

# Lippincott Illustrated Reviews Flash Cards

## PHYSIOLOGY

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# Features: Three-Step Review



## SPOT FLASH

Test your grasp of key concepts or equations on a lecture-by-lecture basis!



## COURSE REVIEW

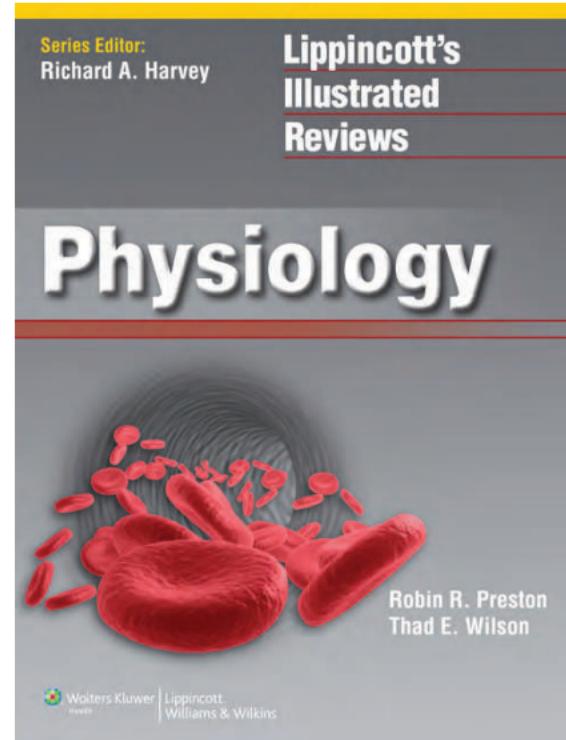
In-depth questions to ensure a thorough understanding of course material. High-yield facts for Course- and Board-exam review!



## CLINICAL CORRELATIONS

Explain how the basic science helps predict outcomes in a clinical setting!

Featuring the same visionary artwork found in  
*Lippincott Illustrated Reviews: Physiology*  
With Lippincott Illustrated Reviews, Seeing is Understanding.





# Preface

*Lippincott Illustrated Reviews Flash Cards: Physiology* is a portable study tool designed for self-assessment and review of medical physiology. The flash cards were developed primarily for use by medical students studying physiology and preparing for course and U.S. medical licensing exams, but information is presented with a clarity and level of detail that suits them as supplements for any of the allied health sciences. The deck contains two card types: Question (Q) cards and Summary cards.

## Q CARDS

The majority of cards comprise Q cards that prompt the reader with questions to assess level of understanding and depth of knowledge.

Each Q card contains three-tiered questions or sets of questions on a common topic: The first tests for retention of basic facts, whereas the next two build on the basics to test understanding of concepts and clinical presentations. The three question types are denoted by icons.



**SPOT FLASH:** Questions test your grasp of key facts or equations and are intended for use on a lecture-by-lecture assessment and review basis.



**COURSE REVIEW:** In-depth questions ensure a thorough understanding of concepts that may have been revisited several times during a medical physiology course. The answers focus on high-yield facts to help consolidate memory during course- and licensing-exam review.



**CLINICAL CORRELATIONS:** Underscoring how the basic science helps predict outcomes in a clinical setting, these correlations are particularly useful when studying for licensing exams, but sneak peeks can encourage students to persevere during early physiology lectures!

*Continued, over*

# Preface

Q cards include several features to aid learning and memorization:

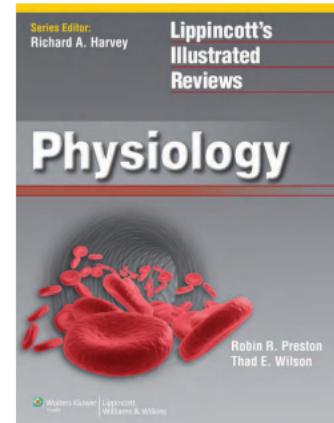
- **Illustrations:** Richly detailed illustrations from the popular companion text, *Lippincott's Illustrated Reviews: Physiology*, appear on both sides of the cards. Many of the illustrations include narrative boxes to help guide readers through complex concepts.
- **A-plus:** Answers may be supplemented with information that goes beyond the need-to-know basics to provide context or to enrich and help cement a medical concept.
- **Emphasis:** Key terms and diseases are bolded for rapid review and assimilation.

## SUMMARY CARDS

Summary cards follow a more traditional flash card design, taking readers step-by-step through a complex physiologic regulatory pathway.

The card deck is designed to be comprehensive, covering all significant physiologic concepts. Key equations are additionally summarized in an appendix for quick and easy reference.

*Note:* Our knowledge and understanding of human physiology evolves constantly in the light of new research discoveries. Future editions of *Lippincott Illustrated Reviews Flash Cards: Physiology* will be updated to take into account such findings and to respond to user feedback. If you have any comments or suggestions for improvement, please contact the author at LIRphysiology@gmail.com.



# Figure Credits

## Card 1.1 Question and Answer:

Modified from Chandar N, Viselli, S. *Lippincott's Illustrated Reviews: Cell and Molecular Biology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.

## Card 1.5 Question and Answer:

Modified from Clarke MA, Finkel R, Rey JA, et al. *Lippincott's Illustrated Reviews: Pharmacology*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.

## Card 2.7 Question and Answer,

## Card 2.15 Question and Answer,

## Card 2.18 Question and Answer,

## Card 2.25 Question and Answer,

## Card 2.29 Question and Answer:

Modified from Krebs C, Weinberg J, Akesson E. *Lippincott's Illustrated Review of Neuroscience*. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.

## Card 2.5 Question and Answer:

Modified from Moore KL, Dalley AF. *Clinical Oriented Anatomy*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.

## Card 2.14 Question and Answer and Card 2.20 Question and Answer:

Modified from Bear MF, Connors BW, Paradiso MA. *Neuroscience: Exploring the Brain*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.

## Card 2.31 Question and Answer:

Modified from Siegel A, Sapru HN. *Essential Neuroscience*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

## Card 3.7 Question and Answer:

Data modified from Kuo KH, Seow CY. Contractile filament architecture and force transmission

in swine airway smooth muscle.

*J Cell Sci.* 2004;117:1503–1511.

## Card 3.10 Question and Answer:

Model (lower) modified from Thurner PJ. Atomic force microscopy and indentation force measurement of bone. *Nanomed. Nanobiotechnol.* 2009;1:624–629.

## Card 4.1 Question and Answer,

## Card 4.2 Question and Answer,

## Card 4.10 Question and Answer, and Card 4.11 Question and Answer:

Modified from Klabunde RE. *Cardiovascular Physiology Concepts*. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.

## Card 4.30 Question and Answer:

Data modified from Harper AM.

The inter-relationship between aPco<sub>2</sub> and blood pressure in the regulation of blood flow through the

# Figure Credits

cerebral cortex. *Acta Neurol Scand Suppl.* 1965;14:94.

Card 4.31 Question, Card 6.2 Question and Answer, Card 6.5 Question and Answer, and Card 9.1 Question and Answer: Modified from Rhoades RA, Bell DR. *Medical Physiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.

Card 5.1 Question and Answer, Card 5.5 Question and Answer, Card 5.7 Question and Answer, Card 5.18 Question and Answer, Card 6.28 Question and Answer, Card 6.29 Question and Answer, Card 6.30 Question and Answer, and Card 6.31 Question and Answer: Modified from West JB. *Respiratory Physiology: The Essentials*. 7th ed.

Philadelphia, PA: Lippincott Williams & Wilkins; 2005.

Card 5.13 Question and Answer, Card 5.14 Question and Answer, Card 8.3 Question and Answer, and Card 9.15 Question and Answer: Modified from Harvey RA, Ferrier DR. *Lippincott's Illustrated Reviews: Biochemistry*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

Card 6.9 Question and Answer: Data modified from Rector FC. Sodium, bicarbonate, and chloride absorption by the proximal tubule. *Am J Physiol.* 1983;244:F461–F471.

Card 8.8 Question and Answer: Modified from Rubin E, Farber JL.

*Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.

Card 8.17 Question and Answer: Modified from Anatomical Chart Company. Philadelphia, PA: Wolters Kluwer Health, 2013.

Card 9.5 Question and Answer: Modified from West JB. *Best and Taylor's Physiological Basis of Medical Practice*. 12th ed. Baltimore, MD: Williams & Wilkins; 1991.

Card 9.14 Question and Answer: Yochum TR, Rowe LJ. *Yochum And Rowe's Essentials of Skeletal Radiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.

# Contents

UNIT 1	<b>Principles of Physiologic Function</b>	1.1
UNIT 2	<b>Sensory and Motor Systems</b>	2.1
UNIT 3	<b>Musculoskeletal and Integumentary Systems</b>	3.1
UNIT 4	<b>Cardiovascular System</b>	4.1
UNIT 5	<b>Respiratory System</b>	5.1
UNIT 6	<b>Urinary System</b>	6.1
UNIT 7	<b>Gastrointestinal System</b>	7.1
UNIT 8	<b>Endocrine System</b>	8.1
UNIT 9	<b>Living and Dying</b>	9.1
APPENDIX	<b>Key Equations and Abbreviations</b>	A-1



# Membrane Proteins

## 1.1 Question



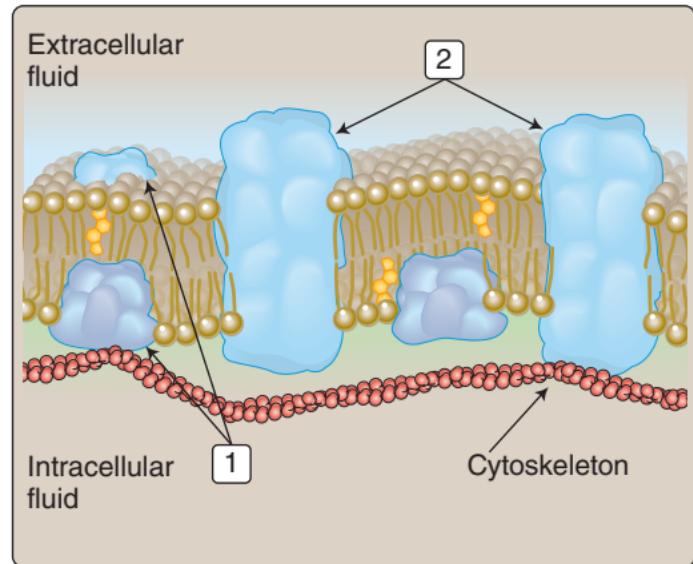
What two protein classes are indicated by boxed numerals?



What is a GPI-anchored protein?



What hemolytic disease is caused by a GPI synthetic pathway defect?



**Two protein classes:**

1. **Peripheral:** Peripheral proteins localize to the membrane surface and may be weakly associated.
2. **Integral:** Integral proteins span the width of the membrane, penetrating the lipid core.

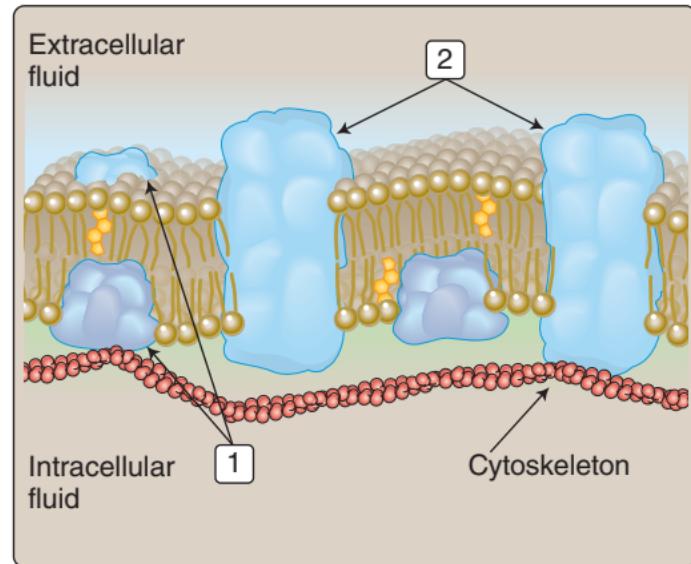


**GPI-anchored proteins** are a subclass of peripheral membrane proteins attached to the cell exterior. They are anchored within the plasma membrane by a glycolipid (i.e., GPI) that is attached during posttranslational modification.

*A-plus:* GPI-anchored proteins include surface antigens, cell adhesion molecules, receptors, and hydrolytic enzymes (e.g., *acetylcholinesterase* and *alkaline phosphatase*).



**Paroxysmal nocturnal hemoglobinuria** results from mutations in the PIG-A gene. PIG-A is required for GPI anchor synthesis. The defect leaves RBCs susceptible to the actions of complement, resulting in a hemolytic anemia.



# Diffusion

## 1.2 Question



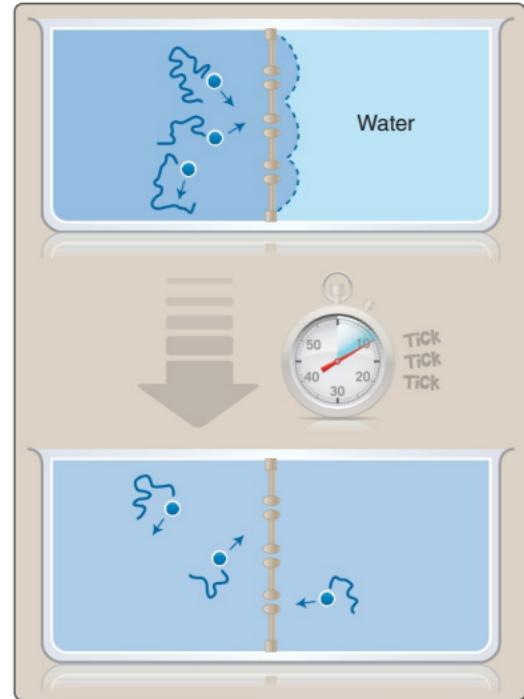
Define the equation used to determine the rate at which molecules diffuse through gases or solutions.



Describe how the cardiovascular, GI, and respiratory systems take advantage of the Fick law.



Why might **celiac disease** be considered a "Fick law defect"?



Simple diffusion of a blue dye through water.



Diffusion rates ( $J$ ) can be calculated using a derivation of the **Fick law** of diffusion:

$$J = P \times A (C_1 - C_2)$$

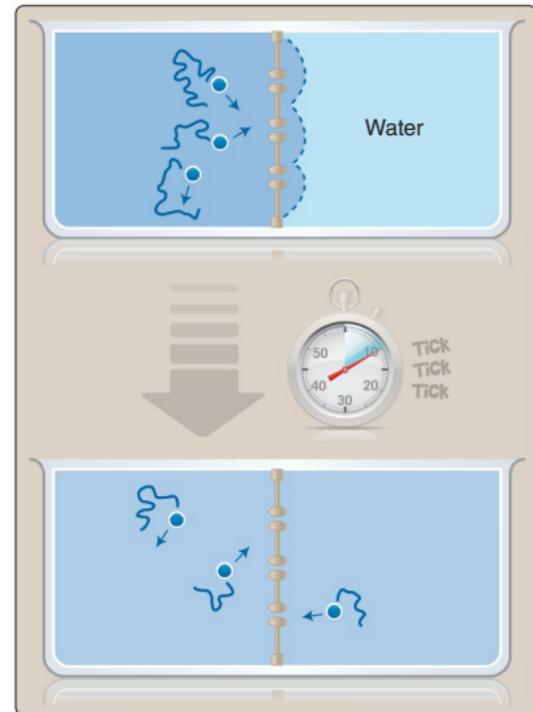
Where  $P$  is a permeability coefficient,  $A$  is surface area, and  $C_1 - C_2$  is the concentration gradient driving diffusion.



The cardiovascular, GI, and respiratory systems all take advantage of the Fick law by maximizing diffusion rates through surface area amplification ( $A$ ). [Note: The lungs also maximize diffusion rates by using an air–gas interface of  $<0.3$  mm (thickness is a component of the permeability coefficient,  $P$ ) and by maintaining the concentration gradients for both  $O_2$  and  $CO_2$  through ventilation and high blood flow.]



**Celiac disease** might be considered a “Fick law defect” insofar as **villar atrophy** reduces small intestine surface area. Atrophy is caused by gluten-induced intestinal inflammation. The disease is typified by chronic diarrhea and weight loss from impaired nutrient absorption.



Simple diffusion of a blue dye through water.



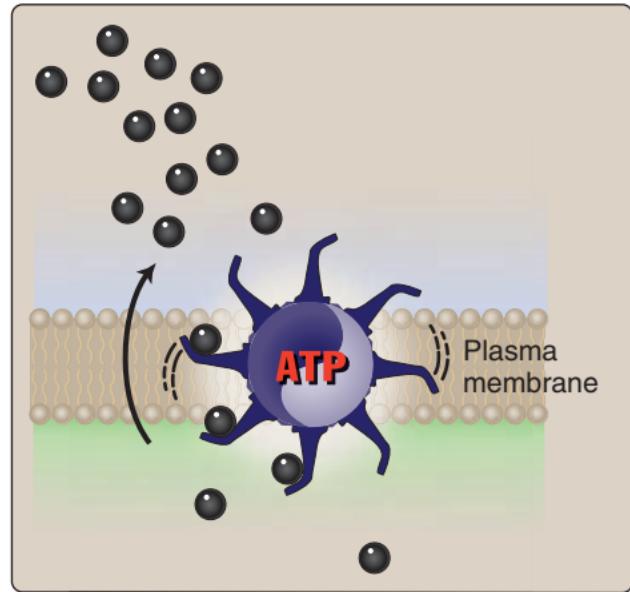
What are the three principal modes of carrier-mediated membrane transport (one example is shown)?



What is an ion pump? What are the three principal pumps found in humans, and how are they distributed?



Cardiac glycosides (e.g., digoxin) may be used to improve output of a heart with **systolic dysfunction** by what mechanism?





Three modes of **carrier-mediated membrane transport**:

1. **Facilitated diffusion**
2. **Primary active transport**
3. **Secondary active transport**
  - **Exchangers** (cotransporters or antiports)
  - **Cotransporters** (symports)

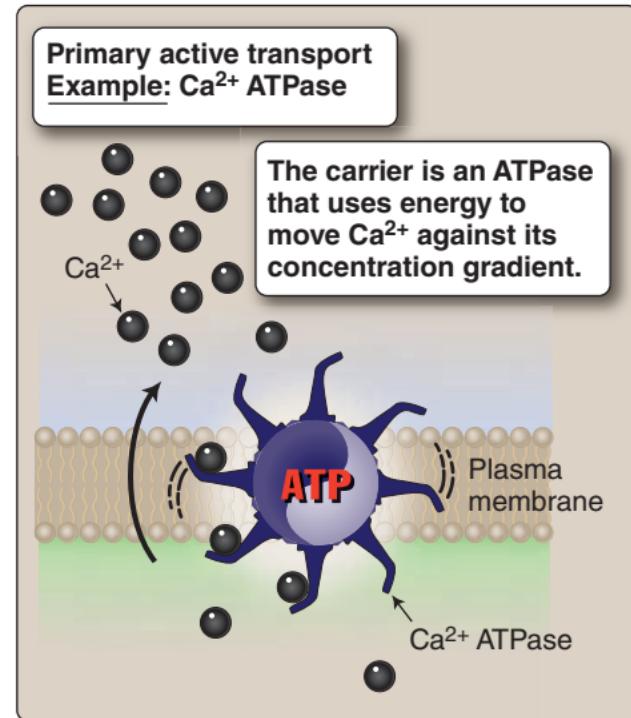


An **ion pump** is a primary active transporter that uses **ATP** to pump ions "uphill" against their electrochemical gradient. The three principal pumps in humans are:

- $\text{Na}^+-\text{K}^+$  ATPase (ubiquitous: creates the  $\text{Na}^+$  gradient used to power secondary active transport)
- $\text{Ca}^{2+}$  ATPase (ubiquitous: keeps intracellular  $\text{Ca}^{2+}$  levels low)
- $\text{H}^+-\text{K}^+$  ATPase (found primarily in the stomach and in osteoclasts)



Digoxin and other glycosides improve **inotropy** by inhibiting the  $\text{Na}^+-\text{K}^+$  ATPase and raising intracellular  $\text{Na}^+$ . This weakens the gradient driving  $\text{Ca}^{2+}$  extrusion via the  $\text{Na}^+-\text{Ca}^{2+}$  exchanger and raises intracellular  $\text{Ca}^{2+}$ . Because  $\text{Ca}^{2+}$  equates with cross-bridge cycle numbers, myocardial inotropy and output are improved.



# Intercellular Communication

1.4 Question



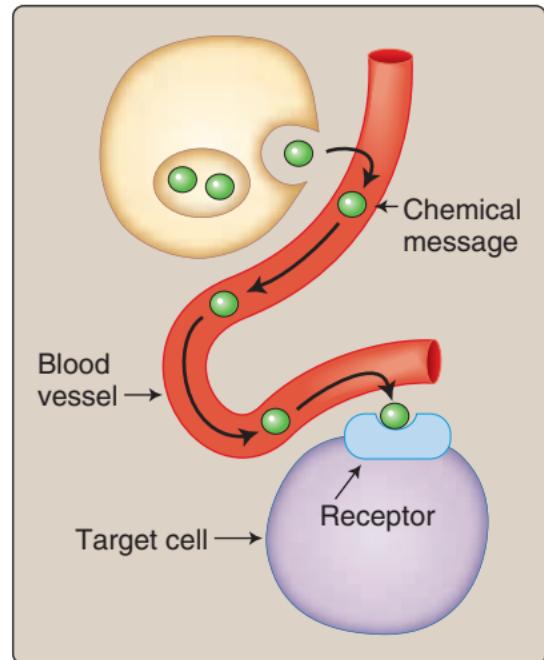
What are the four principal modes of intercellular communication?



What are the main advantages to chemical communication between cells?



Male patients who are infertile may receive a serum sex hormone-binding globulin (SHBG) test. What is the function of SHBG normally?





Four modes of intercellular communication:

1. **Direct contact** (via **gap junctions**)
2. **Hormonal signaling** (via blood)
3. **Paracrine signaling** (close proximity signaling)
4. **Autocrine signaling** (provides a feedback pathway that acts on the cell originating the signal)

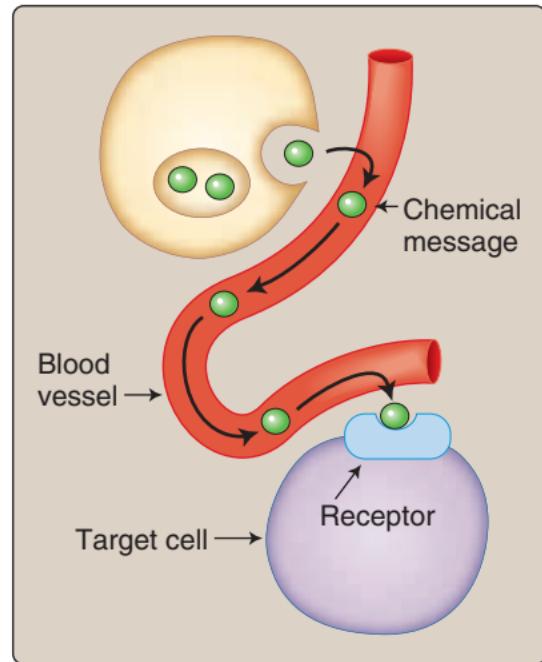


Advantages to chemical communication include:

- **Economy:** Chemical signals can reach every cell in the body via blood. Electrical signaling, by contrast, requires a dedicated network of nerves.
- **Signal gain:** Chemical signals can be amplified (e.g., by hormone-stimulating hormones) en route, whereas electrical signals degrade with distance.



SHBG is a plasma glycoprotein that binds **androgen** and **estrogens** with high affinity. SHBG and related proteins help transport hormones to their target, increase their half-lives, and determine bioavailability. Because SHBG levels control testosterone access to tissues, an inappropriate rise in serum SHBG can cause symptoms similar to **hypogonadism**.



# Intracellular Signaling

## 1.5 Question



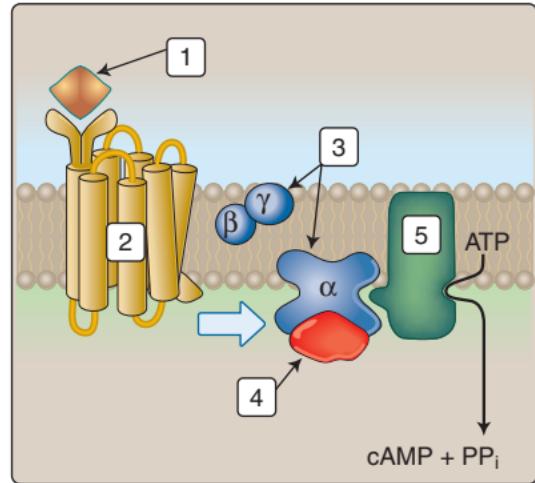
What are the five numbered components of the signal transduction pathway shown?



What is the function of cAMP in this pathway?



*Vibrio* \_\_\_\_\_ causes a watery diarrhea through upregulation of the cAMP signaling pathway and \_\_\_\_\_ efflux via the \_\_\_\_\_ (CFTR).





Five components of the cAMP signal transduction pathway:

1. Hormone or neurotransmitter
2. Receptor
3. GTP-binding protein
4. GTP
5. Active AC

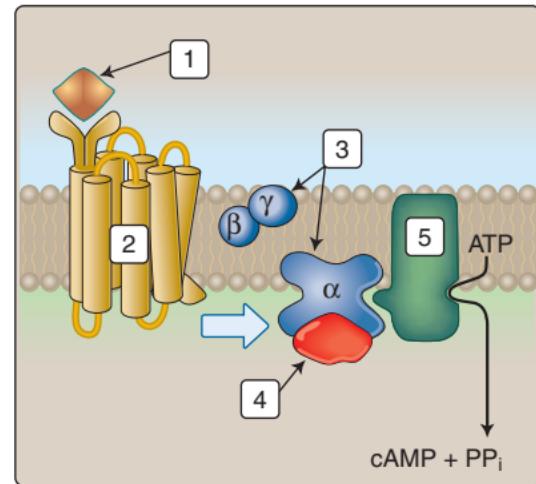


**cAMP** functions as a **second messenger** that couples receptor activation with intracellular effectors such as **PKA**. [Note: The advantage to using second messenger systems is that they allow for massive signal amplification. The cAMP pathway is one of two principal effector pathways in cells. The other uses  $IP_3$  as second messenger.]



*Vibrio cholerae* causes a watery diarrhea through upregulation of the cAMP signaling pathway and  $Cl^-$  efflux via the **cystic fibrosis transmembrane conductance regulator (CFTR)**. [Note: Cholera toxin stimulates ADP-ribosylation and irreversible activation of  $G_{\alpha S}$ , thereby upregulating PKA. PKA then activates CFTR, causing  $Cl^-$  (and obligated water) secretion into the gut lumen.]

**A-plus:** cAMP pathway upregulators can be remembered using **cAMP** as a mnemonic. **Cholera, anthrax, E. coli** (mentally rotate the E 90° to make it an M), and pertussis toxins all upregulate the cAMP pathway.



# Equilibrium Potentials

## 1.6 Question



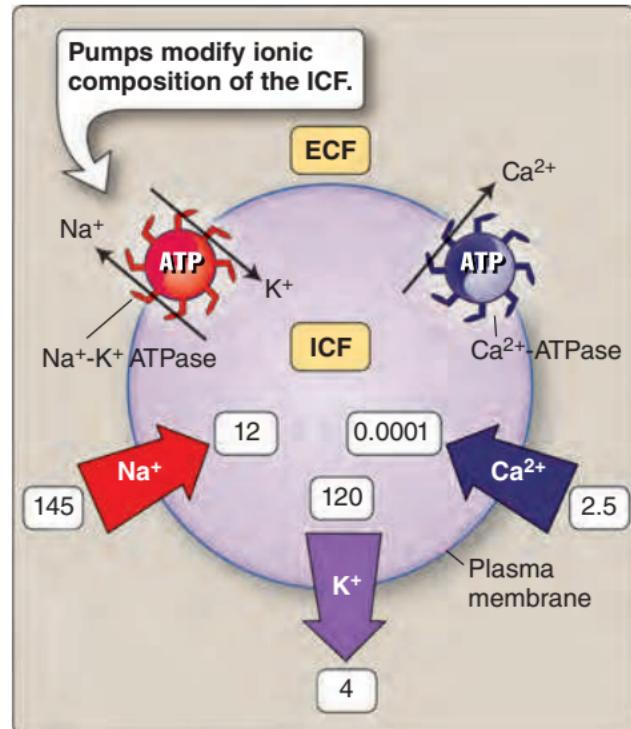
What is the equation used to calculate an ion equilibrium potential ( $E_x$ )? Calculate  $E_{Na}$  for the cell shown.



What is the  $Na^+$  gradient created by the  $Na^+-K^+$  ATPase used for *in vivo*?



Acute hyponatremia and hypernatremia can cause neurologic symptoms through rapid changes in cerebral volume by what mechanism?



Ion concentration gradients created by ion pumps. Numerals in boxes are in mmol/L.



An equilibrium potential ( $E_x$ ) is calculated using a simplified form of the **Nernst equation**:

$$E_x = \frac{60}{z} \log_{10} \frac{[X]_o}{[X]_i}$$

Where  $z$  = valence and  $[X]_o$  and  $[X]_i$  are ion concentrations in the ECF and ICF, respectively. For  $\text{Na}^+$ :

$$E_{\text{Na}} = \frac{60}{1} \log_{10} \frac{145}{12} = 65 \text{ mV}$$

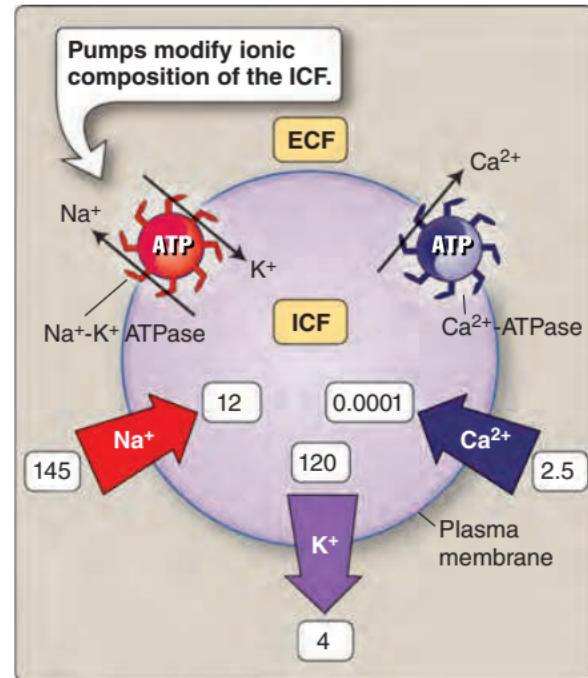


The  $\text{Na}^+$  gradient has two principal uses in vivo:

1. **Electrical signaling** (the upstroke of a nerve AP is driven by  $\text{Na}^+$  influx)
2. Powering **solute transport** by  $\text{Na}^+$ -dependent exchangers and cotransporters



Hypo- and hypernatremia change the osmolality of ECF. If the changes are acute, water shifts rapidly between cells and the ECF, causing cerebral edema (hyponatremia) or demyelination and focal hemorrhages (hypernatremia). Seizures, coma, and death may result.



Ion concentration gradients created by ion pumps.  
Numerals in boxes are in mmol/L.

# Membrane Potentials

1.7 Question



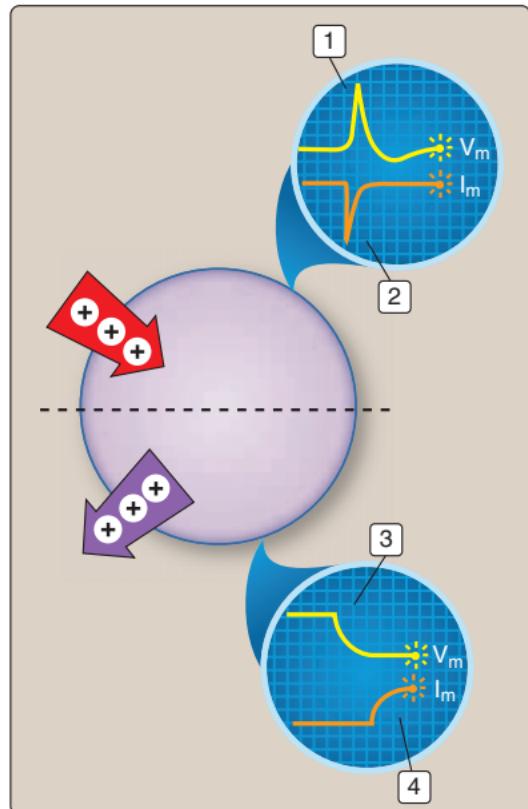
What are the terms used to describe the electrical events indicated by boxed numerals?



Why does membrane potential usually rest close to the  $E_K$ ?



Severe hypokalemia (i.e., serum  $K^+$  of  $<3$  mmol/L) can cause muscle weakness and cardiac rhythm disturbances by what mechanism?





Terms used to describe electrical events:

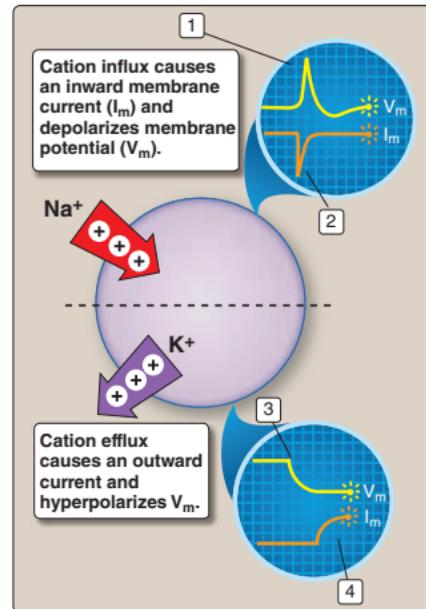
1. **Depolarization**
2. **Inward current**
3. **Hyperpolarization**
4. **Outward current**



$V_m$  usually rests close to  $E_K$  because although all cells express a mix of  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Cl}^-$ , and nonspecific channels in their surface membrane, most of these are closed at rest and, thus, do not contribute to resting potential. The exception is a **K<sup>+</sup> leak channel**, which allows  $\text{K}^+$  to flow out of the cell, pulling  $V_m$  toward  $E_K$ .



Hypokalemia steepens the transmembrane  $\text{K}^+$  gradient and causes membrane hyperpolarization. Severe hypokalemia can cause  $V_m$  to fall to levels so far removed from excitation thresholds that AP formation is inhibited, causing muscle weakness and a variety of cardiac conduction and rhythm abnormalities.



# Action Potentials

## 1.8 Question



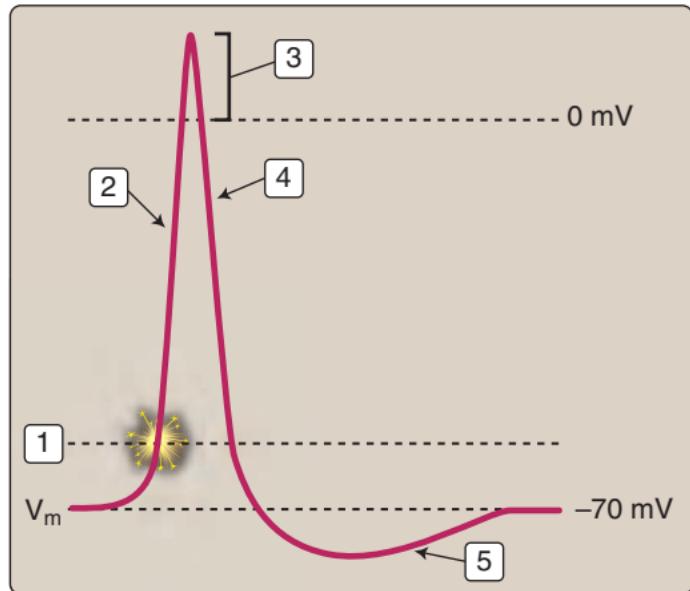
What terms describe AP events (indicated by boxed numerals)?



Nerve APs have durations of 2–3 ms, whereas APs in cardiac myocytes last 200–300 ms. What accounts for the difference?



**Hyperkalemic periodic paralysis (PP)** is a rare inherited channelopathy that affects what ion channel?





Terms used to describe APs:

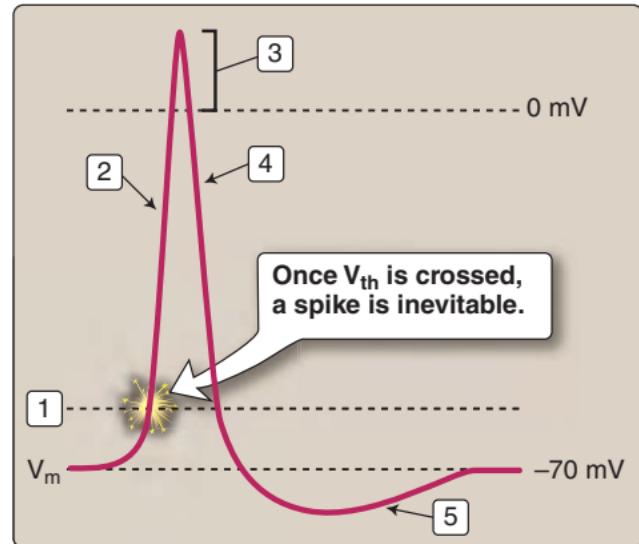
1. **Threshold potential**
2. **Upstroke**
3. **Overshoot**
4. **Downstroke**
5. **Afterpotential** (afterhyperpolarization is shown)



The nerve **AP** is dominated by  $I_{Na}$ , which activates and then inactivates within 2–3 ms. The upstroke of the AP in atrial and ventricular myocytes is also driven by  $I_{Na}$ , but the AP is then sustained for ~300 ms by an  $I_{Ca}$  that activates and deactivates more slowly.



**Hyperkalemic PP** results from a dominant mutation in the  $\text{Na}^+$ -channel gene (*SCN4A*). The mutations delay  $\text{Na}^+$  channel inactivation, thereby prolonging  $\text{Na}^+$  influx and muscle depolarization. Patients suffer recurrent episodes of muscle weakness and paralysis associated with mild hyperkalemia (~5.3 mmol/L).



# Ion Channels

1.9 Question



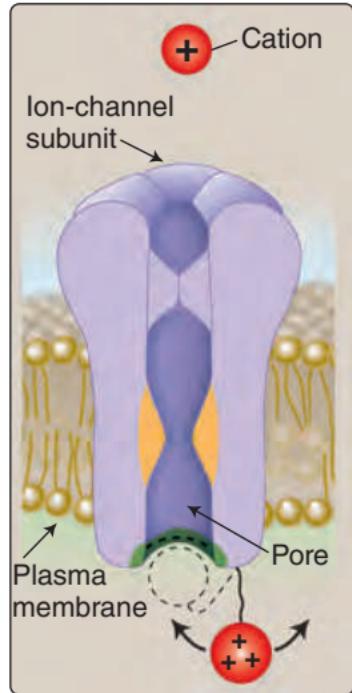
Ion channels possess an \_\_\_\_\_ that allows ions to enter the pore when open and a \_\_\_\_\_ that discriminates between the various ion species.



Identify three or more important roles of  $\text{Ca}^{2+}$  channels in physiology.



Mutations in the gene that encodes the ryanodine receptor (a  $\text{Ca}^{2+}$ -release channel in skeletal muscle) have been linked to **malignant hyperthermia (MH)**, a life-threatening condition. How does MH manifest clinically?





Ion channels possess an **activation gate** that allows ions to enter the pore when open and a **selectivity filter** that discriminates between the various ion species.



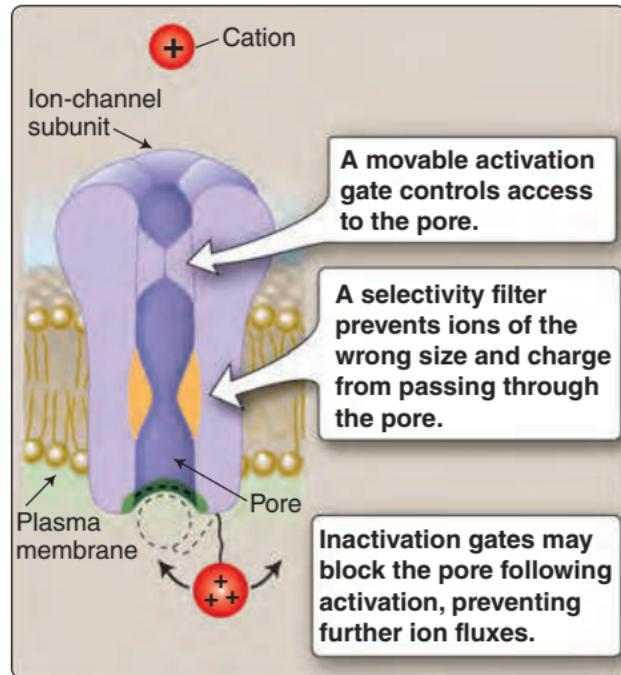
Roles of  $\text{Ca}^{2+}$  fluxes via  $\text{Ca}^{2+}$  channels include:

- **Membrane depolarization** (e.g., cardiac nodal cells)
- **Muscle contraction** (all types)
- **Exocytosis** (neurotransmitters, hormones, enzymes)
- **Secretion, absorption, and reabsorption** across epithelia

[Note:  $\text{Ca}^{2+}$  is an important second messenger whose diverse effects are mediated by  $\text{Ca}^{2+}$ -binding proteins (e.g., calmodulin) and  $\text{Ca}^{2+}$ -dependent enzymes (e.g., PKC).]



**MH** is a hypermetabolic muscle response to inhalation anesthetics (e.g., halothane) or the muscle relaxant succinylcholine. MH manifests acutely as hypercapnia, tachycardia, and a generalized muscle rigidity following inappropriate  $\text{Ca}^{2+}$  release and resulting muscle contraction.



# Ion Channel Types

1.10 Question



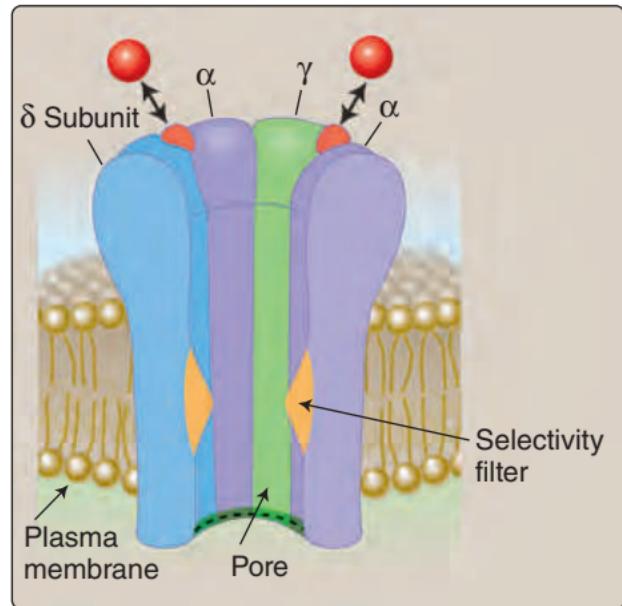
What is a *cys-loop* ion channel (shown)?



The GABA<sub>A</sub> receptor (GABA<sub>AR</sub>) is inhibitory. How do inhibitory channels reduce membrane excitability?



GABA<sub>A</sub>R is the principal target of benzodiazepines, which are used for what?





**Cys-loop channels** are ligand-gated channels with a common pentameric subunit structure. They share a conserved sequence (the cys-loop), which gives them their name.

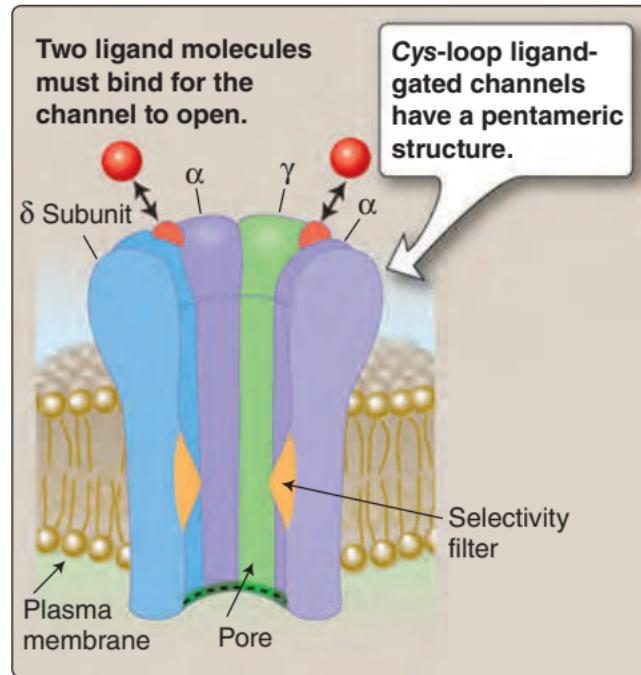
**A-plus:** Principal cys-loop channel family members include nAChR, the 5-HT<sub>3</sub> receptor, GABA<sub>A</sub>R, and the glycine receptor. nAChR and the 5-HT<sub>3</sub> receptor are both **cation channels** and excitatory. GABA<sub>A</sub>R and the glycine receptor are inhibitory **anion channels**.



**GABA<sub>A</sub>R** is an anion channel that supports a Cl<sup>-</sup> flux when open. This flux drives membrane potential toward E<sub>Cl</sub> (~−65 mV), which effectively dampens excitation and reduces AP frequency.



**Benzodiazepines** (e.g., diazepam) are **anxiolytics** used to treat anxiety disorders, muscle spasms, seizures, and sleep disorders and as sedatives prior to some medical procedures.





Define the equation used to determine a solution's osmotic pressure.

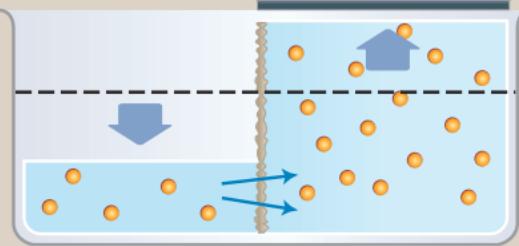


The epithelia lining the small intestine and renal tubule both use osmotic gradients to move water between tube lumen and the vasculature. Which epithelium transports the greater volume on an average day?



A patient with **gastroenteritis** has become volume depleted. Should the patient be rehydrated by oral administration of purified water, a salt and glucose solution, or with isotonic saline administered IV?

**The amount of pressure that would have to be applied to force water back into its original chamber is a measure of osmotic pressure.**



**Osmosis**

**Water moves down its osmotic gradient until the two chambers equilibrate.**



The **osmotic pressure** of a solution ( $\pi$ , measured in mm Hg) is calculated from:

$$\pi = nCRT$$

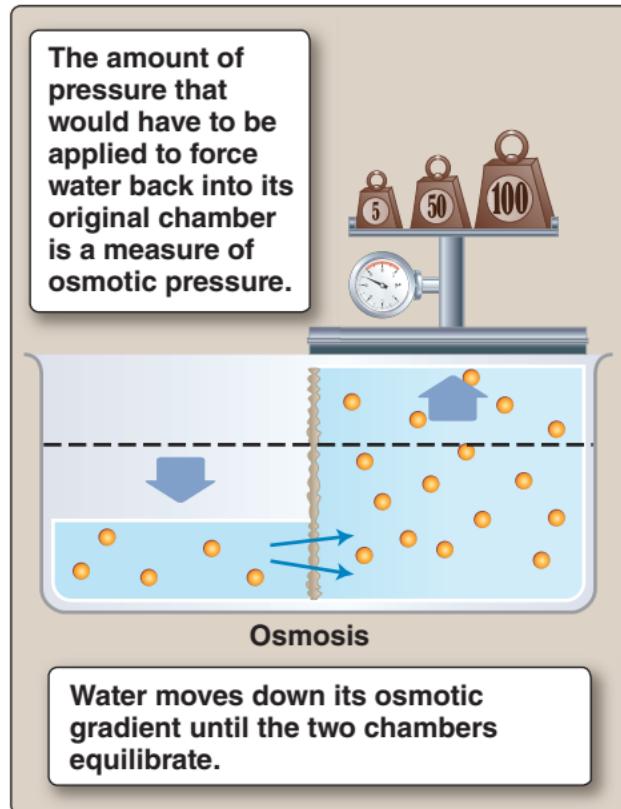
Where  $n$  is particle number,  $C$  is concentration,  $R$  is the universal gas constant, and  $T$  is temperature.



The intestinal epithelium secretes and then reabsorbs  $\sim 6.5$  L/day, along with ingested fluids. The renal tubule reabsorbs  $\sim 180$  L/day. Both epithelia achieve this by manipulating **transepithelial osmotic gradients**.



A salt and glucose solution is a more effective means of rehydration than purified water, because an intestinal  $\text{Na}^+$ -glucose cotransporter creates an osmotic gradient that drives water uptake from the gut lumen. Oral rehydration therapy is appropriate for mild to moderate hypohydration.



# Cell Volume Regulation

1.12 Question



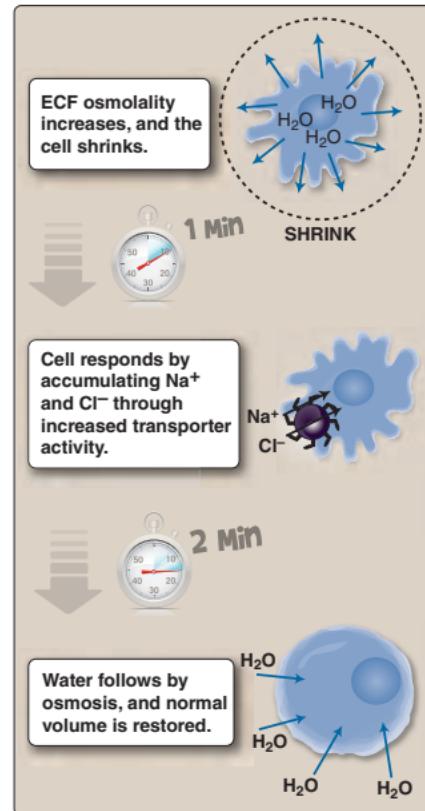
What might the solution that induced shrinkage of the cell shown contain: 200 mmol/L NaCl, 300 mmol/L sucrose, or 400 mmol/L urea?



How do central volume regulatory pathways respond to chronic increases in ECF osmolality?



*Aldose reductase* converts glucose to sorbitol. Clinical trials suggest that *aldose reductase* inhibitors may be helpful in preventing diabetic neuropathy. What is the rationale for such trials?



# Cell Volume Regulation



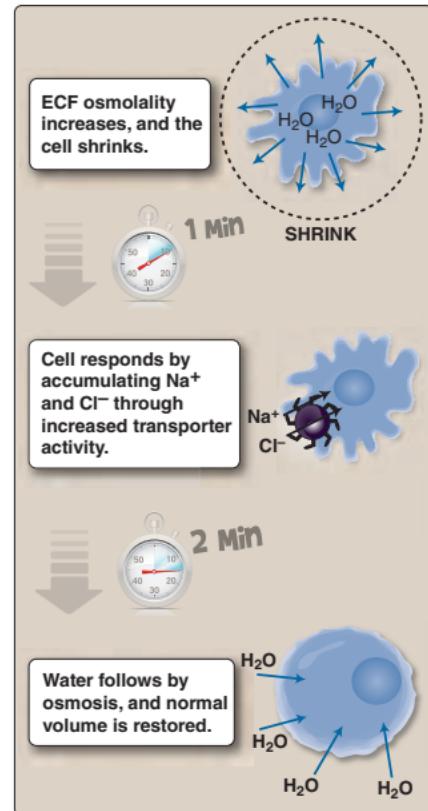
The extracellular solution at right contains 200 mmol/L NaCl. ICF has an **osmolality** of  $\sim 300$  mOsm/kg H<sub>2</sub>O. Because 200 mmol/L NaCl has an osmolality of 400 mOsm/kg H<sub>2</sub>O, it would shrink the cell as shown. Because 300 mmol/L sucrose is **isosmotic**, it would not cause a volume change, and 400 mmol/L urea is **hyperosmotic** but **hypotonic** because urea crosses the cell membrane and raises ICF osmolality (cell would swell as a result).



**Central osmoreceptors** (volume-sensitive neurons) initiate antidiuretic hormone (ADH) release and stimulate thirst. ADH increases water retention by the kidneys, whereas thirst impels water ingestion until ECF osmolality renormalizes (see 6.22).



**Diabetic neuropathy** is associated with neuronal swelling, which has suggested that dysregulation of normal cell volume regulatory pathways may underlie neuronal death. Hyperglycemia stimulates excess sorbitol accumulation by cells. Because sorbitol is an osmoticant normally synthesized during a regulatory volume increase, inhibiting these pathways might help prevent neuropathy.



# Total Body Water

1.13 Question



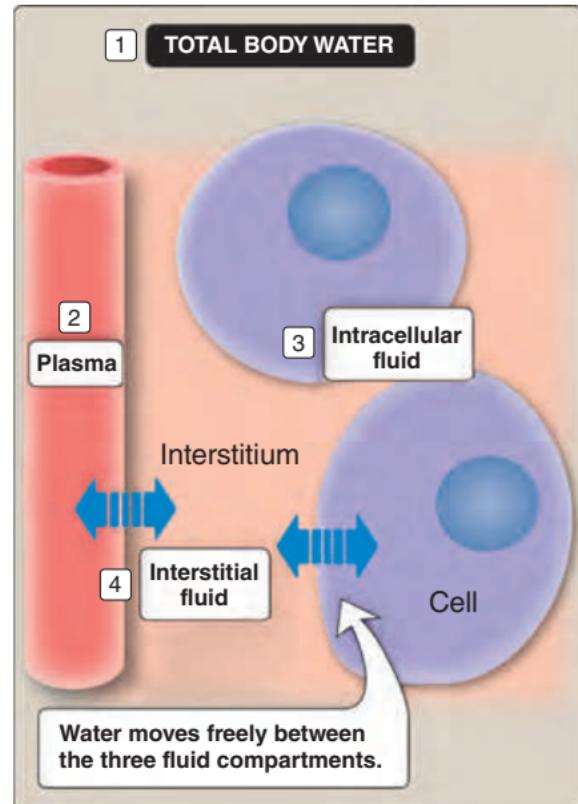
How much water does an average 70-kg male body contain (in L), and how does it distribute between the three different compartments (indicated by boxed numerals)?



How would ingestion of table salt (NaCl) affect water distribution between the three body compartments?



**Kwashiorkor** is an edematous condition caused by inadequate dietary protein intake. How does this cause edema?



# Total Body Water



Body water distribution:

1. Total body water (TBW) = 42 L (~60% of body weight)
2. Plasma = 3.5 L (~8% of TBW)
3. ICF = 28 L (~67% of TBW)
4. Interstitial fluid = 10.5 L (~25% of TBW)

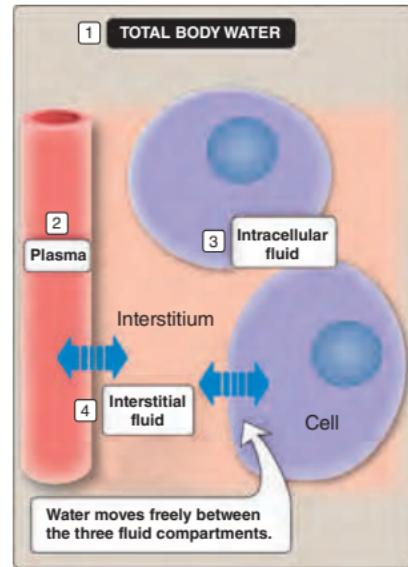


$\text{Na}^+$  is largely confined to the extracellular compartment by the ubiquitous  $\text{Na}^+/\text{K}^+$  ATPase.  $\text{Na}^+$  ingestion raises ECF osmolality and draws water from cells by osmosis. ECF volume increases at the expense of cell volume.

[Note: This redistribution would trigger a compensatory increase in water intake and subsequent  $\text{Na}^+$  excretion by the kidneys.]



Restricting protein intake impairs the body's ability to synthesize new proteins, including **plasma proteins** (e.g., albumin and globulins). Plasma proteins exert a **plasma colloid osmotic pressure** that helps blood retain fluid. When plasma protein concentrations fall, fluid filters out of the vasculature and into the interstitium, manifesting as the **edema** seen in **kwashiorkor**.



# Buffer Systems

1.14 Question



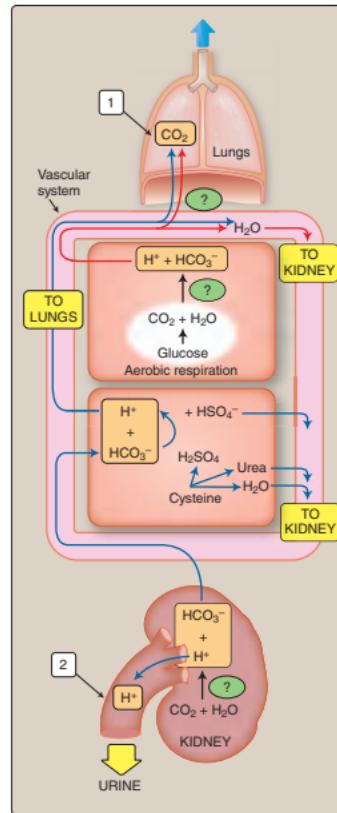
What two types of acid (indicated by boxed numerals) are produced from normal metabolism?



Tissues are protected from acid by three principal buffer systems, one of which is indicated by the green ovals shown. What are these buffer systems?



Acetazolamide is a weak diuretic that affects a primary buffer system by what mode of action?





Two types of acid produced by metabolism:

1. **Volatile acid** (carbonic acid,  $\text{H}_2\text{CO}_3$ ): Carbohydrate breakdown produces  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , which is then converted to  $\text{H}^+$  and  $\text{HCO}_3^-$  to facilitate  $\text{CO}_2$  transport to the lungs.
2. **Nonvolatile (or fixed) acid** (e.g., nitric, phosphoric, and sulphuric acids): Nonvolatile acids are formed through amino acid metabolism.

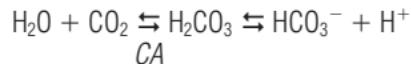


Three principal buffer systems:

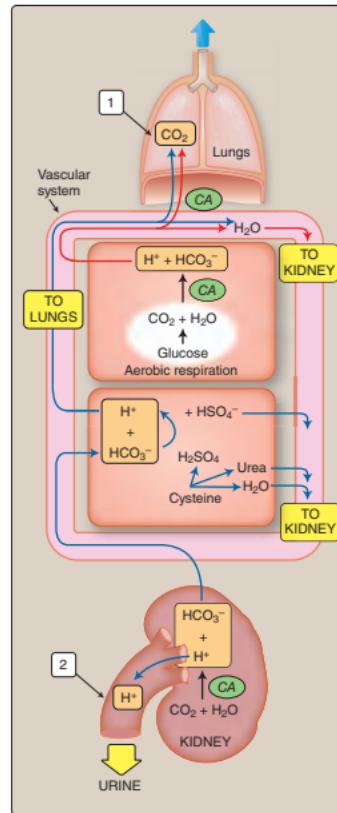
1. **Bicarbonate buffer system**
2. **Phosphate buffer system**
3. **Proteins**



**Acetazolamide** inhibits **carbonic anhydrase (CA)**, which catalyses the reaction below:



The drug impedes  $\text{HCO}_3^-$  (and  $\text{Na}^+$ ) reabsorption by the proximal convoluted tubule to cause an **osmotic diuresis** (see 6.26).





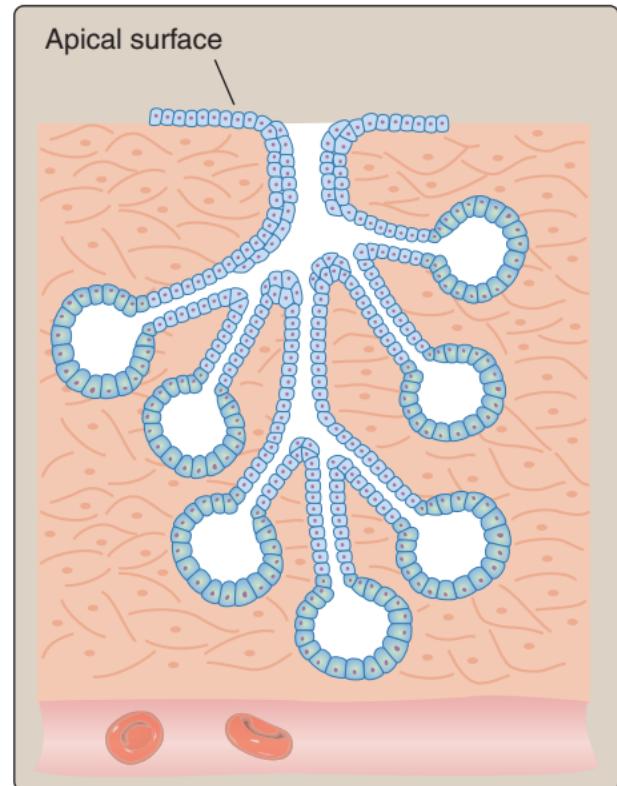
Name the three principal types of epithelia based on morphology.



Many epithelia (e.g., intestinal and respiratory epithelia) contain goblet cells. What are goblet cells, and what is their function?



Patients with **cystic fibrosis (CF)** typically suffer chronic pulmonary infections due to difficulties in clearing thick, viscous secretions from their lungs. How do **CF** mutations affect respiratory epithelial function?





Three principal types of epithelia:

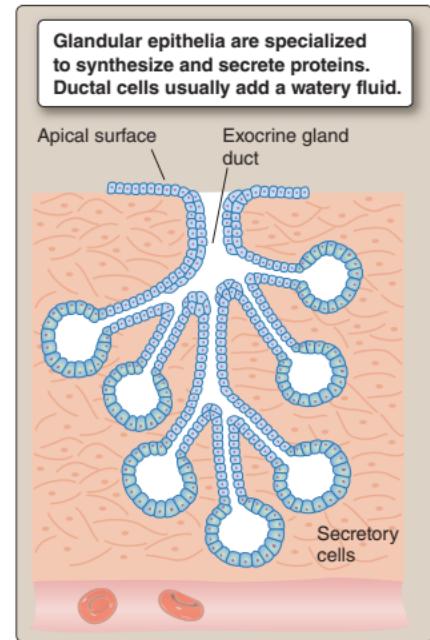
1. **Simple**
2. **Stratified**
3. **Glandular**



**Goblet cells** synthesize and secrete **mucin**, a glycoprotein that dissolves in water to yield **mucus**, which forms a slippery coat that lubricates and protects the epithelial surface. [Note: "Mucous" is the adjectival form of "mucus."]



**CF** is due to abnormal **CFTR** expression and function. CFTR is a  $\text{Cl}^-$  channel, so CFTR gene mutations reduce  $\text{Cl}^-$  and water secretion onto the epithelial surface. Respiratory mucus becomes thick and highly viscous as a consequence, making it difficult to expel. Mucus normally helps trap inhaled particulates, including bacteria, which are then cleared from the lungs by the **mucociliary escalator**. Loss of this protective function leaves patients prone to chronic infection.



# Tight Junctions

1.16 Question



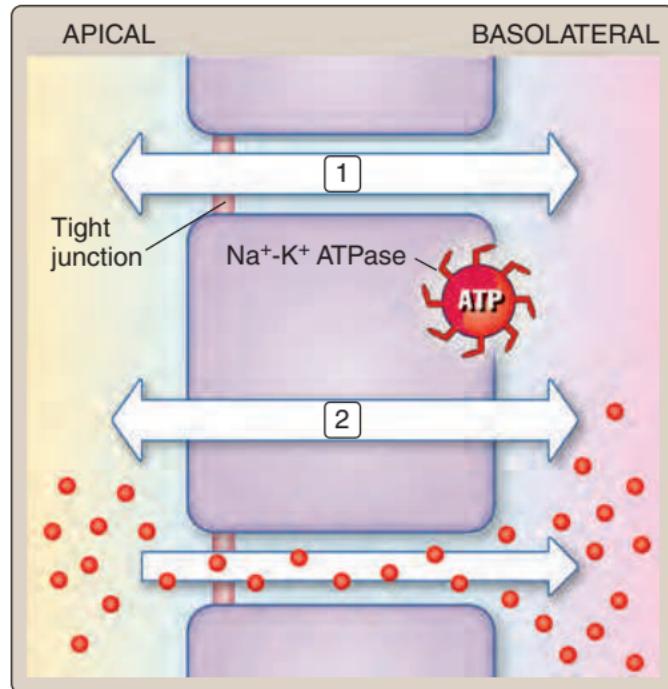
What are the two general pathways (indicated by boxed numerals) for water and solute movement across epithelia?



What are the two main functions of tight junctions?



**Inflammatory bowel diseases (IBDs)**, such as \_\_\_\_\_ and \_\_\_\_\_, are associated with increased intestinal tight junction leakiness and decreased expression of \_\_\_\_\_, a key protein regulator of tight junction permeability.





### Transepithelial transport pathways:

1. Paracellular
2. Transcellular

[Note: Paracellular flow is regulated by tight junctions. The transcellular pathway requires channels and carriers to aid passage across the apical and basolateral membranes.]



### Tight junctions function as:

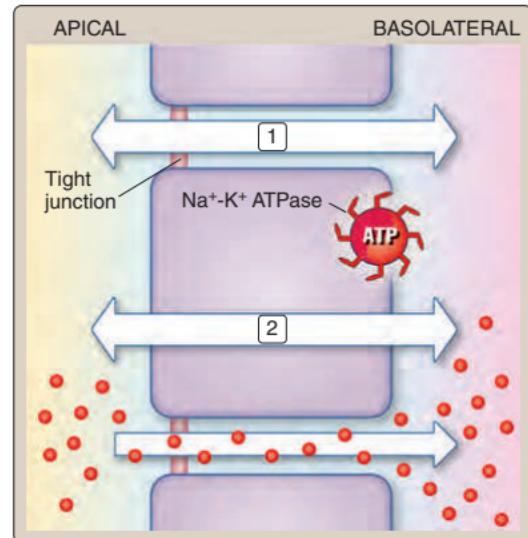
- **Fences:** They encircle epithelial cells to prevent proteins moving between apical and basolateral membranes, allowing for specialization of membrane composition and function.
- **Barriers:** They regulate paracellular water and solute flow and determine epithelial “leakiness.”



**Inflammatory bowel diseases (IBDs)**, such as **Crohn disease** and **ulcerative colitis**, are associated with increased intestinal tight junction leakiness and decreased expression of **occludin**, a key protein regulator of tight junction permeability.

*A-plus:* IBD symptoms include diarrhea due to fluid leakage via tight junctions from the vasculature into the intestinal lumen.

Increased paracellular leakiness correlates with decreased occludin and **claudin** expression, two tight junction proteins with important epithelial barrier functions.



# Gap Junctions

1.17 Question



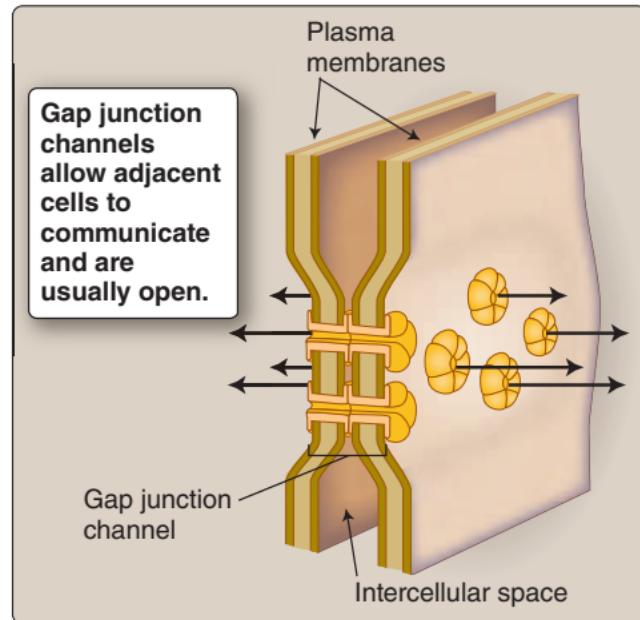
What is the subunit structure of a gap junction channel?



What is a principal function of gap junctions in astrocytes?



An X-linked form of **Charcot-Marie-Tooth disease (CMTX1)** affects a gap junction protein whose expression is essential for myelin formation by Schwann cells. How does **CMTX1** present clinically?





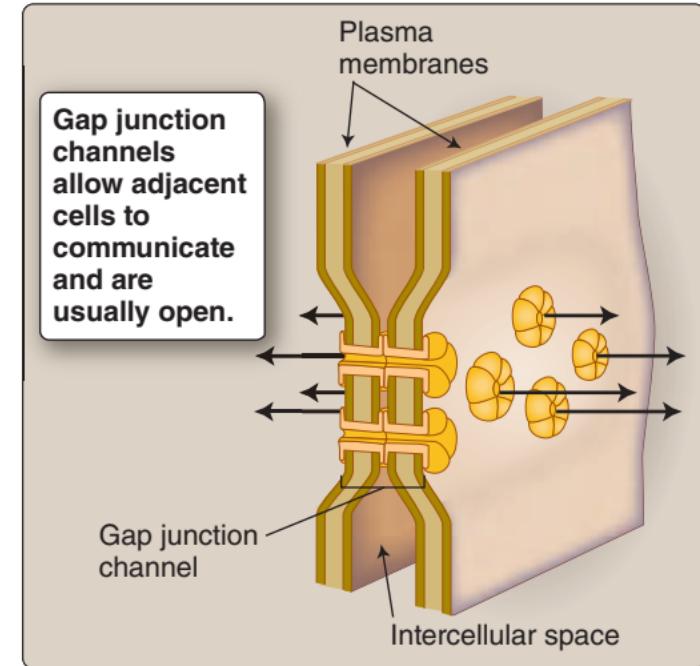
**Gap junction channels** comprise two hemichannels (**connexons**) that align to form a communication pathway between two cells. Each connexon is composed of six **connexin** subunits.



**Gap junctions** provide a pathway through adjacent astrocytes by which  $K^+$  can diffuse from areas of intense neuronal activity and high  $K^+$  concentration to less active CNS regions where  $K^+$  concentrations are low (**spatial buffering**, see 2.4). [Note: Gap junctions similarly serve as important pathways for chemical and electrical communication in most tissues.]



**Schwann cells** myelinate peripheral nerves. **Myelin** insulates axons and increases neuronal signal conduction velocity, so demyelinating diseases typically impair motor and sensory functions. Individuals expressing **CMTX1** have problem gaits and muscle weakness and may show tremors.



# Water Channels

1.18 Question



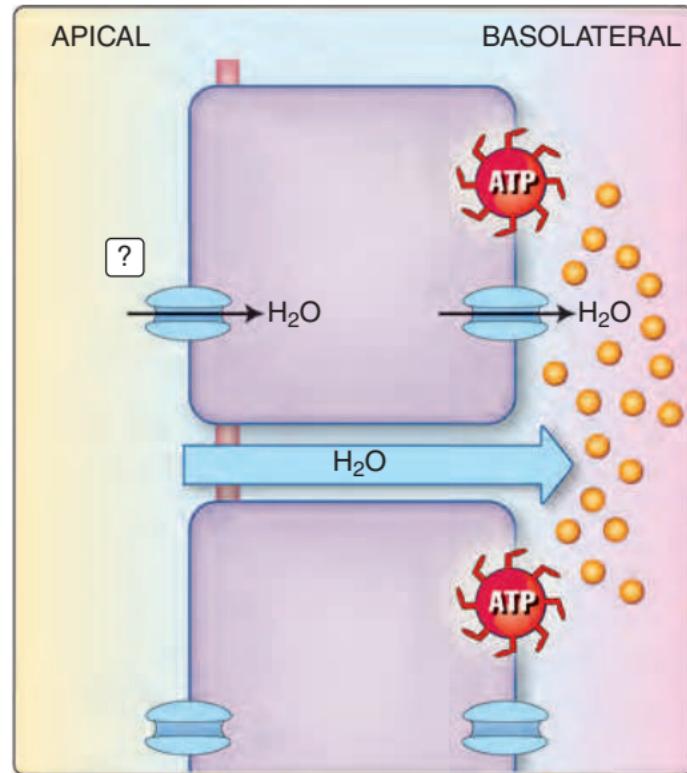
Many epithelia express water channels to permit transcellular water fluxes. What are these channels called, and how many family members are known?



Total body water homeostasis involves regulating kidney water channels by what mechanism?



Mutations in the gene encoding \_\_\_\_\_, a principal water channel in the kidney, reduces the kidney's ability to concentrate urine and leads to a polyuria known as \_\_\_\_\_ (DI).





Water channels are called **aquaporins (AQPs)**. There are 13 known family members, 3 of which are expressed in most body tissues (AQP1, AQP3, and AQP4).

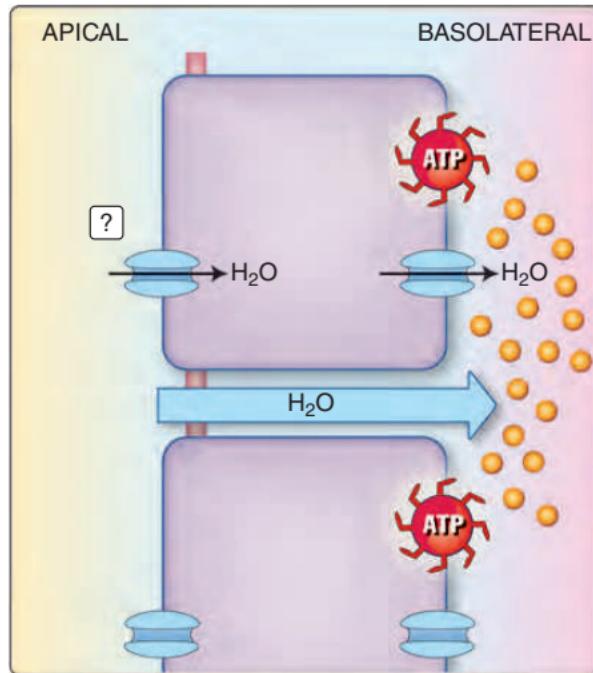


Total body water is controlled through antidiuretic hormone (ADH) regulation of renal collecting duct (CD) permeability. When water conservation is necessary, ADH is released into the circulation. In the kidney, it causes AQPs (AQP2) to be inserted into the CD apical membrane, allowing for water recovery (see 6.20). When total body water is high, AQP2 is removed from the membrane, and excess water is excreted.



Mutations in the gene encoding AQP2, a principal water channel in the kidney, reduces the kidney's ability to concentrate urine and leads to a polyuria known as **diabetes insipidus (DI)**.

**A-plus:** DI is a diuresis induced by excessive water intake (**primary polydipsia**), a defect in ADH release (**central DI**) or renal ADH resistance (**nephrogenic DI**).



# Connective Tissue

1.19 Question



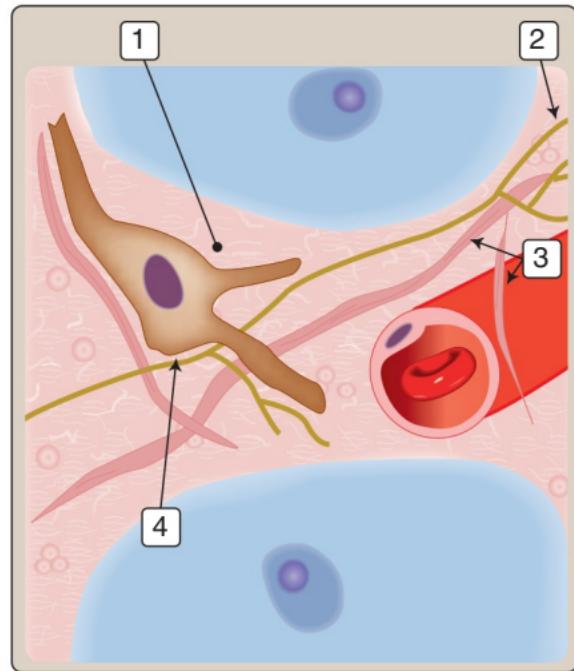
What four principal connective tissue components are indicated by boxed numerals?



The extracellular matrix is filled with a mix of proteins and ECF that together form a gel. What is the importance of this gel?



**Marfan syndrome** is a hereditary disorder of connective tissue. Most affected individuals (>90%) bear a dominant mutation in the fibrillin-1 gene. What is the function of fibrillin?





Connective tissue components:

1. **Ground substance**
2. **Elastic fibers**
3. **Collagen fibers**
4. **Fibroblasts**

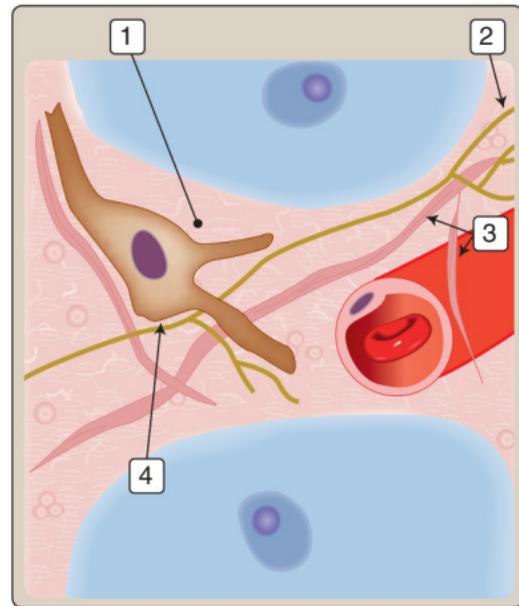


The **ground substance** gel is important in:

- Providing a pathway for chemical diffusion and migration of motile cells such as lymphocytes
- Creating a fluid reservoir that can be recruited to maintain blood volume when total body water is low (see 9.16)



**Fibrillin** is a glycoprotein microfibril secreted by fibroblasts. Together with other microfibrils, it helps form a structural scaffold for elastic fiber formation. Elastic fibers give tissues elasticity. The mechanism by which fibrillin mutation yields the symptoms of **Marfan syndrome** (bone elongation, aortic root disease, and mitral valve prolapse) is not well delineated.





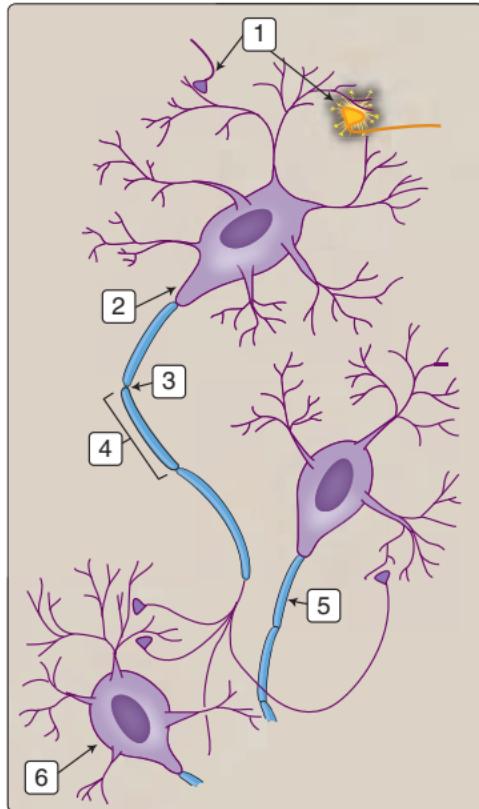
Identify the various features (indicated by boxed numerals) of a neuron.



Neuronal axons contain arrays of microtubules used for transport. What are the two transport modes and molecular motors involved?



Poliovirus is an \_\_\_\_\_ that causes \_\_\_\_\_ paralysis of muscle by proliferating in and destroying \_\_\_\_\_.





Neuron features:

1. **Presynaptic terminals**
2. **Axon hillock**
3. **Node**
4. **Internode**
5. **Myelinated axon**
6. **Cell soma**



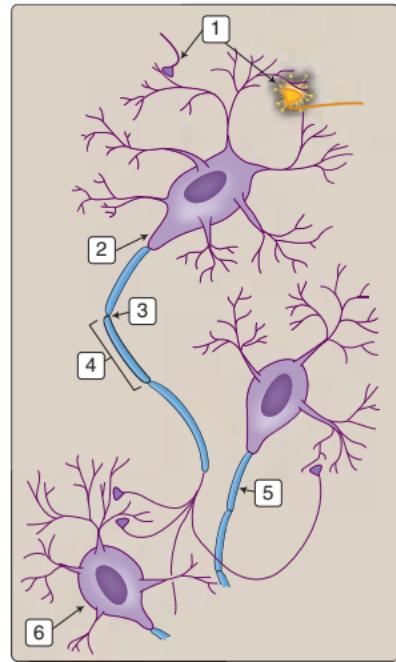
Axonal transport modes and motors:

1. **Anterograde transport:** Vesicles filled with transmitters and other materials attach to the tubule arrays and are then moved toward the terminals by **kinesin**, a molecular motor.
2. **Retrograde transport:** Movement from terminal back to the cell body is powered by **dynein**, the molecular motor that also powers ciliary beating.



Poliovirus is an **enterovirus** that causes **flaccid** paralysis of muscle by proliferating in and destroying **motor neurons**.

*A-plus:* Poliovirus is spread by fecal–oral contact. It is believed to enter a nerve terminal and then be carried back to the cell body by retrograde transport. Here, it proliferates and destroys the motor neuron. Although central neurons can also be infected, patients who succumb to the virus usually die as a result of respiratory muscle paralysis.





# Neuronal Action Potential

2.2 Question



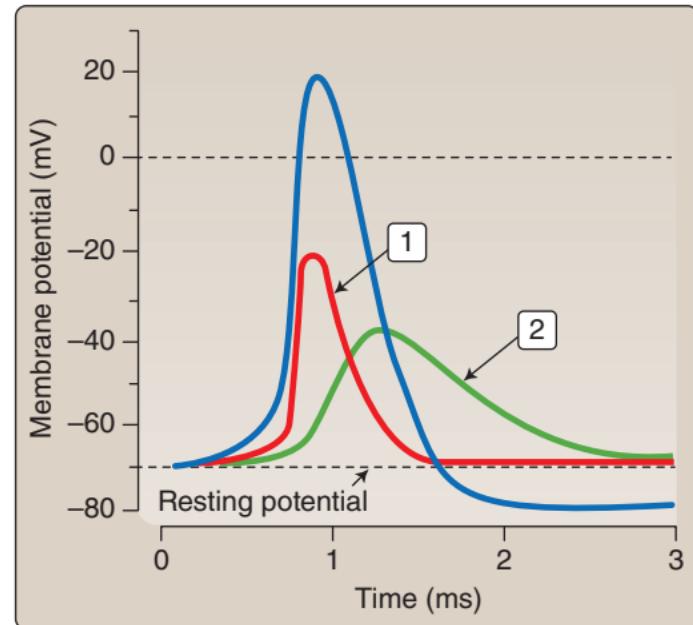
What two voltage-gated ion currents (indicated by boxed numerals) dominate the neuronal AP?



Sensory and motor neurons are specialized for high-velocity conduction. List three or more features that enhance conduction velocity.



Many types of seizure disorder and a severe form of migraine map to the same ion-channel gene. What is this gene, and what is the role of the gene product in the neuronal AP?



## 2.2 Answer

# Neuronal Action Potential



Two currents underlying a neuronal AP:

1. **Voltage-dependent  $\text{Na}^+$  current ( $I_{\text{Na}}$ )**:  $I_{\text{Na}}$  is an inward current that drives  $V_m$  toward the  $\text{Na}^+$  equilibrium potential and then inactivates.
2. **Voltage-dependent  $\text{K}^+$  current ( $I_K$ )**:  $I_K$  is an outward current that helps return  $V_m$  to resting potential, although the AP downstroke largely reflects  $I_{\text{Na}}$  inactivation.

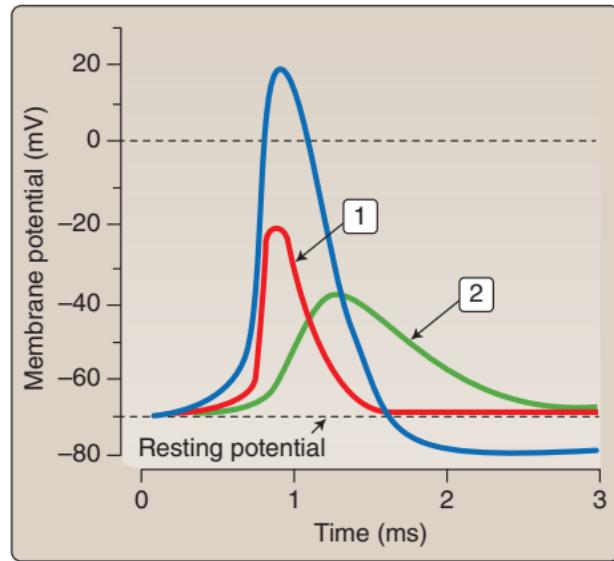


AP conduction velocity is enhanced via:

- **Rapid  $\text{Na}^+$ -channel gating kinetics**: Rapid gating allows for a rapid AP upstroke, which speeds conduction.
- **Wide axons**: Wide axons have low internal resistance, which allows electrical signals to travel farther before needing amplification.
- **Myelination**: Electrical insulation reduces leak currents that short-circuit the signal.
- **Saltatory conduction**: The AP jumps electrotonically from node to node, reducing the need for slower active regeneration steps.



Many seizure disorders and **familial hemiplegic migraine type 3 (FHM3)** map to ***SCN1A***, a gene that encodes the pore-forming  $\alpha$ -subunit of the voltage-dependent  $\text{Na}^+$  channel.



*A-plus*: The way in which *SCN1A* mutations produce seizures is highly varied, ranging from complete inhibition of channel activity to slight structural alterations. FHM3 mutations delay  $I_{\text{Na}}$  inactivation and prolong the neuronal AP.

# Neurotransmission

## 2.3 Question



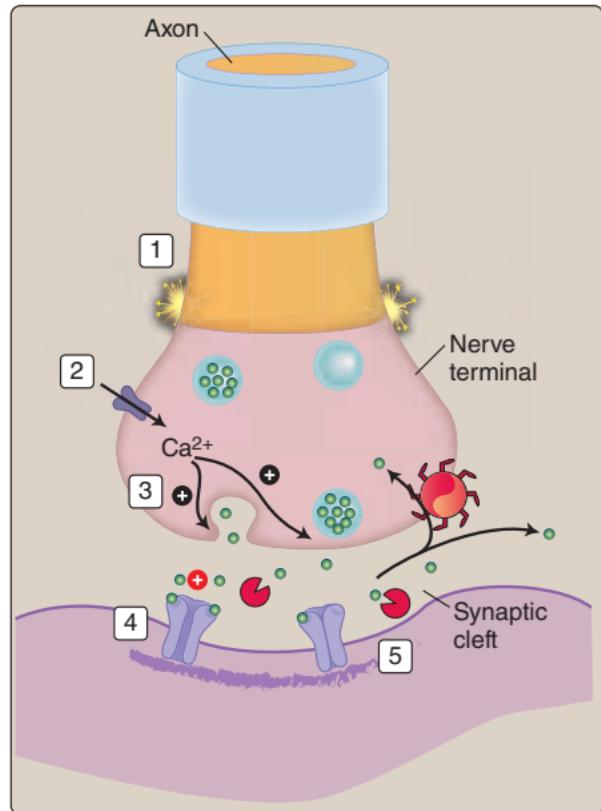
What are the steps in neurotransmission, as indicated by boxed numerals?



What three general mechanisms terminate neurotransmission?



*Clostridium botulinum* and *Clostridium tetani* are related microbes that kill their hosts by interfering with neuromuscular transmission via what mechanism?





### Neurotransmission steps:

1. AP arrives at the nerve terminal.
2. **Voltage-gated  $\text{Ca}^{2+}$  channels** open.
3.  $\text{Ca}^{2+}$  levels rise and cause vesicles to fuse with the synaptic membrane, releasing transmitter into the cleft.
4. Transmitter binds to a receptor on the **postsynaptic membrane**.
5. Transmission is terminated.



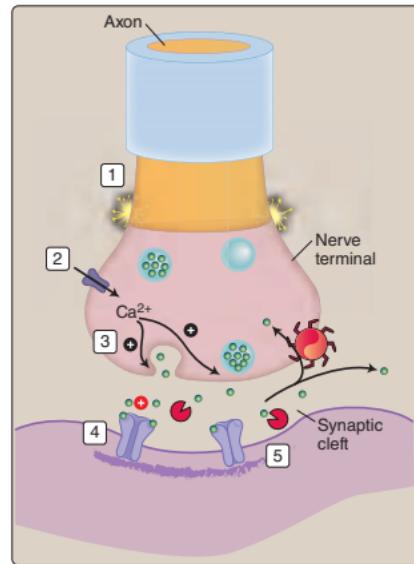
Three general mechanisms for terminating synaptic signaling:

1. **Degradation**: The synaptic cleft usually contains enzymes that degrade the transmitter (e.g., *acetylcholinesterase*).
2. **Recycling**: Transmitter is taken up by the neuron or glia and recycled.
3. **Diffusion**: Transmitter diffuses out of the cleft.



Both microbes produce neurotoxins that prevent synaptic vesicles fusing with the nerve terminal membrane. The toxins are **proteases** that degrade proteins that facilitate vesicle fusion, thereby blocking neuromuscular signaling.

*A-plus*: Botulinum toxin typically acts at the **neuromuscular junction**, causing paralysis by preventing ACh release. *C. tetani* travels to the CNS and prevents glycine and GABA release, thereby disrupting inhibitory pathways that normally limit muscle contractions (see 2.29). Patients may suffer painful muscle spasms and tetanic contractions as a result (e.g., **trismus** and **opisthotonus**).





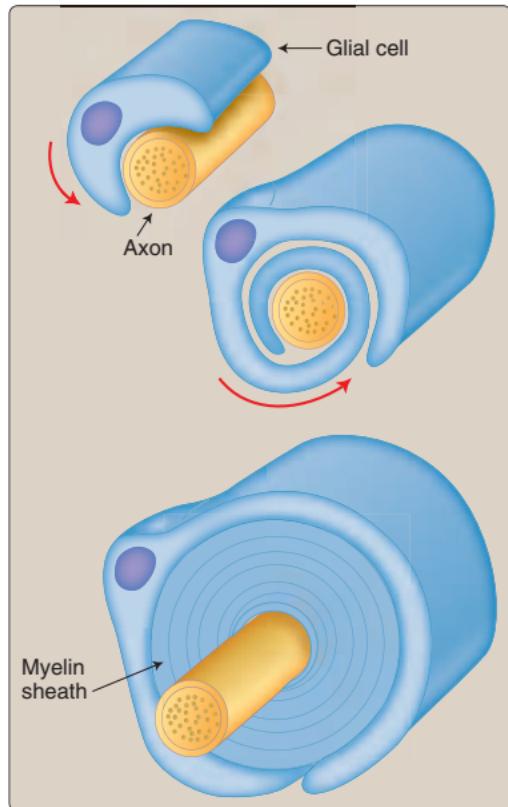
What two principal glial cell types lay down myelin, and how do they differ?



Identify at least three glial cell roles in the peripheral and central nervous systems.



Microglia function like immune cells in the \_\_\_\_\_, \_\_\_\_\_. They mount an inflammatory response to \_\_\_\_\_ and remove injured tissue by \_\_\_\_\_.





### Myelinating glial cells:

1. **Schwann cells** lay down myelin in the periphery and remain dedicated to a single axon.
2. **Oligodendrocytes** lay down myelin in the CNS and extend processes that engulf axons from multiple neurons simultaneously.  
[Note: The glial membrane encircles axons numerous times. Cytoplasm is squeezed out, leaving a cell body and compacted layers of lipid-rich membrane (i.e., myelin).]



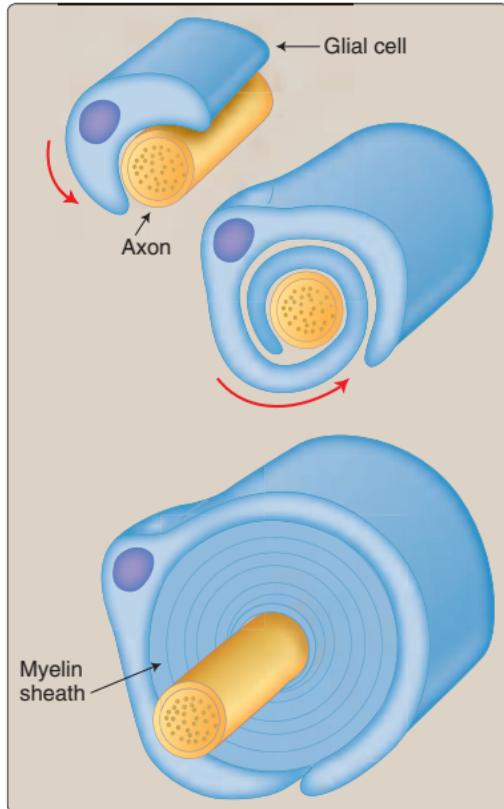
Glia cell functions include:

- **Myelination:** Myelin enhances **conduction velocity**.
- **K<sup>+</sup> homeostasis:** Glia take up K<sup>+</sup> released by neurons and move it to a remote site (**spatial buffering**) to help prevent a local K<sup>+</sup> buildup that would cause neuronal depolarization.
- **Neurotransmitter uptake:** Uptake helps terminate signaling and recycle neurotransmitter.
- **Nutrient supply:** Glia take up glucose from blood and store it as glycogen until needed by neurons.



**Microglia** function like immune cells in the **central nervous system**.

They mount an inflammatory response to infection and remove injured tissue by phagocytosis.





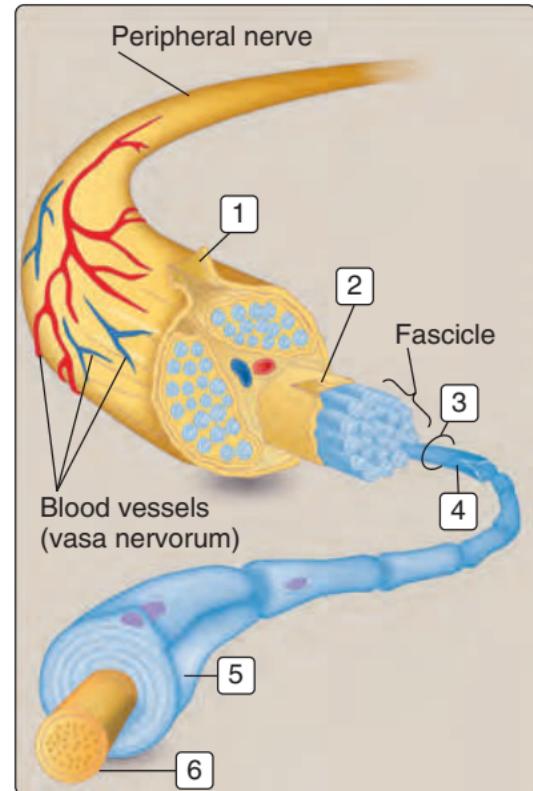
Identify the components of a nerve, as indicated by boxed numerals.



What do "mixed nerve" and "vagovagal reflex" mean?



What are the characteristics and sequelae of chronic nerve compression?





Peripheral nerve structures:

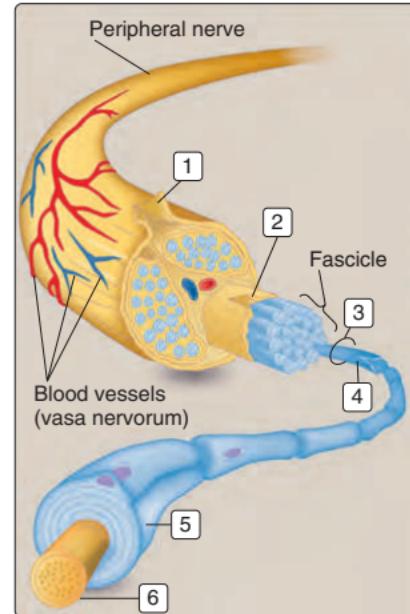
1. **Epineurium** (connective tissue)
2. **Perineurium** (connective tissue)
3. Nerve fiber
4. **Endoneurium** (connective tissue)
5. **Myelin sheath** (compacted lipid layers)
6. **Axon** (nerve cell process)



Nerves contain multiple nerve fibers (axons and their support structures). A **mixed nerve** contains a mix of **afferent** (sensory) and **efferent** (motor) fibers. A **vagovagal reflex** is a reflex arc in which both afferent and efferent arms travel within the vagus nerve, which is possible because the vagus is a mixed nerve. [Note: An example of the vagovagal reflex happens when food entering the stomach is sensed by mechanoreceptors, which signal the CNS via vagal afferents. A response to this sensory input is then signaled via motor fibers that also travel within the vagus nerve. The stomach relaxes as a result, thereby accommodating a meal with minimal increase in gastric pressure.]



Chronic nerve compression (e.g., of the median nerve within the carpal tunnel) causes myelin loss and, potentially, nerve ischemia. The patient experiences pain, numbness, and tingling sensations in the affected areas. Nerve regions distal to the site of the ischemia may undergo **Wallerian degeneration**, causing sensory and motor losses.



# Brain Protective Layers

2.6 Question



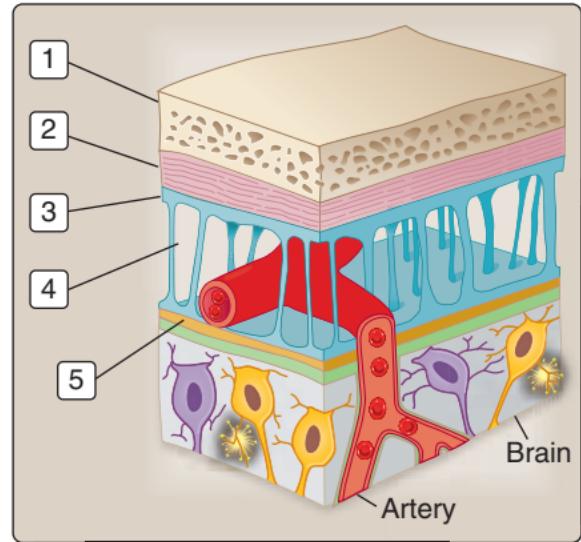
What are the five discrete layers (indicated by boxed numerals) that protect brain tissues from mechanical insult?



The protective layers prevent changes in brain volume, yet increased tissue activity typically causes swelling due to osmolality shifts and changing demands for blood flow. How is this managed in the brain?



Traumatic brain injury can lead to **cerebral edema**. Identify three or more ways in which this might be managed clinically to minimize further brain injury.



## 2.6 Answer

# Brain Protective Layers



Protective layers of the brain:

1. **Cranium** (bone)
2. **Dura mater** (a tough membrane comprising two layers)
3. **Arachnoid mater** (**trabeculae** create a **subarachnoid space** through which CSF flows)
4. **CSF**
5. **Pia mater** (a thin, fibrous membrane adhered to the brain)



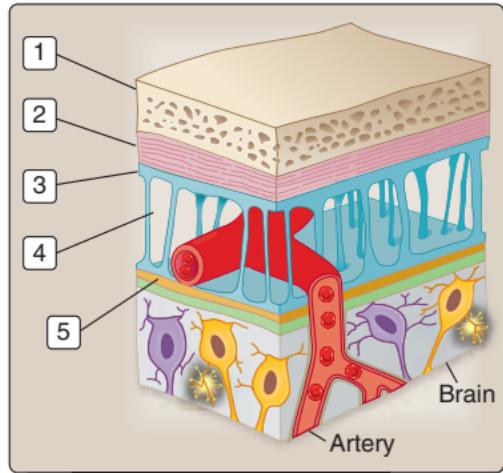
Ways that brain tissue activity levels increase despite the constraints of the cranium:

- A limited degree of brain swelling following osmotic shifts may occur at the expense of CSF volume.
- Limited increases in cerebral blood flow can occur by increasing flow velocity, but changing activity levels also cause flow redistribution from low- to high-activity regions of the brain.



