Netter's
Physiology Flash Cards

Susan Mulroney
Adam Myers

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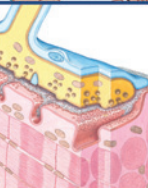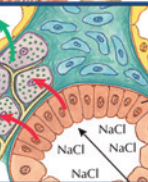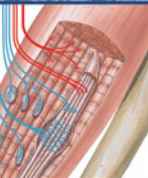
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As a naturally integrative field of study, physiology cannot readily be learned by simple memorization or repetitive study of lecture notes or texts. Most students find that the best understanding of this field comes when multiple learning modalities are utilized. While we recommend that students of physiology start with a standard textbook such as *Netter's Essential Physiology,* many will find that they desire additional learning materials. With this in mind, this set of over 200 cards has been developed to be used in conjunction with textbooks, lectures, and problem sets to cover topics in each of the major areas of physiology: cell physiology, neurophysiology, cardiovascular physiology, respiratory physiology, renal physiology, gastrointestinal physiology, and endocrinology. From the basic physiology and anatomy of these systems to their complex, integrative processes, *Netter's Physiology Flash Cards* provides a visually rich platform for testing one's knowledge of physiology and developing a deeper understanding of physiological concepts. Medical students, allied health students, and undergraduate students taking an advanced course in human physiology will enhance their knowledge of physiology by working with these cards.

Cell Physiology and Fluid Homeostasis

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The cell membrane is made of a lipid bilayer, with many different proteins that regulate cell function and activity. Name the types of proteins represented by numbers 1–4.
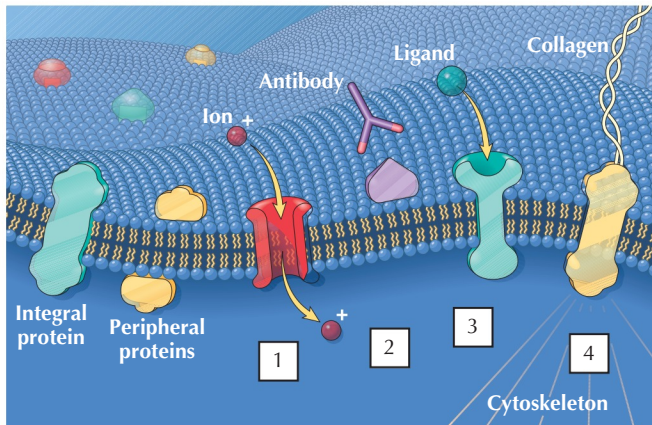
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1. Ion channels
2. Surface antigens
3. Receptors
4. Adhesion molecules

Comment: The amount and types of membrane proteins depend on the cell and on regulatory factors that are subject to change, such as immune status and hormone levels.

1−5. Name the body fluid compartments, based on relative volumes.

6. How much fluid would be associated with each compartment in a 60 kg person?

Body
weight

Cell membrane

Capillary wall

1

2

3

4

5

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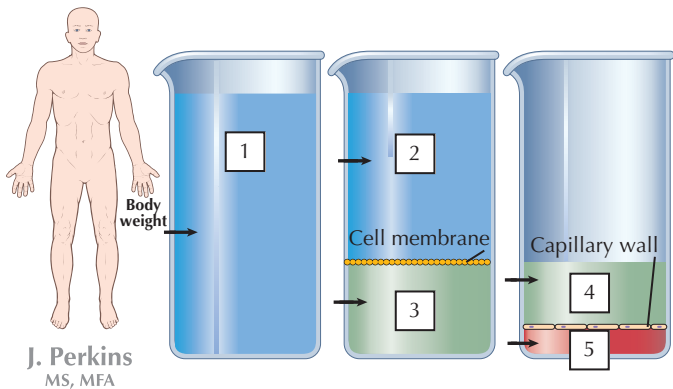
Body Fluid Compartments

1. Total body water (TBW)
2. Intracellular fluid (ICF)
3. Extracellular fluid (ECF)
4. Interstitial fluid (ISF)
5. Plasma volume (PV)
6. TBW is about 60% of body weight, so in a 60-kg person,
   TBW $= 36$ L

ICF is $\frac{2}{3}$ of TBW, or 24 L
ECF is $\frac{1}{3}$ of TBW, or 12 L
ISF is $\frac{3}{4}$ of ECF, or 9 L
PV is $\frac{1}{4}$ of ECF, or 3 L

1–3. Name the indicators that are used to measure plasma volume (1), extracellular fluid volume (2), and total body water (3).

4. Give the formula used to calculate fluid compartment size by the indicator-dilution method.
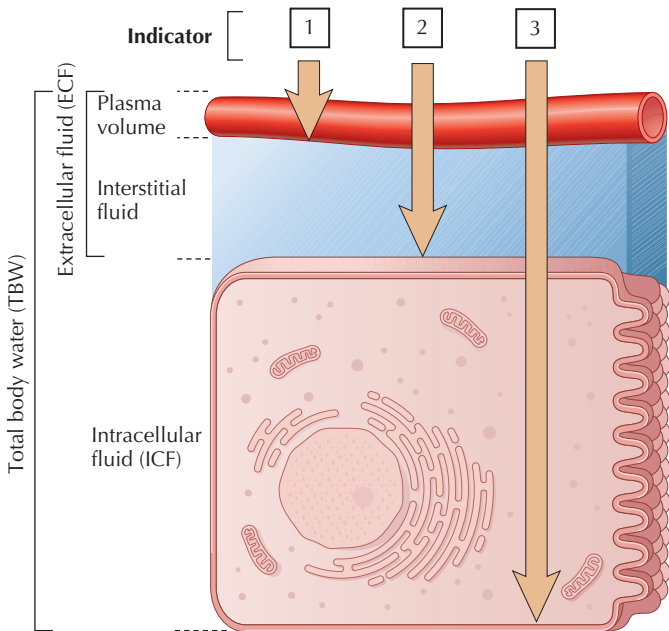
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1. Evans blue dye is used to measure plasma volume.
2. Inulin is used to measure extracellular volume.
3. Antipyrine or tritiated water is used to measure total body water.
4. Compartment volume can be calculated by the formula:

$$\text{Volume (L)} = \frac{\text{amount of indicator injected (mg)}}{\text{Final concentration of indicator (mg/L)}}$$

1. Write the Starling equation for the pressures governing fluid movement into and out of the capillary shown below.

2. Describe the effect on net filtration pressure of: an increase in capillary hydrostatic pressure (P_c) to 40 mm Hg or a reduction in capillary oncotic pressure (π_c) to 20 mm Hg.

Arteriole   Capillary   Venule

$P_i = -3$ mm Hg

$P_c = 30$ mm Hg $P_c = 10$ mm Hg

$\pi_c = 28$ mm Hg

$\pi_i = 8$ mm Hg

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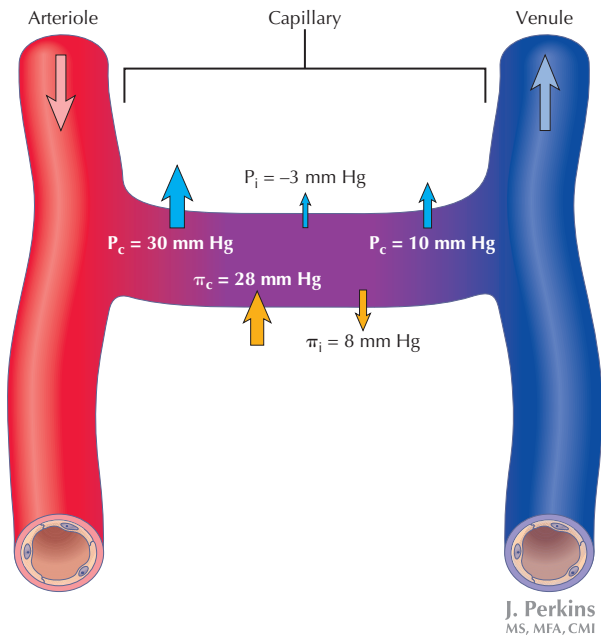
1. Net filtration pressure =
   [(forcing fluid out) − (drawing fluid in)]
   $$(HP_c + \pi_i) - (HP_i + \pi_c)$$
2. Increasing HP_c forces more fluid out of the capillaries. This can result in edema (pooling of fluid in the interstitium). Reducing π_c increases the net filtration pressure, increasing fluid flux into the interstitium.

Fluid balance is necessary for regulation of vascular volume. Referring to the diagram:

1. Describe the effects of a decrease in fluid intake (from 2.5 to 1.5 liters/day) on urine output and thirst.

2. Describe the effects of an increase in fluid intake (from 2.5 to 3.5 liters/day) on urine output and thirst.

Fluid balance

? ← **Excess fluid**   **Fluid deficit** → ?

Intake (~2.5 L/day)

Beverages — 1.3 L
Food — 0.9 L
Oxidation — 0.3 L

Output (~2.5 L/day)

1.5 L — Urine
0.9 L — Sweat and respiration
Excreted in feces (0.1 L)

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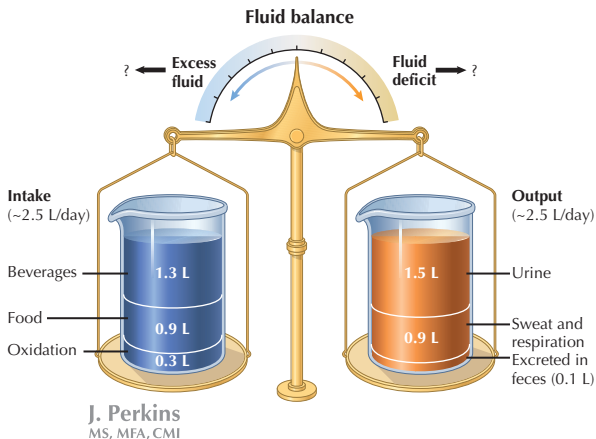
1. A reduction in fluid intake results in dehydration, an imbalance that tips the balance to the right (fluid deficit). Urine volume is greatly reduced, and thirst is stimulated.
2. An increase in fluid intake (without equal losses), tips the balance to the left and results in significantly increased urine output to compensate. Thirst is not stimulated.

Fluid balance

Increased urine output ← **Excess fluid**   **Fluid deficit** → Increased thirst

Intake
(~2.5 L/day)

Beverages — 1.3 L

Food — 0.9 L

Oxidation — 0.3 L

Output
(~2.5 L/day)

1.5 L — Urine

0.9 L — Sweat and respiration

Excreted in feces (0.1 L)

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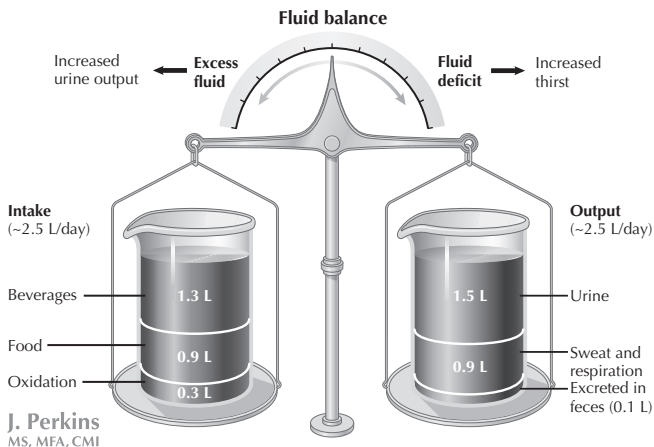
1. Name the type of cellular transport process depicted. Give two examples of this type of transport.

2. What transporter is affected by the substance ouabain?

3. Define primary and secondary active transport.
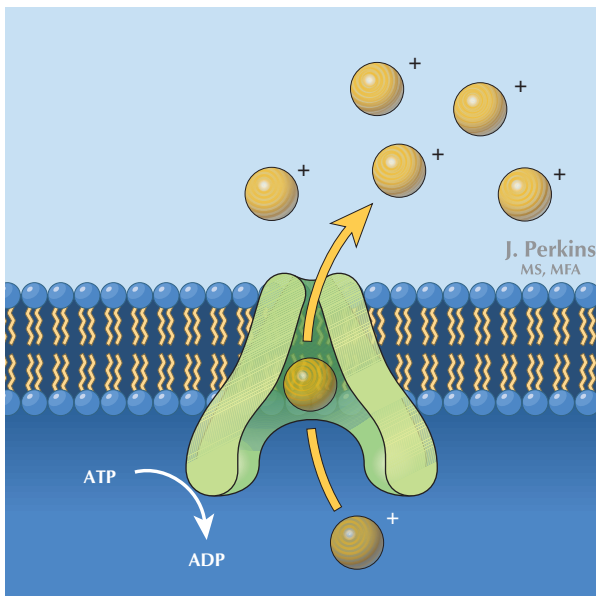
1. **Primary active transport**. Major examples include Na^+/K^+-ATPase, H^+-ATPase, H^+/K^+-ATPase, and Ca^{2+}-ATPase.

2. **Ouabain** is an irreversible blocker of Na^+/K^+-ATPase. Ouabain (also called *digitalis*) is a glycoside that is used to correct cardiac arrhythmias and increase cardiac contractility.

3. **Primary (1°) active transport** is when the transport of ions across a membrane requires a direct expenditure of energy (in the form of ATP). **Secondary (2°) active transport** does not directly use energy (ATP) but instead takes advantage of the electrochemical gradient established by 1° active transport.

A gated ion channel is depicted. Name two types
of gated channels, and the stimuli for gate opening.
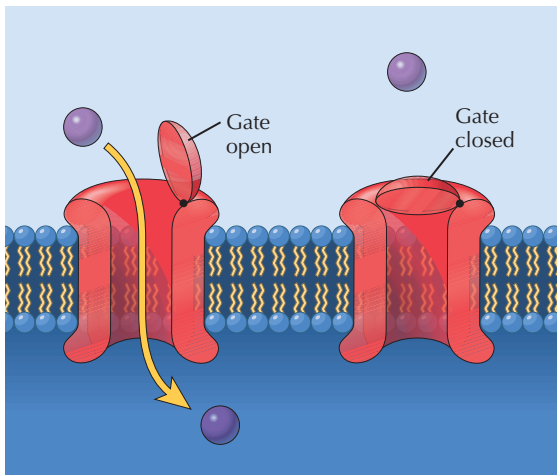
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1. Ligand-gated channels open when a specific ligand (such as acetylcholine) binds to its receptor.
2. Voltage-gated channels open in response to a change in membrane voltage.

Comment: These channels are ion specific; the ions move down their concentration or electrochemical gradients.

Multiple transporters and channels use active transport systems to create a gradient for solute movement. Identify which of the panels depicts a passive channel, a secondary (2°) active symporter, and a 2° active antiporter.
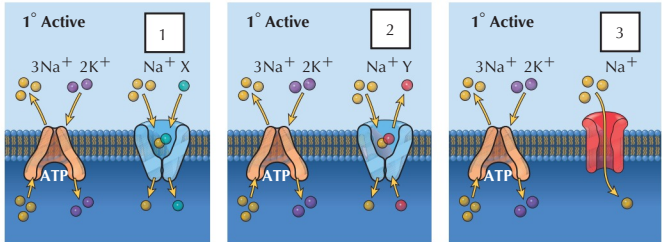
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1. 2° Active symporter
2. 2° Active antiporter
3. Passive channel

Comment: In the cells depicted, the 1° active Na^+/K^+-ATPase (also called the *sodium pump*) maintains low intracellular sodium concentrations, creating an out-to-in gradient for sodium. This allows the 2° active transport of other molecules (*X* and *Y* in the figure) through many different transporters.

Transport of substances through the membrane can occur by the formation and movement of lipid-membrane vesicles. Name the types of vesicular transport represented in each panel.
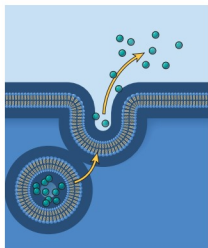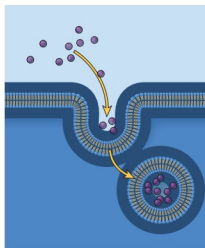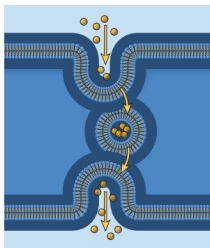
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1. **Exocytosis** involves fusion of the vesicle to the cell membrane for extrusion of vesicle contents.
2. **Endocytosis** involves engulfing substances or particles from the extracellular fluid by the membrane, forming a vesicle within the cell.
3. **Transcytosis** occurs in capillary and intestinal epithelial cells and, using endocytosis and exocytosis, moves the material across the cell membrane.

Comment: Vesicular membrane transport requires energy in the form of ATP. This form of transport is especially important when the material to be transported needs to be isolated from the intracellular environment because of toxicity (e.g., iron, waste) or has the potential to alter signal transduction systems (e.g., Ca^{2+}).

Water flux follows the osmotic pressure gradient, as shown in this diagram:

1. Name the membrane channels through which water movement occurs.

2. What is the function of water channels?

Osmosis

H_2O

H_2O

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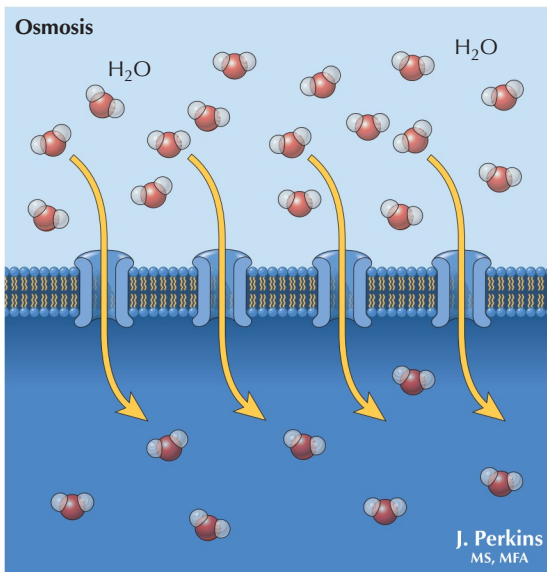
1. **Aquaporins** (AQPs)
2. AQPs are present in all membranes, selectively allowing solute-free water movement. In select membranes such as in the renal collecting ducts, AQPs can be inserted and withdrawn to regulate fluid homeostasis.

Selective Ca^{2+} entry into cells is an important mechanism for initiating intracellular signaling cascades.

1. In this diagram, name the type of channels used in this mechanism.

2. Name the substance calcium binds to in the cell in this pathway.
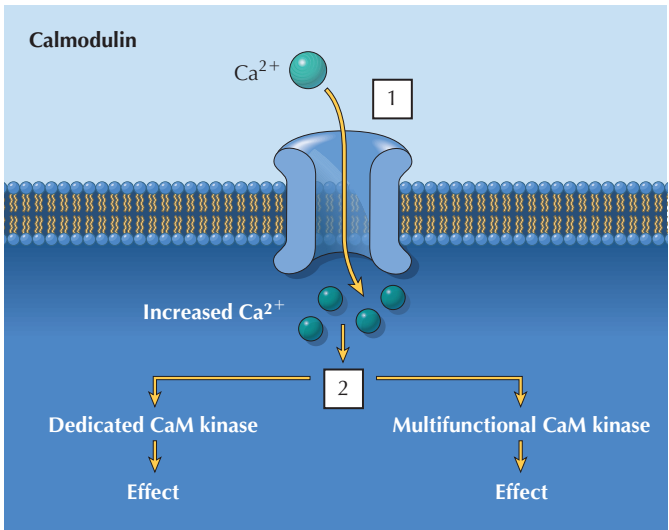
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1. Ligand-gated Ca^{2+} channels
2. Upon entering the cells, calcium binds with calmodulin, activating specific kinases.

Comment: This pathway can initiate smooth muscle contraction, neurotransmitter release, and hormone secretion.

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Two main G-protein coupled transduction systems are illustrated. Name the elements of the transduction systems labeled 1 and 2. What protein kinases are labeled 3 and 4?
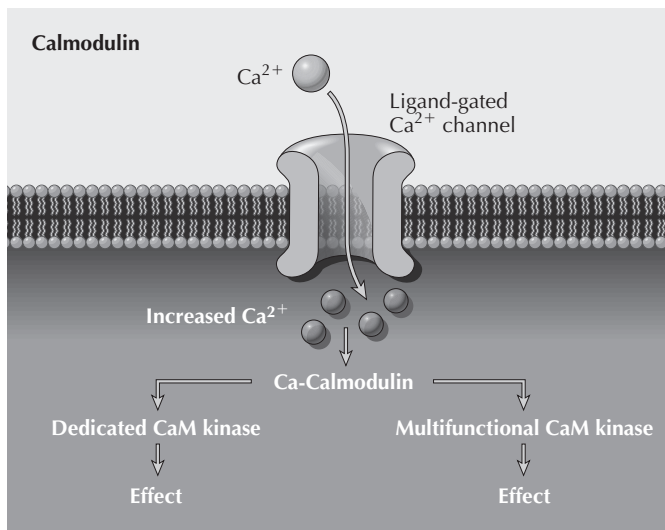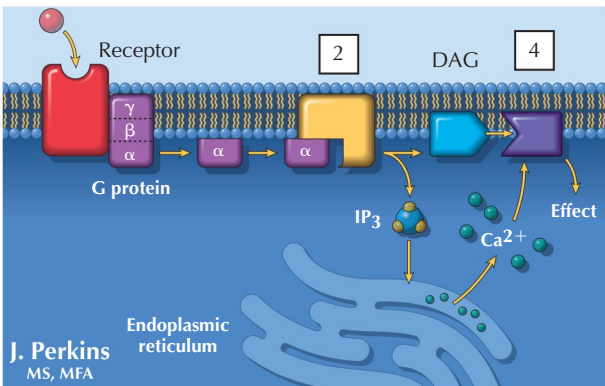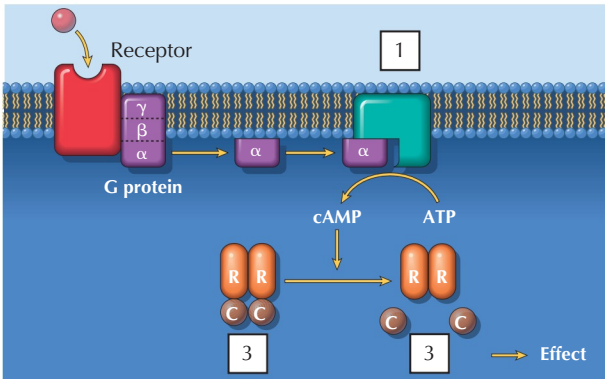
Signal Transduction II: G-Protein-Coupled Receptors

1. Adenylyl cyclase
2. Phospholipase C
3. Protein kinase A (PK-A)
4. Protein kinase C (PK-C)

Comment: Most membrane receptors act through G proteins. Many of their effects are rapid because they do not involve stimulation of transcription factors and protein synthesis.

