. These bacteria produce desired protein from target gene in plasmid.

# TRANSCRIPTION

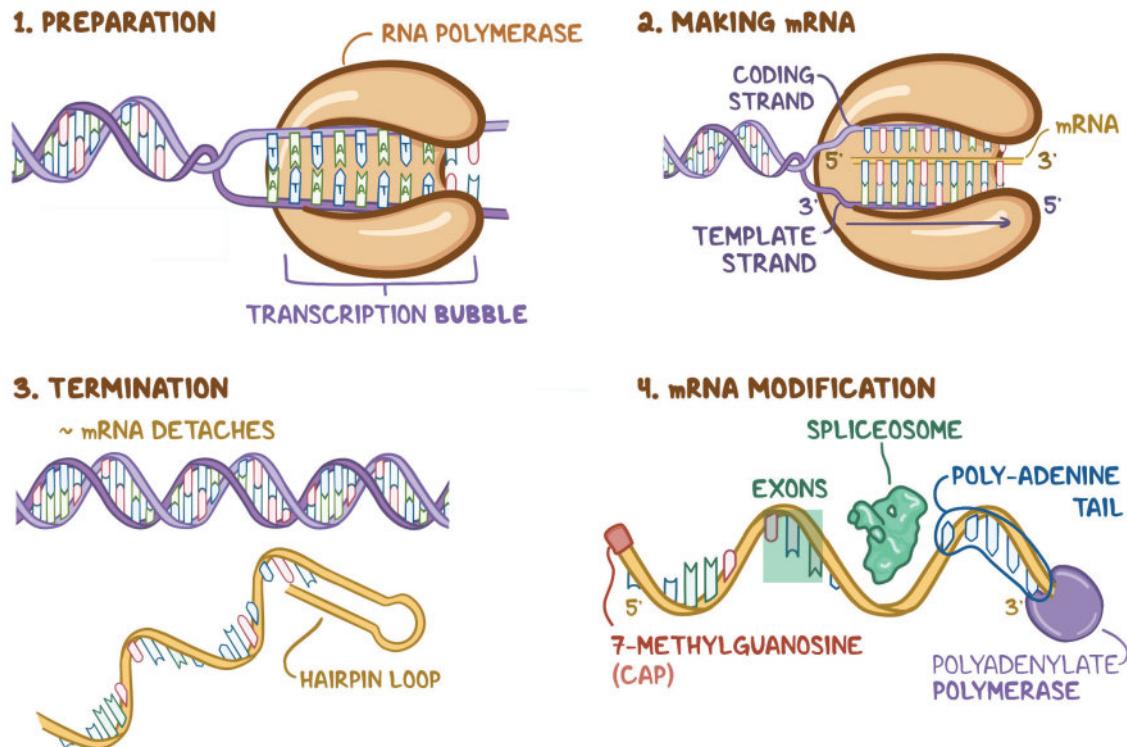
[osms.it/transcription](https://osms.it/transcription)

- First step in creating protein from gene
- Gene read, copied on individual messenger RNA (mRNA)

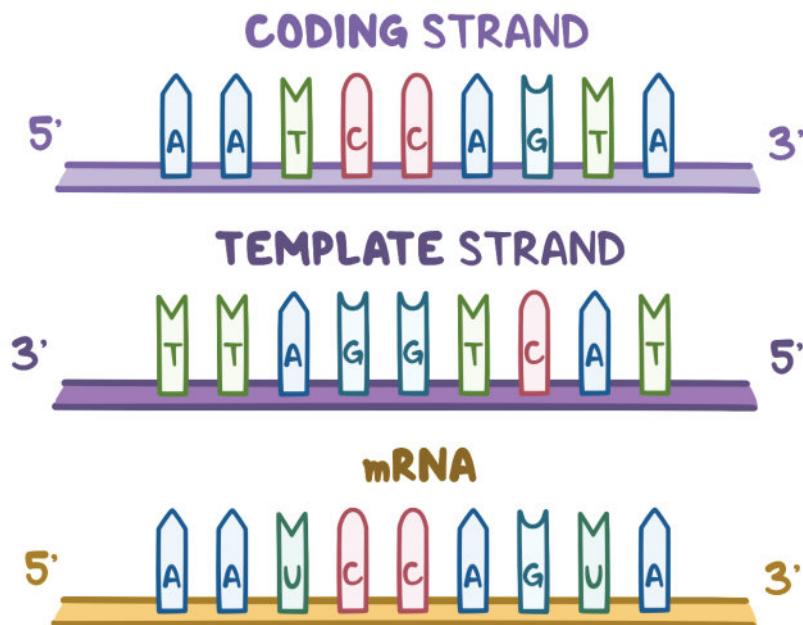
## PROCESS

- DNA unpacked from chromatin, undergoes dehelicization
- Promoter region identifies starting point for transcription (e.g. TATA box)
- RNA polymerase shears hydrogen bonds between two strands → transcription bubble
- RNA polymerase follows template strand to assemble mRNA molecule (complementary to template strand)

- Hydrogen bonds reform on nucleotides (already transcribed)
- Termination sequences contains two complementary sequences → resulting mRNA binds with itself forming hairpin loop
- RNA polymerase detaches, DNA closes back up
- Polyadenylate polymerase adds 7-methyl guanosine cap to 5', polyadenine tail to 3' end of mRNA
- Spliceosomes remove introns (don't code proteins) to leave behind exons (do code proteins)
- Resulting mRNA processed by ribosome to create desired protein (translation)



**Figure 42.7** Transcription. 1: DNA unpackaging, dehelicization; promoter region identified (TATA box); RNA polymerase shears hydrogen bonds between strands → transcription bubble. 2: RNA polymerase assembles mRNA strand complementary to template strand. Hydrogen bonds reform between DNA nucleotides already transcribed. 3: Termination sequence causes mRNA to form hairpin loop, detach. 4: Cap and tail added, introns spliced out.



**Figure 42.8** One strand of DNA is called the coding strand and the other is called the template strand. They have complementary nucleotide sequences. RNA polymerase builds an mRNA molecule by reading the template strand and adding complementary nucleotides. Therefore, the mRNA will have the same sequence and directionality as the coding strand, only with U instead of T.

## TRANSLATION

[osms.it/translation](http://osms.it/translation)

- Second step in creating protein from gene
- Ribosomes assemble protein from mRNA template produced in transcription

### PROCESS

- mRNA floats out of nucleus through pore
- **Initiation:** ribosome grabs mRNA, finds start codon (e.g. AUG)
- **Elongation:** ribosome moves along mRNA, producing specific amino acid for each codon
- **Termination:** ribosome reaches stop codon, releases polypeptide (e.g. UGA)

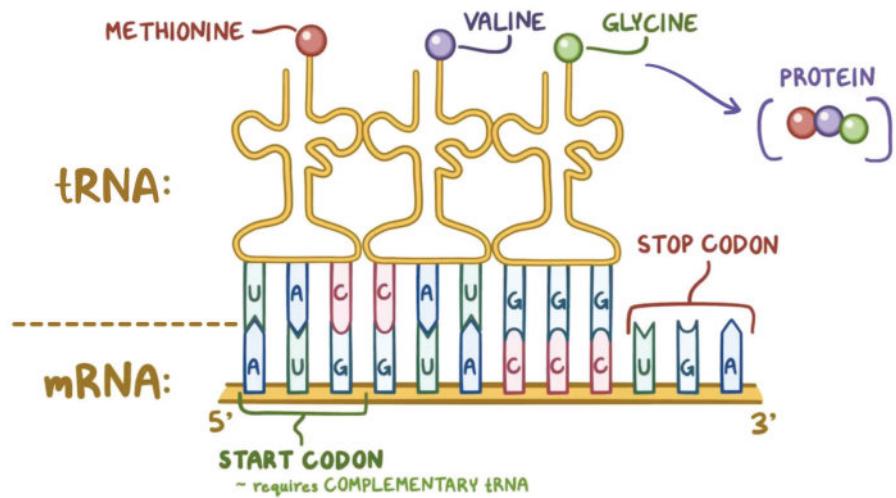
- Binds to ribosome on aminoacyl/peptidyl/exit site
  - Aminoacyl: binds transfer RNA (tRNA) with complementary mRNA codon
  - Peptidyl: holds tRNA with polypeptide
  - Exit: holds tRNA after amino acid released



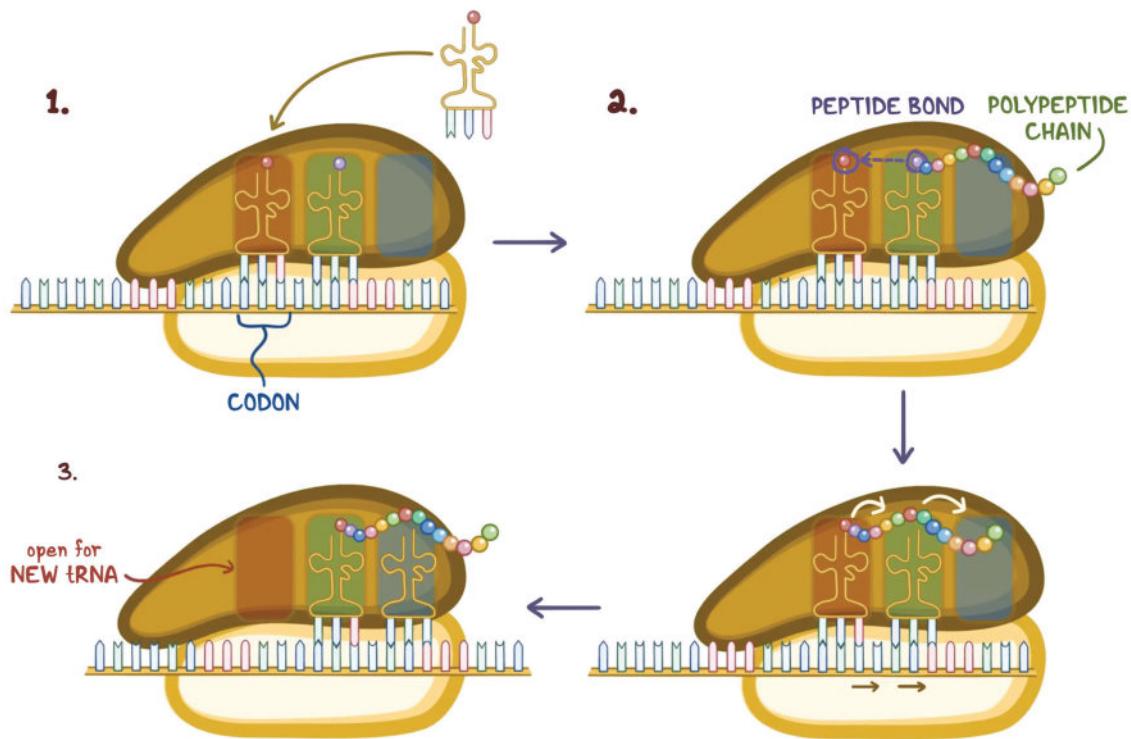
**Figure 42.9** Ribosome binding sites.

### TRANSFER RNA (tRNA)

- Finds, carries amino acids to ribosome
- Three-letter coding sequence (complementary to mRNA)



**Figure 42.10** One strand of DNA is called the coding strand and the other is called the template strand. They have complementary nucleotide sequences. RNA polymerase builds an mRNA molecule by reading the template strand and adding complementary nucleotides. Therefore, the mRNA will have the same sequence and directionality as the coding strand, only with U instead of T.



**Figure 42.11** Translation extending an existing polypeptide chain.

- 1: tRNA with amino acid and codon complementary to that of mRNA binds at ribosome A site.
- 2: Peptide bond forms between amino acid on new tRNA and tRNA in P site holding polypeptide chain, polypeptide chain is transferred to tRNA in A site.
- 3: Everything moves by one site. A site is now open for a new tRNA.

# CELL CYCLE

[osms.it/cell-cycle](https://osms.it/cell-cycle)

- Sequence of events between formation, division of somatic cell
- Two phases
  - Interphase: preparatory phase; cell performs basic functions, replicates DNA
  - Mitosis: cellular division

## GO (G-ZERO) PHASE

- Cells function but not dividing/preparing to divide
- Considered outside cell cycle

## INTERPHASE

- Three subphases: G1, S, G2 phases

### Gap/Growth 1 (G1) phase

- Longest phase
- Cell grows while organelles function as usual

- Terminates with G1 checkpoint
  - Cells with damaged DNA → G0 phase/ apoptosis

### Synthesis (S) phase

- DNA replicated (identical chromatids created)

### Gap/Growth 2 (G2) phase

- Organelles duplicated
- Terminates with G2 checkpoint

## MITOSIS (M) PHASE

- Cell divides into two daughter cells

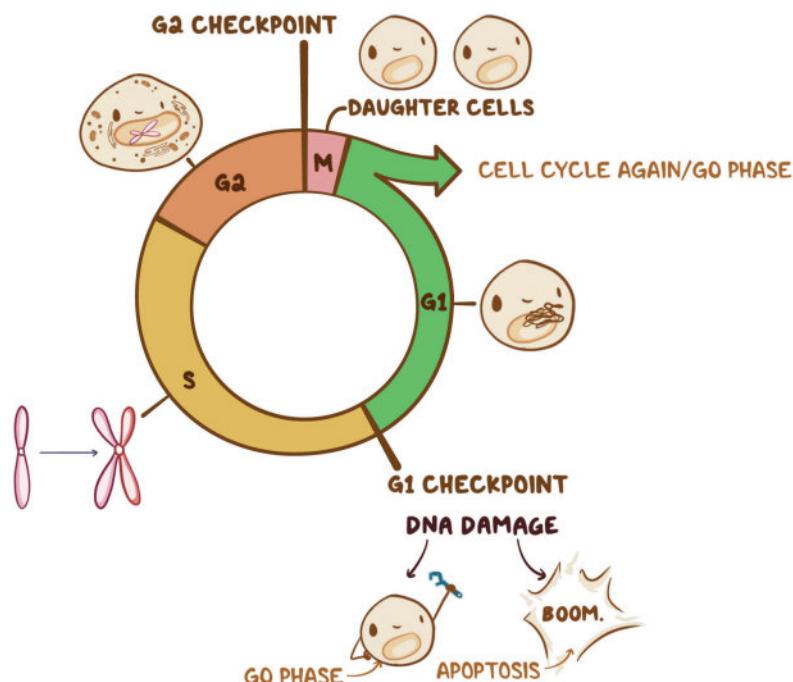


Figure 42.12 Cell cycle summary.

# MITOSIS & MEIOSIS

[osms.it/mitosis-and-meiosis](http://osms.it/mitosis-and-meiosis)

- Two processes of cell division

## MITOSIS

- Division of cell into two identical daughter cells
- Part of cell cycle
- Consists of prophase, metaphase, anaphase, telophase

### Prophase

- Chromatin fibers condense
- Centrioles align chromosomes between centrosomes

### Metaphase

- Prometaphase: nuclear membrane, nucleolus disintegrate
- Metaphase: chromosomes align along metaphase plate, spindle fibers attach to kinetochores

### Anaphase

- Centrosomes pull on spindle fibers to separate chromatids

### Telophase

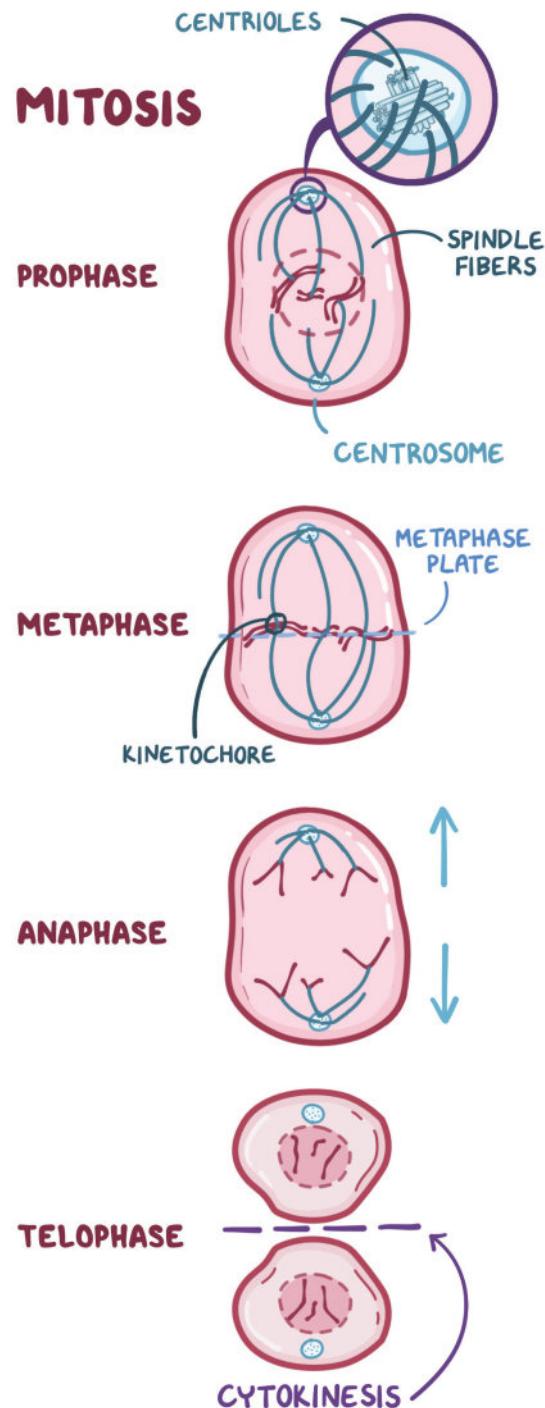
- New nuclear envelopes form

## MEIOSIS

- Division of cell into four haploid daughter cells
- Consists of
  - Meiosis I: prophase I, metaphase I, anaphase I, telophase I
  - Meiosis II: prophase II, metaphase II, anaphase II, telophase II

### Meiosis I

- Prophase I
  - Leptotene: 46 chromosomes condense, nuclear membrane disintegrates
  - Zygote: chromosomes find homologues, bind, forming tetrads (AKA synapsis)

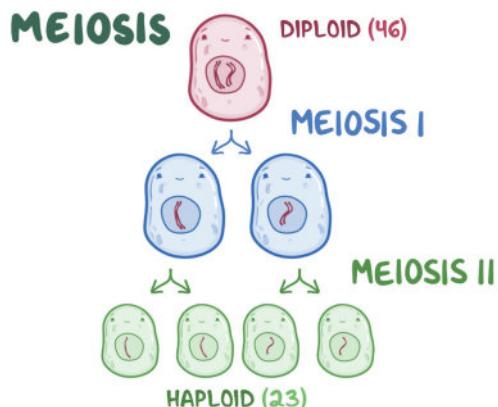


**Figure 42.13** Stages of mitosis: division of one cell into two identical daughter cells.

- Pachytene: homologous chromosomes exchange genetic material (AKA crossing-over)
- Diplotene: homologous chromosomes uncoil, slide toward ends (AKA chiasmata)
- Diakinesis: terminalization completed
- Metaphase I
  - Tetrads migrate to metaphase plate
- Anaphase I
  - Tetrads split up
  - Chromosomes pulled to each pole by spindle fibers
  - Diploid cell → haploid cell
- Telophase I
  - Cleavage furrow appears, cytokinesis occurs
- Followed by interphase without chromosome duplication in S phase

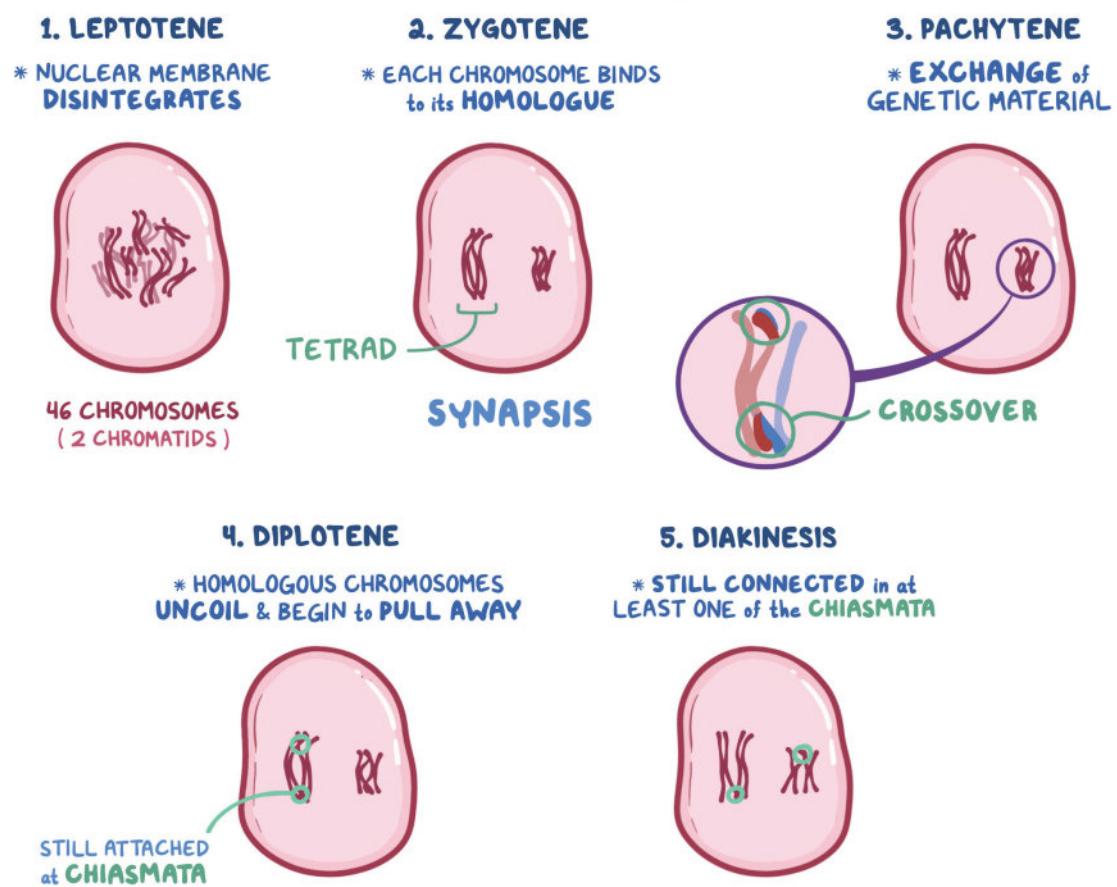
## Meiosis II

- Meiosis II progresses exactly as mitosis
  - Two haploid cells → four haploid cells
  - Same phase names



**Figure 42.15** Meiosis produces haploid daughter cells with 23 chromosomes each.

## MEIOSIS I: PROPHASE I



**Figure 42.14** Steps of meiosis I, prophase I.

# GENETIC MUTATIONS & REPAIR

osms.it/DNA-mutations  
osms.it/DNA-damage-and-repair

## DNA MUTATIONS

- Alterations in nucleotide (A, T, G, C) sequence of  $\geq$  one gene
  - Affect somatic cells (AKA non-reproductive cells), gametes  $\rightarrow$  germline mutations
  - Arise spontaneously/due to mutagens

- Multiples of three  $\rightarrow$  nonframeshift mutation
  - Reading frame displaced by entire codon  $\rightarrow$  remaining amino acids unchanged  $\rightarrow$  similar resulting protein
- **Frameshift mutation:** resulting protein abnormally long/short, most likely nonfunctional

## SMALL-SCALE MUTATIONS

- Single gene
- **Substitutions:** nucleotide replaced by another
- May result in
  - **Silent mutation:** same amino acid
  - **Missense mutation:** different amino acid (e.g. sickle cell disease)
  - **Nonsense mutation:** stop codon

## INSERTIONS & DELETIONS

- Nucleotide added/removed from sequence

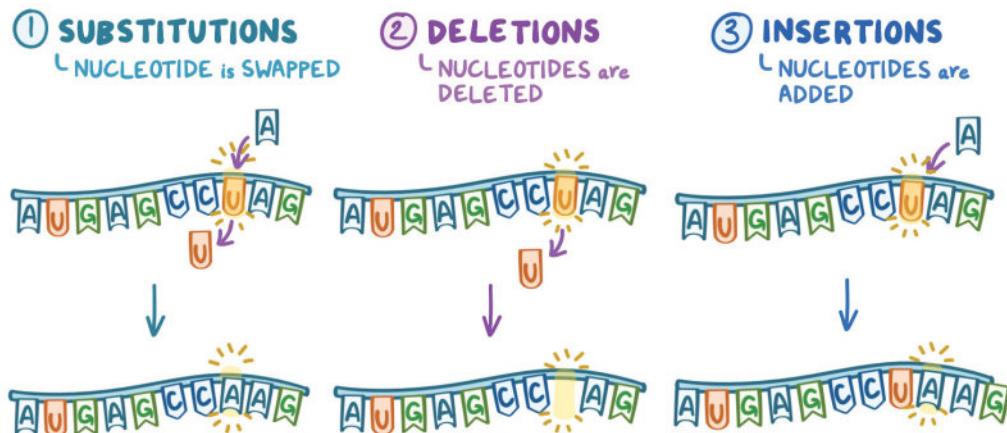
## LARGE-SCALE MUTATIONS

- Often occur due to errors in gamete formation

### Abnormal number of chromosomes

- **Aneuploidy**
  - Additional chromosomes (e.g. Down syndrome)
  - Missing chromosomes (e.g. Turner's syndrome)
- **Polypliody**
  - Increased number of chromosomes per set (e.g. triploidy)

## SMALL MUTATIONS (SINGLE GENE)

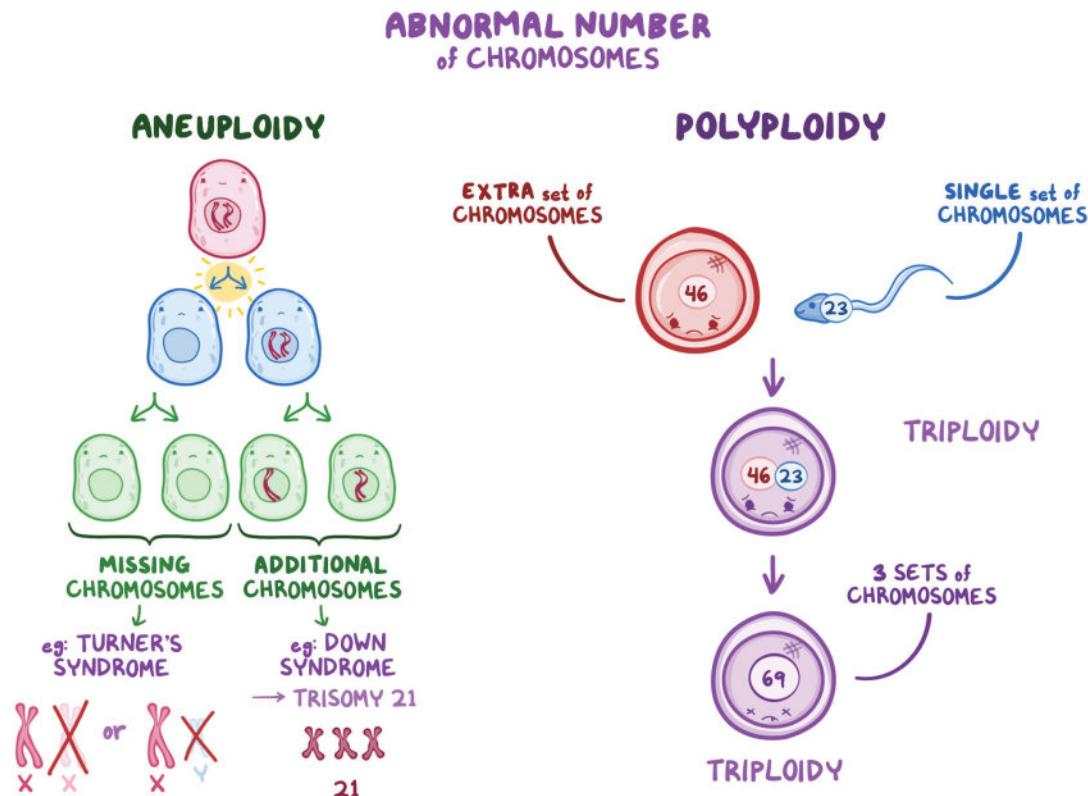


**Figure 42.16** Small-scale mutations include: substitutions, deletions, and insertions. They may have a small or large effect on protein function depending on how the new nucleotide affects the translation of the codon sequence into amino acids.

### Structurally abnormal

- Movement of sections of chromosomes
- Deletion: part of chromosome goes missing (e.g. cri du chat syndrome)
- Duplication: part of chromosome duplicated

- Inversion: part of chromosome breaks off, reattaches
- Translocation: parts of two chromosomes switched

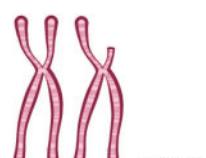


**Figure 42.17** Aneuploidy and polyploidy are types of large-scale mutations which result in an abnormal number of chromosomes.

### STRUCTURAL ABNORMALITIES

#### DELETION

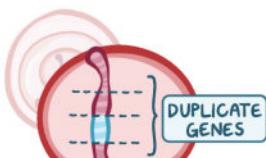
CHUNK of CHROMOSOME goes MISSING



eg: CRI du CHAT or 5p- SYNDROME

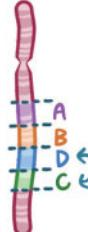
#### DUPLICATION

EXTRA CHUNK of CHROMOSOME ATTACHES to ANOTHER



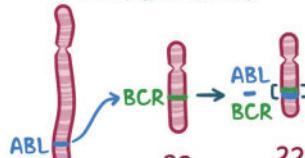
#### INVERSION

CHROMOSOME BREAKS OFF & REATTACHES



#### TRANSLOCATION

PART of 1 CHROMOSOME BREAKS OFF & is EXCHANGED for PART of ANOTHER



eg: PHILADELPHIA CHROMOSOME

**Figure 42.18** Illustration of types of structural abnormalities.

## DNA DAMAGE

- DNA damaged by endogenous, exogenous (environmental) factors
- If damaged DNA cannot be fixed → multiple paths
  - Senescence: stops dividing
  - Apoptosis: programmed cell death
  - Uncontrolled cell division: develops into tumor
- If damaged DNA can be fixed → G0 phase

### Single strand damage

- Causes
  - Endogenous (errors in DNA replication)
  - Exogenous (harmful chemical/physical agents)
- Repaired with mismatch/base excision/nucleotide excision repair
  - Endonucleases cleave damaged segment

- Exonucleases remove damaged segment
- DNA polymerase rebuilds segment
- DNA ligase glues new segment

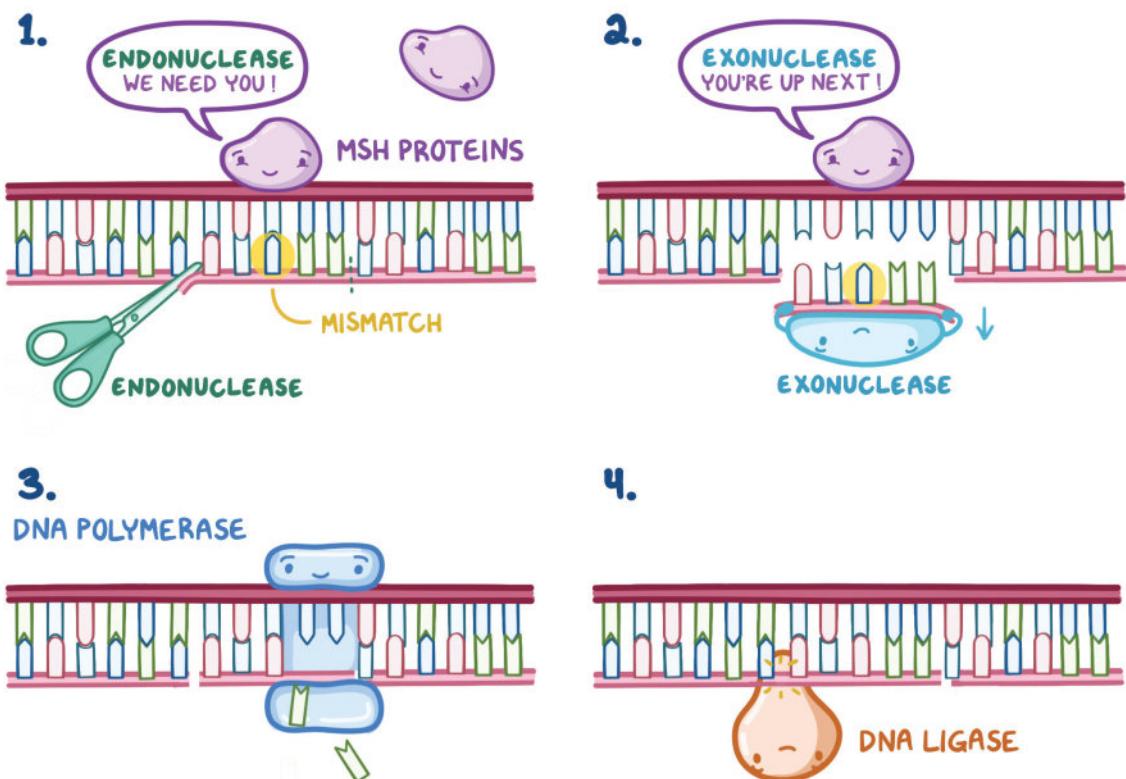
### Double stranded breaks

- May be due to ionizing radiation

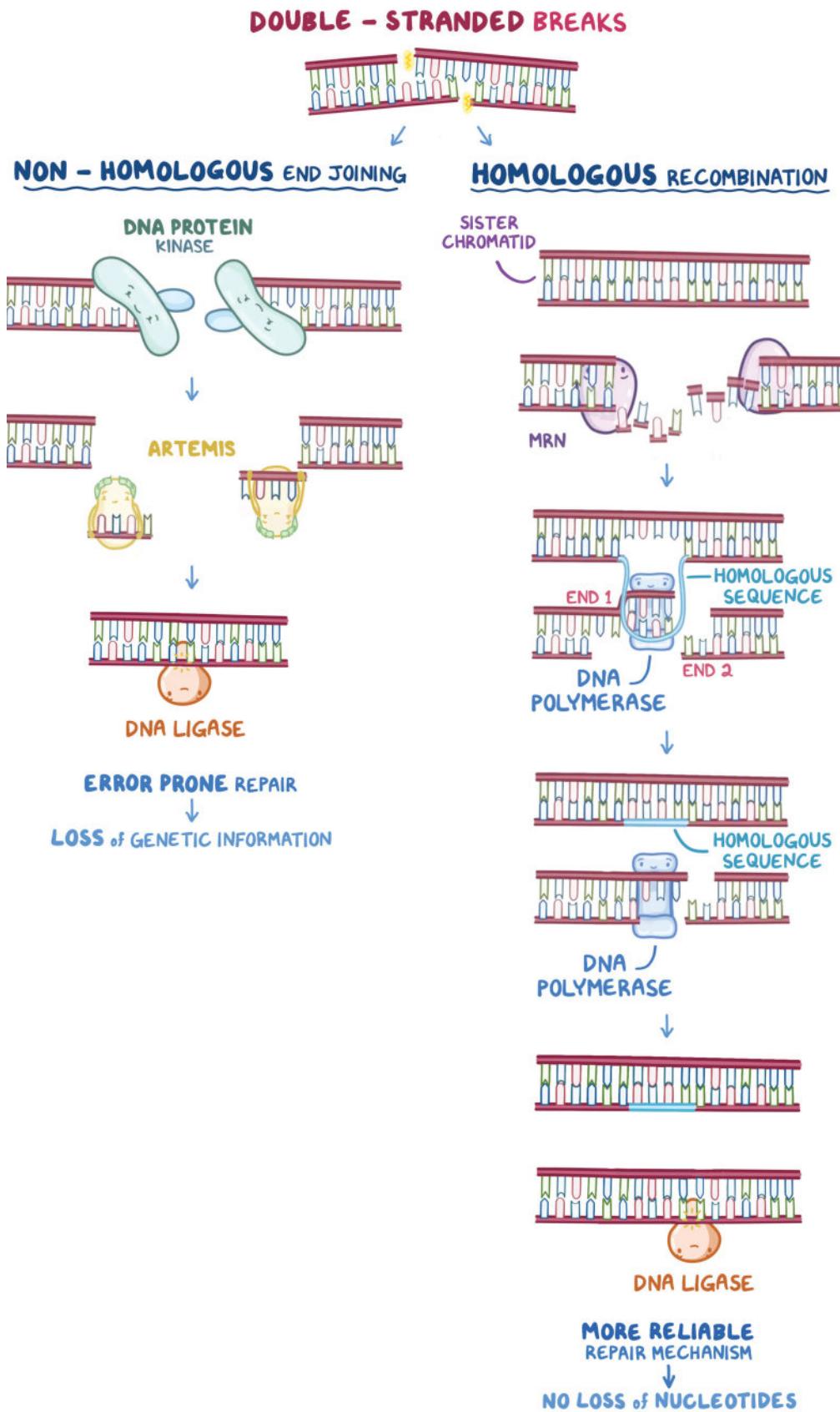
### Repair mechanisms

- Non-homologous end joining
  - DNA protein kinase binds to each end of the broken DNA → artemis cuts off rough ends → ends are rejoined with DNA ligase
- Homologous end joining
  - MRN protein complex binds to each end and removes affected nucleotides → DNA polymerase copies genetic information from sister chromatid

## MISMATCH REPAIR



**Figure 42.19** Repair of a mismatched nucleotide on a newly synthesized DNA strand. **1:** Endonucleases cleave either side of damaged segment; **2:** Exonucleases remove damaged segment; **3:** DNA polymerase rebuilds segment; **4:** DNA ligase connects new segment to strand.



**Figure 42.20** Two repair mechanisms for double-stranded breaks: non-homologous end joining and homologous recombination.



# NOTES

## BLOOD COMPONENTS & FUNCTION

# BLOOD COMPONENTS

[osms.it/blood-components](https://osms.it/blood-components)

### BLOOD COMPONENT SEPARATION

- Blood components separate by density in centrifuge
  - Heaviest layer: erythrocytes
  - Middle layer: buffy coat
  - Lightest layer: plasma

### ERYTHROCYTES

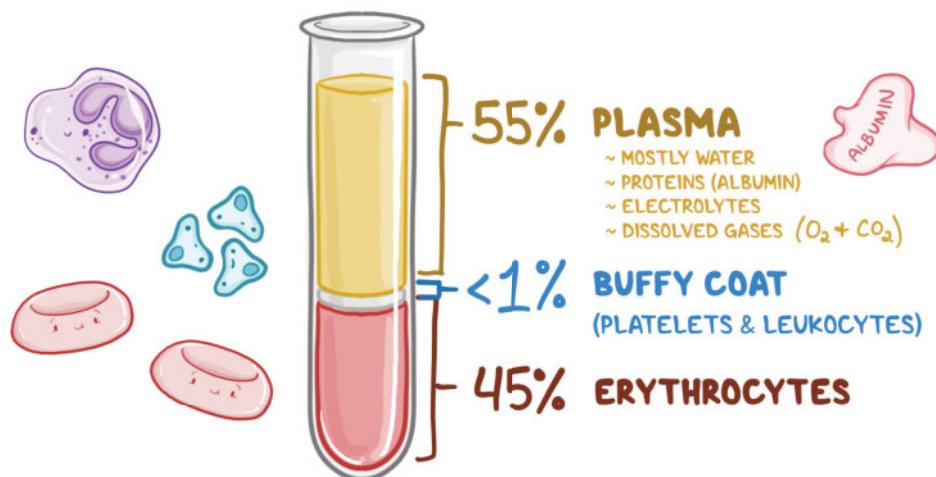
- Comprise 45% (hematocrit) of total blood volume
- Carry  $O_2$  to tissues; bring  $CO_2$  to lungs
- Biconcave discs (depressed center)
  - Fit through vessels, ↑ surface area (for gas exchange)
- No organelles
  - ↑ space for hemoglobins

### BUFFY COAT

- Comprises < 1% of total blood volume
- Contains platelets, leukocytes
- Platelets clump together → seal damaged blood vessels
- Leukocytes ward off pathogens, destroy cancer cells, neutralize toxins

### PLASMA

- Comprises 55% of total blood volume
- No cells: 90% water + proteins, electrolytes, gases
- Albumin: maintains oncotic pressure, acts as transport protein
- Globulins: antibodies, transport proteins
- Fibrinogen: involved in clot formation (helps platelets attach)
- Electrolytes: include sodium, potassium, calcium, chloride, carbonate



**Figure 43.1** Blood components and their relative proportions.

# PLATELET PLUG FORMATION (PRIMARY HEMOSTASIS)

[osms.it/platelet-plug-formation-primary-hemostasis](https://osms.it/platelet-plug-formation-primary-hemostasis)

- Hemostasis: blood-loss prevention
- First two hemostasis steps: platelets clump, form plug around injury site in five steps

## PLATELET PLUG FORMATION STEPS

### 1. Endothelial injury

- Nerves, smooth muscle cells detect injury
- Trigger reflexive contraction of vessel (vascular spasm) → ↓ blood flow, loss
- Secretion of nitric oxide, prostaglandins stop; secretion of endothelin begins → further contraction

### 2. Exposure

- Damage to endothelial cells exposes collagen
- Damaged cells release Von Willebrand factor (binds to collagen)

### 3. Adhesion

- GP1B surface proteins on platelets bind to Von Willebrand factor

### 4. Activation

- Platelet changes shape (forms arms to grab other platelets), releases more von Willebrand factor, serotonin, calcium, ADP, thromboxane A2 (positive feedback loop)
- ADP, thromboxane A2 result in GPIIB/IIIA expression

### 5. Aggregation

- GPIIB/IIIA binds to fibrinogen, links platelets → platelet plug

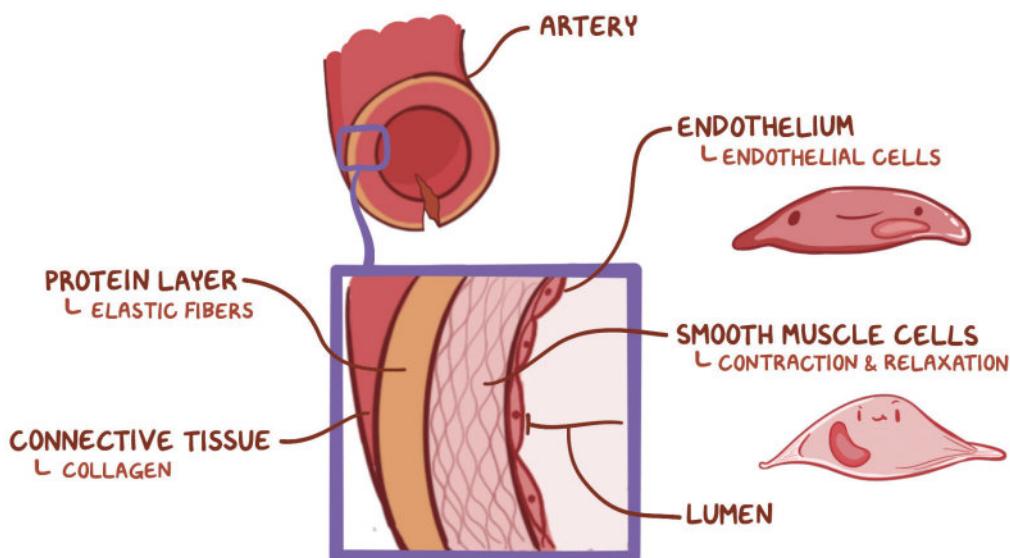


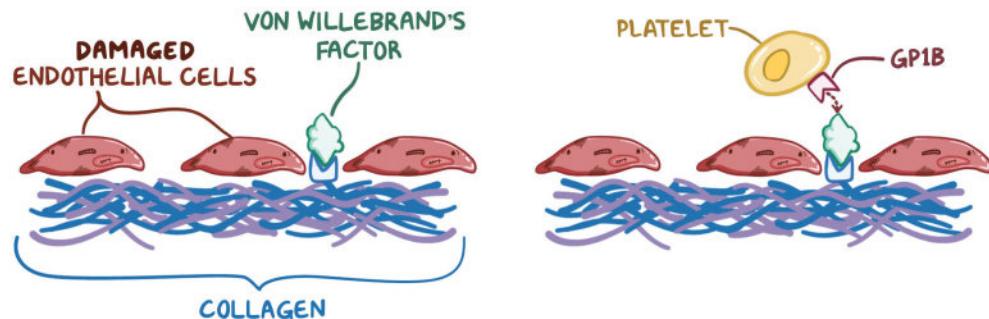
Figure 43.2 Layers of an arterial wall.

## STEPS of PRIMARY HEMOSTASIS

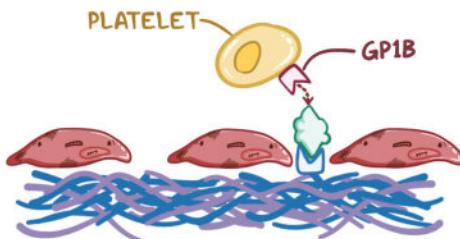
### 1) ENDOTHELIAL INJURY



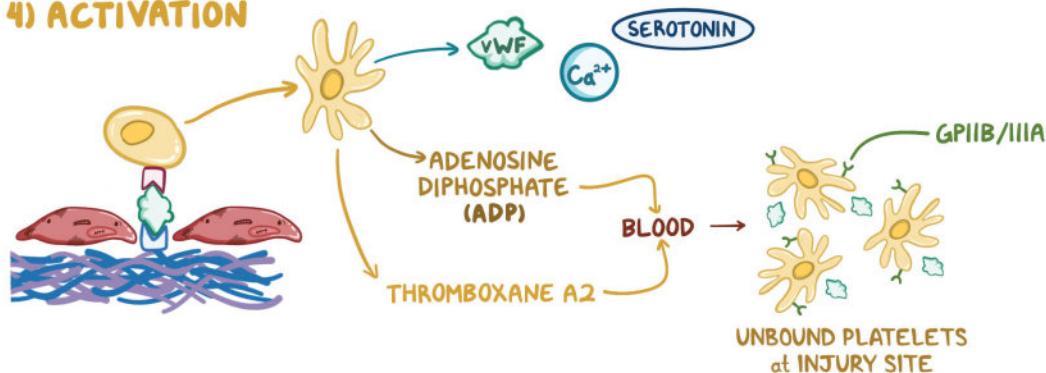
### 2) EXPOSURE



### 3) ADHESION



### 4) ACTIVATION



### 5) AGGREGATION

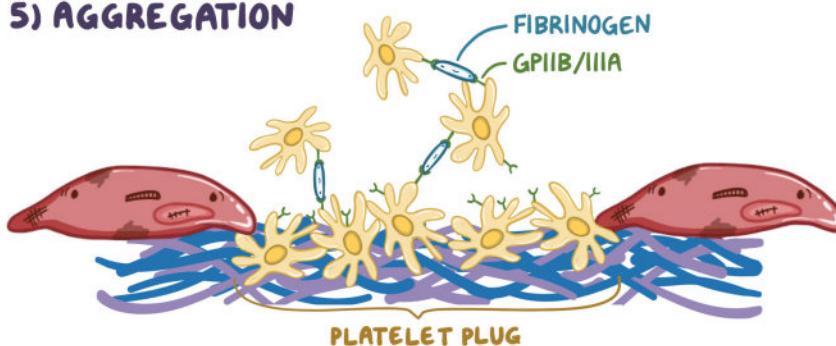


Figure 43.3 Platelet plug formation steps.

# COAGULATION (SECONDARY HEMOSTASIS)

[osms.it/coagulation-secondary-hemostasis](http://osms.it/coagulation-secondary-hemostasis)

- Last two hemostasis steps: clotting factors activate fibrin, build fibrin mesh around platelet plug
- Begins with either extrinsic/intrinsic pathway; factor X activation → coagulation cascade (common pathway)

## EXTRINSIC PATHWAY

- 1.Trauma damages blood vessel, exposes cells under endothelial layer
  - Tissue factor (factor III) embedded in membrane
- 2.Factor VII in blood binds to tissue factor, calcium → VIIa-TF complex

## INTRINSIC PATHWAY

- 1.Circulating factor XII contacts negatively charged phosphates on platelets/ subendothelial collagen → factor XIIa
- 2.Factor XIIa cleaves factor XI → factor XIa
- 3.Factor XIa + calcium cleaves factor IX → factor IXa

- 4.Factor IXa + factor VIIIa (binds to Von Willebrand factor) + calcium → enter the common pathway

## COMMON PATHWAY

- 1.Factor X is cleaved → factor Xa
- 2.Factor Xa cleaves factor V → factor Va
- 3.Factor Xa + factor Va + calcium → prothrombinase complex
  - Prothrombin (factor II) → thrombin (factor IIa)
- 4.Thrombin activates platelets, cofactors (V, VIII, IX); cleaves fibrinogen, stabilizing factor (→ factor XIIIa + calcium → cross-links in mesh)

## COAGULATION TESTS

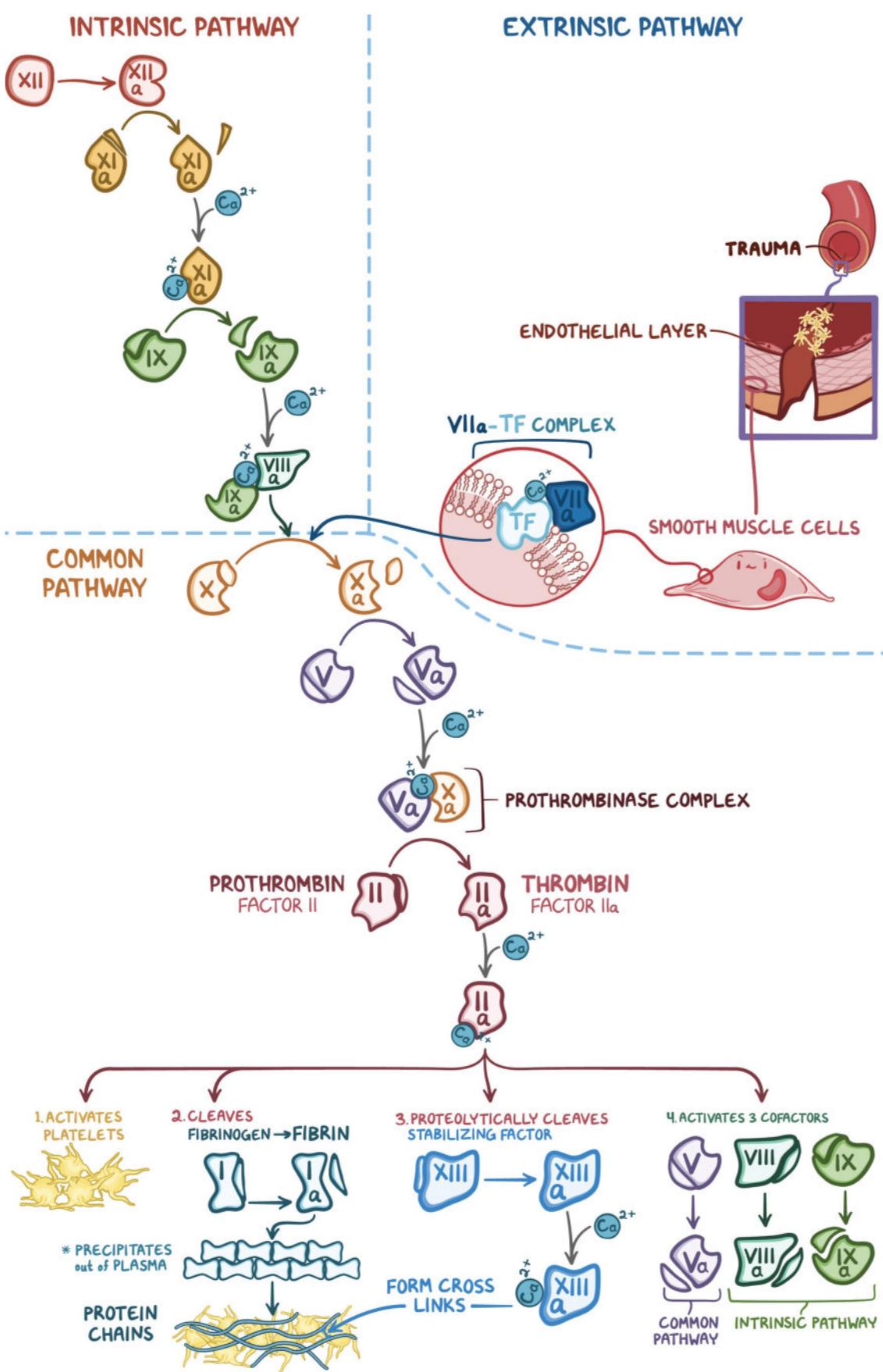
- Prothrombin time (PT): tests extrinsic pathway
- Activated partial thromboplastin time (aPTT): tests intrinsic pathway

# ROLE OF VITAMIN K IN COAGULATION

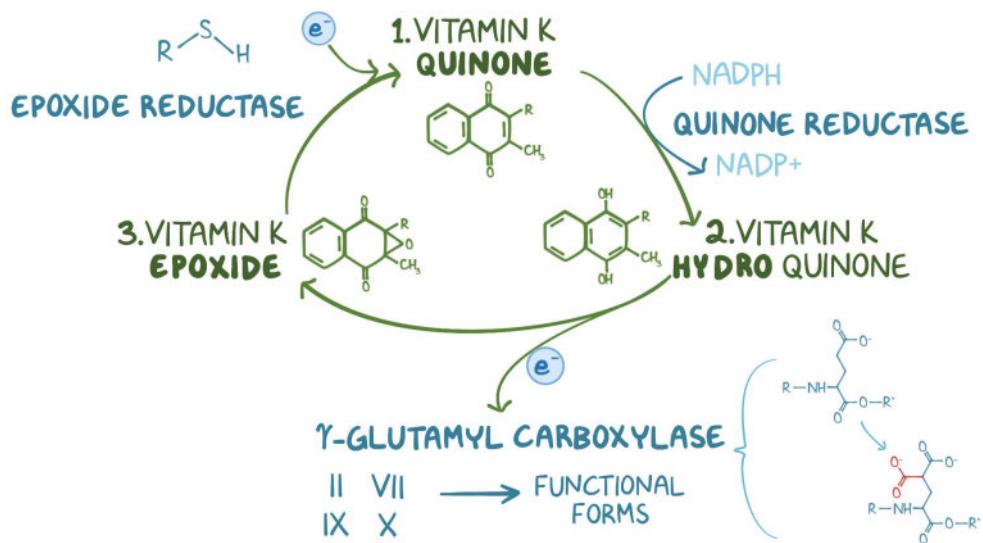
[osms.it/vitamin-k-in-coagulation](http://osms.it/vitamin-k-in-coagulation)

- Vitamin K regulates blood coagulation
  - Converts coagulation factors into mature forms
- 12 coagulation factors: (I–XIII, no factor VI); factors II, VII, IX, X require vitamin K
- Quinone reductase reduces vitamin K quinone (dietary form) into vitamin K hydroquinone
- Vitamin K hydroquinone donates electrons to  $\gamma$ -glutamyl carboxylase, converting

- non-functional forms of II, VII, IX, X into functional forms
  - Adds chemical group made of one carbon, two hydrogens, one oxygen to glutamic acid residues on proteins
- After carboxylation step, vitamin K (as vitamin K epoxide) is converted back into vitamin K quinone via epoxide reductase
- Coagulation factors appear in all coagulation pathways



**Figure 43.4** Coagulation steps, including the intrinsic, extrinsic, and common pathways.



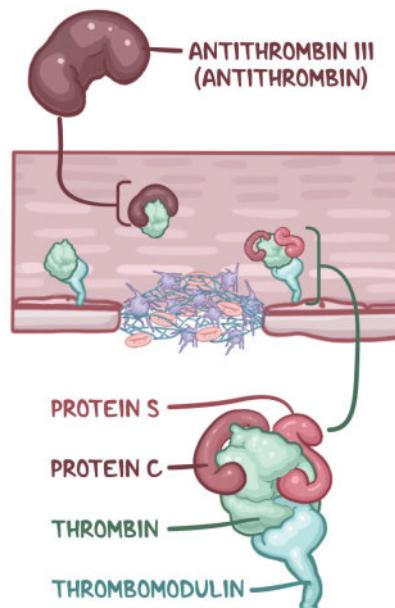
**Figure 43.5** Vitamin K cycle. A single molecule of Vitamin K can be reused many times.

## ANTICOAGULATION, CLOT RETRACTION & FIBRINOLYSIS

[osms.it/clot-retraction-and-fibrinolysis](http://osms.it/clot-retraction-and-fibrinolysis)

### ANTICOAGULATION

- Occurs during primary, secondary hemostasis; regulates clot formation
- Prevents clots from growing too large → block blood flow, form emboli
- Regulation starts with thrombin (factor II)
  - Multiple pro-coagulative functions
  - Proteins C, S bind thrombomodulin-thrombin → cleaves, inactivates factors V, VIII
  - Antithrombin III binds thrombin/factor X → inactivates both (plus factors VII, IX, XI, XII with lower affinity)
- Other factors prevent platelets adhering during primary hemostasis
  - Nitric oxide, prostacyclin → ↓ thromboxane A2



**Figure 43.6** Proteins involved in anticoagulation. Thrombomodulin is found on the surface of intact epithelial cells lining blood vessels.

## CLOT RETRACTION

- Occurs one hour after primary, secondary hemostasis
  - Contracts clot
- Platelets in clot express integrin  $\alpha IIb\beta 3 \rightarrow$  binds to fibrin expressing actin, myosin  $\rightarrow$  lamellipodia contract, fibrin mesh tightens closing wound

## FIBRINOLYSIS

- Occurs two days after primary, secondary hemostasis; degrades clot
- Plasminogen  $\rightarrow$  plasmin (via tissue plasminogen activator)
- Plasmin proteases fibrin  $\rightarrow$  clot dissolves

# BLOOD GROUPS & TRANSFUSIONS

[osms.it/blood-groups-and-transfusions](http://osms.it/blood-groups-and-transfusions)

## BLOOD TRANSFUSIONS

- Blood transfusion: person receives blood/elements of blood (usually through intravenous infusion)
  - Homologous transfusion: anonymous donor
  - Autologous transfusion: self-donor (e.g. in planned surgery)
- Blood is mixed with calcium oxalate to prevent coagulation, refrigerated/frozen for storage

- Immune system produces antibodies against absent glycoproteins
- Type AB: no antibodies  $\rightarrow$  universal recipients
- Type O: no antigens  $\rightarrow$  universal donors

### Rh system

- Determined by presence of Rh protein
  - Rh positive; Rh negative
- Rh+ can receive blood from either group
- Rh- can only receive Rh- blood

## BLOOD TYPING

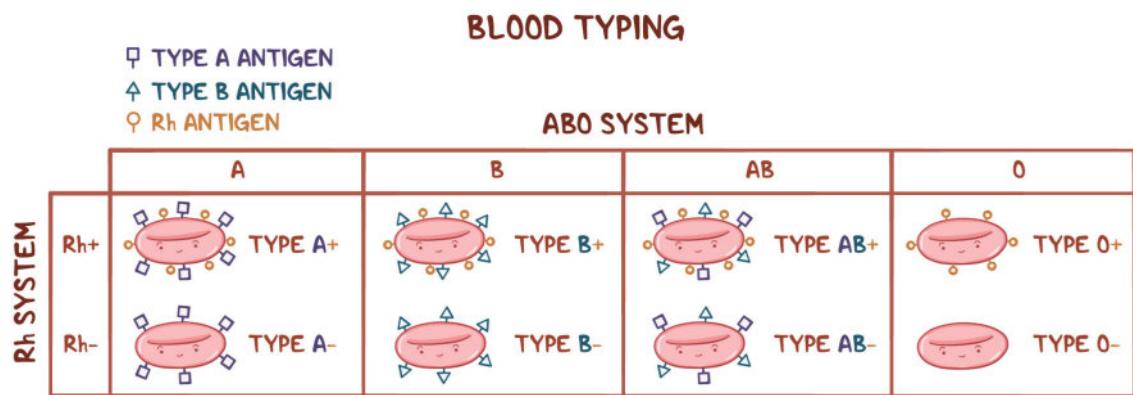
- Transfusion blood types not compatible  $\rightarrow$  autoimmune reaction (hemolytic transfusion reaction)
- Two classification systems (based on presence/absence of proteins)
  - ABO system
  - Rh system

## CROSS MATCHING

- Test to confirm donor's blood is safe for recipient
- Recipient serum is mixed with donor blood
  - Agglutination reaction: cannot receive

### ABO system

- Determined by type of glycoproteins found on red blood cells (RBCs)
  - Type A; type B; type A & B; type O (neither)



**Figure 43.7** Blood types are reported as ABO group and Rh + or -. When both classification systems are combined, there are eight possible blood types: A+, A-, B+, B-, AB+, AB-, O+, O-.



# NOTES

## IMMUNE SYSTEM

# INTRODUCTION TO THE IMMUNE SYSTEM

[osms.it/immune-system-introduction](https://osms.it/immune-system-introduction)

- Includes organs, tissues, cells, molecules
- Protects from microorganisms, removes toxins, promotes inflammation, destroys tumor cells
- Two branches
  - Innate, adaptive

### INNATE IMMUNE RESPONSE

- **Nonspecific** cells: phagocytes, natural killer (NK) cells; **no immunologic memory**
- “Feverishly” **fast** (minutes to hours)

### Noncellular components

- Physical, chemical barriers (e.g. lysozymes in tears, cilia in airways)
- **Inflammation:** stops spread of infection, promotes healing
  - **Four cardinal signs:** redness, heat, swelling, pain
- **Complement system:** cascade of proteins; triggers inflammation, kills pathogens by cytolysis, tags cells for destruction

### ADAPTIVE IMMUNE RESPONSE

- **Highly specific** cells; **immunologic memory**, need priming
- Significantly **slower**, esp. initially (weeks)
- **Clonal expansions:** cells replicate
- **Clonal deletion:** cells die off after immune response; some survive as memory cells

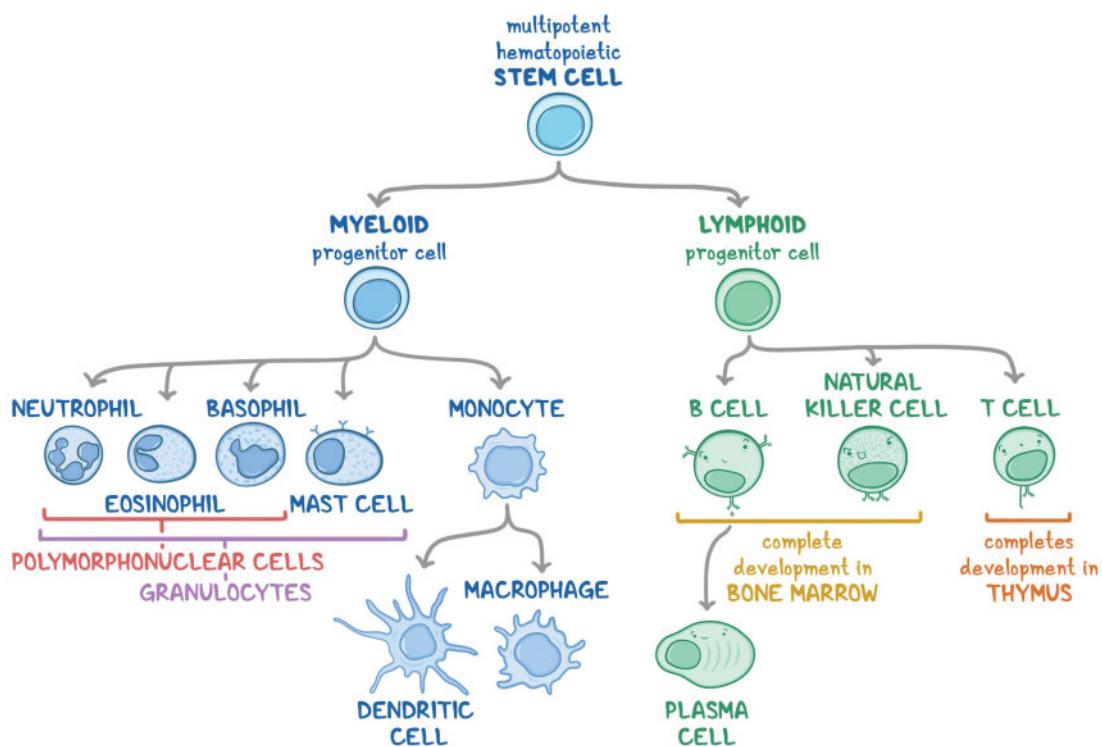
### CELLS OF THE IMMUNE SYSTEM

#### Leukocytes (white blood cells)

- Formed by hematopoiesis in bone marrow
  - Starts with multipotent hematopoietic stem cells
  - Cells develop into myeloid/lymphoid progenitor cells
- **Myeloid cells:** contribute to innate response
  - **Neutrophils:** phagocytes, granulocytes, polymorphonuclear cells (nucleus segmented into 3–5 lobes); stain light pink/reddish-purple; most numerous leukocyte
  - **Eosinophils:** phagocytes, granulocytes, polymorphonuclear cells (nucleus usually bilobed); stain pink with eosin; larger cells fight parasites
  - **Basophils:** nonphagocytes, granulocytes, polymorphonuclear cells (nucleus bilobed/segmented); stain blue-purple with hematoxylin; aid in fighting parasites; granules contain histamine, heparin; involved in inflammatory response; least numerous leukocyte
- **Mast cells:** nonphagocytes, granulocytes; involved in inflammatory response
- **Monocytes:** phagocytes, antigen-presenting cells; release cytokines to recruit other cells; only circulate in blood; differentiate into macrophages/dendritic cells
- **Dendritic cells:** phagocytes, antigen-presenting cells; release cytokines to recruit other cells; circulate in lymph,

- blood, tissue; consume large proteins in interstitial fluid; break bloodborne pathogens into small amino acid chains  
→ move to lymph node → present antigens to T cells
- Macrophages: phagocytes, antigen-presenting cells; release cytokines to recruit other cells; stay in connective tissue, lymphoid organs; not in blood
- Lymphoid cells: contribute to the adaptive response (except NK cells)
  - NK cells: contribute to innate response; complete development in bone marrow; large, contain granules; primarily target infected, cancer cells; kill target cells with **cytotoxic granules** (punch holes in target cell membranes by binding to phospholipids → enter cell, trigger apoptosis, programmed cell death)

- B cells: contribute to adaptive response; complete development in bone marrow; bind to specific antigens (antigen presentation not needed); capable of phagocytosis, antigen presentation; load antigens on major histocompatibility complex (MHC) II, display to T cells; T-cell activation → B cells mature into plasma cells; secrete lots of antibodies/immunoglobulins (B cell receptors in secreted-form, mark pathogens for destruction → "humoral immunity")
- T cells: contribute to adaptive response; complete development in thymus; responsible for **cell-mediated immunity**; bind to specific antigens (antigen presentation needed); naive T cells primed by antigen presenting cells (usually dendritic cells); generally categorized into CD4<sup>+</sup>, CD8<sup>+</sup> T cells; CD4<sup>+</sup> (helper) T cells secrete cytokines to coordinate immune response, only see antigens on MHC II; CD8<sup>+</sup> (cytotoxic) T cells kill target cells, cells with antigens on MHC I



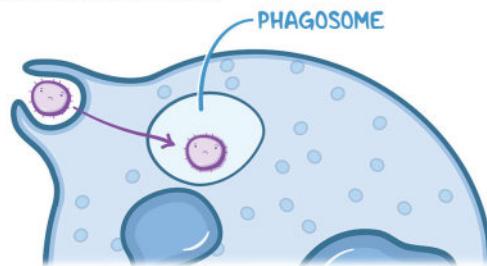
**Figure 44.1** Family tree of immune system cells.

## CLASSIFICATION OF IMMUNE CELLS

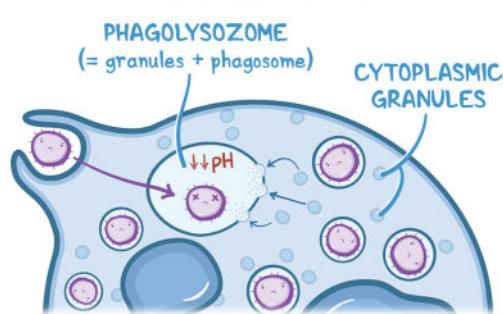
### Phagocytes

- Reach around pathogens with cytoplasm, swallowing whole (phagosome)
- Destroy some pathogens with cytoplasmic granules (phagosomes fuse with granules → phagolysosomes; pH in vesicle drops killing pathogens)
- Continue to swallow pathogens before oxidative burst → produces highly reactive oxygen (e.g.  $H_2O_2$ ; destroys proteins, nucleic acids, killing pathogens, phagocyte)

### 1. PHAGOCYTOSIS



### 2. CYTOPLASMIC GRANULES



### 3. OXIDATIVE BURST

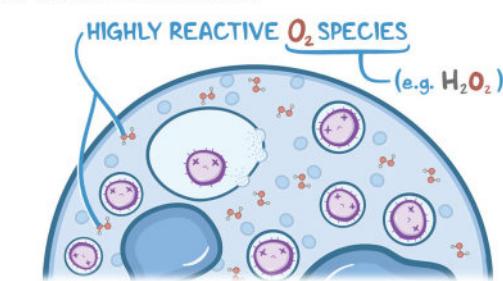


Figure 44.2 Phagocyte activities.

### Granulocytes

- Contain granules in cytoplasm
- All cells (except mast cells) polymorphonuclear

### Antigen-presenting cells

- Present antigens to T cells

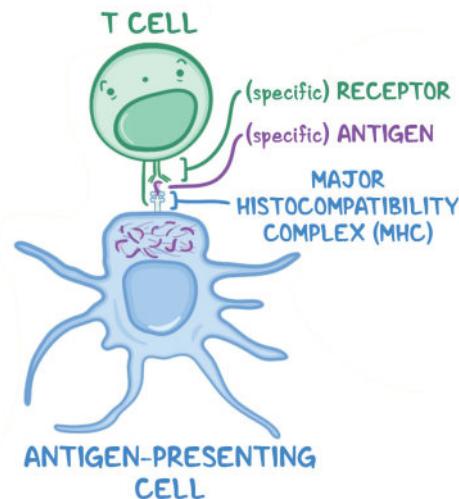


Figure 44.3 Antigen-presenting cell (depicted here as dendritic cell) presenting an antigen to a T cell.

IMMUNE CELL CLASSIFICATIONS		CLASSIFICATIONS	
BASOPHILS			
MAST CELLS		Granulocytes	
NEUTROPHILS			
EOSINOPHILS			
MONOCYTES	Phagocytes		
DENDRITIC CELLS			
MACROPHAGES		Agranulocytes	Antigen-presenting cells
LYMPHOCYTES			

## VACCINES

[osms.it/vaccines](http://osms.it/vaccines)

- Generate protective adaptive immune response against microbes by exposure to nonpathogenic forms/components of microbes
  - Differs from passive immunity (body creates own antibodies)
- Administration: intramuscularly, intradermally, intranasally, subcutaneously, orally
- Immunoglobulin response depends on route, type of vaccine
  - Intramuscular vaccinations → IgG
  - Rotavirus vaccine (oral) → IgA
- Four main types of vaccines
  - Live attenuated, inactivated (whole cell vaccines)
  - Subunit, toxoid (fractionated vaccines)

### LIVE ATTENUATED VACCINES

- Attenuated → pathogen weakened (but still replicates)
- Measles, mumps, rubella, varicella (MMRV); rotavirus; smallpox; yellow fever

### INACTIVATED VACCINES

- Pathogen killed using heat/formalin
- Response humoral/antibody-mediated; no cellular immunity → ↓ response
- Hepatitis A; polio; rabies; influenza

### SUBUNIT VACCINES

- Contain immunogenic portions of pathogens (polysaccharides/proteins)
- Combination of proteins from different pathogens → conjugate subunit vaccines
- Polysaccharide vaccines
  - T cell independent (only respond to protein antigens)
  - Not effective in children < two years old
  - Memory B cells never formed → repeated doses needed
  - Haemophilus influenzae type B; hepatitis B; HPV; Bordetella pertussis (pertussis); Streptococcus pneumoniae; Neisseria meningitidis; Varicella zoster

## TOXOID VACCINES

- Against specific toxins (main cause of illness)
- **Toxoid** fixed/**inactivated** using formalin
- Often combined with subunit vaccines
- Tetanus, diphtheria, and pertussis (TDaP), diphtheria, tetanus, and pertussis (DTaP) vaccine

## CONTRAINdications

- Moderate/severe infection
- Allergy to eggs/previous vaccines
- Guillain–Barré syndrome (vaccines against influenza, DTaP)
- Weakened immune system
  - Pregnant (live attenuated vaccines)



# NOTES B & T CELLS

## ANTIBODY CLASSES

[osms.it/antibody-classes](https://osms.it/antibody-classes)

- B cell receptor, major component of humoral immunity
- Heavy, light chain; fragment antigen-binding region; constant region (Fc)
- B cell develops into plasma cell → B cell receptor secreted as antibody
- Antibodies: monomers, polymers
  - Valence: number of antigen-binding fragments

### FIVE TYPES

- Coded by heavy chain genes

#### Immunoglobulin M (IgM)

- 1<sup>st</sup> antibody response
- Monomer as B cell receptor (valence: 2)
- Pentamer as antibody held together by joining (J) chain (valence: 10)
- Works against carbohydrate, lipid antigens
- Most effective at activating complement pathway

#### Immunoglobulin G (IgG)

- Monomer (valence: 2)
- Four subclasses
  - IgG1, IgG2, IgG3, IgG4 (differ in constant regions)
- Serves as opsonin
- Activates classical complement pathway

#### Immunoglobulin A (IgA)

- Monomer (valence: 2)
- Serves as opsonin (eosinophils, neutrophils, some macrophages)

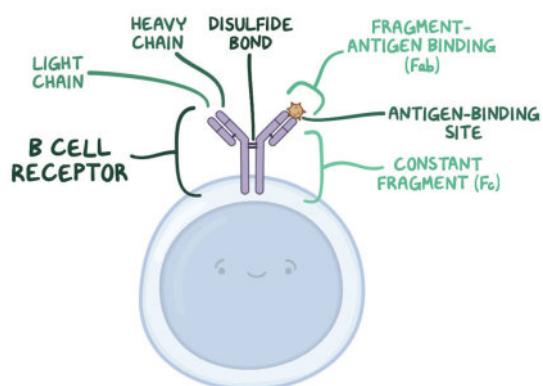
- Main immunoglobulin in mucosal sites; sometimes occurs as dimer (valence: 4)
- Two forms
  - IgA1, IgA2 (differ in constant regions)

#### Immunoglobulin E (IgE)

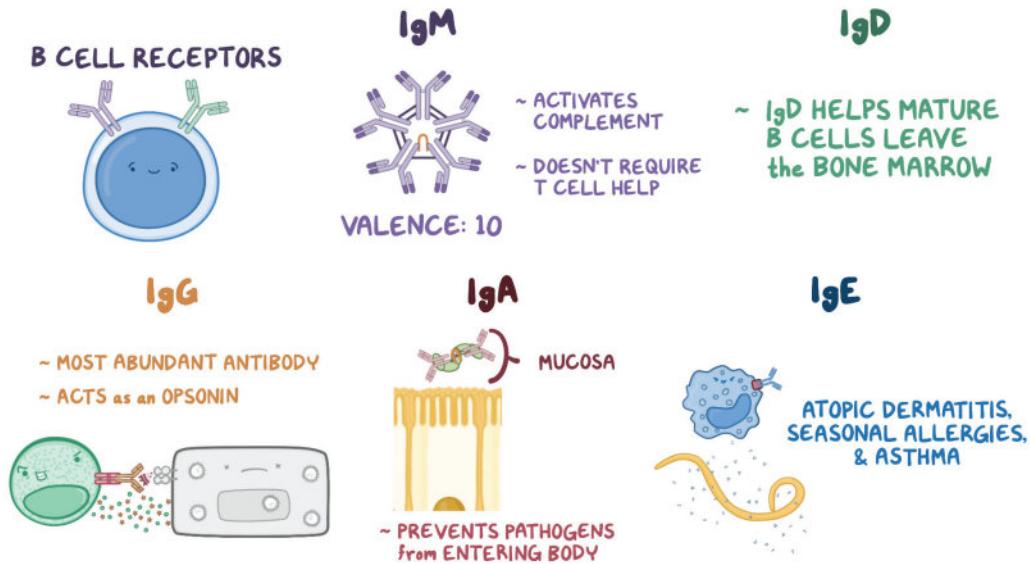
- Monomer (valence: 2)
- Production primarily induced by interleukin 4 (IL-4)
- Triggers granule release from mast cells, eosinophils, basophils
- Responds to nonpathogenic targets (e.g. peanuts) → allergies

#### Immunoglobulin D (IgD)

- Monomer (valence: 2)
- Found alongside IgM antibodies, signals maturation of B cells



**Figure 45.1** B cell receptor components.



**Figure 45.2** Summary of the five classes of antibodies. IgM and IgD can act as B cell receptors.

## B CELL ACTIVATION & DIFFERENTIATION

[osms.it/b-cell-activation-and-differentiation](https://osms.it/b-cell-activation-and-differentiation)

- Developing B cell receptor expresses μ heavy chain → B cell receptors IgM
- Alternative splicing → IgM, IgD expressed on surface → mature, naive B cell explores lymphatic system → B cells enter paracortical region of lymph nodes, migrate to cortical region → form primary follicle

### ACTIVATION

- On activation (antigen-binding), B cell forms germinal center → secondary lymphoid follicle
- Cross-linkage of two B cell receptors → Ig-alpha, Ig-beta, CD19 cluster
  - Blk, Fyn, Lyn phosphorylate tyrosine residues on immunoreceptor tyrosine based activation motif (ITAM) units → transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), nuclear factor of activated T cells (NFAT) → gene expression of cytokines, upregulation of antiapoptotic cell surface markers

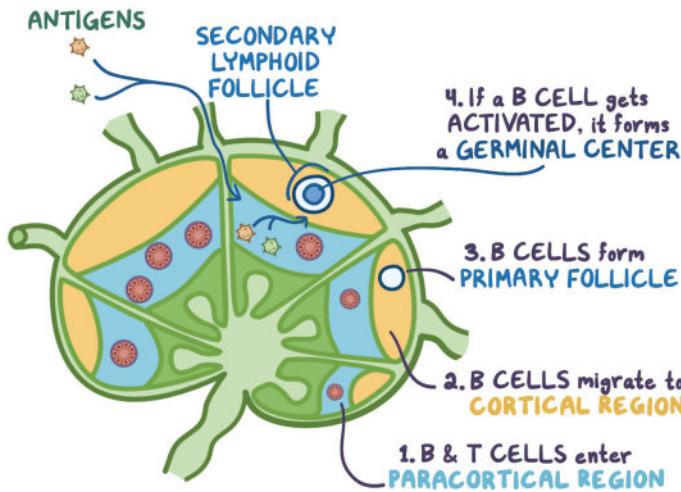
### DIFFERENTIATION

- B cells stimulated by cluster of differentiation 21 (CD21)/complement receptor Type II (CR2) (receptor for C3d complement fragment)
- Activated B cells differentiate into plasma cells, secrete antibodies
  - Plasma cells initially secrete IgM, remain mainly in bone marrow, safeguard against future encounters with same antigen

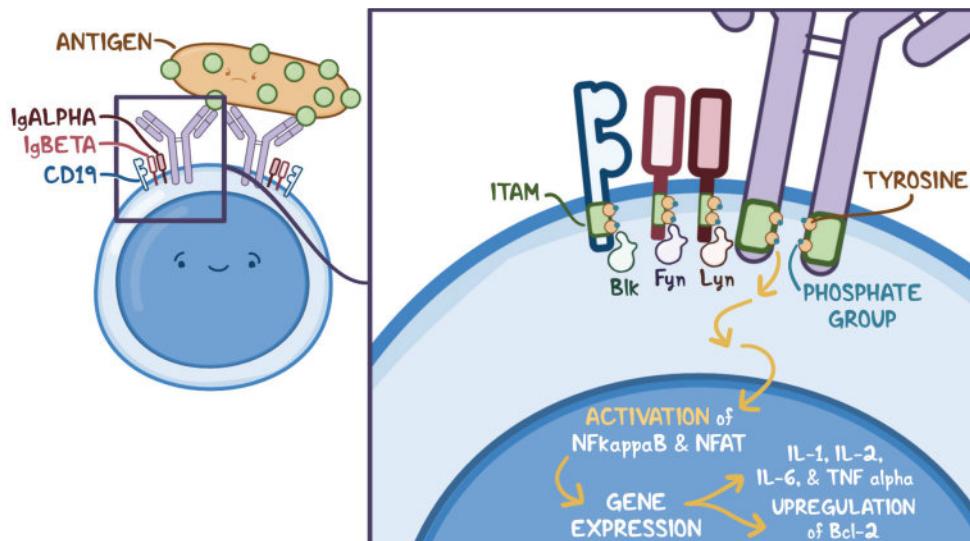
### Activated CD4<sup>+</sup> T cell → class switching

- B cells:** antigen-presenting cells; present antigens on major histocompatibility complex (MHC) class II to helper T cells
- CD40 ligand on T cell binds to CD40 on B cell → cytokines instruct B cell on type of antibody to produce (by activation-induced cytidine deaminase)
  - IL-4, IL-5 → IgE
  - Interferon (IFN) gamma → IgG

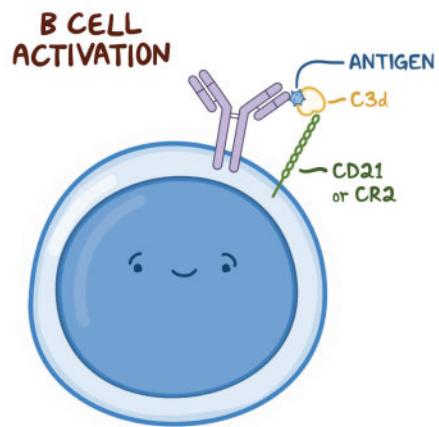
- Activation-induced deaminase removes constant regions during differentiation to leave desired antibody region



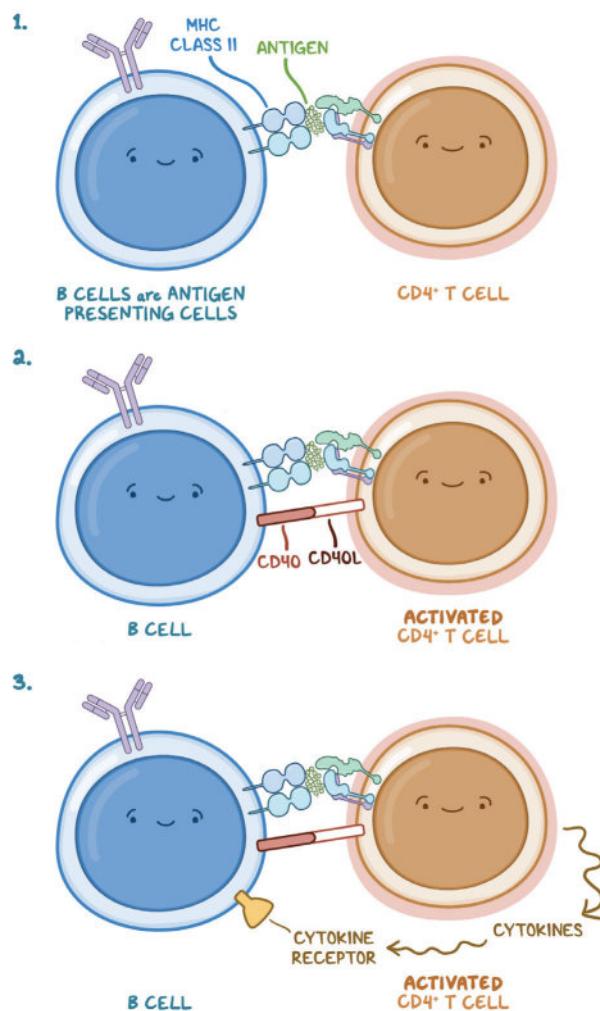
**Figure 45.3** Mature, naive B cells form a primary follicle in the cortical region of a lymph node. When the B cell binds an antigen, it activates and forms a germinal center. The follicle is now called a secondary lymphoid follicle.



**Figure 45.4** Series of events following antigen binding that lead to B cell activation. Ig-alpha, Ig-beta, and CD19 are intracellular side chains of the B cell receptors that cluster when two B cell receptors are cross-linked by an antigen.



**Figure 45.5** Complement fragment C3d can bind an antigen and then be bound by molecule CD21/CR2 on a B cell. B cells can also be activated when they have a B cell receptor that is bound to an antigen, and a CD21 that's bound to an antigen.



**Figure 45.6** B cell differentiation. **1:** B cell presents an antigen to a CD4+ T cell. **2:** If the T cell activates, it expresses CD40L on its surface, which binds to CD40 on the B cell. **3:** CD40L and CD40 binding causes the B cell to express a cytokine receptor and the T cell to release cytokines. The type of cytokine determines what type of antibody the B cell will produce.

# B CELL DEVELOPMENT

[osms.it/b-cell-development](http://osms.it/b-cell-development)

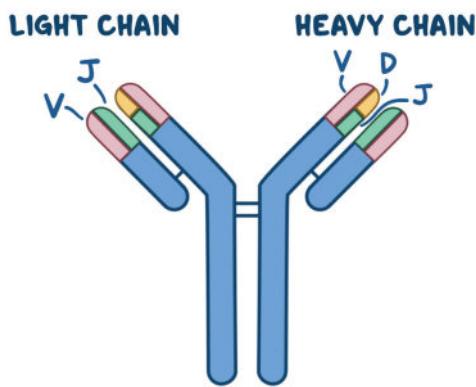
- Lymphopoiesis: development of diverse set of lymphocytes with unique antigen receptors

## CREATION OF SUITABLE RECEPTOR

- B cell receptor contains two chains
  - Heavy, light
- Antigen-binding site made of variable (V), diversity (D), joining (J) protein segments coded by genes of same name
  - Heavy chain: all three segments
  - Light chain: V, J segments

## ANTIGEN BINDING SITE

- VARIABLE
- DIVERSITY
- JOINING



**Figure 45.7** Antigen binding site on heavy chain is composed of V, D, and J segments, while antigen binding site on light chain has only V and J segments.

## STAGES OF DEVELOPMENT

- Six stages: common lymphoid progenitor cell → early pro-B cell → late pro-B cell → large pre-B cell → small pre-B cell → immature B cell

### Early pro-B cell

- Common lymphoid progenitor cell expresses recombination activating gene (RAG) 1, RAG2 → early pro-B cell

### Late pro-B cell

- Heavy chain D, J gene segments spliced together (allelic exclusion: 1<sup>st</sup> chromosome to complete splicing suppresses 2<sup>nd</sup>) → late pro-B cell

### Large pre-B cell

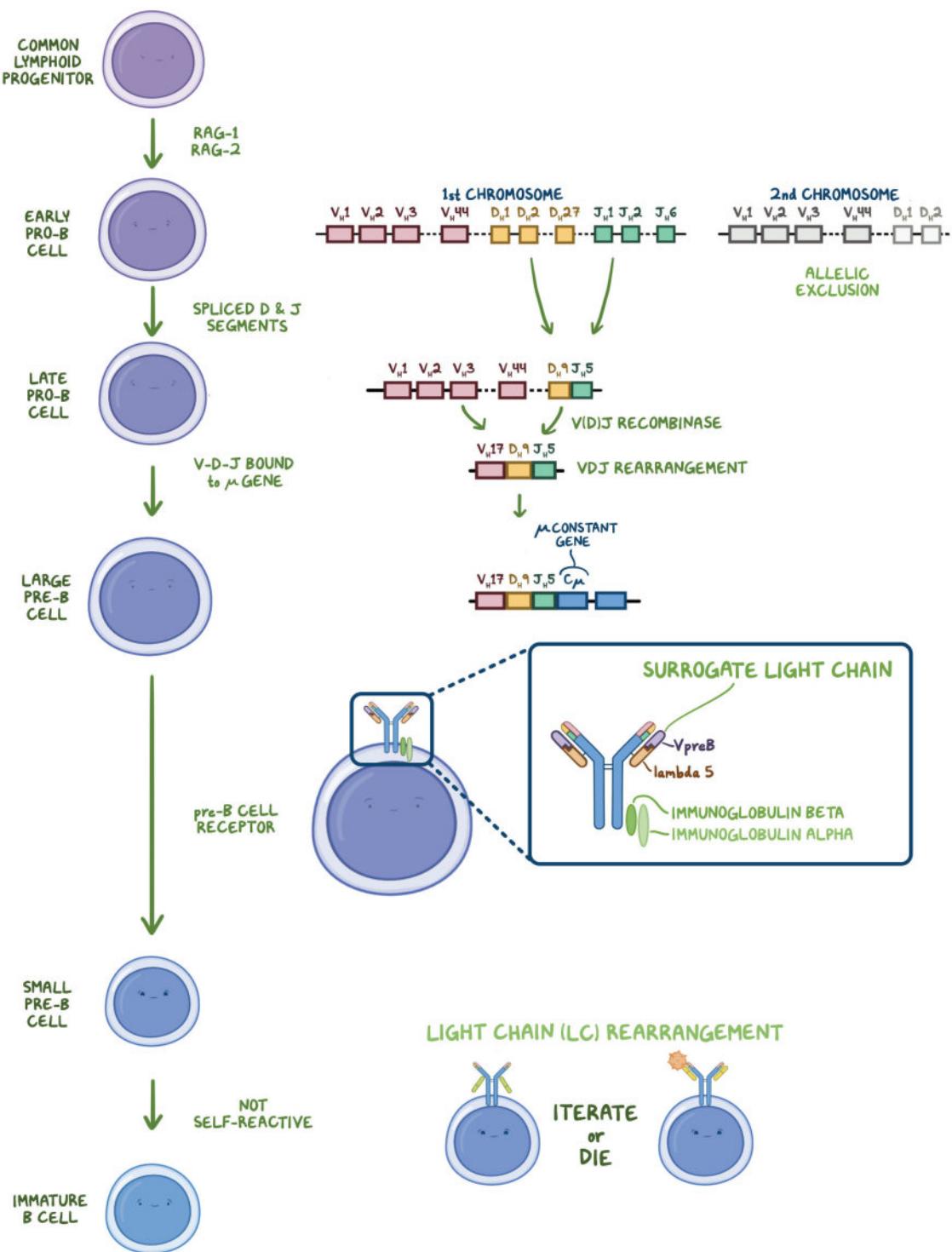
- Late pro-B-cell attaches D-J gene segment to V gene segment via V(D)J recombinase → binding site (heavy chain) recombined with mu gene → large pre-B cell
  - Mu gene codes for IgM constant region protein

### Small pre-B cell

- Functionality of heavy chain tested by binding to surrogate light chain (VpreB, lambda 5) → if successful, cells proliferate → small pre-B cell

### Immature B cell

- Light chain rearranged → functionality of light chain tested by autoimmune regulator (AIRE), identifies self-reactive cells by expressing bodily antigens in lymphoid organs → immature B cell
- Central tolerance/negative selection: elimination of self-reactive cells
  - Strong binding to self-antigen → cell undergoes apoptosis
  - Intermediate binding to self-antigen → light chain repeatedly rearranged with kappa gene on 1<sup>st</sup>, 2<sup>nd</sup> chromosomes, lambda gene 1<sup>st</sup>, 2<sup>nd</sup> chromosomes
  - Failure to eliminate self-reactive cells → autoimmunity
- Immature B cells finally undergo alternative splicing on constant region → IgD constant region replaces IgM constant region → cells released into blood



**Figure 45.8** B cell development stages and the changes that move them to the next stage.

# CELL MEDIATED IMMUNITY OF CD4 CELLS

[osms.it/cell-mediated-immunity-CD4-cells](http://osms.it/cell-mediated-immunity-CD4-cells)

- CD4 cells = **T helper cells** (support other immune cells)
- T cells initially naive
- In response to antigen, T cell primed → effector T cell
  - Two signals: antigen (MHC molecule on antigen-presenting cell), costimulation (CD28 binds to B7 on antigen-presenting cells)
- Activated T helper cell → IL-2 → up-regulates IL-2 alpha receptor
- T helper cell binds to IL-2 (autocrine stimulation) → clonal expansion

→ transcription factors signal transducer and activator of transcription 1 (STAT1), STAT2

## T helper Type II

- Fights parasites
- Eosinophils, basophils, mast cells → IL-4, IL-4, IL-10 → transcription factors STAT6, GATA-binding protein 3 (GATA3)

## T helper Type XVII

- Fights fungal, bacterial infections
- Fungi, bacteria → IL1, IL6, IL23, transforming growth factor (TGF) $\beta$  → transcription factors ROR- $\gamma$ , STAT3

## T follicular helper (Tfh)

- Establishes memory B cells
- Antigen-presenting cells → IL6, IL21, IL27 → transcription factors B cell lymphoma protein 5 (BCL-5), cMaf

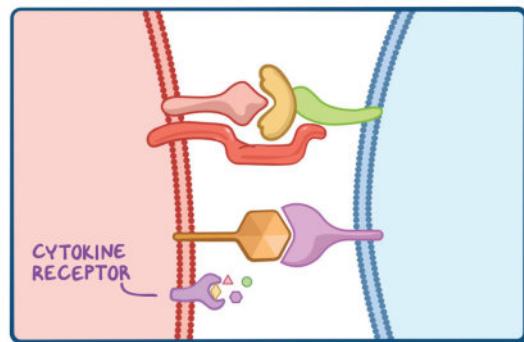
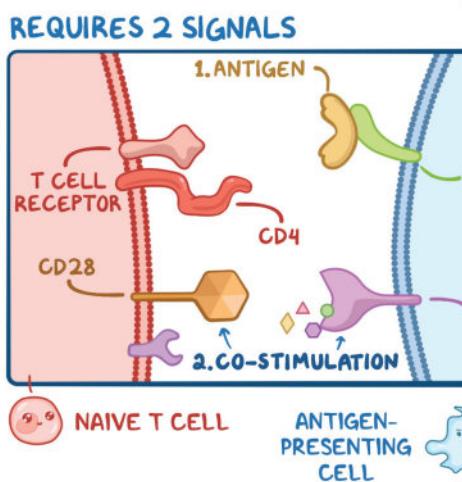
## FOUR TYPES OF T HELPER CELL

- Depends on cytokines in environment

### T helper Type I (Th1)

- Fights intracellular infections
- Macrophages → IL-12, natural killer (NK) cells → IFN- $\gamma$ , infected cells → IFN $\alpha$ , IFN $\beta$

## PRIMING



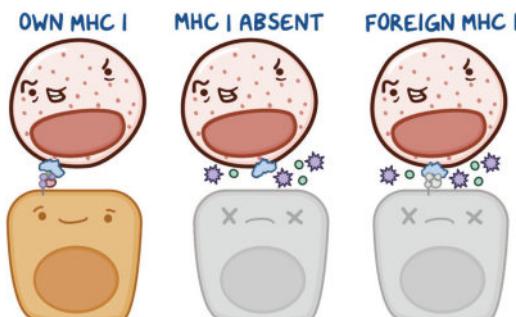
**Figure 45.9** T helper cells require two signals to be primed and become effector T cells: presentation of an antigen and binding of CD28 on T cell to B7 on antigen-presenting cell.

# CELL MEDIATED IMMUNITY OF NATURAL KILLER & CD8 CELLS

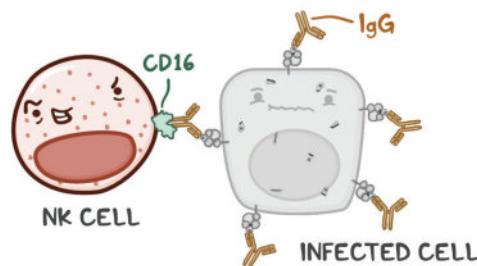
[osms.it/cell-mediated-immunity-NK-CD8-cells](http://osms.it/cell-mediated-immunity-NK-CD8-cells)

## NATURAL KILLER (NK) CELLS

- Identify target cells; deliver perforin, granzymes
- Part of innate response → no need for specific antigen
- Activation receptors recognize surface molecules on infected cells; inhibitory receptors recognize molecules (e.g. native MHC class I molecules)
- Also activated by antibody-dependent cell-mediated cytotoxicity
  - IgG binds to virally-infected cell → CD16 on NK binds to antibody



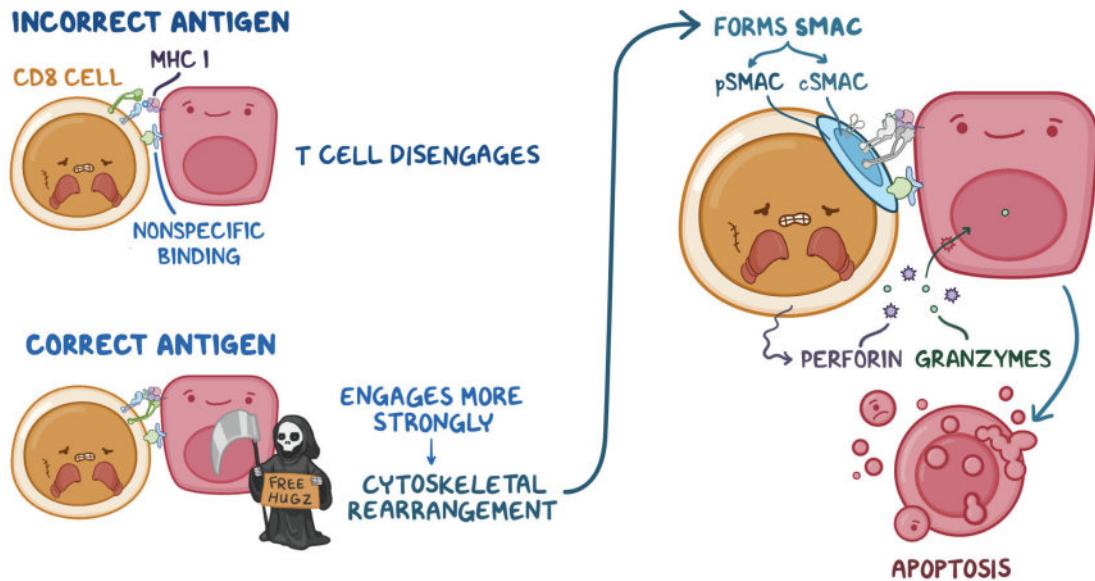
## ANTIBODY DEPENDENT CELL MEDIATED CYTOTOXICITY (ADCC)



**Figure 45.10** NK cells recognize cell surface molecules like MHC I to determine whether or not to kill a cell. They can also kill via ADCC. In this process, the NK cell is stimulated by binding to the constant chain of an IgG antibody attached to a virally infected cell.

## CD8 CELLS

- CD8 cells = cytotoxic T cells
- T cells initially naive
- In response to antigen, T cell primed → effector T cell
  - Two signals: antigen (MHC molecule on antigen-presenting cell), costimulation (CD28 binds to B7 on antigen-presenting cells)
- Activated T helper cell → IL-2 → up-regulates IL-2 alpha receptor
- T helper cell binds to IL-2 (autocrine stimulation) → clonal expansion
- Needs to see antigen in context of MHC I to kill cell (doesn't need CD28)
- Binds nonspecifically to multiple cells with adhesion molecules → fails to bind to MHC I → disengages
- If antigen binds, cytoskeletal rearrangement → forms supramolecular activation cluster (SMAC)
  - Includes central SMAC (cSMAC) for antigen recognition, peripheral SMAC (pSMAC)
- Cytotoxic cell releases granules with perforin, granzymes (caspases → apoptosis)



**Figure 45.11** CD8 cells weakly bind a variety of cells with adhesion molecules. However, they only destroy cells with antigens on their MHC I molecules that allow the CD8 cells to bind tightly.

## CYTOKINES

[osms.it/cytokines](http://osms.it/cytokines)

- Proteins secreted by all types of cells to communicate (bind to receptors, trigger response)

### FIVE TYPES

#### Interleukins (ILs)

- Act as communication between leukocytes, nonleukocytes
- Promote development, differentiation of T, B cells
- Mostly synthesized by helper T cells

#### Tumor necrosis factors (TNFs)

- Bind to cell receptors, cause cells to die (induce apoptosis)
- Heavily involved in inflammatory response (up-regulate expression of adhesion molecules, increase vascular permeability, induce fever)

#### Interferons (IFNs)

- Type I
  - Produced by virally infected cells → affect surrounding cells: degrade messenger RNA (mRNA), inhibit protein synthesis, express MHC

messenger RNA (mRNA), inhibit protein synthesis, express MHC

- Type II
  - Interferon-gamma → promotes anti-viral state, activates macrophages, CD4<sup>+</sup> helper T-cells

#### Colony stimulating factors (CSFs)

- Bind to surface receptors on hematopoietic stem cells → proliferation, differentiation

#### Transforming growth factors (TGFs)

- Control proliferation, differentiation of cells

## MAIN FUNCTIONAL RESPONSES

#### Pro-inflammatory

- Enhance innate, adaptive immune responses
- IL-1, IL-12, IL-18, TNF, IFN-γ

#### Parasite/allergy

- Help immune system handle large parasites, induce allergic responses
- IL-4, IL-5, IL-10, IL13

### Regulatory

- Immunosuppressive
- IL-10, TGF- $\beta$

### Growth and differentiation

- Replenish immune cells
- Granulocyte-macrophage colony-

stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), IL-7

### Chemotactic

- Help cells move towards site of inflammation
- IL-17, IL-8

# MHC CLASS I & MHC CLASS II MOLECULES

[osms.it/MHC-class-I-MHC-class-II](http://osms.it/MHC-class-I-MHC-class-II)

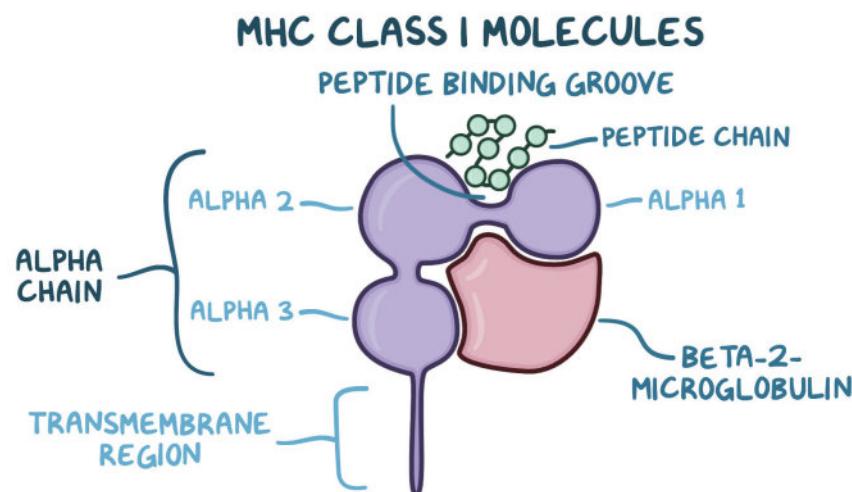
- Major histocompatibility complex (MHC), AKA “human leukocyte antigen”
  - Cell surface proteins, present antigens to T cells

### MHC CLASS I

- Found on all nucleated cells, presents antigens from inside
- Bound by CD8 molecules on cytotoxic T cells
- Includes HLA-A, HLA-B, HLA-C

### Structure

- Contains alpha, beta-2-microglobulin chains
- Alpha chain: peptide binding groove, transmembrane region
  - Binding groove binds peptides 8–10 amino acids long; hydrophobic peptide residues  $\leftrightarrow$  hydrophilic groove amino acids
- Three extracellular domains: alpha-1, alpha-2, alpha-3



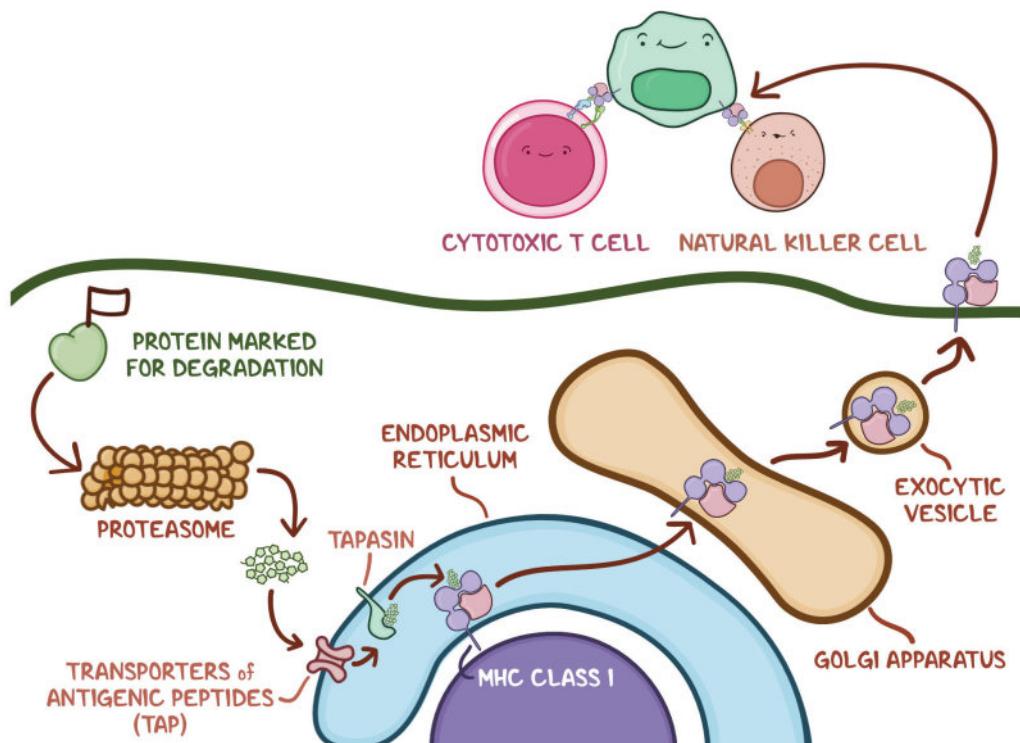
**Figure 45.12** Structure of an MHC class I molecule.