Brain swelling following traumatic injury occurs at the expense of the vasculature, potentially causing **ischemia** and further injury. Strategies to limit swelling may include:

- **Head elevation:** This maximizes venous drainage.
- **Ventricular drainage:** This reduces CSF volume.
- **Osmotic therapy:** Mannitol injected into the vasculature draws water from the brain.
- **Decompressive craniotomy:** A section of the cranium is removed to relieve intracranial pressure and allow swelling to proceed.



# Choroid Plexus

2.7 Question



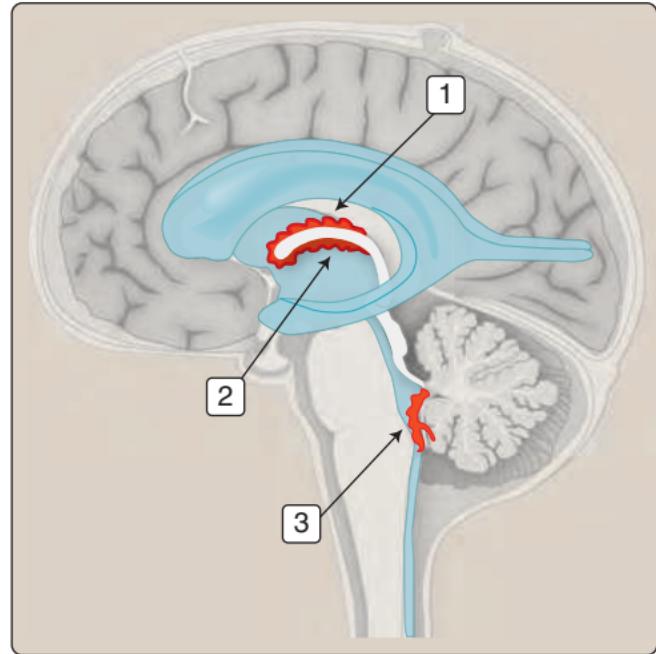
Identify the regions in the brain where choroid plexuses are located, as indicated by boxed numerals.



List three or more features of choroid plexuses that allow them to produce CSF at a rate of  $\sim 500$  mL/day.



What are the consequences of obstructing CSF flow?





### Choroid plexus locations:

1. Lateral ventricles (floor)
2. Third ventricle (roof)
3. Fourth ventricle (roof)

*A-plus:* The lateral ventricles connect with the third ventricle by two **foramina of Monro**. The third ventricle connects with the fourth via the **cerebral aqueduct** (of Sylvius). The **foramen of Magendie** and two lateral **foramina of Luschka** allow CSF to flow from the fourth ventricle into the **subarachnoid space**.

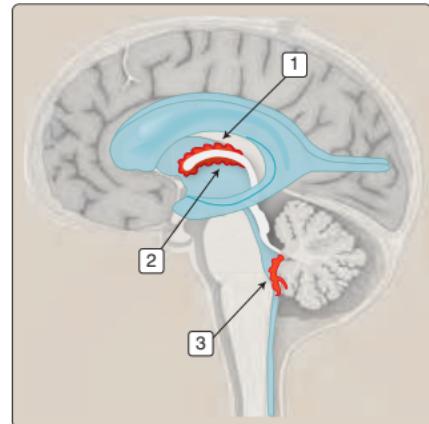


### Choroid plexus specializations:

- **Apical surface area:** The ependymal epithelium is enhanced with villi and microvilli to maximize surface area for fluid secretion.
- Mitochondrial numbers: Numerous **mitochondria** supply energy for ion transport.
- High **blood flow:** Flow to choroid plexuses exceeds that to neurons tenfold.
- Leaky capillaries: **Fenestrations** facilitate fluid movement between blood and ependyma.



If CSF flow or reabsorption is impaired, **hydrocephalus** results, with the accumulating CSF usually raising intracranial pressure and causing ventricular dilation. CSF normally flows from the ventricles over the brain surface and spinal cord via the **subarachnoid space** and is then reabsorbed via **arachnoid villi** into the venous system.



*A-plus:* **Obstructive (noncommunicating) hydrocephalus** is the most common form and is caused by physical obstruction of CSF flow. **Communicating hydrocephalus** develops as a result of impaired CSF reabsorption.



Using the table as a guide, identify the differences between plasma and CSF.



What are the four main functions of CSF?



\_\_\_\_\_ is used to withdraw a sample of CSF when **meningitis** is suspected. Patients typically present with a classic symptom triad that includes \_\_\_\_\_, \_\_\_\_\_, and a change in mental status.

Solute	Plasma	CSF
Na <sup>+</sup>	140	↑ or ↓ ?
K <sup>+</sup>	4	↑ or ↓ ?
Ca <sup>2+</sup>	2.5	1.2
Mg <sup>2+</sup>	1	1.1
Cl <sup>-</sup>	110	↑ or ↓ ?
Glucose	5	3
Proteins (g/dL)	7	↑ or ↓ ?
pH	7.4	7.3

CSF composition compared with plasma. Concentrations are given in mmol/L.

**CSF** and plasma differences:

1.  $\text{Na}^+$  and  $\text{Cl}^-$ : higher in CSF, to compensate osmotically for the lack of protein
2.  $\text{K}^+$ : lower in CSF
3. Proteins: virtually none in CSF  
[Note: CSF is also rich in  $\text{HCO}_3^-$  to help compensate for the lack of protein. Proteins are an important pH buffer in blood and other tissues.]



## CSF functions include:

- **Buoyancy:** The brain floats in CSF, which helps distribute weight evenly and prevents local vascular compression.
- **Shock absorption:** CSF acts as a liquid cushion to reduce trauma.
- **Volume changes:** CSF volume changes to accommodate activity-induced changes in brain volume.
- **Homeostasis:** CSF buffers pH, and constant CSF flow helps remove accumulated ions, metabolites, and transmitters.

Solute	Plasma	CSF
$\text{Na}^+$	140	149
$\text{K}^+$	4	3
$\text{Ca}^{2+}$	2.5	1.2
$\text{Mg}^{2+}$	1	1.1
$\text{Cl}^-$	110	125
Glucose	5	3
Proteins (g/dL)	7	0.03
pH	7.4	7.3



**Lumbar puncture** is used to withdraw a sample of CSF when **meningitis** is suspected. Patients typically present with a classic symptom triad that includes **nuchal rigidity**, **fever**, and a change in mental status. [Note: Meningitis typically also causes an intense headache and aversion to light and noise.]

# Homeostasis

2.9 Question



For what variables are the body's principal homeostatic organs (shown) responsible?



The ANS controls homeostasis via feedback control loops to maintain equilibrium. What are the three fundamental components of a feedback control loop?



Clinical assessment of autonomic function might include monitoring heart rate (HR) during the respiratory cycle. What effect, if any, does respiration have on HR in a normal, healthy individual?

HOMEOSTASIS	
Responsible organ	Regulated variable
	?
<b>SKIN</b>	
	?
<b>LIVER, PANCREAS</b>	
	?
<b>LUNGS</b>	
	?
<b>HEART, VESSELS</b>	
	?
<b>KIDNEYS</b>	



HOMEOSTASIS	
Responsible organ	Regulated variable
	<ul style="list-style-type: none"> <li>Temperature</li> </ul>
<b>SKIN</b>	
	<ul style="list-style-type: none"> <li>Glucose</li> <li>Lipids</li> </ul>
<b>LIVER, PANCREAS</b>	
	<ul style="list-style-type: none"> <li><math>Po_2</math></li> <li><math>Pco_2</math></li> <li>pH</li> </ul>
<b>LUNGS</b>	
	<ul style="list-style-type: none"> <li>Blood pressure</li> </ul>
<b>HEART, VESSELS</b>	
	<ul style="list-style-type: none"> <li>pH</li> <li>Electrolytes (<math>Na^+</math>, <math>K^+</math>, <math>Ca^{2+}</math>, <math>Mg^{2+}</math>, <math>Cl^-</math>)</li> <li>Osmolality</li> <li><math>H_2O</math></li> </ul>
<b>KIDNEYS</b>	



Three components of an ANS control loop:

1. **Sensory system** capable of monitoring the controlled variable
2. **Comparator** that assesses whether the measured variable deviates from a **set point**
3. **Effector mechanism** capable of adjusting the variable  
[Note: Most ANS control pathways use a negative feedback loop, in which a rise in the measured variable stimulates pathways that then decrease that variable.]



**HR** normally rises during inspiration and falls with expiration, producing a **respiratory sinus arrhythmia**.

*A-plus:* Although the physiologic reasons for the HR response to respiration are uncertain, the arrhythmia is a measure of vagal tone and autonomic health. The vagus carries sensory signals to and motor commands from the brainstem comparator that modulates HR.

# Autonomic Neurotransmitters

## 2.10 Question



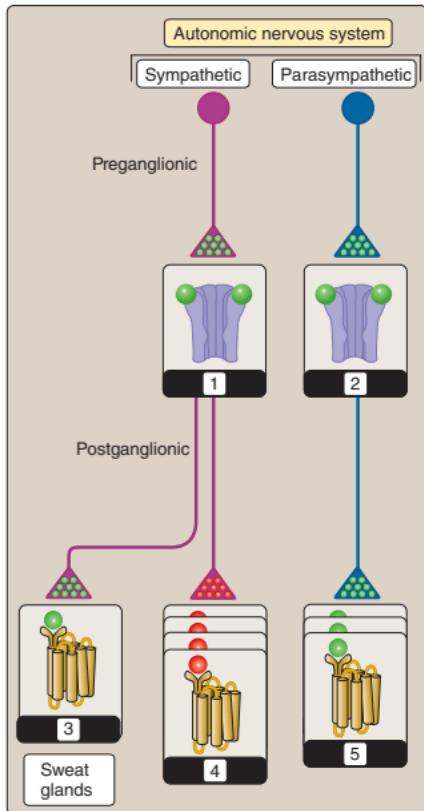
Name the neurotransmitters and their receptor types used in autonomic signaling, as indicated by boxed numerals.



What is the main difference between sympathetic and parasympathetic autonomic pathway organization?



Pancuronium is a potent cholinergic antagonist used as a muscle relaxant during rapid intubation procedures. Why does it not simultaneously inhibit autonomic signaling?



**Autonomic neurotransmitters:**

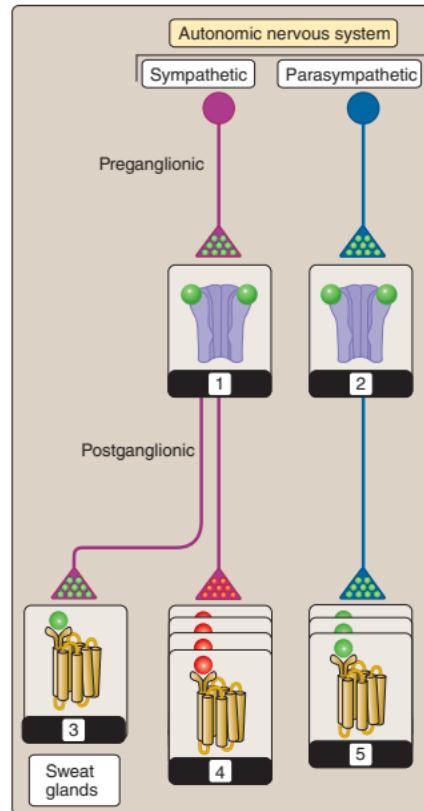
- 1, 2, 3, and 5. ACh binding to AChRs  
4. NE binding to ARs



The cell bodies of autonomic efferent neurons are gathered in ganglia that lie outside the CNS. Because sympathetic ganglia lie close to the vertebral column, postganglionic neurons are relatively long. Parasympathetic ganglia lie close to their target organs, so postganglionic fibers are short.



**Pancuronium** is a competitive antagonist of **type 1 nAChRs**, which are the type found on skeletal muscle. Postganglionic autonomic neurons express **type 2 nAChRs**, which are not blocked by pancuronium at doses used clinically.





Complete the table.

Target Organ	Sympathetic Actions	Parasympathetic Actions
Iris	?	?
Salivary glands	?	?
Lung airways	?	?
Cardiac pacemaker	?	?
Cardiac muscle	?	?
Blood vessels	?	?
Sweat glands	?	?
Stomach	?	?
Pancreas and gallbladder	?	?
Intestinal smooth muscle	?	?
Adrenal glands	?	?
Bladder	?	?
Male reproductive system	?	?
Female reproductive system	?	?



Target Organ	Sympathetic Actions	Parasympathetic Actions
Iris	Pupil dilation	Pupil constriction
Salivary glands	Decreased secretion	Increased secretion
Lung airways	Relaxation	Constriction
Cardiac pacemaker	Increased heart rate	Decreased heart rate
Cardiac muscle	Increased contractility	—
Blood vessels	Constriction	—
Sweat glands	Secretion	—
Stomach	Decreased secretion	Secretion, relaxation
Pancreas and gallbladder	Decreased secretion	Secretion, bile release
Intestinal smooth muscle	Decreased motility	Increased motility
Adrenal glands	Epinephrine release	—
Bladder	Sphincter constriction	Sphincter relaxation, emptying
Male reproductive system	Emission	Erection and arousal
Female reproductive system	Orgasmic muscle contractions	Tissue engorgement and increased vaginal secretion

“—” indicates minimal or no direct effect.

# Autonomic Control Centers

2.12 Question



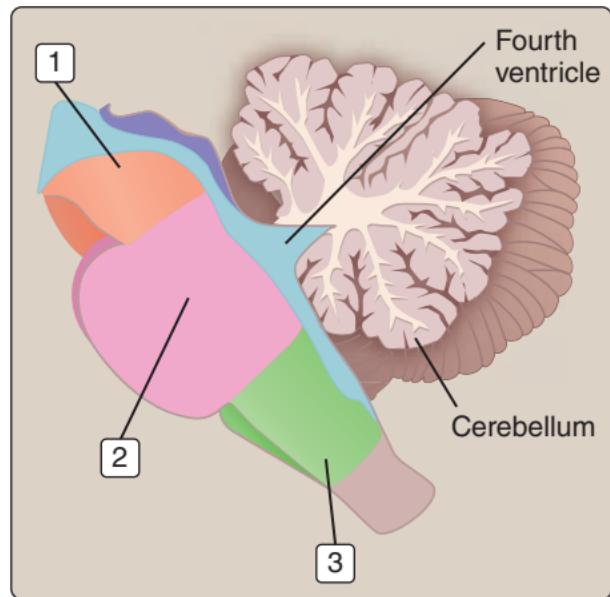
What brainstem areas are indicated by boxed numerals, and what are their corresponding major autonomic control centers?



What are preganglionic nuclei, and how do they contribute to autonomic control? Name and identify the functions of three or more autonomic nuclei.



\_\_\_\_\_ triad is a sign of dangerously elevated intracranial pressure. The three symptoms include \_\_\_\_\_, \_\_\_\_\_, and \_\_\_\_\_.





Brainstem areas and control centers:

1. **Midbrain**: iris (motor control nuclei)
2. **Pons**: apneustic and pneumotaxic centers (respiratory), micturition center (bladder emptying)
3. **Medulla**: respiratory and cardiovascular centers  
[Note: The physiologic role of the pontine respiratory centers is uncertain. The principal respiratory control centers are in the medulla.]

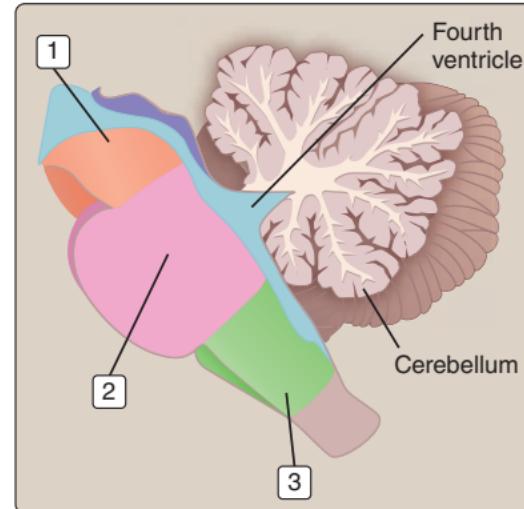


**Preganglionic nuclei** are clusters of nerve cell bodies, the axons of which make up one or more CNs. The nuclei may also contain interneurons that create an autonomic reflex pathway. Principal nuclei include:

1. **Edinger-Westphal nucleus**: iris control
2. **Salivary nuclei**: salivation reflexes
3. **Nucleus ambiguus**: swallowing reflexes and heart rate control
4. **Dorsal motor nucleus of vagus**: GI and respiratory reflexes



**Cushing triad** is a sign of dangerously elevated intracranial pressure. The three symptoms include **bradycardia**, **hypertension**, and **respiratory depression**. [Note: The Cushing response is believed to reflect hypoperfusion and ischemia of brainstem respiratory and cardiovascular control centers. It is a portent of imminent herniation.]



# Circumventricular Organs

2.13 Question



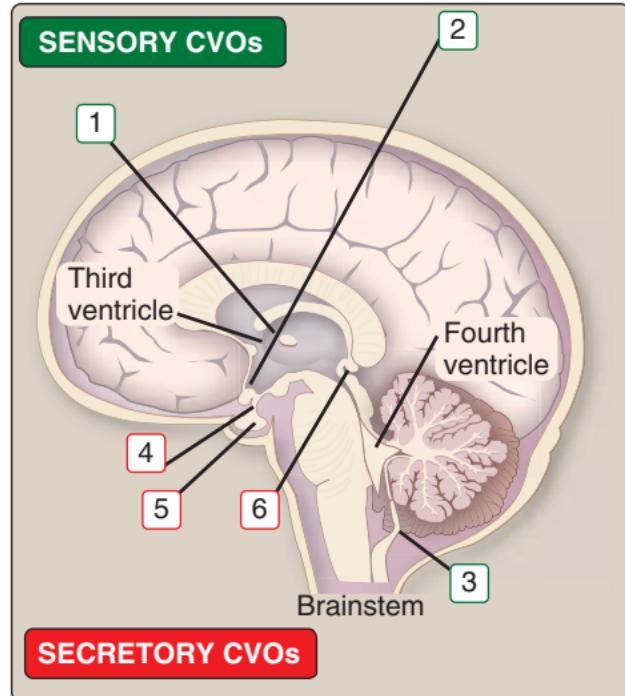
Identify the circumventricular organs (CVOs) indicated by boxed numerals.



Which of these CVOs are osmosensory, and how is osmolality sensed?



An osmosensory defect is believed to underlie about one third of **syndrome of inappropriate antidiuretic hormone secretion (SIADH)** cases. What are the symptoms of SIADH?





CVOs:

1. Subfornical organ (SFO)
2. Organum vasculosum of the lamina terminalis (OVLT)
3. Area postrema
4. Median eminence
5. Posterior pituitary
6. Pineal gland

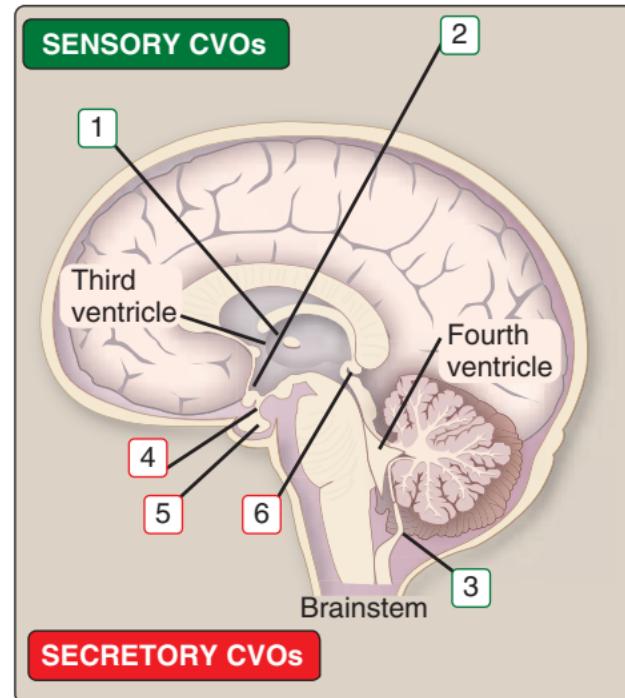


The **SFO** and **OVLT** are osmosensory, both organs containing **osmoreceptor neurons** that monitor ECF osmolality. An ECF osmolality increase causes osmoreceptor cell shrinkage, which stimulates  $\text{Ca}^{2+}$  influx via a mechanosensory channel. The resulting depolarization signals the **hypothalamus** to release **antidiuretic hormone (ADH)** to conserve body water.



The principal symptom of **SIADH** is **hyponatremia**. ADH stimulates water retention. When ADH is released at inappropriately high levels, ECF  $\text{Na}^+$  becomes diluted, manifesting as hyponatremia.

*A-plus:* SIADH can have many causes, including ADH secretion by tumors. The most common such source is a **small cell lung carcinoma**.



# Pituitary Gland

2.14 Question



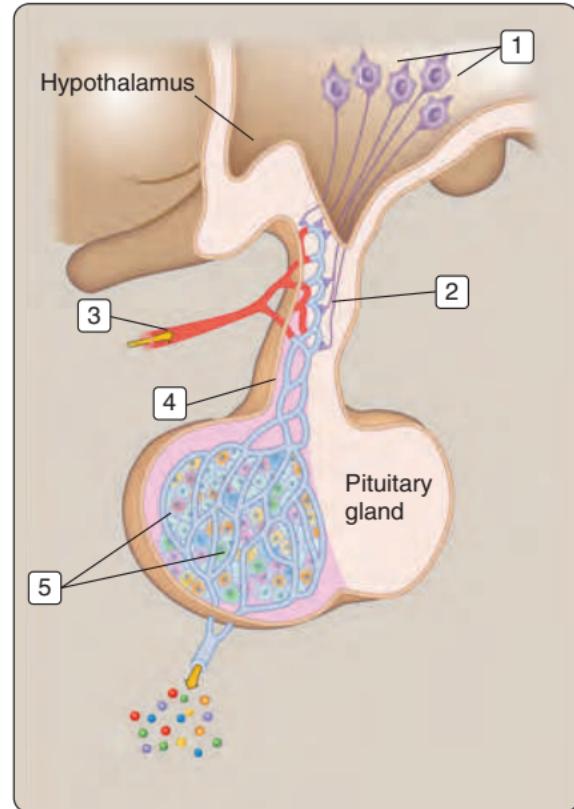
What are the anterior pituitary structures (indicated by boxed numerals) and their functions?



List the six hormones produced and released by the anterior pituitary.



**Pituitary apoplexy** refers to pituitary \_\_\_\_\_. Although the resulting hypopituitarism causes deficiencies in all pituitary hormones, the loss of \_\_\_\_\_ is of grave concern because cortisol is required for vascular tone.





Functions of **anterior pituitary** structures:

1. **Parvocellular neurosecretory cells**: produce hormone-releasing hormones
2. **Median eminence**: blood–brain barrier window for hormone secretion
3. **Superior hypophyseal artery**: supplies portal system
4. **Hypophyseal portal system**: carries hormone-releasing hormones to the tropic cells
5. **Hormone-secreting tropic cells**: synthesize and release anterior pituitary hormones

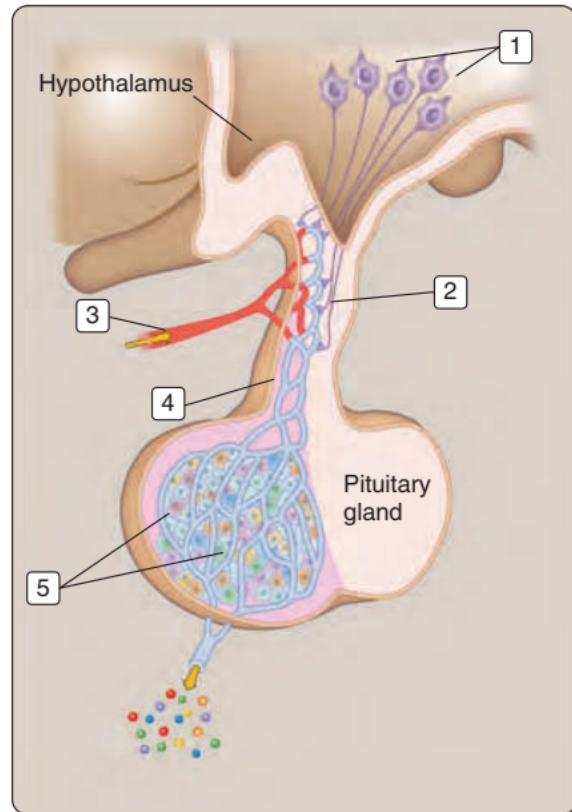


Anterior pituitary hormones:

1. **Adrenocorticotropic hormone**
2. **Thyroid-stimulating hormone**
3. **Follicle-stimulating hormone**
4. **Luteinizing hormone**
5. **Growth hormone**
6. **Prolactin**



**Pituitary apoplexy** refers to pituitary hemorrhage. Although the resulting hypopituitarism causes deficiencies in all pituitary hormones, the loss of adrenocorticotropic hormone is of grave concern because **cortisol** is required for vascular tone. [Note: Cortisol has direct and indirect effects on vascular smooth muscle. Loss of cortisol causes a hypotensive crisis due to vascular collapse.]





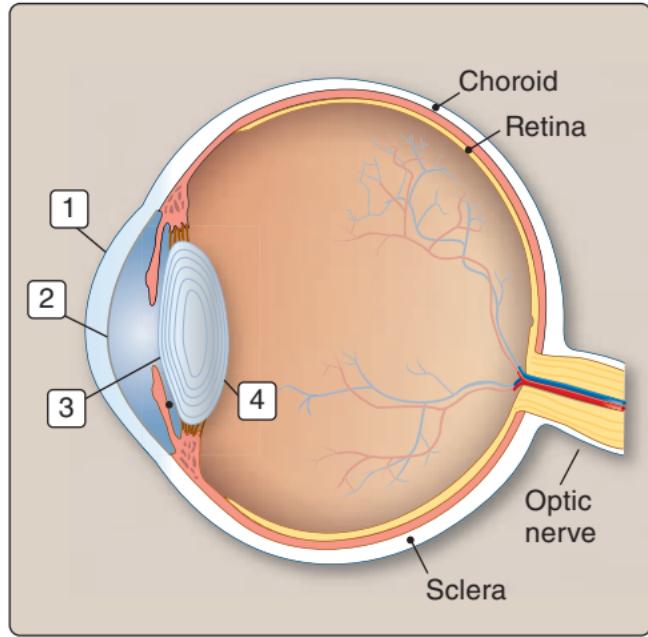
Identify the interfaces (indicated by boxed numerals) where light is refracted during passage through the eye. Where does the greatest degree of refraction occur?



What is the purpose of lens accommodation, and how is it controlled?



How does LASIK surgery improve visual acuity?





Eye's **refractive** interfaces:

1. Air–cornea
2. Cornea–aqueous humor
3. Aqueous humor–lens
4. Lens–vitreous humor

The greatest refraction occurs at the air–cornea interface.

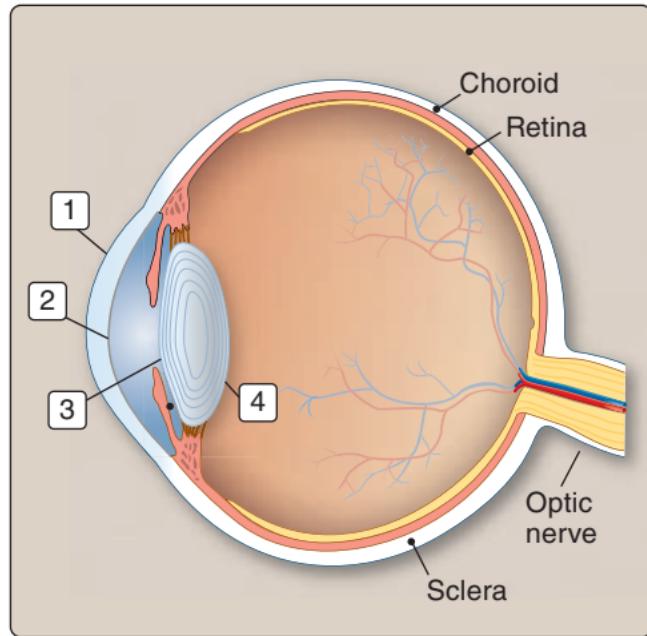
[*Note:* The degree of refraction depends on both disparity in composition of the two materials through which light travels and the degree of interface curvature.]



**Lens accommodation** ensures that the image projected on the retina stays focused when the eye shifts attention from a near to a more distant object, for example. Lens focus is adjusted by changing **lens shape**. In a resting eye, the lens is pulled into an elliptical shape by **zonule fibers**, which are under passive tension. When the eye's focus shifts from distant to near objects, the **ciliary muscle** contracts and releases zonule fiber tension, allowing the lens to assume a more natural spherical shape. The ciliary muscle is under **parasympathetic control**.



The **cornea** is the primary determinant of the eye's ability to focus because the greatest degree of light refraction occurs here. **LASIK surgery** modifies corneal curvature to correct the defects in the eye's optical properties, thus allowing it to focus normally. The laser ablates corneal stroma under computer guidance.



# Pupil Control

2.16 Question



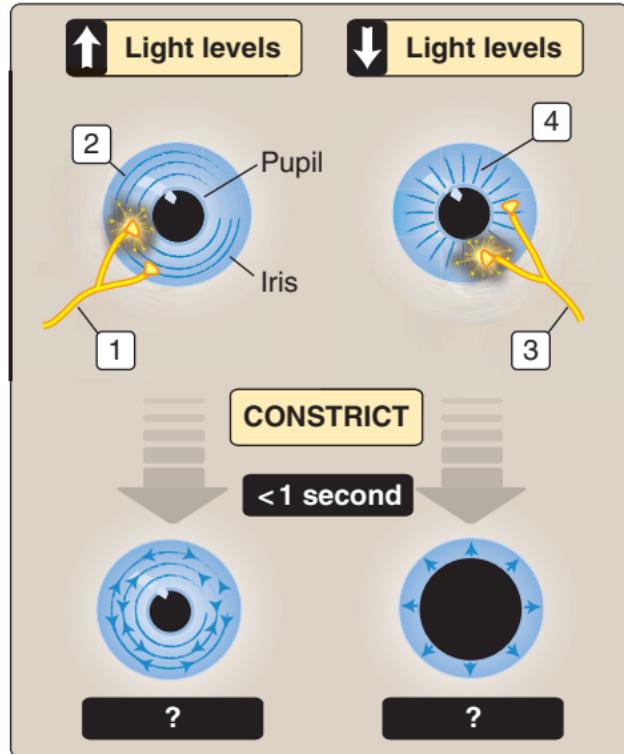
What nerves and muscles (indicated by boxed numerals) mediate pupillary responses to changing light levels? How?



What central pathways are involved in the pupillary light reflex?



A patient presents with **anisocoria** (pupils of unequal size). Is the condition physiologic or an indication of intracranial aneurysm and impending death?





Control of pupil diameter:

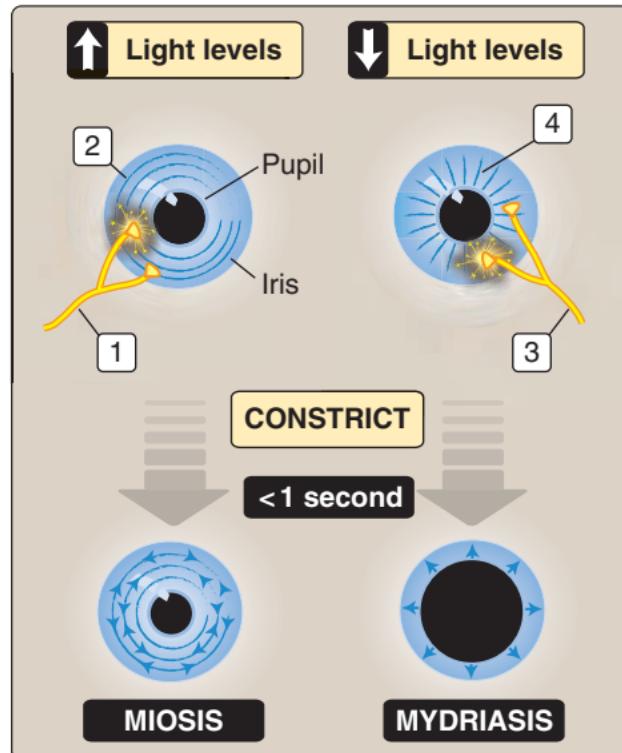
1. The parasympathetic nerve fires.
2. The sphincteric muscle contracts, causing **miosis**.
3. The sympathetic nerve fires.
4. The radial muscle contracts, causing **mydriasis**.



Light falling on photosensitive **retinal ganglion cells** causes them to signal via the **optic nerve** (CN II) to the **prectal nucleus** in the upper midbrain. Axons from the prethalamic nucleus project to the **Edinger-Westphal nucleus** at the head of the oculomotor nerve (CN III). Parasympathetic, preganglionic efferent fibers traveling in CN III project to the **ciliary ganglion**, and then excitatory signals travel via short ciliary postganglionic fibers to iris **sphincteric muscles**.



The condition is probably physiologic. **Anisocoria** is relatively common (~20% of normal individuals), but it can also have pharmacologic or pathologic causes. Conditions associated with anisocoria include **Horner syndrome** (dysfunction of the sympathetic pathways required for mydriasis) and **Adie syndrome** (parasympathetic dysfunction).



# Intraocular Pressure

2.17 Question



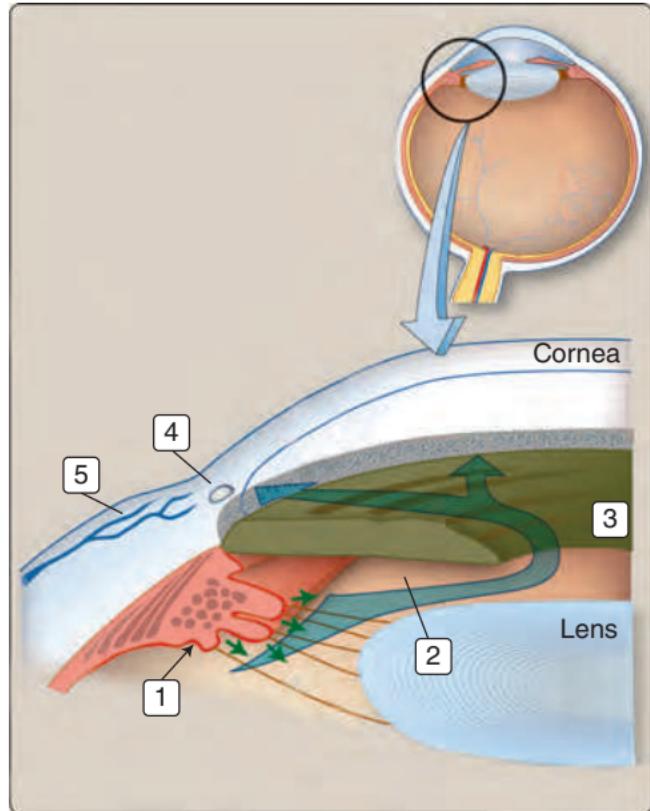
Using the boxed numerals as a guide, trace the source of aqueous humor and its fate following secretion.



What are the functions of aqueous humor?



What is **glaucoma**?



**Aqueous humor:**

1. Secreted by the **ciliary epithelium** that covers the **ciliary body**
2. Flows through the posterior chamber
3. Passes through the iris
4. Flows through the anterior chamber and exits the eye at the “angle” formed between the iris and cornea
5. Drains via the **canal of Schlemm** into the venous system

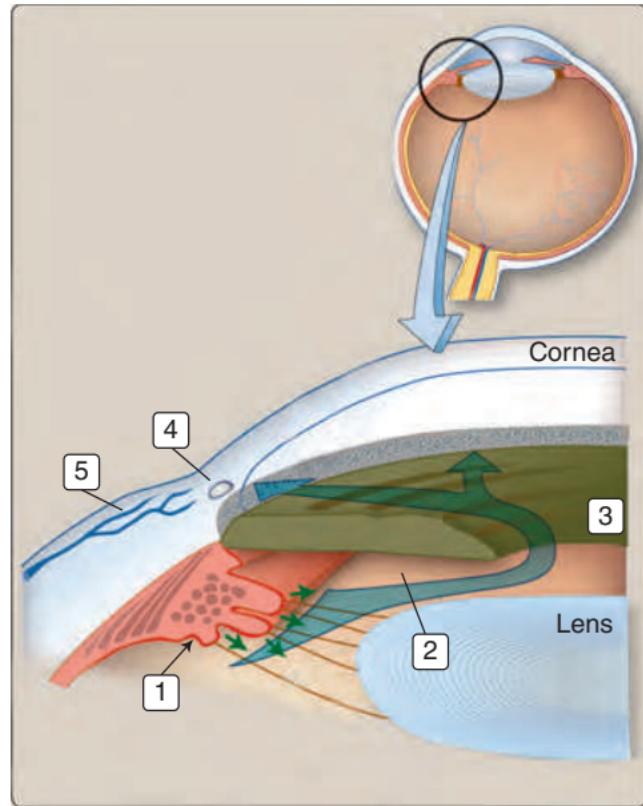
**Aqueous humor** functions include:

- **Nutrition:** It supplies the **cornea** with glucose, amino acids, and other nutrients.
- **Pressure:** Aqueous humor secretion creates an **intraocular pressure (IOP)** of  $\sim 8\text{--}22 \text{ mm Hg}$ , which helps maintain **corneal curvature** (a determinant of eye optics).



**Glaucoma** is an optic nerve neuropathy usually caused by high IOP, resulting in progressive visual loss and blindness if not treated. IOP rises when **aqueous humor** outflow is obstructed. The ciliary epithelium continues secreting fluid despite the obstruction, nerve damage occurring when IOP rises above  $\sim 30 \text{ mm Hg}$ .

**A-plus:** Treatment options include surgery to clear the obstruction or treatment with beta blockers or prostaglandins to decrease secretion or increase outflow, respectively.





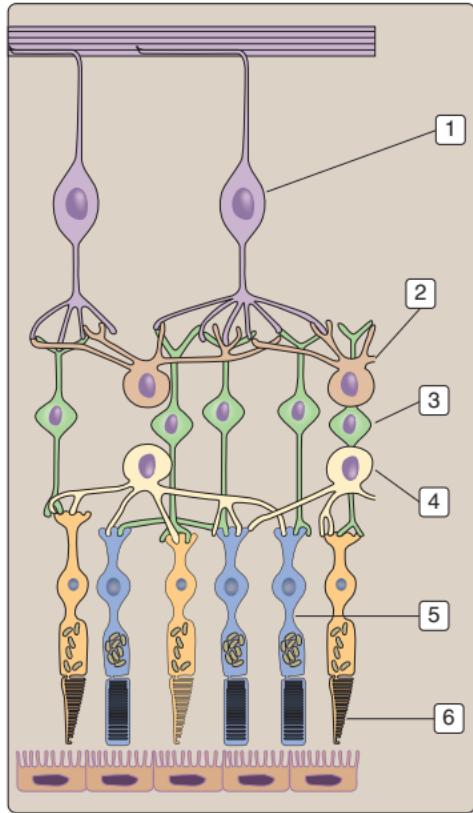
Identify the principal retinal cell types and their functions, as indicated by boxed numerals.



Why is photosensory data from the retina processed extensively before being transmitted to the brain?



What are the three or four most common causes of blindness among elderly adults in developed countries?



**Retinal cell types:**

1. **Ganglion cell**: collates data streams and relays information to the visual cortex
2. **Amacrine cell**: manipulates data
3. **Bipolar cell**: collates data
4. **Horizontal cell**: manipulates data to increase contrast
5. **Rod**: photoreceptor
6. **Cone**: photoreceptor



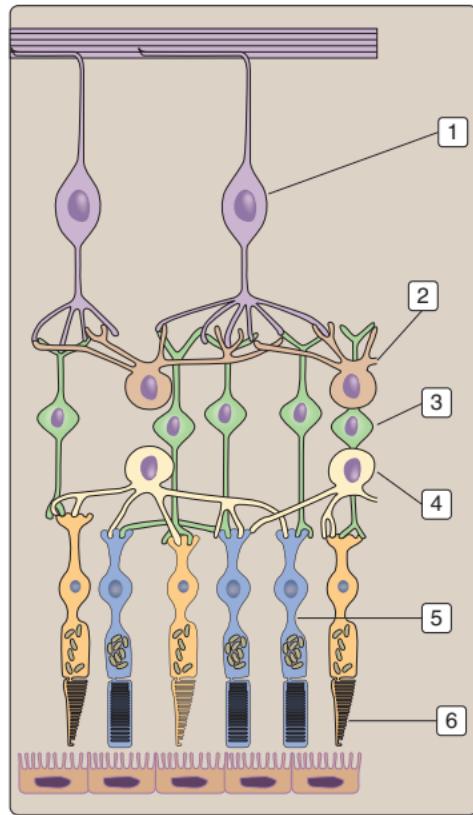
**Photosensory data** is transmitted to the brain via the **optic nerve**, which interrupts the photosensor array and creates a blind spot (**optic disc**). The retina contains  $\sim 10^8$  photoreceptors. If the output from each were transmitted to the brain without processing, the optic nerve would have to be many times wider, which would greatly increase the size of the blind spot.



Common causes of **blindness** in elderly adults include:

- **Macular degeneration**
- **Diabetic retinopathy**
- **Cataracts**
- **Glaucoma**

[Note: Although cataracts are the most common cause of visual impairment among elderly adults, macular degeneration is the most common cause of blindness. Degeneration occurs primarily in the central region of the retina, which impairs an individual's ability to read, drive, and perform many other daily activities.]



# Photosensory Transduction

2.19 Question



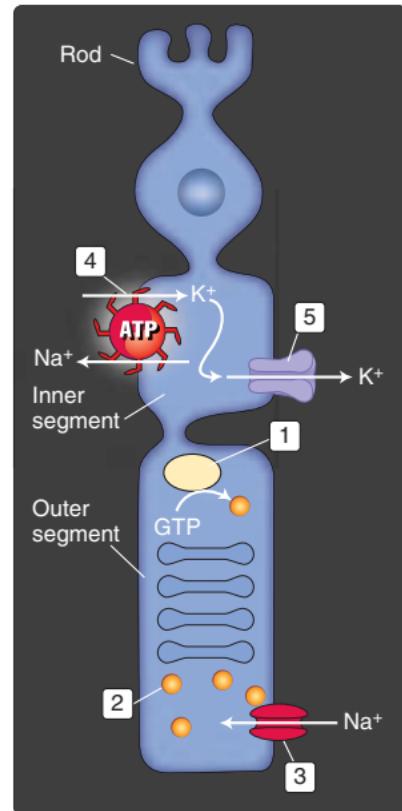
Using the boxed numerals as a guide, trace the origins of the photoreceptor dark current.



Review the sequence of molecular events involved in photoreception.



Vitamin A deficiency is the third most common nutritional deficiency globally. What are the symptoms?



## 2.19 Answer

# Photosensory Transduction



### Dark current origins:

- 1 and 2. **GC** is active in the dark, which keeps **cGMP** levels high.
3. The cell stays depolarized due to  $\text{Na}^+$  influx through a **cGMP-gated channel**.
- 4 and 5. The  $\text{Na}^+/\text{K}^+$  ATPase and a  $\text{K}^+$  channel limit depolarization to  $\sim -40 \text{ mV}$ .

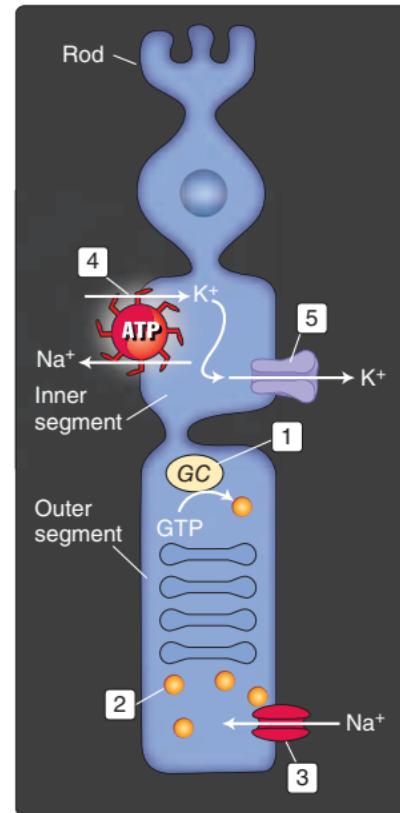


### Photoreception:

- Activation of **rhodopsin** by light activates **transducin**, a **G protein**.
- Transducin activates **PDE**.
- **PDE** hydrolyzes **cGMP**, and intracellular cGMP levels fall.
- $\text{Na}^+$  influx and the **dark current** terminate.
- Continued  $\text{K}^+$  efflux through the  $\text{K}^+$  channel causes membrane hyperpolarization, which constitutes a **photosensory signal**.



Vitamin A deficiency causes night blindness or complete blindness because the vitamin in its **retinol** form is required for visual pigment synthesis. Severe vitamin A deficiency can result in **xerophthalmia**, a pathologic corneal dryness that results from inadequate tear secretion by lacrimal glands.



# Middle Ear

2.20 Question



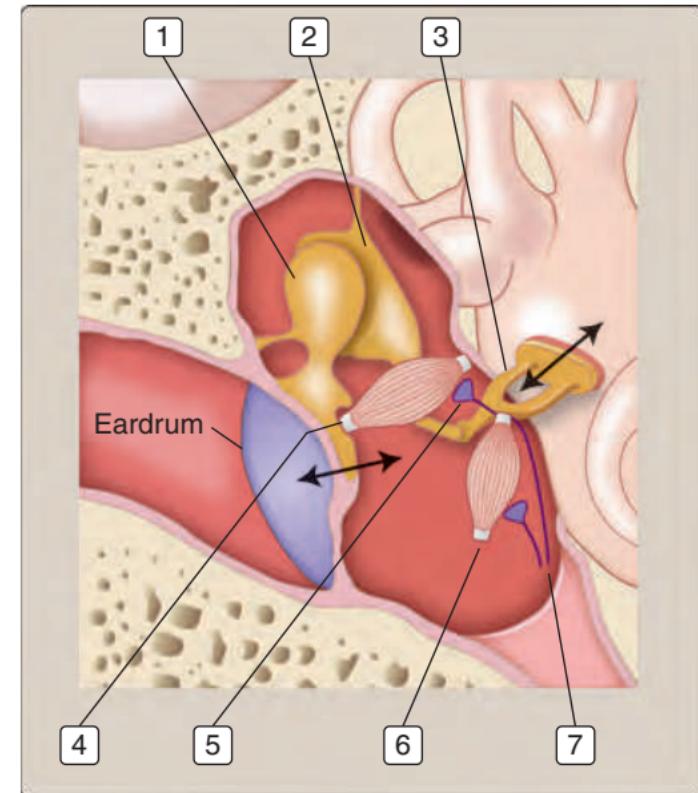
What middle ear structures are indicated by boxed numerals?



How are these ear structures involved in impedance matching and the attenuation reflex?



What is **otosclerosis**, and how does it lead to hearing loss?



**Middle ear** structures:

1. Malleus
2. Incus
3. Stapes
4. Tensor tympani
5. Trigeminal nerve efferent
6. Stapedius
7. Facial nerve efferent

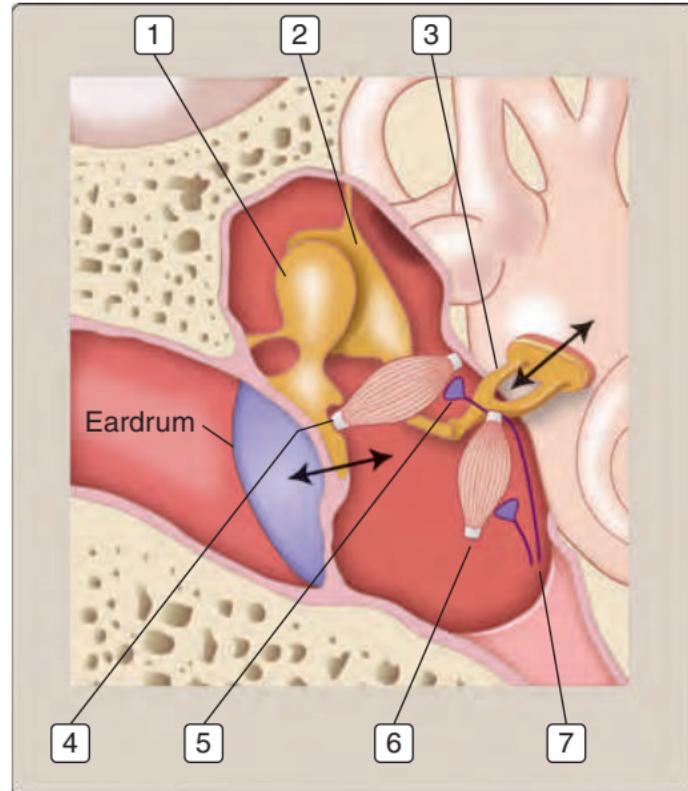


**Impedance matching:** A sound wave traveling in air is amplified and focused to overcome the inertia (or **acoustic impedance**) of fluid filling the inner ear. **Amplification** occurs through the lever system created by the **ossicular chain**. **Focusing** occurs when the energy created by eardrum movement is channeled through the **stapes** foot, which has a much smaller surface area.



**Attenuation reflex:** Contraction of the **tensor tympani** and **stapedius muscles** stiffens the ossicular chain and attenuates energy transfer to the inner ear.

**Otosclerosis** refers to a bony overgrowth that causes the **stapes** foot to become fixed within the **oval window**, preventing normal movement and sound transfer.



# Auditory Hair Cells

2.21 Question



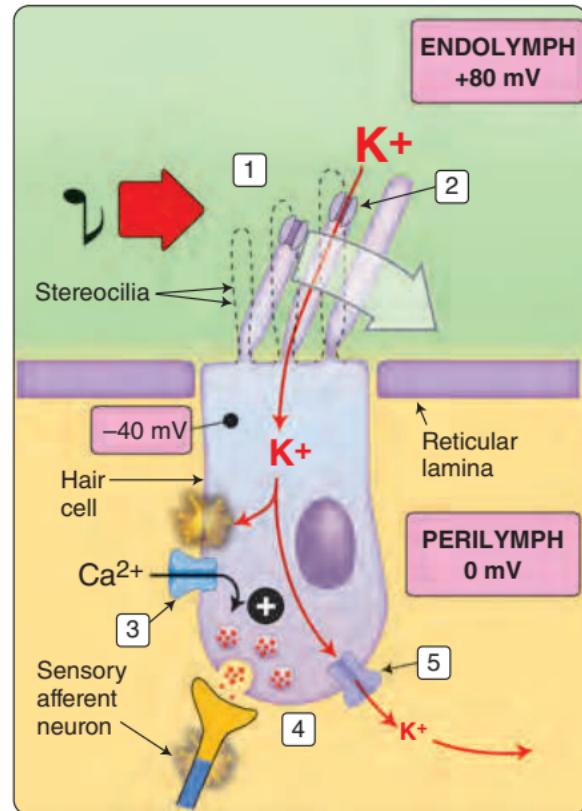
What is the difference between perilymph and endolymph, the two fluids found within the inner ear?



Using the boxed numerals as a guide, summarize the mechanism by which auditory hair cells transduce sounds.



Congenital hearing loss results from mutation in many genes, including an ATP-gated  $K^+$  channel gene (*KCNJ10*) in the stria vascularis. Why would a  $K^+$ -channel gene mutation cause hearing loss?





Difference between inner ear fluids:

- **Perilymph:** fills the space between bony and membranous labyrinths, the **scala vestibuli**, and the **scala tympani** and resembles ECF, with high  $\text{Na}^+$  ( $\sim 140 \text{ mmol/L}$ ) and low  $\text{K}^+$  ( $\sim 5 \text{ mmol/L}$ )
- **Endolymph:** fills the **scala media** and is characterized by very high  $\text{K}^+$  content ( $\sim 150 \text{ mmol/L}$ ) and low  $\text{Na}^+$  ( $\sim 1 \text{ mmol/L}$ )

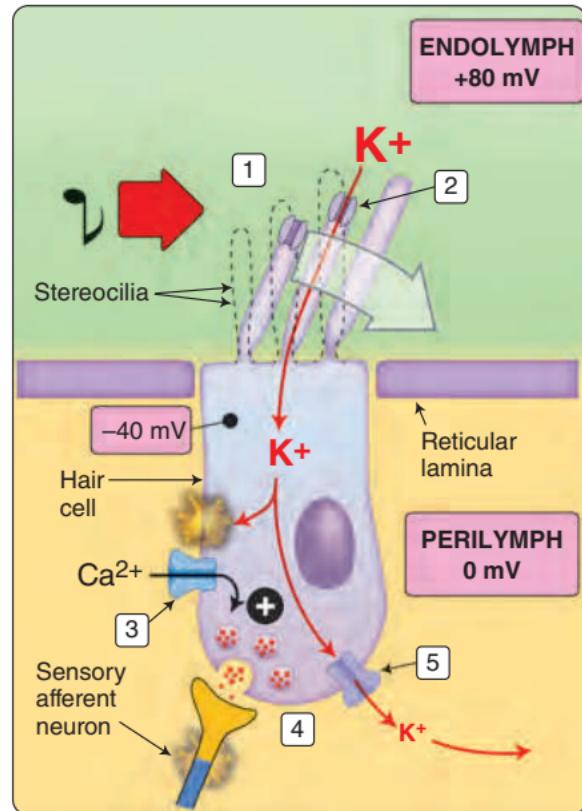


Auditory transduction steps:

1. A sound wave displaces hair cell **stereocilia**.
2. **Tip links tense** and open a **mechanolectric transduction** channel, allowing  $\text{K}^+$  influx.
3. The ensuing hair cell depolarization opens a voltage-gated  $\text{Ca}^{2+}$  channel.
4. A rise in intracellular  $\text{Ca}^{2+}$  triggers **synaptic glutamate release** and signaling via a sensory afferent neuron.
5.  $\text{K}^+$  is **recycled** via a basal  $\text{K}^+$  channel.



**KCNJ10** mutation prevents the 80-mV **endocochlear potential** from forming between endolymph and perilymph. The endocochlear potential is established by the **stria vascularis** and is required for auditory transduction.





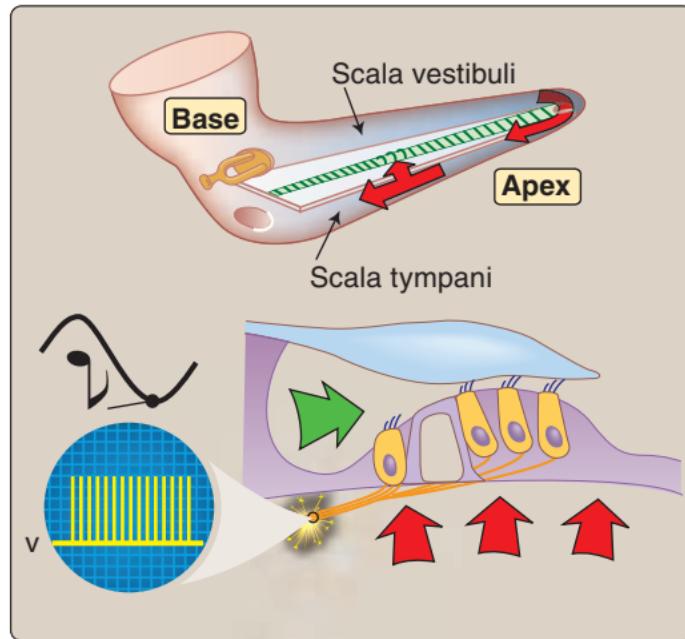
Review how displacement of the oval window leads to auditory nerve afferent activity.



What is the physiologic mechanism of auditory encoding?



Neonatal screening for hearing loss includes otoacoustic emission (OTE) testing. What is the basis for such tests?



Effect of sound waves on hair cells in the organ of Corti.

**Auditory transduction** steps:

1. Displacement of the **oval window** sends a pressure wave down the **scala vestibuli**.
2. The wave buffets the **scala media** and **basilar membrane**, on which rests the **organ of Corti**.
3. Basilar membrane displacement moves **hair cells** relative to the **tectorial membrane**. Hair cell **stereociliary tips** are embedded in this membrane, so the stereocilia are forced to bend.
4. Stereociliary bending activates **tip link channels**. K<sup>+</sup> influx via these channels creates a **receptor potential**. Hair cells then excite the sensory nerve afferents, and auditory nerve activity increases.



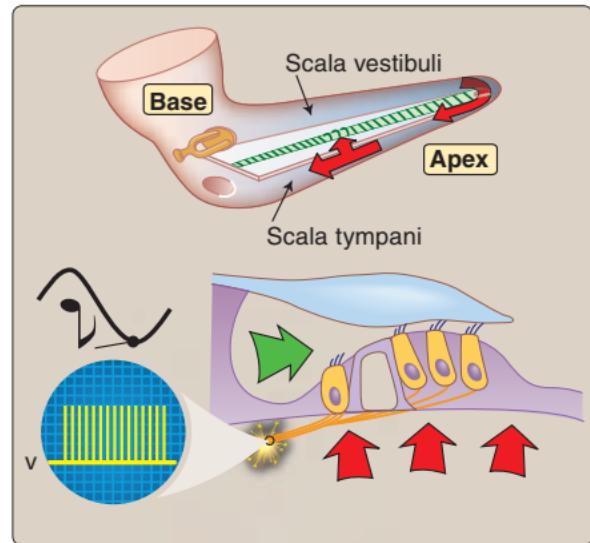
**Auditory encoding** (the two ends of the basilar membrane are attuned to different frequencies):

**Apex:** The membrane is wide and flexible, whereas hair cell stereocilia are long and flexible, which gives maximal responsiveness to low-frequency sounds (~0.5 kHz).

**Base:** The membrane is narrow and inflexible, whereas stereocilia are short and stiff, which produces maximal responsiveness to high-frequency sounds (~16 kHz).



**Outer hair cells** amplify external sounds to enhance auditory discrimination (**cochlear amplifier**). These amplified sounds can be recorded using a microphone placed in the ear canal. During OTE, a series of clicks of varying frequencies are delivered to test the functionality of the amplifier: If responsiveness is diminished, hearing may be impaired.



Effect of sound waves on hair cells in the organ of Corti.

# Vestibular System

2.23 Question



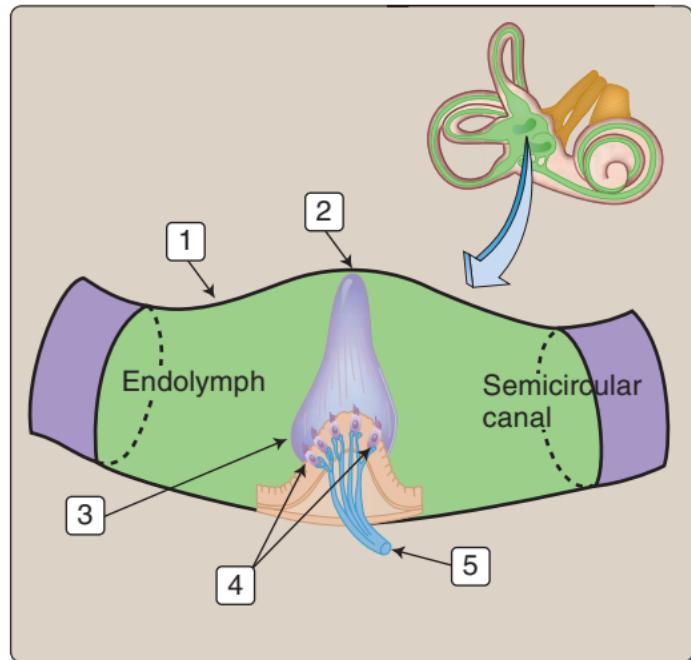
Identify the principal structures in the semicircular canal, as indicated by boxed numerals.



Review the vestibuloocular reflex (VOR).



What causes **benign paroxysmal positional vertigo (BPPV)**, the most common form of vestibular dysfunction?





### Semicircular canal structures:

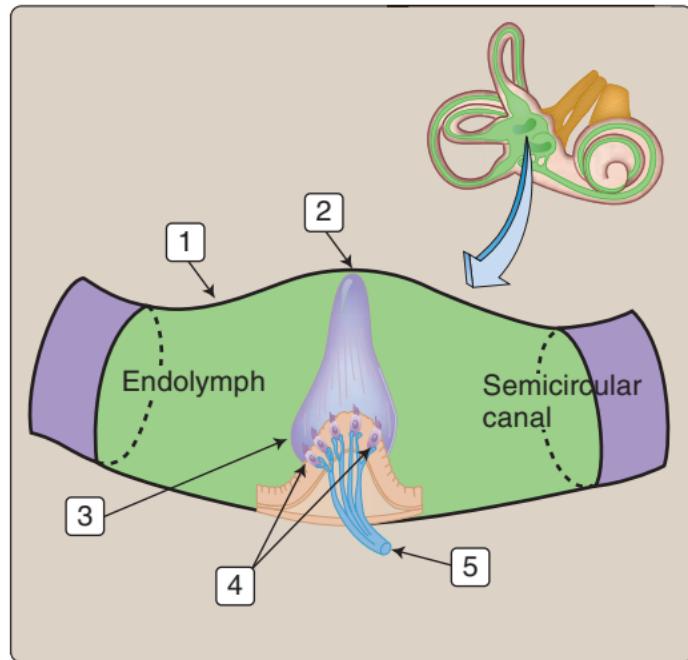
1. Ampulla
2. Cupula
3. Crista ampullaris
4. Sensory hair cells
5. Vestibular nerve afferents



The **VOR** couples semicircular canal sensory output to the **oculomotor muscles** controlling eye movement, thereby helping ensure that retinal images remain stable when the head is moving. When the head turns left, the left horizontal semicircular canal is activated. Sensory signals from this canal are relayed via the **vestibular nucleus** to the contralateral **abducens nucleus** in the brainstem. Contraction of oculomotor muscles that cause the eyes to track right is coordinated by motor signals from the **abducens nucleus** traveling via **CN VI** and from the **oculomotor nucleus** via **CN III**.



**BPPV** is caused by **otoliths** ("ear stones") that have detached from the otolithic membrane of a utricle or saccule and found their way into a **semicircular canal**. Here, they bump against the cupula and stimulate the hair cells inappropriately. The patient experiences dizziness, light-headedness, or vertigo as a result.



# Gustation

2.24 Question



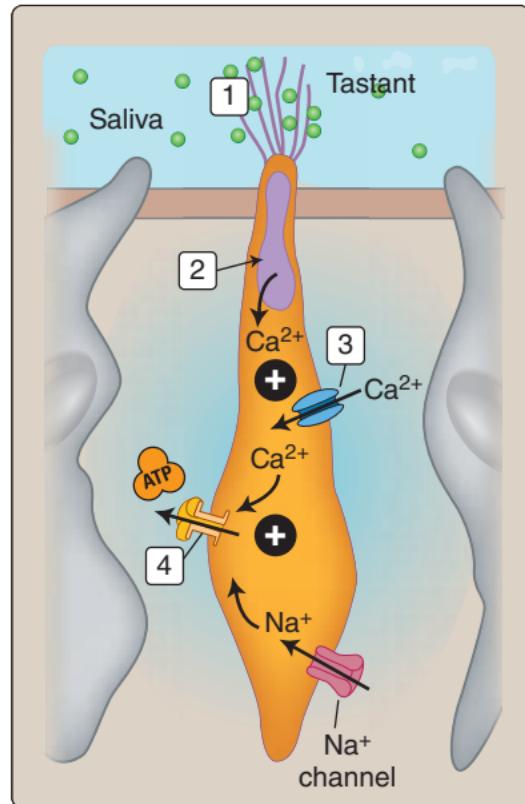
What are the five primary tastes and the receptor cell type responsible for each sensation?



What are the steps (indicated by boxed numerals) involved in taste transduction by a type II-receptor cell?



Patients with **Sjögren syndrome** typically suffer from hypogeusia. What is the underlying pathophysiology?





Primary tastes and receptor types:

- **Salty** (type I receptor)
- **Sweet** (type II receptor)
- **Umami** (type II receptor)
- **Bitter** (type II receptor)
- **Sour** (type III receptor)

[Note: The taste of fats may constitute a sixth basic taste, but the mechanisms involved in fat taste transduction are still under investigation.]

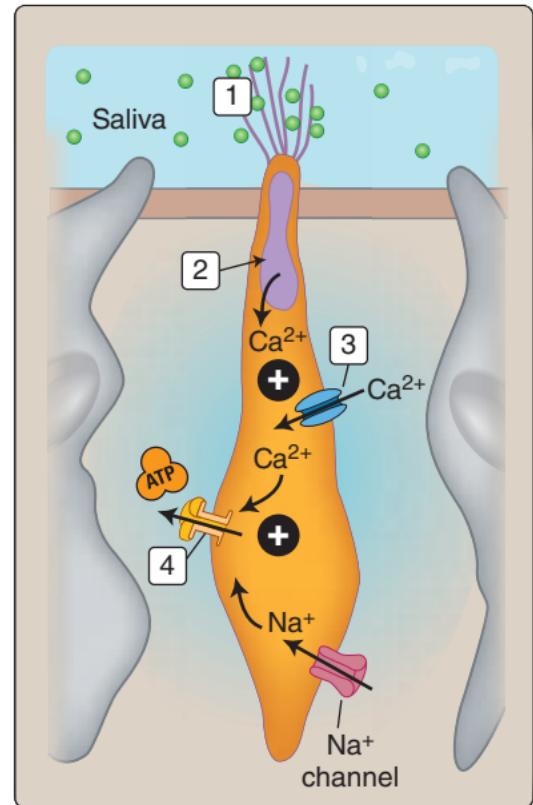


Taste transduction by type II–receptor cells:

1. The tastant binds to a **tastant-specific GPCR**.
2. The **gustducin**  $G_{\beta\gamma}$  subunit initiates  $\text{Ca}^{2+}$  release from intracellular stores via the  **$\text{IP}_3$ -signaling pathway**.
3.  $\text{Ca}^{2+}$  stimulates further  $\text{Ca}^{2+}$  influx via  **$\text{TRPM5}$** .
4.  $\text{Ca}^{2+}$  stimulates ATP release into the taste bud via **pannexin** channels. ATP constitutes a sensory signal.



Taste sensation relies on saliva to dissolve the tastant and deliver it to the receptor cells within a taste bud. Patients with **Sjögren syndrome** have impaired salivary gland function. The resulting salivary deficit causes **xerostomia** (dry mouth) and **hypogeusia** (diminished taste). [Note: Complete taste loss (**ageusia**) is very uncommon. More common is **dysgeusia**, or altered taste.]



# Taste Buds

2.25 Question



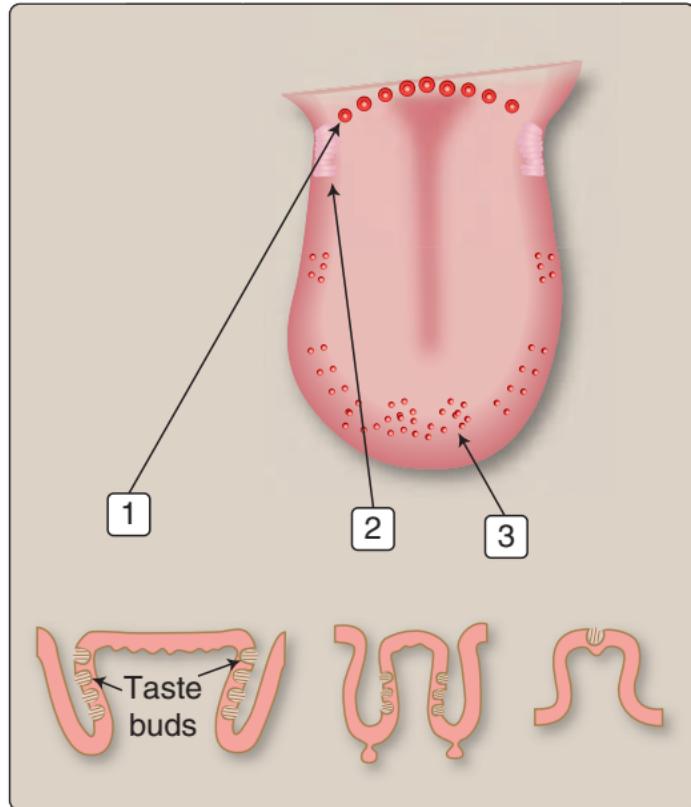
What are the three types of papillae containing taste buds, and what nerves innervate the different gustatory regions?



Only one receptor cell type within a taste bud synapses with a sensory afferent nerve fiber. How do the other receptor cells signal to the brain?



Lithium, metronidazole, and tetracycline all have a troublesome gustatory side effect known as \_\_\_\_\_.





Papillae types:

1. **Circumvallate**
2. **Foliate**
3. **Fungiform**

Sensory signals from the palate and tongue anterior are relayed by the **facial nerve (CN VII)**. The tongue posterior is innervated by the **glossopharyngeal nerve (CN IX)**. The **vagus nerve (CN X)** innervates the pharynx and larynx.

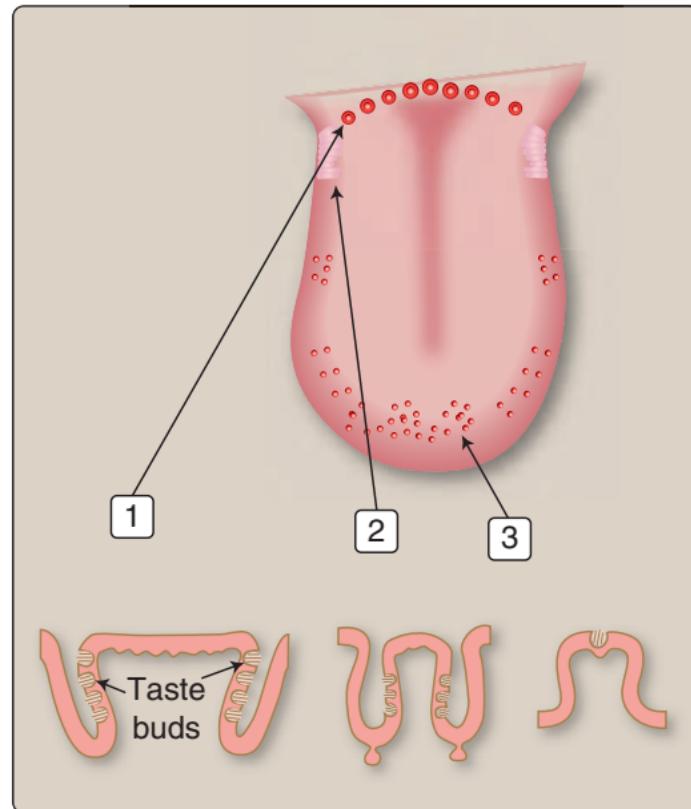


**Taste bud** signaling:

- **Type III cells** (also known as **presynaptic cells**): use **5-HT<sub>3</sub>** as a synaptic transmitter and are the only ones to synapse with a sensory afferent nerve
- **Type II cells**: release **ATP** into the taste bud, where it stimulates **5-HT<sub>3</sub>** release from type III cells (ATP may also stimulate the gustatory nerve directly via a **purinoreceptor**)
- **Type I cells**: may influence gustatory nerve output by releasing an **ecto-ATPase** into the taste bud



Lithium, metronidazole, and tetracycline all have a troublesome gustatory side effect known as **metallic dysgeusia**. [Note: Metallic dysgeusia is a common side effect of many pharmaceuticals, including antifungals and  $\beta$ -lactam antibiotics. In most instances, the mechanisms involved are unknown.]



# Olfaction

2.26 Question



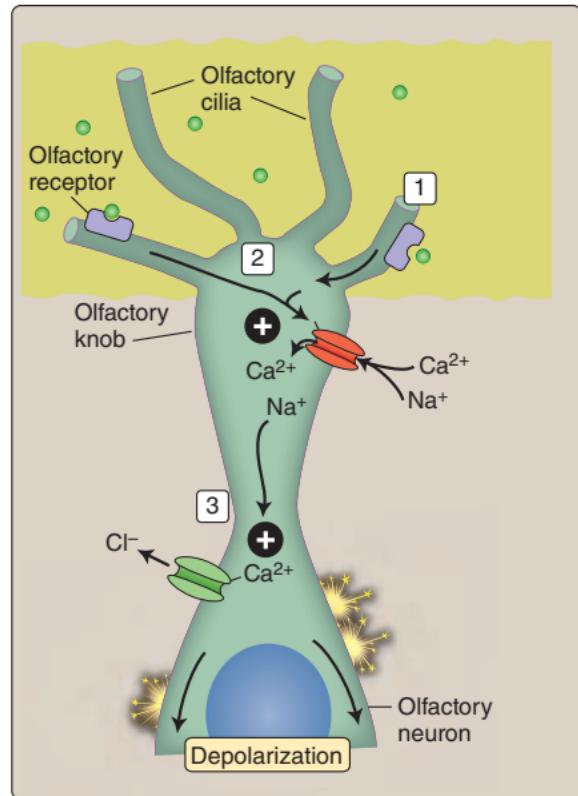
Using the boxed numerals as a guide, trace the steps in olfactory transduction.



The ion channel that mediates olfactory transduction is part of a larger family, one member of which transduces photosensation, whereas another regulates heart rate. Compare the properties of these three channels.



Head trauma accounts for ~30% of cases of **anosmia**. Why is the olfactory system particularly vulnerable to head trauma?





Steps in olfactory transduction:

1. An odorant binds to a **GPCR** and activates  $G_{olf}$ .
2.  $G_{olf}$  activates the **cAMP-signaling pathway**, causing  $\text{Ca}^{2+}$  and  $\text{Na}^+$  influx via a **cAMP-dependent channel**.
3.  $\text{Ca}^{2+}$  activates a  **$\text{Ca}^{2+}$ -dependent  $\text{Cl}^-$  channel**, causing the sensory neuron to depolarize and then spike.

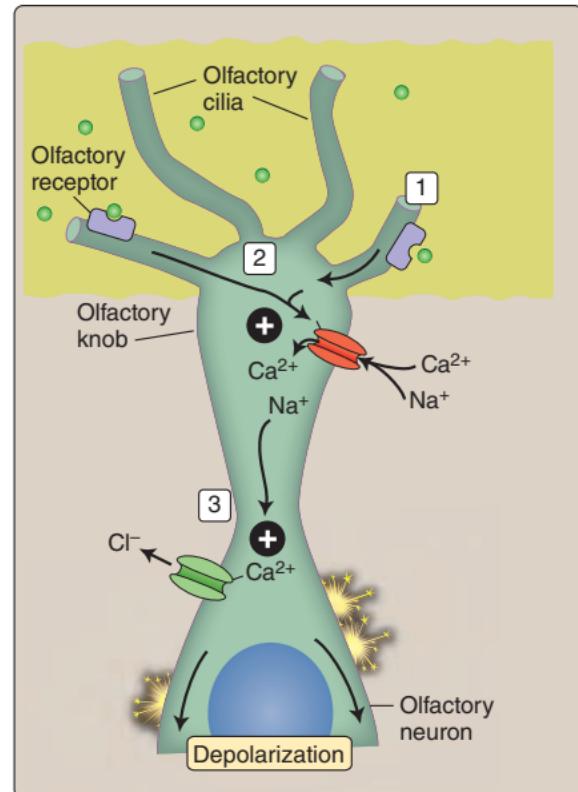


Properties of cyclic nucleotide-gated ion channels:

- **Olfactory system:** relatively nonspecific for cations and gated by **cAMP**
- **Visual system:** relatively nonspecific for cations and gated by **cGMP**
- **Heart:** relatively nonspecific for cations and requires cyclic nucleotides to open but gated by voltage (**hyperpolarization**)  
[Note: All three channels are structurally related to tetrameric voltage-gated channels.]



Olfactory neurons are located on the roof of the nasal cavity, and their axons pass through foramina in the **cribriform plate** (ethmoid bone) en route to the **olfactory bulb**. Rapid movements associated with head trauma can shear these axons, causing **anosmia**. [Note: Although olfactory neurons can regenerate, only  $\sim 10\%$  of such patients with anosmia regain their sense of smell within a year.]



# Sensory and Motor Pathways

2.27 Question



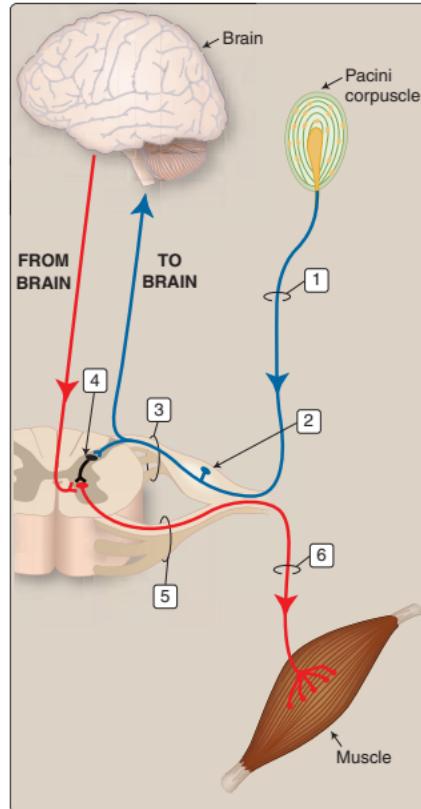
Identify the structures providing pathways for information flow between the peripheral and central nervous systems, as indicated by boxed numerals.



Many reflexes are mediated by spinal circuits involving an interneuron. Review the neural pathways involved in a flexion and crossed-extension reflex.



An extensor plantar reflex, also known as the \_\_\_\_\_, may be an indication of damage to the \_\_\_\_\_ tract when elicited in an adult.





Sensory and motor pathways:

1. **Sensory afferent nerve**
2. **Spinal ganglion** containing nerve cell bodies
3. **Spinal cord posterior root**
4. **Interneuron**
5. **Spinal cord anterior root**
6. **Motor effector nerve**

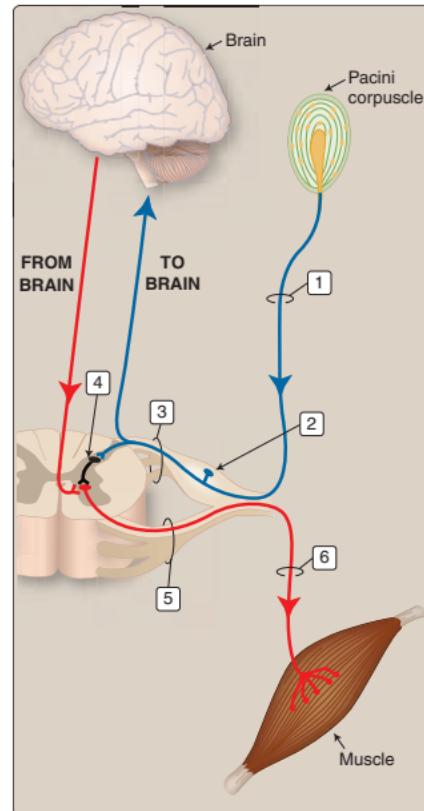


Flexion and crossed-extension reflexes are initiated by limb **nociceptor** activation stimulating afferent fibers projecting to the spinal cord:

- **Flexion reflex:** Motor fibers to ipsilateral flexor muscles are stimulated, whereas extensor muscles are inhibited via a reflex loop involving an inhibitory interneuron.
- **Crossed-extension reflex:** Flexors in the contralateral limb are inhibited, while extensors are activated, again using local spinal reflex loops.



An **extensor plantar reflex**, also known as the **Babinski sign**, may be an indication of damage to the **corticospinal tract** when elicited in an adult. [Note: Toes usually flex when the sole of the foot is stimulated, a reflex mediated by the tibial nerve and circuits in the lumbar and sacral spinal regions. The reflex is subject to modification by motor commands from the cortex via the corticospinal tract. Damage to these pathways can cause the big toe to extend rather than flex and the toes to splay (i.e., exhibit the Babinski sign).]



# Muscle Spindle Receptors

2.28 Question



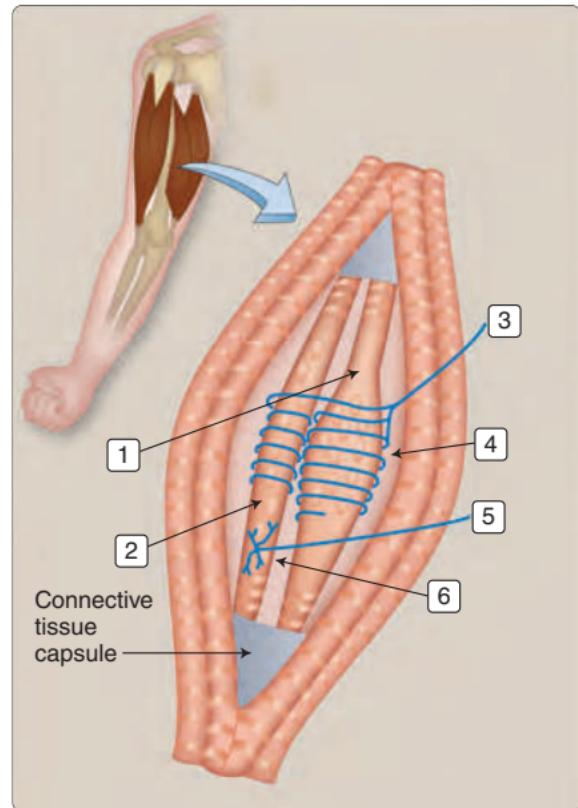
Identify the various muscle and nerve components of a muscle spindle, as indicated by boxed numerals.



Review the role of these various components in muscle spindle function.



Patients with **Guillain-Barré syndrome** commonly suffer muscle weakness and loss of deep tendon reflexes. What is the underlying pathophysiological process?



# Muscle Spindle Receptors



Principal **muscle spindle** components:

1. Nuclear bag fiber
2. Nuclear chain fiber
3. Type Ia sensory nerve
4. Primary receptor
5. Type II sensory nerve
6. Secondary receptor

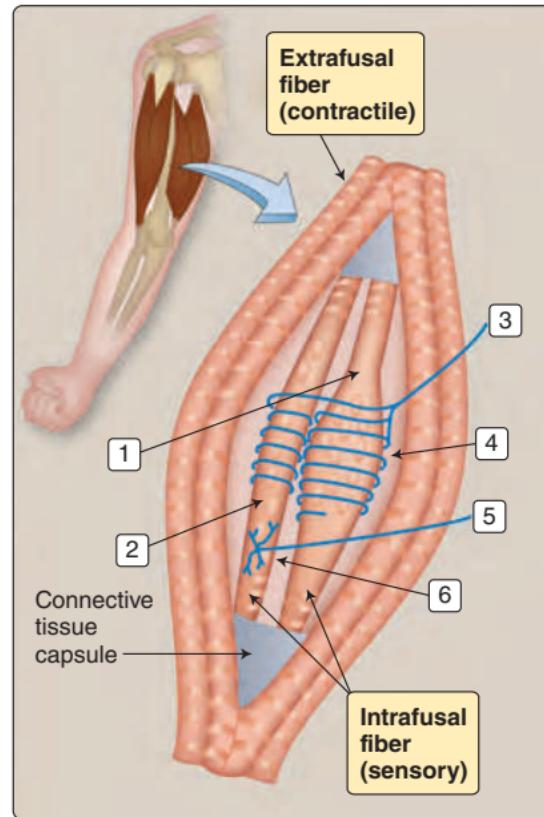


**Muscle spindle** function:

- They monitor muscle length and changes in length.
- They comprise up to 12 **intrafusal muscle fibers** and their associated mechanosensory nerve endings (receptors).
- Nerve endings are stimulated by changes in muscle length. They signal via **fast-conducting sensory afferents**.
- **Slow-conducting  $\gamma$ -motor nerves** adjust muscle spindle length to maintain constant tension and sensory capabilities during **extrafusal contractions**.



**Guillain-Barré** symptoms reflect a polyneuropathy caused by autoimmune responses to axonal membrane constituents or to **myelin**. The result is a progressive sensory and motor deficit, with loss of deep tendon reflexes. [Note: This syndrome is often preceded by an infection, the reaction to which is believed to initiate the autoimmune response.]



# Golgi Tendon Organs

2.29 Question



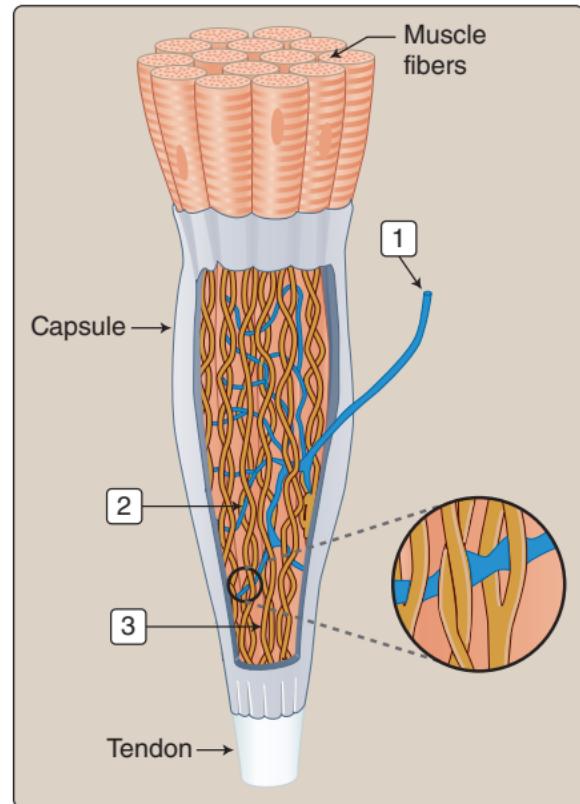
Using the boxed numerals as a guide, identify the structural components of a Golgi tendon organ (GTO) and review how it works.



What is the role of GTOs in an inverse myotatic reflex (also known as a Golgi tendon reflex)?



Tetanus toxin acts by targeting \_\_\_\_\_ cells in the spinal cord. These cells normally limit \_\_\_\_\_ activity and prevent \_\_\_\_\_ contractions.





GTO structure and function:

1. **Group Ib sensory nerve**
2. Sensory nerve endings
3. **Collagen fibers**

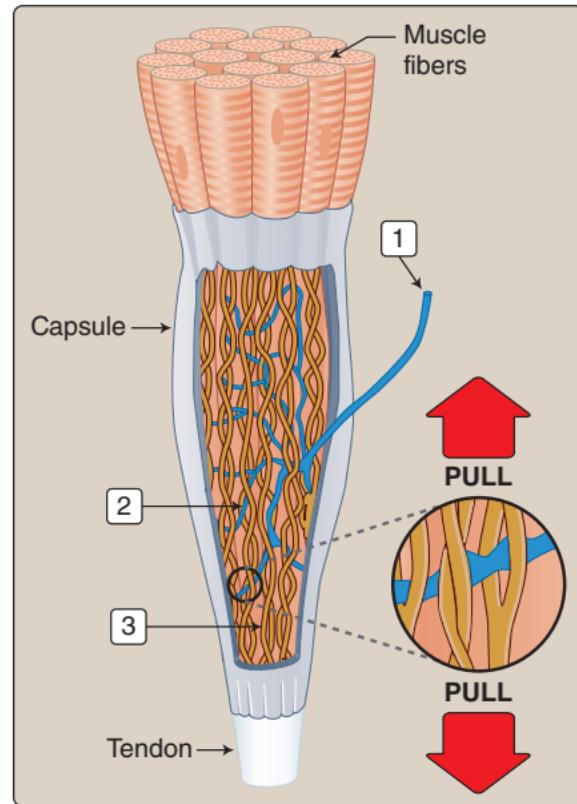
When the muscle tenses, the fibers pinch the sensory nerve endings, causing receptor depolarization and an AP.



**GTOs** help fine-tune limb movements and are involved in posture control. When a muscle contracts, signals from the GTO travel via **group 1b afferents** to the spinal cord, where they excite motor outputs to the heteronymous muscle. The  **$\alpha$ -motor neuron** innervating the homonymous muscle is simultaneously inhibited via an **inhibitory interneuron**. These actions directly oppose and thereby limit the actions of the myotatic reflex.



**Tetanus toxin** acts by targeting **Renshaw cells** in the spinal cord. These cells normally limit  **$\alpha$ -motor neuron** activity and prevent **tetanic contractions**. [Note: The toxin interferes with glycine release, an inhibitory neurotransmitter, at the Renshaw cell's nerve terminal. A Renshaw cell is activated by the same neuron that it inhibits, thereby creating a negative feedback circuit that limits the effects of motor neuron stimulation.]



# Motor Control Centers

2.30 Question



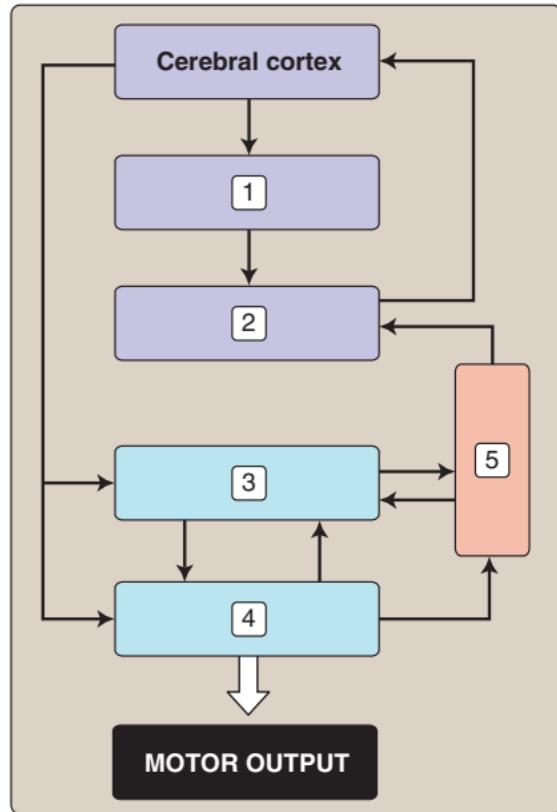
Relationships between what higher motor control centers of the CNS are shown?



What is the role of the cerebral cortex in motor control, and how are the cortical centers organized?



Intention tremors and ataxia are most likely an indication of \_\_\_\_\_ damage.





Higher motor control centers:

1. **Basal ganglia**
2. **Thalamus**
3. **Brainstem**
4. **Spinal cord**
5. **Cerebellum**

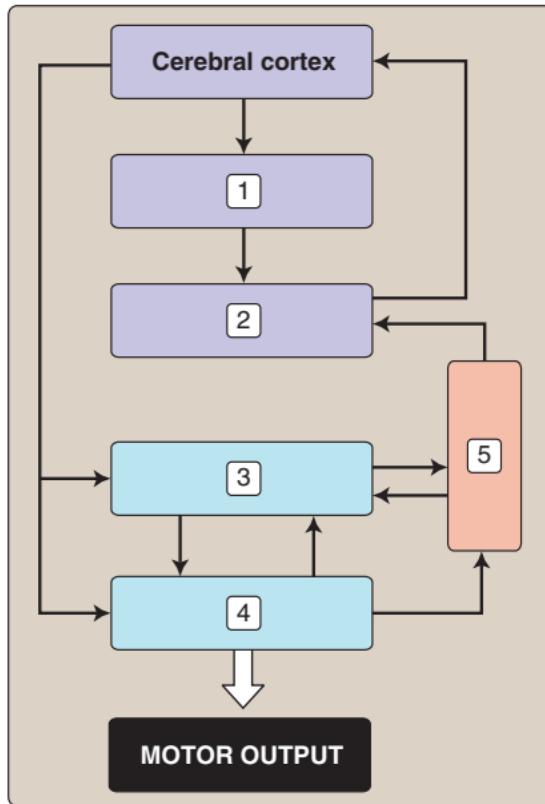


The **cortex** plans voluntary movements and executes them after processing by other regions of the brain.

- **Primary motor cortex:** issues motor commands to the periphery via the **corticospinal tract**
- **Premotor cortex:** may plan movements referencing visual and other sensory cues
- **Supplementary motor area:** coordinates memorized motor sequences



**Intention tremors** and **ataxia** are most likely an indication of **cerebellar** damage. [Note: The cerebellum is involved in fine-tuning motor sequences but is not required for locomotion.]



# Basal Ganglia

2.31 Question



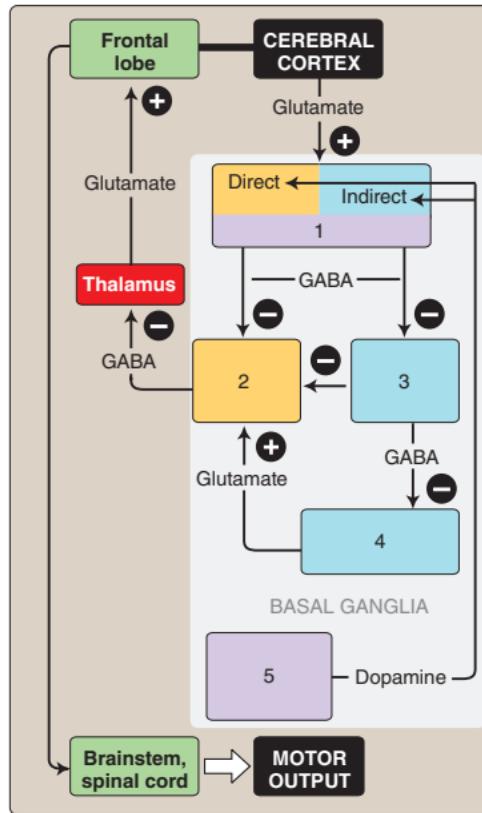
The figure shows the functional relationships among basal ganglia. Identify the nuclei indicated by boxed numerals.

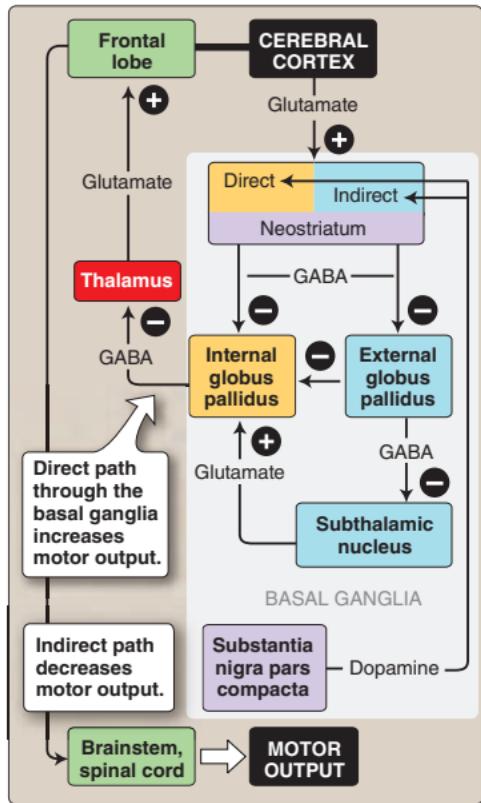


Which one of the basal ganglia derives its name from its color, and why does it contain a high melanin concentration?



The characteristic tremor and shuffling gait of a patient with **Parkinson disease** reflect a defect in the basal ganglia. Which one is affected primarily?





The **substantia nigra** (Latin for “black substance”) appears black due to the presence of **neuromelanin**, a neural form of melanin. The substantia nigra is rich in neurons that synthesize **dopamine**, and neuromelanin is believed to be formed from dopamine breakdown products.



Patients with **Parkinson disease** develop characteristic motor disturbances due to selective loss of large numbers of **dopaminergic neurons** from the **substantia nigra**. The basal ganglia are believed to inhibit motor output until a decision to execute a movement is made by the cerebral cortex. The dopaminergic neurons facilitate disinhibition by the pathways shown. Therefore, loss of these neurons causes **bradykinesia** and other motor disturbances.



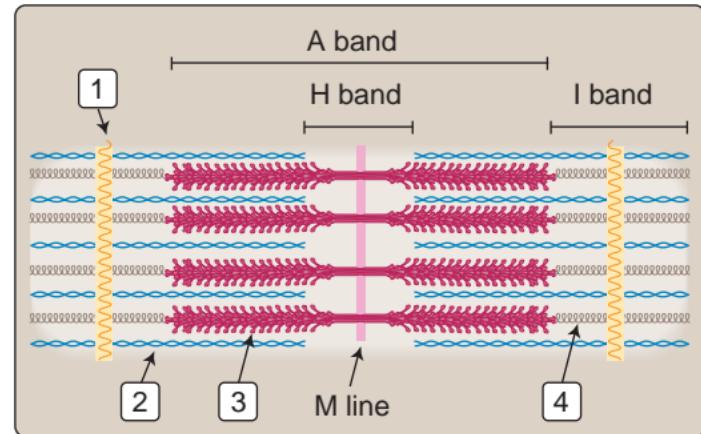
What major structural components of the skeletal muscle sarcomere are indicated by boxed numerals?



What are the two main types of skeletal muscle fiber, and how do they differ?



**Duchenne muscular dystrophy** is caused by mutations in the \_\_\_\_\_ gene. \_\_\_\_\_ normally forms part of a protein complex that localizes to and provides mechanical support for the \_\_\_\_\_.



### 3.1 Answer

## Sarcomere



Sarcomeric structural components:

1. **Z disk** (anchors the thin filaments)
2. **Thin filament** (actin and associated proteins)
3. **Thick filament** (myosin and associated proteins)
4. **Titin** (limits sarcomeric stretch)

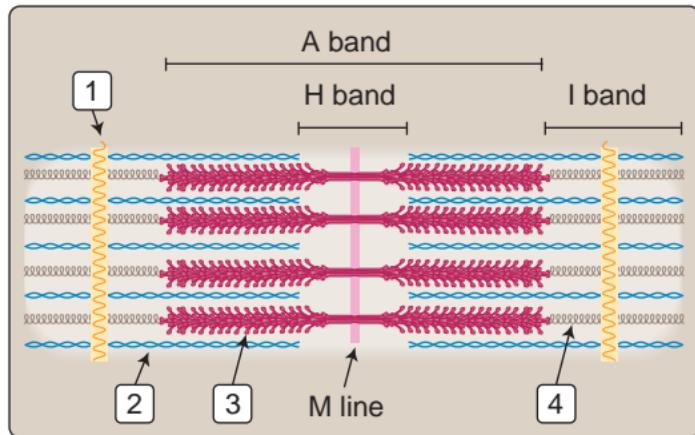


Two broad classes of skeletal muscle fiber:

- **Slow twitch (type I):** Contract slowly, do not fatigue easily, and their energetics are primarily **oxidative**. Uses include posture control, for example. **Myoglobin** gives them a red appearance.
- **Fast twitch (type II):** Contract rapidly but fatigue. They rely on **glycolysis** for energy generation and can be further subdivided into **type IIa** (mixed oxidative and glycolytic energetics) and **type IIx** (glycolytic). The latter are used in rapid sprints, for example.  
[Note: Most muscles contain a mix of fiber types.]



**Duchenne muscular dystrophy** is caused by mutations in the **dystrophin** gene. **Dystrophin** normally forms part of a protein complex that localizes to and provides mechanical support for the **sarcolemma**. [Note: The mutant gene product compromises sarcolemmal integrity and causes muscle fiber necrosis. Muscle wasting results.]