1–4. In the receptor tyrosine kinase pathway, name the elements labeled 1–4.

5. Is this system simple or complex?
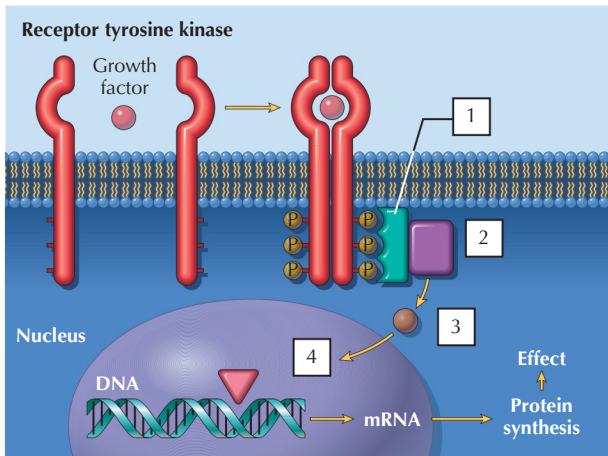
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Signal Transduction III: Receptor Tyrosine Kinase Pathway

1. **Adapter protein**
2. **Monomeric G protein**
3. **Mitogen-activated protein kinase** (MAP-kinase)
4. **Nuclear transcription factors** (activated by MAP-kinase)
5. This is an example of a complex pathway.

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Name the seven major ligands that bind to the nuclear receptor to produce their actions.

Nuclear protein receptor

Nucleus

Effect

DNA

mRNA

Protein synthesis
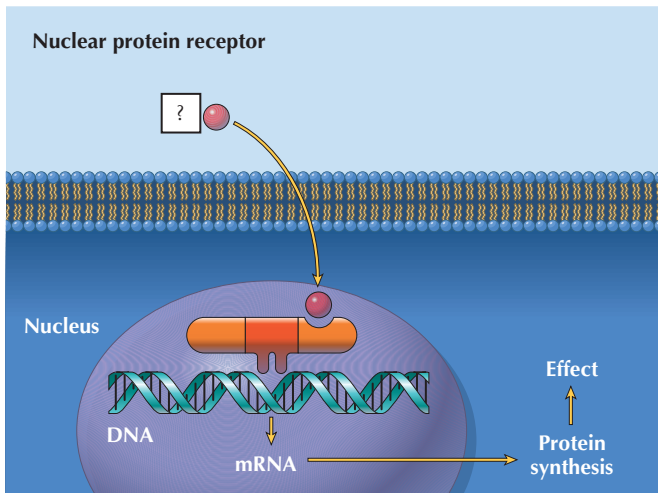
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Signal Transduction IV: Nuclear Protein Receptors

1. Aldosterone
2. Cortisol
3. Calcitriol
4. Estrogen
5. Progesterone
6. Testosterone
7. Thyroid hormones

Comment: In the diagram, these ligands passively diffuse into the cell, bind to a nuclear receptor, and initiate transcription and ultimately protein synthesis. Other than the thyroid hormones, all factors that use the nuclear receptor are steroid hormones (an easy mnemonic is *ACCEPT-T*).

The Nervous System and Muscle

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1. State the formula for the Nernst equation.

2. For the hypothetical cell depicted, assume that the membrane is only permeable to K^+. What is the membrane potential?

3. For the hypothetical cell depicted, assume that the membrane is only permeable to Na^+. What is the membrane potential?

10 K^+
100 Na^+
110 Cl^-

100 K^+
10 Na^+
110 Cl^-

Extracellular fluid

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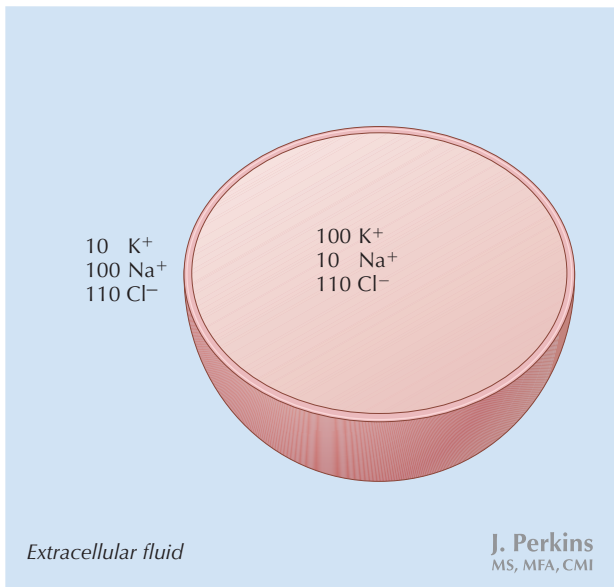
1. The Nernst equation is:

$$E_X = (RT/ZF)\ln([X]_o/[X]_i),$$

   where E_x is the Nernst potential (equilibrium potential) for ion X, $\ln([X]_o/[X]_i)$ is the natural log of the ratio of the concentration of ion X outside a compartment ($[X]_o$) to the concentration of the ion inside the compartment ($[X]_i$), R is the ideal gas constant, T is absolute temperature, Z is the charge of the ion, and F is Faraday's number. In biologic systems at 37°C, this equation can be simplified to:

$$E_X = (61\,mV/Z)\log([X]_o/[X]_i)$$

2. In the hypothetical situation in which only one ion is permeable in a system, the membrane potential will equal the Nernst potential for that ion. The Nernst potential for K^+ in this example (and thus the membrane potential) is:

$$E_{K+} = (61\,mV/1)\log([10]_o/[100]_i) = -61\ mV$$

3. Because only one ion (Na^+) is permeable, the membrane potential will equal the Nernst potential for Na^+:

$$E_{Na+} = (61\,mV/1)\log([100]_o/[10]_i) = 61\ mV$$

Nernst Potential   *See Figure 3.1*

1–3. Identify each ion.

4. Write and explain the Goldman-Hodgkin-Katz equation.
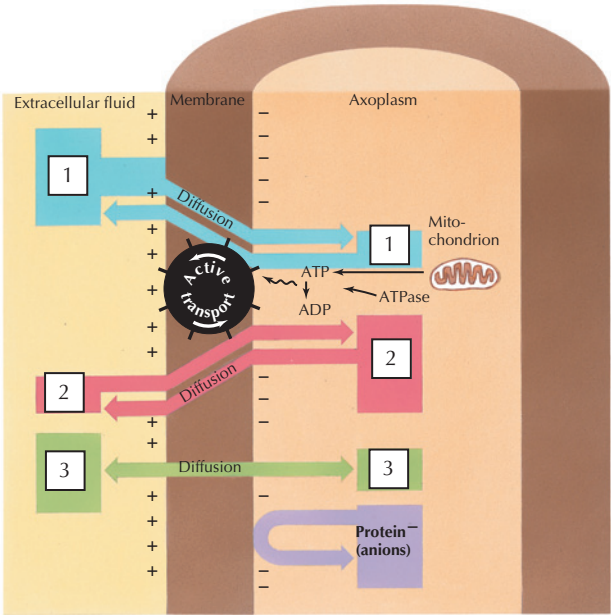
1. **Na$^+$**: Na$^+$ is constantly transported out of the cell by Na$^+$/K$^+$-ATPase.
2. **K$^+$**: K$^+$ is constantly transported into the cell by Na^{a+}/K$^+$-ATPase.
3. **Cl$^-$**: Cl$^-$ is not actively transported, and its concentrations reflect electrochemical equilibrium.
4.

$$V_m = \frac{RT}{F} \ \ln \frac{P_{K+}[K^+_o] + P_{Na+}[Na^+_o] + P_{Cl-}[Cl^-_i]}{P_{K+}[K^+_i] + P_{Na+}[Na^+_i] + P_{Cl-}[Cl^-_o]}$$

where V_m is the resting membrane potential, P_X is the membrane permeability to ion x, $[X]_i$ is the concentration of x inside the cell, $[X]_o$ is the concentration of x outside the cell, R is the ideal gas constant, T is absolute temperature, and F is Faraday's number.

Comment: Although cells contain many ions, this simplified G-H-K equation omits ions that are much less permeable to the cell membrane than K,$^+$ Na$^+$, and Cl$^-$ because their contribution to resting membrane potential is usually negligible. Note also that the concentration of Cl$^-$ inside appears in the top of the right-hand term and the concentration of Cl$^-$ outside appears in the bottom, whereas the situation for K$^+$ and Na$^+$ is opposite that of Cl$^-$, because of the difference in charge of these ions (negative versus positive).

The resting membrane potential for most cells is about -70, whereas in nerve cells, it is about -90 mV.

Identify 1–6.
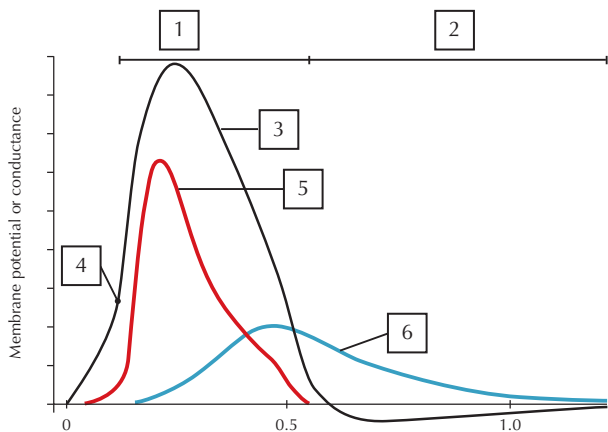
1. Absolute refractory period (the period during which another action potential cannot be elicited)
2. Relative refractory period (the period during which a second action potential can be elicited, but only by a larger than normal stimulus)
3. Action potential
4. Threshold potential; depolarization of the membrane to this level results in an action potential.
5. Na^+ conductance
6. K^+ conductance

Identify each structure.
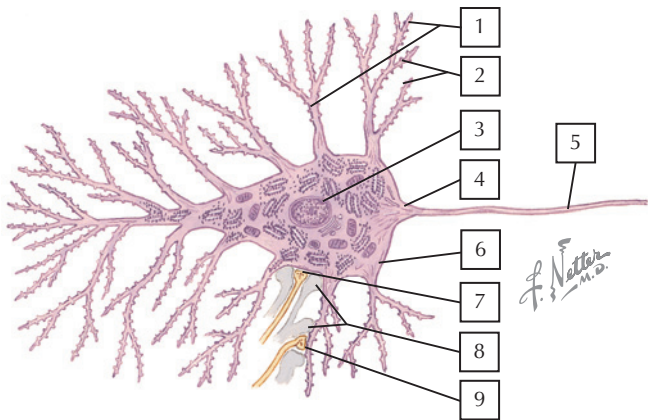
1. Dendrites
2. Dendritic spines (gemmules)
3. Nucleus
4. Axon hillock
5. Axon
6. Soma (cell body)
7. Axosomatic synapse
8. Glial (astrocyte) process
9. Axodendritic synapse

Explain how myelination affects each of these parameters in an axon:

1. **Membrane resistance**
2. **Membrane capacitance**
3. **Conduction velocity**
4. **Explain the term "saltatory conduction" in the context of the diagram.**

A. Unmyelinated fibers

B. Myelinated fibers

Axolemma

Axoplasm

Impulse

Node of Ranvier

Myelin sheath
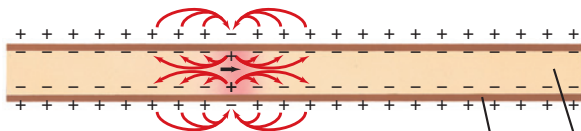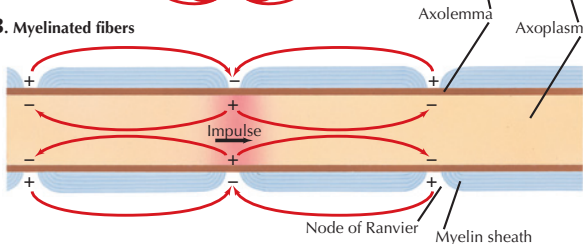
1. Membrane resistance (Rm) is increased by myelinization of axons.
2. Membrane capacitance is greatly reduced by myelinization.
3. Conduction velocity is increased by myelinization. With reduced capacitance and increased membrane resistance, the current travels through the interior of the axon, but not across the membrane in myelinated segments of the axon. The action potential jumps rapidly between the nodes of Ranvier (unmyelinated breaks in the myelin sheath at 1- to 2-mm intervals; compare parts A and B).
4. This process of conduction whereby the action potential jumps between nodes is known as *saltatory conduction* and allows rapid propagation of the action potential despite small axon diameter. Local currents generated at one node during depolarization result in depolarization at the next node, and the action potential skips along the axon, bypassing the highly insulated segments, from one node to the next.

Identify each structure.

Enlarged section of bouton
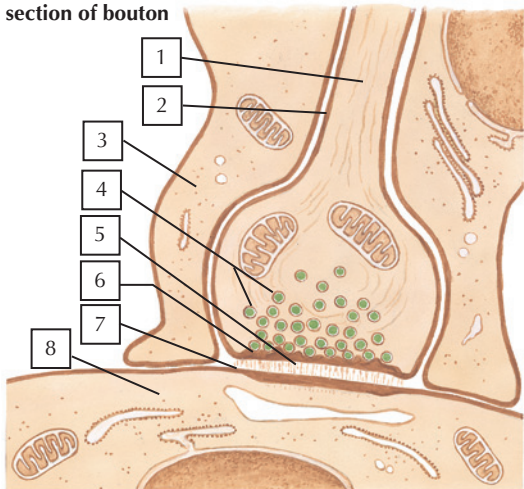
1. Axon (axoplasm)
2. Axolemma
3. Glial process
4. Synaptic vesicles
5. Synaptic cleft
6. Presynaptic membrane (densely staining)
7. Postsynaptic membrane (densely staining)
8. Postsynaptic cell

Describe the steps in chemical transmission that result in excitatory effects (1−3) or inhibitory effects (4−6) at the post-synaptic membrane.
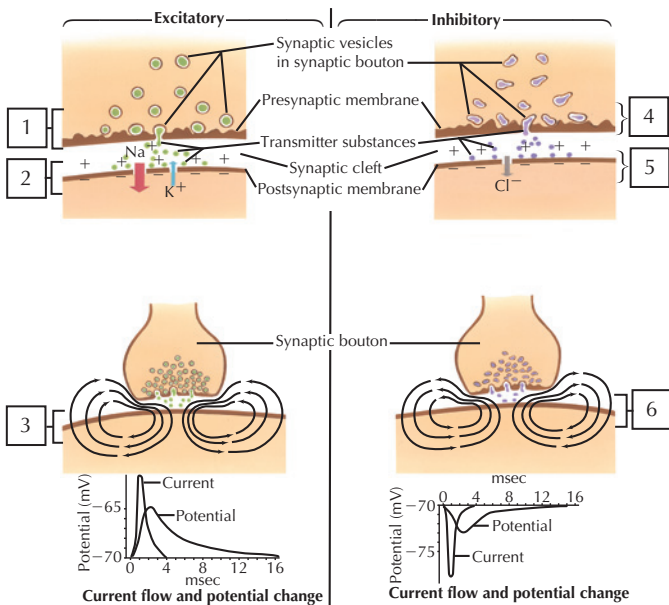
1. An impulse reaching the excitatory synaptic bouton results in release of a transmitter substance into the synaptic cleft.
2. Increased permeability of the postsynaptic membrane to Na^+ and K^+ results in greater Na^+ influx than K^+ efflux, because of the greater electrochemical gradient for Na^+ flux.
3. The resultant current flow is in a direction that tends to depolarize the postsynaptic cell. If threshold is reached, an action potential occurs in the postsynaptic cell.
4. An impulse reaching the inhibitory synaptic bouton results in release of a transmitter substance into the synaptic cleft.
5. Increased permeability of the postsynaptic membrane to Cl^- results in Cl^- influx.
6. The resultant current flow is in a direction that tends to hyperpolarize the postsynaptic cell. As a result, greater depolarization of the postsynaptic cell is required to reach threshold.

Comment: In the bottom left and right panels, current flow and potential change in the postsynaptic membrane are illustrated. An action potential occurs in a postsynaptic cell when local potentials, through spatial and temporal summation, reach the threshold for generation of an action potential.

Identify each structure.
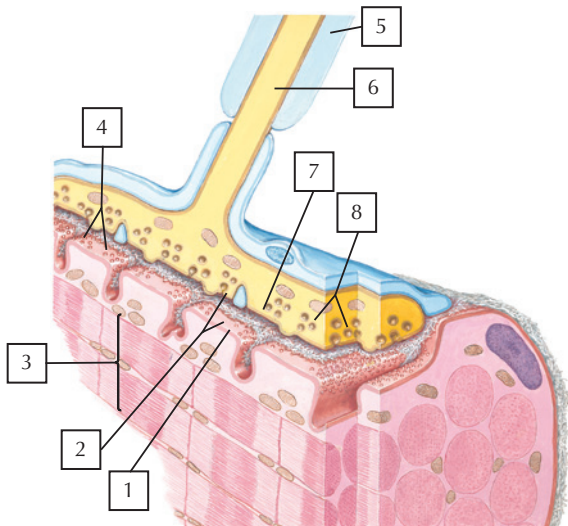
Structure of the Neuromuscular Junction

1. Postsynaptic membrane
2. Synaptic cleft
3. Myofibrils
4. Acetylcholine receptor sites
5. Myelin sheath
6. Axoplasm
7. Presynaptic membrane
8. Synaptic vesicles

Myelin sheath

Axoplasm

Acetylcholine receptor sites

Presynaptic membrane

Synaptic vesicles

f. Netter M.D.

Myofibrils

Synaptic cleft

Postsynaptic membrane

Structure of the Neuromuscular Junction *See Figure 3.10*
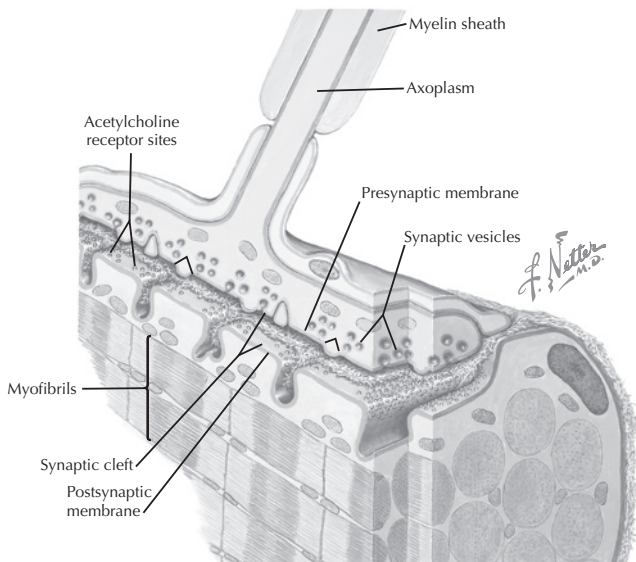
Identify each structure.

Segment of muscle fiber greatly enlarged to show sarcoplasmic structures and inclusions
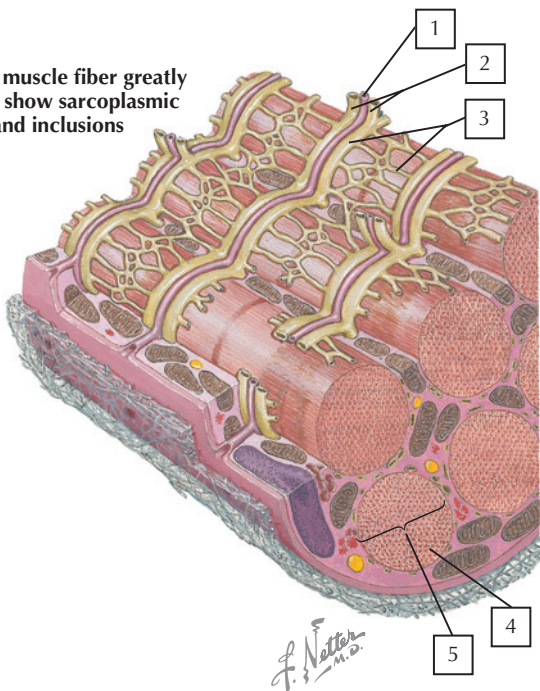
1. Transverse (T) tubule
2. Terminal cisternae
3. Sarcoplasmic reticulum
4. Myofilaments
5. Myofibril

Comment: The T tubules are invaginations of the muscle cell membrane. They form triads with two terminal cisternae of the sarcoplasmic reticulum.

List five major steps in excitation-contraction coupling in the context of this diagram, beginning with an axonal action potential.
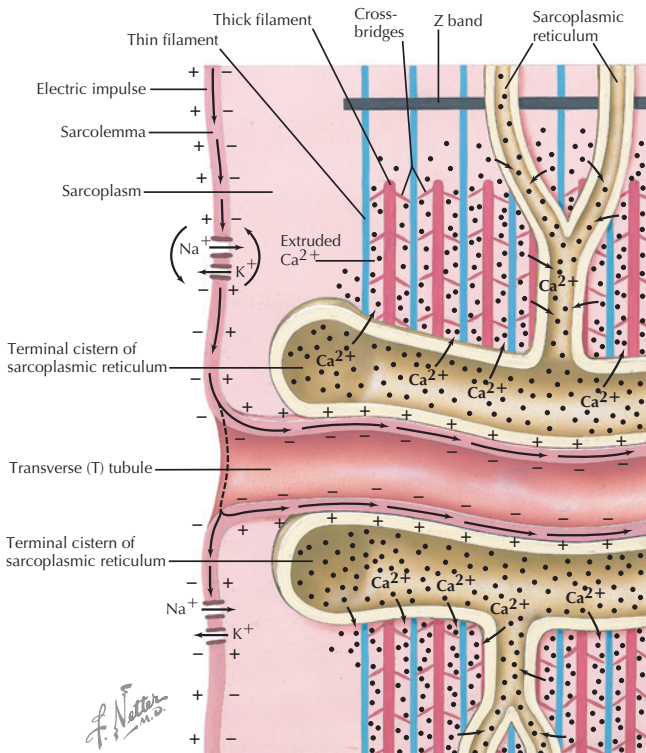
1. The axonal action potential in the motor neuron results in acetyl-choline release at the neuromuscular junction.
2. Acetylcholine is bound on the postsynaptic membrane (sarco-lemma), resulting in opening of a cation channel and influx of Na^+.
3. An action potential is produced and spreads into the transverse tubule, resulting in release of Ca^{2+} from the sarcoplasmic reticulum.
4. Cross-bridge formation is initiated, and muscle contraction is produced.
5. Ca^{2+} is resequestered into the sarcoplasmic reticulum by Ca^{2+}-ATPase, terminating contraction.