**Function**

- Allows immune cells to sample cellular proteins (via **endogenous pathway of antigen presentation**)
  - Marked protein sent to proteasome
  - Proteasome degrades protein → short peptide chains
  - Transporters of antigenic peptides (TAP)

move peptide chains to endoplasmic reticulum

- TAP loads peptide onto MHC class I using tapasin
- MHC class I loaded into exocytic vesicle, sent to cell surface
- Cytotoxic T cells, NK cells interact with peptide (if necessary)



**Figure 45.13** Endogenous pathway of antigen presentation.

**MHC CLASS II**

- Found on antigen-presenting cells, presents antigens from outside
- Bound by CD4 molecules on helper T cells
- Includes HLA-DP, HLA-DQ, HLA-DR

**Structure**

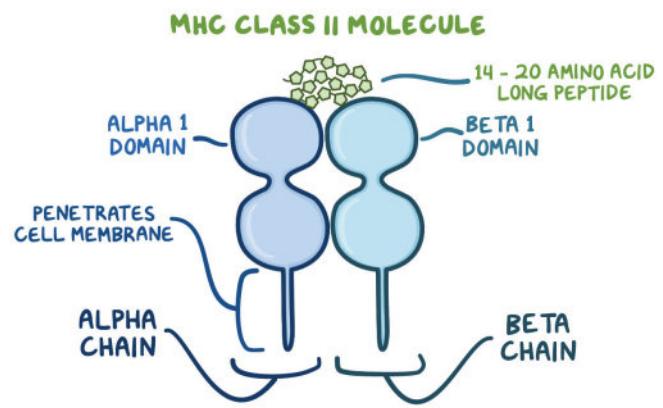
- Contains alpha, beta chains
  - Both penetrate cell membrane
  - Binding groove binds peptides 14–20 amino acids long

**Function**

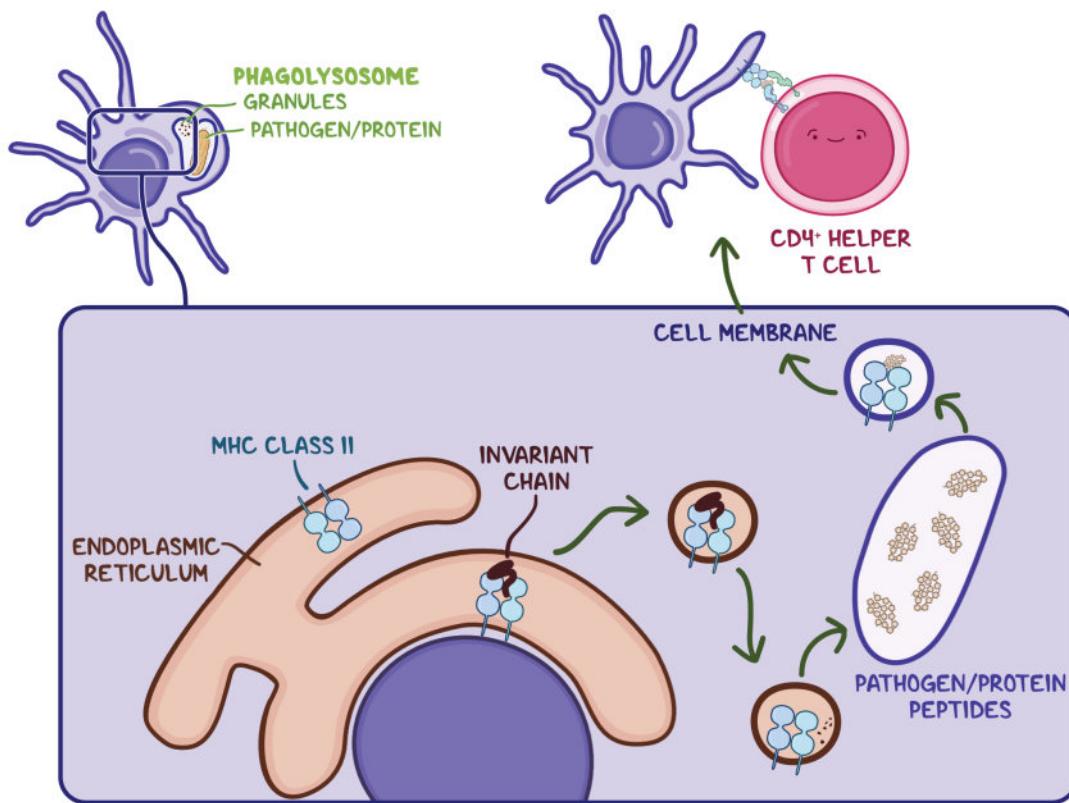
- Engulfs, destroys pathogens; presents antigens to CD4<sup>+</sup> T helper cells (via **exogenous pathway of antigen**)

presentation)

- Antigen-presenting cell ingests antigen → endosome
- Lysosome + endosome → phagolysosome; degrades protein → short peptide chains
- MHC class II binding groove filled temporarily with invariant chain (degrades during vesicular transportation)
- Vesicle fuses with phagolysosome
- MHC class II binds peptide, sent to cell surface
- CD4<sup>+</sup> helper T cells interact with peptide (if necessary)



**Figure 45.14** MHC class II molecule structure.



**Figure 45.15** Exogenous pathway of antigen presentation.

# SOMATIC HYPERMUTATION & AFFINITY MATURATION

[osms.it/somatic-hypermutation-affinity-maturation](http://osms.it/somatic-hypermutation-affinity-maturation)

## SOMATIC HYPERMUTATION

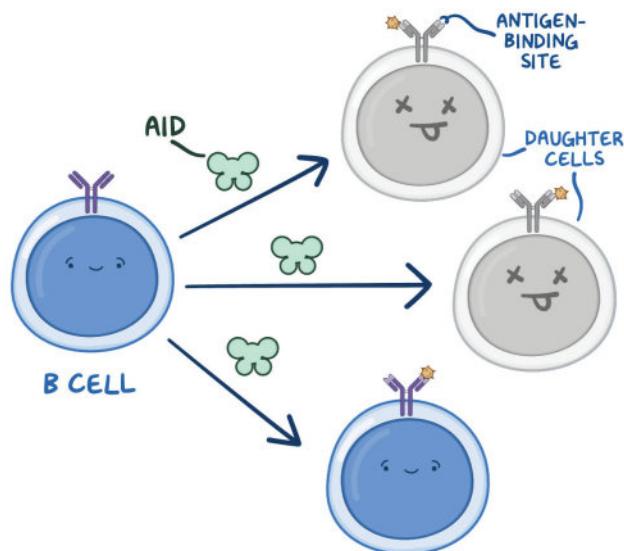
- Intentional mutation of antibody genes to create new antigen specificities → stronger, more specific response to antigen
- Occurs in activated B cells (germinal centers, spleen)
- CD40L on T cell binds to CD40 on B cell → cytokines instruct B cell to produce specific type of antibody
- Activation-induced cytidine deaminase (AID) turns cytidine into uridine (not usually found in DNA) → mismatch/base excision repair to remove uridine
  - Mismatch repair proteins MSH2, MSH6 use nucleases to remove uridine; DNA polymerase replaces nucleotides → mutations

- Base excision: uracil-DNA glycosylase removes uracil from uridine → next round of replication, random nucleotide inserted → mutations
- Only some mutations increase affinity
  - Low affinity B cells die naturally with time
  - High affinity B cells live on (affinity maturation)

## AFFINITY MATURATION

- Process by which B cells increase affinity for antigen during an immune response
- Somatic hypermutation, clonal selection (only high affinity cells activated → only high affinity cells replicate)

### SOMATIC HYPERMUTATION



### AFFINITY MATURATION

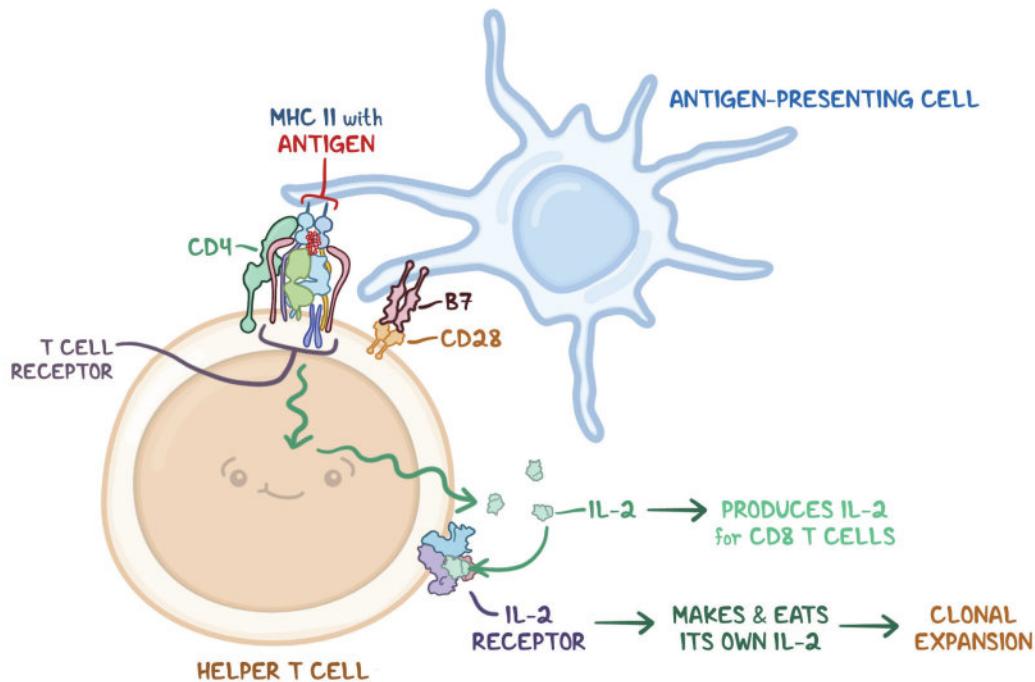


**Figure 45.16** Somatic hypermutation only occurs in B cells which express enzyme AID. AID makes small mutations directly in antigen binding site of B cell receptor, which get expressed in daughter cells of a rapidly proliferating cell. These changes in the variable region change affinity (strength) that B cell receptor has for its antigen. As antigen becomes limited, B cells with lowest affinity will die off first, so only B cells with strongest affinity for their antigen remain.

# T CELL ACTIVATION

[osms.it/t-cell-activation](http://osms.it/t-cell-activation)

- Priming: T cell begins differentiation when exposed to antigen
  - Two signals: antigen (MHC molecule on antigen-presenting cell), costimulation (CD28 binds to B7 on antigen-presenting cells)
- Signal sent to nucleus by CD3 peptide chains
  - Lymphocyte-specific protein tyrosine kinase (LCK) phosphorylates tyrosine residues on immunoreceptor tyrosine based activation motif (ITAM) units
- Zeta-chain-associated protein kinase 70 (ZAP-70) phosphorylates LAT, SLP-76  
→ activation of transcription factors NF- $\kappa$ B, NFAT → gene expression of cytokines, upregulation of antiapoptotic cell surface markers
- Activated T cell → IL-2 → up-regulates IL-2 alpha receptor
- T helper cell binds to IL-2 (autocrine stimulation) → clonal expansion



**Figure 45.17** Summary of T cell activation. T cells need two signals to activate: first, presentation of its antigen by MHC class I (cytotoxic T cells) or class II (helper T cells), and costimulation, which is when CD28 and B7 bind. In helper T cells, this triggers a series of steps that lead to upregulation of the IL-2 alpha receptor and production of IL-2 for itself, causing clonal expansion, and CD8 T cells.

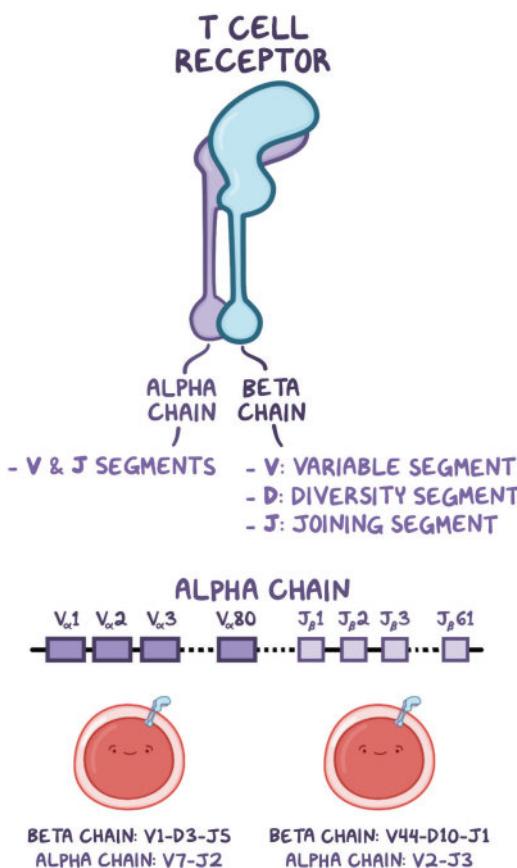
# T CELL DEVELOPMENT

[osms.it/t-cell-development](http://osms.it/t-cell-development)

- Lymphopoiesis: hematopoietic stem cell → common lymphoid progenitor cell → immature B cell (bone marrow)

## CREATION OF SUITABLE RECEPTOR

- T cell receptor contains two chains: alpha, beta
  - Alpha: comparable to B cell's light chain
  - Beta: comparable to B cell's heavy chain
- Antigen-binding site:** V, D, J protein segments coded by genes of same name
  - Beta chain: all three segments
  - Alpha chain: V, J segments



**Figure 45.18** Structure of T cell receptor. Different combinations of V, D, and J segments provide T cell receptors with a wide variety of antigen specificities.

## STAGES OF REARRANGEMENT

- Tracked by CD3, CD4, CD8 cell surface markers

### Double negative/DN stage

- Common lymphoid progenitor initially CD3<sup>-</sup>, CD4<sup>-</sup>, CD8<sup>-</sup> (double negative/DN stage); broken down into DN1, DN2, DN3, DN4)
  - DN1 cell expresses RAG1, RAG2 → DN2 cell
  - Beta chain D, J gene segments spliced together (allelic exclusion) → DN3 cell
  - V gene segment combines with DJ gene segment by V(D)J recombinase → V-D-J gene segment bound to  $\mu$  gene segment → DN4 cell
  - Functionality of beta chain tested by binding to invariant pre-T alpha chain → if successful, cells proliferate

### Double positive/DP stage

- Daughter cells express CD3, CD4, CD8 (double positive/DP stage)

### Single positive/SP stage

- Central tolerance: eliminates potentially self-reactive cells by positive, negative selection
  - Self-reactive cell elimination failure → autoimmunity
- Positive selection
  - T cells recognize/bind to self-MHC molecules
  - Binding failure → apoptosis
- Negative selection
  - Autoimmune regulator gene (AIRE): allows primary lymphoid organs to express antigens normally found throughout body; aids in testing self-reactivity
  - Excessively strong binding to self-antigens → apoptosis

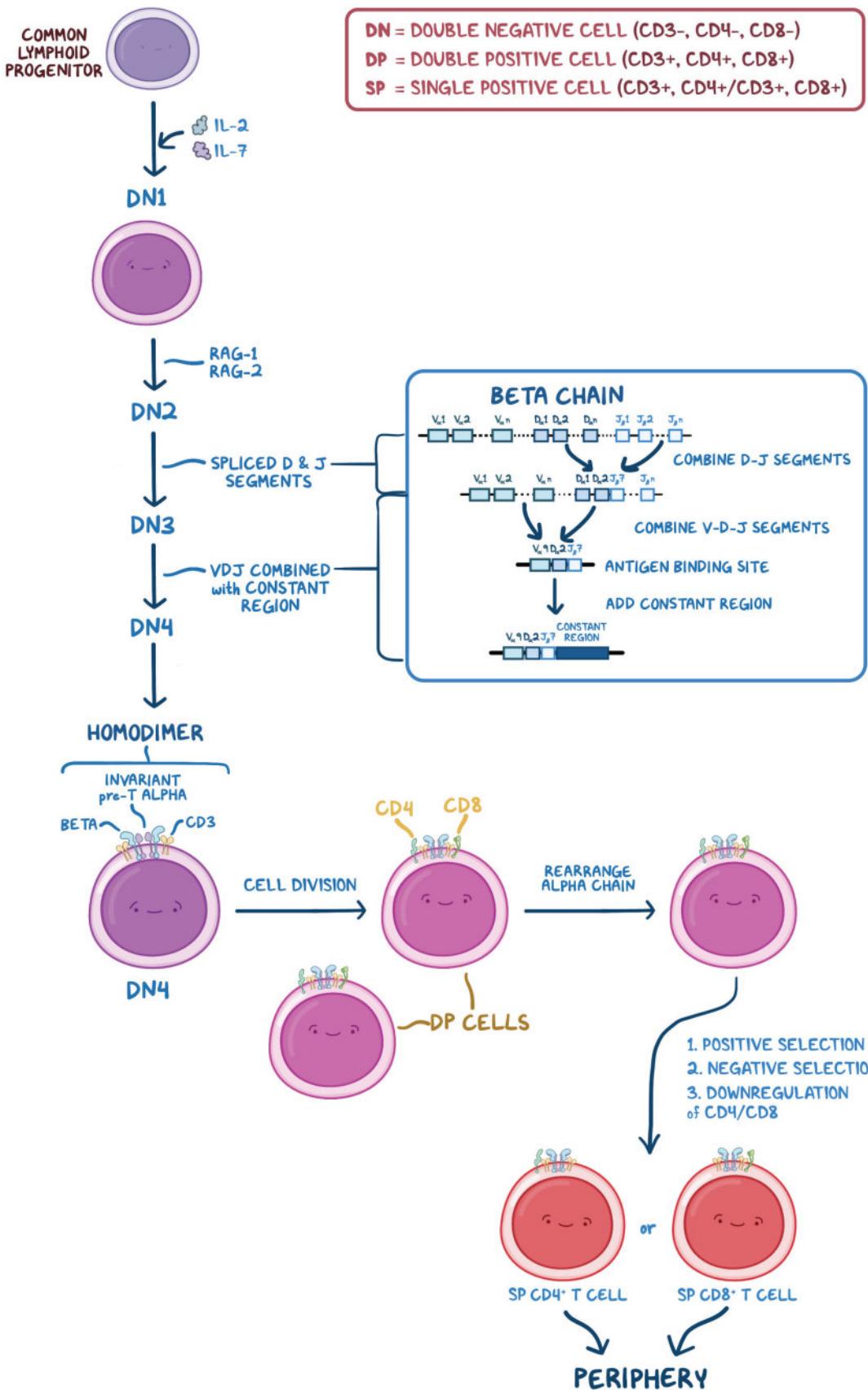


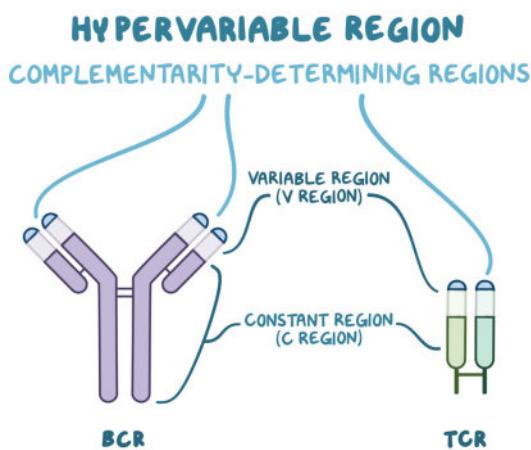
Figure 45.19 T cell development summary.

- DP cells recognize self-MHC but do not recognize self-antigen presented in MHC molecule → downregulate either CD4/CD8 receptor → further development into single positive (SP) cell
  - Strong binding to MHC → CD4 downregulated → SP CD8<sup>+</sup> T cell
  - Weak binding to MHC → CD8 downregulated → SP CD4<sup>+</sup> T cell

## VDJ REARRANGEMENT

[osms.it/VDJ-rearrangement](http://osms.it/VDJ-rearrangement)

- Mechanism used to generate range of B, T cell receptors
- Antigen-binding sites: V, D, J protein segments coded by genes of same name
  - Each cell inherits multiple V, D, J segments → **randomly recombine** → recombinational inaccuracy, random assortment of two chains (heavy/beta chain rearranged first) → new specificities
- V(D)J rearrangement only affects V region (creates variability in hypervariable regions)



**Figure 45.20** Locations of hypervariable regions on BCRs and TCRs affected by V(D)J rearrangement.

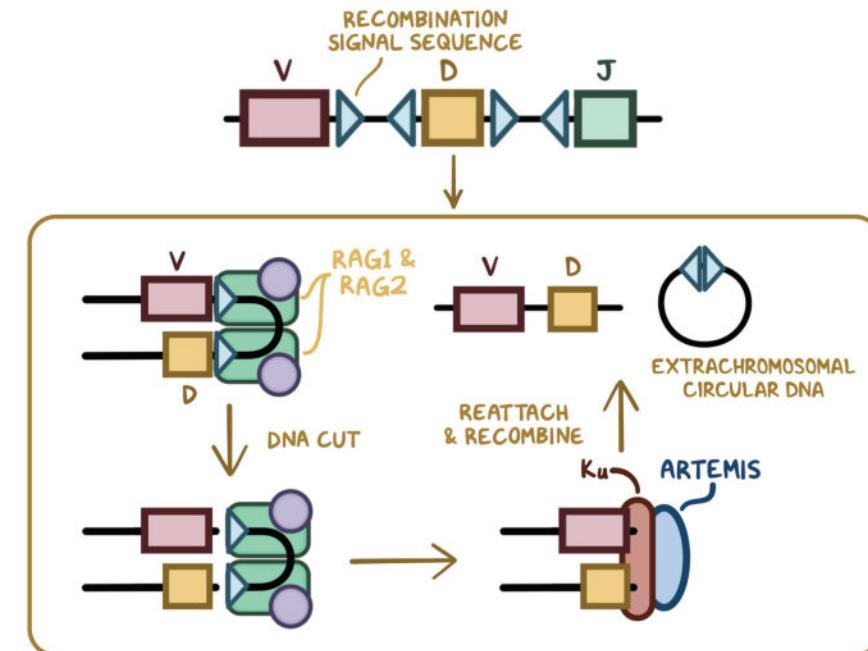
### HEAVY/BETA CHAIN REARRANGEMENT

- Recombination signal sequence
  - Heptamer 5'-CACAGTC-3', 12, 23 nucleotides, nonamer 5'-ACAAAAAACC-3'
  - DNA loops to bring together two recombination signal sequences
  - RAG1, RAG2 cut DNA at recombination signal sequence
  - Recombinases (e.g. ku, artemis) reattach, recombine DNA
- Error-prone process
  - Cut end placed onto **terminal deoxynucleotide transferase (TdT)** to **add random nucleotides** → alters antigen specificity
- Functionality of heavy chain tested → random assortment of chain

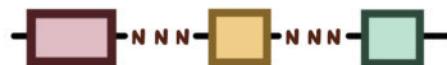
### LIGHT CHAIN REARRANGEMENT

- Rearranged into kappa/lambda light chain (kappa rearranged before lambda)

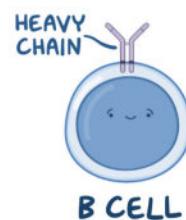
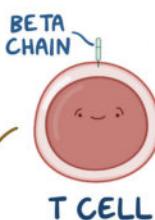
## 1. VDJ REARRANGEMENT of BETA/HEAVY CHAIN



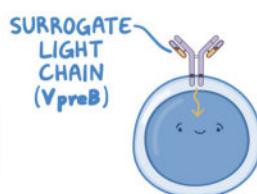
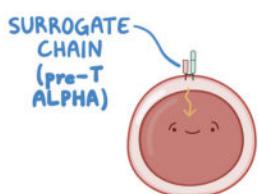
NUCLEOTIDES ADDED by TdT



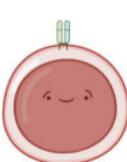
DNA is LIGATED



## 2. BINDING TEST



## 5. PAIRED WITH VARIETY of LIGHT/ALPHA CHAINS



## 3. PROLIFERATION

## 4. ALPHA/LIGHT CHAIN REARRANGEMENT

**Figure 45.21** Summary of the process by which B and T cell receptors are made.



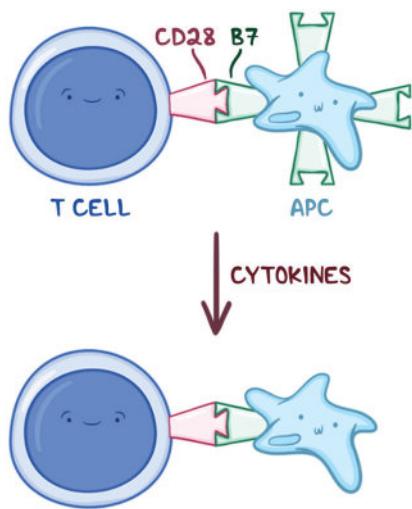
## NOTES CONTRACTION OF THE IMMUNE RESPONSE

# ANERGY, EXHAUSTION, & CLONAL DELETION

[osms.it/contracting-immune-response](http://osms.it/contracting-immune-response)

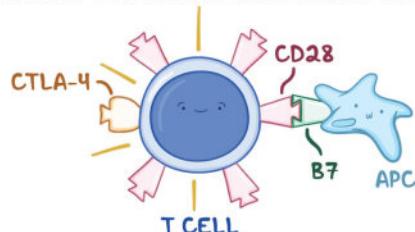
### CLONAL ANERGY

- Functional unresponsiveness to self antigens
- Lymphocytes can bind to antigens, **without costimulation**
- T cells: costimulation involves CD28 binding to B7 on antigen-presenting cells (APCs)
  - T regulatory cells reduce B7 expression on antigen presenting cells
  - Later in immune response, T cells begin to express cytotoxic T-lymphocyte associated protein 4 (CTLA-4) → binds to B7

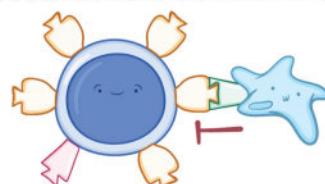


**Figure 46.1** T regulatory cells reduce costimulation by releasing cytokines that reduce B7 expression on antigen-presenting cells (APCs).

### START of IMMUNE RESPONSE: CD28 > CTLA-4



### LATER in IMMUNE RESPONSE: CTLA-4 > CD28



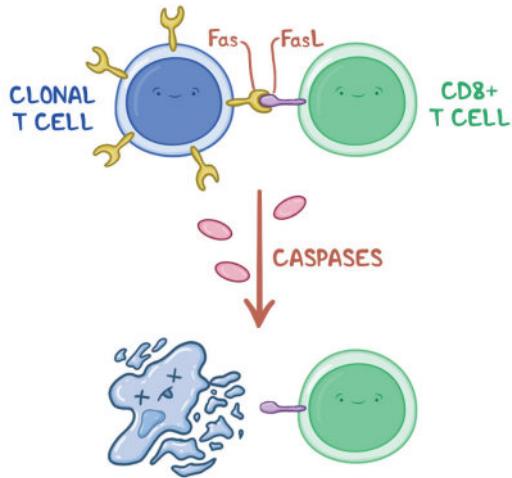
**Figure 46.2** T cells express much more CTLA-4 later in immune response. B7 binds to CTLA-4 more strongly than it does to CD28 and inhibits T cell → T cell inactivation.

### CLONAL EXHAUSTION

- Later in immune response, T cells begin to express program death 1 (PD-1)
- Program death ligand 1 (PD-L1) on antigen-presenting cells bind to PD-1 → T cells shut down

### CLONAL DELETION

- Recognition of self antigens → T cell apoptosis (programmed cell death)
- Later in immune response, T cells express Fas
- Fas ligands on CD8+ T cells, NK cells bind to Fas → activate enzymes called caspases → apoptosis



**Figure 46.3** Clonal deletion. T cells express Fas → bind to Fas ligand on CD8+ T cell/NK cell → caspases activated → apoptosis.

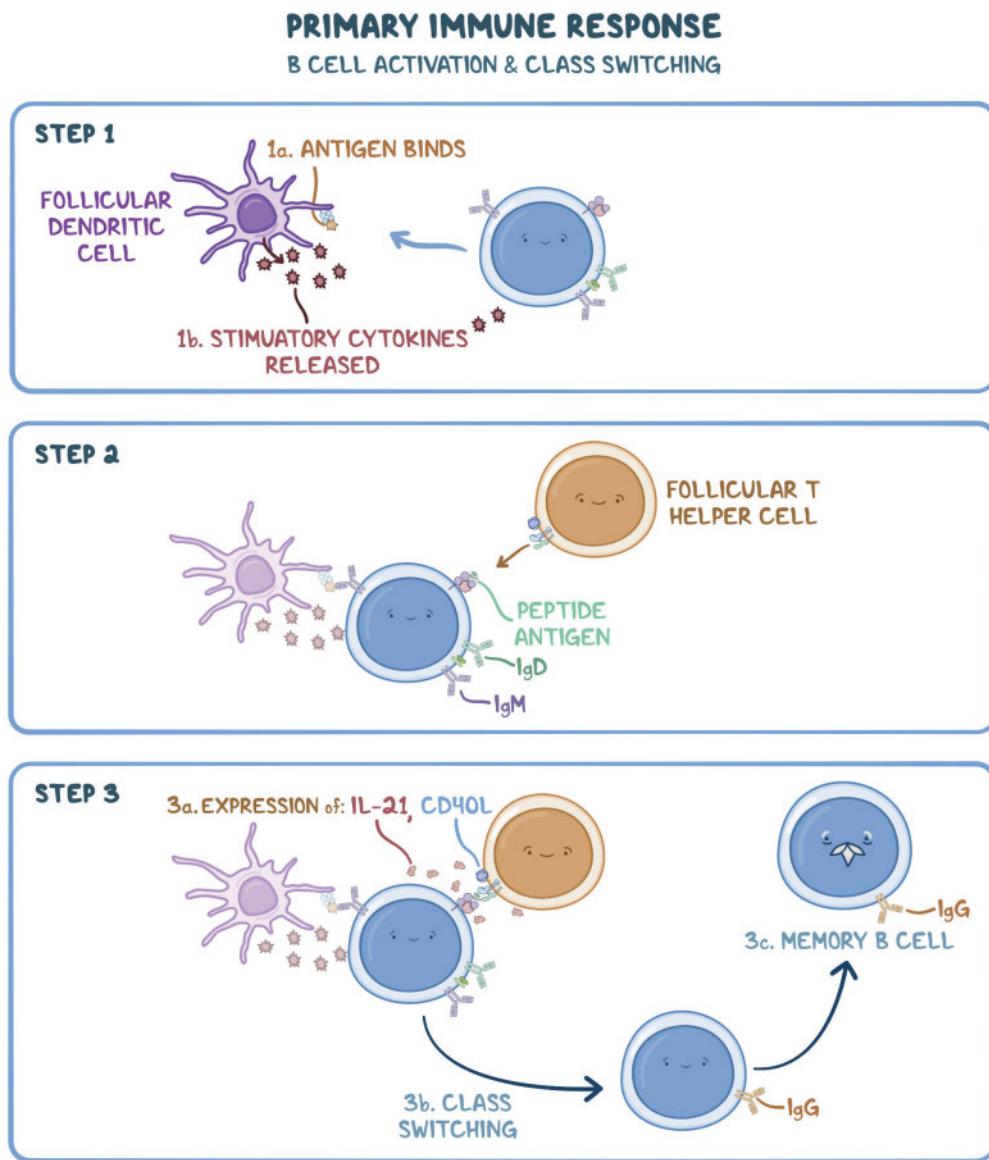
## B & T CELL MEMORY

[osms.it/B-and-T-cell-memory](http://osms.it/B-and-T-cell-memory)

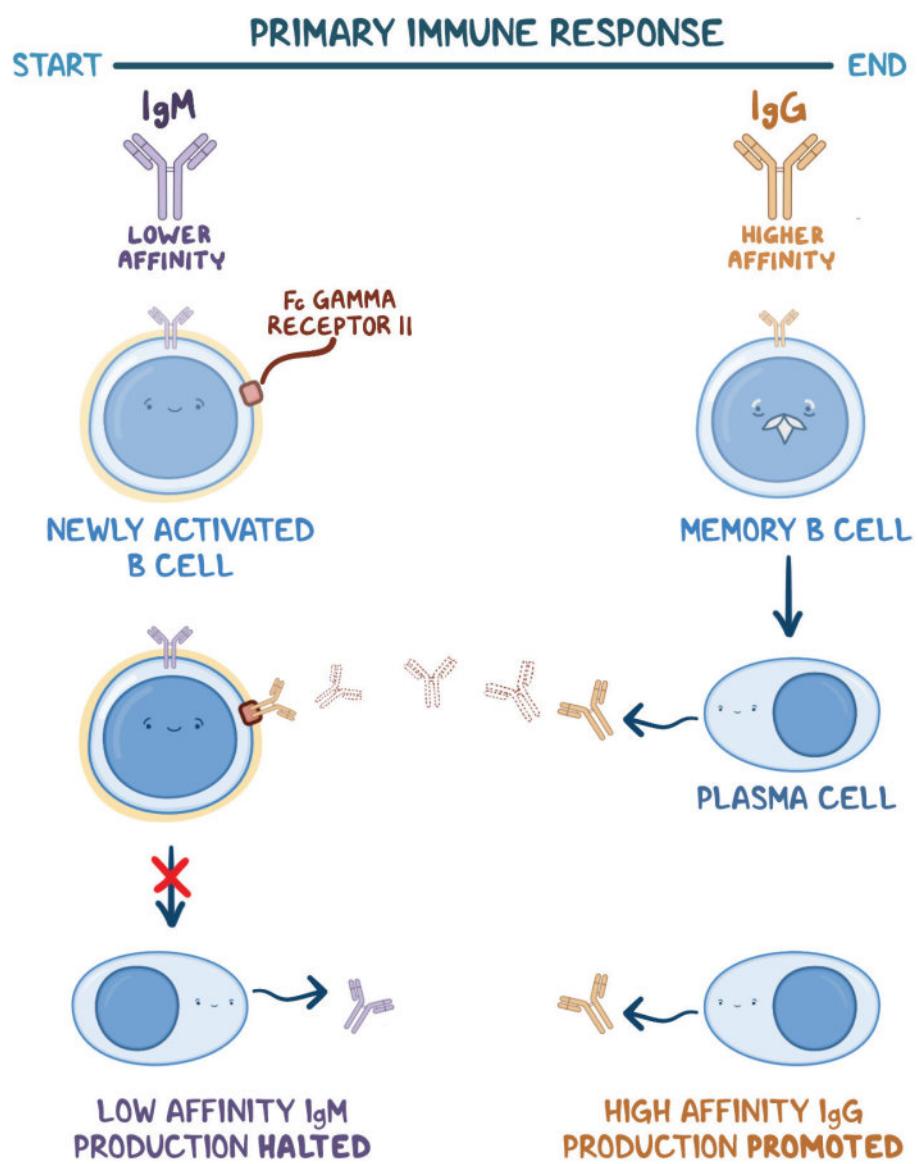
- Ability of B, T cells to “remember” particular antigen
  - B, T cells multiply when receptors detect particular antigen
  - After immune response mounted, excess cells undergo apoptosis
  - Memory B, T cells contain same receptors after immune response
- Immunologic memory → secondary (anamnestic) response
  - Primary response: naive B, T cells require activation before response to pathogen → high pathogen burden (response can take days, weeks)
  - Secondary response: memory B, T cells, antibodies needed to respond to pathogen already exist → low pathogen burden (response occurs right away)

### MEMORY B CELLS

- Only B cells that have undergone **class switching** become memory B cells
  - Memory response limited to peptide antigens (not lipids/carbohydrates)—follicular T helper cells needed for class-switching only respond to peptide antigens
  - Memory B cells don’t produce IgM/IgD
- Live up to 10 years in lymph nodes
- Often differentiate into IgG-producing plasma cells when reactivated
- Due to somatic hypermutation, IgG created late in immune response typically has higher affinity than IgM created early in immune response → IgG binds to Fc gamma receptor II on IgM-producing B cells, prevents differentiation into plasma cells → ↓ IgM production, ↑ IgG production



**Figure 46.4** B cells are activated through interactions with other immune cells. Step 1a: follicular dendritic cell traps antigens and 1b: sends out stimulatory cytokines. Step 2: the B cell presents the antigen to a follicular T helper cell. Step 3a: the follicular T helper cell expresses CD40L on its surface and produces IL-21. 3b: together, they induce the B cell to undergo class switching (shift from expressing a B cell receptor with IgM and IgD to expressing IgG, IgE, or IgA). 3c: some of these B cells become memory B cells.



**Figure 46.5** Process by which higher affinity IgG production is favored over lower affinity IgM production. Memory B cells differentiate into high affinity IgG-producing plasma cells. IgG binds to Fc gamma receptor II on newly activated B cells, which produce low affinity IgM. This prevents them from differentiating into low affinity IgM-producing plasma cells, allowing the proportion of high affinity IgG in the response to be greater.

## MEMORY T CELLS

- Cell surface ligand CD45 used to identify T cells
  - Naive T cells express CD45A
  - Memory T cells express CD45O

### Effector memory T cells

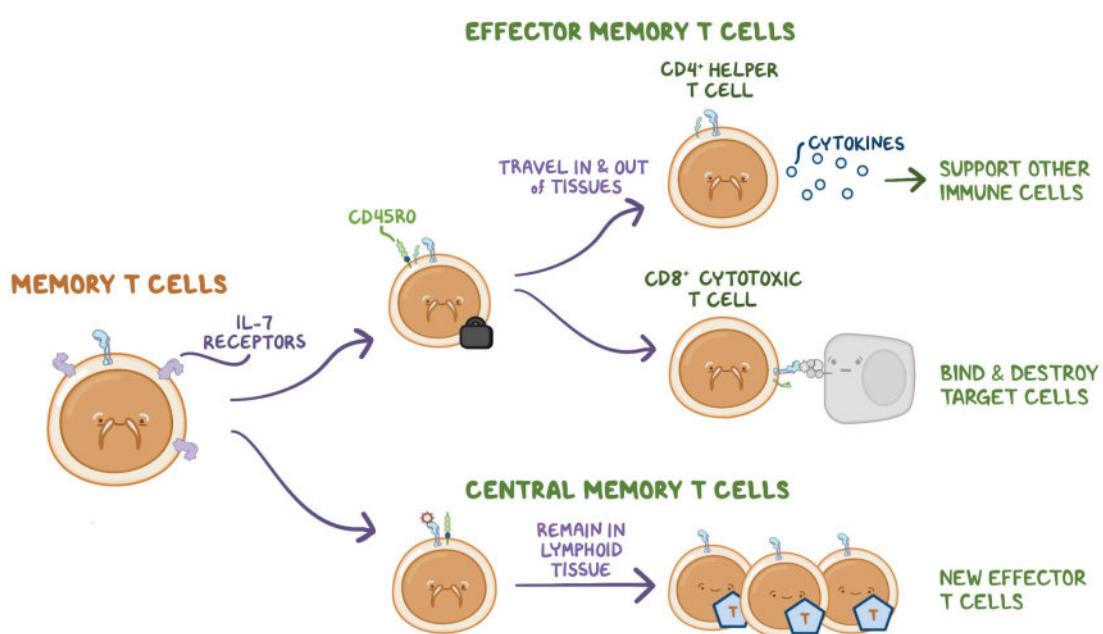
- Move around body looking for pathogens
- Respond as primary response (for CD4+ helper cells, *secretting cytokines*; for CD8+

cytotoxic cells, binding to, destroying target cells)

- IL-7 receptors replaced with IL-2 receptors during activation → cells die shortly after immune response

### Central memory T cells

- Live up to 25 years
- Remain in lymphoid tissues
- High levels of IL-7 receptors maintained → cells live on after immune response



**Figure 46.6** The two types of memory T cells (effector memory T cells and central memory T cells) and their functions.

## CONTRACTING THE IMMUNE RESPONSE

[osms.it/contracting-immune-response](https://osms.it/contracting-immune-response)

- Immune response termination
- Peripheral tolerance to self antigens limits immune response (preventing autoimmune disease)
- Mechanisms directed primarily at T cells; includes use of T regulatory cells, clonal anergy, exhaustion, deletion

### B CELLS

- Similar mechanisms to T cells
- Later in immune response, reduced presence of antigens, T cells prevent B cell activation → anergy
- Surplus IgG binds to FcγR II on B cells → prevent differentiation into plasma cells

### T REGULATORY CELLS

- Inhibit antigen-presenting cells by releasing specific molecules (e.g. indoleamine 2,3 dioxygenase)
- Release cytokines (e.g. IL-10, TGF-beta) → antigen-presenting cells express inhibitory ligand (e.g. PD-L1)
- Express high levels of IL-2, adenosine receptors (competing with other T cells)



# NOTES INNATE IMMUNITY

## INNATE IMMUNE SYSTEM

[osms.it/innate-immune-system](https://osms.it/innate-immune-system)

- Comprises immune system along with adaptive immunity
- Includes barriers to repel pathogens
  - Chemical barriers: **lysozyme** (tears), low stomach pH
  - Physical barriers: epithelium (skin/gut), cilia lining airways

### Key features

- **Nonspecific** cells do not distinguish invaders
- Response occurs within **minutes–hours**
- **No memory**
  - Always responds to pathogen in same manner

### Human microbiome

- Included in innate immunity
- Bacteria, fungi, viruses in/on humans
- May affect host response in own way

## RESPONSE TO PATHOGENS

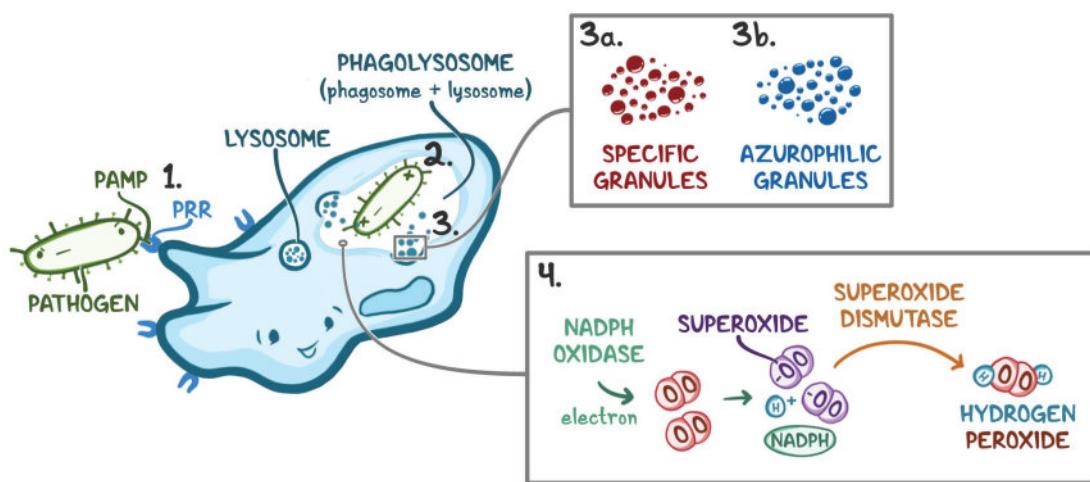
### Phagocyte response to pathogens

- Phagocytes eat, kill pathogens
- Phagocyte consumes pathogen
  - Phagocytic **pattern recognition receptors** (PRRs) on phagocyte **identify pathogen-associated molecular patterns** (PAMPs) on pathogens (e.g. bacterial-wall components)
  - Phagocyte swallows pathogen, traps it in phagosome

- Phagocyte kills pathogen (post-identification)
  - Phagosome binds with lysosome, forms phagolysosome
  - Specific phagolysosome granules (proteases, hydrolases) kill internal microorganisms while decreasing pH
  - Azurophilic granules (hydrolases, oxidative enzymes) activate in acidic environment → more microorganisms killed
  - Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases oxidize oxygen molecules → superoxide ion creation
  - Superoxide dismutase converts superoxide into hydrogen peroxide, killing remaining microorganisms

### Signalling PRRs response to pathogens

- Large amount of pathogens enter → signalling pattern recognition receptors also activated
- Signalling PRRs → phagocytes to release cytokines
- **Toll-like receptors** (TLRs) especially important in signalling PRRs
  - PAMP activation → TLRs activate transcription factor **NF-κB** → proinflammatory cytokines (e.g. TNFα, IL-1β, IL-6) secreted → vasodilation, fever, recruiting leukocytes
  - **Intracellular pathogens**: interferon alpha, beta may be secreted (prevents pathogen multiplication)



**Figure 47.1** Overview of the phagocyte response to pathogens.

1. The phagocyte's pattern recognition receptors (PRRs) identify pathogen-associated molecular patterns (PAMPs) on the pathogen.
2. The pathogen is phagocytosed and trapped in a phagosome, which then
3. binds with lysosomes, forming a phagolysosome.
- 3a. Specific granules from the lysosomes act first to kill pathogens and decrease pH.
- 3b. After the pH is sufficiently lowered, azurophilic granules are activated and kill more pathogens.
4. NADPH oxidases oxidize oxygen molecules to create superoxide ions. The ions are then converted by superoxide dismutase into hydrogen peroxide, which kill the remaining pathogens.

# COMPLEMENT SYSTEM

[osms.it/complement-system](https://osms.it/complement-system)

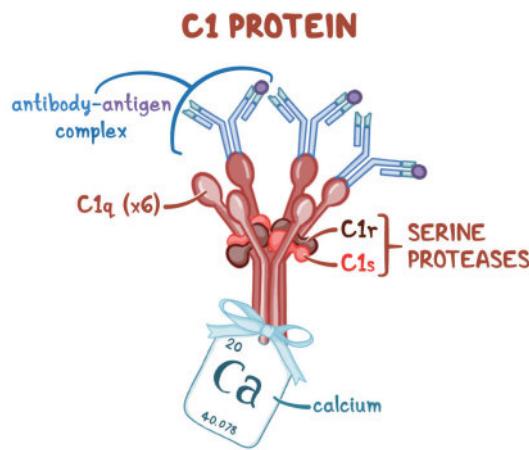
- Collection of plasma proteins called complement proteins
- Produced in **liver**, collectively destroy pathogens

## COMPLEMENT SYSTEM PATHWAYS

- Acts follow one of three pathways
  - Classical, alternative, lectin

### Classical pathway

- Features C1–C9 proteins
- C1
  - Component proteins C1q, C1r, C1s (latter two—serine proteases)



**Figure 47.2** Structure of a C1 protein. Each of the six C1q proteins can bind to an antibody-antigen complex. Calcium ties the protein together.

- Proteins inactive until “cleaved” (portion of protein breaks off)
- Pathway steps
  - C1q proteins bind to Fc portion of antibody when bound to antigen
  - Two C1q proteins bind → C1 changes shapes (conformational change) exposing C1r, C1s

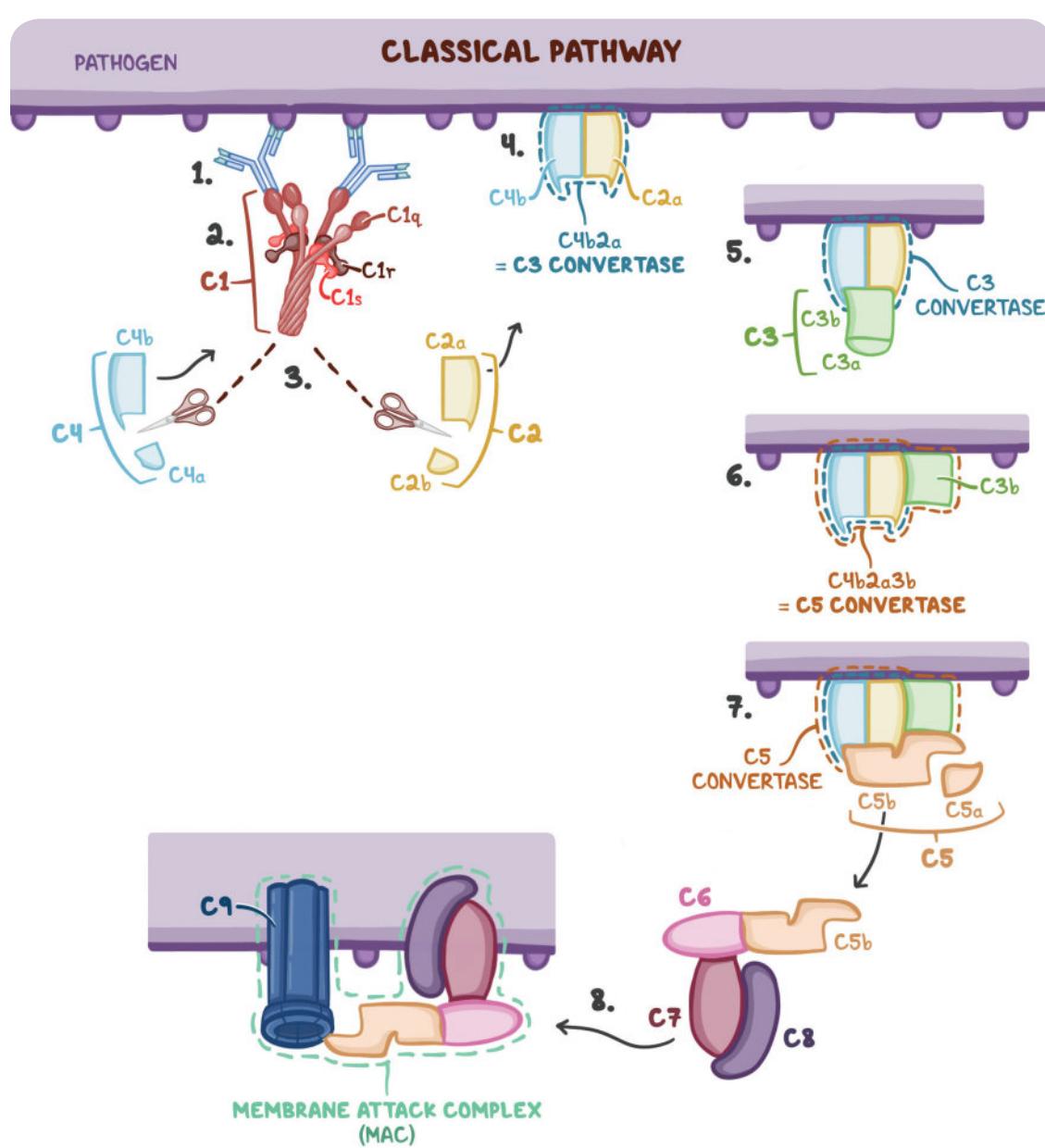
- C1r cleaves C1s (activating C1 molecule) → C1 cleaves C4 into C4a, C4b → C4b binds to pathogen
- C1 also cleaves C2 into C2a, C2b → C2a joins C4b on pathogen → C4b2a (C3 convertase) formed
- C3 convertase cleaves C3 into C3a, C3b
- C3b binds to pathogen near C4b2a/ C3 convertase, creates C5 convertase (C4b2a3b)
- C5 convertase cleaves C5 into C5a, C5b
- C5b binds to **C6, C7, C8, many C9s** → forms **membrane attack complex (MAC)** → penetrates pathogen cell membrane
- C1 consists of six C1q proteins
  - Binds to six antibody-antigen complexes
- Calcium ties together C1
  - Lack of calcium → lack of C1

### Alternative pathway

- Factor B, factor D proteins
- C3 cleaved spontaneously (small amounts)
- Pathway steps
  - C3b binds to pathogen → factor B binds to pathogen
  - Factor D cleaves factor B → forms Ba, Bb → C3bBb formed (C3 convertase)
  - Follows classical pathway
- Constant activation prevention
  - C1-inhibitor protein dissociates C3bBb

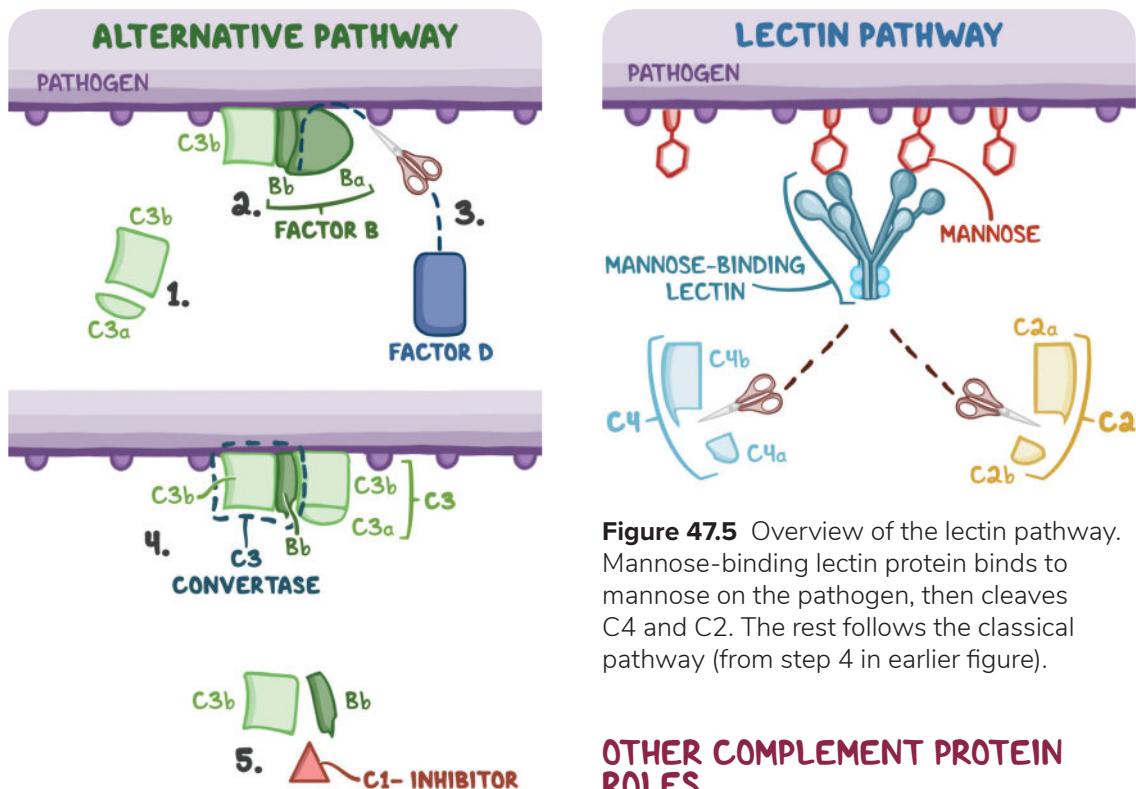
### Lectin pathway

- Features **mannose**-binding lectin protein (binds to bacterial mannose)
- Pathway steps
  - Mannose-binding lectin protein acts similar to C1 → cleaves C4, C2 to eventually establish C4b2a (C3 convertase)
  - Follows classical pathway



**Figure 47.3** Overview of the classical complement pathway.

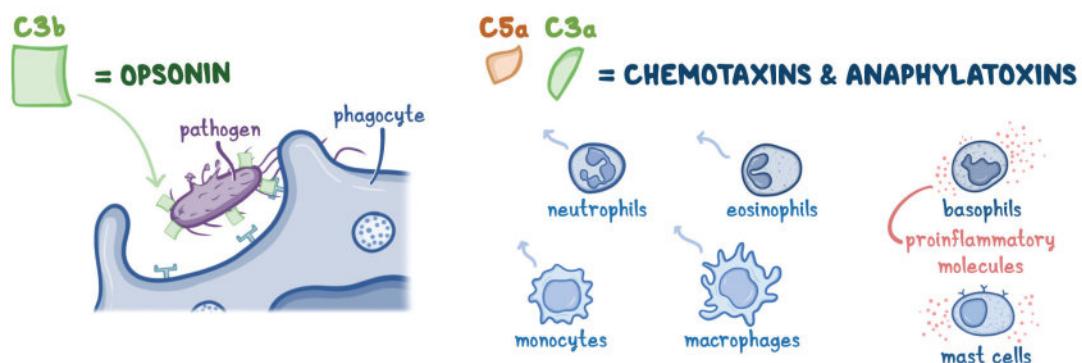
1. C1q binds to an antibody-antigen complex.
2. When two C1q proteins are bound, C1 undergoes a conformational change, exposing C1r and C1s. C1r then cleaves C1s to activate C1.
3. C1 cleaves C4 and C2.
4. C4 and C2 bind to the surface of the pathogen, forming C3 convertase.
5. C3 convertase cleaves C3.
6. C3b binds to the pathogen near the C3 convertase, forming C5 convertase.
7. C5 convertase cleaves C5.
8. C5b joins C6, C7, C8, and then multiple C9s to form the membrane attack complex, penetrating the pathogen cell membrane.



**Figure 47.5** Overview of the lectin pathway. Mannose-binding lectin protein binds to mannose on the pathogen, then cleaves C4 and C2. The rest follows the classical pathway (from step 4 in earlier figure).

## OTHER COMPLEMENT PROTEIN ROLES

- In addition to MAC-formation
  - C3b: **opsonin** → opsonizes pathogens, coats them with molecules, **encourages phagocytosis**
  - C5a, C3a: **chemotaxins** → recruit **neutrophils, eosinophils, monocytes, macrophages**
  - C5a, C3a: **anaphylatoxins** → cause **basophil, mast cell degranulation, releases proinflammatory molecules**



**Figure 47.6** Other roles of complement proteins. C3b acts as an opsonin; it coats pathogens to facilitate phagocytosis. C5a and C3a act as chemotaxins; they recruit neutrophils, eosinophils, monocytes, and macrophages. C5a and C3a also act as anaphylatoxins; they cause basophils and mast cells to degranulate.



# NOTES

## BONES, JOINTS, & CARTILAGE

# SKELETAL SYSTEM ANATOMY & PHYSIOLOGY

[osms.it/skeletal-system-anatomy-physiology](http://osms.it/skeletal-system-anatomy-physiology)

## SKELETAL BASICS

- 206 bones in skeleton
- Separated into axial, appendicular skeleton

### Axial skeleton

- Vertical axis of body; 80 bones (22 in skull, 33 vertebrae, 24 ribs, 1 sternum)

### Appendicular skeleton

- Supports limbs; pectoral girdle (clavicles, scapulae) holds humeri, pelvic girdle (hip bones) holds femora; 126 bones (4 in shoulders, 6 arms, 54 hands, 2 hips, 8 legs, 52 feet)

## TYPES OF BONES

### Long bones

- Length > width
- Humerus, radius, ulna (in arms); metacarpals, phalanges (hands, fingers); femur, tibia, fibula (legs); metatarsals, phalanges (feet, toes)
- Primarily responsible for height

### Short bones

- Similar length, width
- Carpal bones (in wrists); tarsal bones (ankles)
- Support hands, feet

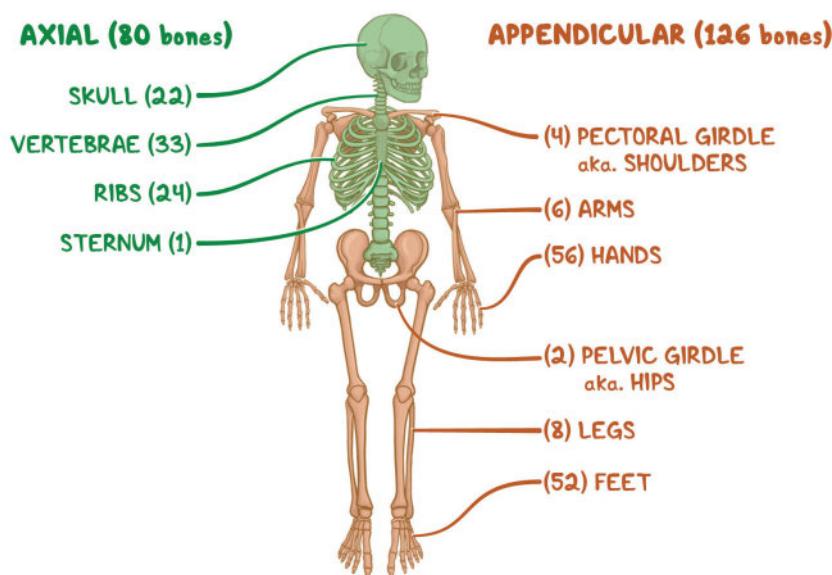


Figure 48.1 Overview of skeleton.

### Flat bones

- Thin, sometimes curved
- Skull bones; scapulae, sternum, ribs
- Protect vital organs

### Sesamoid bones

- Embedded in tendons, shaped like giant sesame seeds
- Pisiform bone (in wrists); patella (knees)
- Support, protect, give additional leverage to tendons

### Irregular bones

- Facial bones; mandible; vertebrae; sacrum, coccyx

## SURFACE FEATURES OF BONES

### Sites of muscle, ligament attachment

- Tubercls, tuberosity: small bumps on bone, serve as attachment sites for muscles; large tubercle → tuberosity; deltoid tuberosity (on humerus)
- Process: bony prominence; xiphoid process (sternum)
- Crest: narrow ridge; iliac crest (ilium)

### Projections

- Part of joints
- Condyle: rounded, articular projection; lateral, medial condyles (femur); epicondyle → raised portion on/above condyle (lateral, medial epicondyles)
- Ramus: arm-like section; mandibular ramus (mandible)

### Openings, passageways, depressions

- Foramen: holes in bone, allow blood vessels/nerves through; foramen magnum (in occipital bone of skull)
- Canal/meatus: tunnels, allow blood vessels/nerves through; optic canal (sphenoid bone); external auditory meatus (temporal bone of ear)
- Sinuses, cavities: empty spaces within/between bones; nasal cavity, paranasal sinuses
- Fossa: depressions where other structures rest; hypophyseal fossa (sphenoid bone)

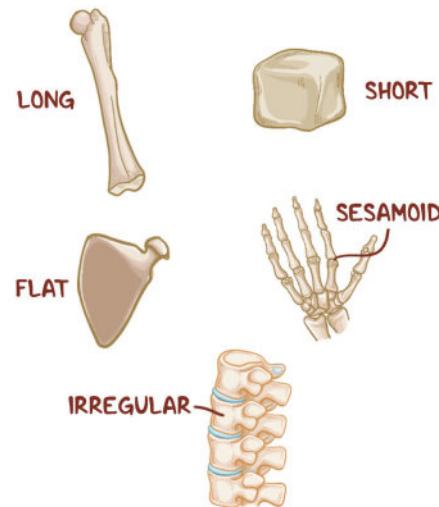


Figure 48.2 Types of bones.

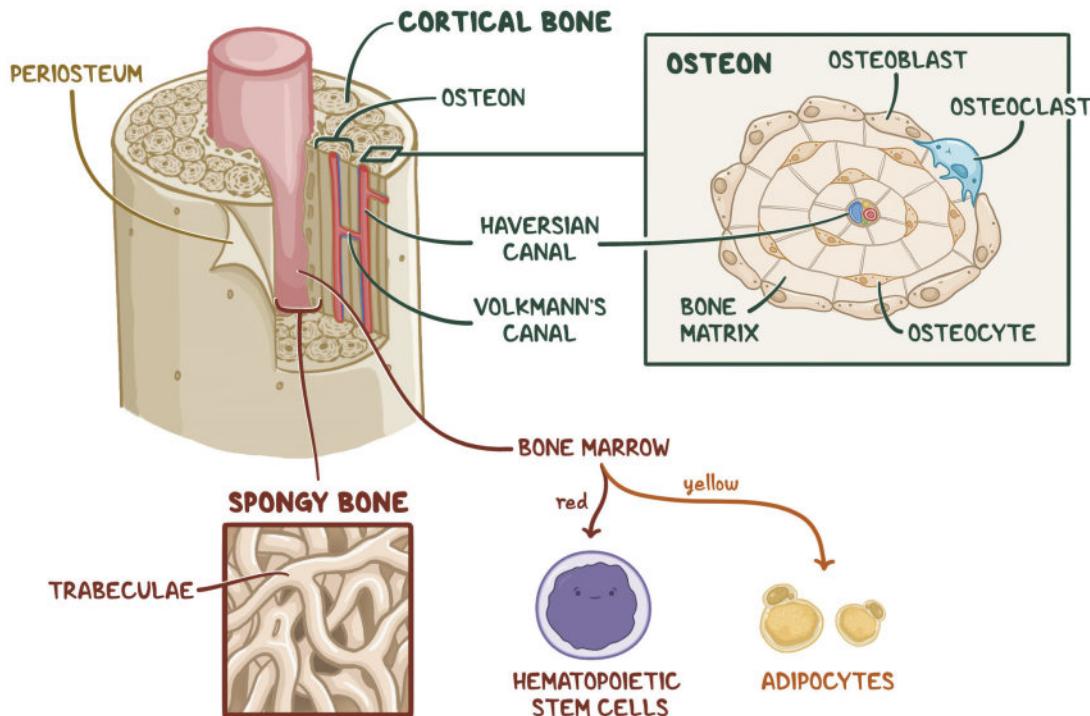
## STRUCTURE OF BONE

### Cortical/compact bone

- Surrounded by periosteum
- Contains pipe-like structures called osteons
- Osteons contain hollow centers (Haversian canals) for nerves, blood cells; connected laterally by Volkmann's canals
- Osteon walls made of bone matrix (type I collagen reinforced with hydroxyapatite), produced by osteoblast cells
- Some osteoblasts get trapped in bone matrix → mature into osteocytes → repair old/broken bone
- Osteoclast cells secrete enzymes → break down bone matrix → release calcium, phosphate into blood

### Trabecular/spongy bone

- Similar material to cortical bone
- Looser structure; branching rods called trabeculae
- Contains bone marrow, consists of hematopoietic stem cells ("red marrow"), adipocytes/fat cells ("yellow marrow")
  - Appendicular bones often contain red marrow at tips, yellow marrow in hollow medullary cavity (center)
- Axial bones mostly red marrow



**Figure 48.3** Bone cross-section showing structure which consists of cortical bone and spongy bone. Spongy bone contains two types of bone marrow, each made up of a different kind of cell.

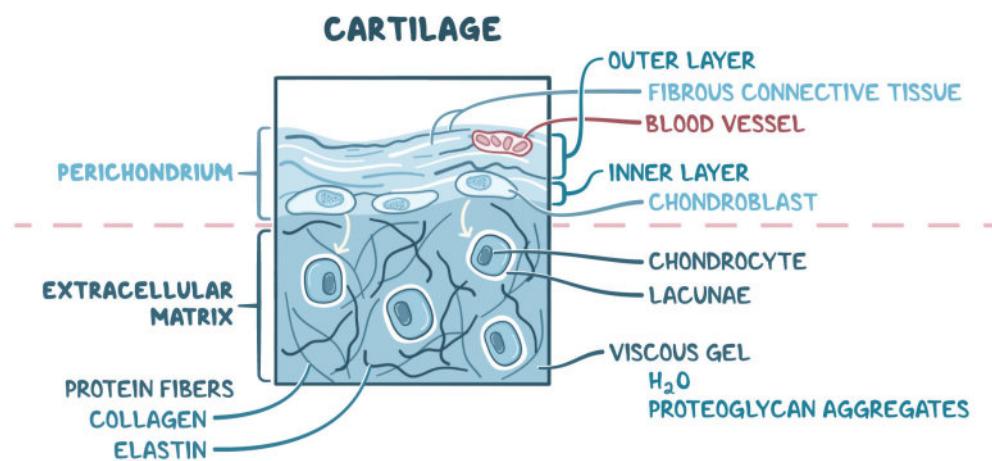
## CARTILAGE

[osms.it/cartilage](https://osms.it/cartilage)

### WHAT IS CARTILAGE?

- Strong, flexible connective tissue
  - Comprises part of nose, ears
  - Provides cushioning between joints
  - Supports/connects body parts (e.g. costal cartilage connects ribs to sternum)
- **Perichondrium**: connective tissue that wraps around cartilage
  - Outer layer contains fibrous connective tissue, blood vessels
  - Inner layer contains chondroblasts → secrete proteins that make extracellular matrix

- **Extracellular matrix**: protein fibers (collagen for strength; elastin for flexibility) suspended in viscous gel (water, proteoglycan aggregates)
  - **Chondrocytes**: chondroblasts trapped in lacunae (small holes) of matrix; maintain, repair extracellular matrix
  - **Proteoglycan aggregates**: hyaluronan (long chain of hyaluronic acid molecules) with hundreds of proteoglycans (proteins + long chains of glycosaminoglycan sugars—GAGS) branching off



**Figure 48.4** Cross-section through cartilage showing its histological structure. Perichondrium wraps around extracellular matrix. Chondroblasts originally in perichondrium become chondrocytes as they become trapped in the extracellular matrix.

## TYPES

- Three main cartilage types

### Elastic cartilage

- Least common type
- ↑ chondrocyte density; ↓ protein fiber density (mostly loose **elastin** fibers, some type II collagen fibers)
- Softest, most flexible cartilage
- Ear pinnae, throat epiglottis

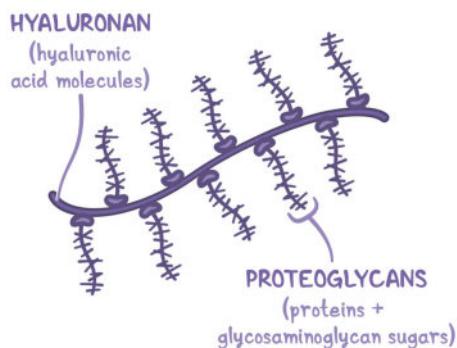
### Hyaline cartilage

- Most common type
- Medium chondrocyte density; medium protein fiber density (mostly **type II collagen** fibers, some loose elastin fibers)
- Stronger, but less flexible cartilage; ↓ friction surface
- Embryonic skeleton (eventually replaced by bone); nose; larynx walls; tracheal, costal cartilages; growth plates; articular cartilages

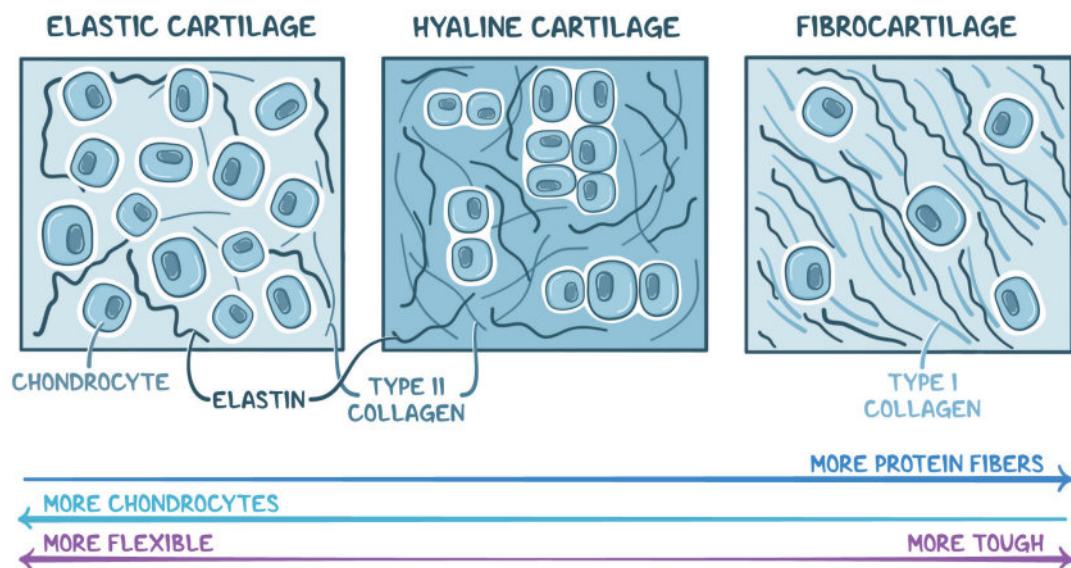
### Fibrocartilage

- ↓ chondrocyte density; ↑ protein fiber density (mostly **type I collagen** fibers)
- Most tensile strength; resistant to compression, stretching; ↓ flexible
- Meniscus of knee, spinal intervertebral discs

## PROTEOGLYCAN AGGREGATE



**Figure 48.5** Proteoglycan aggregate, found in viscous gel of the extracellular matrix.



**Figure 48.6** Histology, characteristics of the three main cartilage types.

## GROWTH PATTERNS

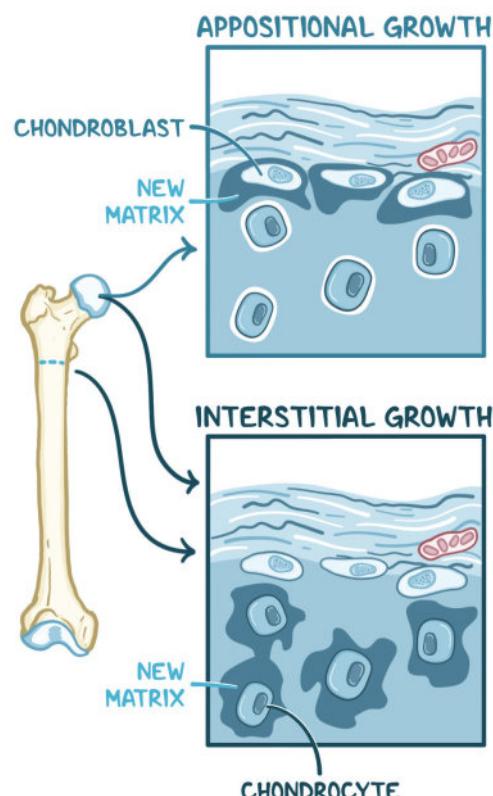
- Two cartilage growth patterns
- Both growth patterns present in growing bones of children, teenagers (e.g. femur)
  - Chondrocytes in growth plate → interstitial growth → cartilage lengthens → **osteoblasts turn cartilage into bone**
  - Articular cartilage on tips of bone experience both appositional, interstitial growth

### Appositional growth

- Chondroblasts secrete new matrix on existing surfaces → cartilage expands, widens

### Interstitial growth

- Chondrocytes secrete new matrix within cartilage → cartilage grows in length



**Figure 48.7** The two cartilage growth patterns. Both types of growth occur in articular cartilage. In the growth plate, only interstitial growth occurs.

# BONE REMODELING & REPAIR

[osms.it/bone-remodeling-repair](https://osms.it/bone-remodeling-repair)

## BONE REPAIR

- Old bone removed/resorbed (broken down) before new tissue replaces it

- Osteoblasts sense microcracks, secrete receptor activator of nuclear factor  $\kappa\beta$  ligand (RANKL)
- RANKL binds to RANK receptors on monocytes → causes them to fuse, form multinucleated osteoclast cells
- Osteoclasts secrete lysosomal enzymes (mostly collagenase) → digest collagen in bone matrix → create surface holes (Howship's lacunae), hydrochloric acid → dissolves hydroxyapatite into soluble calcium, phosphate

(Howship's lacunae), hydrochloric acid → dissolves hydroxyapatite into soluble calcium, phosphate

- Osteoblasts secrete osteoprotegerin → deactivates RANKL, slows down osteoclast activity (before osteoclast apoptosis), osteoid seam (mostly collagen) → fill in Howship's lacunae
- Calcium, phosphate deposit on seam forming hydroxyapatite
- Some osteoblasts get trapped within lacunae → turn into osteocytes

## BONE REPAIR

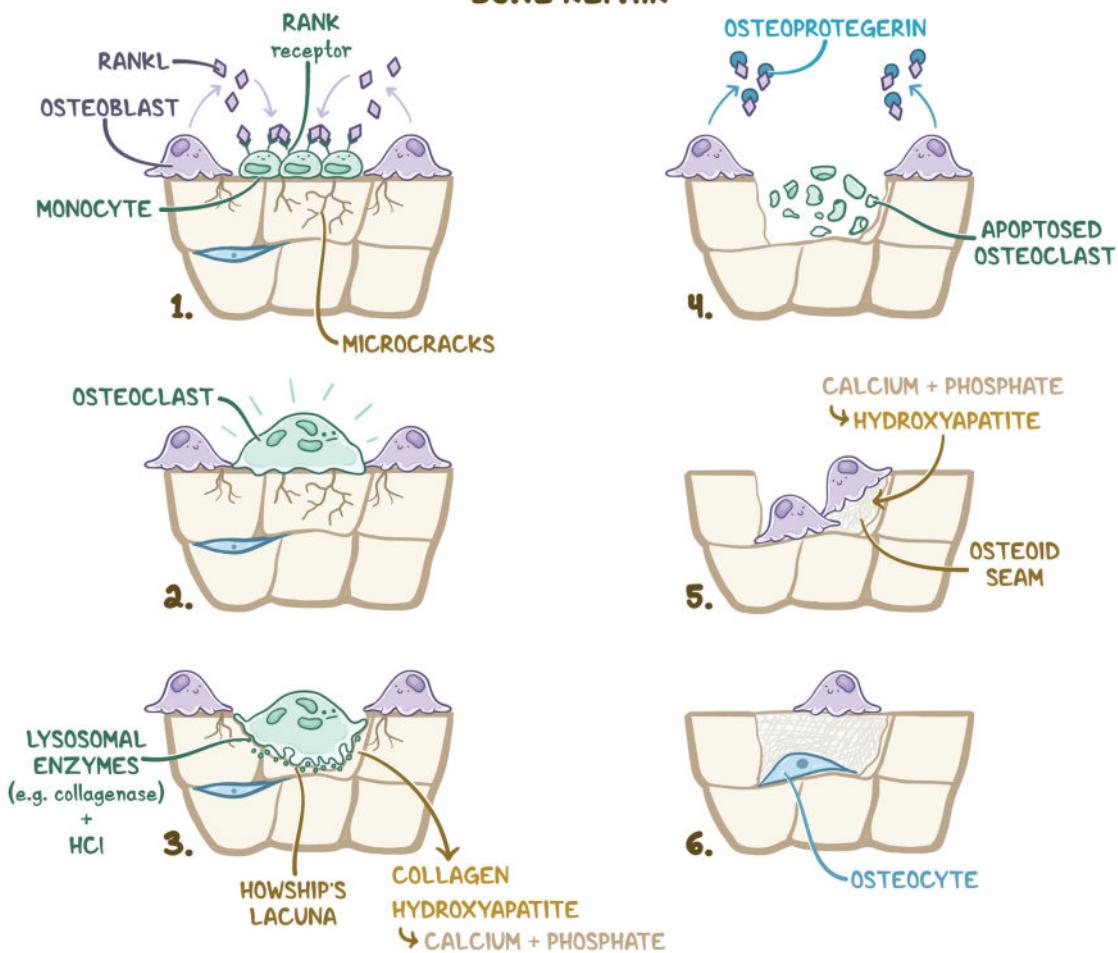


Figure 48.8 Summary of bone repair.

## REMODELING FACTORS

- Hormonal
  - Parathyroid hormone enhances bone resorption
  - Calcitonin inhibits bone resorption
  - Vitamin D ( $\rightarrow \downarrow$  calcitonin) enhances bone resorption
- Mechanical (physical stress)
  - Wolff's law: bones that bear more weight remodel more

# FIBROUS, CARTILAGE, & SYNOVIAL JOINTS

[osms.it/fibrous-cartilage-synovial-joints](https://osms.it/fibrous-cartilage-synovial-joints)

## TYPES

- Classification based on movement of three main groups
  - Fibrous joints: no movement
  - Cartilaginous joints: some movement
  - Synovial joints: freely movable

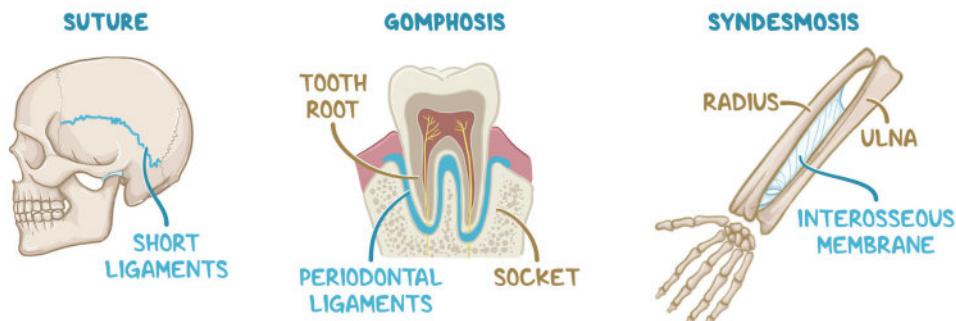
## FIBROUS JOINTS

- Synarthrosis/fixed joints
- Bones are connected by ligaments

### Three main categories (based on location)

- Sutures: junctions between adjacent skull bones; Sharpey's fibers connect bones; fixed (non-fused in babies  $\rightarrow$  partially movable)
- Gomphoses: peg-and-socket joints for teeth; periodontal ligaments connect roots of teeth to sockets; slightly movable
- Syndesmoses: remaining fibrous joints; connected by interosseous membrane (e.g. between radius, ulna); slightly movable

## FIBROUS JOINTS



**Figure 48.9** Three main categories of fibrous joints.

## CARTILAGINOUS JOINTS

- Hyaline cartilage connects bones, stretches to allow some movement
- **Synchondrosis:** costochondral joint, where cartilage attaches rib to sternum; growth plates between bone diaphysis, epiphysis
- **Symphysis:** symphysis pubis in pelvic bone (fibrous cartilage)
  - ↑ strength, ↓ flexibility

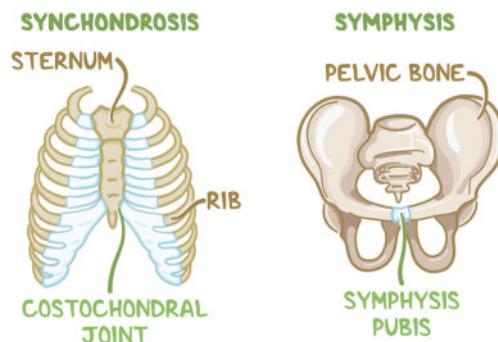
## SYNOVIAL JOINTS

- Joint capsule connects bones
  - Composed of outer fibrous capsule, inner synovial membrane
  - Filled with synovial fluid: lubricates joint, absorbs shock; made of hyaluronic acid, lubricin, proteinases, collagenases
  - Articular cartilage covers tips of bones (same function)
- Allow for abduction, adduction, rotation about axis

### Six main categories (based on structure, movement)

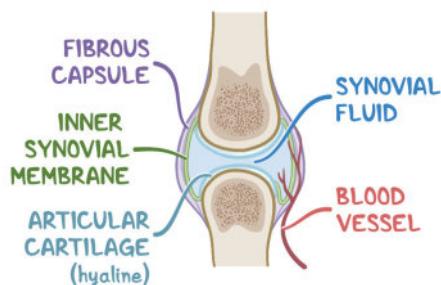
- **Hinge joints:** allow movement only in one axis (e.g. between humerus, ulna)
- **Pivot joints:** allow for rotation (e.g. between head of radius, groove of ulna)
- **Plane (gliding) joints:** allow flat bones to glide across one another (e.g. in carpal, tarsal bones)
- **Ball and socket joints:** allow all movements (e.g. shoulder joint)
- **Condyloid (ellipsoid) joints:** allow most movements, but not rotation (e.g. metacarpophalangeal, metatarsophalangeal joints)
- **Saddle joints:** allow most movements, with limited rotation (e.g. carpometacarpal joint)

## CARTILAGINOUS JOINTS



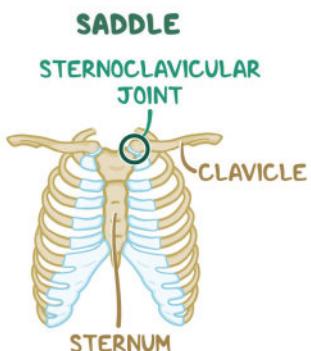
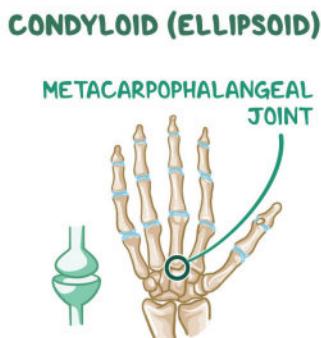
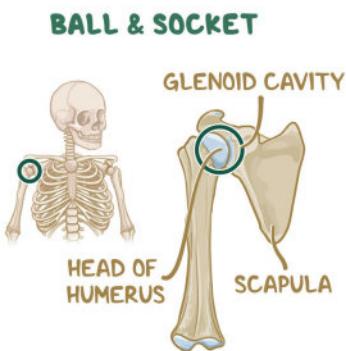
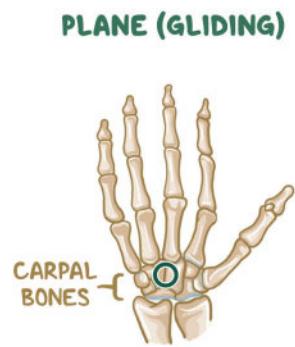
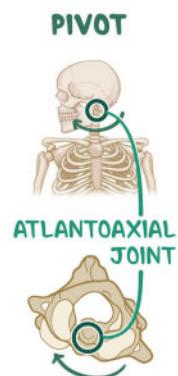
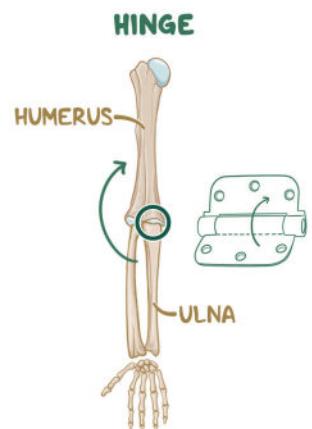
**Figure 48.10** The two categories of cartilaginous joints (with examples).

## JOINT CAPSULE



**Figure 48.11** Synovial joint cross-section showing joint capsule.

## SYNOVIAL JOINTS



**Figure 48.12** The six categories of synovial joints (with examples). Joints circled in green.



# NOTES MUSCLES

## MUSCULAR SYSTEM ANATOMY & PHYSIOLOGY

[osms.it/muscle-anatomy-physiology](https://osms.it/muscle-anatomy-physiology)

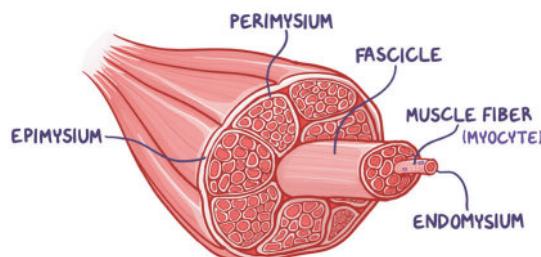
- Three types of muscle cell/tissue
  - Skeletal, cardiac, smooth
- Differ in location, innervation, cell structure
  - All cells excitable, extensible, elastic

### SKELETAL MUSCLE

- Attaches to bone/skin; mostly voluntary; maintains posture, stabilizes joints, generates heat
- Most muscles consist of belly (contracts), tendons

### Connective tissue

- Layers of connective tissue separate muscle belly
  - Epimysium: wrapped around muscle
  - Perimysium: wrapped around fascicles in muscle
  - Endomysium: wrapped around muscle fibers/cells (e.g. myocytes in fascicles)



**Figure 49.1** Cross section of skeletal muscle illustrating connective tissue layers, fascicles, muscle fibers.

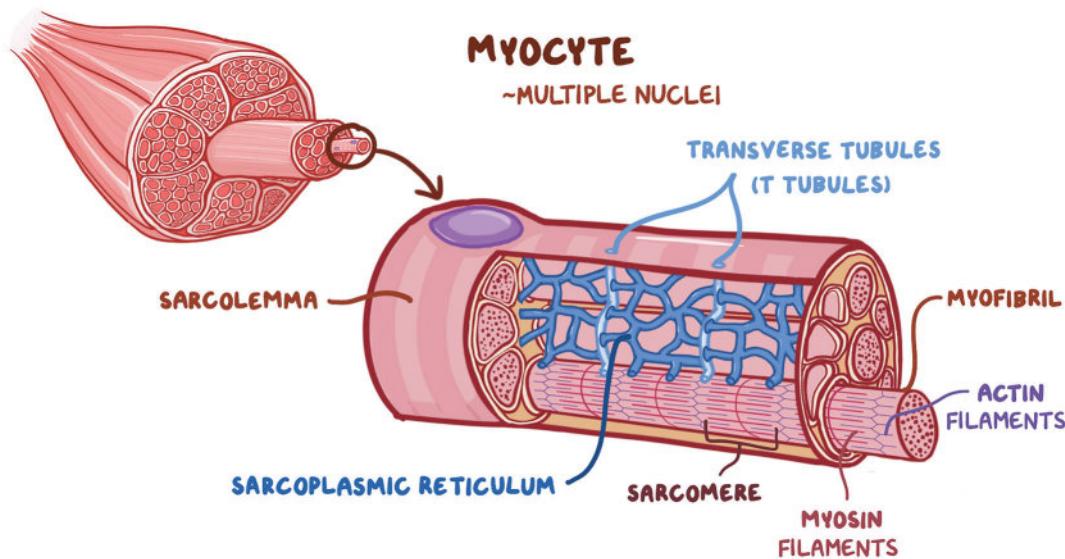
- Combine at end to form tendons
  - Origin attaches to stationary bone; insertion attaches to moving bone

### Myocytes

- Long cylindrical cells with multiple nuclei
- Cell membrane → sarcolemma
- Cytoplasm → sarcoplasm
  - Contains smooth endoplasmic reticulum → sarcoplasmic reticulum (stores calcium)
- Transverse tubules (T tubules) project from sarcolemma to center of muscle
- Long filaments called myofibrils fill sarcoplasm, contain thin actin filaments, thick myosin filaments (arranged into sarcomeres)

### Motor signals

- Brain's motor signals control skeletal system
- Motor neurons release acetylcholine receptors onto sarcolemma → rapid ion shifts across sarcolemma, down T tubules → calcium enters myocyte → sarcoplasmic reticulum releases calcium into sarcoplasm → actin, myosin bind → sarcomeres contract → myocyte contracts → sarcoplasmic reticulum grabs calcium → muscle relaxes



**Figure 49.2** Composition of a myocyte.

## CARDIAC MUSCLE

- Involuntary, striated muscle; found only in heart walls
- Shorter than skeletal muscle; branched and interconnected
- 1–2 central nuclei per fiber
- Numerous mitochondria provide resistance to fatigue
- Pacemaker cells demonstrate automaticity; generate action potentials

### Intercalated discs

- Composed of gap junctions and desmosomes
  - Gap junctions: areas of low resistance, allows fast signal propagation between cardiomyocytes (coordinated contraction of cells)
  - Desmosomes: anchor the cells together; keeps cells from pulling apart during contraction
  - Allows heart to work as a unit (functional syncytium; syn = together, citos = cell)

### T tubules/transverse tubules

- Invaginate from sarcolemma
- Also serve faster propagation
  - Help conduct signal deeper into cell, enabling more synchronized contraction
  - Run along Z bands, communicate with sarcoplasmic reticulum ( $\text{Ca}^{2+}$  storage)

### Thick and thin filaments

- Like skeletal muscle, cardiac myofibrils contain sarcomeres bounded by Z bands
  - Z bands: perpendicular to myofibril, attached to thin filaments
  - Thick filaments lie between Z bands
  - All proteins involved are globular
- Thick, thin filaments slide over each other  
→ contraction

### Thick filaments

- Myosin: tail with two heads
  - Each head has ATPase, actin binding sites

### Thin filaments

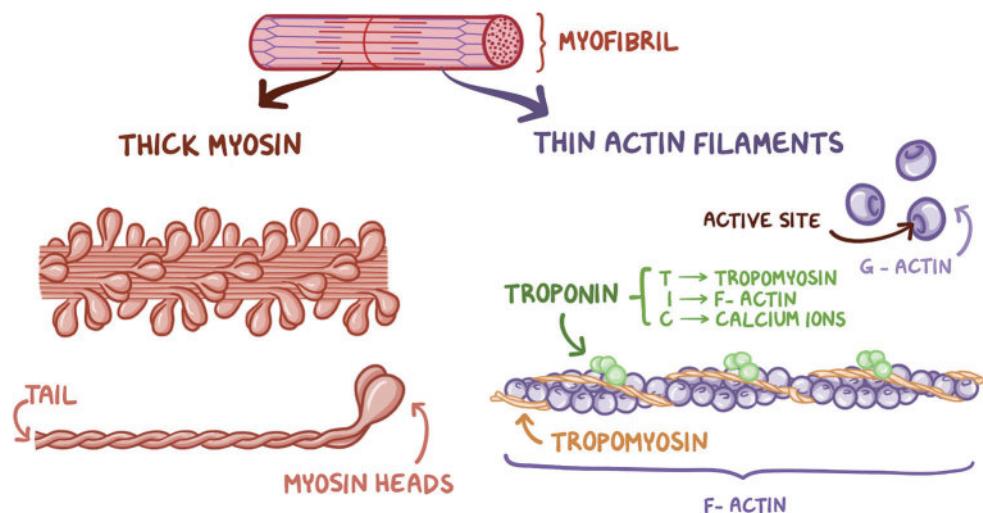
- Actin: globular/G-actin polymerizes into a strand of filamentous/F-actin
  - Two F-actins twist into strand with myosin binding site
- Tropomyosin: site blocker, prevents contraction by disabling attachment of myosin to actin
- Troponin: molecule composed of three subunits:
  - C:  $\text{Ca}^{2+}$  binding → stops troponin inhibition of actin
  - I: Inhibitory → inhibits ATPase
  - T: → relaxed state attachment of troponin complex to actin; myocardial infarction marker in blood

### Endomysium (intercellular connective tissue)

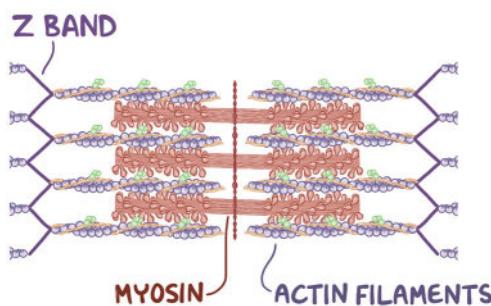
- Contains capillaries, nerves
- Provides support, elasticity; separates cells
- Maintained by fibroblasts

### SMOOTH MUSCLE

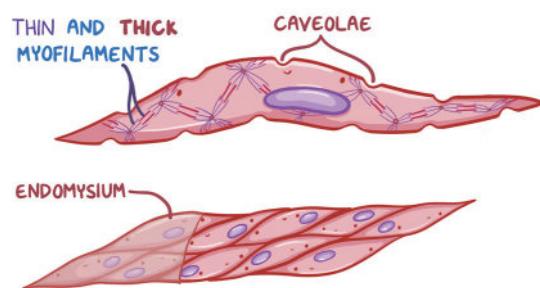
- Often found in hollow organs (e.g. intestines, bladder, uterus, blood vessels); involuntary muscle
- Smooth muscle cells fusiform, only one nucleus
- No T tubules; invaginations called caveolae
- Thin, thick myofilaments; no sarcomeres → "smooth" appearance



**Figure 49.3** Appearance of myosin and actin filaments.



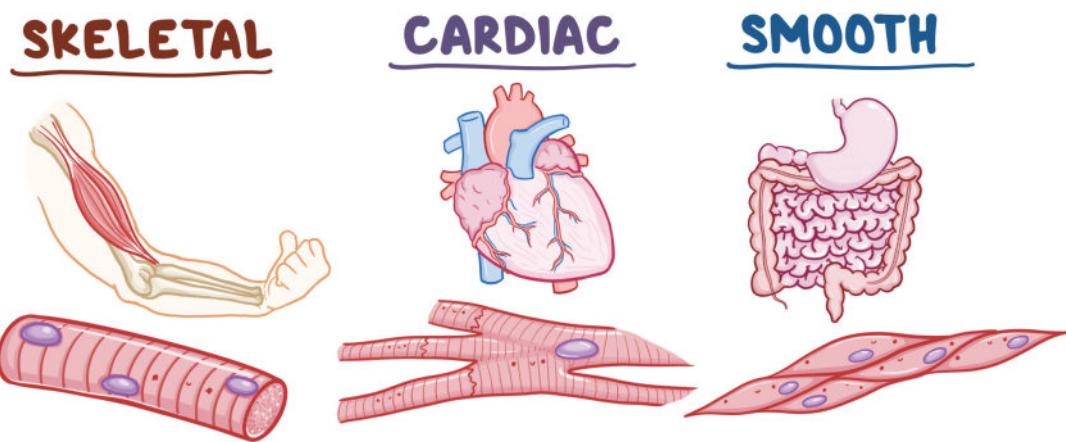
**Figure 49.4** Z bands are the boundaries between sarcomeres in skeletal and cardiac muscles.



**Figure 49.5** Features of smooth muscle cells.

## TYPES OF MUSCLE

	SKELETAL	SMOOTH	CARDIAC
LOCATION	Attached to bones	Forms walls of hollow organs Lines blood vessels, glands	Heart
NEUROLOGICAL CONTROL	Voluntary  Involuntary (reflexes, shivering)  Innervation: somatic nervous system  Neurotransmitter: ACh	Involuntary  Innervation: autonomic nervous system  Neurotransmitter: ACh, NE  Also regulated by hormones (e.g. oxytocin), locally-produced substances (e.g. histamine)  Autorhythmicity (e.g. visceral smooth muscle in digestive tract)  Contracts in response to being stretched	Involuntary  Innervation: autonomic nervous system  Neurotransmitter: ACh  Autorhythmicity: pacemaker cells
FUNCTIONS	Movement, posture, stabilization of body  Shivering thermogenesis  Voluntary control of micturition (external sphincter)	Wide distribution  Digestive tract: movement of food  Urinary: bladder emptying  Vascular: vessel diameter  Sensory: pupil size changes  Endocrine: contraction of glands	Propulsion of blood
CELL CHARACTERISTICS	Long, cylindrical, striated	Spindle-shaped	Cylindrical, striated, branched
NUCLEUS	Multiple	One, centrally located	One, centrally located
SPECIAL CELL-TO-CELL CHARACTERISTICS	None	Gap junctions in some visceral cells	Intercalated discs  Desmosomes  Gap junctions



**Figure 49.6** An illustration of the three types of muscle: skeletal, cardiac, and smooth.

## SLOW TWITCH & FAST TWITCH MUSCLE FIBERS

[osms.it/slow-fast-twitch-muscle-fibers](https://osms.it/slow-fast-twitch-muscle-fibers)

- Each action potential generates brief muscle contraction (AKA twitch)
- Twitches overlap to create longer, smooth muscle contractions

### Skeletal muscle fibers

- Slow twitch (AKA slow oxidative)
- Fast twitch (AKA fast oxidative, fast glycolytic)
- Slow twitch fibers → slow-functioning ATPases → slower individual twitches
- Fast twitch fibers → fast-functioning ATPases → longer individual twitches

### SLOW OXIDATIVE FIBERS

- AKA Type I fibers
- Have aerobic respiration pathway for metabolizing glucose
- Relatively small → weakest contractions
- ↑ blood vessels, ↑ myoglobin → red color
  - AKA “slow red muscle fibers”
- ↑ mitochondria supports aerobic respiration
- Generate lots of ATP, use little; ↓ glycogen storage
- Sustain muscle ability for long time

### FAST OXIDATIVE FIBERS

- AKA Type IIa fibers
- Have aerobic respiration pathway for metabolizing glucose
- Larger than slow fibers → stronger contractions
- ↑ blood vessels, ↑ myoglobin → red color
  - AKA “fast red muscle fibers”
- ↑ mitochondria supports aerobic respiration
- Generate lots of ATP, use more; ↑ glycogen storage
- Fatigue quickly

### FAST GLYCOLYTIC FIBERS

- AKA Type IIx fibers
- Have anaerobic respiration pathway for metabolizing glucose
- Largest fibers → stronger contractions
- ↓ blood vessels, ↓ myoglobin → white color
  - AKA “white muscle fibers”
- ↓ mitochondria
- Generate little ATP, use lots; ↑ glycogen storage
- Fatigue fastest

# SLIDING FILAMENT MODEL OF MUSCLE CONTRACTION

[osms.it/sliding-filament-model](http://osms.it/sliding-filament-model)

## MECHANISM OF MUSCLE CONTRACTION AFTER POWER STROKE

- Thick myosin filaments pull thin actin filaments towards M-line → sarcomere shortens; A-band of the muscle does not change, but H-, I-bands shorten
- At max contraction, almost complete overlap of thick, thin filaments; H-, I- bands almost completely gone

## FACTORS DETERMINING CONTRACTION FORCE

### Size of muscle fibers

- Larger muscle fibers → ↑ filaments → ↑ cross-bridges → stronger contraction

### Number of active muscle fibers

- ↑ muscle fibers → stronger contraction

### Frequency of stimulation (force-frequency relationship)

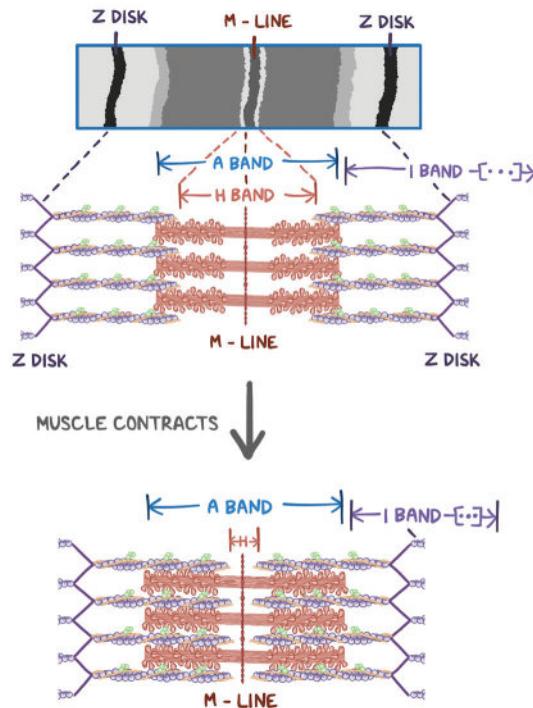
- ↑ frequency of stimulation → ↑ calcium ions flow from sarcoplasmic reticulum into sarcoplasm → ↑ bind to troponin regulatory proteins on actin filaments → ↑ myosin binding → stronger contraction

### Length of sarcomere

- AKA length-tension relationship
- Longer sarcomere → stronger contraction; directly proportional

### Velocity of muscle shortening

- AKA force-velocity relationship
- Slower contraction → stronger contraction



**Figure 49.7** The changes that occur when muscle contracts.

# ATP & MUSCLE CONTRACTION

[osms.it/ATP-and-muscle-contraction](https://osms.it/ATP-and-muscle-contraction)

## MUSCLE TONE

- Force applied to muscles at rest

## MUSCLE TENSION

- Pulling force when muscles act

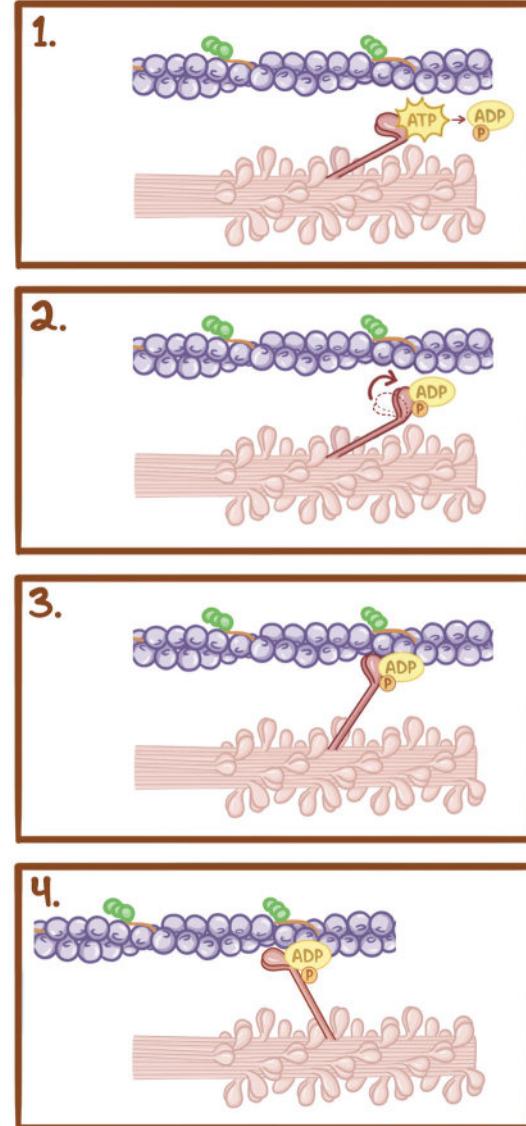
## MUSCLE CONTRACTION

- Action potential travels along sarcolemma, reaches T-tubule, stimulating dihydropyridine (DHP) receptors
- DHP receptor stimulation opens ryanodine receptors
  - AKA calcium channels
- Calcium from sarcoplasmic reticulum flows into sarcoplasm, binds to C-subunits of troponin regulatory proteins
- Troponin changes shape, moving tropomyosin out of the way, allowing actin to be bound by myosin head's cross-bridge formation
- Energy cocks myosin head backwards → high-energy position
- Myosin head can then launch towards M-line, pulling actin filament with it
  - AKA power stroke
- Action potential ends → calcium ions pumped back into sarcoplasmic reticulum → C-subunit of troponin no longer bound → tropomyosin, troponin cover back up actin's active sites → no myosin binding (cross-bridge detaches) → muscle relaxes

## ISOTONIC VS. ISOMETRIC CONTRACTIONS

- Isotonic: muscle length changes but tension stays same
- Isometric: muscle length stays same but tension increases

## SAITO SAYS HI



**Figure 49.8** Muscle contraction.

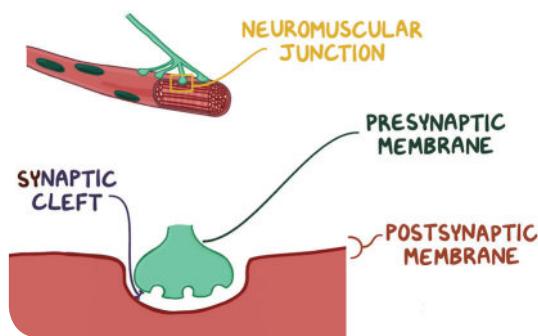
- 1: Part of myosin head is an ATPase; it cleaves ATP into ADP and phosphate ion.
- 2: Myosin head uses this energy to tip back into its high-energy position.
- 3: Myosin head binds to active site on actin, triggering release of stored energy in myosin head.
- 4: Power stroke (myosin head launches, pulling actin with it).