# Neuromuscular Junction

## 3.2 Question



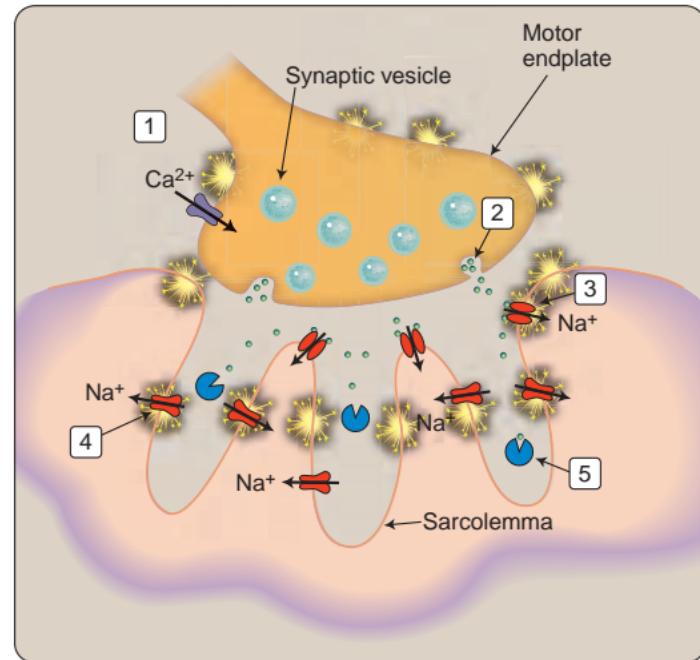
Using the boxed numerals as a guide, trace the steps involved in neuromuscular signaling.



How does the neurotransmitter receptor found at the skeletal neuromuscular junction (NMJ) differ from that at a bronchiolar NMJ?



What causes muscle weakness in patients with **myasthenia gravis (MG)**?



## 3.2 Answer

# Neuromuscular Junction



Neuromuscular signaling steps:

1. An AP arrives at the **motor endplate** and opens a voltage-dependent  $\text{Ca}^{2+}$  channel.
2.  $\text{Ca}^{2+}$  influx initiates **ACh release** from synaptic vesicles.
3. **AChR** activates and mediates a cation influx that creates a **motor endplate potential**.
4. Voltage-dependent  $\text{Na}^+$  channels open and an AP propagates across the sarcolemma.
5. **AChE** helps terminate signaling.



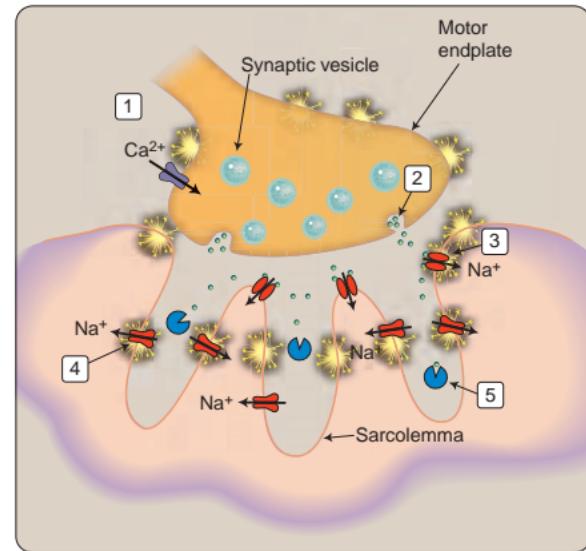
Differences in AChR types:

- **Skeletal muscle:** The AChR is an ion channel (i.e., an **ionotropic receptor**) that mediates  $\text{Na}^+$  influx and membrane depolarization when occupied. It is blocked by **nicotine** (a **nAChR**).
- **Smooth muscle:** This **metabotropic receptor** signals occupancy via a **G protein** and is blocked by **muscarine** (a **mAChR**).



**MG** is an autoimmune disease. Antibodies directed against the nAChR or proteins required for AChR clustering on the postsynaptic membrane (e.g., *muscle-specific receptor tyrosine kinase*) prevent normal neuromuscular signaling and thereby cause muscle weakness.

**A-plus:** Most patients with AChR-specific antibodies have thymus abnormalities (hyperplasia or a carcinoma), and their symptoms often improve with thymectomy.



# Excitation–Contraction Coupling

3.3 Question



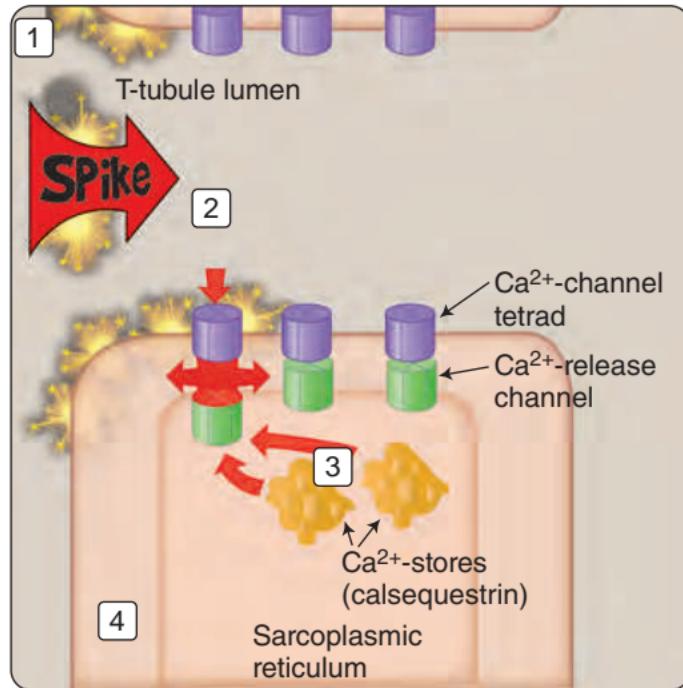
List the steps (indicated by boxed numerals) that follow ACh binding at the neuromuscular junction and initiate muscle contraction.



How is contractile force regulated in skeletal muscle?



**Hypokalemic** \_\_\_\_\_ (PP) is a hereditary condition characterized by periods of muscle weakness. Hypokalemic PP mutations map to \_\_\_ and \_\_\_ channel genes.



Excitation–contraction coupling.

### 3.3 Answer

## Excitation–Contraction Coupling



Excitation–contraction coupling steps:

1. A  $\text{Na}^+$ -dependent AP (spike) carries the signal into T tubules.
2. Voltage-dependent  $\text{Ca}^{2+}$  channel tetrads (**dihydropyridine [DHP] receptors**) open.
3. A conformational change in the DHP receptors forces open  $\text{Ca}^{2+}$ -release channels (**ryanodine receptors**) in the sarcoplasmic reticulum.  $\text{Ca}^{2+}$  floods out of the stores into the sarcoplasm.
4.  $\text{Ca}^{2+}$  binds to myosin and initiates contraction.



Contractile force is regulated through:

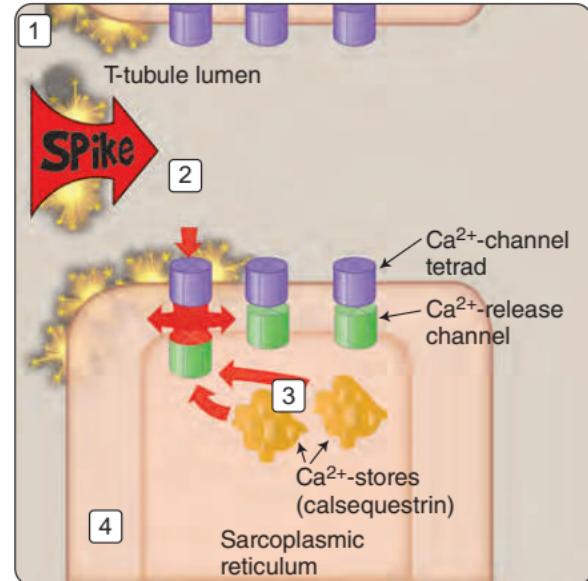
- Muscle **stimulation frequency**
- Number of **motor units** involved

Single APs produce twitch responses that develop minimal tension. APs summate during a volley, however, and contractile force increases. The use of motor units provides for additional force regulation.



**Hypokalemic periodic paralysis (PP)** is a hereditary condition characterized by periods of muscle weakness. Hypokalemic PP mutations map to  $\text{Na}^+$  and  $\text{Ca}^{2+}$  channel genes. [Note: Hypokalemic PP is rare and usually maps to the L-type  $\text{Ca}^{2+}$ -channel gene.]

**A-plus:** Affected individuals experience muscle weakness when serum  $\text{K}^+$  concentrations are low (e.g., when fasting or following exercise). Hypokalemia-induced **membrane hyperpolarization** prevents voltage-gated channel activation and excitation, thereby paralyzing the muscle.



# Crossbridge Cycling

3.4 Question



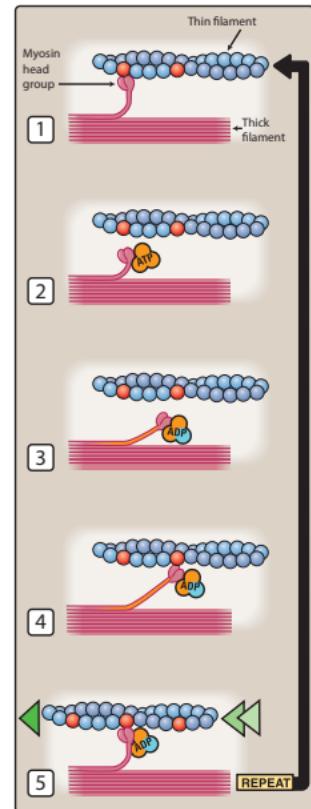
Trace the steps involved in crossbridge cycling, as shown.



How do changes in muscle preload and afterload affect crossbridge cycling?



What is **rigor mortis**?





### Crossbridge cycling steps:

1. The myosin head is bound to the actin thin filament.
2. ATP binds to myosin and decreases actin-binding affinity. The head group releases from the thin filament as a result.
3. ATP hydrolysis causes myosin to reach forward.
4. An actin–myosin crossbridge forms at the new location.
5. The myosin head repositions and displaces the thin filament. The cycle then repeats.

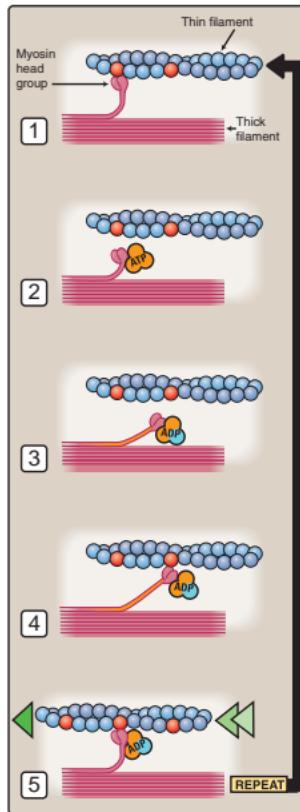


Preload and afterload affect different aspects of the crossbridge cycle:

- **Preload** determines the degree of actin and myosin filament overlap prior to contraction. Overlap, in turn, determines the number of crossbridges that can be formed and the amount of **active tension** that can be developed upon contraction.
- **Afterload** determines **shortening velocity**. Maximal shortening velocity occurs with minimal afterload and decreases with increasing load.



**Rigor mortis** is a muscle rigidity that typically develops ~2–6 hours after death. Rigor is due to thick and thin filament immobilization by crossbridges that form when sarcoplasmic  $\text{Ca}^{2+}$  levels rise. With ATP reserves depleted, the myosin head groups remain locked in place for 1 or 2 days until the myocyte deteriorates.





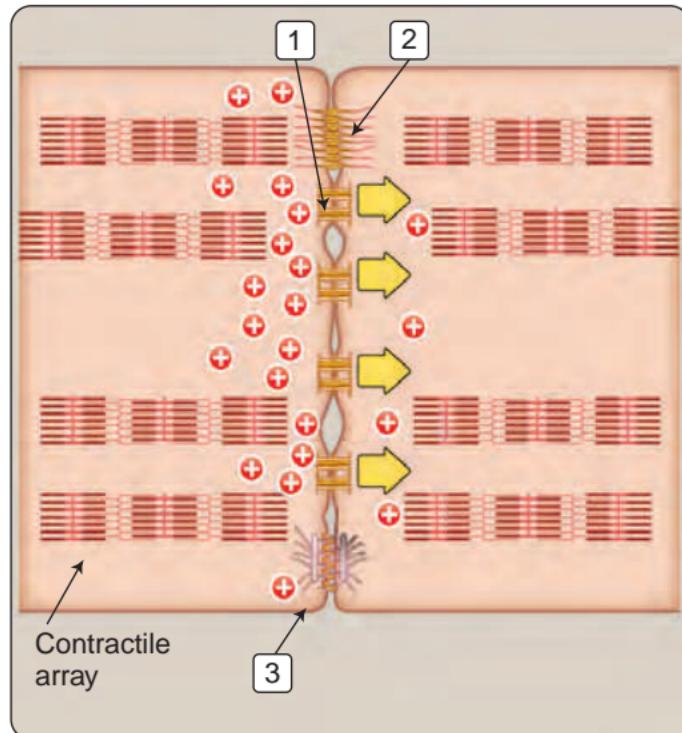
What three junctional structures (indicated by boxed numerals) connect adjacent cardiac myocytes, and what are their main functions?



Skeletal muscle fibers contract when excited by dedicated \_\_\_\_\_, whereas cardiac myocytes are excited by a signal from the \_\_\_\_\_ that spreads via \_\_\_\_\_ across the entire myocardium.



How does **hypertrophic cardiomyopathy (HCM)** affect cardiac muscle fiber communication?





Junctional structures:

1. **Gap junction** (creates a pathway for communication between myocytes)
2. **Fascia adherens** (adhesion, strength)
3. **Desmosome** (adhesion, strength)

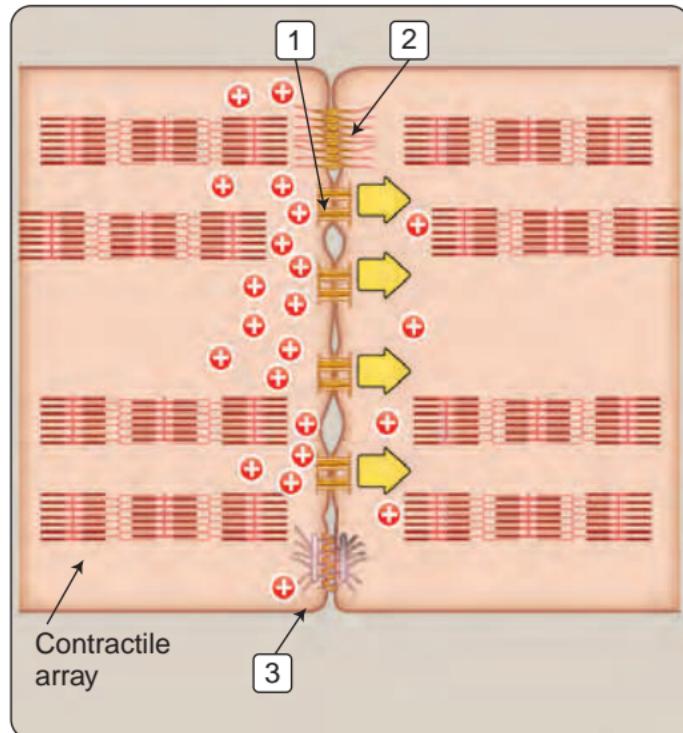


Skeletal muscle fibers contract when excited by dedicated **motor neurons**, whereas cardiac myocytes are excited by a signal from the **sinoatrial node** that spreads via gap junctions across the entire myocardium.



**HCM** disrupts normal electrical communication pathways, which predisposes patients to rhythm abnormalities and **sudden cardiac death**. Histological samples taken from the myocardium of patients with HCM show grossly enlarged myocytes in disarray. Spaces between myocytes may be filled with scar tissue due to microscopic ischemic events.

**A-plus:** HCM is an inherited disorder affecting sarcomeric proteins. The most common form maps to the gene encoding the myosin heavy chain.



# Cardiac Excitation–Contraction Coupling

3.6 Question



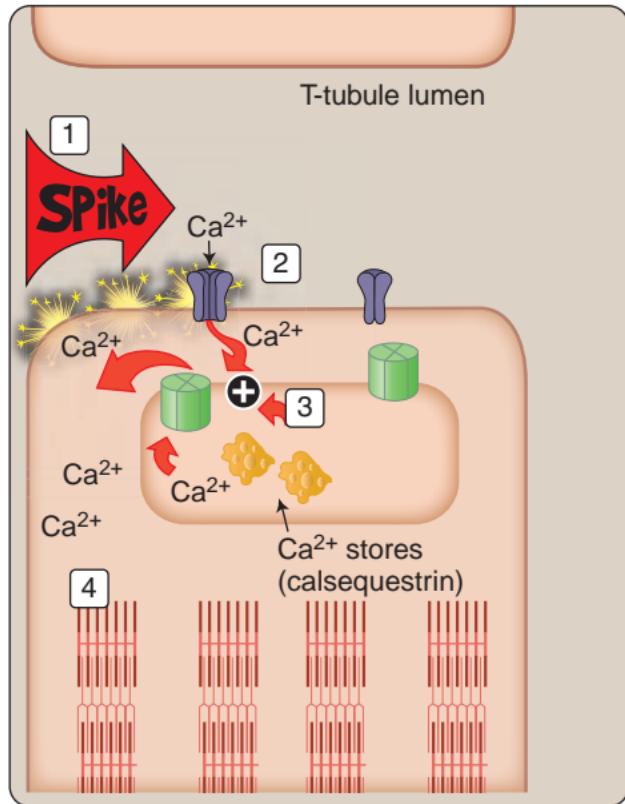
Trace the steps in cardiac muscle excitation–contraction coupling, as indicated by boxed numerals.



How is contractile force regulated in cardiac muscle?



What are the three classes of inotropes used clinically to increase myocardial performance, and how do they act?





Excitation–contraction coupling steps:

1. A  $\text{Na}^+$ -dependent AP (spike) carries the signal into T tubules.
2. L-type  $\text{Ca}^{2+}$  channels (**dihydropyridine receptors**) open to create a  **$\text{Ca}^{2+}$ -trigger flux**.
3. The  $\text{Ca}^{2+}$ -trigger flux opens  **$\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$ -release channels** in the sarcoplasmic reticulum, and  $\text{Ca}^{2+}$  stores empty.
4.  $\text{Ca}^{2+}$  binds to myosin and initiates contraction.

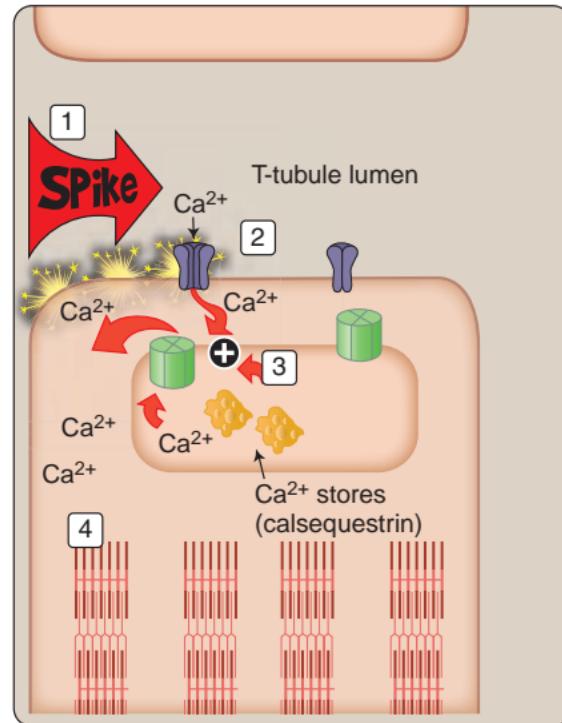


Contractility is regulated through a  $\beta$ -AR and changes in  $\text{Ca}^{2+}$  availability. Receptor occupancy activates *PKA*, which then phosphorylates and increases  $\text{Ca}^{2+}$ -trigger fluxes through the L-type  $\text{Ca}^{2+}$  channel. *PKA* also increases the amount of  $\text{Ca}^{2+}$  deposited into and subsequently released from the  $\text{Ca}^{2+}$  stores.



The three inotrope classes are **cardiac glycosides**,  **$\beta$ -adrenergic agonists**, and **PDE inhibitors**, all of which enhance myocardial contractility by increasing  $\text{Ca}^{2+}$  availability.

- **Cardiac glycosides:** Digoxin and related drugs reduce the  $\text{Na}^+$  gradient used by the  $\text{Na}^+-\text{Ca}^{2+}$  exchanger to remove  $\text{Ca}^{2+}$  from the sarcoplasm following excitation (see 1.3).
- **$\beta$ -Adrenergic agonists:** Dobutamine activates the  $\beta$ -AR and increases  $\text{Ca}^{2+}$  availability by the *PKA* pathway delineated above.
- **PDE inhibitors:** Inamrinone and related drugs prevent cAMP degradation and thereby potentiate *PKA* effects on  $\text{Ca}^{2+}$  availability.



# Smooth Muscle

3.7 Question



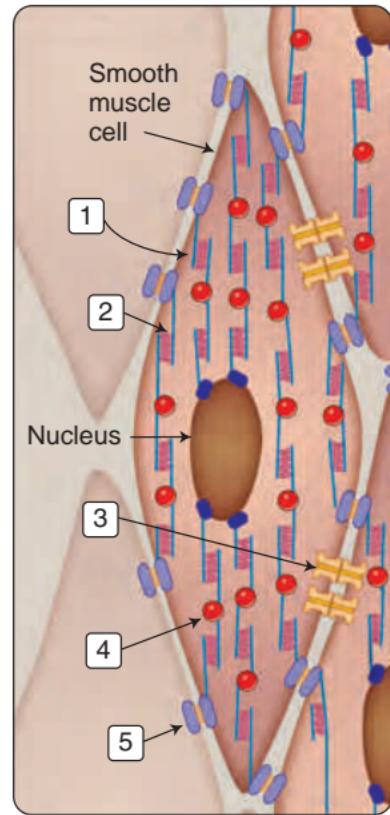
What muscle structures are indicated by boxed numerals?



Contrast sarcomeric structure in striated and smooth muscle.



The lower esophageal sphincter maintains basal tone. Dysfunctions in this smooth muscle result in \_\_\_\_\_ (difficulty swallowing) and \_\_\_\_\_ (GERD).





Smooth muscle cell structures:

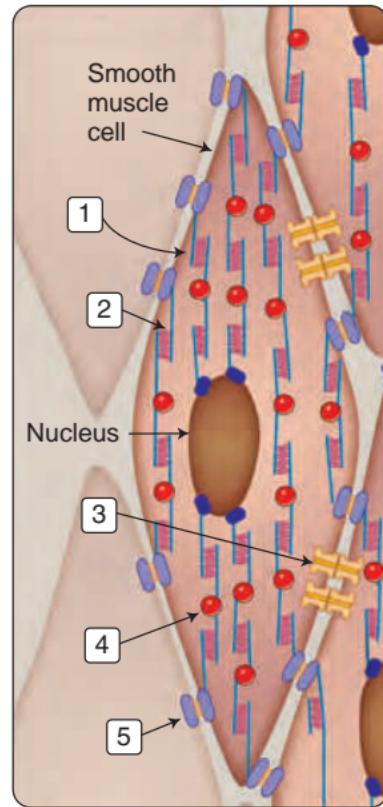
1. **Actin thin filament**
2. **Myosin thick filament**
3. **Gap junction**
4. **Dense body**
5. **Dense plaque**



Striated muscle sarcomeres are highly ordered. Thick and thin filament length is consistent from one sarcomere to the next, and sarcomeres are aligned by their z-discs to give the muscle a striated appearance. In smooth muscle by contrast, thin filament length changes constantly, and there is no consistent ordering of the sarcomere-like thick and thin filament assemblies relative to one another.



The lower esophageal sphincter maintains basal tone. Dysfunctions in this smooth muscle result in **achalasia** (difficulty swallowing) and **gastroesophageal reflux disease (GERD)**. [Note: The role of smooth muscle dysfunction in disease is an area currently under intense investigation, and most of the pathways involved have yet to be delineated fully.]



# Smooth Muscle Excitation–Contraction Coupling

## 3.8 Question



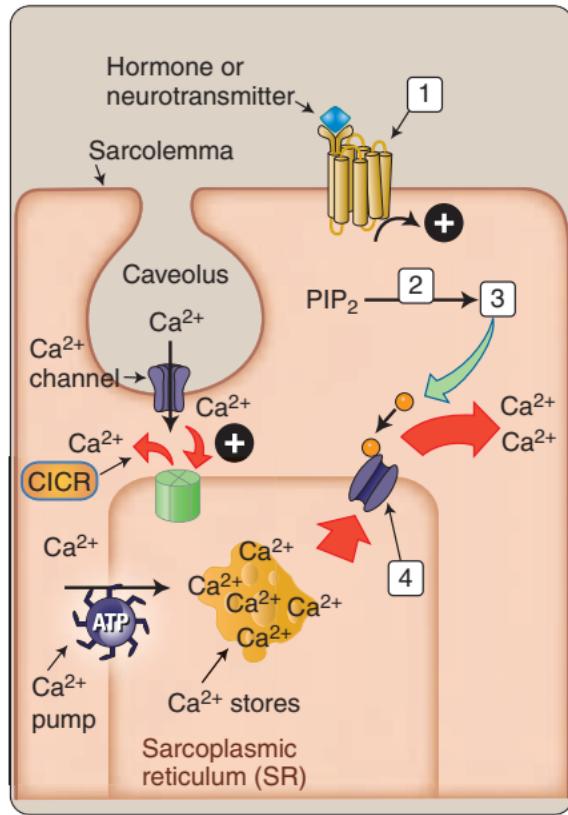
Identify the components of the  $\text{Ca}^{2+}$ -release pathway indicated by boxed numerals.



Why does ACh constrict most types of smooth muscle but relax vascular smooth muscle?



An ophthalmic examination often includes pupil dilation using atropine eye drops to better visualize the retina. How does atropine cause mydriasis?



### 3.8 Answer

## Smooth Muscle Excitation–Contraction Coupling



$\text{Ca}^{2+}$ -release pathway components:

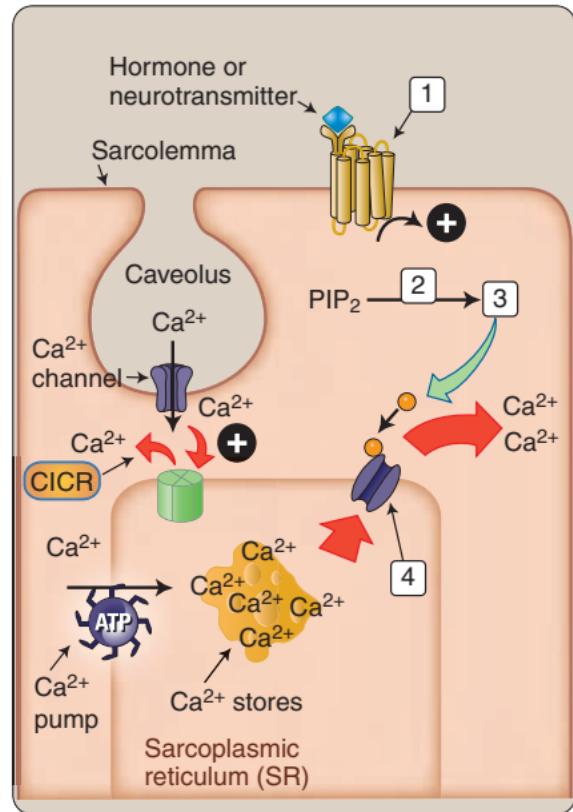
1. **GPCR**
2. **PLC**
3.  **$\text{IP}_3$**
4.  **$\text{IP}_3$ -gated  $\text{Ca}^{2+}$  channel**



ACh released from parasympathetic nerve terminals binds to a mAChR and stimulates intracellular  $\text{Ca}^{2+}$  release and contraction in most smooth muscle types. However, in the vasculature, ACh from nerve terminals acts as a paracrine to stimulate NO formation by the endothelial lining. NO reduces intracellular  $\text{Ca}^{2+}$  in the smooth muscle cells that make up the vessel wall, and they relax (see 4.24).



**Atropine** is an mAChR antagonist that blocks parasympathetic stimulation of iris sphincter muscles. These smooth muscles normally decrease pupil diameter when they contract. The pupil then dilates due to radial muscle contraction under the influence of tonic sympathetic activity (see 2.16).



# Smooth Muscle Contraction

3.9 Question



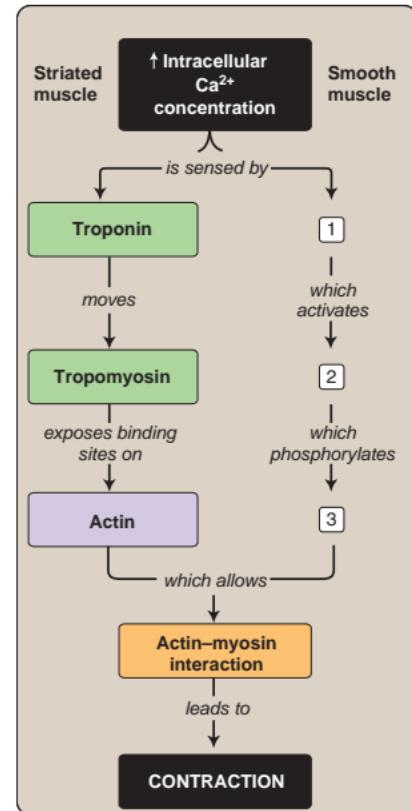
What are the molecular mediators of contraction in smooth muscle, as indicated by boxed numerals?



The pathway shown causes smooth muscle contraction, but how is contraction terminated?



Clinical trials of drugs that potentially could be used to treat vasospasm and angina have focused on pathways that regulate smooth muscle contraction. What are the two main regulatory pathways?



## 3.9 Answer

# Smooth Muscle Contraction



Smooth muscle contraction mediators:

1. **Calmodulin**
2. **MLCK**
3. **Myosin**

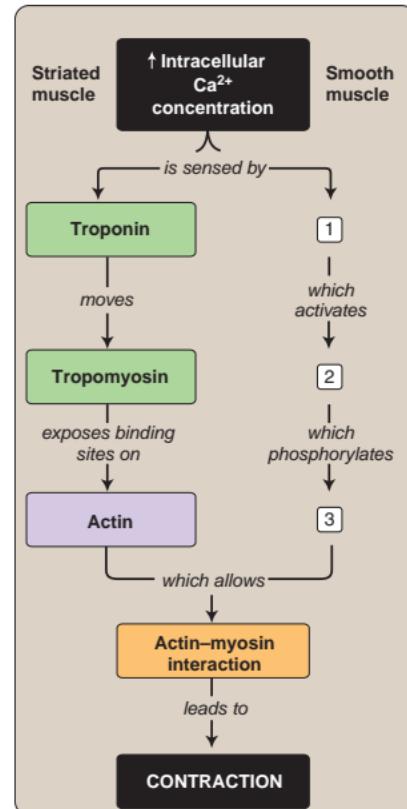


Smooth muscle contraction is terminated by ***myosin phosphatase*** when it dephosphorylates the 20-kDa myosin regulatory light chain (MLC<sub>20</sub>). Dephosphorylation inactivates myosin's intrinsic ATPase activity, and the muscle then relaxes. [Note: Smooth muscle tone reflects a balance between *MLCK* activity, which promotes contraction, and *myosin phosphatase*, which facilitates relaxation.]



Two principal pathways regulating smooth muscle contraction:

- **PLC**: PLC causes Ca<sup>2+</sup> release from intracellular stores through IP<sub>3</sub> production but also releases DAG, which activates PKC. PKC further potentiates contraction by inhibiting *myosin phosphatase*.
- **ROCK**: ROCK directly phosphorylates and inhibits *myosin phosphatase*, which promotes contraction.



# Bone Composition

## 3.10 Question



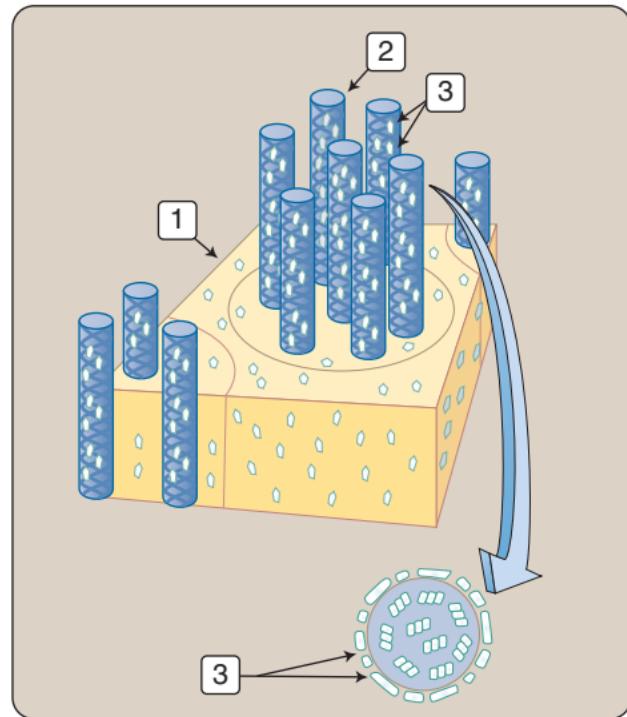
What are the three main bone components, as indicated by boxed numerals?



What are bone components' strengths and weaknesses? How do the components work together to give bone its unique characteristics?



\_\_\_\_\_ (OI), also known as **brittle bone disease**, results from \_\_\_\_\_ gene mutations.



## 3.10 Answer

# Bone Composition



Bone structural components:

1. **Ground substance**
2. **Collagen fibril**
3. **Hydroxyapatite crystals**



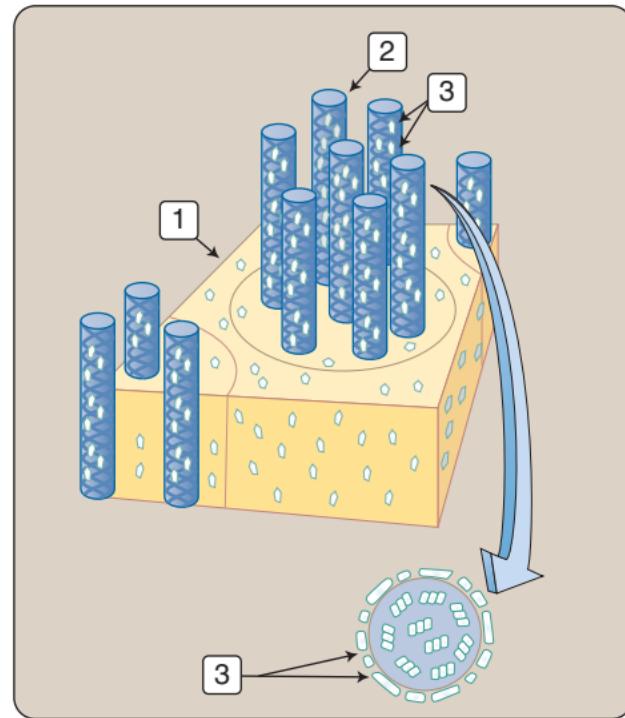
Bone component strengths and weaknesses:

- **Collagen**: little resistance to compression but flexible and has a high resistance to tensile and shear stress
- **Hydroxyapatite**: shears easily but high resistance to compression
- **Ground substance**: mineralized cementing material

Ground substance cements collagen and mineral together in a composite resembling reinforced concrete. Together, they create a material that can support heavy loads but is sufficiently flexible to torque and bend without fracturing.



**Osteogenesis imperfecta (OI)**, also known as **brittle bone disease**, results from collagen gene mutations. [Note: The most common form of OI results from mutations that prevent normal assembly of collagen monomers, which weakens collagen fibrils. Bones formed from such fibrils fracture easily as a result.]



# Bone Types

## 3.11 Question



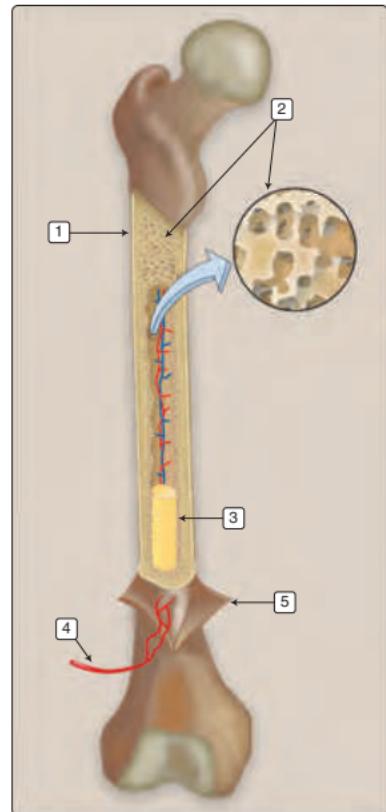
Identify the components of a long bone, as indicated by boxed numerals.



What are the two main types and functions of lamellar bone?



**Osteoporosis** affects both sexes in later years, so why are the clinical effects observed predominantly in women?





Long bone components:

1. **Cortical bone**
2. **Trabecular bone**
3. **Yellow marrow**
4. **Supply artery**
5. **Periosteum**



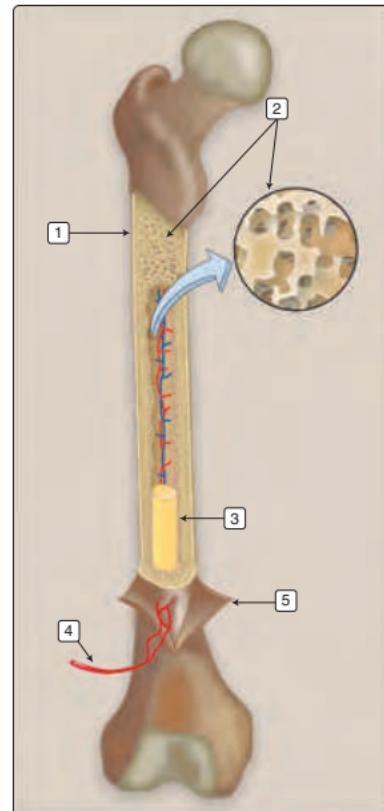
Lamellar bone comes in two forms:

- **Cortical (or compact) bone** is very dense and imparts strength. It is found at a bone's periphery.
- **Trabecular (or cancellous, spongy) bone** also provides mechanical support, but its porous structure creates a large surface area for rapid bone resorption or deposition. This yields a mineral bank that can be mobilized to optimize plasma  $\text{Ca}^{2+}$  and phosphate levels.



Although both men and women lose bone mass with age, men achieve a greater bone mass during their early years, so the effects of **osteoporosis** (i.e., increased incidence of fractures) do not manifest until later in life.

*A-plus:* Loss of bone mass is due to declining estrogen and androgen levels with age. These hormones promote bone deposition, so when levels drop, the normal balance between deposition and resorption tips in favor of bone loss.



# Bone Remodeling

## 3.12 Question



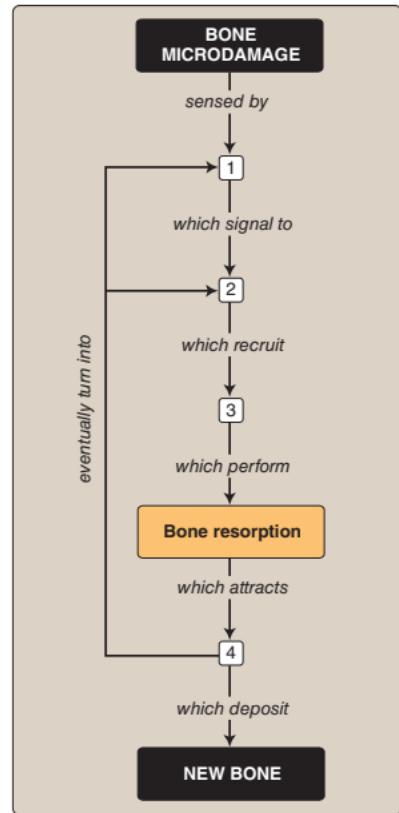
What are the cellular mediators of bone remodeling, as indicated by boxed numerals?



What are the principal causes of bone remodeling?



What are the clinical features of **Paget disease**?





Bone remodeling mediators:

1. **Osteocytes**
2. **Bone lining cells**
3. **Osteoclasts**
4. **Osteoblasts**

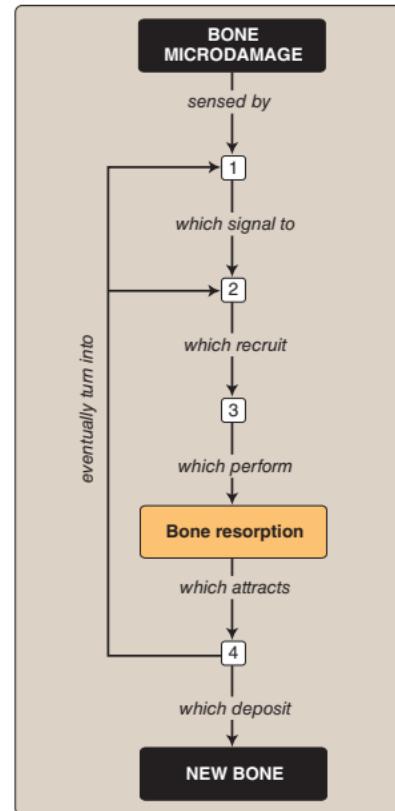


Bone remodeling occurs in response to:

- **Mechanical stress:** Stressing a bone stimulates remodeling to increase its mass and strength along the stress lines.
- **Microdamage:** Normal stresses and aging cause microfissures and microcracks.
- **Hormones:** Plasma  $\text{Ca}^{2+}$  and phosphate homeostasis involves constant bone remodeling. Remodeling is controlled by **parathyroid hormone**, **calcitonin**, and **vitamin D**.



Most patients with **Paget disease** remain asymptomatic, but some present with deformities, **arthritis**, and pain associated with nerve compression and bone remodeling. [Note: Paget disease is a bone remodeling disorder. Osteoclasts resorb and then osteoblasts rebuild bone at accelerated rates, leaving insufficient time for bone maturation.]



# Skin Layers

3.13 Question



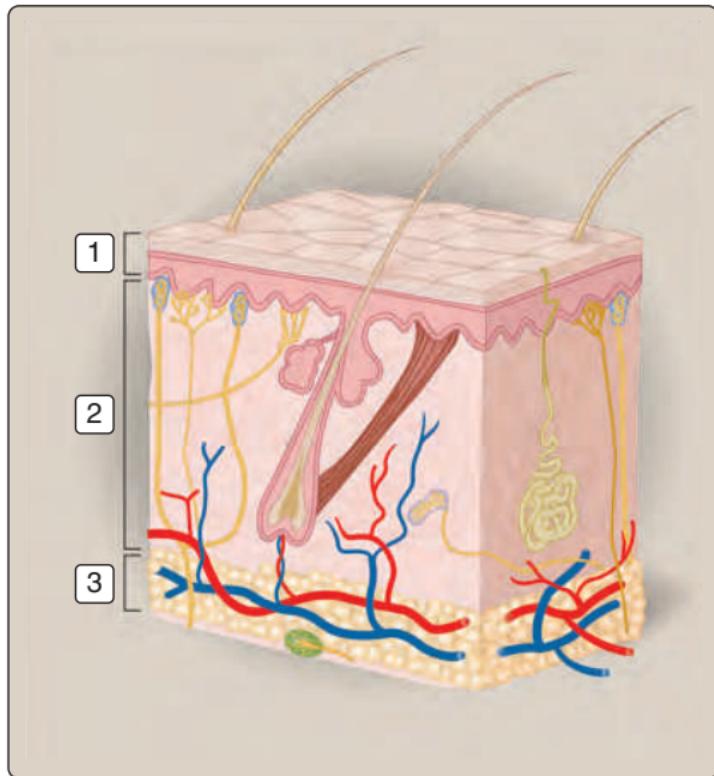
What are the three skin layers (indicated by boxed numerals) and their functions?



What are the principal skin barrier functions?



How are skin burn injuries classified?





Skin layers:

1. **Epidermis:** acts as a barrier between internal and external environments
2. **Dermis:** supports the epidermis structurally and gives skin elasticity
3. **Hypodermis:** houses the vasculature, nerves, and fat stores



Skin's barrier functions include:

- **Physical:** Skin resists mechanical abrasion and shields underlying tissue from chemicals and toxins.
- **Photoprotective:** Melanin absorbs UV radiation and helps prevent photodamage.
- **Antimicrobial:** Skin resists microbial invasion and provides backup (immune cells) if breached.
- **Water-resistive:** Skin repels water externally (lipid secretions) and reduces evaporative water loss from below.



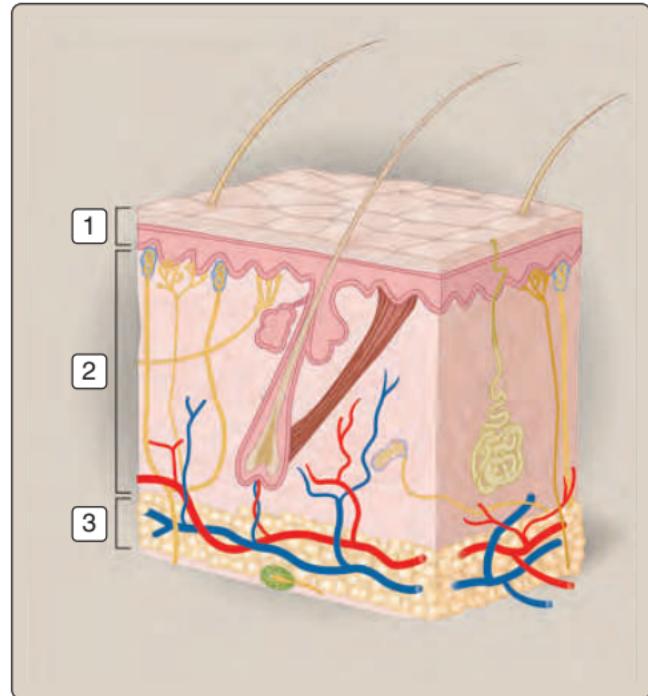
Burn injuries are classified according to depth of injury:

**Superficial (first degree):** epidermal damage only

**Partial thickness (second degree):** involves the epidermis and dermis

**Full thickness (third degree):** all three tissue layers

**Deep tissue (fourth degree):** involves the underlying muscle or bone



# Skin Appendages

3.14 Question



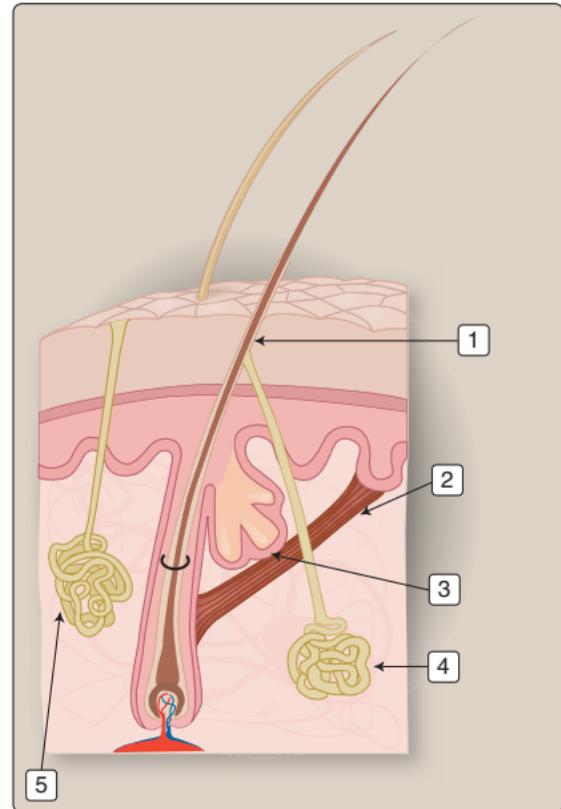
What skin appendages and associated structures are indicated by boxed numerals?



What is the origin of sebum, and what is its main function?



**Acne vulgaris** is a very common and embarrassing adolescent skin disorder. What is the pathophysiology underlying acne pimple formation?



### 3.14 Answer

## Skin Appendages



Skin structures/appendages:

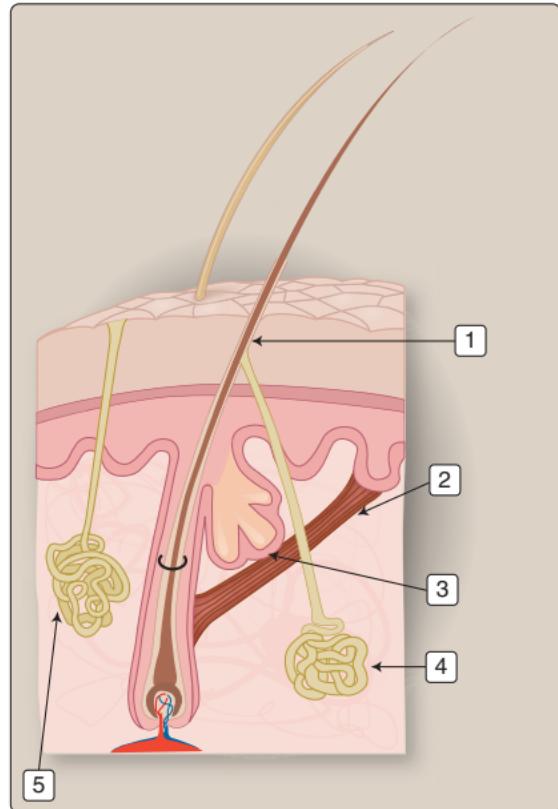
1. Hair
2. Arrector pili muscle (raises hair)
3. Sebaceous gland (secretes sebum)
4. Apocrine sweat gland (pheromonal?)
5. Eccrine sweat gland (cooling)



**Sebum** is a lipid-based secretion produced by **sebocytes**, which are located within **sebaceous glands**. Sebum is secreted onto the hair shaft and then flows onto the epidermal surface. It is believed to help skin retain water, and it also has antimicrobial actions.



Acne lesions occur when skin cells plug a hair follicle's opening, forming a **closed comedone**. Sebum continues to accumulate and provides a substrate that sustains proliferation of *Propionibacterium acnes*, a normal constituent of skin flora. The follicle typically ruptures and precipitates an inflammatory response that manifests as a skin pustule.



# Sweat Glands

3.15 Question



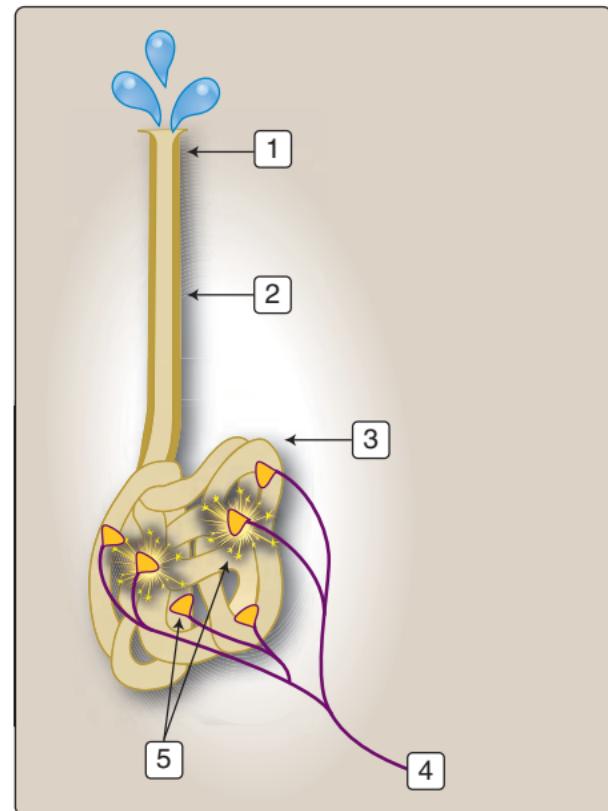
Identify the components and type of innervation (indicated by boxed numerals) in the eccrine sweat gland shown.



Review the ionic and cellular events involved in sweat formation by an eccrine sweat gland.



Why are sweat glands stimulated during shock, including during hypovolemic shock (e.g., hemorrhage)?





Eccrine sweat gland components:

1. **Acrosyringium** (pore opening)
2. **Duct**
3. **Secretory coil**
4. **Sympathetic nerve efferent**
5. **Cholinergic nerve terminals**

[Note: Not shown is a layer of mesangial cells that surround the coil.]

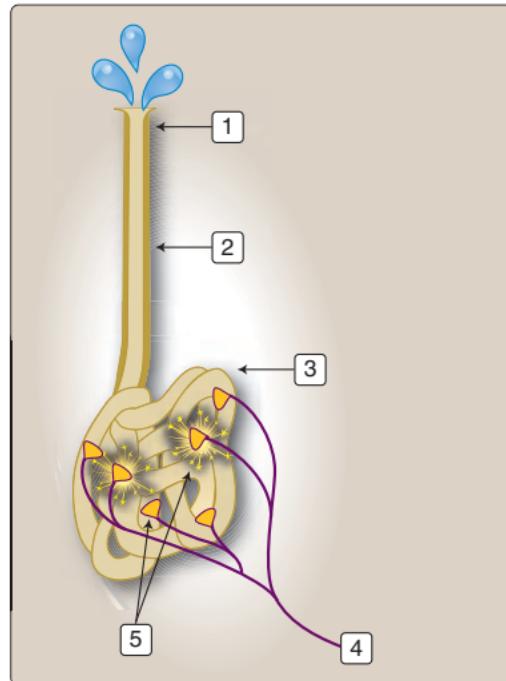


Steps in sweat formation:

- ACh is released from sympathetic terminals.
- ACh binding to clear cells activates the IP<sub>3</sub>-signaling pathway and raises intracellular Ca<sup>2+</sup>.
- Ca<sup>2+</sup> stimulation of the Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter raises intracellular Cl<sup>-</sup>.
- Cl<sup>-</sup> is secreted into the duct via apical Cl<sup>-</sup> channels.
- Na<sup>+</sup> follows Cl<sup>-</sup> via gap junctions.
- Water follows Cl<sup>-</sup> and Na<sup>+</sup> via aquaporins.
- Ions are largely reabsorbed by ductal cells.
- Mesangial cells contract and brace the coil, causing sweat to be forced under pressure onto the skin surface.



Sweat formation is controlled by the SNS, so when the SNS activates to help sustain arterial pressure during shock, sweat glands are invariably activated also (the SNS is nonselective in what it activates). Sweat is formed from blood, however, and cutaneous blood flow is reduced to near zero during intense SNS activity. At most, the skin becomes clammy to the touch.



# Cutaneous Sensory Receptors

3.16 Question



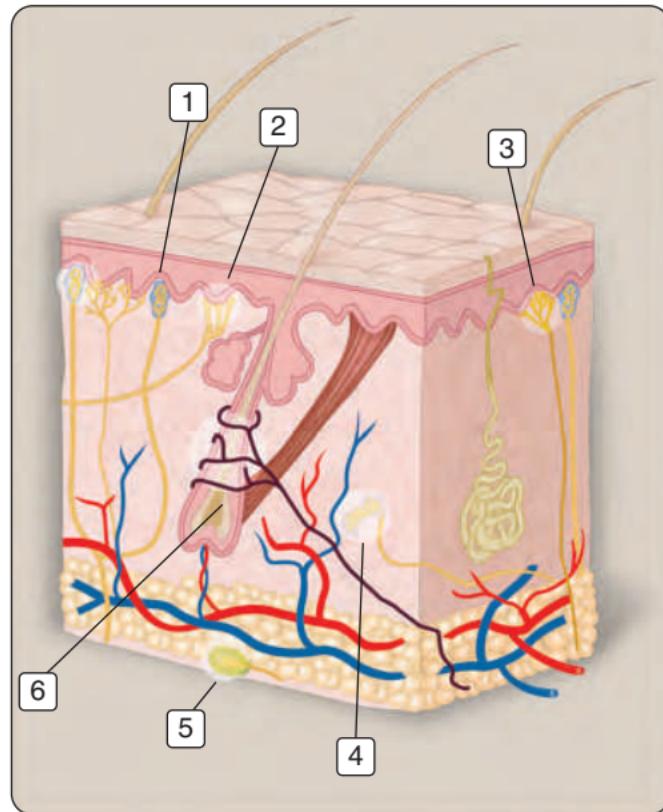
What are the six types of skin sensory receptors (indicated by boxed numerals), and to what type of stimuli are they attuned?



What is meant by "first pain" and "second pain"?



Lidocaine is commonly used topically to relieve skin itching and pain and as a local anesthetic prior to dental surgery. What is its mode of action?





Cutaneous receptors:

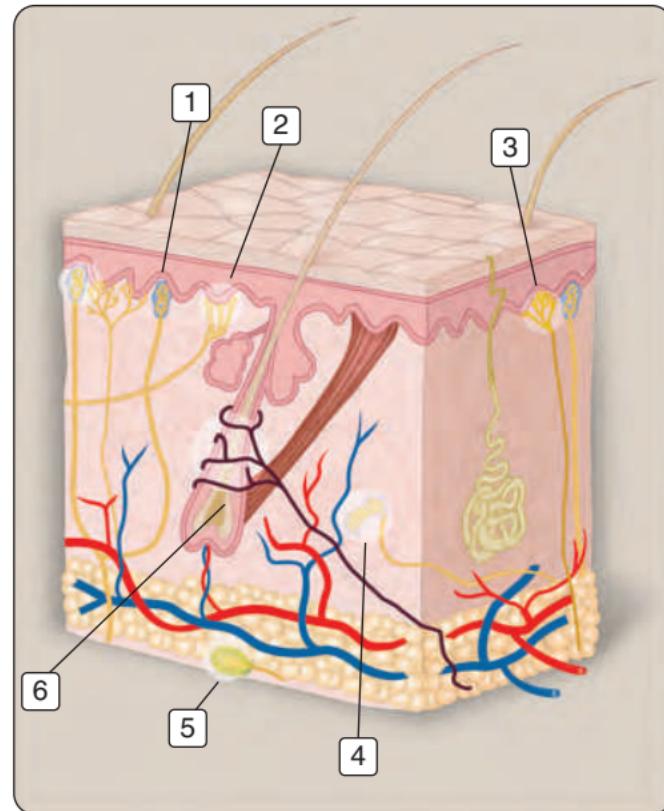
1. **Meissner corpuscle** (touch)
2. **Merkel disk** (light pressure)
3. **Free nerve ending** (touch, pain, itch, temperature)
4. **Ruffini ending** (stretch)
5. **Pacini corpuscle** (vibrations)
6. **Hair sensory nerve** (hair displacement)



**“First pain”** is a sharp and intense pricking sensation caused by **nociceptors** relaying sensory information to the CNS by fast **A<sub>δ</sub> nerve fibers**. **“Second pain”** is sensory information received by the CNS via slower **C fibers** and is perceived as a prolonged and dull throbbing sensation.



**Lidocaine** and related drugs block the voltage-gated Na<sup>+</sup> channel that mediates a nerve AP, thereby preventing pain signals from reaching the CNS. [Note: Lidocaine is often used in conjunction with epinephrine to promote local vasoconstriction. The latter reduces drug washout and prolongs anesthesia time.]





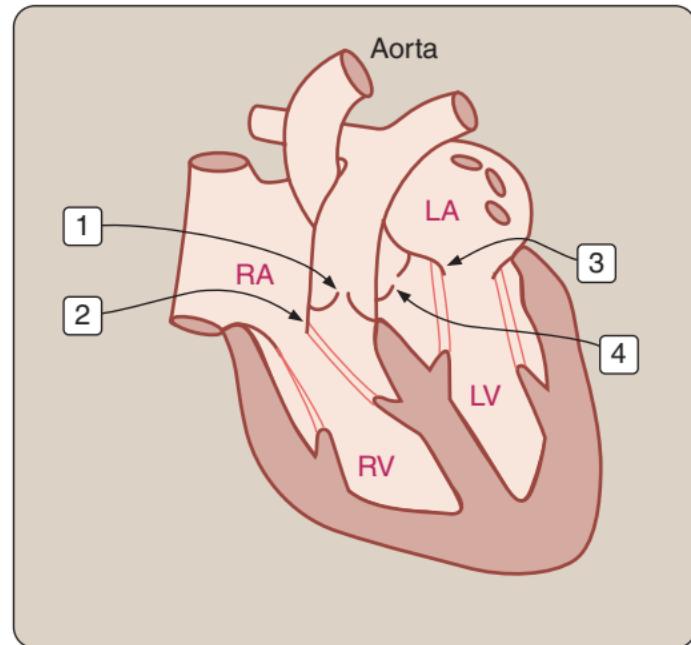
Identify the four heart valves, as indicated by boxed numerals.



What sounds are associated with normal valve function, and which valves are responsible?



A \_\_\_\_\_ valve impairs forward blood flow, whereas an \_\_\_\_\_ valve allows retrograde flow.



LA = left atrium; LV = left ventricle; RA = right atrium;  
RV = right ventricle.



Four heart valves:

1. **Pulmonary valve**
2. **Tricuspid valve**
3. **Mitral valve**
4. **Aortic valve**

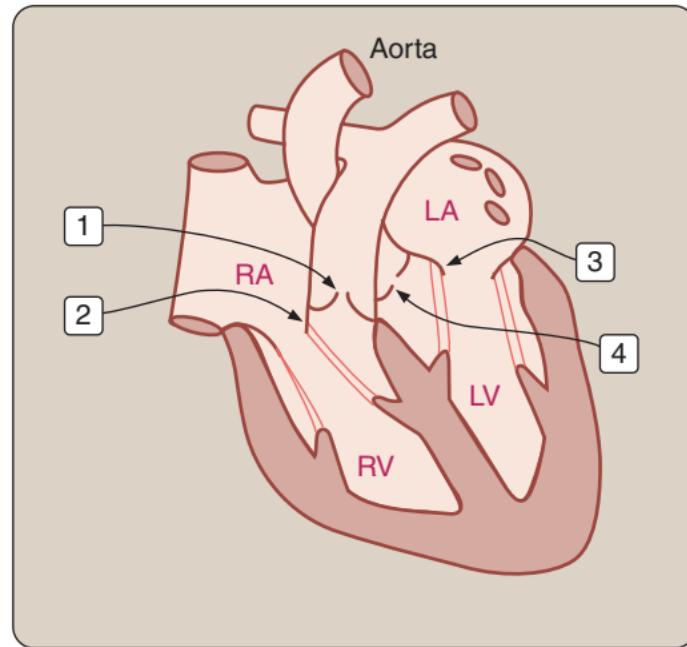


The first and second heart sounds (**S<sub>1</sub>** and **S<sub>2</sub>**) are associated with normal valve function. **S<sub>1</sub>** occurs upon tricuspid and mitral valve closure. **S<sub>2</sub>** coincides with pulmonary and aortic valve closure. [Note: **S<sub>2</sub>** may split into two distinct valve sounds (**A<sub>2</sub>** and **P<sub>2</sub>**) with inspiration (see 4.11).]



A **stenotic** valve impairs forward blood flow, whereas an **incompetent** (or **regurgitant**) valve allows retrograde flow.

**A-plus:** Aortic valve calcification and stenosis is common with age. Mitral valve incompetence (or **insufficiency**) is a common congenital heart valve defect.



LA = left atrium; LV = left ventricle; RA = right atrium;  
RV = right ventricle.

# Pressures in the Cardiovascular System

4.2 Question



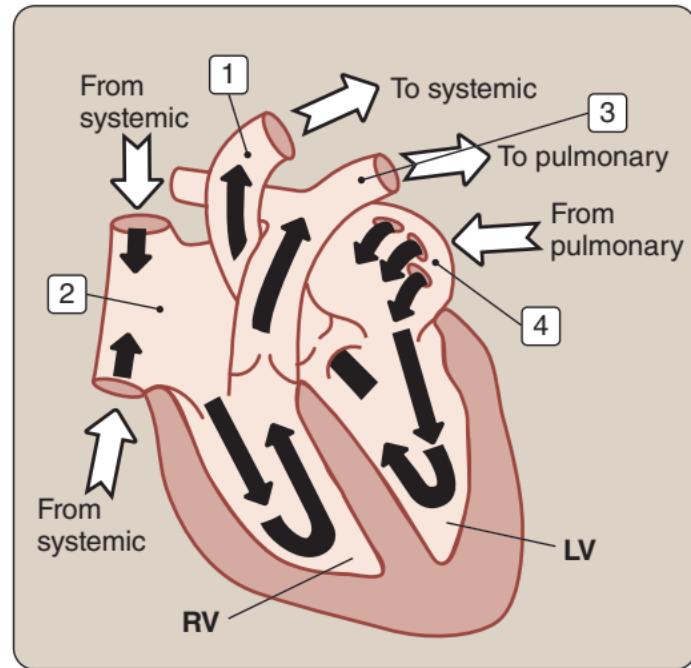
Give approximate values for blood pressure in the regions indicated by boxed numerals.



What would be the immediate effects of increasing pressure in areas [1] and [2] on cardiac output (CO)?



What are the consequences of **atrial septal defect (ASD)** (a common congenital heart abnormality) for the pulmonary circulation?



LV = left ventricle; RV = right ventricle.



Approximate blood pressure values:

1. Mean systemic arterial pressure (MAP) = 70–105 mm Hg
2. Right atrial pressure (RAP) = 4–6 mm Hg
3. Mean pulmonary arterial pressure = 10–20 mm Hg
4. Left atrial pressure = 4–12 mm Hg

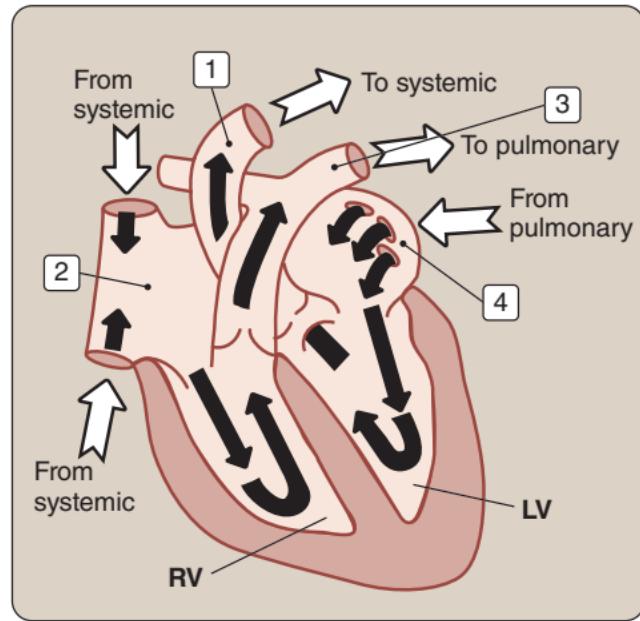


Immediate effects of increasing MAP and RAP:

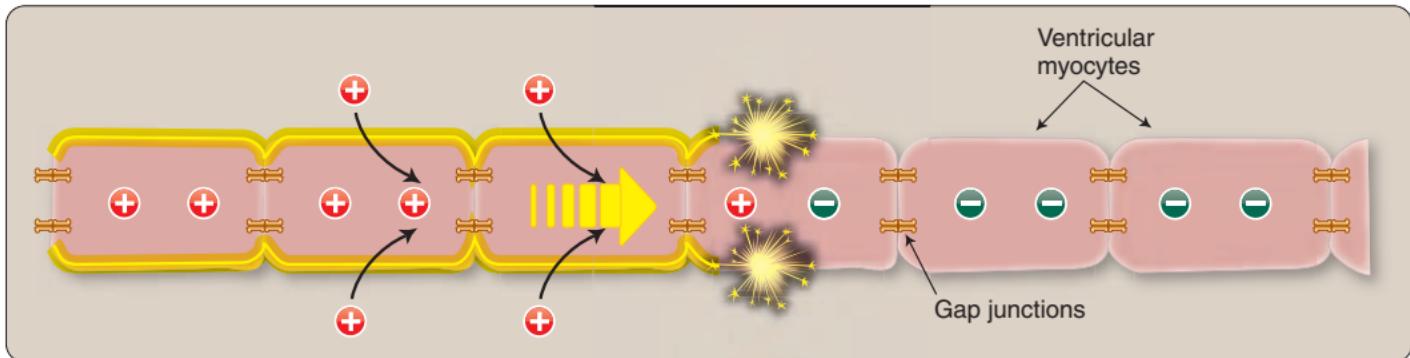
1. Increasing MAP decreases CO because it increases left ventricular (LV) afterload.
2. Increasing RAP increases LV preload and would increase CO.



**ASD** creates a shunt between the two sides of the heart. Oxygenated blood flows from the left atrium to the right, which is at slightly lower pressure. The shunt thereby creates a volume load on the right ventricle and increases pulmonary flow. The pulmonary vasculature adapts to the volume load through capillary recruitment and angiogenesis. [Note: Unless the shunt is severe (right:left volume flow >8:1), patients usually remain asymptomatic until the sixth decade.]



LV = left ventricle; RV = right ventricle.



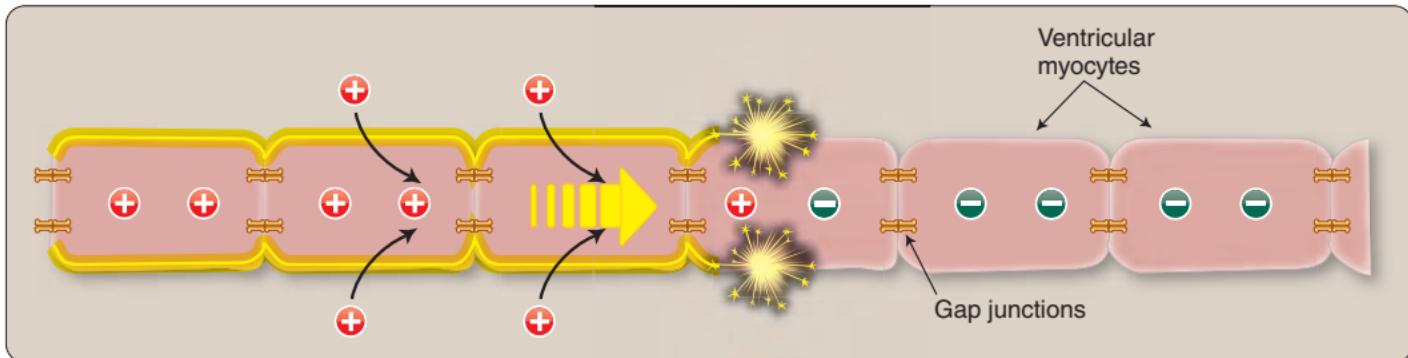
What is the function of gap junctions in signal propagation through the myocardium?



What are the advantages and disadvantages to using gap junctions in signal propagation?



A heartbeat originating in a region of the heart other than the \_\_\_ node is known as an \_\_\_\_\_.



Gap junctions' function is to couple adjacent myocytes electrically, which allows an AP to propagate from its point of origin throughout the entire myocardium. [Note: The cytoplasmic bridges between adjacent myocytes created by gap junctions turn the entire myocardium into a functional syncytium.]



An advantage of using gap junctions is that by allowing signals from the SA node to spread throughout the myocardium, they obviate the need for a nerve plexus to coordinate excitation. However, their disadvantage is in allowing APs generated outside the SA node to propagate and pace the heart.



A heartbeat originating in a region of the heart other than the **SA** node is known as an **ectopic pacemaker**.

# Ventricular Excitation

4.4 Question



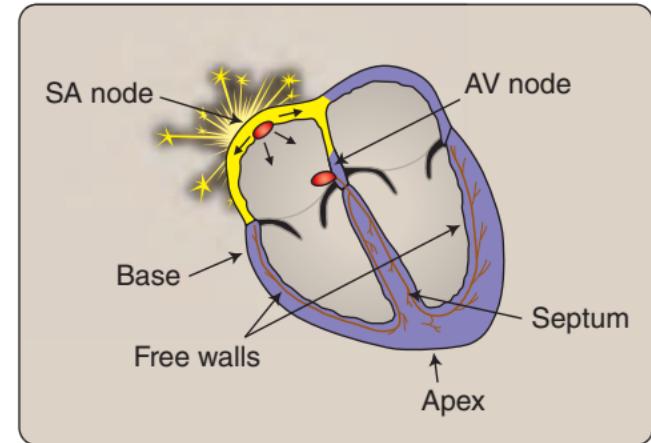
How does ventricular excitation and contraction proceed once a wave of excitation emerges from the AV node?



What are Purkinje fibers, and how are they optimized for high-velocity signaling?



What is **Wolff-Parkinson-White (WPW) syndrome**, and how does the ventricular excitation sequence differ in patients with WPW compared with normal individuals?





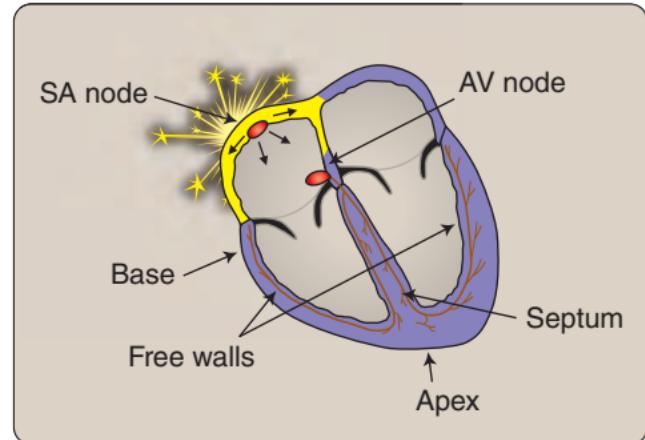
Ventricular excitation proceeds from **septum → apex → free walls → base**. This excitation sequence yields a similarly sequenced ventricular contraction that forces blood up toward the valve outlets (i.e., the aorta and pulmonary artery).



**Purkinje fibers** relay an excitation signal from the AV node to the contractile myocytes. Purkinje fibers conduct signals at 2–4 m/s, compared with ~1 m/s for ventricular myocytes. Transmission speed is enhanced through increased **Na<sup>+</sup>-channel density**, and increased **fiber diameter**. [Note: Purkinje cells also express a funny current, which allows them to function as backup pacemakers.]



**WPW syndrome** is caused by a tract of excitable tissue between atria and ventricles (the **bundle of Kent**). This tract allows electrical signals from the atria to bypass the AV node and excite the ventricles prematurely, which may lead to periods of supraventricular tachycardia and syncope. [Note: Premature ventricular excitation can yield a delta wave on an ECG.]





# Ion Currents in Cardiac Myocytes

4.5 Question



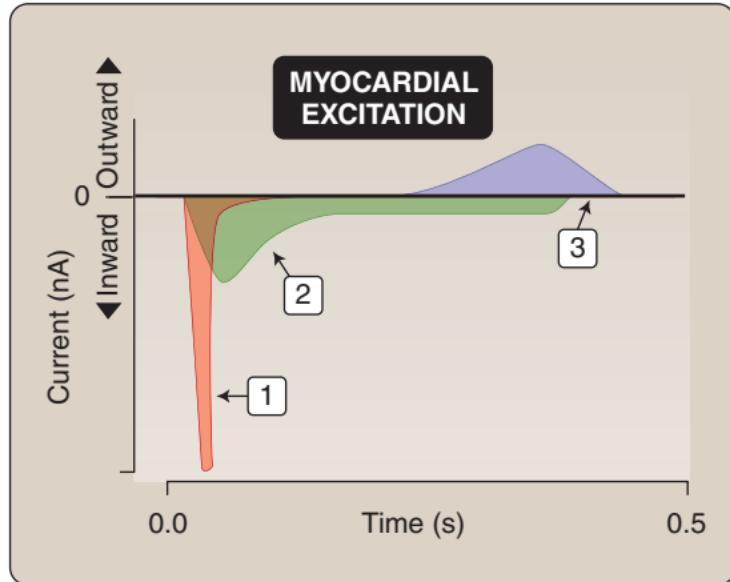
Identify the three principal ion currents active during ventricular excitation, as indicated by boxed numerals.



What are the two main functions of current [2]?



What is **long QT syndrome (LQTS)**, and what is the most common cause of the congenital form?





Three principal ion currents:

1. **Voltage-activated  $\text{Na}^+$  current ( $I_{\text{Na}}$ )**: activates rapidly and then inactivates
2. **Voltage-activated  $\text{Ca}^{2+}$  current ( $I_{\text{Ca}}$ )**: slower to activate
3. **Delayed  $\text{K}^+$  current ( $I_{\text{K}}$ )**: also voltage-activated



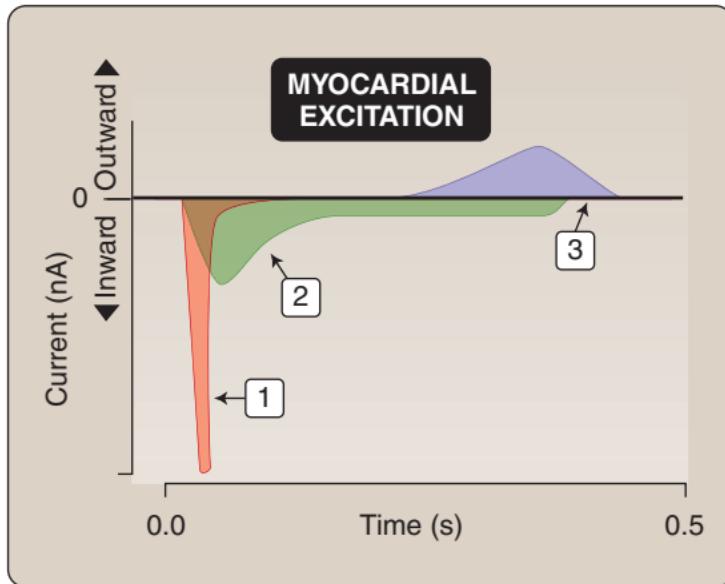
The functions of  $I_{\text{Ca}}$  include:

- Facilitates a rise in intracellular  $\text{Ca}^{2+}$  concentration that initiates contraction
- Prolongs the AP to ensure that intracellular  $\text{Ca}^{2+}$  rises sufficiently to support myocardial contraction before excitation terminates



**LQTS** presents as an increase in the time between the Q wave (ventricular excitation) and T wave (recovery) on an ECG. The most common congenital form is due to mutations in the  $\text{K}^+$ -channel genes underlying  $I_{\text{K}}$ , the current that helps membrane repolarization following excitation.

*A-plus:* LQTS increases the risk of **torsades de pointes**, a form of ventricular tachycardia that can result in cardiac arrest.





What are the principal ion currents or channel events underlying the five numbered phases (shown) of the fast cardiac AP?

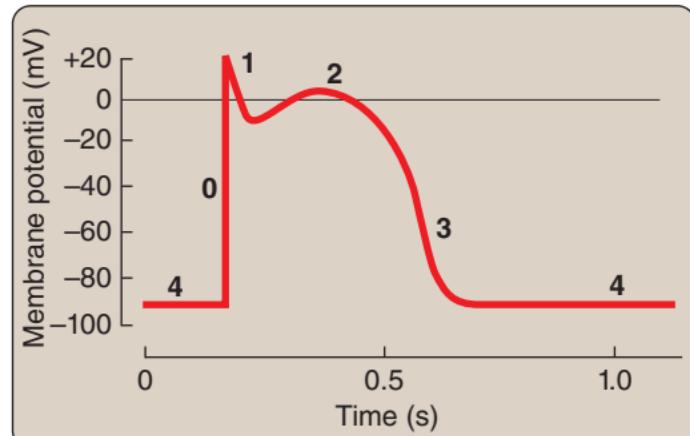


How would inactivation of the channel responsible for phase 0 affect the AP?

How would prolongation of phase 2 affect myocardial performance?



Which phase corresponds most closely to an ECG's ST segment?



## 4.6 Answer

### Fast Cardiac AP



Fast cardiac AP phases:

- 0:  $\text{Na}^+$  influx ( $I_{\text{Na}}$ ) occurs.
- 1:  $\text{Na}^+$  channels inactivate, and a transient outward  $\text{K}^+$  current ( $I_{\text{to}}$ ) activates.
- 2:  $\text{Ca}^{2+}$  influx ( $I_{\text{Ca}}$ ) occurs.
- 3:  $\text{Ca}^{2+}$  channels inactivate, and a delayed  $\text{K}^+$  current ( $I_{\text{K}}$ ) activates.
- 4:  $\text{Na}^+$  and  $\text{Ca}^{2+}$  channels recover from inactivation, and ion pumps renormalize transmembrane ion gradients.

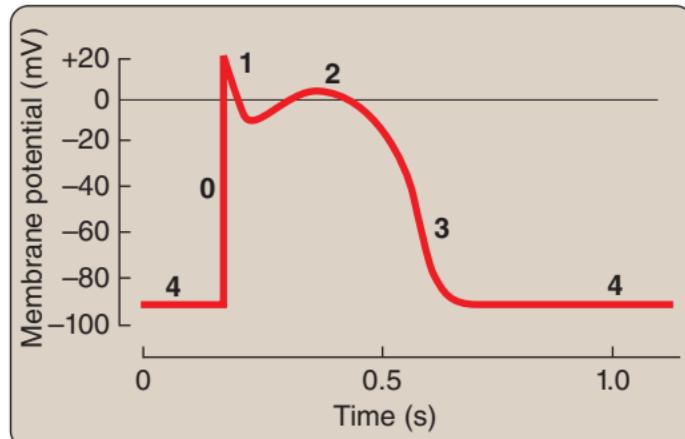


$\text{Na}^+$ -channel inactivation would slow AP conduction. The  $\text{Na}^+$  channel mediates the rapid upstroke of a fast cardiac AP, which, in turn, determines AP conduction velocity. Myocytes lacking functional  $\text{Na}^+$  channels express a slow AP, the upstroke of which is mediated by the  $\text{Ca}^{2+}$  channel. Slow APs are normally seen only in nodal cells.

Phase 2 prolongation would enhance myocardial inotropy. Phase 2 correlates with  $\text{Ca}^{2+}$  influx, so prolonging this phase increases intracellular  $\text{Ca}^{2+}$  availability, crossbridge cycling, and contractility.



The ECG's ST segment correlates with AP phase 2.



# Slow Cardiac AP

## 4.7 Question



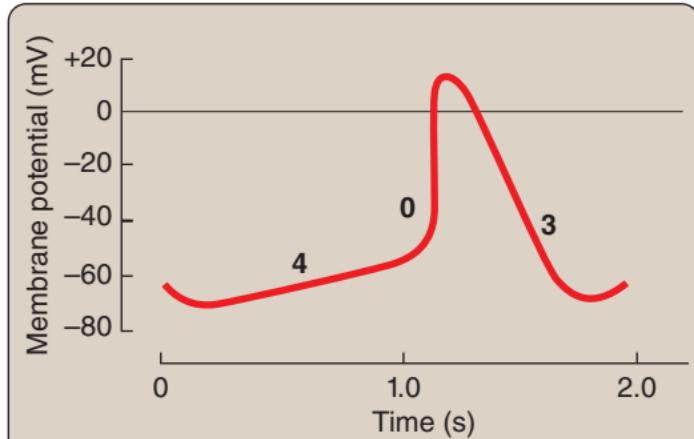
What are the principal ion currents or channel events underlying the three numbered phases (shown) of the slow cardiac AP?



What channel type is responsible for the rising phase 4, and why is the ionic event it mediates known as a “funny current”?



The hearts of patients with **AV block** or other cardiac conduction system interruptions may show escape rhythms. Where do escape rhythms originate typically?



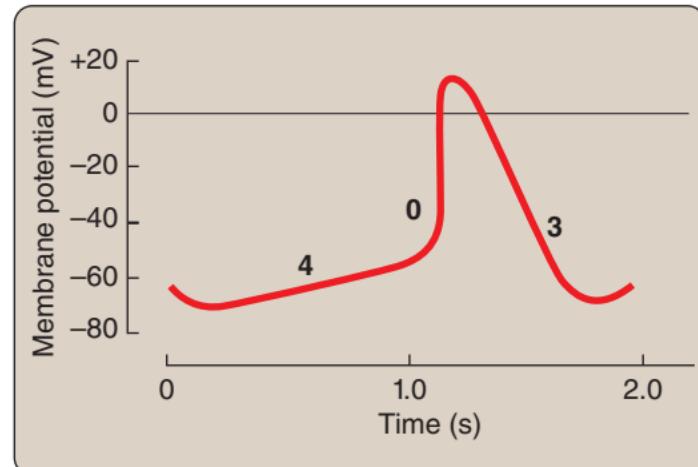


Slow AP phases:

- 0:  $\text{Ca}^{2+}$  influx ( $I_{\text{Ca}}$ ) occurs.
- 3:  $\text{Ca}^{2+}$  channels inactivate, and a delayed  $\text{K}^+$  current ( $I_K$ ) activates.
- 4:  $\text{Ca}^{2+}$  channels recover from inactivation, and ion pumps renormalize transmembrane ion gradients. A pacemaker current (the funny current or  $I_f$ ) activates, and the membrane depolarizes toward threshold.  
[Note: The channel responsible for  $I_f$  mediates simultaneous  $\text{Na}^+$  influx and  $\text{K}^+$  efflux.  $\text{Na}^+$  influx dominates the exchange, causing membrane depolarization.]



Slow phase 4 depolarization is mediated by a **hyperpolarization-activated, cyclic nucleotide-dependent, nonspecific ion channel (HCN)**. The “funny current” is so described because it activates following membrane repolarization rather than upon depolarization.



*A-plus:* HCN is also regulated by cAMP, thereby providing a way for the ANS to regulate heart rate through stimulation or inhibition of AC activity.



Escape rhythms typically originate from the **AV node** or **Purkinje system**. Nodal cells and Purkinje cells both express  $I_f$  and have pacemaker capability. AV nodal cells have a higher intrinsic rate than Purkinje cells (~40 beats/min, compared with ~20 beats/min, respectively), but either cell type can generate escape rhythms when the sinus node fails or normal conduction is blocked.

# Refractory Periods

4.8 Question



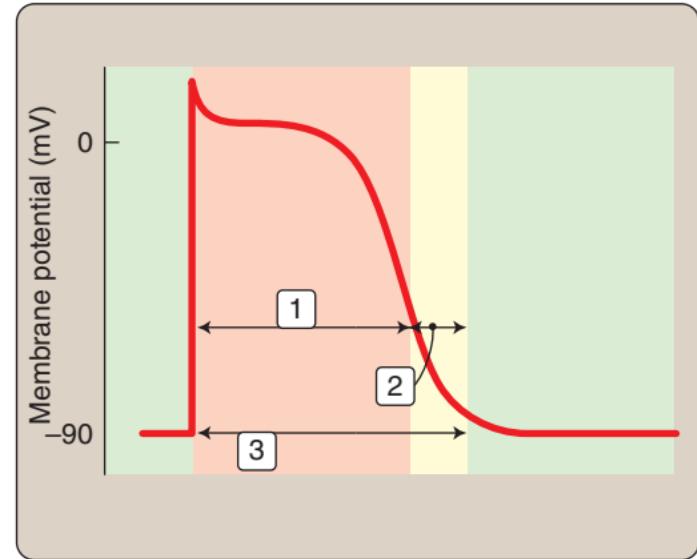
What three refractory periods are indicated by boxed numerals, and what do they represent in terms of membrane excitability?



Refractory periods are common to both neurons and myocytes. What is their function?



**Short QT syndrome** is associated with a short ventricular \_\_\_\_\_ that predisposes patients to ventricular \_\_\_\_\_ and sudden cardiac death.



## 4.8 Answer

# Refractory Periods



Three refractory periods (RPs):

1. **Absolute:** APs cannot be initiated.
2. **Relative:** APs can be initiated but only by suprannormal stimuli.
3. **Effective (ERP):** APs cannot be initiated under physiologic conditions.

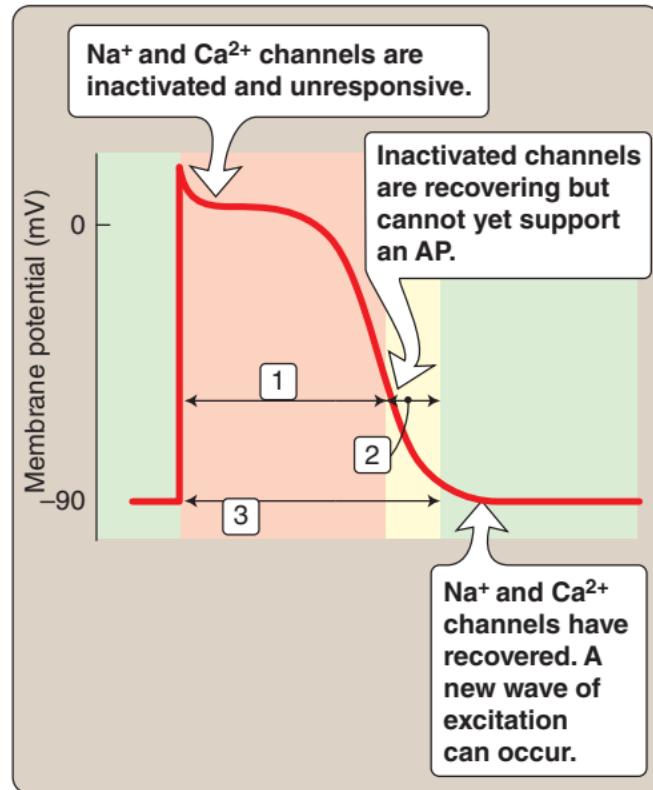


RPs create timeouts between periods of excitation. In neurons, this prevents APs from boomeranging back and forth along an axon. In cardiac muscle, RPs also prevent **tetany** and loss of pump function. [Note: RPs correspond to time periods during which ion channels inactivate and then slowly recover from inactivation.]



**Short QT syndrome** is associated with a short ventricular **action potential** that predisposes patients to ventricular **tachycardia** and sudden cardiac death.

**A-plus:** Short QT syndrome is an ion channelopathy that truncates the AP and decreases the QT interval from a normal 300–430 ms to as low as 220 ms. Reducing AP duration also reduces the ERP, which sets up the potential for the heart to be reexcited by **ectopic foci** or **reentrant circuits**, resulting in periods of tachycardia.





# Electrocardiogram

4.9 Question



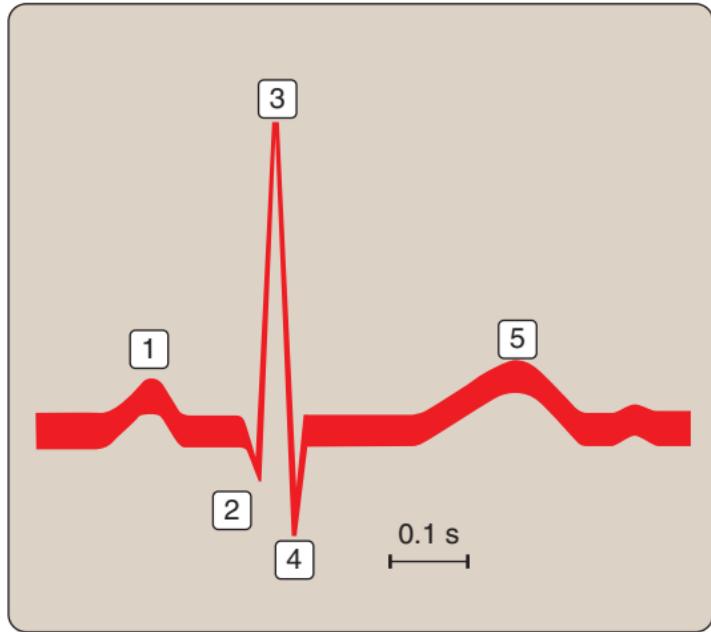
Name the ECG waves (indicated by boxed numerals) and their correlating cardiac events.



What conditions might increase the height of wave [1]?



Acute **myocardial infarction (MI)** may manifest as \_\_\_\_\_ on an ECG. This is caused by an \_\_\_\_\_ that shifts the isoelectric line.





Five ECG waves and corresponding cardiac events:

1. **P wave**: atrial excitation
2. **Q wave**: intraventricular septal excitation
3. **R wave**: excitation of ventricular free walls
4. **S wave**: ventricular base excitation
5. **T wave**: myocardial repolarization



ECG wave height reflects the mass of underlying tissue that produced it. An increase in P-wave height suggests atrial enlargement, perhaps because the ventricle requires additional preload (e.g., due to **hypertension**), or preloading is impaired (e.g., **AV valve stenosis** or **ventricular wall stiffening**).



Acute myocardial infarction may manifest as **ST-segment elevation** on an ECG. This is caused by an **injury current** that shifts the isoelectric line.

**A-plus:** An injury current flows between healthy and ischemic myocardium, even at rest. The isoelectric line, which normally rests at 0 mV, is displaced as a result. The current disappears when the myocardium is fully depolarized (i.e., during the ST segment) at which point the offset between true zero and the isoelectric line becomes apparent, manifesting as ST-segment elevation.





What are the names and origins of the venous pressure waves indicated by boxed numerals?



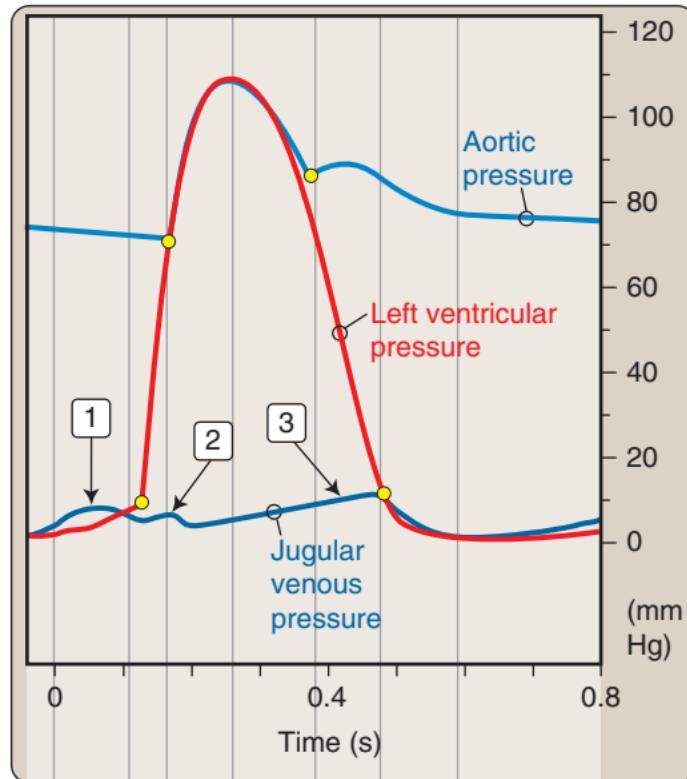
What is the primary determinant of right atrial pressure (RAP)?



Why does blood not flow backward into the veins during atrial systole?



Why are patients with **atrial fibrillation (AF)** anticoagulated in addition to being treated for the rhythm disturbance?





Three venous pressure waves and their origins:

1. **a wave**: atrial systole
2. **c wave**: ventricular contraction
3. **v wave**: damming of venous blood within the atria during ventricular systole

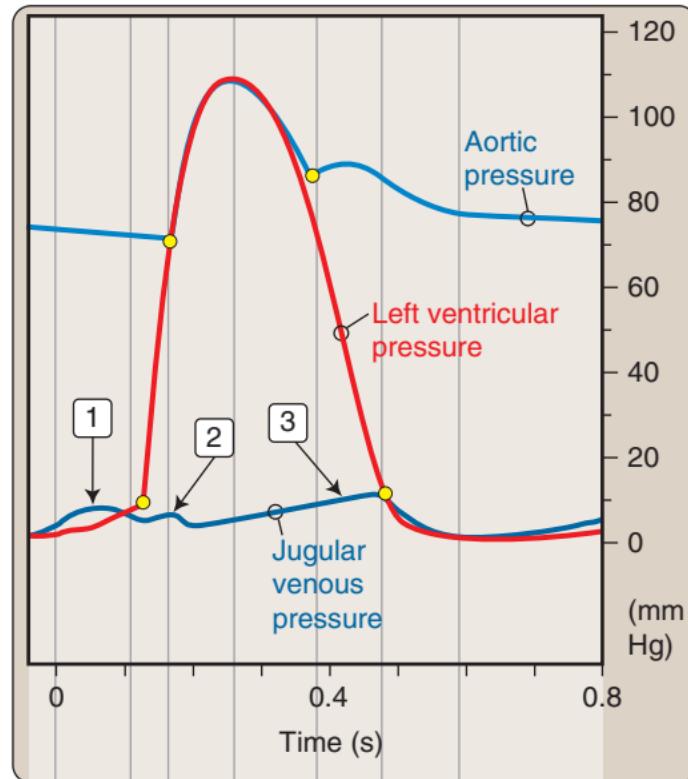


RAP is determined by **central venous pressure**, which, in turn, is determined by venous compliance and filling volume.

Retrograde flow during atrial systole is minimal because the large volume of blood contained within the venous compartment has high inertia.



AF prevents coordinated atrial contraction and emptying. This allows blood to pool and stagnate within the two atria (e.g., behind the AV valves), which then leads to thrombus formation. When left atrial thrombi embolize, they enter the systemic circulation and place the patient at grave risk of stroke. Anticoagulation therapy lessens this risk.





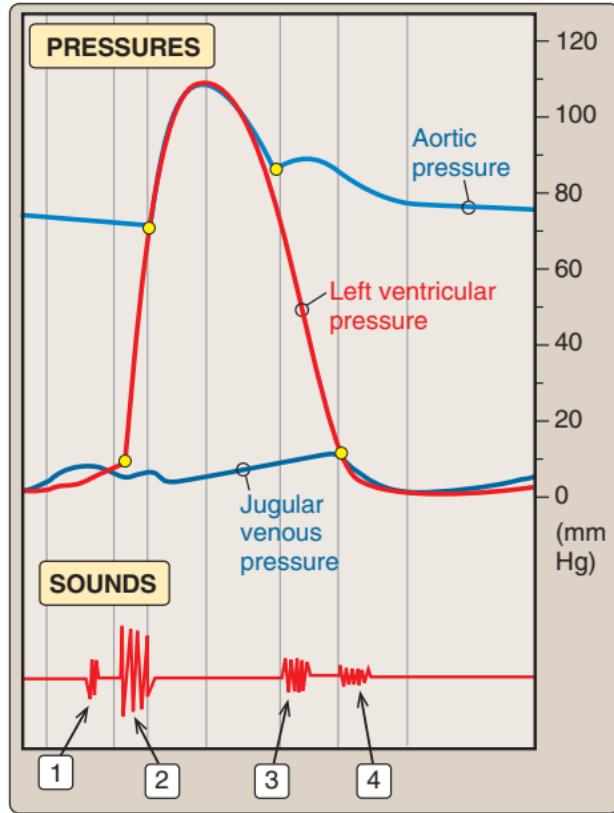
What are the names and origins of the four heart sounds indicated by boxed numerals?



Which heart sound often splits during inspiration? Why?



Although aortic pressure (AoP) and left ventricular pressure (LVP) normally track closely during systole, why might systolic LVP exceed AoP by >100 mm Hg in patients with **aortic valve (AoV) stenosis**?