Identify each structure.
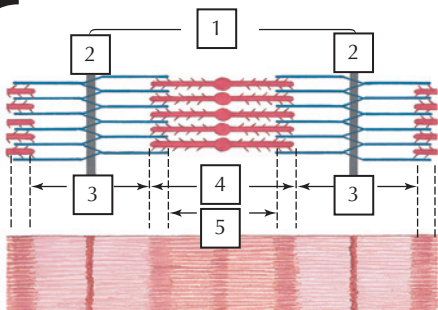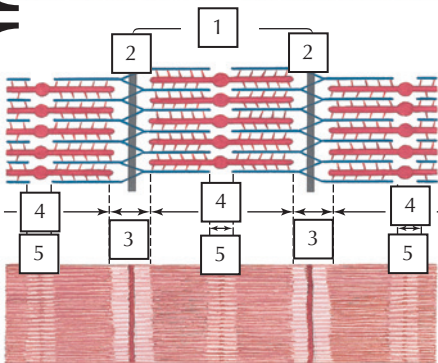
1. Sarcomere
2. Z band
3. I band
4. A band
5. H zone

Comment: During contraction of skeletal muscle, the thick myosin filaments that extend through the A band cyclically form cross-bridges with the thin actin filaments, resulting in sliding of the inter-digitated myosin and actin filaments and shortening of sarcomeres. As a result, Z bands move closer together, and I bands and H zones narrow.

Describe the biochemical and mechanical steps in actin and myosin crossbridge formation and recycling.
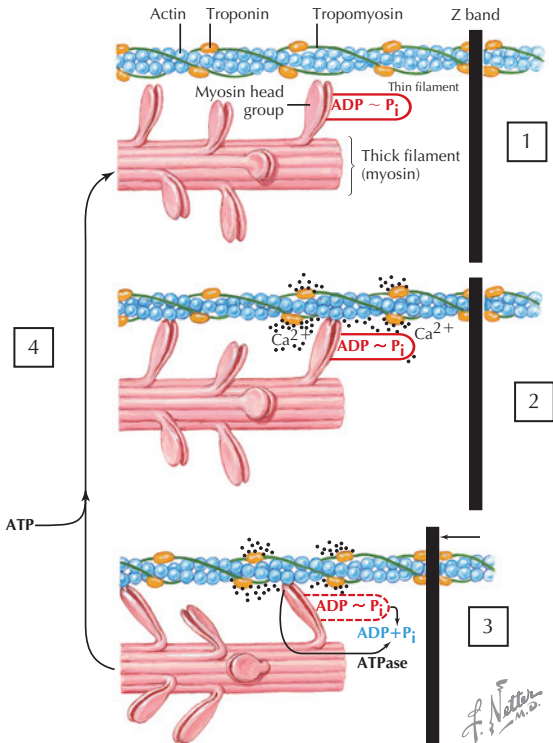
1. In resting muscle, adenosine triphosphate (ATP) is bound to myosin head groups and is partially hydrolyzed, producing a high-affinity binding site for actin. However, tropomyosin blocks the binding site for the myosin head group on actin, and the muscle remains relaxed.

2. Ca^{2+} is released from the sarcoplasmic reticulum in response to an action potential and binds to troponin. Tropomyosin is displaced from the myosin binding site of actin, allowing cross-bridge formation between the myosin head group and actin.

3. Adenosine diphosphate (ADP) and (P_i) are released from the myosin head group, and the head group flexes, producing sliding of the filaments and shortening of the sarcomere.

4. ATP binds to the myosin head group, releasing it from the actin. Partial hydrolysis of the ATP results in recocking of the head group and produces a high-affinity actin binding site. As long as Ca^{2+} remains elevated, the cross-bridge will reform, and the cycle will continue (1), producing further shortening; otherwise, the muscle will relax.

1–7. Identify the major regulatory ions, molecules or enzymes involved in excitation-contraction coupling of smooth muscle.
   8. Explain their role in this process.

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Excitation-Contraction Coupling of Smooth Muscle
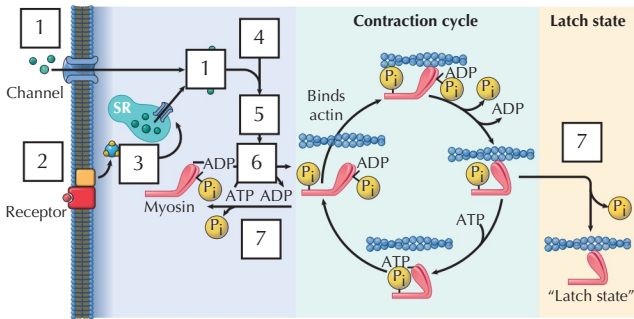
1. Ca^{2+}
2. Phospholipase C
3. Inositol trisphosphate (IP_3)
4. Calmodulin
5. Ca-calmodulin
6. Myosin kinase
7. Myosin phosphatase
8. Intracellular free Ca^{2+} (1) can be elevated by depolarization of the cell membrane and opening of Ca^{2+} channels. It can also be elevated by binding of a ligand to a membrane receptor. In the latter case, this activates phospholipase C (2), which cleaves phosphatidyl inositol to produce IP_3 (3); IP_3 binds to the sarcoplasmic reticulum causing release of stored Ca^{2+}. In either case, Ca^{2+} binds to the calcium binding protein calmodulin (4), forming Ca-calmodulin (5). The Ca-calmodulin activates myosin kinase (6), initiating cross-bridge formation and the contraction cycle, which continues as long as Ca^{2+} is elevated. Otherwise, dephosphorylation of myosin by myosin phosphatase (7) ends the cycle. The latch state occurs when myosin is dephosphorylated while bound to actin, resulting in sustained contraction without requirement for additional ATP hydrolysis.

Identify each structure.

Cardiac Muscle Structure
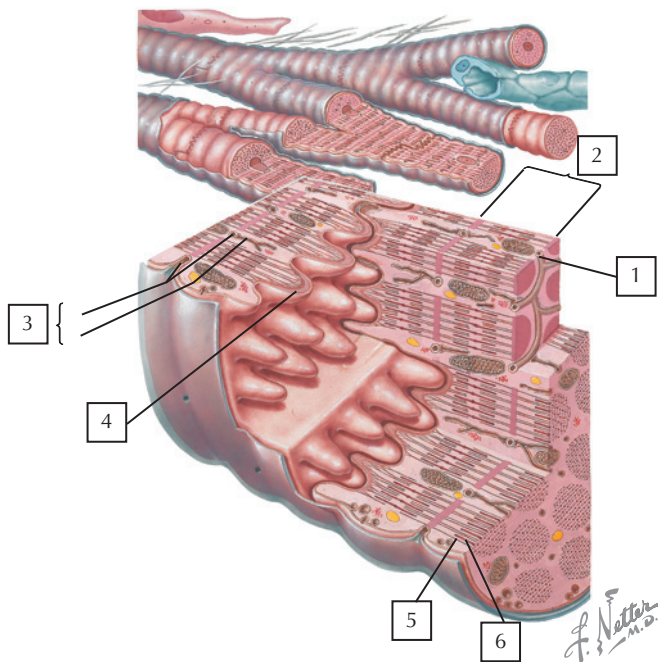
1. T tubule
2. Sarcomere
3. Sarcoplasmic reticulum
4. Intercalated disk
5. Thin filament (mainly actin)
6. Thick filament (myosin)

Identify each structure.

Left lateral view
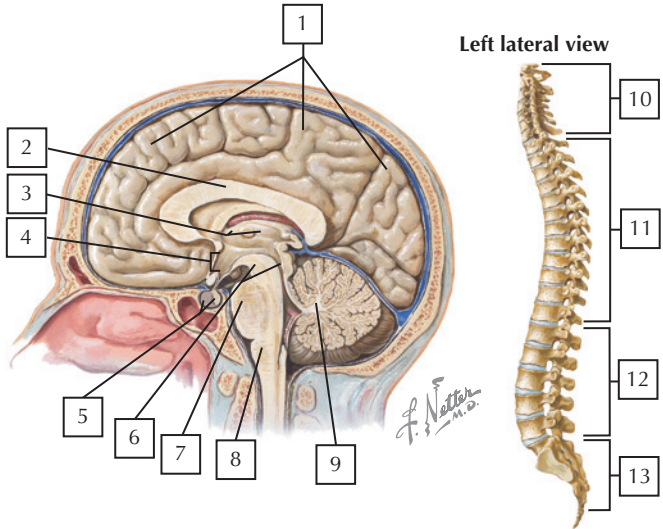
Major Parts of the Central Nervous System and the Vertebral Column

1. Cerebral cortex
2. Corpus callosum
3. Thalamus
4. Hypothalamic area
5. Pituitary gland (anterior and posterior)
6. Midbrain
7. Pons
8. Medulla oblongata
9. Cerebellum
10. Cervical vertebrae, C1–C7
11. Thoracic vertebrae, T1–T12
12. Lumbar vertebrae, L1–L5
13. Sacral vertebrae, S1–S5

Major Parts of the Central Nervous System and the Vertebral Column   *See Figure 4.1*

List the major functions of each of the hypothalamic areas.

Major functions of the hypothalamus	
Hypothalamic area	**Major functions**
Preoptic and anterior	?
Posterior	?
Lateral	?
Ventromedial	?
Supraoptic (subfornical organ and organum vasculosum)	?
Paraventricular	?
Periventricular	?

MAJOR FUNCTIONS OF THE HYPOTHALAMUS

HYPOTHALAMIC AREA	MAJOR FUNCTIONS*
Preoptic and anterior	Heat loss center: cutaneous vasodilation and sweating
Posterior	Heat conservation center: cutaneous vasoconstriction and shivering
Lateral	Feeding center: eating behavior
Ventromedial	Satiety center: inhibits eating behavior
Supraoptic (subfornical organ and organum vasculosum)	Antidiuretic hormone (ADH) and oxytocin secretion
Paraventricular	ADH and oxytocin secretion
Periventricular	Secretion of releasing hormones for the anterior pituitary

*Stimulation of the center causes the responses listed.
Reprinted with permission from Hansen J: Netter's Atlas of Human Physiology.
Philadelphia, Elsevier, 2002.

1–10. Identify each structure.

11. Explain the general organization of the somatic component of the peripheral nervous system.

Somatic Component of the Peripheral Nervous System
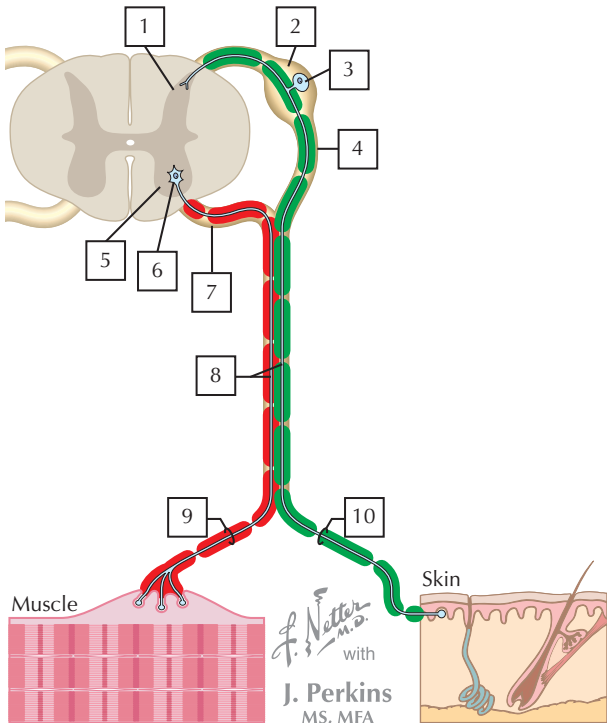
1. Posterior horn of the spinal cord (gray matter)
2. Dorsal root ganglion
3. Sensory neuron cell body
4. Dorsal root
5. Anterior horn of the spinal cord (gray matter)
6. Motor neuron cell body
7. Ventral root
8. Axons of motor (left) and sensory (right) neurons
9. Motor neuron
10. Sensory neuron
11. The peripheral nervous system includes somatic and autonomic components and contains motor nerves and sensory nerves innervating the skin and muscles. The soma (cell bodies) of motor nerves and sensory nerves are located in the gray matter of the anterior horn of the spinal cord and the dorsal root ganglia, respectively.

1. Identify this cutaneous receptor. Describe its characteristics, including location and the type of stimulus transduced.
2. Identify these structures. What type of stimuli do they detect?
3. Identify this structure. What type of receptor is associated with it? Describe the characteristics of the receptor and the type of stimulus transduced.
4. Identify this cutaneous receptor. Describe its characteristics, including the type of stimulus transduced.
5. Identify the receptor in the bottom panel. Describe the characteristics of the receptor and the type of stimulus transduced.
6. What are Ruffini's corpuscles (not illustrated)? What type of stimuli do they respond to?

Epidermis

Dermal papilla (of papillary layer)

Reticular layer

Dermis

Subcutaneous tissue
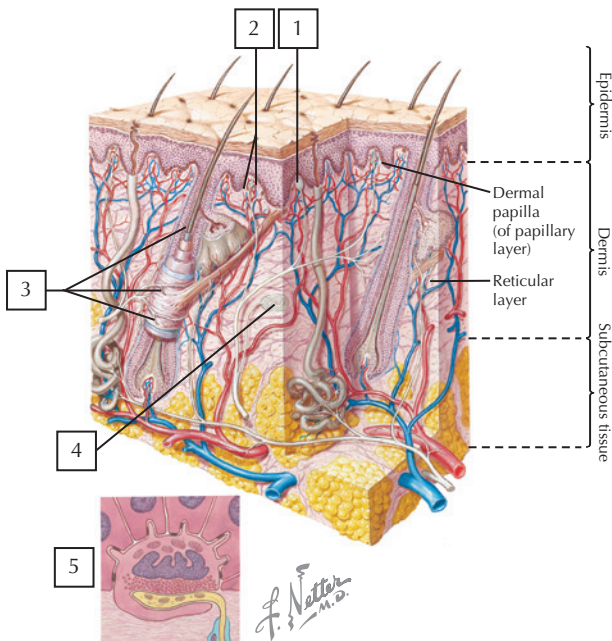
1. Meissner's corpuscle, located in the dermal papillae, especially in fingertips, palms, soles, lips, face, tongue, and genital skin (non-hairy skin). These are rapidly adapting receptors with small receptive fields that allow point discrimination and detection of low-frequency stimuli such as flutter.
2. Free nerve endings. Temperature and painful stimuli are detected by these nociceptors.
3. Hair follicle. Associated hair follicle receptors consist of nerve endings wrapped at the base of the follicle. The receptors are rapidly adapting and detect movement across the skin.
4. Pacinian corpuscle. These are rapidly adapting mechanoreceptors. The lamellated capsules allow response to rapid changes in pressure and vibration.
5. Merkel's disks are slowly adapting receptors with small receptive fields; they respond to pressure and touch, especially to indentation of the skin.
6. Ruffini's corpuscles (not illustrated) are mechanoreceptors located in the dermis and joints. These slowly adapting receptors respond to stretch.

Identify each cell type in the section through the retina. For the cells that act as photoreceptors, identify their roles in light perception.

A. Eyeball
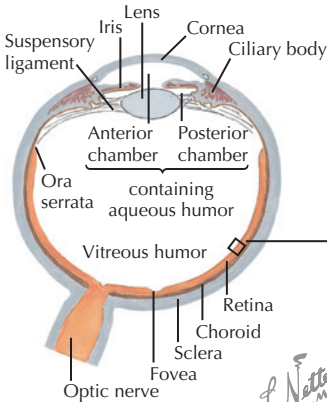
B. Section through retina

Visual Receptors
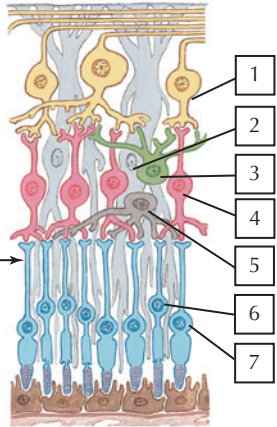
1. Ganglion cell
2. Müller cell (supporting glial cell)
3. Amacrine cell
4. Bipolar cell
5. Horizontal cell
6. Rod; rods are sensitive photoreceptors adapted to respond to light at low intensity.
7. Cone; color perception is mainly mediated by cones.

Comment: Light reception by photoreceptors (rods and cones) ultimately results in reduced Na^+ permeability and hyperpolarization of the photoreceptor membrane, which inhibits release of either inhibitory or excitatory neurotransmitters at synapses between photoreceptors and bipolar and horizontal cells. Signals generated by this system are ultimately transmitted by ganglion cells, whose axons form the optic nerves.

1. **Describe the pathway whereby sound waves reach the inner ear.**

2. **Describe how vibration caused by sound waves is transduced into neural signals within the inner ear in the context of this illustration.**

A. Membranous labyrinth within bony labyrinth (path of sound waves)

- Cochlear nerve
- Utricle
- Saccule
- Semicircular canals
- Scala vestibuli
- Cochlear duct (scala media)
- Scala tympani
- Round window
- Oval window and stapes
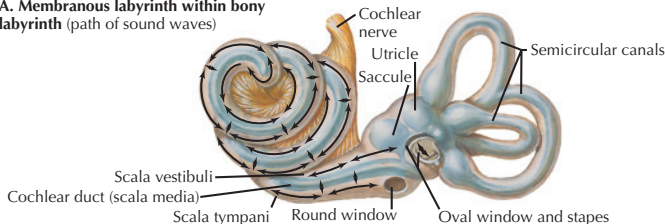
B. Section through turn of cochlea

- Scala vestibuli (perilymph); weakly positive
- +80 mV
- Vestibular (Reissner's) membrane
- Cochlear duct (scala media; endolymph)
- Tectorial membrane
- Spiral ligament
- Bone
- Efferent nerve fibers
- Scala tympani (perilymph); 0 mV
- Outer hair cells; −60 mV
- Basilar membrane
- Inner hair cell; −60 mV
- Afferent nerve fibers
- Spiral ganglion

C. Spiral organ of Corti

- Hair cells
- Inner   Outer
- Tectorial membrane
- Stereocilia
- Rods and tunnel of Corti
- Basilar membrane
- Supporting cells
- Spiral lamina
- Afferent nerve fibers
- Efferent nerve fibers
- Spiral ganglion

1. Before reaching the inner ear, sound waves reaching the external ear (auricle) are directed through the external acoustic meatus to the tympanic membrane, causing it to vibrate. This vibration is transmitted by bones of the air-filled middle ear (malleus, incus, stapes) to the fluid-filled inner ear via the oval window.

2. Sound waves reaching the inner ear travel through the membranous labyrinth of the cochlea (**A**), which consists of three ducts (**B**). Vibration caused by sound results in periodic displacement of the basilar membrane relative to the tectorial membrane, causing bending of stereocilia and depolarizing hair cells within the spiral organ of Corti, resulting in transduction of sound into neural signals (**C**).

Identify each structure and explain its role in balance and equilibrium.

Membranous labyrinth
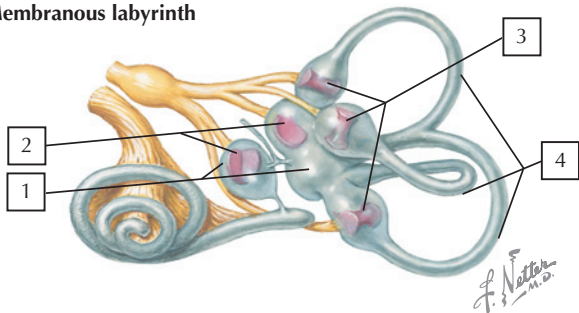
1. Saccule (*top branch*) and utricle (*bottom branch*). These otolithic organs detect linear acceleration of the head.
2. Maculae within the otolithic organs. The maculae, like the cristae, contain sensory hair cells; in the maculae, they respond to endolymph movement during linear acceleration of the head.
3. Cristae within ampullae of the semicircular canals. Cristae contain sensory hair cells that respond to endolymph movement during angular acceleration.
4. Semicircular canals (superior, horizontal, and posterior); respond to angular acceleration of the head.

1–4. Identify each structure.