# NEUROMUSCULAR JUNCTION & MOTOR UNIT

[osms.it/neuromuscular-junction-motor-unit](https://osms.it/neuromuscular-junction-motor-unit)

## NEUROMUSCULAR JUNCTION

- Where axon terminal meets muscle fiber
- Presynaptic membrane
  - Membrane of axon terminal
- Postsynaptic membrane
  - AKA motor end plate
  - Membrane of skeletal muscle fiber
- Synaptic cleft
  - Gap between membranes



**Figure 49.9** Illustration of the neuromuscular junction.

## ACTION POTENTIAL GENERATION IN MUSCLE FIBER

- Action potentials in axon terminal stimulate voltage-gated calcium channels in presynaptic membrane → extracellular calcium ions flow into the axon terminal
- Calcium binds to acetylcholine-containing vesicles in axon terminal → vesicles fuse with presynaptic membrane, acetylcholine released into synaptic cleft
- Two acetylcholine molecules bind to one ligand gated ion channel
  - AKA nicotinic receptor
  - On motor end plate → sodium ions flow into muscle

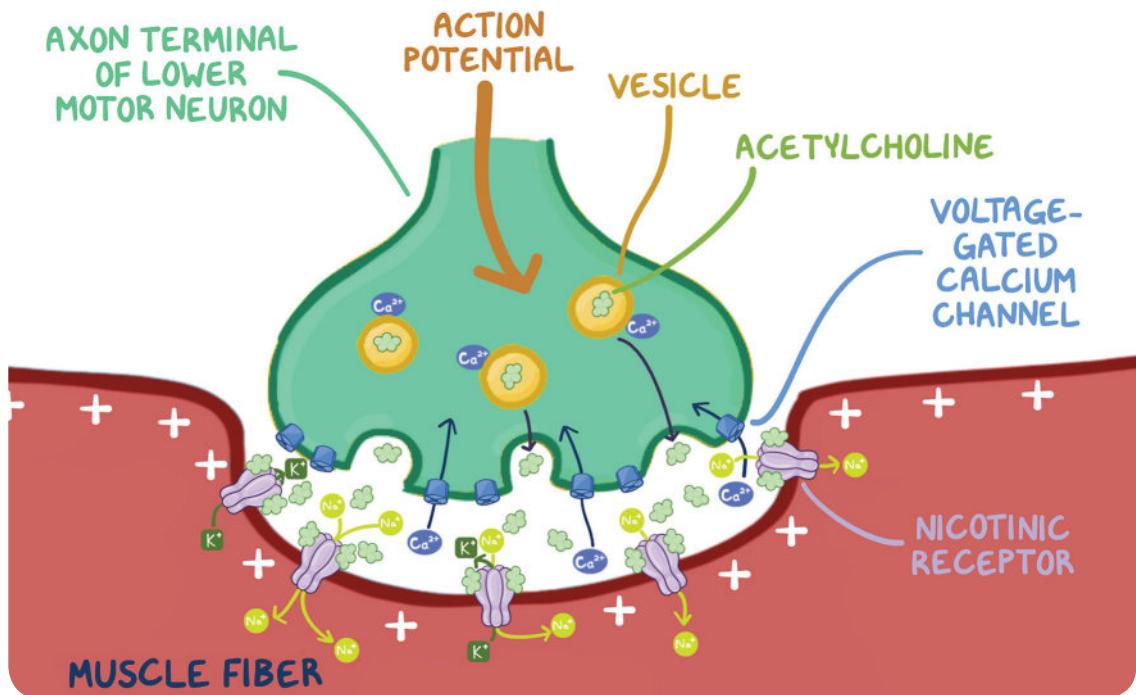
- Positive charge builds up inside muscle fiber → creates end plate potential
  - AKA depolarization
- Resting potential of membrane: -100mV → -60mV
- Voltage-gated sodium channels open up → more sodium ions flow in, generating action potential in muscle fiber

## ACTION POTENTIAL CESSATION IN MUSCLE FIBER

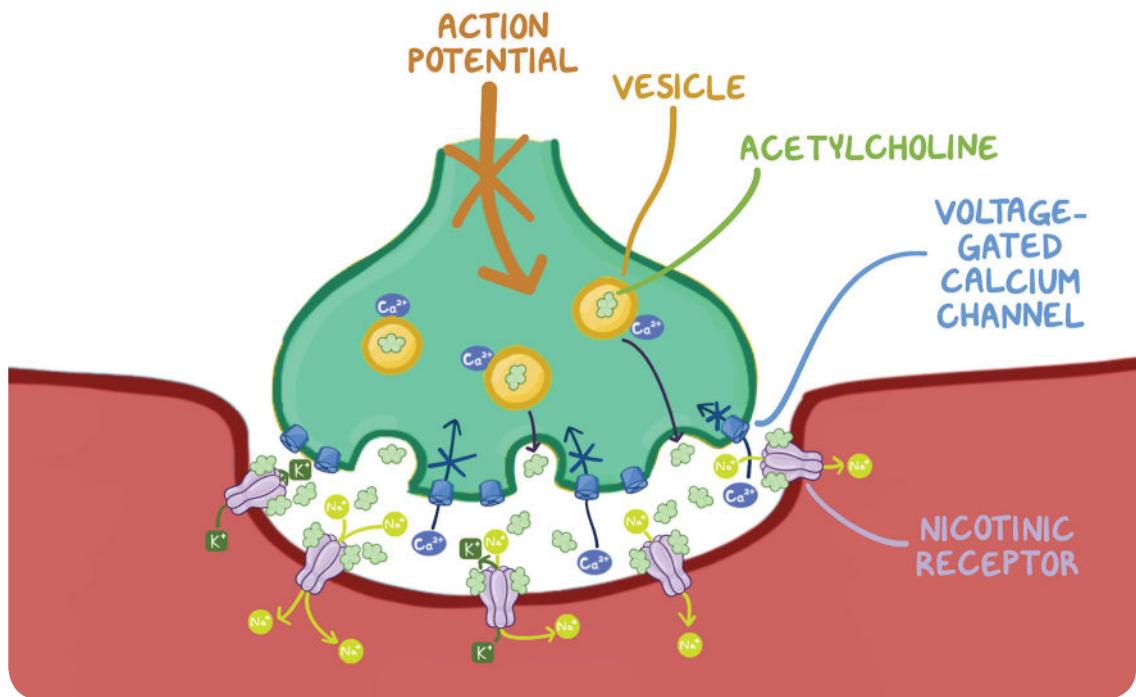
- Action potential in axon stops → voltage-gated calcium channels close → influx of calcium ions to axon terminal stops → synaptic vesicles stop fusing with membrane
- Remaining acetylcholine in cleft degraded by acetylcholinesterase into choline, acetate → choline taken back into axon terminal → acetylcholine transferase makes new acetylcholine → acetate diffuses away

## MOTOR UNITS

- One lower motor neuron, fibers it innervates form single motor unit
- On average, one lower motor neuron innervates 150 skeletal muscle fibers
- More precise muscles → smaller motor units; e.g. 10–15 muscle fibers per neuron in eye
- Less precise muscles → larger motor units (e.g. ≤ 2000 muscle fibers per neuron in bicep)



**Figure 49.10** Action potential generation in muscle fiber. Influx of sodium ions leads to buildup of positive charge inside muscle fiber. Action potential generated → muscle fiber contracts.



**Figure 49.11** Action potential cessation in muscle fiber. Action potential in axons stops → voltage-gated calcium channels close → influx of calcium stops → synaptic vesicles stop fusing with membrane.



# NOTES

## ANATOMY & PHYSIOLOGY

# NERVOUS SYSTEM ANATOMY & PHYSIOLOGY

[osms.it/nervous-system-anatomy-physiology](https://osms.it/nervous-system-anatomy-physiology)

## THE NERVOUS SYSTEM

- Network of brain, spinal cords, nerves
- Sensory/afferent, integrative, motor/efferent functions

### Sensory/afferent

- Receptors monitor external, internal environment
  - Conscious stimuli (e.g. vision, hearing, touch)
  - Unconscious stimuli (e.g. pH, blood pressure)

### Integrative

- Sensory/afferent input received by central nervous system → information processed → interpreted → response initiated

### Motor/efferent

- Brings motor information from central nervous system to periphery
- Controls actions of effector organs (e.g. muscles, glands)

## ORGANIZATION OF THE NERVOUS SYSTEM

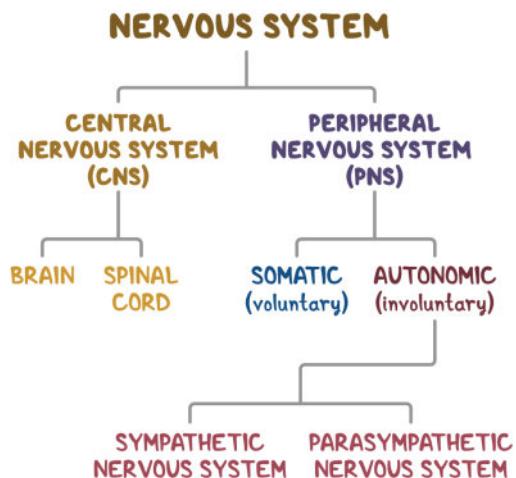
### Central nervous system (CNS)

- Brain, spinal cord

### Peripheral nervous system (PNS)

- Nerves connect PNS with CNS
- Includes 12 pairs of cranial nerves, 31 pairs of spinal nerves
- Efferent (motor), afferent (sensory) divisions

- Efferent divided into somatic (voluntary), autonomic (involuntary) nervous systems
- Autonomic nervous system comprised of sympathetic, parasympathetic nervous systems
- Sensory receptors: structure at nerve ending; detects physical, environmental stimulus; e.g. pain, temperature
- Ganglia/ganglion (plural/singular): collection of neuron cell bodies outside CNS
- Plexuses/plexus (plural/singular): network of nerves outside CNS



**Figure 50.1** Organization of the nervous system.

## CELLS OF THE NERVOUS SYSTEM: NEURON

- Specialized, excitable cell; receives, transmits signals, AKA action potentials
- Very long longevity; can last a lifetime with adequate nutrition
- Amitotic, except olfactory epithelium, some areas of hippocampus
- High metabolic rate; require steady supply of oxygen, glucose
  - Oxygen deprivation → death within minutes

### Cell body/soma

- Contains endoplasmic reticulum (ER: chromatophilic substance, Nissl bodies), Golgi apparatus, mitochondria, neurofibrils, microtubules, pigments (e.g. melanin, lipofuscin); surrounds nucleus
- Site of protein synthesis, processing

### Dendrite

- Short processes, project from cell body
- Receive information from adjacent neurons, contain receptors
- Brings information to cell body via graded potentials
- One neuron may have numerous dendrites

### Axon

- Projection from specialized region of cell body, AKA axon hillock
  - Axon hillock: site of action potential generation

- Neuron's conducting region; forms synapses with dendrites
- Each neuron has only one axon
  - May be as long as 1m/3ft
  - Nerve fiber: one long axon
- Axon collaterals: axon branches
- Carries action potential from cell body to target cell (e.g. other neurons)
- Lacks rough ER, golgi apparatuses
- Cytoplasm contains numerous microtubules/microfilaments
  - Site of materials migration between cell body, axon terminus
- May be insulated with myelin sheath
- Axolemma: plasma membrane of axon
  - Responsible for maintaining neuron's membrane potential via ion channels
- Axon terminals: ends of axons, release neurotransmitters
- Clusters of axons
  - In PNS: nerves
  - In CNS: tracts

### Myelin sheath

- Only axons are myelinated
- Functions
  - Protects fibers; ↑ transmission speed
- Produced by oligodendrocytes in CNS, by Schwann cells in PNS
- Nodes of Ranvier: gaps in myelin where action potential jumps from one node to next

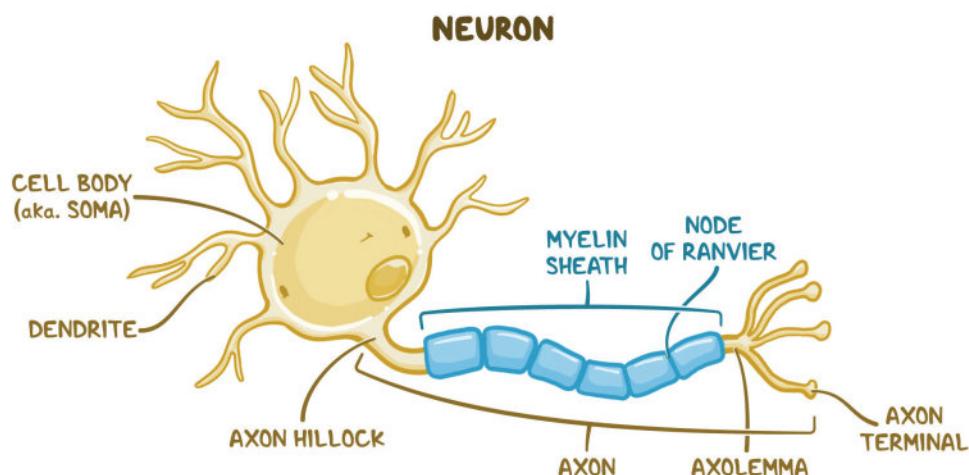


Figure 50.2 Structure of a neuron.

- Saltatory conduction → ↑ speed of propagation
- Gray matter: CNS regions containing nerve cell bodies, unmyelinated axons
- White matter: CNS regions containing myelinated axons

### Structural and functional classification

- Unipolar neurons
  - One process, divides into two branches
  - Mostly function in PNS as first-order sensory neurons; conduct impulses along afferent pathways
- Bipolar neurons
  - Two processes (axon, dendrite) on opposite sides of cell body
  - Sensory neurons found in special sense organs (e.g. olfactory mucosa, retina)
- Multipolar neurons
  - ≥ three processes: one axon, rest are dendrites
  - Primary functions: interneurons within CNS; motor neurons (conduct impulses along efferent pathways)

## CNS GLIAL CELLS (NEUROGLIA)

### Astrocytes

- Most abundant; multiple functions
  - Provide structural, metabolic support for neurons
  - Determine capillary permeability (essential for blood-brain barrier via formation of tight junctions)
  - Control chemical environment (clean up spilled neurotransmitters, potassium ions)

### Microglial cells

- Protective role
- Phagocytize microbes, debris

### Oligodendrocytes

- Forms myelin sheath

### Ependymal cells

- Line cavities of brain, spinal cord
- Form partially permeable barrier between cerebrospinal fluid (CSF), tissue
- Cilia assist in CSF circulation

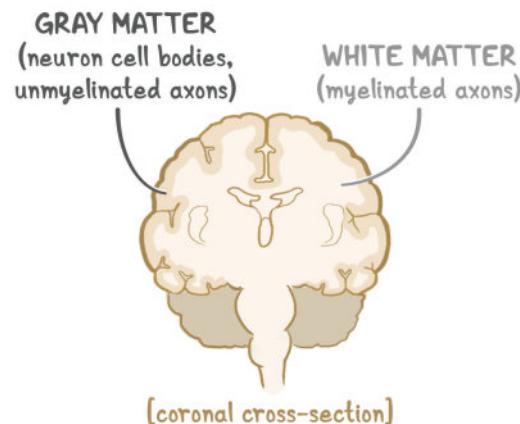
## PNS NEUROGLIA

### Satellite cells

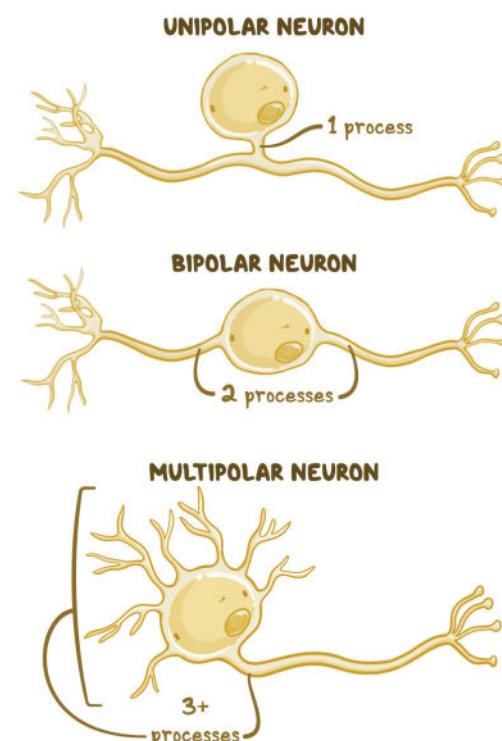
- Similar function as astrocytes

### Schwann cells, AKA neurolemmocytes

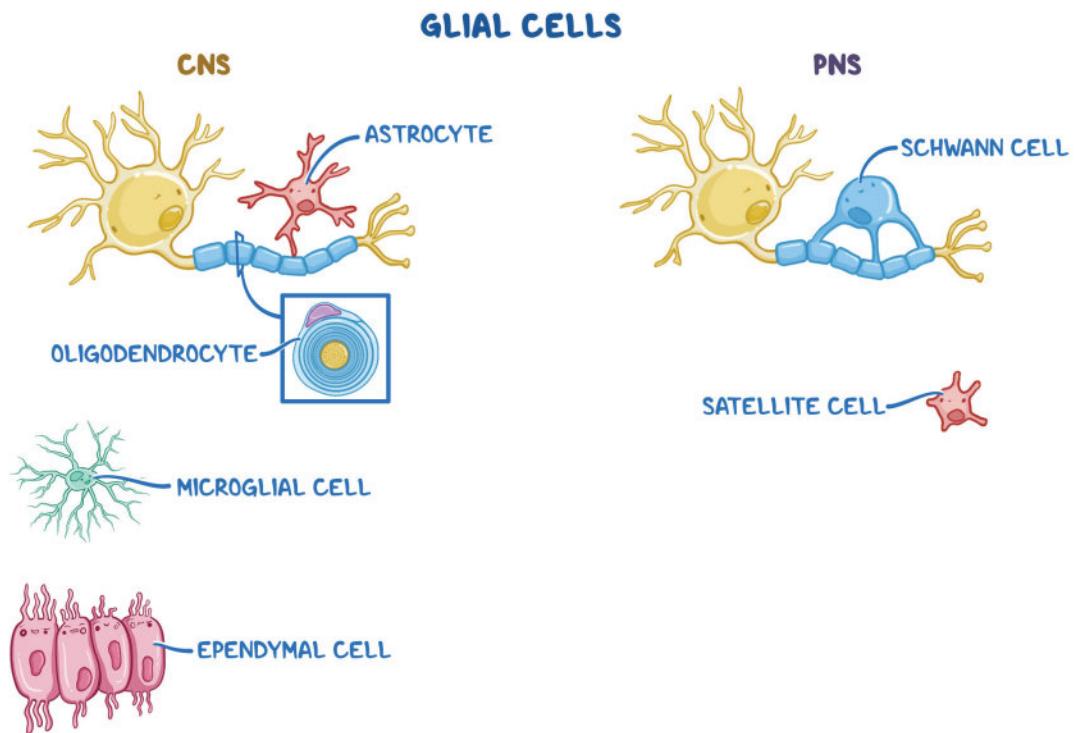
- Form myelin sheath
- Involved in regeneration of damaged peripheral nerve fibers



**Figure 50.3** Coronal cross-section of the brain showing gray matter and white matter.



**Figure 50.4** Structures of unipolar, bipolar, and multipolar neurons.



**Figure 50.5** Glial cells of the CNS and PNS.

## SYNAPSES

- Junction point from one neuron to next
- Presynaptic neuron: conducts impulse toward synapse
- Postsynaptic neuron: conducts impulse away from synapse

### Chemical synapse

- Most common type of synapse
- Information exchanged unidirectionally via neurotransmitters (e.g. serotonin, glutamate, glycine, epinephrine, GABA, histamine)
- Action potential spreads along presynaptic neuron → depolarizes presynaptic neuron → voltage-gated calcium channels open → trigger release of neurotransmitter in vesicles via exocytosis → neurotransmitter binds to postsynaptic membrane receptor → generation of action potential → excitation/inhibition (depending on neurotransmitter)
- Neurotransmitter removed from synaptic cleft by diffusion, degradation, cellular uptake

### Electrical synapse

- Open channels conduct electricity via gap junctions composed of connexons (protein channels); connecting cytoplasm of adjacent neurons
- Rapid, unidirectional or bidirectional transmission
- Examples
  - Cardiac muscles (promote synchronized activity)
  - Hypothalamic hormone-secreting neurons (creates burst of hormone release)

## SPINAL CORD

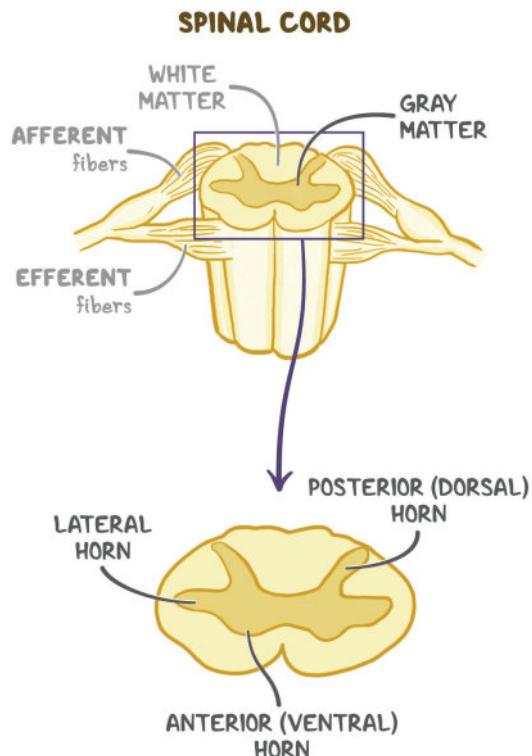
- Long, tubular bundle of nervous tissue; protected by bony vertebral column, meninges, CSF
- Central canal continuous with fourth ventricle; carries CSF through spinal cord
- Extends from brainstem to lumbar region
  - Information travels up spinal cord via afferent (sensory) fibers, down via efferent (motor) fibers

- White matter: afferent, efferent fibers
- Gray matter: cell bodies
- Cell bodies arranged in three columns, AKA horns
  - Anterior (ventral) horns: receive information from brain's **motor** cortex → send it to skeletal muscles → trigger voluntary movement
  - Posterior (dorsal) horns: take **sensory** information → send it to brain's sensory cortex
  - Lateral horns: help regulate processes like urination, digestion, heart rate (mostly **sympathetic** activity)
- **31 pairs of nerves**
  - Nerve pairs: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal
  - Cauda equina: nerve roots at end of vertebral canal
- Nerves arising from spinal column innervate specific bodily regions
  - Each spinal nerve (except C1) provides cutaneous sensory perception
  - Dermatome: **section of skin supplied by pair of spinal nerves**

## STRUCTURES OF THE BRAIN

### Brainstem: medulla, pons, midbrain

- Posterior part of brain continuous with spinal cord
- Responsible for **basic life-sustaining body functions**; e.g. breathing, blood pressure, consciousness, swallowing
- 10/12 cranial nerves (**cranial nerves III-XII arise in brainstem**)
- Medulla
  - Vasomotor (cardiovascular) center, respiratory center, swallowing/coughing/vomiting centers
  - All ascending sensory, descending motor tracts connecting spinal cord with other parts of brain
  - **Pyramids** on anterior surface of medulla; **descending corticospinal tracts** cross (**decussate**) to opposite side
- Pons
  - Controls **facial expressions, sensations**
  - Controls body equilibrium, posture
  - Works with medulla to regulate

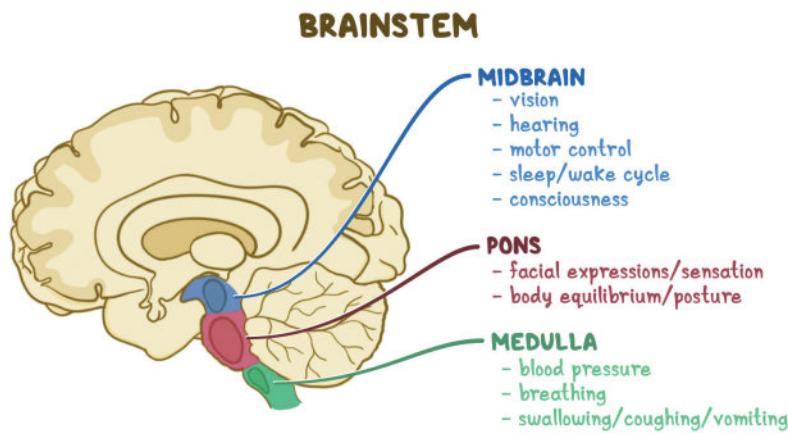


**Figure 50.6** Cross-section of the spinal cord showing its structure.

- breathing (pneumotaxic center), relay information between cerebellum, cerebral hemispheres
- Midbrain (mesencephalon)
  - Participates in **vision, hearing, motor control, sleep-wake cycle, consciousness**
- Reticular formation (RF) scattered throughout brainstem
  - Responsible for consciousness; maintaining posture, general muscle tone, major visceral functions; interpretation, processing of noxious stimuli

### Cerebellum

- AKA "little brain"
- Responsible for coordinating, planning, executing movements; balance, posture, spatial perception
- Integrates sensory information; fine-tunes motor activity (e.g. learned motor skills), stores it as muscle memory



**Figure 50.7** Sagittal section of the brain showing the brainstem, which includes the midbrain, pons, and medulla.

### Diencephalon

- Thalamus
  - Relay station for sensory, motor information going to/from cerebral cortex, brainstem, spinal cord; screens insignificant information
- Hypothalamus
  - Major homeostatic control system
  - Links nervous system to endocrine system via pituitary gland
  - Thermostatic control of body temperature
  - Along with limbic system, participates in emotions such as anger, emotional response to pain, sexual arousal-related behaviors
  - Regulates circadian rhythms
  - Plays role in regulating eating, drinking; contains thirst center, which senses osmotic pressure of extracellular fluid
- Pineal gland
  - Produces melatonin

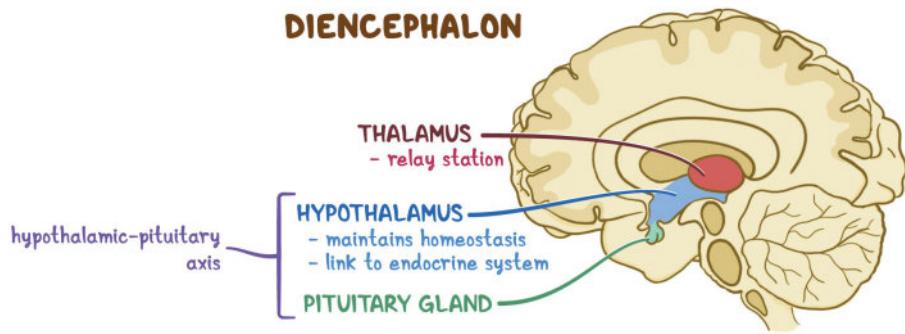
### Cerebrum

- Divided into right, left hemispheres
- Separated by corpus callosum: connects left side to right side
- Contain folds (gyri): increase surface area
- Sulci: grooves between gyri
- Four lobes: frontal, parietal, temporal, occipital
- Frontal
  - Primary motor cortex: voluntary movement (motor homunculus)

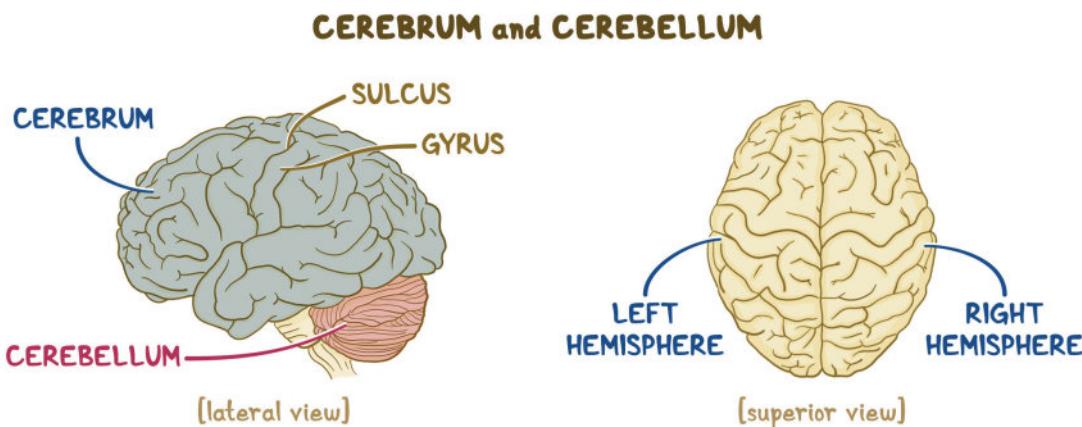
- Premotor cortex: orientation of body
- Supplementary motor area: planning sequence of movement
- Parietal
  - Somatosensory processing
  - Has homunculus pattern similar to motor cortex
- Temporal
  - Functions in hearing, olfaction, visual recognition
- Occipital
  - Responsible for analyzing, interpreting visual information

### Cerebral cortex

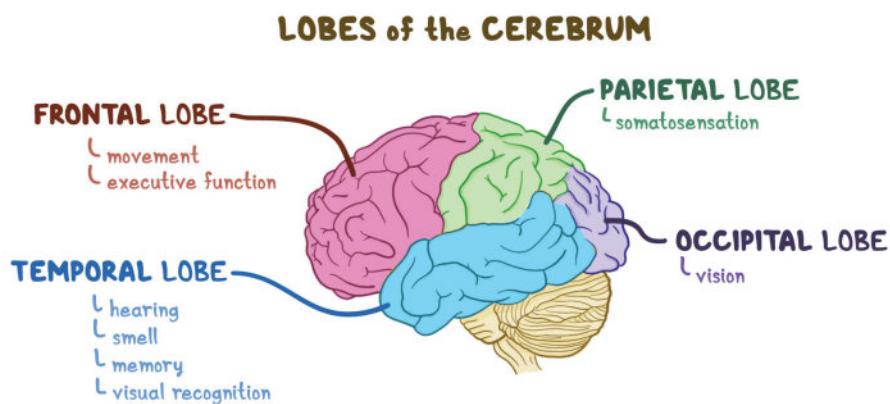
- Gray matter (cell bodies, dendrites) on outer surface of cerebrum: information processing
  - Motor association area: determines appropriate movements for specific tasks
  - Primary somatosensory: receives sensory input; somatosensory association area provides discrete interpretation
- Language processing
  - Broca's area: generation of spoken word (moving muscles to speak)
  - Wernicke's area: comprehension of speech
- White matter: axons; carry information to other parts of brain



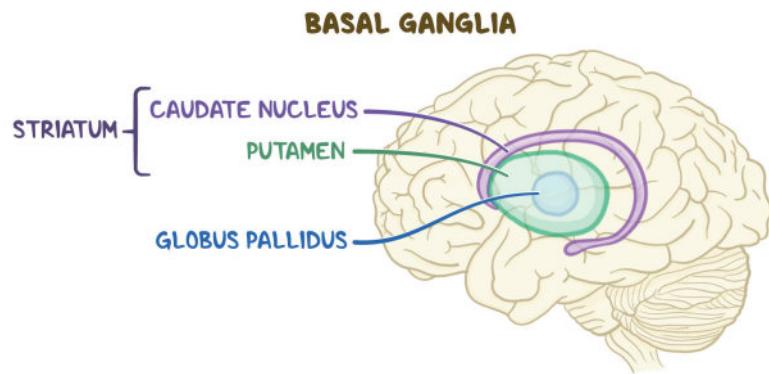
**Figure 50.8** Sagittal section of the brain showing the diencephalon, which includes the thalamus, hypothalamus, and pituitary gland.



**Figure 50.9** The structure of the cerebrum and cerebellum. The cerebrum contains gyri (which are the folds) and sulci (which are the grooves between the folds).



**Figure 50.10** The four lobes of the cerebrum and some of their functions.



**Figure 50.11** The structures of the basal ganglia.

### Basal nuclei (ganglia)

- Gray matter deep within brain; deep nuclei of cerebral hemispheres
- Contains caudate nucleus, globus pallidus, putamen nucleus
- Mainly responsible for regulating movement, tone, [motor control](#)

## VENTRICLES & CSF

### Ventricles

- Four interconnected spaces filled with CSF
- **Two lateral ventricles:** located in frontal lobes, extend posteriorly into parietal lobes
- **Interventricular foramen (foramen of Munro):** connects lateral ventricles to each other, to third ventricle
- **Third ventricle:** lies between thalamic bodies, surrounded by hypothalamus
- **Cerebral aqueduct (aqueduct of Sylvius):** connects third, fourth ventricles
- **Fourth ventricle:** located between cerebellum, pons
- **Two lateral apertures (foramina of Luschka), one medial aperture (foramen of Magendie):** connect fourth ventricle to subarachnoid space

### CSF

- CSF similar in composition to blood with most proteins removed
- **Made by ependymal cells of choroid plexuses**
- **Circulates throughout ventricles, central canal;** also covers brain, meninges
- **Protects brain** (brain “floats” in cushioning fluid), provides nutrients to tissues in CNS

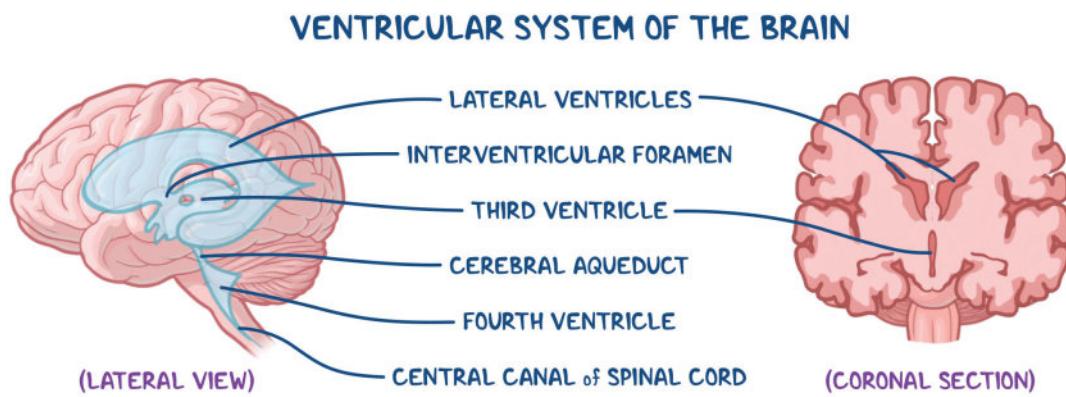
### Flow of CSF through ventricles

- CSF produced by choroid plexus in lateral, third, fourth ventricles → lateral ventricle → through interventricular foramen to third ventricle → through cerebral aqueduct to fourth ventricle → through lateral, median apertures to subarachnoid space (some CSF enters central canal of spinal cord) → superior sagittal sinus, venous circulation

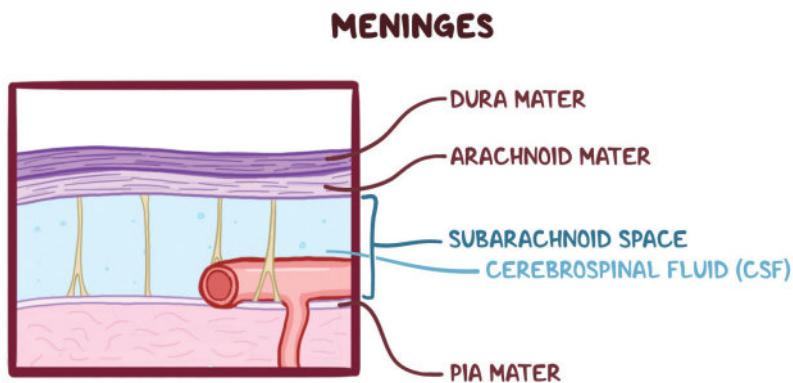
## MENINGES

### Anatomy

- Made up of three layers
- From superficial to deep: dura mater, arachnoid mater, pia mater
- **Dura mater:** [tough](#), inflexible layer
  - Separates brain into compartments, forms sinuses for major veins of brain
  - **Falx cerebri:** separates right, left major veins of brain
  - **Falx cerebelli:** separates right, left lobes of cerebellum
  - **Tentorium cerebelli:** separates right, left lobes
- **Arachnoid mater:** middle layer that projects into sinuses (arachnoid [villi](#))
  - Subarachnoid space: lies between arachnoid, pia mater
  - Contains CSF
  - Contains all blood vessels, cranial nerve of brain
- **Pia mater:** innermost layer
  - [Adheres to brain](#)
  - Fuses with meninges, forming choroid plexus, which produce CSF



**Figure 50.12** Ventricular system of the brain.



**Figure 50.13** The meninges: three tissue layers which protect the brain and spinal cord.

## AUTONOMIC NERVOUS SYSTEM

- Involuntary branch of PNS
- Extends from CNS to target organ via two-neuron chain; interact at autonomic ganglion
  - Preganglionic fiber: synapses with cell body of second neuron
  - Postganglionic fiber: innervates effector organ
- Both systems are active; one dominates other depending on situation
- Dual innervation of organs by both sympathetic and parasympathetic divisions
  - Exceptions: most arterioles, veins, sweat glands only innervated by sympathetic nerve fibers

### Sympathetic

- “Fight or flight” functions: activated when individual exposed to stressful situation
- Originates in thoracic, lumbar region of spinal cord (T1-L2)
- **Preganglionic** axon length: short
- **Postganglionic** axon length: long
- Neurotransmitters, receptors
  - Preganglionic fibers release acetylcholine → binds to nicotinic receptor in **postganglionic** neuron → releases **norepinephrine** → binds to alpha/beta receptors on effector organs → releases acetylcholine → binds to muscarinic receptors on sweat glands
  - Preganglionic fibers release acetylcholine → binds to nicotinic receptor on adrenal medulla → epinephrine released → binds to alpha/beta receptors on effector organs

## Parasympathetic

- “Rest and digest” functions: conserves, stores energy; maintains “housekeeping” functions
- Originates in **craniosacral** areas of spinal cord (CN III, VII, IX, X; S2-S4)
- **Preganglionic** axon length: long
- **Postganglionic** axon length: short
- Neurotransmitters, receptors
  - **Preganglionic** fiber releases **acetylcholine** → binds to nicotinic receptor in **postganglionic** neuron → releases **acetylcholine** → binds to muscarinic receptor on effector organ

## Enteric nervous system (GI)

- “Second brain:” autonomous function independently from autonomic nervous system
- Neurons collected into two ganglia
  - Myenteric (Auerbach’s), Meissner’s plexus
- Coordinates peristalsis, GI tract secretions

## Sympathetic vs. parasympathetic effects on organs

- Some organs only innervated by sympathetic division, but many innervated by both sympathetic, parasympathetic divisions → work cooperatively to regulate normal function
- Heart
  - **Sympathetic:** beta-1 receptors → ↑ heart rate, contractility → ↑ cardiac output
  - **Parasympathetic:** muscarinic (M) receptors → ↓ heart rate, contractility (atria only) → ↓ cardiac output
- Vascular smooth muscle
  - **Sympathetic:** skin/splanchnic alpha-1 receptors → constriction; skeletal muscle vascular beta-2 receptors → dilation; skeletal muscle vascular alpha-1 receptors → constriction
  - **Parasympathetic:** no direct effect
- Bronchial tree
  - **Sympathetic:** beta-2 receptors → dilation
  - **Parasympathetic:** M receptors → constriction
- Eye

▫ **Sympathetic:** beta-2 receptors → ciliary muscle relaxation for far vision; alpha-1 → radial muscle contraction → pupil dilation

▫ **Parasympathetic:** M receptors → ciliary muscle contraction for near vision + sphincter muscle constriction → pupil constriction

### ▪ GI tract

▫ **Sympathetic:** alpha-2, beta-2 receptors → GI tract smooth muscle wall relaxation, ↓ GI motility; alpha-1 → ↑ sphincter tone

▫ **Parasympathetic:** M receptors → ↑ GI smooth muscle wall contraction and motility, ↓ sphincter tone; ↑ gastric secretion

### ▪ Bladder

▫ **Sympathetic:** beta-2 receptors → detrusor muscle relaxation, urinary sphincter contraction

▫ **Parasympathetic:** M receptors → detrusor muscle contraction, urinary sphincter relaxation

### ▪ Liver

▫ **Sympathetic:** beta-2, alpha-1 receptors → gluconeogenesis, glycogenolysis

▫ **Parasympathetic:** no direct effect

### ▪ Adrenals

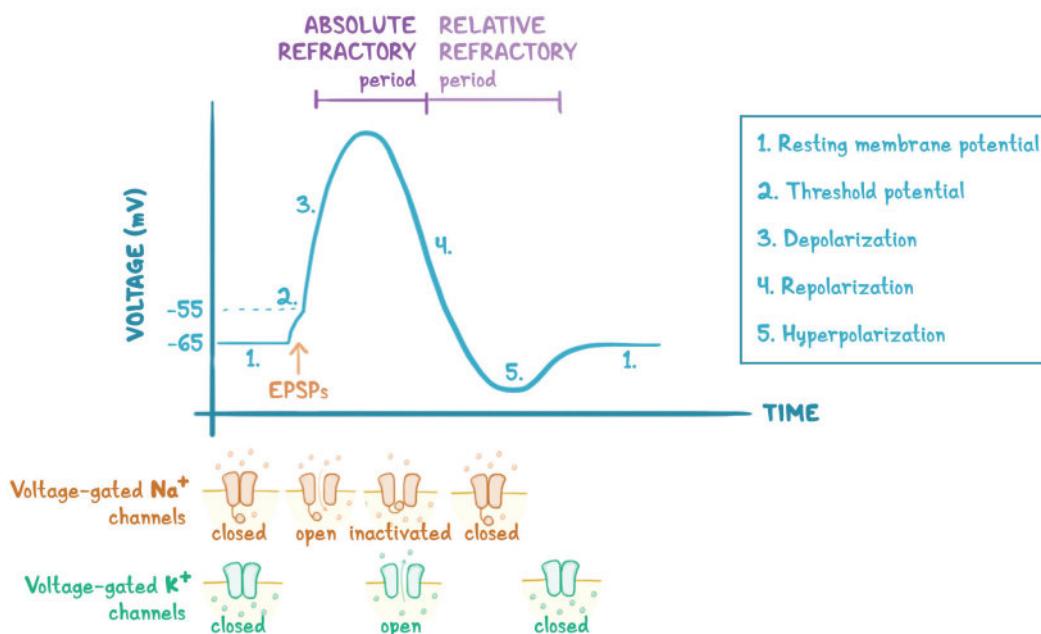
▫ **Sympathetic:** nicotinic receptors → release of epinephrine, norepinephrine

▫ **Parasympathetic:** no direct effect

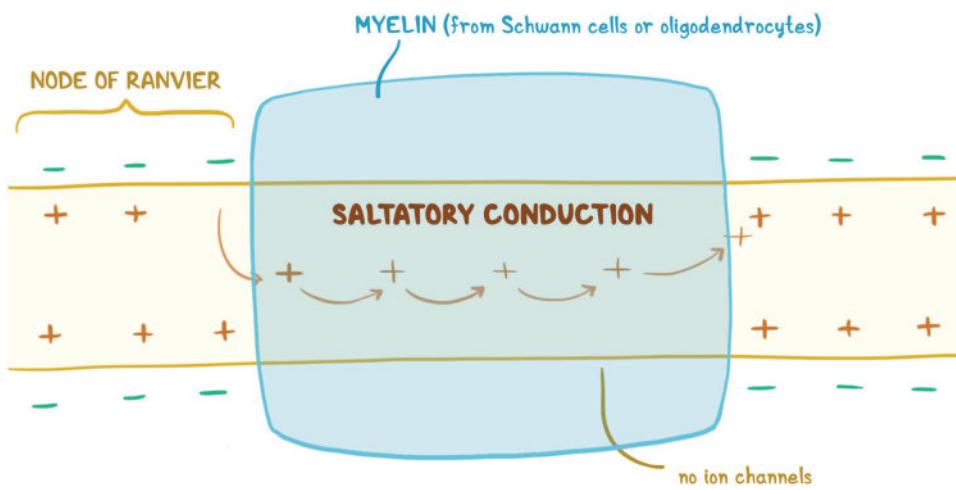
# NEURON ACTION POTENTIAL

[osms.it/neuron-action-potential](https://osms.it/neuron-action-potential)

- Electric signals sent down axons
- Generated by rapid rising, falling of membrane potential
- Resting membrane potential (approx. -65mV) determined by intra, extracellular ion concentrations
  - Ion channels open → depolarization of neuron (net influx of positive charge/excitatory postsynaptic potential)
  - Depolarization to approx. -55mV → voltage-gated sodium channels open at axon hillock → sodium rushes into cell → action potential (neuron is positively charged to approx. +40mV)
- Sodium channel becomes inactivated (absolute refractory period)
- Voltage-gated potassium channels then act → potassium flows out
- Sodium/potassium pump moves sodium out of cell, potassium in → hyperpolarization
- Sodium channels remain closed but can be activated (relative refractory period); hyperpolarization → stronger stimulus needed
- In myelinated areas, electrical force of moving ions pushes subsequent ions along (saltatory conduction)



**Figure 50.14** Graphical summary of the voltage changes that occur during a neuron action potential and the accompanying states of voltage-gated sodium and potassium channels. The action potential is initiated by a net influx of excitatory postsynaptic potentials (EPSPs). Not shown above are sodium/potassium pumps, which help to maintain the resting membrane potential, as well as help to return to that resting potential through repolarization.



**Figure 50.15** Saltatory conduction through myelinated areas of an axon increases the speed of signal conduction down the axon.

## ANATOMY & PHYSIOLOGY OF THE EYE

[osms.it/eye-anatomy-physiology](http://osms.it/eye-anatomy-physiology)

### ANATOMY OF THE EYE

#### Conjunctiva

- Mucous membrane rich with lymphatic channels
- Portions
  - **Palpebral conjunctiva:** lines interior of eyelid adhered to tarsus
  - **Bulbar conjunctiva:** lines surface of the eye; nonkeratinized stratified squamous epithelium
- Functions
  - Protects cornea from friction via mucus production
  - Contributes to immune surveillance by preventing microbes from entering eye

#### Lacrimal apparatus

- Consists of lacrimal gland, draining ducts

#### Lacrimal gland

- Paired, almond-shaped exocrine glands located at upper lateral portion of each orbit

- Compound tubuloacinar structure, contains serous cells producing watery serous secretions, AKA tears
- Innervated by parasympathetic fibers from facial nerve (CN VII)
- Lacrimal secretions contain lysosomes, antibodies, mucus to moisten, protect eye surface
- Pathway of tears
  - Produced in lacrimal gland → blinking causes spread of tears across eyeball → lacrimal canaliculi via lacrimal puncta → lacrimal sac → nasolacrimal duct → empties into inferior nasal meatus inside nasal cavity

### CHAMBERS & FLUIDS

- Anterior, posterior segments separated by lens

#### Posterior segment

- Largest segment
- Filled with gel-like vitreous humor

- Transmits light
- Holds neural layer of retina against retinal pigmented layer
- Maintains shape of eyeball
- Contributes to intraocular pressure

### Anterior segment

- Divided into anterior and posterior chambers
- Filled with aqueous humor

### Anterior chamber

- Larger chamber
- Bounded by cornea anteriorly, trabecular meshwork laterally, iris posteriorly

### Posterior chamber

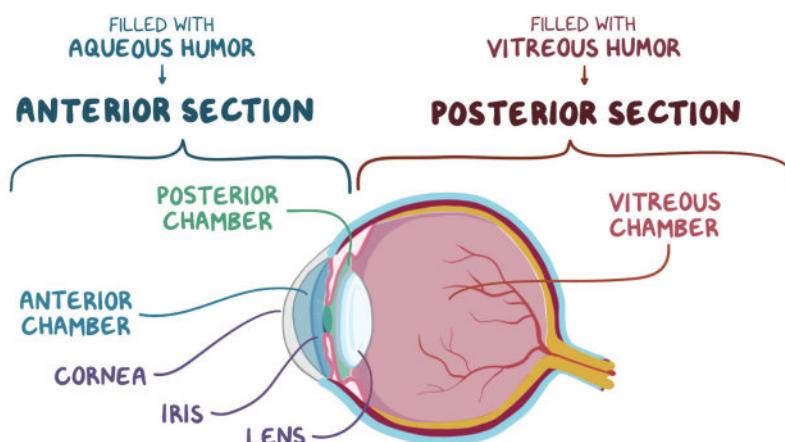
- Smaller chamber; irregularly shaped; size changes during accommodation
- Bounded by iris anteriorly, lens posteriorly
- Base formed by the ciliary processes

### Aqueous humor

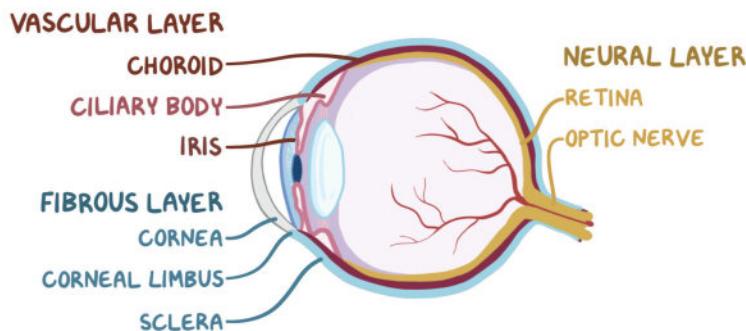
- Continually produced by ciliary processes
- Composed of filtered plasma
- Transports needed metabolites to avascular cornea, lens; removes metabolic wastes
- Pathway of flow: enters posterior chamber → passes through pupil → anterior chamber → trabecular network → scleral venous sinus (canal of Schlemm) → venous blood
  - Small amount diffuses into vitreous humor
- Intraocular pressure primarily depends on balance between production and drainage

### LAYERS OF EYE WALL

- Divided into fibrous layer, vascular layer, innermost layer (retina)
  - Superficial → deep



**Figure 50.16** Three eye chambers. Anterior and posterior chambers are filled with aqueous humor. Vitreous chamber is filled with vitreous humor.



**Figure 50.17** The three layers of the eye.

## Fibrous layer

- Sclera
  - "White" of eye
  - Composed mainly of collagen, elastic fibers
  - Attachment point for extrinsic eye muscles
  - Continuous with cornea, dura mater of brain
- Limbus
  - Intersection between sclera, cornea
- Cornea
  - Anterior, transparent avascular portion of fibrous layer
  - Makes up major refractive surface of eye
  - Layers: anterior → posterior
- Corneal (sub) layers
  - Stratified squamous epithelium: derived from neural crest cells
  - Bowman layer: acellular; serves as barrier, protecting underlying stroma from malignant cells in epithelium
  - Stroma: transparent due to lack of blood vessels, lymphatics
  - Descemet membrane: basement layer separating epithelium from Bowman layer; protective function; epithelial stem cells located in this layer
- Simple squamous epithelium: AKA corneal endothelium; contains sodium pumps to pump water out of cornea, preserving its clarity

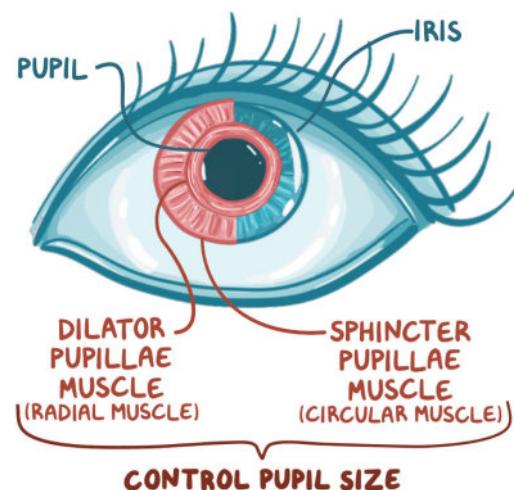
## Vascular layer

- AKA uvea
- Choroid, iris, ciliary body
- Pigmented middle layer
- Choroid
  - Richly vascularized
  - Contains melanocytes to absorb light
  - Discontinued by optic nerve posteriorly
- Iris
  - Visible colored portion surrounding pupil (central opening in iris; allows light to enter eye)
  - Composed of two smooth muscle layers: sphincter pupillae (contracts during close vision, bright light, parasympathetic activation to constrict pupil), dilator pupillae (contracts during

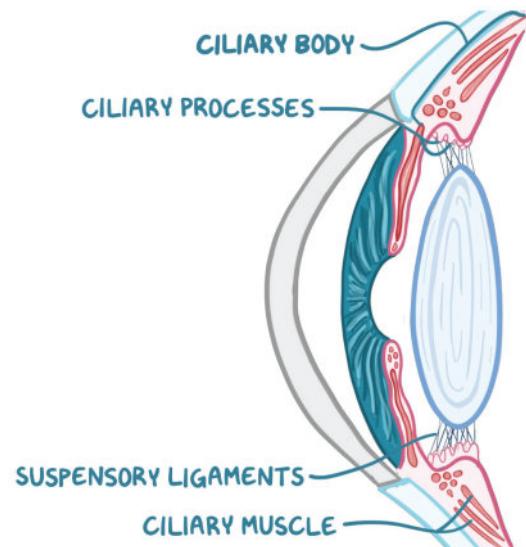
distance vision, dim light, sympathetic activation to dilate pupil)

## Ciliary body

- Ciliary muscles: smooth muscles that control shape of lens
- Ciliary processes: secrete aqueous humor
- Ciliary zonule/suspensory ligament: fibers extending from ciliary processes to lens (secures lens in place)



**Figure 50.18** The iris is composed of two smooth muscle layers, the dilator pupillae and the sphincter pupillae.



**Figure 50.19** Components of the ciliary body.

## Retina

- Innermost layer
  - Further divided into outer pigmented layer, inner neural layer
- Sub-layers: superficial → deep
  - Pigment cell → photoreceptor → outer nuclear → outer plexiform → inner nuclear → inner plexiform → ganglion cell → optic nerve layer

## Retina: outer pigmented layer

- Pigmented epithelial cells absorb light, store vitamin A for photoreceptor cells to use
- Function: photoreceptor maintenance

## Retina: inner neural layer

- Extends anteriorly to ciliary body
- Three types of neurons: photoreceptors, bipolar cells, ganglion cells
  - Night-vision photoreceptors (rods): dim-light, non-color vision; more numerous, more sensitive to light than cones; not present on fovea; do not create sharp, clear images/low acuity
  - Day-vision photoreceptors (cones): bright-light, color vision; present on fovea; high resolution/high acuity
  - Bipolar cells: synapse with ganglion cells
  - Ganglion cells: where action potentials are generated; leave eye as optic nerve

## Optic disc

- Spot where optic nerve (CN II) exits eye
- AKA “blind spot”
- Not noticeable since each blind spot is compensated by other eye

## Macula lutea

- Area of greatest visual acuity
- Contains mainly cones
- Only portion of eye with enough cone density to allow detailed color vision, hard focus
- Lateral to blind spots

## Fovea centralis

- Center of macula lutea
- Contains only cones
- Region of greatest visual acuity in macula

## Optic nerve

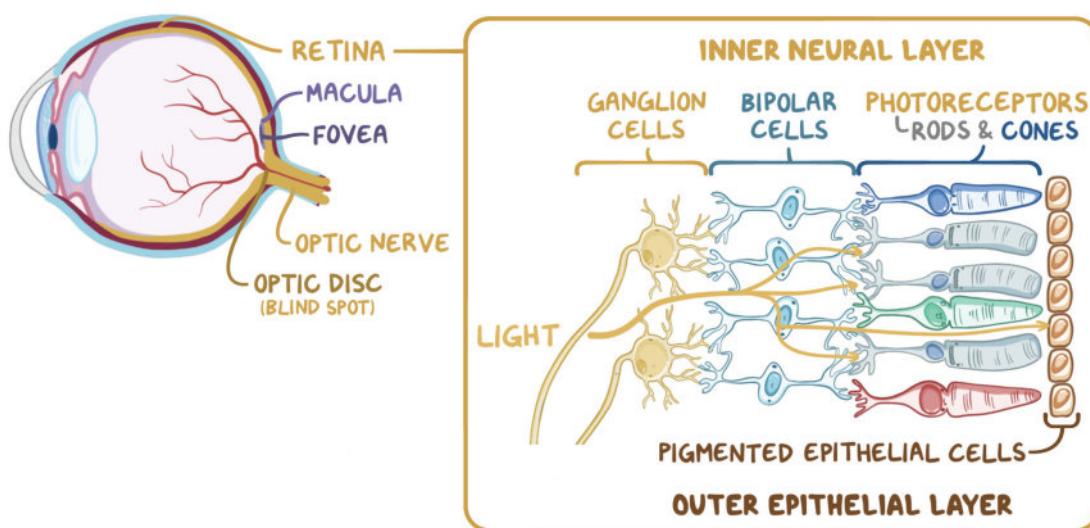
- Composed of retinal ganglion cell axons
- Exits retina via optic disc

## Optic chiasm

- X-shaped structure where optic nerves meet
- Axons from nasal retina cross over to opposite sides → optic tracts

## Optic tract

- Synapses with cells in lateral geniculate nucleus in both sides of thalamus



**Figure 50.20** Components of the neural layer of the eye.

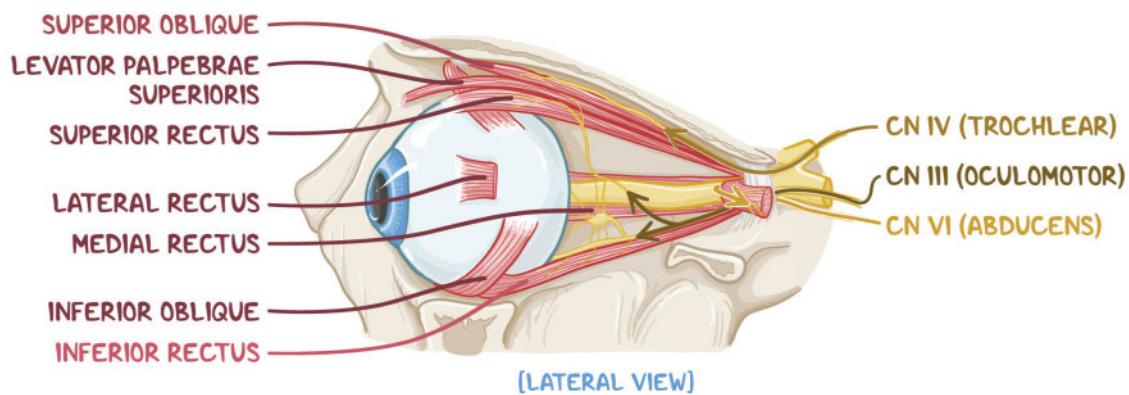
- Sharpens contrasts, enhances depth perception
- Optic radiations sent to primary visual cortex, AKA occipital lobe

## VASCULAR SUPPLY

- Choroidal vessels supply external  $\frac{1}{3}$  of eye
- Retinal central artery and central vein supply internal  $\frac{2}{3}$  of the eye

## EXTRAOCULAR MUSCLES

- Orbicularis oculi
  - Circular muscle that encircles eye
  - Closes eyelid when contracted
- Levator palpebrae superioris
  - Located inside eyelid
  - Raises eyelid
- Extrinsic eye muscles
  - Control eye movement
  - Originate from walls of orbit (common tendinous/annular ring), insert onto surface of eye



**Figure 50.21** Lateral view of the left eye showing the extraocular muscles. Not shown: orbicularis oculi.

## EXTRINSIC EYE MUSCLES

	FUNCTION	INNERVATION
SUPERIOR RECTUS	Elevation, intorsion	Oculomotor nerve (CN III)
INFERIOR RECTUS	Depression, extorsion	Oculomotor nerve (CN III)
LATERAL RECTUS	Abduction	Abducens nerve (CN VI)
MEDIAL RECTUS	Adduction	Oculomotor nerve (CN III)
SUPERIOR OBLIQUE	Depression, intorsion	Trochlear nerve (CN IV)
INFERIOR OBLIQUE	Elevation, extorsion	Oculomotor nerve (CN III)

## PHYSIOLOGY OF VISION: PHOTORECEPTION & PHOTOTRANSDUCTION

- Photoreceptors, ganglion cells, bipolar cells generate excitatory (EPSPs), inhibitory postsynaptic potentials (IPSPs) instead of action potentials
- Light hits retina, 11-cis retinal converted to all-trans retinal → production of metarhodopsin II → activation of transducin → activation of phosphodiesterase, converting cGMP to 5-GMP → ↓ cGMP → closure of sodium channels → hyperpolarization of photoreceptor membrane → ↓ glutamate release (excitatory neurotransmitter) from photoreceptors → either inhibition or excitation
  - Depends on which type of glutamate receptor activated

### Glutamate receptors

- Ionotropic receptor: excitatory/depolarizing
  - ↓ excitatory glutamate response → hyperpolarization of bipolar, horizontal cells → inhibition
- Metabotropic receptor: inhibitory/hyperpolarizing
  - ↓ inhibitory glutamate response → depolarization of bipolar, horizontal cells → excitation
- Establish on-off patterns of visual fields

## LIGHT VS. DARKNESS

### Light

- Photoreceptors hyperpolarize → ↓ glutamate release
  - Glutamate: inhibitory
- → Lack of IPSPs causes bipolar cells to depolarize, release neurotransmitter onto ganglion cells → ganglion cells propagate EPSPs → action potential transmitted to brain via optic nerve

### Darkness

- Photoreceptors depolarize → increased glutamate release → glutamate causes IPSPs → IPSPs cause bipolar cells to hyperpolarize, inhibits release of neurotransmitters onto ganglion cells → ganglion cells do not propagate EPSPs

→ no action potentials carried along optic nerve to brain

### Focusing light on retina

- Light → cornea → aqueous humor → lens → vitreous humor → neural layer of retina
  - Excites photoreceptors of pigmented layer → photoreception, AKA conversion of light into electrical impulses
- Light bent three times:
  - Entering cornea, AKA major refractive step; entering lens; exiting lens
  - Refractive power of cornea is constant, whereas lens' refractive power can be changed

### Distant vision

- Normal resting status of human eye: preset for distant vision
- Ciliary muscles relaxed → ciliary zonule fibers taut → lens is flat (lowest refractive power) → parallel rays focus on retina
- Sympathetic activation causes ciliary muscle relaxation, pupillary dilation
- Far point of vision: distance beyond which no accommodation/change in lens shape required for focusing

### Near vision

- Involves accommodation, pupillary constriction, convergence
- Lens accommodation
  - Ciliary muscles contract → ciliary zonule fibers relaxed → lens becomes spherical (increases refractory power of lens)
  - Parasympathetic activation → ciliary muscle contraction
- Pupil constriction
  - Mediated by sphincter pupillae muscles of iris
  - Parasympathetic activation
  - ↑ depth of focus
- Convergence of eyes
  - Eyes rotate medially as object moves closer
  - Mediated by extrinsic eye muscles via oculomotor nerve (CN III)

### Visual field

- Everything seen by single eye
  - Overlap → central "binocular" visual field

- Split into two parts
  - Nasal visual field: projected onto temporal retina, axons stay on that side of brain
  - Temporal visual field: projected onto nasal retina, axons cross to opposite side of brain at optic chiasm
- Information from left visual fields of both eyes travel to right half of brain, vice versa
  - Cause: axons from nasal retina crossing over
- Some nerve fibers synapse at superior colliculi instead of lateral geniculate body, ascend to midbrain

# ANATOMY & PHYSIOLOGY OF THE EAR

[osms.it/ear-anatomy-physiology](http://osms.it/ear-anatomy-physiology)

## EXTERNAL EAR ANATOMY

### Pinna/auricle

- Composed of elastic cartilage covered with thick skin
- Function
  - Captures sound waves, guides them into auditory canal

### External auditory meatus

- AKA auditory canal
- Contains ceruminous glands
  - Secretes cerumen (ear wax); with small hairs, traps foreign objects
- Function
  - Guides sound waves to tympanic membrane

### Tympanic membrane

- AKA eardrum
- Thin, connective tissue membrane covered by skin (external), mucous membrane (internal)
- Separates external, middle ear
- Vibrates when hit by sound waves → **vibrates ossicles**

## MIDDLE EAR ANATOMY

### Auditory ossicles

- Linked by synovial joints in chain; **transmit vibration of tympanic membrane to oval window**
- **Malleus/“hammer”:** connected to tympanic membrane, incus

- **Incus/“anvil”:** connects malleus, stapes
- **Stapes/“stirrup”:** footplate inserts onto oval window; connects middle, inner ear
- **Stapedius, tensor tympani:** two skeletal muscles attached to auditory ossicles; protect ears from prolonged, loud noises; not brief explosive, noise (e.g. gunshot)

### Oval window

- Membrane-covered opening connecting middle, inner ear; transforms vibrations into fluid waves

### Round window

- Membrane-covered opening relieves pressure created by fluid waves

### Mastoid antrum

- Canal in posterior wall of tympanic cavity, communicates with mastoid air cells

### Pharyngotympanic/eustachian tube

- Canal links middle ear, nasopharynx
- Swallowing/yawning opens tube to equalize middle ear cavity, atmospheric air pressure
- Pathogens may travel through tube → otitis media

## INNER EAR ANATOMY

- **Bony labyrinth:** system of channels/cavities, houses membranous labyrinth, fluid filled
- **Three semicircular canals:** rotational acceleration in three planes of movement (lateral, superior, posterior)

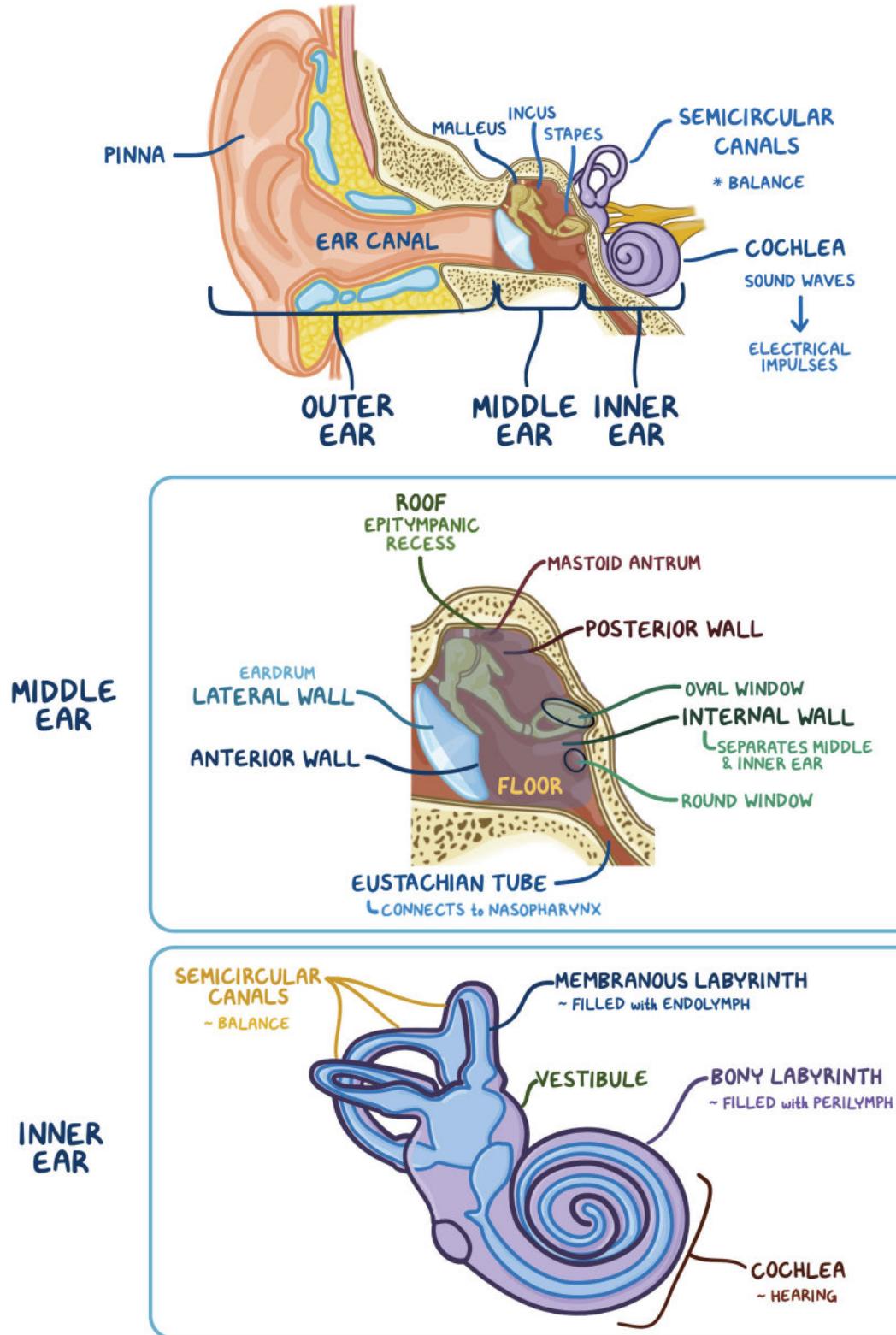


Figure 50.22 Parts of the ear with parts of the middle, inner ear.

### Cochlea

- Spiral bony chamber, coils around central axis
- Contains organ of Corti: site of auditory transduction
- Two receptors
  - Inner hair cells: mechanoreceptors with protruding cilia; arranged in single rows embedded in basilar membrane
  - Outer hair cells: mechanoreceptors with protruding cilia; arranged in parallel rows; more numerous; body embedded in basilar membrane
- All hair cell cilia attached to tectorial membrane above

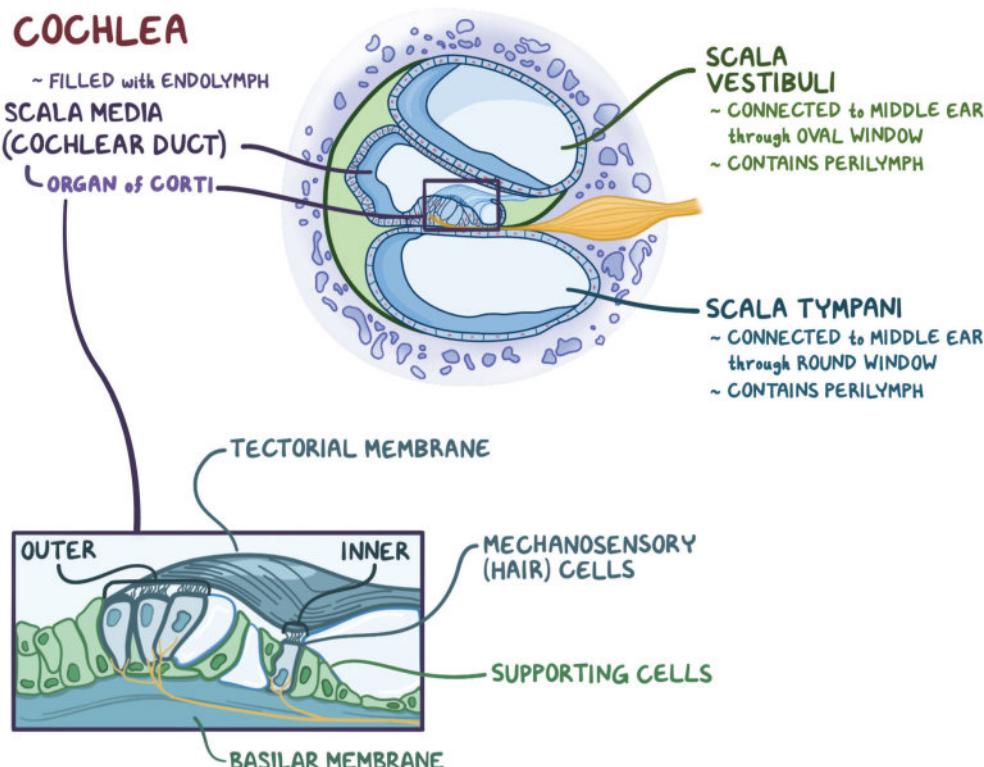
### Basilar membrane

- Narrow, thick near oval window/base; wide, thin near cochlea (apex)
- Function
  - Sound reception

- Cochlear nerve (part of cranial nerve VIII) carries information from basilar membrane to brain; cell bodies in spiral ganglia

### Three chambers (scalae)

- Scala vestibuli
  - Superior chamber superior to cochlea; with vestibule next to oval window
  - Filled with perilymph: similar to cerebrospinal fluid (CSF), extracellular fluid
  - Conducts sound vibrations for hearing, proprioception
- Scala media
  - Middle chamber
  - Cochlear duct
  - Filled with endolymph
- Scala tympani
  - Inferior chamber in cochlea
  - Attaches to round window
  - Filled with perilymph



**Figure 50.23** Anatomy of the cochlea and organ of Corti.

## AUDITORY SYSTEM

### Pathway of sound waves

- Sound waves travel through external ear → vibrate tympanic membrane
- Tympanic membrane vibrates ossicles → ossicles amplify sound → stapes vibrates oval window
- Perilymph in scala vestibuli moves → pressure waves travel through perilymph towards helicotrema → cochlear duct → vibrates basilar membrane
- Hair cells bend by shearing force, cilia pushes against tectorial membrane → cilia bend in one direction → ↑ potassium conduction → depolarization (cilia bends in other direction → ↓ potassium → hyperpolarization) → action potential generated in cochlear nerve → sends signals to brain
- Sounds waves > 20Hz
  - Pressure waves → cochlear duct → perilymph of scala tympani → cochlear duct → vibrates basilar membrane → sound waves converted to electrical signal → hearing sensation
- ↑ intensity of sound = ↑ distal membrane displaced in vibratory motion

### Amplification of sound waves

- Pressure exerted on oval window > pressure exerted on tympanic membrane (due to smaller size of oval window)
- Ossicles

### Frequency mapping (tonotopic map)

- Sound frequencies displace basilar membrane at different locations
- **Base (short, stiff fibers):** 20,000Hz; nearest to stapes, responds best to **high frequencies**
- **Apex (long, floppy fibers):** 20Hz; responds best to **low frequencies**

### Central connections

- Hair cell receptors in organ of Corti → primary cell bodies located in spiral/auditory ganglion (bipolar cells in spiral of cochlea) → axon carries signal → dorsal, ventral cochlear nuclei in pons → secondary axons project via lateral lemniscus → inferior colliculus in midbrain → medial geniculate nucleus in thalamus → projects to primary

auditory cortex located at transverse gyrus of Heschl in temporal lobe

- Accessory auditory nuclei
- Superior olivary nucleus: sound localization; integration, interpretation of sound received in both ears at slightly different times

## VESTIBULAR SYSTEM

- Sensory information from vestibular system → generates visual images for retina → posture adjustments to maintain balance
- Vestibular organ located within temporal bone adjacent to cochlea; three semicircular canals, otolith organs (utricle, saccule)

### Semicircular ducts

- Function
  - Rotational/angular acceleration to maintain balance
- Three canals at right angles to one another in each plane of space (anterior, posterior, lateral)
- Filled with **endolymph**: similar to intracellular fluid (↑ potassium; ↓ sodium)
- **Ampulla:** dilated portion at one end; contains hair cells, protrudes into gelatinous substance, cupula
- **Hair cells:** tonic rate of electrical firing
  - Fire constantly when head not moving
- Head rotation → endolymph deflects hair cells in certain direction in semicircular canals → change in baseline electrical firing rate → propagation down vestibular nerve → brainstem

### Otolith organs: utricle, saccule

- Function
  - Linear acceleration
- Contain
  - Hair cells with calcium carbonate crystals
  - Maculae (balance receptor, responds to changes in head position)
- Moving head in any direction → gravity deflects calcium carbonate crystals, attached hair cells → stereocilia bends toward/away from kinocilium → depolarization/hyperpolarization respectively → excitation/inhibition respectively
- **Head upright:** macula horizontal, saccule vertical

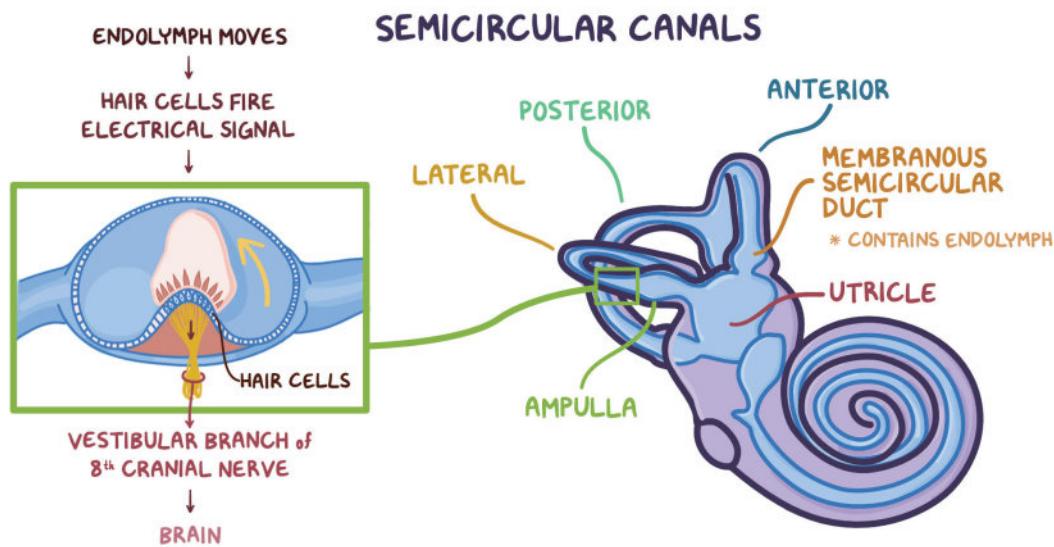
- Tilting head forward/laterally: ipsilateral utricle excited
- Tilting head backward/medially: ipsilateral utricle inhibited
- Forward movement of head: saccule excited
- Lateral, medial movement of head: saccule excited

#### Pathway of signal centrally

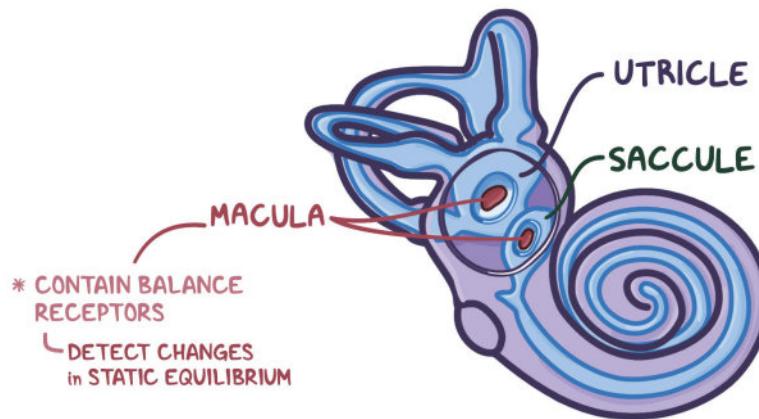
- Hair cells receptor → propagation of signal → vestibular/Scarpa's ganglion (primary sensory cell bodies of vestibular system; bipolar cell type) → vestibular nuclei in pons

(superior, inferior, lateral) → secondary sensory axons project to five areas in central nervous system (CNS)

- Spinal cord via medial, lateral vestibulospinal tracts
- Cerebellum via vermis, flocculonodular lobe
- Extraocular muscles via medial longitudinal fasciculus (MLF), CN nuclei III, IV, VI
- Reticular formation in medulla (vomiting center)
- Medial geniculate body/cortex: provides orientation of body in space



**Figure 50.24** The semicircular canals measure rotational/angular acceleration to maintain balance. Movement of endolymph displaces hair cells in the ampulla. Hair cells then transmit this information as an electrical signal along the vestibular branch of CN VIII to the brain.



**Figure 50.25** The otolith organs, the utricle and saccule, measure linear acceleration using balance receptors in the macula.



# NOTES

## AUTONOMIC NERVOUS SYSTEM

- Part of peripheral nervous system (PNS); regulates basic visceral processes necessary to homeostasis
- Autonomic nervous system (ANS) affects visceral organs, glands, involuntary muscles → regulates heart rate, respiration rate, digestion, urination, salivation, sexual arousal, etc.
- Divided into two systems
  - Sympathetic, parasympathetic
- Unlike somatic nervous system, in ANS
  - Neurotransmitters synthesized, stored, released in varicosities (analogous to presynaptic nerve terminals in somatic nervous system)
  - Target organ's tissue can be innervated by multiple postganglionic neurons
  - Postsynaptic receptors widely scattered on target organ

### NEURONS

- Two neuron types in both sympathetic, parasympathetic systems
  - Preganglionic, postganglionic

- Preganglionic neurons → preganglionic fibers → synapse with autonomic ganglia (postganglionic neurons) → postganglionic fibers → target organ

#### Preganglionic neurons

- General visceral efferent (GVE) neurons
- Located in central nervous system (CNS) (spinal cord)
- Release acetylcholine (ACh)

#### Postganglionic neurons

- GVE, general visceral afferent (GVA) neurons
- Located outside central nervous system
- Release acetylcholine/norepinephrine/neuropeptides

#### Autonomic ganglia

- Contain neuron cell body clusters (postganglionic neurons)
- Synapse points between preganglionic fibers, postganglionic fibers

# SYMPATHETIC NERVOUS SYSTEM

[osms.it/sympathetic-nervous-system](http://osms.it/sympathetic-nervous-system)

- ANS component; controls visceral functions requiring fast response (i.e. "fight or flight")
- Ganglia close to spinal cord → short preganglionic fibers, long postganglionic fibers

#### Preganglionic neurons

- Located: thoracolumbar spinal cord's intermediate horn (T1-L2)
- Cholinergic neurons → release ACh

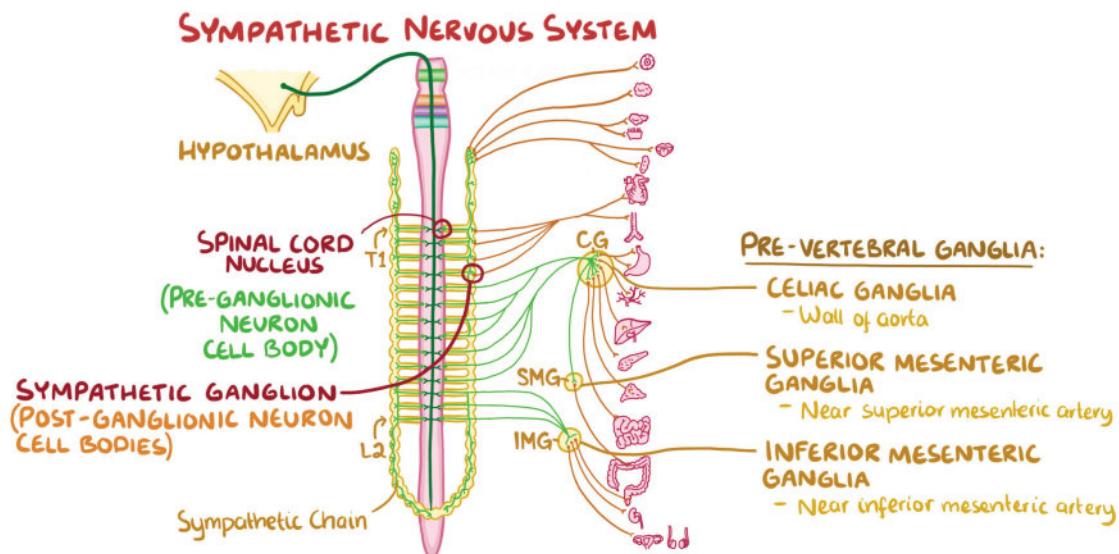
#### Postganglionic neurons

- Located close to spinal cord
  - Paravertebral ganglia (cervical, thoracic, rostral lumbar, caudal lumbar, pelvic ganglia)
  - Prevertebral ganglia (celiac, aorticorenal, superior mesenteric, inferior mesenteric ganglion)
  - Chromaffin cells of adrenal medulla (modified sympathetic ganglion)

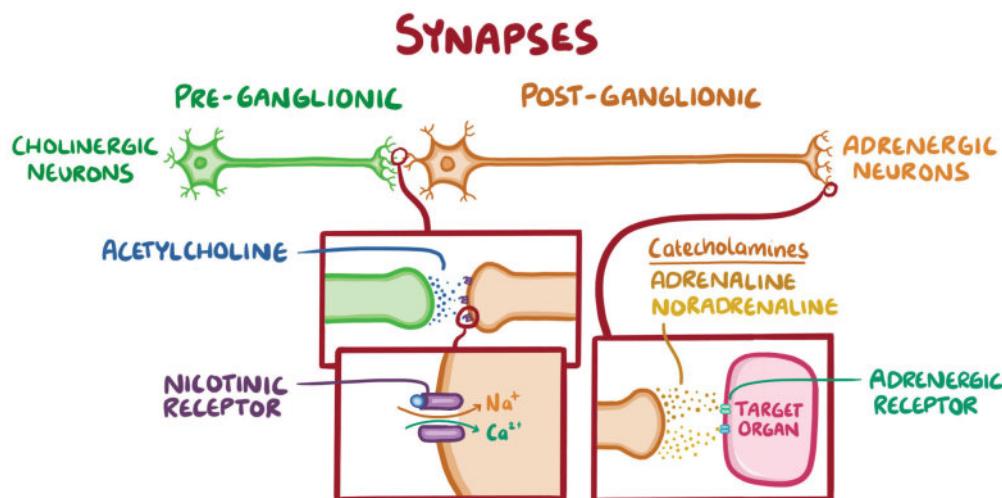
- Either adrenergic/cholinergic
  - Adrenergic neurons → release norepinephrine/epinephrine (adrenal medulla)
  - Cholinergic → release ACh
- Effector organ receptors:  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ ,  $\beta_2$ ,  $\beta_3$

### Sympathetic nervous system effects

- Cardiovascular: ↑ heart rate, ↑ cardiac output, vasoconstriction
- Respiratory: bronchodilation
- Gastrointestinal: ↓ motility, ↓ secretions
- Genitourinary: ↓ bladder's detrusor muscle activity, ejaculation
- Metabolic: ↑ gluconeogenesis
- Glands: ↓ salivation, ↑ sweating
- Pupils: mydriasis



**Figure 51.1** Neurons originating in the hypothalamus synapse with sympathetic pre-ganglionic cell bodies in spinal cord nuclei. Some pre-ganglionic neurons synapse in the paravertebral ganglia of the sympathetic chain; others synapse in the pre-vertebral ganglia.



**Figure 51.2** Sympathetic preganglionic neurons release acetylcholine, which bind to nicotinic receptors on postganglionic neurons. Postganglionic neurons release catecholamines, which are received by adrenergic receptors on target organs.

# PARASYMPATHETIC NERVOUS SYSTEM

[osms.it/parasympathetic-nervous-system](https://osms.it/parasympathetic-nervous-system)

- ANS component controls visceral functions not requiring fast response (i.e. "rest and digest")
- Ganglia close to target organ → long preganglionic fibers, short postganglionic fibers

## Preganglionic neurons

- Located in brainstem (nuclei of cranial nerves II, VII, IX, X), sacral spinal cord (S2–S4)
- Cholinergic neurons → release ACh

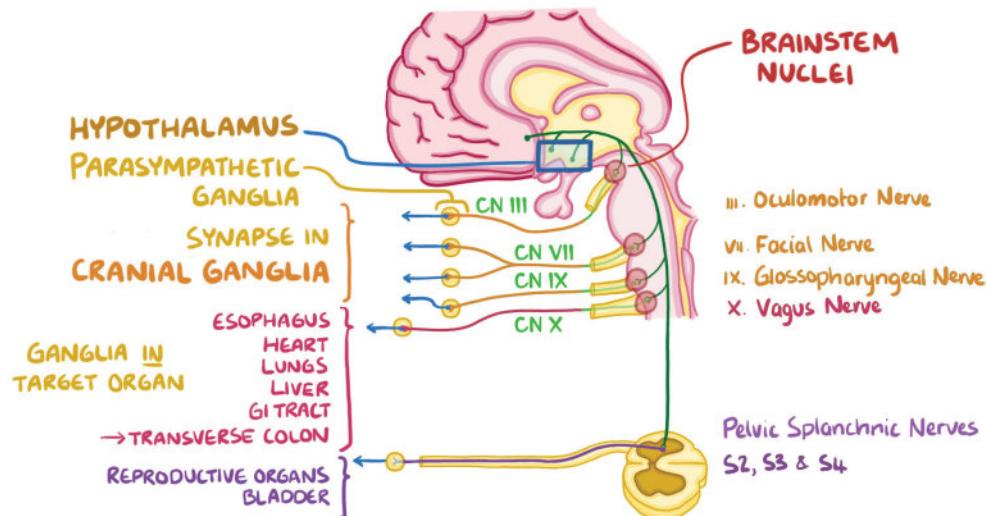
## Postganglionic neurons

- Located **close to target organs**
  - Ciliary ganglion (cranial nerve III)
  - Submandibular ganglion (cranial nerve VII)
  - Otic ganglion (cranial nerve IX)
  - Near/inside target organ (cranial nerve X, sacral nerves)

- Mostly cholinergic, but **some** non-adrenergic, non-cholinergic → release neuropeptides
- Effector organ receptors are muscarinic

## Parasympathetic nervous system effects

- Cardiovascular: ↓ heart rate, ↓ cardiac output
- Respiratory: bronchoconstriction
- Gastrointestinal: ↑ motility, ↑ secretions
- Genitourinary: ↑ bladder's detrusor muscle activity, erection
- Metabolic: ↓ glycogenesis
- Glands: ↑ salivation
- Pupils: miosis

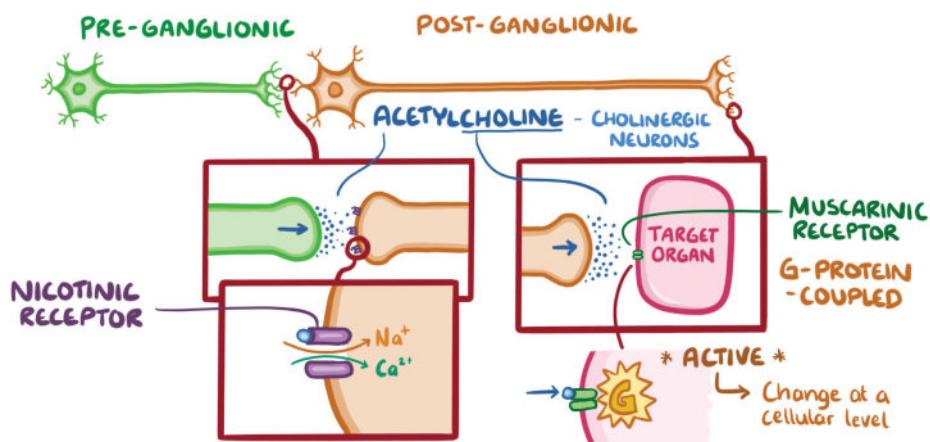


**Figure 51.3** Neurons originating in the hypothalamus synapse with parasympathetic pre-ganglionic cells bodies in brainstem, spinal cord at levels S2, S3, and S4. Pre-ganglionic neurons synapse in cranial ganglia and near/in target organ.

NERVE	GANGLIA	LOCATION	INNERVATION
OCULOMOTOR NERVE	CILIARY GANGLIA	BEHIND EYE	PUPIL
FACIAL NERVE	PTERYGOPALATINE GANGLION	PTERYGOPALATINE FOSSA, BEHIND MAXILLA	SUBLINGUAL & SUBMANDIBULAR SALIVARY GLANDS
	SUBMANDIBULAR GANGLION		LACRIMAL GLANDS GLANDS IN NASAL CAVITY
GLOSSOPHARYNGEAL NERVE	OTIC GANGLIA	INFRATEMPORAL FOSSA, BELOW & MEDIAL TO ZYGOMATIC ARCH	PAROTID SALIVARY GLAND

**Figure 51.4** Summary of parasympathetic components of cranial nerves III (oculomotor), VII (facial), and IX (glossopharyngeal).

## SYNAPSES



**Figure 51.5** Parasympathetic preganglionic neurons release acetylcholine, which binds to nicotinic receptors on the post-ganglionic neuron. The post-ganglionic neuron also releases acetylcholine, which binds to muscarinic (G-protein coupled) receptors on target organs.

## SYMPATHETIC & PARASYMPATHETIC NERVOUS SYSTEMS OVERVIEW

	NEURONS	FIBER LENGTH	NEURO-TRANSMITTERS	RECEPTORS
SYMPATHETIC NERVOUS SYSTEM	Preganglionic	Short	ACh	Muscarinic
	Postganglionic	Long	Norepinephrine, ATP, neuropeptide Y	Adrenergic ( $\alpha_1, \alpha_2, \beta_1, \beta_2$ )
PARASYMPATHETIC NERVOUS SYSTEM	Preganglionic	Long	ACh	Nicotinic (N <sub>n</sub> , N <sub>m</sub> )
	Postganglionic	Short	ACh	Muscarinic (M <sub>1</sub> , M <sub>2</sub> , M <sub>3</sub> , M <sub>4</sub> , M <sub>5</sub> )

## SYMPATHETIC VS. PARASYMPATHETIC: EFFECTS ON EFFECTORS

EFFECTOR	SYMPATHETIC NERVOUS SYSTEM		PARASYMPATHETIC NERVOUS SYSTEM	
	RECEPTOR	EFFECT	RECEPTOR	EFFECT
PUPILS	$\alpha_1$	Dilation	M <sub>3</sub>	Constriction
HEART	$\beta_1$	Positive inotropic, chronotropic, dromotropic effect	M <sub>2</sub>	Negative inotropic, chronotropic, dromotropic effect
LUNGS	$\beta_2$	Bronchodilation	M <sub>3</sub>	Bronchoconstriction, $\uparrow$ gland secretion
GI TRACT	$\alpha_1$	Vasoconstriction, sphincter contraction	M <sub>3</sub>	$\uparrow$ motility, sphincter relaxation, $\uparrow$ gland secretion
URINARY TRACT	$\alpha_1, \beta_1$	Bladder sphincter contraction, $\uparrow$ renin secretion	M <sub>3</sub>	Bladder sphincter relaxation
SKELETAL MUSCLE	$\beta_2$	Vasodilatation	-	None
SKIN	$\alpha_1$	Vasoconstriction	-	None
GLANDS	$\alpha_1$	$\uparrow$ sweating, $\downarrow$ pancreatic activity	M <sub>1</sub> , M <sub>3</sub>	$\uparrow$ salivation, $\uparrow$ lacrimation, $\uparrow$ pancreatic activity

# ADRENERGIC RECEPTORS

[osms.it/adrenergic-receptors](http://osms.it/adrenergic-receptors)

- Metabotropic receptors: respond to catecholamines (norepinephrine, epinephrine)
- Located on sympathetic effector organs → stimulated → sympathetic/sympathomimetic response
- Types
  - $\alpha$ ,  $\beta$  adrenergic receptors:  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ ,  $\beta_2$ ,  $\beta_3$

## $\alpha_1$ Adrenergic receptors (stimulatory effect)

- Gastrointestinal tract blood vessels, skin blood vessels → vasoconstriction
- Bladder, gastrointestinal (GI) tract sphincters → contraction
- Radial (dilator) muscle of iris → contraction
- Pancreas → ↓ secretion
- Liver → ↑ glycogenolysis

## $\alpha_2$ Adrenergic receptors (inhibitory effect)

- Presynaptic nerve terminals (autoreceptors) → presynaptic inhibition of neurotransmitter release
- Postganglionic parasympathetic nerve terminals in GI tract (heteroreceptors) → ↓ insulin secretion
- ↓ platelet aggregation

## $\beta_1$ Adrenergic receptors (stimulatory effect)

- Heart
  - Sinoatrial (SA) node → ↑ heart rate (positive chronotropic effect)
  - Atrioventricular (AV) node → ↑ conduction (positive dromotropic effect)
  - Ventricular muscle → ↑ contractility (positive inotropic effect)
- Salivary glands → ↓ salivation
- Adipose tissue → lipolysis
- Kidney → ↑ renin secretion

## $\beta_2$ adrenergic receptors (stimulatory effect)

- Skeletal muscle blood vessels → vasodilation
- Bronchioles → relaxation
- Pancreas → ↑ secretion
- Liver → ↑ glycogenolysis, ↑ gluconeogenesis

## $\beta_3$ adrenergic receptors (stimulatory effects)

- Adipose tissue → lipolysis, thermogenesis
- Detrusor muscle → relaxation

## Adrenergic receptor mechanism

- Catecholamines binding →  $G_q$  (stimulatory) or  $G_i$  (inhibitory) protein activation → second messenger cascade → ↑ phospholipase C or ↓ adenylate cyclase → effect
- $\alpha_1$  adrenergic receptors
  - $G_q$  protein activation → second messenger cascade → ↑ phospholipase C → ↑ IP<sub>3</sub>, DAG, Ca<sup>2+</sup> → stimulatory effect
- $\alpha_2$  adrenergic receptors
  - $G_i$  protein activation → ↓ adenylate cyclase → ↓ cAMP → inhibitory effect
- $\beta_1$  adrenergic receptors
  - $G_s$  protein activation → ↑ adenylate cyclase → ↑ cAMP → stimulatory effect
- $\beta_2$  adrenergic receptors
  - $G_s$  protein activation → ↑ adenylate cyclase → ↑ cAMP → stimulatory effect

## CATECHOLAMINES

- Neurotransmitters synthesized, released by adrenergic neurons
- Include epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine

**Synthesis**

- Tyrosine → L-dopa; catalyzed by tyrosine hydroxylase
- L-dopa → dopamine; catalyzed by dopa decarboxylase
- Dopamine → norepinephrine; catalyzed by  $\beta$  hydroxylase
- Norepinephrine → epinephrine; catalyzed by phenylethanolamine-N-methyltransferase (PNMT); only in adrenal medulla

**Degradation**

- All catecholamines can be degraded by deamination by monoamine oxidase (MAO)/methylation by catechol-O-methyltransferase (COMT)/both
- Norepinephrine
  - MAO: dihydroxyphenylacetic acid
  - COMT: normetanephrine
  - Both: 3-methoxy-4-hydroxyphenylacetic acid (VMA)

**Epinephrine**

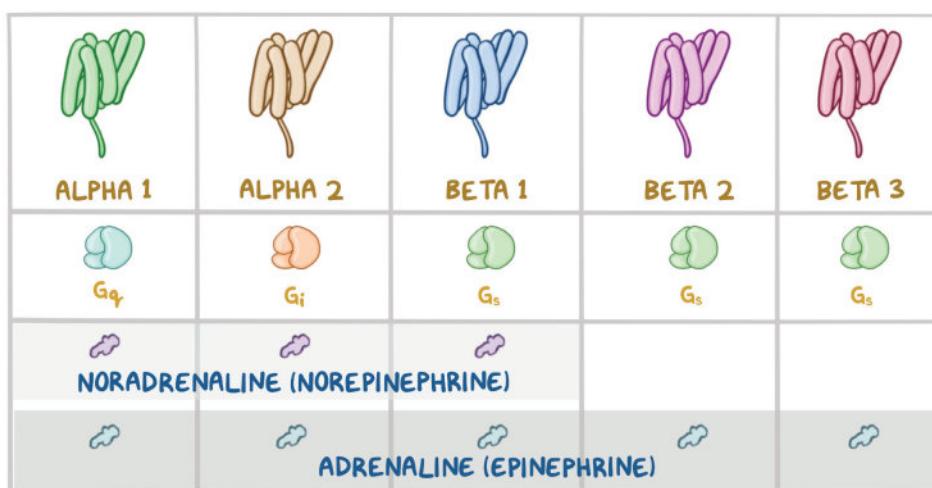
- MAO: dihydroxyphenylacetic acid
- COMT: metanephrine
- Both: 3-methoxy-4-hydroxyphenylacetic acid (VMA)

**Dopamine**

- MAO: dihydroxyphenylacetic acid
- COMT: 3-methoxytyramine
- Both: homovanillic acid (HVA)

**Adrenergic transmission**

- Present in
  - Most postganglionic sympathetic neurons (norepinephrine)
  - Adrenal medulla's chromaffin cells (epinephrine)
  - Ventral tegmental area, substantia nigra (dopamine)



**Figure 51.6** Types of adrenergic receptors, the G-proteins with which they can be coupled, and the catecholamines that bind with them.

# CHOLINERGIC RECEPTORS

[osms.it/cholinergic-receptors](http://osms.it/cholinergic-receptors)

- Receptors respond to neurotransmitter acetylcholine
- Located on parasympathetic effector organs, CNS → stimulated → parasympathetic/parasympathomimetic response

## Nicotinic receptors

- Ionotropic receptors
- Type: location
  - Nm: neuromuscular junction (non autonomic)
  - Nn: autonomic ganglia and adrenal medulla
- Mechanism
  - Acetylcholine binding →  $\text{Na}^+$ ,  $\text{K}^+$  diffusion → depolarization → voltage  $\text{Na}^+$  channel activation → action potential → stimulatory effect

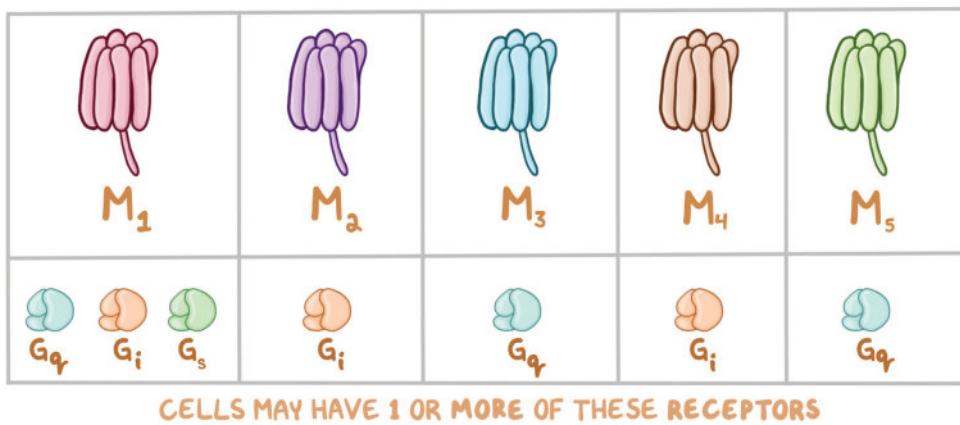
## Muscarinic receptors

- Metabotropic receptors (G-protein coupled receptors)
- Located in CNS, all parasympathetic effector organs, some sympathetic effector organs
- Type: location
  - $\text{M}_1$ : autonomic ganglia, exocrine glands, CNS
  - $\text{M}_2$ : heart, sweat glands, CNS
  - $\text{M}_3$ : smooth muscle (blood vessels, lungs), glands, eyes, CNS
  - $\text{M}_4$ : CNS, sweat glands
  - $\text{M}_5$ : CNS

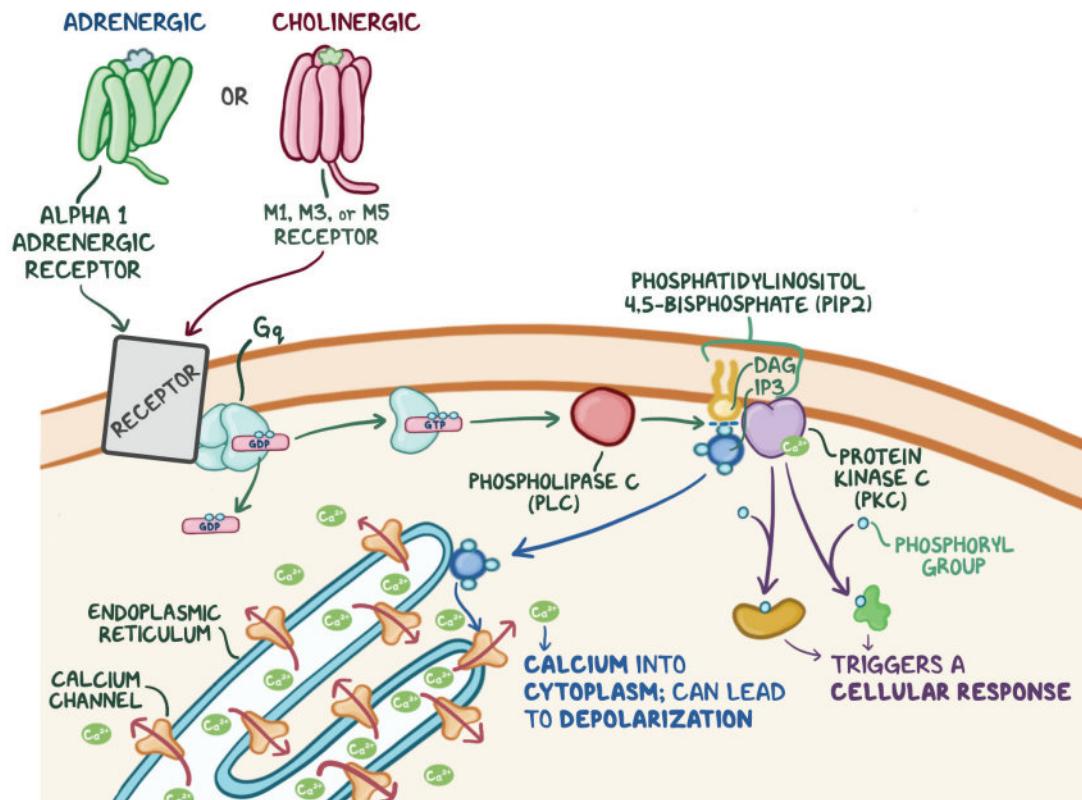
- Mechanism
  - Acetylcholine binding →  $\text{G}_q$  (stimulatory) or  $\text{G}_i$  (inhibitory) protein activation  
→ second messenger cascade → ↑ phospholipase C/↓ adenylate cyclase → stimulatory/inhibitory effect
  - $\text{M}_1$ ,  $\text{M}_3$ ,  $\text{M}_5$  →  $\text{G}_q$  protein activation → ↑ phospholipase C → ↑  $\text{IP}_3$ , DAG,  $\text{Ca}^{2+}$  → stimulatory effect
  - $\text{M}_4$  →  $\text{G}_i$  protein activation → ↓ adenylate cyclase → ↓ cAMP → inhibitory effect
  - $\text{M}_2$  →  $\text{G}_i$  protein activation →  $\text{K}^+$  channel activation → inhibitory effect

## ACETYLCHOLINE (ACh)

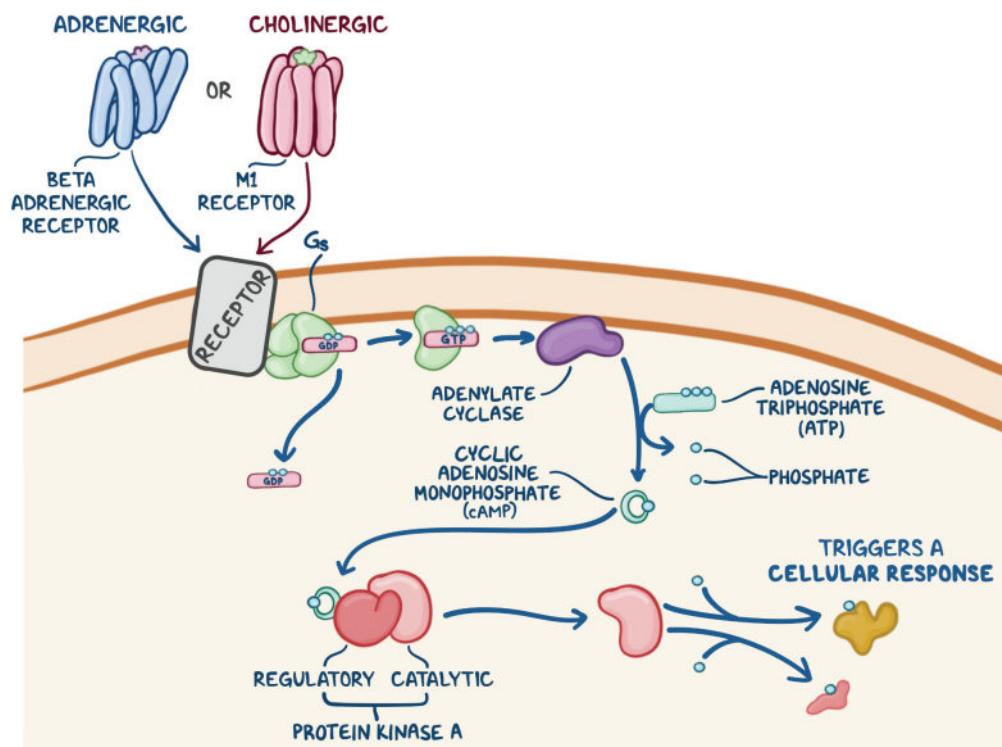
- Neurotransmitter synthesized, released by cholinergic neurons
- Synthesis
  - Acetyl CoA + choline → acetylcholine; catalyzed by choline acetyltransferase
- Degradation
  - Acetylcholine → acetylcholine CoA + choline; catalyzed by cholinesterase
- Cholinergic transmission is present in
  - Basal ganglia, hippocampus, cerebral cortex
  - All neuromuscular junctions
  - All preganglionic neurons (both parasympathetic, sympathetic neurons)
  - All postganglionic parasympathetic neurons
  - Some postganglionic sympathetic neurons (sweat glands)



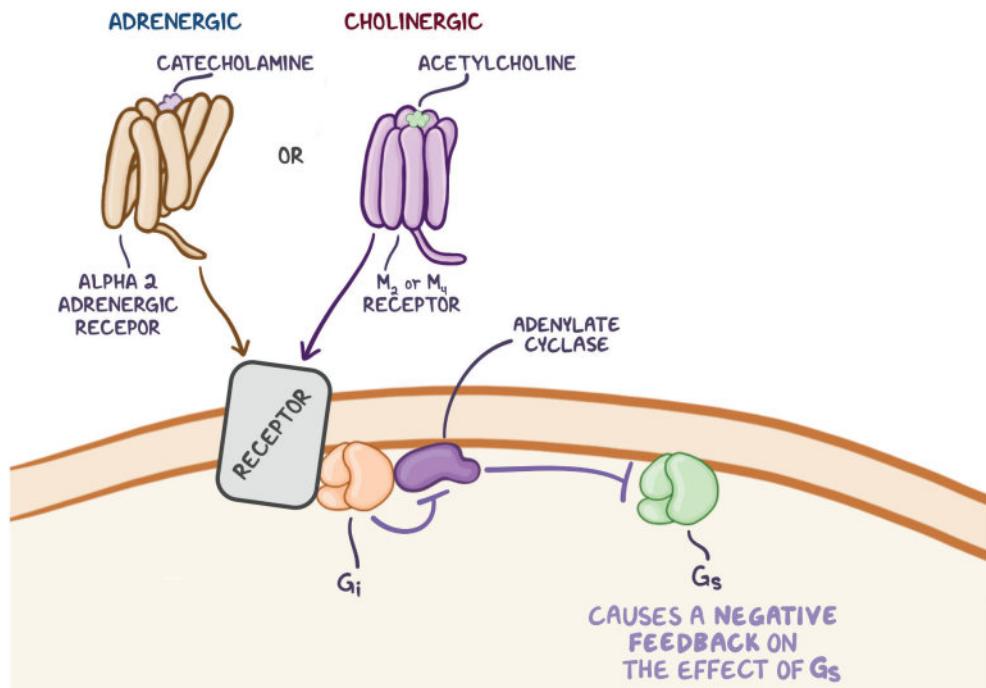
**Figure 51.7** Types of muscarinic receptors and the G-proteins with which they can be coupled.