Heart sounds and their origins:

1. **S<sub>4</sub>** = atrial systole (pathologic)
2. **S<sub>1</sub>** = mitral and tricuspid valve closure
3. **S<sub>2</sub>** = aortic and pulmonary valve closure
4. **S<sub>3</sub>** = ventricular filling (in children and healthy thin adults, otherwise pathologic)

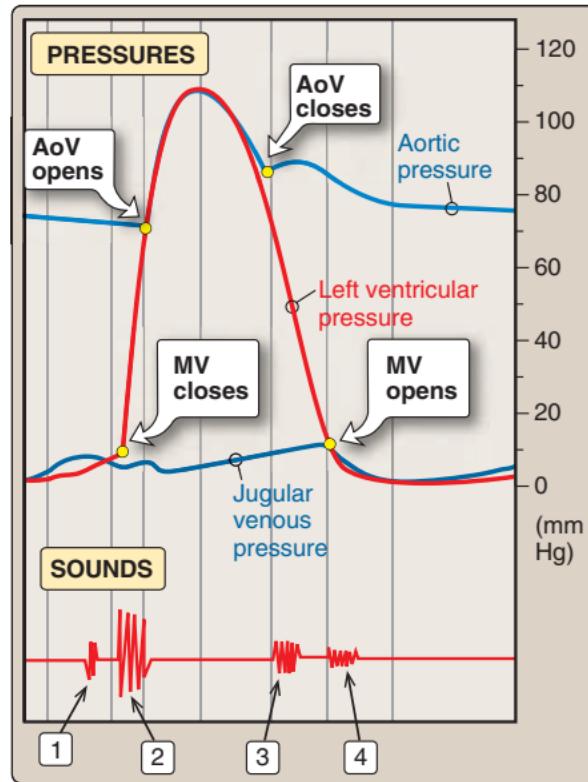


**S<sub>2</sub>** may split into separate aortic ( $A_2$ ) and pulmonary ( $P_2$ ) valve components during inspiration. Intrathoracic pressure falls during inspiration, enhancing the pressure gradient driving blood flow from the venous system to the right heart. The right ventricle preloads to a greater extent than the left as a result, and the added volume takes longer to eject, thus delaying  $P_2$ .



**AoV stenosis** reduces the valve orifice and impairs ventricular ejection. LVP necessarily rises in order to maintain a normal stroke volume and AoP. Severe stenosis can reduce orifice surface area to <25% of normal and lead to >100-mm Hg systolic pressure differences across the valve.

**A-plus:** Patients with AoV stenosis may also present with a **systolic ejection murmur** associated with high-velocity flow through the reduced valve orifice and **LV hypertrophy** in response to the chronic afterload increase.



MV = mitral valve.

# Cardiac Output Determinants

4.12 Question



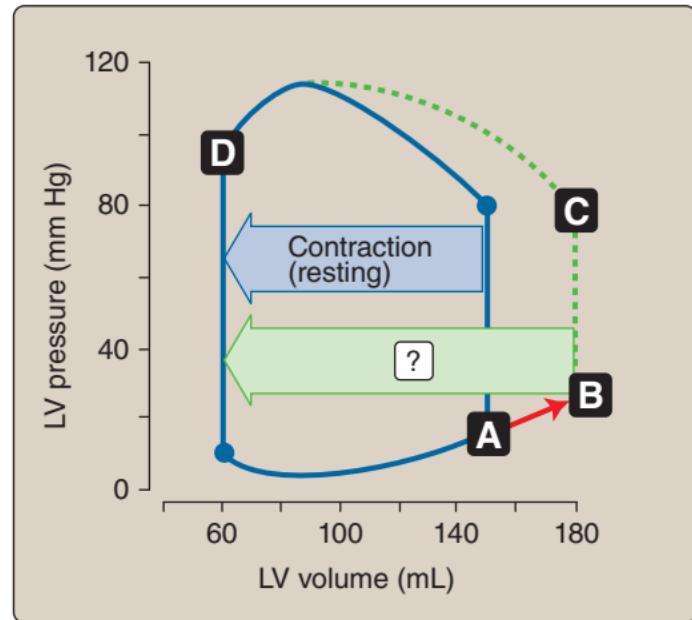
What is the mechanism responsible for increasing left ventricular (LV) stroke volume (SV), as indicated by the dashed green line and the shift from [A] to [B]?



Cardiac output (CO) is a product of heart rate (HR) and SV ( $CO = HR \times SV$ ). SV is determined by \_\_\_\_\_, \_\_\_\_\_, and myocardial \_\_\_\_\_ state.



Patients with **cardiac tamponade** typically present with dyspnea and chest pain. How does tamponade impair cardiac function?





The shift from point A to B occurs through increased LV preloading. Preloading increases SV through the Frank-Starling mechanism. [Note: Increasing end-diastolic volume stretches the myocardium and causes length-dependent activation of the sarcomere.]

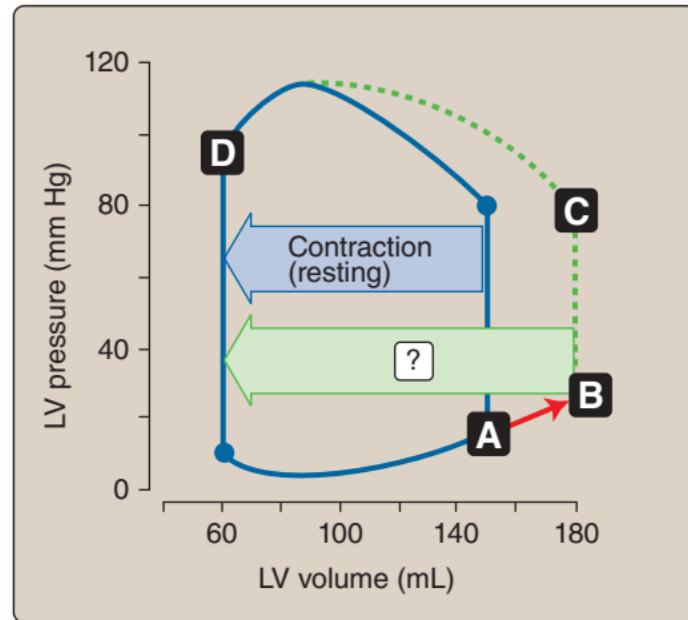


CO is a product of HR and SV ( $CO = HR \times SV$ ). SV is determined by **preload**, **afterload**, and myocardial **inotropic** state. [Note: Preload and inotropy both raise CO when increased, whereas increasing the afterload decreases CO.]



**Tamponade** impairs ventricular filling and limits preload. Dyspnea reflects the resulting CO limitations.

**A-plus:** A healthy pericardium is elastic to permit functional increases in cardiac volume, but **pericardial sac scarring** or a **pericardial fluid effusion** can limit elasticity and impair filling. Accumulation of pericardial fluid under pressure can also cause the relatively thin-walled atria to collapse.





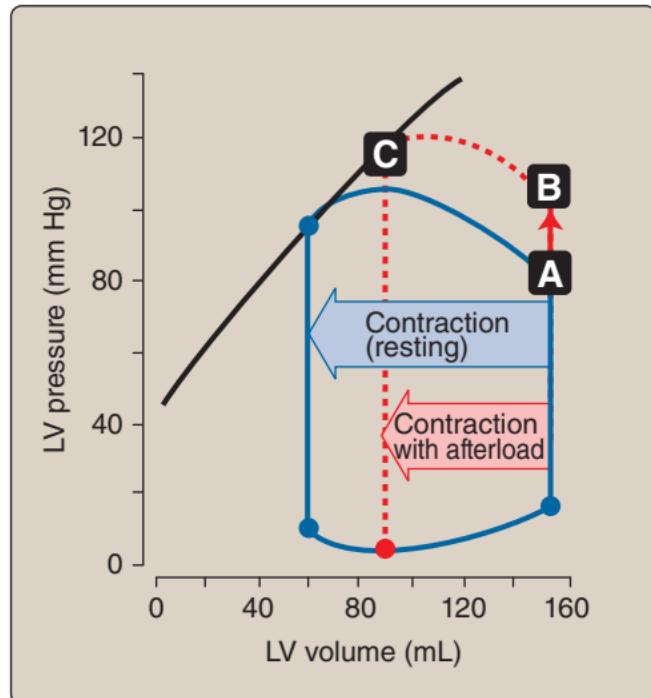
How does increasing afterload (as shown) affect left ventricular (LV) performance, as measured by ejection fraction (EF)?



Name three or more determinants of LV afterload.



How might **mitral valve (MV) regurgitation** be expected to affect LV afterload and EF?



## 4.13 Answer

# Cardiac Afterload



The afterload increase shown decreases EF from 60% to 40%.

EF = stroke volume (SV) ÷ end diastolic volume (EDV).

EF at rest =  $90 \text{ mL} \div 150 \text{ mL} = 60\%$ .

EF with afterload =  $60 \text{ mL} \div 150 \text{ mL} = 40\%$ .

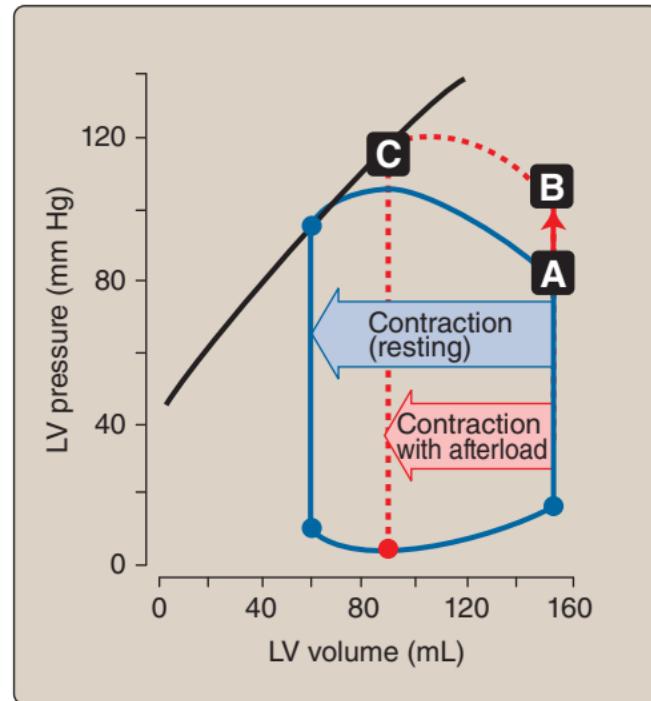


Afterload is the tension that the LV must develop in order to eject blood into the aorta, although it may be easier to think of it as a resistance that the LV must overcome. Contributors to afterload include:

- Aortic pressure
- Chamber size (see 4.15)
- Vascular resistance (see 4.16)
- Hct (see 4.18)
- Valve orifice surface area



Afterload equates with LV wall tension during systole. Because a **prolapsed MV** provides a low-resistance pathway for blood to exit the LV during systole, LV wall tension and afterload is reduced. **MV regurgitation** increases EF, because the blood that escapes backward into the left atrium increases stroke volume. [Note: MV regurgitation is a relatively common disorder affecting ~2% of the population.]



# Cardiac Inotropy (Contractility)

4.14 Question



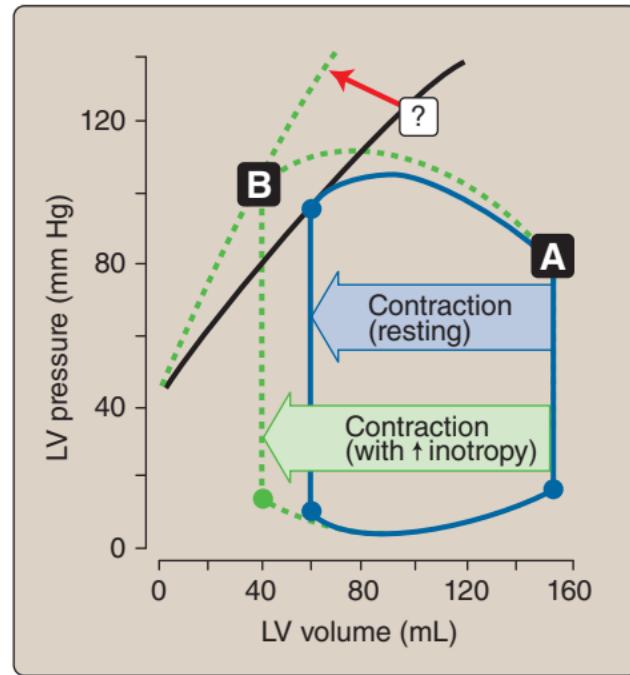
The effects of increasing inotropy on left-ventricular stroke volume are shown, but what does the line indicated by the question mark represent, and why does it shift?



Inotropy is modulated by the SNS. What are the three principal targets of sympathetic stimulation within a ventricular myocyte?



How is ionotropic state measured clinically?



LV = left ventricular.

## 4.14 Answer

# Cardiac Inotropy (Contractility)



The line is the end-systolic pressure–volume relationship. It defines the maximal pressure that a ventricle can develop for a given preload and inotropic state. Increasing inotropy increases the ventricle's ability to develop pressure and makes it a more efficient pump.



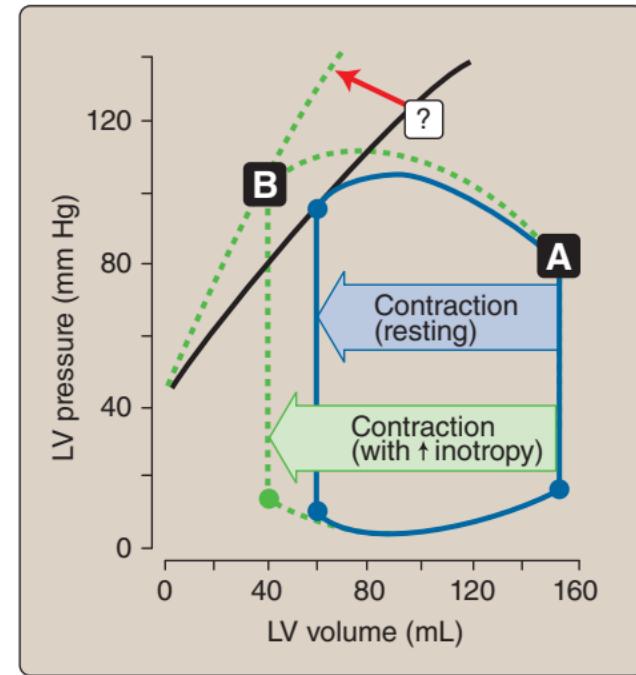
Three principal targets of sympathetic stimulation within a ventricular myocyte:

1. **L-type  $\text{Ca}^{2+}$  channels** (dihydropyridine receptors)
2.  **$\text{Ca}^{2+}$ -release channels** (ryanodine receptors)
3. **Sarcoplasmic reticulum (SR)  $\text{Ca}^{2+}$  ATPase**

Sympathetic effects are mediated by the cAMP-signaling pathway and effected by *PKA*. Phosphorylation increases  $\text{Ca}^{2+}$  fluxes through the L-type  $\text{Ca}^{2+}$  channels and enhances  $\text{Ca}^{2+}$  storage and subsequent release from the SR through actions on the  $\text{Ca}^{2+}$  pump and  $\text{Ca}^{2+}$ -release channels. All three actions increase sarcoplasmic free  $\text{Ca}^{2+}$  during excitation, and  $\text{Ca}^{2+}$  equates with contractility.



Inotropic state can be assessed using Doppler ultrasound techniques that estimate myocardial shortening velocity or blood ejection velocity.



LV = left ventricular.

# Ventricular Wall Tension

4.15 Question



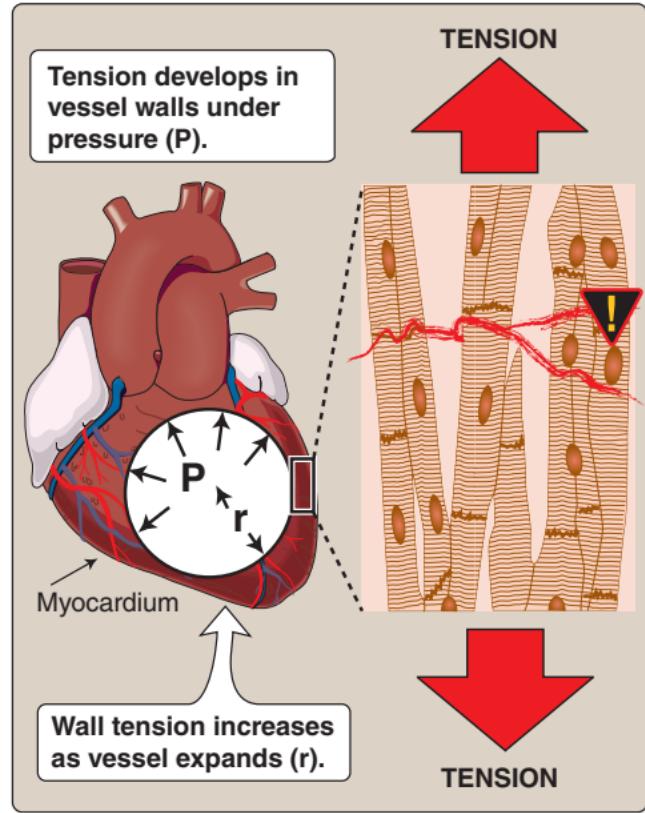
Name and define the equation that relates ventricular wall stress ( $\sigma$ ) to left ventricular pressure (P), radius (r), and wall thickness (h).



How do increases in preload and afterload affect wall tension?



**Congestive heart failure** is associated with increased ventricular wall tension. How is this treated?





The **law of Laplace** relates ventricular wall stress ( $\sigma$ ) to left ventricular pressure (P), radius (r), and wall thickness (h):

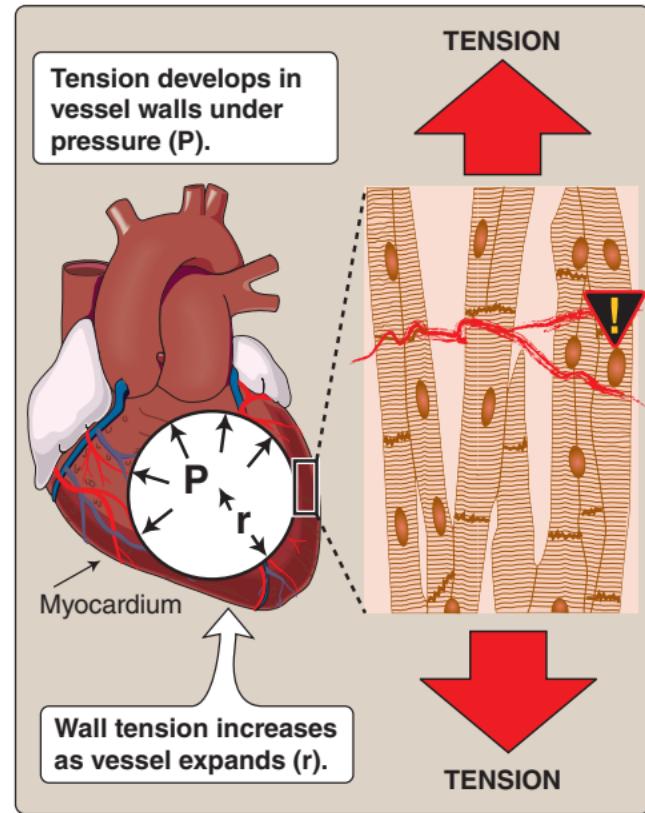
$$\sigma = P \times \frac{r}{2h}$$



Preload and afterload both increase wall tension: Preload increases chamber diameter, whereas afterload increases ejection pressures.



Diuretics are used to reduce ECF volume, which decreases preload and wall tension (see 4.29).





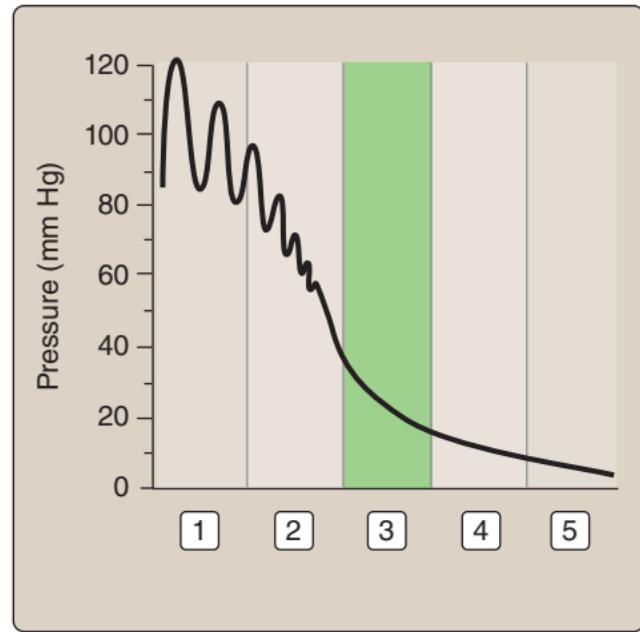
The figure shows how pressure drops as blood traverses the systemic vasculature. Identify the vessel types indicated by boxed numerals and explain the steep pressure drop that occurs when blood flows through [2].



How can the Ohm law be used to quantify vascular resistance of the systemic circulation?



Which type of **circulatory shock** is associated with a profound drop in vascular resistance?





Five blood vessel classes:

1. Large arteries
2. Small arteries and arterioles
3. Capillaries
4. Venules and small veins
5. Larger veins

Small arteries and arterioles are small-bore **resistance vessels**, the function of which is to step down pressure and regulate blood flow to the dependent capillaries.



The hemodynamic form of the Ohm law states that resistance of a vessel or vascular circuit equals the pressure drop across it divided by flow through the circuit:

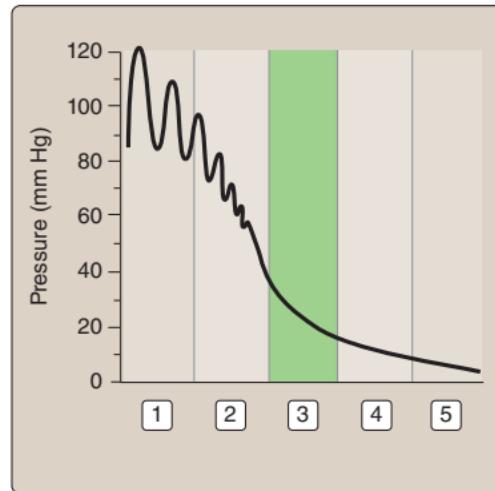
$$\text{SVR} = \frac{\text{MAP} - \text{CVP}}{\text{CO}}$$

Where SVR is **systemic vascular resistance**, MAP = mean arterial pressure (mm Hg), CVP = central venous pressure (mm Hg), and CO = cardiac output (L/min). Using physiologic values:

$$\text{SVR} = \frac{95 - 5}{6} = 15 \text{ mm Hg} \cdot \text{min} \cdot \text{L}^{-1}$$



**Septic shock** is associated with a profound drop in vascular resistance. During shock, sympathetic stimulation of the vasculature increases SVR in order to preserve MAP (see 9.16). In septic shock, the resistance vessels are compromised and dilated, so SVR typically falls.





How is mean arterial pressure (MAP) calculated? Calculate MAP using the values shown.

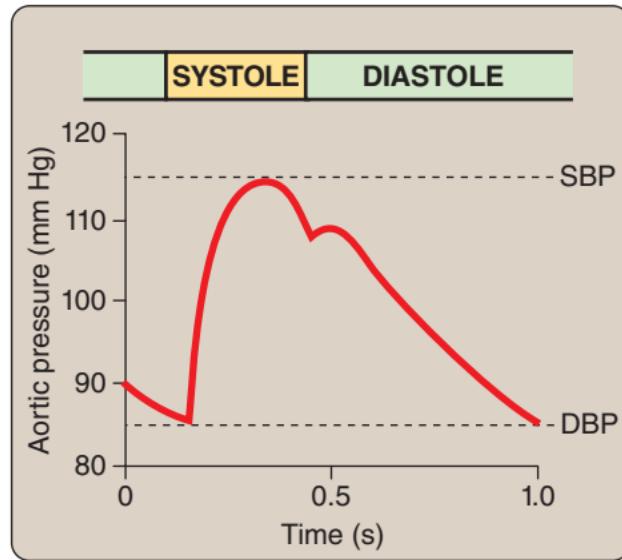


What governs the extent to which systolic blood pressure (SBP) rises and diastolic blood pressure (DBP) falls during the cardiac cycle?

What does "widening of pulse pressure" mean?



**Hypertension (HTN)** is a common medical condition. How is HTN defined, and what is of greater concern in terms of mortality risk: a high SBP or a high DBP?





Calculate MAP:

$$\text{MAP} = \text{DBP} + \frac{(\text{SBP} - \text{DBP})}{3}$$

Using values shown:

$$\text{MAP} = 85 + \frac{(115 - 85)}{3} = 95 \text{ mm Hg}$$

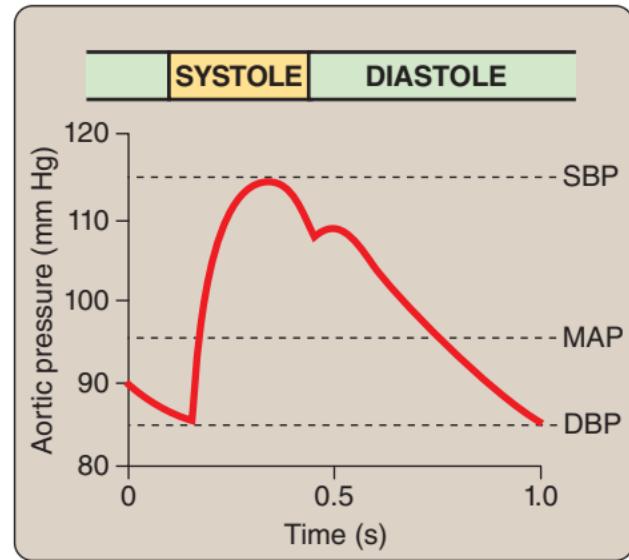


SBP is determined by left ventricular pressure. DBP is governed by systemic vascular resistance (SVR). If SVR is low, DBP falls lower than normal, and, if SVR is high, DBP remains high.

Pulse pressure (PP) = SBP – DBP. If the difference between the two increases (e.g., through a fall in DBP), PP widens.



HTN is defined as a SBP  $\geq 140$  mm Hg and/or DBP  $\geq 90$  mm Hg. A normal blood pressure is <120 mm Hg SBP and <80 mm Hg DBP. Mortality risks are age-dependent. For individuals younger than age 50 years, an elevated DBP is of concern, whereas a high SBP is of greater concern after age 50 years.



# The Poiseuille Law

4.18 Question



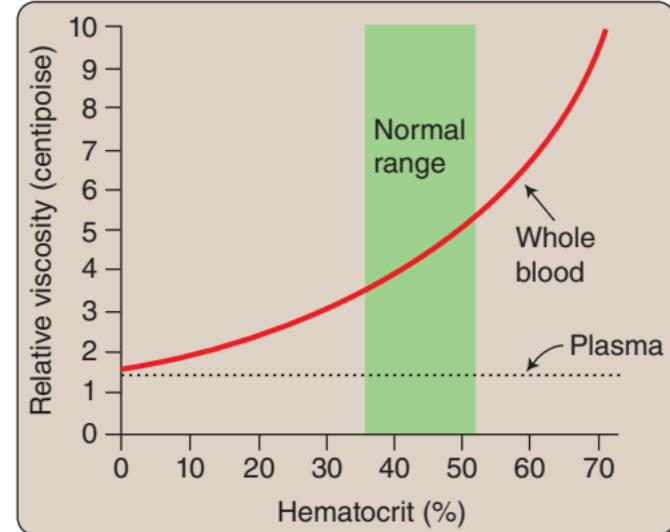
What are the principal determinants of flow through blood vessels, as defined by the Poiseuille law?



What explains the relationship between Hct and viscosity, as shown? How does this limit the ability to live at altitude?



**Sickle cell disease** is an inherited Hb disorder. Does it increase or decrease blood viscosity?





Flow (Q) is driven by pressure (P) against a vascular resistance. Resistance is determined by **vessel radius (r)**, **length (L)**, and **blood viscosity ( $\eta$ )**. The relationship is summarized in the Poiseuille law:

$$Q = \frac{P \times \pi r^4}{8L\eta}$$

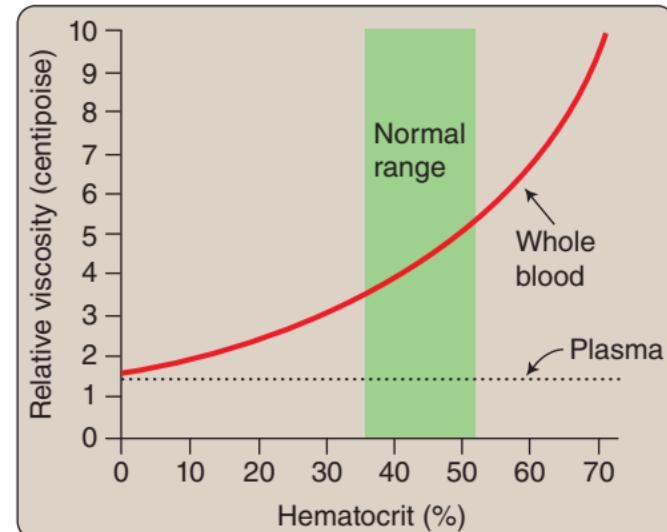


Blood viscosity is due to interactions between proteins covering the RBC surface and other blood components. These interactions increase with Hct, which increases viscosity and resistance to flow.

Living at altitude stimulates **polycythemia** to compensate for reduced O<sub>2</sub> availability. When Hct reaches ~60%, viscosity becomes so great that the heart is unable to generate pressures necessary to maintain adequate perfusion, which places an upper limit for human habitation at ~6,000 m.



RBCs from individuals with the sickle cell trait distort and become rigid at low O<sub>2</sub> tensions. Rigidity causes normally flexible RBCs to lodge in smaller vessels, manifesting as an apparent viscosity increase that precipitates a painful vasoocclusive crisis. However, sickled RBCs are prone to hemolysis, producing anemia and lowered blood viscosity.



# Reynolds Equation

## 4.19 Question



What formula predicts the likelihood of turbulence occurring in the cardiovascular system?



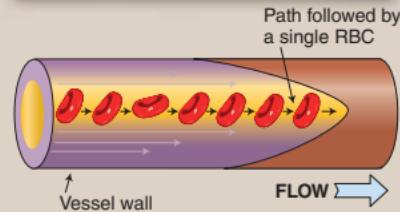
Where in the cardiovascular system is turbulence most likely to occur?  
In what other organ system is turbulence of concern under physiologic conditions?



Why do women manifest functional murmurs during pregnancy?

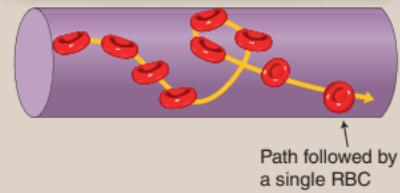
### Streamline flow

- Normal pattern of flow in vasculature
- Highly efficient
- Follows the Poiseuille law



### Turbulent flow

- Occurs in regions where flow velocity is high
- Inefficient, energy is wasted in chaotic movement
- Cannot apply the Poiseuille law





Reynolds equation:

$$N_R = \frac{vd\rho}{\eta}$$

Where  $N_R$  is the Reynolds number,  $d$  is vessel diameter, and  $v$ ,  $\rho$ , and  $\eta$  are blood velocity, density, and viscosity, respectively. [Note: Blood density ( $\rho$ ) does not change *in vivo* and can be considered a constant. The threshold for turbulence in the cardiovascular system is  $\sim 1,600$ .]



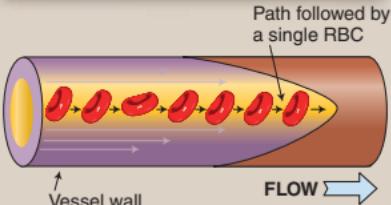
Turbulence occurs where blood velocity is high. In practice, this means turbulence is only likely during flow through the heart and major blood vessels. Turbulence is also a significant source of airflow resistance in the lungs.



Functional murmurs during pregnancy occur due to an Hct decline and associated viscosity decrease (a **physiologic anemia**, see 9.4). The murmurs are associated with ventricular filling and high-velocity systolic flow through heart valves.

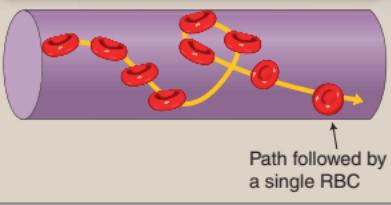
**Streamline flow**

- Normal pattern of flow in vasculature
- Highly efficient
- Follows the Poiseuille law



**Turbulent flow**

- Occurs in regions where flow velocity is high
- Inefficient, energy is wasted in chaotic movement
- Cannot apply the Poiseuille law



# Vascular Compliance

## 4.20 Question



What formula defines vascular compliance?



How is the compliance of arteries and veins of physiologic benefit?



Vessels stiffen with age due to calcification and collagen deposition.  
How does this manifest clinically?

### Noncompliant

Rigid tubes resist expansion when internal pressure rises.

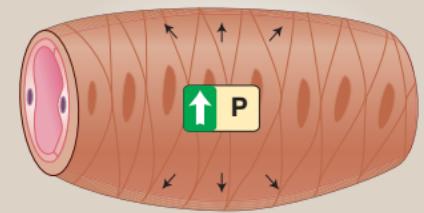
Examples: Capillaries, arterioles, copper pipe.



### Compliant

Tubes with elastic walls swell when internal pressure rises.

Examples: Arteries, veins, rubber tire inner tubes.





Formula for vascular compliance:

$$\text{Compliance} = \frac{\Delta V}{\Delta P}$$

Compliance is a measure of a vessel's ability to accommodate volume (V) when pressure (P) is applied.



The compliance of the aorta and larger arteries allows them to expand to accommodate ventricular stroke volume during systole, then use the energy stored in their elastic walls to drive flow during diastole (**diastolic runoff**). Veins are 6–10 times more compliant than arteries. They expand to create a blood reservoir that can be mobilized when needed to support ventricular preload.



**Arteriosclerosis** decreases the arterial tree's ability to expand during systole, forcing the ventricle to generate higher pressures to sustain basal flow. This manifests as age-related HTN.

### Noncompliant

Rigid tubes resist expansion when internal pressure rises.

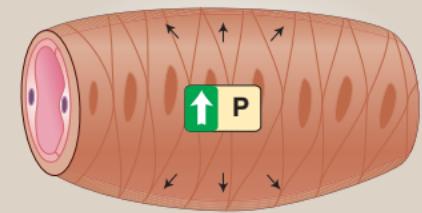
Examples: Capillaries, arterioles, copper pipe.



### Compliant

Tubes with elastic walls swell when internal pressure rises.

Examples: Arteries, veins, rubber tire inner tubes.





# Exchange Pathways in the Microcirculation

4.21 Question



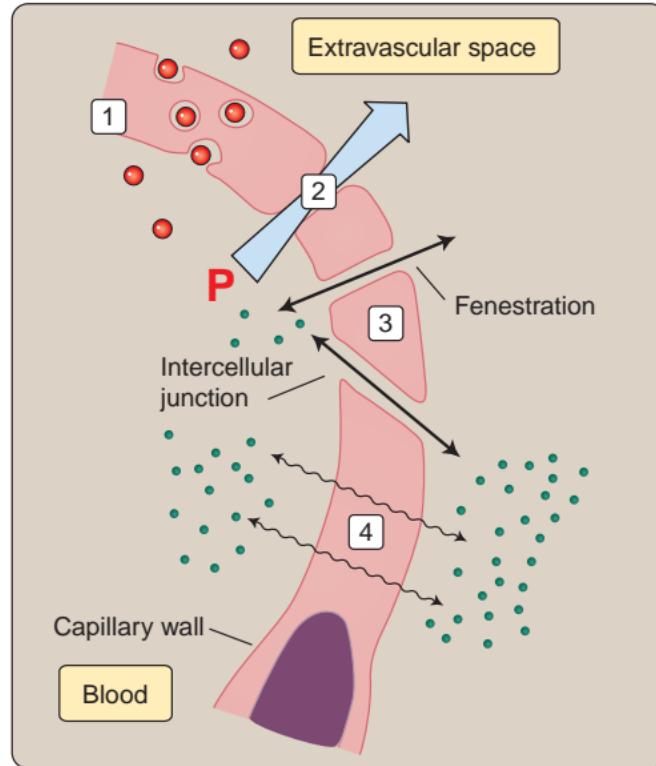
What are the four general pathways for exchanging materials across a capillary wall, as indicated by boxed numerals?



In the cerebral circulation, pathways for exchange are limited by the blood–brain barrier. How do  $O_2$  and nutrients reach CNS neurons?



Treatment of malignant gliomas is hampered by \_\_\_\_\_, a transporter expressed by capillary \_\_\_\_\_ cells that prevents cytotoxic drugs from reaching the tumor.





Four pathways:

1. Pinocytosis and endocytosis
2. Pressure-driven bulk flow via junctions and fenestrations
3. Diffusion via junctions and fenestrations
4. Diffusion across cells (lipid-soluble materials only)

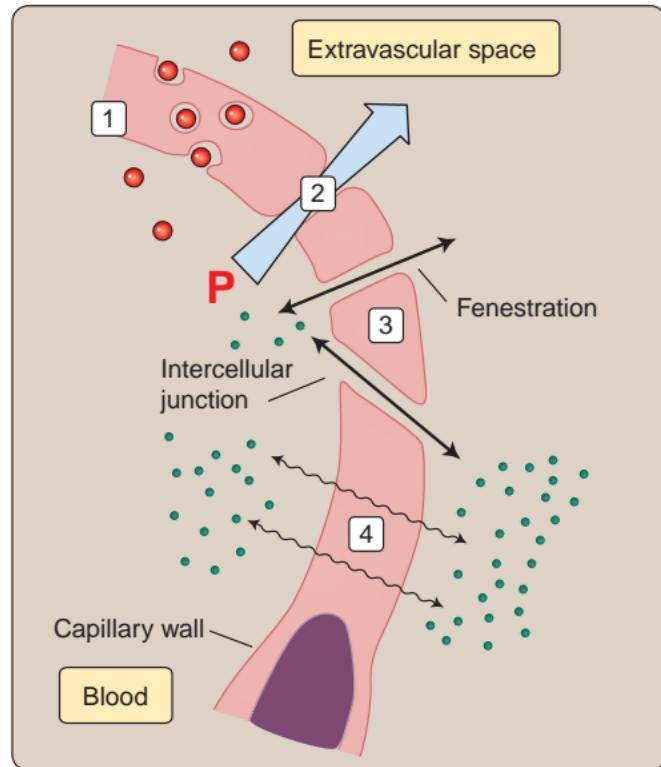


$O_2$  and other lipid-soluble molecules reach the brain by diffusion across capillary endothelial cells. Channels and transporters provide regulated access pathways for other materials. Cerebral capillaries are not fenestrated, and the junctions between cells are tightly sealed to prevent unregulated access to CNS neurons.



Treatment of malignant gliomas is hampered by **P-glycoprotein**, a transporter expressed by capillary endothelial cells that prevents cytotoxic drugs from reaching the tumor. [Note: P-glycoprotein is also known as multidrug resistance transporter.]

**A-plus:** Cerebral capillary endothelial cells also contain *monoamine oxidase*, *peptidase*, *acid hydrolase*, and other enzymes to degrade hormones, transmitters, and other compounds that might influence neuronal activity.



# Starling Equilibrium

## 4.22 Question



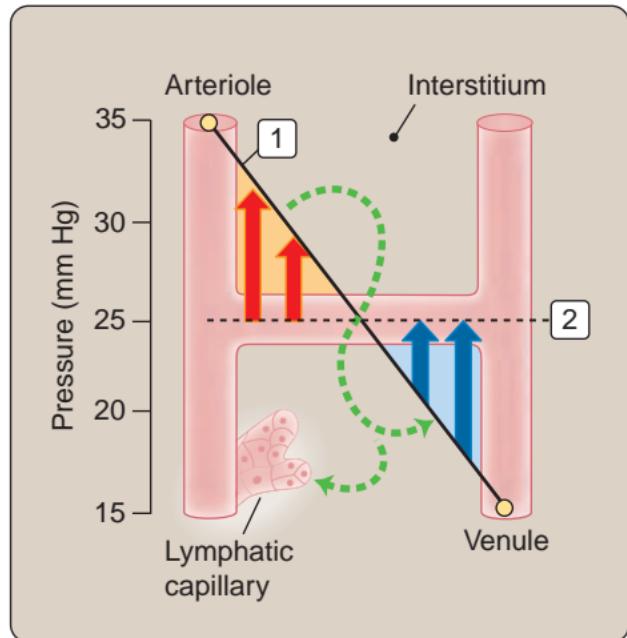
What are the two largest forces controlling fluid movement between blood and the interstitium in most circulations (indicated by boxed numerals)? Define the Starling equation used to quantify fluid flow across the capillary wall.



How is an imbalance in Starling forces used to functional advantage in the renal circulation?



How does repeated infection by the parasitic nematode *Wuchereria bancrofti* cause the gross disfigurements associated with **elephantiasis?**





Two largest forces controlling fluid movement:

1. Capillary hydrostatic pressure ( $P_c$ )
  2. Plasma colloid oncotic pressure ( $\pi_c$ )

Starling law of the capillary:

$$Q = K_f [(P_c - P_{if}) - (\pi_c - \pi_{if})]$$

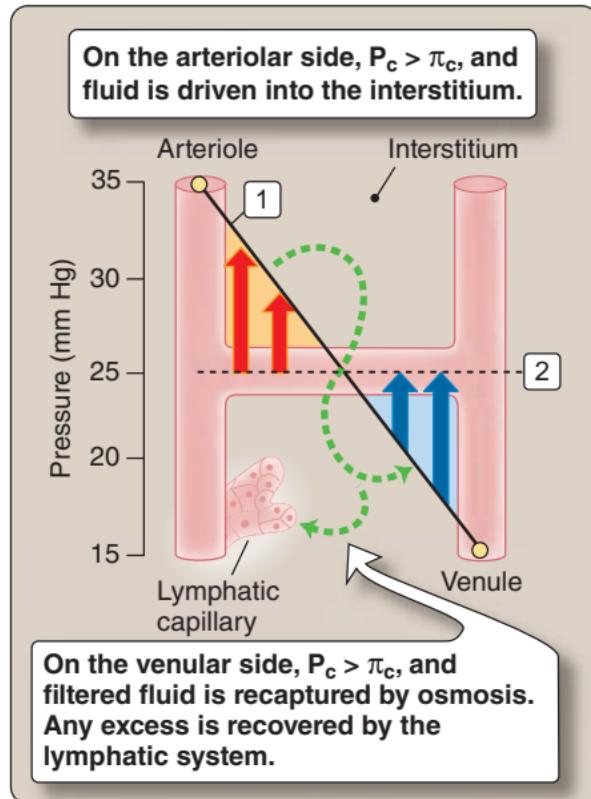
Where  $Q$  = net fluid flow,  $K_f$  is a filtration constant,  $P_{if}$  is interstitial hydrostatic pressure, and  $\pi_{if}$  is interstitial colloid oncotic pressure.  $P_{if}$  and  $\pi_{if}$  are usually near zero.



Blood enters and leaves glomerular capillaries at much higher pressure than  $\pi_c$  ( $P_c \sim 60$  mm Hg), causing massive fluid filtration into the renal tubule. The rise in  $\pi_c$  that accompanies filtration is subsequently used by the peritubular capillary network to recover fluid from the tubule lumen.



Filarial *W. bancrofti* larvae establish themselves in lymph vessels and block normal interstitial drainage. Tissues become edematous and swollen as a result (**lymphedema**). In time, the tissues undergo the inflammatory hardening and thickening characteristic of **elephantiasis**.





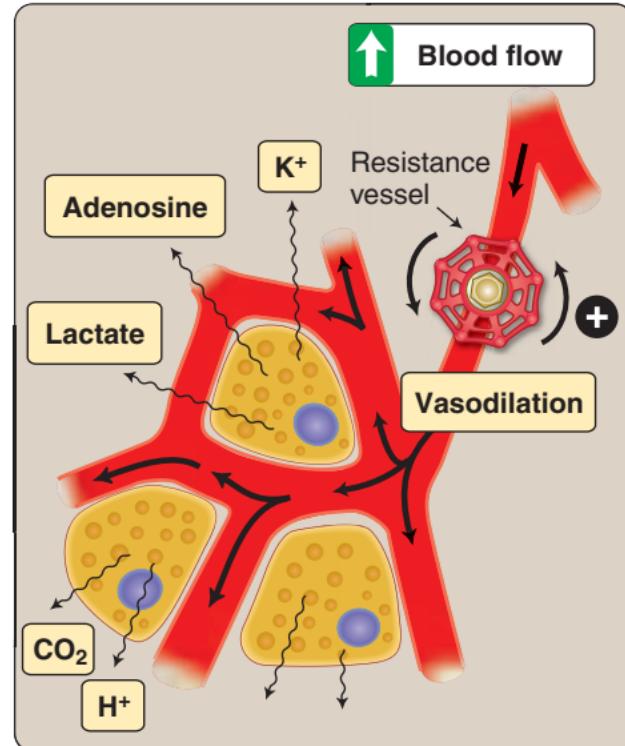
Resistance vessels can be likened to vascular taps that control flow to capillaries (as shown). What two local resistance-vessel control mechanisms allow for autoregulation?



Contrast resistance-vessel control in the coronary and cutaneous circulations.



Patients in **traumatic shock** may show prolonged capillary refill times and narrowing of the pulse pressure (PP). What is the significance of such findings?





Two local control mechanisms allowing for **autoregulation**:

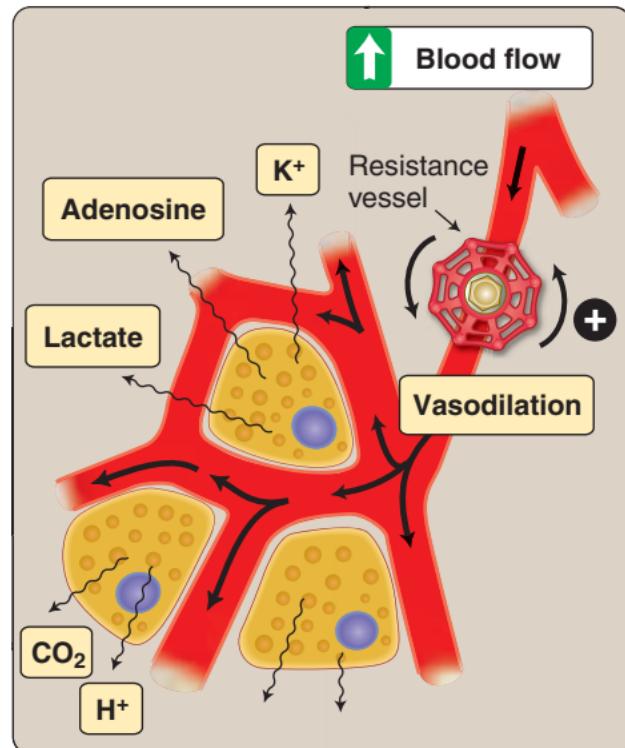
1. **Metabolic:** Rising metabolite levels cause resistance vessels to dilate and thereby increase blood flow to dependent capillaries. Falling metabolite levels cause reflexive vasoconstriction.
2. **Myogenic:** Vessels constrict reflexively in response to arterial pressure surges.  
[Note: The two mechanisms allow tissues to maintain stable blood flow tailored to their metabolic needs independently of central control.]



Coronary resistance vessels are under local control with flow closely paralleling the metabolic needs of cardiac myocytes. Central controls are largely ineffective. By contrast, cutaneous resistance vessels are controlled primarily by the CNS, which adjusts flow to meet thermoregulatory and circulatory needs.



During shock, the CNS restricts flow to nonessential circulations, including the cutaneous circulation. Prolonged capillary refill times reflect curtailed cutaneous arterial flow. CNS-induced vasoconstriction raises systemic vascular resistance, which, in turn, raises diastolic blood pressure. PP narrows as a result.



# Nitric Oxide

4.24 Question



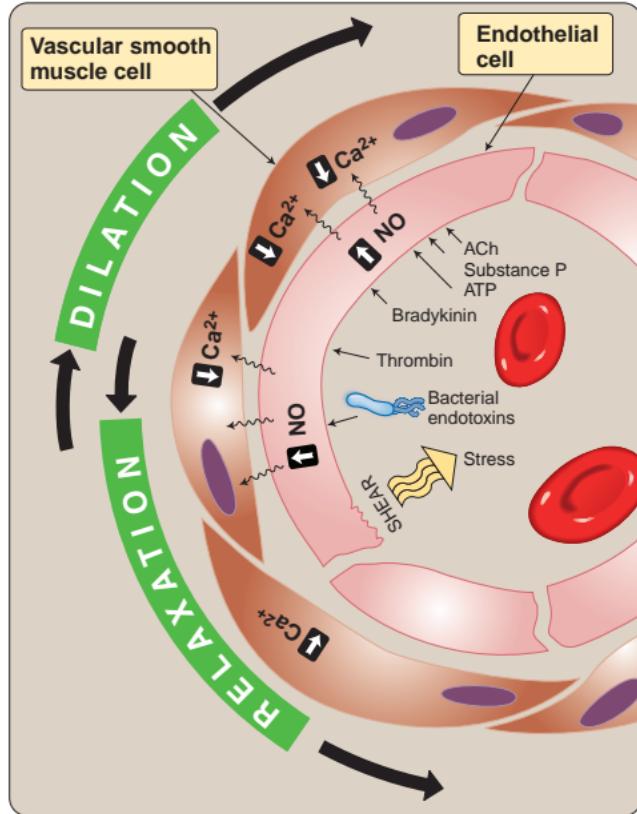
How does nitric oxide (NO) reduce internal  $\text{Ca}^{2+}$  concentration in vascular myocytes during responses to vasodilatory stimuli (as shown)?



What is the physiologic significance of vasodilatory responses to shear stress?



**Angina pectoris** is chest pain associated with inadequate  $\text{O}_2$  supply to the myocardium. How do oral nitrates such as nitroglycerin help alleviate this pain?





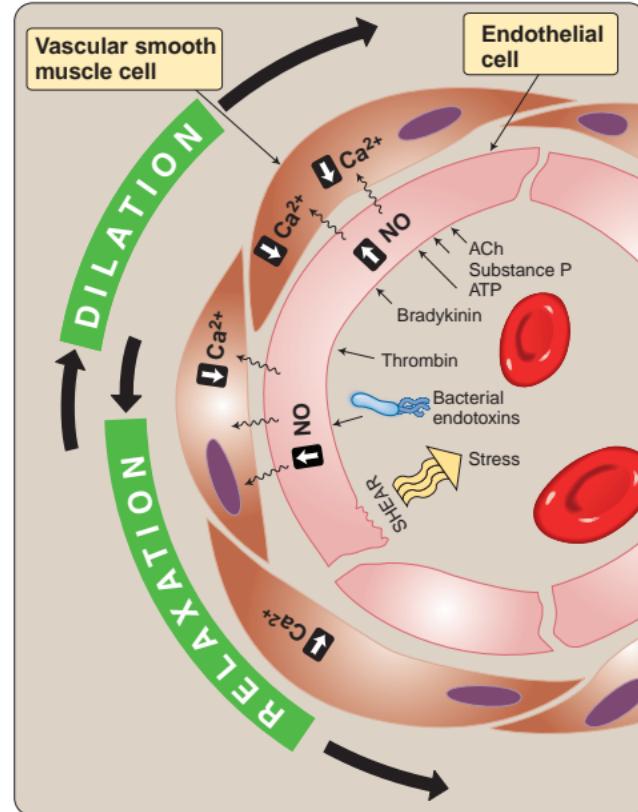
NO is a volatile gas that diffuses to vascular smooth muscle cells from its site of synthesis. Here, it stimulates cGMP production by *GC*. cGMP activates *PKG*, which phosphorylates and raises SERCA activity, causing sarcoplasmic  $\text{Ca}^{2+}$  levels to fall. *PKG* also phosphorylates and reduces *MLCK* activity. Both actions promote muscle relaxation.



Shear stress–induced vasodilation is protective. Shear stress is a force exerted on the vascular endothelium by blood flow. Stress levels increase with flow velocity to the point where they can damage the endothelium, so vasodilation simultaneously decreases flow velocity ( $V = Q \div a$ ) and the associated shear stress and facilitates flow to tissues whose increased need for blood precipitated the velocity increase.



Nitrates are degraded *in vivo* to release NO, which dilates both arteries and veins. The former reduces left ventricular afterload, whereas the latter reduces preload. Both actions reduce myocardial workload and  $\text{O}_2$  demand.



# Baroreflexes

4.25 Question



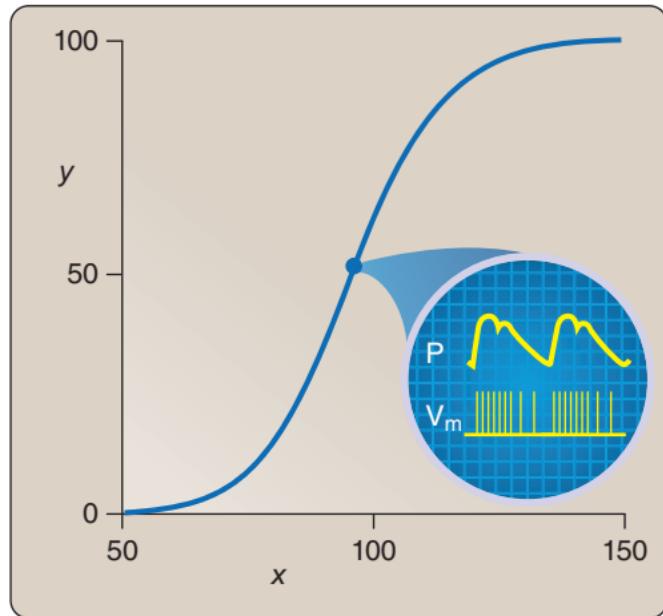
Identify the two axes shown.



What three receptor groups are involved in arterial baroreflexes, and where are the receptors located?



Orthostatic hypotension is a common condition among older adults and may become incapacitating if not treated. What are the symptoms?





Two axes:

x: mean arterial pressure (mm Hg)

y: arterial baroreceptor afferent firing rate (% of maximum)

[Note: Baroreceptors are phasic, so highest firing rates are recorded during the rapid rise in aortic pressure that occurs during early ejection (inset).]

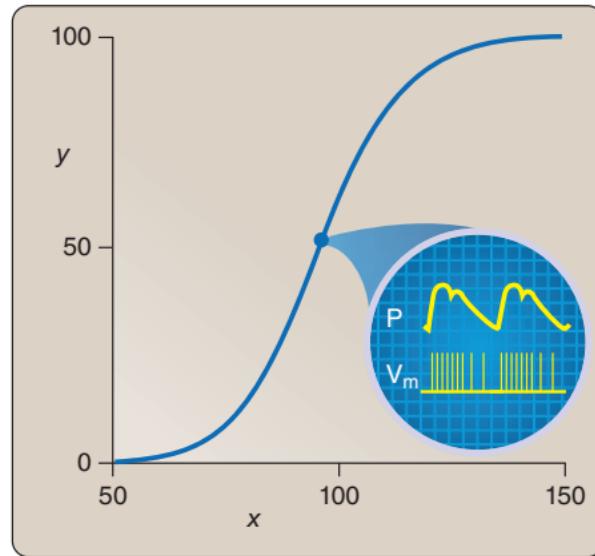


Three receptor types involved in arterial baroreflexes and their locations:

- Arterial baroreceptors:** Stretch-sensitive neurons in the wall of the **aorta** and **carotid sinus** are the primary pressure sensors.
- Cardiopulmonary receptors:** Located in the low-pressure areas of the cardiovascular system (**atria** and **pulmonary vasculature**), they monitor vascular fullness.
- Chemoreceptors:** Chemoreceptor cells located in **aortic** and **carotid bodies** monitor blood gas composition and provide information about flow rates, which reflects arterial pressure.

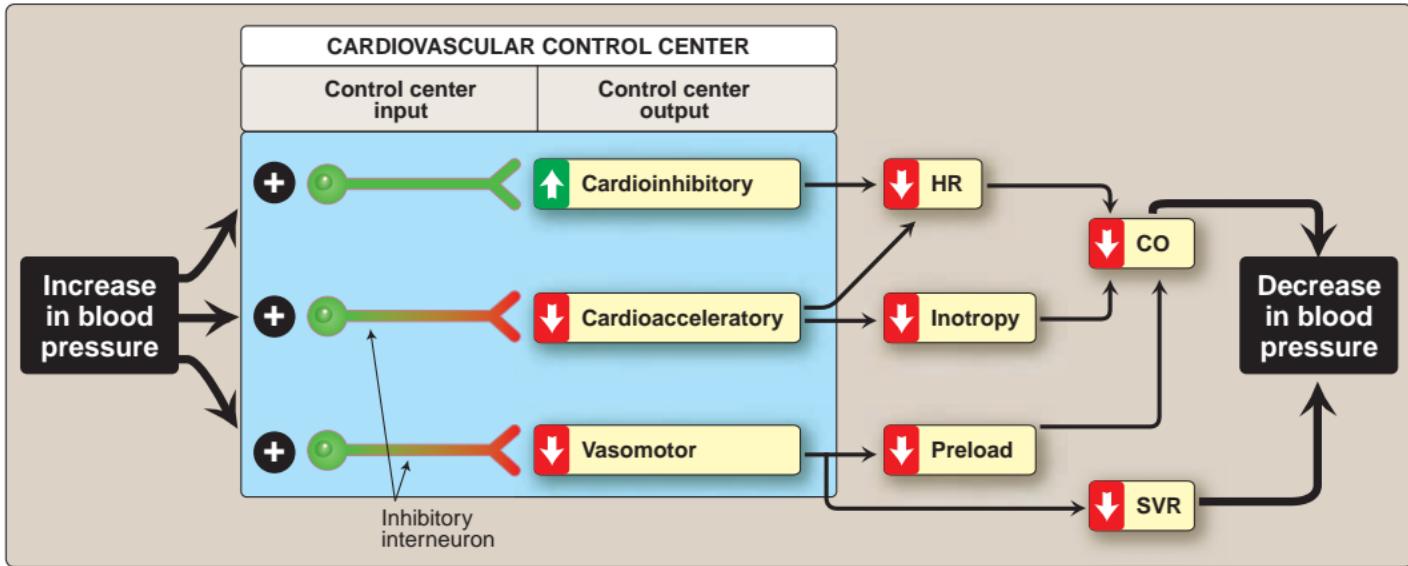


**Orthostatic hypotension** is a fall in blood pressure that occurs upon standing, causing symptoms associated with cerebral hypoperfusion (dizziness, light-headedness, syncope). It reflects an impaired ability to sense and compensate for pooling of venous blood in the lower extremities upon standing, resulting in reduced ventricular preload and output.



# Arterial Blood Pressure Regulation

4.26 Summary



CO = cardiac output; HR = heart rate; SVR = systemic vascular resistance.



### Sensors

1. Arterial baroreceptors: located in the aortic arch and carotid sinus; relay information to the integrator via CN IX (glossopharyngeal) and CN X (vagus)
2. Cardiopulmonary receptors: located in atria, pulmonary artery and vein, and vena cavae; atrial receptors are sensitive to atrial wall tension (A receptors) and stretch (B receptors)
3. Chemoreceptors: located in aortic and carotid bodies; monitor blood gases

### Integrator

Brainstem medulla oblongata contains the cardiovascular control center and is organized into three functional regions:

1. Vasomotor center: vasoconstricts when active
2. Cardioacceleratory center: increases heart rate (HR) and cardiac inotropy
3. Cardioinhibitory center: slows HR

### Effectors

1. Sinoatrial and atrioventricular nodes: control HR
2. Myocardium: contractile strength determines cardiac output (CO)
3. Veins: vasoconstriction forces blood toward the heart and preloads the ventricles
4. Resistance vessels: vasoconstriction limits output from the arterial tree and raises systemic vascular resistance (SVR)
5. Adrenal medulla: releases epinephrine and norepinephrine into the circulation

### Response

Baroreflex acts to keep mean arterial pressure (MAP) stable, and  $\text{MAP} = \text{CO} \times \text{SVR}$ .  $\text{CO} = \text{HR} \times \text{stroke volume}$ :

1. Low MAP:  $\uparrow$  HR,  $\uparrow$  inotropy,  $\uparrow$  venoconstriction,  $\uparrow$  SVR
2. High MAP:  $\downarrow$  HR,  $\downarrow$  inotropy,  $\downarrow$  venoconstriction,  $\downarrow$  SVR

# Renin–Angiotensin–Aldosterone System

4.27 Question



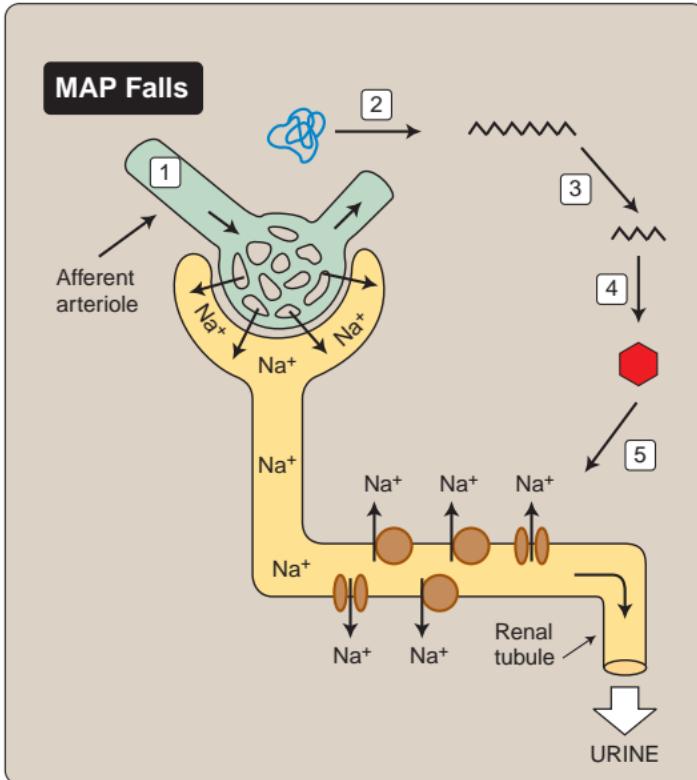
Using the boxed numerals as a guide, trace the steps leading to increased  $\text{Na}^+$  recovery from the renal tubule following a drop in mean arterial pressure (MAP).



A fall in MAP stimulates water recovery from the tubule by what pathway?



Two drugs commonly used to treat hypertension target the pathway shown by what mechanism of action?





A fall in MAP initiates the *renin–angiotensin–aldosterone system* (RAAS):

1. *Renin* release from afferent arteriolar granular cells
2. *Renin* proteolyses angiotensinogen to release angiotensin I (Ang-I)
3. Ang-I is converted to Ang-II in the lungs by *angiotensin-converting enzyme (ACE)*.
4. Ang-II stimulates aldosterone release from the adrenal cortex.
5. Aldosterone upregulates  $\text{Na}^+$  channel and  $\text{Na}^+$  pump expression by the renal tubule, thereby increasing  $\text{Na}^+$  recovery.



A drop in MAP stimulates antidiuretic hormone (ADH) release from the posterior pituitary. ADH promotes aquaporin incorporation into the renal epithelium, which enhances water recovery. [Note: Ang-II also stimulates ADH release.]

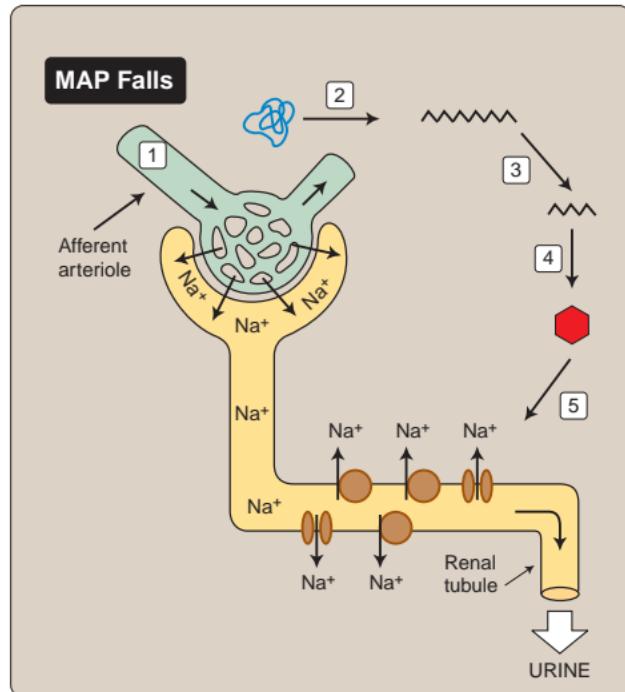


The two classes of antihypertensive drugs that target RAAS are:

1. *ACE* inhibitors (e.g., captopril)
2. Ang-II–receptor blockers (e.g., losartan)

Ang-II is both a vasoconstrictor and also stimulates  $\text{Na}^+$  retention via aldosterone. Thus, blocking Ang-II synthesis and binding has potent antihypertensive effects.

*A-plus:* A *renin* inhibitor (aliskiren) is now also available. Its efficacy is similar to that of *ACE* inhibitors and Ang-II–receptor blockers.





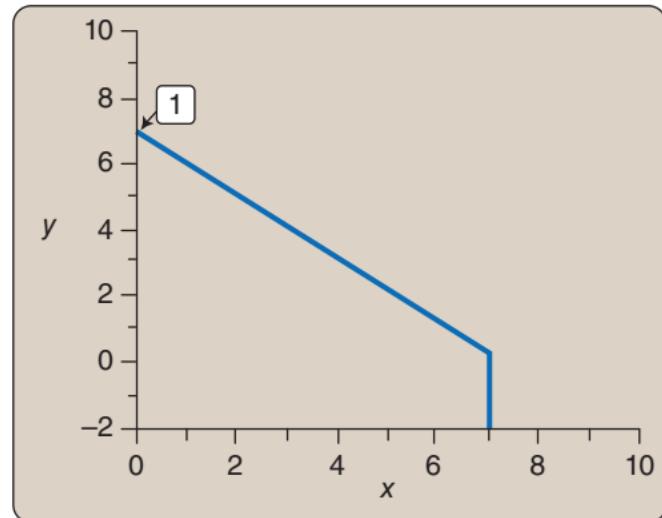
What are the axes for the vascular function curve shown? What does the intersect indicated by [1] represent?



Identify three or more effects of sympathetic stimulation on the venous system.



Pregnancy carries a risk of developing **varicose veins** in the lower extremities, causing leg heaviness, pain, and swelling. What causes varicose veins?





Two axes:

x: cardiac output (L/min)

y: central venous pressure (mm Hg)

The intersect [1] represents **mean circulatory pressure** (i.e., the pressure in the cardiovascular system after flow has been arrested for some minutes and the system has equilibrated).



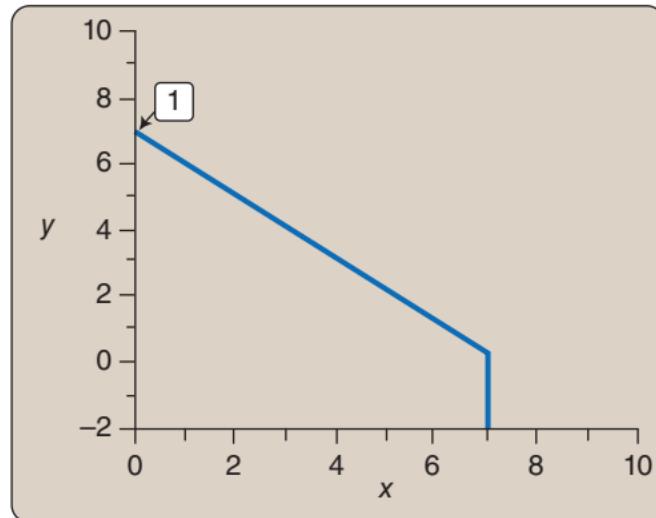
The effects of sympathetic stimulation on veins include:

- Increased central venous pressure
- Decreased venous capacity
- Mobilization of venous reservoirs
- Decreased transit time through the system

[*Note:* Venoconstriction has minimal effects on flow resistance, which contrasts with the effects of constricting small arteries and arterioles.]



Varicose veins are caused by high venous pressure. They are typically superficial veins of the lower extremities that become enlarged and tortuous. Venodilation can render their valves incompetent, which allows retrograde flow and further increases venous pressure in the lower regions. In pregnant women, the gravid uterus compresses and impedes flow through veins returning blood from the feet and legs, which increases the likelihood of varicose vein formation.





# Cardiovascular Function Curves

4.29 Question



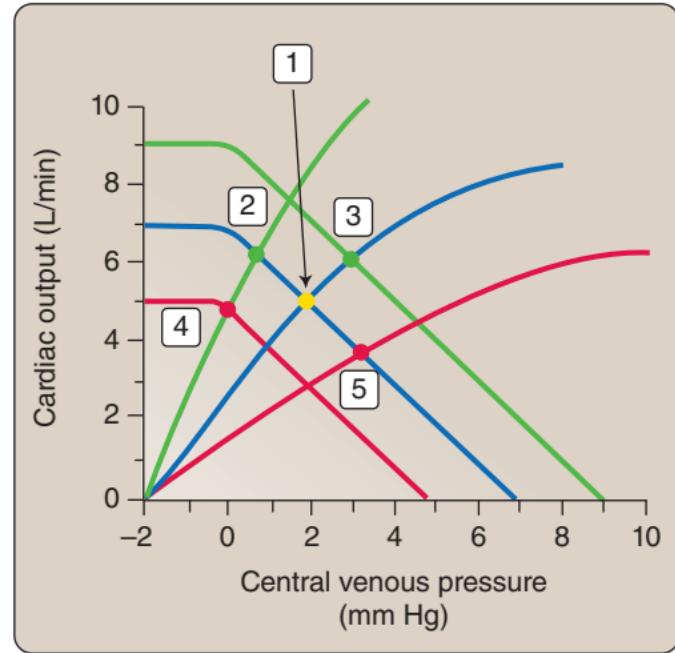
In the graph, if [1] is normal, what do the other four points represent?



How would SNS activation affect the cardiovascular function curve?



Patients in **congestive heart failure** are typically \_\_\_\_\_ to reduce the volume load and given a \_\_\_\_\_ to reduce heart rate and cardiac workload.



# Cardiovascular Function Curves



Four points represent:

2. ↑ Cardiac inotropy
3. ↑ Blood volume
4. Hemorrhage, after compensation
5. Acute myocardial infarction, before compensation



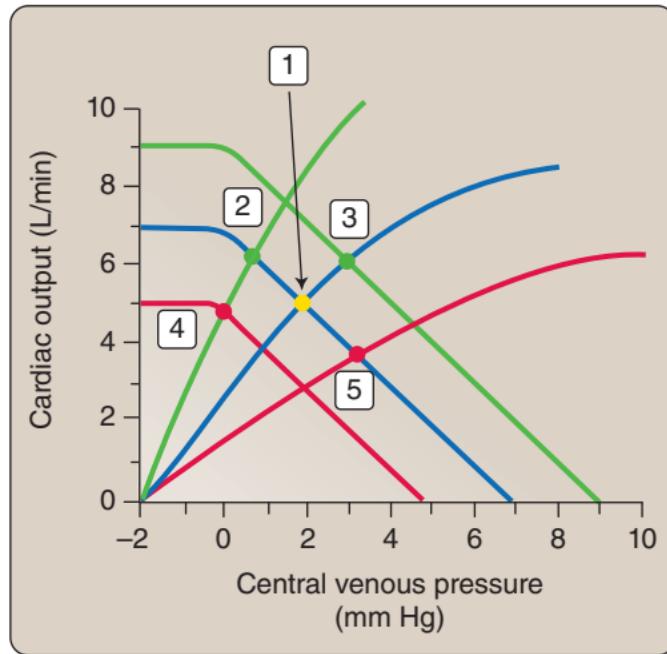
Sympathetic activation would affect cardiac performance and the vasculature:

- ↑ Myocardial inotropy, so the cardiac function curve shifts up and to the left (i.e., toward [2])
- ↑ Central venous pressure through vasoconstriction (i.e., vascular function curve shifts toward [3])

*A-plus:* ↑ Systemic vascular resistance would also rotate the vascular function curve counterclockwise and partly offset the effects of an inotropy increase on cardiac output by increasing left ventricular afterload.



Patients in congestive heart failure are typically **diuresed** to reduce the volume load and given a **beta blocker** to reduce heart rate and cardiac workload. [Note: Although beta blockers also reduce inotropy and promote volume loading, clinical trials have shown significant benefits in long-term survival rates and reducing heart failure progression.]





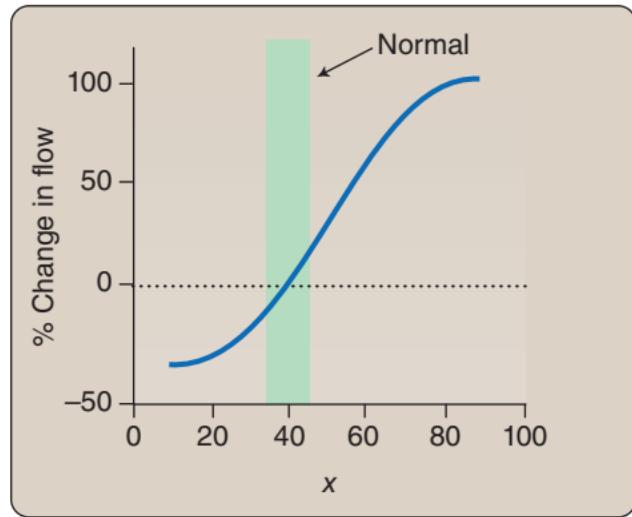
Cerebral circulatory control is primarily local, dominated by changes in levels of what metabolite ( $[x]$ )?



Strenuous exercise requires that flow to most organs be reduced to meet the demands for cardiac output created by active skeletal muscles. How much is cerebral flow reduced?



What are the two main **stroke** categories?





Metabolite ( $[x]$ ) is:

Arterial CO<sub>2</sub> (P<sub>a</sub>CO<sub>2</sub>; mm Hg)

[Note: Although cerebral resistance vessels are sensitive to all metabolites, they are particularly sensitive to P<sub>a</sub>CO<sub>2</sub>. Hyperventilation can reduce P<sub>a</sub>CO<sub>2</sub> levels to the point where they cause reflex cerebral vasoconstriction. Light-headedness and syncope may result.]

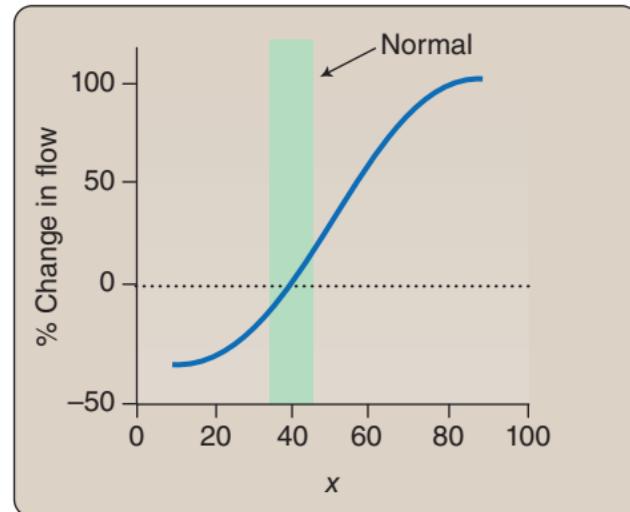


Cerebral flow is minimally affected by the sympathetic activation that accompanies strenuous exercise. Local control mechanisms predominate under normal circumstances.



Two main stroke categories:

1. **Hemorrhagic:** Cerebral or subarachnoid hemorrhage allows blood to accumulate in the brain, compressing arterial supply vessels and impeding flow.
2. **Ischemic:** Emboli or thrombi block arterial supply vessels and impair brain function. Ischemic stroke can also result from cerebral hypoperfusion caused by systemic arterial pressure inadequacy.





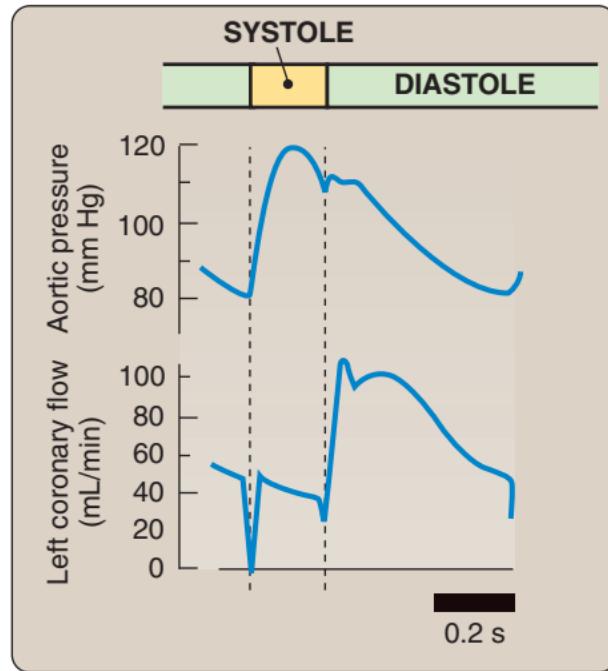
Flow through most vascular beds follows the aortic pressure curve, except in the left coronary circulation. What explains the unusual flow pattern shown?



Myocardial excitation proceeds from endocardium to epicardium, producing a positive deflection on a lead I ECG (i.e., the R wave). How does the flow pattern shown explain why the T wave is also positive?



**Left ventricular infarction** often damages the subendocardial regions to a greater extent than subepicardial areas. How does this correlate with the flow pattern shown?





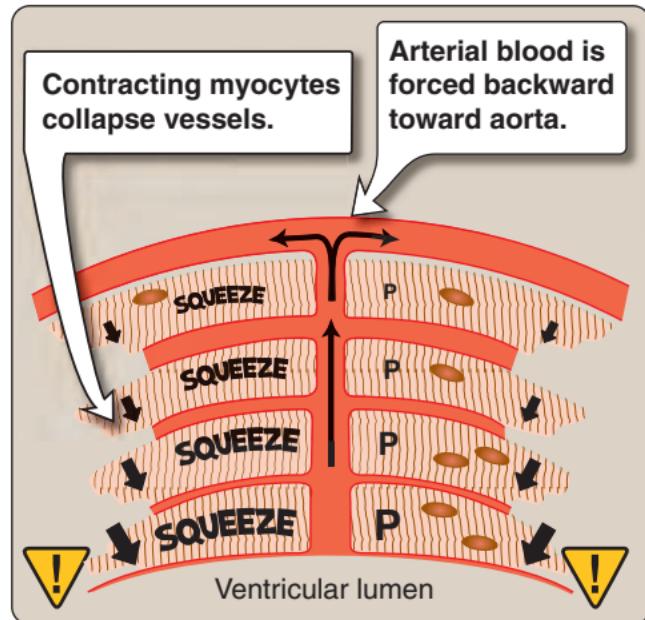
The left ventricle must generate luminal pressures that exceed aortic pressure (AoP) to eject blood. Individual myocytes contract and bear down on each other, the force increasing progressively toward the lumen. This force collapses the coronary supply vessels, whose patency relies on AoP. Blood is forced backward in early systole, with maximal forward flow occurring when the compressive forces are removed during diastole.



Myocytes in the subendocardial regions suffer the greatest compressive forces and blood flow deprivation during systole. Therefore, myocardial recovery proceeds from the epicardium inward toward the lumen. The electrical dipole generated during this time yields an upward T wave, rather than a downward one as might be expected if recovery followed the direction of excitation (i.e., from the subendocardium toward the epicardium).



Because myocytes in the subendocardial regions suffer maximal flow deprivation during systole, they are more likely to necrose when a supply vessel is occluded. Myocytes in the subepicardial regions maintain flow throughout the cardiac cycle and are, thus, more likely to survive ischemia caused by supply vessel occlusion.



# Splanchnic Circulation

4.32 Question



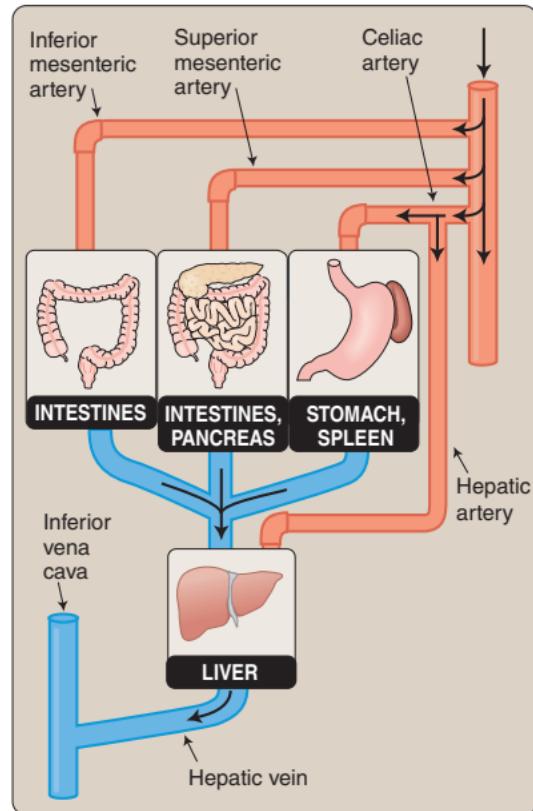
What features of the splanchnic circulation make it anatomically and functionally notable?



What does "autoregulatory escape" mean?



What causes the postprandial hypotension experienced by many elderly patients?





Splanchnic circulation notable features:

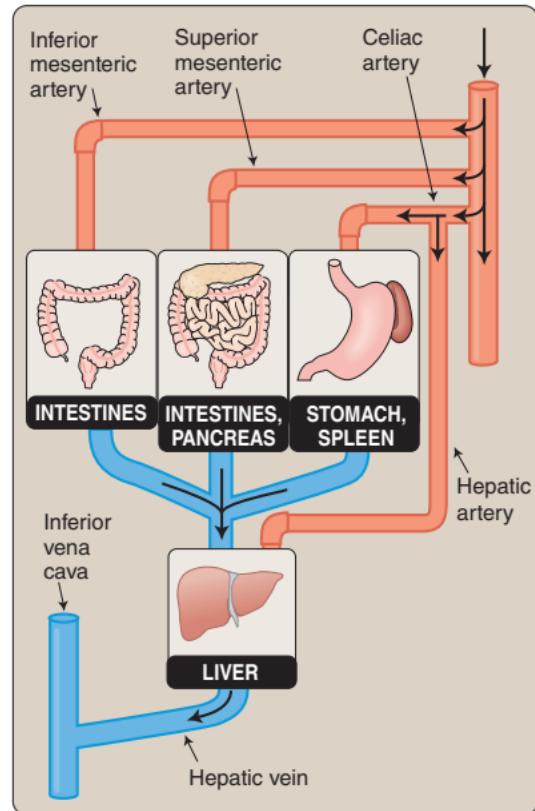
- Includes a **portal circulation** (liver receives venous blood from intestines)
- Extensive **collateralization** (helps protect tissues during local ischemia)
- Commands 20%–30% of cardiac output (CO) at rest
- Commands >100% of resting CO during a meal
- Contains 15% of blood volume, creating a significant **reservoir**
- Flow can be redirected for use elsewhere in the circulation for prolonged periods by sympathetic activation.



Autoregulatory escape refers to the observation that while mild sympathetic stimulation curtails blood flow through splanchnic resistance vessels, the resulting rise in metabolite levels cause a reflexive dilation and normal flow resumes. Thus, local autoregulatory mechanisms allow the tissue to escape from central control.



**Postprandial hypotension** is due to impaired baroreflexes or other autonomic dysfunction that prevents normal compensation for the fall in splanchnic vascular resistance that occurs during a meal. When the splanchnic vasculature becomes a low resistance pathway for blood flow, CO must be increased to maintain arterial pressure at levels adequate to perfuse all tissues. Elderly patients commonly experience light-headedness and syncope following a meal as a result of impaired compensation.



# Lung Airways

## 5.1 Question



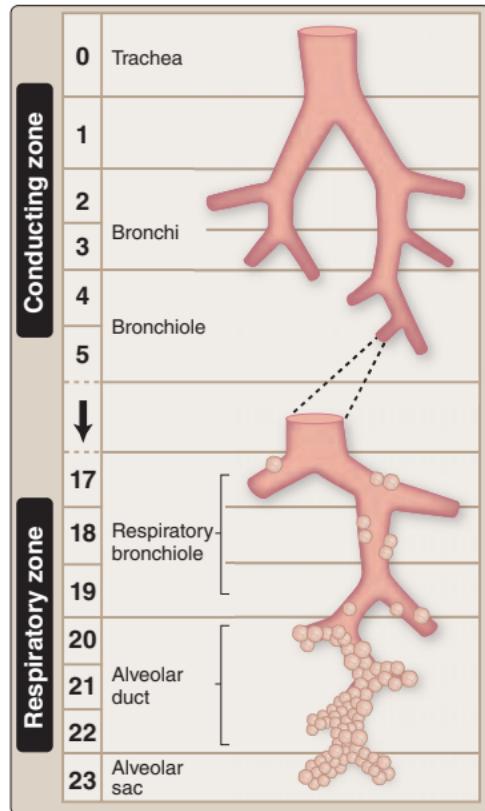
Contrast the properties of airways that make up the bronchial tree's conducting zone with those of the respiratory zone.



Which airways create the greatest resistance to airflow in a normal lung, and why?



Why are smokers prone to coughing episodes and **bronchitis**?





Conducting zone versus respiratory zone airways:

### Conducting zone

- Do not participate in gas exchange
- Mechanically supported with cartilage (larger airways)
- Lined with a ciliated epithelium

### Respiratory zone

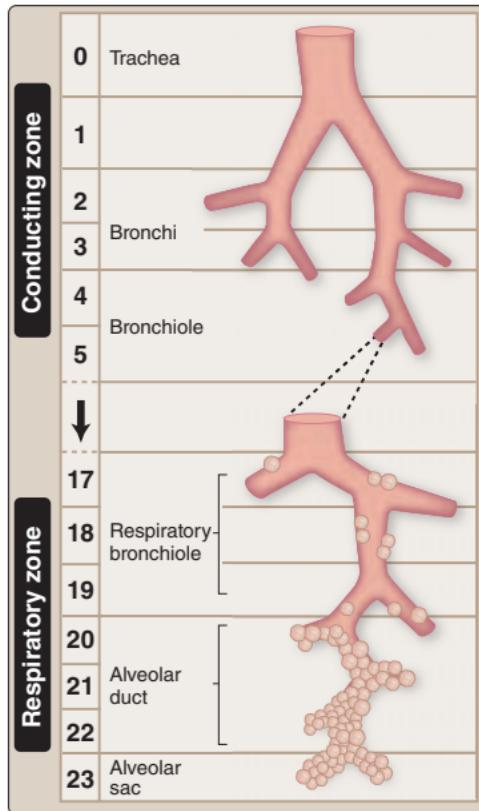
- Houses the blood–gas interface



The sites of highest resistance to airflow are the pharynx and larger airways (generations 0 through ~7). Resistance is proportional to cross-sectional area. Although larger airways are wider than smaller airways, the latter are far more numerous so their collective cross-sectional area is proportionally greater. [Note: Airflow resistance is calculated with the Poiseuille law (see 4.18).]



Tobacco smoke immobilizes respiratory cilia, which normally propel mucus with entrapped particulates, including bacteria, upward and out of the lungs (the **mucociliary escalator**). When allowed to accumulate, these inhaled irritants cause epithelial inflammation and infection, thereby predisposing smokers to coughing and bronchitis.



# Blood–Gas Interface

## 5.2 Question



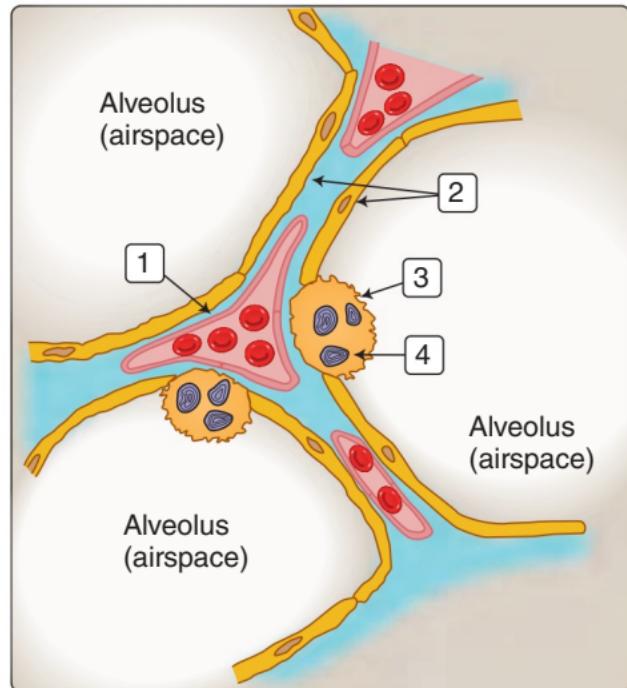
What are the functions of the structures located at the blood–gas interface, as indicated by boxed numerals?



How does the pulmonary circulation differ from the bronchial circulation?



What effect does aspirating freshwater have on pulmonary function, as seen in a case of nonfatal drowning?





Blood–gas interface structures and their functions:

1. **Pulmonary capillary**: brings the circulation into close proximity to air
2. **Type I pneumocyte**: creates a thin barrier between air and the pulmonary interstitium
3. **Type II pneumocyte**: synthesizes surfactant and repairs alveolar damage
4. **Lamellar inclusion body**: contains surfactant



Pulmonary versus bronchial circulations:

### Pulmonary

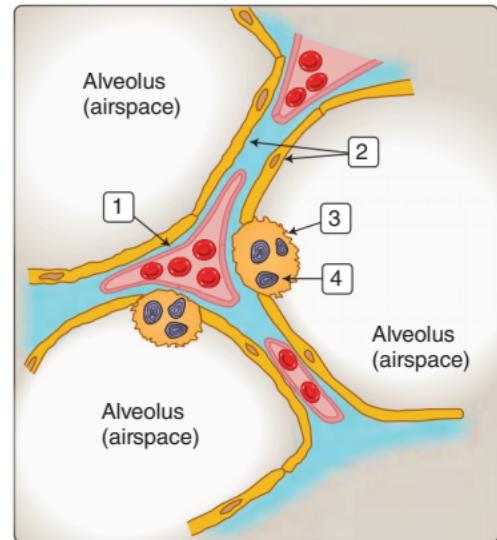
- Low-pressure circuit
- Presents the entire contents of the circulation to the blood–gas interface

### Bronchial

- Circuit of the high-pressure systemic circulation
  - Provides the airways with nutrients
- [Note: The bronchial circulation drains O<sub>2</sub>-poor venous blood into the pulmonary veins, creating a **physiologic shunt**.]



Aspirating freshwater **decreases pulmonary compliance**, which increases the **work of breathing**. Fluid in the airways additionally prevents gas exchange, resulting in **hypoxia**. The compliance effects are due to water entering the pulmonary vasculature under the influence of colloid oncotic pressure ( $\pi_c$ ). Capillary hydrostatic pressure is very low in the pulmonary circulation, so  $\pi_c$  dominates. [Note: Drowning victims do not absorb sufficient water to affect serum electrolyte levels and ventricular function, as originally hypothesized.]



# Surfactant

5.3 Question



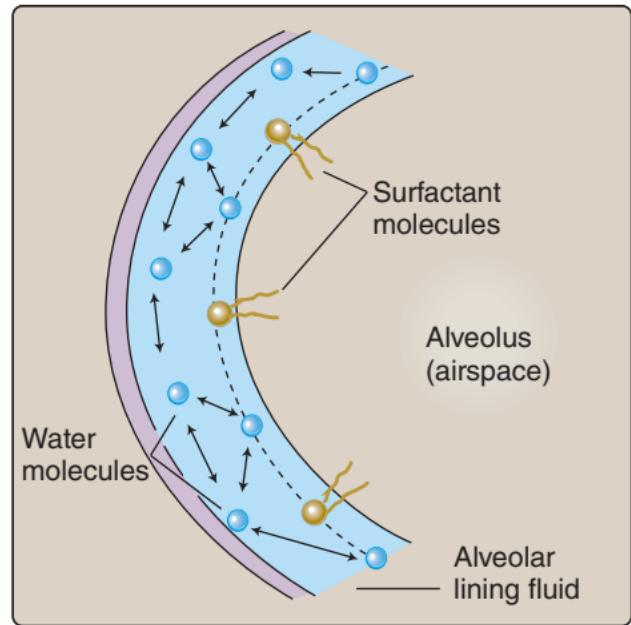
What is surfactant's composition and origin?



In what ways does surfactant assist lung function?



What is the cause and what are the symptoms of **infant respiratory distress syndrome (IRDS)**?





Surfactant is a mixture of phospholipids and a small number of essential proteins (~5% by weight) that is produced and secreted by **type II pneumocytes**. Surfactant phospholipids are **amphipathic**, causing them to localize to the air–water interface when secreted into the alveolar lumen.

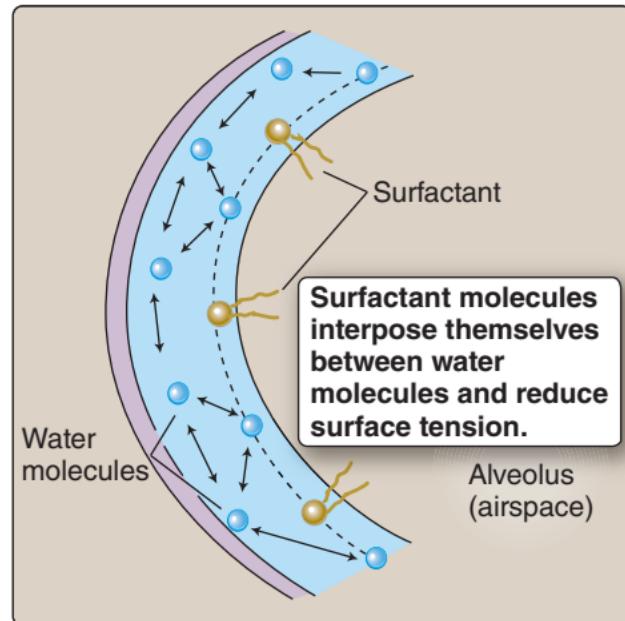


Surfactant reduces **alveolar lining fluid surface tension**, which has several benefits, including:

- **Helps stabilize alveolar size.** Surface tension favors alveolar collapse, but collapse concentrates the surfactant molecules which negates the effects of surface tension. Alveolar inflation has the opposite effect.
- **Increases lung compliance.** Decreasing surface tension decreases the **work of breathing**.
- **Helps keep lungs dry.** Surface tension promotes fluid movement from the vasculature into alveoli. Surfactant reduces this tendency.



**IRDS** is caused by surfactant deficiency in preterm infants. Immature lungs secrete inadequate amounts of surfactant, so work of breathing is high. Such infants show signs of respiratory distress and hypoxia, including tachypnea, use of accessory respiratory muscles, and cyanosis.





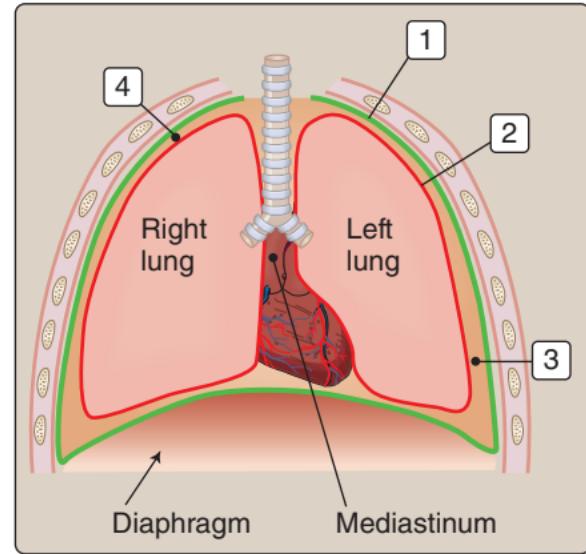
Identify the structures and compartments indicated by the boxed numerals.



Compartments [3] and [4] are filled with fluid. What are its principal functions?



What happens if air is introduced into either compartment [3] or [4]?





Four structures:

1. **Parietal pleura**
2. **Visceral pleura**
3. Left pleural space
4. Right pleural space

[Note: The right and left lungs are completely enclosed within their own pleura.]

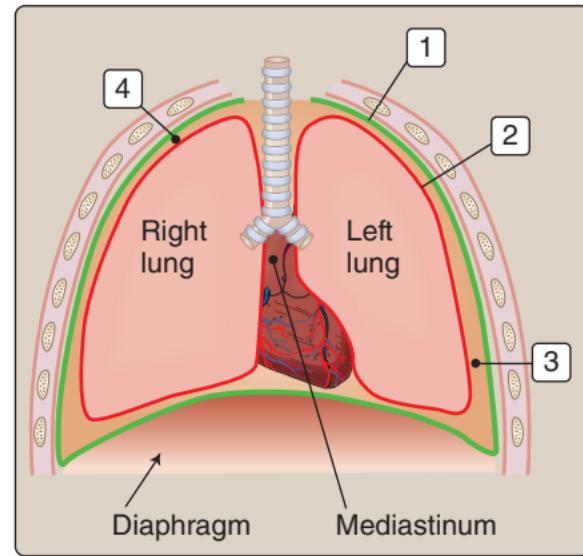


Pleural spaces are filled with ~10 mL of **pleural fluid**, whose functions include:

- **Lubrication:** The fluid allows the pleurae to slide over each other during breathing movements.
- **Cohesion:** Fluid is spread in a thin film that creates cohesion between the two pleurae, allowing forces generated by chest wall movement to be transferred to the underlying lungs.



If air is allowed to enter the pleural space (**pneumothorax**), the lung collapses, causing dyspnea and chest pain. Pneumothorax occurs when the pleurae are breached following chest wall trauma, for example, or spontaneously as a result of underlying lung disease. The lung's elastic recoil holds the pleural space at a negative pressure relative to the atmosphere, which is why air flows in when the pleurae are compromised.



# Pressure–Volume Loop

5.5 Question



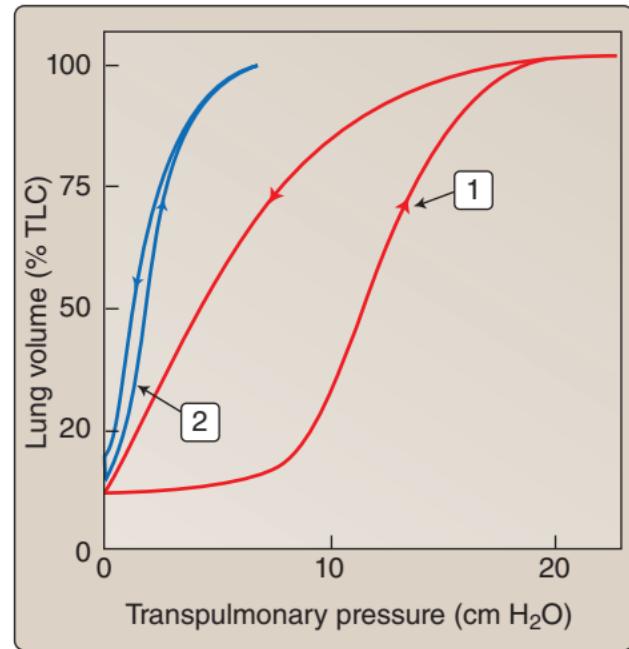
What do the red [1] and blue [2] plots in the graph represent?



Explain the features of the red plot. Why does the loop begin and end at a positive value?



How might **restrictive pulmonary disease** (e.g., **pulmonary fibrosis**) affect a pressure–volume loop compared with a healthy lung?





Plots represent:

1. Lung–volume changes during inspiration (ascending limb, right) and expiration (descending limb, left)
2. Volume changes in a saline-filled lung

The difference between the two reflects the effects of **alveolar lining fluid surface tension** on lung **compliance**.