5. Name the five known types of taste receptors.

B. Section through vallate papilla

A. Tongue

Foliate papillae

Fungiform papillae

Taste buds

Duct of gustatory (Ebner's) gland

Vallate papillae

C. Taste bud

Epithelium

Basement membrane

1

2

3

4
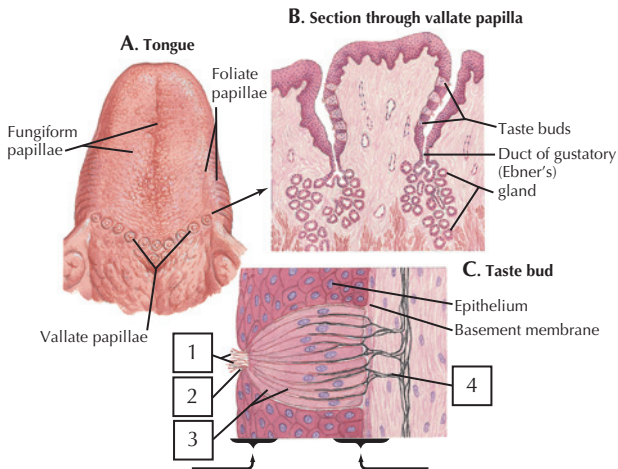
1. Microvilli
2. Taste pore
3. Taste cells
4. Nerve fibers
5. Sweet, salty, sour, bitter, and umami (savory)

1–7. **Identify each structure.**
   8. **Identify the specific location of the olfactory receptors among these structures.**
   9. **Explain how smell is transduced into neural signals.**

A. **Distribution of olfactory epithelium** (*blue* area)

Olfactory bulb

Cribriform plate of ethmoid bone

Lateral nasal wall

Septum
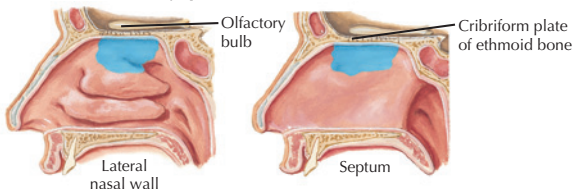
B. **Schema of section through olfactory mucosa**

1
2
3
4
5
6
7
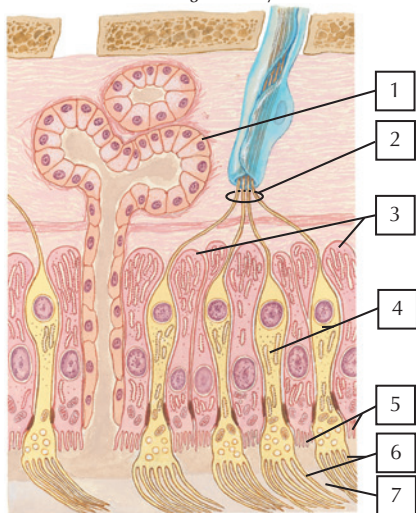
1. Olfactory gland
2. Olfactory axons
3. Sustentacular cells
4. Olfactory cells
5. Villi
6. Cilia
7. Mucus
8. Olfactory receptors are located on the cilia of the olfactory cells.
9. These G-protein-coupled receptors bind odorants. Binding activates signal transduction mechanisms resulting in opening of ion channels and depolarization. These olfactory cells are afferent neurons, which send signals via their axons to the olfactory bulb.

Comment: The six basic types of odors we sense are camphor, floral, ethereal, musky, putrid, and pungent. An olfactory receptor may bind a range of odorant molecules, and an odorant may be bound by more than one receptor type.

Identify each neuron and the function of each.

Efferent fibers
Afferent fibers
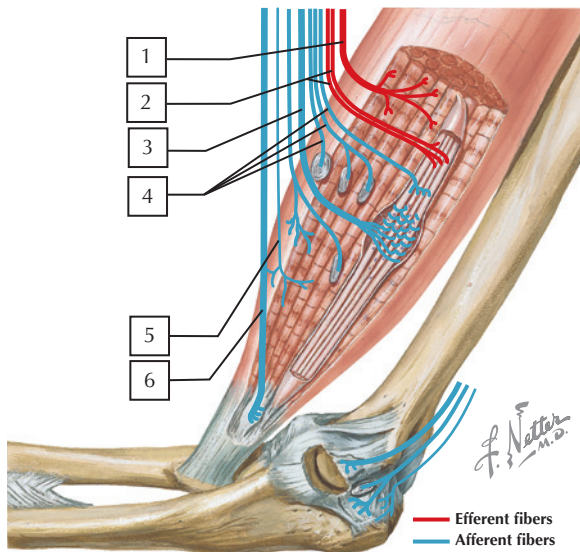
1. α-Motor neurons; contract muscle through innervation of extra-fusal fibers
2. γ-Motor neurons; innervate intrafusal striated muscle endplates
3. Fibers from annulospiral endings; function in proprioception
4. Fibers from flower spray endings and from paciniform and pacinian corpuscles; function in proprioception and detect pressure, respectively
5. Fibers from free nerve endings; detect pain
6. Fibers from Golgi tendon organs; function in proprioception

Identify the spinal reflexes associated with the illustrated pathways. Explain the physiology of the reflex.

From extensor spindle receptor (Ia, II fibers)

Axosomatic or axodendritic inhibitory synapse

Excitatory synapse

To extensors

To flexors

1

From extensor tendon organ (Ib fibers)

Inhibitory synapse

Excitatory synapse

To extensors

To flexors

2

Contralateral extension

Nociceptive fibers

Ipsilateral flexion

Inhibitory synapse

Excitatory synapse

To extensors

To flexors

Excitatory synapse

Inhibitory synapse

To extensors

To flexors

3

1. **Stretch reflex.** Afferent nerves synapse directly with α-motor neurons in the spinal cord, making this a monosynaptic reflex. An example is the knee jerk reflex. A tap on the patellar tendon stretches muscle spindles within the quadriceps; type Ia afferent nerves conduct the signal to the spinal cord, where they synapse directly to α-motor neurons, which conduct the signal back to the quadriceps producing contraction. Simultaneously, activation of interneurons results in relaxation of opposing muscles.

2. **Golgi tendon reflex.** It is a bisynaptic reflex and constitutes a mechanism for preventing muscle damage due to excessive tension. Stretch of Golgi tendon organs activates type Ib afferent sensory nerves, which synapse in the spine with interneurons that subsequently inhibit α-motor neurons, causing relaxation. Simultaneously, antagonistic muscles contract.

3. **Flexor withdrawal reflex**. This reflex occurs in response to pain or other noxious stimuli. Afferent signals are conducted through sensory nerves to the spine, where activation of multiple interneurons produces simultaneous flexion and relaxation of the appropriate muscles to withdraw the limb.

Identify each structure as you trace the descending pathway for voluntary motor control through the corticospinal (pyramidal) tract.

1

2

Midbrain

3

Pons

4

Medulla

5

Medulla

JOHN A.CRAIG__AD

Decussation of pyramids

8

Above mid-thoracic level

Motor endplate

Spinal cord

7

6

Below mid-thoracic level

Motor endplate

8

Corticospinal Tract
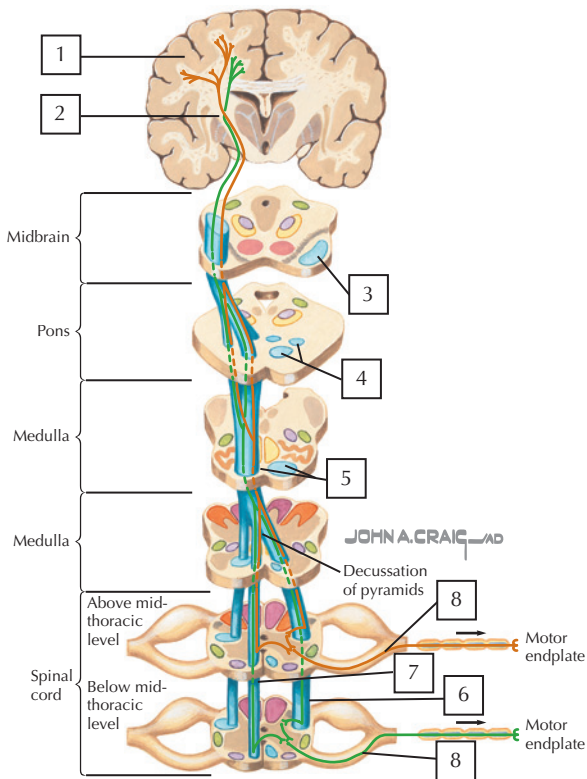
1. Fibers originate in the **motor cortex.**
2. Fibers descend via the posterior limb of the **internal capsule.**
3. Fibers reach the **basis pedunculi** of the midbrain.
4. Longitudinal bundles branch upon entering the **basis pontis.**
5. Bundles rejoin to enter the **pyramids** of the medulla.
6. At the lower medulla, the bulk of fibers cross the median plane to form the **lateral corticospinal tract**, whereas some fibers continue downward in the ipsilateral lateral corticospinal tract.
7. Other fibers descend via the ipsilateral **anterior corticospinal tract**.
8. Synapse occurs at the spinal level, and **secondary motor neurons** innervate muscles at the motor endplates.

Identify the three functional subdivisions of the cerebellum.
Explain the role of each in the cerebellum's accessory role
to the motor cortex in regulation of posture and balance,
movement, and planning and initiation of movement.

1 {
Lingula
Flocculus
Nodule

2 {
Uvula
Pyramid
Vermis

3 {
Middle vermis
Hemisphere

Schema of
theoretical
"unfolding"
of cerebellar
surface in
derivation of
above diagram

1. The **archicerebellum** is composed of the lingula, flocculus, and nodule. It is involved in regulation of posture and balance and control of eye and head movement. It receives afferent signals from the vestibular apparatus and sends efferent signals through the relevant descending pathways.

2. The **paleocerebellum** (spinocerebellum) is composed of the uvula, pyramid, and vermis. It is involved in regulation of proximal limb movement. Afferent sensory signals regarding position and movement of limbs are used to fine-tune limb motion through relevant descending pathways.

3. The **neocerebellum** (pontocerebellum) is composed of the middle vermis and hemisphere. It has a coordinating role in the regulation of distal limb movement. It receives input from the cerebral cortex (via the pontine nuclei) and aids in the planning and initiation of motor activity through its efferent fibers.

Comment: The cerebellum has also been conceptualized as anterior, middle, and flocculonodular lobes. These subdivisions cannot be directly equated to the subdivisions described above.

Complete the table by describing the location of preganglionic nerve cell bodies, location of ganglia, and neurotransmitters of the parasympathetic and sympathetic nervous systems.

General characteristics of the parasympathetic and sympathetic nervous systems		
Characteristic	**Parasympathetic nervous system**	**Sympathetic nervous system**
Location of preganglionic nerve cell bodies	?	?
Location of ganglia	?	?
Neurotransmitter of preganglionic neurons	?	?
Major neurotransmitter released by postganglionic neuron	?	?

GENERAL CHARACTERISTICS OF THE PARASYMPATHETIC AND SYMPATHETIC NERVOUS SYSTEMS

CHARACTERISTIC	PARASYMPATHETIC NERVOUS SYSTEM	SYMPATHETIC NERVOUS SYSTEM
Location of preganglionic nerve cell bodies	Brainstem (nuclei of cranial nerves II, VII, IX, and X) or sacral spinal cord (S2–S4; sacral parasympathetic nucleus)	Intermediolateral and intermediomedial cell columns of the thoracolumbar spinal cord (T1–L3)
Location of ganglia	In or adjacent to target organs	Paravertebral and prevertebral
Neurotransmitter of preganglionic neurons	Acetylcholine (acts at nicotinic receptors)	Acetylcholine (acts at nicotinic receptors)
Major neurotransmitter released by postganglionic neuron	Acetylcholine (acts at muscarinic receptors)	Norepinephrine (acts at $\alpha-$ and β-adrenergic receptors)

Identify the action at each site.

Actions of the autonomic nervous system		
	Parasympathetic nervous system	**Sympathetic nervous system**
Site of action	**Action**	**Action**
Cardiac pacemaker	?	?
Cardiac muscle	?	?
Cardiac AV node	?	?
Vascular smooth muscle	?	?
Gastrointestinal smooth muscle	?	?
Gastric parietal cells	?	?
Pancreas	?	?
Lung, bronchial smooth muscle	?	?
Sweat glands	?	?
Male reproductive system	?	?
Female reproductive system	?	?
Pupil	?	?

ACTIONS OF THE AUTONOMIC NERVOUS SYSTEM

SITE OF ACTION	PARASYMPATHETIC NERVOUS SYSTEM	SYMPATHETIC NERVOUS SYSTEM
	ACTION	ACTION
Cardiac pacemaker	Decreases heart rate	Increases heart rate
Cardiac muscle	Decreases contractility of atria; limited effects on ventricles	Increases contractility
Cardiac atrioventricular (AV) node	Decreases conduction velocity	Increases conduction velocity
Vascular smooth muscle	Indirect vasodilation (genital organs and lower gastrointestinal tract only) by nitric oxide released from endothelium	α_1 Constriction (predominant effect in most vascular beds) β_2 Vasodilation
Gastrointestinal smooth muscle	Increases motility	Reduces motility
	Relaxes sphincters	Constricts sphincters
Gastric parietal cells	Acid secretion	
Pancreas	Exocrine secretion	
Lung, bronchial smooth muscle	Constricts	Dilates
Sweat glands		Secretion
Male reproductive system	Erection	Emission during orgasm
Female reproductive system	Vasocongestion, vaginal lubrication	Orgasmic smooth muscle constriction
Pupil	Miosis (constriction)	Mydriasis (dilation)

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What are the approximate resting systolic and diastolic blood pressures (mm Hg) at points 1, 2, 3 and 4 for a normal, healthy person?

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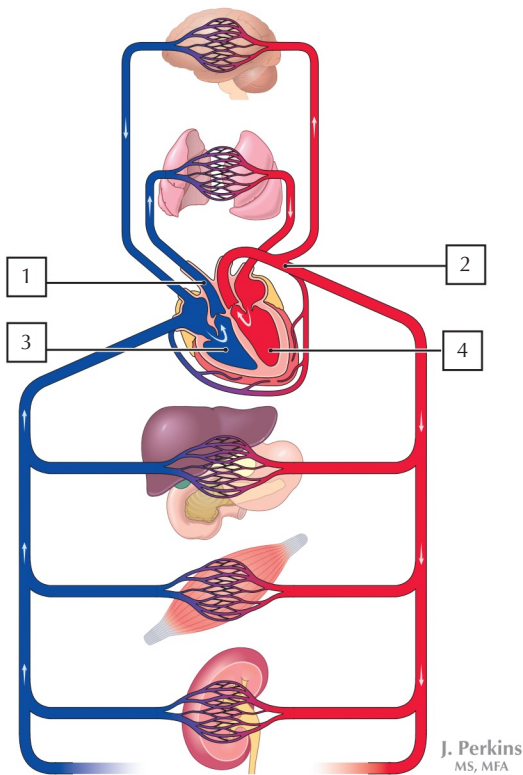
1. Pulmonary artery pressure, 25/10 mm Hg
2. Aortic pressure, 120/80 mm Hg
3. Right ventricular pressure, 25/0 mm Hg
4. Left ventricular pressure, 120/0 mm Hg

Comment: The left ventricle generates high pressure (120 mm Hg) during systole, resulting in flow of blood into the aorta. During diastole, when the aortic valve is closed, pressure is low (near 0 mm Hg), allowing return of blood from the pulmonary circulation, thus resulting in filling of the ventricle. The right ventricular pressure follows a similar pattern, but with lower systolic pressure (25 mm Hg) required for pumping of blood into the pulmonary circulation.

1. **What is cardiac output and its normal, resting value?**

2. **Give the approximate percentage of cardiac output received by the organs at A through G.**

A — Brain
B — Lungs
C — Coronary circulation
D — Liver and gastro-intestinal tract
E — Skeletal muscle
F — Kidney
G — Skin and other organs
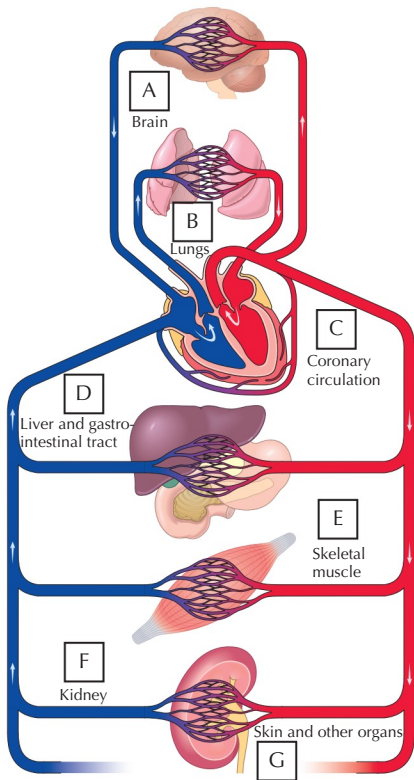
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Distribution of Cardiac Output

1. Cardiac output (CO) is the flow from one side of the heart (flow from the right ventricle equals flow from the left ventricle). At rest, normal CO is about 5 L/min.
2. The approximate percentages of CO delivered to various organs are:
   A. Brain, 13%
   B. Lungs, 100%
   C. Coronary circulation, 4%
   D. Liver and gastrointestinal tract, 24%
   E. Skeletal muscle, 21%
   F. Kidneys, 20%
   G. Skin and other organs, 18%

Comments: These values are for the resting state and are altered with exercise. The lungs always receive 100% of the right ventricular output.

**Identify the chambers and valves of the heart
and note whether the blood coursing through the
chambers is oxygenated or deoxygenated.**
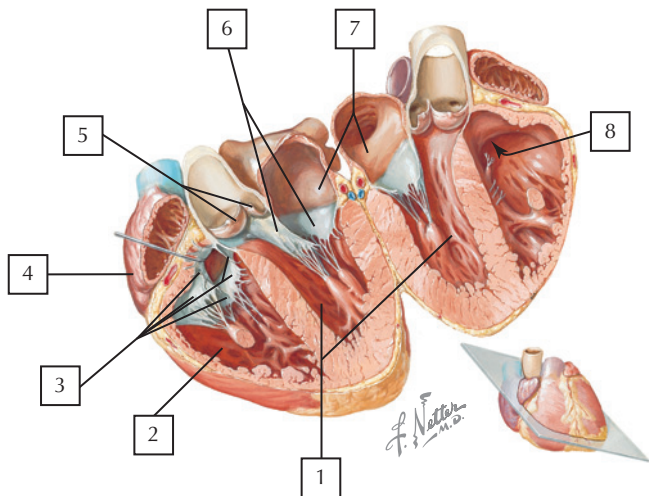
1. Left ventricle, oxygenated
2. Right ventricle, deoxygenated
3. Tricuspid valve
4. Right atrium, deoxygenated
5. Aortic valve
6. Mitral valve
7. Left atrium, oxygenated
8. Outflow track to the pulmonic valve

Comment: Deoxygenated blood returns from the systemic circulation to the right atrium, flowing into the right ventricle during diastole. The right ventricle pumps blood into the pulmonary circulation. Oxygenated blood returns from the lungs to the left atrium, flowing into the left ventricle during diastole. The left ventricle pumps this oxygenated blood into the systemic circulation.

The pulmonic valve is not visible in this illustration.

Identify the components of the cardiac conduction system and describe the sequence of conduction through these structures.
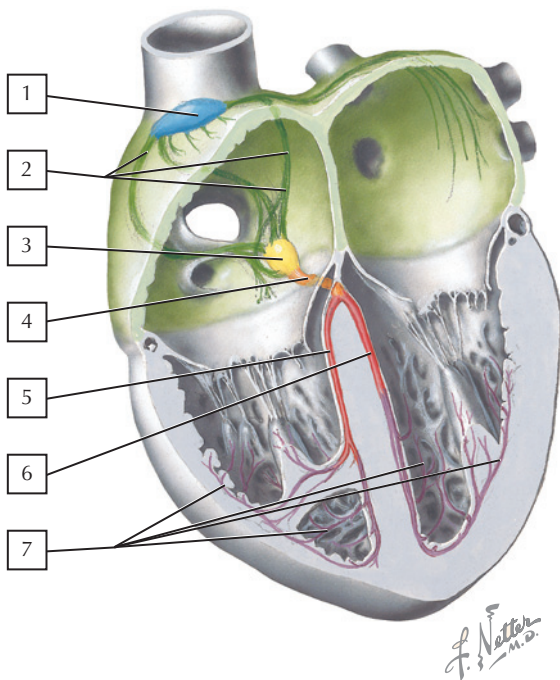
1. Sinoatrial (SA) node
2. Internodal tracts
3. Atrioventricular (AV) node
4. Common AV bundle (bundle of His)
5. Right bundle branch
6. Left bundle branch
7. Purkinje fibers

Comment: The SA node is the pacemaker of the heart. Depolarization of this node results in subsequent conduction of the wave of depolarization along internodal tracts to the AV node. Conduction through the AV node is slow, allowing a pause between depolarization and contraction of the atria, and the subsequent depolarization and contraction of the ventricles. After the signal is conducted through the AV node, it is propagated rapidly along the bundle of His, to the bundle branches and Purkinje fibers, resulting in depolarization and contraction of the ventricular myocardium.

Identify the three ionic currents and describe their contribution to the action potential illustrated in the top tracing.
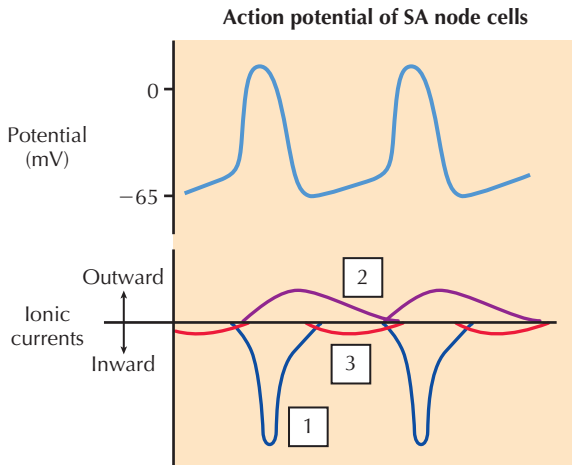
Action potential of SA node cells

1. Ionic current i_{Ca2+} is an inward calcium current. The upstroke of the action potential is caused by opening of T-type and L-type Ca^{2+} channels and the resultant calcium current. Closing of these channels, along with increased conductance of K^+, causes repolarization.

2. Ionic current i_{K+} is an outward potassium current; an increase in this current is responsible for repolarization of the SA node cells along with reduced inward Ca^{2+} current.

3. Ionic current i_f is an inward current mainly carried by Na^+ and is responsible for the gradual, spontaneous depolarization of the AV node, leading to threshold and generation of an action potential. Influx of Ca^{2+} and reduced activity of the inward potassium current also contribute to spontaneous depolarization.

Identify the three ionic currents and describe their contribution to the action potential illustrated in the top tracing.

Action potential of ventricular myocytes

1. Ionic current i_{Na+} is an inward sodium current. The phase 0 up-stroke of the action potential (*top panel*) is caused by opening of sodium channels when ventricular cells reach threshold. Inactivation of these channels contributes to the phase 1 rapid repolarization to the plateau (phase 2).

2. Ionic current i_{K+} is an outward potassium current; this current is reduced during much of the action potential. Increased outward potassium current leads to the rapid repolarization of phase 3 (*top panel*).

3. Ionic current i_{Ca2+} is an inward calcium current. Opening of voltage-sensitive slow L-type Ca^{2+} channels and the resulting inward calcium current are responsible for the phase 2 plateau (*top panel*). Gradual inactivation of these channels leads to activation of K^+ channels and therefore rapid repolarization owing to the increased outward potassium current.