**Figure 51.8** Mechanism of action of receptors coupled with G<sub>q</sub> protein. The type of adrenergic receptor that couples with G<sub>q</sub> protein is the alpha 1 receptor. The types of cholinergic muscarinic receptors that couple with G<sub>q</sub> protein are the M<sub>1</sub>, M<sub>3</sub>, and M<sub>5</sub> receptors.



**Figure 51.9** Mechanism of action of receptors coupled with  $G_s$  protein. The type of adrenergic receptor that couples with  $G_s$  protein is the beta receptor. The type of cholinergic muscarinic receptor that couples with  $G_s$  protein is the  $M_3$  receptor.



**Figure 51.10** Mechanism of action of receptors coupled with  $G_i$  protein. The type of adrenergic receptor that couples with  $G_i$  protein is the alpha 2 receptor. The types of cholinergic muscarinic receptors that couple with  $G_i$  protein are the  $M_2$  and  $M_4$  receptors.



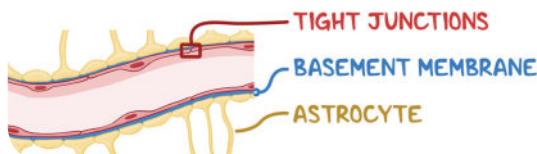
# NOTES

## BLOOD BRAIN BARRIER & CSF

# BLOOD BRAIN BARRIER (BBB)

[osms.it/blood-brain\\_barrier](https://osms.it/blood-brain_barrier)

- Selective barrier separating blood, interstitial liquid in central nervous system (CNS)
- Molecular transport keeps harmful substances out, allows metabolic waste products to diffuse from brain → plasma
- Formed by
  - Tight junctions between endothelial cells of brain capillaries
  - Astrocyte projection ("feet") supporting, maintaining structure
  - Basal (basement) membrane
- Passive transport: no energy needed (e.g. passive diffusion of **lipid-soluble molecules**)
- Active transport: energy needed (e.g. facilitated diffusion of **glucose, amino acids**)
- Primary function: CNS homeostasis
  - Providing selective nutrient passage
  - Controlling fluid movement
  - Protecting from toxins, microbes



**Figure 52.1** Components of the blood brain barrier.

### BBB PERMEABILITY

- May change due to inflammation, irradiation, tumors
- Permeant molecules (lipid-soluble molecules)
  - Steroid hormones; oxygen; carbon dioxide; water; glucose, essential amino acids; certain electrolytes
- Impermeant molecules
  - Non-essential amino acids; waste products; microbes, toxins; proteins; certain electrolytes (e.g. potassium); water-soluble drugs

### BBB IN CIRCUMVENTRICULAR ORGANS

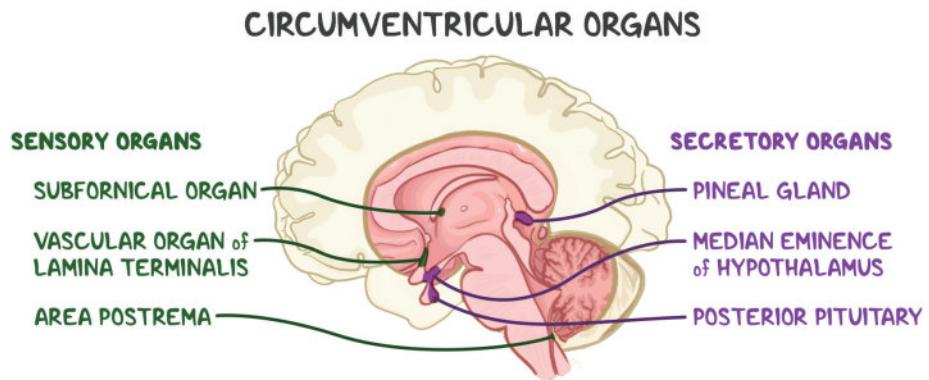
- Absent in circumventricular organs → connection between CNS, blood
- Includes sensory, secretory organs

#### Sensory organs

- Sense plasma molecules, coordinate response to them
  - **Area postrema/vomiting center** (senses harmful substances in blood → vomiting reflex)
  - Subfornical organ
  - **Vascular organ of lamina terminalis**

#### Secretory organs

- Receive stimuli, secrete substances directly in plasma
  - Posterior pituitary gland
  - Median eminence of hypothalamus
  - Pineal gland



**Figure 52.2** Sensory and secretory circumventricular organs.

## CEREBROSPINAL FLUID (CSF)

[osms.it/cerebrospinal-fluid](https://osms.it/cerebrospinal-fluid)

- Body fluid found within CNS
- Fills, circulates through
  - **Ventricular system** (lateral ventricles, third ventricle, fourth ventricle, central canal of spinal cord)
  - **Subarachnoid space** surrounding brain, spinal cord

### CIRCULATION

- Lateral ventricles → interventricular foramina → third ventricle → cerebral aqueduct → fourth ventricle → lateral, median apertures → subarachnoid space, cisterns (some enters spinal column) → arachnoid granulations (arachnoid mater outpouching) → venous system circulation
- Kept in motion by cilia of ependymal cells lining ventricle system

### PRODUCTION

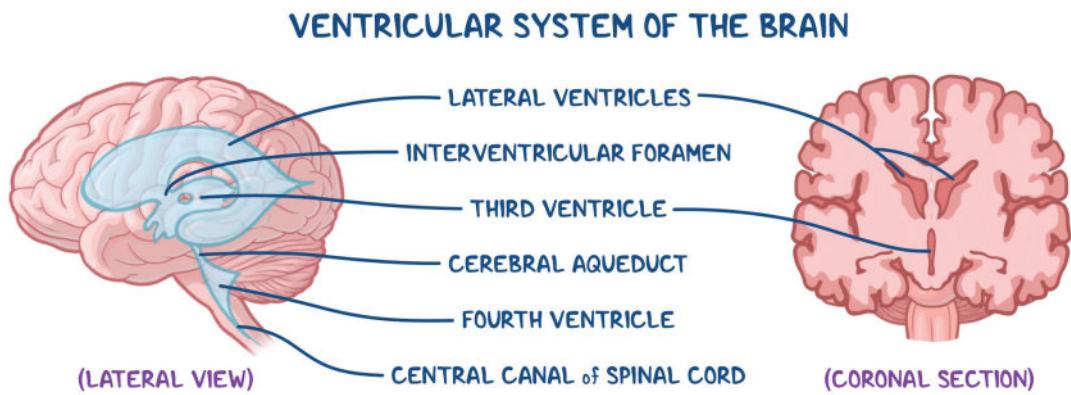
- Mostly produced by choroid plexuses
  - Network of capillaries, modified ependymal cells in ventricles
  - Also functions as blood-CSF barrier
- Rate
  - 500mL/day
- Regulated by
  - Hormones, blood pressure, autonomic nervous system

### CHARACTERISTICS

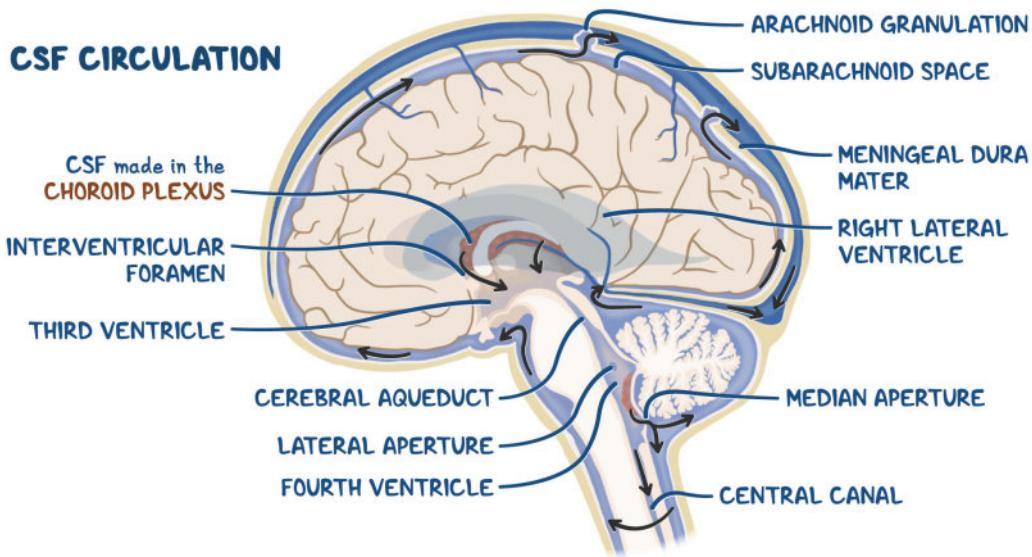
- Quantity: 125mL in total
- Color: limpid
- Pressure: range from 8–15mmHg (supine) to 16–24mmHg (sitting)
- pH: 7.33
- Protein content: 35mg/dL (< serum)
- Glucose: 60mg/dL (< serum)
- Electrolytes (mEq/L)
  - Sodium: 138
  - Potassium: 2.8
  - Calcium: 2.1
  - Magnesium: 2.0
  - Chloride: 119 (> serum)
- Sampled by lumbar puncture
  - Lumbar cistern puncture at end of spinal cord; between second, third lumbar vertebrae (L2–L3)

### FUNCTIONS

- CNS protection
  - Trauma → absorbs mechanical energy
  - Own weight → provides buoyancy
  - Ischemia → decreases quantity, relieves intracranial pressure
  - Toxic metabolites → clears them out
- Transportation medium for chemical signals, nutrients



**Figure 52.3** Ventricular system of the brain through which CSF flows.



**Figure 52.4** CSF circulation. CSF is produced by the choroid plexuses of the ventricles and is reabsorbed through the arachnoid granulations.



# NOTES

## BRAIN FUNCTIONS

### WHAT ARE BRAIN FUNCTIONS?

- Normal brain functions: continuous neuronal electrical activity
- Measured by electroencephalogram (EEG) for research, diagnostics
  - Electrodes on scalp record brain activity (measure voltage differences between cortical regions)

### BRAIN WAVES

- Brain wave activity altered by mental state
  - Slower brain waves: prominent during relaxation
  - Higher brain waves: prominent during wakefulness/alertness
  - Extreme ↑/↓ frequencies: suggest damaged cerebral cortex
- Spontaneous brain waves controlled by autonomic nervous system, continue to appear during unconsciousness, coma (if some brain, body functions continue)
  - Lack of spontaneous brain waves (i.e. "flat EEG" without peaks/troughs) suggests brain death
- Four characteristic EEG brain wave patterns: different consciousness/sleep stages
  - Appearance: continuous peaks/troughs
  - Wave frequency: number of peaks/second (hertz (Hz))
  - Wave amplitude/intensity: indicates synchronicity of many neurons

#### Alpha waves (8–13Hz)

- Low amplitude, rhythmic, regular, synchronous waves
- Appear during relaxed consciousness states

#### Beta waves (14–30Hz)

- Rhythmic, but ↑ frequency, ↓ regularity compared to alpha waves
- Appear during alert consciousness states

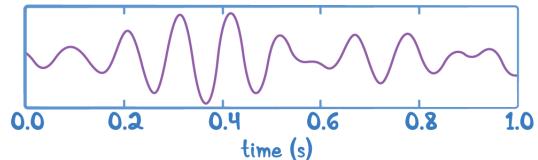
#### Theta waves (4–7Hz)

- Irregular waves
- Often appear in children, may appear in conscious, alert-stage adults

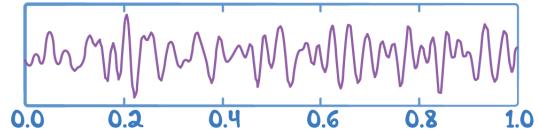
#### Delta waves (<4Hz)

- ↑ amplitude waves
- Often appear during deep sleep stages, anesthesia
- In awake adults, may indicate brain damage

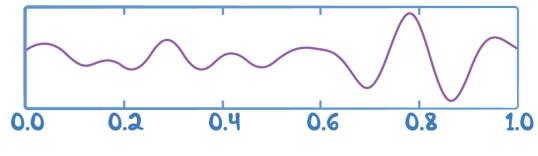
#### ALPHA WAVES



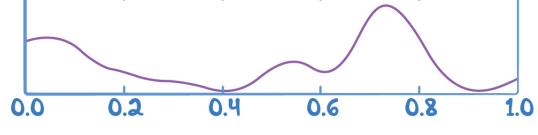
#### BETA WAVES



#### THETA WAVES



#### DELTA WAVES



**Figure 53.1** Four types of brain waves. From top to bottom: alpha waves (awake but relaxed), beta waves (awake and alert), theta waves (common in children), delta waves (deep sleep).

# SLEEP

[osms.it/sleep](https://osms.it/sleep)

## WHAT IS SLEEP?

- Naturally recurring partially-unconscious state (inhibited response to external stimuli)
  - Coma: unconscious state (no response to external stimuli)
- Depressed cortical, continued brain stem activity → continued autonomic nervous system functions (e.g. controlling heart rate, respiration, blood pressure)
- Alternating stages based on EEG patterns

## SLEEP STAGES

### Non-rapid eye movement (NREM) sleep

- Little/no eye movement, thought-like brain activity, less voluntary muscle inhibition
- Stage 1
  - Immediately after falling asleep
  - EEG: irregular waveforms: slow frequencies, ↑ amplitudes
- Stage 2
  - First 30–45 minutes of sleep; occurs with **deeper sleep**
  - EEG: theta waves present
- Stages 3/4
  - Slow-wave sleep (SWS)
  - 90 minutes into sleep
  - EEG: activity slows down progressively
  - Decreased heart rate, blood pressure
  - Important for restorative functions

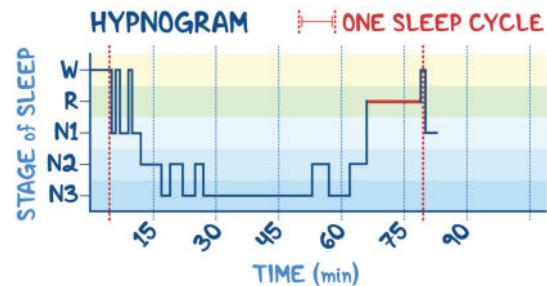
### Rapid eye movement (REM) sleep

- Characterized by irregular brain waves → alpha waves (typically seen when awake)
- ↑ heart rate, blood pressure, respiratory rate; ↓ gastrointestinal function
  - Paradoxical sleep: although most body function activity increases/mimics wakefulness, individual is asleep
- **Brain oxygen use: REM sleep > awake**
- Spinal cord interneurons inhibit motor neurons → temporary skeletal muscle paralysis
- Most **dreaming** occurs
- Associated with **memory consolidation**;

important for learning, cognitive performance

## SLEEP PATTERNS

- Hypothalamus controls sleep cycle timing
  - Retina directly connected to hypothalamus, controls pineal gland (produces melatonin)
  - Decreasing light → melatonin release → sleepiness
- Alternating sleep/wake cycles = body's natural circadian rhythm
- Young/middle-aged adults: sleep starts in 4-stage NREM sleep → alternating REM, NREM cycles
- REM occurs approximately every 90 minutes; each cycle ↑ time
  - First REM: 5–10 minutes
  - Last REM: 20–50 minutes
  - Early in the night: deep sleep → awake periods (SWS sleep dominant)
  - Later in the night: REM sleep dominant
- Sleep patterns change over lifetime; ↑ age = ↓ sleep needs
  - Infants: 16 hours
  - Adults: 7.5–8.5 hours
  - ↑ age = ↑ length of each sleep cycle
  - Children spend more time in SWS than adults



**Figure 53.2** Hypnogram illustrating progression through one sleep cycle. **W** = wakefulness, **R** = REM sleep, **N1** = stage 1 NREM, **N2** = stage 2 NREM, **N3** = stage 3 NREM.

# CONSCIOUSNESS

[osms.it/consciousness](https://osms.it/consciousness)

## WHAT IS CONSCIOUSNESS?

- Awake, responsive state; simultaneous cerebral cortex electrical activity
- Associated with stimuli perception, voluntary movement control, high mental processing levels
- Superimposed by different neuron activities
  - E.g. same neurons involved in cognition, motor control
- Holistic, interconnected (e.g. memories can be triggered by smells, locations, people, etc.)
- Clinically, consciousness used to assess response (range: conscious → coma)
- Commonly assessed based on response to stimuli (movements, sounds, touch, etc.)

## CONSCIOUSNESS STAGES

- Alertness: information processing, physical arousal
- Sleep: partially unconscious state (reduced sensory activity)
- Dreaming: mental experiences during sleep
- Altered: hypnosis, meditation, drug-induced, brain diseases, age → brain wave activity changes

# LEARNING

[osms.it/learning](https://osms.it/learning)

## WHAT IS LEARNING?

- Respond to stimulus → acquire new/adjust existing knowledge/skills/information/behaviors
- Influenced by single/repeated events
- Active process
  - Absorb knowledge by experiencing,

exploring, interacting with world

- Begins at birth, ends at death
- Can occur in different forms
- Affected by internal, external factors
  - External: genetics, environment
  - Internal: attention, attitude, goals, values, behavior, emotions

# ATTENTION

[osms.it/attention](https://osms.it/attention)

## WHAT IS ATTENTION?

- Behavioral, cognitive process
  - Selective concentration on information
- Attention placed on subset of all perceived stimuli (e.g. one person in a crowd)

- Limited by capacity, duration
- Involves allocating processing resources (e.g. while multitasking)
- Integral component of cognitive system for environmental responses

# MEMORY

[osms.it/memory](https://osms.it/memory)

## WHAT IS ATTENTION?

- Information storage, retrieval
  - Important for learning, behavior, consciousness

## MEMORY STAGES

- Sensory memory
  - Visual, auditory memory
  - Generally lasts 1 second without rehearsal, but recalled information very detailed
- Short-term memory (STM) (AKA working memory)
  - Generally fades over 30 seconds without rehearsal
  - Limited capacity
- Working memory
  - Information kept in consciousness for manipulation, integration

- Long-term memory (LTM)
  - Vast information amounts stored, recalled on demand
  - Short-term → long-term memory transfer influenced by emotional states; repetition; new, old information association; automatic memory

## MEMORY TYPES

- Declarative (explicit/fact) memory
  - Explicit information learned, requires conscious recall
- Non-declarative memory
  - Procedural (skills) memory; motor memory; emotional memory; conditioned responses from repetition, experience

# LANGUAGE

[osms.it/language](https://osms.it/language)

## WHAT IS LANGUAGE?

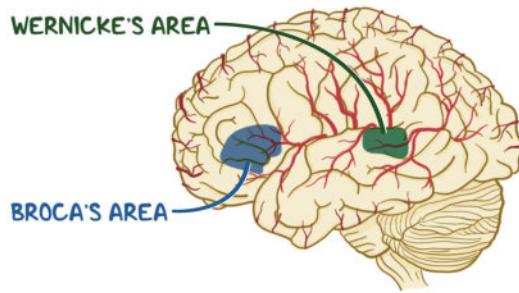
- System that communicates ideas, feelings through words

## COMPONENTS OF LANGUAGE

- Phonology: language's auditory sound
- Morphology: word structure
- Semantics: word meaning
- Syntax: words combined into sentences
- Pragmatics: language depends on context, pre-existing knowledge, audience

## BRAIN'S LANGUAGE PROCESSING

- Processed in dominant left hemisphere, especially Broca's area, Wernicke's area (connected by arcuate fasciculus)
  - Broca's area: controls speech's motor functions
  - Wernicke's area: language comprehension
- Non-dominant right hemisphere: body language (language's nonverbal component)
- Aphasia: inability to produce/comprehend language



**Figure 53.3** Lateral view of the left side of the brain showing the locations of Wernicke and Broca's areas. These areas are responsible for language comprehension and production, respectively.

## EMOTION

[osms.it/emotion](https://osms.it/emotion)

### WHAT IS EMOTION?

- Conscious experience involving mental activity, pleasure/displeasure levels
- Associated with mood, motivation, behavior
- Involves experience, processing, behavior, psychological changes, behavioral changes

### EMOTIONAL RESPONSE

- **Physiological response:** arousal → heart rate, body temperature, blood pressure changes
- **Behavioral response:** facial expressions, body language
- **Cognitive response:** interpretation depends on past experience

## STRESS

[osms.it/stress](https://osms.it/stress)

### WHAT IS STRESS?

- Body's physical, mental, emotional response to change requiring adaptation
- **Positive stress (eustress):** motivation, alertness
- **Negative stress (distress):** decreased performance, anxiety
- **Stress level severity:** dependent on individual's skills, abilities, coping mechanisms

### STRESSORS

- Biological elements, external stimuli, causal events
  - Environment: uncomfortable temperature, loud noises
  - Daily events: losing keys, forgetting items
  - Work/academic events: assignments, time management
  - Social events: family-, friend-, society-related demands

- Chemical/biological: diet, alcohol, drugs
- Psychological: pressure, lack of control, unpredictability, frustration, conflict

## STRESS RESPONSES

- Physiological
  - Alarm stage: initial reaction activates sympathetic nervous system (to maintain body functions enabling response)
  - Resistance stage: continuous hormone release (e.g. cortisol to maintain blood sugar levels; epinephrine to stimulate sympathetic nervous system) to continue engaging body
  - Exhaustion stage: body unable to maintain increased sympathetic nervous system activity
- Emotional
  - Individual may feel irritable, tense, helpless
  - May affect concentration, memory
- Behavioral
  - Individual may withdraw, abuse substances, become aggressive, suicidal
  - Chronic stress may lead to mental health disorders



# NOTES

## MOTOR NERVOUS SYSTEM

# MOTOR CORTEX

[osms.it/motor-cortex](https://osms.it/motor-cortex)

### MOTOR CORTEX BASICS

- Cerebral cortex region dedicated to voluntary movement planning, control, execution
- Location: posterior precentral gyrus, anterior to central sulcus

### THREE INTERCONNECTED REGIONS

#### Premotor cortex

- Movement preparation, sensory guidance
- Emphasis on control of proximal, trunk muscles

#### Supplementary motor cortex

- Internally generates movement planning sequences
- Programs complex motor sequences
  - Active during mental movement rehearsal (even without physical execution)
- Coordinates two sides of body, bilateral

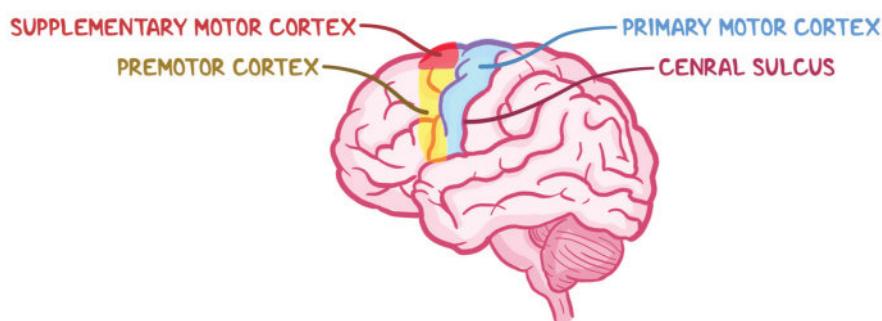
movement

#### Primary motor cortex (area four)

- Topographically organized into motor homunculus
- Origin of programmed motor neuron activation patterns → movement execution
- Upper motor neurons in motor cortex become excited → transmit to brain stem, spinal cord → activate lower motor neurons → coordinated appropriate muscle contraction (voluntary movement)

### MOTOR ACTIVATION PATTERN

- Supplementary motor, premotor cortices develop motor plan (specific muscles to contract, extent, sequence) → upper motor neurons in primary motor cortex → descending nerve tracts → lower motor neurons in spinal cord
- Basal ganglia, cerebellum provide additional fine tuning of motor output



**Figure 54.1** The three regions of the motor cortex.

# MOTOR NEURONS & MUSCLE SPINDLES

[osms.it/motor-neurons-and-muscle-spindles](https://osms.it/motor-neurons-and-muscle-spindles)

## MOTOR NEURONS

### Motor unit

- Single motor neuron, muscle fibers it innervates
- All muscle fibers in motor unit are same fiber type (slow vs. fast twitch)
- **Fine control:** few muscle fibers per neuron (e.g. eye muscles)
- **Coarse control:** thousands of muscle fibers per neuron (e.g. postural muscles)
- **Motor neuron pool:** motor neuron collection innervating muscle fibers in same muscle

### Force of contraction

- Graded action; determined by number of motor units recruited
- **Small motor neurons:** innervate few muscle fibers (generate relatively small amounts of force) → low threshold to activation → typically fire first
- **Large motor neurons:** innervate many muscle fibers (generate relatively large amounts of force) → require large action potentials to activate → typically fire last
- **Size principle:** more motor units recruited → larger motor neurons involved → greater tension developed

## MUSCLE SPINDLE FIBERS

### Extrafusal fibers

- Majority of skeletal muscle
- Innervated by  $\alpha$  motor neurons
  - Large, myelinated multipolar (one axon, many dendrites) neurons that innervate extrafusal muscle fibers of skeletal muscles
  - Directly responsible for muscle contraction
  - Generate force

### Intrafusal fibers

- Innervated by  $\gamma$  motor neurons
  - Small myelinated neurons that don't directly innervate muscle
  - Innervate intrafusal fibers → keep muscle spindles tight → allows for accurate detection of degree of stretch
- Too small to generate significant force
- Encapsulated in sheaths → form muscle spindles
  - Run parallel to extrafusal fibers
  - Abundant in muscles used for fine movements
  - Spindle-shaped organs composed of intrafusal muscle fibers
  - Innervated by sensory, motor nerve fibers
  - Attached to connective tissue

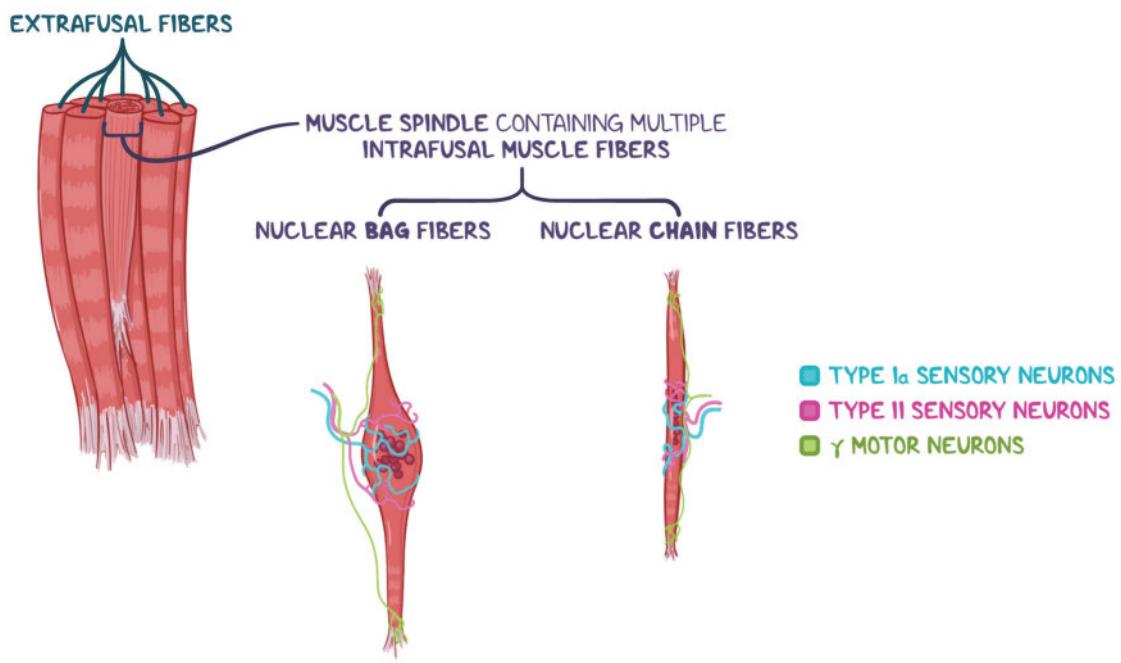
### Intrafusal muscle spindle types

- Both subtypes present in every spindle
- Nuclear bag fibers
  - Larger, nuclei accumulate in central "bag" region
- Nuclear chain fibers
  - Smaller, nuclei arranged in rows (chains), more common

## MUSCLE SPINDLES INNERVATION

### Sensory (afferent) nerves

- Group Ia afferent nerves
  - Innervates central region of both intrafusal muscle spindle subtypes
  - Relatively large nerves → fast conduction velocity
  - Form primary endings in spiral-shaped terminal around central region of muscle spindle fibers



**Figure 54.2** Muscles are composed of muscle fibers bundles with extrafusal muscle fibers on the outside and intrafusal fibers on the inside. There are two intrafusal fiber subtypes: nuclear bag fibers and nuclear chain fibers, determined by the nuclei arrangement within.

- Group II afferent nerves
  - Primarily innervate nuclear chain fibers
  - Intermediate diameter → intermediate conduction velocity
  - Form secondary endings on nuclear chain fibers (primarily)

#### Motor (efferent) nerves

- Two types
  - Dynamic  $\gamma$  motor neurons → synapse on nuclear bag fibers → “plate endings”
  - Static  $\gamma$  motor neurons → synapse on nuclear chain fibers → form “trail endings” → spread out over longer distances

#### MUSCLE SPINDLES FUNCTION

- Stretch receptors
- Extrafusal muscle fibers contract/stretch → muscle spindles correct for changes in muscle length → return muscle to resting length after shortening/lengthening

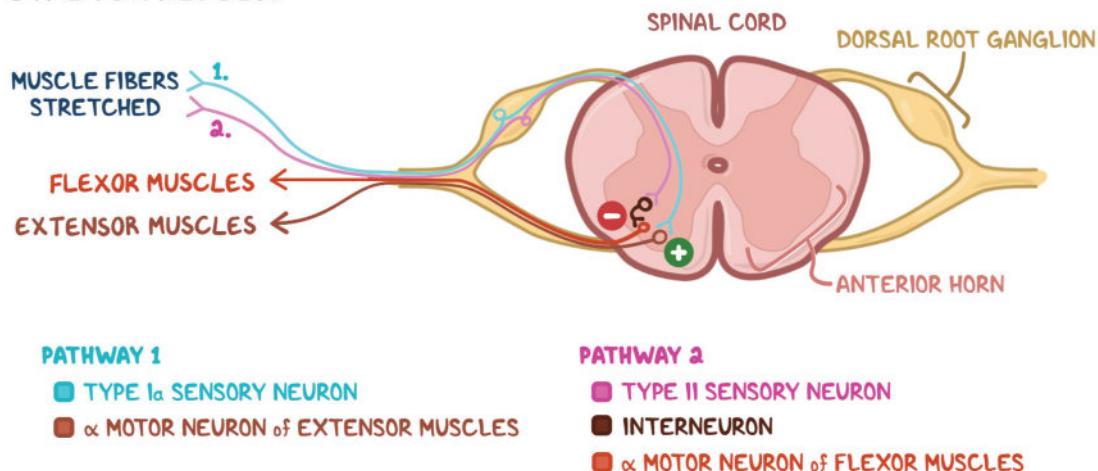
- Muscle stretch → extrafusal muscle fibers lengthen, parallel intrafusal fibers stretch
- Increased length of intrafusal fibers detected by sensory afferent fibers innervating them; increase in length of intrafusal fibers activates group Ia, group II sensory afferent fibers (group Ia afferent fibers detect velocity of length change; group II afferent fibers detect length of muscle fibers)
- Activation of group Ia afferent fibers stimulates  $\alpha$  motor neurons in spinal cord → innervation of extrafusal fibers in same muscle → muscle contraction → original stretch is opposed when reflex causes muscle to contract
- $\gamma$  motor neurons coactivated with  $\alpha$  motor neurons → muscle spindle remains sensitive to muscle length changes (even during contraction)

## MOTOR NEURONS CLASSIFICATION

- $\alpha$  motor neurons
  - Innervate extrafusal skeletal muscle fibers → contraction
- $\gamma$  motor neurons
  - Smaller, slower
  - Regulate sensitivity of intrafusal muscle fibers

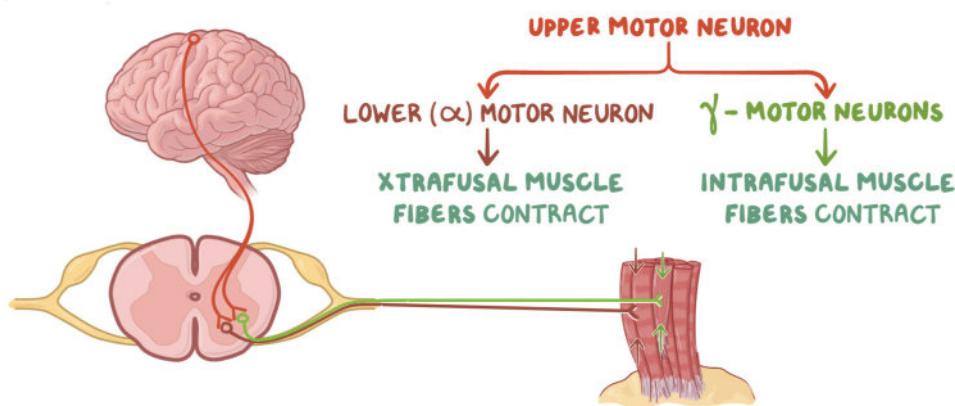
- Innervate specialized intrafusal muscle fibers (part of muscle spindles that sense muscle length) → adjust sensitivity of muscle spindles → ensures appropriate response as extrafusal fibers contract
- $\alpha, \gamma$  motor neurons are co-activated → muscle spindles remain sensitive to muscle length changes as muscle contracts

## STRETCH REFLEX



**Figure 54.3** Stretch reflex when extensor muscles are stretched. Type Ia sensory neurons synapse with  $\alpha$  motor neurons of extensor muscles, causing extensor muscle contraction. Type II sensory neurons synapse with an interneuron, which inhibits the  $\alpha$  motor neurons to the flexor muscles → flexor muscles relax. These actions together oppose the original stretch.

## $\alpha$ - $\gamma$ COACTIVATION



**Figure 54.4** Coactivation of lower motor neurons and gamma motor neurons by upper motor neurons ensures that muscle spindle remains sensitive to muscle length changes (even during contraction).

# PYRAMIDAL & EXTRAPYRAMIDAL TRACTS

[osms.it/pyramidal-and-extrapyramidal-tracts](https://osms.it/pyramidal-and-extrapyramidal-tracts)

- Motor neurons descend from cerebral cortex (cortical motor areas, associated modulatory areas), brainstem via pyramidal, extrapyramidal tracts

## PYRAMIDAL TRACTS

- Pass through medullary pyramids → descend onto lower motor neurons in spinal cord

### Corticospinal tract

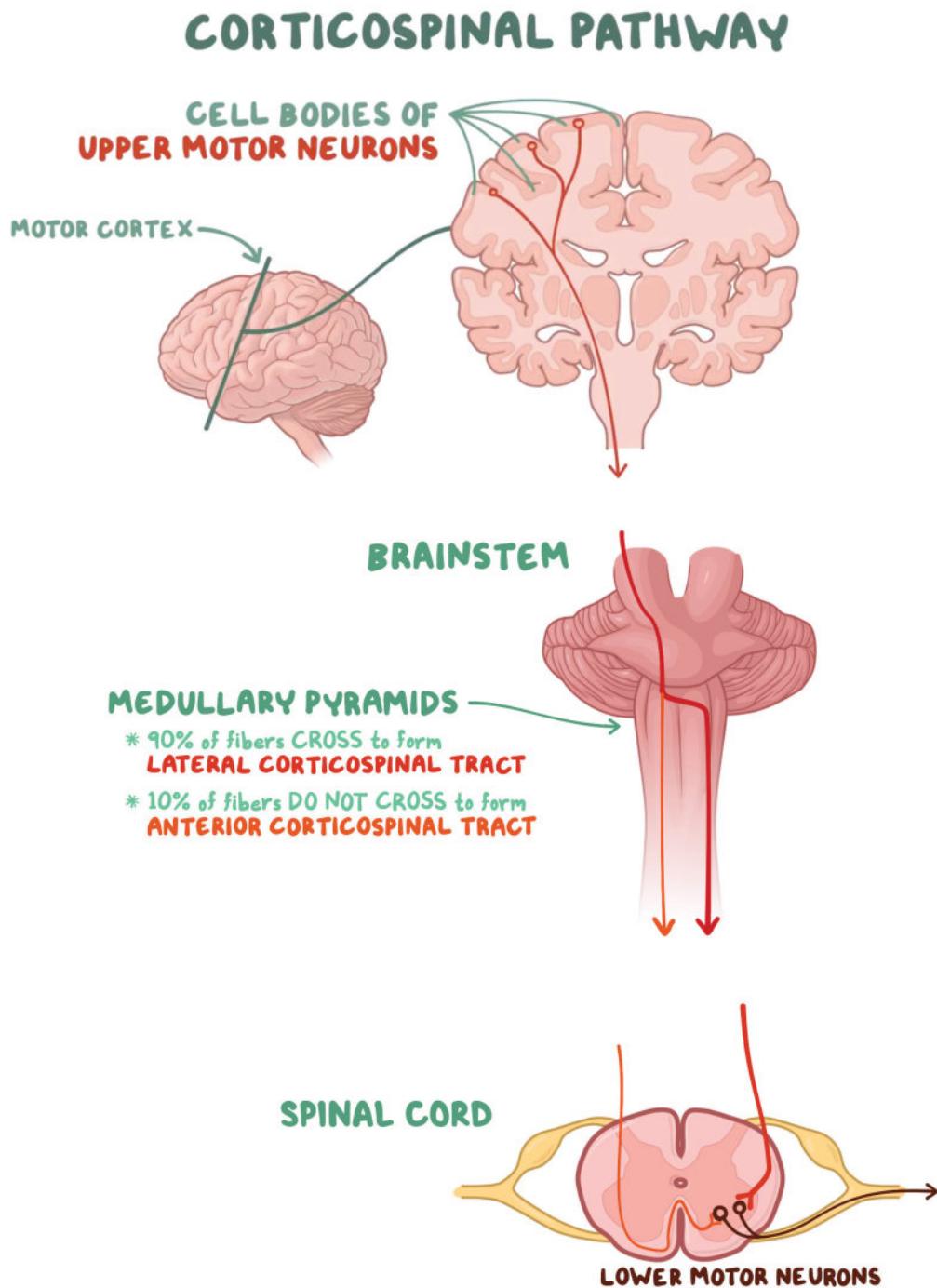
- Forms efferent nerve fibers of upper motor neurons → conduct impulses from brain to spinal cord
- Cortical motor areas (primary motor cortex, premotor cortex, supplementary motor areas), modulating sensory areas (somatosensory cortex, parietal lobe, cingulate gyrus) → posterior limb of internal capsule → cerebral peduncle (base of midbrain) → pons → medulla → spinal cord → synapse directly onto alpha motor neurons → control voluntary movement
- Forms two tracts based on where fibers cross over (decussate) to opposite side of body in medulla oblongata (decussation → muscles controlled by contralateral side of brain)
  - Lateral corticospinal tract, anterior corticospinal tract
- **Lateral corticospinal tract:** responsible for fine-motor movement of upper, lower limbs
  - Forms at level of medullary pyramids → 90% of corticospinal tract fibers decussate → lateral corticospinal tract
- **Anterior corticospinal tract:** responsible for gross, postural movement of trunk, proximal musculature

- Forms at level of medullary pyramids → 10% of corticospinal tract fibers do not decussate → forms anterior tract; eventually decussate at spinal level they innervate

- Damage → upper motor neuron syndrome

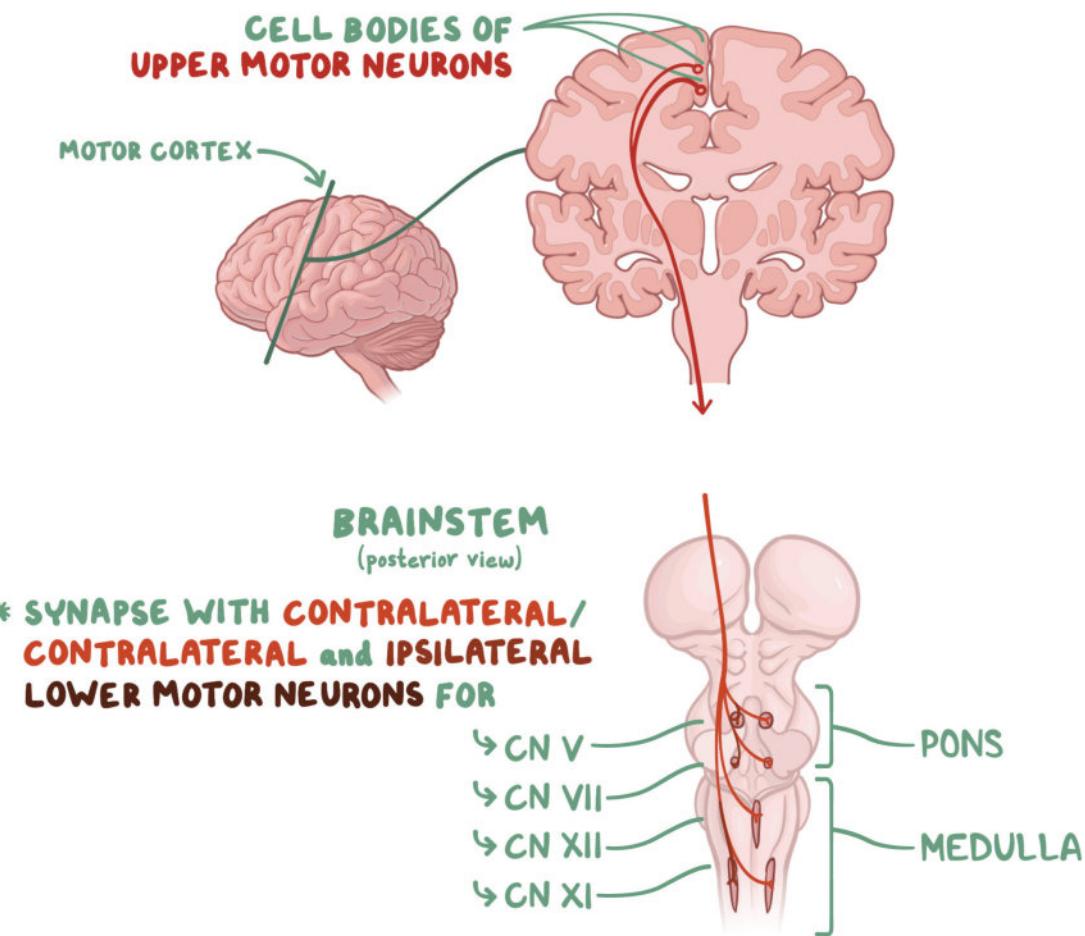
### Corticobulbar tract

- Conducts impulses from brain → cranial nerves
- **Primary motor cortex:** projects through corona radiata, genu of internal capsule/ some fibers through posterior limb of internal capsule → midbrain
- **Midbrain:** internal capsule becomes cerebral peduncles, ventral white matter of cerebral peduncles form crus cerebri → middle third of crus cerebri forms corticobulbar (and corticospinal fibres) → corticobulbar fibers exit brainstem at appropriate level to synapse on lower motor neurons of cranial nerves
- Controls facial, neck muscles (expression, mastication, swallowing)
- Only nerves controlling muscles of lower face decussate
- **Damage:** unilateral → only involves lower face; bilateral → pseudobulbar palsy (inability to control facial muscles)
  - **Pseudobulbar palsy signs, symptoms:** slow, indistinct speech; dysphagia; small/stiff/spastic tongue; brisk jaw jerk, labile affect with/without evidence of upper motor lesion also affecting limbs



**Figure 54.5** Upper motor neuron pathway in corticospinal tract. Lateral corticospinal tract fibers decussate in medulla, while anterior corticospinal tract fibers decussate at the level of the lower motor neuron (which they synapse with).

## CORTICOBULBAR PATHWAY



**Figure 54.6** Pathway of upper motor neurons in corticobulbar tract. The fibers that decussate do so at the cranial nerve level (which they synapse with). Cranial nerve lower motor neurons that receive upper motor neuron branches from both ipsilateral, contralateral sides include: CN V, XI, and portion of VII (that innervates muscles of the face's upper half). Cranial nerves that only receive upper motor neuron signals from the contralateral side include: CN XII and the part of VII that controls muscles of the face's lower half.

## EXTRAPYRAMIDAL TRACTS

- Motor neurons from motor cortex that don't pass through pyramids of medulla; tracts run through pons, medulla, target lower motor neurons in spinal cord
- Control reflexes, locomotion, complex movements, posture
- Modulated by nigrostriatal pathway, basal ganglia, cerebellum, vestibular nuclei, sensory areas of cerebral cortex
- **Extrapyramidal tract damage:** various types of dyskinesias (involuntary movement disorders)

### Rubrospinal tract

- Originates in red nucleus of midbrain, projects to motor neurons in lateral spinal cord (runs adjacent to lateral corticospinal tract), terminates in cervical spinal cord
- Mediates voluntary movement (primarily upper limbs)
- Activates flexor muscles
- Inhibits extensor muscles
- Can assume function of corticospinal tract if corticospinal tract is injured
- Damage: temporary slowness of movement

**Lateral vestibulospinal tract**

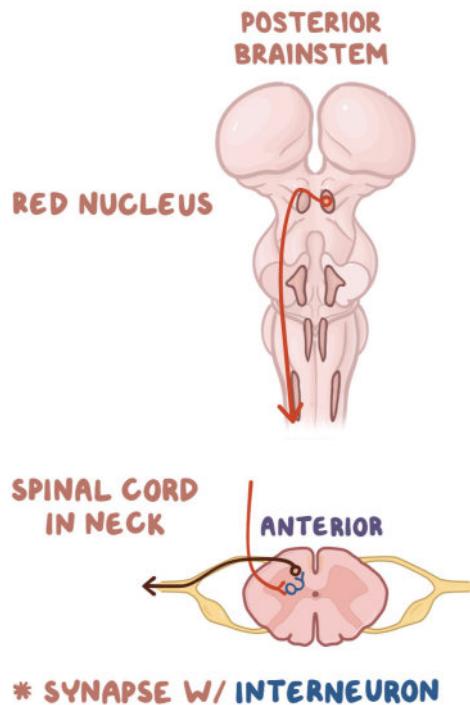
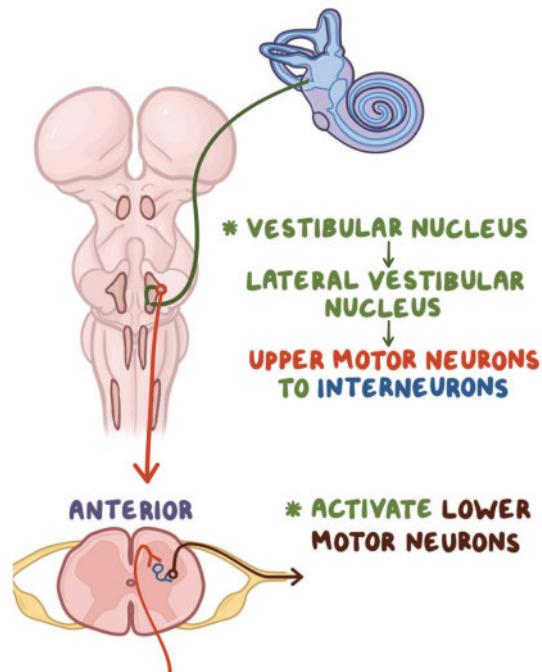
- Originates in lateral vestibular nucleus (Deiters nucleus), projects to ipsilateral motor neurons in spinal cord
- Activates extensors; inhibits flexors
- Maintains upright balance, posture through action on muscles of trunk, legs
- Receives input from cerebellum

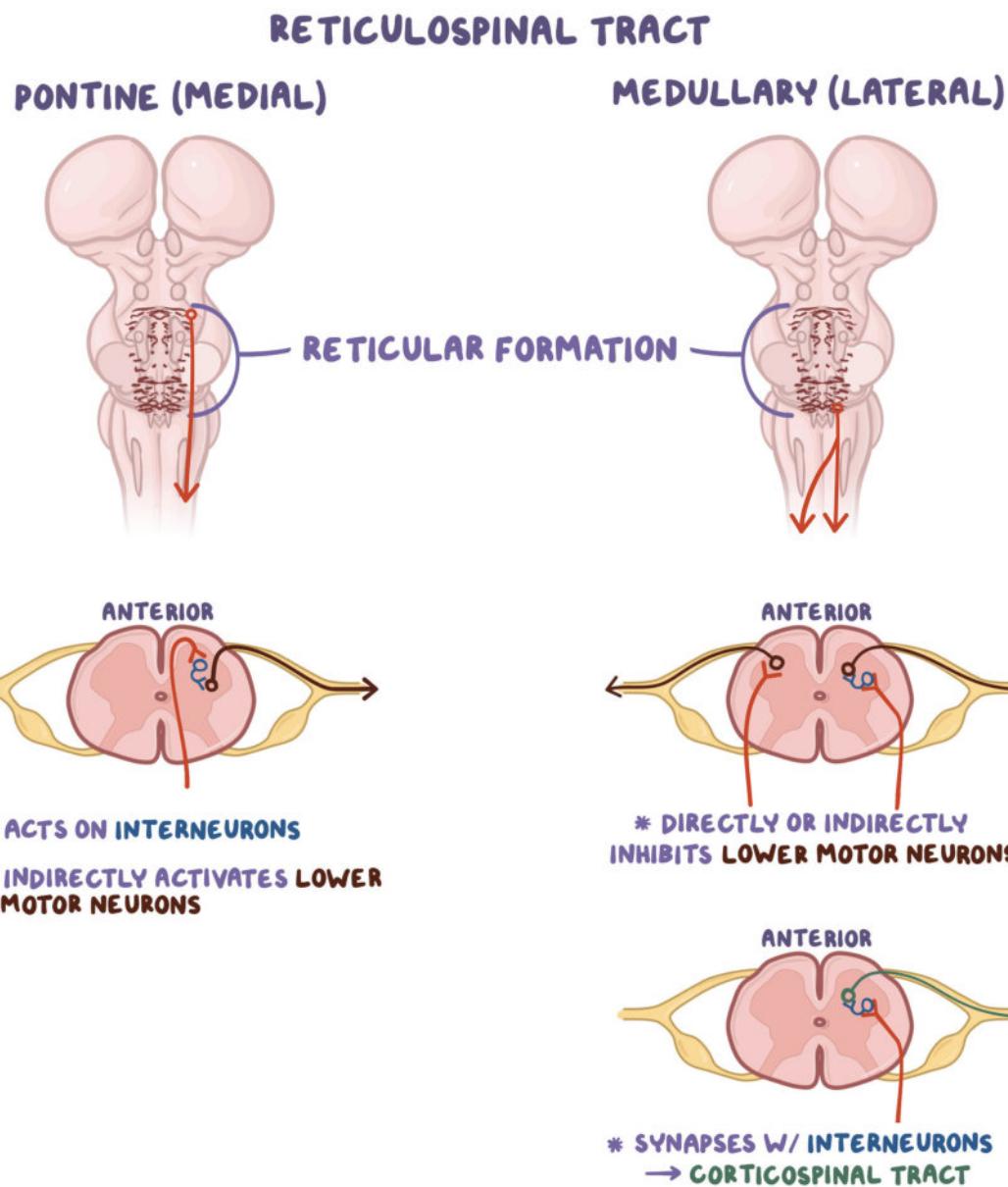
**Reticulospinal tract**

- Coordinates automatic locomotion, posture movements
- Facilitates, inhibits voluntary movement
- Mediates autonomic function
- Modulates pain
- Damage at/just below level of red nucleus
  - Decerebration: unopposed extension of head, limbs
- Pontine (medial) reticulospinal tract: originates in nuclei of pons, projects to ventromedial spinal cord; activates anti-gravity extensor muscles
- Medullary (lateral) reticulospinal tract: originates in medullary reticular formation, projects to spinal cord; inhibits excitatory axial extensors

**Tectospinal tract (colliculospinal tract)**

- Originates in superior colliculus, projects to cervical spinal cord
- Controls neck muscles: mediates reflex, postural movements of head in response to visual, auditory stimuli

**RUBROSPINAL TRACT****Figure 54.7** Rubrospinal tract.**LATERAL VESTIBULOSPINAL TRACT****Figure 54.8** Lateral vestibulospinal tract.



**Figure 54.9** Pontine and medullary reticulospinal tracts.

## SIGNS OF UPPER VS. LOWER MOTOR NEURON LESIONS

	UPPER MOTOR NEURON LESION	LOWER MOTOR NEURON LESION
LESION	Lesion anywhere in motor tract above anterior horn cell of spinal cord	Lesion affects nerve fibers travelling from anterior horn of spinal cord to relevant muscle
TONE	↑  Spasticity: (↑, involuntary, velocity-dependent muscle tone, causes resistance to movement)  Clonus: (involuntary, rhythmic, muscular contractions, relaxation)  Clasp-knife response: initial higher resistance to movement followed by lesser resistance	↓
POWER	Upper limb → primarily extensor weakness  Lower limb → primarily flexor weakness	Distal > proximal distribution  Flexors, extensors equally affected
DEEP TENDON REFLEXES	↑	↓/absent
BABINSKI REFLEX*	Babinski sign present	Absent
MUSCLE WASTING	Not notably wasted	Present
MUSCLE FASCICULATION	Absent	Present

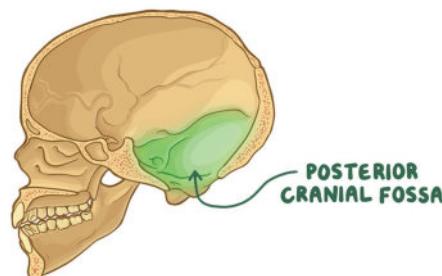
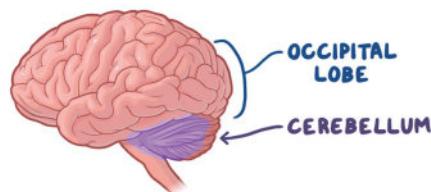
\*Babinski reflex: sole of the foot is stimulated with a pointed instrument → hallux flexion (normal) or extension (sign of pathology)

# CEREBELLUM

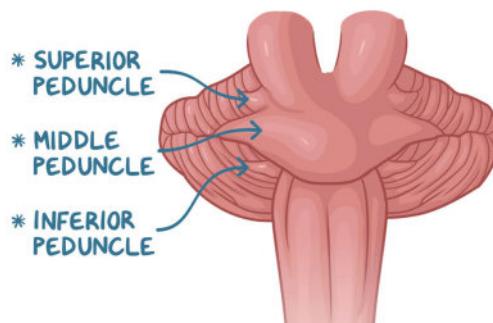
[osms.it/cerebellum](https://osms.it/cerebellum)

## CEREBELLUM

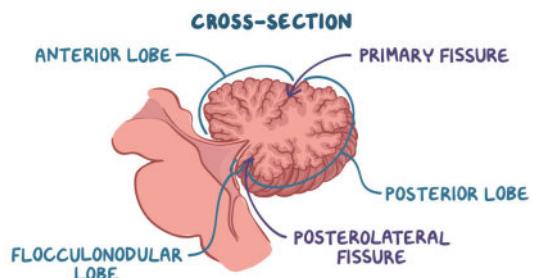
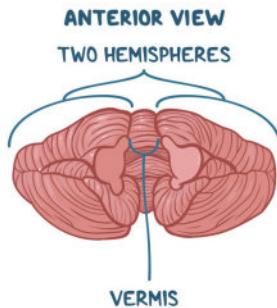
- Location: posterior fossa below occipital lobe
- Connected to brain stem by three **cerebellar peduncles** containing afferent, efferent fibers
- Regulates movement, posture: controls movement synergy (rate, range, force, direction)



**Figure 54.10** Cerebellum location relative to brain and skull.



**Figure 54.11** Superior, middle, inferior peduncles attach cerebellum to brain stem.



**Figure 54.12** Cerebellum divisions from anterior, lateral views. The vermis is the narrow ridge separating the two hemispheres, fissures separate the lobes.

## FUNCTIONAL DIVISIONS

### Vestibulocerebellum

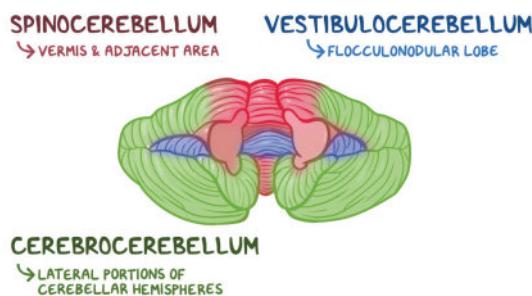
- Anatomical components: flocculonodular lobe (plus immediately adjacent vermis)
- Vestibular input: **balance, eye movement**

### Spinocerebellum

- Anatomical components: vermis, intermediate parts of hemispheres
- Spinal cord input (proprioception): regulation of movement synergy

### Pontocerebellum

- Anatomical components: lateral part of cerebellar hemispheres
- Cerebral input (via pontine nuclei): controls planning, movement initiation



**Figure 54.13** Functional cerebellum divisions (anterior view).

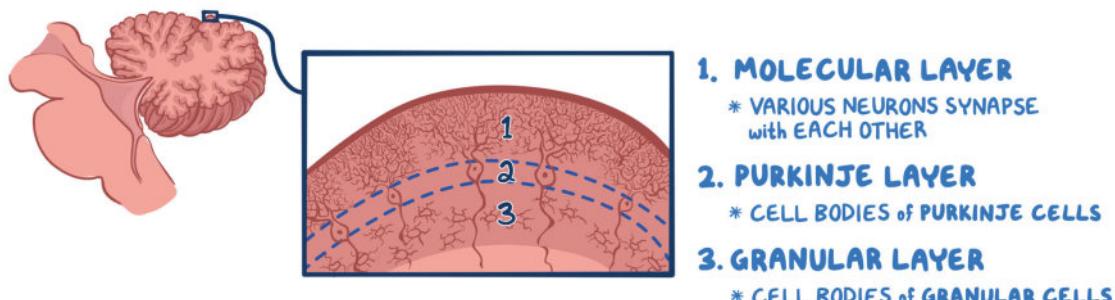
## CEREBELLAR CORTEX

### Three layers

- Molecular layer
  - Outermost layer: contains outer stellate cells, basket cells, dendrites of Purkinje, Golgi II cells, axons of granule cells
  - Two inhibitory interneuron types: stellate cells, basket cells (inhibit Purkinje cells, basket cells, outer stellate cells, Golgi type II cells)
- Purkinje cell layer
  - Middle layer: contains Purkinje cells
  - Primary integrative neurons of cerebellar cortex
  - Provides sole output of cerebellar cortex
  - Exclusively inhibitory output onto deep cerebellar neurons, vestibular nuclei of brainstem

## OUTER LAYER = CORTEX

\* THREE LAYERS

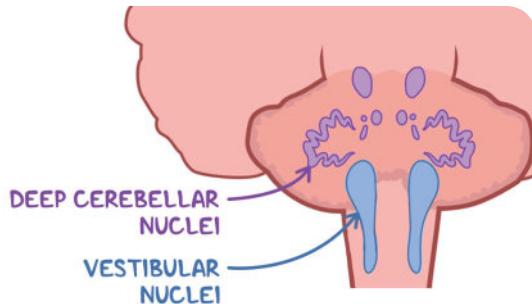


**Figure 54.14** The three layers of the cerebellar cortex, from superficial to deep.

- Granular layer
  - Innermost layer: contains granule cells, Golgi II cells, glomeruli
  - Excitatory mossy fibers from pontine nuclei enter granular layer, deep cerebellar nuclei; in glomeruli axons of mossy fibers from spinocerebellar, pontocerebellar tracts synapse on dendrites of granules, Golgi type II cells

### Cerebellar cortex output

- Purkinje cell axons → always inhibitory (GABAergic)
- Purkinje cells axons project topographically to **deep cerebellar nuclei**, lateral vestibular nuclei
- Regulates movement synergy



**Figure 54.15** Deep cerebellar and vestibular nuclei, to which Purkinje cells project. The lateral vestibular nuclei are in the medulla.

### Excitatory input to cerebellar cortex

- Arises from two systems: climbing fibers, mossy fiber system (both project to deep cerebellar nuclei)
- Climbing fibers: originate in inferior olive of medulla, project directly to Purkinje cells in 1:1 ratio
  - Single action potential → multiple excitatory bursts of descending amplitude (complex spikes) in Purkinje dendrites
  - Modulate Purkinje cell response to mossy fiber input
  - May be involved in cerebellar learning
- Mossy fiber system: majority of cerebellar input
  - Vestibulocerebellar, spinocerebellar pontocerebellar afferents
  - Project to granule cells (excitatory interneurons) → found in synapse collections which form glomeruli → axons from granule cells ascend to molecular layer → bifurcate → form parallel fibers
  - Parallel fibers synapse with many Purkinje cell dendrites → excitation beams across Purkinje cell row
  - Each Purkinje cell's dendritic tree may receive input from up to 250, 000 parallel fibers (contrast with climbing fiber input to Purkinje dendrites → 1:1)
  - Mossy fiber input produces single action potential (AKA simple spikes)
  - Parallel fibers also synapse on cerebellar

interneurons (basket, stellate, Golgi II)

- Excitatory projection from cerebellar cortex → activates secondary circuits → modulate output of cerebellar nuclei via Purkinje cells

### Cerebellar interneurons

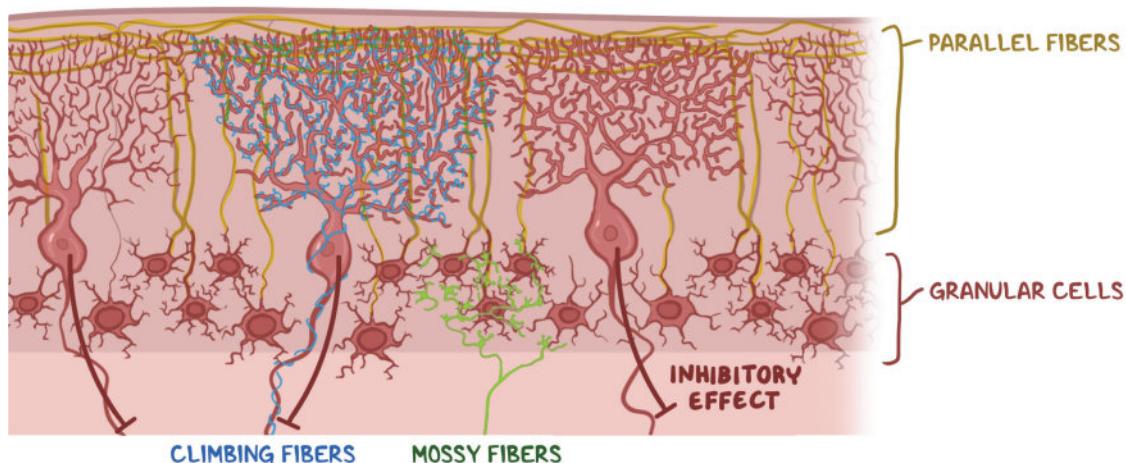
- Modulate Purkinje cell output
- All cerebellar interneurons are inhibitory (except granule cells)
  - Granule cells offer excitatory input for basket cells, stellate cells, Golgi II cells, Purkinje cells
  - Basket, stellate cells inhibit Purkinje cells (parallel fibers)
  - Golgi II cells inhibit granule cells → reduce excitatory effect on Purkinje cells

## LESION DISORDERS

- Lesions → lack of voluntary coordination of muscle movements, limbs, posture, gait (ataxia)

### General signs and symptoms

- Lack of coordination → errors in fine movement control
- Delayed onset of movement/poor execution of sequences
- Overshoot target, stop before reaching
- Dysdiadochokinesia: unable to perform rapid alternating movements
- Intention tremor: tremor perpendicular to direction of voluntary movement, increases near end of movement



**Figure 54.16** Projection destinations for climbing and mossy fibers.

- Rebound phenomenon: inability to stop movement

#### Specific signs and symptoms

- According to affected portion of cerebellum
  - Posterior (flocculonodular lobe): **nystagmus**, poor postural control, gait dysfunction

- Midline (vermis): **truncal**, gait ataxia
- Lateral (hemispheric): **limb ataxia**, dysmetria, dysdiadochokinesia, intention tremor, dysarthria, hypotonia

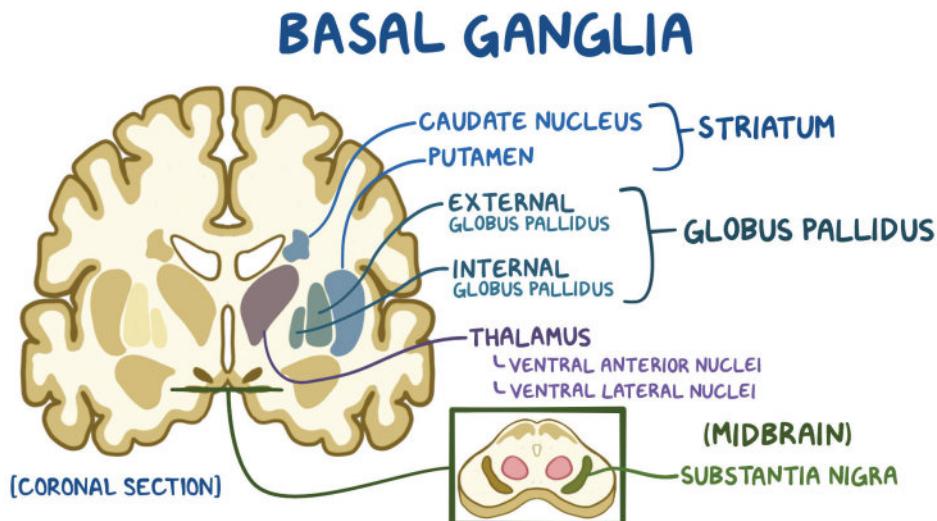
## BASAL GANGLIA: DIRECT & INDIRECT PATHWAY OF MOVEMENT

[osms.it/basal-ganglia-direct-indirect-pathways](https://osms.it/basal-ganglia-direct-indirect-pathways)

#### BASAL GANGLIA

- Collection of subcortical nuclei
- Consists of **globus pallidus**, **striatum** (**caudate** nucleus, **putamen**, amygdala)
- Associated nuclei: ventral anterior, ventral lateral nuclei of thalamus; subthalamic nucleus of diencephalon; substantia nigra of midbrain

- Function: influence motor cortex via pathways through thalamus
  - Aid in planning, **execution of smooth movements**; contribute to affective, cognitive function



**Figure 54.17** Location of basal ganglia and associated structures in coronal slice of the brain.

## COMPLEX AFFERENT & EFFERENT PATHWAYS

- Excitatory pathways use glutamate as neurotransmitter
- Inhibitory pathways use **GABA** ( $\gamma$ -aminobutyric acid) as neurotransmitter
- Almost all cerebral cortex areas project topographically onto striatum, input from motor cortex  $\rightarrow$  striatum  $\rightarrow$  thalamus  $\rightarrow$  back to the cortex via indirect/direct pathways
- Outputs of indirect, direct pathways from basal ganglia to motor cortex are opposed, balanced
  - Disturbance of output  $\rightarrow$  upsets balance of motor control  $\rightarrow$  activity increases/ decreases
- Back-and-forth connection between striatum, pars compacta of substantia nigra are dopaminergic
  - **Dopaminergic pathway is inhibitory via D2 receptors on indirect pathway;** excitatory effect via D1 receptors on direct pathway

### Direct pathway (excitatory)

- Striatum  $\rightarrow$  **inhibits**  $\rightarrow$  internal segment of globus pallidus, pars reticulata of **substantia nigra** (structures that would inhibit otherwise excitatory structures)
- Substantia nigra  $\rightarrow$  inhibitory input to thalamus
- Thalamus  $\rightarrow$  excitatory input to motor cortex
- Overall input is excitatory

### Indirect pathway (inhibitory)

- Striatum  $\rightarrow$  inhibits  $\rightarrow$  external segment of globus pallidus  $\rightarrow$  **inhibits**  $\rightarrow$  **subthalamic nucleus**
- Subthalamic nucleus projects excitatory input to internal segment of **globus pallidus**  $\rightarrow$  internal segment of globus pallidus, pars reticulata of substantia nigra  $\rightarrow$  inhibits  $\rightarrow$  thalamus
- Thalamus  $\rightarrow$  excitatory input to motor cortex
- Overall input of **indirect pathway is inhibitory**

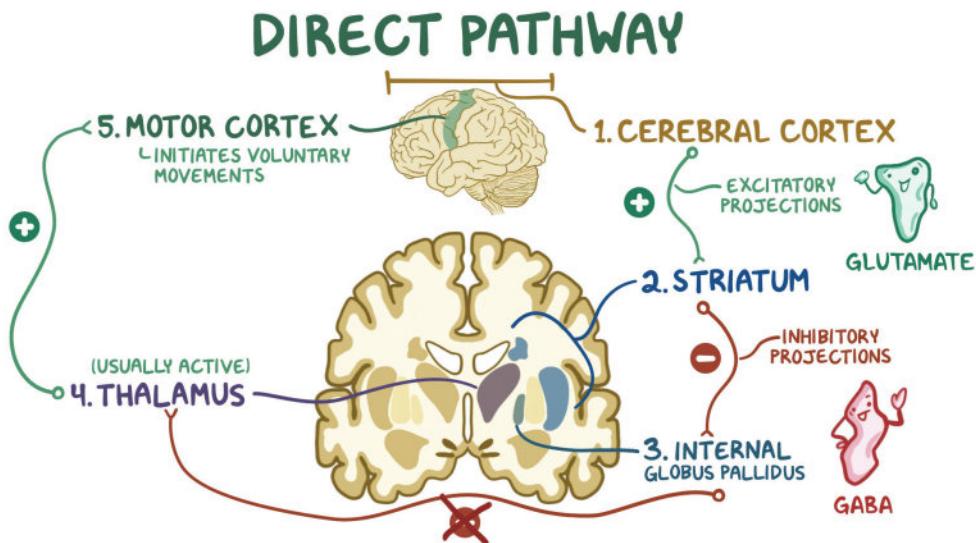
## BASAL GANGLIA DISEASES

### Parkinson's disease

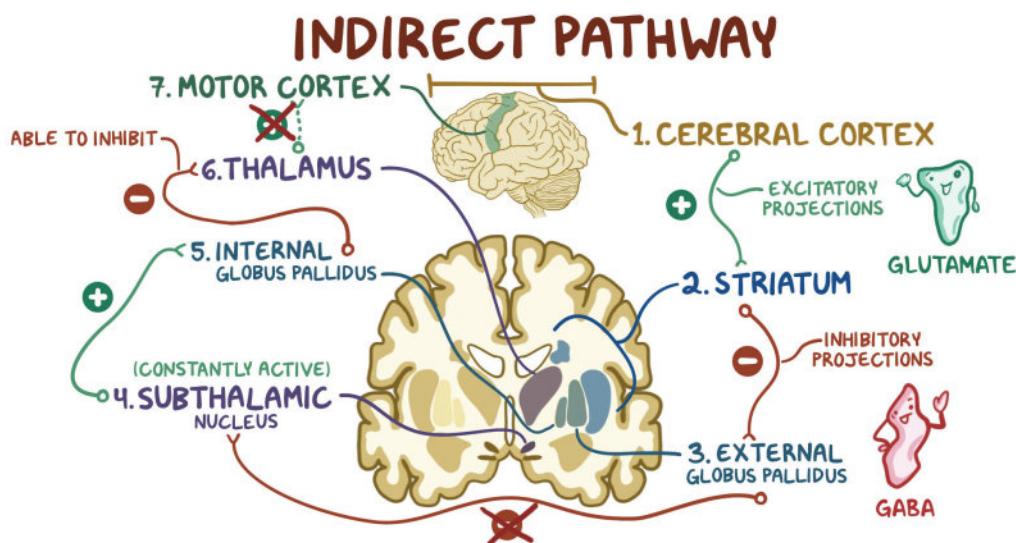
- Cellular damage  $\rightarrow$  cells of pars compacta of **substantia nigra degenerate**  $\rightarrow$  reduce inhibition via indirect pathway, reduce excitation via direct pathway
- Initial accumulation in olfactory bulb, medulla oblongata, pontine tegmentum; early non-motor symptoms (loss of smell, sleep disturbances, autonomic dysfunction)
- Progression: affects midbrain, basal forebrain, neocortex, typical Parkinson's symptoms (resting **tremor**; movement slowness, delay; **shuffling gait**)
- Treatment: aim to  $\uparrow$  dopamine level in brain/mimic its action with dopaminergic drugs
  - L-DOPA (dopamine precursor)  $\rightarrow$  remaining dopamine neurons produce, secrete more dopamine
  - Dopamine agonists (e.g. bromocriptine)  $\rightarrow$  bind to postsynaptic dopaminergic receptors
  - MAO-B inhibitors  $\rightarrow$  impede dopamine breakdown

### Huntington's disease

- Hereditary disorder caused by **destruction of** striatal, cortical cholinergic neurons, inhibitory **GABAergic neurons**
- Presents with **chorea** (writhing movements), **dementia**
- No known cure



**Figure 54.18** Direct pathway. Cerebral cortex sends excitatory projections to striatum → sends inhibitory projections to internal globus pallidus → sends inhibitory projections to thalamus. When striatum inhibits internal globus pallidus, internal globus pallidus can't inhibit thalamus → thalamus is free to send excitatory signals to motor cortex.



**Figure 54.19** Indirect pathway. Cerebral cortex sends excitatory projections to striatum → sends inhibitory projections to external globus pallidus → sends inhibitory projections to subthalamic nucleus. When striatum inhibits external globus pallidus, external globus pallidus can't inhibit subthalamic nucleus → subthalamic nucleus is free to send excitatory signals to internal globus pallidus. Internal globus pallidus inhibits thalamus, preventing it from sending excitatory signals to the motor cortex.

# SPINAL CORD REFLEXES

[osms.it/spinal-cord-reflexes](https://osms.it/spinal-cord-reflexes)

## Intrinsic reflex

- Involuntary, unlearned, rapid, predictable response to stimulus
  - Prevents need for conscious thought about all actions (e.g. staying upright, withdrawing from pain, controlling visceral reactions)
  - Subject to modification if necessary

## Acquired reflex

- Acquired after sufficient repetition (e.g. complex sequence of reactions that occur while driving a car)
  - Process is automatic, but had to be learned initially

## REFLEX ARC COMPONENTS

- Receptor: detects stimulus
- Sensory neuron: transmits afferent impulse to central nervous system (CNS)
- Integration center: processes information, dictates response
  - Simple reflex arcs: single synapse between sensory neuron, motor neurons (monosynaptic reflex)
  - Complex reflex arcs: multiple synapses with chains of interneurons (polysynaptic reflex)

- Motor neuron: conducts efferent impulse from integration center to effector
- Effector: muscle fiber/gland that responds to efferent impulse (contracts/secretes)

## CLASSIFICATION

### Somatic

- Activates skeletal muscle
- Voluntary; occasionally non-voluntary (reflexes)

### Autonomic (visceral)

- Activates visceral organ effectors
  - Smooth muscle: involuntary; forms walls of hollow organs, glands, blood vessels, tracts of respiratory, urinary, reproductive systems
  - Cardiac muscle: involuntary; forms heart walls



# NOTES

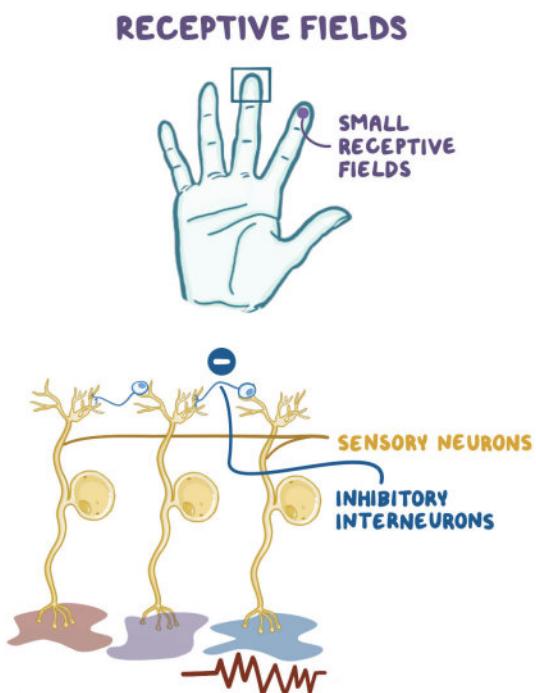
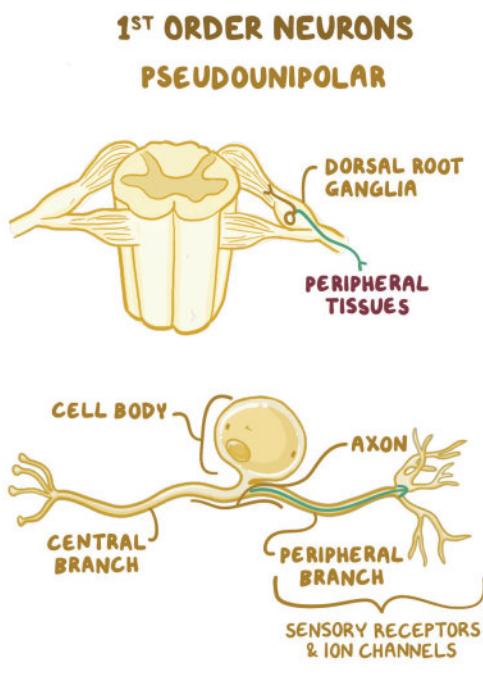
## SENSORY NERVOUS SYSTEM

### SENSORY RECEPTOR FUNCTION

[osms.it/sensory-receptor-function](https://osms.it/sensory-receptor-function)

- 1<sup>st</sup> order neurons carry information from somatosensory receptors
  - Pseudounipolar: no separate dendrites, axons
  - Single axon splits into central branch, peripheral branch
  - Peripheral branch goes from cell body in dorsal root ganglia to receptive field on peripheral tissue
  - Small receptive field = ↑ resolution
  - Large receptive field = ↓ resolution
  - Ion channels open, close in response to stimulus → membrane depolarizes →

- voltage gated channels open → triggers action potential
- To prevent multiple neurons firing, neurons have inhibitory interneurons, AKA lateral inhibition
- Stimulus strength, duration determined by frequency of nerve firing
- Adaption: fewer signals sent in response to same stimulus over time
  - Fast adapting/phasic: high sensitivity; falls off quickly
  - Slow adapting/tonic: constant sensitivity



**Figure 55.1** Features of 1<sup>st</sup> order neurons and lateral inhibition. Interneurons suppress activity of the neurons next to one that has received a stimulus (lateral inhibition) → pin points stimulus by defining its boundaries.

# SOMATOSENSORY PATHWAYS

[osms.it/somatosensory-pathways](http://osms.it/somatosensory-pathways)

- Somatic senses: touch, proprioception, pain, temperature
- Types of somatosensory fibers
  - Non-myelinated fibers (type C): slowest; sense burning pain, hot temperature
  - Small myelinated fibers (type A $\delta$ ): faster; sense sharp pain, gross touch, cold temperature
  - Large myelinated fibers (type A- $\alpha$ ; A- $\beta$ ): fastest; sense proprioception, vibration, fine touch

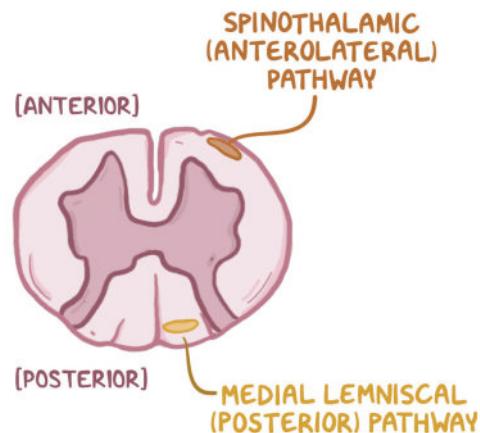
## SOMATOSENSORY PATHWAYS

- Carry somatosensory input up spinal cord to brain
- Consist of 4-neuron relay
  - 1<sup>st</sup> order neuron/afferent sensory neuron: has sensory receptors, converts stimuli into impulse
  - 2<sup>nd</sup> order neuron: cell body in spinal cord or brainstem, synapses with 3<sup>rd</sup>-order neuron
  - 3<sup>rd</sup> order neuron: cell body in thalamus, sends signal to somatosensory cortex
  - 4<sup>th</sup> order neuron/cortical neuron: cell body in sensory cortex
- Includes medial lemniscal/posterior pathway, spinothalamic/anterolateral pathway

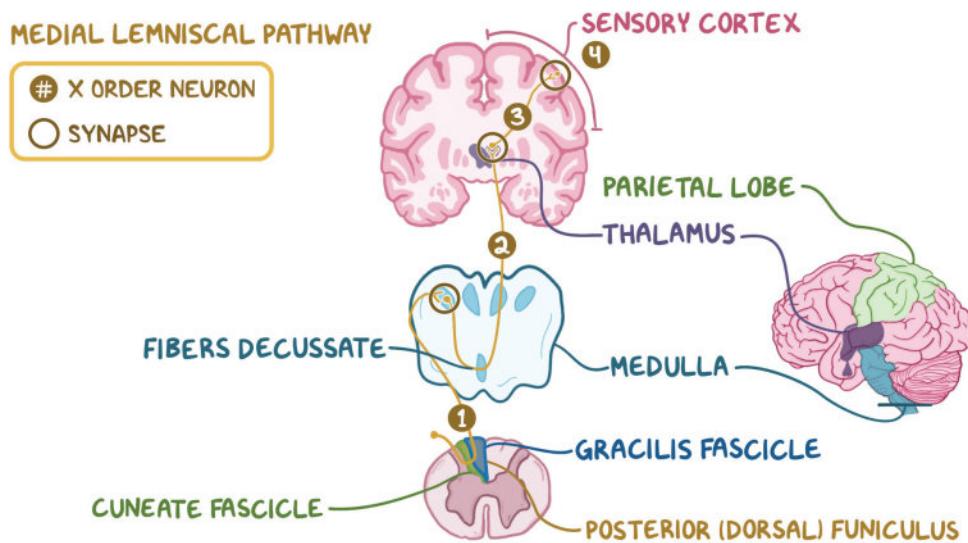
## MEDIAL LEMNISCAL PATHWAY

- Carries information about fine touch, proprioception
- Large myelinated fibers of 1<sup>st</sup> order neurons run to spinal cord
- Neurons run through posterior/dorsal

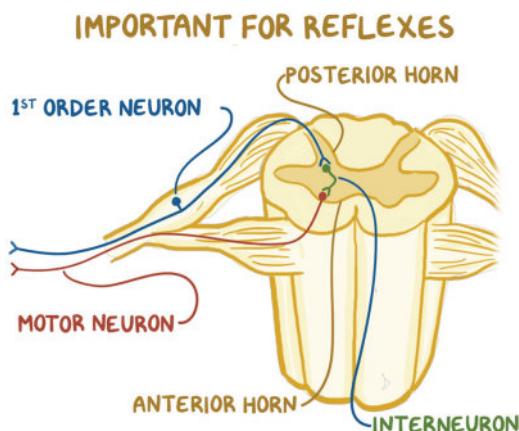
- funiculus of spinal cord
- Via cuneate fascicle for arms, chest
- Via gracilis fascicle for trunk, legs
- 1<sup>st</sup>, 2<sup>nd</sup> order neurons synapse in medulla
  - 1<sup>st</sup> synapse
- 2<sup>nd</sup> order neurons run to medial lemniscus, decussate; run through pons, midbrain to the thalamus
- 2<sup>nd</sup>, 3<sup>rd</sup> order neurons synapse in thalamus
  - 2<sup>nd</sup> synapse
- 3<sup>rd</sup> order neurons run to sensory cortex in parietal lobe
- 3<sup>rd</sup>, 4<sup>th</sup> order neurons synapse in sensory cortex
  - 3<sup>rd</sup> synapse
- Some 1<sup>st</sup> order neurons synapse with interneurons at posterior horn
  - Axons run to anterior horn, synapse directly with motor neuron
  - Important for reflexes



**Figure 55.2** The two somatosensory pathways.



**Figure 55.3** The medial lemniscal pathway carries information about fine touch and proprioception. It includes three synapses between four neurons.



**Figure 55.4** Reflex pathway occurs at the level of the spinal cord: 1<sup>st</sup> order neuron synapses with an interneuron, which synapses with a motor neuron.

- 1<sup>st</sup>, 2<sup>nd</sup> order neurons synapse in posterior horn of spinal cord/1<sup>st</sup> synapse
  - Small myelinated fibers: enter through dorsal root, bend upwards, travel through two vertebral segments
  - Non-myelinated fibers: follow same pathway but synapse with interneurons first, AKA before reaching posterior horn
- 2<sup>nd</sup> order neurons decussate, cross to anterior horn through central canal
- Neurons then carried through one of two tracts to thalamus
  - Lateral tract: carries information for pain, pressure, temperature through lateral funiculus
  - Anterior tract: carries information for crude touch through anterior funiculus
- 2<sup>nd</sup>, 3<sup>rd</sup> order neurons synapse in thalamus/2<sup>nd</sup> synapse
- 3<sup>rd</sup> order neurons run to sensory cortex in parietal lobe
- 3<sup>rd</sup>, 4<sup>th</sup> order neurons synapse in sensory cortex/3<sup>rd</sup> synapse

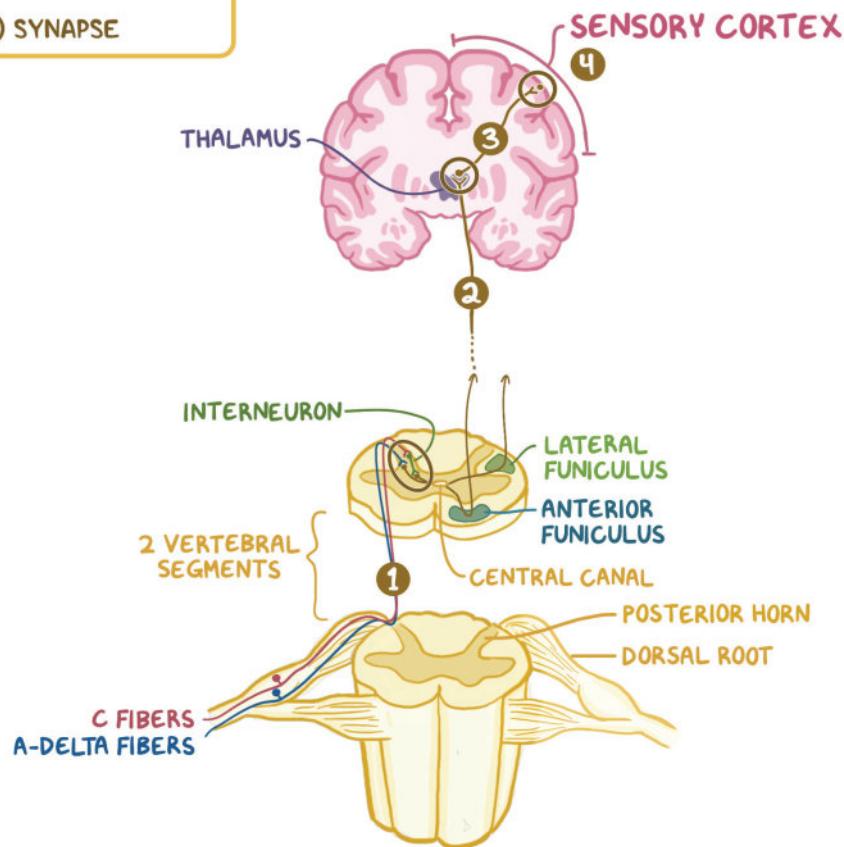
## SPINOTHALAMIC PATHWAY

- Carries information about pain, temperature, crude touch
- Small/non-myelinated fibers of 1<sup>st</sup> order neurons run to spinal cord
  - Small myelinated fibers: sharp pain, cold temperature
  - Non-myelinated fibers: hot temperature, burning pain, crude touch

## SPINOthalamic PATHWAY

# X ORDER NEURON

○ SYNAPSE



**Figure 55.5** The spinothalamic pathway carries information about pain, temperature, and crude touch. It includes three synapses between four neurons. The 1<sup>st</sup> order C fibers synapse with an interneuron, which then synapses with the 2<sup>nd</sup> order neuron.

# SOMATOSENSORY RECEPTORS

[osms.it/somatosensory-receptors](https://osms.it/somatosensory-receptors)

- Perceive general somatic senses
- Include mechanoreceptors, AKA both mechanosensors and proprioceptors, thermoreceptors, nociceptors

### MECHANOSENSORS

- Used for touch; several types

#### Meissner/tactile corpuscles

- Sensitive to light touch
- Encapsulated; located in dermis of hairless skin

- Fast adapting; small receptive fields

#### Merkel (tactile) discs

- Sensitive to pressure
- Non-encapsulated; located in epidermis of hairless skin
- Slow adapting; small receptive fields

#### Ruffini (bulbous) corpuscles

- Sensitive to skin stretching
- Encapsulated; located in dermis of all skin
- Slow adapting; big receptive fields

**Pacinian (lamellar) corpuscles**

- Sensitive to vibration
- Encapsulated; located deep in dermis/subcutaneous tissue of all skin
- Fast adapting; big receptive fields

**PROPRIOCEPTORS**

- Used for proprioception; several types

**Muscle spindle**

- Detect when muscle stretched

- Located throughout perimysium, AKA connective tissue around muscle cells

**Golgi tendon organ**

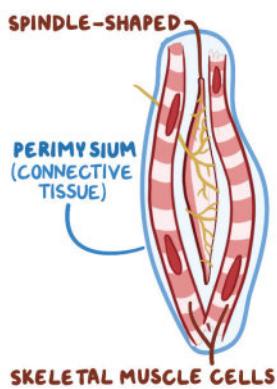
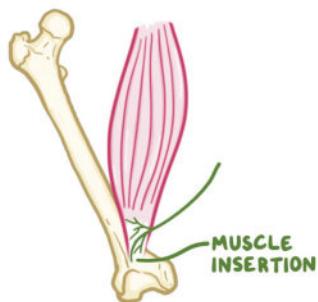
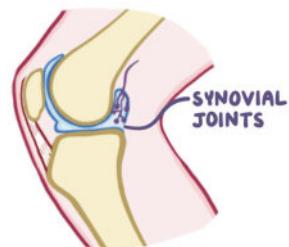
- Detect when tendon stretched
- Located in tendons close to muscle insertion

**Joint receptors**

- Detect joint position, motion
- Located in joint

**MECHANOSENSORS**

**Figure 55.6** The four types of mechanosensors. Only Pacinian and Ruffini corpuscles are present in all kinds of skin (hairless and hairy).

**3 TYPES OF PROPRIOCEPTORS****MUSCLE SPINDLE****GOLGI TENDON ORGAN****JOINT RECEPTORS**

**Figure 55.7** The three types of proprioceptors.

## THERMORECEPTORS

- Used for temperature
- Transient receptor potential channels mediate sensations
  - Transduction of heat involves TRPV channels; activated at 32–48°C/90–118°F
  - Transduction of cold involves TRPM8; activated at 10–40°C/ 50–104°F
- At extremely cold/hot temperatures, nociceptors take over

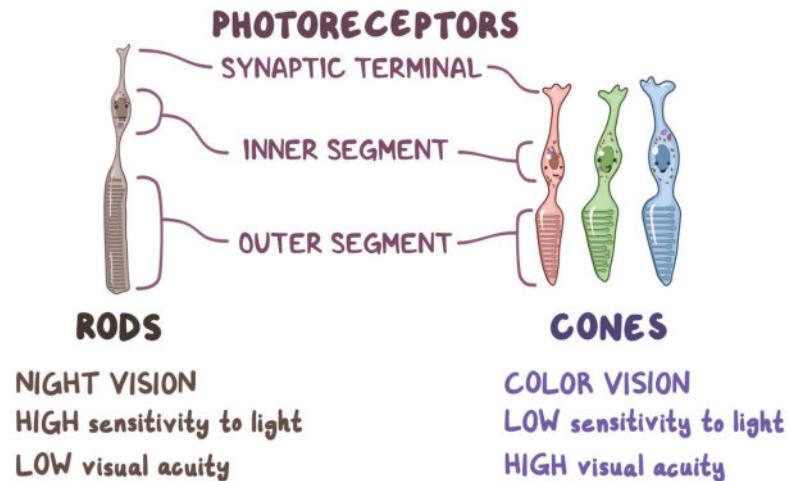
## NOCICEPTORS

- Used for pain; several types
  - Thermals: sense extremely cold/hot temperatures
  - Mechanical: sense excess pressure/deformation
  - Polymodal: Sense combination of both

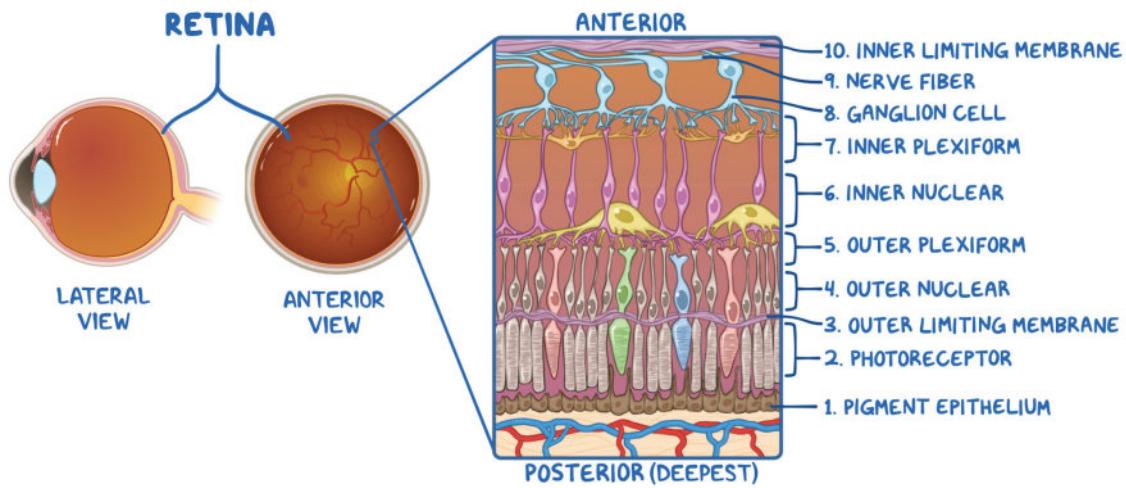
# PHOTORECEPTION

[osms.it/photoreception](https://osms.it/photoreception)

- Process by which rods, cones convert light waves into electrical signals
- Photoreceptors: modified neurons, AKA rods/cones
  - Have outer segment: detects light
  - Inner segment: cell body
  - Synaptic terminal: connects to interneurons
- Photoreceptors located in retina
- 10 retina layers; numbered from deepest outwards
  - Pigment epithelium
  - Photoreceptor
  - Outer limiting membrane
  - Outer nuclear
  - Outer plexiform
  - Inner nuclear
  - Inner plexiform
  - Ganglion cell
  - Nerve fiber
  - Inner limiting membrane



**Figure 55.8** The two types of photoreceptors (rods and cones) and their main features.



**Figure 55.9** Retina = light-sensitive neural layer of tissue at back of eye, composed of 10 layers. Axons of ganglion cells exit eye through optic disc, form optic nerve (CN II).

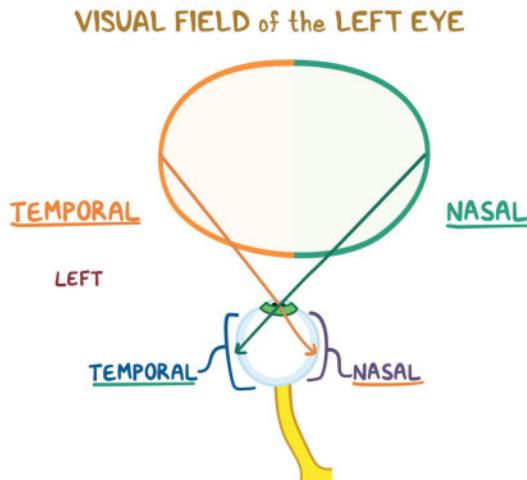
## OPTIC PATHWAYS

[osms.it/optic-pathways-and-visual-fields](http://osms.it/optic-pathways-and-visual-fields)

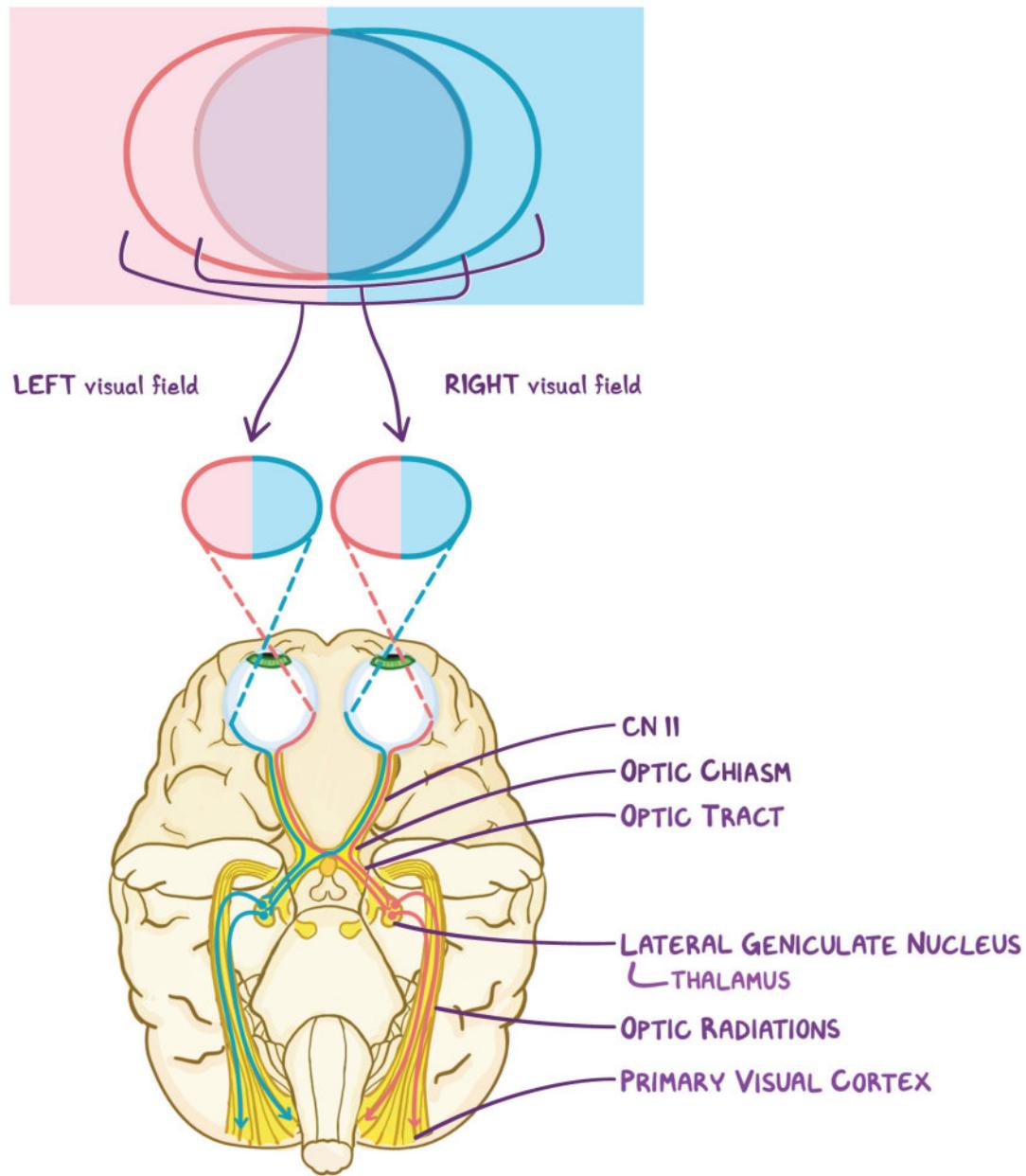
- Visual phototransduction: light waves on retina → electrical signals
- Rods, cones send electrical signal through optic nerve (cranial nerve II)
  - Exits via the optic disc on the retina
- Optic nerves meet at optic chiasm
- Axons from nasal retina cross over to opposite sides → optic tract (synapses with cells in lateral geniculate nucleus in both sides of thalamus) → primary visual cortex/occipital lobe

### VISUAL FIELD

- Everything seen by single eye
- Split into two parts
  - Nasal visual field: projected onto temporal retina, axons stay on that side of brain
  - Temporal visual field: projected onto nasal retina, axons cross to opposite side of brain at optic chiasm
- Information from left visual fields of both eyes goes to right half of brain, vice versa
  - Due to axons from nasal retina crossing over



**Figure 55.10** The nasal portion of the eye's visual field is projected onto the temporal retina, and the temporal portion of the eye's visual field is projected onto the nasal retina. Axons from the nasal retina cross to the opposite side of the brain at the optic chiasm so that all the information from the left and right visual fields stay together.



**Figure 55.11** Visual field projections onto the retinas and the primary optic pathway, which carries information from the retina to the primary visual cortex in the occipital lobe of the brain.

# AUDITORY TRANSDUCTION & PATHWAYS

[osms.it/auditory-transduction-and-pathways](https://osms.it/auditory-transduction-and-pathways)

- Process by which ear converts sound waves into electrical pulses

## OUTER EAR

- Amplifies sound, directs sound waves
  - Pinna → external auditory canal → eardrum vibrates

## MIDDLE EAR

- Transmits airborne sound waves to inner ear
  - Malleus (attached to eardrum) → incus → stapes → oval window → cochlea/inner ear

## COCHLEA

- Coils around the modiolus/bone
- Base is contiguous with middle ear through vestibule
- Has bony outer shell
  - Contains perilymph
- Cochlear duct is inside bony shell

- Contains endolymph
- Above is scala vestibuli, below is scala tympani
- Cochlear duct, scala vestibuli, scala tympani communicate through helicotrema
- Oval window amplifies, transfers sound waves to scala vestibuli → perilymph → helicotrema → cochlear duct → displaces **basilar membrane** towards scala tympani
  - Higher frequencies: **early** membrane
  - Lower frequencies: **late** membrane

## ORGAN OF CORTI

- Stimulated by vibration of basilar membrane
- Made up of mechanosensory/hair cells
- Project out 30–300 stereocilia, AKA sensory organelles
  - Tips of stereocilia embedded in tectorial membrane
- Inner hair cells closer to medialis
  - Innervated by sensory nerve fibers

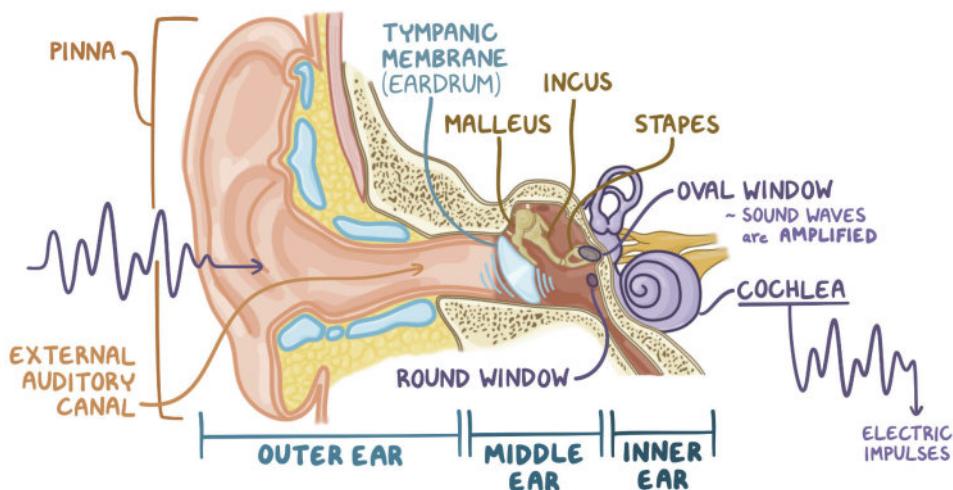
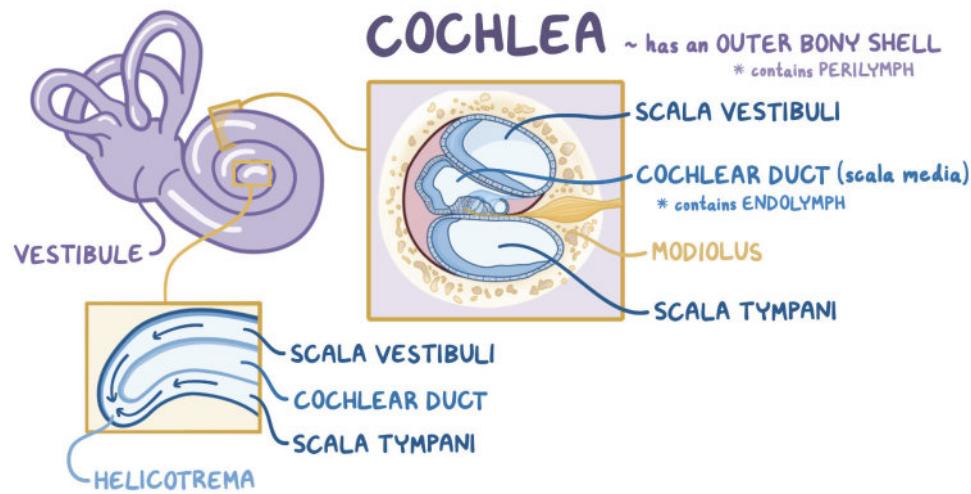
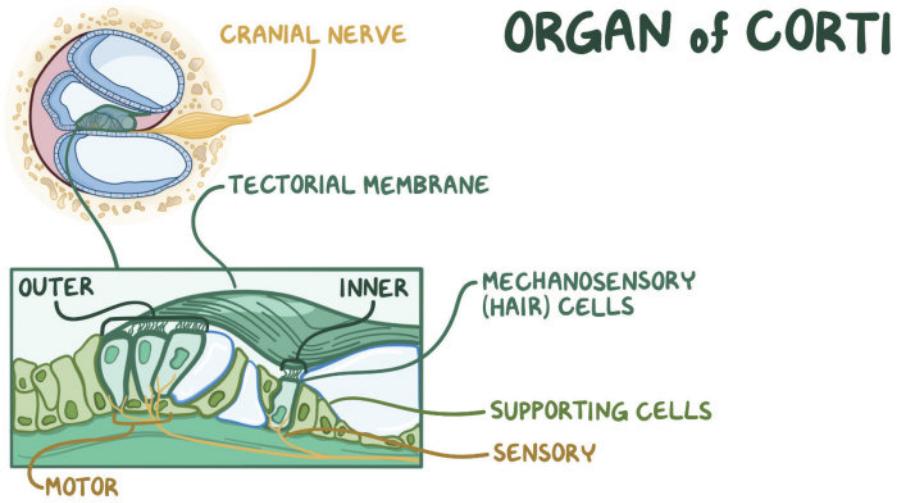


Figure 55.12 Anatomy of the ear.