Features of the pressure–volume loop:

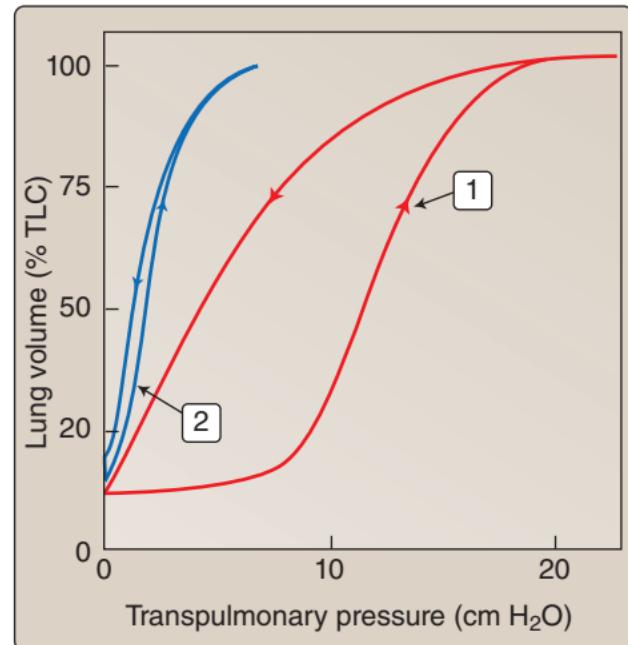
**Inspiration:** Smaller airways are collapsed and sealed by surface tension at low lung volumes. After sufficient pressure has been applied to reopen them, lung inflation proceeds linearly.

**Hysteresis:** Inflation recruits surfactant to the alveolar lining, decreasing the force favoring lung deflation.

**Offset:** Airway collapse seals and traps air within alveoli, so lung volume does not fall to zero upon expiration.



**Pulmonary fibrosis** and other restrictive diseases impair lung expansion, so higher transpulmonary pressures are required to achieve inflation, which manifests as a rightward shift in the loop.





# Airflow During Inspiration

5.6 Question



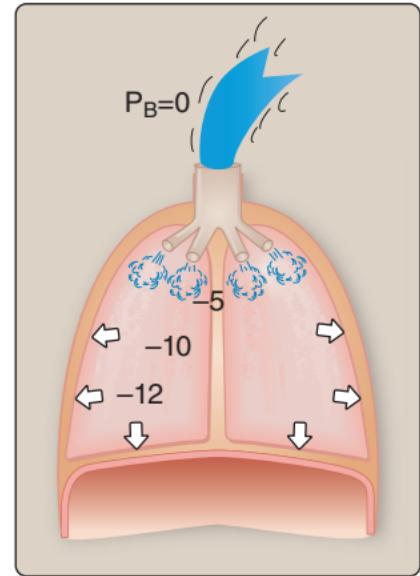
List the steps that result in air being drawn into the lungs during inspiration, as shown.



What is the main factor limiting airflow in the lungs, and how does it account for the apex-to-base intrapulmonary pressure gradient shown?



Short-acting beta-agonists (SABs) provide quick short-term relief of **asthma** symptoms by what mechanism of action?



Numerals indicate pressure in cm H<sub>2</sub>O.  
 $P_B$  = barometric pressure.

## 5.6 Answer

# Airflow During Inspiration



Steps causing airflow:

1. Diaphragm and external intercostal muscles contract.
2. Intrapleural pressure ( $P_{pl}$ ) becomes more negative.
3. Negative  $P_{pl}$  causes the lungs to expand, decreasing alveolar pressure ( $P_A$ ).
4. Air flows into lungs, driven by the barometric  $>$  alveolar pressure gradient.



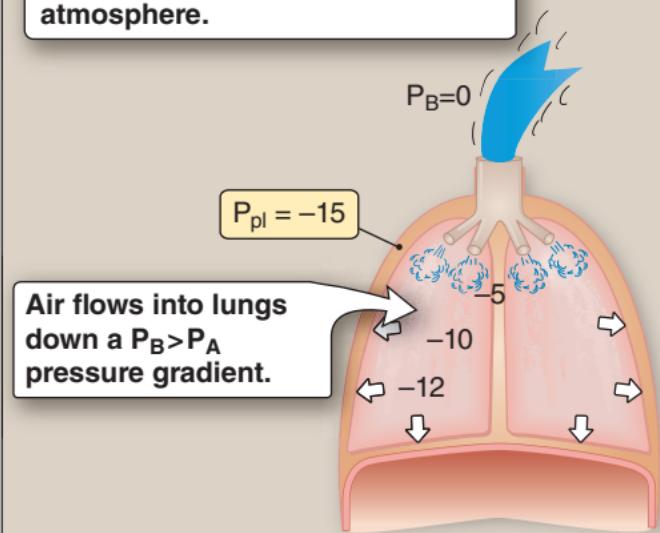
**Airway diameter** is the principal airflow-limiting factor (see 4.18). The large airways have a high resistance to airflow and are a significant determinant of lung inflation rate. In practice, this means that  $P_A$  at the lung base may remain lower than toward the apex for some time.

[Note: Airflow is also influenced by gas viscosity and turbulence within airways.]



**Asthma** symptoms are caused by bronchoconstriction, which limits airflow. SABs bind to  $\beta_2$ -ARs on parasympathetic nerve terminals and inhibit ACh-mediated airway smooth muscle contraction.  $\beta_2$ -Receptors normally mediate bronchodilation during sympathetic activation.

**Negative  $P_{pl}$  expands lungs, and  $P_A$  becomes negative as a result, creating a pressure gradient between alveoli and the external atmosphere.**



Pressures are in cm H<sub>2</sub>O.



# Airflow During Expiration

5.7 Question



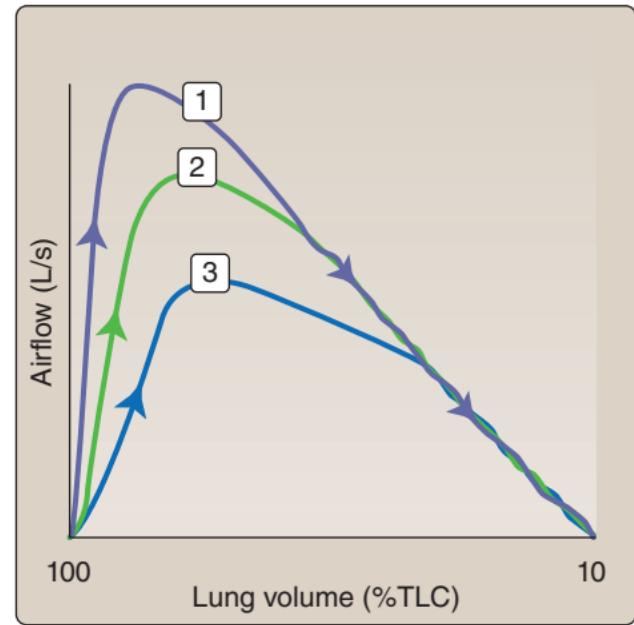
How does “radial traction” decrease airway resistance to airflow during inspiration?



What do the three plots at right demonstrate?



Why do patients with **chronic obstructive pulmonary disease (COPD)** often demonstrate pursed-lip breathing?



## 5.7 Answer

# Airflow During Expiration



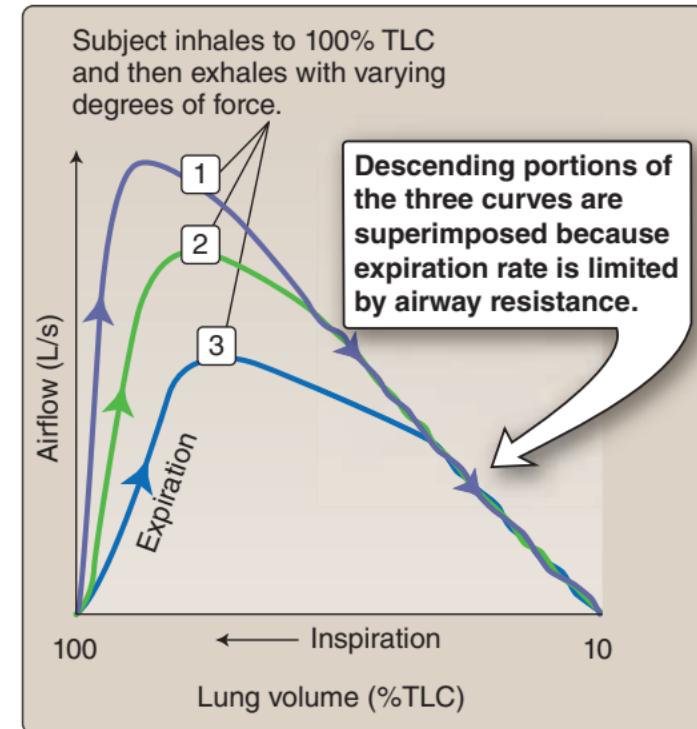
Airways and surrounding alveoli are all linked mechanically. During inspiration, alveoli and airways expand as one, causing airway resistance to fall. During expiration, alveoli deflate and airway diameter decreases, which increases resistance to airflow.



A forceful expiration raises intrapleural pressure to increase airflow, but it also collapses airways which limits maximal flow rates. Thus, while progressive increases in exhalation force do initially increase airflow (as shown), the three curves inevitably superimpose when airway collapse occurs.



**Pursed-lip breathing**, or “puffing,” moves the main site of airway resistance close to the lips, which prolongs the time during which airway pressure remains high. This delays airway collapse and coincident reduction in airflow, partly offsetting the negative effects of disease on ventilation.





# Pulmonary Function Tests

5.8 Question



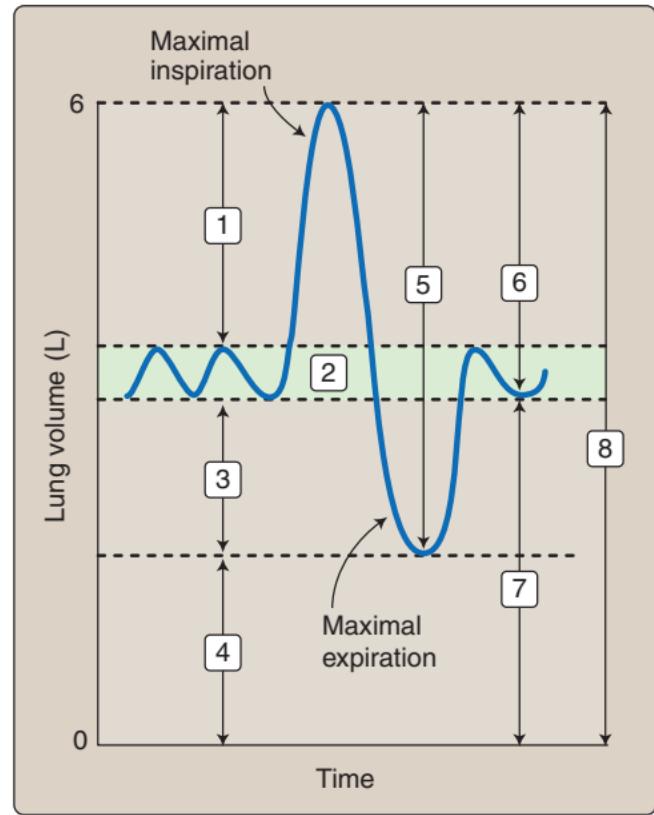
Identify the lung volumes and capacities indicated by boxed numerals.



Because spirometry alone is insufficient to determine all eight volumes and capacities, what additional tests are needed and what information do they provide?



Contrast the effects of **obstructive** and **restrictive** pulmonary disease on measured lung volumes.





Eight lung volumes and capacities:

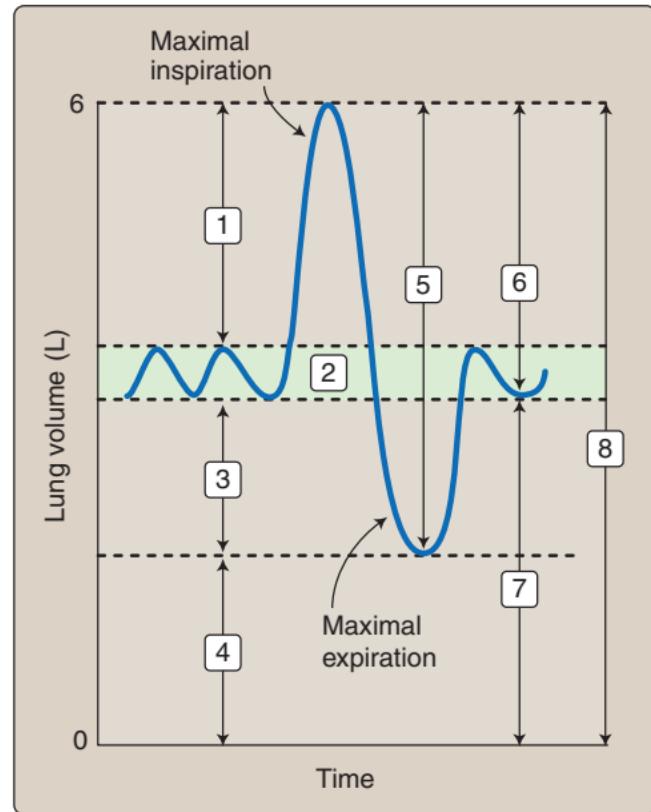
1. **Inspiratory reserve volume (IRV)**
2. **Tidal volume (TV)**
3. **Expiratory reserve volume (ERV)**
4. **Residual volume (RV)**
5. **Vital capacity (VC)**
6. **Inspiratory capacity (IC)**
7. **Functional residual capacity (FRC)**
8. **Total lung capacity (TLC)**



Spirometry cannot measure RV. A full set of **pulmonary function tests (PFTs)** includes body plethysmography, helium-dilution tests, or nitrogen-washout assays to yield RV, from which TLC and FRC can be calculated. [Note: PFTs also measure forced expiratory volume in 1 second (**FEV<sub>1</sub>**), which is useful in documenting obstructive pulmonary disease.]



Patients with **obstructive pulmonary disease** typically work at high lung volumes because exhalation is impaired by obstruction. RV is increased and FEV<sub>1</sub> markedly reduced. In contrast, **restrictive pulmonary disease** makes the lungs noncompliant and difficult to expand, reducing TLC.



# Partial Pressures

5.9 Question



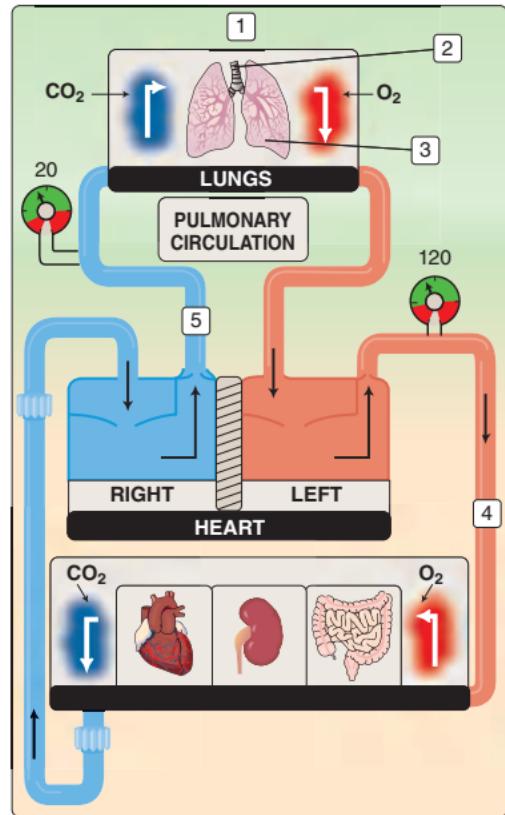
What are the partial pressures of O<sub>2</sub> and CO<sub>2</sub> in the following regions (as shown): [1] air, [2] conducting airways during inspiration, [3] alveoli, [4] aorta, and [5] pulmonary artery?



What is more likely to increase ventilation, a rise in P<sub>a</sub>CO<sub>2</sub> or a fall in P<sub>a</sub>O<sub>2</sub>?



Breathing air at depths of >40 m can cause \_\_\_\_\_, with effects on the CNS similar to those resulting from excess \_\_\_\_\_ consumption.





Partial pressures:

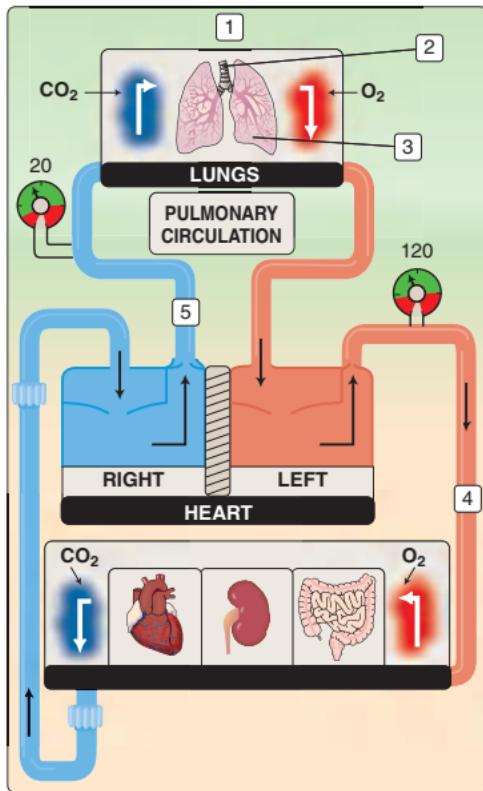
1. 160 mm Hg O<sub>2</sub>, 0 mm Hg CO<sub>2</sub>
2. 150 mm Hg O<sub>2</sub>, 0 mm Hg CO<sub>2</sub>
3. 100 mm Hg O<sub>2</sub>, 40 mm Hg CO<sub>2</sub>
4. ~98 mm Hg O<sub>2</sub>, 40 mm Hg CO<sub>2</sub>
5. 40 mm Hg O<sub>2</sub>, 45 mm Hg CO<sub>2</sub>



A rise in P<sub>a</sub>CO<sub>2</sub> is more likely to increase ventilation. P<sub>a</sub>CO<sub>2</sub> impacts blood pH, which is tightly controlled in part through ventilatory changes. Ventilation is much less sensitive to P<sub>a</sub>O<sub>2</sub>, which can fall to ~60 mm Hg without producing major ventilation changes (see 5.18).



Breathing air at depths of >40 m can cause **nitrogen narcosis**, with effects on the CNS similar to those resulting from excess **alcohol** consumption. [Note: The partial pressure of all gases increases with depth below water. At depths of >40 m, the partial pressure of N<sub>2</sub> rises to the point where significant amounts of N<sub>2</sub> are taken up by the body. N<sub>2</sub> has narcotic-like actions when it dissolves in neuronal membranes.]



# Pulmonary Vascular Resistance

5.10 Question



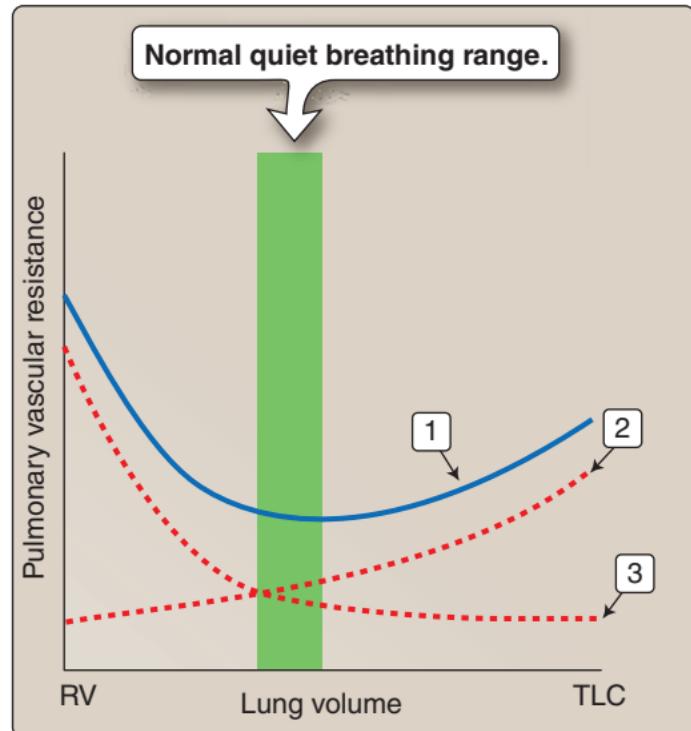
Explain the differences between the three plots indicated by boxed numerals.



What is the primary physiologic regulator of pulmonary vascular resistance (PVR) and pulmonary blood flow?



What is **pulmonary hypertension (PH)**, and how might it be induced by chronic exposure to high altitude?





Three plots represent:

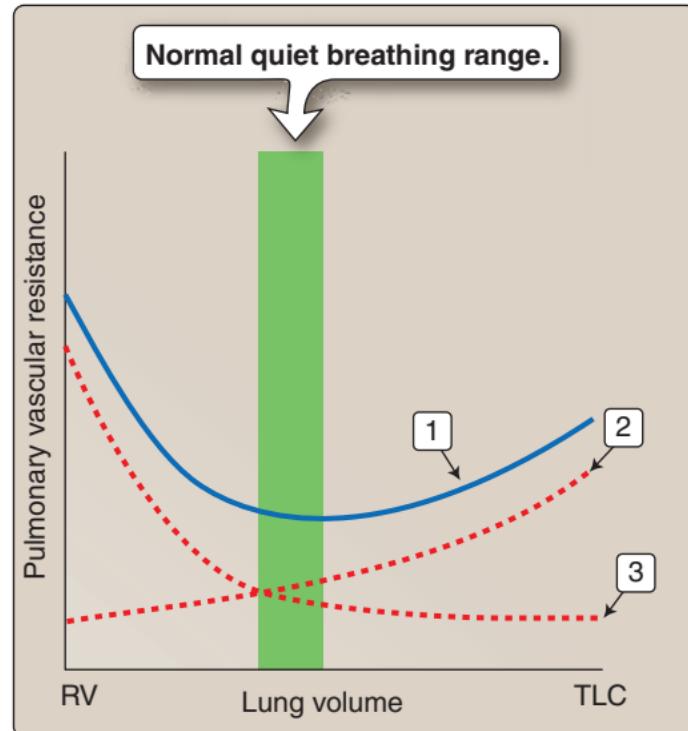
1. PVR dependence on lung volume
2. Capillary contribution to PVR (alveolar inflation stretches and compresses capillaries, increasing flow resistance)
3. Supply vessel effects on PVR (vessels dilate by radial traction when lungs inflate, reducing flow resistance)



$O_2$  is a primary physiologic regulator of pulmonary resistance vessels and PVR. A decrease in alveolar  $O_2$  causes **hypoxic vasoconstriction** and shunting of blood to well-ventilated regions. [Note: Pulmonary resistance vessels are relatively insensitive to sympathetic activity or humoral factors.]



**PH** is indicated by a mean pulmonary artery pressure of  $\geq 25$  mm Hg at rest (normal is  $\leq 20$  mm Hg). Living at high altitude causes a chronic increase in PVR through hypoxic vasoconstriction. Right ventricular pressure rises as a result, causing PH. In time, vascular remodeling may cause a persistent decrease in pulmonary vessel lumen diameter and precipitate **right heart failure**.



# Gravitational Effects on Lung Function

5.11 Question



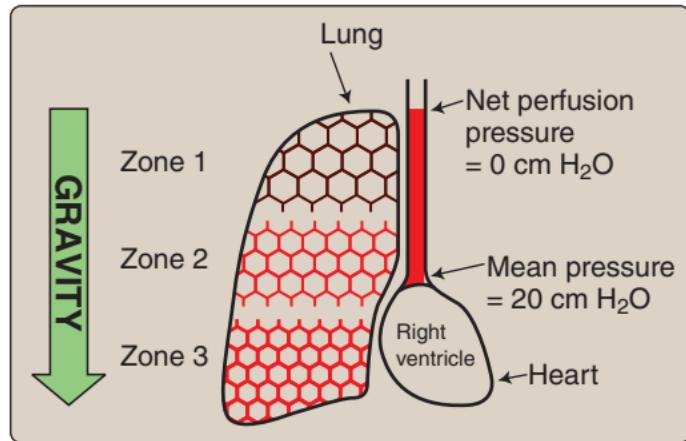
Explain how gravity affects alveolar perfusion, referencing the three zones shown.



How do the regional differences in perfusion and alveolar size affect local  $\dot{V}_A/\dot{Q}$  ratios?



*Mycobacterium tuberculosis* typically establishes itself in the lung apices. How is this related to regional differences in ventilation and perfusion?





The right ventricle generates a pressure of  $\sim 20$  cm H<sub>2</sub>O. Gravity reduces pulmonary arterial pressure at the lung apex to zero and creates negative pulmonary venous pressures, which impacts capillary perfusion.

Zone 1: Mean pulmonary capillary hydrostatic pressure ( $P_{pc}$ ) is negative, so capillaries are collapsed and nonperfused.

Zone 2:  $P_{pc}$  is high enough to maintain patency and perfusion begins.

Zone 3:  $P_{pc}$  and flow is maximal.



Lung mass is forced downward by gravity. In an upright lung, apical alveoli are expanded by the downward force, whereas alveoli in the base are compressed by the mass of tissue above. This affects the extent to which alveoli ventilate during inspiration.

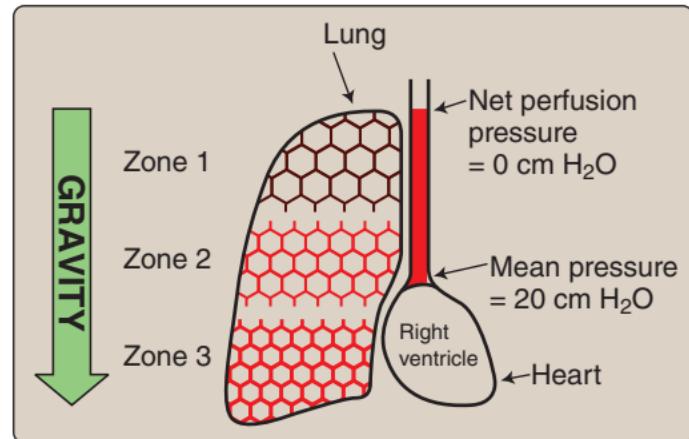
Zone 1: Alveoli are expanded at rest and ventilate poorly upon inspiration. They are also poorly perfused.  $V_A/Q$  approaches infinity.

Zone 2: Ventilation and perfusion both increase rapidly with decreasing height in the lung.

Zone 3: Compressed alveoli ventilate very well and are maximally perfused.  $V_A/Q$  is optimal.



The lung apex is poorly perfused, so alveolar gas composition here resembles inspired air. *M. tuberculosis* favors regions where O<sub>2</sub> levels are high, so often establishes itself in this region.



# Gas Exchange

## 5.12 Question



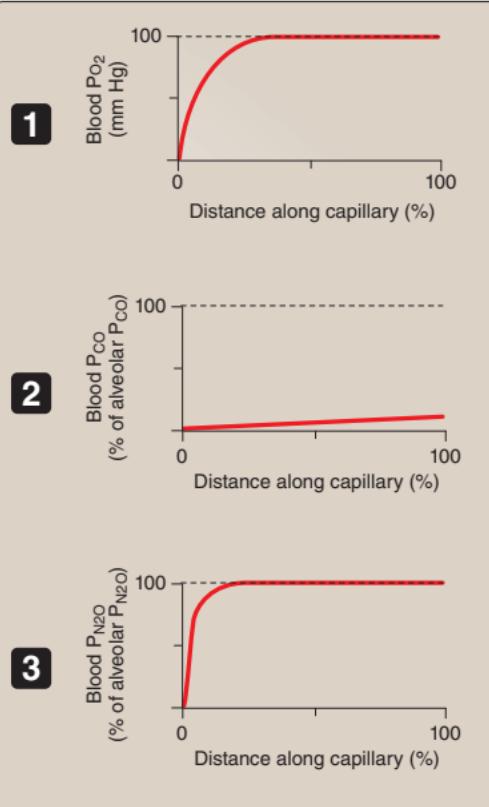
What do the three graphs at right demonstrate?



Referring to the graphs, how would increasing ventilation and perfusion affect gas exchange?



How do **obstructive** and **restrictive pulmonary diseases** affect gas exchange?





All three graphs describe characteristics of gas exchange between the alveolus and pulmonary blood:

1. Normal O<sub>2</sub> uptake
2. Diffusion-limited exchange (CO binds to Hb with high affinity, so alveolar P<sub>CO</sub> and blood P<sub>CO</sub> never equilibrate)
3. Perfusion-limited exchange (Hb does not bind N<sub>2</sub>O, so equilibration occurs rapidly)



Effects of increasing ventilation and perfusion:

Graph 1: ↑ Ventilation: no practical effect

↑ Perfusion: O<sub>2</sub> uptake increase

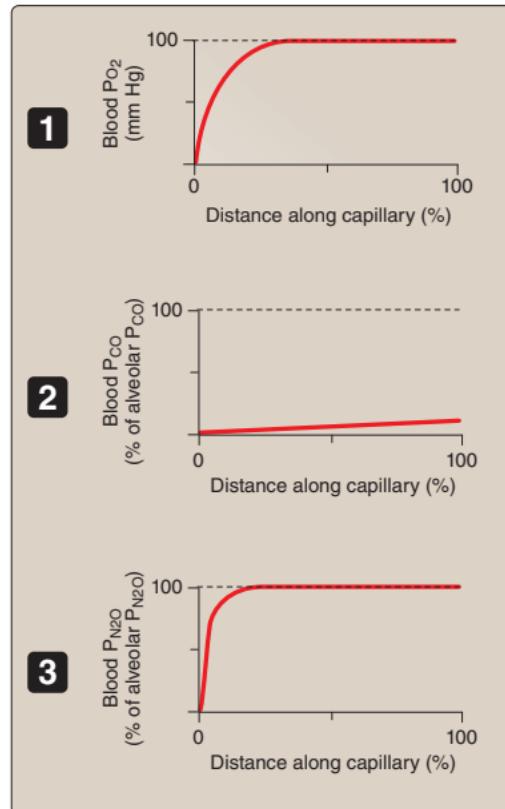
Graph 2: No practical effect for either (exchange is limited by exchange barrier properties)

Graph 3: ↑ Ventilation: no practical effect

↑ Perfusion: N<sub>2</sub>O uptake increase



Both **obstructive** and **restrictive pulmonary diseases** reduce gas exchange by reducing lung diffusing capacity (D<sub>L</sub>). However, obstructive diseases reduce surface area available for exchange, whereas restrictive diseases increase exchange barrier thickness.



# Oxygen Transport I

5.13 Question



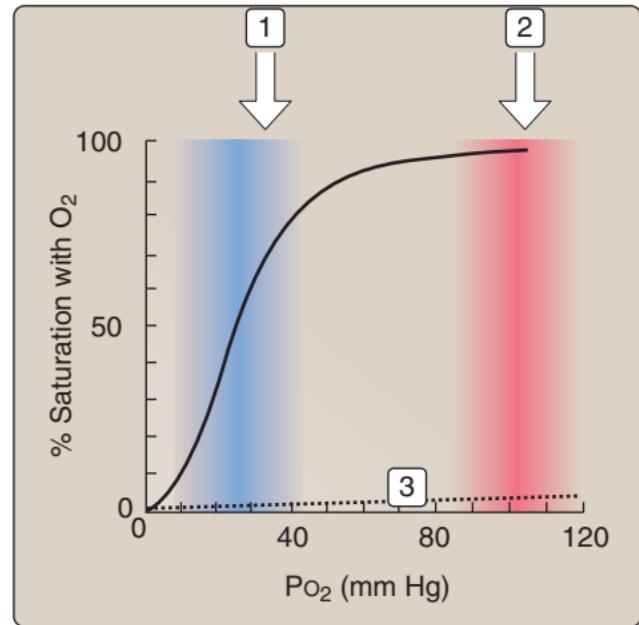
What do the colored bands and the dotted line indicated by boxed numerals represent?



How would a ~10% decrease in Hb concentration affect blood O<sub>2</sub> saturation and O<sub>2</sub>-carrying capacity?



A trauma patient has sustained a class IV hemorrhage involving loss of ~50% of blood volume. The patient's family is refusing transfusion on religious grounds. What is of greater concern, the fluid volume loss or the Hb loss?





Boxed numerals represent:

1. Range of  $P_{O_2}$  values observed in tissues
2. Range of  $P_{O_2}$  values in lungs
3. Amount of  $O_2$  dissolved in blood

[Note: The dissociation curve's steepest portion coincides with tissue  $O_2$  levels, allowing for efficient  $O_2$  unloading.]



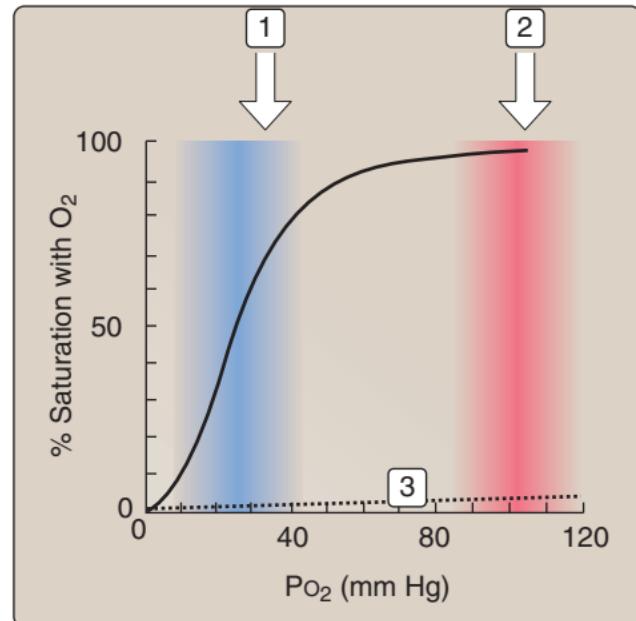
10% decrease in Hb effects:

**$O_2$  saturation:** No effect. Saturation reflects the number of occupied Hb  $O_2$ -binding sites, not total Hb content.

**$O_2$  capacity:** 10% decrease.  $O_2$ -carrying capacity is dependent on Hb concentration.



Blood volume loss is of greater concern with a class IV hemorrhage. Hemorrhages affecting blood volume by >40% cause tissue hypoperfusion and impaired mental status due to an inability to sustain adequate arterial pressure. By contrast, Hb levels can fall from a normal 15 g/dL to 7 g/dL with no significant risk of increased mortality.



# Oxygen Transport II

## 5.14 Question



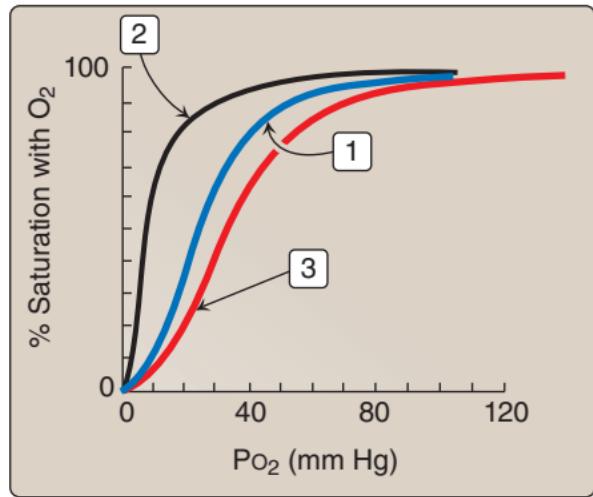
In the graph, if [1] is a normal oxyhemoglobin-dissociation curve, what might cause the shifts indicated by [2] and [3]?



What are the characteristics of HbF, and how do they aid fetal growth and development?



Why is CO, the leading cause of poisoning deaths in the United States, such a lethal gas?





Oxyhemoglobin-dissociation curve shifts:

**Leftward (increased affinity)** [2]: decreased body temperature, acidity,  $\text{PCO}_2$ , or 2,3-diphosphoglycerate (2,3-DPG) levels

**Rightward (decreased affinity)** [3]: increased temperature,  $\text{PCO}_2$ , or acidity—conditions associated with increased metabolism (rightward shifts facilitate  $\text{O}_2$  unloading, and a rise in 2,3-DPG levels decreases Hb  $\text{O}_2$  affinity)

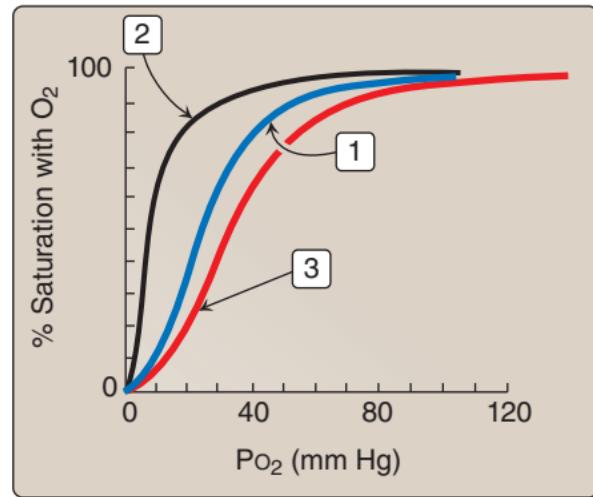


The fetal oxyhemoglobin-dissociation curve is shifted leftward compared with HbA. This shift helps compensate for the limitations inherent in  $\text{O}_2$  delivery via the placenta ( $\text{PO}_2$  rarely exceeds 40 mm Hg) and allows HbF to achieve 80%  $\text{O}_2$  saturation.

*A-plus:* HbF contains two  $\gamma$ -chains in place of the two  $\beta$ -chains common to HbA.  $\gamma$ -Chains bind 2,3-DPG weakly and have an increased  $\text{O}_2$  affinity compared with  $\beta$ -chains.



CO is so lethal because it binds to Hb with high affinity and prevents  $\text{O}_2$  binding. It also shifts the oxyhemoglobin-dissociation curve leftward, which decreases  $\text{O}_2$  unloading. [Note: CO is a common pollutant. Carboxyhemoglobin makes up ~3% of total Hb concentration in nonsmokers.]





# Carbon Dioxide Transport

5.15 Question



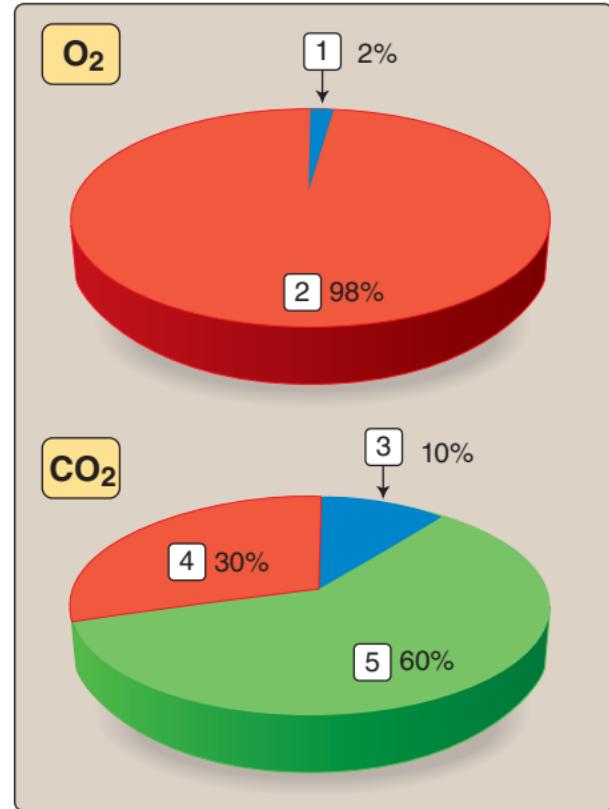
The figure compares modes of O<sub>2</sub> and CO<sub>2</sub> transport by blood. Identify the modes of transport indicated by the boxed numerals.



What is the Haldane effect and why is it important in respiratory physiology?



What does an arterial blood gas (ABG) test measure?





O<sub>2</sub> and CO<sub>2</sub> transport modes:

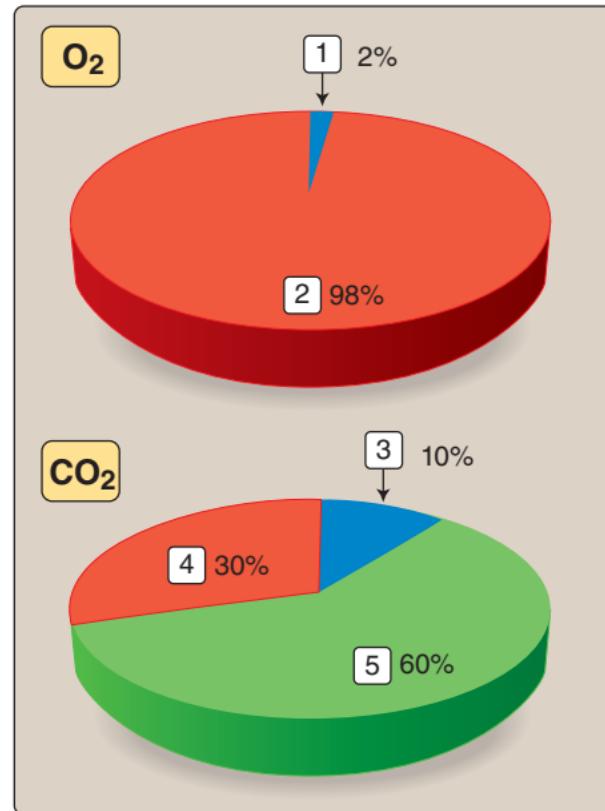
1. Dissolved O<sub>2</sub>
2. O<sub>2</sub> bound to Hb
3. Dissolved CO<sub>2</sub>
4. CO<sub>2</sub> bound to Hb and other proteins
5. HCO<sub>3</sub><sup>-</sup>



When Hb unloads O<sub>2</sub>, its CO<sub>2</sub>-carrying capacity is increased, a phenomenon known as the **Haldane effect**. CO<sub>2</sub> is carried primarily in carbamino form. This is advantageous because it allows Hb to carry significant amounts of CO<sub>2</sub> back to the lungs, where O<sub>2</sub> loading promotes CO<sub>2</sub> release to the atmosphere.



An ABG measures P<sub>a</sub>O<sub>2</sub>, P<sub>a</sub>CO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup> concentration, oxyhemoglobin saturation, and the pH of arterial blood. [Note: The sample must be iced and analyzed within 15 minutes to minimize the effects of gas loss by diffusion through plastic sample tubes and O<sub>2</sub> use by blood's cellular components.]



# Carbon Dioxide and pH Balance

5.16 Question



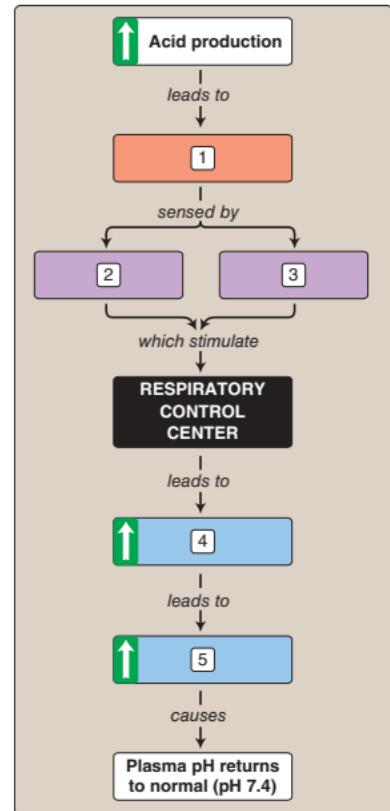
Identify the five numbered steps in the ventilatory response to acid, as shown.

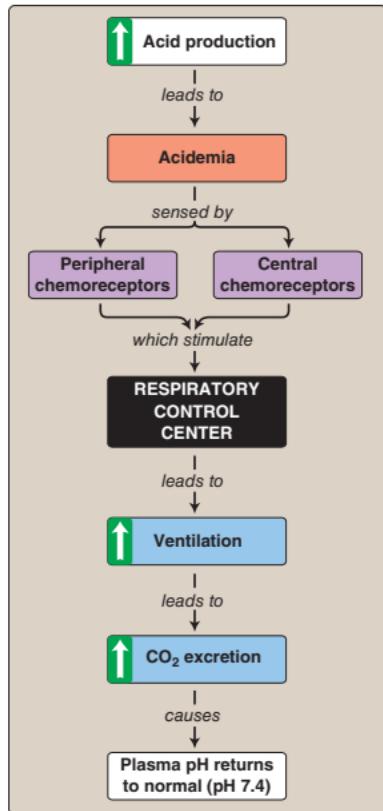


CO<sub>2</sub> dissolves in water to form carbonic acid, which then dissociates to give H<sup>+</sup> and HCO<sub>3</sub><sup>-</sup>. How can the effects of volatile acid production on blood pH be calculated?



**Salicylate** (\_\_\_\_) poisoning causes a combined **metabolic** and **respiratory** \_\_\_\_\_, the latter through suppression of the medullary \_\_\_\_\_ center.





The **Henderson-Hasselbalch** equation shows the relationship between pH and dissolved concentrations of CO<sub>2</sub> and HCO<sub>3</sub><sup>-</sup>:

$$\text{pH} = \text{pK} + \log \frac{[\text{HCO}_3^-]}{[\text{CO}_2]}$$

where pK is the dissociation constant for carbonic acid. Using normal blood values ([HCO<sub>3</sub><sup>-</sup>] = 24 mmol/L, [CO<sub>2</sub>] = P<sub>CO<sub>2</sub></sub> × CO<sub>2</sub> solubility constant = 40 mm Hg × 0.03):

$$\text{pH} = 6.1 + \log \frac{24}{40 \times 0.03} = 7.4$$



**Salicylate (aspirin) poisoning** causes a combined **metabolic** and **respiratory acidosis**, the latter through suppression of the medullary **respiratory** center.

# Peripheral Chemoreceptors

5.17 Question



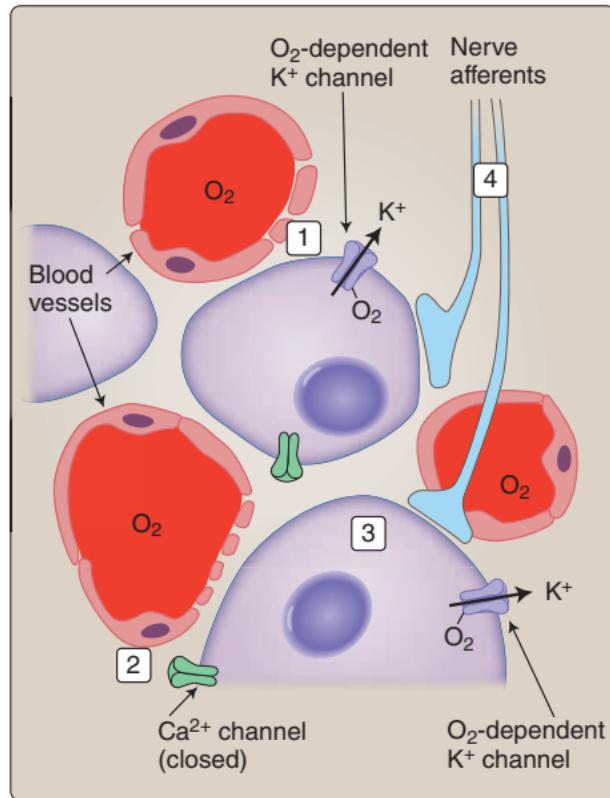
What is the location and function of peripheral chemoreceptors involved in respiratory (and cardiac) control?



Using the boxed numerals as a guide, list the events that culminate in peripheral chemoreceptor afferent nerve signaling following a drop in arterial  $Po_2$ .



**Carotid body tumors**, or \_\_\_\_\_, are generally nonmalignant, but they may cause eyelid ptosis and pupil miosis (\_\_\_\_ syndrome) by pressing on \_\_\_\_\_ nerves.



# Peripheral Chemoreceptors



Peripheral chemoreceptors are highly vascularized bodies located in the carotid sinus and along the inside of the aortic arch. They monitor and signal when  $P_{a}O_2$  falls, but they are also sensitive to  $P_{a}CO_2$  and plasma pH. They signal via the glossopharyngeal nerve (CN IX, carotid bodies) and vagus nerve (CN X, aortic bodies). [Note: The carotid bodies are the primary peripheral chemoreceptors. Aortic bodies may not have a significant role in adult respiratory control.]

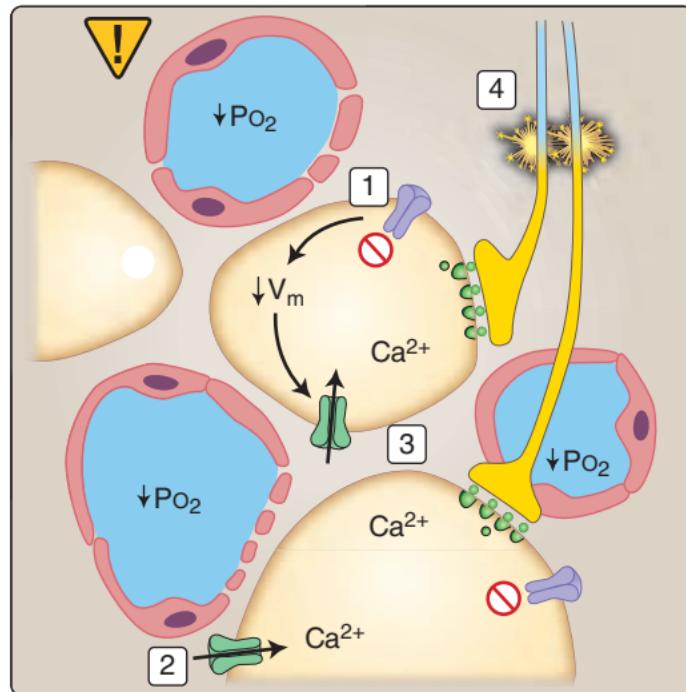


Consequences of a drop in arterial  $Po_2$ :

1.  $O_2$ -dependent  $K^+$  channel closes and the glomus cell depolarizes.
2. Depolarization activates voltage-gated  $Ca^{2+}$  channels.
3.  $Ca^{2+}$  influx triggers neurotransmitter release.
4. Sensory afferents signal to the CNS.



**Carotid body tumors**, or **paragangliomas**, are generally nonmalignant, but they may cause eyelid ptosis and pupil miosis (**Horner syndrome**) by pressing on **sympathetic** nerves.



# Central Chemoreceptors

5.18 Question



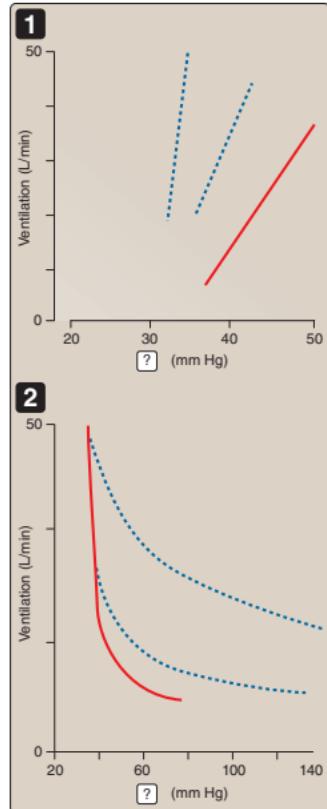
In the graphs, what are the missing *x* axes variables? If the red lines are normal, what do the broken blue lines indicate?



Central chemoreceptors monitor pH changes caused by variations in  $P_a\text{CO}_2$ . How is this possible when central chemoreceptor neurons are located behind the blood–brain barrier (BBB), which is impermeant to  $\text{H}^+$ ?



Why might patients with **chronic obstructive pulmonary disease** and with hypercapnia lose ventilatory drive when given supplemental  $\text{O}_2$ ?





Graphs show ventilatory responses to  $\text{CO}_2$  and  $\text{O}_2$ .

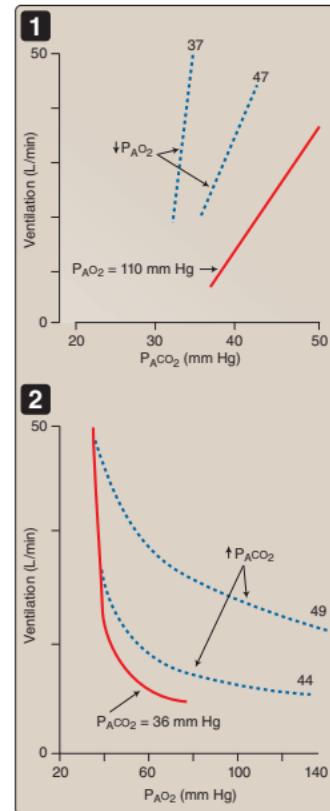
1.  **$\text{P}_{\text{ACO}_2}$ :** Ventilation increases with  $\text{P}_{\text{ACO}_2}$ , a response mediated primarily by central chemoreceptors. The red line shows responses at a normal  $\text{P}_{\text{AO}_2}$ . The line shifts leftward as  $\text{P}_{\text{AO}_2}$  is lowered.
2.  **$\text{P}_{\text{AO}_2}$ :** Ventilation increases sharply once  $\text{P}_{\text{AO}_2}$  drops below  $\sim 60$  mm Hg (red line; normal  $\text{P}_{\text{ACO}_2}$ ), a response mediated primarily by peripheral chemoreceptors. Raising  $\text{P}_{\text{ACO}_2}$  shifts the curve rightward.



Although the BBB is  $\text{H}^+$ -impermeant,  $\text{CO}_2$  readily crosses the barrier and dissolves in CSF to form carbonic acid. The chemoreceptors sense the pH drop and increase ventilation to compensate. [Note: The BBB's  $\text{H}^+$  impermeability allows the chemoreceptors to distinguish changes in  $\text{P}_{\text{aCO}_2}$  from background changes in ECF pH.]



Patients with **chronic hypercapnia** become dependent on monitoring  $\text{P}_{\text{aO}_2}$  to sustain ventilatory drive. Thus, supplemental  $\text{O}_2$  administration removes this drive and may precipitate **hypercapnic respiratory failure**.



# Pulmonary Receptors

5.19 Question



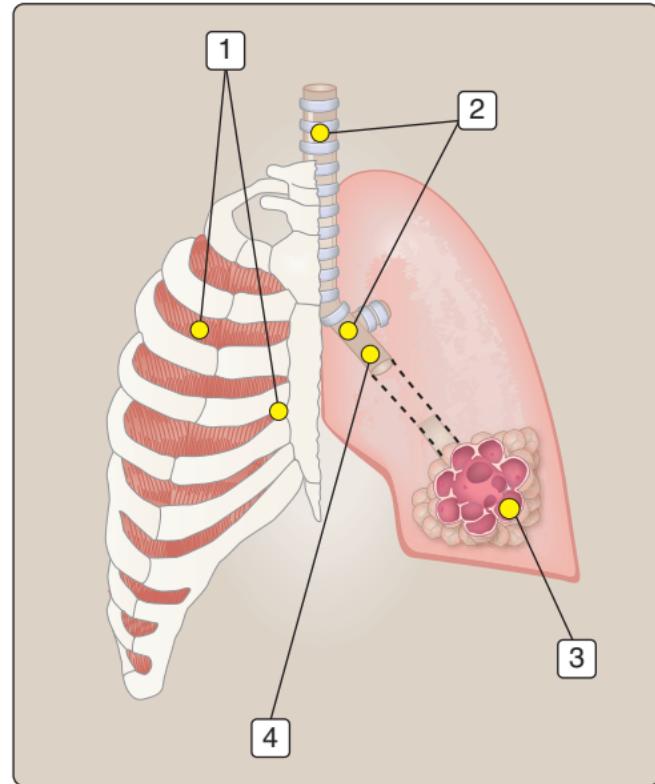
Identify the four general classes of sensory receptor associated with the lung and chest wall, indicated by boxed numerals.



Which of these receptors might be involved in controlling ventilation during exercise, for example, and which might be involved in responses to smoke inhalation?



What is **dyspnea**? Is dyspnea caused by chemoreceptor activation or by stimulation of receptors associated with the lung and chest wall?





Four sensory receptor classes:

1. **Muscle and joint** receptors
2. **Irritant receptors** in the epithelium of the larger airways
3. **Juxtapulmonary capillary receptors (J receptors)**
4. **Stretch receptors**



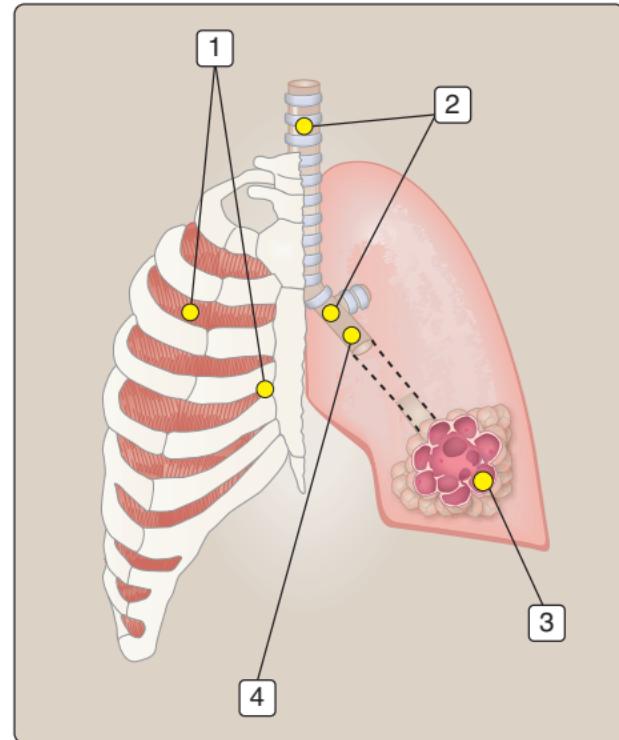
Receptors active during exercise and smoke inhalation:

**Exercise:** Primarily muscle and joint receptors and airway stretch receptors. Muscle spindles plus stretch and tension receptors in joints inform the respiratory centers about chest wall position and effort required for breathing movements. Stretch receptors are slow-adapting sensory fibers in airway walls that provide information about lung volume during inspiration.

**Smoke inhalation:** Primarily irritant and J receptors. Nerve endings located in the larger conducting airways and C-fibers in alveolar walls respond to irritants, although they are also sensitive to lung inflation.

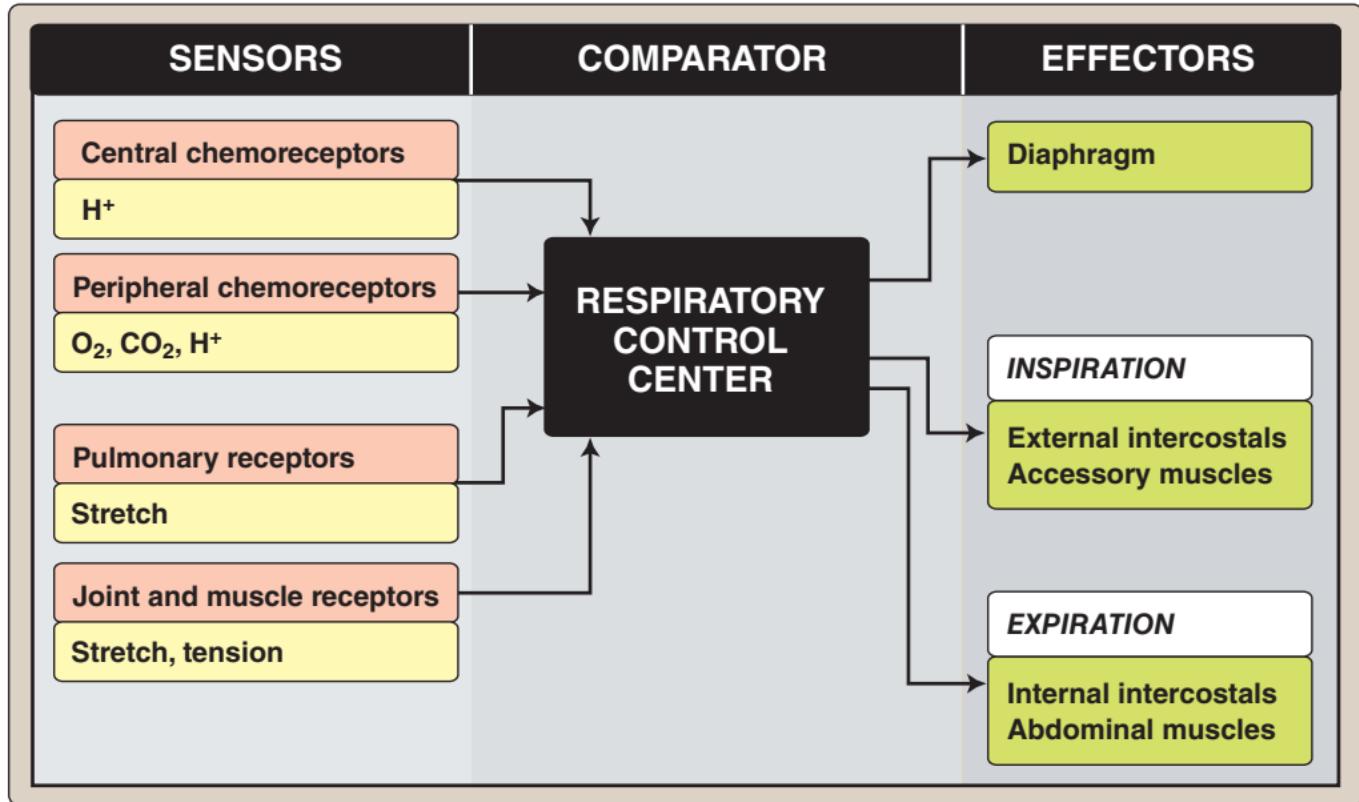


**Dyspnea** is a term used to describe breathing discomfort, which may involve numerous physiologic and psychologic contributing factors. Although dyspnea can be induced by chemoreceptor activation alone, the other pulmonary (and systemic) receptors contribute, particularly to sensations of chest “tightness.”



# Respiratory Regulation

5.20 Summary





## Sensors

1. Central chemoreceptors: Located in the brainstem medulla, they monitor  $\text{Pco}_2$  through changes in ECF pH.
2. Peripheral chemoreceptors: Located in aortic and carotid bodies, they monitor  $P_a\text{O}_2$ ,  $P_a\text{CO}_2$ , and pH. Information is relayed to the integrator via CN IX (carotid bodies) and CN X (aortic bodies).
3. Pulmonary receptors: Stretch receptors in the airways monitor lung inflation. Receptors in the alveolar walls (J receptors) respond to chemicals and alveolar inflation.
4. Joint and muscle receptors: These measure joint position and muscle tension (spindles).

## Integrator

1. Brainstem medulla has two groups of cells based on function:
  - Dorsal respiratory group controls diaphragm during inspiration.
  - Ventral respiratory group coordinates accessory muscles (inspiration and expiration).
2. Pons: Apneustic center and pneumotaxic centers (role in adult is uncertain).
3. Cortex allows for conscious control of breathing movements.

## Effectors

1. Inspiration:
  - Diaphragm pushes down on abdominal contents. It is innervated by the phrenic nerve.
  - External intercostals pull ribs upward and outward.
  - Accessory muscles elevate the upper two ribs and sternum and dilate upper airways.
2. Expiration:
  - Abdominal muscles push the diaphragm up during forced expiration.
  - Internal intercostals pull the ribs downward and inward.

# The Kidney

## 6.1 Question



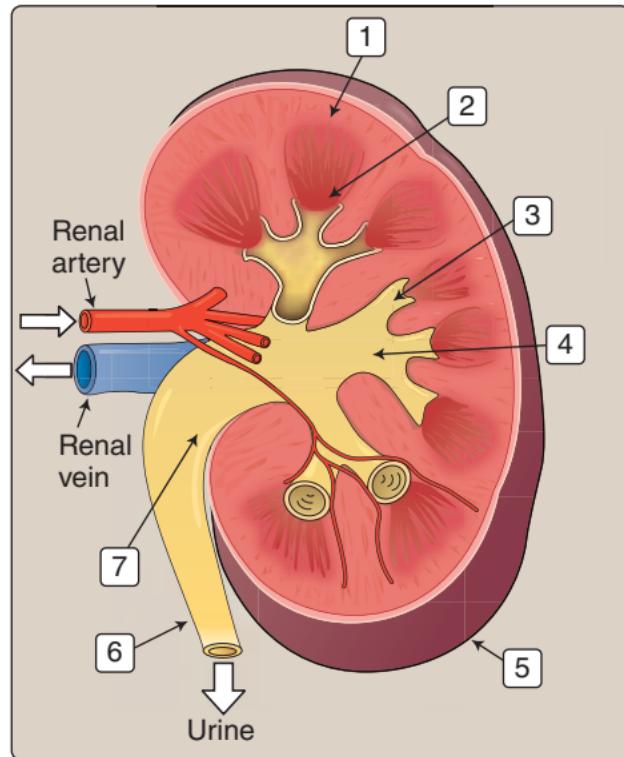
Identify the gross anatomical features of the kidney indicated by boxed numerals.



What are the kidney's three principal functions?



\_\_\_\_\_ (AIN) is an inflammatory condition commonly induced by drug therapy that affects the kidney interstitium. Symptoms may include an acute rise in plasma \_\_\_\_\_ levels and proteinuria.



## 6.1 Answer

# The Kidney



Kidney anatomical features:

1. **Pyramid**: a collection of renal tubules
2. **Papilla**: urine emerges at tip
3. **Minor calyx**: funnels urine
4. **Major calyx**: funnels urine
5. **Capsule**: connective tissue
6. **Ureter**: conveys urine to bladder
7. **Renal pelvis**: funnels urine

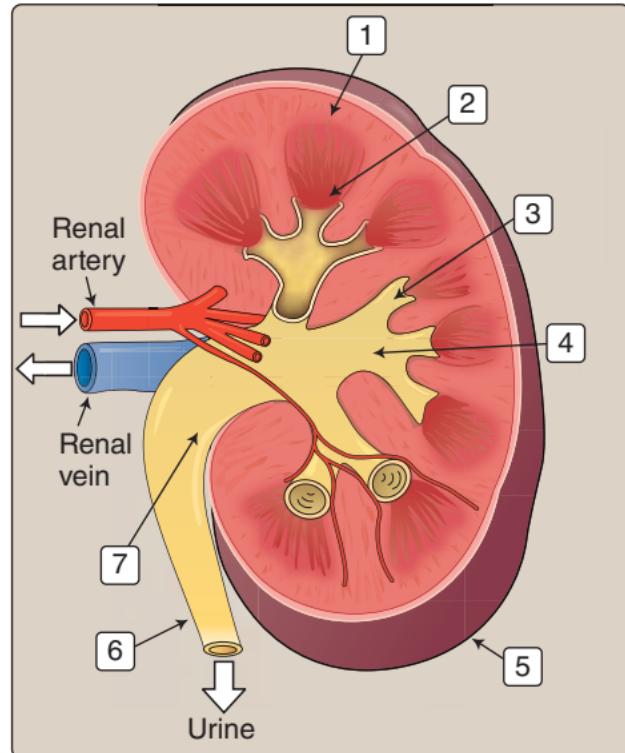


Kidney's three principal functions:

- **Endocrine control**: controls release of angiotensin II (involved in salt and water balance and blood pressure control) and produces hormones regulating blood cell production (e.g., erythropoietin)
- **Excretion**: filters blood and excretes waste products as urine
- **Homeostasis**: helps maintain electrolyte balance, acid–base balance, and blood pressure



**Acute interstitial nephritis (AIN)** is an inflammatory condition commonly induced by drug therapy that affects the kidney interstitium. Symptoms may include an acute rise in plasma creatinine levels and proteinuria. [Note: AIN can also be caused by autoimmune disorders such as **sarcoidosis**, but antibiotics are the most common cause.]



# Nephrons

## 6.2 Question



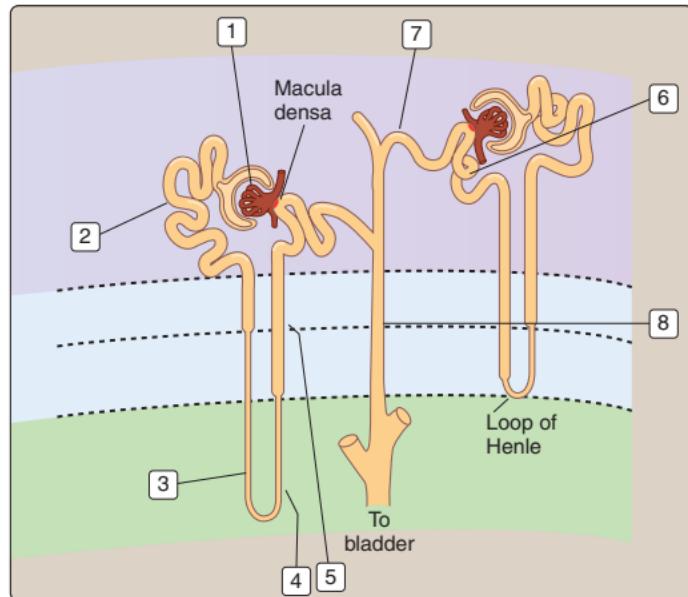
Identify the structures indicated by boxed numerals.



What are the kidney's two main nephron types and how do they differ?



What is **polycystic kidney disease**?





Nephron structures shown are:

1. **Glomerulus**
2. **Proximal convoluted tubule**
3. **Descending thin limb of Henle**
4. **Ascending thin limb of Henle**
5. **Thick ascending limb**
6. **Distal convoluted tubule**
7. **Connecting duct**
8. **Collecting duct**

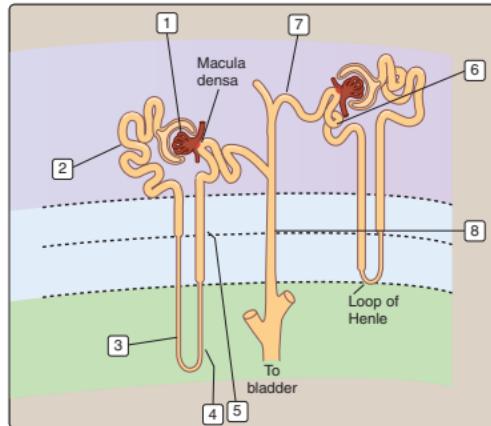


The kidney's two main nephron types are distinguished by location and loop length:

- **Superficial:** They have short nephron loops (**loop of Henle**) that extend into the outer medulla but not the inner medulla. They receive ~90% of renal arterial blood and outnumber juxtamedullary nephrons by the same degree.
- **Juxtamedullary:** Their glomeruli are located at the border between cortex and medulla, and their nephron loops dip deep into the inner medulla. Although they receive ~10% of renal blood supply and their numbers are low, they are primarily responsible for the kidney's ability to concentrate urine.



**Polycystic kidney disease** is an inherited disorder that causes fluid-filled cysts to form within the kidney and other organs. The cysts progressively enlarge until they compromise kidney function and precipitate organ failure. No effective treatment exists.



# Blood Supply

## 6.3 Question



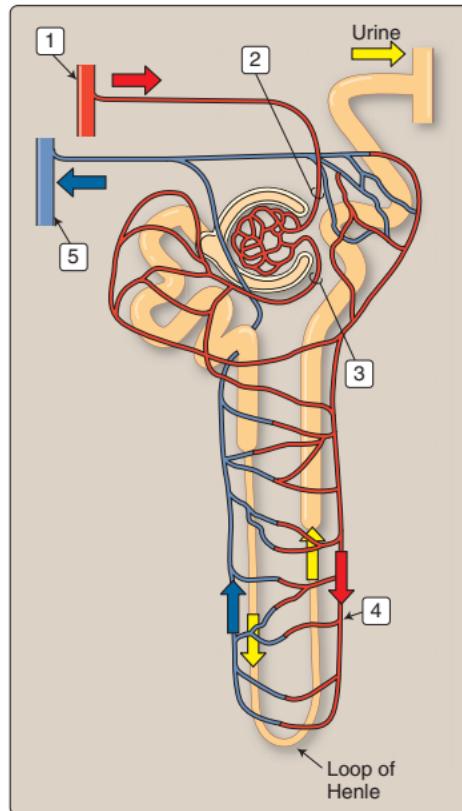
Identify the blood vessels indicated by boxed numerals.



What are the functions of the glomerular and peritubular capillary networks?



How can renal blood flow be quantified clinically?





Blood vessels shown:

1. **Interlobular artery**
2. Glomerular **afferent arteriole**
3. Glomerular **efferent arteriole**
4. **Peritubular capillary network**
5. **Interlobular vein**

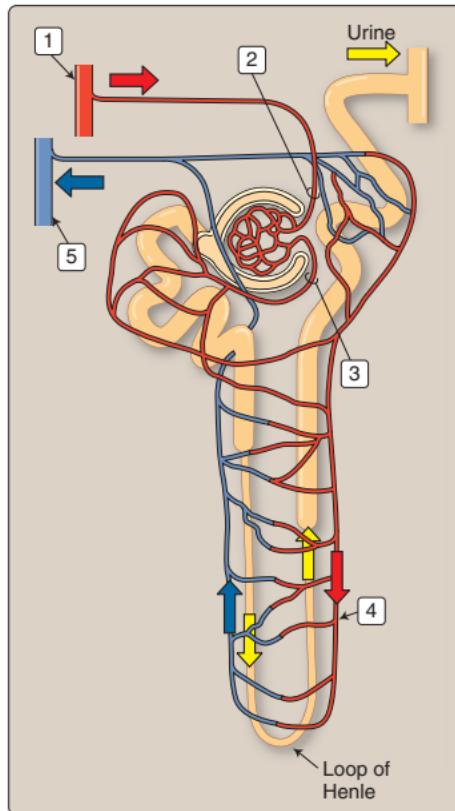


Glomerular and peritubular capillary networks have distinct functions:

- **Glomerular network:** biologic filter used to separate fluid from the cellular and proteinaceous blood components. The capillary walls are highly fenestrated and capillary hydrostatic pressure is relatively high to facilitate ultrafiltration.
- **Peritubular network:** delivers  $O_2$  and nutrients to the nephron. Peritubular capillaries also carry away water and other materials reabsorbed by the tubule.  
 [Note: The glomerular and peritubular capillary networks form a serial circuit. In practice, this means that the glomerular resistance vessels control flow through both networks.]



Renal blood flow can be estimated from a knowledge of renal plasma flow (RPF) and Hct. RPF can be determined experimentally using *para*-aminohippurate clearance (see 6.10), although such determinations enjoy little practical clinical use.



# Glomerular Filtration

6.4 Question



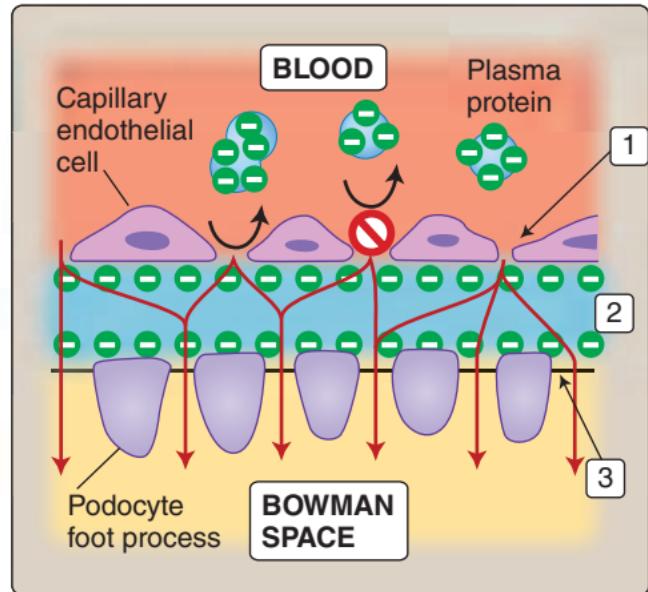
What are the three functional layers of the glomerular ultrafiltration barrier, as shown?



What are the four principal forces governing ultrafiltrate flow across the filtration barrier, and how are they related?



What are the clinical features of **nephritic syndrome**?



## 6.4 Answer

# Glomerular Filtration



Three glomerular ultrafiltration barrier layers:

1. **Capillary endothelium:** has fenestrations that create a molecular filter preventing proteins of ~70 nm or larger from entering the Bowman space
2. **Glomerular basement membrane:** carries a negative charge that repels proteins
3. **Filtration slit diaphragm:** proteinaceous membrane between podocyte foot processes



Four main determinants of ultrafiltrate flow:

- **Capillary hydrostatic pressure ( $P_c$ )**
- **Capillary oncotic pressure ( $\pi_c$ )**
- **Hydrostatic pressure within the Bowman space ( $P_{BS}$ )**
- **Ultrafiltrate oncotic pressure ( $\pi_{BS}$ )**

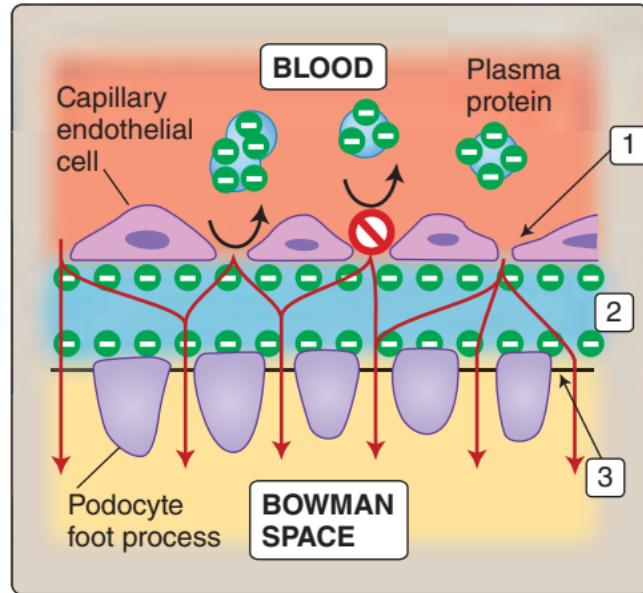
These four forces are related in the **Starling law** ( $K_f$  is a filtration constant):

$$\text{Flow} = K_f [(P_c - P_{BS}) - (\pi_c - \pi_{BS})]$$

[Note: The net pressure favoring ultrafiltration drops from ~20 mm Hg to ~8 mm Hg across the length of a glomerular capillary, largely because plasma proteins become concentrated as a consequence of fluid filtration.]



**Nephritic syndrome** results from breaches in the glomerular filtration barrier caused by inflammation of glomerular capillaries or their supporting structures. These breaches allow proteins and cellular blood components to enter the nephron. Urinalysis reveals **proteinuria** and the presence of RBCs or **cell casts**.



# Autoregulation

## 6.5 Question



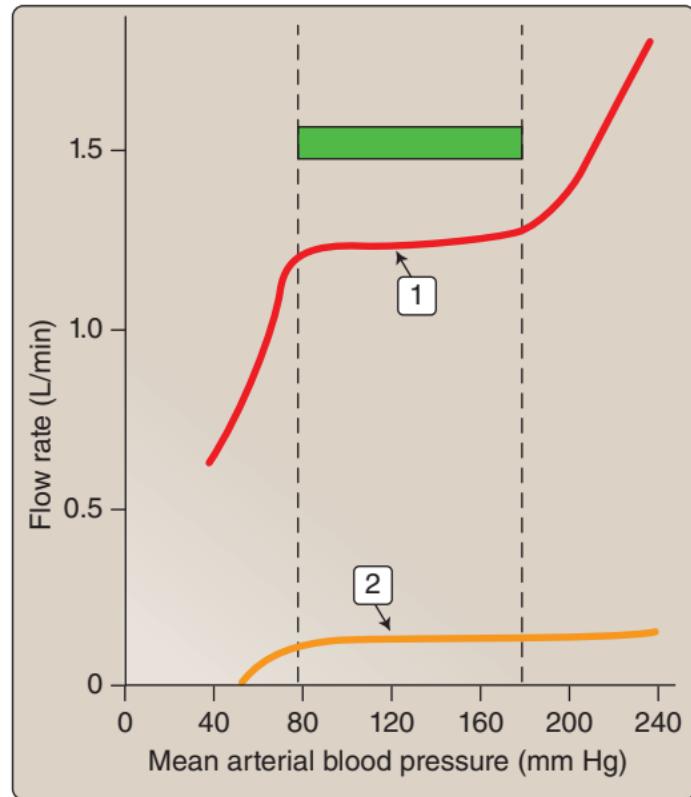
What do the two lines indicated by boxed numerals and the green bar represent?



What are the four principal pathways regulating glomerular blood flow?



What happens to renal blood flow during **mild hemorrhage**?





Plots shown represent:

1. **Renal blood flow (RBF)**
2. **Glomerular filtration rate (GFR)**

The green bar highlights a wide RBF autoregulatory range. GFR is also maintained at a relatively constant 125 mL/min over this same range, due in part to RBF autoregulation.

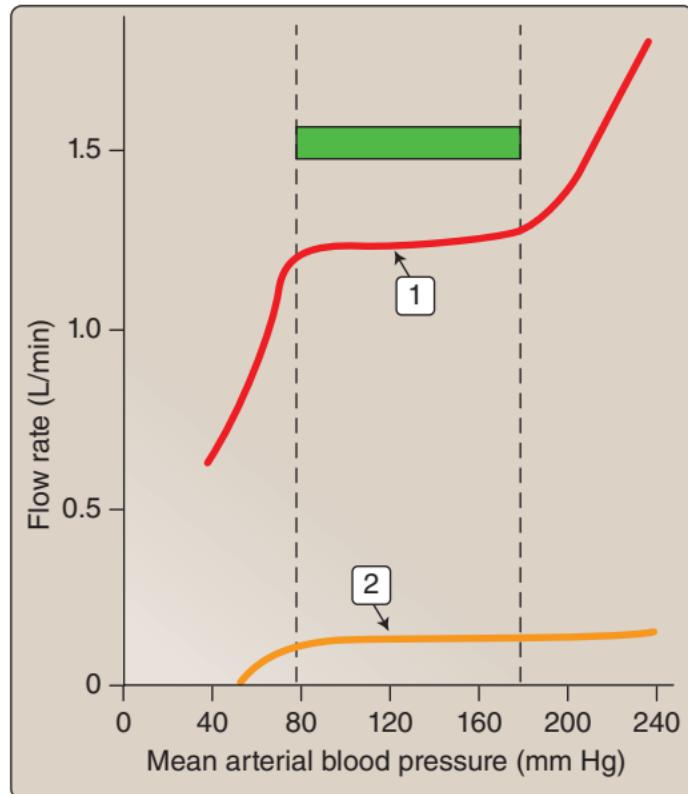


Four principal pathways controlling glomerular blood flow:

- **Autoregulation:** Reflex constriction of glomerular arterioles (a **myogenic response**) restricts flow when arterial pressure rises.
- **Tubuloglomerular feedback (TGF):** Glomerular pressure is adjusted through TGF to maintain a constant GFR. TGF is dependent on the rate of NaCl presentation to the **macula densa** (see 6.6).
- **Hormones and paracines:** Humoral mediators include angiotensin II, dopamine, prostaglandins, and epinephrine.
- **Central control:** Glomerular arterioles are innervated by the SNS, which restricts flow when arterial pressure is low.



**Mild hemorrhage** activates the SNS, which restricts RBF. The resultant drop in glomerular filtration pressure permits salt and water retention to help maintain ECF volume and blood pressure.



# Tubuloglomerular Feedback

## 6.6 Question



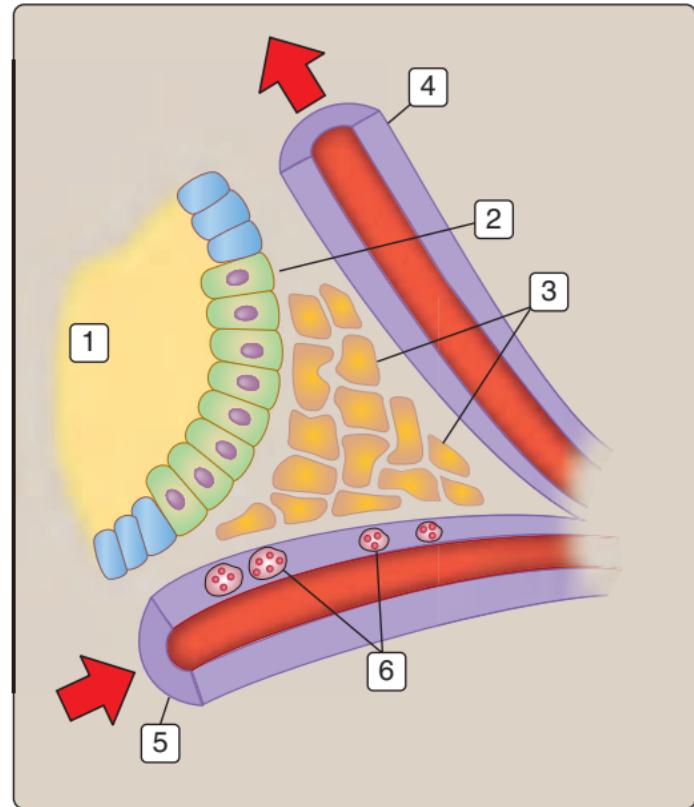
What are the components of the juxtaglomerular apparatus (JGA) indicated by boxed numerals?



What is the role of the JGA in tubuloglomerular feedback (TGF)? What happens when tubule flow rises above optimal levels?



What effect would loop diuretics have on TGF?





JGA components:

1. Distal **thick ascending limb (TAL)**
2. **Macula densa**
3. **Mesangial cells**
4. Glomerular **efferent arteriole (EA)**
5. Glomerular **afferent arteriole (AA)**
6. **Renin-filled granular cells**

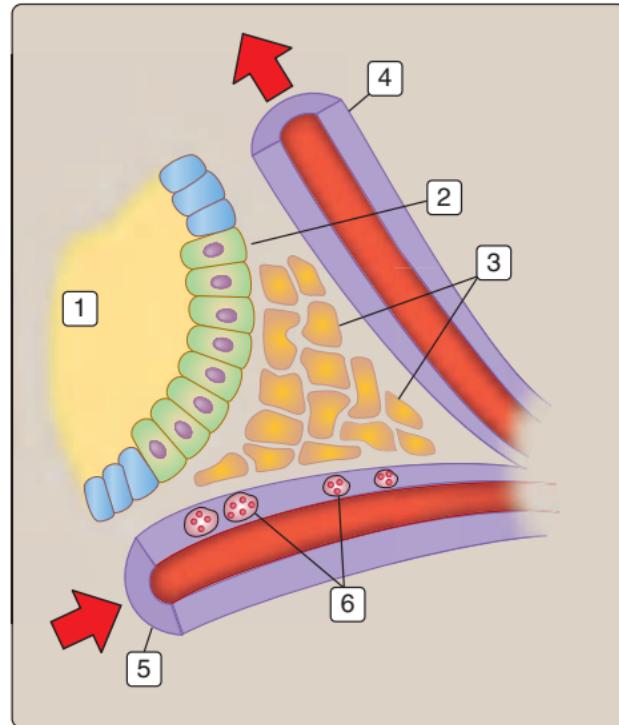


The JGA mediates TGF, which helps optimize glomerular filtration rate (GFR).

- When GFR is high, macula densa cells are depolarized by the high levels of NaCl flowing through the TAL, causing  $\text{Ca}^{2+}$  influx via voltage-gated  $\text{Ca}^{2+}$  channels.
- $\text{Ca}^{2+}$  diffuses via mesangial cells to AA granular cells and inhibits *renin* release. *Renin* normally raises GFR via angiotensin II-mediated constriction of the EA.
- Adenosine (paracrine that constricts the AA and dilates the EA) production by the macula densa rises also. Ultrafiltration pressure falls as a result, causing GFR and NaCl presentation to the macula densa to fall back toward normal.



Loop diuretics (e.g., furosemide) inhibit TGF by inhibiting the  $\text{Na}^+-\text{K}^+-2\text{Cl}^-$  cotransporter that mediates NaCl-induced depolarization of the macula densa. Inhibiting this cotransporter also impairs  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  reabsorption from the TAL, which is the primary reason to administer a loop diuretic.



# Renal Clearance

## 6.7 Question



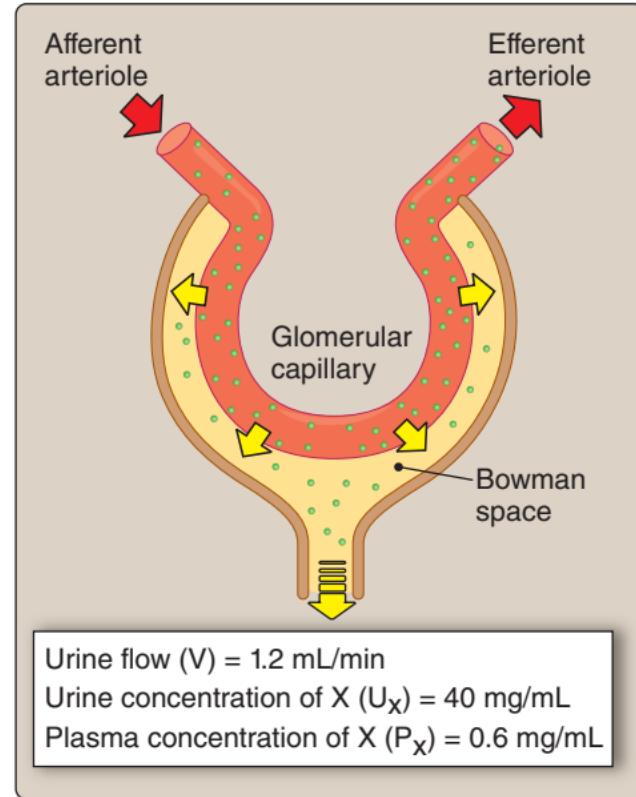
What is clearance? Calculate clearance for substance X ( $C_x$ ) using the data shown.



Why is inulin used in studies of clearance, and how is clearance related to filtered load?



What are the advantages and limitations to using creatinine clearance ( $C_{Cr}$ ) values clinically to estimate renal function?



## 6.7 Answer

# Renal Clearance



**Clearance** refers to the amount of plasma that is completely cleared of a given substance per unit time. Using the given values,  $C_x$  is calculated as:

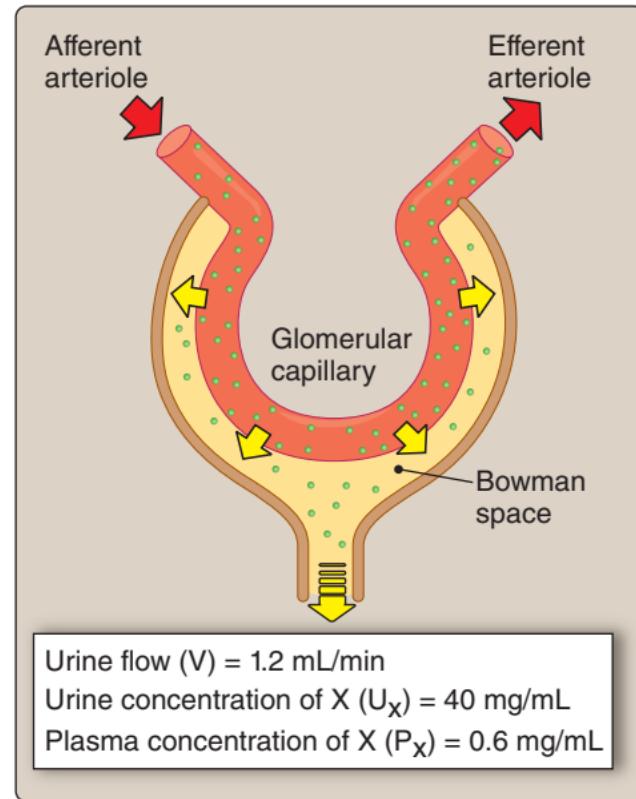
$$C_x = \frac{U_x \times V}{P_x} = \frac{40 \times 1.2}{0.6} = 80 \text{ mL/min}$$



Inulin represents an ideal substance that is freely filtered from plasma and then passes through the tubule without being reabsorbed and without tubule fluid levels being increased by secretion. Inulin clearance can thus be used to determine glomerular filtration rate (GFR). The **filtered load** of substance X is a product of GFR and  $P_x$ .



Creatinine is produced continually by muscle. It is freely filtered from plasma and not reabsorbed during passage through the tubule, so  $C_{Cr}$  provides a way of determining GFR that avoids having to infuse a patient with a synthetic marker. However, creatinine is secreted by transporters in the proximal tubule, which introduces a source of error that overestimates GFR (which is then cancelled out by a near equal and opposite error in the creatinine assay).



# Urinary Bladder

6.8 Question



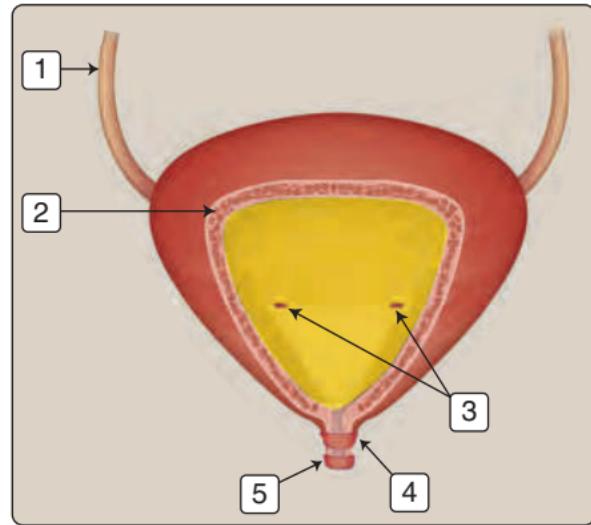
Identify the structures indicated by boxed numerals.



What four ways is the urinary bladder adapted to store urine until micturition?



What is meant by "overactive bladder"?



## 6.8 Answer

# Urinary Bladder



Structures shown:

1. **Ureter**: conveys urine from the kidney
2. **Detrusor muscle**: contracts to increase intraluminal pressure when voiding
3. **Ureteral opening**
4. **Internal sphincter** (involuntary)
5. **External sphincter** (voluntary)



Four bladder storage adaptations:

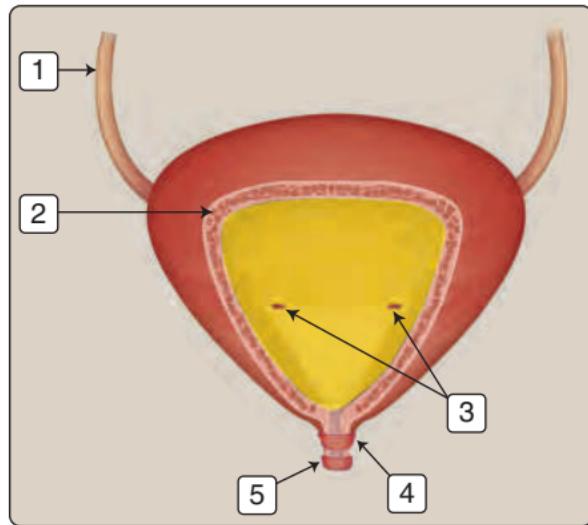
- The bladder is lined with **transitional epithelium** that stretches without tearing.
- **Rugae** in the bladder wall “unfold” to allow for volume expansion.
- **Internal and external sphincters** prevent urine leaking via the urethra until micturition.
- Ureters enter the bladder at an angle to create **pressure valves** that prevent urine backflow.



“**Overactive bladder**” refers to a sense of increased urinary urgency, increased voiding frequency, and **nocturia**.

[Note: Although the causes are uncertain, the condition is believed to reflect increased detrusor muscle activity.

Decreased inhibition of the micturition reflex due to a defect in the pontine micturition center may be one possible cause.]



# Proximal Tubule I—Reabsorption

6.9 Question



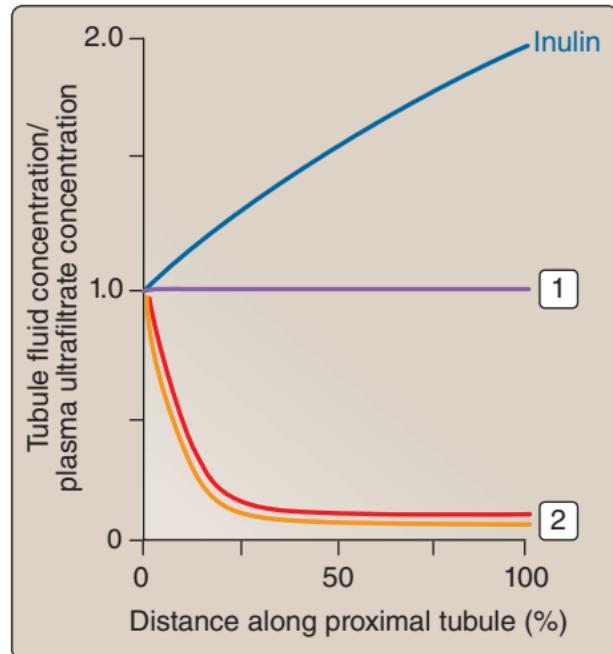
The fate of various solutes during passage through the proximal tubule (PT) is shown. What might the lines indicated by boxed numerals represent, and why does inulin concentration increase?



List two or more ways in which the PT is specialized for reabsorption.



\_\_\_\_\_ syndrome refers to a generalized PT dysfunction, leading to aminoaciduria, glucosuria, and hypouricemia. Impaired ability to reabsorb  $\text{HCO}_3^-$  results in \_\_\_\_\_.





Fate of solutes:

1.  $\text{Na}^+$ ,  $\text{K}^+$ , or **osmolality**
2. **Organic compounds** such as **amino acids**, **proteins**, and **glucose**. Transporters in the early part of the PT recover >98% of the filtered load.

Inulin concentration rises with distance along the PT because water is reabsorbed. Inulin remains trapped within the tubule lumen and is ultimately excreted.

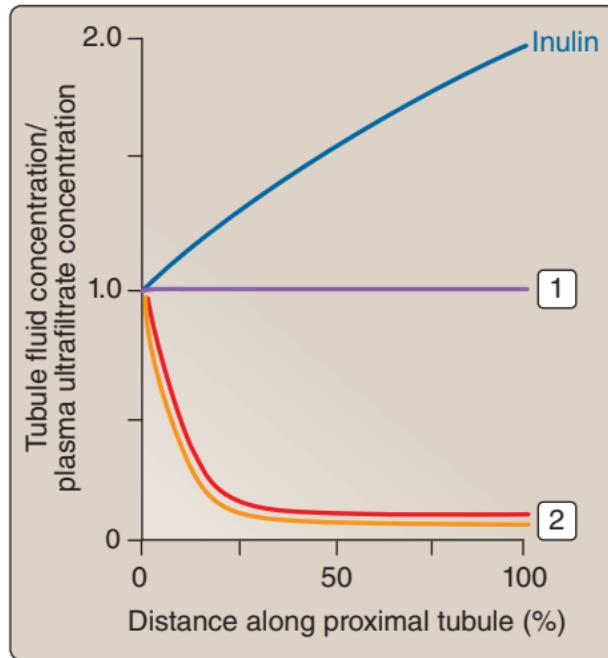


Three PT reabsorption adaptations:

- Contains **numerous mitochondria** to supply transporters with ATP
- **Surface area amplification** of both the apical (which bears dense microvilli that form a “**brush border**”) and basolateral (which has numerous infoldings) epithelial surfaces
- **Leaky tight junctions** between epithelial cells facilitate bulk paracellular uptake  
[Note: The PT reabsorbs ~67% of the fluid filtering into the Bowman space. Reabsorption is isosmotic.]