Name each pressure in this tracing of arterial pressure and determine the value for each.

J. Perkins
MS, MFA
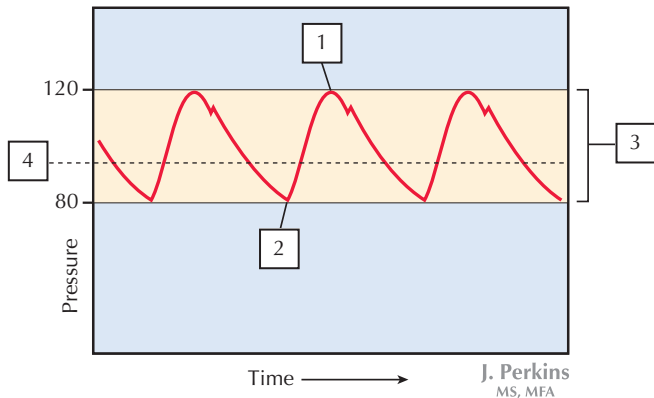
1. Systolic pressure, 120 mm Hg
2. Diastolic pressure, 80 mm Hg
3. Pulse pressure, 40 mm Hg, calculated as systolic pressure minus diastolic pressure
4. Mean arterial pressure (MAP), 93 mm Hg, calculated by the formula:

$$MAP = \text{diastolic pressure} + \tfrac{1}{3} \text{ pulse pressure}$$

Comment: The formula, MAP = diastolic pressure + $\tfrac{1}{3}$ pulse pressure, yields an approximation of MAP at normal heart rates, when the duration of diastole is about twice that of systole.

Identify the likely site of measurement of pressure waves shown based on the systolic and diastolic pressure and wave form, assuming that these tracings were obtained in a normal, resting subject.

J. Perkins
MS, MFA, CMI

1. Left ventricular pressure, 120/0 mm Hg
2. Aortic pressure, 120/80 mm Hg
3. Right ventricular pressure, 25/0 mm Hg

1. Give the formula for flow (Q) based on Poiseuille's law.

2. Give a simplified formula for the relationship among flow (Q), pressure, and resistance.
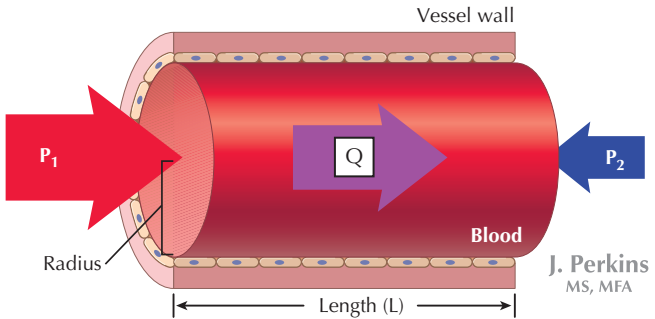
1.

$$Q = \frac{\Delta P \Pi r^4}{\eta 8 L}$$

where P is pressure, r is radius of the tube, η is viscosity of the fluid, and L is length of the tube.

2. $Q = (P_1 - P_2)/R$ or $Q = (\Delta P)/R$

Predict the effect on flow (Q) for each of these changes, assuming that other parameters are held constant:

1. **A doubling of the pressure gradient, ΔP**
2. **A doubling of the length of the tube, L**
3. **A doubling of the radius of the tube, r**

Vessel wall

P_1

$\Delta P = P_1 - P_2$

P_2

Blood

Radius

J. Perkins
MS, MFA
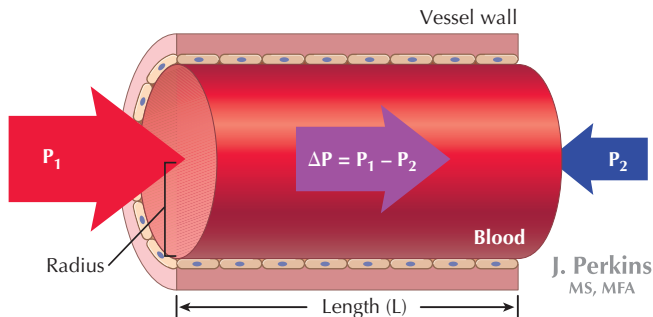
Length (L)

1. Q will double with a doubling of the pressure gradient.
2. Q will be halved by a doubling of the length of the tube.
3. Q will be increased 16-fold by a doubling of the radius of the tube.

Comment: The effect on flow of a change in the pressure gradient, tube length, or tube radius can be calculated on the basis of Poiseuille's law:

$$Q = \frac{\Delta P \Pi r^4}{\eta 8L}$$

A doubling of the viscosity of the fluid will cause a halving of flow.

1. What is the relative velocity of fluid in the large tube (V_1) compared with the velocity of fluid in one of the small tubes (V_2), assuming that each of the nine small tubes has a cross sectional area equal to one ninth the area of the large tube?

2. Give the appropriate equation for determining the answer.

A

B
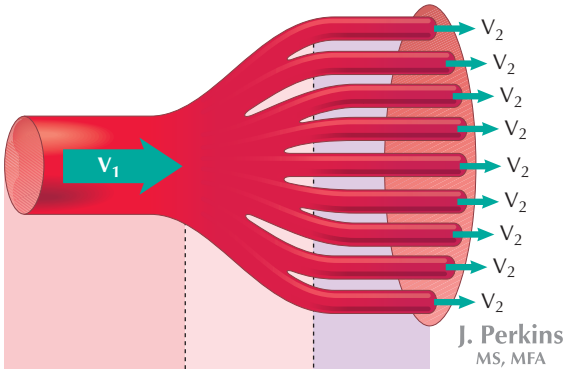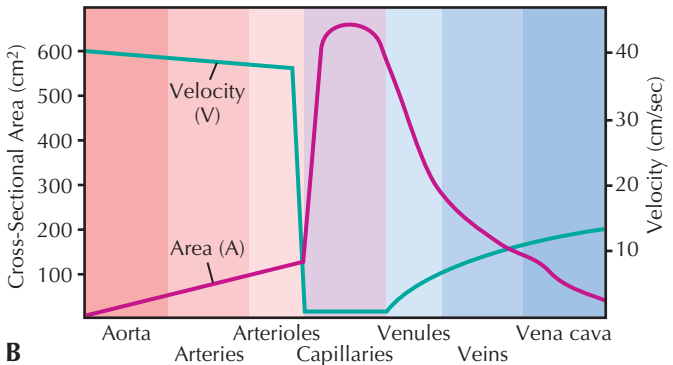
1 Velocity of flow in the large tube (V_1) is the same as velocity of flow in each of the small tubes (V_2).

2.

$$Q = vA$$

or rearranging,

$$v = Q/A$$

where Q is flow, v is velocity, and A is cross-sectional area.

Comment: The equation can only be used to compare velocities based on cross-sectional area when the flow rate (or relative flow rate) is known. In the cardiovascular system (**B**), velocity is greatest in the aorta and large arteries, where total cross-sectional area is smallest; velocity is lowest in the capillaries, where the total cross-sectional area is greatest.

1. **Give the formula that predicts whether flow in a tube will be laminar or turbulent.**

2. **Explain how each of the variables in the formula affects the probability that flow will be laminar or turbulent.**

Laminar flow
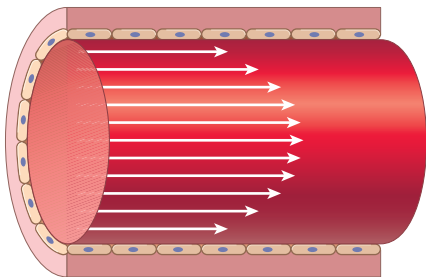
Turbulent flow
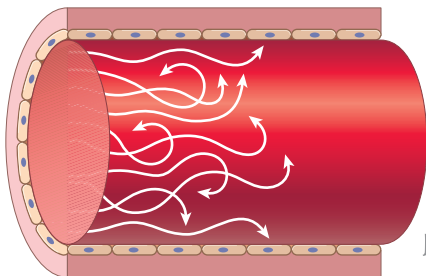
J. Perkins
MS, MFA

1. Reynold's number (R_e) determines whether flow in a tube will be laminar or turbulent:

$$R_e = \frac{vD\partial}{\eta}$$

where v is velocity, D is diameter of the tube, ∂ is density of the fluid, and η is viscosity of the fluid.

2. Assuming other variables are held constant, increased velocity, tube diameter, and density of fluid are associated with greater likelihood of turbulence; increased viscosity is associated with greater likelihood of laminar flow.

Note the change in vessel diameter in the area of the ruptured aneurysm.

1. What is the formula for wall tension in a vessel?

2. Explain why an aneurysm of this type is prone to rupture based on this formula.

Ascending aorta

Rupture of aneurysm

Dissection of aortic wall

Descending aorta
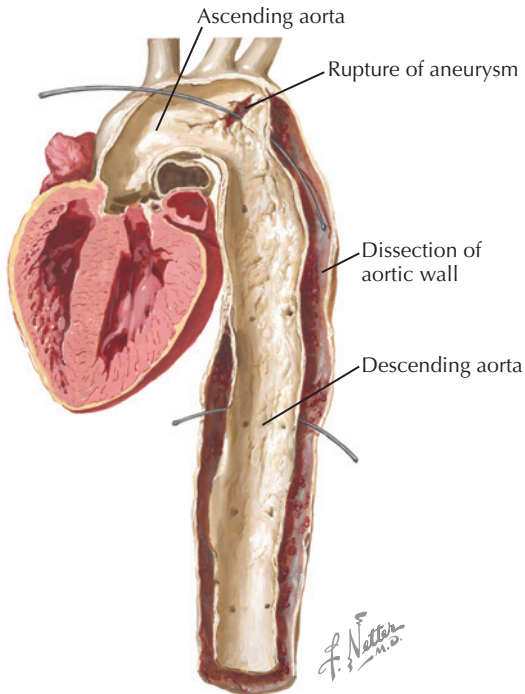
1. Wall tension is determined by the formula:

$$T = P_t r$$

   where P_t is the transmural pressure (the difference between pressure inside and outside the vessel or the pressure gradient across the vascular wall), and r is vessel radius.
2. Wall tension can be conceptualized as the force necessary to hold together a theoretical slit occurring in the wall of a vessel. In the case of an aneurysm, the increased vessel radius results in greater wall tension, and the vessel becomes susceptible to rupturing.

In this cardiac cycle diagram, identify the three waves of the atrial pressure curve (dashed line). Explain the cause of each of these waves.
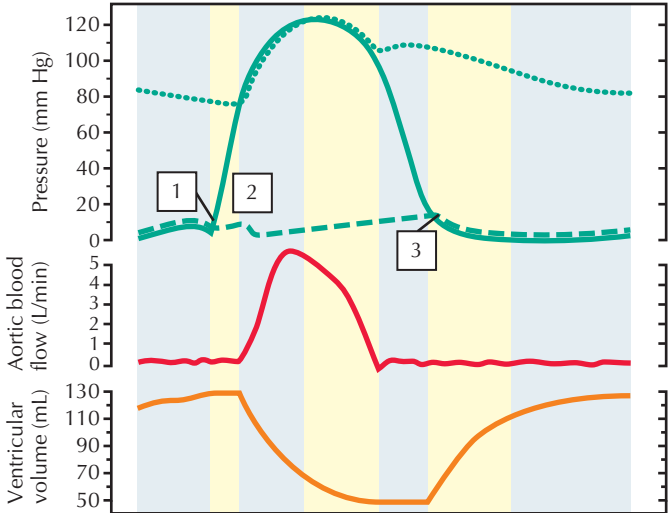
J. Perkins
MS, MFA

1. The **a** wave of the atrial pressure curve is caused by atrial contraction.
2. The **c** wave occurs during isovolumetric contraction and is caused by bulging of the mitral valve back into the left atrium as the ventricle attempts to contract against a fixed volume.
3. The **v** wave occurs during the ejection phase of the cardiac cycle as left atrial pressure rises slowly while venous return from the pulmonary circulation fills the atrium.

In this cardiac cycle diagram, identify the valve opening or closure occurring at points 1–4.
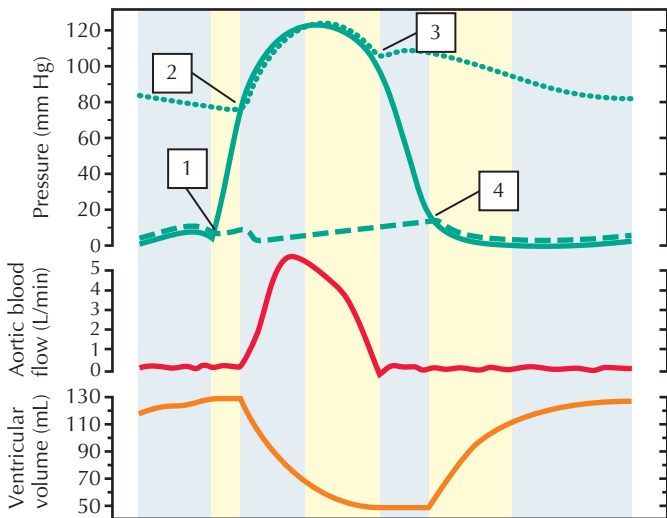
J. Perkins
MS, MFA

1. Mitral valve closure
2. Aortic valve opening
3. Aortic valve closure
4. Mitral valve opening

In this cardiac cycle diagram, identify the heart sounds that might be heard at points 1–4 and the cardiac event associated with each sound.
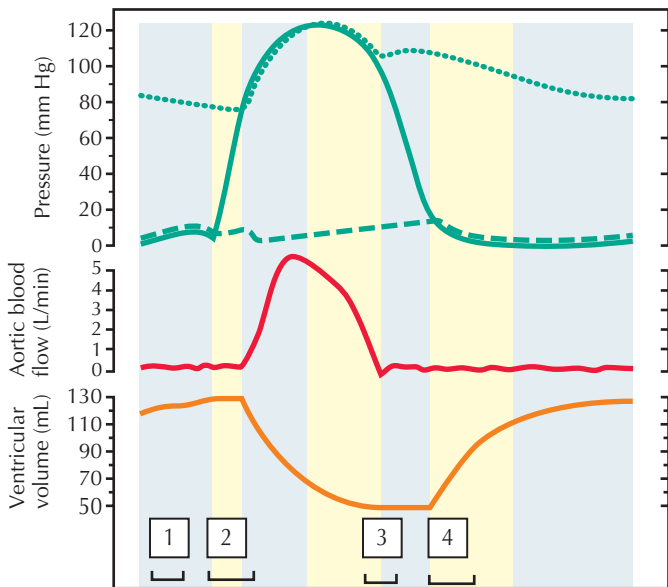
J. Perkins
MS, MFA

1. S4, associated with active ventricular filling (atrial contraction); it is not heard in healthy adults
2. S1, associated with closure of the mitral and tricuspid valves
3. S2, associated with closure of the aortic and pulmonic valves
4. S3, associated with rapid, passive ventricular filling; it is often heard in children but not in healthy adults
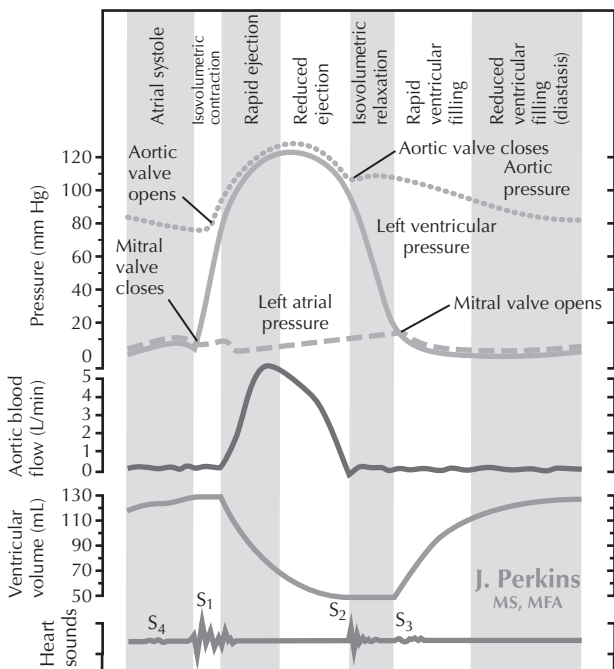
Identify the major neurotransmitters released at points 1–4.
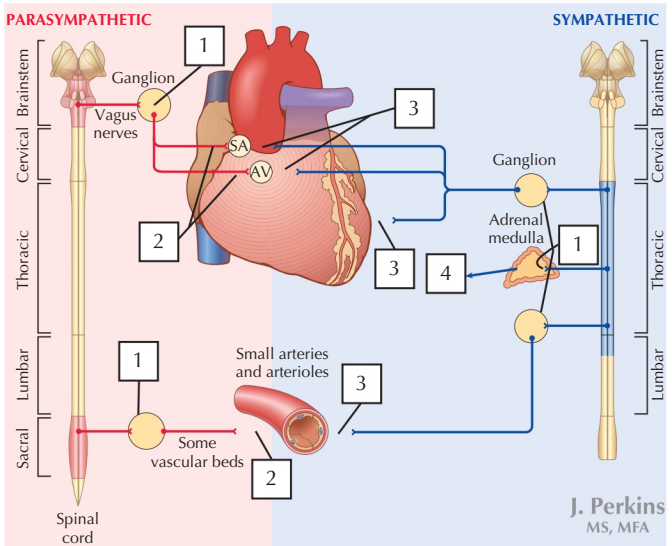
1. Acetylcholine (ACh) is released by preganglionic fibers of both the sympathetic and parasympathetic nervous systems.
2. ACh is released by postganglionic fibers of the parasympathetic nervous system at the SA and AV nodes of the heart and in some vascular beds (in the genital region and lower gastrointestinal tract).
3. Norepinephrine (NE) is released by postganglionic fibers of the sympathetic nervous system at the SA and AV nodes, ventricular myocardium, and blood vessels.
4. Epinephrine (two thirds) and NE (one third) are released by the adrenal medullary chromaffin cells in response to sympathetic nervous system activation.

Indicate the direction of change in the variables at points 1–8, and explain the sequence of events that occurs as a result of the baroreceptor reflex following a rise in mean arterial pressure (MAP).

J. Perkins
MS, MFA
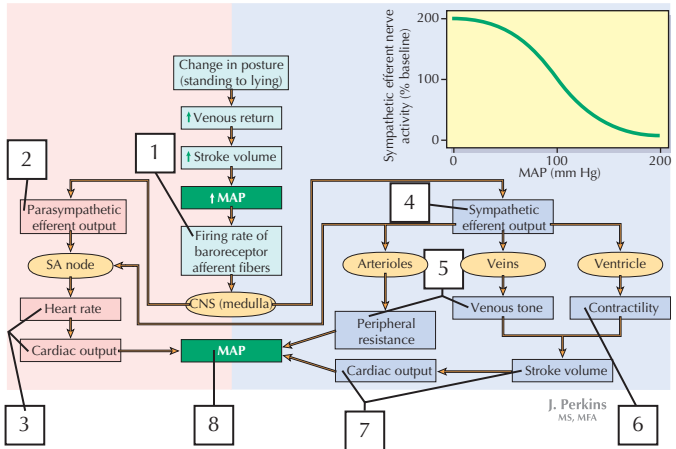
1. Increase in firing rate of baroreceptor afferent fibers. The rise in MAP produces stretch of the arterial baroreceptors, which initiate signals to the medullary cardiovascular center.
2. Increase in parasympathetic efferent output occurs in response to the increased firing of baroreceptor afferent fibers.
3. Decrease in heart rate, and therefore cardiac output, as a result of increased parasympathetic stimulation of the heart.
4. Decrease in sympathetic efferent output occurs in response to increased firing of baroreceptor afferent fibers.
5. Decrease in peripheral resistance and venous tone are produced by vasodilation in response to reduced sympathetic efferent activity.
6. Decrease in contractility of the ventricle as a result of reduced sympathetic stimulation of the heart.
7. Decrease in stroke volume, and therefore cardiac output, in response to reduced venous tone and myocardial contractility.
8. Decrease in MAP is the result of reduced peripheral resistance and cardiac output.

Comment: Heart rate decreases as the result of increased parasympathetic outflow, as illustrated, and as a result of reduced sympathetic efferent activity. The decrease in stroke volume is the result of both reduced contractility and reduced preload. The latter is caused by the decrease in venous tone.

Normal cardiac function curve is illustrated in A. Identify the changes or events that would produce a displacement of the curve to 1 or 2 in B.
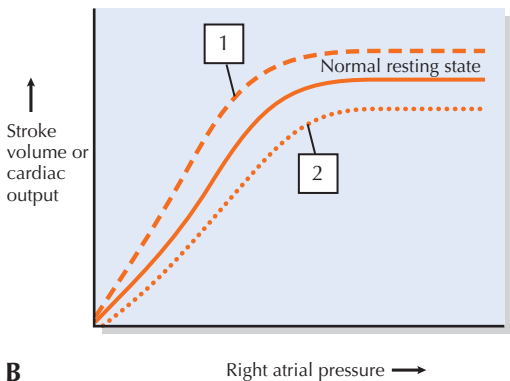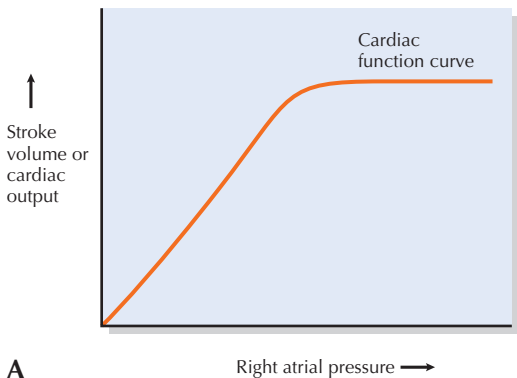
1. Cardiac function curve is shifted upward by sympathetic stimulation or administration of drugs that enhance myocardial contractility (inotropic agents).
2. Cardiac function curve is depressed by myocardial ischemia, infarction, and heart failure.