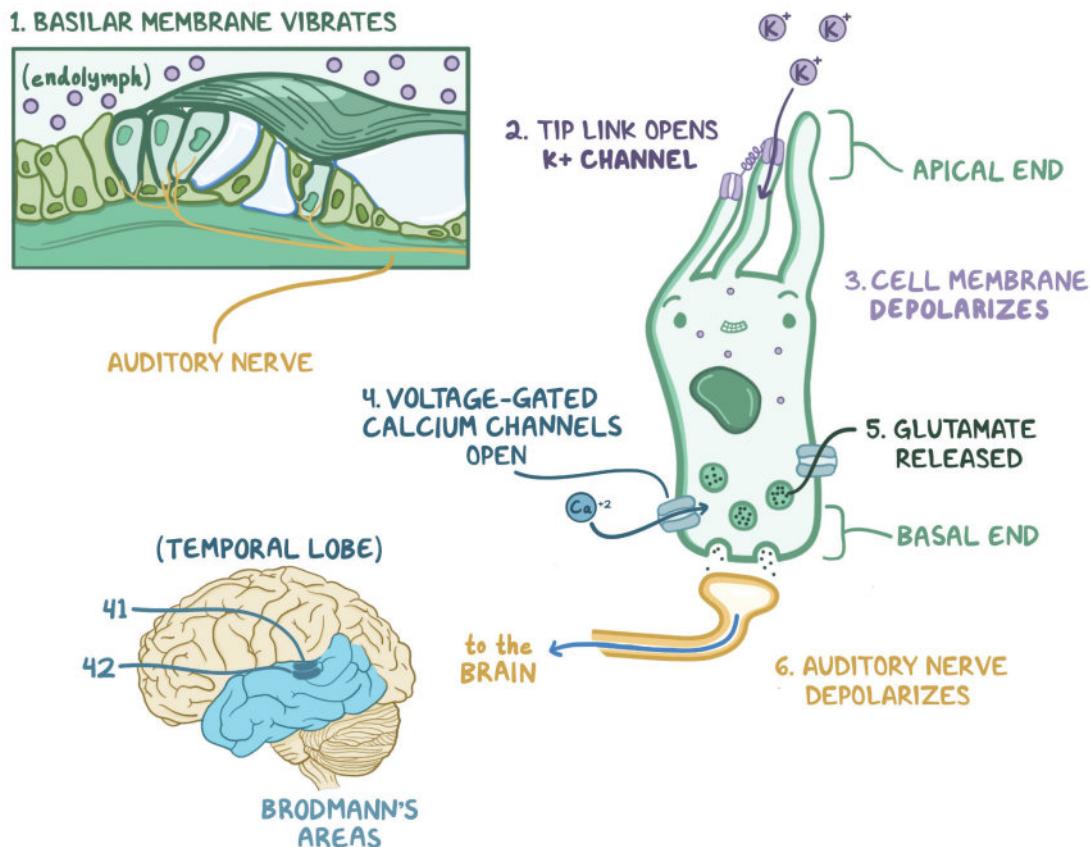
- Outer hair cells closer to spiral ligament
  - Innervated by motor nerve fibers
  - Changes stiffness of membrane to adjust auditory signal
- Vibration of basilar membrane pushes organ of Corti, hair cells against tectorial membrane
- Pressure on basilar membrane allows protein filaments/tip links to reach, open potassium channels
- Potassium flows in → membrane depolarizes → voltage-gated calcium channels open → glutamate vesicles released into synaptic space → sends electrical impulse to auditory cortex, AKA Brodmann's areas 41 and 42, via auditory nerve



**Figure 55.13** Anatomy of the cochlea.



**Figure 55.14** Anatomy of the organ of Corti.



**Figure 55.15** Electrical impulse production via organ of Corti hair cells.

## VESTIBULAR TRANSDUCTION

[osms.it/vestibular-transduction](http://osms.it/vestibular-transduction)

- Process by which the ear determines spatial equilibrium and converts it into electrical signals
  - Signals are sent to brain via vestibular branch of vestibulocochlear nerve
- Vestibular apparatus located in inner ear
  - Includes semicircular canals (dynamic equilibrium), utricle, saccule (static equilibrium)
- Tips of cilia embedded in otolithic membrane
- Bottom of each cell connected to sensory neurons
- Striola divides hair cells into two sections
  - Receptors arranged to face striola
- Movement pushes protein filaments/tip links on cilia on one side of striola to reach, open potassium channels on kinocilium
  - Potassium flows in → membrane depolarizes → voltage-gated calcium channels open → glutamate vesicles are released into the synaptic space → sends electrical impulse to brain

### STATIC EQUILIBRIUM

- Managed by otolith organs (utricle, saccule)
  - Both contain round macula
- Contains balance receptors/hair cells with stereocilia, kinocilium

## UTRICULAR MACULA

- Horizontally oriented: detects horizontal movement
- Receptors arrangement: kinocilia face towards striola

## SACCULAR MACULA

- Vertically oriented: detects vertical movement
- Receptor arrangement: kinocilia face away from striola

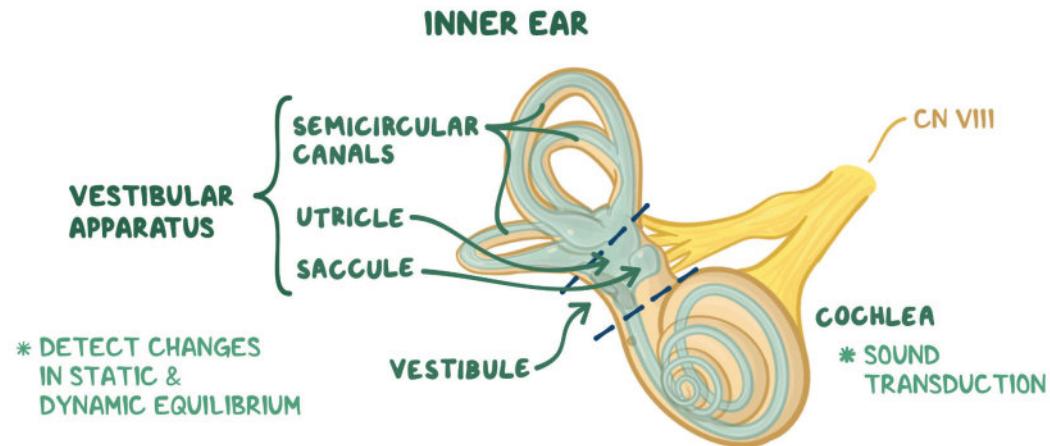


Figure 55.16 Anatomy of the inner ear.

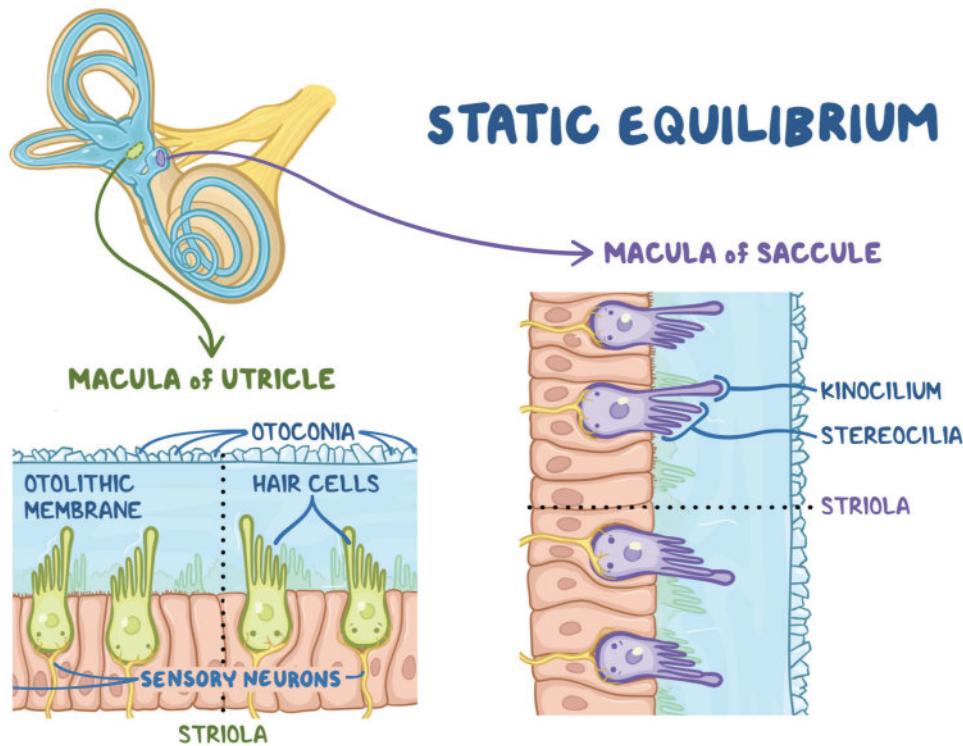


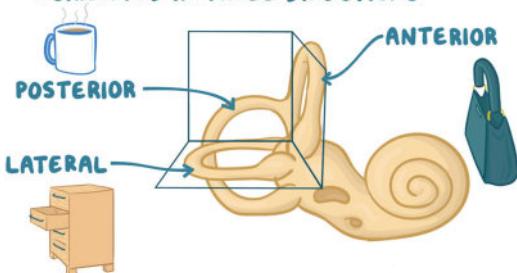
Figure 55.17 Orientation of hair cells relative to the striola in the macula and saccule.

## DYNAMIC EQUILIBRIUM

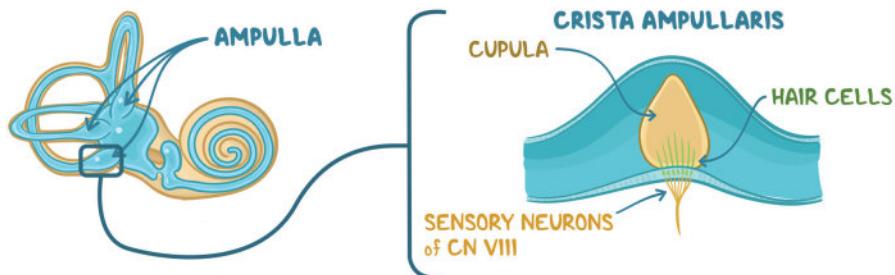
- Managed by semicircular canals
  - U-shaped ducts containing endolymph; oriented at 90° to each other
- Ampulla
  - Houses crista ampullaris
  - Contains balance receptors/hair cells with stereocilia, surrounded by cupula
  - Bottom of each cell connected to sensory neurons
  - Axial rotation in plane of a semicircular canal drags cupula in opposite direction due to inertia → depolarization/hyperpolarization of hair cells → sends electrical impulse to brain
- Brain uses combination of signals from both ears to determine equilibrium

## SEMICIRCULAR CANALS

↳ ORIENTED IN THREE DIRECTIONS



**Figure 55.18** Orientation of the three semicircular canals.



## DYNAMIC EQUILIBRIUM

### A. SUPERIOR VIEW

DIRECTION of ENDOLYMPH MOVEMENT



LEFT SEMICIRCULAR CANAL

DIRECTION of ROTATION



RIGHT SEMICIRCULAR CANAL

### B. ANTERIOR VIEW

DEPOLARIZES HAIR CELL → ↑ FREQUENCY of NERVE IMPULSES



LEFT SEMICIRCULAR CANAL

HYPERPOLARIZES HAIR CELL → ↓ FREQUENCY of NERVE IMPULSES



RIGHT SEMICIRCULAR CANAL

**Figure 55.19** Simultaneous depolarization, hyperpolarization of hair cells in left, right ears allows brain to determine direction of movement.

# VESTIBULO-OCULAR REFLEX & NYSTAGMUS

[osms.it/vestibulo-ocular\\_reflex\\_nystagmus](http://osms.it/vestibulo-ocular_reflex_nystagmus)

- Reflex occurs in response to head movement by the vestibular apparatus; results in eye movement in the opposite direction of the head
  - Stabilizes position of the eye in the line of sight during head movement
- Semicircular canals within the vestibular apparatus respond to rotation and angular acceleration/deceleration of the head
- Contains hair cells (receptors) that create action potential when stimulated

## AFFERENT PATHWAY

- Sensory signals generated by hair cells → action potential travels along nerves → vestibular branch of the vestibulocochlear nerve (CN VIII) → vestibular nuclei in pons

## EFFERENT PATHWAY

- From the right vestibular nucleus, nerves cross over to contralateral (left) abducens nucleus → lateral rectus muscle stimulated via abducens nerve/CN VI → left lateral rectus muscle contracts → left eye moves to left
- Other fibers from left abducens act as interneurons → travel to right oculomotor nucleus → left lateral, right medial rectus muscles move eyes to left
- Eyes move all the way to the left → creates physiological form of nystagmus (involuntary back-and-forth eye movement) where eyes move slowly to the left, then rapidly to the right

# OLFACTORY TRANSDUCTION & PATHWAYS

[osms.it/olfactory-transduction-and-pathways](http://osms.it/olfactory-transduction-and-pathways)

## OLFACTION

- Process by which nose converts smells into electrical signals
- Perceived by sensory neurons in roof of nasal cavity, AKA olfactory region
- Carried by olfactory nerve (CN I)

## OLFACTORY REGION

- Lined by olfactory epithelium
- Consists of olfactory receptor cells
  - AKA chemoreceptors; respond to odorants
- Supported by columnar epithelial cells

- Mucus produced in Bowman's glands in connective tissue below, AKA lamina propria

## OLFACTORY RECEPTOR CELLS

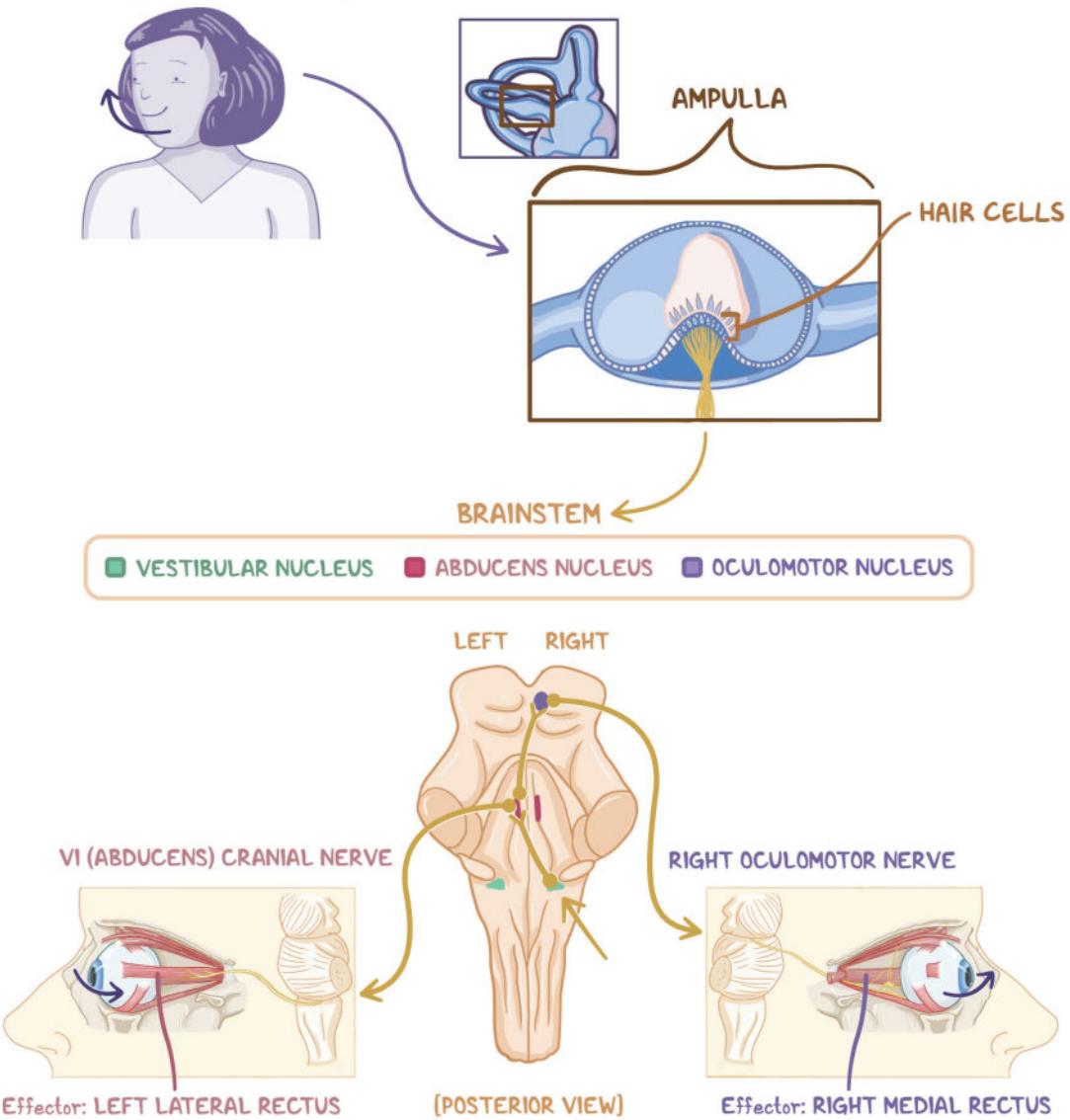
- Bipolar neurons
- Send dendrites to bottom of the epithelium
  - Dendrites project out as cilia
- Olfactory receptor proteins/G-protein coupled receptors embedded in cilia
- Specific odorants bind onto receptors → G-olfactory protein activates → opens calcium, sodium channels via G-protein coupled receptor pathway

- Calcium-activated chloride channels open  
→ chloride ions flow out → cell membrane depolarizes → neuron fires
- Neuron sends axons that join up to form olfactory nerves (collectively called CN1)
- CN1 passes through olfactory foramina to olfactory bulb
  - Second order neurons send signals to olfactory cortex via olfactory tract

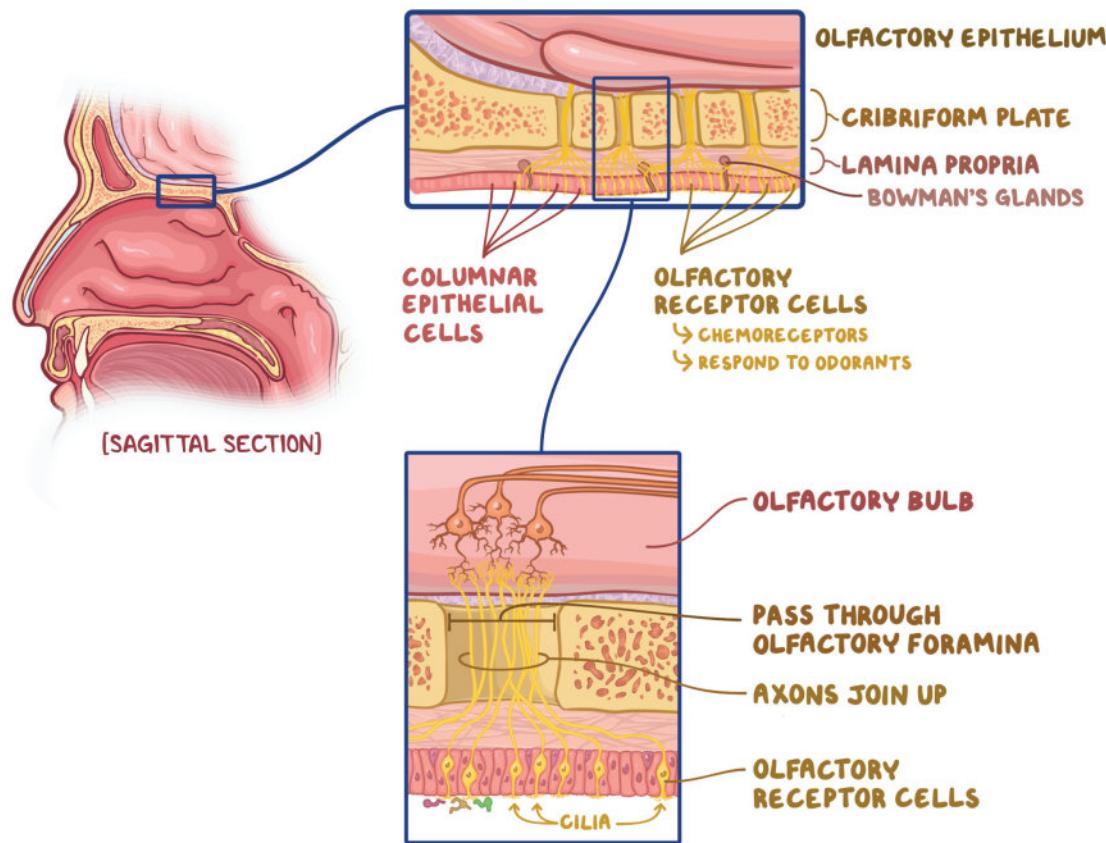
## OLFACTORY TRACT

- Lateral tract runs to ipsilateral piriform complex
  - Some fibers go to limbic system
- Medial tract crosses to contralateral piriform complex
- Adaption: fewer signals sent in response to same odorants over time

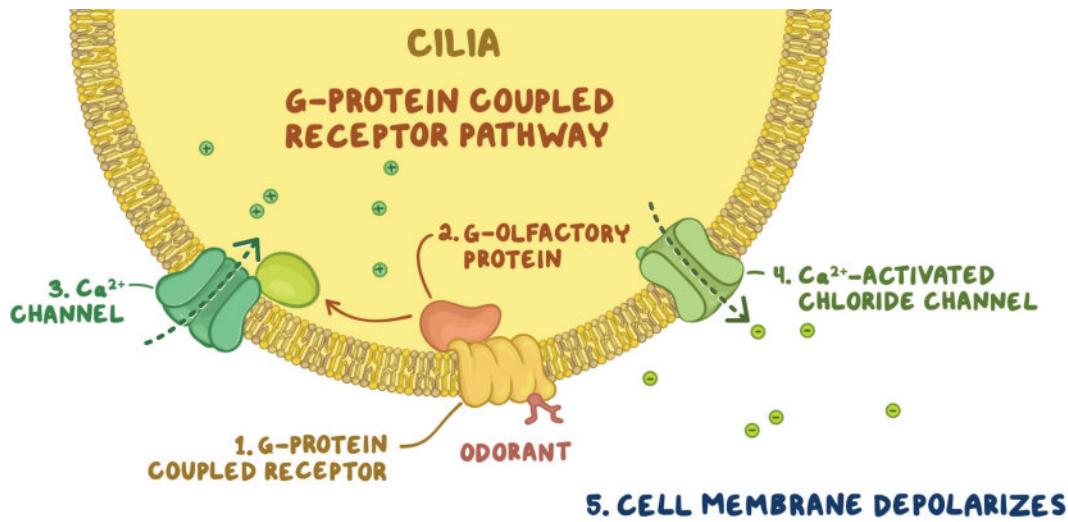
### TURNING HEAD to the RIGHT



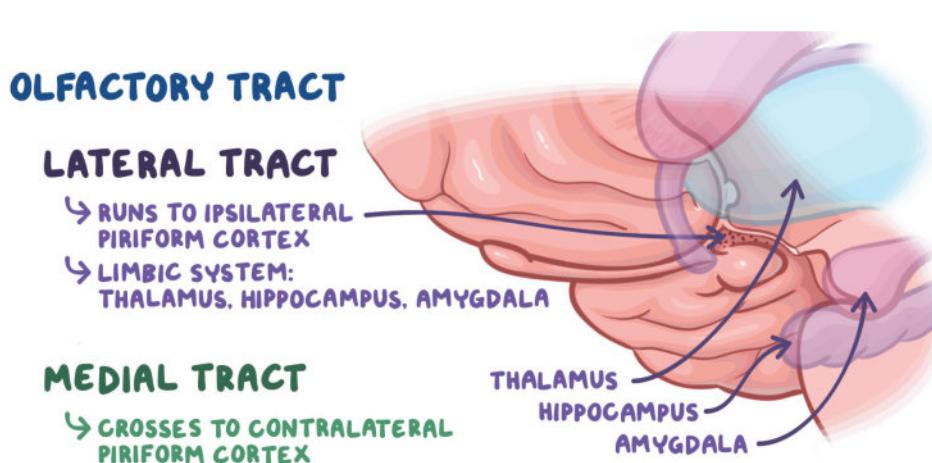
**Figure 55.20** Vestibulo-ocular reflex pathway at work when an individual turns their head to the right.



**Figure 55.21** Anatomy of the olfactory region.



**Figure 55.22** The cilia of bipolar olfactory receptor cells use a G-protein coupled receptor pathway to generate a signal.



**Figure 55.23** Destinations of the olfactory tract.

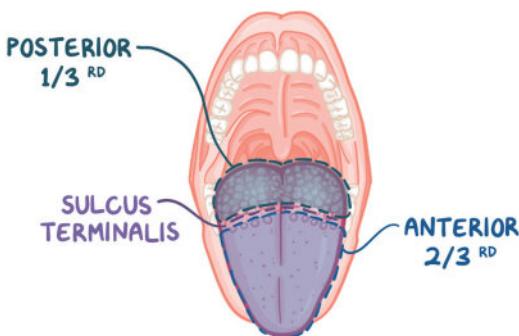
## TASTE & THE TONGUE

[osms.it/taste-and-the-tongue](https://osms.it/taste-and-the-tongue)

- Taste: sensation produced when substances react with taste receptor cells, AKA gustation
  - Five primary tastes of bitter, salty, sour, sweet, umami/savory

### TONGUE

- Surface is covered by mucosa
- Contains both intrinsic, extrinsic muscles
  - Intrinsic muscles: start, end within tongue; help change shape
  - Extrinsic muscles: attach to structures outside tongue; help guide movement
- Divided by a V-shaped group, AKA sulcus terminalis, into posterior third, an anterior two-thirds
- Covered with papillae
  - Small bumps/projections



**Figure 55.24** Sulcus terminalis divides tongue into posterior third and anterior two thirds.

- Contain taste buds
  - More sensitive to sweet, umami

### Foliate papillae

- On sides of tongue
- Contain taste buds
  - More sensitive to salty, sour

### Circumvallate papillae

- On back of anterior two-thirds
- Contain taste buds
  - More sensitive to bitter

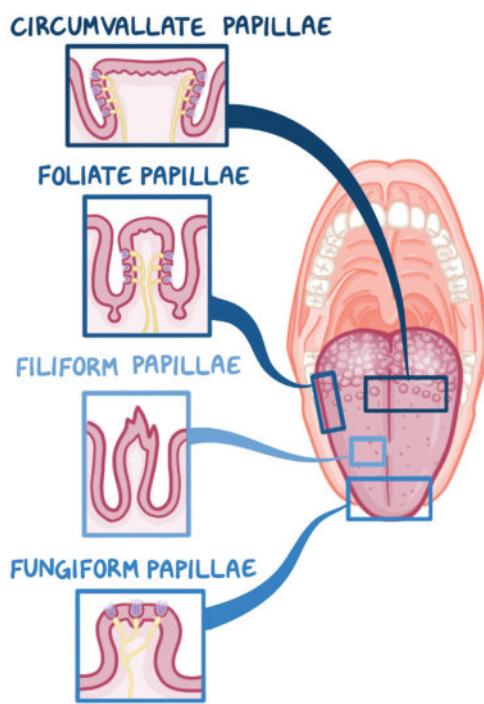
### TYPES OF PAPILLAE

#### Filiform papillae

- On anterior two-thirds
- Used for sensation of touch

#### Fungiform papillae

- On tip of tongue



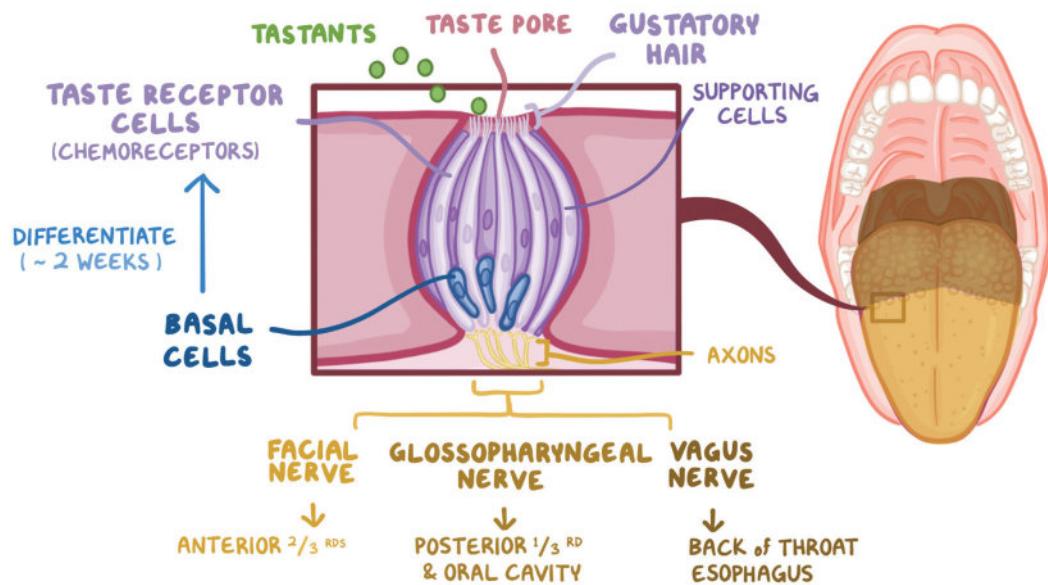
**Figure 55.25** The four types of papillae and their locations on the tongue.

## TASTE BUDS

- Small structures housing taste receptor cells, basal cells that differentiate into taste receptor cells
- Found on tongue as well as soft palate, pharynx, epiglottis, larynx, upper esophagus

## TASTE RECEPTOR CELLS

- Used to perceive taste, AKA respond to tastants
- Arranged like orange wedges with supporting cells between
- Have thin, hair-like microvilli/gustatory hair protruding out of taste pore
- Send signals to brain via axons
  - Anterior two-thirds innervated by facial nerve
  - Posterior third, oral cavity innervated by glossopharyngeal nerve
  - Back of throat, esophagus innervated by vagus nerve



**Figure 55.26** Anatomy of a taste bud.

## PERCEPTION OF TASTE

- Chewed up particles → mix with saliva → travel to papillae → make contact with gustatory hairs
- For salty/sour tastes
  - $\text{Na}^+$ ,  $\text{H}^+$  ions make contact with gustatory hair
  - Ion channels allow these ions into cell
  - Membrane depolarizes
  - Voltage gated channels open
  - Extracellular calcium flows inside
  - Neurotransmitters fuse with cell membrane
  - Nerves tell brain
- For sweet, bitter, umami tastes
  - Tastants bind to G-protein coupled receptors
  - Triggers G-protein coupled pathway
  - Calcium channels on endoplasmic reticulum open
  - Intracellular calcium ions flow into cell
  - Neurotransmitters fuse with cell membrane
  - Nerves tell brain

- Complex tastes: combination of taste receptors
- Adaption: fewer signals sent in response to same tastants over time
- Factors affecting taste
  - Hunger: ↑ sensitivity to sweet, salty tastes
  - Infections, allergies: ↓ sensitivity
  - Age: ↓ sensitivity; because receptor cells not replaced as quickly

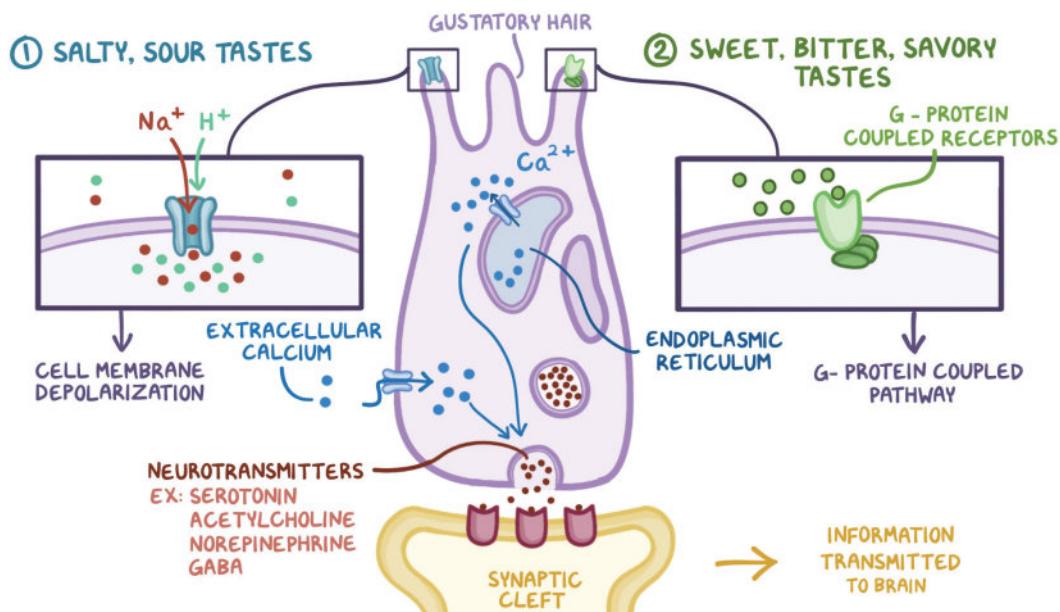


Figure 55.27 The two taste perception methods.



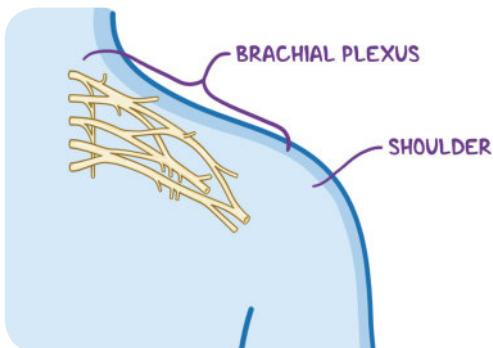
# NOTES

## SPINAL CORD & NERVES

# BRACHIAL PLEXUS

[osms.it/brachial-plexus](https://osms.it/brachial-plexus)

- Network of nerves innervating shoulder, arm, hand (supply afferent/sensory, efferent/motor nerve fibers); one on each side of body
- Begins as five roots → combine to three trunks → split into six divisions (three anterior, three posterior) → combine into three cords → end in five terminal branches; also preterminal (collateral) branches



**Figure 56.1** Brachial plexus location in body.

### ROOTS

- First four: from last four cervical nerves (C5, C6, C7, C8)
- Last one: from first thoracic nerve (T1)
- Long thoracic nerve (LT) branches off from C5, C6, C7
  - Innervates serratus anterior
- Dorsal scapular (DS) nerve branches off from C5
  - Innervates rhomboid muscles
- Phrenic nerve contributed to by C5
  - Innervates diaphragm

### TRUNKS

- C5, C6 form superior trunk
- C7 remains as middle trunk
- C8, T1 form inferior trunk
- Suprascapular nerve branches off from superior trunk
  - Innervates supraspinatus, infraspinatus, acromioclavicular, glenohumeral joints

### DIVISIONS

- Each trunk splits into anterior, posterior division

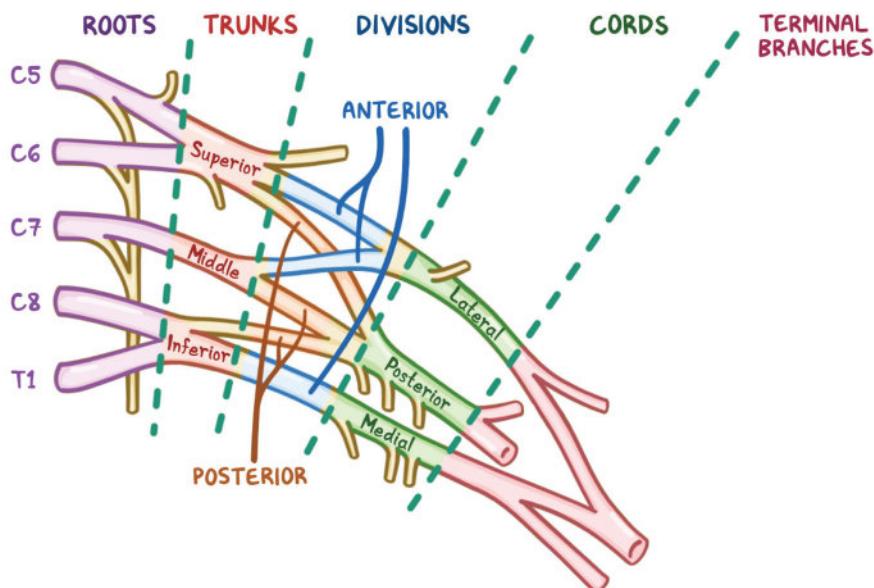
### CORDS

- Lateral cord
  - Superior, middle trunk anterior divisions
- Posterior cord
  - All three trunk posterior divisions
- Medial cord
  - Inferior trunk anterior division
- Lateral pectoral nerve branches off from lateral cord
- Upper, middle, lower subscapular nerves branch off from posterior cord
- Medial cutaneous nerves of arm, forearm, medial pectoral nerve branch off from medial cord

### TERMINAL BRANCHES

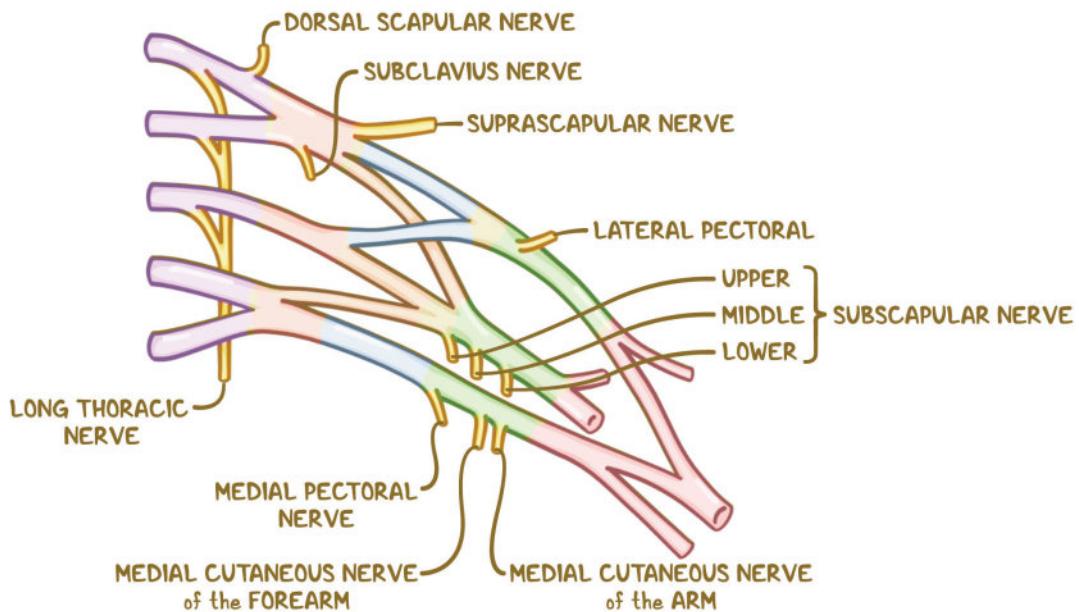
- Musculocutaneous nerve comes from lateral cord
  - Innervates biceps brachii, brachialis, coracobrachialis
- Median nerve formed from lateral, medial cords
  - Innervates flexors of forearm, hand

- Axillary, radial nerves split out from posterior cord
  - Axillary nerve innervates deltoid, teres minor
  - Radial nerve innervates triceps brachii, brachioradialis, forearm extensors
- Ulnar nerve off from medial cord
  - Innervates wrist, fingers



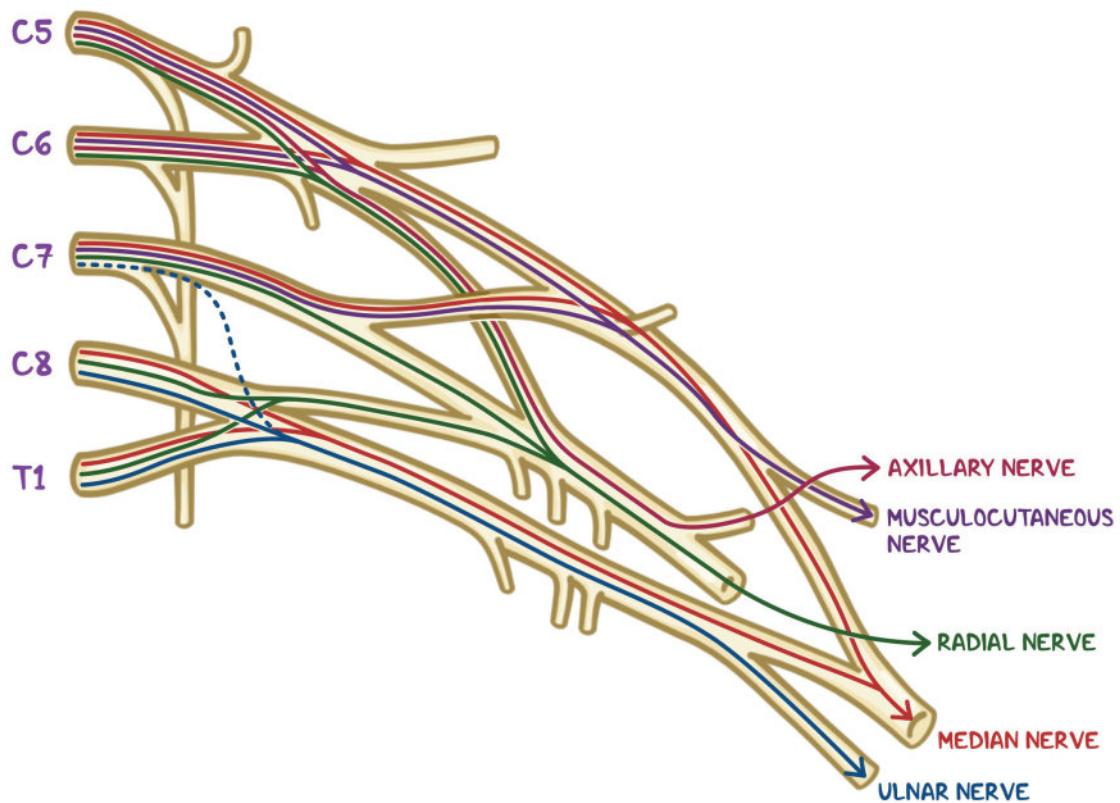
**Figure 56.2** Divisions of the brachial plexus.

### PRETERMINAL (COLLATERAL) BRANCHES



**Figure 56.3** Names and locations of brachial plexus' collateral branches.

### ORIGINS OF TERMINAL BRANCHES



**Figure 56.4** Contributions of the spinal nerves to the brachial plexus' terminal branches.



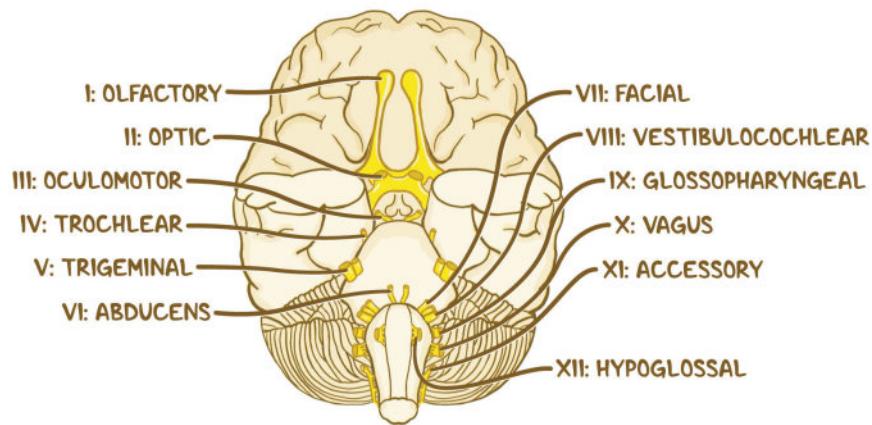
**Figure 56.5** A simplified diagram of the brachial plexus with mnemonics for names and order of divisions (Remember To Drink Cold Beer) and the terminal branches (MARMU).

# CRANIAL NERVES

[osms.it/cranial-nerves](https://osms.it/cranial-nerves)

- 12 nerve pairs originating in brain, brainstem
  - Supply body (primarily head, neck) with motor, sensory information
- Includes olfactory, optic, oculomotor, trochlear, trigeminal, abducens, facial, vestibulocochlear, glossopharyngeal, vagus, accessory, hypoglossal nerves

## 12 PAIRS of CRANIAL NERVES



**Figure 56.6** The cranial nerves originate from the brain (including brainstem).



### MNEMONIC:

Cranial Nerve Names  
**O**n  
**O**ld  
**O**lympus  
**T**owering  
**T**op,  
**A**  
**F**ine  
**V**ictorian  
**G**entleman  
**V**iewed  
**A**  
**H**awk



### MNEMONIC:

Cranial Nerve Functions  
(S = sensory, M = motor)  
**S**ome  
**S**ay  
**M**arry  
**M**oney  
**B**ut  
**M**y  
**B**rother  
**S**ays  
**B**ig  
**B**rains  
**M**atter  
**M**ore

## I - OLFACTORY NERVE (SENSORY)

- Function: smell
- Arises from primary olfactory cortex (temporal lobe)
- Neurons form olfactory tracts → run to olfactory bulb (above cribriform plate of ethmoid bone)
- Receives information from sensory nerve fibers (axons from nasal cavity's olfactory neurons) which synapse with olfactory bulb's neurons

midbrain, follows oculomotor nerve through superior orbital fissure

- Innervates superior oblique muscles (abducts, depresses, internally rotates eyeball)

## V - TRIGEMINAL NERVE (SENSORY/MOTOR)

- Function: facial movement, chewing, temperature, touch, pain
- Emerges from pons; travels to trigeminal ganglion
- Splits into ophthalmic, maxillary, mandibular nerves
  - Ophthalmic nerve exits through superior orbital fissure, gives sensory innervation to upper eyelid, nose, forehead, scalp
  - Maxillary nerve exits through foramen rotundum, gives sensory innervation to maxilla, nasal cavity, palate, cheeks' skin
  - Mandibular nerve exits through foramen ovale, gives sensory innervation to tongue (not taste buds), lower lip, lower teeth, chin, temporal scalp. Gives motor innervation to chewing muscles

## VI - ABDUCENS NERVE (MOTOR)

- Function: eyeball movement
- Emerges from pons; runs through superior orbital fissure
- Innervates lateral rectus muscle (abducts eye)

## VII - FACIAL NERVE (SENSORY/MOTOR)

- Function: taste, saliva, tears, facial movement (i.e. facial expressions)
- Emerges from pons; enters temporal bone through internal acoustic meatus
- Runs within bone to geniculate ganglion
- Splits into greater petrosal nerve, stapedius nerve, chorda tympani
  - Greater petrosal nerve provides autonomic fibers to lacrimal, nasal, palatine, pharyngeal glands
  - Stapedius nerve sends motor fibers to middle ear's stapedius
  - Chorda tympani gives sensory innervation to taste buds of tongue's anterior two thirds

## III - OCULOMOTOR NERVE (MOTOR)

- Function: eye movement
- Arises from ventral midbrain; runs through superior orbital fissure to eye
- Splits into superior, inferior branch
  - Superior branch innervates levator palpebrae superioris (raises upper eyelid), superior rectus (elevates eye)
  - Inferior branch innervates inferior oblique (abducts eyeball), inferior rectus (depresses, adducts eyeball), medial rectus (adducts eyeball) with proprioception; controls pupil constriction (sphincter pupillae), visual focusing (ciliaris) via ciliary ganglion

## IV - TROCHLEAR NERVE (PRIMARILY MOTOR/SOME SENSORY)

- Function: eyeball movement
- Arises from dorsal midbrain; runs around

- Remaining nerve exits skull through stylomastoid foramen
- Splits again into temporal, zygomatic, buccal, mandibular, cervical branches (innervating forehead, nose, cheeks, around eyes/lips, chin)

## VIII - VESTIBULOCOCHLEAR NERVE (SENSORY)

- Function: hearing, equilibrium
- Emerges from pons; runs through internal acoustic meatus
- Splits into cochlear, vestibular nerves
  - Cochlear nerve supplies cochlea's hearing receptors
  - Vestibular nerve supplies vestibule's equilibrium receptors

## IX - GLOSSOPHARYNGEAL NERVE (SENSORY/MOTOR)

- Function: swallowing, monitoring blood pressure/oxygen/carbon dioxide
- Arises from medulla; runs through jugular foramen
- Innervates tongue, pharynx
- Sends motor fibers to stylopharyngeus (elevates pharynx in swallowing), parasympathetic motor fibers to parotid salivary glands, sensory fibers to tongue's posterior third
- Conveys information from carotid bodies' chemoreceptors (blood oxygen, carbon dioxide levels), carotid sinus' baroreceptors (blood pressure)

## X - VAGUS NERVE (SENSORY/MOTOR)

- Function: smooth muscle control, digestive enzyme secretion
- Arises from medulla; runs through jugular foramen
- Dips down into thorax, abdomen
- Sends somatic motor innervation to pharynx, larynx (swallowing), parasympathetic fibers to heart, lungs, abdominal organs (heart rate, breathing, digestion)

- Brings in sensory information from thoracic, abdominal organs; aortic arch's baroreceptors; chemoreceptors in carotid, aortic bodies; epiglottis' taste buds

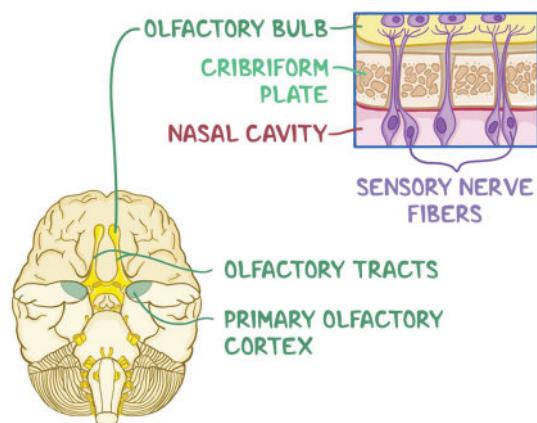
## XI - ACCESSORY NERVE

- Function: swallowing; head, shoulder movement
- Considered vagus nerve accessory
- Forms from rootlets emerging from spinal cord; enters skull via foramen magnum, emerges from medulla, runs through jugular foramen
- Innervates trapezius, sternocleidomastoid muscles (head, neck movement); carries sensory proprioceptive information from larynx, pharynx

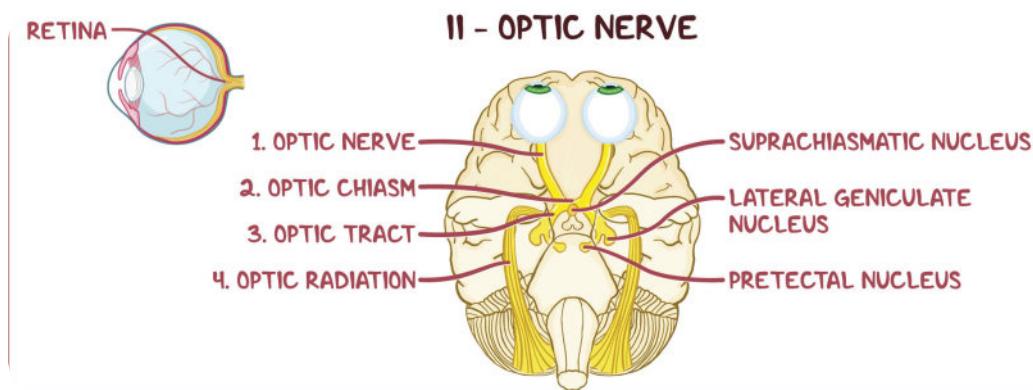
## XII - HYPOGLOSSAL NERVE

- Function: tongue movement, speech, swallowing
- Arises from medulla; runs through hypoglossal foramen
- Sends motor fibers to tongue muscles, carries sensory proprioceptive information

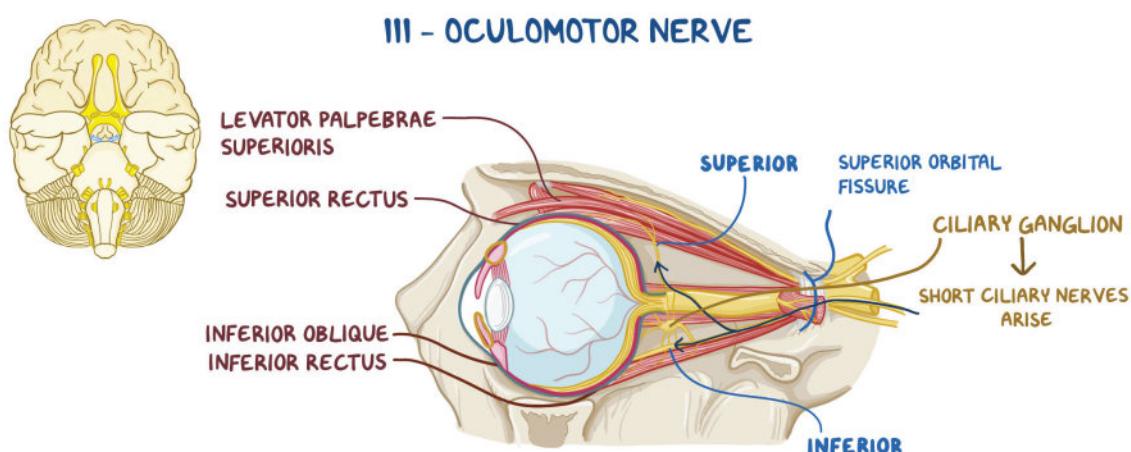
## I - OLFACTORY NERVE



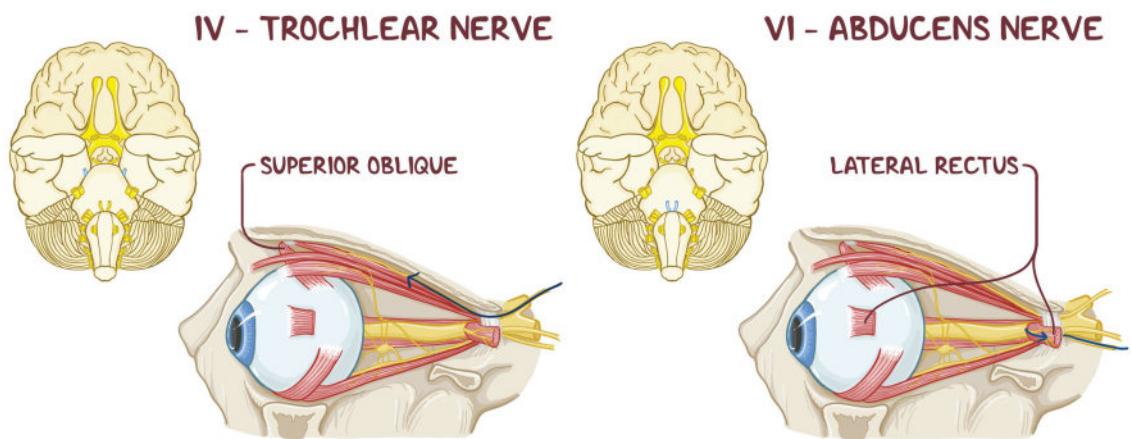
**Figure 56.7** CN I: olfactory nerve.



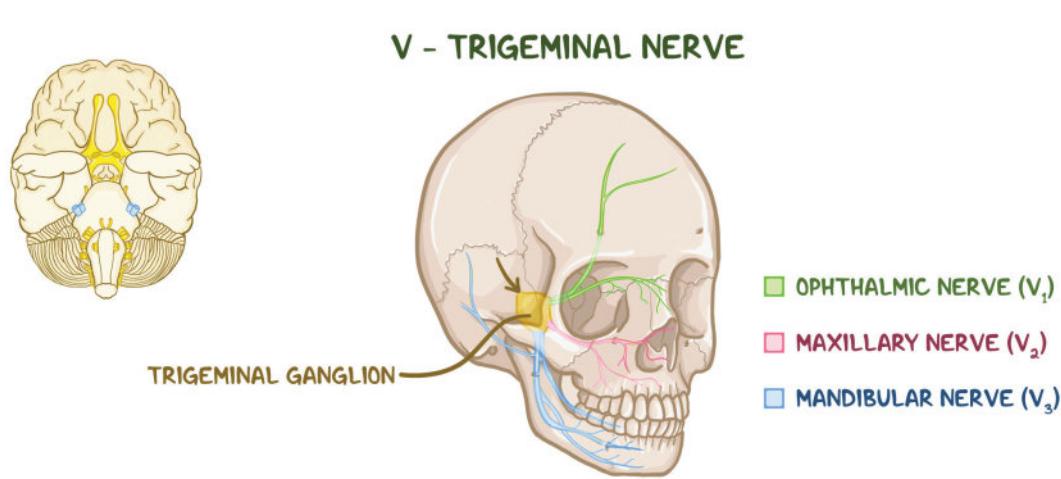
**Figure 56.8** CN II: optic nerve.



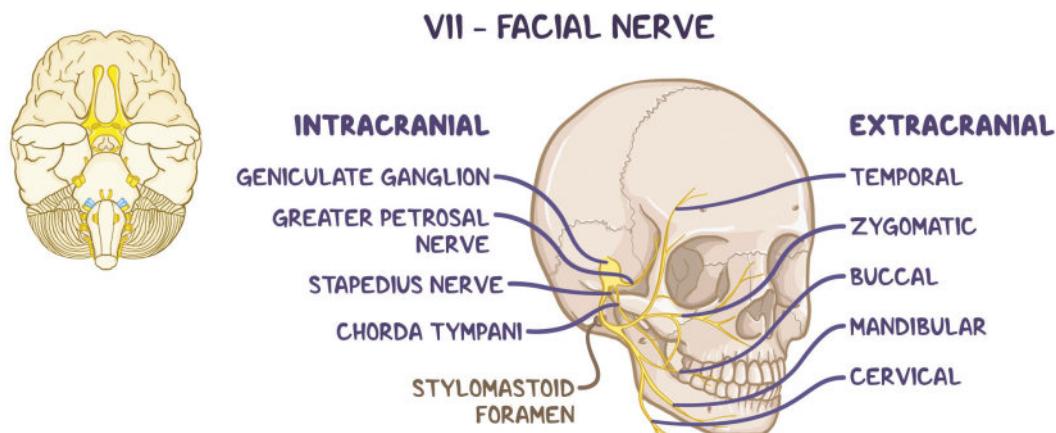
**Figure 56.9** CN III: oculomotor nerve.



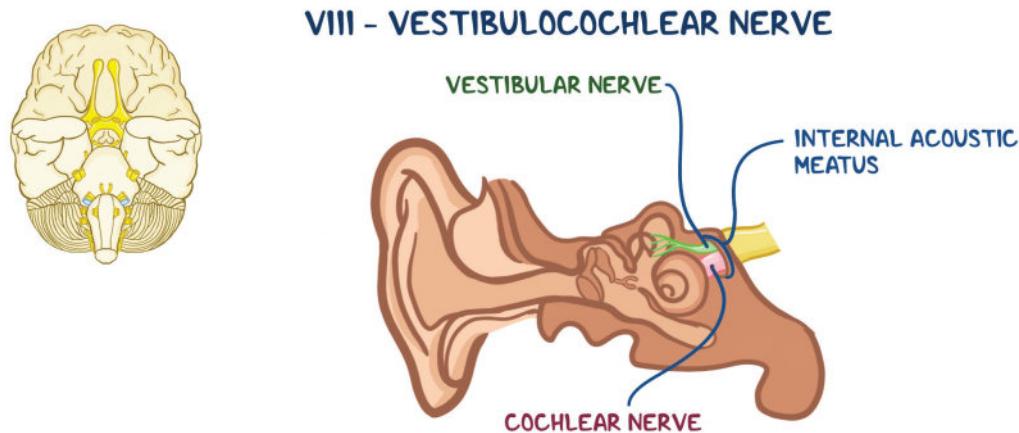
**Figure 56.10** CN IV: trochlear nerve and CN VI: abducens nerve. Together, CN III, IV, and VI control eye movement.



**Figure 56.11** CN V: trigeminal nerve. The three branches include the ophthalmic nerve ( $V_1$ ), maxillary nerve ( $V_2$ ), and mandibular nerve ( $V_3$ ).

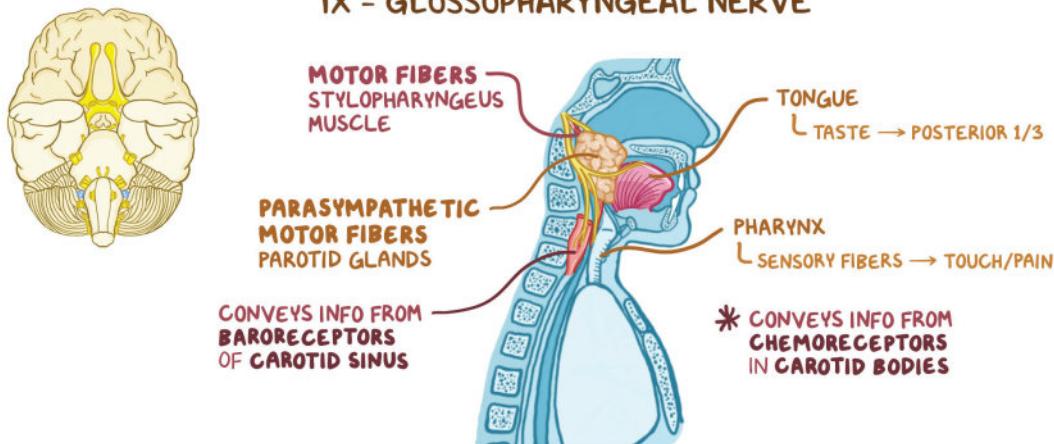


**Figure 56.12** CN VII: facial nerve, including the intracranial and extracranial branches.



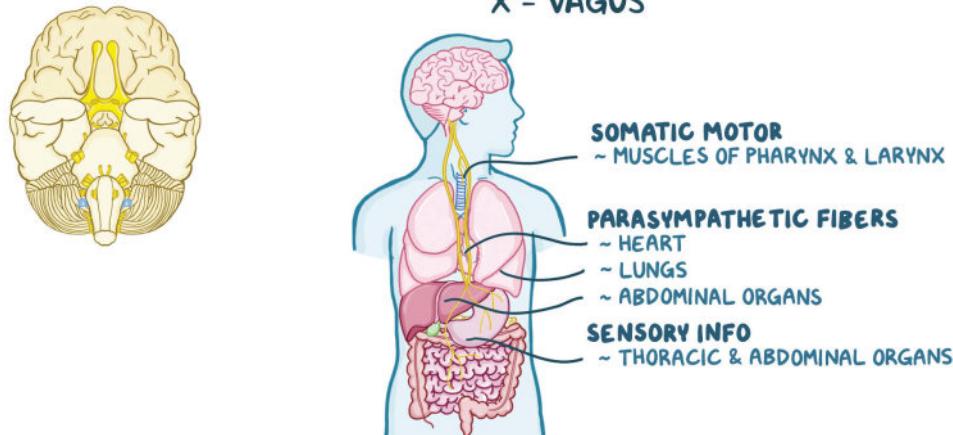
**Figure 56.13** CN VIII: vestibulocochlear nerve, which splits into the vestibular and cochlear nerves once it passes through the internal acoustic meatus.

## IX - GLOSSOPHARYNGEAL NERVE



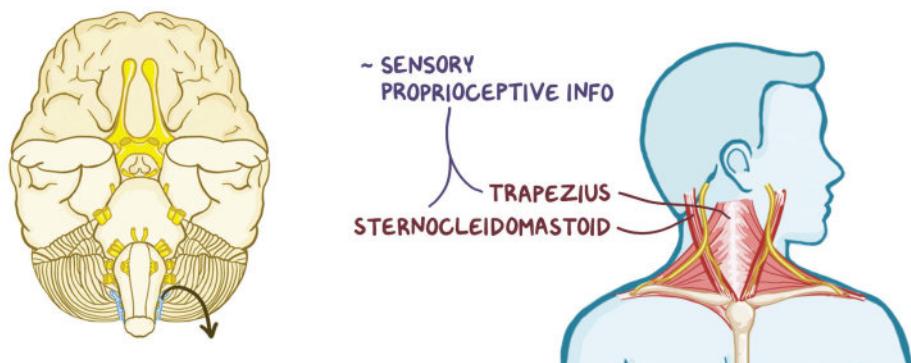
**Figure 56.14** CN IX: glossopharyngeal nerve has sensory and motor functions.

## X - VAGUS

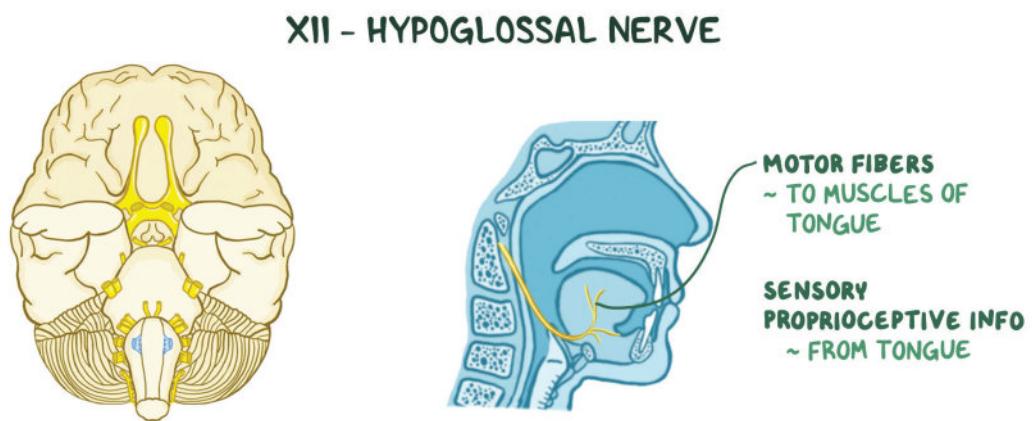


**Figure 56.15** CN X: vagus nerve also has sensory and motor functions.

## XI - ACCESSORY NERVE



**Figure 56.16** CN XI: accessory nerve enters the skull through foramen magnum, then exits again through the jugular foramen. It innervates the trapezius and sternocleidomastoid muscles.



**Figure 56.17** CN XII: hypoglossal nerve innervates the tongue and has both motor and sensory function.



# NOTES ANATOMY & PHYSIOLOGY

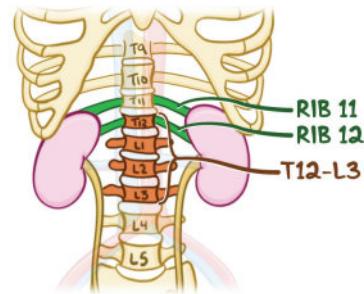
## RENAL ANATOMY & PHYSIOLOGY

[osms.it/renal-anat-phys](http://osms.it/renal-anat-phys)

### RENAL SYSTEM

- Two kidneys
  - Filter the blood from harmful substances
  - Regulate blood pH, volume, pressure, osmolality
  - Produce hormones
- Located between T12, L3 vertebrae; partially protected by ribs 11, 12; behind peritoneal membrane (retroperitoneal)
- Right kidney slightly lower due to larger portion of the liver on right side
- Filter 150 liters of blood everyday; receive  $\frac{1}{4}$  of cardiac output from renal arteries (from aorta)
  - Renal arteries divide → segmental arteries → interlobar arteries (between renal columns) → arcuate arteries (cover bases of renal pyramids) → cortical radiate arteries (supply the cortex) → afferent arterioles (supply nephrons)

- Renal capsule (inner)
  - Dense connective tissue
  - Gives kidney shape



**Figure 57.1** Kidney placement in relation to ribs and vertebrae.

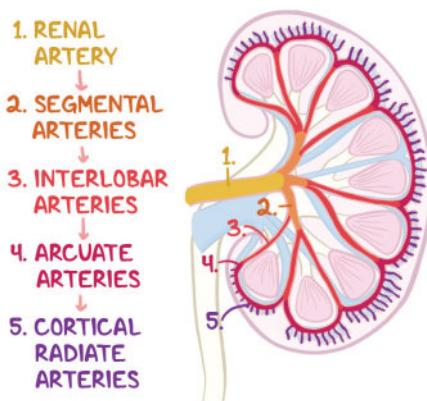
### MORPHOLOGY

#### Renal hilum

- Indentation in the middle of each kidney
- Entry/exit point for ureter, arteries, veins, lymphatics, nerves

#### Surrounding tissue (three layers)

- Renal fascia (outer)
  - Dense connective tissue
  - Anchors kidney
- Adipose capsule (middle)
  - Fatty tissue
  - Protects kidney from trauma



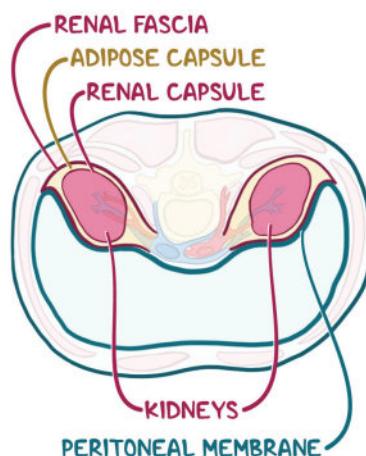
**Figure 57.2** Arterial bloodflow in the kidney.

**Renal cortex (outer portion)**

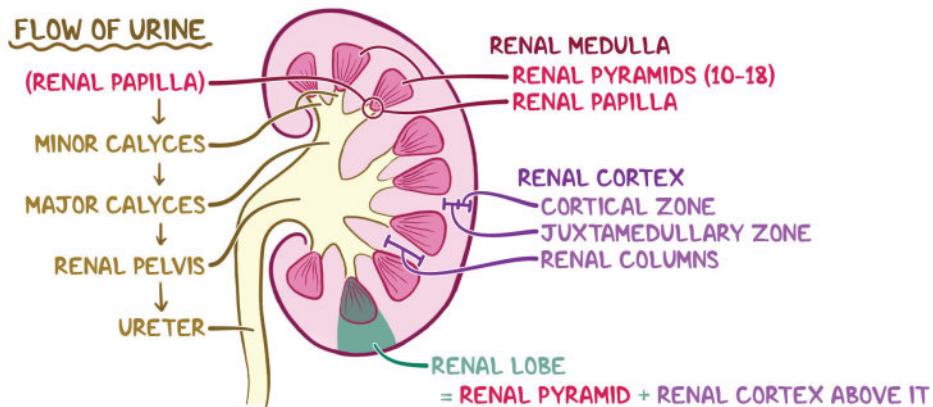
- Outer cortical zone
- Inner juxtamedullary zone
- Renal columns project into the kidney, separating medulla

**Renal medulla (inner portion)**

- 10-18 renal pyramids with pointy ends (renal papilla/hipples) towards center of kidney
- **Renal lobes:** renal pyramids including cortex above them
- Renal papilla → minor calyces → major calyces → renal pelvis → ureter



**Figure 57.3** Transverse cross-section showing retroperitoneal position of kidneys, surrounding tissue layers.

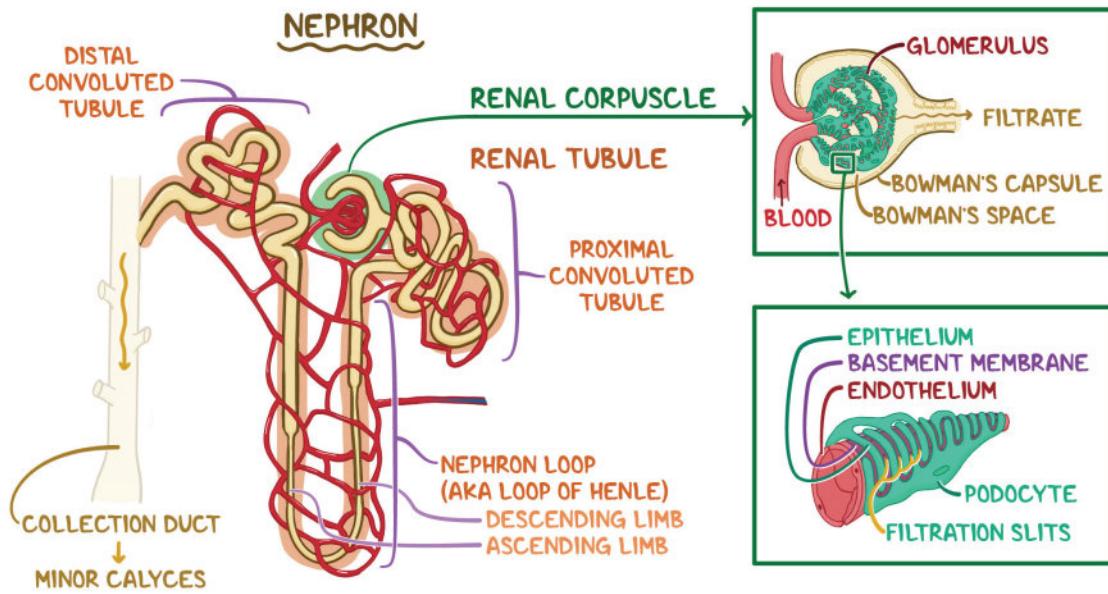


**Figure 57.4** Cross-section through kidney showing renal medulla, renal cortex, and urine flow through kidney.

**Nephron**

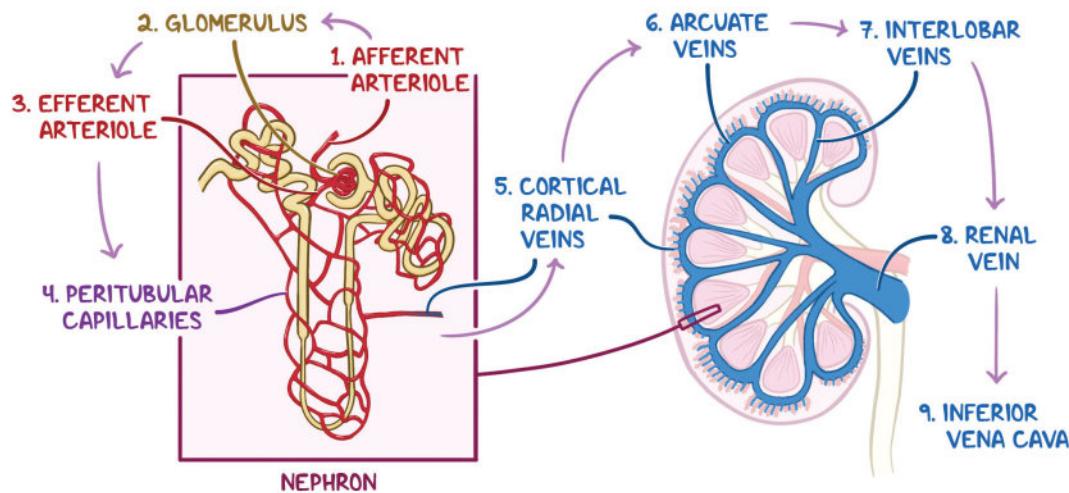
- Functional unit of kidney (about one million in each kidney)
- Composed of renal corpuscle, renal tubule
- Blood filtration starts in renal corpuscle
  - Includes glomerulus, a tuft of capillaries supplied by afferent arteriole, and Bowman's capsule
  - Blood flows into glomerulus → water, solutes (e.g. sodium) pass through capillary endothelium → through basement membrane → through epithelium → into Bowman's space (becoming filtrate)

- Epithelium comprises podocytes wrapped around basement membrane; gaps called filtration slits allow small solutes through but block large proteins, red blood cells
- Blood leaving glomerulus enters efferent arteriole → divides into peritubular capillaries → these reunite into cortical radiate veins → arcuate veins → interlobar veins → renal veins → inferior vena cava



**Figure 57.5** Nephron anatomy.

- Filtrate from Bowman's capsule enters renal tubule
  - Made up of proximal convoluted tubule, descending/ascending limbs of nephron loop (loop of Henle), distal convoluted tubule, collection ducts (which send urine to minor calyces)
  - Filtrate is further filtered by passing water, solutes between filtrate, blood in peritubular capillaries
- Blood pressure, glomerular filtration rate regulated by juxtaglomerular complex
  - Located between distal convoluted tubule and afferent arteriole
  - Contains three types of cells: macula densa, extraglomerular mesangial, juxtaglomerular (granular) cells

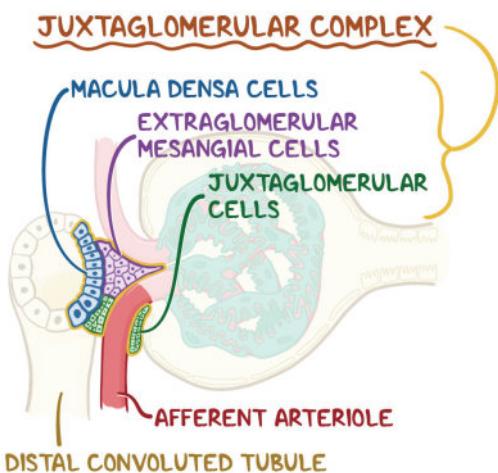


**Figure 57.6** Blood flow through nephron and venial bloodflow in kidney.

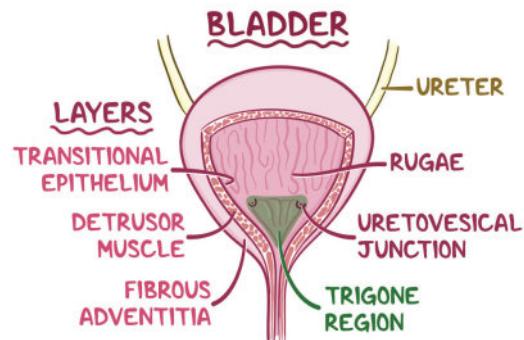
- Macula densa cells in distal convoluted tubule sense ↓ sodium/blood pressure → juxtaglomerular cells secrete renin → ↑ sodium reabsorption, constricting blood vessels → ↑ blood pressure via the renin–angiotensin–aldosterone system (RAAS)
- Urine from renal tubules enters minor calyces → major calyces → renal pelvis → ureter

### Bladder

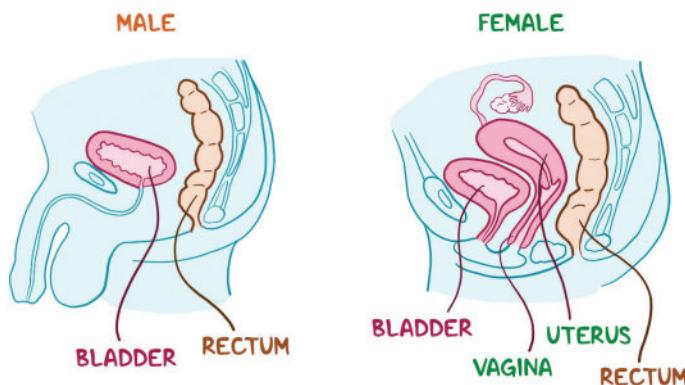
- Bladder receives urine from ureter
  - Urine enters at ureterovesical junctions
  - Muscular walls fold into rugae as bladder empties
- Bladder wall contains multiple layers
  - **Transitional epithelium:** allows bladder to distend while maintaining a barrier
  - **Detrusor muscle:** helps with bladder contraction
  - **Fibrous adventitia:** holds bladder loosely in place
- Located in front of rectum in biologically-male individuals; in front of vagina, uterus, and rectum in biologically-female individuals
- Holds 750mL of urine
  - **Biologically-female individuals:** slightly less due to crowding from uterus
- Contains smooth triangular region (trigone region) on bladder floor
  - Bounded by two ureterovesical junctions and internal urethral orifice
  - Highly sensitive to expansion → signals brain as bladder fills



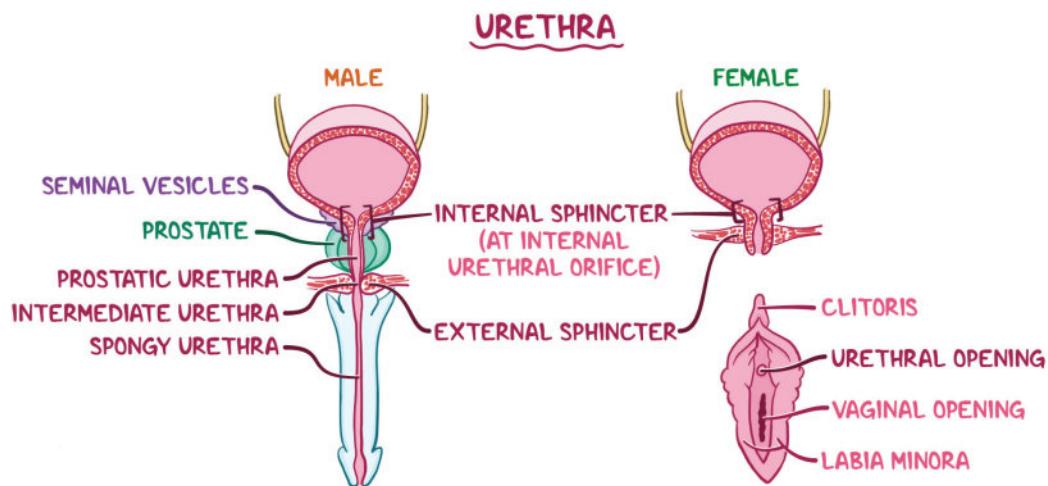
**Figure 57.7** Cross-section through renal capsule showing juxtaglomerular complex.



**Figure 57.8** Bladder anatomy.



**Figure 57.9** Sagittal cross-section showing placement of bladder in relation to other organs.



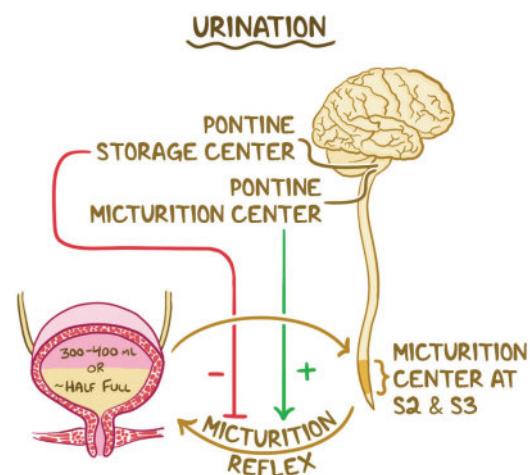
**Figure 57.10** Coronal cross-section through bladder showing urethra anatomy.

### Urethra

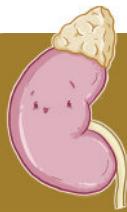
- Drains urine from bladder
- Structured differently in biologically male and female people
  - Starts at internal urethral orifice
  - Male: passes through prostate (prostatic urethra), deep peritoneum (intermediate urethra), penis (spongy urethra); also used during ejaculation (semen enters via seminal vesicles)
  - Female: passes through perineal floor of pelvis, exits between labia minora (above vaginal opening but below clitoris)
  - Detrusor muscle thickens at internal urethral orifice forming internal sphincter (involuntary control; controlled by autonomic nervous system; keeps urethra closed when bladder isn't full)
  - External sphincter is located at level of urogenital diaphragm in floor of pelvis (voluntary control; can be used to stop urination with kegel exercises)

### Urination

- Involves close coordination between nervous system and bladder muscles
- Bladder volume of > 300–400mL, sends signals to micturition center in spinal cord (located at S2 and S3) → micturition reflex causes contraction of bladder and relaxation of both sphincters
  - Pontine storage center in pons of brain can be activated to stop micturition reflex
  - Pontine micturition center can be activated to allow micturition reflex



**Figure 57.11** Signal pathways of micturition reflex.



# NOTES

## ACID-BASE PHYSIOLOGY

# ACID-BASE MAP & COMPENSATORY MECHANISMS

[osms.it/acid-base\\_map\\_and\\_compensatory\\_mechanisms](https://osms.it/acid-base_map_and_compensatory_mechanisms)

### ACID-BASE MAP

- Main physiologic pH factors
  - $\text{HCO}_3^-$ ,  $\text{CO}_2$
- Acid-base map
  - $\text{HCO}_3^-$  concentration (x-axis)/ $\text{CO}_2$  partial pressure (y-axis) diagram
- Henderson-Hasselbalch equation
  - $\text{pH} = 6.1 + \log ([\text{HCO}_3^-]/0.03\text{PCO}_2)$
  - $\text{P}_{\text{CO}_2}$  is partial pressure of  $\text{CO}_2$
- Diagonal lines
  - Drawn where each point on graph has same pH (isohydric lines)
- Drawing lines for  $\text{pH} = 7.35$ ,  $\text{pH} = 7.45$ 
  - Comprises area where all  $\text{HCO}_3^-$ ,  $\text{CO}_2$  combinations correspond to "normal" pH

### pH out of normal range

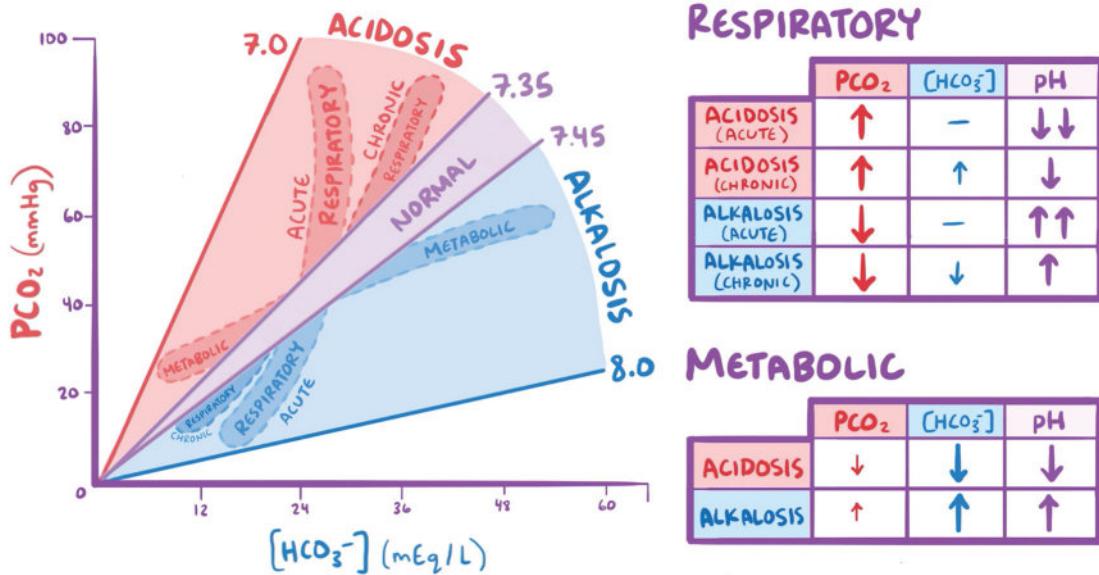
- One of two ways
  - Acidosis:  $\text{pH} \downarrow 7.35$ , enters top-left portion of map
  - Alkalosis:  $\text{pH} \uparrow 7.45$ , enters bottom-right portion of map
- One of two reasons
  - Respiratory:  $\text{P}_{\text{CO}_2}$  too  $\uparrow/\downarrow$
  - Metabolic:  $[\text{HCO}_3^-]$  too  $\uparrow/\downarrow$

### COMPENSATORY MECHANISMS

- Simple acid-base disorder
  - Single problem changing pH
- Mixed acid-base disorder
  - Multiple problems compounding/cancelling out

### Multiple compensatory mechanisms

- Respiratory acidosis
  - Kidneys retain more  $\text{HCO}_3^-$
- Respiratory alkalosis
  - Kidneys excrete more  $\text{HCO}_3^-$
- Metabolic acidosis
  - Lungs blow off  $\text{CO}_2$  (deeper, more frequent breaths)
- Metabolic alkalosis
  - Lungs retain  $\text{CO}_2$  (shallower, less frequent breaths)



**Figure 58.1** An acid-base map shows the relationship between pH, bicarbonate concentration, and partial pressure of carbon dioxide in respiratory and metabolic acidosis or alkalosis, and how these values are adjusted when there is renal or respiratory compensation. The accompanying tables depict the changes in PCO<sub>2</sub>, [HCO<sub>3</sub><sup>-</sup>], and pH associated with respiratory/metabolic acidosis/alkalosis.

## BUFFERING & HENDERSON-HASSELBALCH EQUATION

[osms.it/buffering\\_and\\_henderson-hasselbalch\\_equation](https://osms.it/buffering_and_henderson-hasselbalch_equation)

### BUFFERING

- Buffers: pH change-resisting solutions
- Can comprise
  - Acidic buffer: weak acid, conjugate base
  - Basic buffer: weak base, conjugate acid
- Weak acids, bases do not dissociate fully → equilibrium formation (e.g. HA ⇌ H<sup>+</sup> + A or B + H<sub>2</sub>O ⇌ BH<sup>+</sup> + OH<sup>-</sup>)
  - Le Chatelier's principle: equilibria move forward/backward, balance products/reactants' gain/loss

### Resisting pH change

- Acidic, basic buffers resist all pH changes
- Strong base added to acidic buffer
  - OH<sup>-</sup> ions react with H<sup>+</sup> ions → ↑ pH
  - H<sup>+</sup> ion loss shifts acid's equilibrium →

more H<sup>+</sup> ions created, resists pH change

- Strong acid added to acidic buffer
  - H<sup>+</sup> ions would ↓ pH
  - Shifts acid equilibrium in opposite direction → conjugate base reacts with H<sup>+</sup> ions → resists pH change
- Strong acid added to basic buffer
  - H<sup>+</sup> ions would ↓ pH, also reacts with excess OH<sup>-</sup> ions
  - OH<sup>-</sup> loss shifts base's equilibrium → ↑ OH ion creation → resists pH change
- Strong base added to basic buffer
  - OH<sup>-</sup> ions would react with H<sup>+</sup> ions to ↑ pH
  - Shifts base's equilibrium in opposite direction → conjugate acid reacting with OH<sup>-</sup> ions → resists pH change

## HENDERSON-HASSELBALCH EQUATION

- Henderson-Hasselbalch equation determines buffer's pH
  - $\text{pH} = \text{pK} + \log([\text{A}^-]/[\text{HA}])$
- This is derived
  - Weak acid equilibrium: equilibrium constant  $K \rightarrow K = [\text{H}^+][\text{A}^-]/[\text{HA}]$

- Solving for  $\text{H}^+$  →  $[\text{H}^+] = K([\text{HA}]/[\text{A}^-])$
- Negative log of both sides →  $\text{pH} = \text{pK} + \log([\text{A}^-]/[\text{HA}])$
- Note
  - If  $[\text{A}^-] = [\text{HA}]$ , then  $\text{pH} = \text{pK}$

# PHYSIOLOGIC pH & BUFFERS

[osms.it/physiologic-pH-and-buffers](https://osms.it/physiologic-pH-and-buffers)

## PHYSIOLOGIC pH

- Measures balance between acids, bases in body
- pH:  $-\log[\text{H}^+]$ 
  - $[\text{H}^+]$ : hydrogen ion concentration
- Ideal:  $[\text{H}^+] = 40 \times 10^{-9}$  Eq/L = 40 nEq/L → pH = 7.4 (slightly alkaline)
  - Acidemia: pH < 7.4
  - Alkalolemia: pH > 7.4
- $\uparrow [\text{H}^+] \rightarrow \downarrow \text{pH}$  (negative sign in equation)
- pH,  $[\text{H}^+]$  has logarithmic (not linear) relationship

- Equilibrium reaction
 
$$\text{H}_2\text{O} + \text{CO}_2 \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$$
- Excess
  - $\text{CO}_2$  blown off by lungs
  - $\text{HCO}_3^-$  eliminated by kidneys

## Phosphate buffer system (extracellular)

- Acidic buffer: dihydrogen phosphate ( $\text{H}_2\text{PO}_4^-$ )
- Conjugate base: monohydrogen phosphate ( $\text{HPO}_4^{2-}$ )
- Equilibrium reaction
 
$$\text{H}_2\text{PO}_4^- \rightleftharpoons \text{H}^+ + \text{HPO}_4^{2-}$$

## Protein buffer system (extracellular)

- Protein amino acids may have exposed carboxyl (-COOH), amine ( $\text{NH}_2$ ) groups
- Results in separate acidic ( $-\text{COOH} \rightleftharpoons -\text{COO}^- + \text{H}^+$ ), basic ( $-\text{NH}_2 + \text{H}^+ \rightleftharpoons -\text{NH}_3^+$ ) buffers

## Intracellular buffer systems

- Hemoglobin: buffer in red blood cells (selectively binds  $\text{H}^+$  ions)
- Organic phosphates (e.g. ATP) can buffer similarly

## PHYSIOLOGIC BUFFERS

- Physiologic buffers occur naturally in body
  - Maintains stable pH between 7.35–7.45

### Bicarbonate buffer system

- Extracellular, most important
- Acidic buffer: carbonic acid ( $\text{H}_2\text{CO}_3$ )
- Conjugate base: bicarbonate ion ( $\text{HCO}_3^-$ )
- Carbonic acid can be formed from  $\text{H}_2\text{O}$ ,  $\text{CO}_2$  (carbonic anhydrase catalyzes reaction)

# PLASMA ANION GAP

[osms.it/plasma-anion-gap](https://osms.it/plasma-anion-gap)

## PLASMA ANION GAP

- Cations, anions coexist within plasma
  - To keep plasma electrically neutral sum of cation charges must equal sum of anion charges
- Not all cation, anion concentrations can be measured
  - Often gap (“plasma anion gap”) between measured cation charges (mainly  $\text{Na}^+$ ), smaller measured anion charges sum (mainly  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ )
- Plasma anion gap range: 3–11 mEq/L
  - High gap → high unmeasured anion number
  - Low gap → low unmeasured anion number
- Unmeasured anions include anion component of several organic acids, negatively charged plasma proteins (e.g. albumin)

## DIAGNOSTIC TOOL

- Plasma anion gap serves as useful diagnostic tool

## Metabolic acidosis

- Organic acids’  $\text{H}^+$  ions convert  $\text{HCO}_3^-$  into  $\text{H}_2\text{CO}_3$

- Organic anions aren’t measured → plasma anion gap ↑
- Organic acids include lactic acid, ketoacids, oxalic acid, formic acid, hippuric acid
- Some cases (e.g. diarrhea/renal tubular acidosis)
  - Kidneys reabsorb more  $\text{Cl}^-$  ions → plasma anion gap remains normal (hyperchloremic metabolic acidosis)

## High gap may suggest

- Unmeasured anion buildup (e.g. hyperphosphatemia, hyperalbuminemia)
- Metabolic alkalosis (high pH triggers albumin to release  $\text{H}^+$  ions → negative charge ↑ on unmeasured albumin molecules)

## Low gap may suggest

- Unmeasured anion ↓ (e.g. hypoalbuminemia)
- Unmeasured cation ↑ (rarely)
  - E.g. hyperkalemia, hypercalcemia, hypermagnesemia

# THE ROLE OF THE KIDNEY IN ACID-BASE BALANCE

[osms.it/kidney\\_and\\_acid-base\\_balance](https://osms.it/kidney_and_acid-base_balance)

## KIDNEYS' FUNCTION

- Kidneys maintain acid-base balance in two ways
  - $\text{HCO}_3^-$  reabsorption: urine into blood
  - $\text{H}^+$  secretion: blood into urine

- Kidneys consist of nephrons
  - Each has glomerulus (capillaries clump)
- During filtration, plasma leaves glomerulus entering renal tubule (consists of proximal convoluted tubule, loop of Henle, distal convoluted tubule)

- Tubules lined with brush border cells (apical surface facing tubular lumen, basolateral surface facing peritubular capillaries)

### $\text{HCO}_3^-$ reabsorption

- Primarily in proximal convoluted tubule
  - $\text{Na}^+$  ions exchanged for  $\text{H}^+$  ions through apical surface → bind with  $\text{HCO}_3^-$  → form  $\text{H}_2\text{CO}_3$
  - Carbonic anhydrase type 4 splits  $\text{H}_2\text{CO}_3$  into  $\text{H}_2\text{O}$ ,  $\text{CO}_2$
  - $\text{H}_2\text{O}$ ,  $\text{CO}_2$  diffuse across membrane
  - Carbonic anhydrase type 2 recombines them into  $\text{H}_2\text{CO}_3$
  - $\text{H}_2\text{CO}_3$  dissolve into  $\text{H}^+$ ,  $\text{HCO}_3^-$

- Sodium/chloride bicarbonate cotransporters on basolateral surface snatch up  $\text{HCO}_3^-$ , nearby sodium/chloride ion, moving both into blood

### $\text{H}^+$ secretion

- Primarily in proximal convoluted tubule
  - Sodium-hydrogen countertransport:  $\text{H}^+$  ions exchanged for  $\text{Na}^+$  ions through apical surface
- Another mechanism in distal convoluted tubule, collecting ducts involving alpha-intercalated cells
- Chemical buffers (ammonia, phosphate) prevent urine pH from dropping too low in tubules (< 4.5)

# METABOLIC ACIDOSIS

[osms.it/metabolic-acidosis](https://osms.it/metabolic-acidosis)

## METABOLIC ACIDOSIS

- $\text{HCO}_3^-$  ion reduction → blood pH ↓ to < 7.35

## TYPES

- Distinguished by high/normal anion gap
  - Measured cation concentration
  - E.g.  $\text{Na}^+$  ions, minus measured anion concentration (e.g.  $\text{Cl}^-$ ,  $\text{HCO}_3^-$  ions)

### High anion gap

- $\text{H}^+$  ions from organic acids convert  $\text{HCO}_3^-$  to  $\text{H}_2\text{CO}_3$ 
  - ↓  $\text{HCO}_3^-$  ion concentration (measured in anion gap), ↑ organic anion concentration (not measured)
  - Naturally-occurring organic acids: e.g. lactic acid production (lactic acidosis), ketoacid production (diabetic ketoacidosis), excessive uric, sulfur-containing acid retention (chronic renal failure)
  - Ingestible organic acids: e.g. oxalic acid (antifreeze), formic acid (methanol), hippuric acid (toluene)

### Normal anion gap

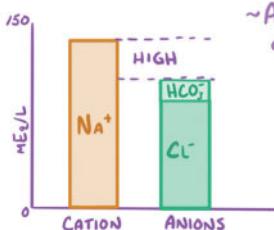
- $\text{HCO}_3^-$  lost in various ways,  $\text{Cl}^- \uparrow$  prevents anion gap change (hyperchloremic metabolic acidosis)
- Possible causes
  - Diarrhea, renal tubular acidosis

## REGULATORY MECHANISMS

- Body has several regulatory mechanisms to reverse ↓ pH
  - $\text{H}^+$  ions moved from blood into cells, exchanged for  $\text{K}^+$  ions (may cause hyperkalemia); if organic anions present, can enter cells with  $\text{H}^+$  ions →  $\text{K}^+$  ions are not released
  - Chemoreceptors fire more in low pH → ↑ respiratory rate, breath depth → ↑ ventilation,  $\text{CO}_2$  movement out of body
  - $\text{H}^+$  ions excreted by kidneys →  $\text{HCO}_3^-$  reabsorbed (with normal renal function)

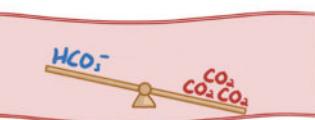
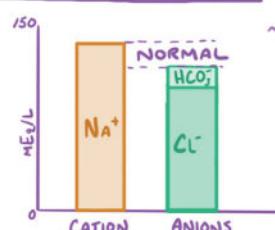
## ~DECREASED $\text{HCO}_3^-$ IN THE BLOOD

### HIGH ANION GAP



- ~ACCUMULATION OF ORGANIC ACIDS
- L<sup>↑</sup> PRODUCTION IN BODY
- L<sup>↓</sup> EXCRETION
- L<sup>↓</sup> EXOGENOUS INGESTION

### NORMAL ANION GAP



- ~LOSS of  $\text{HCO}_3^-$
- L DIARRHEA
- L TYPE II RENAL TUBULAR ACIDOSIS

**Figure 58.2** Illustration depicting the two kinds of metabolic acidosis: high anion gap (where  $\text{H}^+$  from organic acids converts  $\text{HCO}_3^-$  to  $\text{H}_2\text{CO}_3$ ), and normal anion gap (where a  $\text{Cl}^-$  increase maintains the normal anion gap).

# METABOLIC ALKALOSIS

[osms.it/metabolic-alkalosis](http://osms.it/metabolic-alkalosis)

## METABOLIC ALKALOSIS

- $\text{HCO}_3^-$  ion gain  $\rightarrow$  blood pH  $\uparrow > 7.45$

## CAUSES

- Associated with direct  $\text{HCO}_3^-$  ion gain/loss of  $\text{H}^+$  ion loss (thus  $\rightarrow \text{HCO}_3^-$  ion gain), usually both
- Hypokalemia
  - Metabolic alkalosis cause
  - May also be result of other root causes

## Excessive $\text{H}^+$ ion loss causes

- Vomiting (gastric secretions acidic)
  - Also causes  $\text{HCO}_3^-$  ion buildup in pancreas (would normally neutralize gastric secretions)
- Abnormal renal function
  - E.g. adrenal tumors secrete aldosterone  $\rightarrow$  distal convoluted tubule dumps  $\text{H}^+$  ions, reabsorbs  $\text{HCO}_3^-$  ions

## Excessive $\text{HCO}_3^-$ ion gain causes

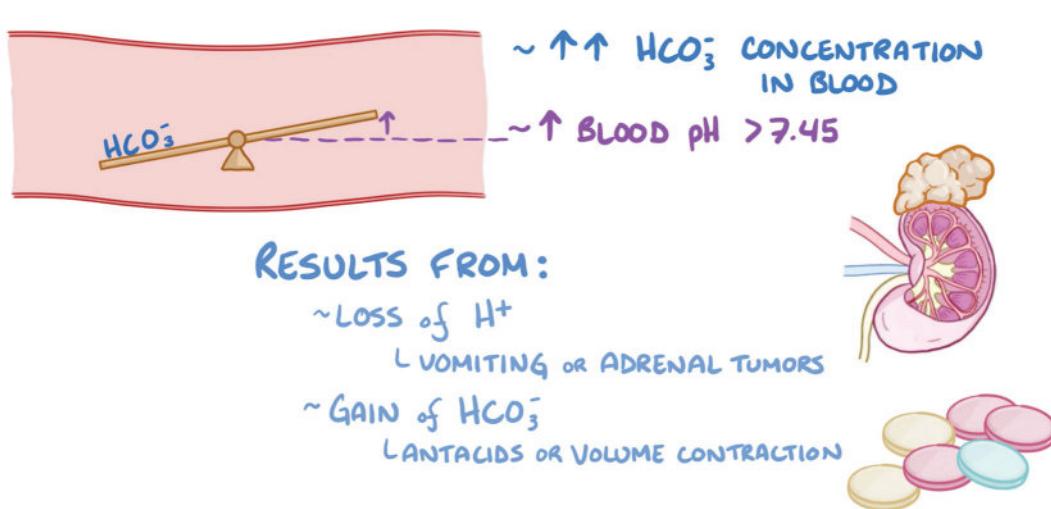
- ↑ kidney reabsorption
  - Volume contraction with loop/thiazide

diuretics/severe dehydration cases  
(contraction alkalosis)

- Hypokalemia
  - Diarrhea/diuretic use, triggering renin-angiotensin-aldosterone mechanism  $\rightarrow$  distal convoluted tubule dumps  $\text{H}^+$  ions, reabsorbs  $\text{HCO}_3^-$  ions
- $\text{HCO}_3^-$  ion ingestion
  - E.g. excessive antacid use ( $\text{NaHCO}_3$ )

## REGULATORY MECHANISMS

- Body has regulatory mechanisms to reverse  $\uparrow$  pH
  - $\text{K}^+$  ions move from blood into cells  $\rightarrow$  exchanged for  $\text{H}^+$  ions (may contribute to hypokalemia)
  - Chemoreceptors fire less in high pH  $\rightarrow$  ↓ respiratory rate, breathing depth  $\rightarrow$  ↓ ventilation,  $\text{CO}_2$  retention
  - $\text{HCO}_3^-$  ions excreted by kidneys  $\rightarrow$   $\text{H}^+$  reabsorbed (normal renal function)



**Figure 58.3** Illustration summarizing the definition and causes of metabolic alkalosis.

## RESPIRATORY ACIDOSIS

[osms.it/respiratory-acidosis](https://osms.it/respiratory-acidosis)

### RESPIRATORY ACIDOSIS

- $\text{CO}_2$  gain  $\rightarrow$  blood pH  $\downarrow < 7.35$

### CAUSES

- Ventilation  $\downarrow$  (frequency, breath depth) for variety of reasons  $\rightarrow$  lungs blow off too little  $\text{CO}_2$ 
  - Stroke/medication overdose/etc.  $\rightarrow$  respiratory-center abnormality in brainstem
  - Obesity, trauma, neuromuscular disorders (myasthenia gravis), etc.  $\rightarrow$  respiratory muscle-contraction failure
  - Airway obstruction
  - Alveoli damage (chronic obstructive pulmonary disease); alveoli fluid buildup

(pneumonia); fluid buildup between alveoli, capillary walls (pulmonary edema)  $\rightarrow$  impaired gas exchange between alveoli, capillary

### REGULATORY MECHANISMS

- Body has several regulatory mechanisms to reverse pH  $\downarrow$ 
  - Low pH  $\rightarrow$  chemoreceptors fire more  $\rightarrow$  attempted  $\uparrow$  in respiratory rate, breathing depth  $\rightarrow$   $\uparrow$  ventilation
  - $\text{H}^+$  ions bind to basic protein molecules (mainly exposed hemoglobin  $-\text{NH}_2$  groups), although in small amounts
  - $\text{H}^+$  ions excreted by kidneys,  $\text{HCO}_3^-$  reabsorbed

# RESPIRATORY ALKALOSIS

[osms.it/respiratory-alkalosis](https://osms.it/respiratory-alkalosis)

## RESPIRATORY ALKALOSIS

- $\text{CO}_2$  loss → blood pH  $\uparrow > 7.45$

## CAUSES

- Ventilation  $\uparrow$  (frequency, breath depth) for variety of reasons → lungs blowing off too much  $\text{CO}_2$ 
  - Respiratory-center abnormality in brainstem
  - Pneumonia, pulmonary embolism, etc. → low oxygen levels (hypoxia)
  - Anxiety, panic attacks, sepsis, salicylates overdose

- Incorrectly-set ventilator → medical intervention

## REGULATORY MECHANISMS

- Body has several regulatory mechanisms to reverse pH  $\uparrow$ 
  - High pH → chemoreceptors fire less → attempted  $\downarrow$  in respiratory rate, breathing depth →  $\downarrow$  ventilation
  - $\text{H}^+$  ions released from acidic protein molecules (mainly exposed hemoglobin -COOH groups), although in small amounts
  - $\text{HCO}_3^-$  ions excreted by kidneys,  $\text{H}^+$  are reabsorbed



# NOTES

## FLUIDS IN THE BODY

### BODY FLUID COMPARTMENTS

[osms.it/body-fluid-compartments](https://osms.it/body-fluid-compartments)

#### GENERAL CHARACTERISTICS

- Fluid divisions in body
  - Includes intracellular fluid, extracellular fluid
- “60-40-20 rule”
  - Total body water is 60% of body weight, of which two thirds is intracellular → total intracellular fluid is 40% of body weight, total extracellular fluid is 20% of body weight
- Due to macroscopic electroneutrality principle, fluid compartments have same concentration of positive charges as negative charges

#### INTRACELLULAR & EXTRACELLULAR FLUID

- Large difference between intracellular fluid and extracellular fluid (e.g.  $\text{Na}^+$ - $\text{K}^+$  ATPases establish high concentration of  $\text{K}^+$  inside cell and high concentration of  $\text{Na}^+$  outside cell)

##### Intracellular fluid

- Dissolves cations (esp.  $\text{K}^+$  and  $\text{Mg}^{2+}$ ) and anions (esp. proteins and organic phosphates e.g. ATP)

##### Extracellular fluid

- Includes interstitial fluid (around cells) and plasma (aqueous part of blood, containing about 10% proteins e.g. albumin)
  - Both dissolve cations (esp.  $\text{Na}^+$ ) and anions (esp.  $\text{Cl}^-$  and  $\text{HCO}_3^-$ )
  - Solutes and water travel between the interstitial fluid and plasma through pores in endothelial cells of capillaries

- Negative plasma proteins are too big to travel through pores; electroneutrality is maintained by repelling small anions into interstitial fluid and attracting small cations into plasma (Gibbs–Donnan effect) → interstitial fluid has ↑ small anion concentration (e.g.  $\text{Cl}^-$ ) and ↓ small cation concentration (e.g.  $\text{Na}^+$ )

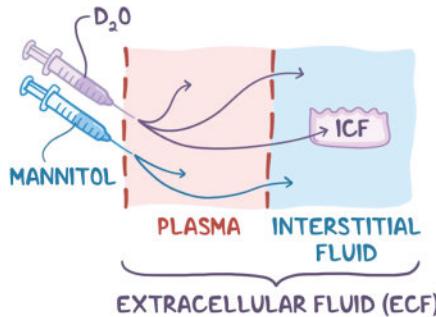
#### VOLUMES OF BODY FLUID COMPARTMENTS

- Determined by administering and measuring concentration of substances that are known to settle in specific compartments (dilution method)
  - Radiolabeled albumin for plasma (cannot pass into interstitial fluid)
  - Smaller molecules like mannitol and inulin for interstitial fluid (cannot pass through cell membranes)
  - Heavy water ( $\text{D}_2\text{O}$ ) for total body water (knowing this and above, intracellular fluid can be calculated too)
  - Measuring concentration of these substances in their respective body fluid compartments allows us to calculate volume ( $= \frac{\text{AmountGiven}}{\text{Concentration}}$ )

- To account for loss of these substances in urine, subtract amount lost from amount given and use this value in formula

## DILUTION METHOD SAMPLE PROBLEM

A 70 kg man is injected with 150mCi of D<sub>2</sub>O and 650mg of mannitol. During a two hour equilibration period, he excretes 10% of the D<sub>2</sub>O and 10% of the mannitol in his urine. After that, the concentration of D<sub>2</sub>O in the plasma is 0.32mCi/100 mL, and the concentration of mannitol is 4.6 mg/100mL. Calculate the total body water (TBW), extracellular fluid (ECF), and intracellular fluid (ICF) volumes.