**Fanconi syndrome** refers to a generalized PT dysfunction, leading to aminoaciduria, glucosuria, and hypouricemia. Impaired ability to reabsorb  $\text{HCO}_3^-$  results in **renal tubular acidosis**.



## Proximal Tubule II—Secretion

### 6.10 Question



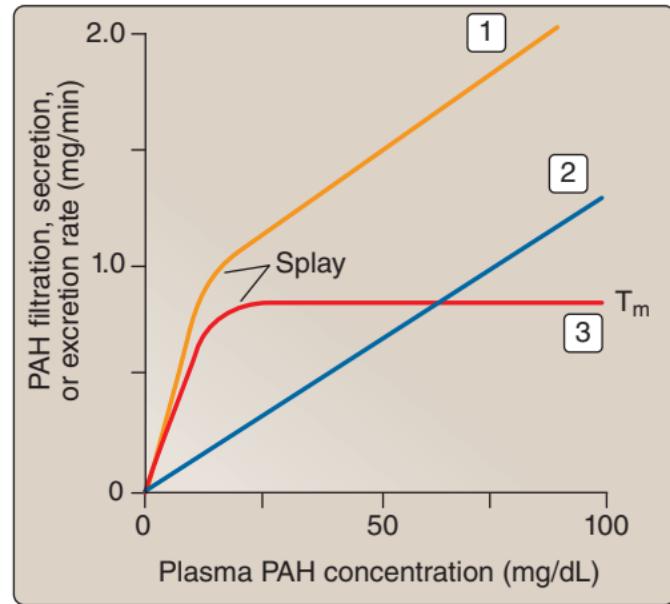
What do the three colored lines shown represent, and why do the two curves "splay"?



How can *para*-aminohippurate (PAH) secretion by the proximal tubule (PT) be used to estimate renal blood flow (RBF)?



Why does the PT's ability to secrete organic anions and cations create a risk of **acute kidney injury (AKI)** during chemotherapy?





Lines represent:

1. Excreted PAH
2. Filtered PAH
3. Secreted PAH

“Splay” occurs because PAH secretion and excretion relies on transporters. Transporter numbers are finite and once maximal transporter capacity ( $T_m$ ) has been reached, secretion saturates. Splay reflects the presence of two or more transporter classes with differing transport maxima and also nephron heterogeneity.



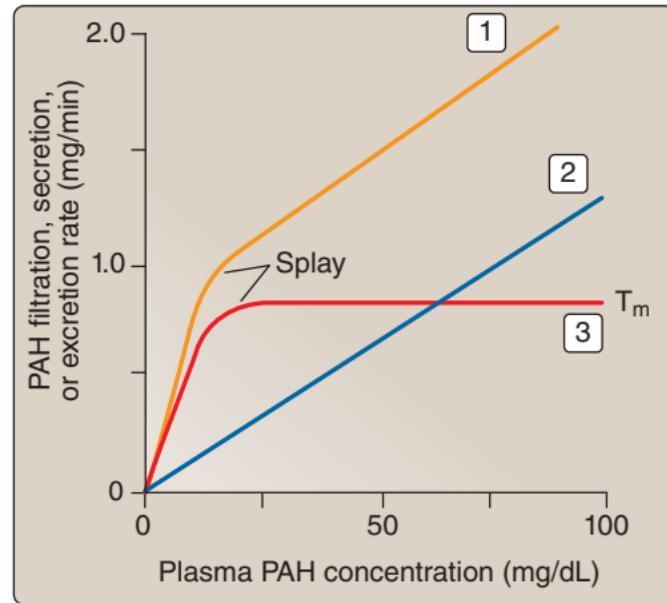
The PT epithelium captures and secretes >90% of PAH contained in blood flowing through the peritubular network. Therefore, PAH clearance ( $C_{PAH}$ ) is close enough to 100% that it can be used to determine renal plasma flow (RPF):

$$RPF = C_{PAH} = \frac{U_{PAH} \times V}{P_{PAH}}$$

where  $U_{PAH}$  and  $P_{PAH}$  are urine and plasma PAH concentrations, respectively, and  $V$  is urine flow. RBF is then calculated as  $RPF \div (1 - Hct)$ .



**AKI** is a common side effect of chemotherapy, because the transporters that the PT uses to take up and subsequently secrete uric acid, oxalic acid, and other bloodborne waste products also transport many pharmaceuticals, including cytotoxic chemotherapy agents. These chemicals become sufficiently concentrated in the PT epithelium to cause nephrotoxicity and AKI.



# Glucose Reabsorption

6.11 Question



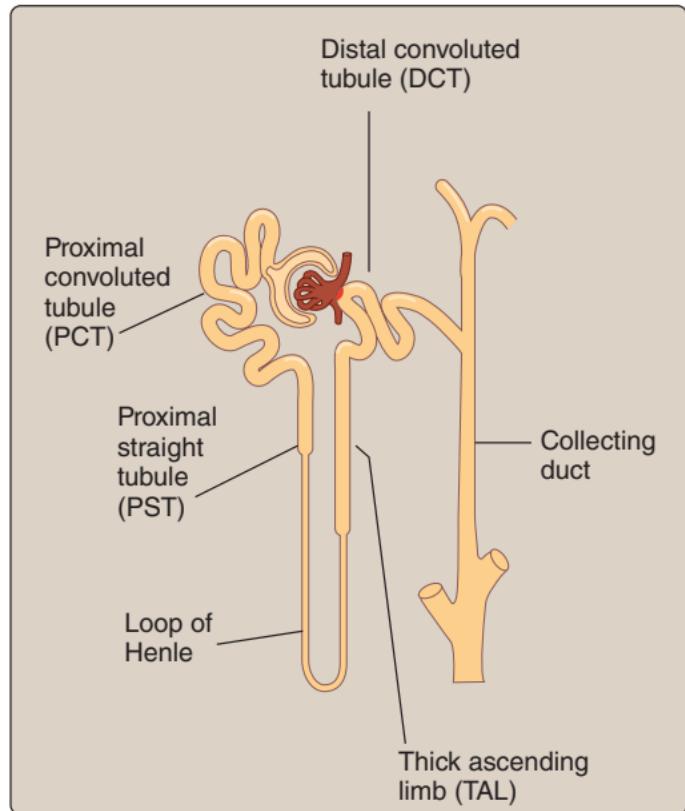
What is the main site of glucose reabsorption by the renal nephron?



What are the pathways for glucose reabsorption?



What is the mechanism by which glucose causes diuresis in patients with untreated **diabetes mellitus**?





Glucose is reabsorbed primarily in the early proximal tubule (PT; ~98%). The late PT reabsorbs the remainder.



Glucose reabsorption occurs **transcellularly**, but the early and late regions of the PT use different transporter classes for recovery.

### Early PT

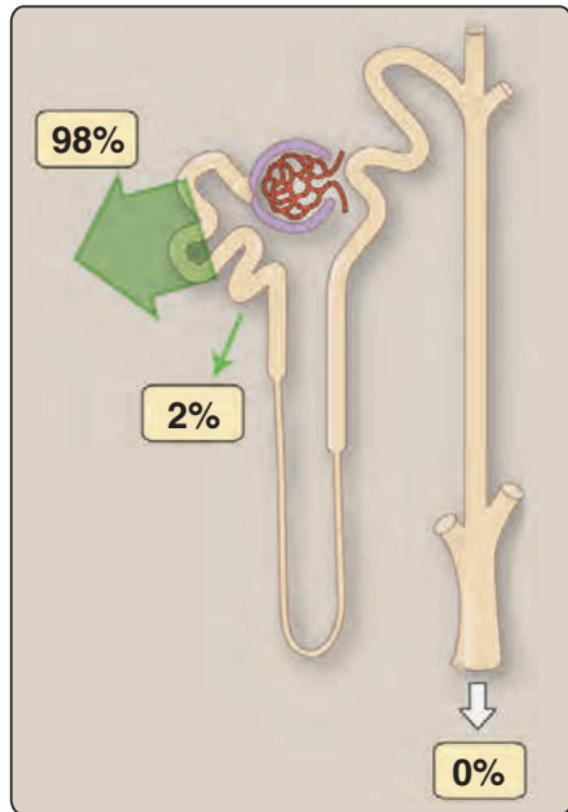
- Apical membrane: low-affinity, high-capacity  $\text{Na}^+$ -glucose cotransporter (SGLT2)
- Basolateral membrane: facilitated diffusion via GLUT2

### Late PT

- Apical membrane: high-affinity, low-capacity  $2\text{Na}^+$ -glucose cotransporter (SGLT1)
- Basolateral membrane: facilitated diffusion via GLUT1



In patients with uncontrolled **diabetes mellitus**, glucose filters into the renal tubule at rates that exceed maximal glucose transporter capacity. The excess remains in the tubule lumen and causes an **osmotic diuresis**.



# Peptide Reabsorption

6.12 Question



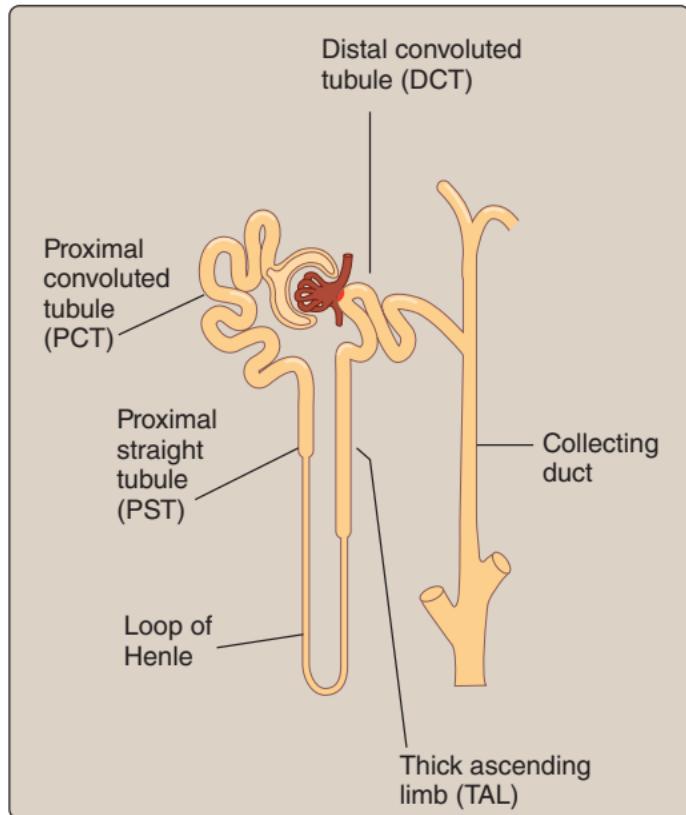
What is the main site of peptide reabsorption by the renal nephron?



What are the pathways for peptide reabsorption?



Heavy proteinuria ( $>3.5$  g/day), lipiduria, and edema may be an indication of \_\_\_\_\_ syndrome. Normal urinary protein excretion should be less than \_\_\_ mg/day.





Proteins and peptides are reabsorbed primarily in the early proximal tubule (PT; ~99%). The late PT reabsorbs the remainder.



Peptide reabsorption occurs **transcellularly**, but the early and late PT regions use different transporter types.

### Early PT

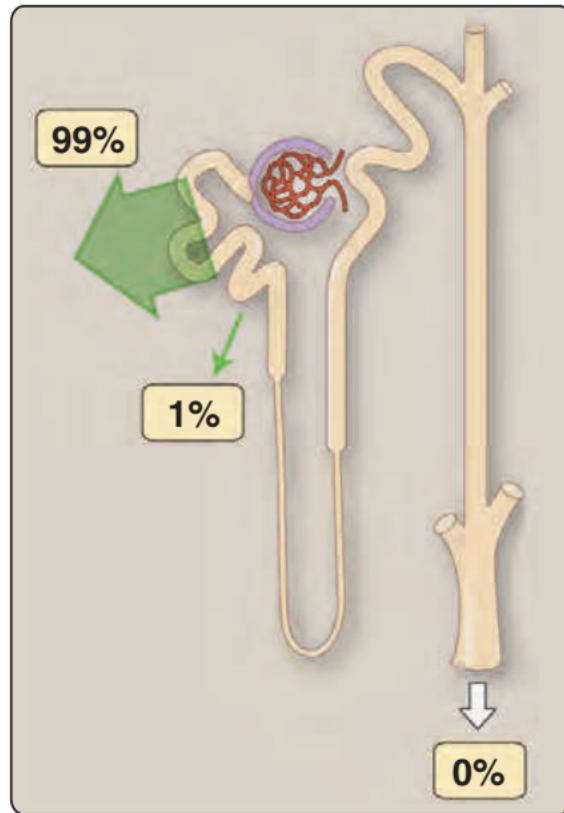
- Apical membrane: low-affinity, high-capacity H<sup>+</sup>-peptide cotransporter (PepT1) takes up di- and tripeptides, which are then degraded by intracellular *proteases*
- Basolateral membrane: facilitated diffusion via amino acid transporters

### Late PT

- Apical membrane: high-affinity, low-capacity H<sup>+</sup>-peptide cotransporter (PepT2)
- Basolateral membrane: facilitated diffusion via amino acid transporters
- The late PT also captures filtered proteins by endocytosis



Heavy proteinuria (>3.5 g/day), lipiduria, and edema may be an indication of **nephrotic syndrome**. Normal urinary protein excretion should be less than 150 mg/day. [Note: Nephrotic syndrome reflects increased leakiness and deterioration of the glomerular filtration barrier.]



# Urea Reabsorption

6.13 Question



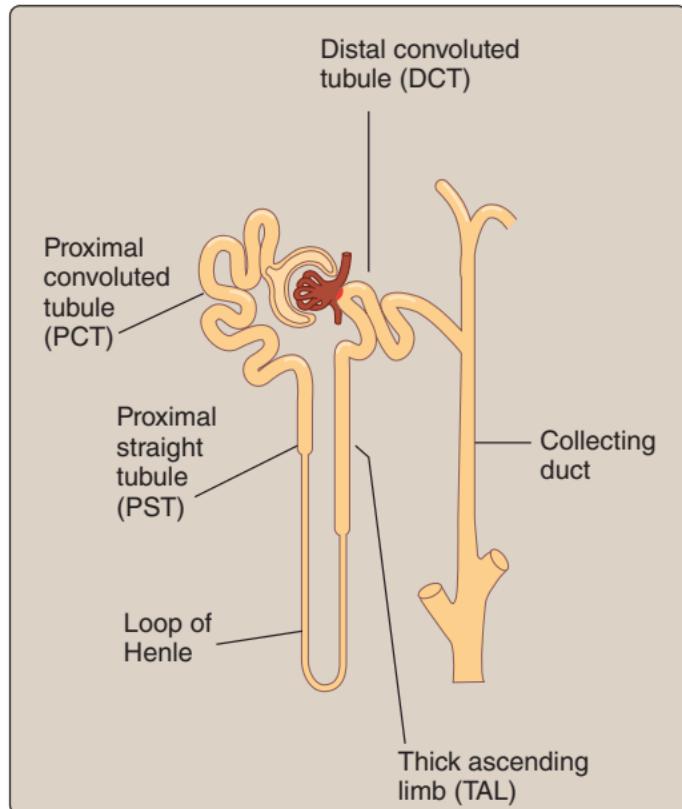
What are the main sites of urea handling by the renal nephron?



What is the purpose of and pathways involved in urea recycling?



What is the difference between "azotemia" and "uremia"?





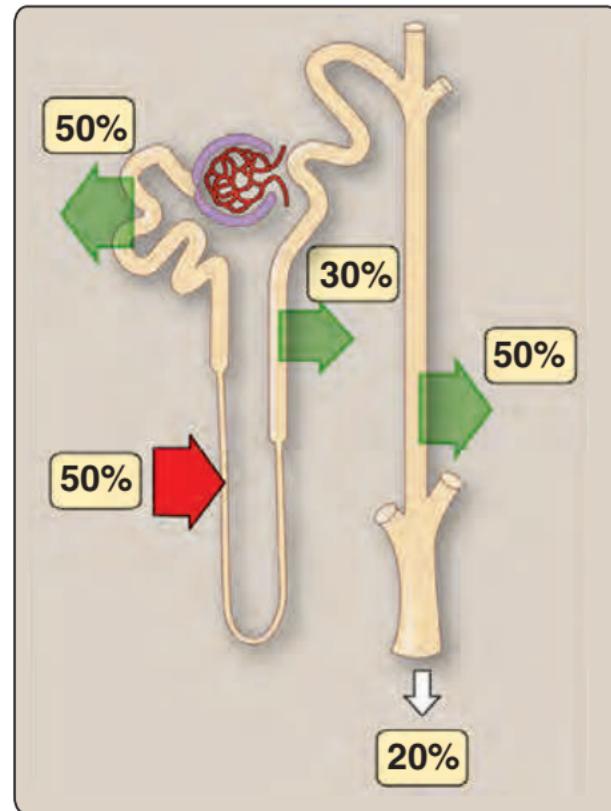
Urea is reabsorbed principally by the proximal tubule. Reabsorption occurs **paracellularly** by chemical **diffusion** and **solvent drag**. The loop of Henle and collecting ducts also handle urea, but these pathways are primarily concerned with maintaining the osmotic gradients that facilitate water recovery, as discussed in the following answer.



**Urea recycling** helps maintain and enhance the **corticopapillary osmotic gradient** used to recover water from the renal tubule and collecting ducts. Urea is recycled from the collecting ducts through the renal medulla. It then enters the loop of Henle and is carried through the distal segments back to the collecting ducts. Urea passage across the walls of the collecting duct and loop is assisted by urea transporters (UTs). [Note: UT expression is regulated by antidiuretic hormone as a way of modulating water recovery.]



**Azotemia** refers to abnormally high levels of nitrogenous wastes (including urea) in blood. Although **uremia** also pertains to nitrogenous wastes, the term more usually describes a set of clinical symptoms associated with renal failure, including electrolyte and acid-base disturbances, hypertension, and certain neurologic disorders.



# Calcium Reabsorption

6.14 Question



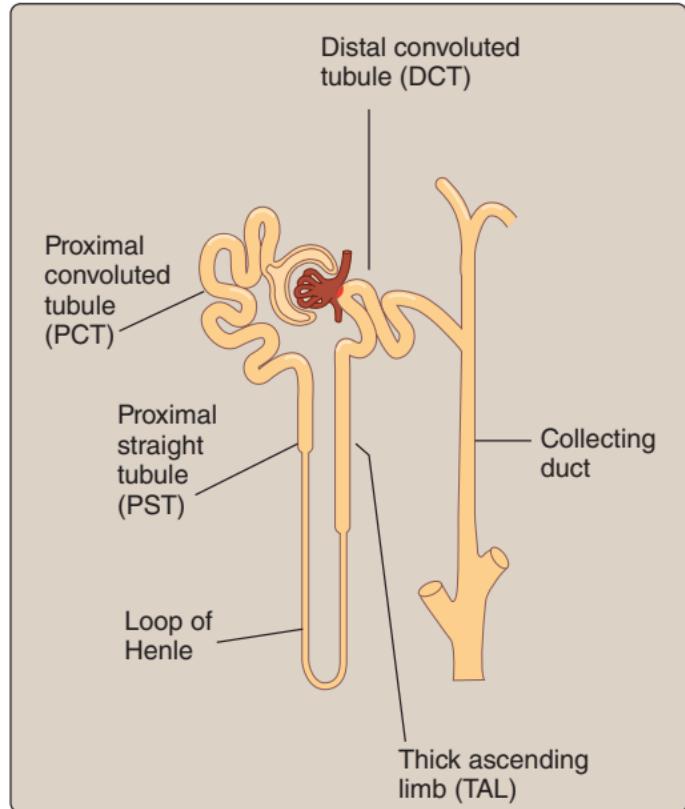
What are the main sites of  $\text{Ca}^{2+}$  reabsorption by the renal nephron?



What is the main site for regulated  $\text{Ca}^{2+}$  reabsorption, and how is reabsorption controlled?



Familial \_\_\_\_\_ calciuric \_\_\_\_\_ calcemia (FHH) is caused by mutations in the \_\_\_\_\_ - \_\_\_\_\_ receptor gene.



## 6.14 Answer

## Calcium Reabsorption



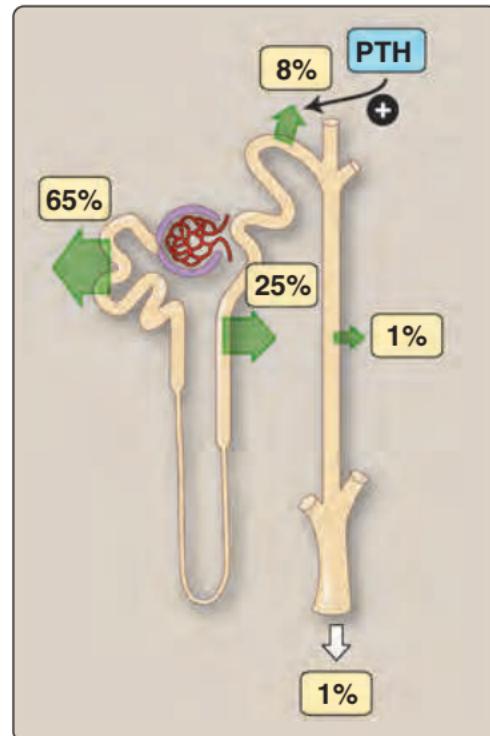
The bulk of  $\text{Ca}^{2+}$  reabsorption occurs in the proximal tubule (~65%) and thick ascending limb (~25%), movement being driven **paracellularly** by the **transepithelial voltage gradient**.



Regulated  $\text{Ca}^{2+}$  reabsorption occurs in the distal convoluted tubule in response to **parathyroid hormone (PTH)**.  $\text{Ca}^{2+}$  is reabsorbed **transcellularly** via a **TRPV5 channel** in the apical membrane and a  $\text{Ca}^{2+}$  pump and  $\text{Na}^+-\text{Ca}^{2+}$  exchanger in the basolateral membrane. PTH increases  $\text{Ca}^{2+}$  reabsorption by increasing TRPV5 open probability. [Note:  $\text{Ca}^{2+}$  crosses the epithelial cell interior bound to calbindin to keep intracellular free levels low.]



**Familial hypocalciuric hypercalcemia (FHH)** is caused by mutations in the **calcium-sensing receptor (CaSR)** gene. [Note: FHH is a rare disorder. The CaSR is expressed in multiple tissues, including parathyroid glands, kidney, and bone. FHH mutations affect PTH secretion and may also directly interfere with  $\text{Ca}^{2+}$  reabsorption by the renal tubule.]



# Magnesium Reabsorption

6.15 Question



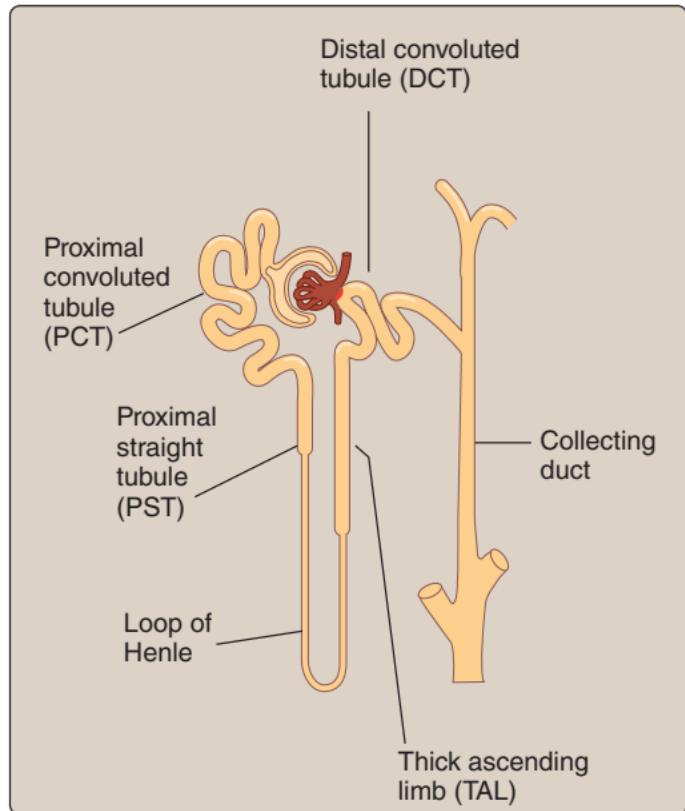
What are the main sites of Mg<sup>2+</sup> reabsorption by the renal nephron?



What is the main site for regulated Mg<sup>2+</sup> reabsorption, and how is Mg<sup>2+</sup> reabsorption regulated?



What is the underlying cause of the inherited disorder, **familial hypomagnesemia with hypercalcioria and nephrocalcinosis (FHHNC)**, and why do patients with FHHNC form calculi?



## 6.15 Answer

# Magnesium Reabsorption



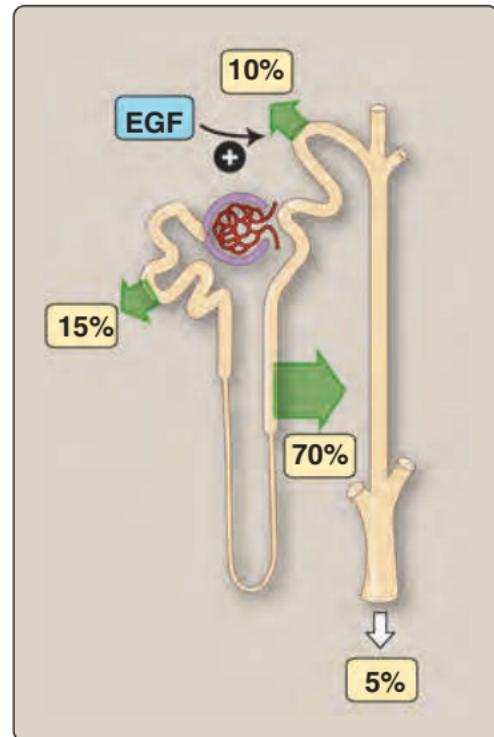
The bulk of Mg<sup>2+</sup> reabsorption occurs in the proximal tubule (~15%) and thick ascending limb (~70%), movement being driven **paracellularly** by the **transepithelial voltage gradient**.



Regulated Mg<sup>2+</sup> reabsorption occurs in the distal convoluted tubule in response to **epidermal growth factor (EGF)**, although other hormones may be involved also. Mg<sup>2+</sup> is reabsorbed transcellularly via an apical **TRPM6** channel whose activity is regulated by EGF.



**FHHNC** is caused by mutations in the **claudin-16** gene. Claudin-16 forms a specific pathway (**paracellin-1**) for paracellular Mg<sup>2+</sup> and Ca<sup>2+</sup> reabsorption in the thick ascending limb. Disrupting this pathway prevents normal Mg<sup>2+</sup> and Ca<sup>2+</sup> recovery, so urinary concentrations of both ions may rise to the point where their respective salts precipitate and grow as **renal or ureteral calculi**.



# Phosphate Reabsorption

6.16 Question



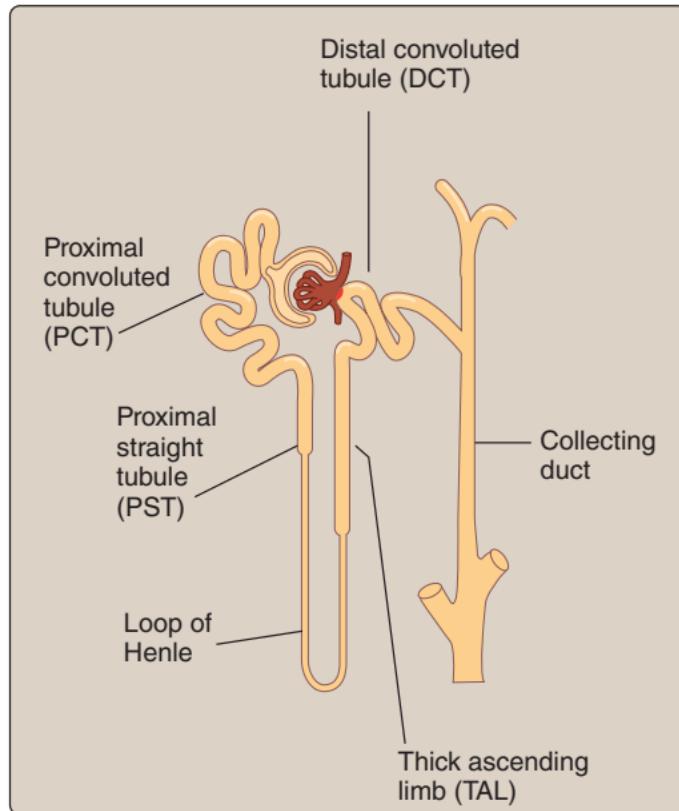
Where in the renal nephron is the majority of the filtered load of phosphate reabsorbed?



What is the main site for regulated phosphate reabsorption, and how is it regulated?



What are the symptoms of severe hypophosphatemia, often associated with chronic alcoholism or excessive antacid ingestion?



## 6.16 Answer

## Phosphate Reabsorption



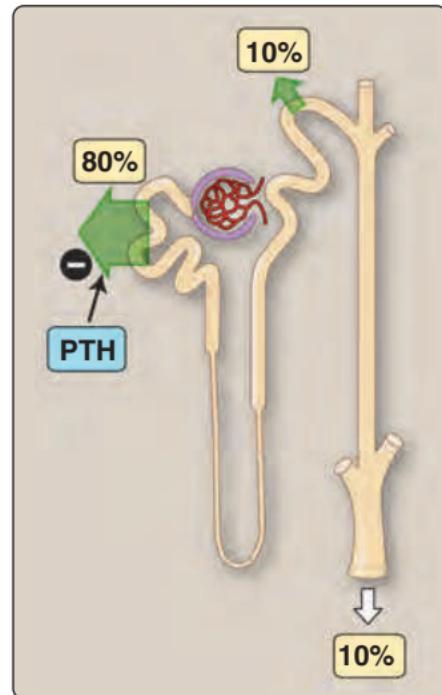
Most phosphate reabsorption occurs **transcellularly** in the proximal tubule (PT; ~80%). A small percentage (~10%) is recovered by the distal convoluted tubule and the rest excreted to help buffer nonvolatile acid (see 6.27).



Phosphate reabsorption in the PT is regulated by **parathyroid hormone (PTH)**. PTH inhibits reabsorption by promoting internalization and degradation of  $\text{Na}^+-\text{P}_i$  cotransporters that are expressed in the renal epithelium's apical membrane. The transporters provide a pathway for phosphate retention when ECF levels are suboptimal.



Phosphate is required for synthesis of ATP and 2,3-diphosphoglycerate (2,3-DPG). The latter facilitates  $\text{O}_2$  release to tissues by reducing Hb's  $\text{O}_2$  affinity (see 5.14). Phosphate depletion thus reduces ATP availability and  $\text{O}_2$  delivery. Symptoms include a general muscle weakness affecting the myocardium, diaphragm, gastrointestinal tract, and skeletal musculature. There may also be effects on CNS function, causing an altered mental status and seizures.



# Potassium Reabsorption

6.17 Question



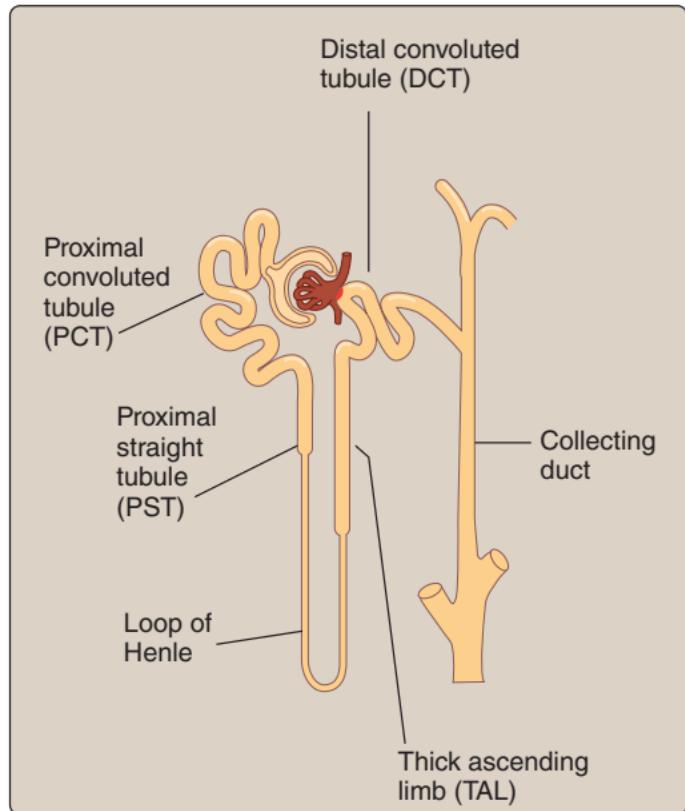
Where in the renal nephron is the majority of the filtered load of  $K^+$  reabsorbed?



The distal segments normally secrete  $K^+$  into the tubule, but, when intake is restricted, these same segments reabsorb  $K^+$ . What is the mechanism by which  $K^+$  is reabsorbed by the distal segments?



Hypokalemia can cause a metabolic acidosis and vice versa. In what two ways are  $K^+$  balance and acid–base balance linked?





Most K<sup>+</sup> reabsorption occurs **paracellularly** in the proximal tubule (~77%) and thick ascending limb (~10%). Movement is powered by a **voltage gradient** and **solvent drag**. The distal segments also actively reabsorb K<sup>+</sup> when intake is restricted, as discussed in the following answer.



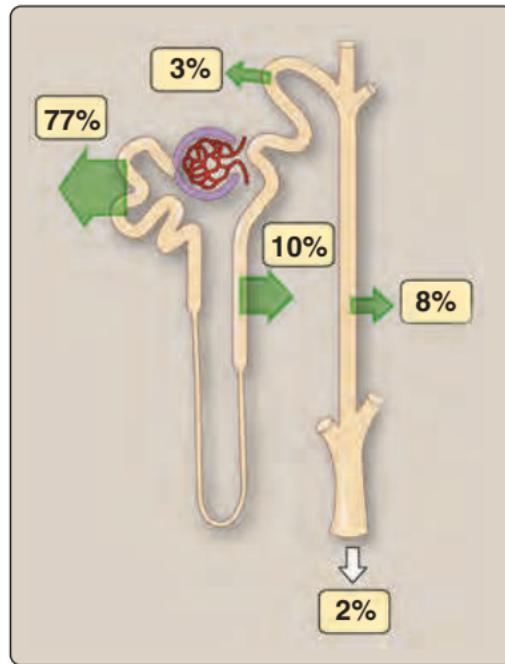
K<sup>+</sup> reabsorption in the distal segments is the responsibility of  **$\alpha$ -intercalated cells**. K<sup>+</sup> is exchanged for H<sup>+</sup> using an apical H<sup>+</sup>-K<sup>+</sup> ATPase, and then crosses the basolateral membrane via a K<sup>+</sup> channel. When K<sup>+</sup> intake is restricted, pump activity is upregulated to facilitate K<sup>+</sup> reabsorption.

[Note: Hypokalemia simultaneously reduces K<sup>+</sup> secretion by distal segment principal cells. Secretion is regulated through an aldosterone-dependent pathway (see 6.18).]



K<sup>+</sup> balance and acid–base balance are coupled on two levels:

- **Cellular:** When plasma K<sup>+</sup> levels are low, K<sup>+</sup> moves out of cells and H<sup>+</sup> moves in to compensate for the loss of positive charge, causing metabolic alkalosis. Metabolic alkalosis similarly causes hypokalemia.
- **Renal:** H<sup>+</sup> excretion and K<sup>+</sup> reabsorption are linked through the H<sup>+</sup>-K<sup>+</sup> ATPase expressed on the apical membrane of  $\alpha$ -intercalated cells. Hypokalemia thus promotes H<sup>+</sup> excretion and potentiates the metabolic alkalosis caused by H<sup>+</sup> moving into cells.



# Potassium Secretion

6.18 Question



Which renal tubule segments are involved in  $K^+$  secretion?

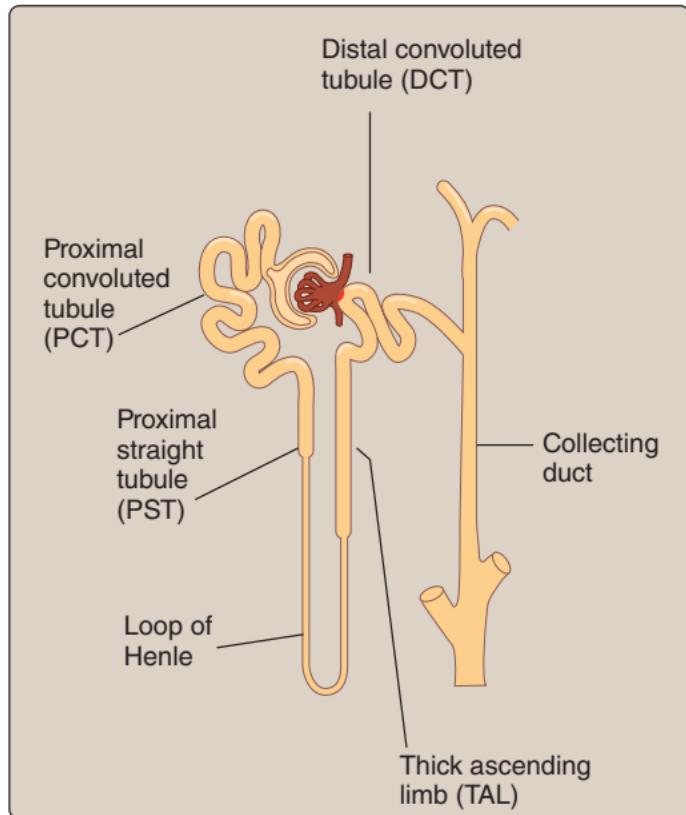


How are plasma  $K^+$  concentrations buffered during a meal?



How is renal  $K^+$  excretion regulated?

Renal impairment can result in hyperkalemia.  
What are the main concerns in a patient with hyperkalemia?





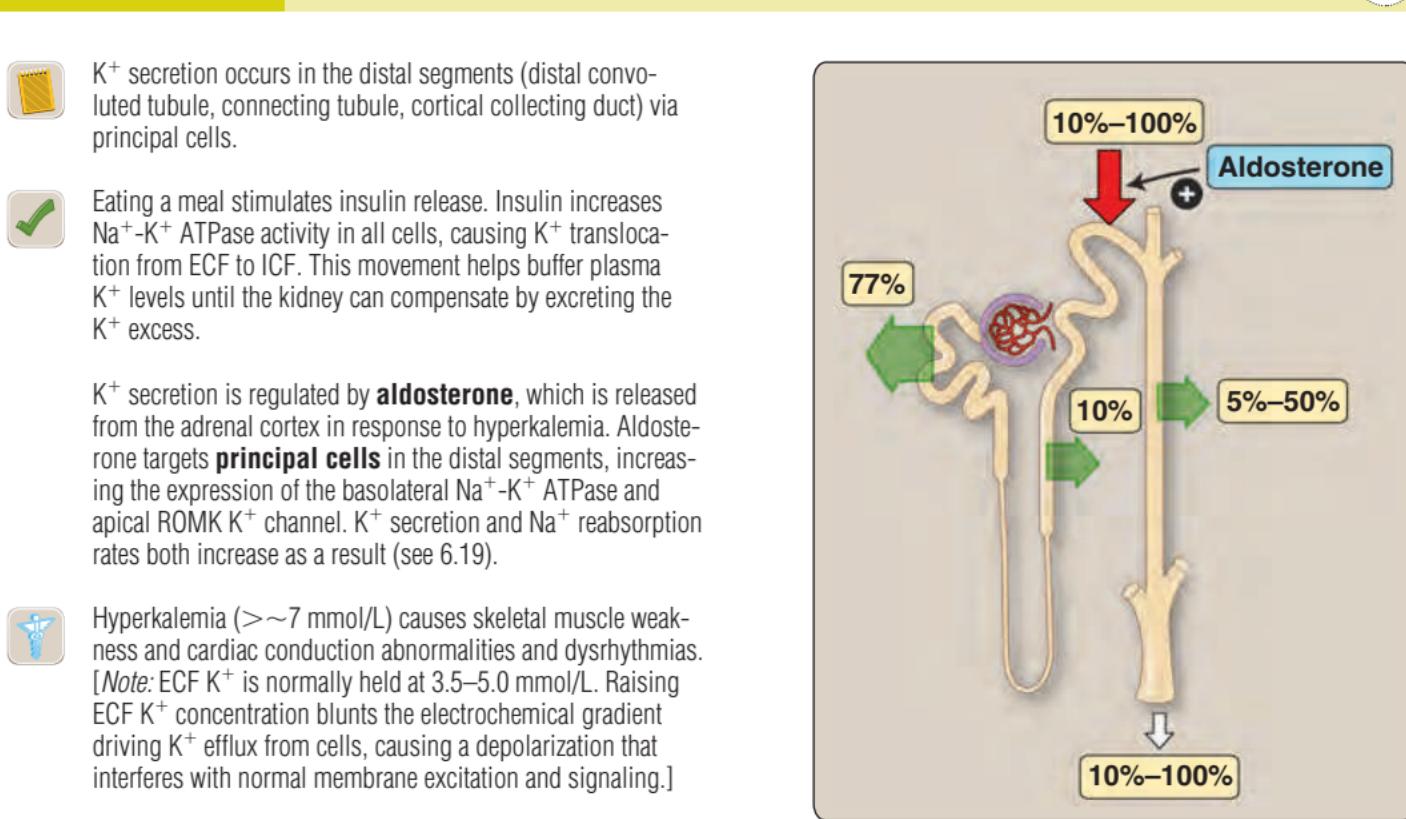
$K^+$  secretion occurs in the distal segments (distal convoluted tubule, connecting tubule, cortical collecting duct) via principal cells.



Eating a meal stimulates insulin release. Insulin increases  $Na^+-K^+$  ATPase activity in all cells, causing  $K^+$  translocation from ECF to ICF. This movement helps buffer plasma  $K^+$  levels until the kidney can compensate by excreting the  $K^+$  excess.



$K^+$  secretion is regulated by **aldosterone**, which is released from the adrenal cortex in response to hyperkalemia. Aldosterone targets **principal cells** in the distal segments, increasing the expression of the basolateral  $Na^+-K^+$  ATPase and apical ROMK  $K^+$  channel.  $K^+$  secretion and  $Na^+$  reabsorption rates both increase as a result (see 6.19).



# Sodium Reabsorption

6.19 Question



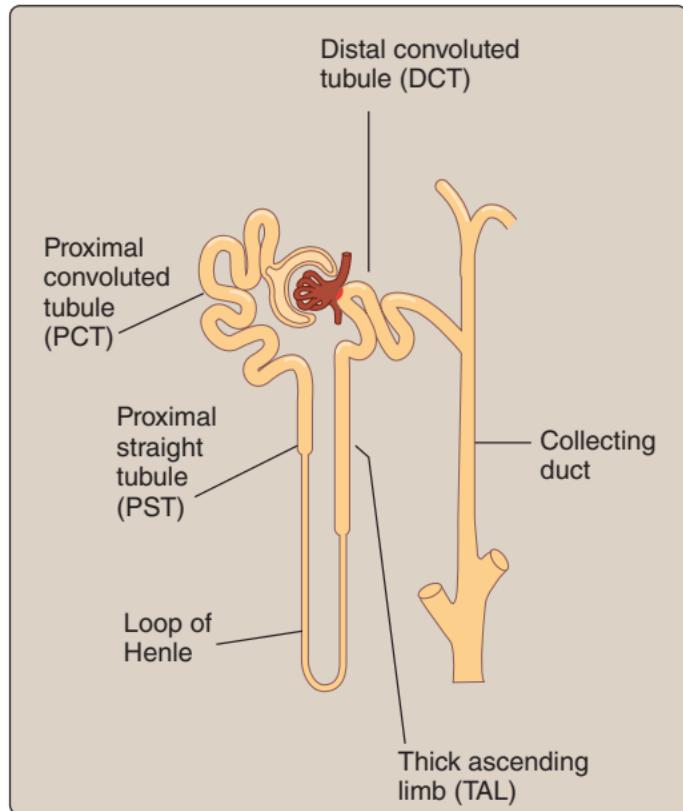
What are the main sites of  $\text{Na}^+$  reabsorption by the renal tubule?



What is the cellular mechanism by which aldosterone regulates  $\text{Na}^+$  reabsorption?



What are the clinical features of **Liddle syndrome**?





Most of the  $\text{Na}^+$  filtered load is reabsorbed **transcellularly** in the proximal tubule (~67%) during **cotransport** of organic and inorganic solutes, or in exchange for  $\text{H}^+$ . The thick ascending limb absorbs  $\text{Na}^+$  paracellularly, and transcellularly via an apical  $\text{Na}^+-\text{K}^+-2\text{Cl}^-$  cotransporter.

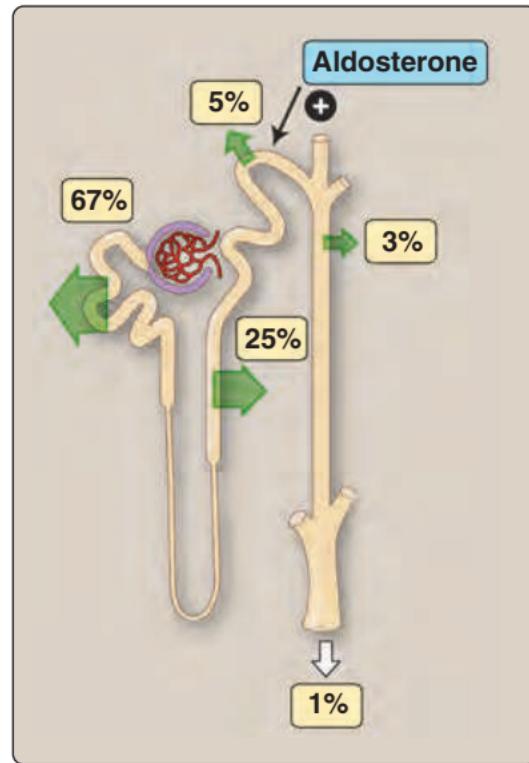


**Aldosterone** regulates  $\text{Na}^+$  reabsorption through changes in the expression levels of various  $\text{Na}^+$  channels and  $\text{Na}^+$  pumps.  $\text{Na}^+$  is recovered from the distal segments via an apical **epithelial  $\text{Na}^+$  channel (ENaC)** found in **principal cells**. Movement is powered by the concentration gradient created by the basolateral  $\text{Na}^+-\text{K}^+$  ATPase. Aldosterone binding to a mineralocorticoid receptor increases expression levels of numerous proteins involved in uptake, including ENaC and the  $\text{Na}^+-\text{K}^+$  ATPase.



**Liddle syndrome** is characterized by increased renal  $\text{Na}^+$  reabsorption, causing **hypertension**. Some patients may also show hypokalemia and metabolic alkalosis through concurrent aldosterone-stimulated changes in  $\text{K}^+$  handling by principal cells.

**A-plus: Liddle syndrome** is caused by recessive mutations in the ENaC gene that prevent the channel being degraded by intracellular *proteases*. ENaC is normally removed from the apical membrane and degraded when extracellular  $\text{Na}^+$  concentrations are optimal.



# Water Reabsorption

## 6.20 Question



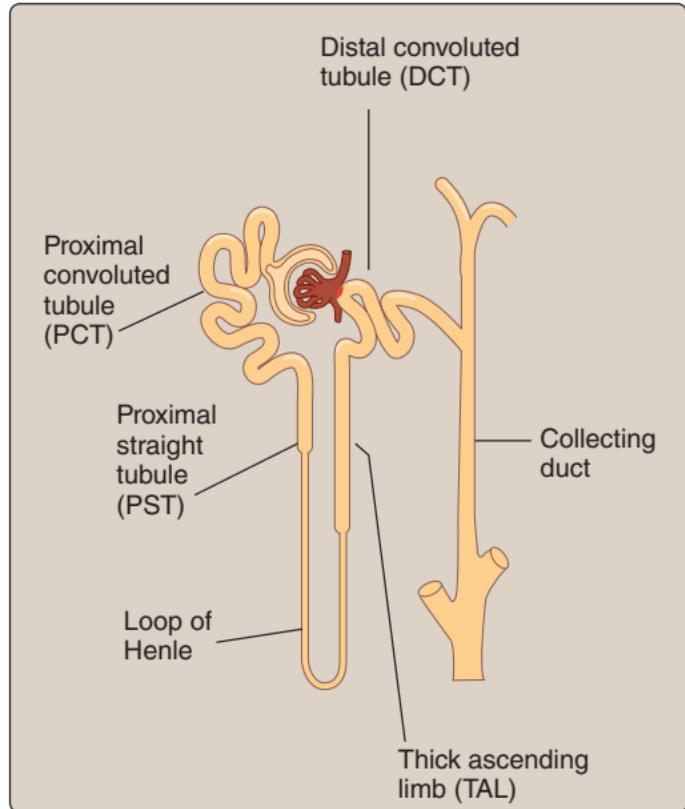
Where in the renal tubule is the majority of filtered water recovered?



What is the cellular mechanism by which water recovery is increased when ECF volume is low?



What is the difference between neurogenic and nephrogenic **diabetes insipidus**?





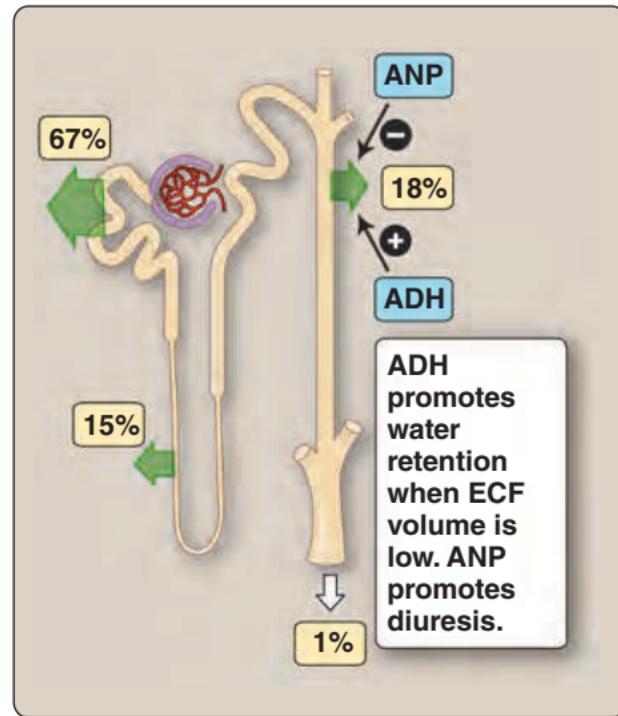
Most H<sub>2</sub>O reabsorption occurs in the proximal tubule (~67%) driven by the osmotic gradient created by solute reabsorption. Another ~15% is recovered during passage through the loop of Henle. Regulated H<sub>2</sub>O recovery (~18%) occurs in the collecting ducts.



Water recovery is regulated by **antidiuretic hormone (ADH)**, also known as **arginine vasopressin**) acting through V<sub>2</sub> receptors in the collecting ducts. ADH binding causes **aquaporins (AQP2)** to be inserted into the ductal apical membrane from intracellular vesicles. The basolateral membrane contains AQP3 water channels, so water is then free to flow from the lumen into the renal medulla down a strong osmotic gradient. **Atrial natriuretic peptide (ANP)** inhibits ADH release.



**Neurogenic (central) diabetes insipidus (DI)** is a polyuria caused by a defect in the ADH release pathway that normally activates when ECF osmolality increases, whereas **nephrogenic DI** is caused either by impairment of the kidney's ability to concentrate urine or through ADH resistance. [Note: Hereditary forms of ADH resistance include those that map to genes encoding the V<sub>2</sub> receptor and AQP2 water channel.]



# Corticopapillary Osmotic Gradient

6.21 Question



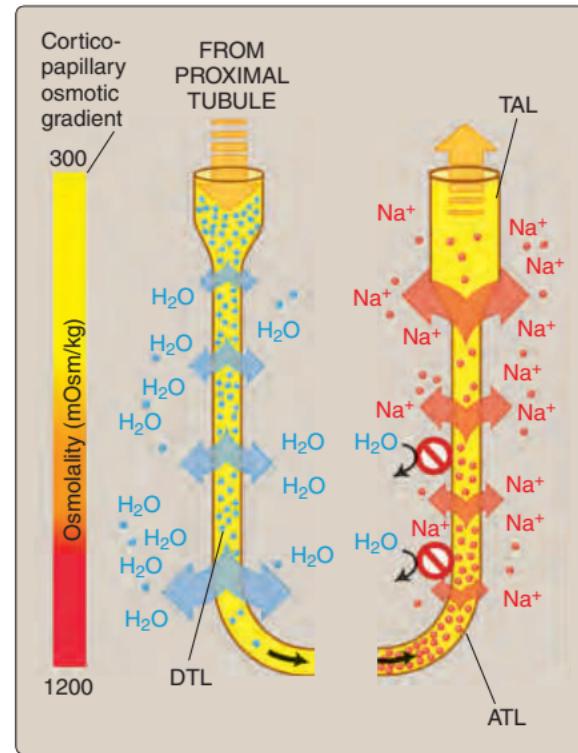
What three characteristics of the loop of Henle allow for water extraction from tubule fluid?



How is the corticopapillary (CP) osmotic gradient established?



Where do loop diuretics act? Why are they so effective in producing diuresis?



Loop of Henle. ATL = ascending thin limb;  
DTL = descending thin limb; TAL = thick ascending limb.

# Corticopapillary Osmotic Gradient



Three loop characteristics that facilitate H<sub>2</sub>O recovery:

- The loop travels through the medulla, which exposes its contents to the **CP osmotic gradient**.
- The DTL has high H<sub>2</sub>O permeability. H<sub>2</sub>O leaves the tubule and moves into the interstitium by osmosis.
- The ATL is H<sub>2</sub>O-impermeant. H<sub>2</sub>O is prevented from reentering the tubule, so it rejoins the circulation and is carried away by the **vasa recta**.

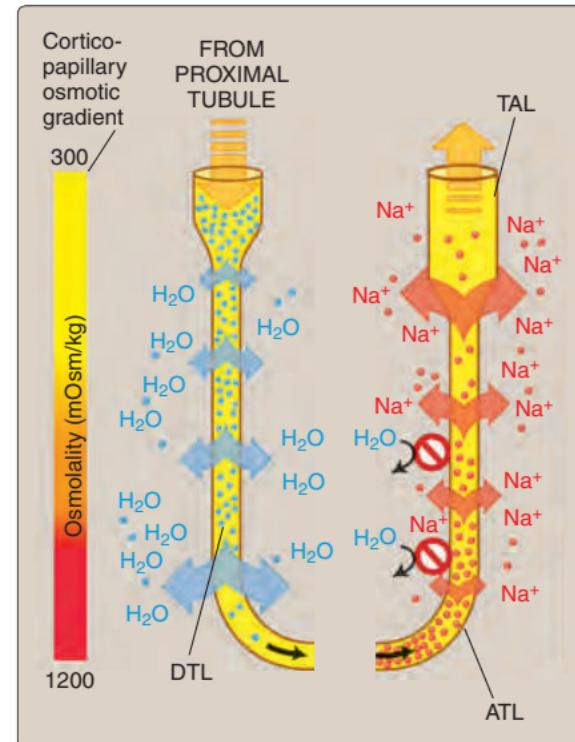


The CP gradient is established by transporters and channels in the TAL.

- Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>-</sup> are reabsorbed from the tubule by a Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter (NKCC).
- Na<sup>+</sup> is transferred to the interstitium by the Na<sup>+</sup>-K<sup>+</sup> ATPase, and K<sup>+</sup> and Cl<sup>-</sup> follow via channels, which raises interstitial osmolality and draws water from fluid within the DTL.
- High osmolality fluid in the loop is carried into the medulla as flow proceeds, raising local interstitial osmolality. It is also pushed into the TAL where Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>-</sup> are extracted and transferred to the interstitium to further raise osmolality. The CP osmotic gradient thus slowly builds by **countercurrent multiplication**.



Loop diuretics inhibit the NKCC and prevent the CP gradient being established. The gradient is required for water recovery in the loop of Henle and the distal segments.



Loop of Henle. ATL = ascending thin limb;  
DTL = descending thin limb; TAL = thick ascending limb.

### Tally Sheet

- **Intake:** H<sub>2</sub>O is ingested with food and by drinking beverages, plus ~300 mL/day is generated through carbohydrate metabolism. H<sub>2</sub>O intake is regulated through the sensation of thirst.
- **Output:** H<sub>2</sub>O is lost to the environment in urine and through evaporation from the skin and lungs (**insensible losses**). Variable amounts of H<sub>2</sub>O are excreted with feces. H<sub>2</sub>O output is regulated through urine production.

### Sensory Mechanism

Total body water (TBW) is sensed through changes in ECF osmolality. **Osmosensation** is the responsibility of osmoreceptor neurons associated with two CNS **circumventricular organs**: (1) the **organum vasculosum of the lamina terminalis** and (2) the **subfornical organ**.

When TBW falls, ECF osmolality rises (normal = 275–295 mOsm/kg H<sub>2</sub>O), causing osmoreceptor neuron shrinkage and triggering Ca<sup>2+</sup> influx and depolarization via mechanosensitive TRPV4 channels. Signals from the osmoreceptors converge on the hypothalamus.

Pathway	mL/day
<i>Intake</i>	
Metabolism	300
Food	800
Beverages	500*
Total	1,600
<i>Output</i>	
Feces	200
Skin	500
Lungs	400
Urine	500*
Total	1,600

\*Regulated steps.



### Regulation

Hypohydration prompts the hypothalamus to stimulate thirst ( $\uparrow H_2O$  intake) and release **antidiuretic hormone (ADH)**; also known as **arginine vasopressin**) from the posterior pituitary ( $\downarrow H_2O$  output).

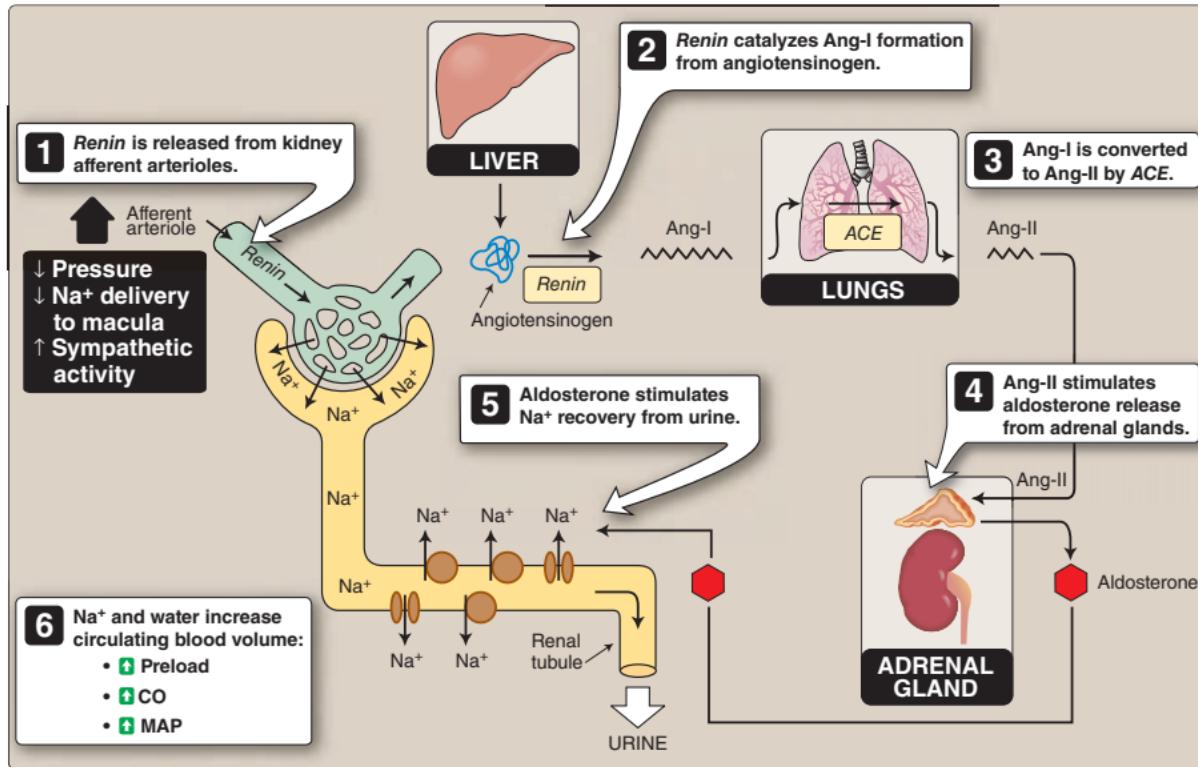
- **Intake:** Thirst compels fluid intake. Thirst sensation is mediated by higher cortical areas, including the anterior cingulate cortex and the insular cortex.
- **Output:** ADH binds to  $V_2$  receptors in the renal collecting ducts and stimulates **aquaporin** water channel (AQP2) insertion into the ductal apical membrane. AQP2 plus AQP3 in the basolateral membrane provide a pathway for water to leave the collecting ducts and reenter the renal interstitium and vasculature.

### Negative Feedback

**Atrial natriuretic peptide (ANP)** opposes the actions of ADH. ANP is released from atrial myocytes when ECF volume and cardiac preload is high.

# Sodium Balance

6.23 Summary



The renin-angiotensin-aldosterone system.



### Tally Sheet

- **Intake:** Dietary  $\text{Na}^+$  intake usually exceeds homeostatic needs.
- **Output:** Output is regulated through urinary excretion. Small amounts of  $\text{Na}^+$  are lost in feces and through sweat formation.

### Sensory Mechanisms

- **Direct:** Tubule  $\text{Na}^+$  levels are monitored by the **macula densa** (a component of the **juxtaglomerular apparatus [JGA]**).
- **Indirect**
  - $\text{Na}^+$  determines ECF osmolality, which is sensed by **central osmoreceptors**.
  - $\text{Na}^+$  determines ECF volume, which governs cardiac output and mean arterial pressure (MAP).

MAP is monitored by **arterial baroreceptors** and by the **glomerular afferent arteriole (AA)**.

### Regulation (Response to Hyponatremia)

- **Intake:** Salt craving impels  $\text{Na}^+$  intake. The pathways involved are not well defined.
- **Output:** Output is regulated through the **renin–angiotensin–aldosterone system**.
  - *Renin* is released following  $\downarrow$  AA pressure or  $\downarrow \text{Na}^+$  delivery to the JGA.
  - *Renin* is also released by sympathetic stimulation of the AA following  $\downarrow$  MAP.

Aldosterone increases  $\text{Na}^+$  reabsorption by distal segments via a mineralocorticoid receptor. Angiotensin II (Ang-II) potentiates these effects and stimulates water retention.

### Negative Feedback

**Atrial natriuretic peptide (ANP)** opposes the actions of aldosterone and Ang-II. ANP is released from atrial myocytes when ECF volume and cardiac preload is high.

# Potassium Balance

## 6.24 Summary

### Tally Sheet

- **Intake:**  $K^+$  is ingested as a part of a normal diet. Fruit and vegetables are  $K^+$ -rich.
- **Output:** Kidneys are the principal route for  $K^+$  output.

### Sensory Mechanism

No direct evidence for a  $K^+$ -specific sensory mechanism.

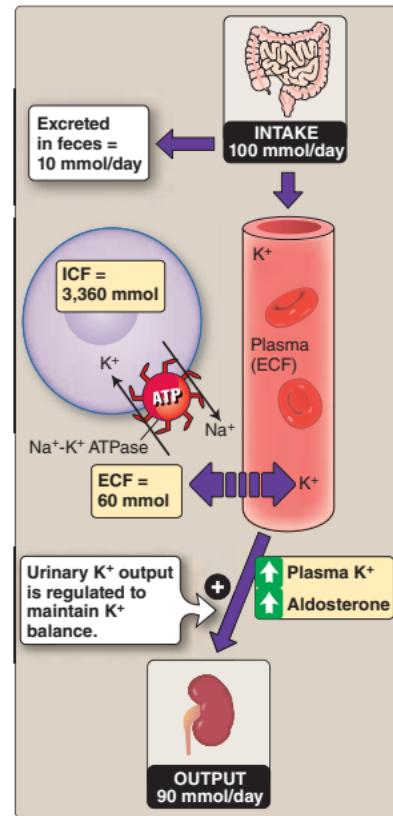
### Regulation (Response to Hypokalemia)

- **Intake:** Intake is unregulated.
- **Output:** Hypokalemia stimulates the  $H^+-K^+$  ATPase in collecting duct  **$\alpha$ -intercalated cells**, which increases  $K^+$  reabsorption.

### Regulation (Response to Hyperkalemia)

- **Intake:** Intake is unregulated.
- **Output:** Hyperkalemia stimulates **aldosterone** release from the adrenal cortex. Aldosterone increases  $K^+$  secretion by **principal cells** in the distal segments ( $\uparrow$  basolateral  $Na^+-K^+$  ATPase and  $\uparrow$  apical ROMK  $K^+$  channel expression).

continued...





### Uncoupling K<sup>+</sup> Balance from Na<sup>+</sup> Balance

Na<sup>+</sup> reabsorption is coupled to K<sup>+</sup> secretion through the principal cell Na<sup>+</sup>-K<sup>+</sup> pump in the distal segments. Functional uncoupling is required when ECF volume needs adjusting. Uncoupling depends on tubule flow rate:

- **Euvolemia, low tubule flow:** K<sup>+</sup> accumulates in the tubule lumen and blunts the driving force for further K<sup>+</sup> secretion. Secretion rate decreases as a result.
- **Euvolemia, high tubule flow:** K<sup>+</sup> is swept through the tubule during high flow and secretion rate is increased correspondingly.
- **Hypovolemia:** Hypovolemia activates the *renin*-angiotensin-aldosterone system (RAAS). Aldosterone increases Na<sup>+</sup> reabsorption, but coincident K<sup>+</sup> secretion is prevented because hypovolemia also reduces tubule flow rate
- **Hypervolemia:** Hypervolemia suppresses RAAS and increases tubule flow. Inappropriate K<sup>+</sup> secretion is prevented because the pathways involved in both Na<sup>+</sup> absorption and K<sup>+</sup> secretion are downregulated when aldosterone levels fall.

# Internal Potassium Balance

6.25 Question



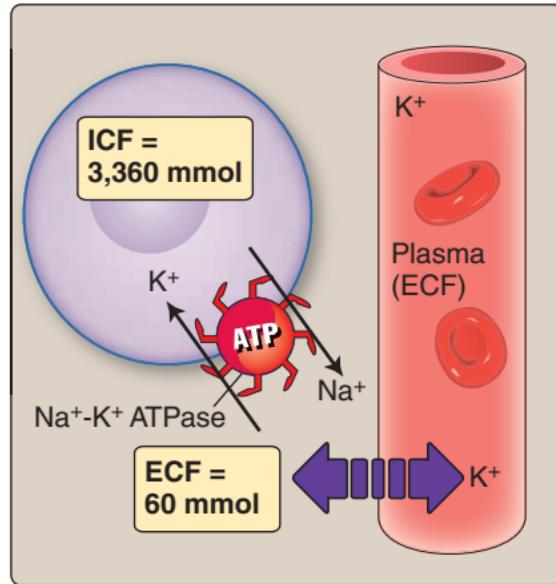
What is meant by "internal K<sup>+</sup> balance"?



How do strenuous exercise, insulin secretion, and acidosis affect internal K<sup>+</sup> balance? Do they cause hypokalemia or hyperkalemia?



How do traumatic crush injuries affect internal K<sup>+</sup> balance and kidney function?





"Internal K<sup>+</sup> balance" refers to the relative distribution of K<sup>+</sup> between ICF and ECF. The majority of K<sup>+</sup> is located in cells (primarily muscle) due to the actions of the Na<sup>+</sup>-K<sup>+</sup> ATPase. A shift from ICF to ECF causes **hyperkalemia**. A reverse shift causes **hypokalemia**.

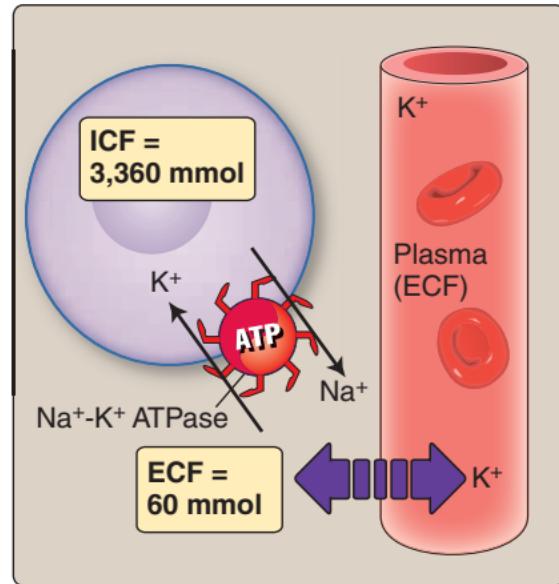


Effects of various events on internal K<sup>+</sup> balance:

- **Exercise:** Muscle cells release K<sup>+</sup> during membrane excitation, causing hyperkalemia.
- **Insulin secretion:** Insulin stimulates Na<sup>+</sup>-K<sup>+</sup> ATPase activity. K<sup>+</sup> moves from ECF to ICF, causing hypokalemia.
- **Acidosis:** H<sup>+</sup> enters cells and K<sup>+</sup> moves into the ECF to compensate for the charge movement, causing hyperkalemia.



Traumatic crush injuries can cause a life-threatening hyperkalemia. Traumatizing muscle causes **rhabdomyolysis** and release of myocytic contents, including K<sup>+</sup>, Ca<sup>2+</sup>, and myoglobin. Hyperkalemia and hypercalcemia may both cause cardiac rhythm disturbances. Myoglobin is excreted by the kidney and colors urine red or reddish brown. Myoglobin may also obstruct tubule flow through cast formation, resulting in **acute kidney injury**.



# Bicarbonate Reabsorption

## 6.26 Question



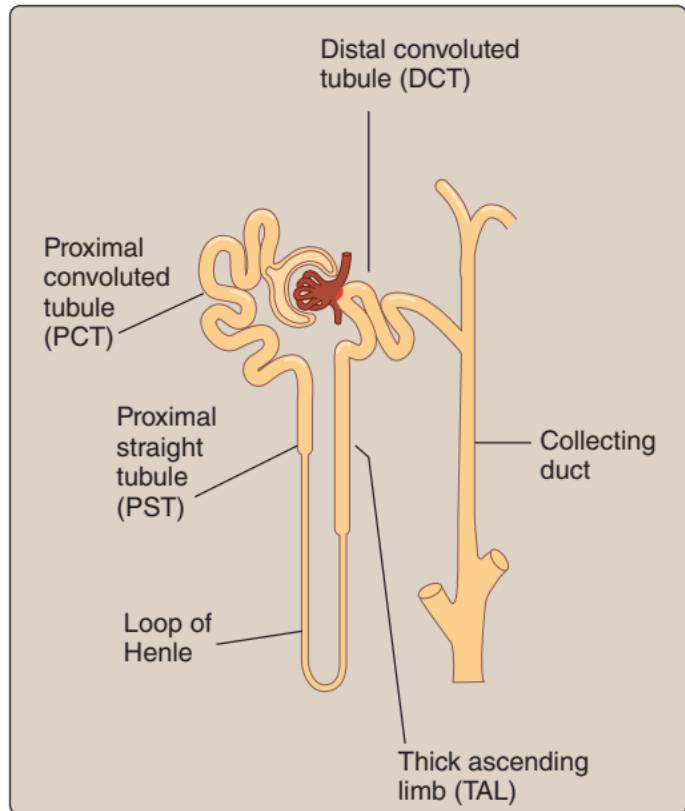
What is the relative contribution of the various renal tubule segments to  $\text{HCO}_3^-$  reabsorption?



The renal tubule generates “new”  $\text{HCO}_3^-$ . What is the purpose and site of new  $\text{HCO}_3^-$  formation?



Why is acetazolamide rarely used as a diuretic even though it inhibits  $\text{HCO}_3^-$  reabsorption and causes an osmotic diuresis?



# Bicarbonate Reabsorption



Most  $\text{HCO}_3^-$  reabsorption occurs in the proximal tubule (PT; ~80%) and thick ascending limb (~10%). The remainder is recovered in the distal segments.  $\text{HCO}_3^-$  is reabsorbed as  $\text{H}_2\text{O}$  and  $\text{CO}_2$  after titration with acid.

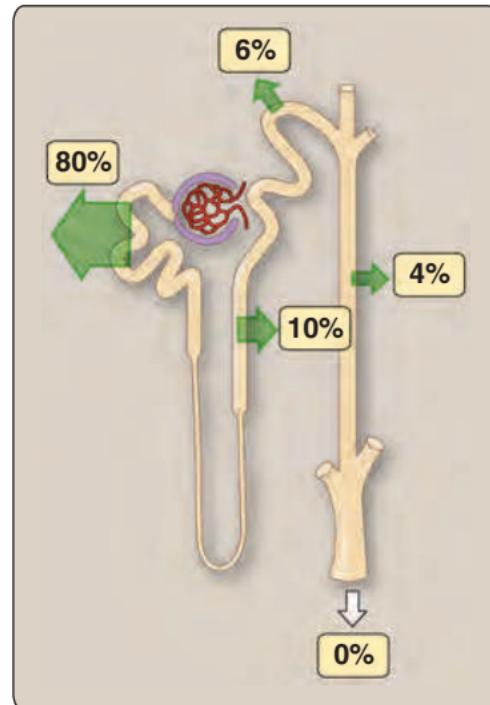


"New"  $\text{HCO}_3^-$  is synthesized by the renal tubule epithelium to facilitate nonvolatile acid excretion. Most of the ~50–100 mmol/day of new  $\text{HCO}_3^-$  generated by the kidney originates from the PT, and the remainder from the distal segments. [Note: A portion of the new  $\text{HCO}_3^-$  generated by the PT is a byproduct of  $\text{NH}_3$  synthesis.  $\text{NH}_3$  is used to excrete nonvolatile acid in the form of  $\text{NH}_4^+$ .]



Acetazolamide has limited use as a diuretic because:

1. Acetazolamide's principal target is the PT, but later segments are able to compensate by increasing water reabsorption.
2. Loop diuretics are more effective at controlling total body water.
3. Inhibiting  $\text{HCO}_3^-$  reabsorption causes a metabolic acidosis. The lungs compensate by increasing ventilation, so plasma  $\text{HCO}_3^-$  levels fall. Reduced amounts of  $\text{HCO}_3^-$  appear in the glomerular filtrate as a result, so the diuretic potential of acetazolamide wanes over time.



### Tally Sheet

- Intake:** Metabolism generates ~15–22 mol of **volatile acid** and 70–100 mmol of **nonvolatile acid** per day.
- Output:** The lungs excrete the volatile acid ( $\text{H}_2\text{CO}_3$ ), and the kidneys excrete the nonvolatile acid (including nitric, phosphoric, and sulphuric acids).

### Sensory Mechanism

- Central:** Chemoreceptors in the **medulla oblongata** monitor  $\text{P}_{\text{a}}\text{CO}_2$  and control ventilatory responses to pH.
- Peripheral: Aortic and carotid bodies** monitor  $\text{P}_{\text{a}}\text{CO}_2$  and pH (in addition to  $\text{P}_{\text{aO}_2}$ ) and contribute to ventilatory responses.
- Renal:** pH changes have direct effects on renal epithelial function.

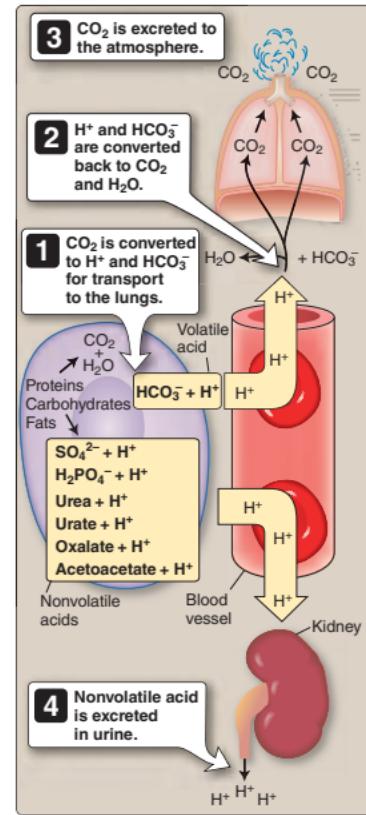
### Regulation (Response to Acidosis)

- Acute:** ↑ ventilation to transfer volatile acid to the atmosphere at increased rates
- Chronic:** ↑ renal  $\text{H}^+$  excretion

### Regulation (Response to Alkalosis)

- Acute:** ↓ ventilation to reduce the rate of volatile acid transfer to the atmosphere
- Chronic:** ↓ renal  $\text{H}^+$  excretion

continued...





### Renal Mechanisms

- **Proximal tubule:**

- A  $\text{Na}^+ \text{-H}^+$  exchanger uses the  $\text{Na}^+$  gradient to secrete  $\text{H}^+$  into the tubule lumen (also found in the thick ascending limb [TAL]).
- A V-type  $\text{H}^+$  ATPase pumps  $\text{H}^+$  into the lumen (also found in the TAL).
- $\text{NH}_3$  is synthesized from glutamine to help excrete  $\text{H}^+$  as  $\text{NH}_4^+$ .

- **Titratable acids** (e.g., hydrogen phosphate, creatinine): These buffer  $\text{H}^+$  during passage through the renal tubule.

[Note: Acidosis upregulates expression of these pathways and increases  $\text{NH}_3$  production. Alkalosis has the opposite effect.]

- **Distal segments:**

- $\alpha$ -Intercalated cells secrete  $\text{H}^+$  into the tubule lumen using a  $\text{H}^+ \text{-K}^+$  ATPase.
- $\beta$ -Intercalated cells secrete  $\text{HCO}_3^-$  into the tubule lumen using a  $\text{Cl}^- \text{-HCO}_3^-$  exchanger.

[Note: Acidosis increases the relative proportion of  $\alpha$ -intercalated cells to  $\beta$ -intercalated cells, which increases  $\text{H}^+$  excretion rate. Alkalosis reverses this effect.]

# Acid–Base Disorders: Respiratory Acidosis

6.28 Question



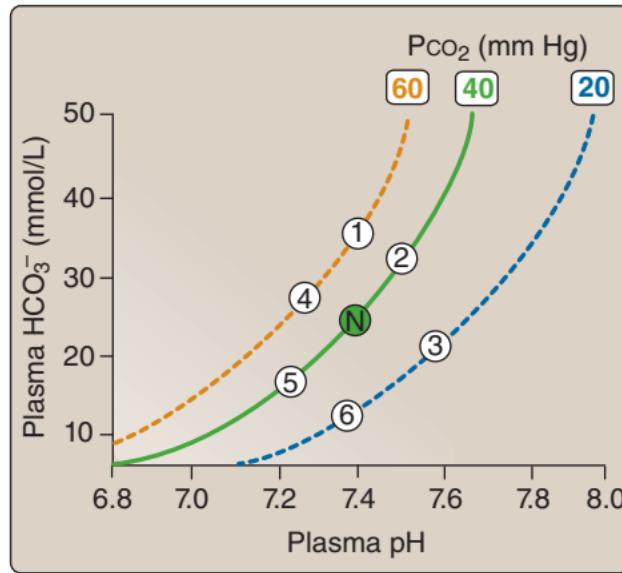
Referring to the graph, how would acute and compensated respiratory acidosis change plasma pH,  $\text{HCO}_3^-$ , and  $\text{Pco}_2$ ?



What is the main cause of respiratory acidosis? What are three others?

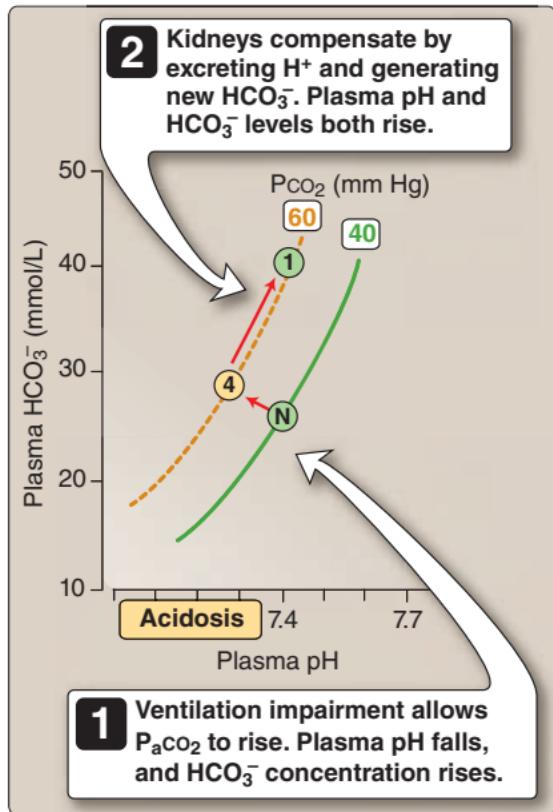


What two features of the CNS make its function unusually sensitive to acute hypercapnia, and what are the typical hypercapnia symptoms?



N = normal.

# Acid–Base Disorders: Respiratory Acidosis



Respiratory acidosis is usually caused by **hypoventilation** but can result from any condition that prevents  $CO_2$  excretion, including:

- ↓ **Ventilatory drive** due to suppression of brainstem function (e.g., tumors, drugs)
- **Air pump impairment** due to reduced respiratory muscle or motor nerve function (e.g., **muscular dystrophy, amyotrophic lateral sclerosis, polio**)
- **Airway obstructions** that prevent gas exchange (e.g., **pneumonia, chronic obstructive lung disease**)



Two features of the CNS make brain function susceptible to hypercapnia:

- $CO_2$  diffuses rapidly across the blood–brain barrier and acidifies CSF, which has only modest buffering capacity. The pH change may cause agitation, depressed mental activity, or predispose a patient to seizures.
- Cerebral blood vessels are unusually sensitive to  $P_{CO_2}$ . Hypercapnia-induced increases in cerebral flow may cause headaches as a result of increased intracranial pressure.



# Acid–Base Disorders: Respiratory Alkalosis

6.29 Question



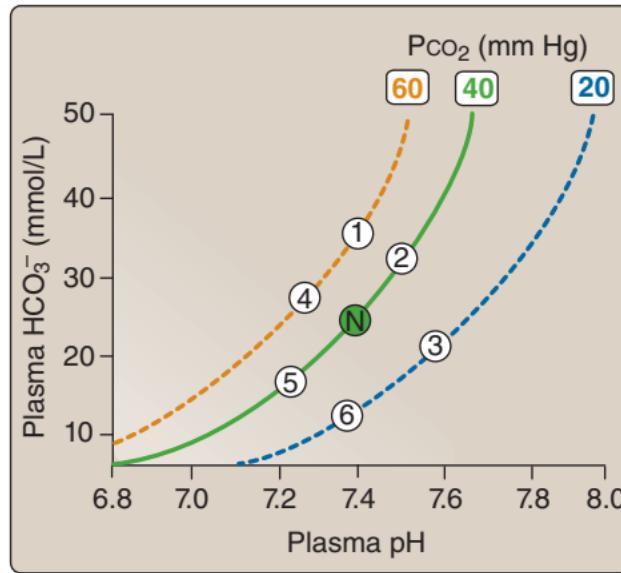
Referring to the graph, how would acute and compensated respiratory alkalosis change plasma pH,  $\text{HCO}_3^-$ , and  $\text{PCO}_2$ ?



What causes respiratory alkalosis?

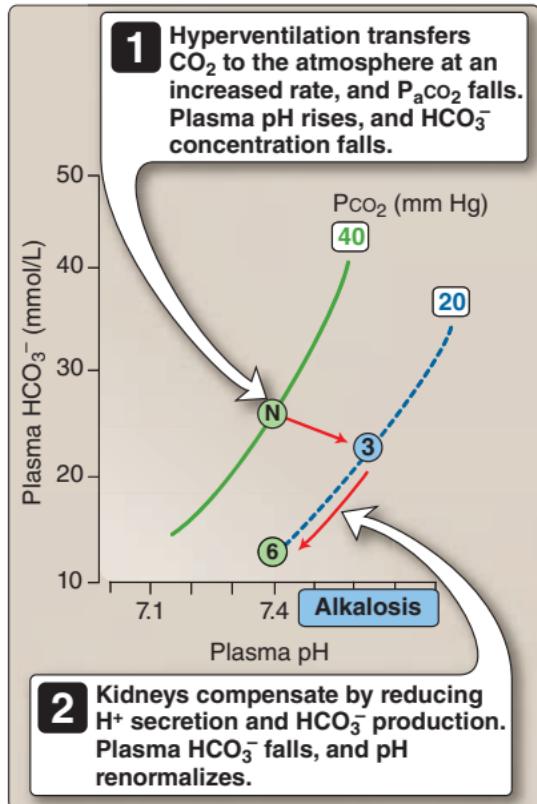


Mild respiratory alkalosis is a common finding during pregnancy. What are its causes and consequences?



N = normal.

# Acid–Base Disorders: Respiratory Alkalosis



Respiratory alkalosis is *always* due to **hyperventilation** but numerous underlying causes may exist, including:

- Pain and anxiety
- Drugs affecting the respiratory centers (e.g., salicylates)
- Hypoxia (e.g., at altitude)
- Hypoxemia (e.g., **anemia** or **pulmonary embolism**)



O<sub>2</sub> consumption increases by ~30% during pregnancy, a need met by a ~50% increase in **minute ventilation**. The increase is achieved largely through increased **tidal volume**. P<sub>a</sub>CO<sub>2</sub> falls to ~32 mm Hg as a result and is compensated by the kidneys. P<sub>a</sub>O<sub>2</sub> simultaneously rises to ~104 mm Hg.

*A-plus:* An increased respiratory drive during pregnancy is believed to be mediated by progesterone effects on the brainstem respiratory centers.

# Acid–Base Disorders: Metabolic Acidosis

6.30 Question



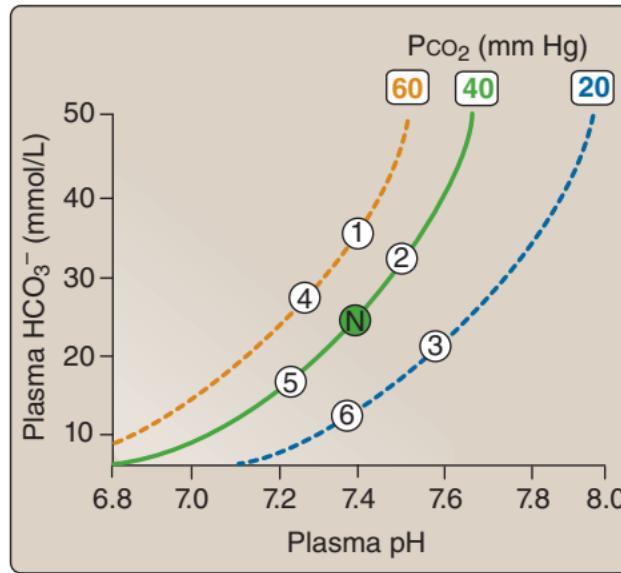
Referring to the graph, how would acute and compensated metabolic acidosis change plasma pH,  $\text{HCO}_3^-$ , and  $\text{PCO}_2$ ?



List two or more common causes of metabolic acidosis.



How do anion gap measurements help clinicians diagnose metabolic acid–base disorders?

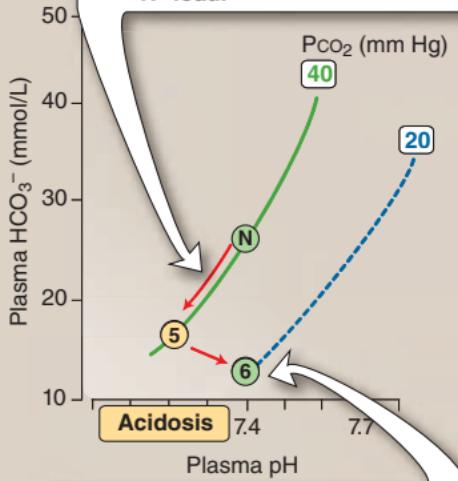


N = normal.

# Acid–Base Disorders: Metabolic Acidosis



**1** Nonvolatile acid production or accumulation is buffered at source by  $\text{HCO}_3^-$ , so plasma  $\text{HCO}_3^-$  levels fall. Plasma pH falls also due to increased  $\text{H}^+$  load.



**2** Respiratory centers compensate by increasing ventilation.  $\text{P}_{\text{a}}\text{CO}_2$  decreases as a result. Plasma  $\text{HCO}_3^-$  falls further, but pH renormalizes.



Metabolic acidosis can be caused both by nonvolatile acid accumulation and excessive  $\text{HCO}_3^-$  loss. Possible culprits are numerous, including:

- ↑ **Acid production** (e.g., lactic acid): Metabolism of ketone bodies causes **ketoacidosis**.
- **Drugs and poisons**: Methanol and ethylene glycol yield nonvolatile acids when metabolized.
- ↑  **$\text{HCO}_3^-$  excretion**: Excessive  $\text{HCO}_3^-$  loss can result from proximal tubule dysfunction or from diarrhea.
- ↓  **$\text{H}^+$  excretion**: Drugs, toxins, and familial disorders that impair  $\text{H}^+$  excretion cause renal tubular acidosis.



The anion gap is a measure of minor serum anions such as proteins, lactate, citrate, and phosphate. Accumulation of lactic acid, keto acids, and other anions widens the gap and is indicative of a metabolic acidosis. The gap is determined by subtracting total serum  $\text{Cl}^-$  and  $\text{HCO}_3^-$  from  $\text{Na}^+$  concentration. [Note: Normal = 8–16 mmol/L.]



# Acid–Base Disorders: Metabolic Alkalosis

6.31 Question



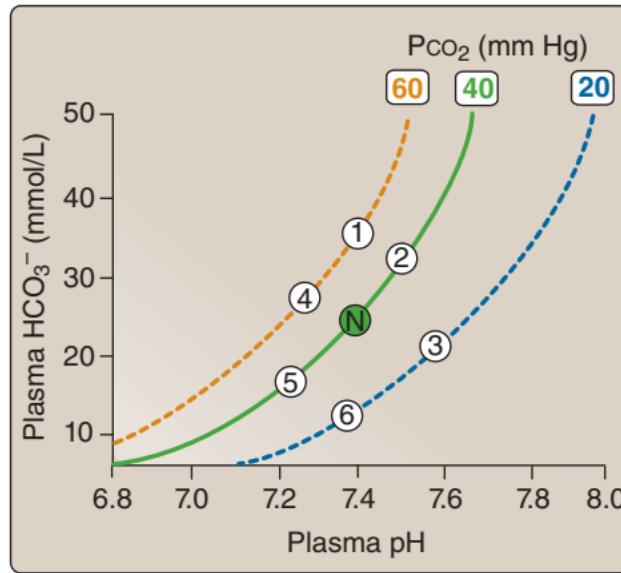
Referring to the graph, how would acute and compensated metabolic alkalosis change plasma pH,  $\text{HCO}_3^-$ , and  $\text{PCO}_2$ ?



What are two common causes of metabolic alkalosis?



A patient's arterial blood gas values are pH = 7.15,  $\text{PCO}_2$  = 50 mm Hg, and  $\text{HCO}_3^-$  = 20 mmol/L. He has an anion gap of 21 mmol/L. What is his acid–base status?

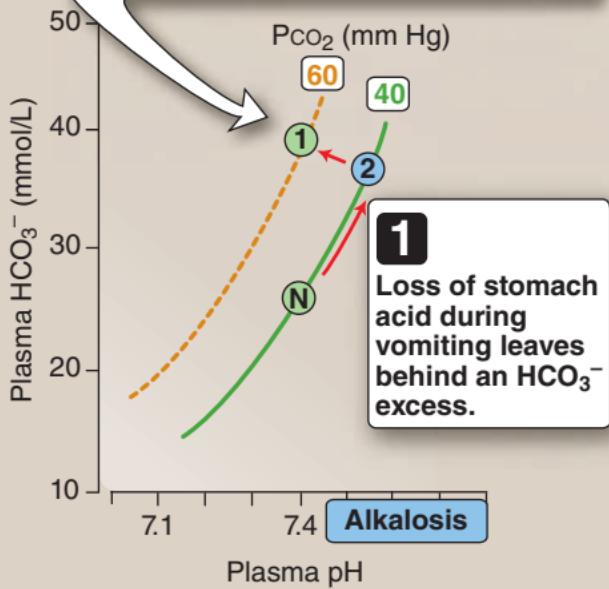


N = normal.

# Acid–Base Disorders: Metabolic Alkalosis



**2** Respiratory centers compensate by decreasing ventilation to retain  $\text{CO}_2$ .  $\text{P}_{\text{aCO}_2}$  rises, and volatile acid accumulation helps renormalize plasma pH.

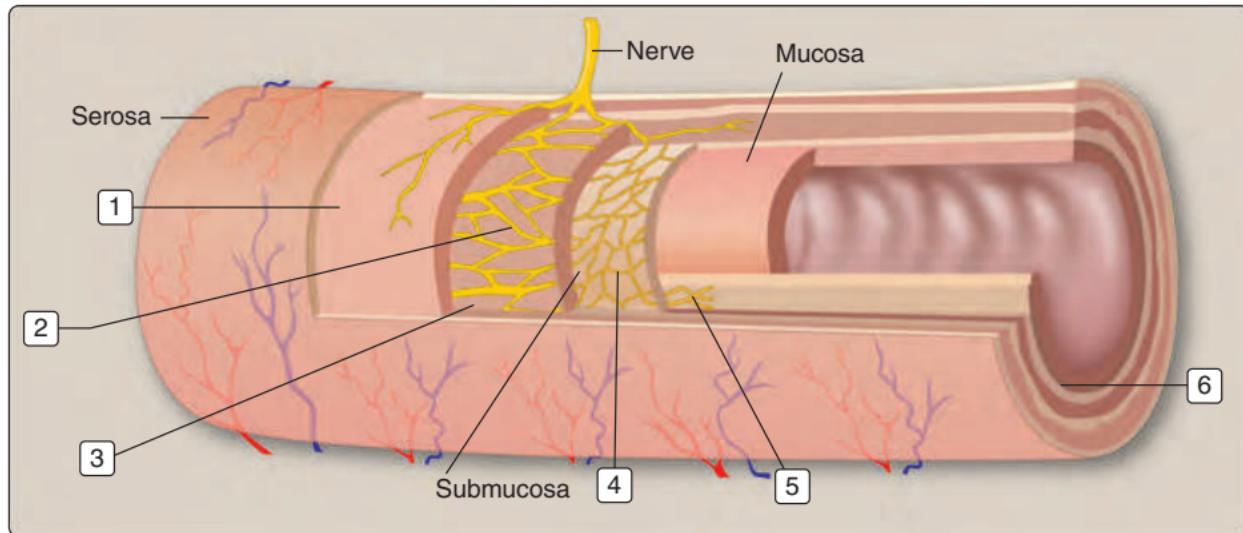


Two common causes of metabolic alkalosis:

- The most common cause is loss of stomach acid to the body exterior through prolonged vomiting or nasogastric suction.
- Some diuretics may also cause metabolic alkalosis by increasing  $\text{H}^+$  renal excretion.  
[Note: Ingestion of  $\text{NaHCO}_3$  (an antacid) is a less common cause.]



The patient has mixed respiratory acidosis and metabolic acidosis. The pH of 7.15 indicates acidosis (normal = 7.35–7.45). The anion gap of 21 mmol/L indicates an underlying metabolic acidosis (normal = 8–16 mmol/L), which should increase ventilation and cause hypcapnia. However, a  $\text{P}_{\text{CO}_2}$  of 50 mm Hg is abnormally high (normal = 36–44 mm Hg), indicating that there is also an underlying respiratory acidosis.



Identify the muscle layers and nerve plexuses indicated by boxed numerals.



What is the role of the individual muscle layers within the GI tract?



What is **Chagas disease**, and how does it cause **megaesophagus**?



GI tract layers:

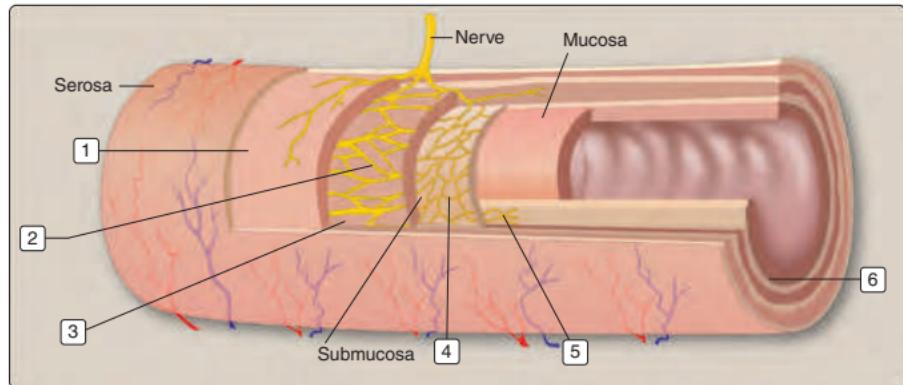
1. **Longitudinal muscle**
2. **Myenteric (Auerbach) nerve plexus**
3. **Circular muscle**
4. **External submucosal nerve plexus**
5. **Internal submucosal nerve (Meissner) plexus**
6. **Muscular layer of mucosa**



Longitudinal muscle shortens an intestinal segment, whereas circular muscle increases luminal pressure

when it contracts. Together, these actions produce **propulsive** and **mixing movements**.

- **Propulsive:** Peristaltic waves of circular muscle contraction propel food through the intestines. Movement usually proceeds anally, but orad movements can occur also.
- **Mixing:** Segmentation contractions help mix food with secretions and facilitate nutrient absorption.



The muscular layer of mucosa produces localized contractions that help expel secretions from crypts and propel lymph through villi, for example.



**Chagas disease** is caused by *Trypanosoma cruzi*, a parasitic protozoan. Infection typically causes **cardiomyopathy**, but destruction of enteric neurons can also prevent normal peristalsis. Food accumulating in the esophagus increases luminal pressure, causing distention and **megaesophagus**.

# Chemical Signaling

## 7.2 Question



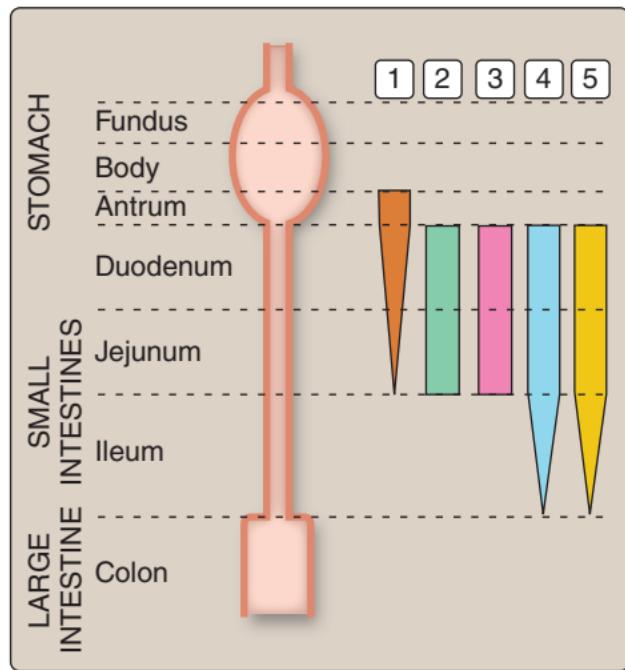
Identify the GI hormones indicated by boxed numerals.



What are the three principal GI paracrines regulating gastric acid secretion, and what is their mode of action?