The solid line in A and B illustrates normal force-velocity curve. Identify the change that would produce a displacement of the curve to 1 or 2.
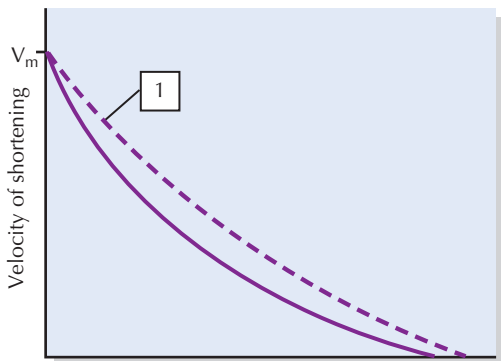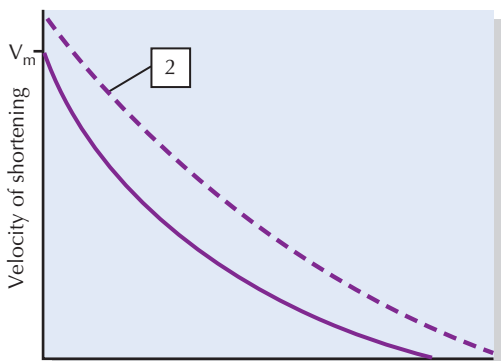
1. Increased preload
2. Increased contractility

Comment: Force-velocity curves are altered when preload or contractility is changed. When preload is increased, the curve is shifted upward, but V_m (the maximal velocity, occurring at zero afterload) is unchanged. Increased contractility, however, results in a shift in the curve with an increase in V_m.

Normal left ventricular pressure-volume relationship for the heart is illustrated in A. Identify the manipulation that would change this relationship to those represented in B.
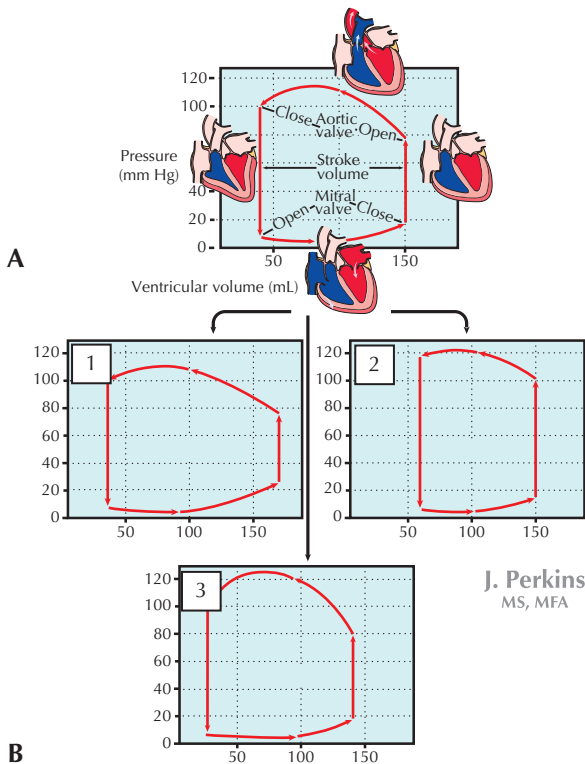
1. Increased preload (end-diastolic volume)
2. Increased afterload (arterial pressure)
3. Increased contractility

Comment: The *top panel* illustrates the normal, resting left ventricular pressure-volume relationship during a cardiac cycle. An increase in preload (end-diastolic volume) results in greater stroke volume through the Frank-Starling mechanism (1). An increase in afterload results in opening of the aortic valve at a higher left ventricular pressure; stroke volume is reduced (2). Increase in contractility produces a greater stroke volume that is not dependent on a change in end-diastolic volume (3).

The solid lines illustrate the normal, resting cardiac function and vascular function curves. Identify the manipulation or event that would result in vascular function curves 1 and 2. What effect would the altered vascular function have on cardiac output?
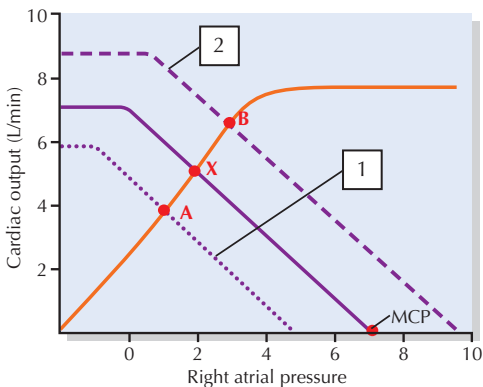
J. Perkins
MS, MFA

1. Hemorrhage (hypovolemia); decreased cardiac output
2. Increased blood volume or venoconstriction; increased cardiac output

Comment: Hemorrhage results in a downward shift in the vascular function curve. The new equilibrium between the cardiac and vascular function curves at point A reflects lower preload (as reflected by lower right atrial pressure) and cardiac output. Hypervolemia causes an upward shift in the vascular function, and the new equilibrium at point B is at higher preload and cardiac output. Venoconstriction also causes an upward shift in the vascular function curve.

The solid lines illustrate the normal, resting cardiac function and vascular function curves. Identify the manipulation or event that would result in cardiac function curves 1 and 2.
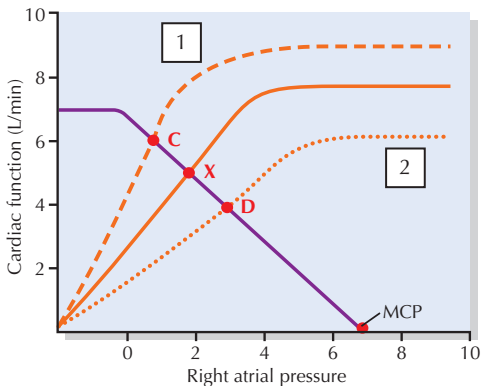
J. Perkins
MS, MFA

1. Sympathetic stimulation or administration of inotropic drugs
2. Heart failure, ischemia, infarction

Comment: With sympathetic stimulation or inotropic drug administration, the cardiac function is shifted upward; the new equilibrium point (C) is at higher cardiac output and lower preload (as reflected by right atrial pressure). With heart failure, the cardiac function curve shifts downward, resulting in lower cardiac output and higher preload (D).

Name each tissue layer in the wall of this vessel. For each, name the predominant cell or tissue types.

J. Chovan
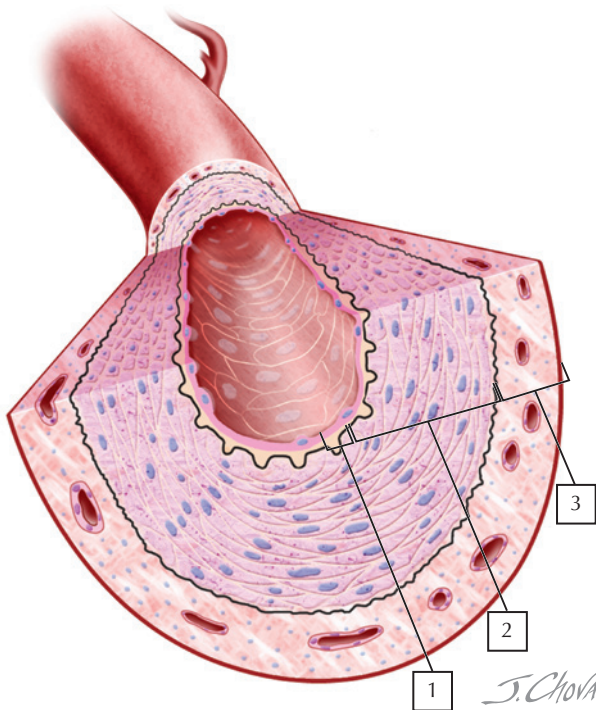
1. Tunica intima; this innermost layer consists of a single endothelial cell layer resting on a basement membrane
2. Tunica media; the media consists mainly of smooth muscle
3. Tunica adventitia; consists mainly of connective tissue

Comment: Absolute and relative thickness of media and adventitia varies between arteries and veins, and between small and large vessels. Connective tissue and cellular constituents of these layers vary between vessel types as well. Walls of large arterial vessels are rich in elastic tissue, with relatively thick adventitia compared with smaller arteries. Smaller arteries have a relatively thicker tunica media. Capillaries contain no media or adventitia, and their vascular walls consist only of endothelial cells and basement membrane. The illustrated vessel is a small artery.

Identify the structures in microcirculation.
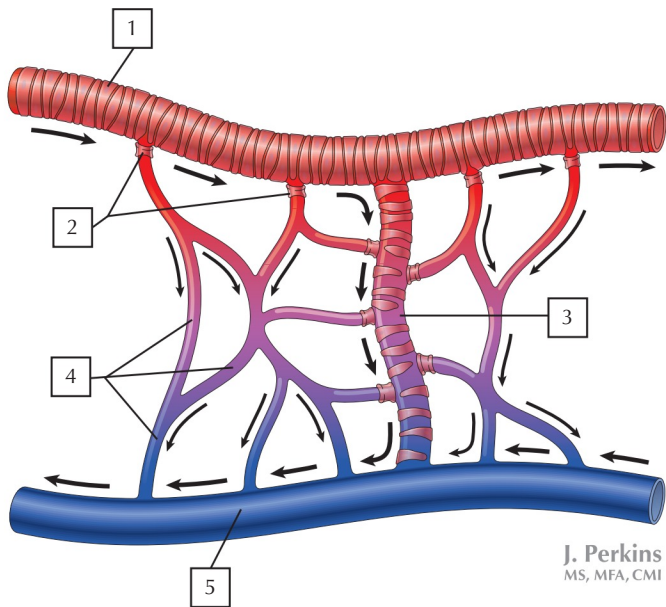
J. Perkins
MS, MFA, CMI

1. Arteriole
2. Precapillary sphincters
3. Metarteriole
4. Capillaries
5. Venules

1. **What is the Starling equation for net filtration pressure for diffusion of fluid out of a capillary?**

2. **Use the Starling equation to calculate the net filtration pressure for the arteriolar end of the capillary illustrated.**

Lymphatic flow

$\pi_c = 28$ mm Hg
$P_c = 30$ mm Hg $P_c = 10$ mm Hg

$\pi_i = 8$ mm Hg $P_i = -3$ mm Hg

$\sigma = 0$ $\pi_L = 8$ mm Hg $P_L = -4$ mm Hg

Lymph vessel

Arteriole   Venule

Lymphatic circulation

Interstitial fluid

Capillary wall

Plasma

8–12 L/day

1–4 L/day

4–8 L/day

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Lymph node
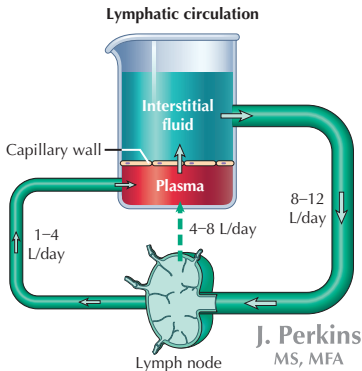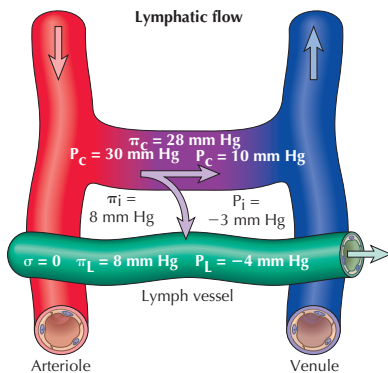
1. Net filtration pressure = $(P_c - P_i) - (\pi_c - \pi_i)$,
   where P_c is capillary hydrostatic pressure, P_i is interstitial hydrostatic pressure, π_c is capillary oncotic pressure, and π_i is oncotic pressure in the interstitium.

2. Net filtration pressure =
   (30 mm Hg − [−3 mm Hg]) − (28 mm Hg − 8 mm Hg) = 13 mm Hg

Comment: Filtration pressure is higher at the arteriolar end of capillaries than at the venular end because hydrostatic pressure falls as blood flows through capillaries. In the illustration, the net filtration pressure at the venular end of the capillary is −7 mm Hg.

Identify and explain the mechanisms of local regulation of blood flow illustrated in 1 through 3.
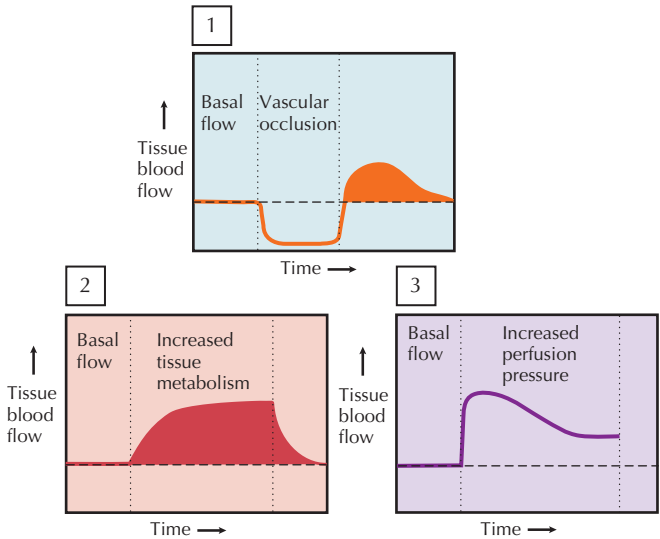
1. **Reactive hyperemia.** Occlusion of blood flow to a region results in buildup of metabolic products; when flow is restored, the accumulated vasodilator metabolites produce increased blood flow.
2. **Active hyperemia.** Increased tissue metabolism results in greater local blood flow, caused by increased metabolic products with vasodilatory actions.
3. **Myogenic regulation (autoregulation).** Arterial smooth muscle constricts in response to increased transmural pressure, resulting in autoregulation of local flow. Thus, when perfusion pressure is artificially increased, although flow immediately rises, in many vascular beds it subsequently returns toward normal.

Identify the constituents of the renin-angiotensin-aldosterone system and explain their role in the response to decreased blood volume and pressure.

Response to Decreased Blood Volume and Pressure

J. Perkins
MS, MFA

Sympathetic nerve activity

Thirst

ADH

Brain

CN IX, X

Heart and lungs

1

Liver

2

3

Adrenals

4

(decreases NaCl excretion)

5

(stimulates renin secretion and decreases NaCl excretion)

(decreases water excretion)

Kidneys

(increased H₂O intake)

NaCl and H₂O excretion → Blood volume and pressure
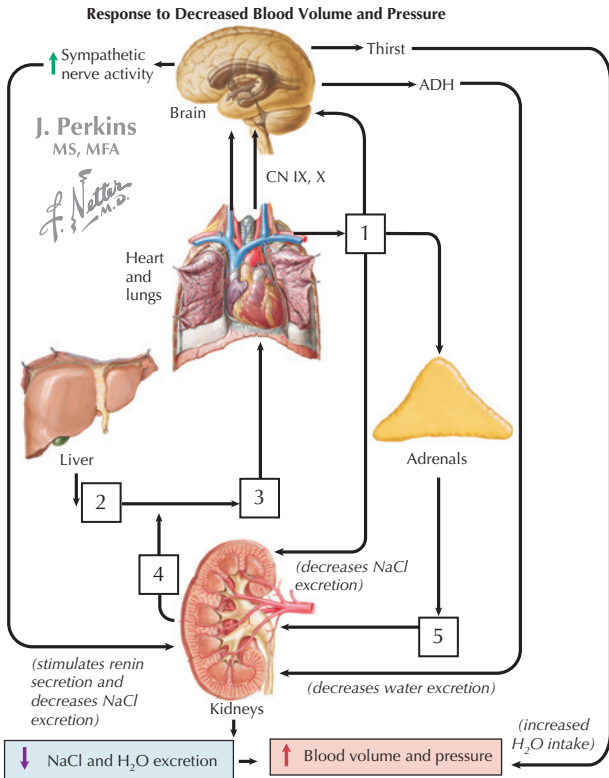
1. **Angiotensin II**. Angiotensin-converting enzyme (ACE) is found on the surface of endothelial cells, particularly in the lungs, and converts angiotensin I to angiotensin II. Through its various renal effects, angiotensin II reduces NaCl and water excretion.
2. **Angiotensinogen.** The liver produces angiotensinogen, the precursor for angiotensin I and II.
3. **Angiotensin I.** Angiotensin I is produced by the action of the enzyme renin on angiotensinogen.
4. **Renin.** This enzyme is released by the kidney in response to reduced renal blood flow and sympathetic nerve activity; it cleaves angiotensinogen to form angiotensin I.
5. **Aldosterone.** This steroid is produced by cells of the zona glomerulosa of the adrenal cortex in response to angiotensin II. At the kidney, its actions result in retention of NaCl and water.

Comment: Angiotensin II is a vasoconstrictor but does not play a role in the normal regulation of vascular smooth muscle tone in most vascular beds. However, in states such as hemorrhagic shock, the vasoconstriction by angiotensin II may be important as one of the mechanisms that raise total peripheral resistance.

Note that in contrast to other vascular beds, in the kidney, angiotensin II does have a physiologic role in regulating the tone of afferent and efferent arterioles.

Identify coronary arteries labelled 1−4. In the bottom panel, explain the basis for the changes in left coronary artery flow at 5 and 6.
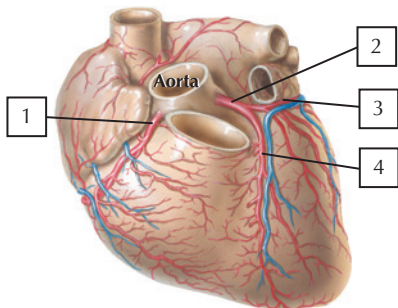
Sternocostal aspect
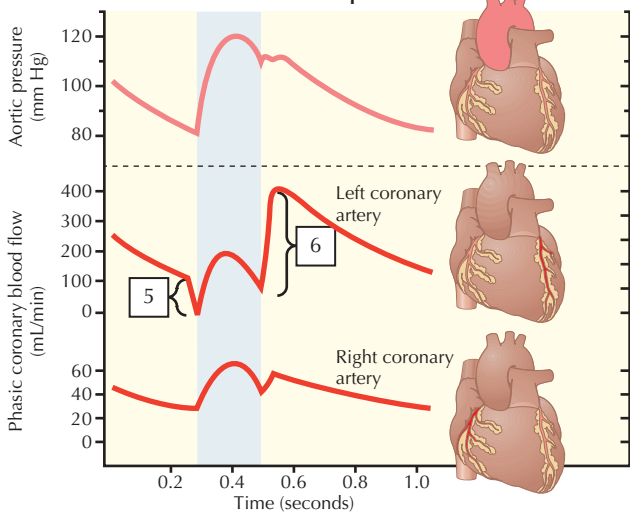
1. Right coronary artery
2. Left coronary artery
3. Circumflex branch of the left coronary artery
4. Anterior descending (anterior interventricular) branch of the left coronary artery
5. This fall in left coronary flow occurs at the beginning of cardiac systole during isovolumetric contraction. It is caused by extravascular tissue pressure, which compresses the coronary vasculature in the wall of the left ventricle as the heart contracts. For the remainder of systole, left coronary flow remains low and follows the pattern of the systolic aortic pressure curve.
6. The great rise in left coronary flow during early diastole is caused by the fall in extravascular tissue pressure as the heart relaxes, along with vasodilator effects of metabolites (particularly adenosine) that build up during systole, when flow is low.

Comment: The pattern of right coronary artery flow follows that of aortic pressure. This is because extravascular tissue pressure in the right ventricular wall is much lower than in the left ventricular wall and therefore has only a modest effect on coronary flow.

Identify the structures in fetal circulation, and for each explain the basis for its closure after birth.
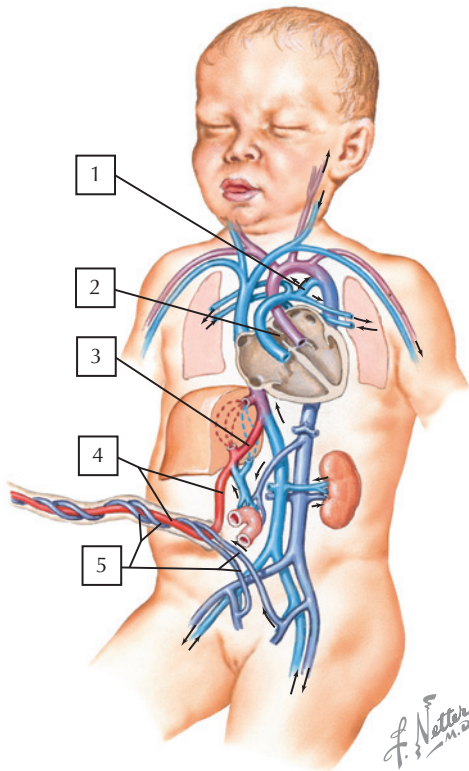
1. **Ductus arteriosus.** In the fetus, blood flows from the pulmonary artery to the aorta through this structure. With inflation of the lungs and reduced pulmonary artery pressure, and with increased systemic arterial pressure due to closing of the umbilical circulation, flow through the ductus is reversed. With higher oxygen tension in arterial blood, vasodilator prostaglandins formed in the ductus fall, resulting in vasoconstriction and closure of the ductus.

2. **Foramen ovale.** In the fetus, right atrial pressure exceeds left atrial pressure, keeping the foramen open. With inflation of the lungs after birth and, therefore, greater flow of blood to the left atrium from the pulmonary circulation, this pressure gradient is reversed, functionally closing the foramen as the tissue flap covers the opening.

3. **Ductus venosus.** This structure shunts a fraction of the blood from the umbilical vein directly to the inferior vena cava, bypassing the liver. It closes after the return of blood from the placental circulation falls, although the mechanism is not well understood.

4. **Umbilical vein.** Closure of this vessel occurs after umbilical artery closure, and is probably caused by catecholamines and other factors.

5. **Umbilical arteries.** The paired umbilical arteries close in response to vasoconstrictor catecholamines, cold, and other factors associated with delivery of the baby and placenta.