	INJECTED	EXCRETED	CONCENTRATION
D <sub>2</sub> O	150 mCi	10%	0.32 mCi/100 mL
MANNITOL	650 mg	10%	4.6 mg/100 mL

### STEP 1: CALCULATE VOLUME<sub>TBW</sub> (D<sub>2</sub>O) & VOLUME<sub>ECF</sub> (MANNITOL)

#### STEP 1a: Determine amount remaining in body after excretion

Amount remaining = amount injected - amount excreted

$$\begin{aligned} \text{Amount}_{\text{D}_2\text{O}} &= 150\text{mCi} - (10\% \times 150\text{mCi}) \\ &= 150\text{mCi} - 15\text{mCi} \\ &= 135\text{mCi} \end{aligned}$$

$$\begin{aligned} \text{Amount}_{\text{mannitol}} &= 650\text{mg} - (10\% \times 650\text{mg}) \\ &= 650\text{mg} - 65\text{mg} \\ &= 585\text{mg} \end{aligned}$$

#### STEP 1b: Divide remaining amount by concentration

$$\begin{aligned} \text{Volume}_{\text{TBW}} &= \text{Volume}_{\text{D}_2\text{O}} \\ &= 135\cancel{\text{mCi}} \times \frac{100\text{mL}}{0.32\cancel{\text{mCi}}} \\ &= 42.2\text{L} \end{aligned}$$

$$\begin{aligned} \text{Volume}_{\text{ECF}} &= \text{Volume}_{\text{mannitol}} \\ &= 585\cancel{\text{mg}} \times \frac{100\text{mL}}{4.6\cancel{\text{mg}}} \\ &= 12.7\text{L} \end{aligned}$$

### STEP 2: CALCULATE VOLUME<sub>ICF</sub>

$$\begin{aligned} \text{Volume}_{\text{ICF}} &= \text{Volume}_{\text{TBW}} - \text{Volume}_{\text{ECF}} \\ &= 42.2\text{ L} - 12.7\text{ L} \\ &= 29.5\text{ L} \end{aligned}$$

**Figure 59.1** A sample problem demonstrating how to solve for total body water, extracellular fluid, and intracellular fluid volumes using information gained from D<sub>2</sub>O and mannitol.

# WATER SHIFTS BETWEEN BODY FLUID COMPARTMENTS

[osms.it/water-shifts-between-body-fluid-compartments](https://osms.it/water-shifts-between-body-fluid-compartments)

## Key features

- Movement of water between body fluid compartments to maintain constant osmolarity
- Shifts are characterized by change in volume and concentration of extracellular fluid
  - ECF volume:  $\uparrow$  = expansion;  $\downarrow$  = contraction
  - ECF osmolarity:  $\uparrow$  = hyperosmotic;  $\downarrow$  = hyposmotic; no change = isosmotic
- Six possible combinations

## VOLUME CONTRACTION

### Isosmotic volume contraction

- Loss of isosmotic fluid from ECF
- Volume  $\downarrow$  but osmolarity is constant  $\rightarrow$  no water shift
- $\downarrow$  plasma volume and arterial pressure;  $\uparrow$  plasma protein concentration and hematocrit
- E.g. diarrhea

### Hyperosmotic volume contraction

- Loss of hyposmotic fluid from ECF
- Volume  $\downarrow$  and osmolarity  $\uparrow$   $\rightarrow$  water shifts from ICF (net effect is still volume contraction)
- $\downarrow$  plasma volume and arterial pressure;  $\uparrow$  plasma protein concentration but hematocrit is unchanged (since red blood cells lose volume too)
- E.g. heavy sweating (sweat is hyposmotic relative to ECF)

### Hyposmotic volume contraction

- Loss of solutes/hyperosmotic fluid from ECF
- Volume  $\downarrow$  and osmolarity  $\downarrow$   $\rightarrow$  water shifts to ICF
- $\downarrow$  plasma volume and arterial pressure;  $\uparrow$  plasma protein concentration and hematocrit

- E.g. adrenal insufficiency (deficiency in several hormones, including aldosterone). Aldosterone important for sodium reabsorption from kidneys;  $\downarrow$  aldosterone =  $\uparrow$  sodium loss in urine

## VOLUME EXPANSION

### Isosmotic volume expansion

- Gain of isosmotic fluid in ECF
- Volume  $\uparrow$  but osmolarity is constant  $\rightarrow$  no water shift
- $\uparrow$  plasma volume and arterial pressure;  $\downarrow$  plasma protein concentration and hematocrit
- E.g. receiving an infusion of isotonic NaCl solution

### Hyperosmotic volume expansion

- Gain of solutes or hyperosmotic fluid in ECF
- Volume  $\uparrow$  and osmolarity  $\uparrow$   $\rightarrow$  water shifts from ICF
- $\uparrow$  plasma volume and arterial pressure;  $\downarrow$  plasma protein concentration and hematocrit
- E.g. eating salty chips

### Hyposmotic volume expansion

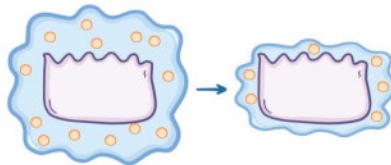
- Gain of hyposmotic fluid in ECF
- Volume  $\uparrow$  and osmolarity  $\downarrow$   $\rightarrow$  water shifts to ICF (net effect is still volume expansion)
- $\uparrow$  plasma volume and arterial pressure;  $\downarrow$  plasma protein concentration but hematocrit is unchanged
- E.g. too much antidiuretic hormone causing excessive water reabsorption

## **TYPES of VOLUME CONTRACTION**

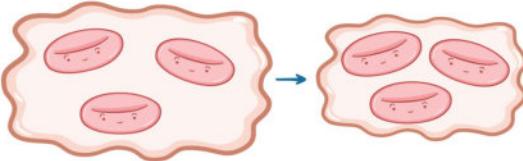
## ISOSMOTIC VOLUME CONTRACTION (Example: Diarrhea)

## 1. ISOSMOTIC FLUID LOST FROM ECF

→ ECF VOLUME ↓



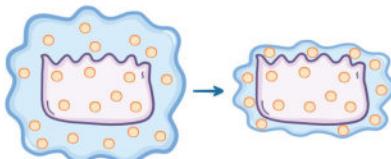
PLASMA VOLUME ↓ → PLASMA PROTEIN [ ] ↑  
HEMATOCRIT ↑



2. ECF OSMOLARITY = ICF OSMOLARITY → NO ICF WATER MOVEMENT

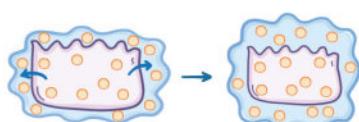
### **HYPEROSMOTIC VOLUME CONTRACTION (Example: Running a marathon)**

1. HYPOOSMOTIC FLUID LOST FROM ECF → ECF VOLUME ↓, ECF OSMOLARITY ↑

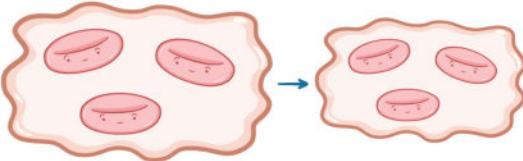


2. ECF OSMOLARITY > ICF OSMOLARITY → WATER MOVES FROM ICF TO ECF

→ ECF & ICF VOLUME ↓  
ECF & ICF OSMOLARITY ↑

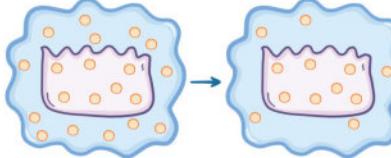


PLASMA VOLUME ↓ → PLASMA PROTEIN [ ] ↑  
HEMATOCRIT UNCHANGED



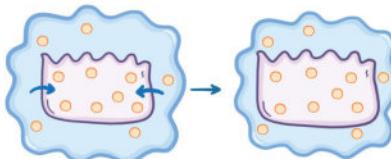
### **HYPONATROMIC VOLUME CONTRACTION (Example: Adrenal insufficiency)**

## 1. ↓ ECF SOLUTES → ECF OSMOLARITY ↓

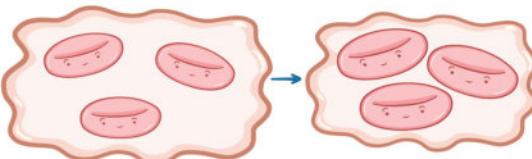


2. ECF OSMOLARITY < ICF OSMOLARITY → WATER MOVES FROM ECF TO ICF

→ ECF VOLUME ↓, ICF VOLUME ↑  
ECF & ICF OSMOLARITY ↓



PLASMA VOLUME ↓ → PLASMA PROTEIN [ ] ↑  
HEMATOCRIT ↑



**Figure 59.2** Visualization of the types of volume contraction.

## TYPES of VOLUME EXPANSION

### ISOSMOTIC VOLUME EXPANSION (Example: Isotonic NaCl infusion)

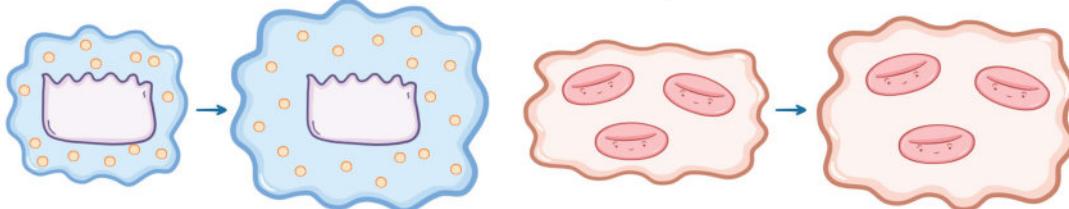
#### 1. ISOSMOTIC FLUID ADDED TO ECF

→ ECF VOLUME ↑

OSMOLARITY UNCHANGED

PLASMA VOLUME ↑ → PLASMA PROTEIN [ ] ↓

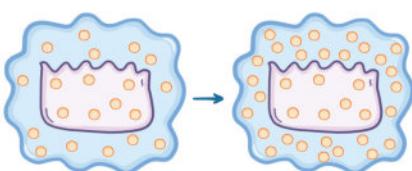
HEMATOCRIT ↓



#### 2. ECF OSMOLARITY = ICF OSMOLARITY → NO ICF WATER MOVEMENT

### HYPEROSMOTIC VOLUME EXPANSION (Example: Eating salty chips)

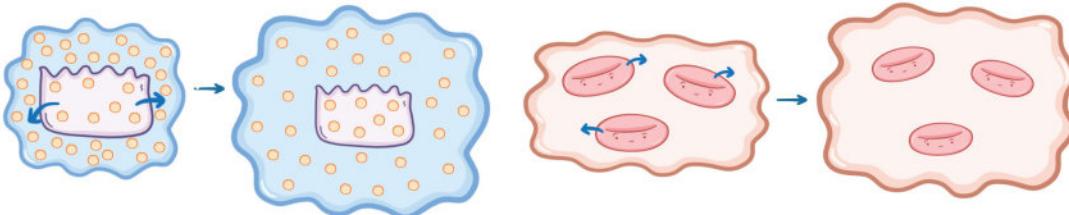
#### 1. ECF SOLUTES ↑ → ECF OSMOLARITY ↑



#### 2. ECF OSMOLARITY > ICF OSMOLARITY → WATER MOVES FROM ICF TO ECF

→ ECF VOLUME ↑, ICF VOLUME ↓  
ECF & ICF OSMOLARITY ↑

PLASMA VOLUME ↑ → PLASMA PROTEIN [ ] ↓  
HEMATOCRIT ↓

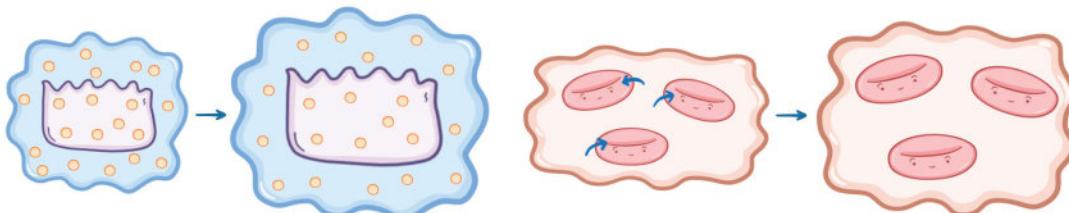


### HYPONOSMOTIC VOLUME EXPANSION (Example: SIADH)

#### 1. ↑↑ WATER REABSORPTION, EXCESS WATER DISTRIBUTED THROUGHOUT TOTAL BODY WATER

→ ECF & ICF VOLUME ↑  
ECF & ICF OSMOLARITY ↓

PLASMA VOLUME ↑ → PLASMA PROTEIN [ ] ↓  
HEMATOCRIT UNCHANGED



**Figure 59.3** Visualization of the types of volume expansion.

# RENAL CLEARANCE

[osms.it/renal-clearance](http://osms.it/renal-clearance)

- Rate at which kidneys clear blood plasma of substance
- For substance “x”, renal clearance

$$C = \frac{[U]_x \times V}{[P]_x}$$

- $[U]_x$ : urine concentration of x
  - $[P]_x$ : plasma concentration of x
  - V: urine flow rate
- To measure reabsorption/secretion of substance in kidneys, **inulin** can be used as reference point
    - Inulin is **freely filtered**
    - Inulin is **not reabsorbed/secreted**
  - Clearance ratio for substance x is

$$C_{H_2O} = V - \frac{U_{osm}}{P_{osm}} V$$

- $U_{osm}$ : urine osmolarity
- $P_{osm}$ : plasma osmolarity

$$\frac{C_x}{C_{inulin}}$$

- $= 1 \rightarrow x$  is freely filtered, not secreted
- $> 1 \rightarrow x$  is freely filtered, secreted
- $< 1 \rightarrow x$  is not freely filtered/is reabsorbed

## RENAL CLEARANCE SAMPLE PROBLEM

### PART 1

In a **24 hour** period, a man has **2 liters** of urine. His plasma  $\text{Na}^+$  concentration is **145mEq/L**, whereas his urine  $\text{Na}^+$  concentration is **190mEq/L**. What is the man's **renal clearance** for sodium?

$$C = \frac{[U]_x \times \dot{V}}{[P]_x}$$

#### STEP 1: CALCULATE $\dot{V}$

$$\dot{V} = \frac{\text{URINE VOLUME}}{\text{TIME}} = \frac{2000\text{mL}}{1440\text{min}} = 1.39\text{mL/min}$$

#### STEP 2: CALCULATE $C_{\text{Na}^+}$

$$C_{\text{Na}^+} = \frac{[U]_x \times \dot{V}}{[P]_x} = \frac{190\text{mEq/L} \times 1.39 \text{ mL/min}}{145\text{mEq/L}} = 1.43\text{mL/min}$$

→ 1.43mL of plasma is cleared of  $\text{Na}^+$  per minute.

### PART 2

Returning to the scenario in Part 1, let's assume we gave that man an infusion of **inulin** over **2 hours**. The urine concentration of inulin is **140mg/mL**, and the plasma concentration of inulin is **1mg/mL**. The urine flow rate is **1.39mL/min** (the value calculated in Part 1). What is the man's clearance of inulin? What is the clearance ratio for  $\text{Na}^+$ ?

$$C = \frac{[U]_x \times \dot{V}}{[P]_x}$$

#### STEP 1: CALCULATE $C_{\text{INULIN}}$

$$C_{\text{INULIN}} = \frac{[U]_x \times \dot{V}}{[P]_x} = \frac{140\text{mg/mL} \times 1.39 \text{ mL/min}}{1\text{mg/mL}} = 194.6\text{mL/min}$$

→ 194.6mL of plasma is cleared of inulin per minute.

#### STEP 2: CALCULATE CLEARANCE RATIO FOR $\text{Na}^+$

$$C_{\text{Na}^+} = \frac{C_{\text{Na}^+}}{C_{\text{INULIN}}} = \frac{1.43\text{mL/min}}{194.6\text{mL/min}} = 0.007$$

→ 0.007 << 1, so very little  $\text{Na}^+$  is excreted in the urine. Since it is freely filtered, it must be extensively reabsorbed by the nephron to have such a low clearance ratio.

## FREE WATER CLEARANCE SAMPLE PROBLEM

A woman has a urine flow rate of **1.5mL/min**, a urine osmolarity of **130mOsm/L**, and a plasma osmolarity of **280mOsm/L**. What is her free water clearance?

$$\text{CH}_2\text{O} = \dot{V} - C_{\text{OSM}}$$

$$\begin{aligned} \text{CH}_2\text{O} &= \dot{V} - \frac{[U]_{\text{OSM}} \times \dot{V}}{[P]_{\text{OSM}}} \\ &= 1.5\text{mL/min} - \frac{130\text{mOsm/L} \times 1.5\text{mL/min}}{180\text{mOsm/L}} \\ &= 1.5\text{mL/min} - 0.7\text{mL/min} \\ &= 0.8\text{mL/min} \end{aligned}$$

→ 0.8mL of plasma is cleared of solute-free water every minute by the kidneys.

**Figure 59.4** Sample questions solving for renal clearance of a solute and free water clearance.



# NOTES

## RENAL BLOOD FLOW REGULATION

# RENAL BLOOD FLOW REGULATION

[osms.it/renal-blood-flow-regulation](http://osms.it/renal-blood-flow-regulation)

- Blood enters kidney via renal artery, leaves via renal vein
  - Blood enters glomerulus via afferent arteriole, leaves via efferent arteriole
- Renal blood flow: volume of blood that reaches kidneys in unit time; determined by pressure gradient (pressure in renal artery - pressure in renal vein) divided by arteriolar resistance
  - ↑ blood pressure → ↑ pressure in renal artery → ↑ renal blood flow
  - ↓ arteriolar resistance → ↑ renal blood flow
- Renal blood flow determines glomerular filtration rate (GFR)
  - ↑ renal blood flow → ↑ GFR
- Regulation of renal blood flow: increasing/decreasing arteriolar resistance
  - Binds to angiotensin receptors along afferent, efferent arterioles → smooth muscle cells contract
  - Efferent arterioles more sensitive to angiotensin II → constrict more → blood builds up in glomerulus → GFR constant
  - High levels of angiotensin II → afferent arterioles constrict equally → ↓ GFR

### Key hormones: increasing arteriolar resistance (decreasing renal blood flow)

- Adrenaline (epinephrine)
  - Secreted by adrenal gland in response to sympathetic stimulation
  - Binds to alpha-1 adrenergic receptors along afferent, efferent arterioles → smooth muscle cells contract
- Angiotensin II
  - Renin produced by juxtaglomerular cells in afferent arteriole → released into blood, becomes angiotensin I in response to low blood pressure
    - converted into angiotensin II by angiotensin-converting enzyme (ACE), synthesized in endothelial cells (esp. in lungs)

- Binds to angiotensin receptors along afferent, efferent arterioles → smooth muscle cells contract
- Efferent arterioles more sensitive to angiotensin II → constrict more → blood builds up in glomerulus → GFR constant
- High levels of angiotensin II → afferent arterioles constrict equally → ↓ GFR

### Key hormones: decreasing arteriolar resistance (increasing renal blood flow)

- Atrial natriuretic peptide
  - Secreted by atria of heart in response to increased cardiac workload
  - Binds to natriuretic peptide receptors along afferent, efferent arterioles → smooth muscle cells relax
- Brain natriuretic peptide
  - Secreted by ventricles of heart in response to increased cardiac workload
  - Binds to natriuretic peptide receptors along afferent, efferent arterioles → smooth muscle cells relax
- Prostaglandins (e.g. prostaglandin E2, I2)
  - Produced by kidneys in response to sympathetic stimulation
  - Binds to prostaglandin receptors along afferent, efferent arterioles → smooth muscle cells relax
  - Prevents kidney damage during sympathetic stimulation
- Dopamine
  - Synthesized in brain, kidneys
  - Binds to dopaminergic receptors along afferent, efferent arterioles → smooth muscle cells relax

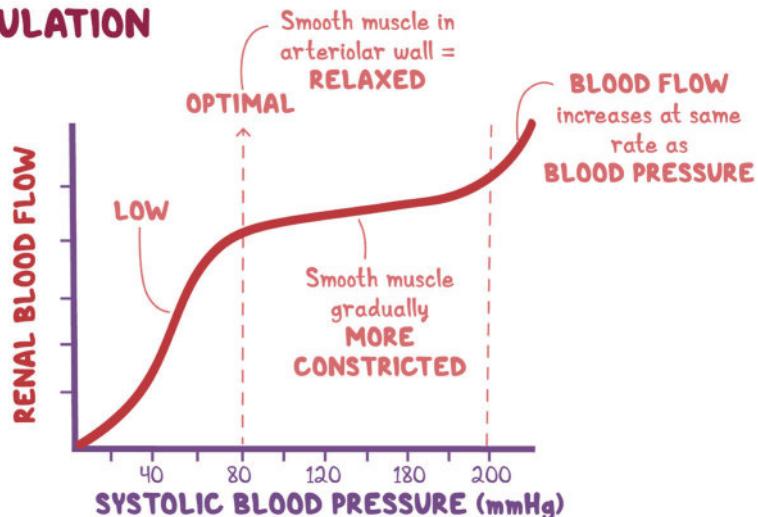
## AUTOREGULATION OF RENAL BLOOD FLOW

- Keeps renal blood flow, GFR constant over range of systemic blood pressures (80–200mmHg)
  - 80mmHg: smooth muscle cells in arterioles completely relaxed, renal blood flow optimal
  - Systemic blood pressure increases → smooth muscle cells contract to maintain optimal renal blood flow

### Mechanisms for autoregulation

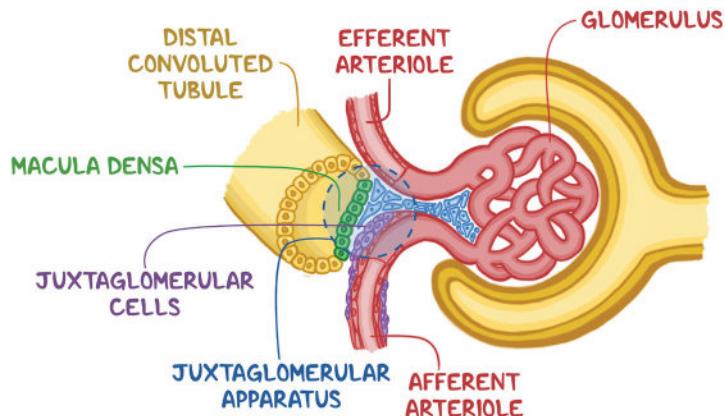
- Myogenic mechanism:** smooth muscle cells in arterioles automatically contract when stretched by high blood pressure (related to increased renal blood flow)
- Tubuloglomerular mechanism:** macula densa cells release adenosine → increases resistance in afferent arteriole when more sodium, chloride ions detected in distal convoluted tubule (related to increased GFR, renal blood flow)

## AUTOREGULATION



**Figure 60.1** Graph displaying the relationship between systolic blood pressure and renal blood flow. The kidneys achieve consistency between 80–200mmHg by adjusting their own arteriole resistance.

## TUBULOGLOMERULAR MECHANISM



**Figure 60.2** The region where the distal convoluted tubule and the afferent arteriole are close to one another is called the juxtaglomerular apparatus. This proximity allows adenosine from the macula densa cells to diffuse over to the juxtaglomerular cells of the afferent arteriole, alerting them to ↑ GFR. This increases arteriolar resistance → ↓ GFR.

# MEASURING RENAL PLASMA FLOW & RENAL BLOOD FLOW

[osms.it/measuring-renal-plasma-blood-flow](https://osms.it/measuring-renal-plasma-blood-flow)

- Fick principle: amount of substance in blood that flows into organ = amount that flows out (if organ doesn't produce/degrade that substance)

## True renal plasma flow

- Add para-aminohippuric acid (PAH) to body (isn't made in body, doesn't affect renal function)
- Fick principle: amount of PAH that flows into kidneys through renal artery = amount of PAH that flows out (through urine, renal veins)
  - Inwards flow of PAH = outwards flow of PAH
  - $[PAH]_{\text{artery}} \times \text{renal plasma flow} = ([PAH]_{\text{vein}} \times \text{renal plasma flow}) + ([PAH]_{\text{urine}} \times \text{urine flow})$
  - $\text{Renal plasma flow} \times ([PAH]_{\text{artery}} - [PAH]_{\text{vein}}) = [PAH]_{\text{urine}} \times \text{urine flow}$
  - $\text{Renal plasma flow} = \frac{[PAH]_{\text{urine}} \times \text{Urine flow}}{[PAH]_{\text{artery}} - [PAH]_{\text{vein}}}$
- Measure concentration of PAH in renal artery/vein, urine; measure urine flow

## Effective renal plasma flow

- Two assumptions
  - 90% of PAH leaves kidneys in urine → 10% leaves in renal vein negligible
  - Concentration of PAH in renal artery = concentration of PAH in any peripheral vein

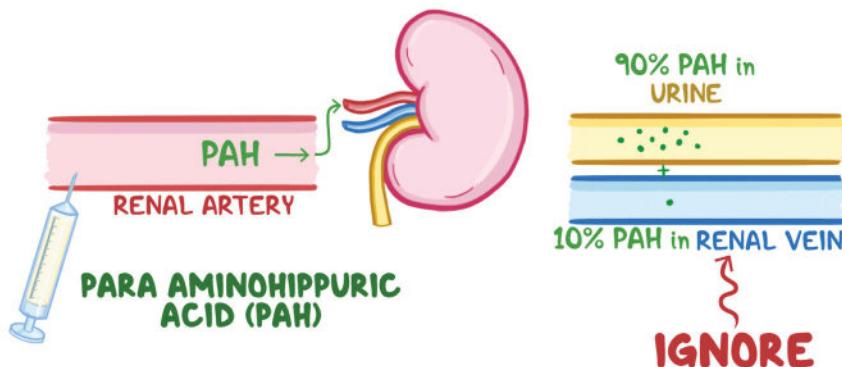
$$\text{Effective renal plasma flow} = \frac{[PAH]_{\text{urine}} \times \text{Urine flow}}{[PAH]}$$

- Effective renal plasma flow = 90% of true renal plasma flow

## Renal blood flow

$$\text{Renal blood flow} = \frac{\text{Renal plasma flow}}{(1 - \text{hematocrit})}$$

- Hematocrit: blood volume fraction occupied by red blood cells (i.e. fraction of blood volume not plasma)



**Figure 60.3** Para-aminohippuric acid (PAH) is used to measure effective renal plasma flow. It is assumed that about 90% of PAH that enters kidneys through renal artery is excreted in urine, and only 10% enters the renal vein → ignore this, assume that effective renal plasma flow = 90% of true renal plasma flow.



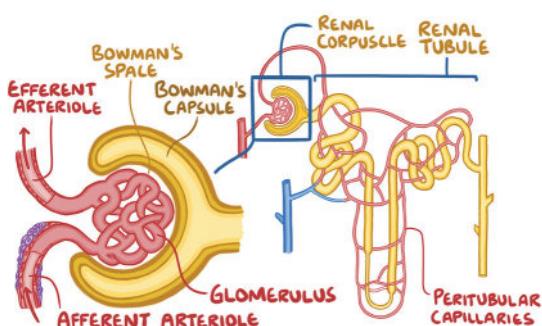
# NOTES

## RENAL ELECTROLYTE REGULATION

### GLOMERULAR FILTRATION

[osms.it/glomerular-filtration](https://osms.it/glomerular-filtration)

- Fluid passage through glomerular filtration barrier; approx. 125mL/min
- **Glomerular filtrate:** fluid that passes through all glomerular filtration barriers
  - Blood minus red blood cells, plasma proteins
- Anything remaining in glomerulus carried away by efferent arteriole
- Starling forces → glomerular filtration
  - Different pressures of fluids, proteins in glomerular capillaries, Bowman's space
- Most filtration occurs at beginning of glomerulus, nearer afferent arteriole



**Figure 61.1** An illustration depicting the glomerulus and its relationship to the rest of the nephron.

#### GLOMERULAR FILTRATION BARRIER

- Capillary walls of glomerulus
  - **Glomerulus:** tuft of capillaries in nephron's renal corpuscle
  - Blood enters glomerulus through afferent arteriole → leaves through efferent arteriole → divides into

peritubular capillaries

- Separates blood in capillaries from Bowman's space, Bowman's capsule
- Allows only water, some solutes to pass into Bowman's space
- **Three layers:** endothelium, basement membrane, epithelium
- **Juxtaglomerular apparatus:** secretes renin

#### Endothelium

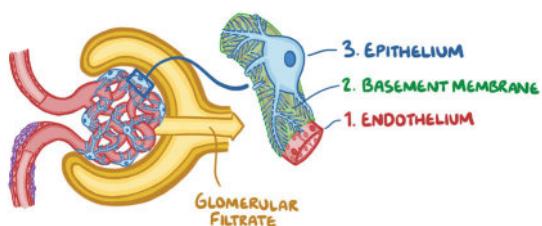
- Comprised of glomerular capillary endothelial cells featuring pores (AKA fenestrations)
- Allows passage of solutes, proteins
- Blocks red blood cell passage

#### Basement membrane

- Gel-like layer with tiny pores
- Blocks plasma protein passage
  - Due to pore size, negative membrane charge

#### Epithelium

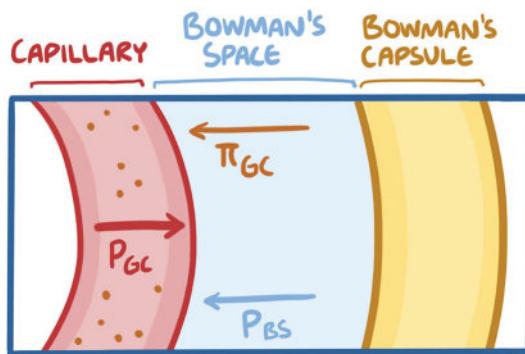
- Comprised of podocytes (wrap around basement membrane)
- Also blocks plasma protein passage



**Figure 61.2** The three layers of the glomerular filtration barrier.

## STARLING FORCES

- Determine fluid movement through capillary wall
- Includes hydrostatic/fluid pressures, oncotic/protein pressures
- Three Starling forces at play in glomerular filtration barrier
  - Hydrostatic pressure of blood in capillary ( $P_{gc}$ )
  - Hydrostatic pressure of filtrate in Bowman's space ( $P_{bs}$ )
  - Oncotic pressure of proteins in capillary ( $\pi_{gc}$ )
- Determines net ultrafiltration pressure of glomerulus:  $P_{uf} = P_{gc} - (P_{bs} + \pi_{gc})$ 
  - Net ultrafiltration pressure  $\downarrow$  along each glomerular capillary—as fluid removed, proteins remain ( $\uparrow \pi_{gc}$ )
  - At filtration equilibrium, net ultrafiltration pressure equals 0 (no fluid filtered)



**Figure 61.3** Illustration depicting the three Starling forces at play in the glomerular filtration barrier.

## GLOMERULAR FILTRATION RATE (GFR)

- Filtrate volume produced by all of body's glomeruli in one minute
- $GFR = P_{uf} \times K_f$  where  $K_f$  is filtration coefficient
  - $K_f$ : indicates capillary's fluid permeability
  - Fenestrations, large surface area  $\rightarrow$  high  $K_f$  for glomerular capillaries
- Depends on all three Starling forces

### Hydrostatic blood pressure in capillary

- Positive relationship
- Afferent arteriole vasoconstriction  $\rightarrow \downarrow$  renal blood flow
  - $\downarrow$  hydrostatic blood pressure in capillary ( $\downarrow GFR$ )
- Afferent arteriole vasodilation  $\rightarrow \uparrow$  renal blood flow
  - $\uparrow$  hydrostatic blood pressure in capillary ( $\uparrow GFR$ )
- Efferent arteriole vasoconstriction  $\rightarrow \uparrow$  fluid in glomerular capillary
  - $\uparrow$  hydrostatic blood pressure in capillary ( $\uparrow GFR$ )
- Efferent arteriole vasodilation  $\rightarrow \downarrow$  fluid in glomerular capillary
  - $\downarrow$  hydrostatic blood pressure in capillary ( $\downarrow GFR$ )

### Hydrostatic filtrate pressure in Bowman's space

- Negative relationship
- Doesn't normally occur
- Urine flow blockage  $\rightarrow$  urine backup (e.g. stone lodged in ureter)
  - $\uparrow$  hydrostatic filtrate pressure in Bowman's space ( $\downarrow GFR$ )

### Oncotic protein pressure in capillary

- Negative relationship
- $\uparrow$  plasma protein concentration can  $\uparrow$  oncotic protein pressure in capillary ( $\downarrow GFR$ )
- $\downarrow$  plasma protein concentration can  $\downarrow$  oncotic protein pressure in capillary ( $\uparrow GFR$ )

## FILTRATION FRACTION (FF)

- Ratio of glomerular filtration rate to renal plasma flow
  - $FF = GFR / RPF$
- Indicates how much fluid reaching kidneys is filtered into renal tubules

# PROXIMAL CONVOLUTED TUBULE

[osms.it/proximal-convoluted-tubule](https://osms.it/proximal-convoluted-tubule)

- First renal tubule segment
- Receives filtrate from renal corpuscle
- Passes filtrate to loop of Henle
- Lined by brush border cells
  - Apical surface faces lumen; lined with microvilli
  - Basolateral surface faces interstitium
- Surrounded by peritubular capillaries → reabsorption, secretion of solutes to/from blood via interstitium
- Reabsorbs  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Cl}^-$ ,  $\text{Mg}^{2+}$  into bloodstream

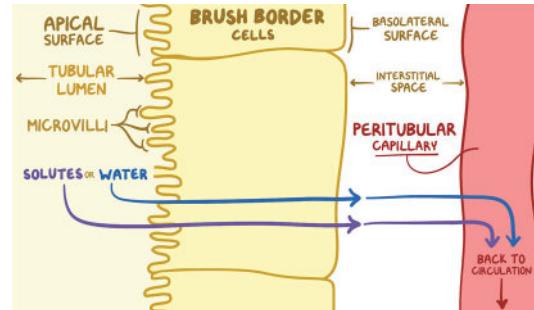
## $\text{Na}^+$ MOVEMENT

### Natural concentration gradient from lumen into cells

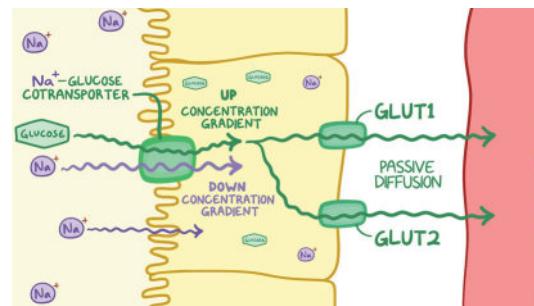
- Cotransporters: use this energy to move other solutes (e.g.  $\text{Na}^+$ -glucose cotransporter)
- $\text{Na}^+/\text{K}^+$  ATPase: pumps  $3\text{Na}^+$  from cell into interstitium,  $2\text{K}^+$  from interstitium into cell
  - Movement against two concentration gradients → ATP required
- $\text{Na}^+/\text{H}^+$  exchanger: pumps  $\text{Na}^+$  from cell into cell,  $\text{H}^+$  from cell into lumen
  - Assists  $\text{HCO}_3^-$  reabsorption by creating  $\text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2$

### Paracellular route

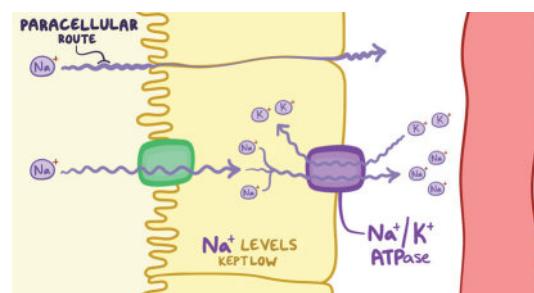
- Leaky tight junctions → some  $\text{Na}^+$  movement between cells
  - ↓ claudin proteins → ↑ permeability
- Urea, water diffuse straight across cells → interstitium
- Glutamine breakdown inside cell →  $\text{NH}_4^+$  (cell → lumen) +  $\text{HCO}_3^-$  (cell → interstitium)
- Organic acids, some medications diffuse directly from capillaries into lumen (e.g. penicillin)



**Figure 61.4** The relationship between the proximal convoluted tubule's brush border cells and a peritubular capillary.



**Figure 61.5** The  $\text{Na}^+$ -glucose cotransporter uses the concentration gradient of  $\text{Na}^+$  to transport glucose against its concentration gradient.



**Figure 61.6**  $\text{Na}^+/\text{K}^+$  ATPase and the paracellular route of  $\text{Na}^+$  movement.

# LOOP OF HENLE

[osms.it/loop-of-henle](http://osms.it/loop-of-henle)

- Receives filtrate from proximal convoluted tubule
- Passes filtrate to distal convoluted tubule
- Composed of descending, thin ascending, thick ascending limbs
- Establishes osmotic gradient; allows varying urine concentration
- Lined by epithelial cells
  - Apical surface faces lumen
  - Basolateral surface faces interstitium
- Surrounded by peritubular capillaries
  - AKA vasa recta
  - Reabsorption, secretion of solutes to/ from blood via interstitium

## Descending limb

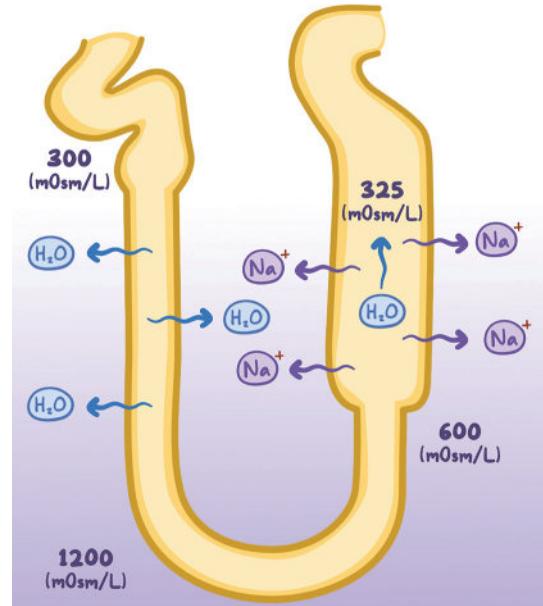
- Filtrate that enters has osmolarity of ~300mOsm/L (interstitial osmolarity)
- Squamous epithelial cells have aquaporins on both surfaces
  - Water moves across cells into interstitium
- Osmolarity ↑ to ~1200mOsm/L at bottom of loop

## Thin ascending limb

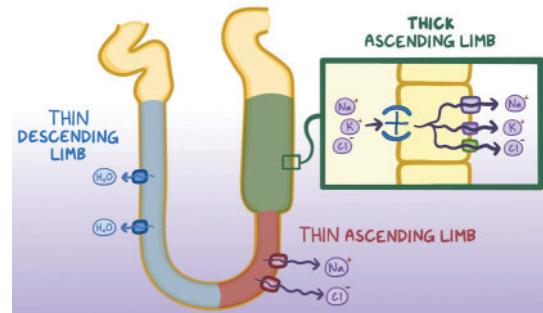
- No aquaporins on thin ascending limb;  $\text{Na}^+$ ,  $\text{Cl}^-$  channels instead
  - Move from lumen into interstitium along concentration gradient
- Osmolarity ↓ to ~600mOsm/L at top of thin loop

## Thick ascending limb

- Cuboidal epithelium in thick ascending limb has  $\text{Na}-\text{K}-2\text{Cl}$  cotransporters
  - $\text{Na}^+$ ,  $\text{K}^+$ ,  $2\text{Cl}^-$  moved from lumen into cells using  $\text{Na}^+$  concentration gradient
- $\text{Na}^+/\text{K}^+$  ATPase works as previously
- $\text{K}^+$ ,  $\text{Cl}^-$  channels → move from cell into interstitium along concentration gradient
- Osmolarity ↓ to ~325mOsm/L at top of thick loop
- **Countercurrent multiplication:** process of creating concentration gradient along loop



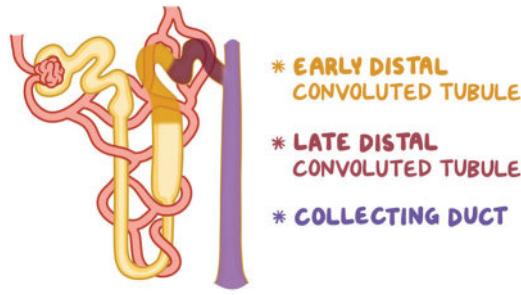
**Figure 61.7** Countercurrent multiplication is the process of creating the concentration gradient along the loop of Henle. It uses ATP.



**Figure 61.8** Aquaporins transport  $\text{H}_2\text{O}$  out of the thin descending limb; channel proteins transport  $\text{Na}^+$  and  $\text{Cl}^-$  out of the thin ascending limb;  $\text{Na}-\text{K}-2\text{Cl}$  cotransporters and channels transport  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  out of the thick ascending limb.

# DISTAL CONVOLUTED TUBULE

[osms.it/distal-convoluted-tubule](http://osms.it/distal-convoluted-tubule)

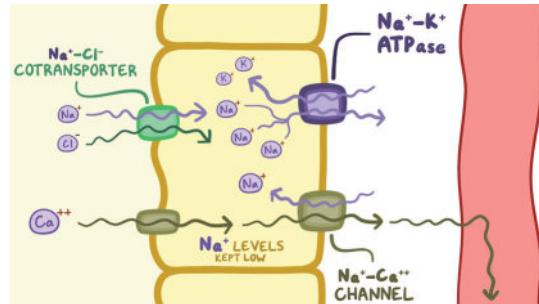


**Figure 61.9** Filtrate passes through the early and late portions of the distal convoluted tubule, then reaches the collecting duct.

- Receives filtrate from loop of Henle
- Passes filtrate to collecting ducts
- Composed of early, late distal convoluted tubules
- Lined by brush border cells
  - Apical surface faces lumen; not lined with microvilli
  - Basolateral surface faces interstitium
- Surrounded by peritubular capillaries → reabsorption, secretion of solutes to/from blood via interstitium

## Early distal convoluted tubule

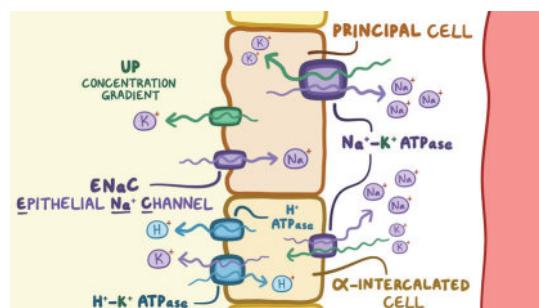
- Impermeable to water
- $\text{Na}^+$ : natural concentration gradient from lumen → cells
- Cotransporters use this energy to move other solutes (e.g.  $\text{Na}^+ \text{-Cl}^-$  cotransporter)
- $\text{Cl}^-$  moves from cells → interstitium through direct channels
- $\text{Ca}^{2+}$  moves across cells → interstitium through direct channels
  - On basolateral surface:  $\text{Na}^+ \text{-Ca}^{2+}$  channel pumps  $\text{Na}^+$  from interstitium → cell,  $\text{Ca}^{2+}$  from cell → interstitium
- $\text{Ca}^{2+}$  reabsorption regulated by parathyroid hormone
  - Creates more  $\text{Na}^+ \text{-Ca}^{2+}$  channels
- $\text{Na}^+ \text{/K}^+$  ATPase works as previously



**Figure 61.10** Illustration of transporters present in the early distal convoluted tubule.

## Late distal convoluted tubule

- → collecting ducts
- Principal cells,  $\alpha$ -intercalated cells dispersed among brush border cells
- Aldosterone upregulates pump synthesis
- Principal cells have
  - $\text{K}^+$  pumps (cell → lumen; uses ATP)
  - $\text{Na}^+$  pumps ("ENaC"; lumen → cell)
  - $\text{Na}^+ \text{/K}^+$  ATPases
- Aquaporin 2 in principal cells allows for water reabsorption in response to antidiuretic hormone
- $\alpha$ -intercalated cells have
  - $\text{H}^+ \text{ATPases}$ ,  $\text{H}^+ \text{-K}^+$  ATPases (movement against concentration gradients → ATP required)
  - $\text{Na}^+ \text{/K}^+$  ATPases



**Figure 61.11** Illustration of transporters present in the late distal convoluted tubule.

# TF/P<sub>x</sub> RATIO & TF/P<sub>INULIN</sub>

[osms.it/TF\\_Px-ratio-TF\\_Pinulin](http://osms.it/TF_Px-ratio-TF_Pinulin)

## [TF/P]<sub>x</sub> RATIO

- Refers to concentration of substance (X) in tubular fluid (TF) and plasma (P) at given point in nephron

### Helps determine substance net secretion/absorption

- $[TF/P]_x = 1$ 
  - X: not reabsorbed/secreted (e.g. freely filtered)
  - X: reabsorbed in proportion to water
    - E.g.  $[TF/P]_{\text{glucose}} = 1$  when glucose, water reabsorbed equally in Bowman's space
- $[TF/P]_x < 1$ 
  - X: reabsorbed more than water
    - E.g.  $[TF/P]_{\text{glucose}} < 1$  when glucose reabsorbed more than water along proximal tubule
- $[TF/P]_x > 1$ 
  - X: reabsorbed less than water/X secreted into tubular fluid
    - E.g.  $[TF/P]_{\text{urea}} > 1$  in presence of antidiuretic hormone (ADH) at collecting ducts (water reabsorbed, not urea)

## [TF/P]<sub>INULIN</sub>

- Inulin (inert substance—neither reabsorbed nor secreted) concentration throughout nephron helps determine how much is reabsorbed

- Inulin concentration will ↑ as water is reabsorbed
- Determined using this formula:

$$\text{Fraction of filtered water reabsorbed} = 1 - \frac{1}{[TF / P]_{\text{inulin}}}$$

- Fraction of filtered water reabsorbed =  $1 - 1/2 = 0.5$  (50%)

- $[TF/P]_{\text{inulin}} = 2$  when 50% of water is reabsorbed (inulin concentration doubles)

- Double ratio formula determines fraction of filtered load of substance in nephron at any point

$$\frac{[TF / P]_x}{[TF / P]_{\text{inulin}}}$$

- If  $[TF/P]_{\text{Na}^+}$  divided by  $[TF/P]_{\text{inulin}} = 0.3$ , then 30% sodium remains in tubule, 70% reabsorbed

# CALCIUM HOMEOSTASIS

[osms.it/calculus-homeostasis](https://osms.it/calculus-homeostasis)

- 1%  $\text{Ca}^{2+}$  found in intracellular fluid (ICF), extracellular fluid (ECF); 99% in bones, teeth
- Functions: cell membrane permeability, blood clotting, muscle contraction
- 40% plasma  $\text{Ca}^{2+}$  bound to protein
  - Unbound is physiologically active
  - Regulated by parathyroid hormone (PTH)

## $\text{Ca}^{2+}$ HANDLING

### Filtration

- Only unbound  $\text{Ca}^{2+}$  (60%) is filtered
- Calculation of  $\text{Ca}^{2+}$  filtered load if total plasma  $\text{Ca}^{2+} = 5\text{mEq/L}$  and  $\text{GFR} = 180\text{L/day}$ 
  - $180 \times 5 \times 0.6 = 540\text{mEq/day}$

### Filtered load reabsorption

- Coupled with  $\text{Na}^+$  reabsorption in proximal tubule, loop of Henle (passively reabsorbed via electrochemical gradient created by  $\text{Na}^+$ , water)
  - 67% reabsorbed by proximal tubule
  - 25% reabsorbed in thick ascending limb of loop of Henle (paracellular route); loop diuretics  $\downarrow$  reabsorption/ $\uparrow$  secretion
- 8% reabsorbed in distal tubule
  - Reabsorptive  $\text{Ca}^{2+}$  regulation site: only nephron segment not coupled with  $\text{Na}^+$  reabsorption; PTH, thiazide diuretics  $\rightarrow \uparrow \text{Ca}^{2+}$  reabsorption (hypocalciuric action)

### Excretion

- < 1%

# MAGNESIUM HOMEOSTASIS

[osms.it/magnesium-homeostasis](https://osms.it/magnesium-homeostasis)

- < 1%  $\text{Mg}^{2+}$  found in ECF; 60% in bones, 20% in skeletal muscle, 19% in soft tissues, remainder found in ICF
- Functions: neuromuscular activity; enzymatic reactions within cells; ATP production;  $\text{Na}^+$ ,  $\text{Ca}^{2+}$  transport across cell membranes
- 20% plasma  $\text{Mg}^{2+}$  bound to protein
  - Unbound is physiologically active

## $\text{Mg}^{2+}$ HANDLING

### Filtration

- Only unbound  $\text{Mg}^{2+}$  (80%) is filtered

### Filtered load reabsorption

- 30% reabsorbed by proximal tubule
- 60% reabsorbed by thick ascending limb of loop of Henle
  - Loop diuretics  $\downarrow$   $\text{Mg}^{2+}$  reabsorption ( $\uparrow$  excretion)
- 5% reabsorbed by distal tubule

### Excretion

- 5%

# PHOSPHATE HOMEOSTASIS

[osms.it/phosphate-homeostasis](https://osms.it/phosphate-homeostasis)

- ICF phosphate (15%) used for DNA, ATP synthesis, other metabolic processes
  - ECF phosphate (<0.5%) serves as buffer for H<sup>+</sup>
  - 85% in bones

## PHOSPHATE HANDLING

### Filtration

- Freely filtered across glomerular capillaries

### Filtered load reabsorption

- 70% reabsorbed by proximal tubule; 15% by proximal straight tubule via Na<sup>+</sup>-phosphate cotransporter in luminal membrane
- Excess phosphate excreted when T<sub>m</sub> (transport maximum) is reached
- PTH inhibits Na<sup>+</sup>-phosphate cotransporter → ↓ phosphate T<sub>m</sub> → phosphaturia

### Excretion

- 15%

# POTASSIUM HOMEOSTASIS

[osms.it/potassium-homeostasis](https://osms.it/potassium-homeostasis)

- Potassium (K<sup>+</sup>): primary intracellular cation
  - Regulates intracellular osmolarity
  - Concentration gradient across cell membrane establishes resting membrane potential, essential for excitable cell function (e.g. myocardium)

## INTERNAL K<sup>+</sup> BALANCE

- Difference between intracellular K<sup>+</sup> concentration (98% of total K<sup>+</sup>), extracellular K<sup>+</sup> concentration (2% of total K<sup>+</sup>) maintained by Na<sup>+</sup>-K<sup>+</sup> ATPase
- K<sup>+</sup> shifts in/out of cells
  - Potentially causes hypo-/hyperkalemia

### Outward K<sup>+</sup> shifts

- ↓ insulin
  - ↓ Na<sup>+</sup>-K<sup>+</sup> ATPase activity → ↓ cellular K<sup>+</sup> uptake
- Cell lysis
  - K<sup>+</sup> released from ICF
- H<sup>+</sup>-K<sup>+</sup> exchange in acidosis
  - ↑ blood H<sup>+</sup> → H<sup>+</sup> leaves cell → K<sup>+</sup> moves from ICF to ECF

- ↑ ECF osmolarity
  - Osmotic gradient causes H<sub>2</sub>O movement out of cells → ↑ intracellular K<sup>+</sup> → diffusion of K<sup>+</sup> from ICF to ECF (H<sub>2</sub>O brings K<sup>+</sup> with it)

- Exercise
  - Cellular ATP stores depleted → K<sup>+</sup> channels open in muscle cell membrane → K<sup>+</sup> moves down concentration gradient to ECF
- α-adrenergic receptor activation
  - Hepatic Ca<sup>2+</sup>-dependent-K<sup>+</sup>-channel activation → K<sup>+</sup> moves from ICF to ECF

### Inward K<sup>+</sup> shifts

- Insulin
  - ↑ Na<sup>+</sup>-K<sup>+</sup> ATPase activity → ↑ cellular K<sup>+</sup> uptake
- H<sup>+</sup>-K<sup>+</sup> exchange in alkalosis
  - ↓ blood H<sup>+</sup> → H<sup>+</sup> leaves cell → K<sup>+</sup> enters cell
- ↓ ECF osmolality
  - Osmotic gradient causes H<sub>2</sub>O movement into cells → ↓ ICF K<sup>+</sup> concentration → diffusion of K<sup>+</sup> from

- ECF to ICF
- $\beta_2$ -adrenergic receptor activation
  - $\uparrow$   $\text{Na}^+ \text{-K}^+$  ATPase activity  $\rightarrow$   $\text{K}^+$  enters cell

## EXTERNAL $\text{K}^+$ BALANCE

- Dietary  $\text{K}^+$  intake = renal excretion of  $\text{K}^+$  via renal mechanisms

## $\text{K}^+$ HANDLING

### Filtration

- Freely filtered across glomerular capillaries

### Filtered load reabsorption

- 67% reabsorbed by proximal tubule (isosmotic fluid reabsorption along with water,  $\text{Na}^+$ )
- 20% reabsorbed by thick ascending limb
  - $\text{K}^+$  reabsorbed without water (impermeable to water) via  $\text{Na}^+ \text{-K}^+ \text{-}2\text{Cl}^-$  cotransporter
  - $\text{K}^+$  diffuses through  $\text{K}^+$  channels across basolateral membrane (reabsorption)/ $\text{K}^+$  diffuses into lumen (no reabsorption)
- Fine-tuning of  $\text{K}^+$  balance at distal tubule, collecting duct depending on current physiological requirements

- Reabsorbed by  $\alpha$ -intercalated cells/secreted by principal cells
  - Dietary  $\text{K}^+$ : high  $\text{K}^+$  diet— $\text{K}^+$  enters cells (via insulin)  $\rightarrow$   $\uparrow$  intracellular  $\text{K}^+$   $\rightarrow$   $\uparrow \text{K}^+$  in principal cells  $\rightarrow$   $\uparrow \text{K}^+$  secretion across luminal membrane  $\rightarrow$   $\uparrow \text{K}^+$  excretion; low  $\text{K}^+$  diet— $\downarrow \text{K}^+$  secretion by principal cell,  $\uparrow \text{K}^+$  reabsorption by  $\alpha$ -intercalated cells
  - Aldosterone effects on principal cells: presence of aldosterone/hyperaldosteronism ( $\uparrow \text{K}^+$  secretion); hypoaldosteronism ( $\downarrow \text{K}^+$  secretion)
- Acid-base imbalance effects on principal cells: alkalosis ( $\uparrow \text{K}^+$  secretion); acidosis ( $\downarrow \text{K}^+$  secretion)
- Diuretic effects on principal cells: loop, thiazide ( $\uparrow \text{K}^+$  secretion);  $\text{K}^+$  sparing (inhibit aldosterone effects  $\rightarrow \downarrow \text{K}^+$  secretion)
- Luminal anions (e.g. sulfate,  $\text{HCO}_3^-$ ) in distal tubule, collecting duct ( $\uparrow$  lumen electronegativity by non-reabsorbable anions  $\rightarrow \uparrow \text{K}^+$  secretion)

### Excretion

- Varies from 1–110% of filtered load

# SODIUM HOMEOSTASIS

[osms.it/sodium-homeostasis](https://osms.it/sodium-homeostasis)

- Sodium ( $\text{Na}^+$ ): primary cation in ECF
  - Determines ECF osmolarity

## $\text{Na}^+$ BALANCE REGULATION

- $\text{Na}^+$  balance ( $\text{Na}^+$  excretion =  $\text{Na}^+$  intake) determines ECF volume, blood volume, blood pressure (BP)
  - Positive  $\text{Na}^+$  balance:  $\uparrow \text{Na}^+$  retained  $\rightarrow \uparrow \text{Na}^+$  in ECF  $\rightarrow$  ECF expansion  $\rightarrow \uparrow$  blood volume,  $\uparrow$  blood pressure
  - Negative  $\text{Na}^+$  balance:  $\uparrow$  excreted, lost in urine  $\rightarrow \downarrow \text{Na}^+$  in ECF  $\rightarrow$  ECF contraction  $\rightarrow \downarrow$  blood volume,  $\downarrow$  blood pressure

### Effective arterial blood volume (EABV)

- ECF volume with arterial system perfuses tissue
- Normal ECF changes  $\rightarrow$  parallel EABV changes (e.g.  $\uparrow$  ECF =  $\uparrow$  EABF)
- Edema: fluid filtered into interstitial space  $\rightarrow \uparrow$  ECF  $\rightarrow \downarrow$  EABV ( $\downarrow$  BP)  $\rightarrow$   $\text{Na}^+$  excretion altered by kidneys (attempts to restore normal EABF, BP)

### $\text{Na}^+$ excretion regulation ( $\uparrow/\downarrow$ ) mechanisms

- Sympathetic nervous system activity
  - Baroreceptors detect  $\downarrow$  BP  $\rightarrow$  sympathetic nervous system activation  $\rightarrow$  afferent arteriole vasoconstriction,  $\uparrow$

$\text{Na}^+$  reabsorption by proximal tubule

- **Natriuretic hormones:** respond to  $\uparrow$  ECF volume  $\rightarrow \uparrow$  GFR, natriuresis (renal  $\text{Na}^+$ , water excretion)  $\rightarrow \downarrow$  ECF
  - Atrial natriuretic peptide (ANP): volume receptors detect atrial wall stretching  $\rightarrow$  ANP secreted by cells in atria
  - Brain natriuretic peptide (BNP): volume receptors in ventricles detect stretching  $\rightarrow$  BNP secreted by cells in ventricles
  - Urodilatin: synthesized in distal tubular cells  $\rightarrow$  paracrine actions on kidney
- Peritubular Starling forces
  - $\uparrow$  ECF volume  $\rightarrow$  ECF dilution,  $\downarrow \pi_c$  (capillary oncotic pressure);  $\downarrow$  proximal tubule  $\text{Na}^+$  reabsorption
  - $\downarrow$  ECF volume  $\rightarrow$   $\uparrow$  ECF concentration,  $\uparrow \pi_c$ ;  $\uparrow$  proximal tubule  $\text{Na}^+$  reabsorption
- **Renin-angiotensin-aldosterone system (RAAS):**  $\downarrow$  arterial blood pressure (BP)  $\rightarrow$   $\downarrow$  renal perfusion  $\rightarrow$  juxtaglomerular apparatus secretes renin  $\rightarrow$  angiotensinogen (plasma protein) converted to angiotensin I  $\rightarrow$  angiotensin I converted to angiotensin II  $\rightarrow$  adrenal cortex secretes aldosterone, vasoconstriction  $\rightarrow \uparrow \text{Na}^+, \text{Cl}^-$ , water reabsorption  $\rightarrow \uparrow$  ECF volume,  $\uparrow$  BP

#### Excess $\text{Na}^+$ intake response

- $\rightarrow \text{Na}^+$  ECF distribution  $\rightarrow \uparrow$  ECF,  $\uparrow$  EABV,  $\downarrow \pi_c \rightarrow \downarrow$  sympathetic activity,  $\uparrow$  ANP (and other natriuretic hormones),  $\downarrow$  RAAS  $\rightarrow \uparrow \text{Na}^+$  excretion

#### Decreased $\text{Na}^+$ intake response

- $\rightarrow \downarrow$  ECF,  $\downarrow$  EABV,  $\uparrow \pi_c \rightarrow \uparrow$  sympathetic activity,  $\downarrow$  ANP (and other natriuretic hormones),  $\uparrow$  RAAS  $\rightarrow \downarrow \text{Na}^+$  excretion

## $\text{Na}^+$ HANDLING

### Filtration

- Freely filtered across glomerular capillaries

### Filtered load reabsorption

- 67% reabsorbed by proximal tubule
  - Isosmotic reabsorption of water,  $\text{Na}^+$
  - Water reabsorption coupled with  $\text{Na}^+$  reabsorption ( $[\text{TF}/\text{P}]_{\text{Na}^+} = 1$ )
- 25% reabsorbed by thick ascending limb
  - $\text{Na}^+$  reabsorbed without water (impermeable to water) via  $\text{Na}^+-\text{K}^+-2\text{Cl}^-$  cotransporter
  - Influenced by ADH, loop diuretics
- 5% reabsorbed by early distal convoluted tubule
  - $\text{Na}^+$  reabsorbed without water (impermeable to water) via  $\text{Na}^+-2\text{Cl}^-$  cotransporter
  - Influenced by thiazide diuretics
- 3% reabsorbed by late distal convoluted tubule
  - Influenced by aldosterone

### Excretion

- $< 1\%$  excreted (99% net  $\text{Na}^+$  reabsorption)



# NOTES

## RENAL REABSORPTION & SECRETION

# TUBULAR REABSORPTION & SECRETION

[osms.it/tubular-reabsorption-secretion](http://osms.it/tubular-reabsorption-secretion)

- Blood chemistry balanced, urine formed through glomerular filtration, tubular reabsorption, secretion
  - Filtered blood continues through glomerulus, substances reabsorbed/ secreted according to body's needs
  - Entire plasma volume filtered approx. 60 times/day

## REABSORPTION

- Retention of substances contained in filtrate back into peritubular capillary blood

### Filtration only/no reabsorption

- Occurs with: products of metabolism (e.g. urea, creatinine), foreign substances (e.g. drugs)

### Filtration with partial reabsorption

- Electrolytes (e.g. sodium, bicarbonate) easily reabsorbed, may be partially reabsorbed, secreted

### Filtration with complete reabsorption

- Nutritional substances (e.g. glucose, amino acids) completely reabsorbed

## SECRETION

- Substances not reabsorbed (e.g. organic acids), secreted into tubular fluid to become urine

# TUBULAR REABSORPTION OF GLUCOSE

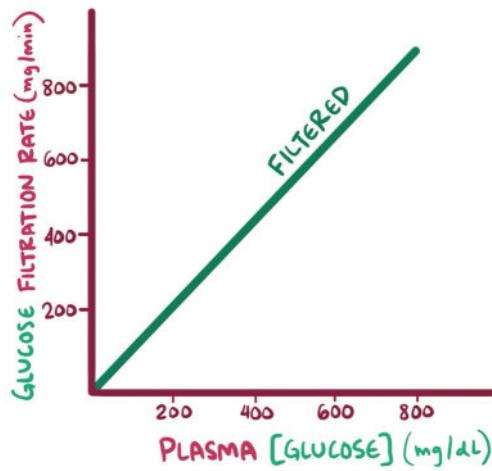
[osms.it/tubular-reabsorption-glucose](http://osms.it/tubular-reabsorption-glucose)

- Filtration rate of glucose: mass of glucose filtered through kidneys per day (depends on plasma glucose concentration)
- Kidney filtrate passes through renal tubules in nephron before becoming urine
  - Tubules lined by brush border cells with apical surface (lined with microvilli),

basolateral surface; peritubular capillaries surround tubules

## GLUCOSE REABSORPTION

- Occurs primarily in proximal convoluted tubule



**Figure 62.1** Graph showing glucose filtration rate as a function of plasma glucose. As the plasma glucose concentration increases, the filtered load of glucose increases linearly.

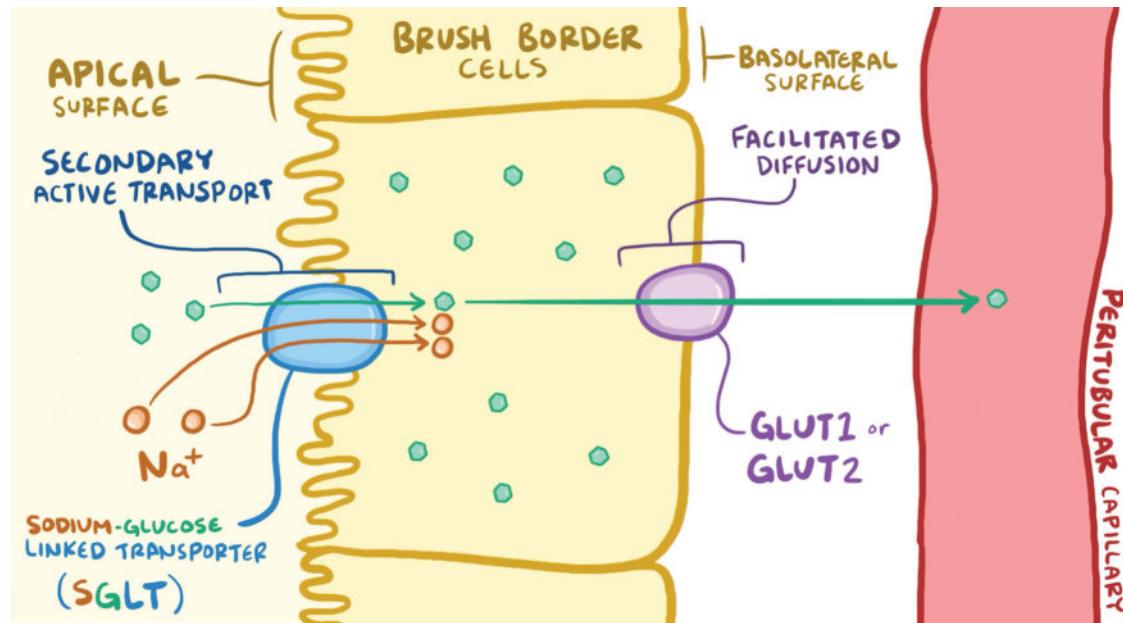
#### Two steps

- 1. Glucose moves across apical membrane into brush border cells
  - Glucose concentration inside cells typically higher than outside → sodium-glucose linked transporters use energy from existing sodium concentration

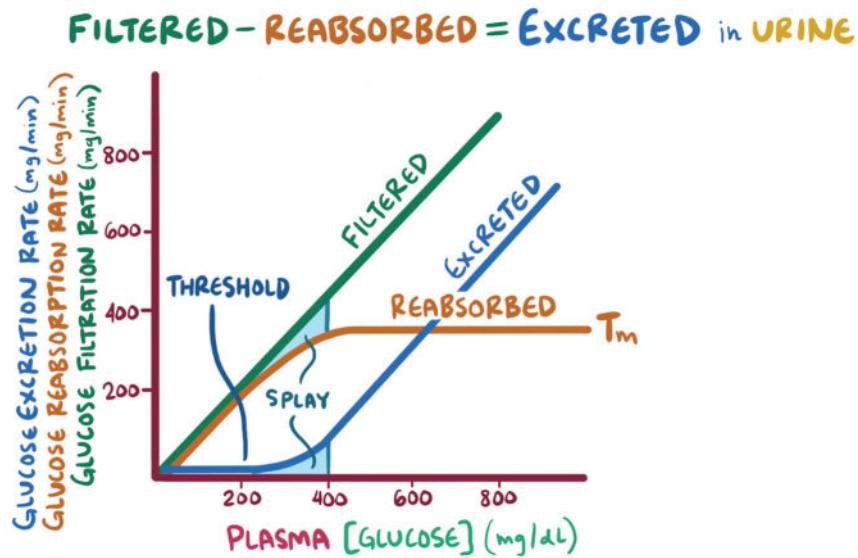
- gradient to move glucose against concentration gradient
- 2. Glucose diffuses across basolateral membrane into peritubular capillaries (facilitated diffusion with GLUT1/GLUT2)
  - Normal plasma glucose levels ( $< 200\text{mg/dL}$ ): glucose reabsorption matches filtration
  - High plasma glucose levels ( $> 200\text{mg/dL}$ ): limited number of glucose transporter proteins prevents reabsorption from keeping up with filtration
  - Higher glucose levels ( $> 350\text{mg/dL}$ ): glucose transporter proteins fully saturated, reabsorption cannot go faster; transport maximum ( $T_m$ )

#### GLUCOSE EXCRETION

- Excess glucose excreted in urine
  - Threshold: plasma glucose level at which glucose excretion starts
  - Splay: initial, nonlinear increase in urine excretion
- Glycosuria (glucose excreted in urine) may be caused by diabetes mellitus ( $\downarrow$  insulin →  $\uparrow$  plasma glucose)/hormonal changes during pregnancy ( $\uparrow$  renal blood flow →  $\uparrow$  glucose filtration)



**Figure 62.12** An illustration depicting the two steps of glucose reabsorption that occur in the proximal convoluted tubule: transport across the apical membrane of the brush border cells, followed by transport across the basolateral membrane of the brush border cells by GLUT1 or GLUT2.

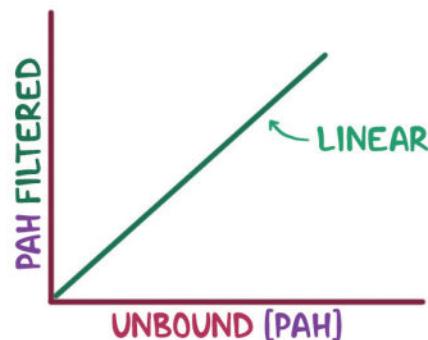


**Figure 62.2** A graph showing glucose reabsorption and secretion rates as a function of plasma glucose. The glucose reabsorption line plateaus because the plasma [glucose] has been reached where all the GLUT1/GLUT2 transporters in virtually all the nephrons are occupied by glucose molecules.

## TUBULAR SECRETION OF PARA-AMINOHIPPURIC ACID (PAH)

[osms.it/tubular-secretion-PAH](http://osms.it/tubular-secretion-PAH)

- Body's entire plasma volume, including some para-aminohippuric acid (PAH), filtered approx. 60 times/day
  - PAH: organic acid; approx. 90% bound to plasma proteins, cannot be filtered
  - Filtration rate of PAH: mass of PAH filtered through kidneys per day (depends on plasma concentration of unbound PAH)
- Kidney filtrate passes through renal tubules in nephron before becoming urine
  - Tubules lined by brush border cells with apical surface (lined with microvilli), basolateral surface; peritubular capillaries surround tubules



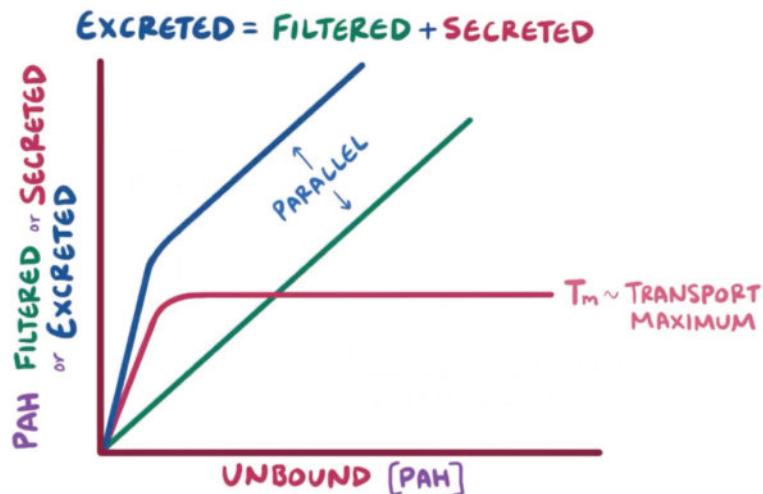
**Figure 62.3** Graph showing PAH filtration rate as a function of unbound plasma PAH.

- No renal reabsorption of PAH
- PAH secretion occurs primarily in proximal convoluted tubule
  - Special carrier proteins on basolateral membrane transport PAH, other organic anions directly into tubules
- Low plasma PAH levels: PAH secretion increases linearly with PAH concentration
- Higher plasma PAH levels: limited number of carrier proteins prevents secretion from increasing, even with increasing PAH concentration ( $T_m$ ) → some PAH left behind in peritubular capillaries
- Both filtered, secreted PAH excreted in urine

#### Using PAH to estimate renal plasma flow (RPF)

- Fick's principle:  $\text{PAH}_{\text{entering}} = \text{PAH}_{\text{leaving}}$
- PAH enters kidney via renal artery; leaves via renal vein/urine

- Low PAH concentrations ( $< T_m$ ): all PAH leaves via urine
- $\text{PAH}_{\text{entering}} = \text{PAH}_{\text{excreted}}$
- $[\text{PAH}]_{\text{R.A.}} \times \text{RPF} = [\text{PAH}]_{\text{urine}} \times \text{urine flow rate (UFR)}$ 
  - Renal, urine concentrations of PAH both measured in milligrams per millilitre
  - RPF, urine flow rate (UFR) both measured in liters per minute
- $\text{RPF} = ([\text{PAH}]_{\text{urine}} \times \text{UFR}) / [\text{PAH}]_{\text{R.A.}}$  (milliliters of plasma per minute)
- Some PAH may remain in renal vein → estimate usually accurate to 10% of true RPF
- Renal plasma flow can be used to calculate renal blood flow (RBF)
  - $\text{RBF} = \text{RPF} / (1 - \text{Hct})$
  - Hematocrit (Hct): volume of blood occupied by red blood cells (RBCs)



**Figure 62.4** Graph showing PAH secretion and excretion rates as a function of plasma PAH.

# UREA RECYCLING

[osms.it/urea-recycling](https://osms.it/urea-recycling)

- Urea: one of body's waste products (byproduct of amino acid breakdown)
- Freely filtered across kidneys' glomerular capillaries, travels through renal tubule
- Part of reabsorbed urea secreted back into loop of Henle → "urea recycling"
  - Helps establish corticopapillary gradient (reabsorbs water from kidneys back into blood)

## Four steps to urea recycling

- 50% of urea reabsorbed by simple diffusion in proximal convoluted tubule (leaving behind 50% of initial urea), together with water
- Urea from medullary interstitium secreted back into tubule in descending limb of loop

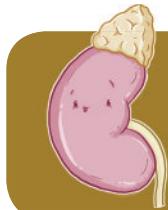
- of Henle (resulting in 110% of initial urea in bottom of loop of Henle)
  - Occurs due to higher urea concentration in medullary interstitium
- Ascending limb of loop of Henle, early distal convoluted tubule impenetrable to urea, water (urea levels stay same)
- 70% of initial urea reabsorbed into interstitium in late distal convoluted tubule, cortical, outer medullary collecting ducts (leaving behind 40% of initial urea to be excreted in urine)
  - Occurs due to antidiuretic hormone (ADH)-induced water reabsorption through aquaporins → concentration gradient of urea towards interstitium

# WEAK ACIDS & BASES - NON-IONIC DIFFUSION

[osms.it/non-ionic\\_diffusion](https://osms.it/non-ionic_diffusion)

- Many substances secreted by proximal tubule weak acids/bases
- Exist in uncharged (nonionic)/charged (ionized) forms; amount depends on pH of tubular fluid
  - Urine with low pH: nonionic forms dominate
  - Urine with higher pH: ionized forms dominate

- Nonionic weak acids, bases lipid soluble, able to passively diffuse back into blood from urine
- Ionized weak acids, bases not lipid soluble, remain in tubular fluid to be excreted
- Excretion of unwanted substances, toxins accomplished by manipulating urine pH, promoting ionization



# NOTES

## WATER REGULATION

### OSMOREGULATION

[osms.it/osmoregulation](http://osms.it/osmoregulation)

- Regulation of body fluid solute concentrations
  - Concentrations measured in osmolarity (mOsm/L)
  - Osmole: single ion in solution

#### BLOOD PLASMA OSMOLARITY

- 290–300 mOsm/L
- Main components
  - Sodium, glucose, urea
- Osmolarity =  $2[\text{Na}^+] + [\text{Glucose}]/18 + [\text{BUN}]/2.8$ 
  - Glucose, blood urea nitrogen (BUN) measured in mg/dL

#### HYDRATION

- Changes in hydration affect plasma osmolarity, blood pressure
  - Osmoreceptors in supraoptic nuclei of anterior hypothalamus detect changes in plasma osmolarity
  - Baroreceptors in cardiovascular system detect changes in blood pressure
- Osmoreceptors, baroreceptors regulate production of ADH in hypothalamus

#### Overhydration

- Plasma osmolarity decreases, blood pressure increases
- Osmoreceptors, baroreceptors fire less, stimulating less ADH production
- Less/no water reabsorbed from kidneys

#### Dehydration

- Plasma osmolarity increases, blood pressure decreases
- Osmoreceptors, baroreceptors fire more, stimulating greater ADH production
- More water reabsorbed from kidneys

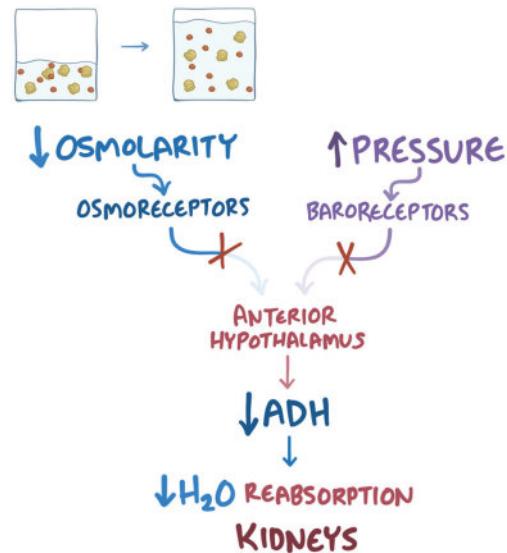


Figure 63.1 Body response to overhydration.

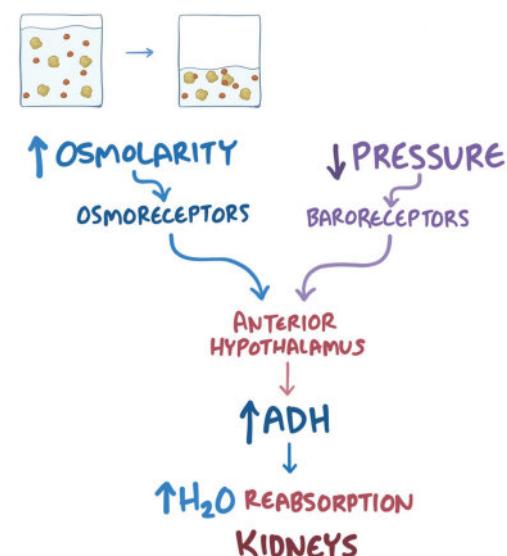


Figure 63.2 Body response to dehydration.

# KIDNEY COUNTERCURRENT MULTIPLICATION

[osms.it/kidney-countercurrent-multiplication](https://osms.it/kidney-countercurrent-multiplication)

- Concentration gradient (corticopapillary gradient) established in medulla of kidney

## TWO STEPS

- In nephron loop of Henle

### Single effect

- Takes advantage of ascending limb being impermeable to water
- Sodium, potassium, chloride ions enter tubule cells along ascending limb via  $\text{Na}^+ \text{K}^+ \text{2Cl}^-$  cotransporters on apical surface
- Na/K ATPase pumps sodium ions through basolateral surface into interstitium in exchange for potassium ions
- Potassium, chloride ions enter interstitium
- Osmosis → ions in interstitium diffuse into descending limb → fluid concentration

### Flow of fluid

- Uses new fluid to distribute ions
- New fluid pushes existing fluid around loop
- Concentrated fluid (previously in descending limb) enters ascending limb

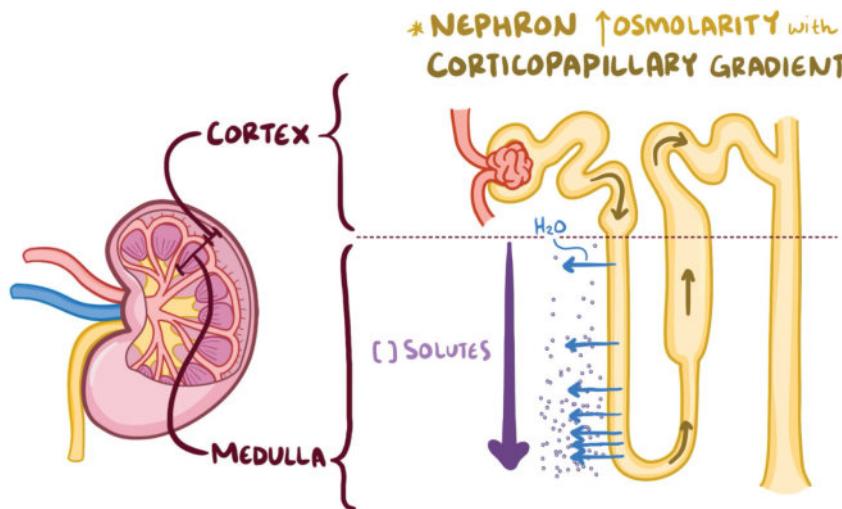
- Single effect recurs, fluid more concentrated at bottom of ascending limb → more ions enter interstitium at bottom

### Two steps repeat

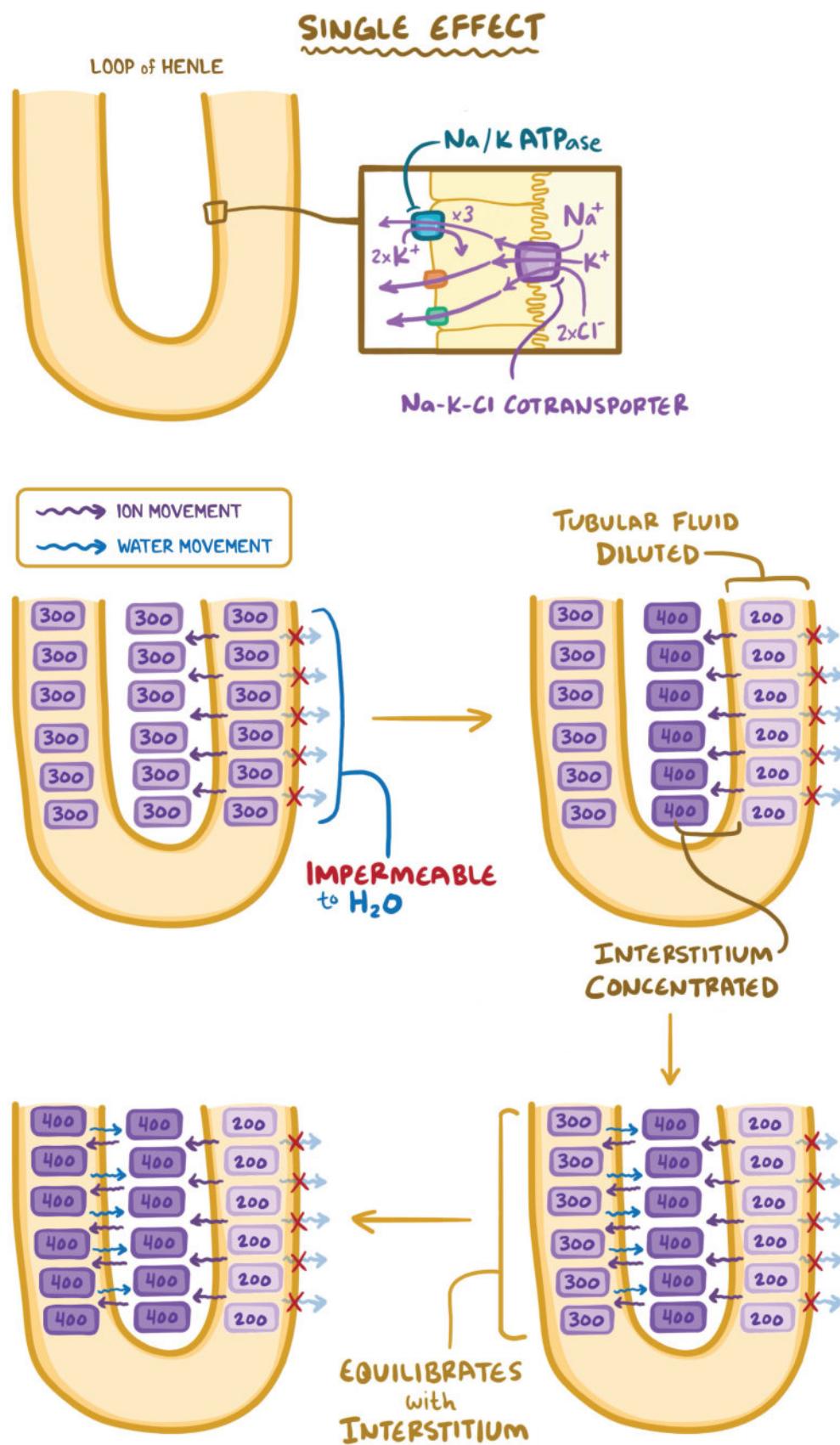
- Form concentration gradient of 1200mOsm/L at inner medulla, 300mOsm/L at outer cortex

## COUNTERCURRENT EXCHANGE

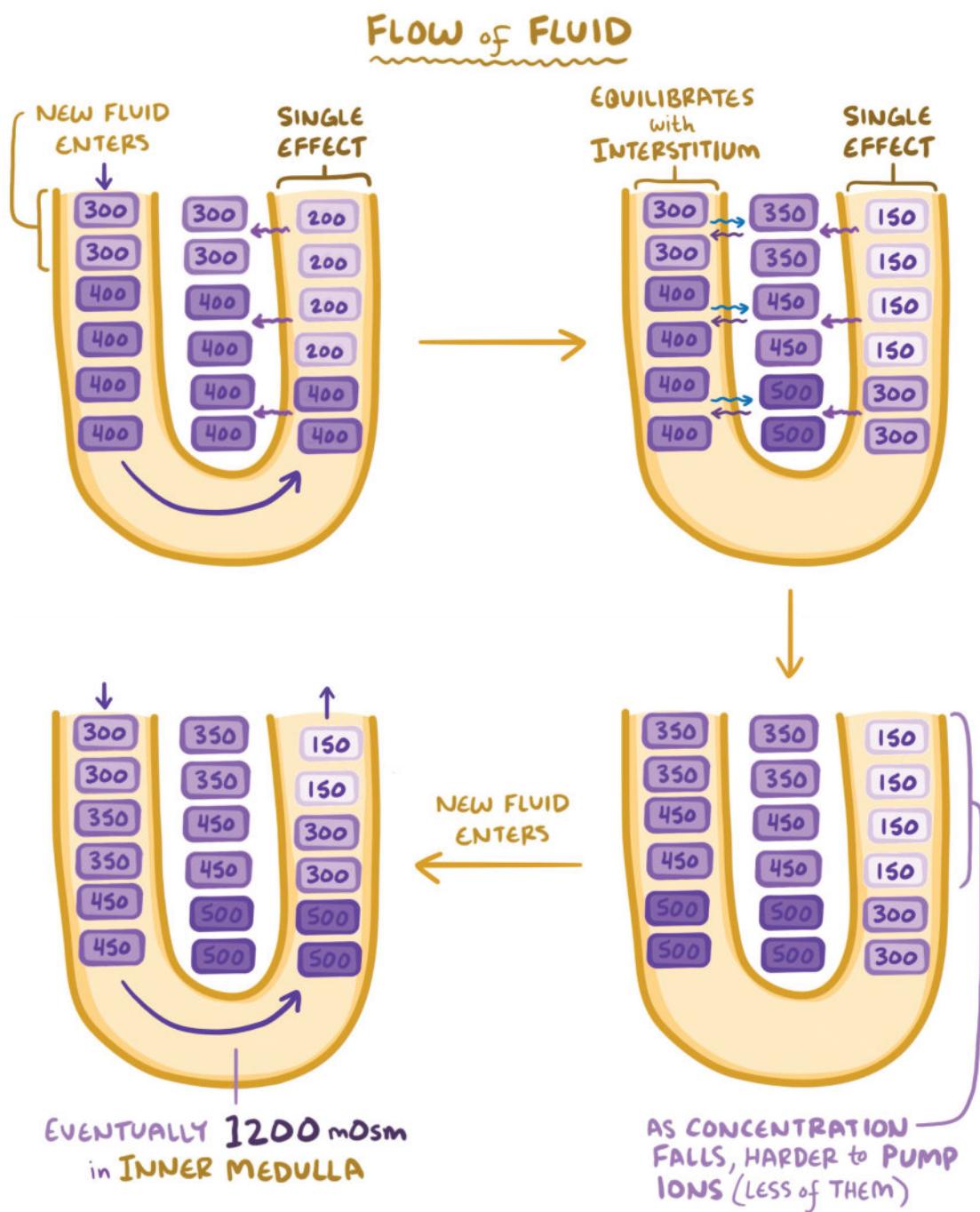
- Important process for corticopapillary gradient
- Peritubular capillaries permeable to water, solutes
- Osmosis would destroy corticopapillary gradient if capillaries only ran along descending limb → peritubular capillaries run down descending limb, up ascending limb → allow extra solutes pulled from interstitium near descending limb to return to interstitium near ascending limb (as corticopapillary gradient decreases) → water diffused from capillary into interstitium returns



**Figure 63.3** To increase urine osmolarity, nephrons rely on the corticopapillary gradient. The interstitium becomes increasingly hypertonic relative to the lumen of the tubule.

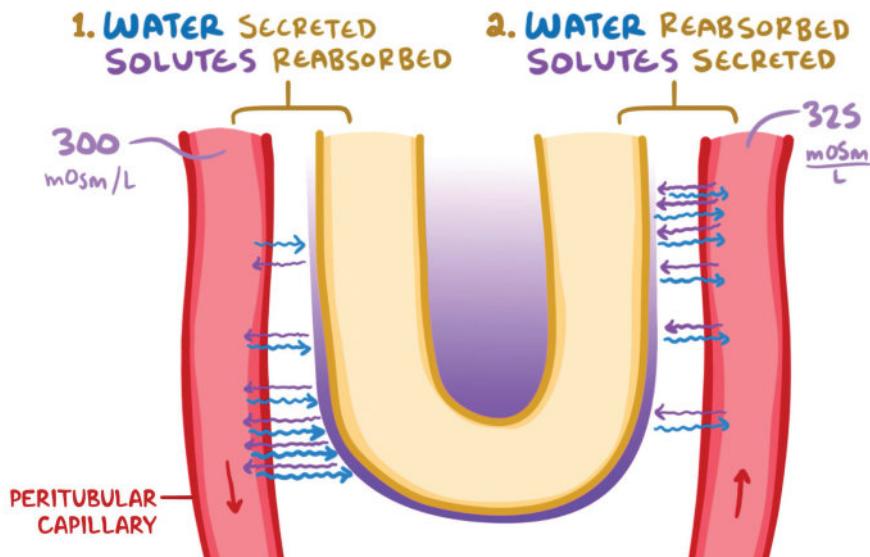


**Figure 63.4** Single effect: ions leave ascending limb, but water can't follow → urine osmolarity in ascending limb decreases. Water can pass through descending limb → descending limb equilibrates with the interstitium. Numeric values = number of mOsm/L (e.g. 300 = 300mOsm/L).



**Figure 63.5** Flow of new fluid into the loop of Henle + single effect = corticopapillary gradient.  
Numeric values = number of mOsm/L (e.g. 300 = 300mOsm/L).

## COUNTERCURRENT EXCHANGE



**Figure 63.6** Countercurrent exchange: peritubular capillaries run down the descending limb and up the ascending limb to maintain the corticopapillary gradient.

# ANTIDIURETIC HORMONE

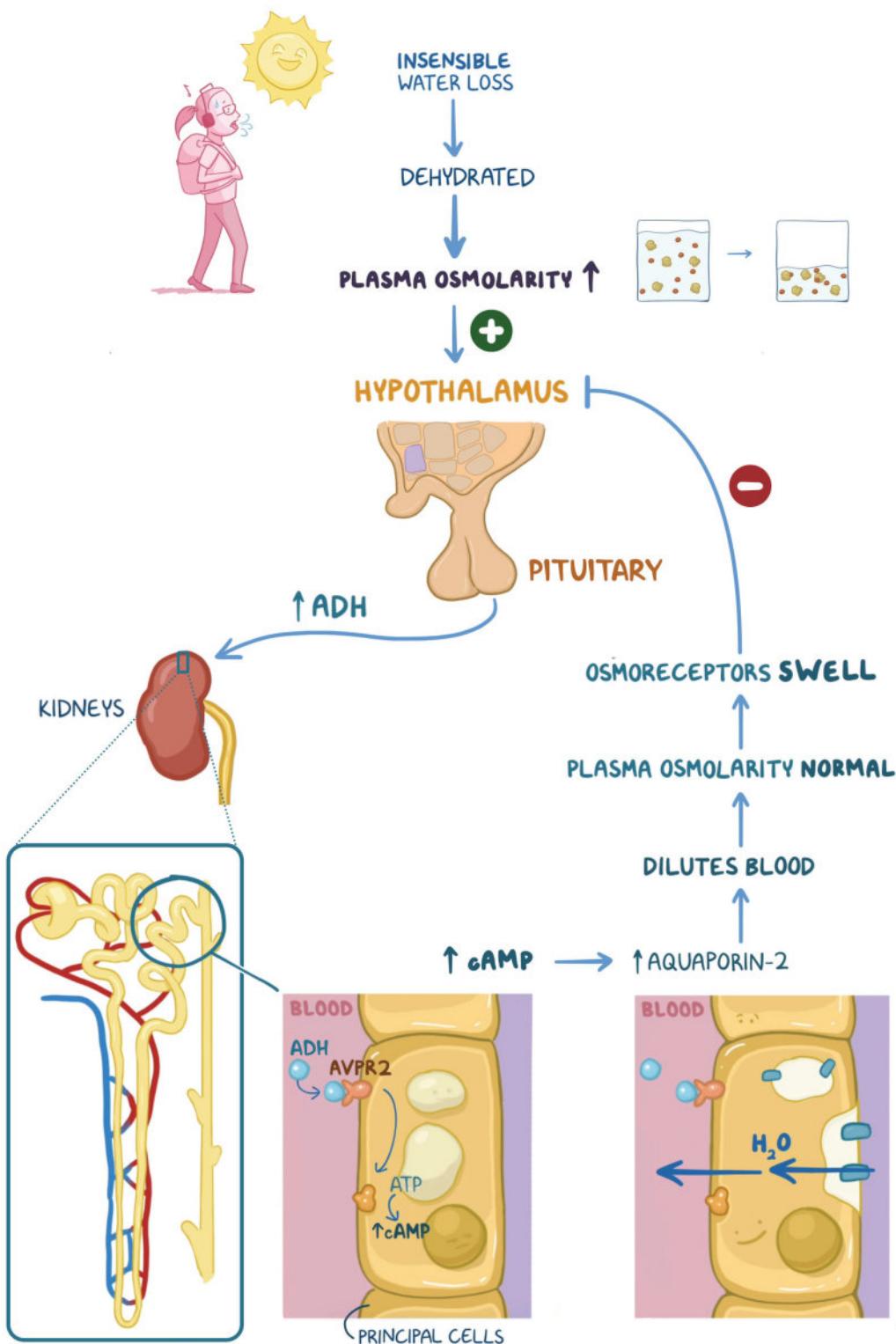
[osms.it/antidiuretic-hormone](https://osms.it/antidiuretic-hormone)

- Peptide hormone prevents excessive urine production by reabsorbing water from kidneys
- Allows body to control amount of fluid retention
- Antidiuretic hormone (ADH) production triggered by osmoreceptors in supraoptic nuclei of anterior hypothalamus, baroreceptors in cardiovascular system; stimulated by angiotensin II
- ADH (AKA vasopressin) also causes smooth muscles cells in arteries to constrict

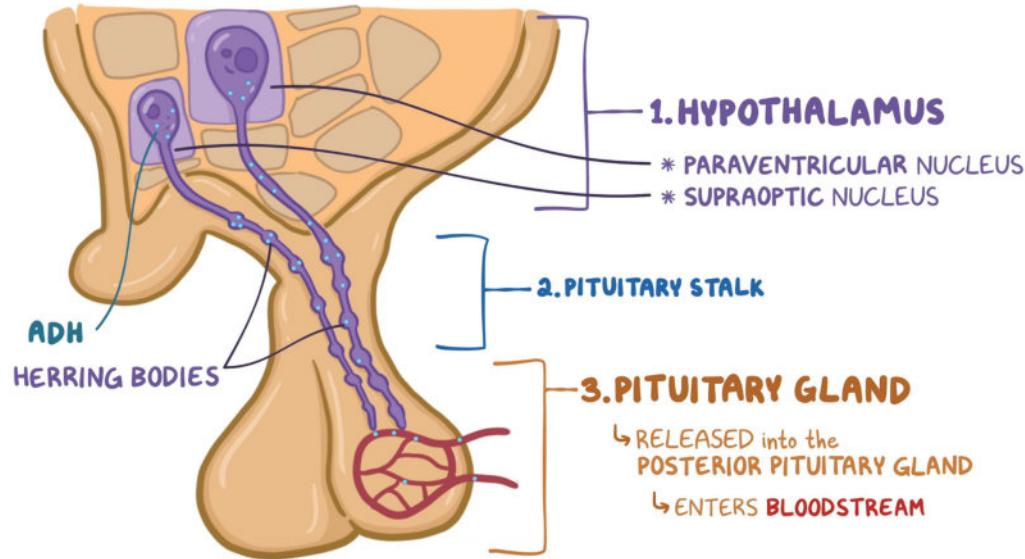
- capillaries → binds to V2 receptors (AVPR2) on basolateral membrane of principal cells (along collecting ducts of nephrons)
- AVPR2 signals adenylyl cyclase to convert ATP to cAMP → cell produces water protein channels called aquaporins, opens existing aquaporins (in apical membrane) of principal cells → osmosis pulls water from lumen of ducts into interstitium, reabsorbed into circulation

## ADH PATHWAY

- Produced in paraventricular, supraoptic neurons of hypothalamus → travels down axons through infundibulum → stored in posterior pituitary gland
- When needed, released into blood, travels to kidneys
- In kidneys, travels through peritubular



**Figure 63.7** The ADH pathway. Increased plasma osmolarity triggers ADH release from the posterior pituitary. ADH acts on the principal cells of the distal convoluted tubule, collecting ducts → ↑ aquaporins in the cell membranes → ↑ water reabsorption → ↓ plasma osmolarity.



**Figure 63.8** ADH is produced in the paraventricular and supraoptic nuclei in the hypothalamus, stored in Herring bodies in paraventricular and supraoptic neurons, and released into the bloodstream from the posterior pituitary gland.

## FREE WATER CLEARANCE

[osms.it/free-water-clearance](https://osms.it/free-water-clearance)

- Free water: water without solutes
- Free water clearance: rate at which kidneys filter free water out of blood plasma

### PATHWAY

- Free water filtered out of blood plasma in ascending limbs, distal convoluted tubules of kidneys' nephrons, solutes removed
- Free water reabsorbed into circulation through aquaporin protein channels in collecting ducts

### ANTIDIURETIC HORMONE EFFECTS

- High amounts of ADH → lots of free water reabsorbed, retained (negative free water clearance) → hyperosmotic urine
- Low amounts of ADH → little free water reabsorbed, excreted (positive free water clearance) → hypoosmotic urine
- Free water clearance, 0: excreted urine has same osmolarity as blood plasma
- $C_{H_2O} = V - (U_{osm}/P_{osm})V$ 
  - $V$ : urine flow rate (mL/min)
  - $U_{osm}$ : urine osmolarity
  - $P_{osm}$ : plasma osmolarity



# NOTES

## FEMALE REPRODUCTIVE SYSTEM

# ANATOMY & PHYSIOLOGY OF THE FEMALE REPRODUCTIVE SYSTEM

[osms.it/female-reproductive-system](http://osms.it/female-reproductive-system)

### EXTERNAL ORGANS

- Labia minora, labia majora, clitoris (erectile tissue), mons pubis
  - Vulvar vestibule: space between labia minora; includes vaginal, urethral opening

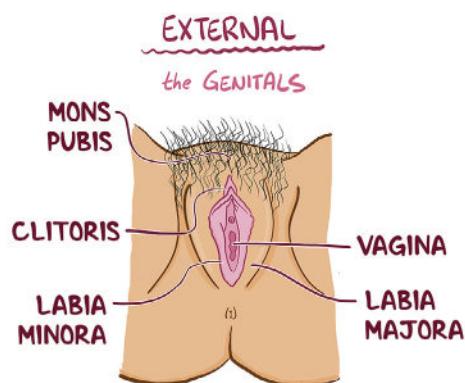
### INTERNAL ORGANS

#### Ovaries (female gonads)

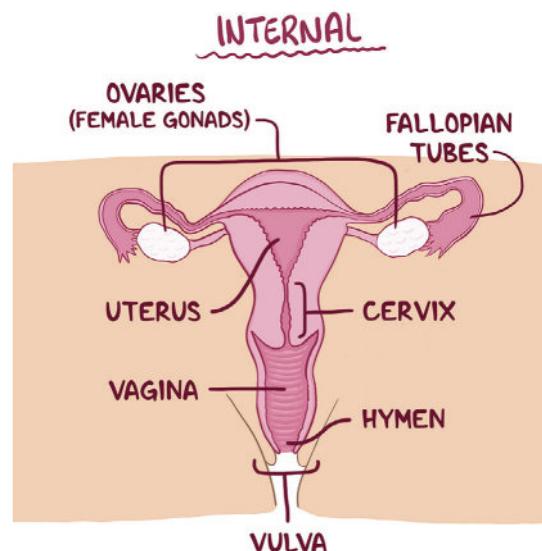
- Epithelial, follicular, granulosa, theca, oocyte cells
- Secrete estrogen, progesterone
- Located superior, lateral to uterus
- Held in place by ovarian, broad, suspensory ligaments
  - Suspensory ligaments contain ovarian artery, vein, nerve plexus
- Made up of outer cortex, inner medulla
  - Cortex contains ovarian follicles (oocytes surrounded by granulosa cells); medulla contains blood vessels, nerves

#### Fallopian tubes (uterine tubes)

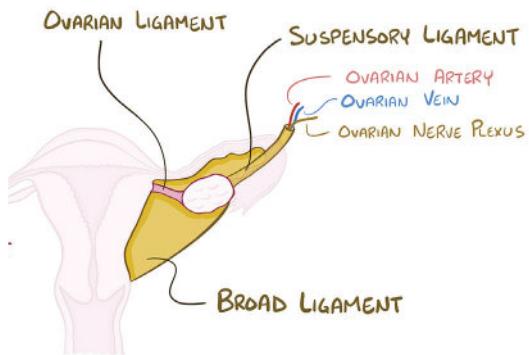
- Two tubes, each associated with one ovary, on side of uterus
- Flattened mesothelial, epithelial, secretory, intercalary cells
- Fimbriae around ovary → infundibulum → ampulla (where fertilization most commonly occurs) → isthmus region opens into uterine cavity
- Covered by peritoneum, supported by mesosalpinx
- Lined with smooth muscle, cilia to sweep zygote towards uterus; inner mucosa provides nutrients for oocyte



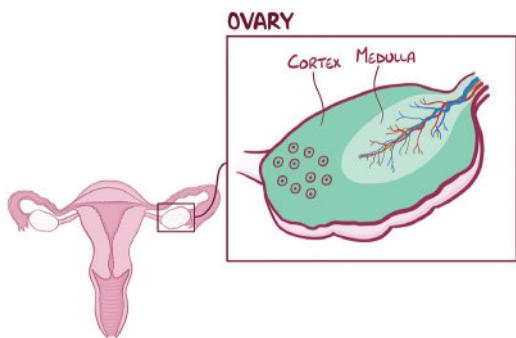
**Figure 8.1** External organs of the female reproductive system.