Aspirin and other nonsteroidal analgesics (NSAIDs) can irritate and erode the gastric mucosa by interrupting which chemical signaling pathway? How do they produce gastric symptoms?



Sites of GI hormone release.



GI hormones:

1. **Gastrin** (released by G cells)
2. **Gastric inhibitory peptide** (released by K cells)
3. **Motilin** (released by M cells)
4. **Cholecystokinin** (released by I cells)
5. **Secretin** (released by S cells)

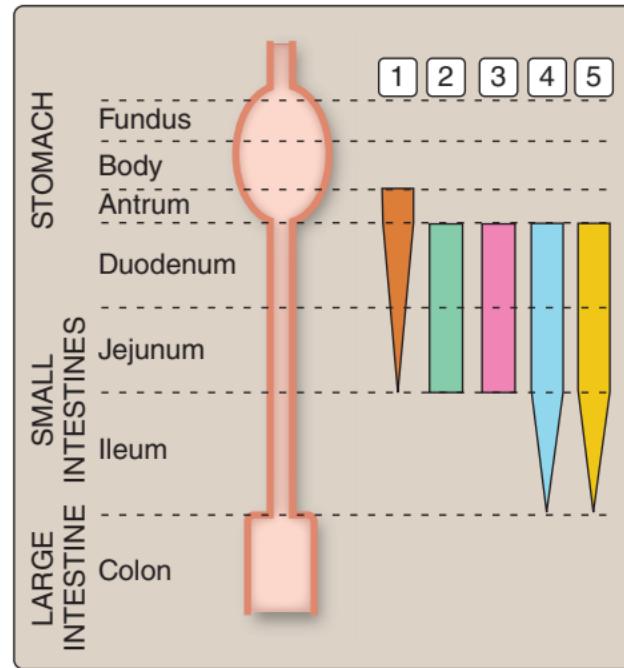


Paracrines regulating acid secretion:

- **Histamine**: released from enterochromaffin-like cells and mast cells in the stomach to increase acid secretion
- **Somatostatin**: released from D cells located in the stomach and pancreas to inhibit acid secretion
- **Prostaglandins (PGs)**: inhibit acid secretion ( $\text{PGE}_2$ )



NSAIDs inhibit  $\text{COX}1$  and  $\text{COX}2$ , enzymes involved in PG synthesis. PGs normally limit gastric acid release and help sustain a mucous layer that protects the GI lining. Inhibiting PG synthesis reduces the protective layer and leaves the gastric epithelium vulnerable to gastric acid and pepsin. [Note: Aspirin and other NSAIDs are acidic and irritate the gastric lining directly.]



Sites of GI hormone release.



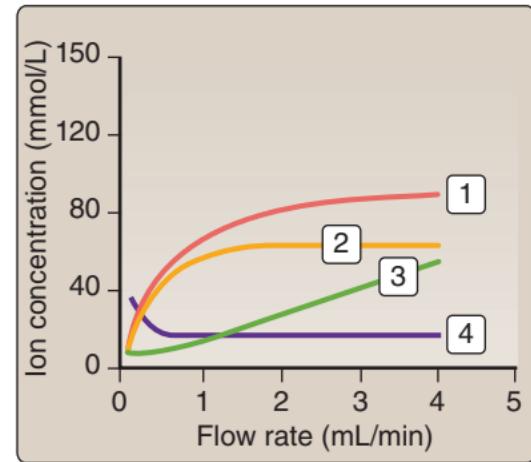
Identify the ions indicated by boxed numerals. Why is ionic composition affected by salivary flow rate?



Saliva contains several other components in addition to water and ions. Name four or more and review their functions.



**Sjögren syndrome** is an \_\_\_\_\_ disorder. First symptoms include \_\_\_\_\_ and dry eyes due to reduced \_\_\_\_\_ and \_\_\_\_\_ gland function.



## 7.3 Answer

# Saliva



Ions:

1.  $\text{Na}^+$
2.  $\text{HCO}_3^-$
3.  $\text{Cl}^-$
4.  $\text{K}^+$

Salivary ductal cells modify the primary secretion by reabsorbing  $\text{Na}^+$  and  $\text{Cl}^-$  and secreting  $\text{HCO}_3^-$  and  $\text{K}^+$ . Higher flow rates reduce the time available to modify the secreted fluid, so saliva's composition increasingly resembles the primary secretion.

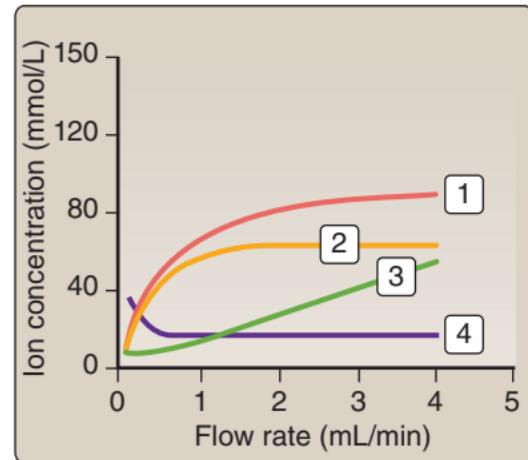


Other salivary components:

- **Lysozyme:** antimicrobial enzyme that attacks the bacterial cell wall
- **Lactoferrin:** antimicrobial
- **Immunoglobulin A:** antimicrobial
- **Proline-rich proteins:** antimicrobial and aid tooth enamel formation
- **Salivary amylase:** carbohydrate digestion
- **Lingual lipase:** lipid digestion



**Sjögren syndrome** is an autoimmune disorder. First symptoms include xerostomia and dry eyes due to reduced salivary and lacrimal gland function. [Note: The combination of dry mouth and dry eyes is also known as the "sicca complex."]



# Swallowing

7.4 Question



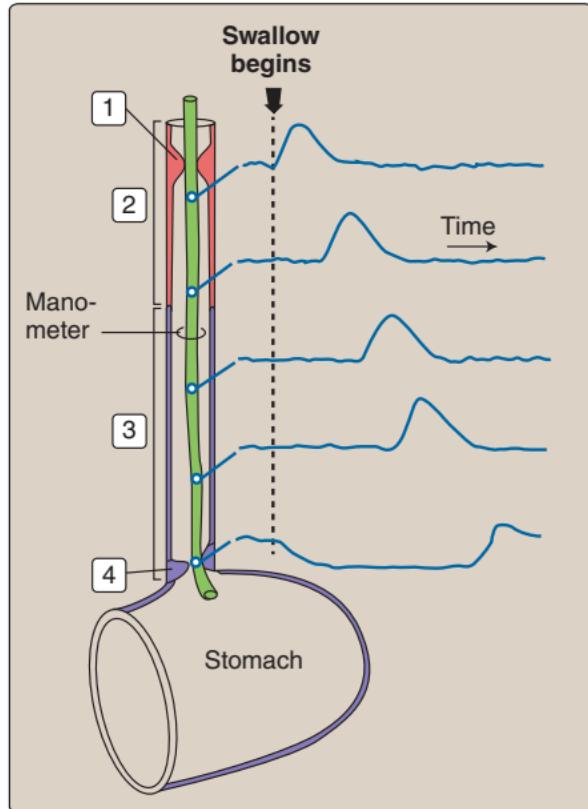
What types of muscle are involved in swallowing (indicated by boxed numerals), and what is the significance of the blue manometric traces?



How is swallowing regulated?



What is the difference between “**dysphagia**” and “**achalasia**,” and what structures are involved?





Muscles:

1. **Upper esophageal sphincter (UES)**; smooth muscle
2. Striated esophageal muscle
3. Smooth esophageal muscle
4. **Lower esophageal sphincter (LES)**; smooth muscle

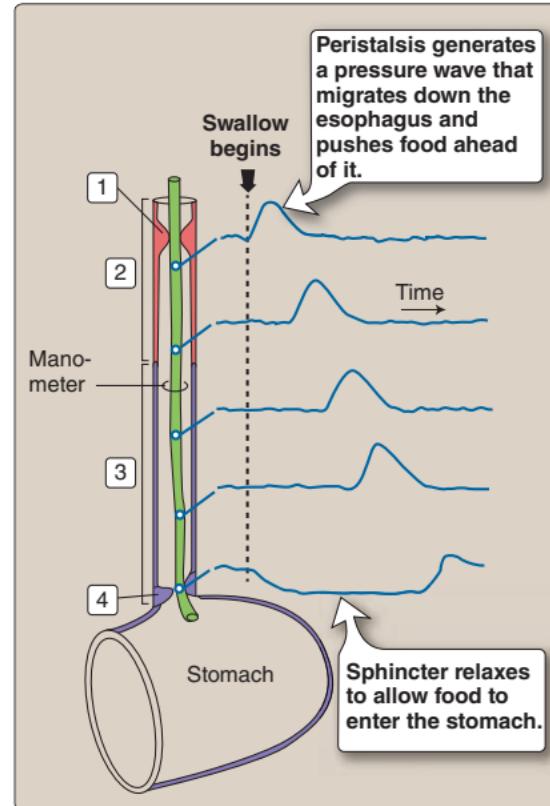
The manometric traces record a wave of positive pressure migrating down the esophagus during a swallow (**peristaltic pressure wave**). The LES relaxes ahead of this wave to allow food to enter the stomach, which is recorded as a pressure decrease.



Swallowing is initiated voluntarily by forcing food against the pharynx, triggering a swallowing reflex that is coordinated by the **medullary swallowing center**. The center sequences muscle contractions that propel food (pharyngeal and esophageal peristalsis), coordinates relaxation of the UES and LES, and transiently inhibits respiration during food passage through the pharynx.



**Dysphagia** describes difficulty swallowing or initiating a swallowing reflex. Because the reflex involves multiple pathways, numerous underlying causes may exist. **Achalasia** symptoms primarily reflect LES relaxation failure. The LES is a tonically contracted smooth muscle under neural control.





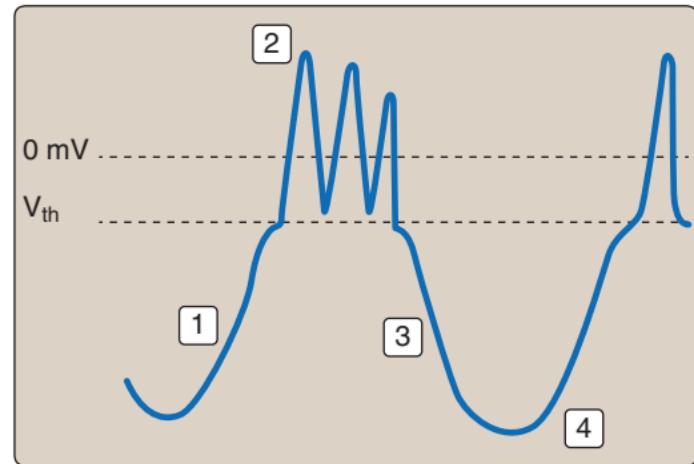
Using the boxed numerals as a guide, explain the ionic mechanisms by which gastric slow waves are generated and sustained.



Identify three or more important physiologic functions of the stomach.



What is **functional dyspepsia (FD)**?





Slow wave origins:

1. The membrane spontaneously depolarizes toward  $V_{th}$ .
2. A voltage-gated  $I_{Ca}$  activates at  $V_{th}$  to generate an AP.
3.  $Ca^{2+}$  influx activates a  $Ca^{2+}$ -dependent  $I_K$ , and the membrane repolarizes.
4.  $Ca^{2+}$  channels close,  $I_K$  terminates, and the membrane again depolarizes toward  $V_{th}$ .



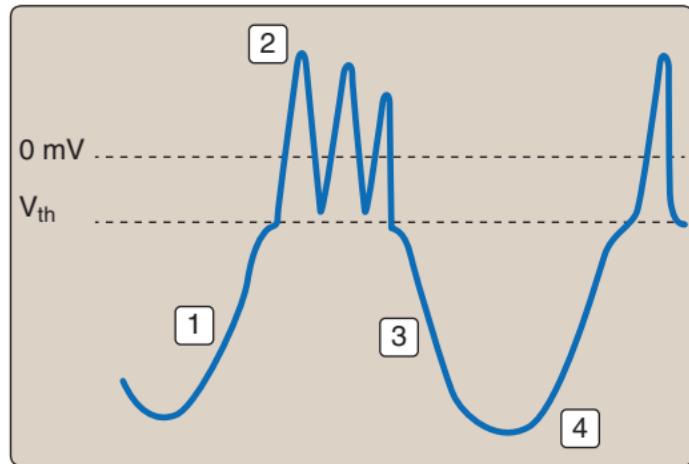
Stomach functions include:

- **Reservoir:** fundal **receptive relaxation** creates a storage reservoir, delaying solid food delivery to the small intestine
- **Mixing and grinding:** grinds food (**gastric mill**) and mixes it with secretions
- **Secretion:** primarily gastric acid plus some enzymes
- **Hormonal:** releases gastrin and somatostatin
- **Antimicrobial:** low pH prevents microbial overgrowth and small intestine colonization



**FD** is a common complaint with unclear origins. Symptoms include a troubling sensation of postprandial fullness, early satiety, and epigastric pain or burning sensations.

[Note: Although there is usually no clear cause, and endoscopy typically fails to reveal any structural changes, reduced gastric motility has been documented in patients with FD.]



# Gastric Secretions

## 7.6 Question



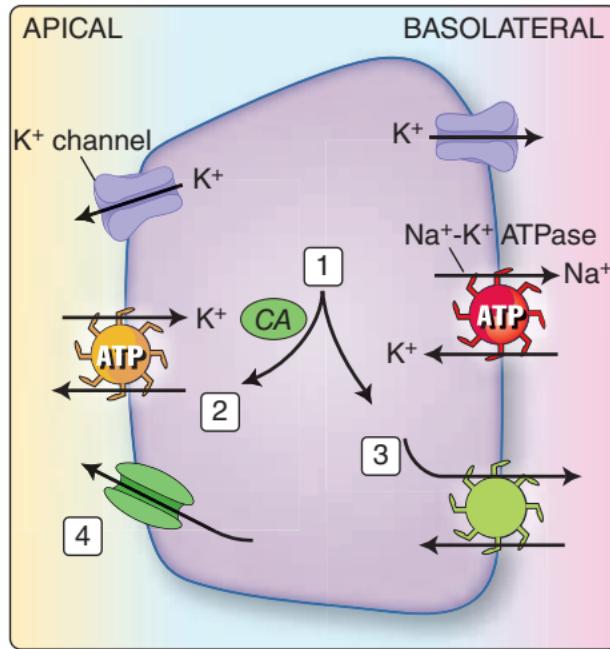
Using the boxed numerals as a guide, explain the steps in acid secretion by a gastric parietal cell.



Review three or more mechanisms that help protect the stomach against auto-digestion by gastric acid and *pepsin*.



What is the most common cause of **peptic ulcers**?



Acid secretion by a parietal cell.

## 7.6 Answer

# Gastric Secretions



HCl secretion steps:

1.  $\text{H}^+$  and  $\text{HCO}_3^-$  form from  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , facilitated by CA.
2.  $\text{H}^+$  is pumped into the gastric lumen by an  $\text{H}^+ \text{-} \text{K}^+$  ATPase.
3.  $\text{HCO}_3^-$  is exchanged for  $\text{Cl}^-$ .
4.  $\text{Cl}^-$  is released into the gastric lumen via a  $\text{Cl}^-$  channel.



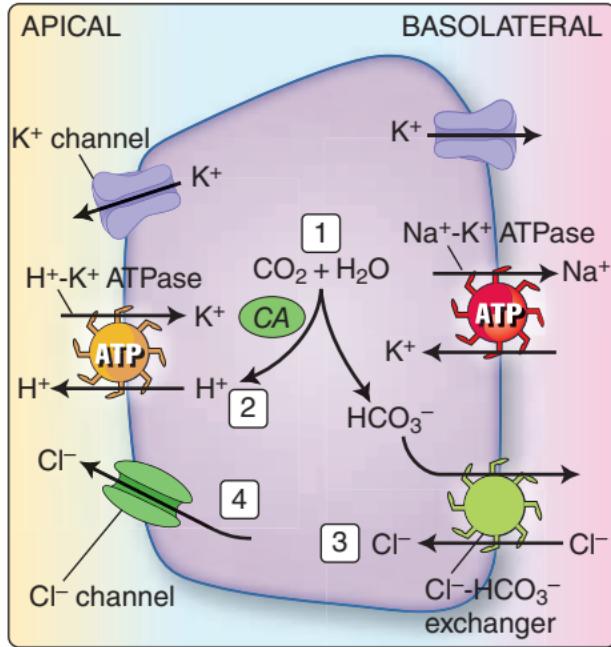
Stomach protective mechanisms:

- Pepsin is secreted in inactive form (**pepsinogen**).
- A **viscous mucous layer** creates a physical barrier to acid and enzymes.
- $\text{HCO}_3^-$  is secreted onto the epithelial surface which, with assistance of mucus, creates an **alkaline buffer layer**.
- **Somatostatin** release from gastric D cells provides negative feedback that limits acid production.



Most **peptic ulcers** are due to ***Helicobacter pylori***, which migrates to and colonizes the  $\text{HCO}_3^-$ -rich mucous layer at the epithelial surface. Inflammatory responses to the infection cause chronic gastritis and, ultimately, gastric mucosa erosion. [Note: The stomach is well protected against acid and enzymes under normal circumstances.]

**A-plus:** Smoking, stress, and NSAID use are also principal risk factors for peptic ulcer disease.



Acid secretion by a parietal cell.

# Parietal Cell Regulation

7.7 Question



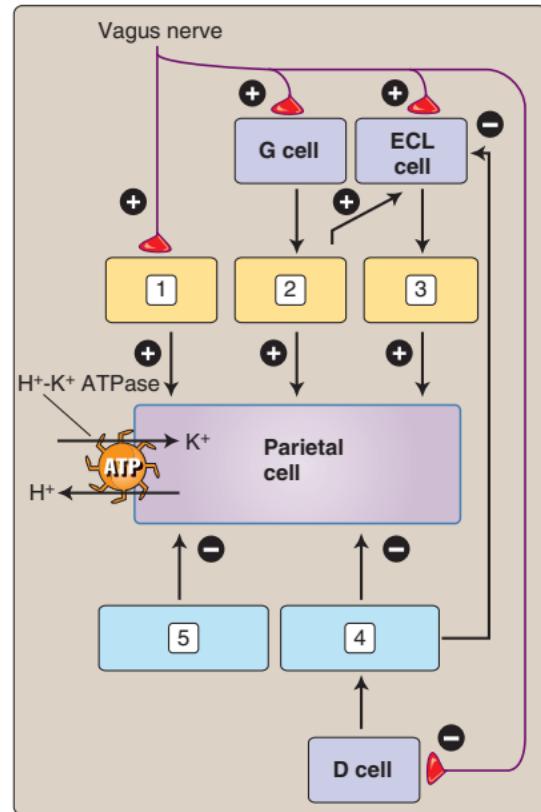
What are the hormones and paracrines that regulate acid production by parietal cells (indicated by boxed numerals)?



Integration and fine-tuning of acid release during parietal cell stimulation involves what two intracellular signaling pathways?



What is **Zollinger-Ellison syndrome (ZES)**?



## 7.7 Answer

# Parietal Cell Regulation



Regulatory factors:

1. ACh
2. Gastrin
3. Histamine
4. Somatostatin
5. Prostaglandins (PGs)



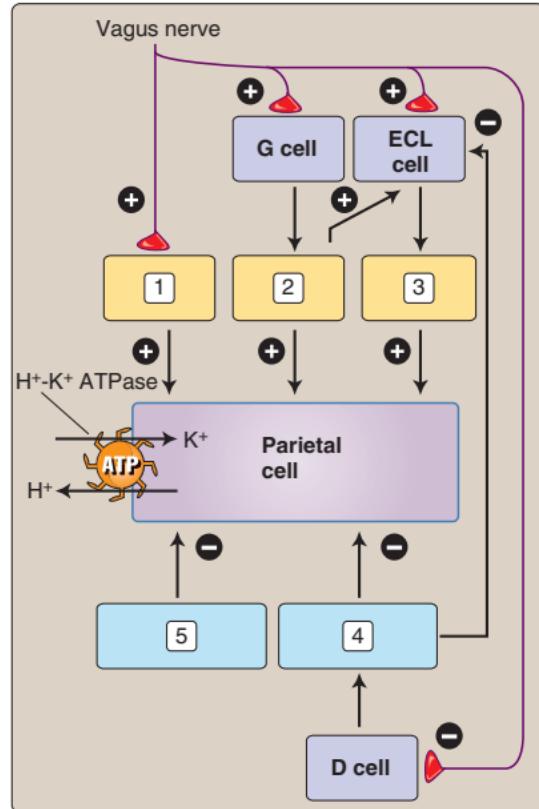
Two pathways regulating acid release:

- **IP<sub>3</sub> signaling pathway:** Gastrin and ACh both act through GPCRs that initiate intracellular Ca<sup>2+</sup> release and activate PKC. PKC increases H<sup>+</sup>-K<sup>+</sup> ATPase activity and acid secretion.
- **cAMP signaling pathway:** Somatostatin and PGs also act through GPCRs, but they couple to a G<sub>i</sub> that inhibits PKA and acid secretion. Histamine also works through the cAMP pathway but is stimulatory.



The symptoms of **ZES** are caused by a **non-β islet cell gastrinoma** typically located in the pancreas. Unregulated gastrin production by the tumor stimulates gastric acid production in amounts that overwhelm the duodenum's ability to neutralize it. Duodenal and gastric ulcers are common in patients with ZES.

**A-plus:** Gastrinomas typically cause fasting serum gastrin levels to be 10-fold higher than normal, which can prove diagnostic. Paradoxically, gastrin production increases in response to secretin, which provides a basis for the diagnostic **secretin stimulation test**.



# Carbohydrate Digestion and Absorption

7.8 Question



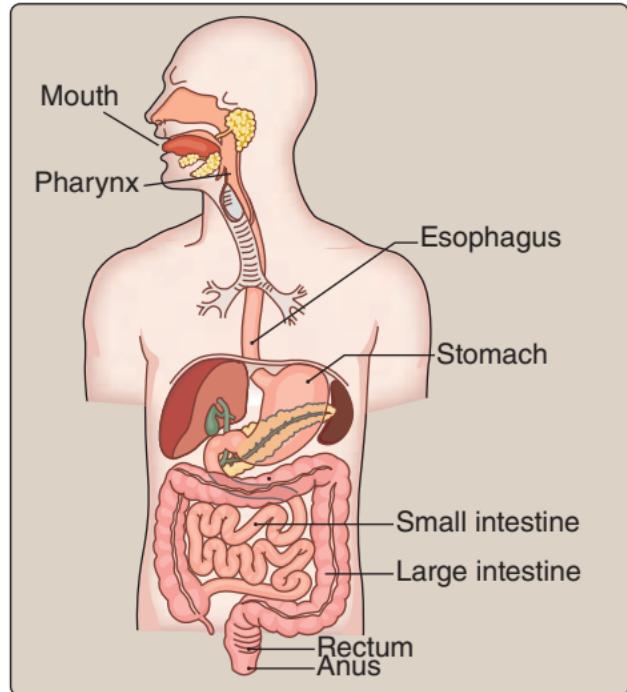
What are the two main GI tract sites of carbohydrate digestion, and where are carbohydrates absorbed?



What is the mechanism by which carbohydrates are absorbed by the GI tract?



How does an H<sub>2</sub> breath test help provide a diagnosis of **lactose intolerance**?





Main sites of digestion and absorption:

- **Mouth.** *Salivary amylase* begins carbohydrate breakdown, although it is not essential for digestion.
- **Small intestine.** *Pancreatic amylase* and membrane-bound *disaccharidases* (*isomaltase*, *glucoamylase*, *lactase*, *sucrase*) complete carbohydrate digestion. The **duodenum** is the principal absorption site.

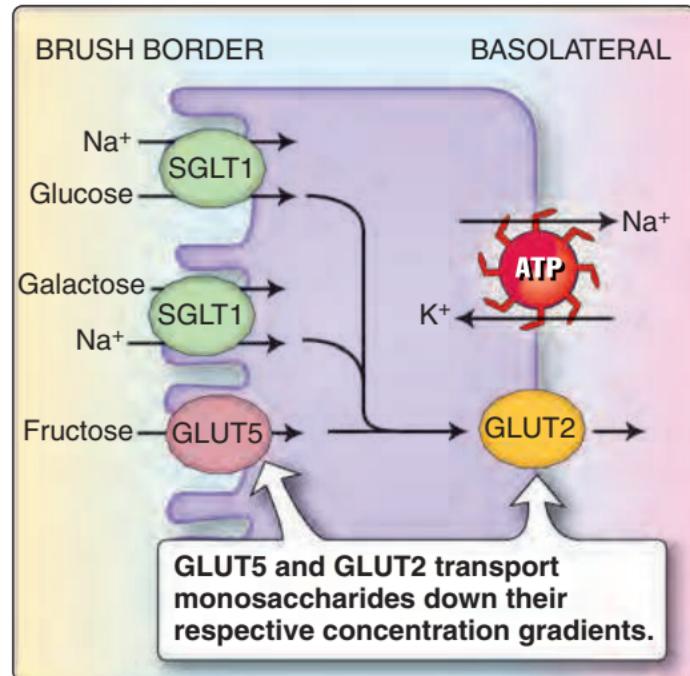


The intestine can only absorb monosaccharides (i.e., glucose, galactose, fructose). They are absorbed by  **$\text{Na}^+$ -glucose cotransport (SGLT1)** and **facilitated transport (GLUT2 and GLUT5)**, as shown.



**Lactose intolerance** reflects a ***lactase deficiency***.

Lactose passes through the small intestine to the colon undigested. Colonic bacteria then digest it to short-chain fatty acids and  $\text{H}_2$ , the latter of which can be detected in breath samples (>20 ppm is considered diagnostic).



Monosaccharide absorption in the small intestine.

# Protein Digestion and Absorption

7.9 Question



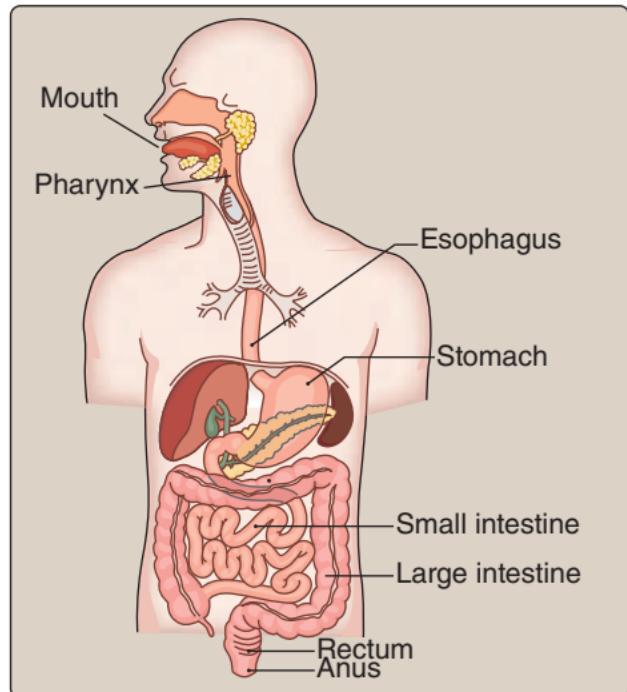
What are the two principal GI tract sites of protein digestion, and where does absorption occur?



What are the two main cellular pathways for peptide absorption by the GI tract?



The **pellagra**-like symptoms of \_\_\_\_\_ disease are the result of a \_\_\_\_\_ deficiency caused by an inability to absorb \_\_\_\_\_ (and other neutral amino acids).





Two principal GI tract sites of digestion:

- **Stomach:** Pepsin begins protein digestion.
- **Small intestine:** Pancreatic proteases (*trypsin, chymotrypsin, elastase, carboxypeptidases A and B*), apical peptidases, and intracellular processing by enterocytes complete digestion.

Protein absorption occurs in the small intestine, principally in the **duodenum**.

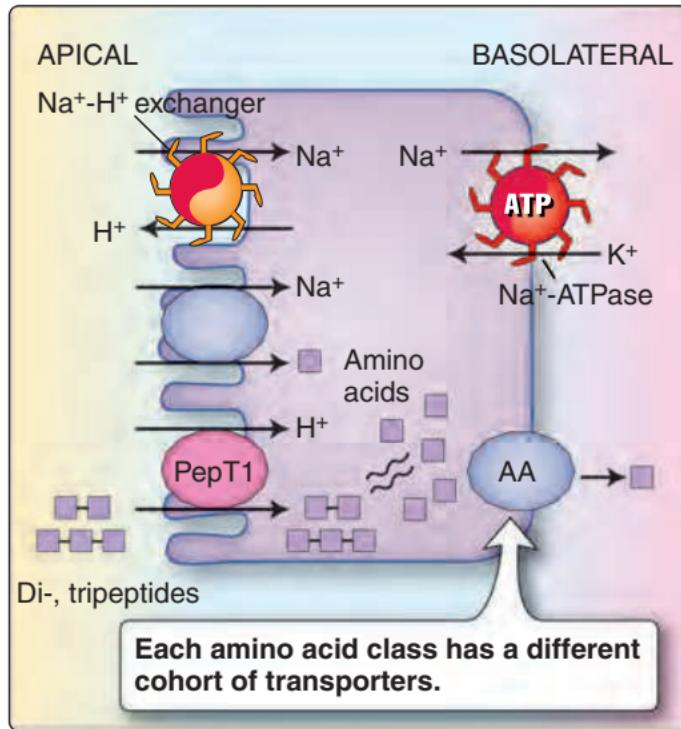


Proteins cross the basolateral membrane as single amino acids. Uptake at the apical membrane occurs by:

- **Na<sup>+</sup>-dependent cotransport** of single amino acids by a range of broad-specificity carriers, and
- **H<sup>+</sup>-dependent cotransport** of oligopeptides via PepT1, as shown.



The **pellagra**-like symptoms of **Hartnup** disease are the result of a niacin deficiency caused by an inability to absorb tryptophan (and other neutral amino acids).



Peptide absorption in the small intestine. PepT1 =  $\text{H}^+$ -oligopeptide cotransporter.

# Lipid Digestion

7.10 Question



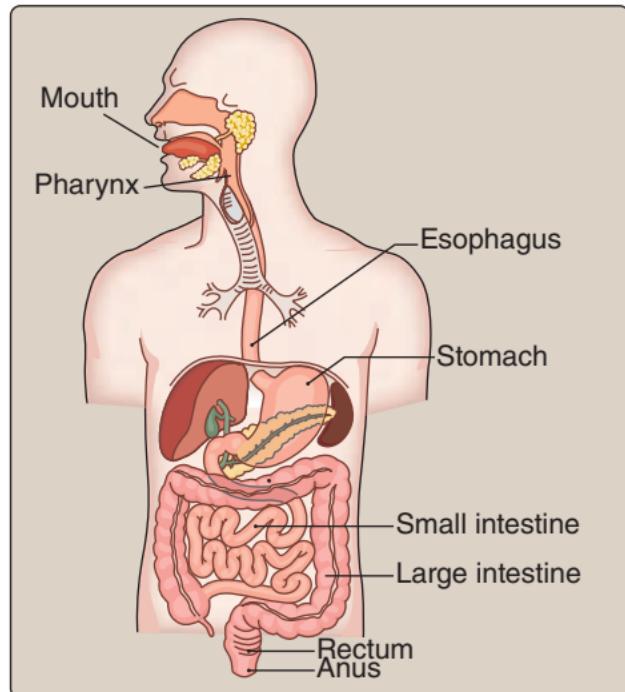
What are the three main GI tract sites of lipid digestion?



What is the physiologic stimulus for *pancreatic lipase* secretion into the intestinal lumen?



Symptoms of **Zollinger-Ellison syndrome (ZES)** include steatorrhea. How does a **gastrinoma** cause fat malabsorption?





Three lipid digestion sites:

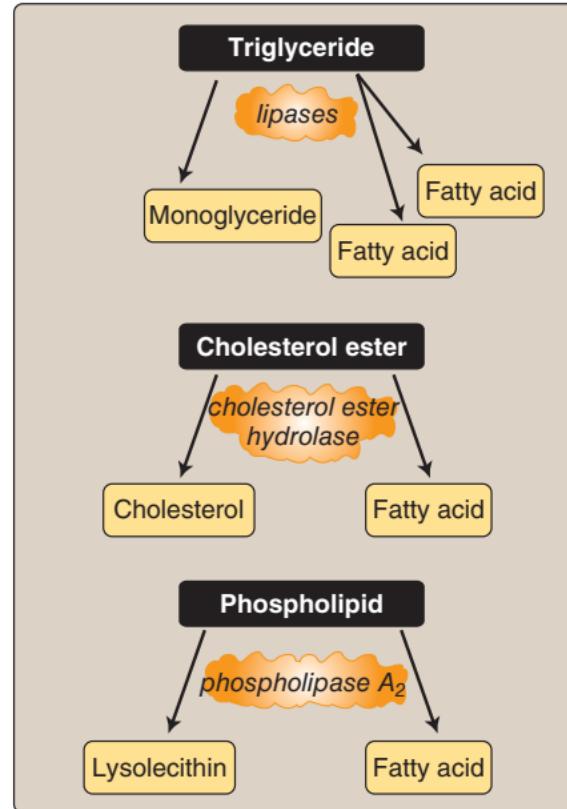
- **Mouth:** Lingual lipase begins digestion.
- **Stomach:** Lingual lipase and gastric lipase continue digestion.
- **Small intestine:** Pancreatic lipase assists the two lipases entering from the stomach, and two additional lipases from the pancreas (*cholesterol ester hydrolase* and *phospholipase A<sub>2</sub>*) help complete digestion.



Lipids entering the duodenum stimulate **cholecystokinin (CCK)** release from I cells. CCK then stimulates enzyme secretion by pancreatic acinar cells. Concurrent CCK-stimulated bile release from the gallbladder facilitates lipid digestion.

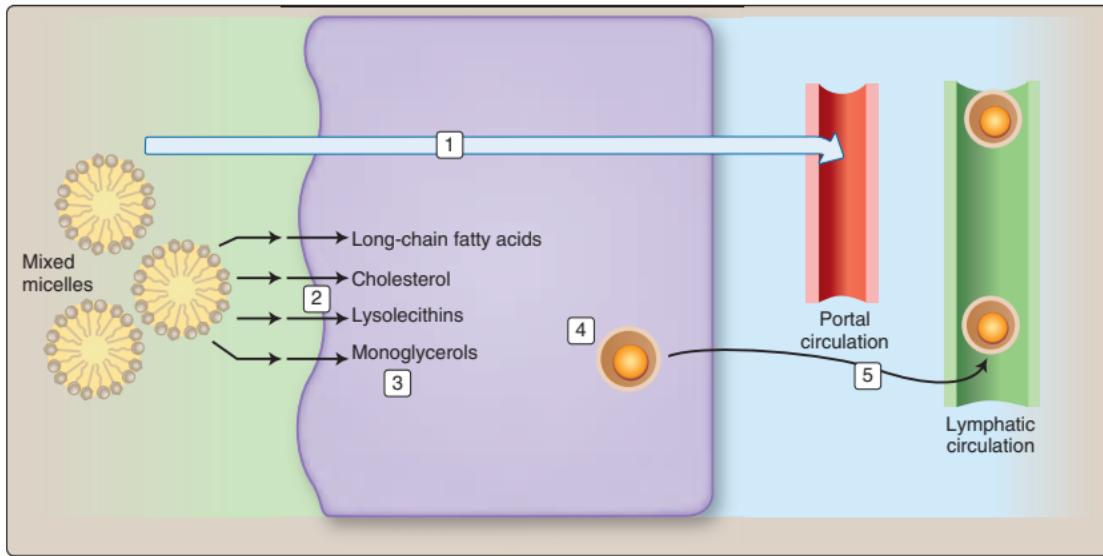


Patients with **ZES** produce gastric acid in amounts that overwhelm duodenal buffering capacity, causing the pH of chyme to fall to levels that inactivate *pancreatic lipase* and bile salts. Fat passes through the small intestine to the colon undigested as a result, causing steatorrhea.



# Lipid Absorption

7.11 Question



Using the boxed numerals as a guide, review the pathways for lipid absorption in the small intestine.



Which vitamins are fat-soluble, and how are they absorbed?

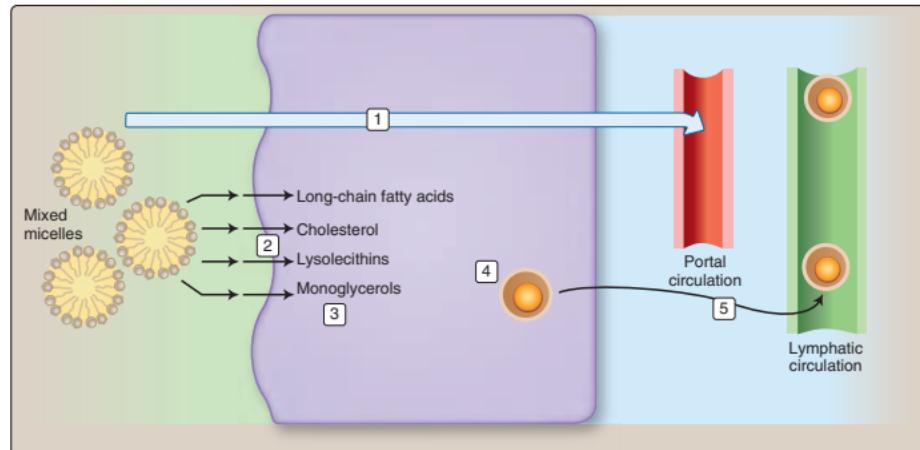


What are the physiologic consequences of vitamin E deficiency?



Pathways for lipid absorption:

1. Short- and medium-chain fatty acids diffuse across the epithelium and enter the circulation directly.
2. Long-chain fatty acids are absorbed by diffusion or transported across the apical membrane in association with fatty acid-binding proteins.
3. Incorporation of fatty acids into triglycerides, phospholipids, and cholesterol esters
4. Triglycerides are packaged into **chylomicrons**.
5. Chylomicrons are exocytosed across the basolateral membrane and enter the lymphatic system.



Vitamins A, D, E, and K are fat-soluble. They are incorporated into micelles and absorbed from the gut lumen by mechanisms similar to those used for other fatty acids (i.e., diffusion and transport). Once inside the enterocyte, they are packaged into chylomicrons and transferred to the lymphatic system for distribution.



Vitamin E deficiency is rare in otherwise healthy populations but can cause hemolysis and neurologic symptoms. Vitamin E is an antioxidant that normally protects membrane fatty acids from peroxidation.

# Electrolyte Absorption

7.12 Question



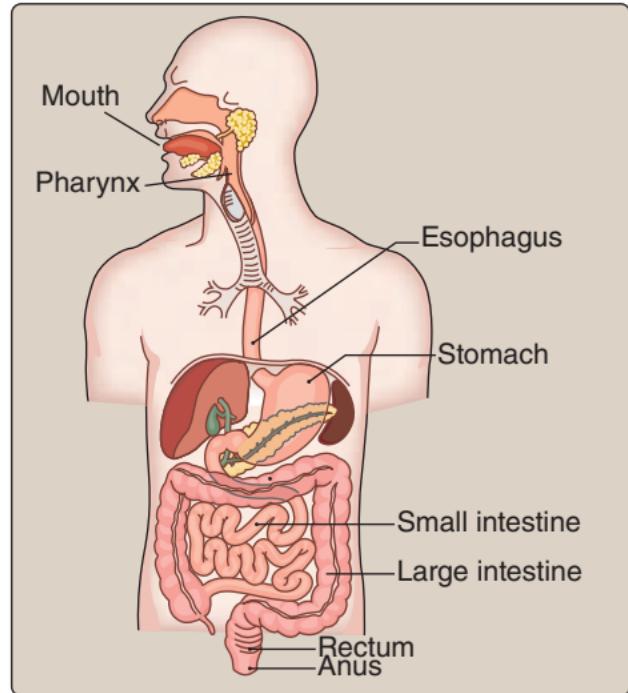
Identify which intestinal segment (i.e., small or large intestine) is the primary site for absorption of each of the following electrolytes:  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ , and  $\text{Cl}^-$ .



Where in the GI tract does regulated uptake of  $\text{Ca}^{2+}$  occur and by what mechanism?



What is **tropical sprue**, and how does it result in hypocalcemia?





Sites of electrolyte absorption by the small and large intestines:

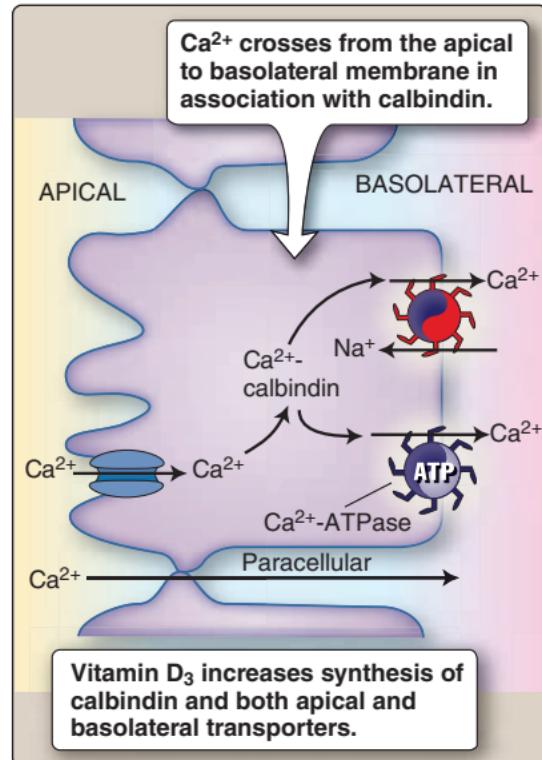
- **Na<sup>+</sup>**: absorbed along with nutrients via Na<sup>+</sup>-dependent cotransport in the small intestine and via Na<sup>+</sup>-H<sup>+</sup> exchange in both intestinal segments. The distal colon absorbs Na<sup>+</sup> via ENaC, an epithelial Na<sup>+</sup> channel that provides an important pathway for Na<sup>+</sup> reabsorption by the renal tubule (see 6.19).
- **K<sup>+</sup>**: absorbed in small and large intestines (latter also actively secretes K<sup>+</sup>)
- **Ca<sup>2+</sup>**: small intestine, both passively and actively (as shown)
- **Mg<sup>2+</sup>**: small intestine, both passively and actively by unknown mechanisms
- **Cl<sup>-</sup>**: linked mainly to Na<sup>+</sup> absorption



Ca<sup>2+</sup> is actively absorbed in the duodenum via apical Ca<sup>2+</sup> channels and basolateral Ca<sup>2+</sup> transporters, as shown. **Vitamin D** stimulates uptake by upregulating expression of these proteins.



**Tropical sprue** is a malabsorption syndrome seen in regions close to the equator. The cause is unknown (possibly infectious), but intestinal villi are stunted as a result, causing malabsorption. Reduced absorption and increased excretion of divalent cations, including Ca<sup>2+</sup>, causes hypocalcemia.



Ca<sup>2+</sup> absorption in the small intestine.

# Water Secretion and Absorption

7.13 Question



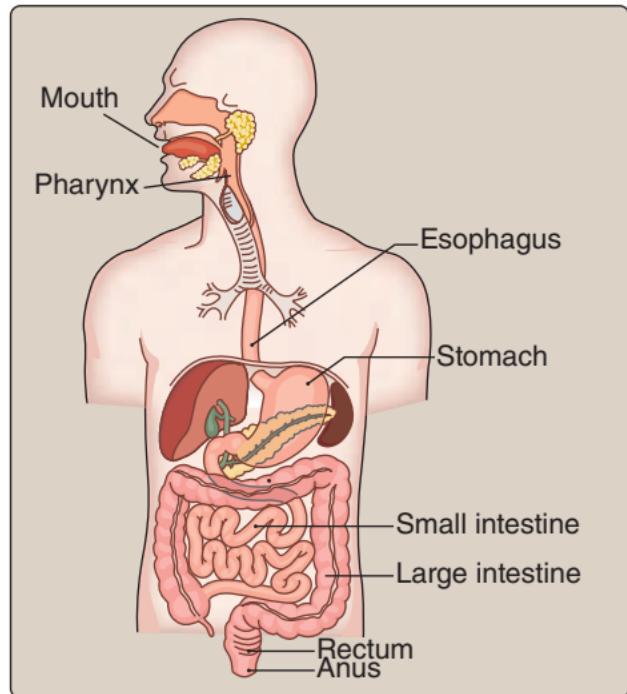
Approximately how much water does the GI system secrete and absorb daily?



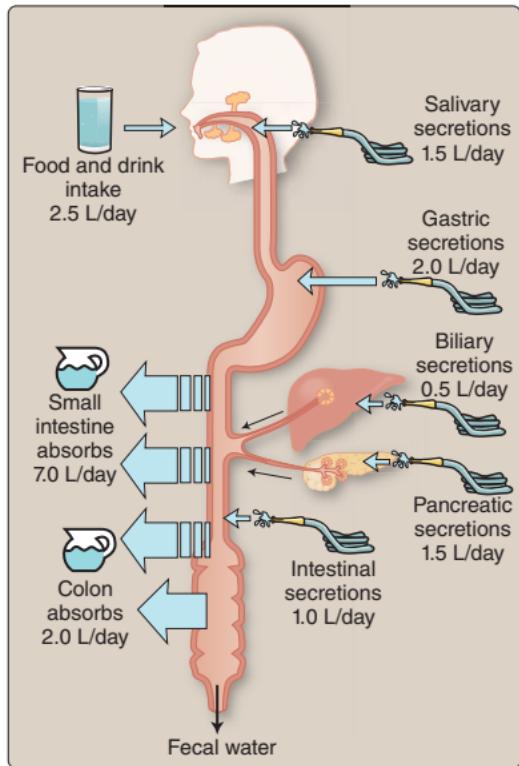
What two main large intestine features allow it to absorb all but ~100 mL of water per day from feces?



What are the four different types of diarrhea (based on stool characteristics) and the mechanisms by which water absorption is impaired?



# Water Secretion and Absorption



Water secretion and absorption by the GI system.



Water absorption by the large intestine:

- The large intestine is lined with a **tight epithelium** that is able to establish strong transepithelial concentration gradients that drive water absorption by osmosis.
- Segmentation contractions** knead residual undigested material, thereby increasing contact between feces and epithelium.

[Note: The contractions yield bead-like haustra.]



Four diarrhea types:

- Osmotic:** Ingestion of osmolytes (e.g.,  $Mg^{2+}$  salts, polyethylene glycol) draws water into the intestinal lumen.
- Fatty:** Nutrient malabsorption prevents normal water recovery.
- Inflammatory:** Inflammatory bowel disease and infections can produce frequent loose stools.
- Secretory:** Various bacterial and other toxins stimulate water secretion by enterocytes.

# Exocrine Pancreas

7.14 Question



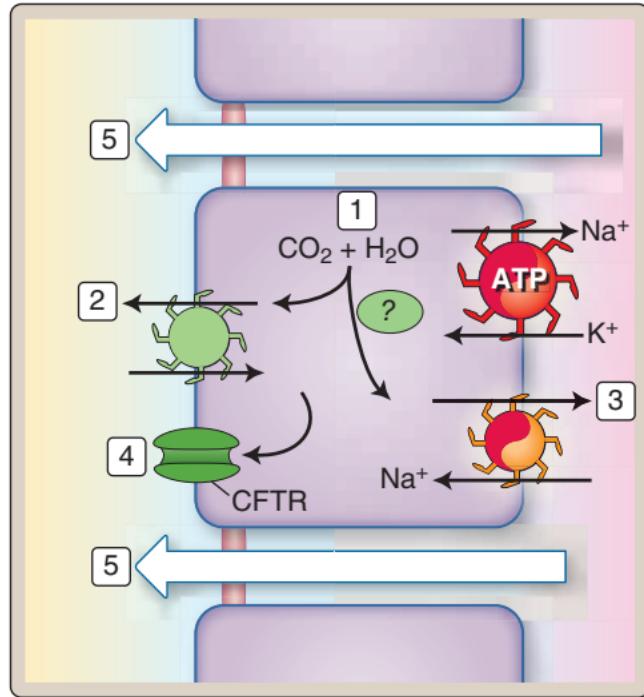
Using the boxed numerals as a guide, identify the composition and steps involved in serous fluid secretion by pancreatic intercalated cells.



What are the three phases of pancreatic secretion, and how does control shift from one phase to the next?



How is pancreatic function affected in patients with **cystic fibrosis**?





Steps in serous fluid secretion:

1.  $\text{H}^+$  and  $\text{HCO}_3^-$  are formed from  $\text{H}_2\text{O}$  and  $\text{CO}_2$ , assisted by CA.
2.  $\text{HCO}_3^-$  is secreted in exchange for  $\text{Cl}^-$ .
3.  $\text{H}^+$  is released to blood in exchange for  $\text{Na}^+$ .
4.  $\text{Cl}^-$  diffuses into the lumen via CFTR.
5.  $\text{Na}^+$  follows the negative charge carried by  $\text{Cl}^-$ , and  $\text{H}_2\text{O}$  is drawn into the lumen by osmosis.

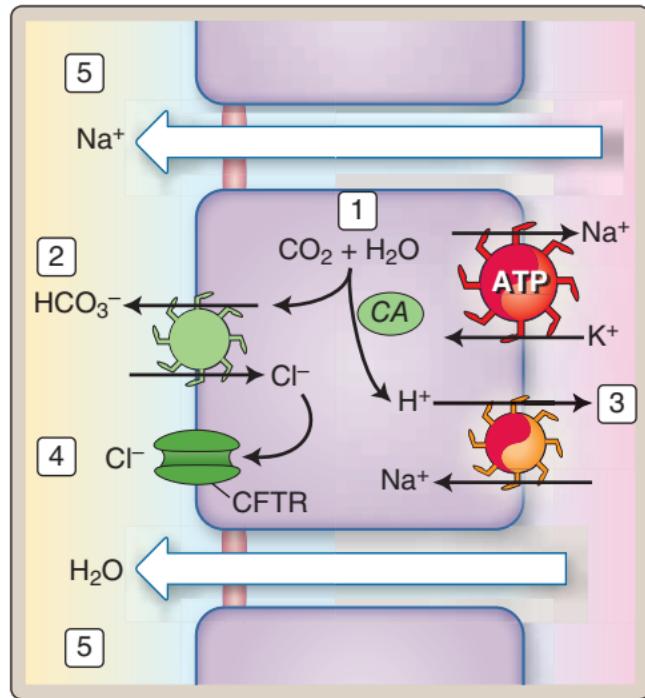


Three pancreatic secretion phases:

- **Cephalic:** Approximately 25% of total secretion occurs in response to the thought of food. Secretion is stimulated by the vagus nerve.
- **Gastric:** Approximately 10% is mediated by a **vagovagal reflex** initiated by gastric distension.
- **Intestinal:** Approximately 65% is stimulated by secretin and cholecystokinin (CCK), which are released in response to  $\text{H}^+$  (i.e., secretin) and fats (i.e., CCK) entering the duodenum.



CFTR mutations impair pancreatic secretion by interfering with  $\text{Cl}^-$ - and  $\text{Cl}^-$ -dependent  $\text{Na}^+$  and  $\text{H}_2\text{O}$  movement into the ducts (step 4 shown). This causes pancreatic insufficiency and can lead to recurrent bouts of **pancreatitis**.





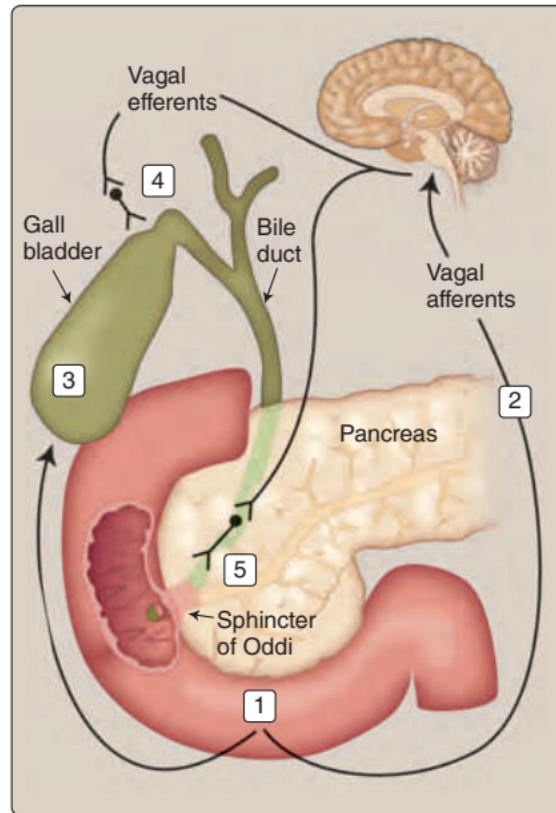
Using the boxed numerals as a guide, explain how bile secretion is controlled.



What is the composition of bile, and what are the three general physiologic functions of bile salts?



What are **gallstones** composed of, and how do they cause symptoms?





Bile secretion control:

1. Fats and proteins in the duodenum stimulate **cholecystokinin (CCK)** release from I cells.
2. Arrival of these nutrients is also relayed vagally to the brain.
3. CCK causes gallbladder contraction.
4. Vagal efferents also stimulate gallbladder contraction via cholinergic terminals.
5. Vagal efferents cause **sphincter of Oddi** relaxation through **vasoactive intestinal peptide** release, permitting bile to flow into the small intestine.



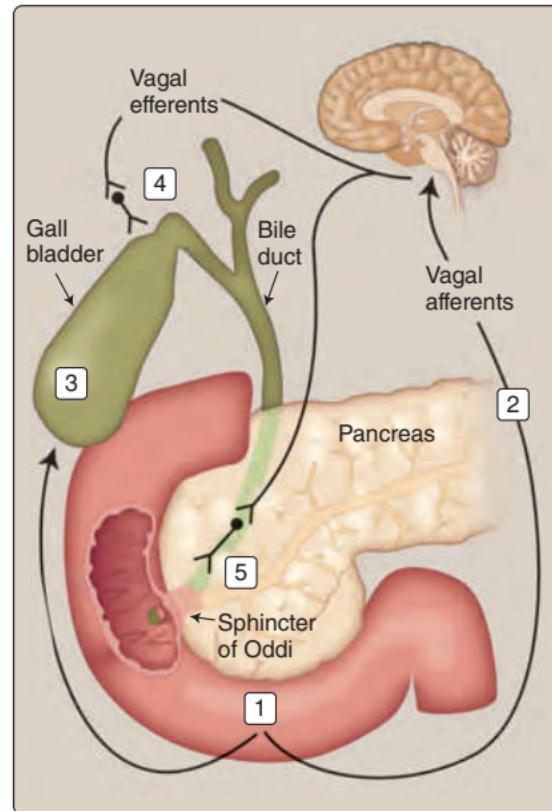
Bile contains water, various electrolytes, bile salts, cholesterol, fatty acids, phospholipids, and bilirubin.



Bile salt functions:

- **Emulsify** fat droplets, making the lipids accessible to *lipases*
- Bile salt micelles ferry lipid digestion products to enterocytes for absorption.
- Facilitate **cholesterol excretion**

Most gallstones (~80%) are yellow and composed of cholesterol. The remaining ~20% are black or brown and composed of bile pigments (e.g., calcium bilirubinate). Symptoms arise when stones enter the bile duct and obstruct flow, causing pain (**biliary colic**). [Note: Many individuals with gallstones remain asymptomatic.]



# Endocrine Pancreas

## 8.1 Question



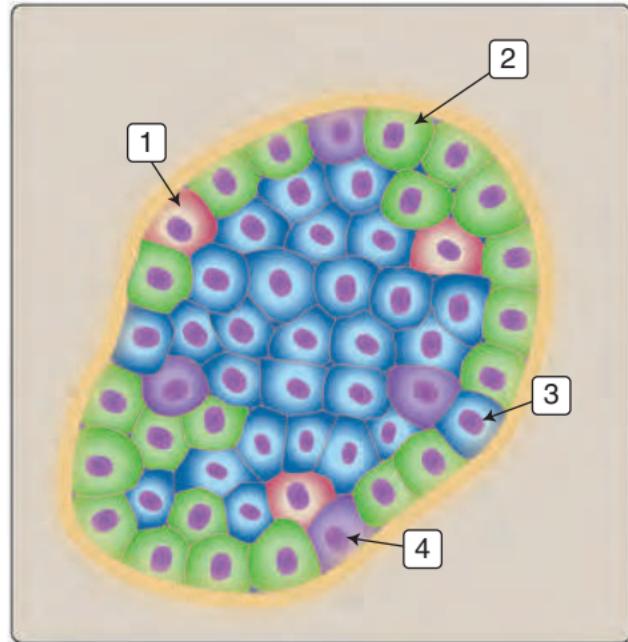
Identify four types of neuroendocrine cell found in pancreatic islets (shown) and the hormones they secrete.



Review three or more mechanisms by which islet neuroendocrine cells are regulated.



What characteristic symptom triad do **somatostatinomas** produce, and what is their etiology?





Neuroendocrine cells and their products:

1. **α-Cells** secrete **glucagon**.
2. **β-Cells** secrete **insulin**, along with proinsulin, C-peptide, and amylin.
3. **δ-Cells** secrete **somatostatin**.
4. **F-Cells** secrete **pancreatic polypeptide**.



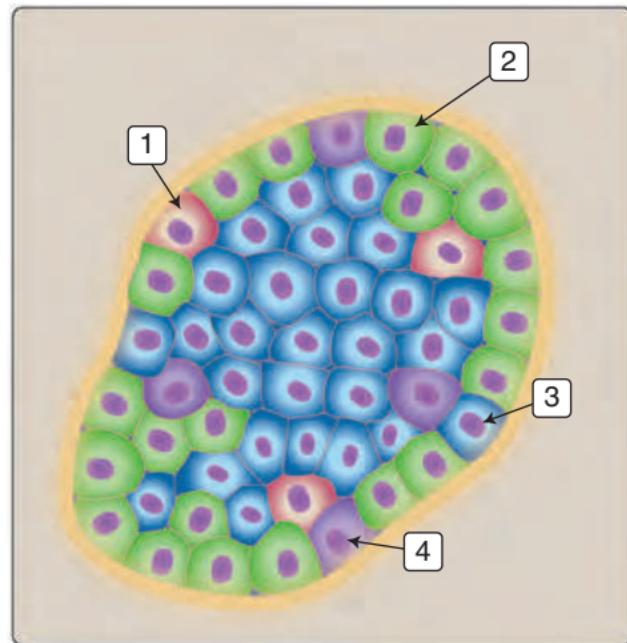
Neuroendocrine cell regulation includes:

- **Nutrients**: Bloodborne glucose, fatty acids, and amino acids modulate release.
- **Hormones**: GI and other hormones modulate release.
- **Paracrines**: Blood enters islets centrally and carries secretory products outward, providing for paracrine signaling.
- **Neural regulation**: Sympathetic and parasympathetic inputs modulate release.
- **Direct communication**: Adjacent islet cells signal via gap junctions.



δ-Cell tumors, or **somatostatinomas**, are rare but classically present as **diabetes mellitus**, **steatorrhea**, and **gallstones**.

Somatostatin's actions are usually inhibitory, and diabetes is caused by inhibition of insulin release. Steatorrhea occurs due to inhibition of pancreatic enzyme and  $\text{HCO}_3^-$  release, and gallstones result from inhibition of cholecystokinin-stimulated gallbladder contraction.



# Glucagon

## 8.2 Question



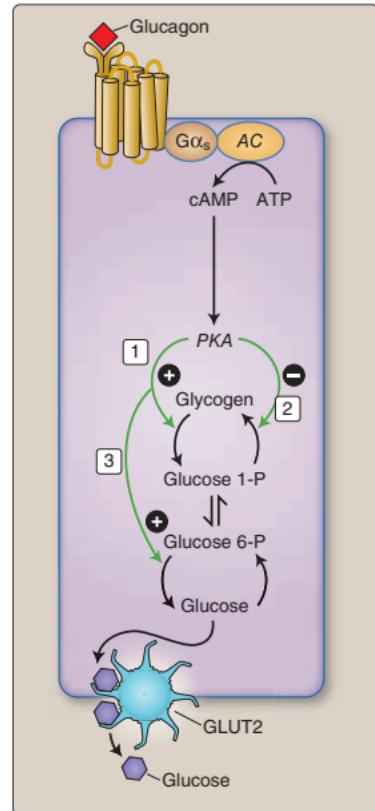
What are glucagon's principal physiologic functions?



The figure shows glucagon's effects on hepatocytes. What are the three enzymes being modulated by glucagon receptor binding, and what are the consequences?



Glucagon is a first-line antidote for \_\_\_\_-\_\_\_\_ overdose. Glucagon is therapeutic because it increases cardiac \_\_\_\_\_ through a rise in intracellular \_\_\_\_\_ and \_\_\_\_\_ concentration.





Glucagon maintains circulating levels of glucose and other energy substrates between meals, when fasting, or following a high-protein meal. Glucagon acts primarily on **hepatocytes** but also on **striated muscle** and **adipocytes**. Glucagon's actions include stimulation of:

- **Glycogenolysis** (shown)
- **Gluconeogenesis**
- **Lipolysis**
- **Ketogenesis**

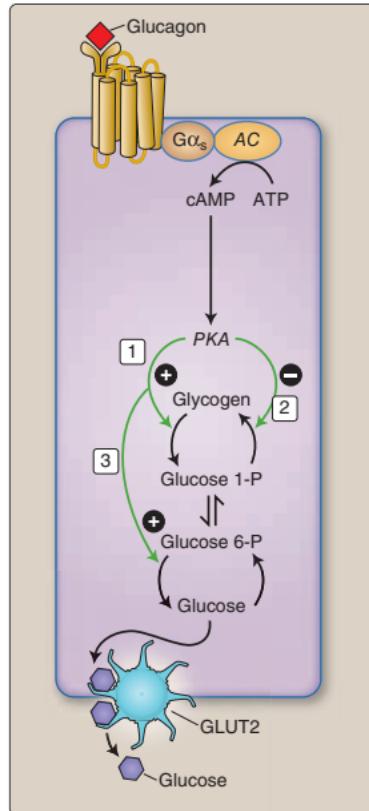


Glucagon effects on the glycogenolysis pathway shown:

1. Stimulates *glycogen phosphorylase* to ↑ glucose 1-P availability
2. Inhibits *glycogen synthase* to ↑ glucose 1-P availability
3. Stimulates *glucose 6-phosphatase* to ↑ circulating glucose levels



Glucagon is a first-line antidote for **beta-blocker overdose**. Glucagon is therapeutic because it increases cardiac inotropy (or output) through a rise in intracellular cAMP and  $\text{Ca}^{2+}$  concentration. [Note: Beta-blocker poisoning is fairly common, presenting as **bradycardia** and **hypotension**.]



# Insulin

## 8.3 Question



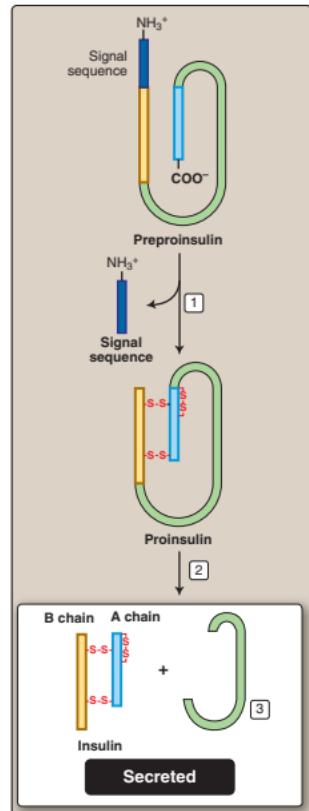
Using the boxed numerals as a guide, indicate where insulin gene product processing occurs and identify the peptide that is co-secreted with insulin.



What are insulin's physiologic functions?



What is the diagnostic value of measuring plasma levels of insulin's co-secreted peptide?





Processing locations and product:

1. Endoplasmic reticulum
2. Golgi apparatus
3. **C-peptide**



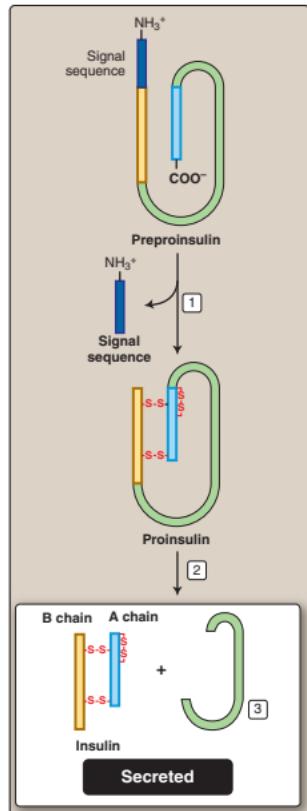
Insulin informs cells that there is an abundance of nutrients (**glucose, fatty acids, glycerol, ketone bodies, amino acids**) available in blood during a meal and stimulates uptake and storage of these nutrients by insulin-sensitive tissues. Principal targets for insulin-stimulated nutrient uptake include:

- Liver
- Skeletal muscle
- Adipose tissue



C-peptide is co-released with insulin. Insulin has a short half-life (~3–8 min), whereas C-peptide persists for ~30 min in the circulation and, therefore, can be used to estimate the rate of endogenous insulin secretion by pancreatic  $\beta$ -cells.

**A-plus:** In patients without a prior history of **diabetes**, a C-peptide test may be useful in determining the possible cause of hypoglycemia (e.g., **insulinoma**). In **type 1 diabetes**, it can be used to assess the amount of residual  $\beta$ -cell secretory function.



# Diabetes Mellitus

## 8.4 Question



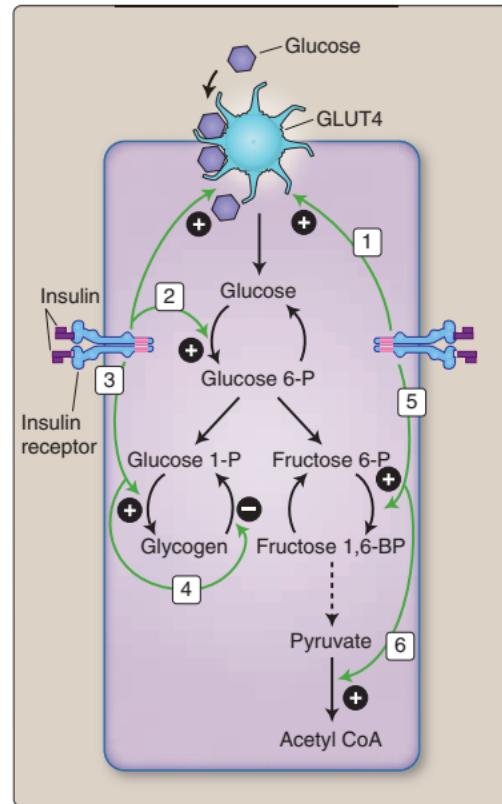
What type of receptor mediates insulin's actions, and how is receptor function affected in patients with **type 2 diabetes mellitus**?



Using the figure as a guide, explain insulin's effects on glucose uptake and disposition in skeletal muscle.



What are the long-term complications of **diabetes mellitus**?



## 8.4 Answer

# Diabetes Mellitus



Insulin's actions are mediated by a heterotetrameric insulin receptor with intrinsic *tyrosine kinase* activity. Insulin binding initiates receptor autophosphorylation and phosphorylation of numerous **insulin receptor substrates** that mediate the hormone's many effects.

**Type 2 diabetes** is characterized by **insulin resistance**, which can have multiple causes. [Note: In cases where cell responsiveness to insulin is decreased, the disease appears to affect events downstream of the receptor, not the receptor itself.]

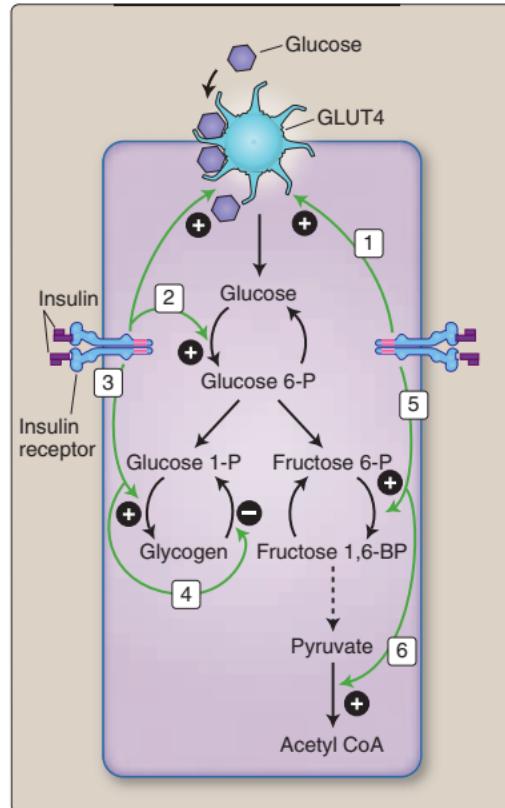


Insulin effects on skeletal muscle include:

1. Upregulates GLUT4 expression to ↑ glucose uptake
2. Stimulates *glucokinase* to ↑ conversion of glucose to glucose 6-P
3. Stimulates *glycogen synthase* to ↑ glycogen levels
4. Inhibits *glycogen phosphorylase* to ↑ glycogen levels
5. Stimulates *phosphofructokinase* to ↑ fructose 6-P formation
6. Stimulates *pyruvate dehydrogenase* to ↑ acetyl CoA formation



**Diabetes** increases risk of **microvascular disease (retinopathy, nephropathy)**, **macrovascular disease (atherosclerosis)**, and **peripheral neuropathy**.  
[Note: The etiology is not well understood.]



# Growth Hormones

8.5 Question



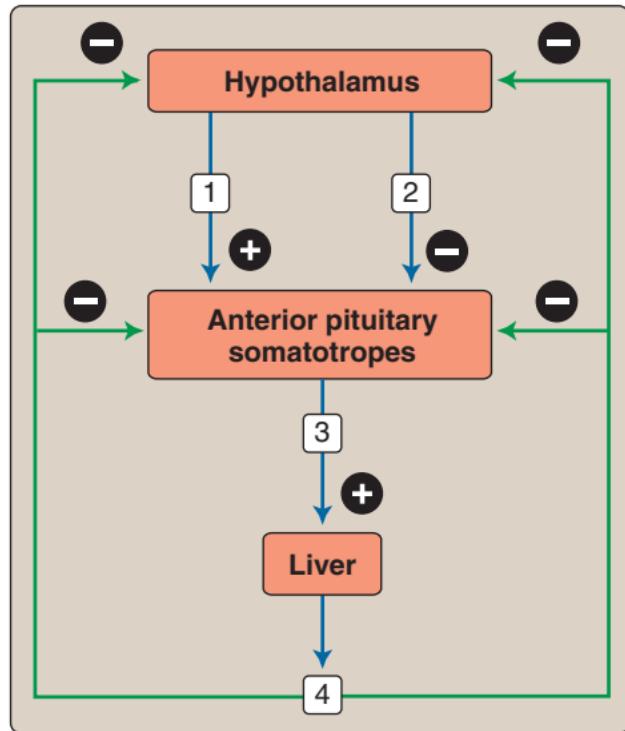
Identify the hormones of the hypothalamic–pituitary–liver axis, as indicated by boxed numerals.



What are the general physiologic functions of the hormones indicated by boxed numerals 3 and 4?



What is the difference between **pituitary gigantism** and **acromegaly**?





Hormones:

1. **Growth hormone-releasing hormone**
2. **Somatostatin**
3. **Growth hormone (GH)**
4. **Insulin-like growth factor 1 (IGF-1)**



GH has a number of short-term, "anti-insulin" effects on multiple tissues, including:

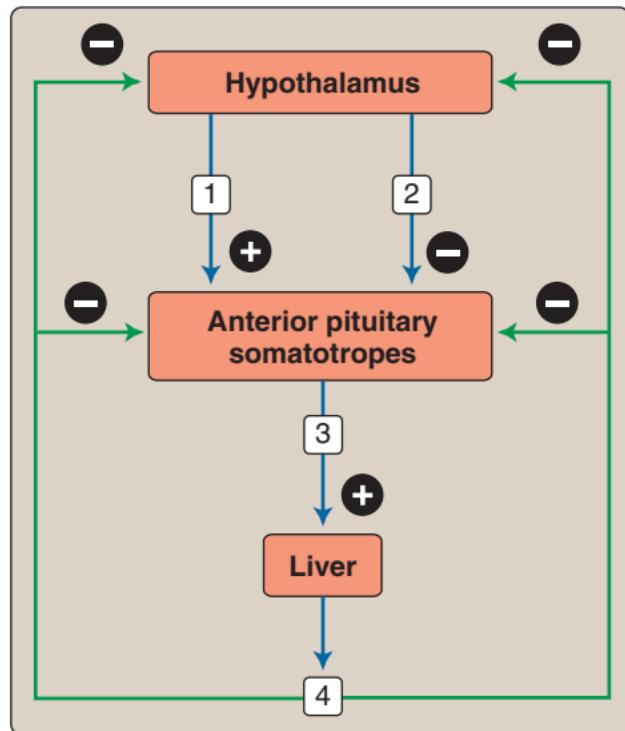
- **Adipose tissue:** ↑ Lipolysis
- **Muscle:** ↓ Glucose uptake
- **Liver:** ↓ Glucose uptake, ↑ gluconeogenesis

IGF-1 mediates many long-term effects of GH, promoting glucose and amino acid uptake, and stimulating protein synthesis and bone growth throughout the body.



**Pituitary gigantism** is a rare condition seen in children before bone epiphyseal growth plates have closed. Abnormally high circulating GH levels stimulate linear bone growth, so that affected individuals achieve an unusually tall stature.

**Acromegaly** is a condition caused by excessive GH secretion after epiphyseal plates have closed. GH and IGF-1 together have numerous effects, including skin thickening, soft tissue overgrowth, and bone overgrowth with excessive mineralization.



# Adrenal Cortex

## 8.6 Question



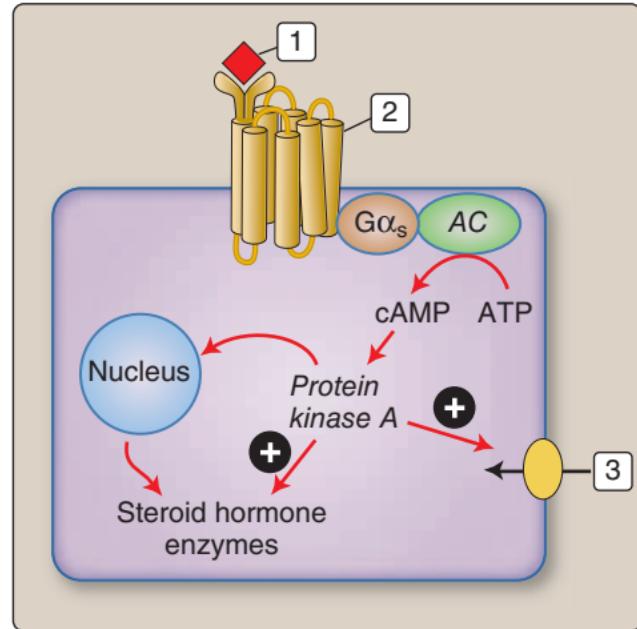
Name the three histologically distinct bands that comprise the adrenal cortex, and identify the hormone or hormones that each produce.



What is the common substrate for adrenocortical hormone synthesis? Using the boxed numerals as a guide, explain how adrenocortical hormone synthesis and release is regulated.



What is the pathophysiology underlying **Addison disease**?





Adrenal cortex organization:

- **Zona glomerulosa** produces **aldosterone**.
- **Zona fasciculata** produces **cortisol**.
- **Zona reticularis** produces the **adrenal androgens dehydroepiandrosterone (DHEA)**, **DHEA sulphate**, and **androstenedione**.

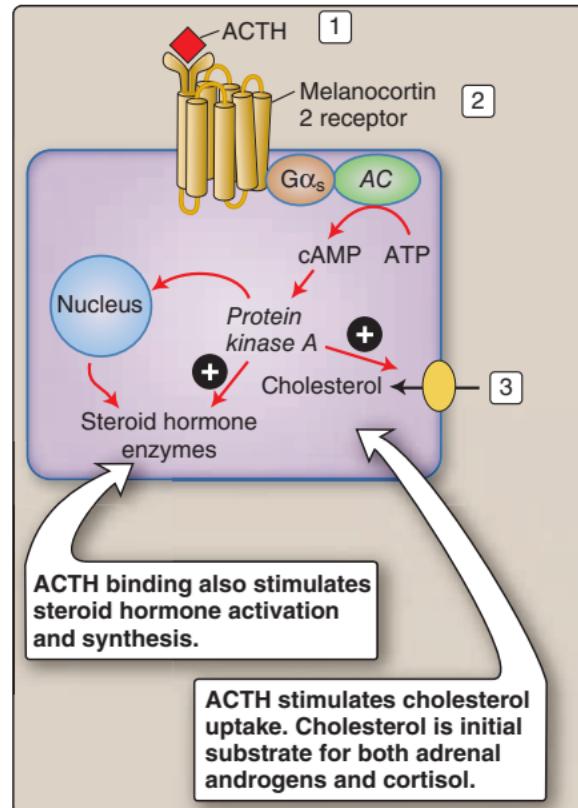


The **adrenal cortex** is regulated via the **hypothalamic–pituitary–adrenal axis**.

1. **Corticotropin-releasing hormone** from the hypothalamus stimulates **adrenocorticotrophic hormone (ACTH)** release from **pituitary corticotropes**. ACTH regulates adrenocortical hormone synthesis and release.
2. ACTH binds to a **melanocortin 2 receptor** (a **GPCR**) and activates the cAMP signaling pathway.
3. **PKA** stimulates cholesterol uptake and promotes adrenocortical hormone synthesis.



**Primary adrenal insufficiency (Addison disease)** is caused by destruction of the adrenal cortex, usually as a result of an autoimmune response, but it may also be caused by infection (e.g., **tuberculosis**).



# Aldosterone

## 8.7 Question



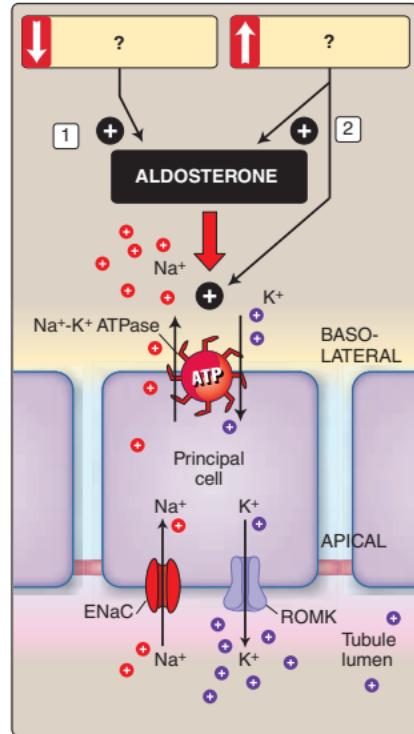
What are aldosterone's functions, and why is aldosterone production restricted to the adrenal glands' zona glomerulosa?



What are the two principal pathways regulating aldosterone synthesis and secretion, as shown?



How does **primary aldosteronism** present clinically?



ENaC = epithelial  $\text{Na}^+$  channel; ROMK = renal outer medullary  $\text{K}^+$  channel.

# Aldosterone



**Aldosterone** regulates  $\text{Na}^+$  and osmotically obligated water absorption and reabsorption from the **small intestine** and **renal tubule**. It also promotes  $\text{K}^+$  secretion by the renal tubule. Aldosterone synthesis is restricted to the **zona glomerulosa** because this is the only cortical region to express significant amounts of **aldosterone synthase (AS)**, the enzyme necessary to convert **corticosterone** to aldosterone.



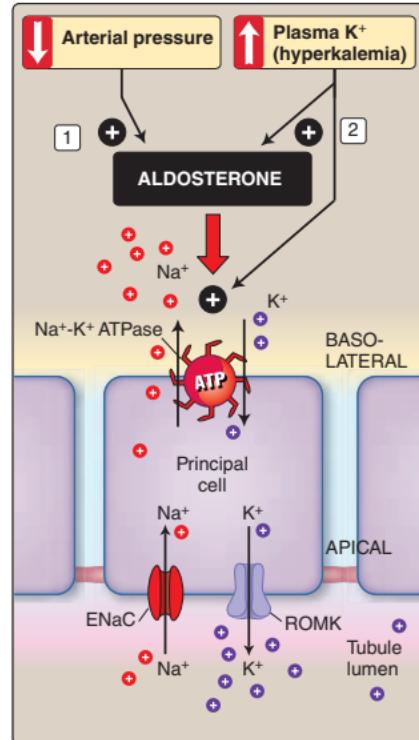
Circulating aldosterone levels are regulated through changes in *AS* expression. Two pathways:

1. Activation of the **renin-angiotensin-aldosterone system** following a fall in **mean arterial pressure** or renal perfusion pressure (see 6.23)
2. Rise in plasma  $\text{K}^+$  concentration (**hyperkalemia**)



**Primary aldosteronism** presents as **hypertension** and, in many cases, **hypokalemia**. The latter may be accompanied by **metabolic alkalosis**.

[Note: The presenting symptoms reflect aldosterone hypersecretion by an **adenoma**, causing inappropriate  $\text{Na}^+$  retention and  $\text{K}^+$  secretion by the renal tubule.]



$\text{ENaC}$  = epithelial  $\text{Na}^+$  channel;  $\text{ROMK}$  = renal outer medullary  $\text{K}^+$  channel.

# Cortisol

## 8.8 Question



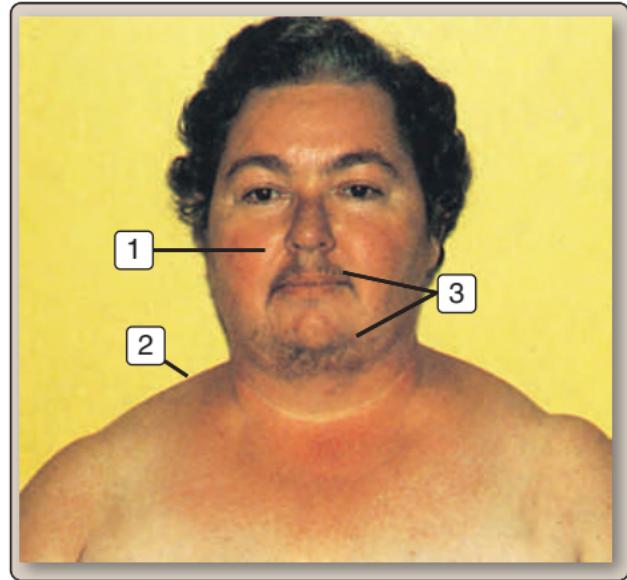
What are the feedforward and feedback systems regulating cortisol secretion?



Review three or more physiologic actions by which cortisol prepares the body for stress.



What causes **Cushing syndrome** and what are three typical symptoms (patient shown)?



## 8.8 Answer

# Cortisol



Cortisol synthesis and secretion is controlled by the **hypothalamic–pituitary–adrenal axis**.

- The hypothalamus releases **corticotropin-releasing hormone (CRH)** in a daily rhythm and in response to stress.
- CRH stimulates **adrenocorticotropic hormone (ACTH)** release from the pituitary to increase cortisol production and secretion.
- ACTH and cortisol both inhibit CRH release (negative feedback).



Cortisol prepares the body for stress through effects on most tissues, including:

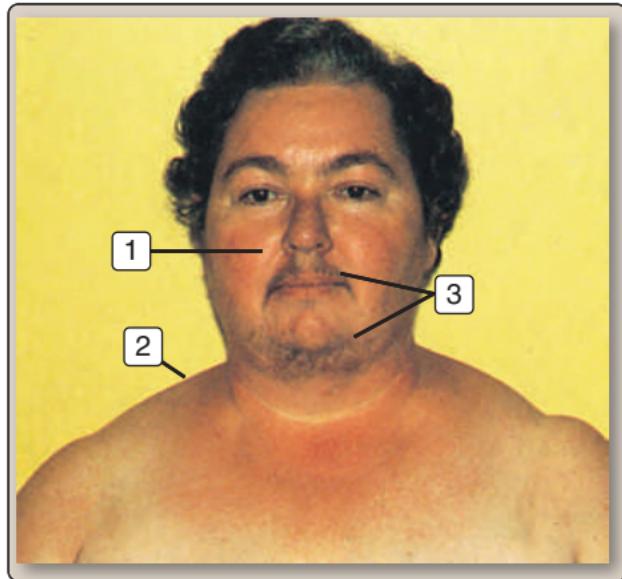
- Tissue metabolism:** increases plasma glucose and fatty acids by breaking down muscle proteins, mobilizing adipose fat stores, and increasing appetite
- Immune system:** suppresses inflammatory responses
- Connective tissue:** increases bone resorption and decreases collagen formation
- Cardiovascular system:** stimulates RBC production and potentiates responses to vasoconstrictors and inotropes



**Cushing syndrome** is caused by a glucocorticoid excess.

Symptoms include:

- Moon facies** (fat deposits that cause facial rounding)
- Fat pads that form above the collarbone and back of the neck
- Hirsutism**



# Adrenal Medulla

## 8.9 Question



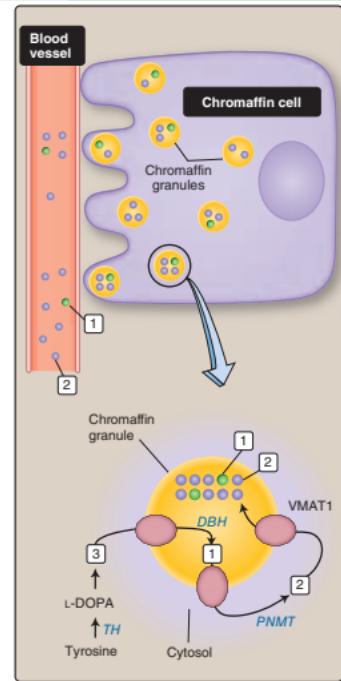
How does the adrenal medulla differ from the adrenal cortex?



Using the figure as a guide, explain what the adrenal medulla's chromaffin cells secrete and how secretion is regulated.



What are **pheochromocytomas**? What is the classic **pheochromocytoma symptom triad**?



DBH = dopamine  $\beta$ -hydroxylase;  
L-DOPA = L-3,4-dihydroxyphenylalanine;  
PNMT = phenylethanolamine  $N$ -methyltransferase;  
TH = tyrosine hydroxylase;  
VMAT1 = vesicular monoamine transporter 1.



The adrenal medulla and cortex have different embryological origins, meaning that their cellular compositions are different. The cortex forms from mesoderm, whereas the medulla forms from the neural crest and is the functional equivalent of an SNS postganglionic neuron.

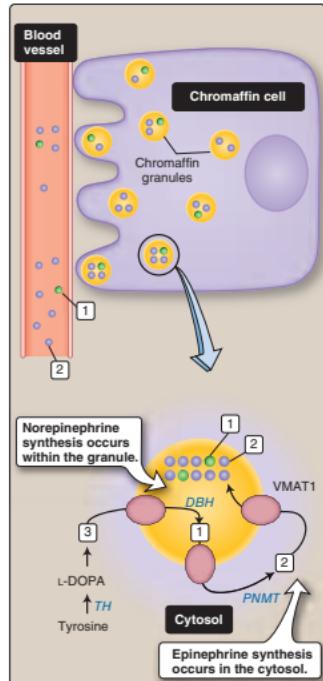


**Chromaffin cells** synthesize and secrete **catecholamines**:

1. **Norepinephrine** (~20% of total)
2. **Epinephrine** (~80% of total)
3. The two catecholamines are synthesized from tyrosine, with a **dopamine** intermediate.  
[Note: Chromaffin cells store catecholamines in chromaffin granules. The granules release their contents into the circulation when stimulated by the SNS.]



**Pheochromocytomas** are catecholamine-secreting tumors of chromaffin cells or sympathetic ganglia. Catecholamine excess mimics SNS activation, producing a symptom triad comprising **headache**, **sweating**, and **tachycardia**. [Note: Many patients also have **paroxysmal hypertension**, **palpitations**, **tremors**, and a sense of **impending doom**.]



DBH = *dopamine β-hydroxylase*; L-DOPA = L-3,4-dihydroxyphenylalanine; PNMT = *phenylethanolamine N-methyltransferase*; TH = *tyrosine hydroxylase*; VMAT1 = *vesicular monoamine transporter 1*.

# Thyroid Hormones

## 8.10 Question



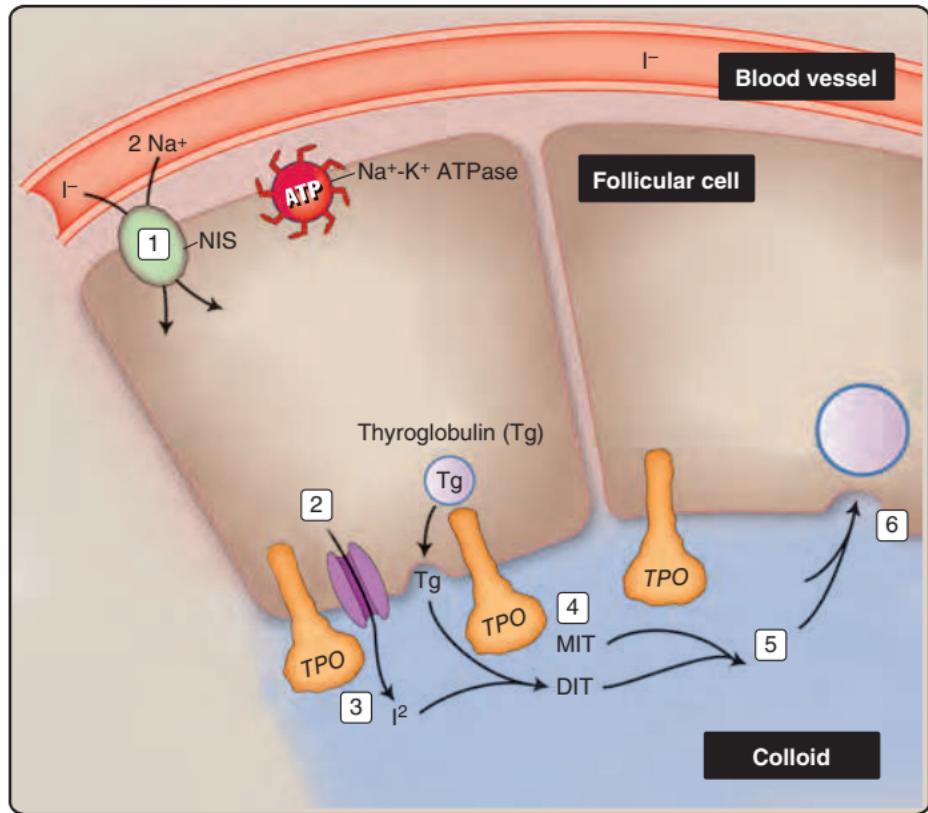
What three hormones does the thyroid gland produce, and what are their principal functions?



Explain the steps involved in thyroid hormone synthesis, using the boxed numerals as a guide.



What is Hashimoto disease?





Three thyroid hormones:

- **Triiodothyronine ( $T_3$ )**: regulates cell metabolism and development
- **Tetraiodothyronine ( $T_4$ ; thyroxine)**: regulates cell metabolism and development
- **Calcitonin (from parafollicular C cells)**: involved in  $\text{Ca}^{2+}$  homeostasis

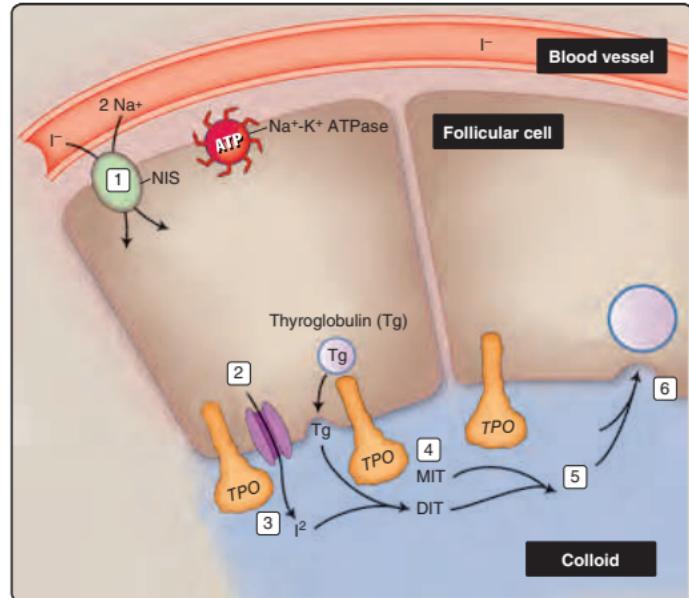


Thyroid hormone synthesis:

1.  $\text{I}^-$  uptake occurs from blood via an  $\text{Na}^+-\text{I}^-$  cotransporter (NIS; " $\text{I}^-$  trapping").
2. **Pendrin** ( $\text{Cl}^--\text{I}^-$  cotransporter) allows  $\text{I}^-$  to enter the colloid. **Thyroglobulin (Tg)** enters via exocytosis.
3. **Thyroid peroxidase (TPO)** catalyzes  $\text{I}_2$  formation from  $\text{I}^-$  and  $\text{H}_2\text{O}_2$ .
4. **TPO** facilitates **organification** of Tg to form **mono- (MIT)** and **diiodotyrosine (DIT)**.
5. MIT and DIT conjugate to form  $\text{T}_3$  and  $\text{rT}_3$ .  $\text{T}_4$  forms from two DIT residues.
6. Hormones are endocytosed back into the follicular cell to await release.



**Hashimoto disease** is a chronic autoimmune thyroiditis that results in **hypothyroidism**. The patients may also develop **goiter** due to infiltration by immune cells, fibrosis, and follicular hyperplasia.





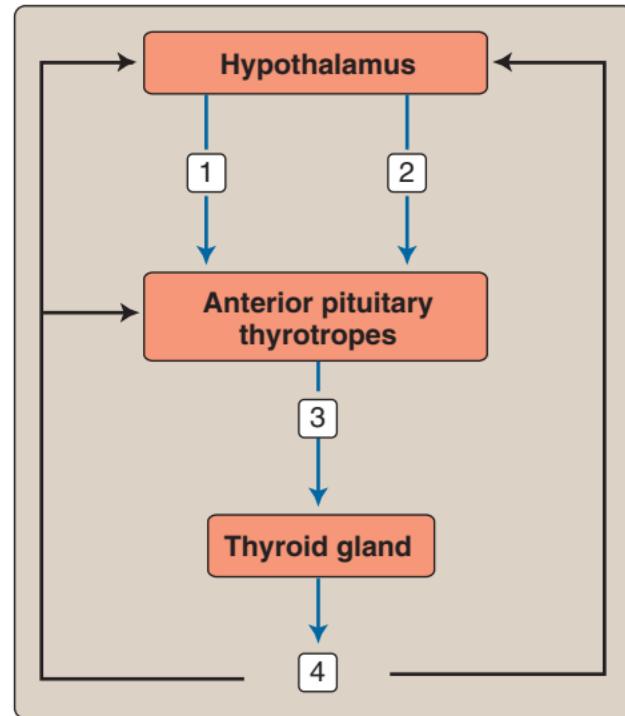
In what form are thyroid hormones  $T_3$  and  $T_4$  distributed by the circulation, and which hormone has the greater physiologic importance?



Using the boxed numerals as a guide, identify the hormones of hypothalamic–pituitary–thyroid axis. What happens to this axis when circulating thyroid hormone levels rise above optimal?



What are the clinical features of **Graves disease**?





**T<sub>3</sub>** and **T<sub>4</sub>** circulate in association with **thyroid hormone-binding globulin**, which protects them from degradation while in blood. T<sub>3</sub> has a greater physiologic effect than T<sub>4</sub> because T<sub>4</sub> is mostly converted to T<sub>3</sub> by the liver, kidneys, and other target tissues.



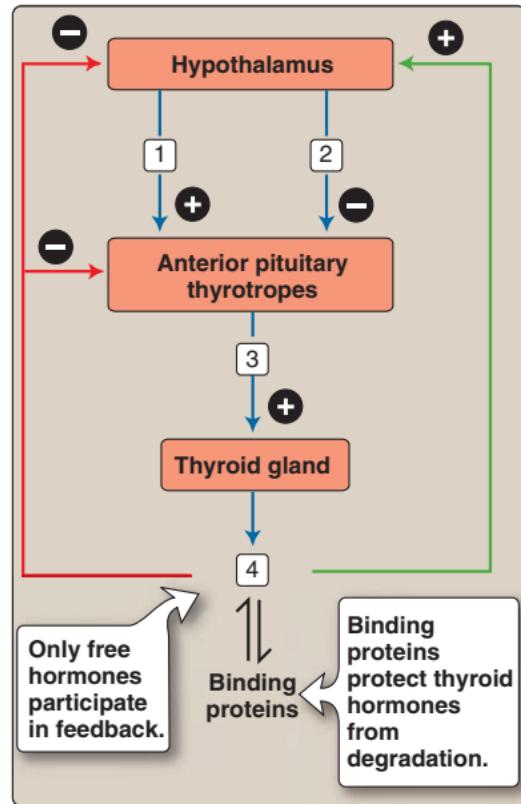
Hypothalamic–pituitary–thyroid axis hormones:

1. **Thyroid-releasing hormone (TRH)**
2. **Somatostatin**
3. **Thyroid-stimulating hormone (TSH)**
4. T<sub>3</sub> and T<sub>4</sub>

T<sub>3</sub> and T<sub>4</sub> inhibit their own secretion through negative hypothalamic feedback. Rising hormone levels suppress TRH secretion, which reduces TSH and thyroid hormone release. T<sub>3</sub> and T<sub>4</sub> also stimulate somatostatin release from the hypothalamus, which exerts additional negative feedback on TSH secretion.



The most conspicuous feature of **Graves disease** is **ophthalmopathy**. Graves is an autoimmune disorder that activates the TSH receptor and causes **hyperthyroidism**, but the autoimmune antibodies also affect retro-orbital tissue and extraocular muscles. Inflammation and mucopolysaccharide deposition within these tissues cause the characteristic swelling and orbital protrusion.



# Thyroid Hormone Responses

## 8.12 Question



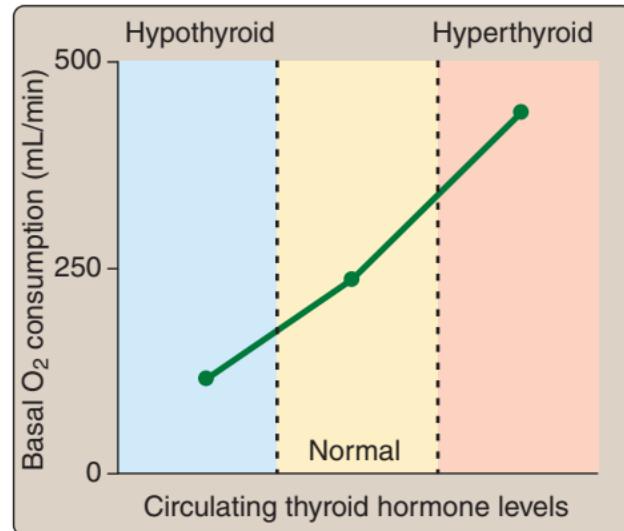
How is thyroid hormone receptor occupancy signaled to downstream effectors?



The figure shows how changes in circulating thyroid hormone levels impact basal O<sub>2</sub> consumption. Identify three or more cellular pathways affected by thyroid hormone to produce the changes shown.