Ligamentum arteriosum (obliterated ductus arteriosus)

Fossa ovalis (obliterated foramen ovale)

Ligamentum venosum (obliterated ductus venosus)

Ligamentum teres (round ligament) of liver (obliterated umbilical vein)

Medial umbilical ligaments (occluded part of umbilical arteries)

Postnatal circulation

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Contrast the approximate resting pressures in the pulmonary circulation and right side of the heart to those of systemic circulation and left side of the heart:

1. Pulmonary artery vs. aorta
2. Right ventricle vs. left ventricle
3. Right atrium vs. left atrium
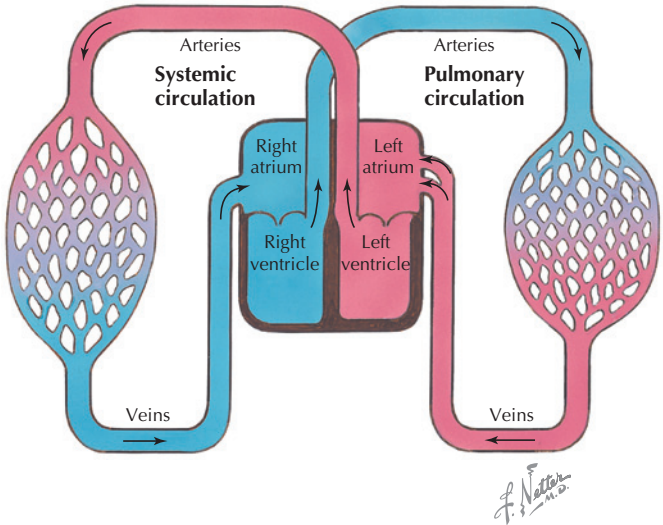
1. Pulmonary artery pressure, 25/10 mm Hg; aortic pressure, 120/80 mm Hg
2. Right ventricular pressure, 25/0 mm Hg; left ventricular pressure, 120/0 mm Hg
3. Right atrial pressure, 2 mm Hg; left atrial pressure, 5 mm Hg

Comment: Pressures in the pulmonary circulation and right side of the heart are significantly lower than those in the systemic circulation and left side of the heart. Pressures given above for the right and left atria are mean pressures.

**Describe the effects of pulmonary artery pressure on pulmonary
vascular resistance, relating these effects to panels 1, 2, and 3.**

Arteriole
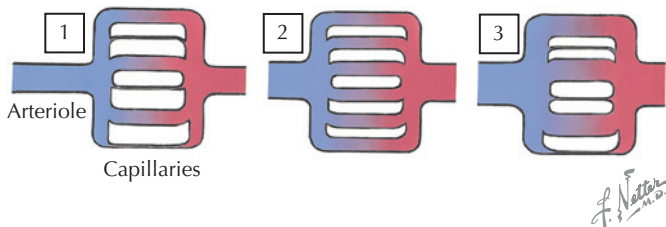
Capillaries

Pulmonary Artery Pressure and Pulmonary Vascular Resistance

1. Not all capillaries in the pulmonary circulation are normally open; collapsed capillaries do not conduct blood.
2. An increase in pulmonary artery pressure results in recruitment of capillaries, whereby collapsed vessels are opened when pulmonary artery pressure increases, resulting in a fall in pulmonary vascular resistance.
3. Higher pressure also results in distention of pulmonary vessels, which also reduces resistance owing to increased radius of the vessels.

Describe how changes in lung volume affect pulmonary vascular resistance, referring to the illustration.

Effects of lung volume
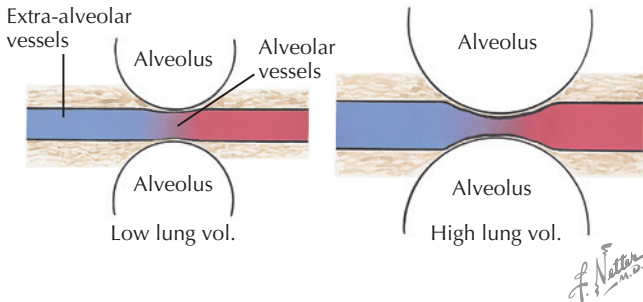
Lung Volume and Pulmonary Vascular Resistance

Comment: As lung volume rises (from left panel to right panel), traction distends extra-alveolar vessels, reducing their resistance. In alveolar vessels, on the other hand, increase in lung volume raises resistance as they are compressed by the enlargement of alveoli. Starting from the collapsed state, as a lung is inflated, pulmonary vascular resistance first falls as a result of distension of extra-alveolar vessels, and then rises as the lung is inflated further and alveolar vessels are compressed.

Identify substances that vasoconstrict (1) and vasodilate (2) pulmonary vessels. Describe the effect of alveolar hypoxia on pulmonary arterioles (3).
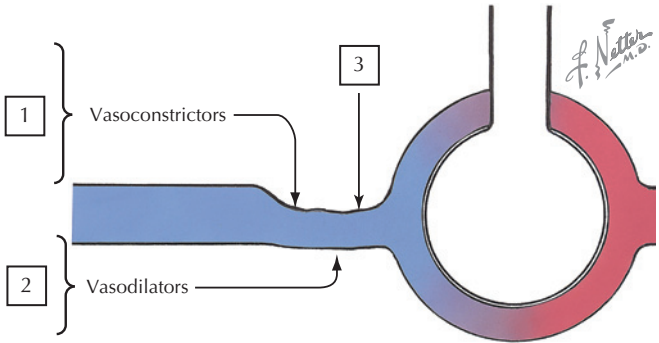
Chemical and Humoral Control of Pulmonary Vascular Resistance

1. α-Adrenergic agonists, thromboxane, norepinephrine, angiotensin II, histamine, and endothelin constrict pulmonary vessels.
2. β-Adrenergic agonists, bradykinin, prostacyclin, and nitric oxide dilate pulmonary vessels.
3. Alveolar hypoxia constricts pulmonary arterioles, redirecting blood flow toward areas of the lung that are better ventilated.

See Figure 13.2
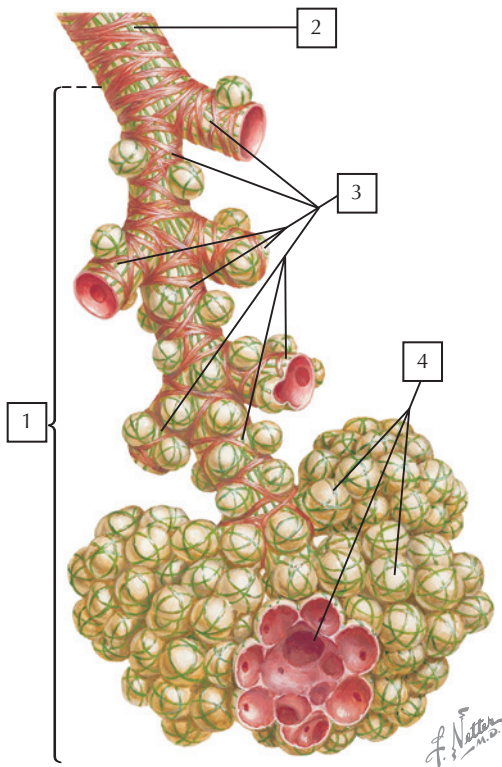
Name the structures labeled 1–4.
5. Which structures (labeled 1–4) constitute the respiratory zone of the lungs?

1. Acinus
2. Terminal bronchiole
3. Respiratory bronchioles
4. Alveolar sacs and alveoli
5. Structures distal to the terminal bronchiole constitute the respiratory zone of the lungs (respiratory bronchioles, alveolar ducts, and alveoli).

Identify each cell type.

A. Trachea and large bronchi.

Mucus

Nerve

1

2

3   4

Nerve

5

6

B. Bronchioles.

Nerves

1

7

7

3

7
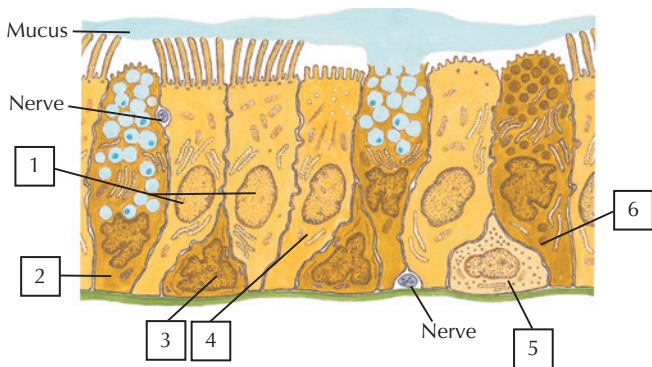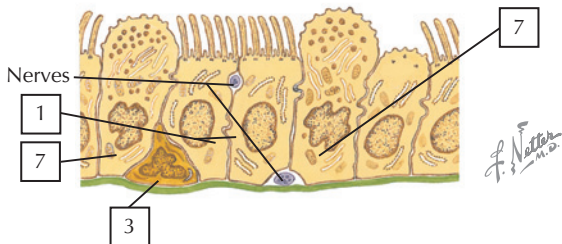
1. Ciliated cells
2. Goblet (mucous) cell
3. Basal cell
4. Brush cell
5. Kulchitsky cell
6. Serous cell
7. Clara cell

Comment: Ciliated cells and goblet cells are predominant in the trachea and large bronchi. Ciliated cells are predominant in the bronchioles; Clara cells increase distally through the airways, whereas goblet cells and serous cells decrease distally and are absent in the terminal bronchioles.

**Identify and describe the lung volumes labeled 1−4
and the capacities labeled 5−8 on this spirometry tracing.**
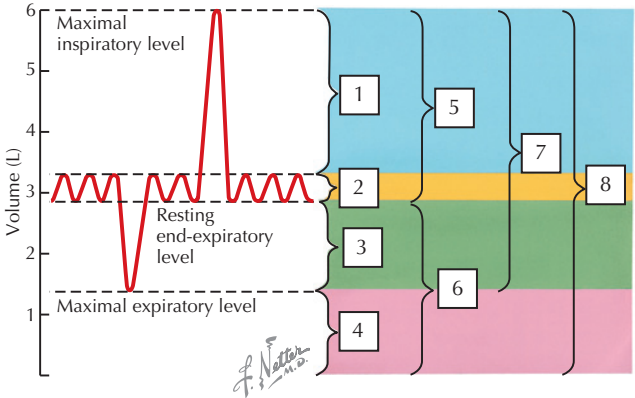
1. **Inspiratory reserve volume (IRV)**: the additional volume that could be inhaled after a normal, quiet inspiration
2. **Tidal volume (V_T)**: the volume of air inhaled and exhaled during breathing. At rest, this is approximately 500 mL.
3. **Expiratory reserve volume (ERV)**: the additional volume that could be exhaled after a normal, quiet expiration
4. **Residual volume (RV)**: the volume remaining in the lung after maximal exhalation
5. **Inspiratory capacity (IC)**: the maximum volume that can be inspired after expiration during normal, quiet breathing
6. **Functional residual capacity (FRC)**: the volume remaining in the lung after expiration during normal quiet breathing
7. **Vital capacity (VC)**: the maximum volume that can be exhaled after a maximal inspiration
8. **Total lung capacity (TLC)**: the volume of air in the lung after maximal inspiration

Comment: Of these parameters, 1, 2, 3, 5, and 7 can be measured directly from a spirometry tracing. RV, FRC, and TLC cannot because the spirometer measures only changes in volume. An additional technique such as nitrogen washout, helium dilution, or body plethysmography must be employed to measure FRC, after which RV and TLC can be calculated.

1–7. Identify the muscles of breathing.

8. Which muscles are involved in normal, quiet breathing?
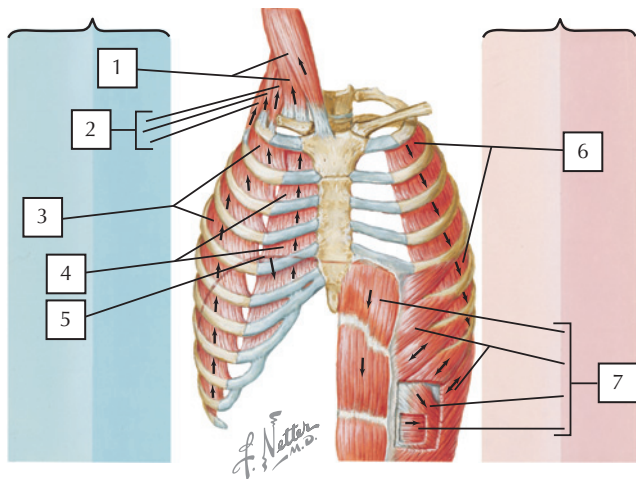
1. Sternocleidomastoid
2. Anterior, middle, and posterior scalenes (from right to left)
3. External intercostals
4. Internal intercostals (interchondral portion)
5. Diaphragm
6. Internal intercostals (except interchondral portion)
7. Abdominal muscles (from top to bottom: rectus abdominis, external oblique, internal oblique, and transversus abdominis)
8. The diaphragm is the main muscle used in normal, quiet breathing.

Comment: The principal muscles of inspiration are the external intercostals, interchondral portion of the internal intercostals, and the diaphragm; the sternocleidomastoid and scalenes play an accessory role. In quiet respiration, the diaphragm is the main muscle involved. The main muscles of expiration are the internal intercostals (except the interchondral portion) and the abdominal muscles. However, in normal, quiet breathing, no muscles are involved; expiration in this case is driven by passive recoil of the lungs.

1. Give the composition of the Earth's atmosphere in terms of percentage O_2, N_2, and CO_2 in our air.

2. Equate these percentages with partial pressures of the gases in dry air at sea level.

3. Explain Dalton's law and how it is used to calculate partial pressure of gases in a mixture.

Atmosphere

Inspired air

Alveolus

Pulmonary artery
(mixed venous
blood)

Pulmonary vein
(arterial blood)

Capillaries
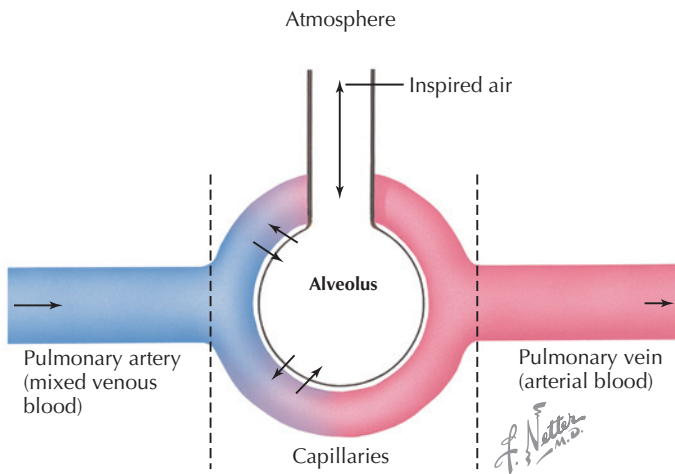
Partial Pressure of Gases in the Atmosphere

1. 21% O_2, 79% N_2, <1% CO_2 and other gases
2. P_{O_2} = 160 mm Hg; P_{N_2} = 600 mm Hg; P_{CO_2} < 1 mm Hg
3. According to Dalton's law, the sum of the partial pressures of gases in a mixture equals the total pressure. Thus, for O_2, which composes 21% of the atmosphere, the partial pressure at sea level in dry air will be 0.21 $\times$ 760 mm Hg, or 160 mm Hg.

Partial Pressure of Gases in the Atmosphere

See Figure 13.12

1. Give the normal partial pressure of O_2 and CO_2 in inspired air at sea level.

2. Explain the basis for the difference in P_{O_2} between the atmosphere and inspired air.

3. Give the normal partial pressure of O_2 and CO_2 in mixed venous blood, alveolar air, and arterial blood.
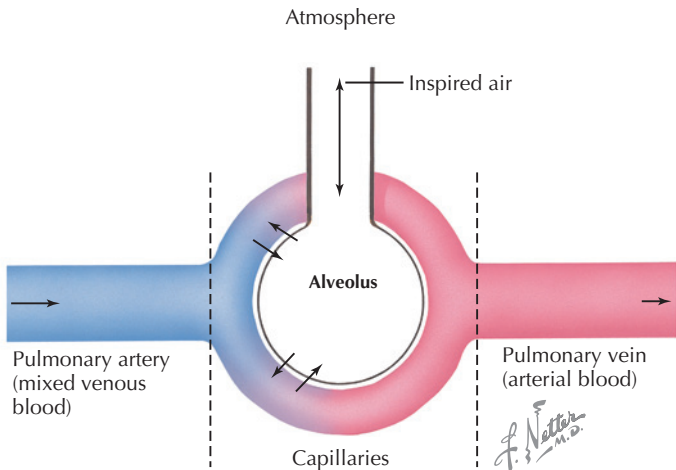
Atmosphere

Inspired air

Alveolus

Pulmonary artery (mixed venous blood)

Pulmonary vein (arterial blood)

Capillaries

1. $P_{O_2} = 150$ mm Hg; $P_{CO_2} < 1$ mm Hg
2. Dry air at sea level contains 21% O_2, and the P_{O_2} is 160 mm Hg (0.21×760 mm Hg). When this air is inspired, it is saturated with water vapor, such that the partial pressure of H_2O is 47 mm Hg. Thus, P_{O_2} in inspired air is 150 mm Hg (0.21×713 mm Hg).
3. For mixed venous blood in a normal, resting individual, P_{O_2} is 40 mm Hg, and P_{CO_2} is 45 mm Hg. For alveolar air and arterial blood, P_{O_2} is 100 mm Hg, and P_{CO_2} is 40 mm Hg.

Comment: P_{O_2} and P_{CO_2} in arterial blood are normally the same as in alveolar air because oxygen and carbon dioxide completely equilibrate between blood and alveolus as blood courses through the alveolar capillaries.

1. **Give the alveolar gas equation for determining partial pressure of oxygen in alveolar air.**

2. **Given the various partial pressures in the diagram below, calculate the partial pressure of oxygen in the alveolar air (P_{AO_2}).**

Atmosphere
P_{O_2} = 160 mm Hg
P_{CO_2} = 0 mm Hg

Inspired air
P_{O_2} = 150 mm Hg
P_{CO_2} = 0 mm Hg

P_{CO_2} = 60 mm Hg

Alveolus

Pulmonary artery
(mixed venous blood)

Pulmonary vein
(arterial blood)

Capillaries
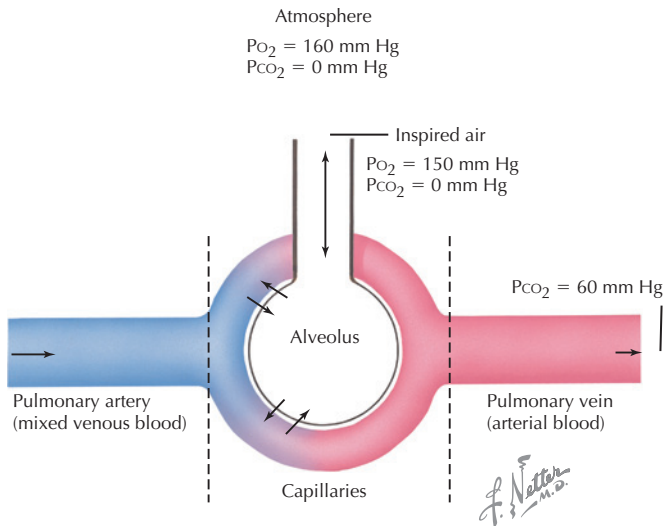
Alveolar Gas Equation

1. $P_{AO_2} = P_{IO_2} - P_{ACO_2}/R$, where R is the respiratory quotient (R usually has a value of 0.8)
2. $P_{AO_2} = 150 \text{ mm Hg} - 60/0.8 \text{ mm Hg} = 75 \text{ mm Hg}$

Comment: The calculation above assumes that the respiratory quotient (R) is 0.8. The alveolar gas equation can be used in a healthy person to predict P_{AO_2} based on P_{aCO_2} measured during arterial blood gas determination, because P_{ACO_2} and P_{aCO_2} will be the same (the partial pressures of oxygen and carbon dioxide completely equilibrate between blood and alveolar air as blood courses through the alveolar capillaries).

Describe the relationship among arterial, alveolar, and venous pressures in the three zones of the lung and how the relationship affects pulmonary blood flow in that zone.

Zone 1: Alveolar pressure exceeds arterial and venous pressure; as a result, there is no blood flow in this zone. Present only when alveolar pressure is raised or arterial pressure is reduced.

Zone 2: Arterial pressure exceeds alveolar pressure; alveolar pressure exceeds venous pressure. Blood flow is determined by the difference between arterial and alveolar pressures.

Zone 3: Arterial pressure exceeds venous pressure; venous pressure exceeds alveolar pressure. Flow through zone 3 is dependent on the a-v pressure gradient. The higher hydrostatic pressure in this region results in distention of vessels and, therefore, reduced resistance.

Identify the lines representing ventilation, blood flow, and $\dot{V}_A/\dot{Q}_C$ from bottom to top of the lung.

1. Line 1 represents blood flow (perfusion) from the bottom to the top of the lung. Note the greater gradient for perfusion than for ventilation (line 3).
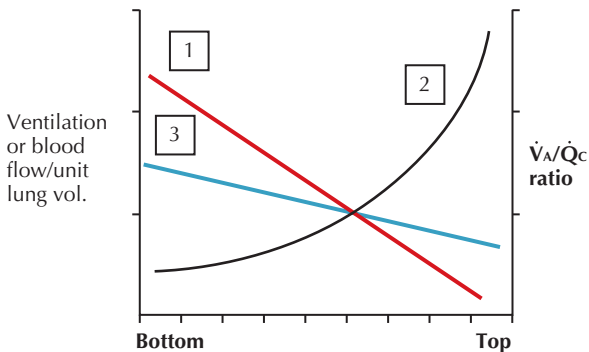
2. Line 2 represents V̇A/Q̇C (the ventilation/perfusion ratio) from bottom to the top of the lung. Note that the ratio is lowest at the bottom of the lung and greatest at the apex of the lung, and that ventilation and perfusion are best matched in the middle of the lung.

3. Line 3 represents ventilation from bottom to top of the lung. The gradient for ventilation is not nearly as steep as the gradient for perfusion.

**Identify the lines 1, 2, and 3, and identify the volumes
or capacities of 4, 5, and 6.**
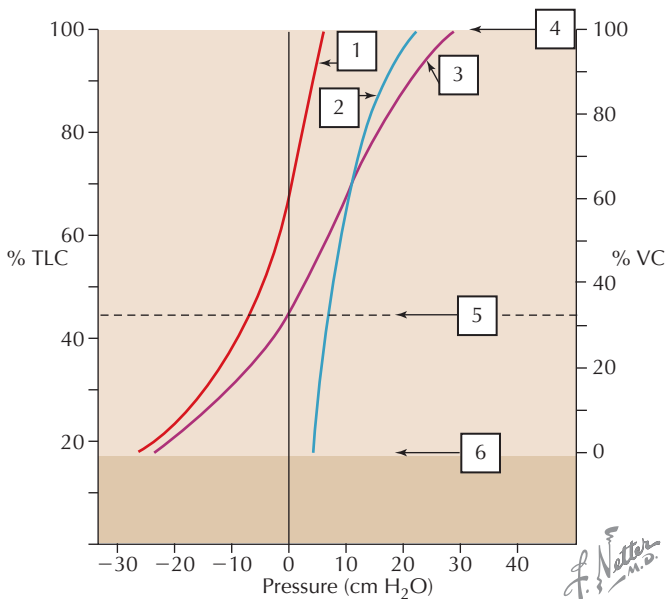
1. Elastic recoil pressure of the chest wall
2. Elastic recoil pressure of the lung
3. Elastic recoil pressure of the lung and chest wall (the algebraic sum of elastic recoil pressure of the chest wall and lung)
4. Total lung capacity
5. Functional residual capacity
6. Residual volume

Comment: At functional residual capacity (FRC), the mechanical system is at rest, with elastic recoil of the lung equal and opposing that of the chest wall. This is the state after quiet expiration in breathing.