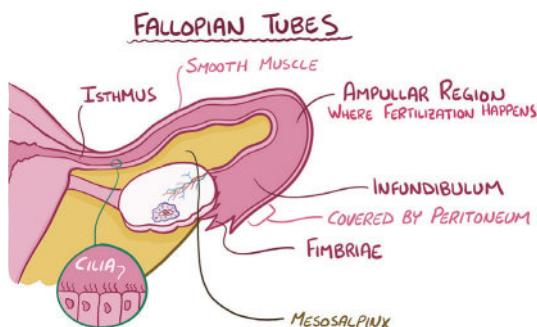
**Figure 8.2** Internal organs of the female reproductive system.



**Figure 8.3** The locations of the ovarian, suspensory, and broad ligaments.



**Figure 8.4** Outer cortex of ovary containing follicles and inner medulla containing blood vessels, nerves.



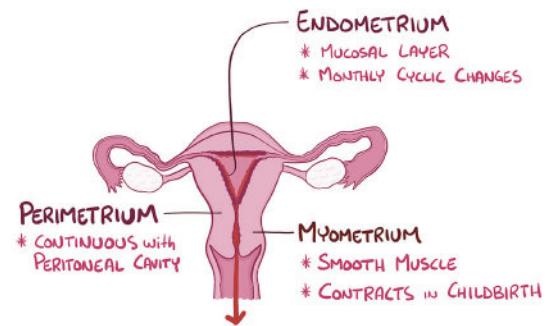
**Figure 8.5** Features of the fallopian tubes.

## Uterus

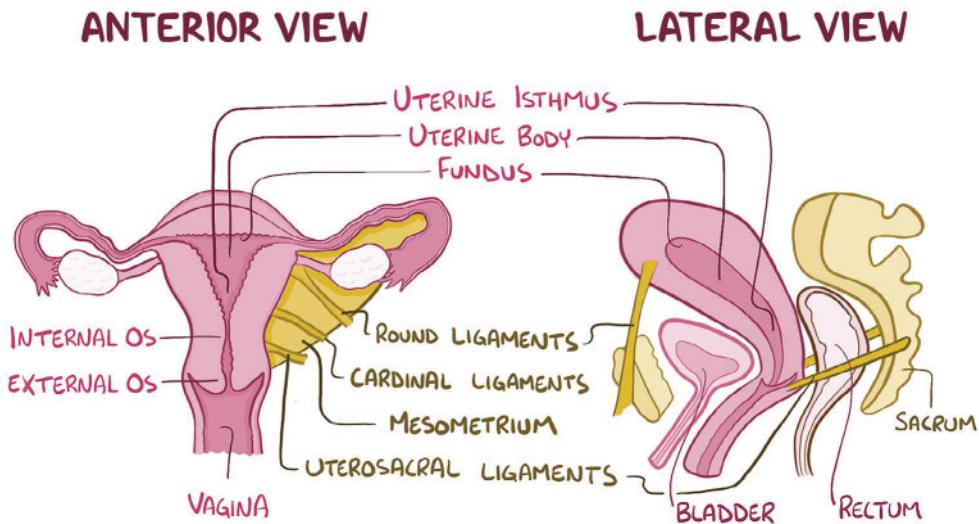
- Located posterior to bladder, anterior to rectum
- Fundus (top) → uterine body → uterine isthmus → cervix (neck of uterus)
  - Cervical opening to vagina: external os; thins, dilates during childbirth
  - Cervical opening into uterine cavity: internal os
- Anchored to sacrum (uterosacral ligaments) → anterior body wall (**round ligaments**)
- Supported by **cardinal ligaments, mesometrium**
- Three layers of uterine wall
  - Perimetrium, myometrium (smooth muscle), endometrium (highly vascular mucosal layer)

## Vagina

- Extends from uterus, opens into vulva (covered by hymen in childhood)
- Outer muscular wall containing rugae; inner mucous membrane of **stratified squamous epithelium**
- Fornix (superior, domed area) connects to sides of cervix



**Figure 8.6** The three layers of the uterine wall. External to internal: perimetrium → myometrium → endometrium.



**Figure 64.7** Anterior view of the uterus and lateral view of the uterus in relationship to surrounding structures.

## OOGENESIS

### Fetal development

- Oogonia (primordial oocyte cell) undergo mitotic division → ↑ oogonia (**diploid cells**)
- 7 months
  - Oogonia begin meiotic division, become **primary oocytes** (diploid cells)

### Follicular development

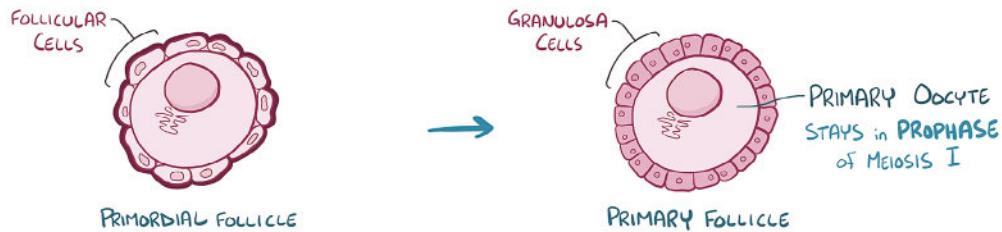
- Infancy to puberty
  - Primary oocyte surrounded by granulosa cells form primary (primordial) follicle
- Menstrual cycle (approx. every 28 days)
  - Primary follicle → secondary follicle → tertiary (Graafian) follicle
- Antrum (fluid-filled cavity) forms in Graafian follicles; granulosa cells secrete nourishing fluid for primary oocyte
- Theca cells produce androstenedione (sex hormone precursor) → converted into estradiol in granulosa cells
- **Follicular phase of menstrual cycle:** Graafian follicles grow
- Follicle with most follicle-stimulating hormone (**FSH**) receptors becomes dominant follicle; primary oocyte → meiosis I completed, secondary oocyte (haploid cell with 23 chromosomes) formed
- **Ovulation:** dominant follicle ruptures → secondary oocyte released → peritoneal cavity → pulled inside fallopian tube
- **Luteal phase:** follicle remains → **corpus luteum** (luteinized granulosa, theca cells)
  - Luteinized granulosa cells secrete inhibin → ↓ FSH → ↓ estrogen → ↓ luteinizing hormone (**LH**)
  - **Luteinized theca cells:** ↑ progesterone → dominant hormone

### Fertilization

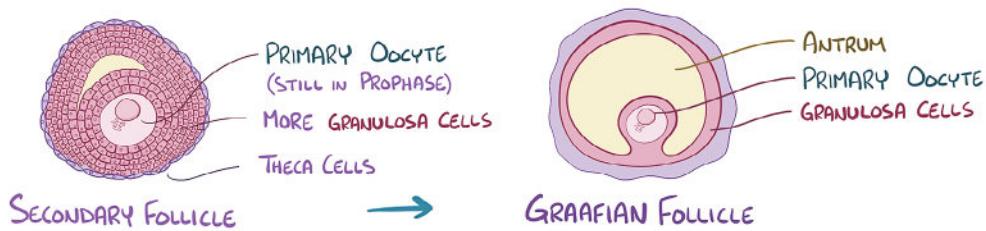
- If fertilization occurs → oocyte becomes mature ovum → progesterone produced until placenta forms
- If fertilization does not occur → corpus luteum → corpus albicans

# FOLLICULAR DEVELOPMENT

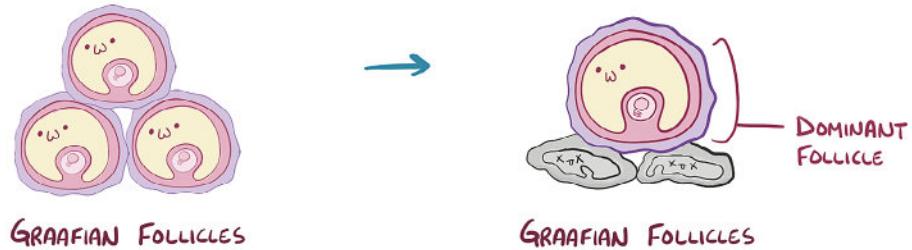
## FIRST STAGE: INFANCY to PUBERTY



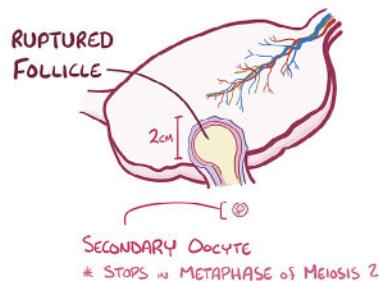
## SECOND STAGE: a FEW PRIMARY FOLLICLES ENTER EACH MENSTRUAL CYCLE



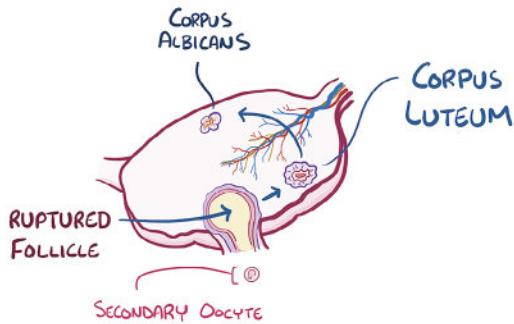
## THIRD STAGE: BEGINS WHEN GRAAFIAN FOLLICLES ARE READY OCCURS DURING FOLLICULAR PHASE



## OVULATION



## LUTEAL PHASE (WEEKS 3 & 4)



**Figure 64.8** Stages of follicular development. Stage one: primordial follicles → primary follicles, meaning that the follicular cells surrounding the primary oocyte develop into granulosa cells. Stage two: primary follicles → secondary follicles → tertiary (Graafian) follicles. This stage results in a few fast-growing Graafian follicles. Stage three: dominant follicle is established. Ovulation: dominant follicle ruptures, releases secondary oocyte into fallopian tube. The secondary oocyte stops in metaphase of meiosis II. Luteal phase: weeks 3 to 4 of menstrual cycle. The remains of the follicle turn into the corpus luteum. If fertilization occurs, the corpus luteum keeps making progesterone until the placenta forms. If not, the corpus luteum stops making hormones after about ten days, becomes fibrotic → corpus albicans.

## OXYTOCIN & PROLACTIN

[osms.it/oxytocin-prolactin](https://osms.it/oxytocin-prolactin)

- Peptide hormones involved in production, release of milk

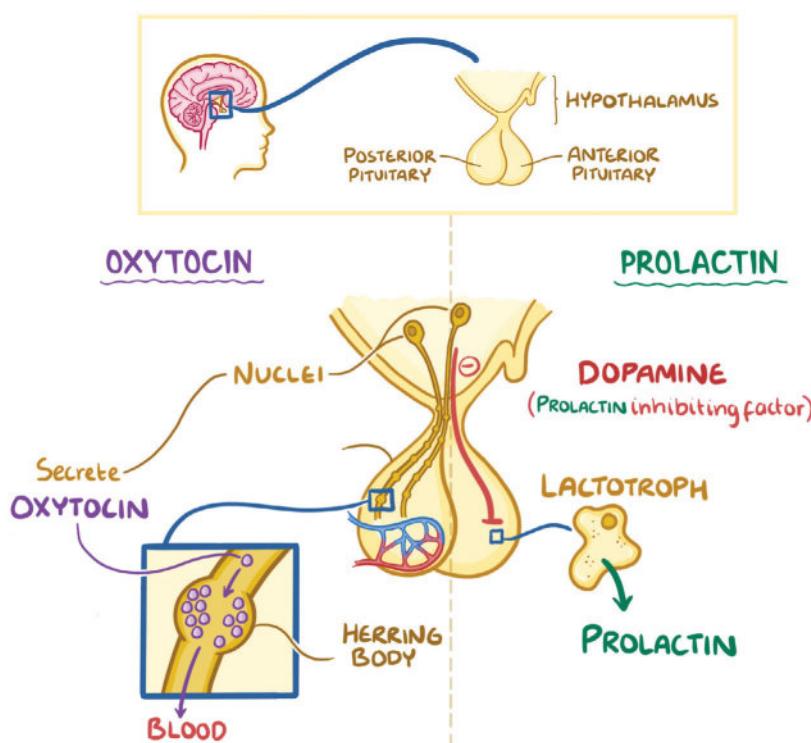
→ stored in Herring bodies → released into blood → target tissues (e.g. breasts, uterus)

### OXYTOCIN

- Essential for **progression of labor**, control of postpartum bleeding, return of uterus to pre-pregnancy state (involution)
- Synthesized, secreted by **hypothalamus** → travels down axons to posterior pituitary

### PROLACTIN (PL)

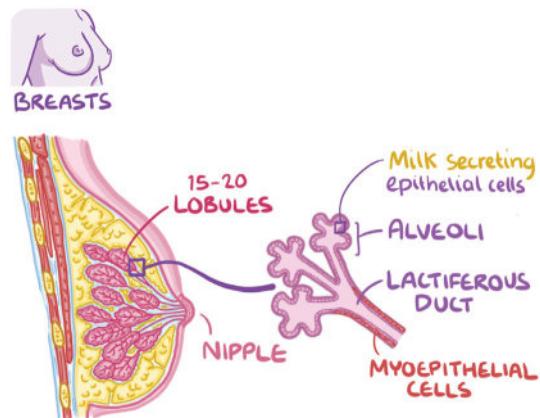
- Synthesized by lactotrophs in anterior pituitary → target tissue (**breasts**)
- Synthesis inhibited by dopamine during non-pregnant/non-breastfeeding state



**Figure 64.9** Synthesis and secretion of oxytocin and prolactin.

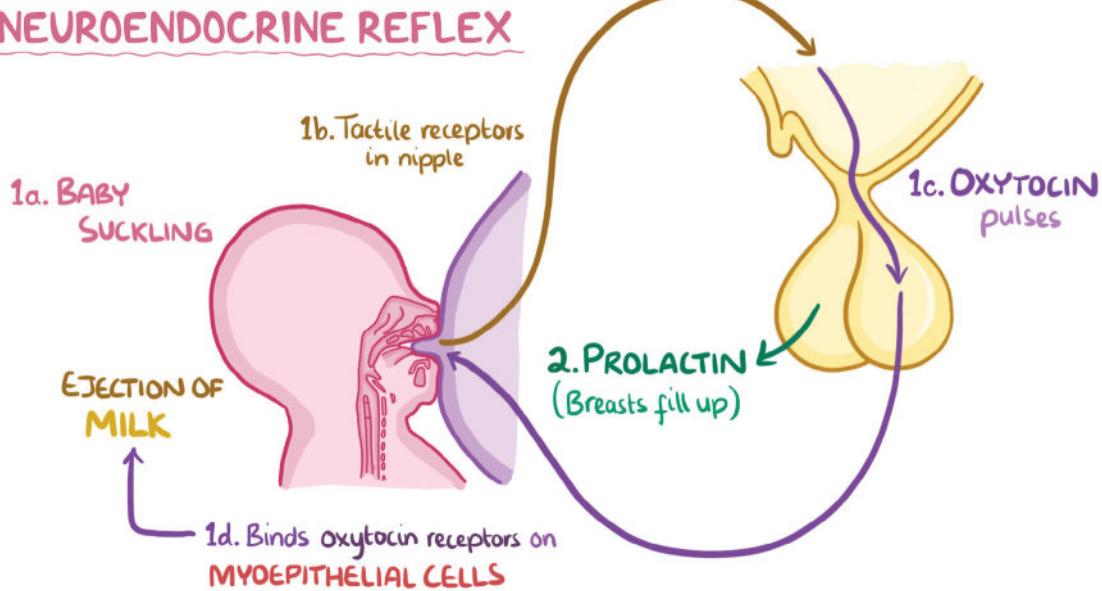
## FUNCTIONS DURING LACTATION

- Neuroendocrine reflex: suckling by infant at breast → stimulates mechanoreceptors in nipple, areola → action potential travels up spinal cord to hypothalamus
- First, burst of oxytocin released from posterior pituitary → enters bloodstream → breasts, uterus
  - Myoepithelial cells surrounding alveoli in breasts contract → **milk ejection from alveolus** (let-down reflex)
  - Stimulates contractile activity of uterine myometrium → ↓ postpartum bleeding; promotes uterine involution
- Second, thyrotropin-releasing hormone (TRH) from hypothalamus → PL released from anterior pituitary → enters bloodstream → breasts → ↑ **milk production**, secretion by alveolar epithelial cells
- ↑ PL inhibits release of GnRH from hypothalamus → ↓ LH, FSH from anterior pituitary → ↓ development of ovarian follicles, ovulation, menstrual periods



**Figure 64.10** Anatomy of the breast.

## NEUROENDOCRINE REFLEX



**Figure 64.11** Illustration of the neuroendocrine reflex. In response to the suckling of a baby, oxytocin released from the posterior pituitary stimulates ejection of milk, and prolactin released from the anterior pituitary increases milk production.

## FUNCTIONS DURING & AFTER LABOR

- Oxytocin (powerful uterine muscle stimulant) produced during pregnancy, does not stimulate uterine contractions due to
  - Rapid degradation by placental oxytocinase
  - Progesterone-induced inhibition of oxytocin receptors on myometrium
- Estrogen-induced oxytocin receptor expression + ↑ myometrial sensitivity to oxytocin promotes uterine contractions during labor

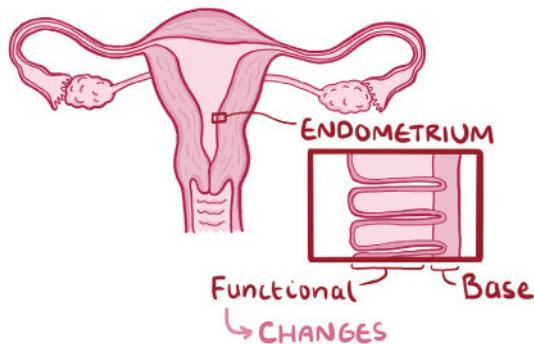
▫ Positive feedback loop: ↑ uterine contractions → fetal head pushes against cervix → neural signal travels to spinal cord → hypothalamus → ↑ oxytocin release from posterior pituitary → ↑ uterine contractions → cycle continues until delivery (baby, placenta)

- After labor, milder contractions continue
  - Clamp down on placental arteries at placental attachment site → ↓ bleeding
  - Gradually ↓ size of uterus (involution)
  - Additional oxytocin released during breastfeeding → speeds involution

# MENSTRUAL CYCLE

[osms.it/menstrual-cycle](http://osms.it/menstrual-cycle)

- Menstruation (menses): shedding of uterine functional endometrium
- Occurs approx. every 28 days



**Figure 64.12** The uterine endometrium consists of a thin base layer and a functional layer. The functional layer is subject to the changes (thickening and shedding) that occur during the menstrual cycle.

## FOLLICULAR PHASE

- Ovulation (days 1–14): maturing follicles, proliferation of uterine mucosa, dominated by estrogen

### Day 1

- Hypothalamus releases gonadotropin-releasing hormone (GnRH) → anterior pituitary releases FSH, LH → one oocyte dominates → develops within primary follicle
- Primary (primordial) follicle: oocyte surrounded by single layer of granulosa cells (nourish oocyte)

### Days 1–13

- Granulosa cells proliferate → follicle grows → develops outer layer of cells (theca layer) → respond to LH by producing estrogen → mature follicle
  - Estrogen acts on uterine endometrium to prepare for fertilized egg → initiates uterine proliferative phase → endometrial lining grows
  - Estrogen also feeds back to hypothalamus, pituitary → turns off GnRH, FSH, LH

### Day 14

- Brief LH surge stimulates ovulation → follicle ruptures → oocyte ejected out of follicle

## LUTEAL PHASE

- After ovulation, empty follicle collapses  
→ turns into **corpus luteum** → produces **progesterone** (approx. 14 days)
  - Endometrium becomes highly vascularized, glycogen-filled tissue (secretory phase)

## Days 15–24

- Egg travels through fallopian tube

## Day 25

- If fertilization does not occur → corpus luteum undergoes apoptosis → progesterone levels fall
- If fertilization does occur → embryonic tissue secretes **human chorionic gonadotropin** (hCG) → signals corpus luteum to continue production of estrogen, progesterone to support pregnancy

# PREGNANCY

[osms.it/pregnancy](http://osms.it/pregnancy)

- Obstetric history (GTPAL)
  - G (**gravida**): number of pregnancies, regardless of duration (including current pregnancy)
  - T: number of term infants born
  - P: number of preterm infants born
  - A: number of spontaneous/induced abortions
  - L: number of currently living children
  - Example: G3P1202 (3 pregnancies, 1 term birth, 2 preterm births, 0 abortions, 2 living children)
- Pregnancy lasts approx. 280 days (40 weeks); divided into three trimesters

activity (6–8 weeks)

## ESTIMATED DATE OF DELIVERY (EDD)

- Calculated from last menstrual period (LMP) to estimated date of delivery (EDD)
- Naegle's rule: add 7 days to 1st day of LMP, subtract 3 months, add 7 days, add 1 year
- Ultrasonic examination
  - Measurement of crown-to-rump length in first trimester
- Measurement of fundal height estimates pregnancy progression
  - Symphysis: 12–14 weeks
  - Umbilicus: 20 weeks
  - Rises above umbilicus 1 cm/week until 36 weeks

## PHYSIOLOGICAL CHANGES IN THE REPRODUCTIVE SYSTEM

### Uterus

- ↑ size, capacity due to hypertrophy, hyperplasia, mechanical stretching
- 20 times larger
- ↑ strength, distensibility, contractile proteins, number of mitochondria
- ↑ volume capacity (10 mL–5 L)
- Softening of uterine isthmus (Hegar's sign)

## SIGNS & SYMPTOMS

### Presumptive

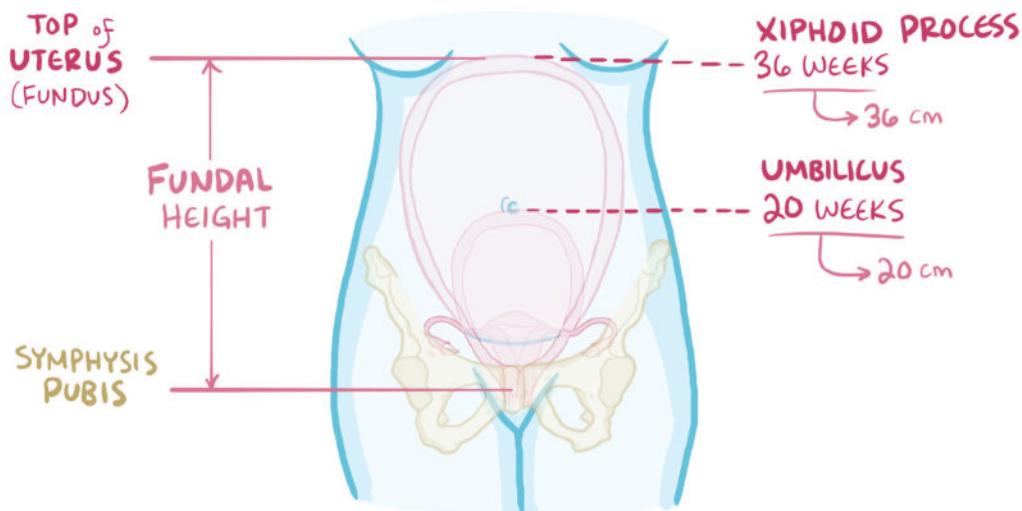
- Amenorrhea; breast fullness, tenderness; nausea/vomiting ("morning sickness"); urinary frequency; fatigue; fetal movement (16–20 weeks of gestation)

### Probable

- Uterine enlargement; softening of uterine isthmus (Hegar sign); vaginal, cervical purplish-blue discoloration (Chadwick sign); positive urine/serum hCG

### Positive

- Auscultation of fetal heart tones (7–8 weeks of gestation); "quickenings" (fetal movements); fetal sac visualized by ultrasound (5–6 weeks); fetal cardiac



**Figure 64.13** Fundal height = distance from symphysis pubis to top of uterus (fundus). Fundal height is a good estimate of gestational age.

### Cervix

- Formation of mucus plug; seals endocervical canal
- ↑ vascularity → purplish-blue color
- Mild softening due to edema, hyperplasia (Goodell's sign); ↑ softening in third trimester

### Placenta

- Develops where embryo attaches to uterine wall
- Expands to cover 50% internal uterine surface
- Functions as maternal-fetal organ for metabolic, nutrient exchange
- Secretes estrogen, progesterone, relaxin, hCG

### Vagina

- ↑ vascularity → bluish-purple color
- Loosening of connective tissue → ↑ distensibility
- Leukorrhea
  - pH of 3.5–6.0 → protects against bacterial infections

### Breasts

- ↑ size, weight, nodularity, blood flow, vascular prominence
- Areola, nipples are a darker pigmentation due to ↑ melanocyte activity
- ↑ activity of Montgomery's tubercles

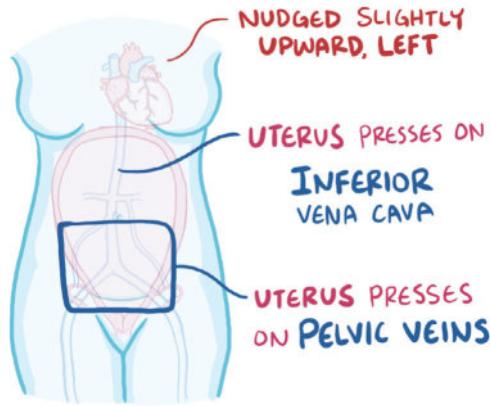
(sebaceous glands)

- Progesterone
  - ↑ alveolar-lobular development; prevents milk production during pregnancy (inhibits prolactin)
- Estrogen
  - ↑ growth of lactiferous ducts
- Secretion of colostrum begins week 16

## PHYSIOLOGICAL CHANGES IN OTHER BODY SYSTEMS

### Cardiovascular

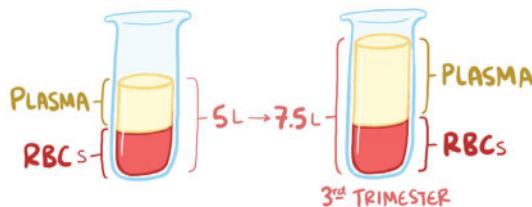
- Mild hypertrophy
- S2, S3 more easily auscultated, split exaggerated
- Heart displaced upward, forward, slightly to left
- ↑ heart rate by 15–20 beats/minute
- Stroke volume ↑ 30%, cardiac output (CO) ↑ 30–50% (by term); ↓ blood pressure (BP) despite ↑ CO due to progesterone-induced vasodilation; BP = CO × systemic vascular resistance (SVR)
- Supine hypotensive syndrome caused by gravid uterus pressing on inferior vena cava (left lateral recumbent position optimal for CO, uterine perfusion)
- Gravid uterus elevates pressure veins draining legs, pelvic organs → slowed venous return, dependent edema, varicose veins, hemorrhoids



**Figure 64.14** Cardiovascular changes during pregnancy. When lying down, uterus presses on inferior vena cava → less blood to right atrium → hypotension. The uterus also presses on pelvic veins → varicose veins, swelling in lower legs, ankles.

### Hematologic

- ↑ blood volume (approx. 1500 mL)
  - Related to sodium, water retention due to changes in osmoregulation, secretion of vasopressin by anterior pituitary, renin-angiotensin-aldosterone system (RAAS)
- ↑ total red blood cell (RBC) volume (approx. 30%), with iron supplementation
  - ↑ volume, oxygen-carrying capacity needed for ↑ basal metabolic rate (BMR), needs of uterine-placental unit (offsets blood loss at delivery)
  - Plasma > RBC volume → hemodilution, ↓ hematocrit (physiologic anemia)
- ↑ white blood cell (WBC) count (approx. 5,000–12,000/mm<sup>3</sup>)
- ↑ clotting factors (fibrin, fibrinogen): **hypercoagulable** state of pregnancy



**Figure 64.15** Pregnancy is a high volume state. Plasma volume ↑ > RBC volume ↑ → ↓ hematocrit (physiologic anemia).

### Respiratory

- ↑ oxygen consumption, subcostal angle, anteroposterior diameter, tidal volume (30–50%), minute ventilatory volume, minute oxygen uptake
- Gravid uterus places upward pressure on diaphragm → elevates approx. 4 cm
- Hyperventilation → mild respiratory alkalosis (renal compensation → maternal blood pH 7.40–7.45)
- Nasal congestion, epistaxis due to estrogen-induced edema

### Gastrointestinal

- Gums bleed easily due to estrogen-induced hyperemia, friability
- Progesterone-induced smooth muscle relaxation, delayed gastric emptying, ↓ peristalsis → nausea, vomiting (AKA “morning sickness”); constipation; heartburn (pyrosis), esophageal reflux; intrahepatic cholestasis of pregnancy due to ↓ gallbladder emptying time → ↑ risk of cholelithiasis
- ↑ saliva production (ptyalism)

### Urinary & renal

- Bladder
  - First trimester: gravid uterus presses on bladder → urinary frequency, nocturia, stress incontinence
  - Second trimester: uterus occupies abdominal space → ↓ urinary frequency
  - Third trimester: presenting part descends into pelvis → urinary frequency, nocturia, stress incontinence
- ↑ glomerular filtration rate (GFR)
  - 40–50% by second trimester; ↑ urinary output (25%)
- ↑ size of kidneys (1–1.5 cm)
- Dilation of urinary collecting system → physiologic hydronephrosis
- Urinalysis
  - Glycosuria (due to ↑ glucose load), ↑ protein excretion (due to altered proximal tubule function + ↑ GFR)

### Integumentary

- Hyperpigmentation (due to estrogen, ↑ melanocyte activity) → melasma (chloasma) brownish “mask of pregnancy”; linea nigra formation on abdomen; darkening of

- nipples, areolae, vulva
- ↑ cutaneous blood flow → ↑ heat dissipation → pregnancy “glow”
- ↓ connective tissue strength secondary to ↑ adrenal steroid levels → stretch marks (striae gravidarum) in breasts, abdomen, thighs, inguinal area
- Estrogen-induced vascular permeability → spider nevi, angiomas, palmar erythema

### Musculoskeletal

- Abdominal distension + shift in center of gravity → lordosis
- Enlarging uterus → separation of abdominal rectus muscles (diastasis recti)
- ↑ progesterone, relaxin → ↑ joint mobility, “waddling” gait
  - Widening of symphysis pubis
  - Facilitates accommodation of fetus into pelvis
- High bone turnover, remodeling

### Endocrine

- ↑ size of pituitary gland; mostly due to proliferation of lactotroph cells
  - ↑ intrasellar pressure → ↑ risk of postpartum infarction (Sheehan syndrome) in setting of postpartum hemorrhage
- ↑ parathyroid hormone (meets calcium need of developing fetal skeleton)
- Physiologic hypercortisolism
  - ↑ need for estrogen, cortisol → ↑ glucocorticoids from adrenal glands → supports fetal somatic, reproductive growth

- “Diabetogenic state” of pregnancy
  - ↑ need for glucose, insulin production → hypertrophy, hyperplasia of pancreatic beta cells
- ↓ thyroid-stimulating hormone (TSH); thyroid gland enlarges; ↑ total T3, T4
- Reproductive hormones
  - hCG from placenta; estrogen, progesterone from corpus luteum (first, second trimesters), placenta (second, third trimesters)
  - Suppressed FSH, LH due to feedback from estrogen, progesterone, inhibin
  - ↓ oxytocin levels throughout pregnancy → ↑ labor onset → ↑ second stage of labor

### NUTRITIONAL NEEDS

- Recommendation of additional 300 kcal/day, weight gain of 25–35 pounds (11.5–16 kg)
  - 11 lb (5 kg): placenta, amniotic fluid, fetus
  - 2 lb (0.9 kg): uterus
  - 4 lb (1.8 kg): ↑ blood volume
  - 3 lb (1.4 kg): breast tissue
  - 5–10 lb (2.3–4.5 kg): maternal reserves
- 600 mcg folic acid/day → RBC synthesis, placental/fetal growth, ↓ risk of neural tube defects
- 1,000–1,300 mg calcium/day supports pregnancy, lactation
- 60g protein daily supports tissue growth
- 27 mg iron/day supports ↑ RBCs

## LABOR

[osms.it/labor](https://osms.it/labor)

- Labor (parturition): uterine contractions → cervical changes → delivery of baby, placenta
- Begins at term (37–42 weeks of gestation)
- Duration of three stages varies with gravidity (nulliparas typically longer than multiparas)

### PREMONITORY SIGNS

- Cervical changes
  - Remodeling of cervix by enzymatic collagen dissolution, ↑ water content → softening, ↑ distensibility
- Cervical softening → expulsion of mucus plug → “bloody show” (pink-tinged mucus)

- Spontaneous rupture of amniotic membranes (ROM)

#### False labor

- AKA Braxton-Hicks contractions
- True labor: regular, increase in frequency, duration, intensity; produce cervical changes (e.g. dilation/opening up, effacement/getting thinner); pain begins in lower back, radiates to abdomen, not relieved by ambulation
- False labor: irregular, intermittent contractions; no cervical changes; pain in abdomen; walking may decrease pain

## FIRST STAGE OF LABOR

#### Early/latent

- 8–12 hours
- Mild contractions every 5–30 minutes
- Duration 30 seconds each
- Gradually increase in frequency, intensity, duration
- Cervical dilation 0–3 cm
- Effacement 0–30%
- Spontaneous ROM

#### Active phase

- 3–5 hours
- Contractions every 3–5 minutes
- Duration ≥ 1 minute
- Cervical dilation 3–7 cm
- Effacement 80%
- Progressive fetal descent

#### Transition phase

- 30 minutes–2 hours
- Intense contractions every 1.5–2 minutes
- Duration 60–90 seconds
- Cervical dilation 7–10cm
- Effacement 100%

## SECOND STAGE

- AKA pushing stage
- Begins with full dilation
- Navigation through maternal pelvis dictated by 3 Ps
  - Power, passenger, passage

#### Power

- Frequency, duration, intensity of uterine contractions
- Physiology of contractions
  - Stimulation of uterine myometrium
  - Alpha-receptors stimulate uterine contractions
  - Numerous **oxytocin** receptors, mostly on uterine fundus
- Contraction steps
  - Wave begins in fundus, proceeds downward to rest of uterus → muscle shortens in response to stimulus → increment (build up) → acme (peak) → decrement (gradual letting up) → relaxation → fetal descent, cervical effacement, dilation → amount of pressure exerted by uterine contractions (intrauterine pressure) measured in millimeters of mercury (mm Hg)

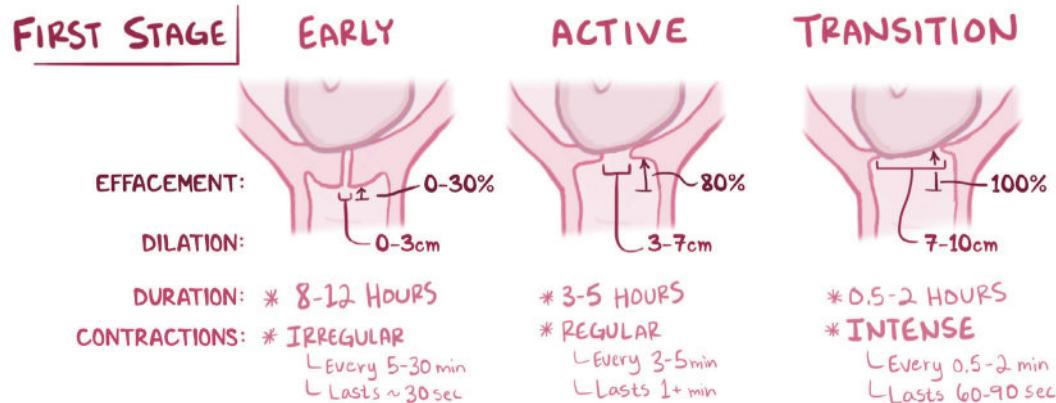


Figure 64.16 Features of the phases of the first stage of labor.

**Passenger**

- Fetal size
    - Fetal head most critical; cephalopelvic disproportion → labor dystocia (difficult/obstructed)
    - Macrosomia (birth weight  $\geq$  90th percentile for gestational age/ $>$  4500 g) associated with shoulder dystocia (fetal shoulder unable to pass below maternal pubic symphysis), birth injuries
  - **Fetal attitude:** relationship of fetal parts to one another
    - Full flexion (chin on chest; rounded back with flexed arms, legs); smallest diameter of head (suboccipitobregmatic diameter) presents at pelvic inlet
  - **Fetal lie:** relationship of fetal cephalocaudal axis (spinal column) to maternal cephalocaudal axis
    - **Longitudinal (ideal):** fetal spine lies along maternal
    - **Transverse:** fetal spine perpendicular to maternal
    - **Oblique:** fetus at slight angle
  - **Fetal presentation:** fetal/presenting part enters pelvic inlet first
  - **Cephalic:** head first
    - **Vertex (most common):** optimal for easy delivery; head completely flexed onto chest → occiput (part of fetal skull covered by occipital bone) is presenting
    - **Brow:** fetal head partially extended; sinciput (part of fetal skull covered by frontal bone, anterior fontanelle to orbital ridge) presenting part
    - **Face:** fetal head hyperextended; fetal face from forehead to chin presenting part
  - **Breech:** head up; bottom, feet, knees present first
    - **Frank breech:** hips flexed, knees extended; bottom presents
    - **Complete breech:** hips, knees flexed; bottom presents
    - **Incomplete breech:** one/both hips not completely flexed; feet present
    - **Shoulder:** transverse lie; shoulders present first
- **Gynecoid:** rounded pelvic inlet, midpelvis, outlet capacity adequate; optimal for vaginal delivery
- **Android:** heart-shaped pelvic inlet; ↓ midpelvis diameters, outlet capacity; associated with labor dystocia
- **Anthropoid:** oval-shaped pelvic inlet; midpelvis diameters, outlet capacity adequate; favorable for vaginal delivery
- **Platypelloid:** oval-shaped pelvic inlet, ↓ midpelvis diameters, outlet capacity adequate; not favorable for vaginal delivery
- **Cardinal movements (mechanisms of labor)**
    - **Descent:** presenting part reaches pelvic inlet (engagement) before onset of labor → degree of descent (fetal station), relationship of presenting part to maternal ischial spines → fetus moves from pelvic inlet (-5 station) down to ischial spines (0 station) to pelvic outlet (+4 station) to crowning at vaginal opening (+5 station)
    - **Flexion:** fetal chin presses against chest, head meets resistance from pelvic floor
    - **Internal rotation:** fetal shoulders internally rotate 45°; widest part of shoulders in line with widest part of pelvic inlet
    - **Extension:** fetal head passes under symphysis pubis (+4 station), moves (+5 station), emerges from vagina
    - **Restitution (external rotation):** head externally rotates as shoulders pass through pelvic outlet, under symphysis pubis, turns to align with back
    - **Expulsion:** anterior shoulder slips under symphysis pubis, followed by posterior shoulder, rest of the body; marks end of second stage

**THIRD STAGE**

- Delivery of placenta, umbilical cord, fetal membranes; uterus contracts firmly, placenta begins to separate from uterine wall

**FOURTH STAGE**

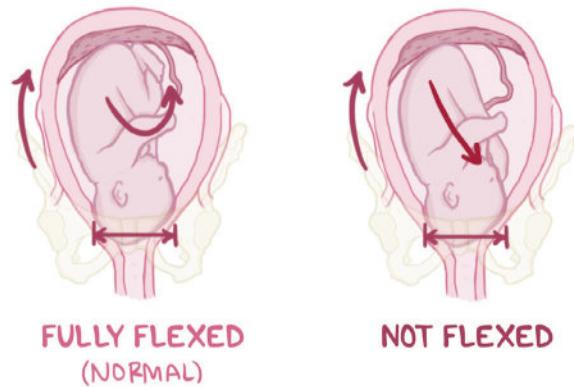
- Physiological adaptation to blood loss, initiation of uterine involution

**Passage**

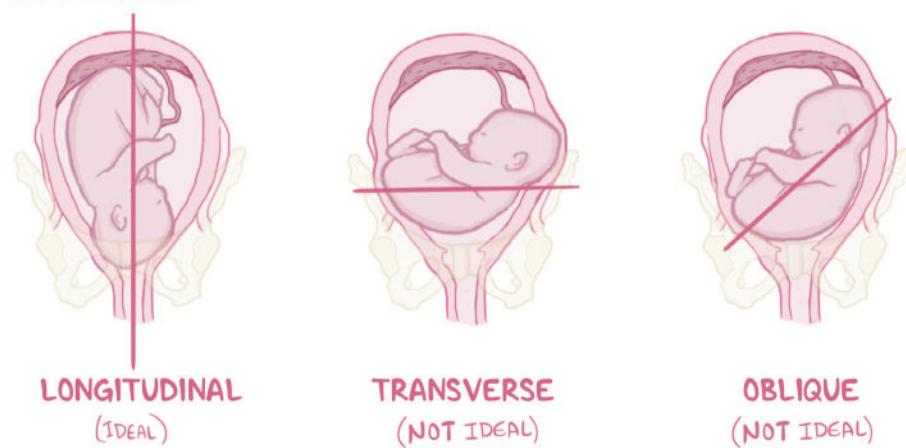
- Route through bony pelvis
- Size, type of pelvis

## SECOND STAGE

### FETAL ATTITUDE



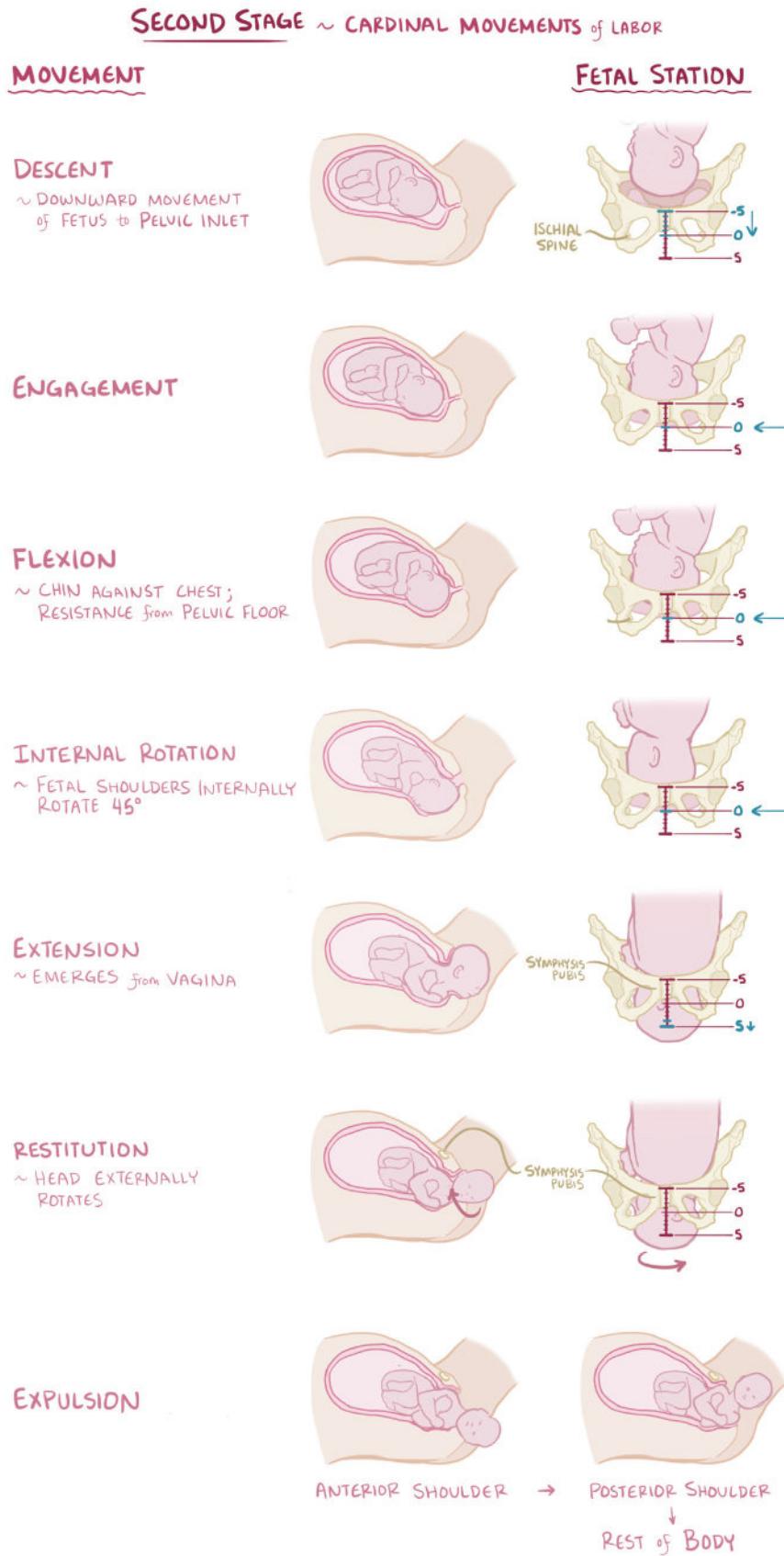
### FETAL LIE



### FETAL PRESENTATION



**Figure 64.17** Fetal attitude, lie, and presentation are all critical factors in determining the fetus' ease of passage through the maternal pelvis.



**Figure 64.18** Second stage cardinal movements: the fetal position changes that occur during labor.

# BREASTFEEDING

[osms.it/breastfeeding](https://osms.it/breastfeeding)

- Provision of breast milk from lactating breast; involves breast tissue development, initiation of milk secretion lactogenesis
- Pregnancy, human placental lactogen (hPL), progesterone released from placenta, + PL released from anterior pituitary gland → stimulates growth of breast glandular tissue → prepares epithelial cells lining alveoli to produce milk
  - Progesterone prevents lactation until after delivery of placenta
- Delivery of baby, placenta → ↓↓ progesterone → **milk synthesized** in alveoli

## INFANT SUCKLING

- Stimulates release of **oxytocin**, PL

### Oxytocin

- Required for milk to be released from alveoli
- Neuroendocrine reflex → let-down reflex (milk ejection)
  - Myoepithelial cells contract → milk ejection from alveolus → drained by milk-collecting ducts → transported to nipple
- **Milk ejection continues** as long as infant continues **suckling**
- Other triggers for **oxytocin release, let-down reflex**
  - Sounds/sights/smells connected to infant (e.g. infant crying)

### PL

- **Continues milk production**
- Amount of milk produced depends on amount removed at feeding (supply meets demand)
- Milk extraction facilitated by good latch of baby onto nipple, frequent emptying of breast
  - **Good latch:** baby's mouth wide open, covering areola, lips flanged out, nipple up against roof of mouth, baby's tongue up against bottom of areola
- Feedings every 1–2 hours at first, then

every 3 hours

- If milk not removed, builds up → ↑ intramammary pressure → ↓ capillary blood flow → glandular tissue involutes → ↓ milk production

## BIOCHEMICAL COMPOSITION OF BREAST MILK

### Benefits for baby

- ↑ whey to casein ratio, enzymes, hormones → ↑ absorption, digestion of milk
- Immunoglobulins
  - ↓ risk of infection; esp. **respiratory, gastrointestinal**, otitis media; ↓ risk of necrotizing enterocolitis in premature infants
- Long-chain polyunsaturated fatty acids (PUFAs)
  - Aids neural, visual development
- ↑ beneficial bacteria (*Lactobacillus*, *Bifidobacterium*) in gut microflora
- Cytokines
  - Anti-inflammatory properties
- **Ideal source of nutrition for newborns**, including **premature** infants
- Milk composition transitions from early postpartum period to mature milk to meet infant needs

### Benefits for mother

- Accelerated uterine involution, ↓ risk of chronic disease (e.g. diabetes Type II, arthritis, heart disease; **cancers of breast, ovaries, uterus**)

### Colostrum

- Small amounts of milk produced during second half of pregnancy
- Thick, yellowish fluid (due to beta-carotene) rich in immune cells, antibodies, antioxidants, protein, fat-soluble vitamins, minerals; low in fat, lactose
- Protects newborn from infection; laxative effect → passage of first stool (meconium),

- formed in fetal gastrointestinal tract
- Helps establish healthy gut microbiome

### **Transitional milk**

- Produced 7–10 days postpartum; thinner than colostrum; light yellow color

### **Mature milk**

- Produces 2 weeks postpartum
- Watery, slight bluish color; fat content increases during feeding
- Biologically complex
  - Protein, fat, sugars (e.g. lactose, oligosaccharides), vitamins, minerals, immunoglobulins, antibodies (esp. secretory IgA), immune cells (e.g. macrophages, neutrophils), immune-modulating factors (e.g. lactoferrin, lysozyme, lactoperoxidase)
- Low in vitamin D; supplementation often recommended
- Continues to be produced until lactation ceases
- Healthy maternal diet supports breast milk production

## **CONTRAINdications & CAUTIONS TO BREASTFEEDING**

### **Contraindications**

- Certain maternal medications (e.g. chemotherapy), illicit drugs (e.g. cannabis, heroin)
- HIV infection (in high-income settings)
- Herpes zoster, herpes simplex
  - If lesions on breast
- Tuberculosis
  - Until approx. 2 weeks of maternal pharmacotherapy

### **Cautions**

- Smoking discouraged ( $\uparrow$  risk of SIDS, respiratory problems)
- Minimize alcohol; if consumed, wait two hours before breastfeeding
- Limit caffeine

## **BREASTFEEDING PROBLEMS**

### **Engorgement**

- Cause: milk accumulation in breast tissue, vascular congestion, resulting in pain

- Presentation: firm, tender breast; may have  $\uparrow$  vascular markings
- Treatment: empty breasts ( $\uparrow$  breastfeeding, pumping); warm shower/compresses before feeding (enhances let-down), cool compresses after feeding; nonsteroidal anti-inflammatory drugs (NSAIDs); application of cool green cabbage leaves
- Prevention: frequent feedings, good latch to ensure emptying breast

### **Sore, cracked nipples**

- Cause: improper latch, positioning
- Presentation: pain; blister/bleb on nipple if pores plugged
- Treatment: cool/warm compresses; apply expressed breast milk to nipple; mild analgesics (e.g. acetaminophen)
- Prevention: good breastfeeding technique

### **Mastitis**

- Cause: bacterial infection
- Presentation: usually unilateral, localized warmth, tenderness/pain, edema, erythema, firmness; acute onset of flu-like symptoms (e.g. fever, fatigue)
- Treatment: continued breastfeeding, NSAIDs, antibiotics
- Prevention: good hygiene

### **Yeast infections**

- Cause: Candida albicans; history of infant oral/diaper candidal infection/maternal vaginal candidal infection
- Presentation: infant may have white plaques in oral area; mother may experience pain, red/sore nipples
- Treatment: for mother, topical antifungal applied after feeding; infant, nystatin solution swabbed into oral mucosa after feeding
- Prevention: good hygiene; avoid excessive moisture by keeping breasts dry between feedings

# MENOPAUSE

[osms.it/menopause](http://osms.it/menopause)

- Diagnosed when menstrual cycles have stopped for entire year, no identified pathological cause
- Caused by natural effects of ovarian follicular depletion during aging process
- Usually begins age 50
- Preceded by perimenopause
  - 4 years before final menstrual period; missed/irregular menstrual cycles, changes in bleeding patterns (heavy, prolonged, light)

## HORMONAL CHANGES

- ↓ estrogen, progesterone → ↓ hypothalamic inhibition → ↑ bursts of GnRH → ↑ FSH, LH

## PHYSIOLOGICAL EFFECTS OF ESTROGEN WITHDRAWAL

### Hot flashes

- Caused by hypothalamus-associated thermoregulatory dysfunction → vasomotor instability
- Sensation of heat (centered on chest, face → generalized), diaphoresis, palpitations, anxiety
- Night sweats
  - Hot flashes occur at night → trouble sleeping
- Avoid triggers (e.g. hot drinks, spicy foods); maintain cool ambient temperature; dress in lighter clothing
- Stops within few years of onset

### Vulvovaginal atrophy

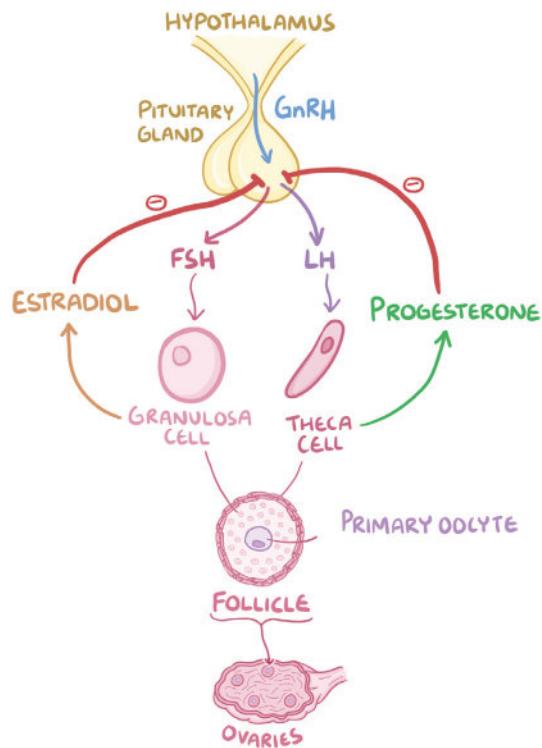
- Vaginal dryness, loss of vaginal rugae → dyspareunia
- Vaginal estrogen creams, lubricants helpful

### ↓ protective effects from estrogen

- ↑ risk of cardiovascular disease
- ↓ bone marrow density → ↑ risk of osteoporosis, bone fractures
  - ↑ vitamin D, calcium (diet, supplements) helpful

### Others

- Urinary tract dysfunction → dysuria, urinary urgency
- Mood instability → depression, anxiety
- Decline in cognitive function, difficulty concentrating
- ↓ collagen content in skin → ↑ skin wrinkling
- ↓ lean body mass
- Individualized approach for menopausal hormone therapy (MHT)
  - Estrogen/estrogen + progestin helpful in some cases



**Figure 64.19** Hormone activity in a regular menstrual cycle. Estrogen and progesterone levels ↓ during menopause because the ovaries run out of functional follicles → no theca or granulosa cells to produce more hormones. So ↓ estrogen, progesterone → ↓ hypothalamic inhibition → ↑ bursts of GnRH → ↑ FSH, LH.

# ESTROGEN & PROGESTERONE

[osms.it/estrogen-progesterone](http://osms.it/estrogen-progesterone)

- Female steroid hormones, produced mainly by ovaries
  - Some estrogen produced in adrenal cortex, **adipose tissue**; secreted by **placenta** during pregnancy
  - Corpus luteum secretes estrogen, progesterone
- Three types
  - **Estradiol** (most biologically active), estrone, estriol

## SYNTHESIS

- Cholesterol → **theca cells** → converted to pregnenolone via cholesterol desmolase → pregnenolone converted into progesterone via 3-beta-hydroxysteroid dehydrogenase (HSD) → released into blood → binds to plasma proteins (e.g. albumin) → transported to target tissues
- Remainder of pregnenolone converted to 17-hydroxypregnenolone → converted into dehydroepiandrosterone (DHEA) → finally converted into androstenedione (testosterone precursor) by 3-beta-HSD
- Androstenedione diffuses to nearby **granulosa cells** → androstenedione converted to testosterone by 17-beta-hydroxysteroid → testosterone converted to 17-beta-estradiol dehydrogenase aromatase (most biologically active type of estrogen during reproductive period)
- 17-beta-estradiol released into blood → binds to sex hormone-binding globulin (**SHBG**)
  - Plasma protein, carries 17-beta-estradiol to target tissues (e.g. uterus, vagina, bones)

## SECRETION

- Regulated by **hypothalamic-pituitary-ovarian** axis through feedback loops
- At puberty, pulsatile release of GnRH from hypothalamus → anterior pituitary secretes FSH, LH → ovarian follicles differentiate into theca, granulosa cells → secrete

estrogen, progesterone

## EFFECTS OF ESTROGEN

- Maturation of **female reproductive organs** (e.g. uterus, fallopian tubes, vagina)
- Secondary sexual characteristics (e.g. **breast** growth, **fat distribution**)
- ↑ estrogen (pre-ovulation) → prepares uterine epithelium for implantation (**endometrial proliferation**); endometrial secretion in collaboration with progesterone
- Dominant hormone during the **follicular phase** of ovarian cycle; follicle maturation; initiates ovulation via FSH, LH surge

## Pregnancy

- Secreted by placenta to support uterus; stimulates development of **myometrium**
- ↑ melanin-stimulating hormones → hyperpigmentation
- ↑ vascularity of upper respiratory tract; hypersecretion of mucus
- Preparation for **labor**
  - Stimulates **development of myometrial gap junctions**, promotes coordinated contractions
  - Promotes cervical ripening
  - ↑ uterine responsiveness to oxytocin (↑ oxytocin receptors), triggering parturition
- **Breasts**
  - Stimulates growth of duct cells

## Systemic

- Required for closure of epiphyseal plates (both sexes)
- Anabolic effect on bones
- ↓ low-density lipoprotein (**LDL**), ↑ high-density lipoproteins (**HDL**)
- Maintains flexibility of blood vessels
- Promotes skin elasticity, fat deposition
- ↓ estrogen during perimenopausal/menopausal years → ↑ risk of **cardiovascular morbidity, osteoporosis, sexual dysfunction**

## EFFECTS OF PROGESTERONE

- Dominant hormone during luteal phase of ovarian cycle
- ↑ progesterone (secretory phase of menstrual cycle) → forms decidual tissue for implantation

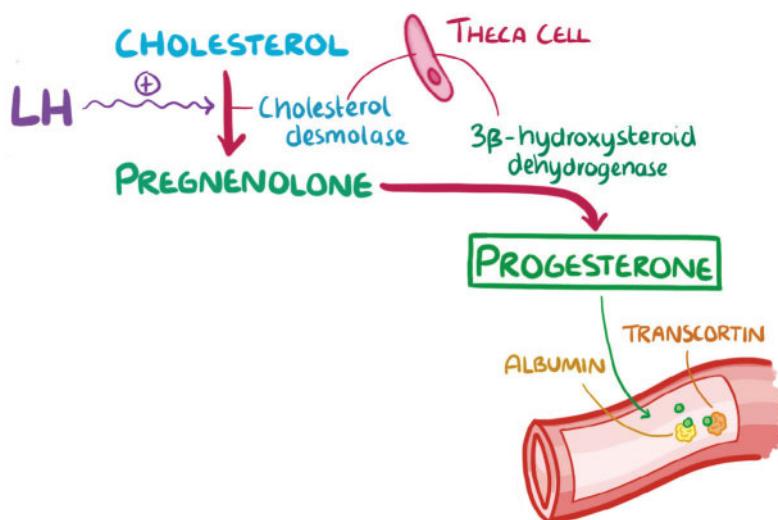
- Breasts: ↑ alveolar-lobular development, prevents milk production during pregnancy (inhibits prolactin)
- Respiratory: ↑ sensitivity to CO<sub>2</sub>, mild hyperventilation, ↓ airway resistance
- ↑ vasodilation

### Pregnancy

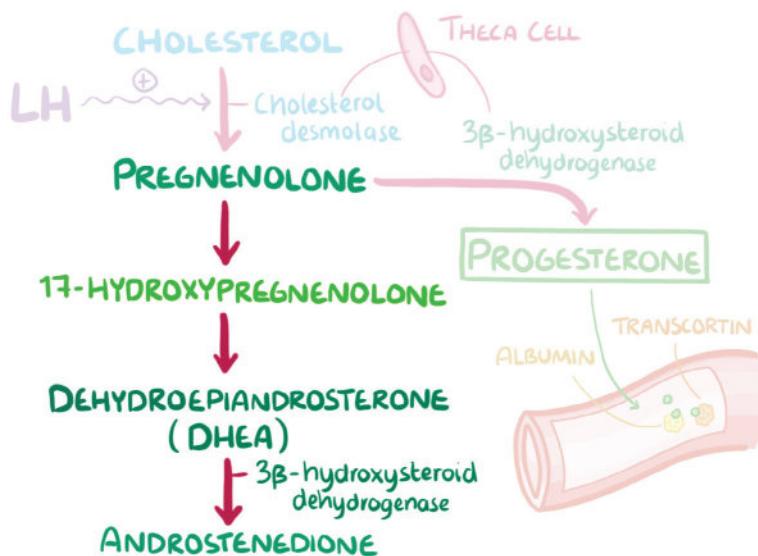
- Maintains pregnancy: ↓ irritability of myometrium → ↓ risk of spontaneous abortion
- Cervix: forms mucus plug

### Systemic

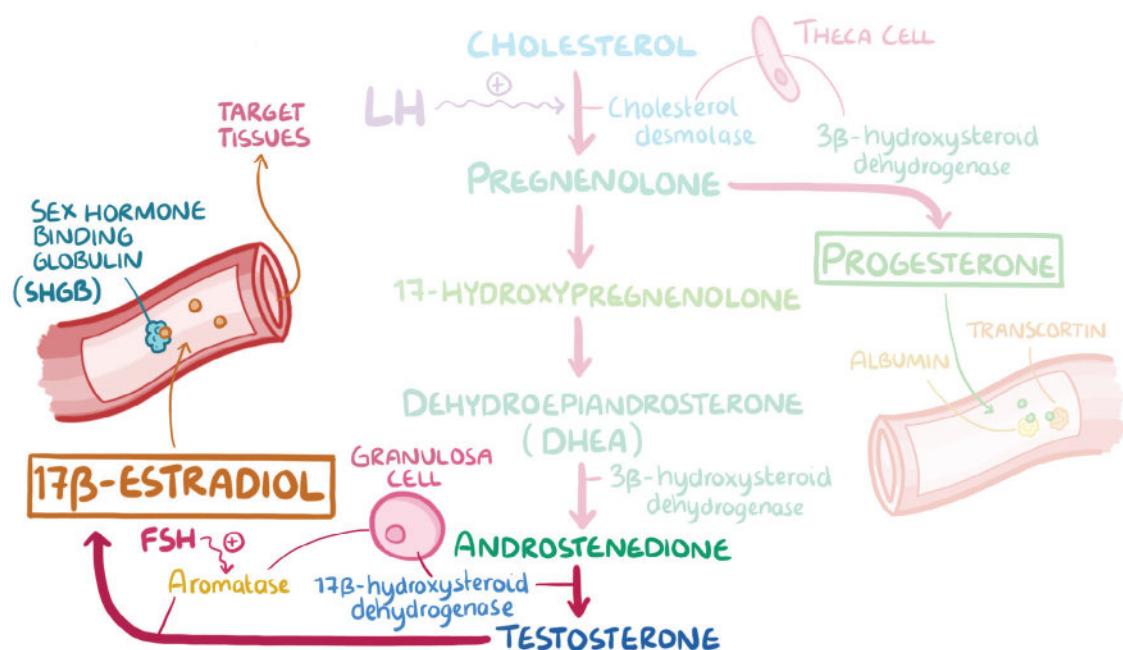
- Works with estrogen to promote bone remodeling → ↑ bone density
- Promotes skin elasticity



**Figure 64.20** The steps of progesterone synthesis. LH stimulates proliferation of theca cells → cholesterol desmolase converts more cholesterol into pregnenolone.



**Figure 64.21** Synthesis of androstenedione from pregnenolone. Androstenedione will be used in the next steps to synthesize 17-beta-estradiol.



**Figure 64.22** Synthesis of 17-beta-estradiol from androstenedione. FSH increases the activity of aromatase. Some target tissues for 17-beta-estradiol include the uterus and vagina, bones, and blood vessels.



## NOTES MALE REPRODUCTIVE SYSTEM

# ANATOMY & PHYSIOLOGY OF THE MALE REPRODUCTIVE SYSTEM

[osms.it/anatomy-physiology-male-reproductive-system](https://osms.it/anatomy-physiology-male-reproductive-system)

### EXTERNAL ORGANS

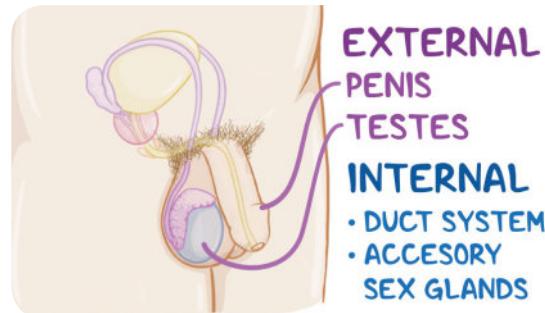
- Penis, scrotum
- Two testes (male gonads) in scrotum

#### Penis

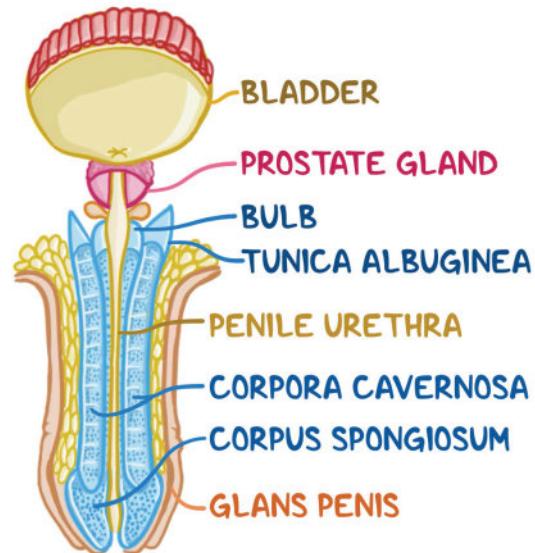
- Smooth muscle cells
- Enlarged tip (glans penis), surrounded by loose skin (foreskin)
- Opens as external urethral orifice
- Three cylindrical bodies of erectile tissue (vascular spaces, surrounded by smooth muscle)
  - Corpus spongiosum, two corpora cavernosa
- Arousal → smooth muscle cells relax, blood flows into vascular spaces, corpora cavernosa distend → veins compress, blood doesn't drain → local engorgement → erection

#### Testes

- Functions: produce sperm (in seminiferous tubules), testosterone (by Leydig cells)
  - Descend into scrotum from abdominal cavity (seventh month of gestation)
  - Scrotum provides cooler environment needed for spermatogenesis
- Contains epithelial, Sertoli, Leydig, sperm cells
- Separated by scrotal raphe
- Covered by tunica albuginea
  - Septa project towards center → 250 lobules (1–4 seminiferous tubules)
- Seminiferous tubules
  - Surrounded by epithelial lining,



**Figure 65.1** External and internal male reproductive system anatomy.



**Figure 65.2** Penis anatomy.

- capillaries, Leydig cells
- Spermatogonia (primordial sperm cells) → spermatocytes (towards lumen) → spermatids → sperm (most central); Sertoli cells (extend from margin to lumen; provide nutrients; establish blood-testis barrier)
- Tubules combine → rete testis (in mediastinum testis) → efferent ducts → epididymis

## INTERNAL ORGANS

- Ducts for sperm, accessory glands (seminal vesicles, prostate gland, bulbourethral glands)

### Sperm

- Acrosome: enzymes to penetrate oocyte (female gamete)
- Neck (midpiece): mitochondria for energy
- Tail: helps sperm swim
- Mature, swim in epididymis head; move through seminiferous tubules, rete testis by peristalsis

### Spermatogenesis

- Begins at puberty
- Hypothalamus secretes gonadotropin-releasing hormone (GnRH) → pituitary secretes luteinizing hormone (LH), follicle-stimulating hormone (FSH)
  - LH binds to Leydig cells → stimulates testosterone production
  - FSH binds to Sertoli cells → produces androgen binding protein (ADP) → more testosterone crosses blood-testis barrier

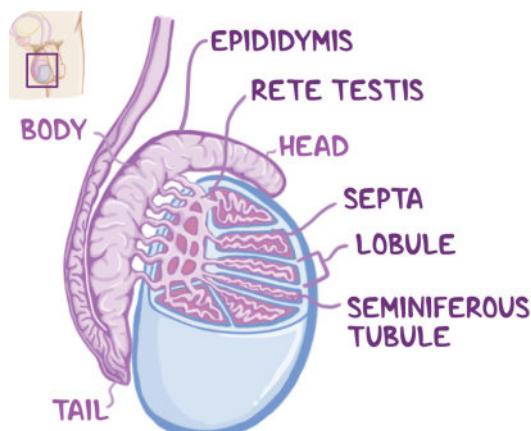


Figure 65.3 Testes anatomy.

- Spermatogonium (diploid cell) undergoes mitosis → two daughter cells (spermatogonia)
  - One spermatogonia cycled back to serve as spermatogonium
  - Second spermatogonia continues on to produce sperm
- **Spermatogonia** (diploid cell) undergoes mitosis → **primary spermatocyte**
- Primary spermatocyte undergoes meiosis I → secondary spermatocytes (haploid cells) emerge
- Secondary spermatocytes undergo meiosis II → spermatids (haploid)
- **Spermatids** enter lumen → cellular

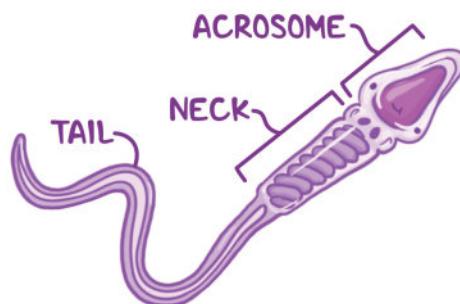


Figure 65.4 Sperm anatomy.

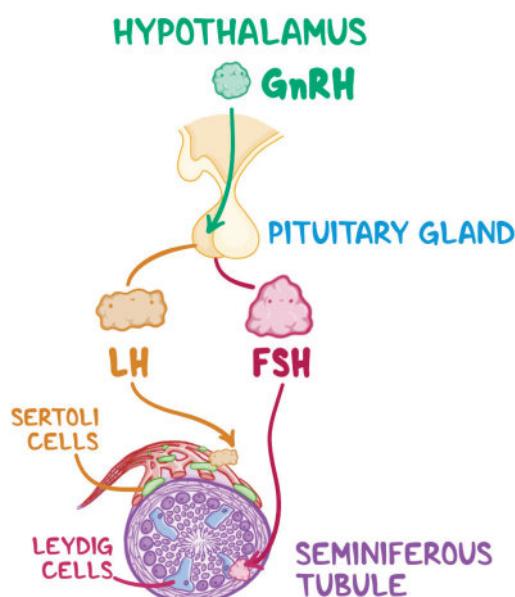


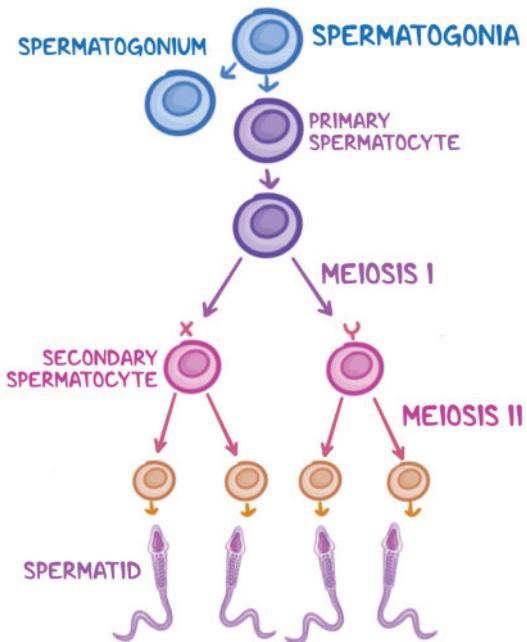
Figure 65.5 Hypothalamus secretes GnRH, stimulates pituitary release of FSH, LH (important to testosterone production).

differentiation → acquire tail → mature sperm

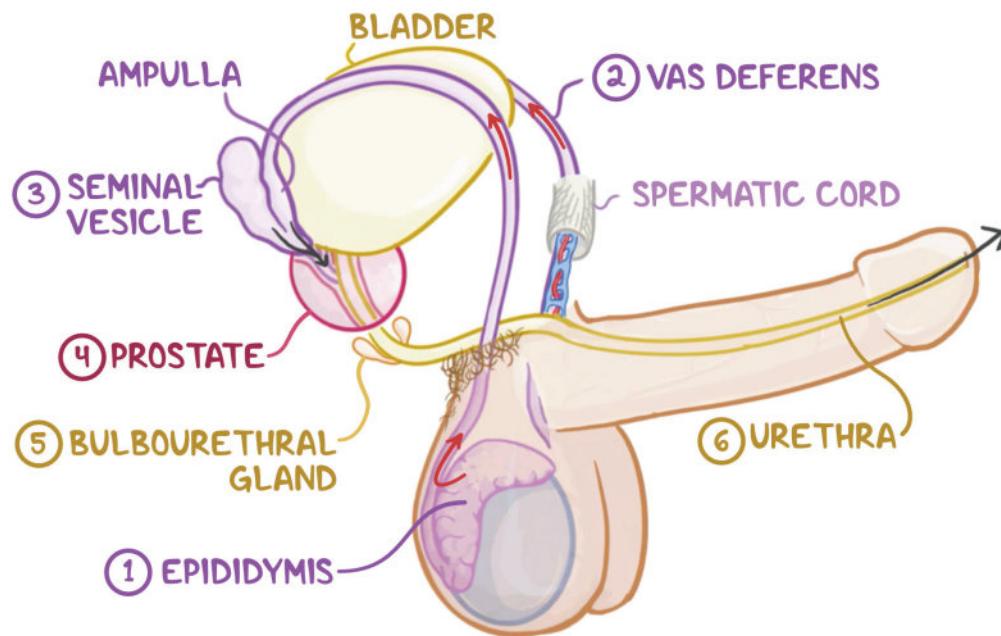
- Regulation via feedback loops
  - Sertoli cells secrete inhibin → negative feedback to pituitary → ↓ FSH
  - Leydig cells secrete testosterone → negative feedback to pituitary → ↓ LH

### Ejaculation

- Mature sperm exit through tail of epididymis → vas deferens → secretions from seminal vesicle at ampulla → ejaculatory ducts → secretions from prostate gland → secretions from bulbourethral glands → empty into urethra
- Accessory glands secrete fluids into urethra
  - Seminal: seminal fluid (contains fructose for energy, prostaglandins for transport)
  - Prostate: prostatic fluid (alkaline → neutralizes acidic vaginal secretions)
  - Bulbourethral: lubricant
- Semen (seminal fluid): final mixture of all fluids with spermatozoa
- During ejaculation, bladder sphincter contracts (prevents urine from mixing with semen)



**Figure 8.6** Spermatogenesis.



**Figure 65.7** Once produced, the mature sperm exit the tail of the epididymis (1) and travel through the vas deferens (2) where they are combined with secretions of the seminal vesicles (3) at the ampulla. The mature sperm then pass through the ejaculatory ducts and secretions of the prostate gland (4). Finally, the bulbourethral gland (5) secretions are added and the semen is ejaculated through the urethra.

# TESTOSTERONE

[osms.it/testosterone](https://osms.it/testosterone)

## WHAT IS TESTOSTERONE?

- Main androgenic hormone
- Produced, released by Leydig cells of testes
- Synthesized from cholesterol in series of steps involving multiple enzymes
- Inactivated in liver → eliminated in urine, bile
- Active locally on Sertoli cells (paracrine action)
  - Sertoli cells produce androgen-binding protein (ABP) → keep testosterone levels high
  - Testosterone reinforces follicle-stimulating hormone (FSH) spermatogenesis stimulation
- Active in rest of body (endocrine action)

## Circulation in bloodstream

- Approx. 98% bound to proteins (albumin, sex-hormone binding globulin)
  - Not biologically active when bound to protein
  - Functions as reservoir of free testosterone
  - Production regulated by androgens, estrogens
- Approximately 2% free, biologically active

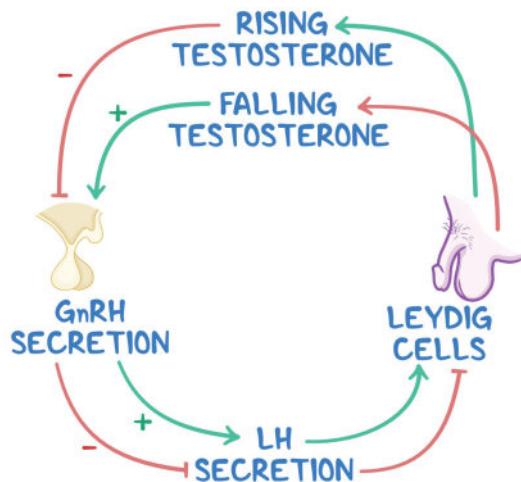
## PRODUCTION

### Regulated by hypothalamic-pituitary axis

- Low testosterone → hypothalamic arcuate nuclei secrete GnRH into hypothalamic-hypophyseal portal blood → GnRH arrives to anterior lobe of pituitary gland → pituitary gland secretes FSH, LH (AKA gonadotropins)
  - LH → Leydig cells produce testosterone by increasing cholesterol conversion into pregnenolone (first step of testosterone production)
  - FSH → spermatogenesis, Sertoli cell function

## NEGATIVE FEEDBACK REGULATION

- High testosterone levels → inhibits hypothalamus from secreting GnRH, pituitary gland from secreting LH
- Sertoli cells in testes secrete glycoprotein called inhibin → inhibits pituitary gland secreting FSH



**Figure 65.8** Testosterone production is regulated through a negative feedback loop by the hormones released by the hypothalamus and the Leydig cells.

## MECHANISM OF ACTION

- Binding on androgen receptor in cell of target tissue → androgen-receptor complex moves into nucleus → gene transcription → generation of new proteins → physiological effects

## EFFECTS OF ANDROGENIC HORMONES TESTOSTERONE & DIHYDROTESTOSTERONE

### Testosterone

- Masculinizes internal genital tract in male fetus; promotes descent of testes before birth

- Puberty: muscle mass increases; epiphyseal plates close; penis, seminal vesicles grow; spermatogenesis; rise of libido; secondary sexual characteristics (thickens vocal cords, deepening voice, male pattern of hair growth)
- Adulthood: maintains reproductive tract; anabolic effect on proteins

#### Dihydrotestosterone (DHT)

- Produced from testosterone by 5 alpha-reductase in target tissues
- Determines
  - Fetal maturation of external male genitalia (penis, scrotum, prostate)
  - Hair distribution (baldness)
  - Sebaceous gland activity
- 5 alpha-reductase inhibitors block testosterone conversion in dihydrotestosterone → treats male pattern baldness, benign prostatic hypertrophy
  - Propecia (finasteride)



# NOTES

## SEXUAL DEVELOPMENT

# DEVELOPMENT OF THE REPRODUCTIVE SYSTEM

[osms.it/reproductive-system-dev](https://osms.it/reproductive-system-dev)

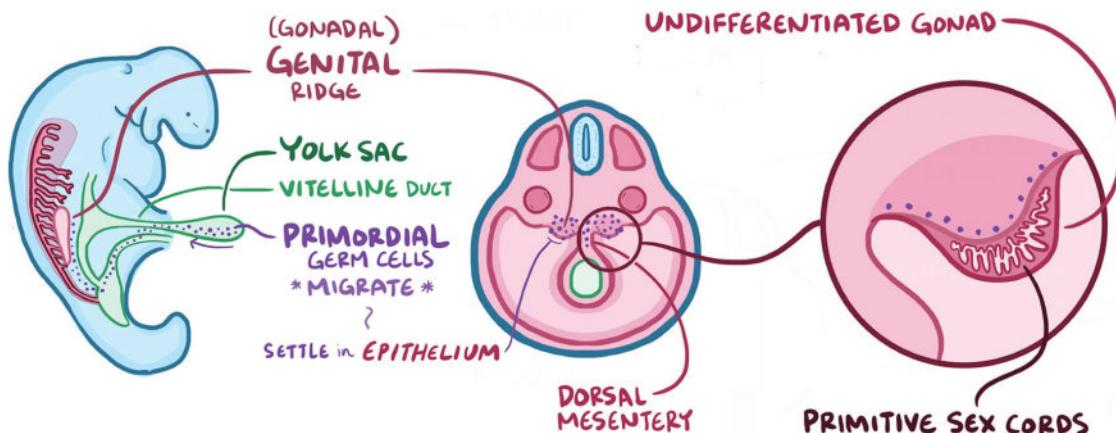
### SEXUAL DIFFERENTIATION

- Series of events begins at conception, ends with sexual characteristics acquisition (designated biologically male/female)
- During first five gestational weeks
  - Gonadal ridge develops, later becomes differentiated gonads
- Week 6
  - Primordial germ cells start migrating from yolk sac towards gonadal ridge
- Week 7
  - Primordial germ cells promote gene expression contained in sex chromosomes
- Wolffian, Müllerian ducts: structures that will develop into rest of reproductive tract; remain undifferentiated until week 8

### MALE DEVELOPMENT

#### Male gonadal development

- Embryo genetically male → gene expression in Sex-determining Region in Y chromosome (SRY) promoted
  - SRY-region genes promote testis-determining factor production → testis-determining factor acts on undifferentiated gonads → gonadal transformation into testes
  - Gonadal ridge becomes seminiferous tubules, rete testis, straight tubules
- Testes contain three functional cell types
  - Germ cells: produce spermatogonia → produce male gametes in puberty
  - Sertoli cells: synthesize anti-Müllerian hormone
  - Leydig cells: synthesize testosterone



**Figure 66.1** Illustration of the migration of primordial germ cells to the gonadal ridge in week 6. At this point, the gonad is undifferentiated, meaning that it can develop into ovaries or testes.

### Male internal reproductive organ development

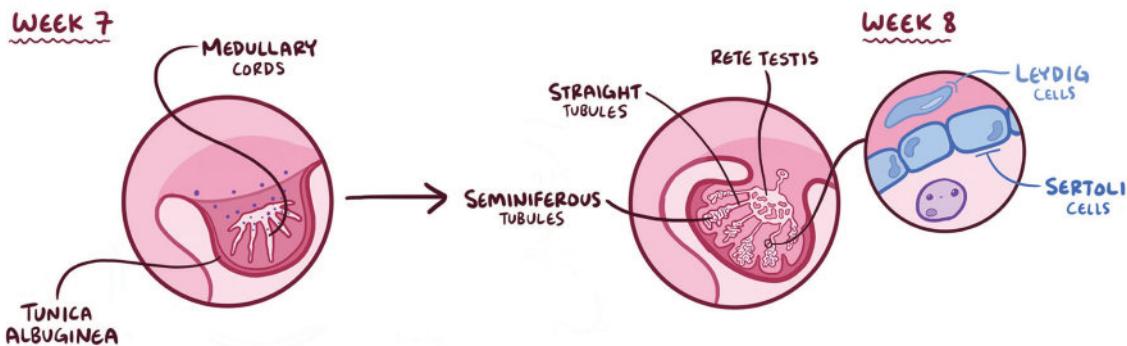
- Wolffian ducts give rise to male internal genitalia
  - AKA mesonephric duct/mesonephros
  - Meso = middle, in between; nephros = kidney
  - Two functions: connects primitive kidney to cloaca; develops into male genitalia
  - Growth, differentiation stimulated by testosterone
- Male internal reproductive organ development depends on Sertoli cells, Leydig cells, urogenital sinus
- Sertoli cells: synthesize, secrete anti-Müllerian hormone; AKA Müllerian inhibiting substance
  - Promotes Müllerian/paramesonephric-duct atrophy
- Leydig cells: synthesize, secrete testosterone → become internal male genitalia

▫ Promotes Wolffian/mesonephric-duct growth, differentiation

- Urogenital sinus: develops into external reproductive organs; undifferentiated until gestational week 9
  - Urethral folds → urethra (both)
  - Labioscrotal swellings → scrotum
  - Primordial phallus → penis

### Male external reproductive organ development

- Male external genitalia differentiation from urogenital sinus depends on testosterone presence
  - 5 alpha reductase in target tissues converts testosterone → more potent dihydrotestosterone
  - Dihydrotestosterone: responsible for masculinizing external genitalia



**Figure 66.2** Biologically male sexual differentiation, week 7: genes in Sex-determining Region of Y chromosome (SRY) code for testis-determining factor (which initiates development of testes). Primitive sex cords → medullary cords that carry primitive germ cells deeper into mesoderm. The surface epithelial layer of each gonad thins out → tunica albuginea. Later, medullary cords → seminiferous tubules, straight tubules, rete testis. The primordial germ cells settle in seminiferous tubules mature into dormant spermatogonia. During puberty, spermatogonia start dividing → sperm (male gametes). During week 8, some cells in the seminiferous tubule walls differentiate into Sertoli cells, and cells between the seminiferous tubules differentiate into Leydig cells.

## FEMALE DEVELOPMENT

### Female gonadal development

- Without functional SRY gene
  - Week 9: ovaries begin developing
  - Week 10: ovarian cortex, inner medulla distinguishable
- Ovaries contain three functional cell types
  - Germ cells: produce oogonia; located in ovarian cortex (oogonia—haploid cells that remain arrested in prophase 1 of meiosis until ovulation)
  - Granulosa cells: synthesize estradiol
  - Theca cells: synthesize progesterone
- Ovarian follicle: oogonium surrounded by granulosa cells, connective tissue

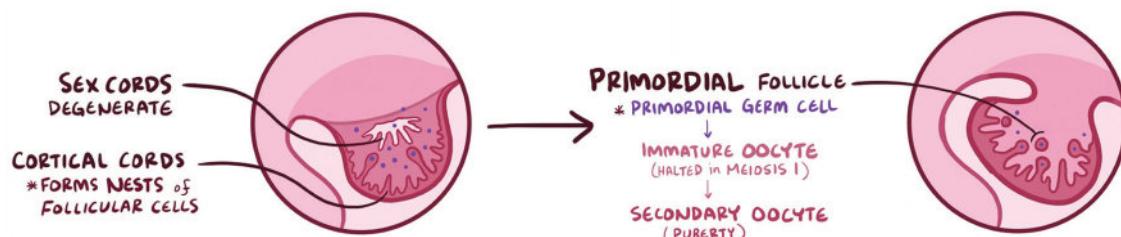
### Female internal reproductive organ development

- Müllerian duct → female genitalia
  - AKA paramesonephric duct/paramesonephros
  - Para = on the side of; meso = middle, in between; nephros = kidney
- Female internal reproductive organ development primarily depends on testes absence

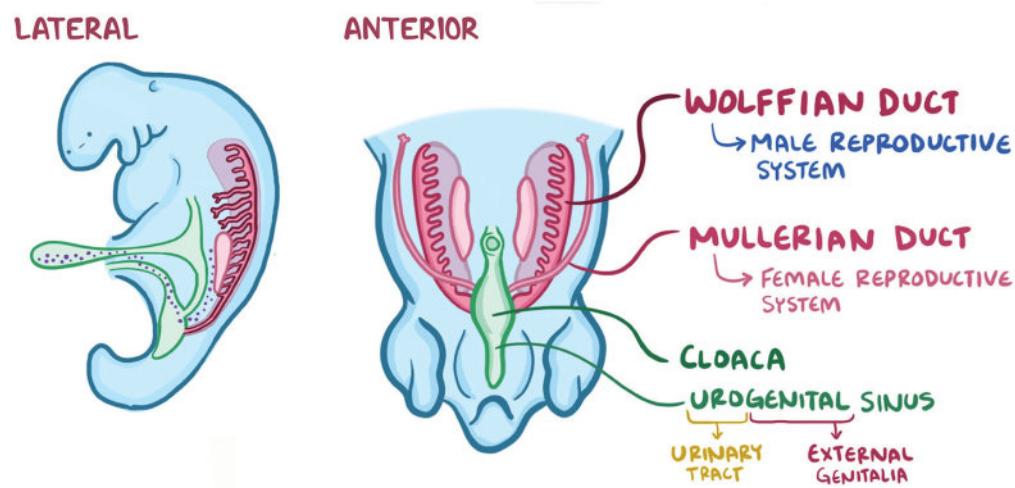
- Lack of testosterone induces Wolffian duct degeneration
- Lack of anti-Müllerian hormone promotes Müllerian ducts persistence → develop into fallopian tubes, uterus, upper 1/3 of vaginal canal
- Rest of female reproductive organs arise from urogenital sinus

### Female external reproductive organ development

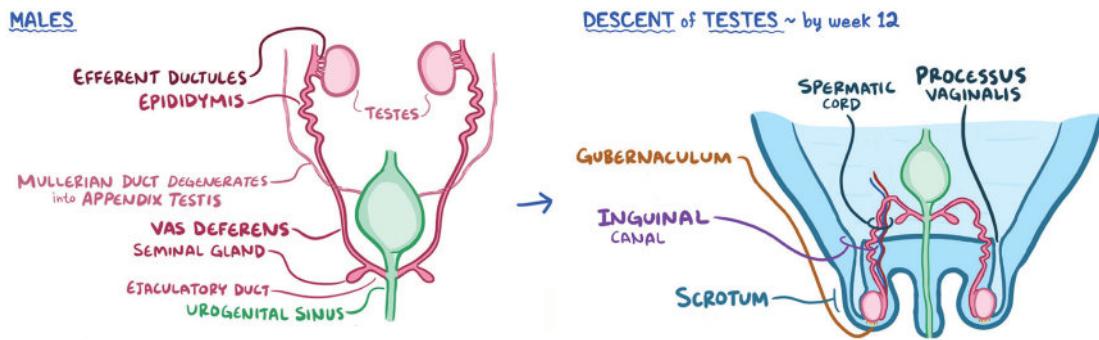
- Urogenital sinus develops into external reproductive organs; undifferentiated until gestational week 9
  - Urethral folds → urethra (both ♂), labia minora
  - Labioscrotal swellings → labia majora, mons pubis
  - Primordial phallus → clitoris
- Female external genitalia differentiation
  - Androgen absence-dependent (testosterone, dihydrotestosterone)
- Phenotypic differentiation complete at week 12 → earliest ultrasound-based sex-determination date



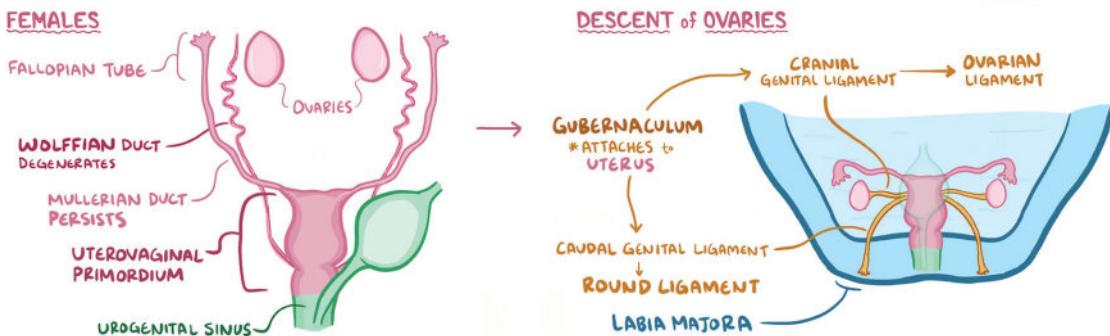
**Figure 66.3** Biologically-female sexual differentiation. Since there is no Y chromosome to secrete Testis-determining factor, the undifferentiated gonads develop into ovaries. The rest of the reproductive tract acquires female characteristics in the absence of testosterone.



**Figure 66.4** The genital ducts are initially undifferentiated, tubular structures that run down the embryo's back inside the two nephrogenic cords on either side of the embryo. The Wolffian and Müllerian ducts start in the thoracic and upper lumbar region and continue down the embryo's back until they open into the part of the cloaca called the urogenital sinus.



**Figure 66.5** Male internal reproductive organ differentiation and descent of gonads.



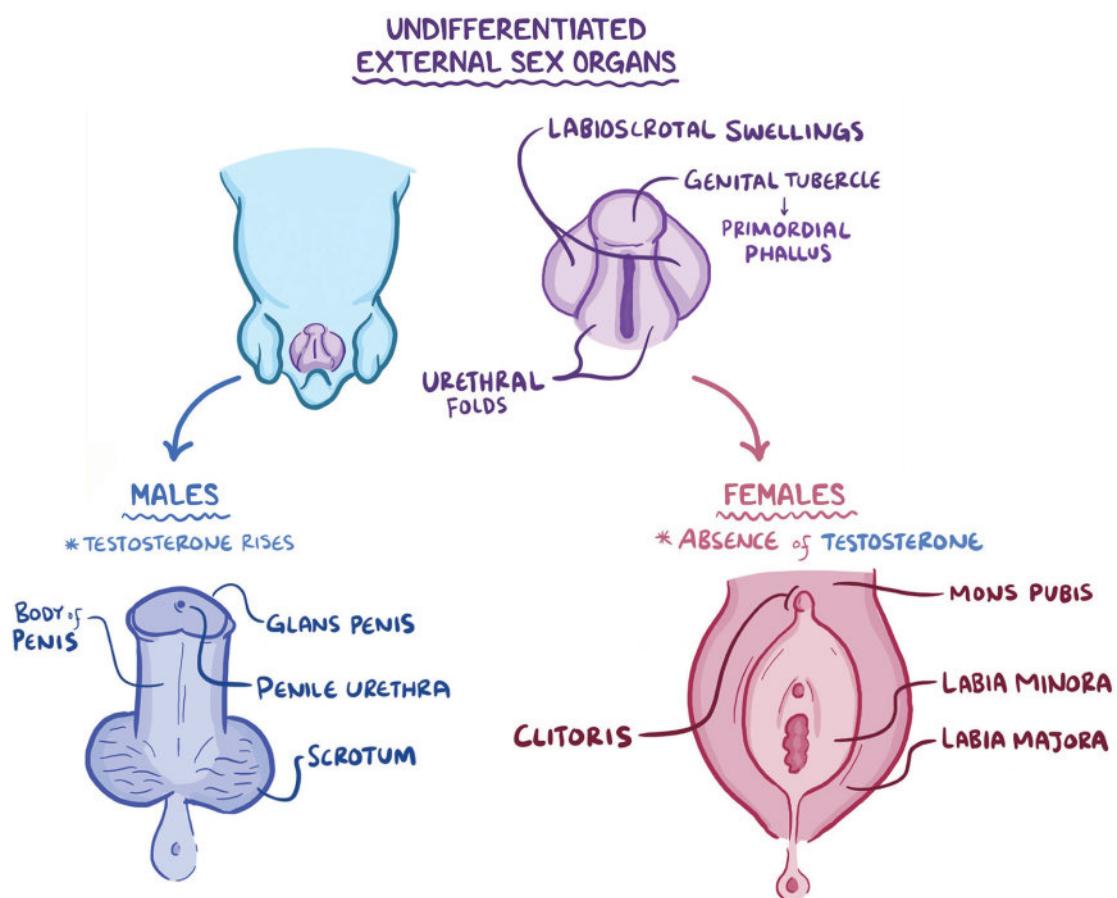
**Figure 66.6** Female internal reproductive organ differentiation and descent of gonads.

## SEX VS. GENDER

- Gender
  - Socially-constructed characteristics/behaviors associated with biologically male/female people
  - E.g. norms, roles, relationships between individuals
- Genetic sex
  - Individual's chromosomal composition
  - XY: males
  - XX: females
  - Established by oocyte, sperm cell fusion
- Gonadal sex
  - Individual's reproductive organs
  - Male: testes
  - Female: ovaries
- Phenotypic sex

## Internal, external reproductive organ structure

- Male genitalia
  - Internal: prostate, seminal vesicles, vas deferens, epididymis
  - External: penis, scrotum
- Female genitalia
  - Internal: fallopian tubes, uterus, upper  $\frac{1}{3}$  vaginal canal
  - External: clitoris, labia majora, labia minora, lower  $\frac{2}{3}$  vaginal canal



**Figure 66.7** Male and female external sex organs. Phenotypical differentiation is complete at week 12.

# PUBERTY & TANNER STAGING

[osms.it/puberty-tanner-staging](https://osms.it/puberty-tanner-staging)

## PUBERTY

- Sexual maturation process involving endocrine, physical changes; controlled by hypothalamic-pituitary-gonadal axis
- Begins between ages 10–14 in females; between age 12–16 in males

## GnRH secretion

- Pulses from hypothalamus regulate luteinizing hormone (LH), follicle-stimulating hormone (FSH) secretion from anterior pituitary → development of sexual characteristics
  - Primary sex characteristics: genitals (organs directly involved in sexual reproduction)
  - Secondary sex characteristics: sex-specific physical characteristic not necessary involved in sexual reproduction (e.g. pubic hair—both sexes, voice changes—males, breast development—females)

## Gamete production

- Oocytes (females); sperm (males)
- Males: LH acts on Leydig cells → produces testosterone; FSH acts on Sertoli cells → produces sperm
- Females: LH acts on ovarian follicles → produces progesterone, androstenedione (converted into estrogen)
  - Estrogen, progesterone levels vary according to menstrual cycle phases

## Gonadal steroid production

- Testosterone (males), estradiol (females) secretion → ↑ circulating sex hormones
- Secondary sexual characteristics develop
- Stimulate bone growth, ossification
- Involved in growth hormone production → growth spurt

## EVENTS OF PUBERTY

### Gonadarche

- Gonadal activation by FSH, LH

### Adrenarche

- ↑ adrenal androgen production by adrenal cortex

### Thelarche

- Breast tissue appears
  - Ovarian estradiol-guided

### Menarche

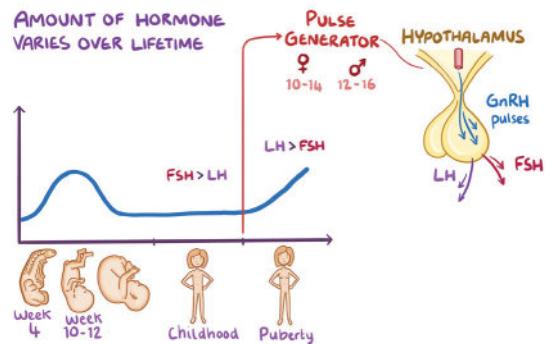
- First menstruation occurs
  - Ovarian estradiol-guided
  - First menstrual cycles tend to be anovulatory

### Spermarche

- First sperm production occurs
  - FSH, LH, testosterone-guided
  - Nocturnal sperm emissions, sperm appears in urine

### Pubarche

- Pubic hair appears
  - Adrenal androgens-guided
  - Association: body hair; acne; apocrine sweat glands activation



**Figure 66.8** Puberty begins when pulse generator in hypothalamus begins secreting GnRH in pulses → pulsatile secretion of FSH and LH. In puberty, GnRH receptors in anterior pituitary become more sensitive to GnRH stimulation: small ↑ GnRH = large ↑ FSH, LH levels.

## TANNER STAGING

- System for describing predictable steps during sexual maturation
- Centers on two, **independent criteria**
  - Appearance: pubic hair in males, females
  - Genital development: ↑ **testicular volume, penile growth** (males); **breast development** (females)

## FIVE CATEGORIES OF TANNER STAGING

### Stage 1: pre-pubertal

- ♀ No pubic hair present in either sex
- ♂ Small penis, testes
- ♀ Have flat-chest

### Stage 2

- ♀ Soft pubic hair appears
- ♂ Measurable testes enlargement
- ♀ Breast buds appear

### Stage 3

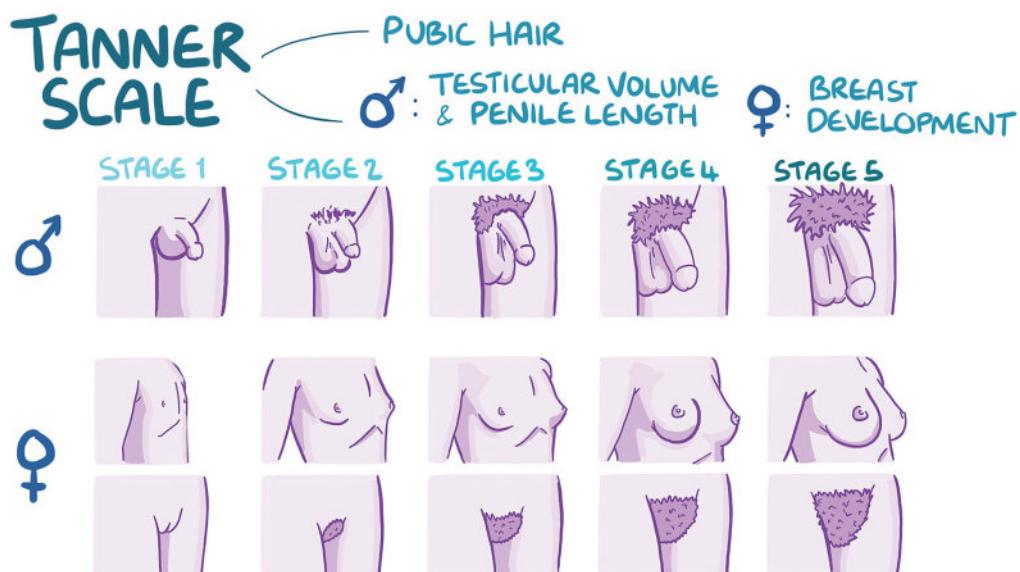
- ♀ Pubic hair becomes coarser
- ♂ Penis begins to enlarge in size, length
- ♀ Breast mounds form

### Stage 4

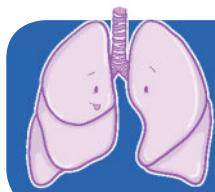
- ♀ Pubic hair begins to cover pubic area
- ♂ Penis begins to widen
- ♀ Breast enlargement forms “mound-on-mound” breast contour

### Stage 5: adult

- ♀ Pubic hair extends to inner thigh
- ♂ Penis, testes enlarged to adult size
- ♀ Breast takes on adult contour



**Figure 66.9** Illustration of the five stages of the Tanner scale in males and females.



# NOTES

## ANATOMY & PHYSIOLOGY

# RESPIRATORY SYSTEM

[osms.it/respiratory-anatomy-physiology](http://osms.it/respiratory-anatomy-physiology)

## RESPIRATORY SYSTEM

- Upper respiratory tract
  - Nose, pharynx, associated structures
- Lower respiratory tract
  - Larynx, trachea, bronchi, lungs

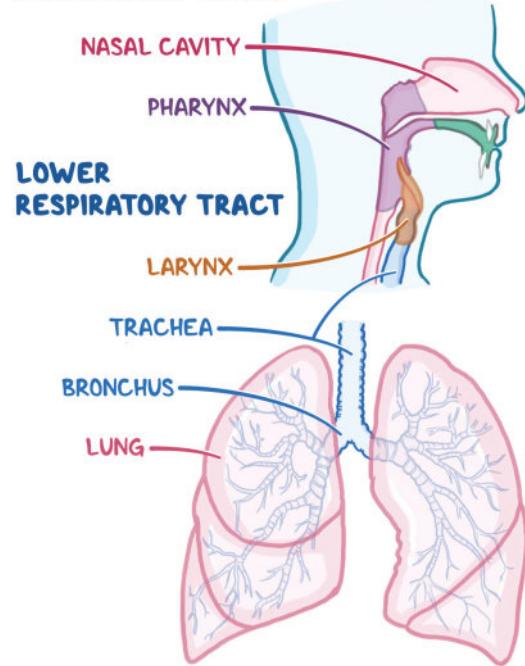
## Respiratory system function

- Gas exchange between blood, atmosphere
- Protection against harmful particles, substances
- pH homeostasis
- Vocalization

## Conducting vs. respiratory zone

- Conducting zone
  - Does not participate in gas exchange
  - Nose to terminal bronchioles
  - Function: inspire, warm, humidify, filter air before gas exchange
  - Smooth muscle layer contains autonomic nervous system (sympathetic, parasympathetic nerves)
  - Smooth muscle along trachea, first few bronchial branches have beta-2-adrenergic receptors
  - Sympathetic nerves stimulate beta-2-adrenergic receptors → ↑ airway diameter
  - Parasympathetic nerves stimulate muscarinic receptors → ↓ airway diameter
- Respiratory zone
  - Participates in gas exchange
  - Lined with alveoli
  - Terminal bronchioles–alveoli

## UPPER RESPIRATORY TRACT



**Figure 67.1** Respiratory system overview, categorized into upper, lower respiratory tracts.

## RESPIRATORY SYSTEM ANATOMY

### Nose

- Function: humidifies, warms, filters inspired air; voice resonance chamber; houses olfactory receptors
- Nasal vibrissae (hairs) coated with mucus → traps large particles (e.g. dust, pollen)

### Nasal cavity

- Nasal cavity division
  - Midline nasal septum: composed of septal cartilage, anteriorly
  - Vomer bone: posteriorly
- Four paranasal sinuses (air-filled spaces inside bones) connected to nasal cavity
  - Ethmoid, frontal, sphenoid, maxillary sinuses
  - Function: warms, moistens inspired air; amplifies voice; lightens skull
- Roof formed by ethmoid, sphenoid bones
- Floor formed by palate
- Two mucous membrane types
  - Olfactory mucosa: olfactory epithelium containing smell receptors
  - Respiratory mucosa: pseudostratified ciliated columnar epithelium containing goblet cells; secretes mucus containing lysozyme, defensins
- Nasal conchae
  - Three mucosa-covered projections (superior, middle, inferior nasal conchae) of nasal cavity's lateral wall
  - Meatus: groove inferior to each conchae (superior, middle, inferior meatus)
  - Function: ↑ turbulence inside cavity to filter, humidify inspired air; reabsorb heat, moisture during nasal expiration

### Palate

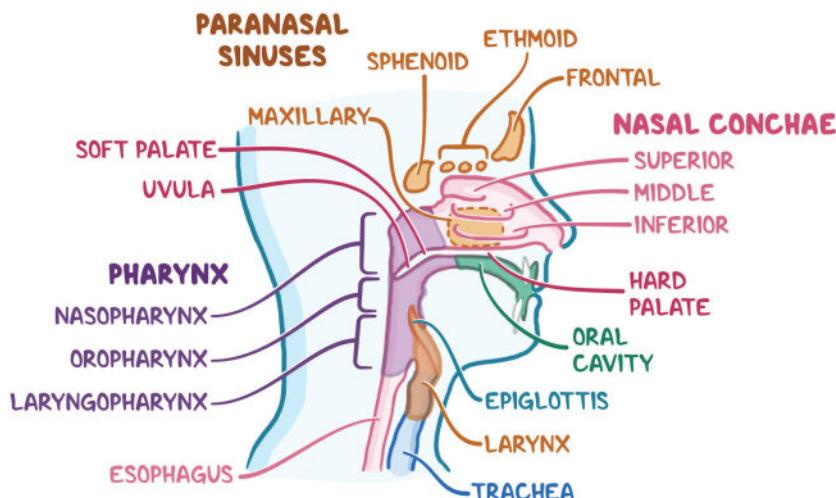
- Separates nasal cavity from oral cavity
  - Hard palate: anterior portion supported by palatine bones
  - Soft palate: posterior portion not supported by bones
  - Soft palate, uvula move together; forms valve that closes nasopharynx when swallowing (prevents food from entering nasopharynx)

### Pharynx

- AKA throat
- Passageway connecting nasal cavity, larynx, oral cavity, esophagus
- Nasopharynx: region connecting nasal cavity to pharynx
  - Posterior to nasal cavity, inferior to sphenoid bone, superior to soft palate
  - Air-only passageway
  - Pharyngeal tonsils (adenoids); located on posterior wall; traps, kills pathogens
  - Pseudostratified ciliated epithelium (part of mucociliary escalator)
- Oropharynx: region connecting pharynx to oral cavity
  - Posterior to oral cavity, continuous with isthmus of fauces
  - Soft palate superior, epiglottis inferior
  - Food, air passageway
  - Pseudostratified columnar epithelium of nasopharynx → stratified squamous epithelium
  - Palatine tonsils located on lateral walls
  - Lingual tonsils cover posterior tongue
- Laryngopharynx: part of pharynx continuous with larynx (voice box)
  - Food, air passageway
  - Stratified squamous epithelium
  - Epiglottis anterior, esophagus posterior

### Larynx

- Cartilage, connective tissue framework
  - Connects pharynx to trachea; houses vocal cords, epiglottis (cartilage flap atop larynx that seals airway off when swallowing—prevents food entering larynx)
- Location
  - Third to sixth cervical vertebra
  - Superior: hyoid bone
  - Inferior: trachea
- Function
  - Routes food, air into appropriate passageway; voice production
- Histology
  - Superior portion: contacts food; stratified squamous epithelium
  - Inferior portion: below vocal folds; pseudostratified ciliated columnar epithelium (part of mucociliary escalator)



**Figure 67.2** Anatomy of upper respiratory tract, surrounding structures.

- Contains nine cartilages
  - Thyroid cartilage: large shield-shaped midline cartilage, produces laryngeal prominence ("Adam's apple")
  - Cricoid cartilage: ring-shaped cartilage inferior to thyroid cartilage, superior to trachea
  - Arytenoid, cuneiform, corniculate cartilages: form posterior, lateral larynx walls (arytenoid cartilages anchor vocal cords)
  - Epiglottis: spoon-shaped cartilage is pulled superiorly to cover laryngeal inlet during swallowing (prevents food from passing through larynx)
- Vocal folds/ligaments
  - Attach arytenoid cartilages to thyroid cartilage
  - True vocal cords: sound production (function); composed of elastic fibers; core of mucosal folds; appears white (avascularity)
  - False vocal cords: superior to true vocal cords; does not participate in sound production; close glottis during swallowing (function)

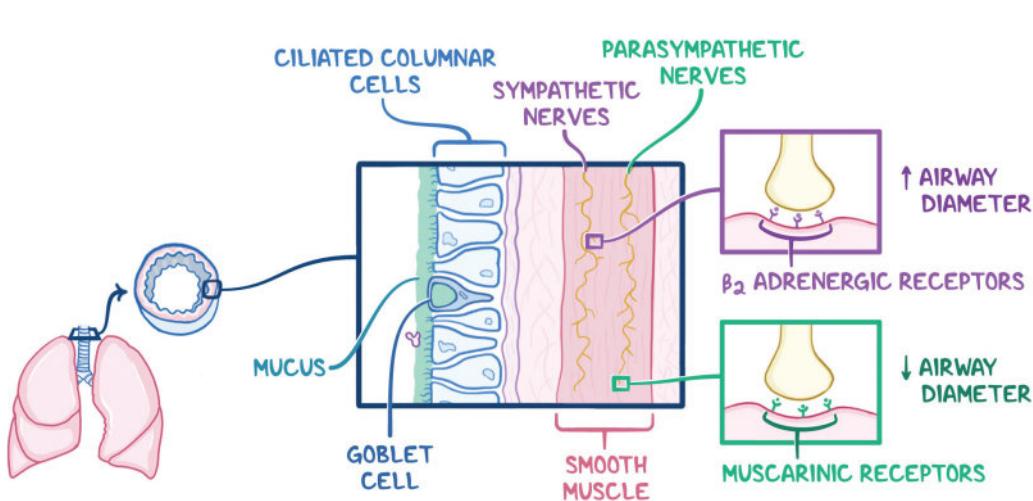
#### Trachea

- AKA windpipe
- Mainstem bronchi, airways
- Trachea
  - Tube smooth muscle, connective tissue, C-shaped cartilage (provides support,

- maintains open passage for air)
- Connected by trachealis muscle
- Runs from larynx, divides into two main bronchi inferiorly at carina
- Layers (superficial to deep)
  - Mucosa: pseudostratified epithelium with goblet cells; mucociliary escalator
  - Submucosa: connective tissue layer (supported by 16–20 C-shaped cartilage rings)
  - Adventitia: connective tissue layer encasing cartilage rings

#### Right & left mainstem bronchus

- Right mainstem bronchus
  - Wider, more vertical
  - Something accidentally inhaled → goes into right lung (more likely)
- Inside lungs
  - Main bronchus subdivides into lobar bronchi → segmental bronchi → terminal bronchioles
- Trachea, first three bronchial generations
  - Wide, supported by cartilage rings
- Large airways lined by ciliated columnar cells, goblet cells (secrete mucus)
  - Mucociliary escalator: mucus traps particles → ciliated columnar cells beat rhythmically → moves mucus, trapped particles towards pharynx → spit out/swallowed



**Figure 67.3** Section of tracheal wall showing its histology. Stimulation by sympathetic nerves dilates airways, stimulation by parasympathetic nerves constricts airways.