What are the consequences of **congenital hypothyroidism** if left untreated after birth? Why is it difficult to detect at birth?



# Thyroid Hormone Responses



Thyroid hormone receptors (TRs) are located in the cell nucleus. The hormones diffuse across the surface membrane, and T<sub>4</sub> is converted to the active form, T<sub>3</sub>, which then binds to a TR and displaces a corepressor protein from a **thyroid-response element** on DNA. The TR–hormone–coactivator protein complex then initiates gene transcription.

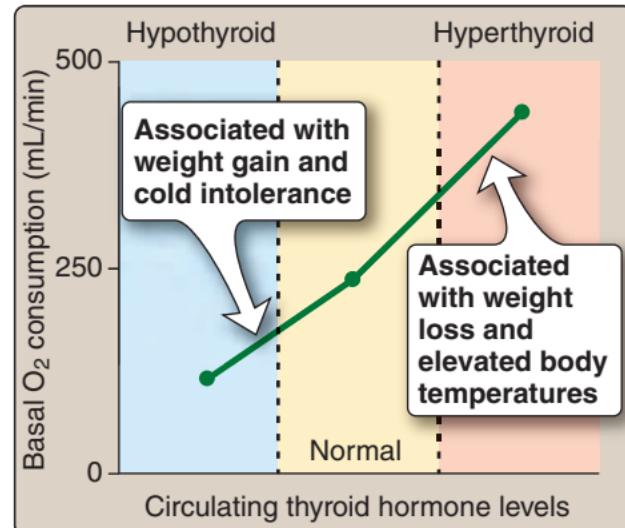


Thyroid hormones increase **basic metabolic rate**, which increases O<sub>2</sub> consumption by numerous cellular pathways, including:

- ↑ Na<sup>+</sup>-K<sup>+</sup> ATPase expression and activity
- ↑ Glycogenolysis and gluconeogenesis
- ↑ Lipolysis and lipogenesis
- ↑ Proteolysis and protein synthesis



Thyroid hormone is required for normal growth and development. If left untreated, **congenital hypothyroidism** causes **cretinism**, a condition characterized by mental retardation and short stature. Congenital hypothyroidism is difficult to detect at birth because maternal thyroid hormones cross the placenta and may support near-normal development in utero.



# Parathyroid Hormone

8.13 Question



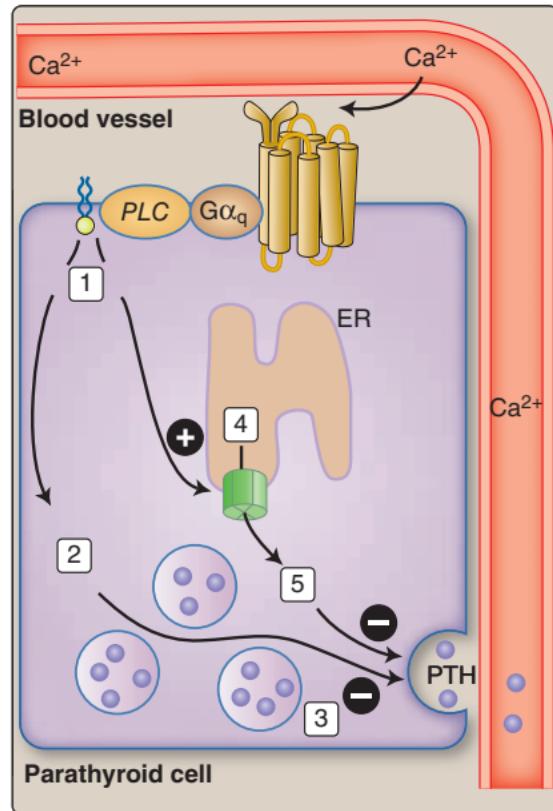
Which two organs are the principal targets of parathyroid hormone (PTH), and how does it affect their function?



Using the boxed numerals as a guide, explain the steps in PTH secretion regulation.



Patients taking lithium to treat a **bipolar disorder** may develop hypercalcemia. How does lithium affect PTH regulation of plasma  $\text{Ca}^{2+}$ ?





PTH targets kidney and bone to raise plasma  $\text{Ca}^{2+}$ :

- PTH stimulates  **$\text{Ca}^{2+}$  reabsorption** by the **renal tubule distal segments** (see 6.14). It also stimulates **vitamin D** synthesis by the kidney.
- PTH stimulates **bone resorption** to liberate bound  $\text{Ca}^{2+}$ .  
[Note: PTH also increases intestinal  $\text{Ca}^{2+}$  uptake, but acts indirectly through vitamin D.]

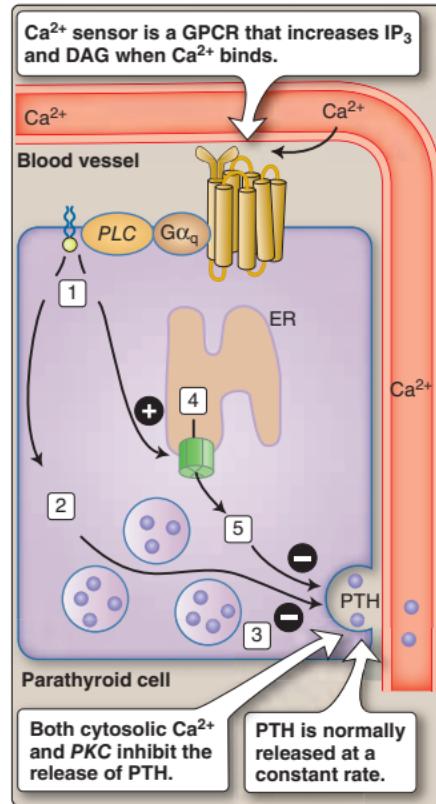


PTH is secreted at basal rates when plasma  $\text{Ca}^{2+}$  levels are normal. Hypocalcemia increases PTH release. Hypercalcemia inhibits PTH secretion:

1.  $\text{Ca}^{2+}$  is sensed by a GPCR linked to *PLC*. *PLC* liberates DAG and  $\text{IP}_3$ .
2. DAG activates *PKC*.
3. *PKC* inhibits PTH release.
4.  $\text{IP}_3$  initiates  $\text{Ca}^{2+}$  release from the ER.
5. A rise in intracellular free  $\text{Ca}^{2+}$  also inhibits PTH secretion. *PKC* and  $\text{Ca}^{2+}$  effects together cause plasma  $\text{Ca}^{2+}$  to fall through reduced recovery from the renal tubule and decreased bone resorption.



Lithium desensitizes parathyroid cells to  $\text{Ca}^{2+}$ , such that higher levels are required to suppress PTH release than previously. PTH secretion increases as a result, causing increased renal  $\text{Ca}^{2+}$  reabsorption and bone resorption.



# Vitamin D

## 8.14 Question



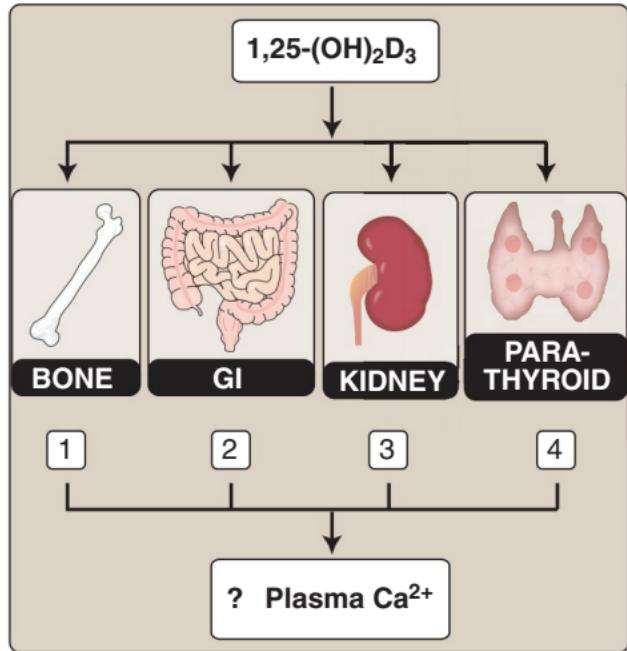
What effect does vitamin D have on each of the four organs shown, and what happens to plasma  $\text{Ca}^{2+}$  levels as a result?



What is vitamin D, and what are its main sources?



What are the clinical features of **rickets**, and how are they related to vitamin D?





Four principal vitamin D actions:

1. ↑ Bone resorption
2. ↑ GI  $\text{Ca}^{2+}$  absorption through  $\text{Ca}^{2+}$  channel and pump upregulation
3. ↑ Reabsorption from the renal distal segments
4. ↓ Parathyroid hormone gene transcription and secretion

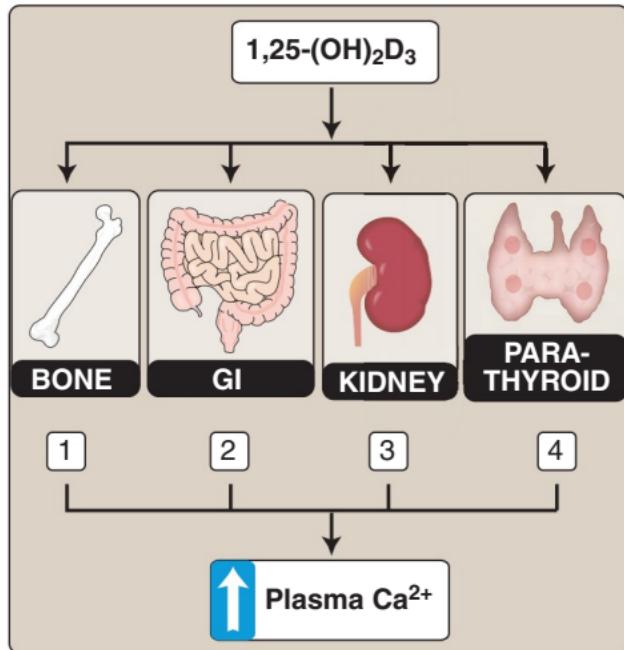


Vitamin D is a mix of vitamin D<sub>2</sub> (**ergocalciferol**), which is obtained from the diet, and vitamin D<sub>3</sub> (**cholecalciferol**), which forms in skin through the actions of ultraviolet light on **7-dehydrocholesterol**. [Note: The active form of vitamin D is 1,25-dihydroxyvitamin D<sub>3</sub>, which is a metabolite of vitamins D<sub>2</sub> and D<sub>3</sub>.]



**Rickets** is condition caused by inadequate bone mineralization at the growth plate. Bones are weakened as a result, causing the long bones of the leg to bow. **Calcipenic rickets** is usually caused by a dietary deficiency in vitamin D.

*A-plus:* **Rickets** can also be caused by renal phosphate wasting (**phosphopenic rickets**).





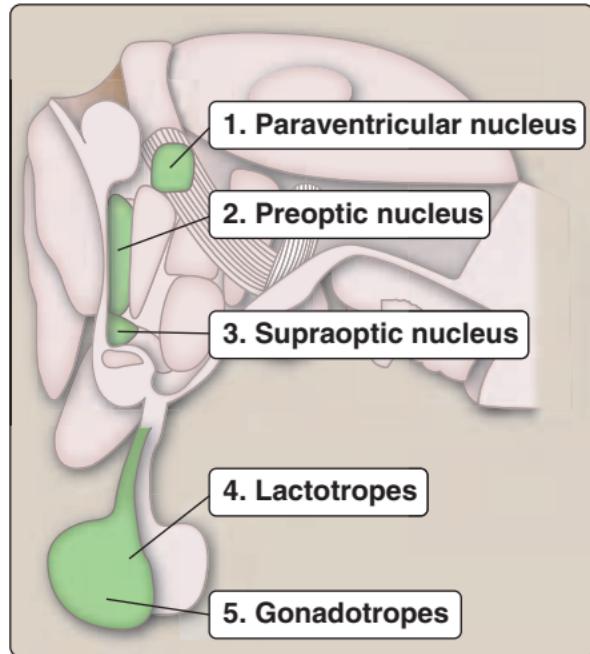
Using the figure as a guide, identify the hormones involved in the hypothalamic–pituitary–ovarian axis.



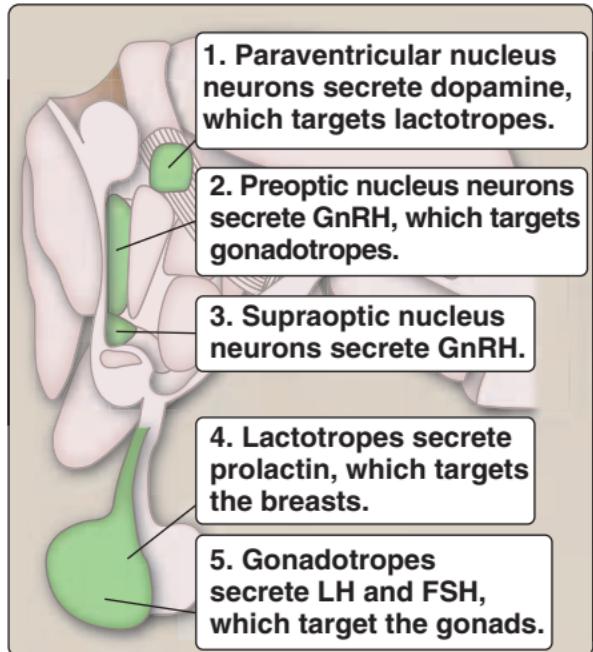
Which two ovarian cell types must cooperate in order to produce estradiol, and what is the nature of the cooperation?



How does an imbalance in the hypothalamic–pituitary–ovarian axis cause the symptoms associated with **polycystic ovary syndrome (POS)**?



# Hypothalamic–Pituitary–Ovarian Axis



GnRH = gonadotropin-releasing hormone



Estradiol production requires cooperation between ovarian **theca cells** and **granulosa cells**.

- Theca cells can produce **androstenedione** and **testosterone**, but they lack the **aromatase** necessary to convert androgens to estradiol.
- Granulosa cells contain *aromatase*, but they rely on theca cells to supply the testosterone and androstenedione needed to form **estradiol**.

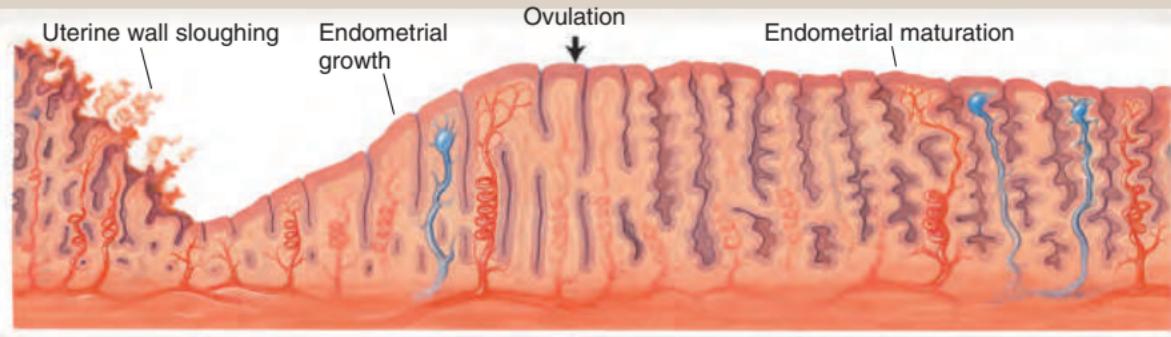
*A-plus:* **Luteinizing hormone (LH)** stimulates conversion of cholesterol to pregnenolone in theca cells, thereby increasing androgen availability to granulosa cells. LH, together with **follicle-stimulating hormone (FSH)**, stimulates *aromatase* in granulosa cells, which facilitates increased production of estradiol.



**POS** is due to an inappropriate increase in LH relative to FSH, leading to an androgen excess. Symptoms include hirsutism and virilization, menstrual irregularities, obesity and associated insulin resistance, and polycystic ovaries.

# Endometrial Cycle

8.16 Question



Menstrual  
Phase

Proliferation  
Phase

Secretory  
Phase



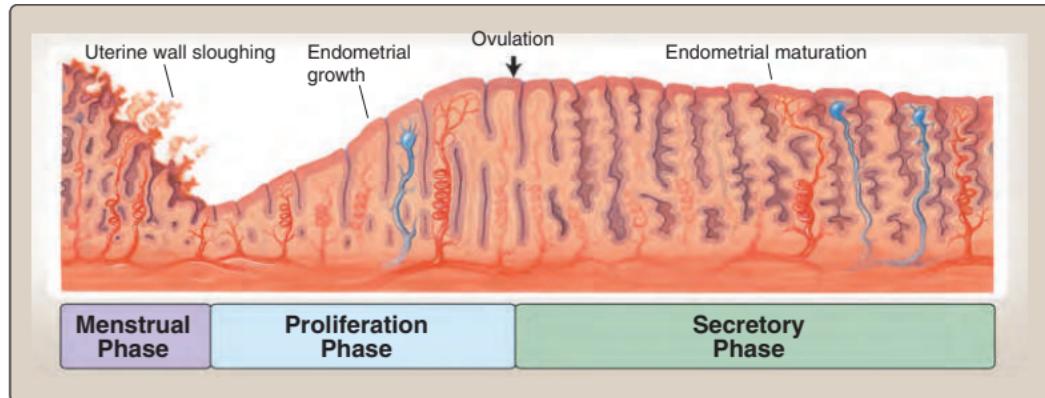
What hormones account for the endometrial changes shown?



Explain the physiology of menstruation.



What are the causes and more common symptoms of **endometriosis**?



Endometrial phases:

- 1. **Menstrual:** Uterine wall sloughing is initiated by declining levels of progestins and estrogens.
- 2. **Proliferation:** Endometrial proliferation is impelled by rising estrogen levels.
- 3. **Secretory:** Proliferation halts with a drop in estrogen levels following ovulation. Rising progestins stimulate glandular growth and increasing vascularization.

Menstruation results from intense **vasospasms** that prevent flow through the **spiral arteries** and cause **local ischemia** and inflammation. Endometrial breakdown ensues, enhanced by inflammatory cell infiltration.

**Endometriosis** refers to the establishment of endometrial tissue at extrauterine sites, possibly due to retrograde travel through the fallopian tubes during menstruation. Common symptoms include pelvic pain, dysmenorrhea, and infertility.

# Testosterone

## 8.17 Question



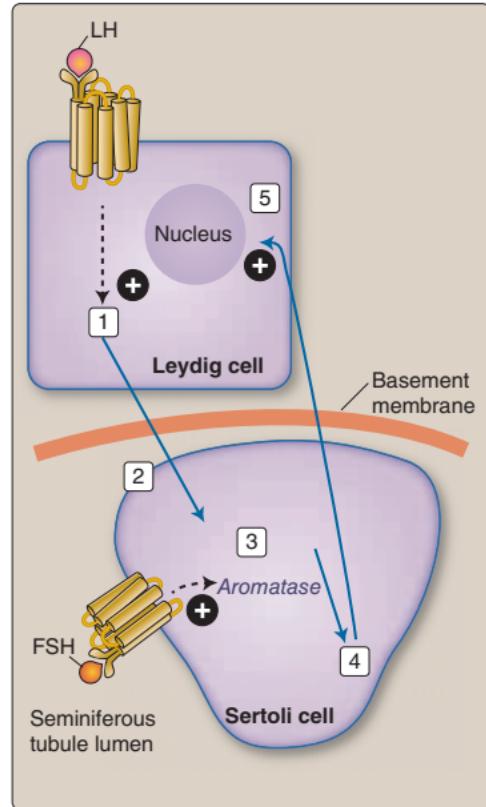
The endocrine functions of the testis require cooperation between Leydig and Sertoli cells. Using the boxed numerals as a guide, indicate the nature of this cooperation.



How does testosterone exert hormonal effects on target organs, and what are these effects?



What are **primary** and **secondary male hypogonadism**?





Leydig and Sertoli cell cooperation:

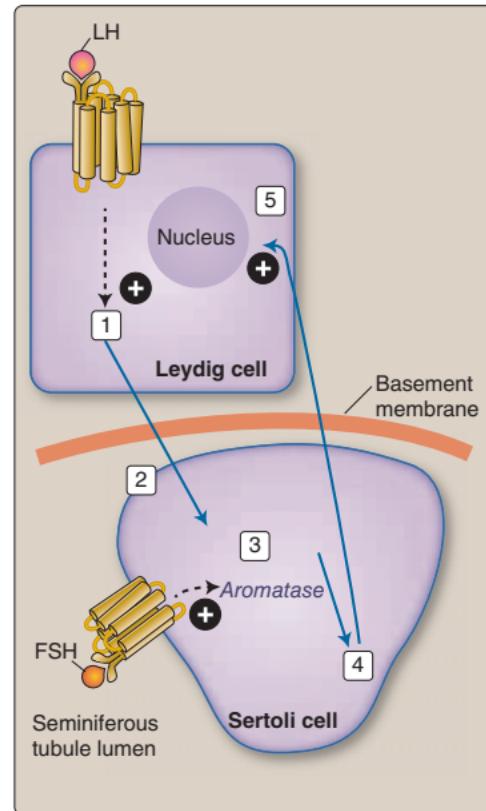
1. **Luteinizing hormone (LH)** stimulates **testosterone** production.
2. Testosterone diffuses out of the Leydig cell and enters Sertoli cells.
3. **Follicle-stimulating hormone (FSH)** activates **aromatase**.
4. Aromatase converts testosterone to **estradiol**.
5. Estradiol regulates protein synthesis in both Sertoli and Leydig cells.



Testosterone binds to an **intracellular androgen receptor** within target tissues. The hormone–receptor complex then binds DNA and influences target gene transcription. Testosterone has **anabolic effects** on bone and muscle and promotes male **secondary sex characteristics** development.



**Hypogonadism** describes a decrease in one or both of the testes' main functions: testosterone synthesis and sperm production. **Primary hypogonadism** is a condition affecting testis function directly. Serum LH and FSH levels may be increased as a result. **Secondary hypogonadism** is generally a result of impaired gonadotropin secretion from the pituitary.





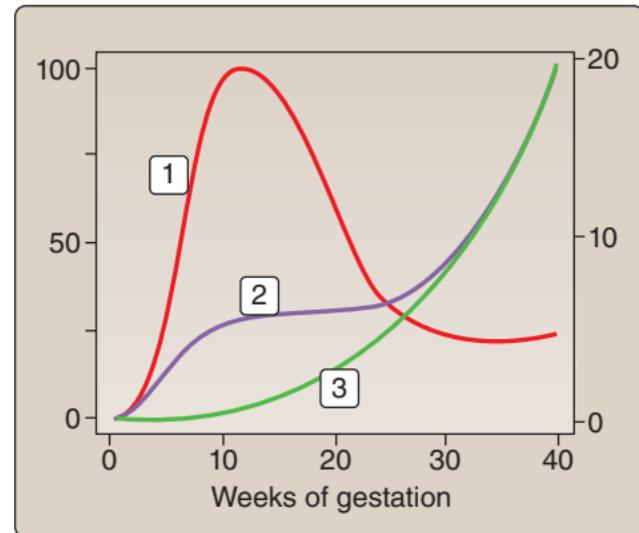
The figure tracks gestational changes in levels of what three principal placental hormones? What are their functions?



The placenta relies on a maternal–placental–fetal unit to produce hormones. What substrates do mother and fetus contribute to the placenta to aid hormone synthesis?



The placental \_\_\_\_\_ produces \_\_\_ in amounts that can be detected within ~\_\_ days of gestation, thereby forming the basis for the home pregnancy test.





Placental hormones:

1. **Human chorionic gonadotropin (hCG):**  
surge in hCG levels prevents menstruation
2. **Estrogens:** stimulate uterine and breast development
3. **Progesterone:** facilitates implantation and suppresses endometrial contractions

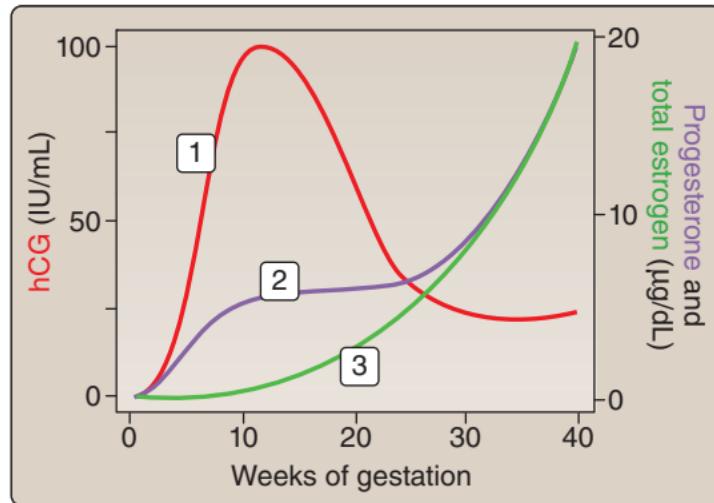


The placenta cannot synthesize steroids without the assistance of mother and fetus.

- **Mother:** contributes cholesterol, the starting point for steroid synthesis
- **Fetus:** contributes *17α-hydroxylase (17,20-lyase)* and *16α-hydroxylase*, enzymes necessary for estrone, estradiol, and estriol synthesis



The placental syncytiotrophoblast produces hCG in amounts that can be detected within ~8–10 days of gestation, thereby forming the basis for the home pregnancy test.



# Placental Exchange

9.2 Question



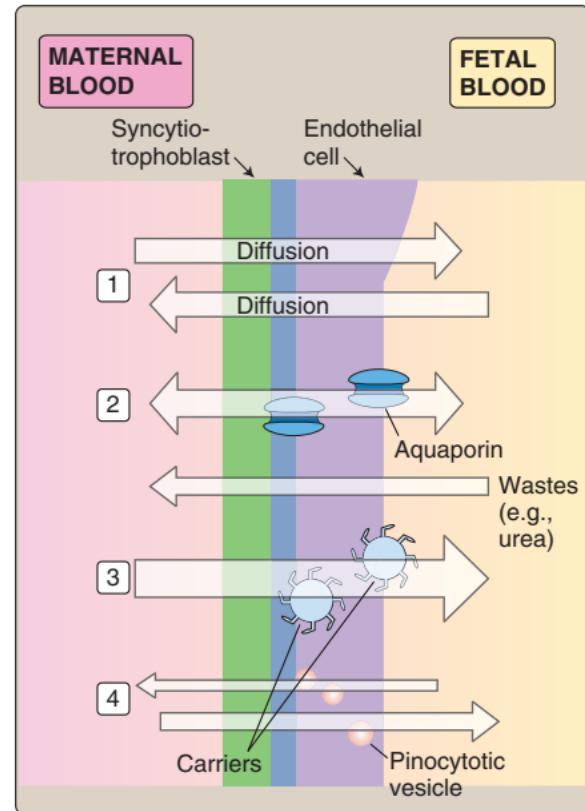
The figure shows four pathways for placental exchange. Identify the primary route by which each of the following substances would cross the placental barrier: amino acids, antibodies, CO<sub>2</sub>, glucose, hormones, O<sub>2</sub>, vitamins, and water.



Identify two or more placental structural features that facilitate nutrient and waste exchange across the placental barrier.



What types of pharmaceuticals are most likely to cross the placental barrier?





Four pathways for placental exchange:

1. **Diffusion:** CO<sub>2</sub>, O<sub>2</sub>, lipophilic materials
2. **Aquaporins:** water
3. **Transporters (carriers):** amino acids, glucose, vitamins, and other organic nutrients
4. **Pinocytosis:** proteins, such as antibodies and protein-bound hormones

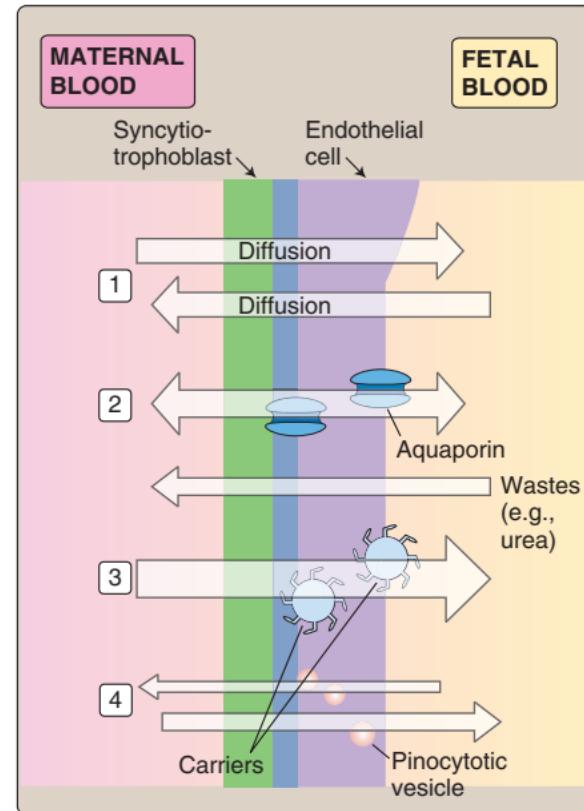


Structural features facilitating placental exchange include:

- **Barrier thickness** is minimal (<5 μm at term).
- **Villi and microvilli** maximize barrier surface area (~10–12 m<sup>2</sup>).
- Villi develop above **eroded spiral arteries**. Blood from these vessels continually washes over the villi to maximize concentration gradients between maternal and fetal blood.  
[Note: Blood flows from eroded spiral arteries at a pressure of ~70 mm Hg to ensure adequate flow through the placental site.]



Pharmaceuticals most likely to cross the barrier are small (<600 Da), lipophilic, and uncharged. By contrast, large charged molecules are unlikely to cross the barrier in significant quantities. [Note: The placental barrier resembles the blood–brain barrier in that it contains drug-metabolizing enzymes, but the adaptations above mean that virtually all pharmaceuticals cross the barrier to some degree.]



# Uterine Blood Flow

9.3 Question



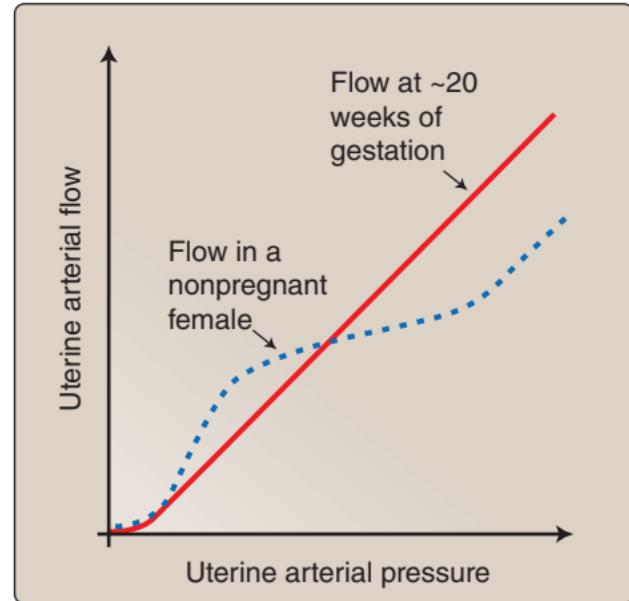
What accounts for the characteristics of uterine blood flow during pregnancy, as shown?



How is the change in uterine blood flow effected, and for what purpose?



How might a defect in the transformation shown result in **preeclampsia**?





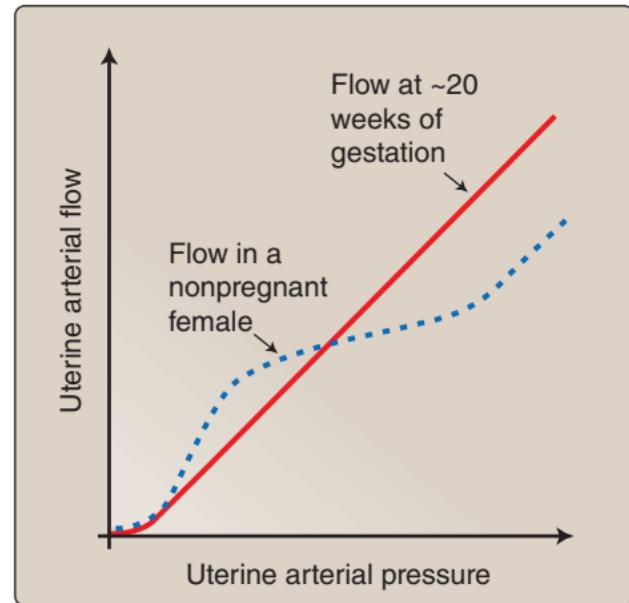
During placentation, uterine **spiral arteries** are eroded. These arteries are resistance vessels that facilitate **autoregulation** of uterine blood flow in a nonpregnant female (broken blue line). Because eradicating these vessels prevents autoregulation, uterine blood flow becomes a linear function of uterine arterial pressure.



Spiral arteries are eroded and remodeled by invading **fetal cytotrophoblast** to effect the change shown. Smooth muscle is replaced by fibrous tissue, and the vessels are widened during remodeling. Remodeling maximizes blood flow to the placental site to ensure adequate delivery of nutrients to the fetus (flow reaches  $\sim 500$  mL/min at term).



**Preeclampsia** is a maternal condition associated with **placental hypoperfusion**. Incomplete transformation of maternal spiral arteries by fetal cytotrophoblast results in flow inadequacy and release of fetal placental factors that damage the maternal vasculature. Symptoms include **hypertension** and **proteinuria** that presents at  $\sim 20$  weeks' gestation.





# Maternal Cardiovascular System

9.4 Question



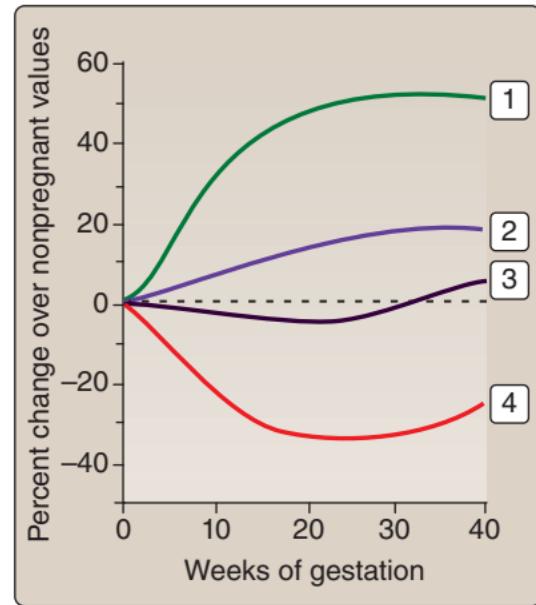
Referring to the figure, identify which plot represents mean arterial pressure, systemic vascular resistance, heart rate, and cardiac output (CO).



How is the change in CO effected, and what are the consequential hemodynamic benefits?



What four sounds associated with maternal blood flow might be expected upon auscultation of a pregnant woman nearing term?





Four plots:

1. CO
2. Heart rate
3. Mean arterial pressure
4. Systemic vascular resistance



The rise in maternal CO occurs primarily through ECF expansion, which increases left ventricular preload. Benefits to volume expansion:

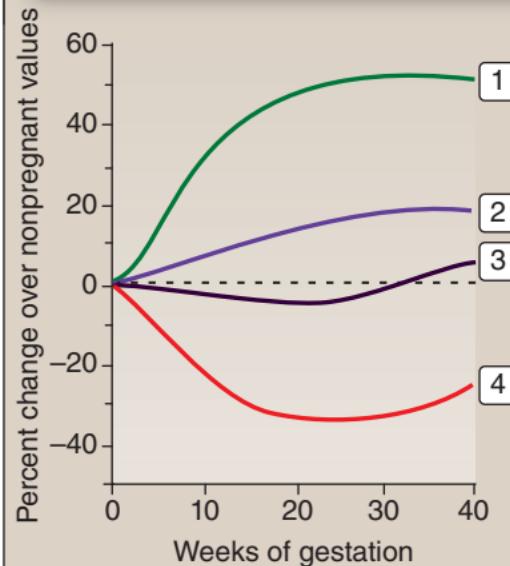
- A ~50% rise in blood volume during gestation allows for ~500 mL blood volume loss at parturition.
- ECF expansion outstrips RBC production, which reduces hematocrit and viscosity (see 4.18). Benefits of the viscosity decrease include:
  - ↓ Flow resistance and cardiac work
  - ↓ Shear stress and vascular damage
  - ↑ Placental perfusion



Four sounds typical in pregnant women:

- **Systolic ejection murmurs** (flow through the aortic and pulmonary valves)
- **S<sub>3</sub>** (ventricular filling)
- **Venous hum** (high-velocity flow through larger veins)
- **Mammary souffle** (heard over the breasts and probably of vascular origin)

**Heart rate and stroke volume increase to maintain cardiac output and arterial pressure when systemic vascular resistance falls.**



# Fetal Circulation

9.5 Question



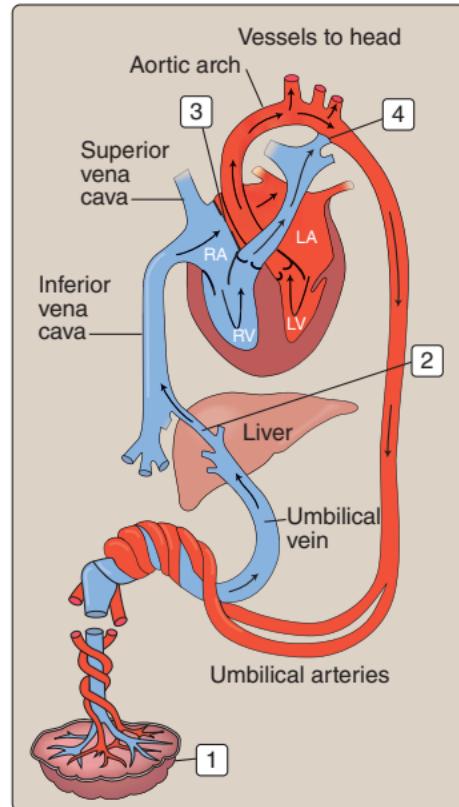
What are the four structures unique to the fetal circulation (indicated by boxed numerals), and what are their purposes?



Compare the level of O<sub>2</sub> saturation in the umbilical arteries and umbilical vein. How is fetal blood adapted to achieve such high levels of O<sub>2</sub> saturation?



**Patent** \_\_\_\_\_ is common in preterm infants. Treatment with a \_\_\_\_\_ inhibitor may be sufficient to induce closure.





Fetal cardiovascular adaptations include:

1. **Placenta**: site of O<sub>2</sub> and CO<sub>2</sub> exchange
2. **Ductus venosus**: shunts blood around the liver
3. **Foramen ovale**: allows O<sub>2</sub>-rich blood to bypass the pulmonary circulation
4. **Ductus arteriosus (DA)**: allows right ventricular output to bypass the pulmonary circulation

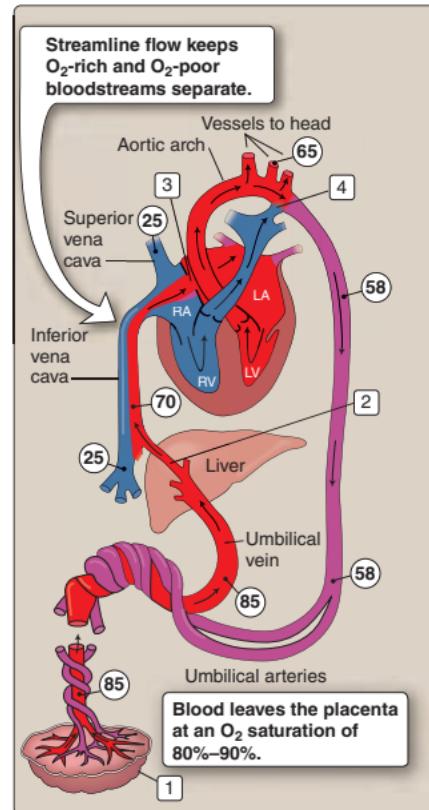


The umbilical arteries and vein exhibit O<sub>2</sub> saturations of ~58% and ~85%, respectively (as shown; O<sub>2</sub> saturation is indicated by circled numerals). Two features of fetal blood help compensate for the inefficiency of placental O<sub>2</sub> transfer:

- Fetal Hb has a left-shifted O<sub>2</sub>-dissociation curve compared with the adult form (see 5.14), which allows relatively high saturation at O<sub>2</sub> partial pressures common to the placenta.
- Fetal blood contains ~20% more Hb compared with adult blood.



**Patent ductus arteriosus** is common in preterm infants. Treatment with a *cyclooxygenase* inhibitor may be sufficient to induce closure. [Note: PGE<sub>2</sub> helps maintain DA patency in the fetus. DA closure can often be induced by blocking PGE<sub>2</sub> synthesis with a *COX* inhibitor (e.g., ibuprofen).]



# Parturition

## 9.6 Question



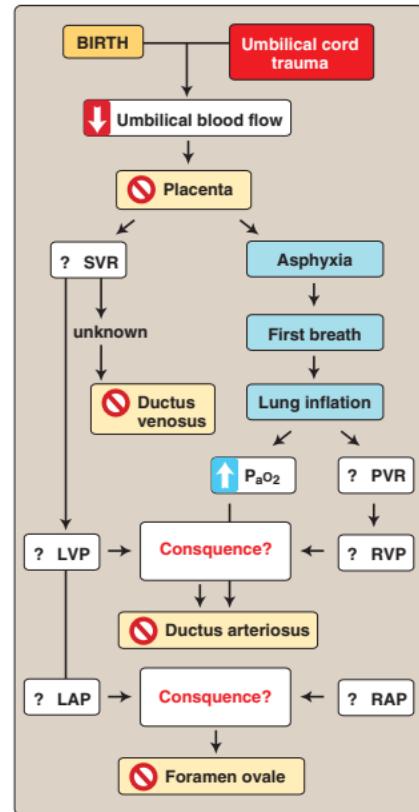
The figure summarizes fetal circulatory events at parturition. What happens to systemic and pulmonary vascular resistance (SVR, PVR), left and right ventricular (LVP, RVP), and atrial (LAP, RAP) pressures?

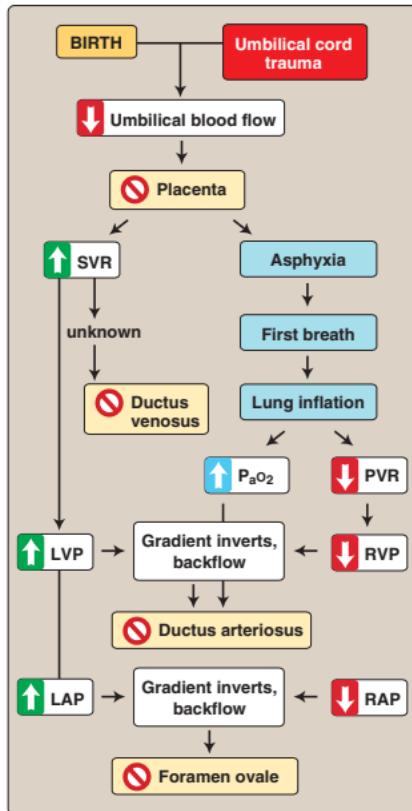


What are the two main factors maintaining PVR in the fetus? Why is the first breath said to be "the most difficult we ever take"?



What are the clinical features of **persistent pulmonary hypertension of the newborn (PPHN)**?





Two main factors maintaining a high fetal PVR:

- Fetal lungs are collapsed, causing **extravascular compression**.
- Absence of ventilation plus fluid in the air spaces causes **hypoxic vasoconstriction**.



Fluid within the airways creates **surface tension** that must be overcome before a lung inflates. This requires a supranormal transpulmonary pressure gradient, thereby making the first breath "the most difficult."



**PPHN** occurs when PVR remains high at birth, causing **right-to-left shunting** through a patent ductus arteriosus and foramen ovale. The neonate presents with hypoxemia and signs of **respiratory distress**. [Note: PPHN may be due to incomplete pulmonary vascular development or pulmonary vasoconstriction as a result of infection or other precipitating factor.]

# Thermoregulation

9.7 Question



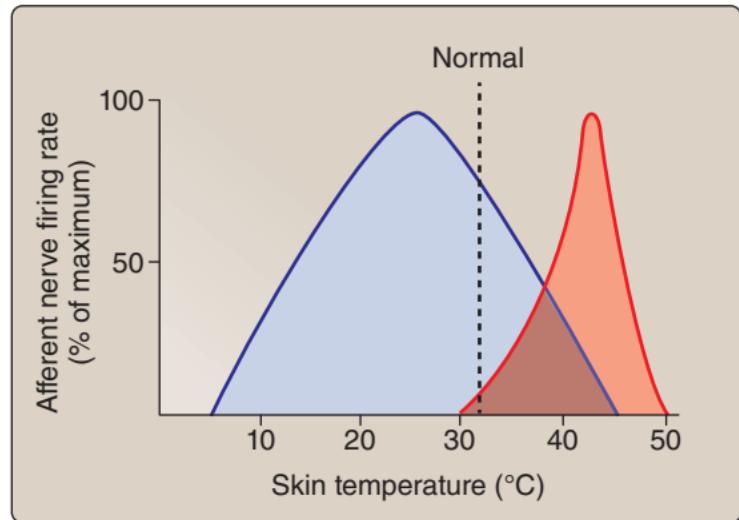
What do the two plots shown demonstrate?



Where is the thermoregulatory control center located, and how does it effect responses to cold stress?



What causes tissue loss during frostbite?





The figure shows output from skin cold and warmth receptors over a range of skin temperatures. [Note: Thermoregulation also relies on thermoreceptors located in the CNS and viscera.]



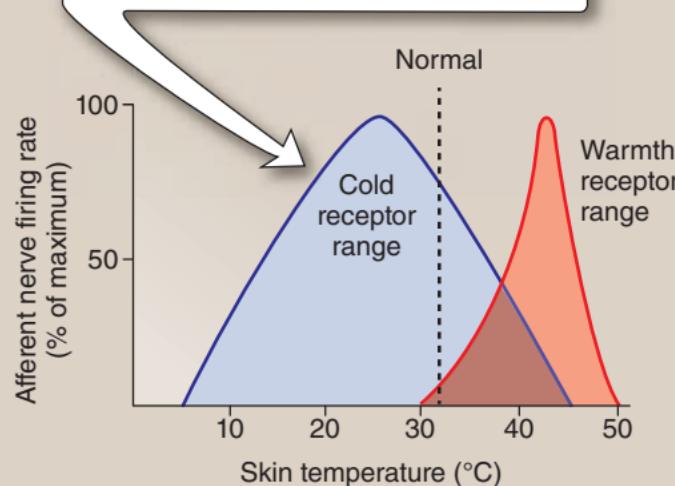
The thermoregulatory control center is located in the **pre-optic area of the hypothalamus**. A response to cold stress has both behavioral and physiologic components:

- **Behavioral**: adding clothing layers to increase insulation, adjusting a room thermostat, exercising to generate heat
- **Physiologic**
  - **Cutaneous blood flow**: reduction decreases heat loss from the skin surface
  - **Shivering**: nonforceful muscle contractions generate heat
  - **Nonshivering thermogenesis**: increases metabolic rate in muscle and other tissues



**Frostbite** is cold-induced tissue damage and necrosis. The ice crystals that form when tissue freezes disrupt cell membranes and provoke inflammatory responses that cause further tissue damage and ischemia. [Note: Frostbite severity is assessed using a four-tier system similar to burns.]

**Cold receptors predominate responses to cold temperature but are also active in warm temperatures.**





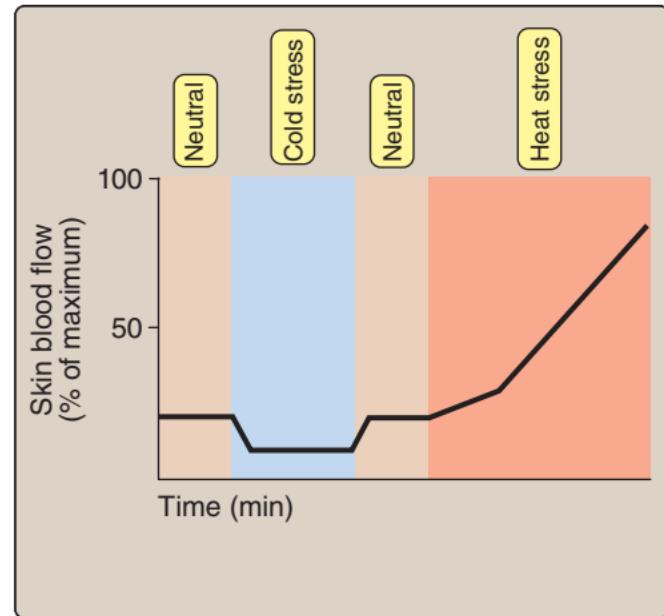
Explain how cutaneous blood flow is regulated during cold and heat stress, as shown.



What are the four mechanisms by which heat is transferred to the external environment? What equation relates the amount of heat transferred to the environment to heat production and storage by the body?



What is **heat stroke**?



## 9.8 Answer

# Heat Transfer



The cutaneous vasculature is regulated by the SNS:

- **Cold stress:** The SNS constricts cutaneous resistance vessels, veins, and arteriovenous anastomoses to shunt blood away from the body surface and conserve heat.
- **Heat stress:** SNS vasoconstrictor influence is removed, and skin flow increases.  
[Note: The pathways underlying an active vasodilatory response to heat stress (as shown) are not well delineated.]



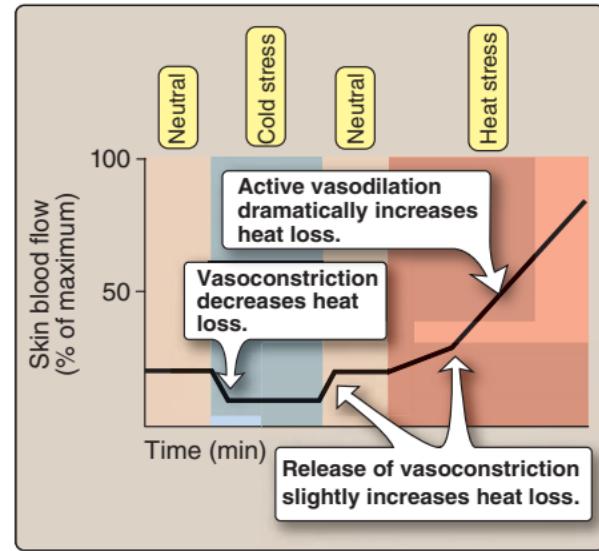
Four routes for heat transfer to the environment:

- **Radiation (R):** to distant external objects
- **Conduction (K):** to objects in close physical contact
- **Convection (C):** via moving fluids (e.g., air or water)
- **Fluid evaporation (E):** from the skin surface

The **heat balance equation** is used to determine how much heat the body stores (S) based on the amount of heat generated and that transferred to (or from) the environment:

$$S = (M - W_k) - (R + K + C) - E$$

where M = metabolism and W<sub>k</sub> = external work.



**Heat stroke** occurs when body temperature rises to  $>40^{\circ}\text{C}$ , resulting in neurologic symptoms, such as headache and confusion. [Note: Heat stroke reflects **thermoregulatory failure** and is usually caused by exposure to excessively high heat. It may result in coma and death if not corrected by medical intervention.]



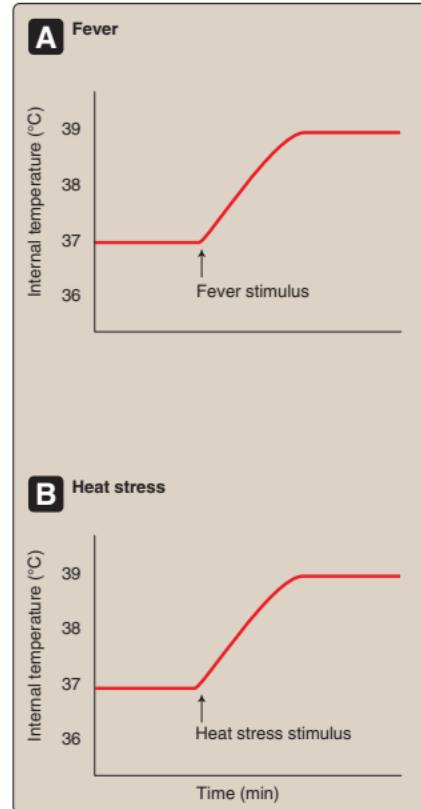
What is the difference between fever and heat stress (which are both characterized by a rise in internal body temperature, as shown)?



How is a fever-induced rise in internal temperature initiated and sustained?



Why are NSAIDs effective in reducing fever?





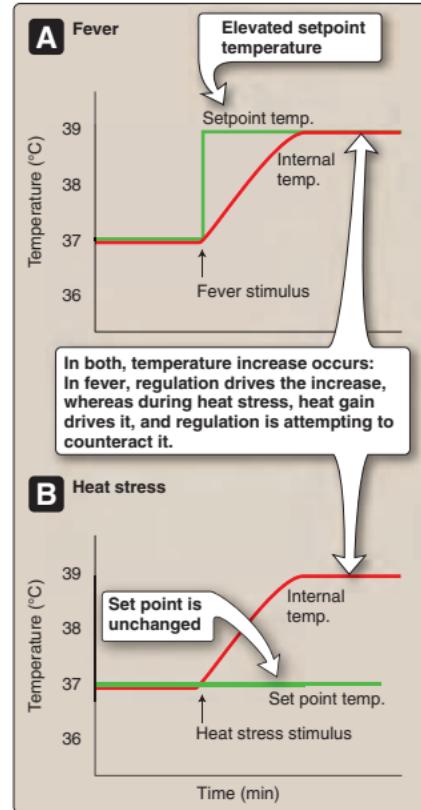
**Fever** is an intentional rise in body temperature sustained by the **hypothalamic thermoregulatory center**. During fever, the body's internal **temperature setpoint** is reset to a higher value. During **heat stress**, the body assumes a heat load that exceeds the thermoregulatory capacity. The setpoint remains unchanged, even though body temperature rises.



Fever is usually a response to infection triggered either by bacterial (**exogenous pyrogens**) or following mast cell activation (**endogenous pyrogens**). The hypothalamic thermoregulatory setpoint resets as a result, and then internal temperature is maintained at the new febrile value using normal thermoregulatory pathways.



NSAIDs inhibit prostaglandin (PG) synthesis. PGs are intermediaries in the pathways that signal the hypothalamus that infection has occurred and that setpoint should be adjusted accordingly. Therefore, inhibiting these pathways causes temperature setpoint to renormalize.





The table lists various forms of exercise. Identify the predominant energy system (i.e., aerobic or anaerobic) used in each case.



What three synthetic pathways do muscles use to generate ATP during exercise, and what are their effective time courses?



The appearance of muscle enzymes in blood can be useful for assessing patients with suspected myopathies. Which muscle enzyme would provide a more effective clinical marker of rhabdomyolysis, *creatine kinase (CK)* or *lactate dehydrogenase*?

Exercise	Type
400-m sprint	?
10-km run	?
Track cycling (1 km)	?
Road cycling (40 km)	?
100-m freestyle swim	?
1,500-m freestyle swim	?



Exercise	Type
400-m sprint	Anaerobic
10-km run	Aerobic
Track cycling (1 km)	Anaerobic
Road cycling (40 km)	Aerobic
100-m freestyle swim	Anaerobic
1,500-m freestyle swim	Aerobic

[Note: Although the table above lists the predominant exercise type, most forms of exercise use both aerobic and anaerobic pathways with overlapping time courses.]



ATP synthetic pathways:

- **Creatine phosphate (CP):** CK uses the high-energy phosphate bond from CP to regenerate ATP. ATP synthesis is rapid but sustains exercise for seconds only.
- **Lactic acid system:** uses glucose as a substrate; generates ATP at half the rate of the CP system but extends muscle contraction time to 0.5–2.5 min
- **Oxidative phosphorylation:** uses glucose as a substrate; generates ATP at half the rate of the lactic acid system but can sustain exercise for hours



*Lactate dehydrogenase* is expressed in most tissues and is not a muscle-specific marker enzyme. Because CK is expressed at high levels in muscle primarily, it is a sensitive indicator of muscle injury.

# Blood Pressure During Exercise

9.11 Question



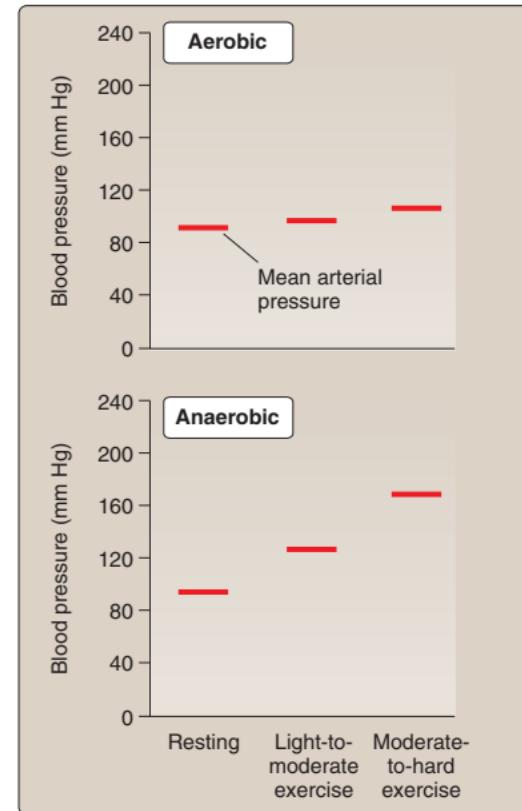
What is meant by "exercise pressor reflex"?



The figure shows that mean arterial pressure (MAP) rises with exercise intensity, but this masks fundamental differences in pulse pressure responses to aerobic and anaerobic exercise. What is the cause and nature of these differences?



The incidence of **cardiac arrest** increases significantly the day after a heavy snowfall in northern climes. Why is shoveling snow so hazardous, especially to elderly individuals?



# Blood Pressure During Exercise



**Exercise pressor reflex** refers to a reflexive rise in blood pressure and associated cardiovascular responses induced by contracting skeletal muscle.

**A-plus:** The reflex is believed to be mediated by muscle sensory afferents responding to mechanical stimuli (class III) and metabolites (class IV).



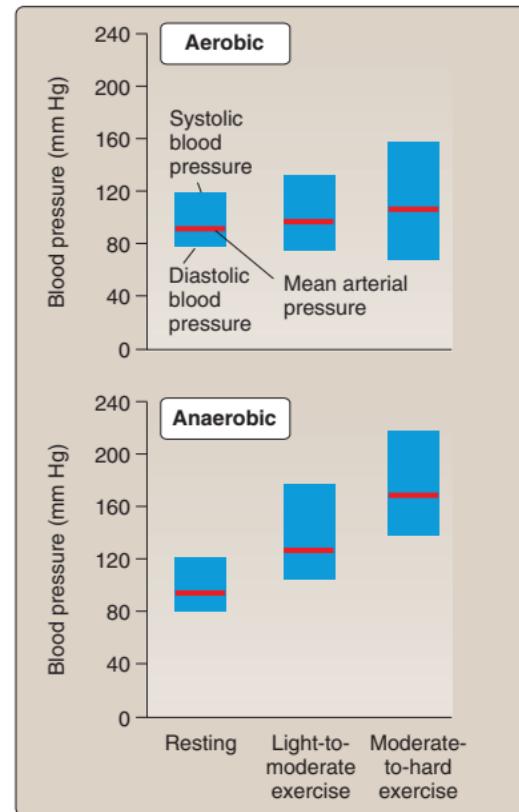
The main difference between responses to aerobic and anaerobic exercise relates to **diastolic blood pressure (DBP)**:

**Aerobic:** Systolic blood pressure (SBP) and MAP both rise with aerobic exercise intensity, whereas DBP falls. The drop in DBP reflects enhanced **diastolic runoff** into the high-capacity, low-resistance vascular beds supplying muscle and skin.

**Anaerobic:** Sustained muscle contractions compress supply arteries and raise vascular resistance. DBP rises along with SBP.



Shoveling snow uses small upper body muscle groups that have relatively low impact on systemic vascular resistance when active. Lifting heavy snow is also an anaerobic activity that induces marked increases in SBP, MAP, DBP, and heart rate. Individuals with preexisting heart disease are at increased risk of arrhythmia and cardiac arrest as a consequence.



# Cardiac Output During Exercise

9.12 Question



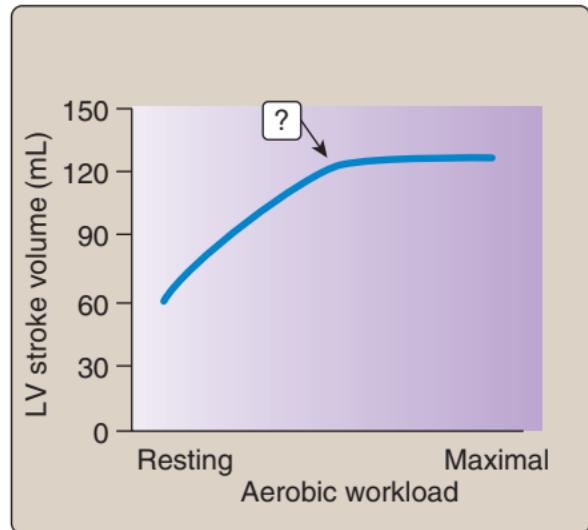
Why does left ventricular (LV) stroke volume plateau at moderate exercise intensities, as shown?



Identify two or more mechanisms by which venous return (VR) is increased to support increased cardiac output (CO) during aerobic exercise.



What is the purpose of an exercise ECG test?



# Cardiac Output During Exercise



The rise in CO during exercise is accomplished by increasing heart rate (HR) and stroke volume (SV):  $CO = HR \times SV$ . Increasing HR shortens diastole and reduces LV preload during moderate to maximal exercise. SV plateaus and may even decline as a consequence.

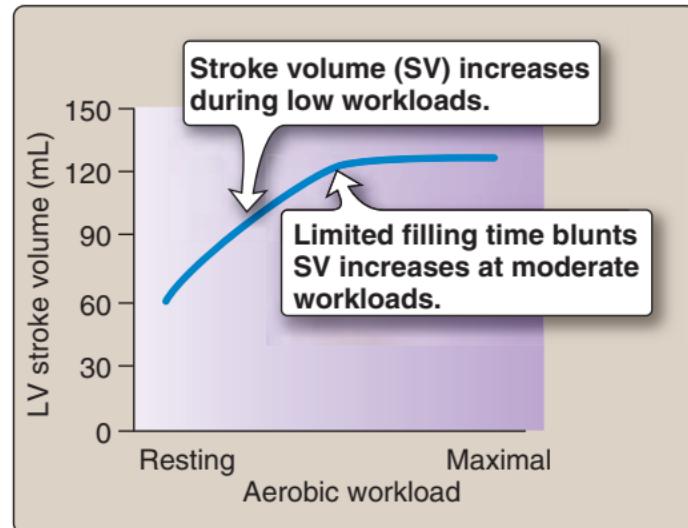


Mechanisms by which VR increases during aerobic exercise:

- ↑ **Venous pumping**: Muscle contractions “pump” blood through the veins at increased rate (“muscle pump”).
- ↓ **Venous capacity**: Sympathetic vasoconstriction reduces capacity and decreases blood transit time through the venous system.
- ↑ **Ventilation**: Deep inspirations enhance the pressure gradient driving flow through the venous system.



An exercise ECG test is used in diagnosing **coronary heart disease**. Coronary flow must increase during exercise to support a rise in CO. Occlusion of coronary vessels limits flow and causes myocardial ischemia, which manifests as changes on an ECG recording.



# Respiratory Function During Exercise

9.13 Question



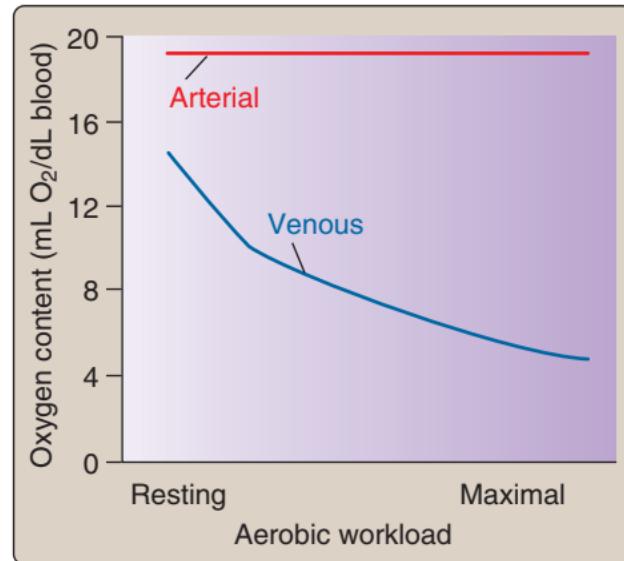
What accounts for the changes in venous blood O<sub>2</sub> content during exercise, as shown?



What three changes in pulmonary function allow P<sub>aO<sub>2</sub></sub> to remain stable during exercise?



Should patients with **chronic obstructive lung disease (COPD)** be advised to refrain from exercise, or is exercise beneficial?



## 9.13 Answer

## Respiratory Function During Exercise



Muscles increase their  $O_2$  consumption during exercise, which lowers venous  $O_2$  content. Increased  $O_2$  extraction is facilitated in two ways:

- Active myocytes decrease  $Po_2$  locally, which steepens the partial pressure gradient driving  $O_2$  delivery.
- Exercising muscles generate heat,  $CO_2$ , and  $H^+$ , all of which lower Hb's  $O_2$  affinity and facilitate unloading (see 5.14).

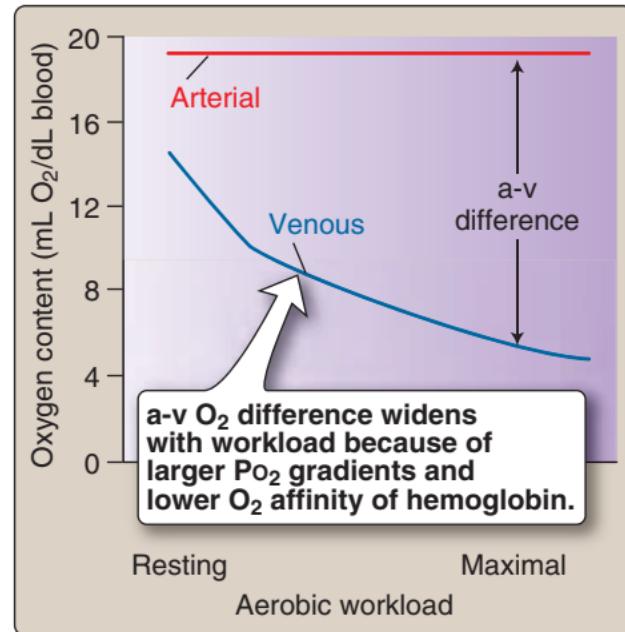


$P_{aO_2}$  remains stable during exercise in the face of increased demand through:

- ↑ **Ventilation**: maintains a steep  $Po_2$  gradient across the blood–gas barrier
- ↑ **Tidal volume**: improves  $\dot{V}_A/\dot{Q}$  ratio at the lung base
- ↑ **Pulmonary flow**: recruits pulmonary capillaries and increases blood–gas interface surface area



Exercise training increases ventilation, increases muscle's ability to extract  $O_2$  from blood, and increases Hb levels in both normal individuals and in patients with **COPD**. Therefore, an exercise program can help alleviate feelings of **dyspnea** that patients with COPD experience upon exertion, allowing for continued mobility.





What is the difference between apoptosis and necrosis?



Aging produces what similar types of change in all tissues? How do they cause increased arterial pressure and a decrease in maximal attainable heart rate?



The radiograph shows an example of severe **senile kyphosis**. How does such extreme curvature affect pulmonary function?



Lateral thoracic spine radiograph.



**Apoptosis** is **programmed cell death**. Cells break into fragments and are then engulfed by phagocytes without significant spillage of cell contents. **Necrosis** is a **pathologic** cell death that culminates in cell lysis. Spilled cell contents trigger an inflammatory response that may damage surrounding cells.



Aging is accompanied by decreased tissue compliance, functionality, and responsiveness to external factors. Loss of arterial compliance due to elastin breakdown and collagen deposition results in **hypertension**. Reduced myocardial sensitivity to autonomic transmitters and hormones limits maximal heart rate to  $220 - \text{age in years}$ .



**Kyphosis** limits chest wall movements, thereby decreasing vital capacity, forced expiratory volume, and other measures of pulmonary function. Patients often present with dyspnea also.



Lateral thoracic spine radiograph.

# Ischemic Cascade

9.15 Question



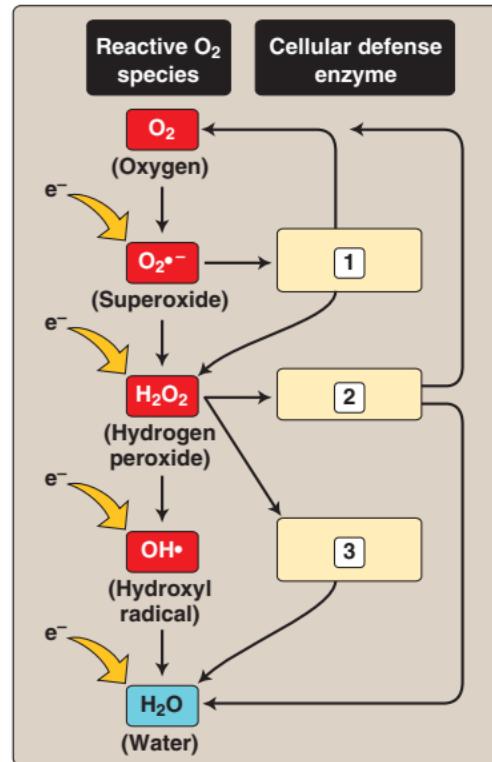
The figure shows reactive O<sub>2</sub> species produced by the mitochondrial electron chain. Using the boxed numerals as a guide, identify the enzymes that help protect cells against such reactive O<sub>2</sub> species.



Identify four or more key events in an ischemic cascade.



What is the rationale behind therapeutic hypothermia following **myocardial infarction**?





Enzymes that protect against reactive O<sub>2</sub> species:

1. **Superoxide dismutase**
2. **Catalase**
3. **Glutathione peroxidase**

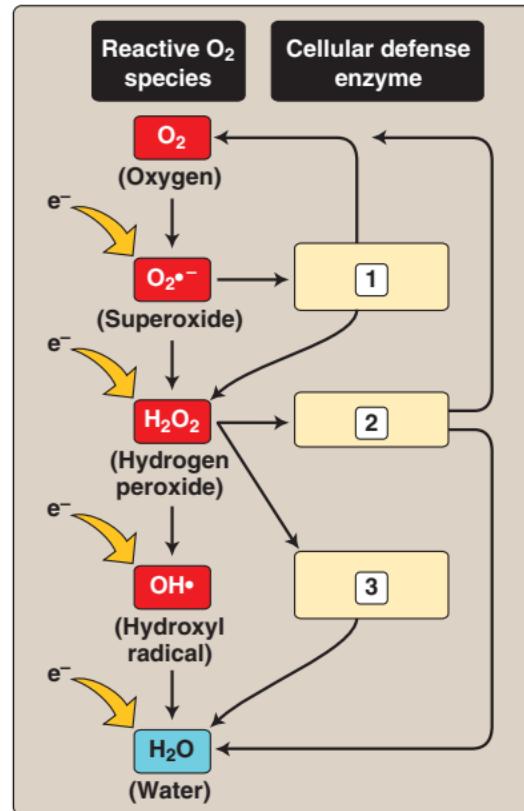


Key events in an ischemic cascade include:

- **O<sub>2</sub> deprivation** forces cells to switch from aerobic to anaerobic metabolism. Lactic acid accumulation causes acidosis.
- **Falling ATP levels** cause ion pumps to slow, allowing ion gradients to dissipate.
- **Rising intracellular Ca<sup>2+</sup>** activates Ca<sup>2+</sup>-dependent degradative enzymes.
- **Mitochondria accumulate reactive oxygen species**, damaging their membranes. Release of electron chain constituents initiates **apoptosis**.
- **Cell breakdown and lysis (necrosis)** initiates inflammatory reactions, causing further tissue damage.



Cooling body temperature to ~32°C for 12–24 hr following cardiac arrest (i.e., **therapeutic hypothermia**) reduces mitochondrial breakdown and limits inflammatory mediator release. These mediators cause **reperfusion injury** and neurologic damage when circulation is restored after an ischemic event.





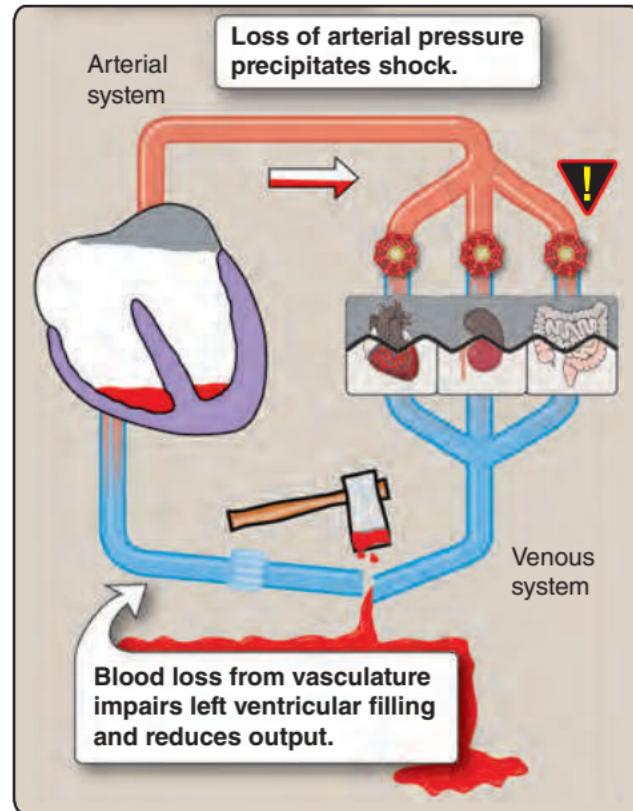
What are the three broad shock categories, and how are they characterized?



What compensatory systems help maintain arterial pressure (e.g., after hemorrhage, as shown)?



What is **sepsis**?





Three broad shock categories:

- **Hypovolemic:** Blood volume falls (e.g., through **hemorrhage** or ECF volume contraction), which compromises cardiac preload and output.
- **Cardiogenic:** Cardiac output (CO) falls due to pump failure (e.g., **arrhythmia, cardiomyopathy**).
- **Distributive:** Loss of vascular tone (e.g., due to inflammatory responses) compromises mean arterial pressure (MAP) and prevents adequate tissue perfusion.

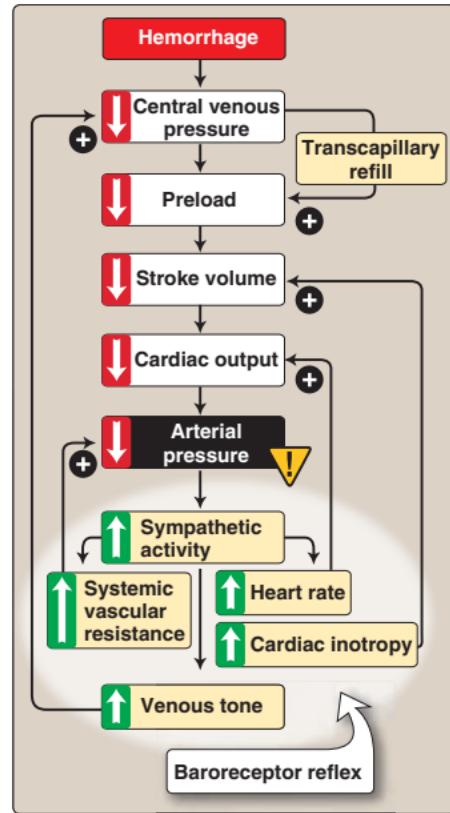


Shock compensation mechanisms:

- **Baroreflex:** ↓ MAP initiates a sympathetic response.
  - ↑ Heart rate and ↑ cardiac inotropy helps support CO.
  - ↑ Venous pressure increases preload and CO.
  - ↑ Systemic vascular resistance helps sustain MAP.
- **Transcapillary refill:** ↓ Venous pressure causes capillary hydrostatic pressure to fall also, allowing for fluid recruitment from the interstitium.
- **↓ Renal fluid loss:** Glomerular filtration rate falls due to a drop in MAP, renal artery pressure, and in response to SNS activation.



**Sepsis** is a systemic inflammatory response to local infection that causes widespread tissue damage and may result in **septic shock**. Shock develops through inappropriate **NO** and **prostacyclin (PGI<sub>2</sub>)** release, causing systemic vasodilation and hypotension.





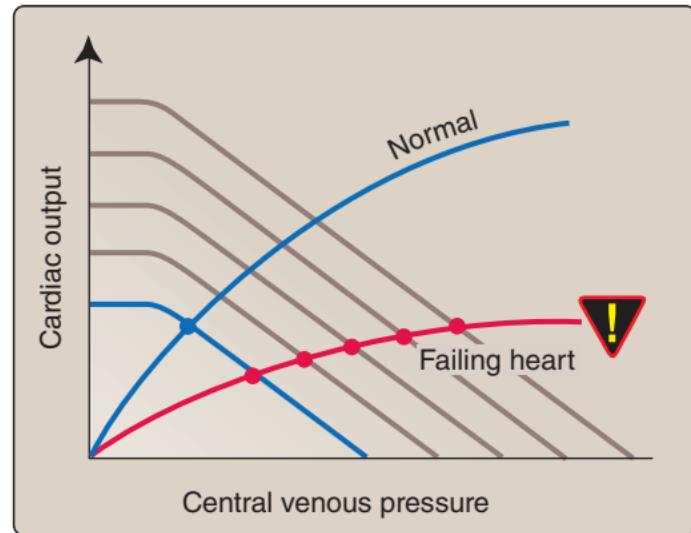
What process is shown?



The process shown results in heart failure if left unchecked by timely medical intervention. Identify three or more disadvantages to the process shown.



What is **Cheyne–Stokes breathing**, and how does it relate to heart failure?





The figure shows ongoing heart failure compensation. A failing heart initiates long-term fluid retention pathways (the **renin–angiotensin–aldosterone system**) to increase ECF volume. Blood volume increases also, which supports cardiac output through increased ventricular preload.



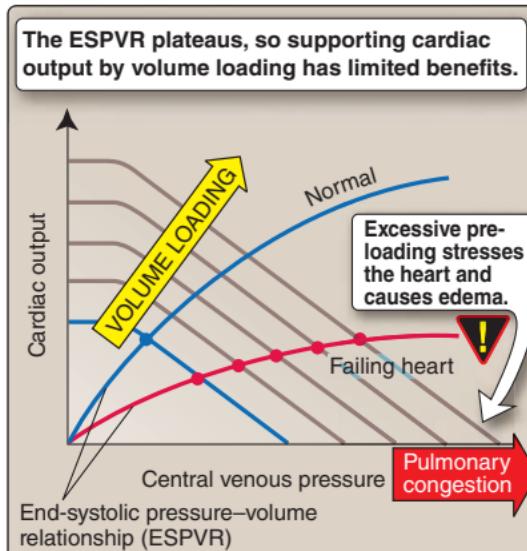
Compensation disadvantages:

- Length-dependent sarcomeric activation has limits, meaning that loading eventually becomes futile (as shown).
- Volume loading increases wall stress (law of Laplace) and cardiac workload.
- Heart enlargement distorts electrical conduction pathways to cause dysrhythmias.
- Heart enlargement may also unseat the heart valves and allow regurgitation.
- Rising venous pressure ultimately causes systemic and pulmonary edema.

[Note: The deleterious effects of volume loading can be reversed by diuresis (see 4.29).]



**Cheyne–Stokes breathing (CSB)** is common in patients with heart failure and is associated with high rates of cardiac mortality compared with failure patients with no breathing disorder. CSB is characterized by periods of apnea followed by breaths with a crescendo–decrescendo airflow pattern.



# Respiratory Failure

9.18 Question



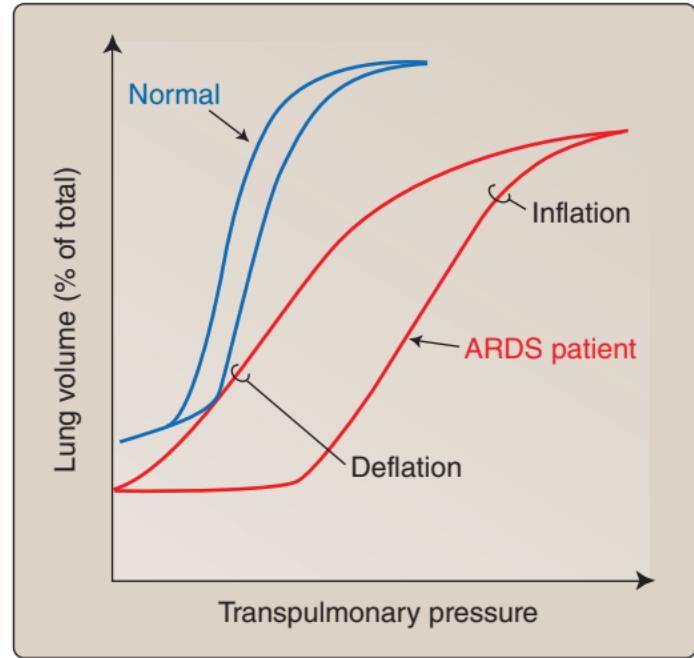
Is fluid in the lungs (e.g., blood, pus, or other exudates) more likely to cause **hypoxemic respiratory failure** or **hypercapnic respiratory failure**?



What is the significance of the rightward shift in the pressure–volume loop in the patient with **acute respiratory distress syndrome (ARDS)** shown, and what causes the shift?



How does severe hypercapnia (e.g.,  $\text{PCO}_2 > 90 \text{ mm Hg}$ ) present clinically?





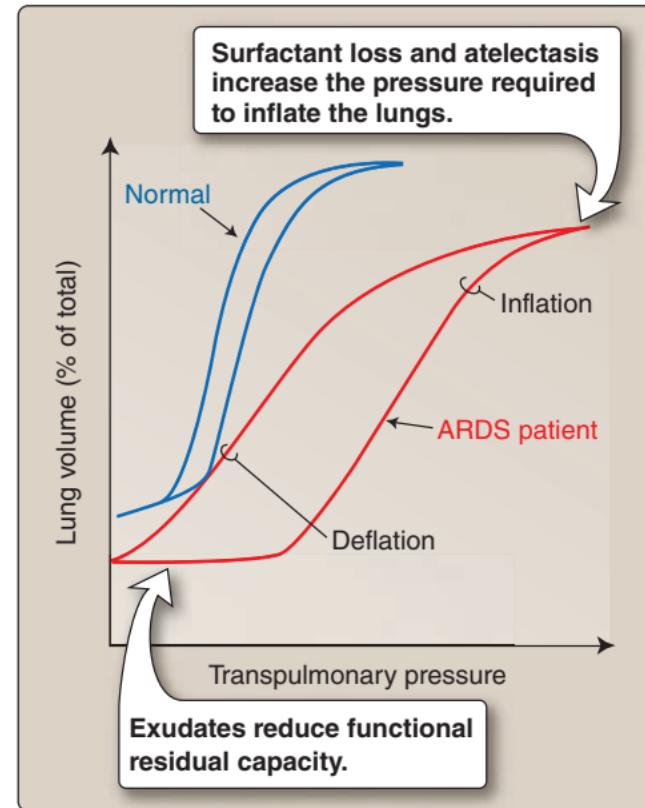
The presence of fluid in the airspaces creates a  **$V_A/Q$  mismatch** and **hypoxemia**, although hypoxemia is typically accompanied by some degree of hypercapnia. [Note: Hypercapnic respiratory failure usually occurs when ventilation is impaired.]



The lungs of patients with **ARDS** are characteristically non-compliant, requiring high transpulmonary pressure to expand. Stiffening occurs due to lung infiltrates that inactivate surfactant and inhibit surfactant synthesis by pneumocytes, causing **atelectasis**. The infiltrates also interfere with gas exchange and reduce functional residual capacity.



**Hypercapnia** has anesthetic-like effects on the CNS (" **$CO_2$  narcosis**"), causing confusion and lethargy. Hypercapnia also depresses the respiratory center and suppresses ventilatory drive, thereby exacerbating the hypercapnia.



# Key Equations

A-1

**Diffusion (Fick law)**

$$J = P \times A (C_1 - C_2)$$

**Compliance**

$$C = \frac{\Delta V}{\Delta P}$$

**Equilibrium potential (Nernst)**

$$E_x = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i}$$

**Cardiac output**

$$CO = HR \times SV$$

**Hemodynamic Ohm law**

$$P = Q \times R$$

**Ejection fraction**

$$EF = \frac{SV}{EDV}$$

**Vascular resistance**

$$SVR = \frac{MAP - CVP}{CO}$$

**Starling law of the capillary**

$$Q = K_f [(P_c - P_{if}) - (\pi_c - \pi_{if})]$$

**Mean arterial pressure**

$$MAP = DBP + \frac{(SBP - DBP)}{3}$$

**Alveolar ventilation**

$$V_A = (TV - V_D) \times \text{breaths/min}$$

**Resistance (Poiseuille)**

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

**Alveolar gas equation**

$$P_{A\text{O}_2} = P_{i\text{O}_2} - \frac{P_{A\text{CO}_2}}{R}$$

**Turbulence (Reynolds)**

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

**Forced vital capacity**

$$FVC = TV + IRV + ERV$$

**Wall stress (Laplace)**

$$\sigma = P \times \frac{r}{2h}$$

**Renal clearance**

$$C = \frac{U \times V}{P}$$

# Key Equations



**Glomerular filtration rate**    
$$\text{GFR} = \frac{[\text{U}]_{\text{Creatinine}} \times \text{V}}{[\text{P}]_{\text{Creatinine}}}$$

**Henderson-Hasselbalch**    
$$\text{pH} = \text{pK} + \log \frac{[\text{HCO}_3^-]}{[\text{CO}_2]}$$

**Serum anion gap**    
$$\text{Anion gap} = [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$$

**Plasma osmolality**    
$$\text{Osmolality} = 2[\text{Na}^+] + \frac{[\text{glucose}]}{18} + \frac{[\text{BUN}]}{2.8}$$

# Abbreviations

ABBREVIATION	EXPANSION	ABBREVIATION	EXPANSION
<b>2,3-DPG</b>	2,3-diphosphoglycerate	<b>AR</b>	adrenergic receptor
<b>5-HT<sub>3</sub></b>	5-hydroxytryptamine	<b>ARDS</b>	acute respiratory distress syndrome
<b>AA</b>	afferent arteriole	<b>AS</b>	<i>aldosterone synthase</i>
<b>ABG</b>	arterial blood gas	<b>ASD</b>	atrial septal defect
<b>AC</b>	<i>adenylyl cyclase</i>	<b>ATP</b>	adenosine triphosphate
<b>ACE</b>	<i>angiotensin-converting enzyme</i>	<b>AV</b>	atrioventricular
<b>ACh</b>	acetylcholine	<b>BBB</b>	blood–brain barrier
<b>AChE</b>	<i>acetylcholinesterase</i>	<b>BPPV</b>	benign paroxysmal positional vertigo
<b>AChR</b>	acetylcholine receptor	<b>CA</b>	<i>carbonic anhydrase</i>
<b>ACTH</b>	adrenocorticotrophic hormone	<b>cAMP</b>	cyclic 3',5'-adenosine monophosphate
<b>ADH</b>	antidiuretic hormone	<b>CaSR</b>	calcium-sensing receptor
<b>ADP</b>	adenosine diphosphate	<b>CCK</b>	cholecystokinin
<b>AF</b>	atrial fibrillation	<b>C<sub>Cr</sub></b>	creatinine clearance
<b>AIN</b>	acute interstitial nephritis	<b>CD</b>	collecting duct
<b>AKI</b>	acute kidney injury	<b>CF</b>	cystic fibrosis
<b>Ang-I</b>	angiotensin I	<b>CFTR</b>	cystic fibrosis transmembrane conductance regulator
<b>Ang-II</b>	angiotensin II	<b>cGMP</b>	cyclic 3',5'-guanosine monophosphate
<b>ANP</b>	atrial natriuretic peptide	<b>CICR</b>	Ca <sup>2+</sup> -induced Ca <sup>2+</sup> release
<b>ANS</b>	autonomic nervous system	<b>CK</b>	<i>creatine kinase</i>
<b>AoP</b>	aortic pressure	<b>CMTX1</b>	Charcot-Marie-Tooth disease
<b>AoV</b>	aortic valve	<b>CN</b>	cranial nerve
<b>AP</b>	action potential	<b>CNS</b>	central nervous system
<b>AQP</b>	aquaporin		

# Abbreviations

ABBREVIATION	EXPANSION	ABBREVIATION	EXPANSION
<b>CO</b>	cardiac output	<b>EF</b>	ejection fraction
<b>COPD</b>	chronic obstructive pulmonary disease	<b>EGF</b>	epidermal growth factor
<b>COX</b>	cyclooxygenase	<b>E<sub>K</sub></b>	potassium equilibrium potential
<b>CP</b>	corticopapillary	<b>E<sub>Na</sub></b>	sodium equilibrium potential
<b>CRH</b>	corticotropin-releasing hormone	<b>ENaC</b>	epithelial Na <sup>+</sup> channel
<b>CSB</b>	Cheyne–Stokes breathing	<b>ER</b>	endoplasmic reticulum
<b>CSF</b>	cerebrospinal fluid	<b>ERP</b>	effective refractory period
<b>CVO</b>	circumventricular organ	<b>ERV</b>	expiratory reserve volume
<b>CVP</b>	central venous pressure	<b>E<sub>x</sub></b>	equilibrium potential
<b>DA</b>	ductus arteriosus	<b>FD</b>	functional dyspepsia
<b>DAG</b>	diacylglycerol	<b>FEV<sub>1</sub></b>	forced expiratory volume in 1 second
<b>DBP</b>	diastolic blood pressure	<b>FHH</b>	familial hypocalciuric hypercalcemia
<b>DHEA</b>	dehydroepiandrosterone	<b>FHHNC</b>	familial hypomagnesemia with hypercalcioria and nephrocalcinosis
<b>DHP</b>	dihydropyridine	<b>FHM3</b>	familial hemiplegic migraine, type 3
<b>DI</b>	diabetes insipidus	<b>FRC</b>	functional residual capacity
<b>DIT</b>	diiodotyrosine	<b>FSH</b>	follicle-stimulating hormone
<b>D<sub>L</sub></b>	lung diffusing capacity	<b>GABA</b>	γ-aminobutyric acid
<b>DTL</b>	descending thin limb	<b>GABA<sub>AR</sub></b>	γ-aminobutyric acid receptor
<b>EA</b>	efferent arteriole	<b>G<sub>αs</sub></b>	stimulatory G protein alpha subunit
<b>ECF</b>	extracellular fluid	<b>GC</b>	<i>guanylyl cyclase</i>
<b>ECG</b>	electrocardiogram	<b>GERD</b>	gastroesophageal reflux disease
<b>ECL</b>	enterochromaffin-like	<b>GFR</b>	glomerular filtration rate
<b>EDV</b>	end diastolic volume		

# Abbreviations

A-5

ABBREVIATION	EXPANSION	ABBREVIATION	EXPANSION
<b>GH</b>	growth hormone	<b>I<sub>Ca</sub></b>	Ca <sup>2+</sup> current
<b>GI</b>	gastrointestinal	<b>ICF</b>	intracellular fluid
<b>G<sub>i</sub></b>	inhibitory G protein	<b>I<sub>f</sub></b>	funny current
<b>GLUT</b>	glucose transporter	<b>IGF-1</b>	insulin-like growth factor 1
<b>GnRH</b>	Gonadotropin-releasing hormone	<b>I<sub>K</sub></b>	K <sup>+</sup> current
<b>G<sub>olf</sub></b>	olfactory G protein	<b>I<sub>m</sub></b>	membrane current
<b>GPCR</b>	G protein-coupled receptor	<b>I<sub>Na</sub></b>	Na <sup>+</sup> current
<b>GPI</b>	glycophosphatidylinositol	<b>IOP</b>	intraocular pressure
<b>GTO</b>	Golgi tendon organ	<b>IP<sub>3</sub></b>	inositol trisphosphate
<b>GTP</b>	guanosine triphosphate	<b>IRDS</b>	infant respiratory distress syndrome
<b>Hb</b>	hemoglobin	<b>IRV</b>	inspiratory reserve volume
<b>HbA</b>	adult hemoglobin	<b>I<sub>to</sub></b>	transient outward K <sup>+</sup> current
<b>HbF</b>	fetal hemoglobin	<b>IV</b>	intravenous, -ly
<b>hCG</b>	human chorionic gonadotropin	<b>JGA</b>	juxtaglomerular apparatus
<b>HCM</b>	hypertrophic cardiomyopathy	<b>LAP</b>	left atrial pressure
<b>HCN</b>	hyperpolarization-activated, cyclic nucleotide-dependent, nonspecific ion channel	<b>LASIK</b>	laser-assisted in situ keratomileusis
<b>Hct</b>	hematocrit	<b>LES</b>	lower esophageal sphincter
<b>HPP</b>	hypokalemic periodic paralysis	<b>LH</b>	luteinizing hormone
<b>HR</b>	heart rate	<b>LQTS</b>	long QT syndrome
<b>HTN</b>	hypertension	<b>LV</b>	left ventricle
<b>IBD</b>	inflammatory bowel disease	<b>LVP</b>	left ventricular pressure
<b>IC</b>	inspiratory capacity	<b>mAChR</b>	muscarinic acetylcholine receptor
		<b>MAP</b>	mean arterial pressure

# Abbreviations

ABBREVIATION	EXPANSION	ABBREVIATION	EXPANSION
<b>MG</b>	myasthenia gravis	<b><math>\pi_{BS}</math></b>	ultrafiltrate oncotic pressure
<b>MH</b>	malignant hyperthermia	<b><math>\pi_c</math></b>	plasma colloid oncotic pressure
<b>MI</b>	myocardial infarction	<b>P<sub>c</sub></b>	capillary hydrostatic pressure
<b>MIT</b>	monoiodotyrosine	<b>Pco</b>	partial pressure of carbon monoxide
<b>MLC<sub>20</sub></b>	20-kDa myosin regulatory light chain	<b>Pco<sub>2</sub></b>	partial pressure of CO <sub>2</sub>
<b>MLCK</b>	<i>myosin light-chain kinase</i>	<b>Pcr</b>	creatine phosphate
<b>MS</b>	multiple sclerosis	<b>PDE</b>	<i>phosphodiesterase</i>
<b>MV</b>	mitral valve	<b>PepT1</b>	peptide transporter 1
<b>nAChR</b>	nicotinic acetylcholine receptor	<b>PepT2</b>	peptide transporter 2
<b>NE</b>	norepinephrine	<b>PFTs</b>	pulmonary function tests
<b>NIS</b>	Na <sup>+</sup> -I <sup>-</sup> symporter	<b>PG</b>	prostaglandin
<b>NKCC</b>	Na <sup>+</sup> -K <sup>+</sup> -2Cl <sup>-</sup> cotransporter	<b>PGE<sub>2</sub></b>	prostaglandin E <sub>2</sub>
<b>NMJ</b>	neuromuscular junction	<b>PGI<sub>2</sub></b>	prostaglandin I <sub>2</sub>
<b>NO</b>	nitric oxide	<b>PH</b>	pulmonary hypertension
<b>NSAID</b>	nonsteroidal anti-inflammatory drug	<b>PIG-A</b>	phosphatidylinositol glycan A
<b>OI</b>	osteogenesis imperfecta	<b>PIP<sub>2</sub></b>	phosphatidylinositol 4,5-bisphosphate
<b>OTE</b>	otoacoustic emission	<b>PKA</b>	<i>protein kinase A</i>
<b>OVLT</b>	organum vasculosum of the lamina terminalis	<b>PKC</b>	<i>protein kinase C</i>
<b>P<sub>A</sub></b>	alveolar pressure	<b>PKG</b>	<i>protein kinase G</i>
<b>P<sub>a</sub>CO<sub>2</sub></b>	arterial Pco <sub>2</sub>	<b>PLC</b>	<i>phospholipase C</i>
<b>PAH</b>	<i>para</i> -aminohippurate	<b>Po<sub>2</sub></b>	partial pressure of O <sub>2</sub>
<b>P<sub>a</sub>O<sub>2</sub></b>	arterial Po <sub>2</sub>	<b>POS</b>	polycystic ovary syndrome
<b>P<sub>BS</sub></b>	hydrostatic pressure within Bowman space	<b>PP</b>	pulse pressure

# Abbreviations

A-7

ABBREVIATION	EXPANSION	ABBREVIATION	EXPANSION
<b>P<sub>pc</sub></b>	pulmonary capillary hydrostatic pressure	<b>SGLT</b>	sodium-dependent glucose transporter
<b>PPHN</b>	persistent pulmonary hypertension of the newborn	<b>SHBG</b>	sex hormone-binding globulin
<b>PP<sub>i</sub></b>	pyrophosphate	<b>SIADH</b>	syndrome of inappropriate antidiuretic hormone release
<b>P<sub>pl</sub></b>	intrapleural pressure	<b>SNS</b>	sympathetic nervous system
<b>PT</b>	proximal tubule	<b>SR</b>	sarcoplasmic reticulum
<b>PTH</b>	parathyroid hormone	<b>SV</b>	stroke volume
<b>PVR</b>	pulmonary vascular resistance	<b>SVR</b>	systemic vascular resistance
<b>RAAS</b>	<i>renin–angiotensin–aldosterone system</i>	<b>T<sub>3</sub></b>	triiodothyronine
<b>RAP</b>	right atrial pressure	<b>T<sub>4</sub></b>	thyroxine
<b>RBC</b>	red blood cell	<b>TAL</b>	thick ascending limb
<b>RBF</b>	renal blood flow	<b>TBW</b>	total body water
<b>ROCK</b>	<i>rho-kinase</i>	<b>TGF</b>	tubuloglomerular feedback
<b>ROMK</b>	renal outer medullary potassium channel	<b>TLC</b>	total lung capacity
<b>RP</b>	refractory period	<b>T<sub>m</sub></b>	maximal transporter capacity
<b>RPF</b>	renal plasma flow	<b>TPO</b>	<i>thyroid peroxidase</i>
<b>RV</b>	residual volume	<b>TR</b>	thyroid hormone receptor
<b>RVP</b>	right ventricular pressure	<b>TRH</b>	thyroid-releasing hormone
<b>SA</b>	sinoatrial	<b>TRPM6</b>	transient receptor potential cation channel, subfamily M, member 6
<b>SABS</b>	short-acting beta-agonists	<b>TRPV5</b>	transient receptor potential cation channel, subfamily V, member 5
<b>SBP</b>	systolic blood pressure	<b>TSH</b>	thyroid-stimulating hormone
<b>SERCA</b>	sarco/endoplasmic reticulum $\text{Ca}^{2+}$ -ATPase		
<b>SFO</b>	subfornical organ		

# Abbreviations

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ABBREVIATION	EXPANSION	ABBREVIATION	EXPANSION
<b>TV</b>	tidal volume	<b>V<sub>m</sub></b>	membrane potential
<b>UES</b>	upper esophageal sphincter	<b>VOR</b>	vestibuloocular reflex
<b>UT</b>	urea transporter	<b>VR</b>	venous return
<b>UV</b>	ultraviolet	<b>V<sub>th</sub></b>	threshold potential
<b>̇V<sub>A</sub>/̇Q</b>	ventilation/perfusion ratio	<b>WPW</b>	Wolff-Parkinson-White
<b>VC</b>	vital capacity	<b>ZES</b>	Zollinger-Ellison syndrome