### Histological changes as conducting tubes decrease

- Cartilage
  - Cartilage amount ↓ while elastic fibers ↑ (bronchioles contain no cartilage)
- Epithelium
  - Mucosal epithelium changes from **pseudostratified columnar** → **columnar** → **cuboidal**
  - **Goblet cells, cilia ↓** (completely absent in bronchioles)
- Smooth muscle ↑

### Bronchioles

- Narrow airways after first three bronchial generations
- **Terminal bronchioles:** last part of terminal bronchioles, end of conducting zone
- **Respiratory bronchioles:** distal to terminal bronchioles, first part of respiratory zone
- Terminal bronchiole → respiratory bronchiole → alveolar ducts → alveolar sac → alveoli

### Alveoli

- Alveolar wall
  - Composed of a single **simple squamous** epithelium layer
- Elastic fibers surround alveoli → allow lung expansion during inspiration, recoil during expiration
  - **Type I pneumocytes:** primary **gas exchange** site; oxygen–carbon dioxide

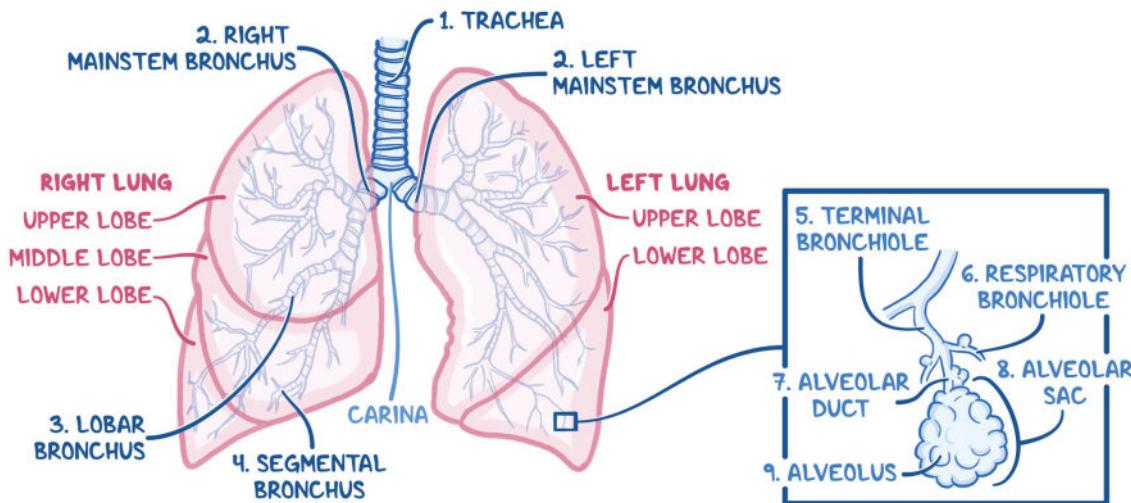
exchange occurs between alveolar gas, pulmonary capillary blood; thin walls, large alveoli surface-area maximizes gas exchange diffusion capabilities

- **Type II pneumocytes:** **secrete surfactant** (↓ surface tension within alveoli → eases expansion, prevents collapsing)
- Alveolar macrophages phagocytize particles inside lungs → conducting bronchioles → mucociliary escalator
- Respiratory membrane
  - Capillary, alveolar walls; basement membranes
- Alveolar pores connect adjacent alveoli
- Blood supply
  - Pulmonary capillary networks

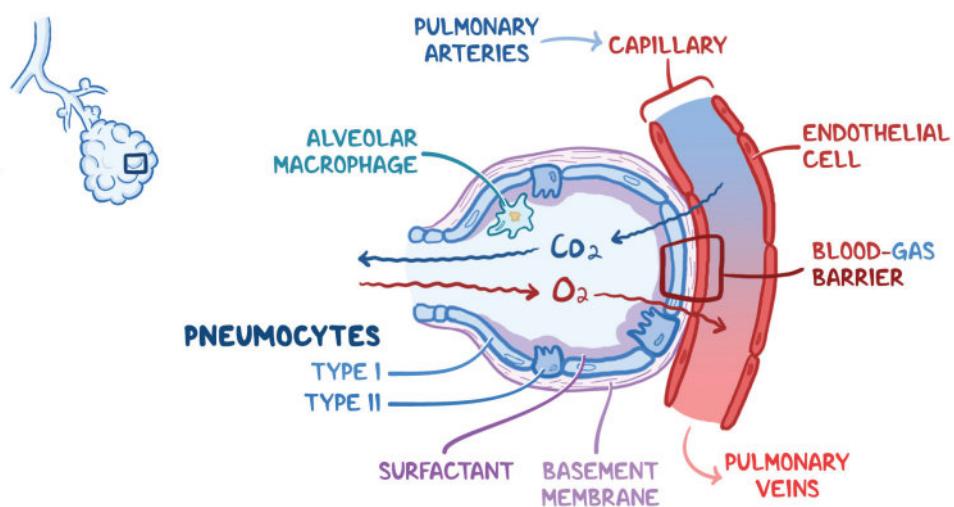
### Lungs

- Main respiration organs
- Right lung
  - **Three lobes:** upper, middle, lower lobe
- Left lung
  - **Two lobes:** upper, lower lobe
- Base of lungs rest on diaphragm
- **Pleura:** **double-layered** serosa covering lungs, pleural fluid lining pleural cavity between two layers
  - **Parietal pleura:** outer layer adherent to thoracic wall, superior surface of diaphragm
  - **Visceral pleura:** inner layer adherent to external lung surface

- Pulmonary circulation
  - Pulmonary veins (anterior to main bronchi) bring oxygen-rich blood to lungs from heart
  - Pulmonary arteries bring oxygen-poor systemic venous blood for oxygenation
  - Low-pressure, high-volume circulation
- Bronchial circulation
  - Bronchial arteries: provide oxygenated systemic blood to lung tissue
  - Bronchial veins: drain deoxygenated
- Innervation
  - Pulmonary plexus
  - Parasympathetic motor causes bronchoconstriction
  - Sympathetic motor causes bronchodilation
  - Visceral sensory
  - Diaphragm innervated by phrenic nerve



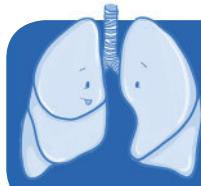
**Figure 67.4** Trachea and lung anatomy. Numbered labels show sequence of airflow going into the airways from (trachea to alveoli).



**Figure 67.5** Alveolus structure. Gas exchange occurs at the blood-gas barrier. De-oxygenated blood from pulmonary arteries are oxygenated then sent to pulmonary veins.

## VENTILATION

- Ventilation (breathing): moving air in, out of lungs
- Oxygen pathway
  - Air inhaled through nostrils → nasal cavity → pharynx → larynx → trachea → mainstem bronchus → conducting bronchioles → terminal bronchioles → respiratory bronchioles → alveolar duct → alveoli → capillary → body
  - Carbon dioxide moves in reverse
- Airflow from atmosphere to lungs
  - Higher pressure → lower pressure
- Muscle movement creates pressure gradient
  - Primary respiration muscles: diaphragm, external intercostals, scalenes
  - Forceful breathing: other muscles recruited
- Airflow resistance: function of respiratory passage diameter
- Passive inhalation: negative pressure inside body generated → moves air into lungs
  - Diaphragm contracts downwards, chest muscles pull ribs outward → ↑ intrathoracic volume → ↓ intrathoracic pressure → air moved into lungs (air flows down pressure gradient)
- Passive exhalation: ↑ intrathoracic pressure generated → moves air out of lungs
  - Diaphragm relaxes (returns to resting position), external intercostal muscles relax, thoracic cage recoils → elastic lung recoil → ↓ intrathoracic volume → ↑ intrathoracic pressure → air pushed out of lungs



# NOTES BREATHING MECHANICS

## LUNG VOLUMES & CAPACITIES

[osms.it/lung-volumes-capacities](https://osms.it/lung-volumes-capacities)

- Spirometry: spirometer used to measure air volume moving in, out of lungs
- Static lung volumes: volumes not involved in airflow rate
- Capacities: combination of > one lung volume
- VT + inspiratory reserve volume = 3.5L
- Vital capacity ( $V_C$ )
  - $V_T + \text{inspiratory reserve volume (IRV)} + \text{ERV} = 4.7\text{L}$
- Total lung capacity (TLC)
  - Combination of all lung capacities = 5.9L

### Volume variations

- Related to age, sex, body size, posture
- Tidal volume ( $V_T$ )
  - 500mL
  - Air volume inspired, expired during quiet breathing
- Inspiratory reserve volume
  - Maximum volume inhaled air above  $V_T = 3\text{L}$
- Expiratory reserve volume
  - Maximum expired air volume below  $V_T = 1.2\text{L}$
- Residual volume (RV)
  - Air remaining in lungs after forced expiration = 1.2L (not measured by spirometry)
- Functional residual capacity (FRC)
  - Expiratory reserve volume (ERV) + RV = 2.4L

### MEASURING FRC

#### Helium dilution method

- Helium placed in spirometer → inhaled
- Helium concentration in lungs equalizes with amount of helium placed in spirometer (helium insoluble in blood) after few breaths
- Total helium mass measured in spirometer = FRC

#### Body plethysmograph method

- Application of Boyle's law ( $P \times V = k$ )
- Person sits inside plethysmograph (airtight box) → breathes in/out through mouthpiece → measures air pressure in mouth
- Mouthpiece closed after expiring  $V_T$ ; as person attempts to breathe FRC calculated using measurements of alveolar pressure, lung volume, pressure changes within plethysmograph

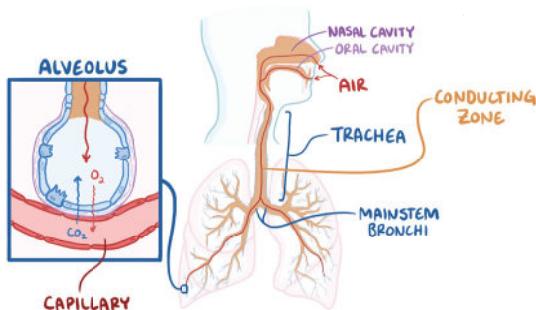
# ANATOMIC & PHYSIOLOGIC DEAD SPACE

[osms.it/anatomic-physiologic-dead-space](https://osms.it/anatomic-physiologic-dead-space)

- Dead space: air volume enters airways, lungs; **no gas exchange** occurs

## ANATOMIC DEAD SPACE

- Air inaccessible to body for gas exchange (due to anatomical structure)
- Air contained in **conducting zone** (nose → terminal bronchioles)
- Conduit for air movement in/out of lungs; warms, humidifies air; removes debris, pathogens
- Volume = 150mL ( $\frac{1}{3}$  of tidal volume)



**Figure 68.1** The volume of air contained in the conducting zone is called anatomic dead space because no gas exchange occurs here; therefore, no oxygen can be extracted from this air.

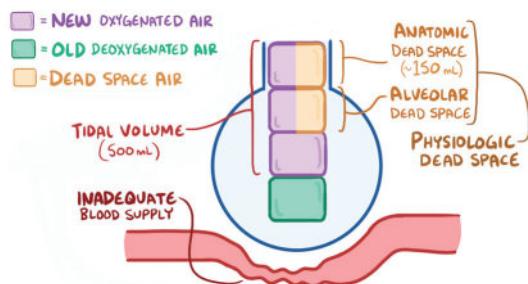
## PHYSIOLOGIC DEAD SPACE

- Air physiologically inaccessible to body for gas exchange
- **Composition:** anatomic dead space + dead space in respiratory zone (respiratory bronchioles, alveolar duct, alveolar sac, alveoli) that does not partake in gas exchange
  - Ventilation/perfusion defect: alveoli ventilated, not well perfused (alveolar dead space)
- Volume = approx. 0 (in healthy adult)

- Anatomic dead space = physiologic dead space

$$V_T = V_D + V_A$$

- $V_T$  = tidal volume
- $V_D$  = physiological dead space volume
- $V_A$  = air volume present in functioning alveoli



**Figure 68.2** The green block represents residual air from the previous inhalation that participated in gas exchange. The purple blocks represent new oxygenated tidal volume inhaled during the current breath. Some of this new air also ends up being dead space air ("alveolar dead space") due to an inadequate blood supply to the alveolus.

## Physiological dead space volume (Bohr equation)

- Assumptions
  - Environmental air  $CO_2 = 0$  (actual amount  $\cong 0.04\%$ )
  - Dead space  $CO_2$  contribution = 0
  - All  $CO_2$  in exhaled air comes from functioning alveoli
- $$V_D = V_T \times \frac{Pa_{CO_2} - Pe_{CO_2}}{Pa_{CO_2}}$$

$$V_D = V_T \times \frac{Pa_{CO_2} - Pe_{CO_2}}{Pa_{CO_2}}$$

# VENTILATION

[osms.it/ventilation](http://osms.it/ventilation)

- Air movement between environment, lungs
- Ventilation rates: measure air volume moving in/out of lungs over period of time

## MINUTE VENTILATION ( $V_E$ )

- $V_E$  = amount of air moved in/out of lungs in one minute; does not factor in physiological dead space

$$V_E = (VT) \times (\text{Respiratory Rate/RR})$$
$$V_E = 500 \text{ mL} \times 15/\text{minute} = 7.5 \text{ L/minute}$$

## ALVEOLAR VENTILATION ( $V_A$ )

- $V_A = V_E$  corrected for physiological dead space

$$V_A = (VT - VD) \times RR$$
$$V_A = (500 \text{ mL} - 150 \text{ mL}) \times 15 = 5.2 \text{ L/minute}$$

- $V_A$  without measuring dead space
  - $V_A = \text{volume of CO}_2 (V_{CO_2}) \div \text{fraction CO}_2 (F_{CO_2})$
  - $VA = (V_{CO_2}) / (F_{CO_2})$

- Partial pressure: proportional to fractional concentration of that gas in mixture; based on constant K

- Assumes gases are saturated with water vapor (normal body temperature, sea-level atmospheric pressure)
- $\text{CO}_2$  partial pressure in alveolar air:  $P_{CO_2} = F_{CO_2} \times K$
- Alveolar ventilation equation:  $V_A = [(V_{CO_2}) / (P_{CO_2})] \times K$
- Replacing  $P_{CO_2}$  with  $P_{aCO_2}$  pressure in arterial blood ( $Pa_{CO_2}$ ) in alveolar equation
- Inverse relationship between alveolar ventilation,  $\text{CO}_2$  partial pressure in alveolar air, pulmonary arteries (e.g. ↑ air ventilating the alveoli → ↓  $\text{CO}_2$  in blood, vice versa)

$$V_A = \frac{V_{CO_2} \times K}{P_{aCO_2}}$$

# ALVEOLAR GAS EQUATION

[osms.it/alveolar-gas-equation](https://osms.it/alveolar-gas-equation)

- Pressure in alveoli = atmospheric pressure ( $P_{atm}$ ); air in alveoli contains water vapor
- Alveolar pressure ( $P_{atm}$ ) = water vapor pressure ( $P_{vapor}$ ) + gas mixture pressure  
→ total alveolar pressure exerted from all gases minus water vapor =  $P_{atm} - P_{vapor}$
- $O_2$  partial pressure dissolved in blood ( $P_{aO_2}$ ) =  $CO_2$  partial pressure in alveoli ( $P_{ACO_2}$ ) ÷ by R (respiratory quotient)  

$$P_{aO_2} = (P_{ACO_2}) / R$$
- Partial pressure of  $O_2$  inside alveolus ( $P_{AO_2}$ ) = partial pressure of inspired oxygen ( $P_{iO_2}$ ) minus partial pressure of oxygen going into blood ( $P_{aO_2}$ )

## Partial pressure: gas particle mixture

- Gas' partial pressure proportional to fractional gas concentration in mixture
- Fractional  $CO_2$  concentration ( $F_{CO_2}$ ) = 0.3
  - Accounts for 30% of gas molecules ( $F_{CO_2} \times$  total pressure of gas mixture  $P_{gases}$ )
- Fractional concentration of  $O_2$  ( $F_{O_2}$ ) = 0.7
  - Accounts for remaining 70% ( $F_{O_2} \times$  total pressure of gas mixture  $P_{gases}$ )

- Pressure exerted by  $O_2$  > pressure exerted by  $CO_2$  (proportional to fractional concentrations)
  - If  $P_{gases} = 20\text{mmHg}$ ; partial pressure of  $O_2 = 14\text{mmHg}$  ( $0.7 \times 20$ ); partial pressure of  $CO_2 = 6\text{mmHg}$  ( $0.3 \times 20$ )
  - Partial pressure of inspired air ( $P_{iO_2}$ ), fractional oxygen concentration in inspired air ( $F_{iO_2}$ ), accounting for water vapor

$$P_{iO_2} = F_{iO_2} \times (P_{atm} - P_{vapor})$$

## Alveolar gas equation

- Relationship between  $O_2$  partial pressure inside alveolus to  $CO_2$  partial pressure in alveolus

$$P_{AO_2} = [F_{iO_2} \times (P_{atm} - P_{vapor})] - [(P_{ACO_2}) / R]$$

$$P_{AO_2} = 150 - (1.25 \times P_{ACO_2})$$

- $F_{iO_2} = 0.21$  (normal air = 21%  $O_2$ )
- Atmospheric pressure = 760mmHg
- Water vapor pressure = 47mmHg
- $R = 0.8$

# COMPLIANCE OF LUNGS & CHEST WALL

[osms.it/compliance-lungs-chest-wall](https://osms.it/compliance-lungs-chest-wall)

- Compliance measures how changes in pressure → lung volume change
- Lung, chest wall compliance: inversely correlated with elastic, "snap back" properties (elastance)
  - Compliance =  $\Delta V / \Delta P$
  - Elastance =  $\Delta P / \Delta V$

- ↑ compliance → lungs easier to fill with air
  - Forces promoting open alveoli: compliance, transmural pressure gradient, surfactant
- ↓ compliance → lungs harder to fill with air
  - Forces promoting collapse of alveoli: elastic recoil/elastance, alveolar surface tension

# COMBINED PRESSURE-VOLUME CURVES FOR THE LUNG & CHEST WALL

[osms.it/pressure-vol\\_curves\\_lung\\_chest\\_wall](http://osms.it/pressure-vol_curves_lung_chest_wall)

- Pressure-volume relationship is curvilinear
- Volume at FRC (zero airway pressure)
  - Lung inward recoil: balanced with chest wall's tendency to expand outward (e.g. at equilibrium with no tendency to collapse/expand)
- Volume > FRC
  - Positive transmural pressure
  - ↑ lung recoiling force
  - ↓ chest wall outward force
- Volume < FRC (forced expiration)
  - Negative transmural pressure
- ↓ lung recoiling force
- ↑ chest wall outward force
- Pressure-volume curves plotted on graph
  - X-axis: pressure
  - Y axis: volume
  - Slope of curve = compliance
- Curve flattens out when lung, chest wall compliance combined
- Hysteresis: compliance for inspiration, expiration are different → slopes will be different

# ALVEOLAR SURFACE TENSION & SURFACTANT

[osms.it/alveolar-surface-tension-surfactant](http://osms.it/alveolar-surface-tension-surfactant)

- Alveoli lined with fluid film; water tends to form spheres (e.g. drops)
  - Due to intrinsic surface tension (caused by attraction of water molecules to each other)
- Surface tension creates pressure → pulls alveoli closed → collapses into sphere → ↓ gas exchange
- Law of Laplace: pressure that promotes lungs' collapse is (1) directly proportional to surface tension, (2) inversely proportional to alveoli radius

$$P = 2T/r$$

- P = pressure on alveolus
- T = surface tension
- r = alveolar radius

- Smaller alveolus ( $r = 1$ ) → ↑ pressure
  - $P = 2 \times 50/1 = 100$
- Larger alveolus ( $r = 2$ ) → ↓ pressure
  - $P = 2 \times 50/2 = 50$
- Alveoli are small (allows ↑ surface area relative to volume), so have ↑ collapsing pressure

## SURFACTANT

- ↓ collapsing pressure in alveoli → ↑ gas exchange, ↑ lung compliance, ↓ work of breathing
  - Lipoprotein mixture primarily containing dipalmitoyl phosphatidylcholine (DPPC)
  - Synthesized by type II pneumocytes, coats inside of alveoli

- Contains both hydrophilic, hydrophobic group (amphipathic nature)— intermolecular forces produced by

repelling hydrophobic groups, attracting hydrophilic groups → ↓ surface tension, collapsing pressure

# AIRFLOW, PRESSURE, & RESISTANCE

[osms.it/airflow-pressure-resistance](http://osms.it/airflow-pressure-resistance)

## AIR FLOW & PRESSURE

- Airflow in lungs determined by Ohm's law
  - Air flow directly proportional to pressure difference between alveoli, mouth/nose; inversely proportional to airway resistance
$$Q = \Delta P/R$$
  - Q = air flow
  - ΔP = change in pressure
  - R = resistance
- Pressure gradient
  - Driving force for air flow
  - Diaphragm contracts during inspiration → creates pressure gradient (↑ lung volume, ↓ alveolar pressure) → air flows into lungs

## RESISTANCE

### Poiseuille's law

- Resistance in lungs determined by Poiseuille's law
  - Air flow directly proportional to resistance along airway

$$R = \frac{8nl}{\pi r^4}$$

- R = resistance
- n = gas viscosity
- l = length of airway
- πr<sup>4</sup> = flow is related exponentially to airway's radius
- Highlights critical importance of airway diameter on airflow
  - E.g. if airway radius ↓ by a factor of 2 → ↑ resistance by 24 (16-fold)

### Resistance changes

- Parasympathetic muscarinic receptor stimulation → bronchial smooth muscle constriction → ↓ airway diameter → ↓ airflow; sympathetic stimulation of β<sub>2</sub> receptors → bronchial smooth muscle relaxation → ↑ airway diameter → ↑ airflow
- ↓ lung volume → ↑ resistance; ↑ lung volume → ↓ resistance
- ↑ viscosity (e.g. deep sea diving) → ↑ resistance; ↓ viscosity (e.g. inhaling helium) → ↓ resistance

# BREATHING CYCLE

[osms.it/breathing-cycle](https://osms.it/breathing-cycle)

- Normal, quiet breathing phases
  - Rest (period between breaths), inspiration, expiration
- Involves changes in air volume, intrapleural pressure, alveolar pressure
- Affected by respiratory system's resistance, compliance

## Rest

- Alveolar pressure ( $P_{alv}$ ) = atmospheric pressure ( $P_{atm}$ ) = 0
- No air movement in/out of lungs
  - Due to pressure gradient's absence
- Air volume in lungs = FRV
- Intrapleural pressure = -0.5cm/0.2in  $H_2O$ 
  - Transmural pressure gradient (intrapleural pressure always less than alveolar pressure) keeps lungs inflated
- Diaphragm relaxed

## Inhalation

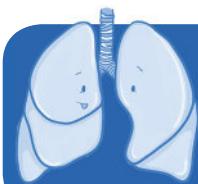
- Active process (requires muscle activity)
- **Diaphragm** (major inspiratory muscle; innervated by phrenic nerve) contracts, moves downward; external intercostal

muscles contract (innervated by intercostal nerves) contract, elevate ribs outward, upward → enlarge thoracic cavity → ↑ lung volume → ↓ pressure in lungs ( $P_{alv} = -1\text{cm}/0.39\text{in } H_2O$ )

- Boyle's law ( $P = k/V$ ): gas pressure ( $P$ ) in container (thorax, alveoli) at constant temperature ( $k$ ) inversely proportional to volume ( $V$ )
- Pressure gradient causes air to flow into lungs until  $P_{alv} = P_{atm}$  at inspiration's end
- Volume in lungs = FRC + VT
- Intrapleural pressure = -8cm/3.1in  $H_2O$  at expiration's end

## Exhalation

- Passive process
- Elastic forces of lungs compress alveolar air volume → ↑ pressure in lungs →  $P_{alv} > P_{atm}$  → pressure gradient causes air to flow out of lungs until  $P_{alv} = P_{atm}$  at inspiration's end
- Diaphragm, external intercostal muscles relax → ↓ thoracic cavity size → ↓ lung volume → ↑ pressure in lungs
- $V_T$  expired → lung volume = FRC



# NOTES

## BREATHING REGULATION

# BREATHING CONTROL

[osms.it/breathing-control](https://osms.it/breathing-control)

### WHAT IS BREATHING CONTROL?

- Breathing (ventilation): movement of gasses in, out of lungs
- Regulation maintains arterial partial pressures of  $O_2$ ,  $CO_2$  ( $PaO_2$ ,  $PaCO_2$ )
- Components: brainstem respiratory centers; peripheral, central chemoreceptors; mechanoreceptors in lungs, muscles of respiration, joints

### BRAINSTEM RESPIRATORY CENTERS

#### Dorsal respiratory group (DRG)

- Inspiratory center, located in dorsal medulla
- Sets basic rhythm of breathing
- Receives sensory input via cranial nerves (CN) IX, X from peripheral chemoreceptors, mechanoreceptors in lungs → sends motor output via phrenic nerve to stimulate contraction of diaphragm
  - DRG neurons generate repeating bursts of action potentials → period of quiescence
  - Bursts occur → action potential frequency “ramps up” → ↑ lung volume

#### Ventral respiratory group (VRG)

- Expiratory center, located in ventral medulla
- Inactive during basic, quiet breathing
- Provides high respiratory drive when ventilation needs to increase (e.g. exercise)

#### Pneumotaxic center

- Located in upper pons
- Limits inspiration by inhibiting DRG
- Limits tidal volume, increases respiratory rate

- Receives input from cerebral cortex

#### Apneustic center

- Located in lower pons
- Prolongs DRG inspiratory signal, diaphragm contraction → inspiratory gasps (apneusis)
- Associated with damage to pons/upper medulla

### VOLUNTARY CONTROL

#### Cerebral cortex

- Sends commands to voluntarily override autonomic control of ventilation
- Hyperventilation
  - Voluntarily breathing at rate > that needed by metabolism
  - Self-limiting: hyperventilation → ↓  $PaCO_2$  (strongly inhibits autonomic respiratory centers, ventilation)
- Hypoventilation
  - Voluntarily breathing at rate insufficient for metabolism
  - Self-limiting: hypoventilation → ↓  $PaO_2$ , ↑  $PaCO_2$

### HYPOTHALAMIC CONTROL

- Strong emotions, pain: act via hypothalamus, limbic system → signal respiratory centers → modify respiratory rate, depth
- Rise in body temperature → ↑ respiratory rate
- Drop in body temperature → ↓ respiratory rate

# PULMONARY CHEMORECEPTORS & MECHANORECEPTORS

[osms.it/pulmonary-central-peripheral-chemoreceptors](https://osms.it/pulmonary-central-peripheral-chemoreceptors)

## CENTRAL CHEMORECEPTORS

- Located in ventral surface of medulla
- Sensitive to changes in  $H^+$  indirectly by sensing acute changes in  $PaCO_2$  (unable to cross blood-brain barrier)
  - $\uparrow PaCO_2 \rightarrow$  conversion to carbonic acid ( $H_2CO_3$ ) by enzyme carbonic anhydrase  $\rightarrow$  dissociation into  $H^+$ ,  $HCO_3^- \rightarrow \downarrow CSF pH$  ( $\uparrow CSF [H^+]$ )  $\rightarrow$  stimulates central chemoreceptors  $\rightarrow$  stimulates DRG  $\rightarrow \uparrow$  ventilation  $\rightarrow \downarrow PaCO_2$  (40mmHg)
- Crucial minute-to-minute control
  - Match ventilation with metabolism by monitoring  $PaCO_2$

## PERIPHERAL CHEMORECEPTORS

- Located in carotid bodies at bifurcation (near aortic arch)
- Responds directly to changes in  $PaO_2$ ,  $PaCO_2$ 
  - Strongly stimulated in linear fashion when  $PaO_2 < 60\text{mmHg}$
  - Weakly stimulated by  $\uparrow PaCO_2$
  - Carotid bodies only: stimulated by  $\uparrow$  arterial  $[H^+]$
- Afferents send information to DRG via CN IX, X  $\rightarrow$  directs ventilatory response to hypoxemia, acidemia, alkalemia

## MECHANORECEPTORS

### Lung stretch receptors

- Located in airway smooth muscle
- Respond to lung inflation  $\rightarrow$  termination of inspiration (Hering-Breuer inspiratory-inhibitory reflex)

### Joint and muscle receptors

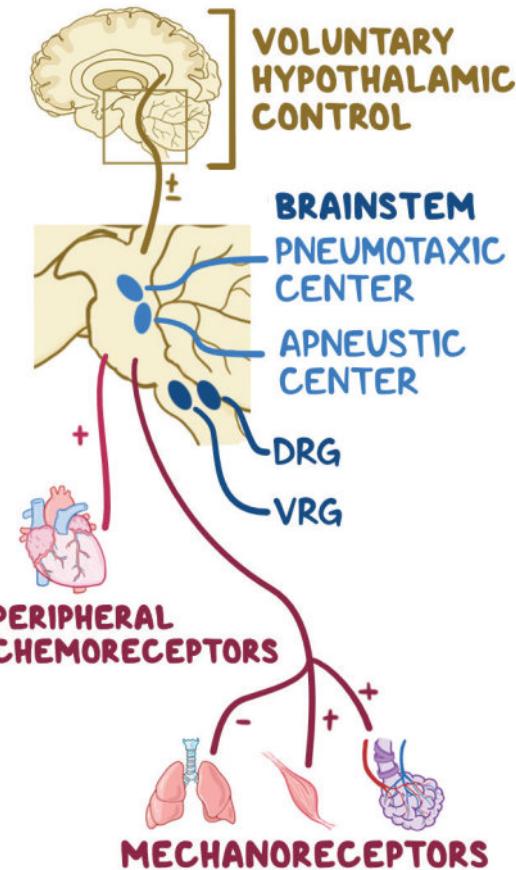
- Respond to bodily movement  $\rightarrow \uparrow$  respiratory rate

### Irritant receptors

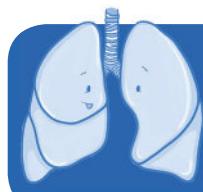
- Respond to noxious gasses; particulates via CN X  $\rightarrow$  coughing, bronchoconstriction

### Juxtagapillary (J) receptors

- Located in alveoli, near capillaries
- Respond to capillary engorgement  $\rightarrow \uparrow$  respiratory rate



**Figure 69.1** The brainstem is the respiratory center of the body. Many receptors throughout the body send signals to the brainstem so that it can regulate the breathing rate accordingly.



# NOTES

## GAS EXCHANGE

### GAS EXCHANGE & LAWS

- Diffusion of oxygen ( $O_2$ ), carbon dioxide ( $CO_2$ ) in lungs, peripheral tissues
- Alveolar  $O_2$  from inhaled gas → pulmonary capillary blood → circulation → tissue capillaries → cells
- $CO_2$  from cells → tissue capillaries → circulation → pulmonary capillary blood →  $CO_2$  for exhalation from alveoli
- Gas exchange, gas behavior in solution is governed by fundamental physical gas properties → represented by gas laws

### FORMS OF GAS IN SOLUTION

#### Dissolved gas

- All gas in solution are to some extent carried in a freely dissolved form
- For given partial pressure, the higher

the solubility of a gas, the higher the concentration in solution

- In solution only dissolved gas molecules contribute to partial pressure
- Of the gases inspired as air, only nitrogen is exclusively carried in dissolved form

#### Bound gas

- $O_2$ ,  $CO_2$ , CO are bound to proteins in blood
- $O_2$ ,  $CO_2$ , CO can all bind to hemoglobin
- $CO_2$  also binds to plasma proteins

#### Chemically modified gas

- The ready back and forth conversion of  $CO_2$  to bicarbonate ( $HCO_3^-$ ) in presence of enzyme carbonic anhydrase allows  $CO_2$  to contribute to gas equilibria despite chemical conversion
- Majority of  $CO_2$  in blood carried as  $HCO_3^-$

## IDEAL (GENERAL) GAS LAW

[osms.it/ideal-gas-law](http://osms.it/ideal-gas-law)

- Relates multiple variables to describe state of a hypothetical “ideal gas” under various conditions
  - Ideal gas: theoretical gas composed of many randomly moving point particles whose only interactions are perfectly elastic collisions
  - All gas laws can be derived from general gas law
- $PV = nRT$ 
  - P = Pressure (millimeters of mercury (mmHg))
  - V = Volume (liters (L))
  - n = Moles (mol)
  - R = Gas constant (8.314 J/mol)
  - T = Temperature (Kelvin [K])

- In gas phase: body temperature, pressure (BTPS) used
  - T = 37°C/98.6°F/310K
  - P = Ambient pressure
  - Gas is saturated with water vapor (47mmHg)
- In liquid phase/solution: standard temperature, pressure (STPD) used
  - T = 0°C/32°F/273K
  - P = 760mmHg
  - Dry gas (no humidity)
- Ideal gas law can be used to interconvert between properties of same gas under BTPS, STPD conditions
  - E.g. gas volume ( $V_1$ ) at BTPS → gas volume at STPD ( $V_2$ )

$$V_2 = V_1 \times \frac{T_1}{T_2} \times \frac{P_1 - P_{w1}}{P_2 - P_{w2}}$$

$$V_2 = V_1 \times \frac{273}{310} \times \frac{760 - 47}{760 - 0}$$

$$V_2 = V_1 \times 0.826$$

## BOYLE'S LAW

[osms.it/Boyles-law](http://osms.it/Boyles-law)

- Describes how pressure of gas ↑ as container volume ↓
- $P_1 V_1 = P_2 V_2$
- For gas at given temperature, the product of pressure, volume is constant
- Inspiration → diaphragm contraction → ↑ lung volume
- If PV constant + lung volume ↑ → pressure ↓
- Pressure ↓ → disequilibrium between room, lung air pressures → air fills lungs to equalize pressure

## DALTON'S LAW

[osms.it/Daltons-law](http://osms.it/Daltons-law)

- Total pressure exerted by gaseous mixture = sum of all partial pressures of gases in mixture → partial pressure of gas in gaseous mixture = pressure exerted by that gas if it occupied total volume of container
- $P_x = P_B \times F$ 
  - $P_x$  = partial pressure of gas (mmHg)
  - $P_B$  = barometric pressure (mmHg)
  - $F$  = fractional concentration of gas (no unit)
- Partial pressure = total pressure X fractional concentration of dry gas
- For humidified gases
- $P_x = (P_B - P_{H2O}) \times F$
- $P_{H2O}$  = Water vapor pressure at 37°C/98.6°F (47mmHg)
- If the sum of partial pressures in a mixture = total pressure of mixture → barometric pressure ( $P_B$ ) is sum of the partial pressures of O<sub>2</sub>, CO<sub>2</sub>, N<sub>2</sub> (nitrogen), and H<sub>2</sub>O
- At barometric pressure (760 mmHg) composition of humidified air is O<sub>2</sub>, 21%; N<sub>2</sub>, 79%; CO<sub>2</sub>, 0%
- Within airways, air is humidified thus water vapor pressure is obligatory = to 47mmHg at 37°C/98.6°F

# HENRY'S LAW

[osms.it/Henrys-law](https://osms.it/Henrys-law)

- For concentrations of dissolved gases
- When gas is in contact with liquid → gas dissolves in proportion to its partial pressure → greater concentration of a particular gas, in gas phase → more dissolves into solution at faster rate
  - $C_x = P_x \times \text{Solubility}$
  - $C_x$  = concentration of dissolved gas (mL gas / 100mL blood)
  - Concentration of gas in solution only applies to dissolved gas that is free in solution
  - Concentration of gas in solution does not include any gas that is presently bound to any other dissolved substances (e.g. plasma proteins/hemoglobin)
  - $P_x$  = partial pressure of gas (mmHg)
  - Solubility = solubility of gas in blood (mL gas / 100mL blood per mmHg)
- Henry's law governs gases dissolved within solution (e.g.  $O_2$ ,  $CO_2$  dissolved in blood)

- To calculate gas concentration in liquid phase
  - Partial pressure of gas in gas phase → partial pressure in liquid phase → concentration in liquid
  - Partial pressure of gas in liquid phase (at equilibrium) = partial pressure of gas in gaseous phase
  - If alveolar air has  $PO_2$  of 100mmHg →  $PO_2$  of capillary blood that equilibrates with alveolar air = 100mmHg

## HYPERBARIC CHAMBERS

- Hyperbaric chambers employ Henry's law
  - Contain  $O_2$  gas pressurized to above 1 atm → greater than normal amounts of  $O_2$  forced into the blood of the enclosed individual
  - Used to treat carbon monoxide poisoning, gas gangrene due to anaerobic organisms (cannot live in presence of high concentrations of  $O_2$ ), improve oxygenation of skin grafts, etc.

# FICK'S LAWS OF DIFFUSION

[osms.it/Ficks-law-of-diffusion](https://osms.it/Ficks-law-of-diffusion)

- Describes diffusion of gases

$$V_x = \frac{DA\Delta P}{\Delta x}$$

- $V_x$  = volume of gas transferred per unit time
- D = gas diffusion coefficient
- A = surface area
- $\Delta P$  = partial pressure difference of gas
- $\Delta x$  = membrane thickness
- Driving force of gas diffusion is difference

in partial pressures of gas ( $\Delta P$ ) across membrane (not the concentration difference)

- If  $P_{O_2}$  of alveolar air = 100mmHg
- $P_{O_2}$  of mixed venous blood entering pulmonary capillary = 40mmHg
- Driving force across membrane is 60mmHg (100mmHg - 40mmHg)
- Diffusion coefficient of gas (D) is a combination of usual diffusion coefficient (dependent on molecular weight) and gas solubility
- Diffusion coefficient dramatically affects

diffusion rate, e.g. diffusion coefficient for CO<sub>2</sub> is approximately 20x greater than that of O<sub>2</sub> → for a given partial pressure difference CO<sub>2</sub> would diffuse across the same membrane 20x faster than O<sub>2</sub>

## LUNG DIFFUSION CAPACITY (DL)

- A functional measurement which takes into account
  - Diffusion coefficient of gas used
  - Membrane surface area
  - Membrane thickness
  - Time required for gas to combine with proteins in pulmonary capillary blood (e.g. hemoglobin)
- Measured using carbon monoxide (CO) → CO transfer across alveolar-capillary barrier exclusively limited by diffusion process
- Lung diffusion capacity of carbon monoxide

(DL<sub>CO</sub>) is measured using a single breath

- Individual breathes a mixture of gases with a low CO concentration → rate of CO disappearance is predictable in different disease states
- Emphysema → destruction of alveoli → decreased surface area for gas exchange → decreased DL<sub>CO</sub>
- Fibrosis/pulmonary edema → increase in membrane thickness (via fluid accumulation in the case of edema) → decreased DL<sub>CO</sub>
- Anemia → reduced hemoglobin → reduced protein binding in a given time period → decreased DL<sub>CO</sub>
- Exercise → increased utilization of lung capacity, increased recruitment of pulmonary capillaries → increased DL<sub>CO</sub>

## GRAHAM'S LAW

[osms.it/Grahams-law](http://osms.it/Grahams-law)

- Diffusion rate of gas through porous membranes varies inversely with the square root of its density
- To compare rate of effusion (movement through porous membrane) of two gases → velocity of molecules determine the rate of spread
- Kinetic temperature in kelvin of a gas is directly proportional to average kinetic energy of gas molecules → at the same temperature, molecule of heavier gas will have a slower velocity than those of lighter gas

▫ Kinetic energy =  $\frac{1}{2}mv^2$

$$\frac{1}{2}m_1v_1^2 = \frac{1}{2}m_2v_2^2$$

$$\frac{v_1^2}{v_2^2} = m_2/m_1$$

$$\frac{v_1}{v_2} = \sqrt{(m_2/m_1)}$$

▫ Which can be rewritten to give Graham's law

$$\frac{\text{Rate}_1}{\text{Rate}_2} = \sqrt{\frac{M_2}{M_1}}$$

# GAS EXCHANGE IN THE LUNGS

[osms.it/gas-exchange-in-lungs](https://osms.it/gas-exchange-in-lungs)

## PULMONARY GAS EXCHANGE

- AKA external respiration
- Pulmonary capillaries perfused with blood from right heart (deoxygenated)
- Gas exchange occurs between pulmonary capillary, alveolar gas
  - Room air → inspired air → humidified tracheal air → alveoli
  - $O_2$  diffuses from alveolar gas → pulmonary capillary blood
  - $CO_2$  diffuses from pulmonary capillary blood → alveolar gas
  - Blood exits the lungs → left heart → systemic circulation

### Dry inspired air

- $P_{O_2}$  is approximately 160mmHg
  - Barometric pressure × fractional concentration of  $O_2$  (21%)
  - $P_{O_2} = 760\text{ mmHg} \times 0.21$
  - Assume no  $CO_2$  in dry inspired air

### Humidified tracheal air

- $P_{O_2}$  of humidified tracheal air is 150mmHg
  - Air is fully saturated with water vapor → “dilution” of partial pressures → calculations must correct for water vapor pressure (subtracted from barometric pressure)
  - At 37°C/98.6°F,  $P_{H_2O}$  is 47mmHg
  - $P_{O_2} = (760\text{ mmHg} - 47\text{ mmHg}) \times 0.21$
  - Assume no  $CO_2$  in humidified inspired air

### Alveolar air

- Pressures of alveolar gas designated “PA”
- Alveolar gas exchange in lungs sees a drop in  $O_2$  partial pressure, increase in  $CO_2$  partial pressure
  - $PA_{O_2} = 100\text{ mmHg}$
  - $PA_{CO_2} = 40\text{ mmHg}$
- Amount of these gases entering/leaving alveoli correspond to physiological body needs (i.e.  $O_2$  consumption,  $CO_2$  production)

### Pulmonary capillaries

- Blood entering pulmonary capillaries is mixed venous blood
- Tissues (metabolic activity alters composition of blood) → venous vasculature → right heart → pulmonary circulation
- $P_{O_2} = 40\text{ mmHg}$
- $P_{CO_2} = 46\text{ mmHg}$

### Systemic arterial blood (oxygenated)

- Gas partial pressures of systemic arterial blood designated “Pa”
- In a healthy individual, diffusion of gas across alveolar, capillary membrane is so rapid that we can assume equilibrium is achieved between alveolar gases, pulmonary capillaries →  $P_{O_2}$  and  $P_{CO_2}$  of blood leaving pulmonary capillaries = alveolar air
- $PA_{O_2} = Pa_{O_2} = 100\text{ mmHg}$
- $PA_{CO_2} = Pa_{CO_2} = 40\text{ mmHg}$
- This blood enters systemic circulation to eventually return to lungs

### Physiological shunt

- Small fraction of pulmonary blood flow bypasses alveoli → physiological shunt → blood not arterialized → systemic blood has slightly lower  $P_{O_2}$  than alveolar air
- Shunting occurs due to
  - Coronary venous blood, drains directly into left ventricle
  - Bronchial blood flow
- Shunting may be increased in various pathologies → ventilation-perfusion defects/mismatches
- As shunt size increases → alveolar gas, pulmonary capillary blood do not equilibrate → blood is not fully arterIALIZED
- A-a difference: difference in  $P_{O_2}$  between alveolar gas (A), systemic arterial blood (a)
  - Physiological shunting → negligible/small differences
  - Pathology → notably increased difference

## FACTORS AFFECTING EXTERNAL RESPIRATION

### Thickness of respiratory membrane

- In healthy lungs, respiratory membrane → 0.5–1 micrometer thick
- Presence of small amounts of fluid (left heart failure, pneumonia) → significant loss of efficiency, equilibration time dramatically increases → the 0.75 seconds blood cells spend in transit through pulmonary circulation may not be sufficient

### Surface area of respiratory membrane

- Greater surface area of respiratory membrane → greater amount of gas exchange
- Healthy adult male lungs have surface area of 90m<sup>2</sup>
- Pulmonary diseases (e.g. emphysema) → walls of alveoli break down → alveolar chambers enlarge → loss of surface area
- Tumors/pneumonia → prevent gas from occupying all available lung → loss of surface area

### Partial pressure gradients and gas solubilities

- Partial pressures of O<sub>2</sub>, CO<sub>2</sub> drive diffusion of these gases across respiratory membrane
- Steep O<sub>2</sub> partial pressure gradient exists
  - PO<sub>2</sub> of deoxygenated blood in pulmonary arteries = 40mmHg
  - PO<sub>2</sub> of 104mmHg in alveoli
  - O<sub>2</sub> diffuses rapidly from alveoli into pulmonary capillary blood
- O<sub>2</sub> equilibrium (PO<sub>2</sub> of 104mmHg on both sides of respiratory membrane) occurs in around 0.25 seconds of transit through lungs (about 1/3 of the time available)
- CO<sub>2</sub> has smaller gradient → 5mmHg (45mmHg vs 40mmHg), although pressure gradient for O<sub>2</sub> is much steeper than for CO<sub>2</sub>, CO<sub>2</sub> is 20x more soluble in plasma, alveolar fluid than O<sub>2</sub> → equal amounts of gas exchanged

### Ventilation-perfusion coupling

- Ventilation: amount of gas reaching alveoli
- Perfusion: amount of blood flow in pulmonary capillaries
- These are regulated by local autoregulatory

mechanisms → continuously respond to local conditions → some control in blood flow around lungs

- Arteriolar diameter controlled by P<sub>O<sub>2</sub></sub>
  - If alveolar ventilation is inadequate → blood taking O<sub>2</sub> away faster than ventilation can replenish it → low local P<sub>O<sub>2</sub></sub> → terminal arteriole restriction → blood redirected to respiratory areas with high P<sub>O<sub>2</sub></sub>, oxygen pickup more efficient
  - In alveoli where ventilation is maximal → high P<sub>O<sub>2</sub></sub> → pulmonary arteriole dilation → blood flow into pulmonary arterioles increases
  - Pulmonary vascular muscle autoregulation is opposite of that in systemic circulation
- Bronchiolar diameter controlled by P<sub>CO<sub>2</sub></sub>
  - Bronchioles connecting areas where PA<sub>CO<sub>2</sub></sub> high → dilation → allows CO<sub>2</sub> to be eliminated from body
  - Those with low CO<sub>2</sub> → constrict
- Independent autoregulation of arterioles, bronchioles → matched perfusion, ventilation
- Ventilation-perfusion matching is imperfect
  - Gravity → regional variation in blood, air flow (apices have greater ventilation but lesser perfusion, bases have greater perfusion, lesser ventilation)
  - Occasionally alveolar ducts may be plugged with mucus → unventilated areas

## INTERNAL RESPIRATION

- Capillary gas exchange in body tissue
- Partial pressures, diffusion gradients are reversed from lungs however physical laws governing the exchanges remain identical
- Cells in body continuously use O<sub>2</sub>, produce CO<sub>2</sub>
  - PO<sub>2</sub> always lower in tissue than arterial blood (40mmHg vs 100mmHg) → O<sub>2</sub> moves rapidly from blood → tissues until equilibrated
  - CO<sub>2</sub> moves rapidly down its pressure gradient (P<sub>CO<sub>2</sub></sub> of 40mmHg in fresh blood arriving at capillary beds vs. P<sub>CO<sub>2</sub></sub> of 45mmHg in tissues) → venous blood → right heart

- Gas exchange at tissue level driven by partial pressures, occurs via simple diffusion

# DIFFUSION-LIMITED & PERFUSION-LIMITED GAS EXCHANGE

[osms.it/diffusion-limited-perfusion-limited-gas-exchange](http://osms.it/diffusion-limited-perfusion-limited-gas-exchange)

## Diffusion-limited gas exchange

- Diffusion is limiting factor determining total amount of gas transported across alveolar-capillary barrier
- As long as partial pressure gradient is maintained, diffusion continues
  - Gas readily diffuses across permeable membrane
  - Blood flow away from alveoli/chemical binding → partial pressure of gas on systemic end does not rise → partial pressure maintenance
  - Given a sufficiently long capillary bed diffusion will continue along entire length as equilibrium is not achieved
- Examples include
  - CO across alveolar-pulmonary capillary barrier
  - Oxygen during strenuous exercise/ emphysema/fibrosis

## Perfusion-limited gas exchange

- Perfusion (blood flow) is the limiting factor determining total amount of gas transported across alveolar-capillary barrier
- Increasing blood flow → increasing amount of gas transported; examples include
  - Nitrous oxide ( $N_2O$ ): not bound in blood → entirely free in solution;  $PA_{N_2O}$  is constant,  $Pa_{N_2O} = 0$  at start of capillary → initial large A-a difference → because no  $N_2O$  binds to any other components of blood, all of it remains free in solution → partial pressure builds rapidly → rapid equilibration, most of capillary length does not participate in gas exchange; new blood must be supplied to partake in further

gas exchange with alveolar  $N_2O$  → “perfusion-limited gas exchange”

- $O_2$  at rest
- $CO_2$

## Limitations of $O_2$ transport

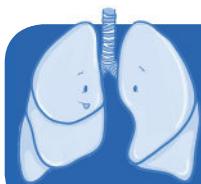
- Under physiological conditions  $O_2$  transport into pulmonary capillaries → perfusion-limited
- Diseased or abnormal conditions → diffusion-limited
- Perfusion-limited  $O_2$  transport
  - $PA_{O_2}$  is constant = 100mmHg
  - At beginning of capillary  $Pa_{O_2} = 40$ mmHg (mixed venous blood) → large partial pressure gradient → drives diffusion
  - As  $O_2$  diffuses into pulmonary capillary blood → increase in  $Pa_{O_2}$
  - Hemoglobin binds  $O_2$  → resists increase in  $Pa_{O_2}$  → initially gradient is maintained; eventually equilibrium is achieved → perfusion-limitation
  - Therefore pulmonary blood flow determines net  $O_2$  transfer (changes in pulmonary blood flow will affect net  $O_2$  transfer)

## Diffusion-limited $O_2$ transport

- Fibrosis → thickening of alveolar walls → increased diffusion distance for  $O_2$  (decreases DL) → slowed rate of diffusion → prevents equilibration → partial pressure gradient maintained along length of capillary
- Increasing capillary length allows for more time for equilibrium to occur → diffusion-limitation

### O<sub>2</sub> transport at high altitude

- High altitude reduces barometric pressure  
→ reduced partial pressures
- Reductions in Pa<sub>O<sub>2</sub></sub> → reduce oxygen amount available to diffuse into blood → reduced rate of equilibration at capillary → more time required for gas exchange, lower peak oxygen concentration reached once equilibrated



# NOTES

## GAS TRANSPORT

# OXYGEN BINDING CAPACITY & OXYGEN CONTENT

[osms.it/oxygen-binding-capacity-oxygen-content](https://osms.it/oxygen-binding-capacity-oxygen-content)

### MEASURES OF OXYGEN AVAILABILITY

#### O<sub>2</sub> binding capacity

- Maximum amount of O<sub>2</sub> bound to hemoglobin when 100% saturated (per blood volume)
  - More hemoglobin → more oxygen (per blood volume)
- Measurement
  - Expose blood to air with high P<sub>O<sub>2</sub></sub> → complete hemoglobin saturation
  - Hemoglobin's oxygen affinity → 1g of hemoglobin A binds 1.34mL of O<sub>2</sub>
  - Normal hemoglobin A concentration in blood → 15g/100mL
  - O<sub>2</sub> binding capacity = hemoglobin concentration × hemoglobin's affinity for oxygen
- Example: O<sub>2</sub> binding capacity = 15g/100mL × 1.34mL O<sub>2</sub>/g hemoglobin = 20.1mL O<sub>2</sub>/100mL blood

#### Oxygen content (CaO<sub>2</sub>)

- Oxygen (mL) per 100mL of blood
- CaO<sub>2</sub> = O<sub>2</sub> binding capacity × % saturation + oxygen dissolved in solution
  - Correction for dissolved O<sub>2</sub> → solubility of O<sub>2</sub> in blood → 0.003mL O<sub>2</sub>/100mL blood per mmHg
- CaO<sub>2</sub> = hemoglobin concentration (g/100mL blood) × hemoglobin oxygen affinity (mL O<sub>2</sub>/g) × SaO<sub>2</sub> (arterial oxygen saturation) + partial pressure of oxygen (mmHg) × solubility of O<sub>2</sub> in blood (mL O<sub>2</sub>/blood/mmHg)

$$\text{CaO}_2 (\text{ml O}_2/100\text{mL blood}) = ([\text{Hb}] \times 1.34 \times \text{SaO}_2) + (\text{PaO}_2 \times 0.003)$$

#### O<sub>2</sub> DELIVERY TO TISSUES

- Dependent on blood flow (determined by cardiac output), blood's oxygen content
- O<sub>2</sub> delivery = cardiac output × oxygen content

### OXYGEN TRANSPORT

- Majority of oxygen in blood bound to hemoglobin, remainder dissolved in solution

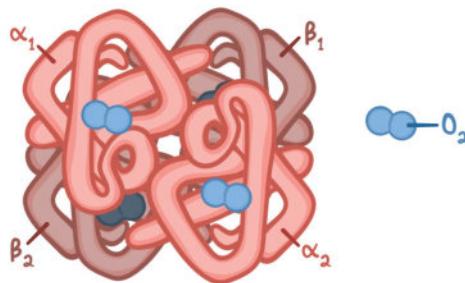
#### Dissolved O<sub>2</sub>

- Free in solution (1.5% of total blood O<sub>2</sub> content)
- Only free O<sub>2</sub> contributes to partial pressure → drives O<sub>2</sub> diffusion
- O<sub>2</sub> solubility in blood = 0.003mL O<sub>2</sub>/100mL blood per mmHg → at normal PaO<sub>2</sub> of 100mmHg → concentration of dissolved O<sub>2</sub> is 0.3mL O<sub>2</sub>/100mL blood
- Normal consumption of O<sub>2</sub> = 250mL O<sub>2</sub>/minute
- Only dissolved O<sub>2</sub> delivered to tissues (cardiac output 5L/min) × dissolved O<sub>2</sub> concentration → 15mL O<sub>2</sub>/min → incompatible with life
- Hemoglobin increases amount of O<sub>2</sub> carried by blood

#### Hemoglobin bound

- Hemoglobin → greater concentrations of O<sub>2</sub> carried to tissues by blood
- 98.5% of O<sub>2</sub> in blood bound to hemoglobin

- Four subunits of hemoglobin molecule
  - Each subunit contains heme moiety: iron-binding porphyrin, polypeptide chain (alpha/beta)
  - Adult hemoglobin subunits ( $\alpha_2\beta_2$ ): two alpha chains, two beta chains → each contains one iron molecule ( $Fe^{2+}$ ) → binds one  $O_2$  molecule → four molecules of  $O_2$  per molecule of hemoglobin → oxyhemoglobin
  - Deoxygenated hemoglobin → deoxyhemoglobin



**Figure 71.1** Each of the four hemoglobin subunits contains a heme group capable of binding one oxygen molecule.

- Heme binds oxygen in lungs → oxyhemoglobin
  - Oxygen diffuses from alveoli → across single cell thick alveolar walls → diffuses into blood → through red blood cell (RBC) membrane → interacts with heme → oxyhemoglobin (bright red blood)
- Oxygen binding to hemoglobin → conformational shift in heme structure → ↑ oxygen binding affinity → sigmoidal (S-shaped) oxygen-binding affinity/dissociation curve
- At tissue level: association process reversed
  - $O_2$  released → deoxyhemoglobin (dark red blood)
  - 20% of dissolved  $CO_2$  → binds with globin amino acids (not heme group) of deoxyhemoglobin → carbaminohemoglobin

#### Fetal oxygen transport

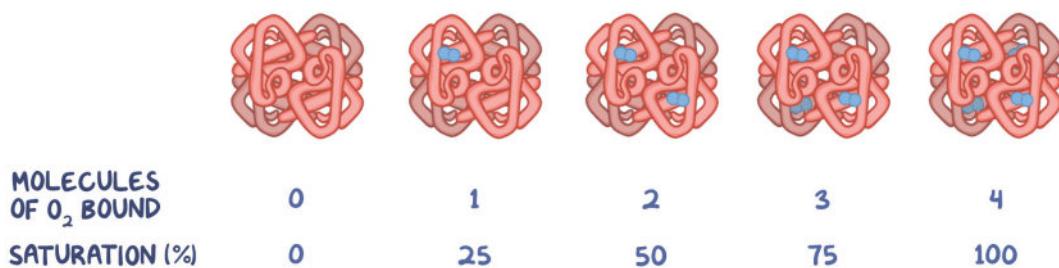
- Fetal blood requires higher affinity for oxygen to facilitate movement of  $O_2$  from maternal to fetal blood
- Fetal variant hemoglobin (hemoglobin F)
  - Contains two alpha chains, two gamma chains ( $\alpha_2\gamma_2$ ) → greater affinity for oxygen

## OXYGEN-HEMOGLOBIN DISSOCIATION CURVE

[osms.it/oxygen-hemoglobin\\_dissociation\\_curve](http://osms.it/oxygen-hemoglobin_dissociation_curve)

- Proportion of saturated hemoglobin plotted against partial pressure of oxygen
- Illustrates how blood carries, releases oxygen as partial pressures vary
  - **Hemoglobin:** primary oxygen transporter in blood
  - Amount of oxygen bound to hemoglobin at any given time determined by environmental partial pressure of oxygen (high in lungs, lower in tissue

- capillary beds) → hemoglobin binds to oxygen in lungs, releases at tissue level
- **Oxyhemoglobin dissociation curve:** determined by hemoglobin affinity for oxygen; rate hemoglobin acquires, releases oxygen into surrounding fluid; plots  $SO_2$  against  $PO_2$



**Figure 71.2** Each hemoglobin molecule can bind four O<sub>2</sub> molecules, but each hemoglobin isn't always 100% saturated, or bound, by O<sub>2</sub>. A hemoglobin molecule with no O<sub>2</sub> bound (0% saturation) is called deoxyhemoglobin.

## SIGMOIDAL SHAPE

- Oxyhemoglobin dissociation curve is sigmoidal
  - Positive cooperativity → each successive oxygen molecule binding to heme group → ↑ affinity
  - Approaches maximum saturation limit → few binding sites remain → little additional binding possible → curve levels off → large ↑ in oxygen partial pressure → no effect on hemoglobin saturation beyond saturation point
  - Partial pressures ↓ at tissue level → oxygen release → with each successive oxygen molecule release, subsequent release eases → rapid oxygen unloading at low partial pressures

## P<sub>50</sub>

- P<sub>50</sub>: partial pressure of oxygen in blood when hemoglobin 50% saturated (e.g. 26.6mmHg)
- Conventional measure of hemoglobin affinity for oxygen
- Physiological/disease processes may shift dissociation curve to left/right, alter P<sub>50</sub>
  - Left shift → lower P<sub>50</sub> → ↑ oxygen affinity
  - Right shift → raised P<sub>50</sub> → ↓ oxygen affinity

## RIGHT SHIFT

- Right shift → lower oxygen affinity → 50% saturation occurs at higher PO<sub>2</sub> → oxygen unloading

## ↑ PCO<sub>2</sub>, ↓ pH

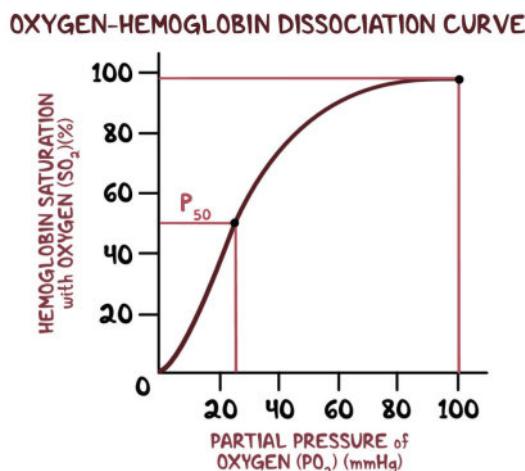
- ↑ metabolic activity of tissues → ↑ CO<sub>2</sub> → ↑ H<sup>+</sup> concentration → ↓ pH → ↓ hemoglobin oxygen affinity → oxygen unloading in metabolically active tissues
- Effect of PCO<sub>2</sub>, pH on oxygen-hemoglobin dissociation curve → Bohr effect

## ↑ temperature

- Very metabolically active tissue (e.g. active muscle → ↑ heat production → ↓ hemoglobin oxygen affinity)

## ↑ 2,3-diphosphoglycerate (2,3-DPG) concentration

- 2,3-DPG (glycolysis byproduct) → binds deoxyhemoglobin beta chains → ↓ oxygen affinity → binds to hemoglobin beta chains → oxygen unloading
- 2,3-DPG production ↑ under hypoxic conditions (e.g. living at high altitude) →



**Figure 71.3** The oxygen-hemoglobin dissociation curve. O<sub>2</sub> saturation is influenced by the PO<sub>2</sub> of the blood. P<sub>50</sub> indicates the partial pressure at which hemoglobin proteins are 50% saturated.

hypoxemia → 2,3-DPG production in red blood cells → greater oxygen delivery to tissues

## LEFT SHIFT

- Left shift → higher oxygen affinity → 50% saturation occurs at lower  $\text{PO}_2$  → impairs oxygen unloading

### $\downarrow \text{PCO}_2, \uparrow \text{pH}$

- $\downarrow$  tissue metabolism →  $\downarrow \text{CO}_2$  production →  $\downarrow \text{H}^+$  concentration →  $\uparrow \text{pH}$  → left shift →  $\text{O}_2$  tightly bound to hemoglobin

### $\downarrow$ temperature

- $\downarrow$  tissue metabolism →  $\downarrow$  heat production →  $\downarrow \text{O}_2$  unloading

### $\downarrow$ 2,3-DPG concentration

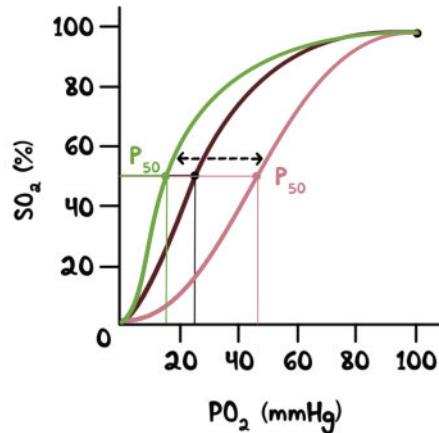
- $\downarrow$  tissue metabolism →  $\downarrow$  2,3-DPG concentration →  $\downarrow \text{O}_2$  unloading

## LEFT SHIFT

### HbA

- \*  $\downarrow \text{P}_{\text{CO}_2}$
- \*  $\downarrow$  TEMPERATURE
- \*  $\downarrow$  2,3 DPG
- \*  $\uparrow \text{pH}$
- \* HbF

HEMOGLOBIN AFFINITY for  $\text{O}_2$  ↑



## RIGHT SHIFT

### HbA

- \*  $\uparrow \text{P}_{\text{CO}_2}$
- \*  $\uparrow$  TEMPERATURE
- \*  $\uparrow$  2,3 DPG
- \*  $\downarrow \text{pH}$

HEMOGLOBIN AFFINITY for  $\text{O}_2$  ↓

**Figure 71.4** Summary of factors that can shift the oxygen-hemoglobin dissociation curve to the left ( $\uparrow$  hemoglobin's affinity for  $\text{O}_2$ ) and to the right ( $\downarrow$  hemoglobin's affinity for  $\text{O}_2$ ).

# ERYTHROPOIETIN (EPO)

[osms.it/erythropoietin](https://osms.it/erythropoietin)

- Glycoprotein cytokine secreted by kidney (cellular hypoxia response) → stimulates erythropoiesis → RBCs

## RENAL INDUCTION OF EPO SYNTHESIS

- ↓ O<sub>2</sub> delivery to kidneys (↓ hemoglobin concentration/PaO<sub>2</sub>) → increased production of alpha subunit of hypoxia-inducible factor 1 (HIF1)
- Hypoxia-inducible factor 1-alpha (HIF1A) → acts on fibroblasts in renal cortex, medulla → upregulation of EPO messenger RNA (mRNA) → increased EPO synthesis
- EPO → promotes proerythroblast differentiation → mature to form erythrocytes (maturation not EPO-dependent)

## RENAL SENSING OF HYPOXIA

- To effectively regulate EPO secretion, kidneys must distinguish between following:

### Decreased blood flow

- → ↓ O<sub>2</sub> availability
  - ↓ renal blood flow → ↓ glomerular filtration → ↓ sodium (Na<sup>+</sup>) filtration/reabsorption → ↓ O<sub>2</sub> consumption (Na<sup>+</sup> resorption closely linked to O<sub>2</sub> consumption in kidney)
  - O<sub>2</sub> delivery, consumption remain matched → EPO production not triggered

### Decreased arterial blood O<sub>2</sub> content

- → ↓ O<sub>2</sub> availability
  - Renal blood flow remains normal → normal glomerular filtration → normal Na<sup>+</sup> filtration/reabsorption → reduced oxygen availability for given metabolic demand → stimulus for EPO secretion

# CARBON DIOXIDE TRANSPORT IN BLOOD

[osms.it/carbon-dioxide-transport-in-blood](https://osms.it/carbon-dioxide-transport-in-blood)

- Carried as dissolved carbon dioxide (CO<sub>2</sub>), carbaminohemoglobin (bound to hemoglobin), bicarbonate (HCO<sub>3</sub><sup>-</sup>)

## DISSOLVED CO<sub>2</sub>

- Small fraction of CO<sub>2</sub> dissolved in blood (similar to oxygen)
- Henry's law: CO<sub>2</sub> concentration in blood = partial pressure × solubility of CO<sub>2</sub>
- Solubility: 0.07mL CO<sub>2</sub>/100mL blood per mmHg
- Partial pressure: 40mmHg

- Concentration = 2.8mL CO<sub>2</sub>/100mL blood (5% of total CO<sub>2</sub> content of blood)

## CARBAMINOHEMOGLOBIN

- CO<sub>2</sub> binds to terminal amino groups on proteins (e.g. albumin, hemoglobin)
- CO<sub>2</sub> bound to hemoglobin → carbaminohemoglobin (3% of total blood CO<sub>2</sub>)
  - CO<sub>2</sub> binding to hemoglobin at different site than oxygen → conformational shift of protein structure → ↓ oxygen affinity

- right shift in dissociation curve
- **Haldane effect:** less O<sub>2</sub> bound to hemoglobin → ↑ CO<sub>2</sub> affinity

## BICARBONATE

- 90% of CO<sub>2</sub> in blood
- **Tissue level:** CO<sub>2</sub> produced by aerobic metabolism → driven by partial pressure gradient → CO<sub>2</sub> diffuses across cell membrane, capillary wall → enters RBCs

### RBC blood pH regulation

- RBCs regulate blood pH via interaction with CO<sub>2</sub> in blood
- RBCs contain enzyme, carbonic anhydrase → catalyzes conversion of CO<sub>2</sub>, water → carbonic acid (also catalyzes reverse reaction)
- Carbonic acid dissociates into bicarbonate, hydrogen ion in blood
  - CO<sub>2</sub> + H<sub>2</sub>O ⇌ H<sub>2</sub>CO<sub>3</sub> ⇌ HCO<sub>3</sub><sup>-</sup> + H<sup>+</sup>
  - Mass action drives reaction to right as tissues continuously supply CO<sub>2</sub>
- H<sub>2</sub>CO<sub>3</sub> dissociates → H<sup>+</sup>, HCO<sub>3</sub><sup>-</sup>
- H<sup>+</sup> remains in RBCs → buffered by deoxyhemoglobin

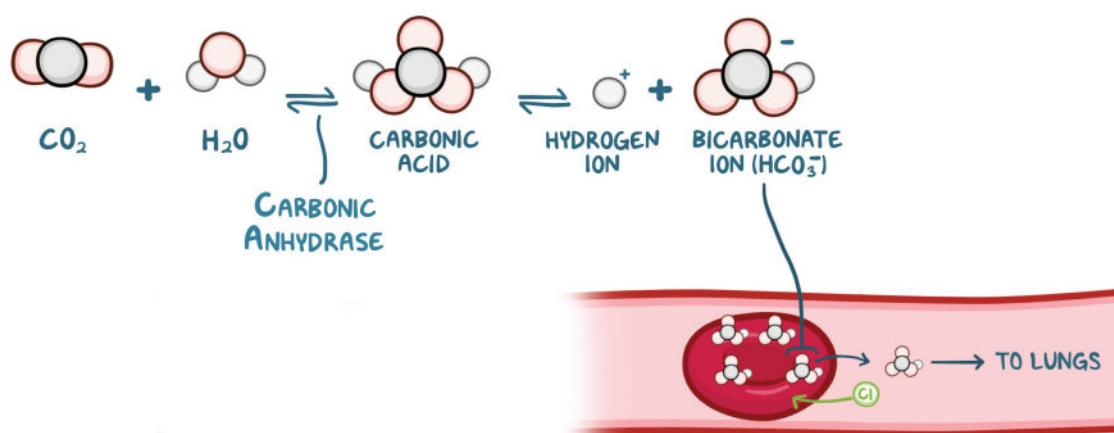
- If H<sup>+</sup> remains free in solution → acidifies RBCs, venous blood → H<sup>+</sup> must be buffered

- H<sup>+</sup> buffered by deoxyhemoglobin, carried in venous blood (deoxyhemoglobin more efficient buffer than oxyhemoglobin)
- H<sup>+</sup> production favors oxyhemoglobin conversion → deoxyhemoglobin (**Bohr effect**)

- HCO<sub>3</sub><sup>-</sup> transported into plasma (exchanged for chloride)
- Band 3 protein facilitates anion exchange of Cl<sup>-</sup> for HCO<sub>3</sub><sup>-</sup> (chloride shift)
- HCO<sub>3</sub><sup>-</sup> carried in plasma to lungs

### Respiratory system blood pH regulation

- Respiratory system further regulates blood pH
  - Controls CO<sub>2</sub> elimination rate → CO<sub>2</sub> elimination ↑ pH by shifting equation to left
  - RBCs, carbonic anhydrase allow rapid reaction in lungs → reverse processes in blood at tissue level



**Figure 71.5** CO<sub>2</sub> transport in the form of bicarbonate. CO<sub>2</sub> undergoes a chemical reaction with H<sub>2</sub>O to form carbonic acid, which then dissociates into hydrogen ions and bicarbonate ions. This reaction can occur in the plasma, but is sped up in red blood cells by the presence of carbonic anhydrase enzymes. Ionic exchange of bicarbonate ions and chloride occurs via facilitated diffusion to ensure charges stay balanced. Bicarbonate then travels to the lungs in the plasma.

# REGULATION OF PULMONARY BLOOD FLOW

[osms.it/pulmonary-blood-flow-regulation](https://osms.it/pulmonary-blood-flow-regulation)

- Regulated by altering arteriole resistance → controlled by arteriolar smooth muscle tone
- Regulatory changes mediated by local vasoactive substance concentrations

## PULMONARY VASOACTIVE SUBSTANCES & STATES

### Nitric oxide (NO)

- Retains similar function on pulmonary vascular beds (compared to systemic) → vasodilation
- Nitric oxide (NO) synthase inhibition → hypoxic vasoconstriction enhancement
- Inhaled NO → reduction in/prevention of hypoxic vasoconstriction

### Thromboxane A<sub>2</sub>

- Product of arachidonic acid metabolism via **cyclooxygenase pathway** (macrophages, leukocytes, endothelial cells)
- Lung injury → potent vasoconstrictor of pulmonary arterioles, veins

### Prostaglandin I<sub>2</sub> (prostacyclin)

- Product of arachidonic acid metabolism via **cyclooxygenase pathway** (endothelium)
- Potent local vasodilator

### Leukotrienes

- Product of arachidonic acid metabolism via **lipoxygenase pathway**
- Potent airway constrictor

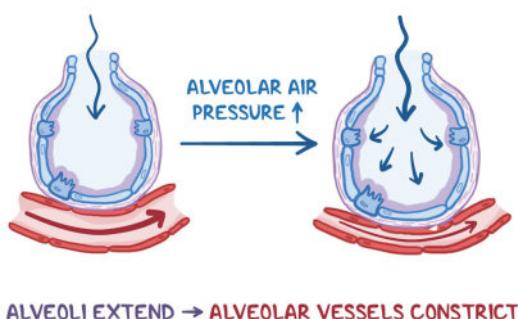
## LUNG VOLUME

- Pulmonary blood vessels → alveolar capillaries that surround alveoli, extra-alveolar vessels which do not (arteries, veins)

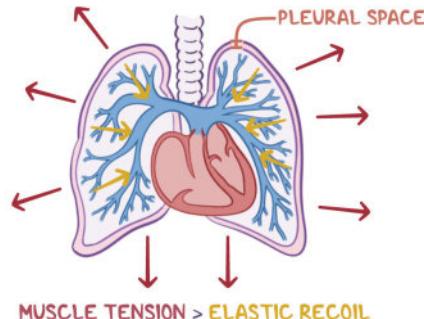
### Increased lung volume

- Crushes alveolar capillaries → ↑ resistance to blood flow
- Intrapleural pressure becomes more negative (↓ resistance) → pulls open extra-alveolar vessels
- Total pulmonary vascular resistance: sum of alveolar, extra-alveolar resistance → increased lung volume effect dependent on larger effect
  - Low lung volumes (extra-alveolar vessels dominate) → ↑ volume → extra-alveolar vessels pulled open → ↓ resistance
  - High lung volume (alveolar capillaries dominate) → ↑ lung volume → alveolar vessels crushed, sharp ↑ resistance

### ALVEOLAR VESSEL RESISTANCE ↑



### EXTRA-ALVEOLAR VESSEL RESISTANCE ↓



**Figure 71.6** Blood vessel resistance associated with increased lung volume.

# ZONES OF PULMONARY BLOOD FLOW

[osms.it/zones-of-pulmonary-blood-flow](https://osms.it/zones-of-pulmonary-blood-flow)

## POSITIONAL EFFECT

- Supine gravitational effect largely uniform
- Upright distribution of blood flow (perfusion), ventilation throughout lungs not uniform
- Blood flow favors gravity-dependent lung regions → ↑ pulmonary arterial hydrostatic pressure moving inferiorly → blood flow in inferior (basal) regions > superior (apical) regions
- Ventilation favors apices → ventilation ↓ with move towards bases of lungs

- $P_A$  generally = atmospheric pressure; can be overcome by low-pressure lung circulation
- Positive pressure ventilation →  $P_A > P_a$  in apices of lung → blood vessels collapse → physiological dead space (ventilated, not perfused)

## Zone II

- $P_a > P_A >$  pulmonary venous pressure ( $P_v$ )
- Capillary compression not problematic
- Perfusion driven by difference between  $P_a$ ,  $P_A$  (not  $P_a$ ,  $P_v$ ; as in systemic vascular beds)

## Zone III

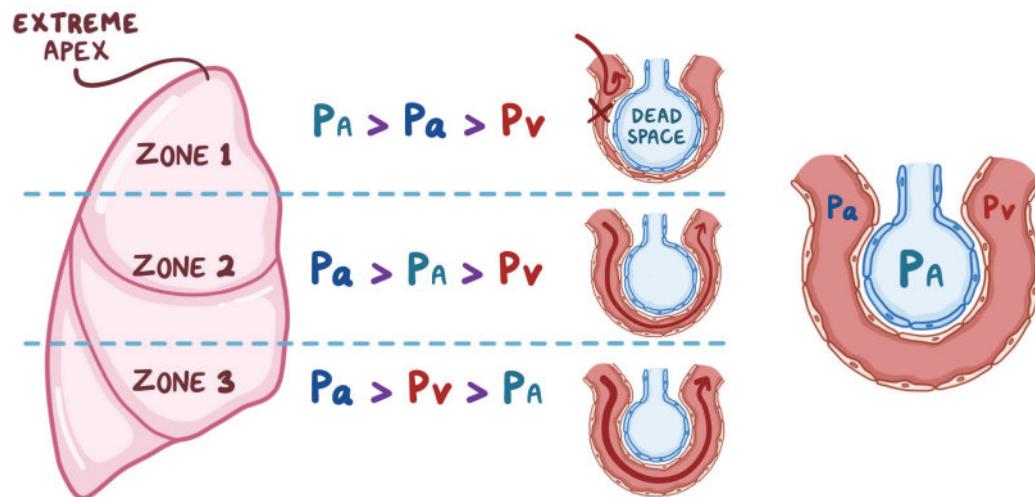
- Majority of healthy lung volume
- No external resistance to blood flow
- Flow determined by  $P_a - P_v$  (both exceed  $P_A$ )

## LUNG ZONES

- Lungs divided into three vertical sections (based on pressure differences between compartments)

### Zone I

- Unobserved in healthy lung: pulmonary arterial pressure ( $P_A$ ) > alveolar pressure ( $P_a$ ) > pulmonary venous pressure ( $P_v$ ) in all parts of lung



**Figure 71.7** Relationships between  $P_A$ ,  $P_a$ , and  $P_v$  in the three lung zones.

# PULMONARY SHUNTS

[osms.it/pulmonary-shunts](https://osms.it/pulmonary-shunts)

- Shunts occur when blood flow redirected from expected route, bypassing circulatory conduit

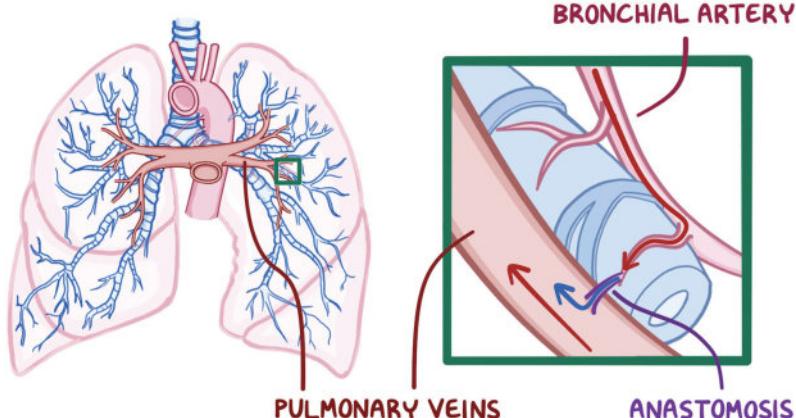
## PHYSIOLOGICAL SHUNTS (ANATOMICALLY NORMAL)

- Bronchial blood flow: fraction of pulmonary blood which **bypasses alveoli** to supply bronchi
- Coronary blood flow: thebesian venous network allows for **alternative myocardium drainage directly into left ventricle** (not reoxygenated)

## LEFT-TO-RIGHT SHUNTS

- More common
- Blood shunted from left to right heart
  - Due to **septal defects** (e.g. trauma, patent ductus arteriosus)
- Blood intended for systemic circulation directly circulated back to lungs → pulmonary blood flow exceeds systemic blood flow → fraction of blood does not reach systemic circulation fully oxygenated → no hypoxia

### BRONCHIAL BLOOD FLOW



### CORONARY BLOOD FLOW

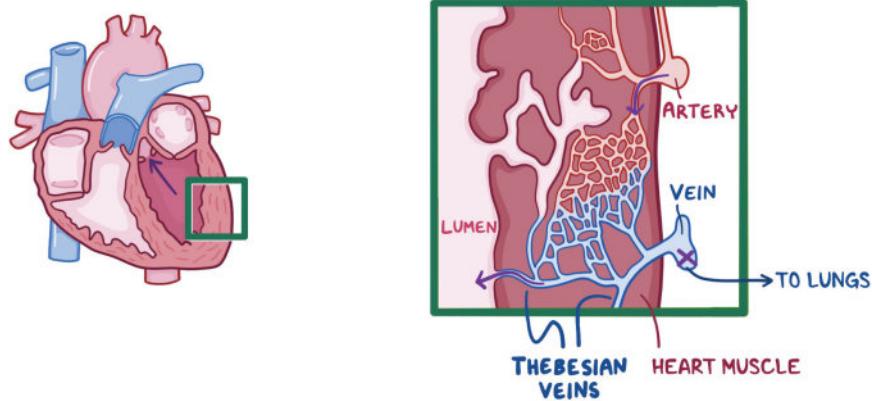


Figure 71.8 Physiologic shunts.

## RIGHT-TO-LEFT SHUNTS

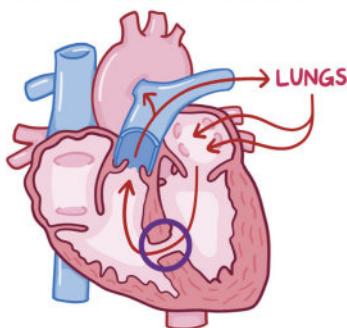
- Defect in wall between right, left sides of heart → blood shunted from right to left side of heart
- Allows for large cardiac output fraction to be shunted (approx. 50%) → bypasses lungs → oxygenated blood diluted with shunted deoxygenated blood → hypoxemia
- Not responsive to high  $P_{O_2}$  gas treatment → complete pulmonary blood saturation doesn't improve shunted blood oxygenation
- Causes minimal  $Pa_{CO_2}$  change → central chemoreceptors responsive to small  $Pa_{CO_2}$  increases (shunted blood not available for gas exchange) → ↑ ventilation rate → extra  $CO_2$  expired
- Central  $O_2$  receptors significantly less sensitive than  $CO_2$  receptors → only ↑ ventilation once  $Pa_{O_2} < 60\text{mmHg}$

## Shunt fraction equation

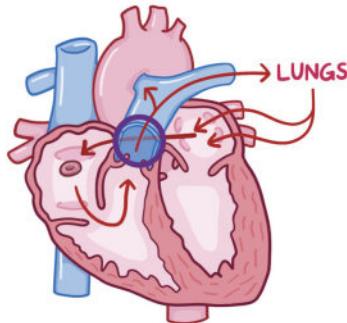
- Oxygenation bypass of venous blood in lung capillaries
- $$\frac{Q_s}{Q_T} = \frac{(C_{CO_2} - C_{AO_2})}{(C_{CO_2} - C_{VO_2})}$$
- $Q_s$ : blood flow through right-to-left shunt (L/min)
- $Q_T$ : cardiac output (L/min)
- $C_{CO_2}$ : oxygen content of nonshunted pulmonary capillary blood
- $C_{AO_2}$ : oxygen content of systemic arterial blood
- $C_{VO_2}$ : oxygen content of venous blood

## LEFT-TO-RIGHT SHUNTS

### VENTRICULAR SEPTAL DEFECT

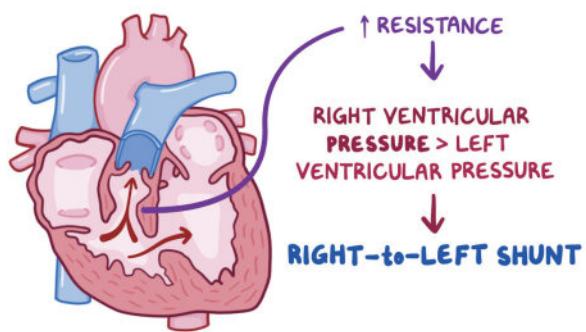
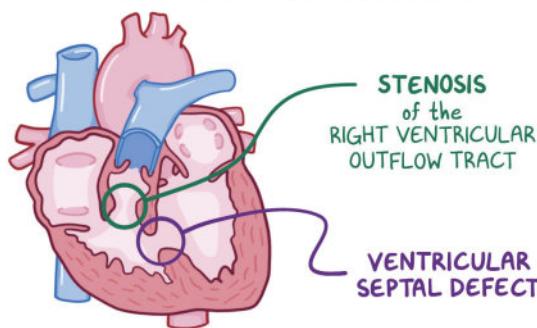


### ATRIAL SEPTAL DEFECT



## RIGHT-TO-LEFT SHUNTS

### EXAMPLE: TETRALOGY OF FALLOT



**Figure 71.9** Pathologic shunts occurring in the left-to-right (more common) and right-to-left directions.

# VENTILATION PERFUSION RATIOS & V Q MISMATCH

[osms.it/ventilation-perfusion-ratios-V-Q-mismatch](http://osms.it/ventilation-perfusion-ratios-V-Q-mismatch)

- Ratio of amount of air to amount of blood reaching alveoli per minute ( $\dot{V}/\dot{Q}$  ratio)

## IDEAL SCENARIO

- Oxygen provided saturates blood fully → ratio of 1

## NORMAL SCENARIO

- Average across entire lung → ratio of 0.8 (apex higher, bases lower)
- Normal breathing rate, tidal volume, cardiac output

## DEFECTS

- Mismatching between ventilation, perfusion → abnormal gas exchange

### Dead space

- Ventilation of lung regions not perfused
- No gas exchange (no blood to facilitate gas exchange)
- Alveolar gas same composition as humidified inspired air ( $PA_{O_2} = 150 \text{ mmHg}$ ,  $PA_{CO_2} = 0$ )
- Pulmonary embolism

### High $\dot{V}/\dot{Q}$

- High ventilation relative to perfusion (ventilation wasted)
- Usually due to ↓ blood flow (limited blood flow → limited gas exchange)
- Relatively high ventilation → pulmonary capillary blood with high  $P_{O_2}$ , low  $P_{CO_2}$
- Emphysema

### Low $\dot{V}/\dot{Q}$

- Low ventilation relative to perfusion (perfusion wasted)
- Usually due to ↓ ventilation → pulmonary capillary blood with low  $P_{O_2}$ , high  $P_{CO_2}$
- Asthma, chronic bronchitis, pulmonary edema, etc.

### Right-to-left shunt

- Perfusion of lung regions not ventilated
- No gas exchange occurs (no gas available to exchange)
- Same blood composition as mixed venous blood ( $Pa_{O_2} = 40 \text{ mmHg}$ ,  $Pa_{CO_2} = 46 \text{ mmHg}$ )
- Airway obstruction, right-to-left cardiac shunts, etc.

V/Q	NORMAL (0.8)	HIGH (can equal ∞)	LOW (can equal zero)
$Pa_{O_2}$	95 mmHg	N/A	↓ to 40 mmHg
$Pa_{CO_2}$	40 mmHg	N/A	↑ to 40 mmHg
$PA_{O_2}$	100 mmHg	150 mmHg	N/A
$PA_{CO_2}$	40 mmHg	0 mmHg	N/A

Figure 71.10 Normal  $\dot{V}/\dot{Q}$ ,  $P_a$ , and  $P_A$  compared to pulmonary embolism and airway obstruction.

# HYPOTENSION & HYPOXIA

osms.it/hypoxemia-and-hypoxia

## HYPOTENSION

- Decrease in arterial  $\text{Pa}_{\text{O}_2}$

### High altitude

- Barometric pressure is decreased → decrease in  $\text{P}_{\text{O}_2}$  of inspired air → decreased  $\text{PA}_{\text{O}_2}$
- Equilibration of alveolar air, pulmonary capillary blood (normal)
- Systemic arterial blood achieves same (lower)  $\text{P}_{\text{O}_2}$  of alveolar air
- Normal alveolar–arterial (A-a) gradient
- High altitude breathing supplemental  $\text{O}_2$  → raised inspired  $\text{P}_{\text{O}_2}$  → raised  $\text{PA}_{\text{O}_2}$  → raised  $\text{Pa}_{\text{O}_2}$

### Hypoventilation

- Less inspired fresh air → decrease in  $\text{PA}_{\text{O}_2}$
- Normal equilibration → pulmonary capillary blood achieves same (lower)  $\text{PA}_{\text{O}_2}$  as A-a gradient
- Hyperventilation: breathing supplemental  $\text{O}_2$  → raised  $\text{PA}_{\text{O}_2}$  → raised  $\text{Pa}_{\text{O}_2}$

### Diffusion defects (fibrosis, pulmonary edema)

- Increased diffusion distance/decreased surface area → impaired equilibration
- Normal  $\text{PA}_{\text{O}_2}$ , decreased  $\text{Pa}_{\text{O}_2}$  → ↑ A-a gradient
- Breathing supplemental  $\text{O}_2$  → raised  $\text{PA}_{\text{O}_2}$  → increased driving force for diffusion → raised  $\text{Pa}_{\text{O}_2}$

### Ventilation/perfusion mismatches

- Regions of well-ventilated (high  $\text{PA}_{\text{O}_2}$ ), poorly-ventilated (low  $\text{PA}_{\text{O}_2}$ ), well-perfused, poorly-perfused lung
- Poor perfusion to well-ventilated areas, adequate perfusion to areas poorly ventilated → low  $\text{Pa}_{\text{O}_2}$
- Supplemental oxygen → raised  $\text{PA}_{\text{O}_2}$  in poorly-ventilated areas with adequate perfusion → increase in  $\text{Pa}_{\text{O}_2}$
- ↑ A-a gradient

## COMMON HYPOTENSION CAUSES/THEIR EFFECT ON GAS EXCHANGE

CAUSE	$\text{Pa}_{\text{O}_2}$	A-a GRADIENT	SUPPLEMENTAL $\text{O}_2$ BENEFICIAL?
HIGH ALTITUDE	↓	Normal	Yes
HYPOVENTILATION	↓	Normal	Yes
DIFFUSION DEFECT	↓	↑	Yes
VENTILATION/PERFUSION MISMATCH	↓	↑	Yes
RIGHT-TO-LEFT-SHUNT	↓	↑	↑ shunt severity → ↓ effect

### Right-to-left shunts (right-to-left cardiac shunts, intrapulmonary shunts)

- Shunted blood completely bypasses alveoli, cannot equilibrate
- Shunted blood mixes with, “dilutes” blood that did pass through alveoli → ↓  $\text{Pa}_{\text{O}_2}$  (even if  $\text{PA}_{\text{O}_2}$  normal)
- ↑ A-a gradient
- Limited supplemental  $\text{O}_2$  effect → raises  $\text{PA}_{\text{O}_2}$ ,  $\text{Pa}_{\text{O}_2}$  of nonshunted blood, does not address underlying shunted blood/oxygenated blood mixing → larger shunt, less effective supplemental  $\text{O}_2$

### HYPOXIA

- ↓  $\text{O}_2$  delivery to/utilization by tissues
- $\text{O}_2$  delivery → determined by cardiac output,  $\text{O}_2$  content of blood
- ↓ cardiac output/localized blood flow → hypoxia
- Hypoxemia (any cause) → ↓  $\text{Pa}_{\text{O}_2}$  → ↓ hemoglobin saturation → ↓ oxyhemoglobin concentration in blood → ↓ oxygen delivery to tissues → hypoxia
- Anemia (↓ hemoglobin concentration) → ↓ oxyhemoglobin concentration in blood → decreased oxygen delivery to tissues → hypoxia

- Carbon monoxide poisoning → irreversible binding with hemoglobin → ↓ oxyhemoglobin concentration in blood → ↓ oxygen delivery to tissues → hypoxia
- Cyanide poisoning → interferes with  $\text{O}_2$  utilization on cellular level

### HYPOXIC VASOCONSTRICTION

- Alveolar partial pressure of oxygen ( $\text{PA}_{\text{O}_2}$ ) major factor controlling pulmonary blood flow
- ↓  $\text{PA}_{\text{O}_2}$  → vasoconstriction (opposite to systemic vasculature where ↓ in  $\text{Pa}_{\text{O}_2}$  → vasodilation)
  - Vasoconstriction in response to poor oxygenation ensures blood flow coupled to areas of good ventilation → optimal gas exchange
  - In localized lung disease, areas of poorly-ventilated, diseased lung circumvented → blood directed towards healthy lung

## COMMON HYPOXIA CAUSES/ARTERIAL OXYGENATION STATUS

CAUSE	MECHANISM	$\text{PaO}_2$
↓ CARDIAC OUTPUT	↓ blood flow	Equilibrated
HYPOTHEMIA	↓ $\text{PaO}_2$ ↓ O <sub>2</sub> saturation of hemoglobin ↓ O <sub>2</sub> content of blood	↓
ANEMIA	↓ hemoglobin concentration ↓ O <sub>2</sub> concentration of blood	Equilibrated
CARBON MONOXIDE POISONING	↓ O <sub>2</sub> concentration of blood Left shift of O <sub>2</sub> -hemoglobin curve	Equilibrated
CYANIDE POISONING	↓ O <sub>2</sub> utilization of blood	Equilibrated

### **Alveolar $P_{O_2}$ direct action on vascular smooth muscle → hypoxic vasoconstriction**

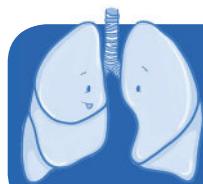
- Pulmonary microcirculation surrounds alveoli
- $O_2$  highly lipid soluble → permeable across cell membranes
- Normal  $PA_{O_2}$  (100mmHg),  $O_2$  diffuses from alveoli → arteriolar smooth muscle → maintains relaxation, dilation of arterioles
- $PA_{O_2}$  decreases (70–100mmHg) → vascular smooth muscle sense change (hypoxia) → vasoconstriction → ↓ pulmonary blood flow to region
  - Vasocnstriction mechanism likely due to hypoxia → vascular smooth muscle depolarization → voltage-gated calcium channels open → calcium enters smooth muscle → contraction

### **HIGH ALTITUDE & HYPOXIC VASOCONSTRCTION**

- Entire lung exposed to ↓  $PA_{O_2}$  (e.g. high altitudes) → global ↑ in pulmonary arteriolar resistance → ↑ pulmonary vascular resistance
- Chronic ↑ pulmonary vascular resistance → ↑ right heart afterload → right heart hypertrophy

### **FETAL HYPOXIC VASOCONSTRCTION**

- Fetal circulation must acquire oxygen from maternal circulation via placenta → significantly lower  $Pa_{O_2}$  → fetal lung vasoconstriction → reduction of blood flow to lungs (15% of cardiac output)
- At birth low pressure placenta circuit removed → ↑ systemic blood pressure → first breath after birth → ↑  $PA_{O_2}$  → 100mmHg → ↓ hypoxic vasoconstriction → ↓ pulmonary vascular resistance → pulmonary blood flow begins to normalize



# NOTES

## NORMAL VARIATIONS

# PULMONARY CHANGES DURING EXERCISE

[osms.it/pulmonary\\_changes\\_during\\_exercise](https://osms.it/pulmonary_changes_during_exercise)

### RESPIRATORY RESPONSE TO EXERCISE

- Exercise → muscle workload increase → **consumption of significant O<sub>2</sub>** amounts, above baseline production of CO<sub>2</sub>, lactic acid
- Increased O<sub>2</sub> demand → hyperpnea (ventilation increases 10–20x to compensate)
- Hyperpnea vs. hyperventilation
  - Hyperpnea: aims to maintain homeostasis → blood O<sub>2</sub>, CO<sub>2</sub> levels remain relatively constant
  - Hyperventilation: excessive ventilation, blowing off too much CO<sub>2</sub> → **low P<sub>CO<sub>2</sub></sub>**, **respiratory alkalosis**
- Exercise-induced ventilation not initially prompted by alterations in blood gases (rising P<sub>CO<sub>2</sub></sub>, declining P<sub>O<sub>2</sub></sub>, pH)
- **Ventilation increases** abruptly as exercise begins due to neural factors
  - Psychological stimuli (conscious exercise anticipation)
  - Simultaneous cortical motor activation of skeletal muscle, respiratory centers
  - Proprioceptors moving muscles, tendons, joints → stimulate respiratory centers
  - Initial neural regulation → early compensation to exercise as opposed to waiting for change in blood values
- Initial abrupt increase in ventilation is followed by gradual increase (reflective of lung CO<sub>2</sub> delivery rate) → eventually, steady state of ventilation appropriate for intensity achieved

- Exercise cessation → initial small abrupt decline in ventilation (higher neurological stimulation ends) → followed by gradual decrease to pre-exercise respiratory rate (gradual decrease in CO<sub>2</sub> flow to lungs)

### PULMONARY CIRCULATORY RESPONSE

- Cardiac output increases to meet tissue O<sub>2</sub> demand → increased right heart output → **increased blood flow through pulmonary circulation** → increased blood return to left heart → increased output to systemic circulation → increased O<sub>2</sub> tissue delivery
- **Exercise** → pulmonary resistance decrease → perfusion of more pulmonary capillary beds → more even distribution of pulmonary perfusion, ventilation → **improved V/Q ratio** (decreased physiological dead space) → increased gas exchange efficiency

### HEMATOLOGICAL RESPONSE

#### Bohr effect

- Hemoglobin's oxygen binding affinity is inversely related to acidity, carbon dioxide concentration
  - **Exercise** → increased tissue P<sub>CO<sub>2</sub></sub>, decreased tissue pH, increased temperature → **right shift of O<sub>2</sub>-hemoglobin dissociation curve** → decreased affinity of hemoglobin for O<sub>2</sub> → greater unloading of oxygen to exercising muscle

### Regulation of blood gases during exercise

- Arterial  $P_{CO_2}$ ,  $P_{O_2}$  remain nearly constant during exercise
- Venous  $P_{CO_2}$ ,  $P_{O_2}$  may change significantly during exercise
  - Ventilation increases sufficiently to blow off all excess  $CO_2$ , maintain arterial homeostasis

### Anaerobic respiration

- Leads to rise in lactic acid levels
- Not due to inadequate respiratory function
- Alveolar ventilation, pulmonary perfusion remain well matched during exercise → hemoglobin fully saturated
- Cardiac output limitation/limits of skeletal muscle to utilize oxygen → rising lactic acid

RESPIRATORY RESPONSE TO EXERCISE OVERVIEW	
VENTILATION RATE	↑
PHYSIOLOGIC DEAD SPACE	↓
V/Q RATIO	More equal distribution throughout lungs
PULMONARY BLOOD FLOW, CARDIAC OUTPUT	↑
O <sub>2</sub> CONSUMPTION	↑
CO <sub>2</sub> CONSUMPTION	↑
ARTERIAL P <sub>O<sub>2</sub></sub> , P <sub>CO<sub>2</sub></sub>	No change
ARTERIAL pH	Light exercise: no change

# PULMONARY CHANGES AT HIGH ALTITUDE & ALTITUDE SICKNESS

[osms.it/pulmonary\\_changes\\_high\\_altitude\\_altitude\\_sickness](https://osms.it/pulmonary_changes_high_altitude_altitude_sickness)

## RESPIRATORY RESPONSE TO ALTITUDE

- Humans typically live at altitudes between sea level and 2400m/7800ft
- Altitudes > 2400m/7800ft → lower overall atmospheric pressure → lower  $P_{O_2}$  → hemoglobin less saturated at baseline
  - At rest at sea level hemoglobin typically unloads 20–25%  $O_2$  content on a single trip through the circulatory system
  - Significant functional reserve allows for survival due to further hemoglobin unloading when poorly saturated

## ACCLIMATIZATION

- Long-term, slow steady move from sea level to higher altitude → respiratory, hematopoietic adaptation
- Decrease in arterial  $P_{O_2}$  → peripheral chemoreceptors more responsive to increases in  $P_{CO_2}$  → chemoreceptors stimulate medullary inspiratory center → increased breathing rate

### Initial (fast) adaptation

- Some changes occur immediately, others over course of days
- Pulmonary
  - Minute ventilation → 2–3L/min higher than sea level
  - Increased ventilation → decreased arterial  $CO_2$  (<40mmHg) → respiratory alkalosis → increased blood pH → inhibition of central, peripheral chemoreceptors → offset increase in ventilation rate (initial effect)
  - As adaptation occurs →  $HCO_3^-$  excretion increases →  $HCO_3^-$  concentration in cerebrospinal fluid (CSF) decreases → CSF pH decreases toward normal → increased ventilation rate resumes
  - Respiratory alkalosis as result of rapid ascent to high altitude managed

with carbonic anhydrase inhibitors  
→ increased  $HCO_3^-$  excretion → mild compensatory metabolic acidosis

- Hematological
  - Increase in 2,3-bisphosphoglyceric acid (2,3-BPG) concentration → hemoglobin affinity for  $O_2$  reduced → increased unloading of  $O_2$  at tissue level (also decreases efficiency of oxygen loading in lungs)
- Cardiac
  - Increased heart rate
  - Right heart hypertrophy: low  $P_{O_2}$  alveolar gas → pulmonary vasculature vasoconstriction → increase in pulmonary vascular resistance → increased right heart strain → right ventricular hypertrophy
- Oxygen conservation
  - Non-essential body functions suppressed → reduction in food digestion efficiency (decreased circulation in favor of perfusing more important organs)

### Late (slow) acclimatization

- Occurs over weeks to months
- Hematological: hypoxia → kidneys produce more erythropoietin → stimulates bone marrow production of red blood cells → total  $O_2$  carrying capacity of blood increased
  - Essential compensation for living at altitude
  - Increases blood viscosity → greater blood flow resistance → greater heart workload
  - Full acclimatization: increase in red blood cell plateaus
- Effect on complete blood count parameters
  - Total red cells: ↑
  - Hemoglobin: ↑
  - Hematocrit: ↑

- Mean corpuscular volume: unchanged
- Mean corpuscular hemoglobin concentration: ↑

### Exercise at altitude

- Adaptations normally serve to achieve homeostasis at rest → unless fully acclimatized intense physical activity → homeostasis loss → severe hypoxia
- This transient intentional hypoxia can be exploited by athletes → further adaptive changes to altitude → blood with greater oxygen carrying capacity → improved performance at lower altitude
- Late phase acclimatization of skeletal muscle includes: increased capillary concentration, increased myoglobin amount, increased mitochondria number, increased aerobic metabolism enzyme concentration

## ACUTE MOUNTAIN SICKNESS

- AKA altitude sickness
- Commonly associated with altitudes above 2400m/7800ft
  - Minor symptoms may occur at as low as 1500m/5000ft
  - Death zone: 5500m/18000ft, altitude considered incompatible with human life; acclimatization not possible
- Caused by sudden transition to altitude without sufficient acclimatization → low atmospheric pressure → low  $P_{O_2}$  → hypoxia
- Contributing factors
  - Rate of ascent
  - Rate of water vapor loss from lungs
  - Activity level
- Sudden increase in altitude without taking time to acclimatize

### Symptoms

- Headache, shortness of breath, nausea, dizziness, peripheral edema

### Complications

- Severe complications of high altitude can be fatal
- High altitude pulmonary edema (HAPE)
  - Low atmospheric pressure → decreased oxygen partial pressures, poor oxygenation → increased pulmonary arterial, capillary pressures, idiopathic increase in permeability of vascular endothelium → fluid extravasation → pulmonary edema
- High altitude cerebral edema (HACE)
  - Hypoxia → increased cerebral microvascular permeability, failure of cellular ion pumps → vasogenic, cytotoxic edema

### Treatment

- Supplemental oxygen/immediate descent

PHYSIOLOGICAL ACCLIMATIZATION TO HIGH ALTITUDE OVERVIEW	
	RESPONSE
ALVEOLAR $P_{O_2}$	↓ (lower barometric pressure → lower atmospheric $P_{O_2}$ )
ARTERIAL $P_{O_2}$	↓ (hypoxemia)
ARTERIAL pH	↑ (respiratory alkalosis due to hyperventilation)
HEMOGLOBIN CONCENTRATION	↑ red blood cell concentration
2,3-DPG CONCENTRATION	↑
MUSCLE METABOLISM	↑ efficiency of aerobic metabolism
$O_2$ -HEMOGLOBIN DISSOCIATION CURVE	Right shift (more oxygen unloaded to tissues)
PULMONARY ARTERIAL PRESSURE	↑ (secondary to increased pulmonary vascular resistance)
PULMONARY VASCULAR RESISTANCE	↑ (vasoconstriction)
VENTILATION RATE	↑