1. Define the term "compliance."

2. Explain the concept of pulmonary compliance in the context of this diagram.
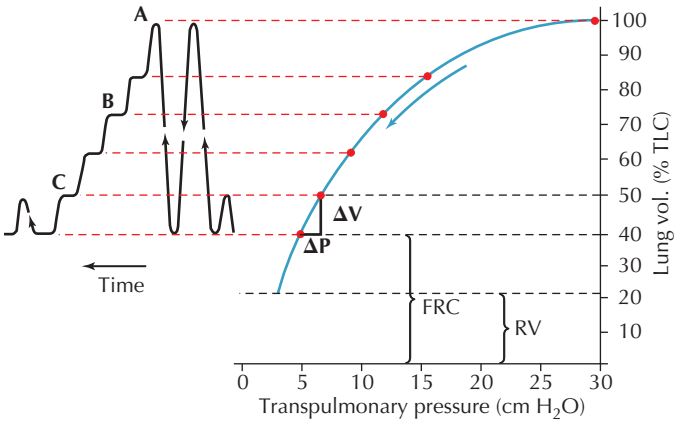
1. Compliance is the change in volume produced by a change in pressure:

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

2. The slope of the pressure–volume relationship in this plot is compliance. In the graph, lung volume (percent total lung capacity, or TLC) is plotted against transpulmonary pressure; the latter is measured during periodic interruptions of a slow expiration from TLC. The spirometry tracing during the procedure is illustrated at the left.

1. **The pressure–volume relationship is measured experimentally Identify which tracing (1 or 2) is obtained in air-filled lungs and which is obtained in saline-filled lungs.**

2. **Explain why the two conditions result in different pressure–volume relationships.**

3. **Define the term "hysteresis" in the the context of this diagram.**
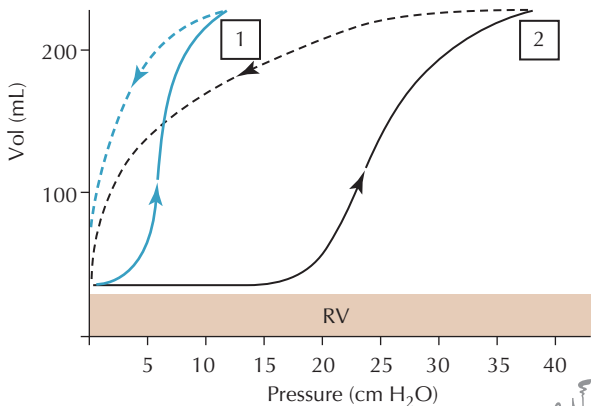
1. Tracing 1 is obtained in saline-filled lungs, whereas tracing 2 is obtained in air-filled lungs.
2. In air-filled lungs, the surface tension associated with the liquid–air interface results in a higher pressure required to maintain a given lung volume.
3. Hysteresis is the difference in the pressure–volume curve obtained during inspiration (indicated in the diagram by *upward arrows*) and the curve obtained during expiration (*downward arrows*). Lung volume associated with any pressure during inspiration is lower than volume at that pressure during expiration, mainly because surface forces must be overcome during inspiration.

1. **In pair 1, which of the two tubes has highest resistance, assuming length is the same? By what factor? Explain.**

2. **In pair 2, which of the two tubes has highest resistance, assuming radius is the same? By what factor? Explain.**

$r = 2$

$r´ = 1$

$L = 2$ $L´ = 4$

Resistance ~2   Resistance ~4
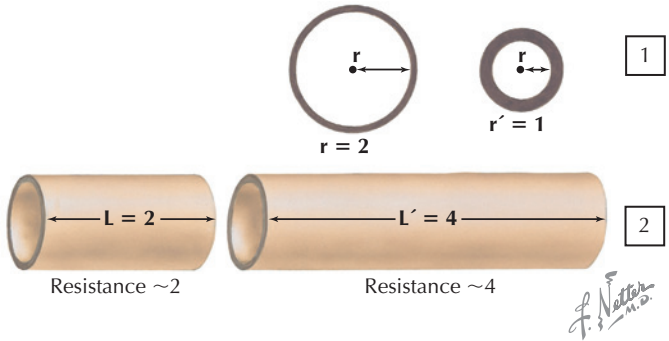
1. The smaller of the two tubes has the highest resistance, 16 times greater than in the larger tube. Flow through airways follows Poiseuille's law, which defines resistance (R) as:

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

   where η is viscosity of the fluid, L is length of the tube, and r is radius of the tube. Thus, resistance is inversely related to the fourth power of the radius, and therefore the smaller tube, with half the radius of the larger tube, has 16 times greater resistance.

2. The longer of the two tubes has twice the resistance of the shorter tube. Resistance is directly related to the length of a tube.

Identify the type of airflow illustrated in each airway. For each, identify the type of airway in which this type of flow is likely to occur.
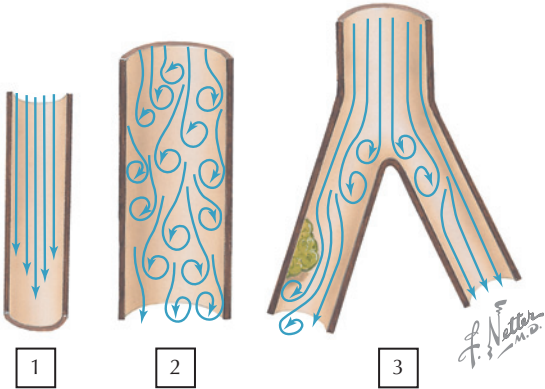
1. Laminar flow; occurs mainly in small airways where diameter and velocity are low, both factors favoring laminar flow
2. Turbulent flow; occurs mainly in trachea and larger airways, where velocity is high and diameter is large, both factors favoring turbulent flow
3. Transitional flow; occurs mainly in larger airways, particularly at branch points and points of narrowing

Comment: Reynold's number (R_e) determines whether flow in a tube will be laminar or turbulent:

$$R_e = \frac{VD\partial}{\eta}$$

where V is velocity, D is diameter of the tube, ∂ is density of the fluid, and η is viscosity of the fluid. Higher R_e is associated with turbulence.

Identify points 1 and 2 on these curves.
Explain the convergence of the down slopes
of the two curves in the segment labeled 3.

Expiratory flow–volume
curves performed with
maximal effort (solid line)
and reduced effort (dotted line)
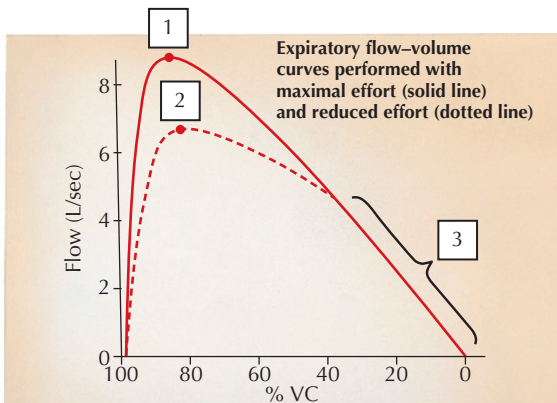
1. Peak expiratory flow rate (PEFR) at maximum effort (during a forced vital capacity maneuver)

2. PEFR at reduced effort

3. The downward slope (expiratory phase) of the flow–volume curve is effort independent. During this phase of the curve, flow is limited by dynamic compression of the airways. Thus, once maximum flow rate is reached, further increases in pleural pressure will only increase resistance proportionally, and the two lines overlap (*solid line* represents a forced vital capacity maneuver; *dotted line* represents the flow–volume curve performed at reduced effort)

1. Identify the category of lung disease characterized by the expiratory flow–volume curve labeled 1.

Describe how the following parameters are affected (increased, decreased, or unchanged) in this type of disease:

2. Total lung capacity (TLC)
3. Functional residual capacity (FRC)
4. Residual volume (RV)
5. Forced vital capacity (FVC)
6. FEV_1 (forced expiratory volume in the first second of a vital capacity maneuver)
7. FEV_1/FVC

Maximum expiratory flow–volume curves
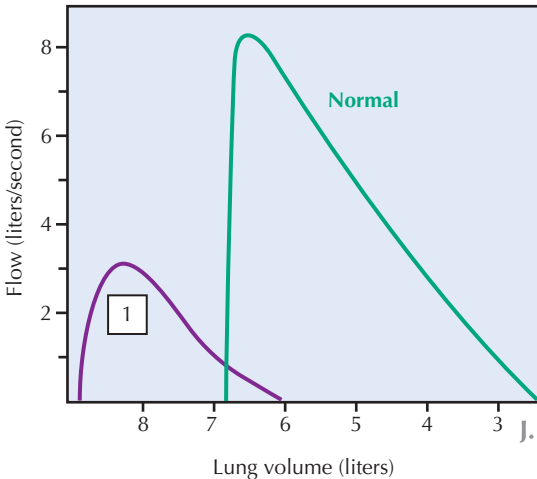
1. Obstructive lung disease
2. TLC is increased in obstructive lung disease.
3. FRC is increased.
4. RV is increased.
5. FVC is reduced slightly.
6. FEV_1 is reduced.
7. FEV_1/FVC is reduced.

1. Identify the category of lung disease characterized by the expiratory flow–volume curve labeled 1.

Describe how the following parameters are affected (increased, decreased, or unchanged) in this type of disease

2. Total lung capacity (TLC)
3. Functional residual capacity (FRC)
4. Residual volume (RV)
5. Forced vital capacity (FVC)
6. FEV_1 (forced expiratory volume in the first second of a vital capacity maneuver)
7. FEV_1/FVC

Maximum expiratory flow–volume curves
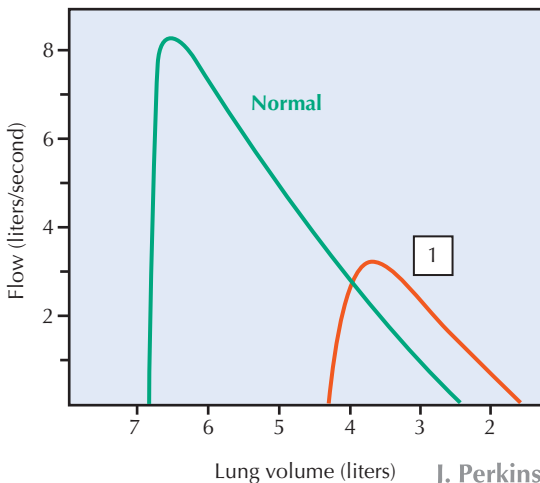
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1. Restrictive lung disease
2. TLC is decreased in restrictive lung disease.
3. FRC is decreased.
4. RV is decreased.
5. FVC is reduced.
6. FEV_1 is reduced.
7. FEV_1/FVC is normal or elevated.

Comment: Lung volumes are reduced in restrictive lung diseases. Although FEV_1 is reduced, the FEV_1/FVC ratio is usually normal or elevated because FVC is also diminished in restrictive disease.

1. **Identify this line. Give the formula for calculation of the maximum amount of oxygen that can be carried in blood in this form.**

2. **Identify this line. Give the formula relating the amount of oxygen carried in blood in this form to partial pressure of oxygen.**

Oxyhemoglobin dissociation curve
(at pH 7.4, P_{CO_2} 40 mm Hg, 37° C)

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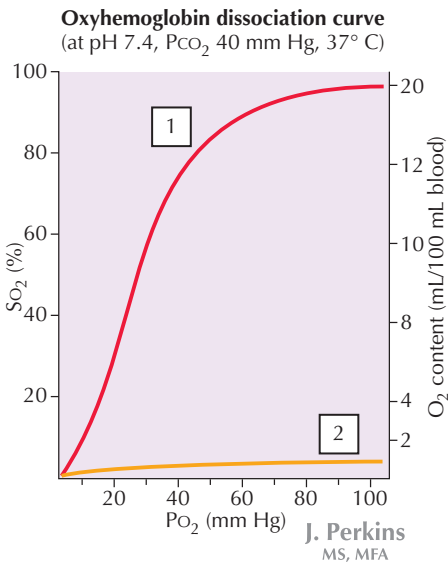
1. Oxygen combined with hemoglobin:

   O_2 binding capacity = (1.34 mL O_2/g Hb) $\times$ (g Hb/100 mL blood)

2. Dissolved oxygen:

   Dissolved O_2 = 0.003 mL O_2/ 100 mL blood/mm Hg P_{O_2}

Comment: At normal blood hemoglobin concentration of 15 g/dL, O_2 binding capacity of blood is 20.1 mL O_2/100 mL blood. Based on P_{O_2} of 100 mm Hg in arterial blood, the concentration of dissolved oxygen will be 0.3 mL O_2/100 mL blood.

The illustration is based on the assumption that hemoglobin content of blood is 15g/100 mL. How would a change in hemoglobin concentration to 12g/100 mL blood affect:

1. So_2 (percentage saturation of hemoglobin with oxygen)?
2. O_2 content of blood?
3. Dissolved O_2 in blood?

Oxyhemoglobin dissociation curve
(at pH 7.4, PCo_2 40 mm Hg, 37° C)

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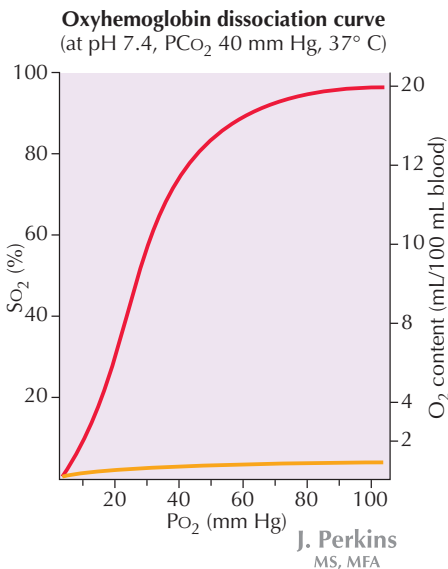
1. A fall in hemoglobin concentration will not affect saturation of hemoglobin with O_2. Thus, looking the top line in the graph (the oxyhemoglobin dissociation curve) at P_{O_2} of 40 mm Hg, for example, hemoglobin will still be 75% saturated with oxygen, but the oxygen content of blood will be reduced (below).

2. A fall in hemoglobin concentration will proportionally reduce the concentration of oxyhemoglobin at a given P_{O_2}. Thus, at P_{O_2} of 40 mm Hg and hemoglobin concentration of 12 g/100 mL (reduced from 15 g/100 mL), hemoglobin will still be 75% saturated with oxygen, but the oxygen content of blood will be reduced by 20% because there is 20% less hemoglobin.

3. Dissolved oxygen (*bottom line* on the graph) will be unaffected by a change in hemoglobin concentration.

The solid lines in graphs 1, 2, and 3 represent the normal oxyhemoglobin dissociation curve. The effect of changes in P_{CO_2}, pH and temperature on the binding of oxygen by hemoglobin are illustrated by the *dotted and dashed* lines in graphs 1, 2, and 3, respectively.

Describe the qualitative effects of an increase or decrease in P_{CO_2}, pH and temperature on the oxyhemoglobin dissociation curve in the context of the graphs.

Effects of P_{CO_2}, pH, and temperature on O_2 dissociation curve
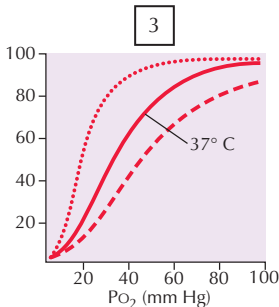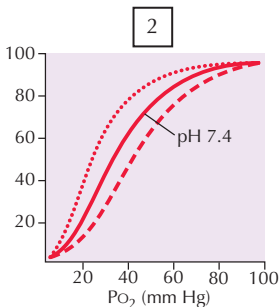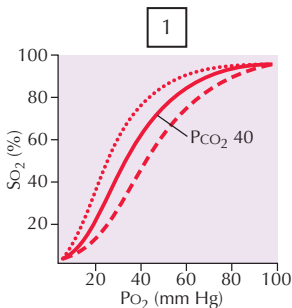
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1. A rise in P_{CO_2} shifts the oxyhemoglobin dissociation curve to the right (*dashed line*), whereas a fall in P_{CO_2} shifts the curve to the left (*dotted line*).

2. A rise in pH shifts the curve to the left (*dotted line*), whereas a fall in pH shifts the curve to the right (*dashed line*).

3. A rise in temperature shifts the curve to the right (*dashed line*), whereas a fall in temperature shifts the curve to the left (*dotted line*).

Comment: Note that the oxyhemoglobin dissociation curve is shifted to the right under conditions of increased P_{CO_2}, low pH and high temperature, conditions that occur locally during tissue hypoxia and increased metabolism (e.g., during exercise). The rightward shift of the curve results in decreased affinity of hemoglobin for oxygen and therefore enhances delivery of oxygen to tissues. 2,3-Disphosphoglycerate (2,3-DPG), a metabolite of red blood cell glycolysis, also shifts the curve to the right and is elevated during hypoxia.

1–3. Identify oxyhemoglobin dissociation curves as curves expected in the normal state (15g Hb/100 mL), anemic state (7.5 g Hb/100 mL) and carbon monoxide poisoning.

4. Describe the effects of anemia on oxygen content of blood.

5. Describe the effects of carbon monoxide poisoning on oxygen content of blood.
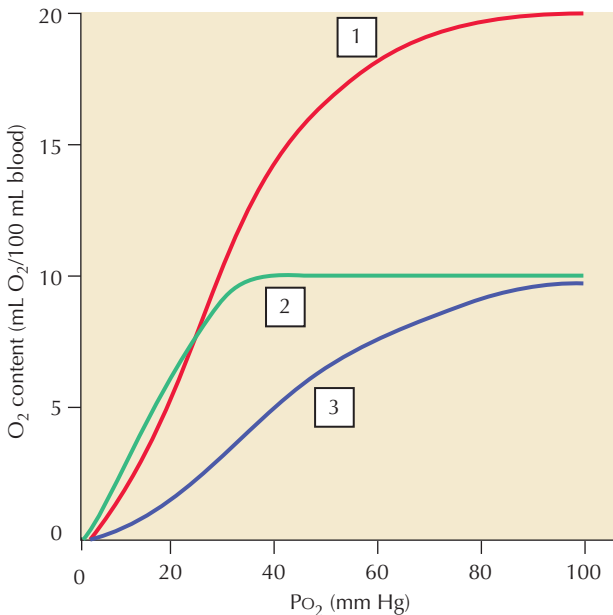
1. Normal Hb (15 g Hb/100 mL)
2. Carbon monoxide poisoning (as illustrated, normal Hb but 50% as carboxyhemoglobin)
3. Anemia (7.5 g Hb/100 mL)
4. In anemia, the content of oxygen in blood is reduced at any P_{O_2} in proportion to the reduction of hemoglobin concentration. Thus, on the graph, at any P_{O_2}, O_2 concentration of the anemic blood (line 3) is half that of normal blood (line 1).
5. Carbon monoxide has much higher affinity for hemoglobin than oxygen. In carbon monoxide poisoning, CO displaces oxygen bound to hemoglobin, forming carboxyhemoglobin and therefore reducing the oxygen carrying capacity of blood.

Comment: Finger-probe and earlobe-probe pulse oximeters used to monitor arterial SO_2 rely on colorimetric measurements, but because carboxyhemoglobin, like oxyhemoglobin, is red, false, high SO_2 readings result when this instrument is used in patients suffering from CO poisoning.

In this illustration, CO_2 is transported as carbaminohemoglobin, bicarbonate and in dissolved form. What is the relative importance of these three forms of CO_2 transport?

Red blood cell

Hb•NH$_2$

Hb•NHCOO$^-$

CO$_2$

Alveoli of lung

Hb•NHCOO$^-$
(carbaminoHb)

Bicarbonate

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Hb•NH$_2$

Hb•NHCOO$^-$

CO$_2$

Carbonic anhydrase
+
H$_2$O

Cl$^-$

HCO$_3^-$ + H$^+$
+ H$_2$O

CO_2 in physical solution

Body tissues
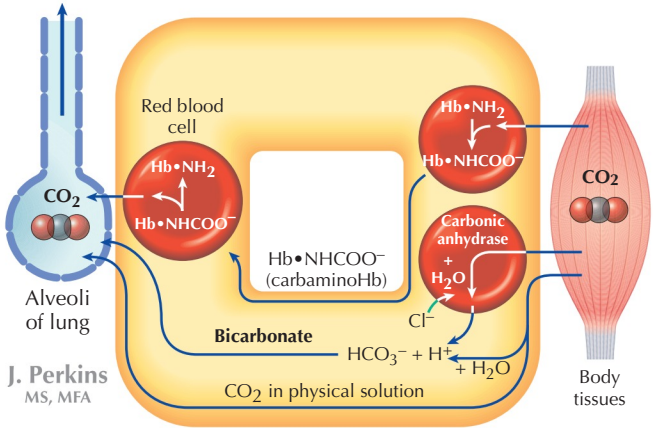
1. About 70% of CO_2 in blood is carried in the form of bicarbonate anion (HCO_3^-).
2. Up to 23% of CO_2 may be combined with protein, including hemoglobin (as **carbaminohemoglobin**). CO_2 binds to terminal amino groups of blood proteins.
3. About 7% of CO_2 in blood is **dissolved CO_2**. Because solubility of CO_2 in plasma is relatively high (20 $\times$ the solubility of O_2), the dissolved form of CO_2 has a significant role in its transport.

Based on this illustration, explain the Haldane effect and how it facilitates transport of CO_2.

CO_2 Equilibrium Curves
(for normal arterial and venous blood)

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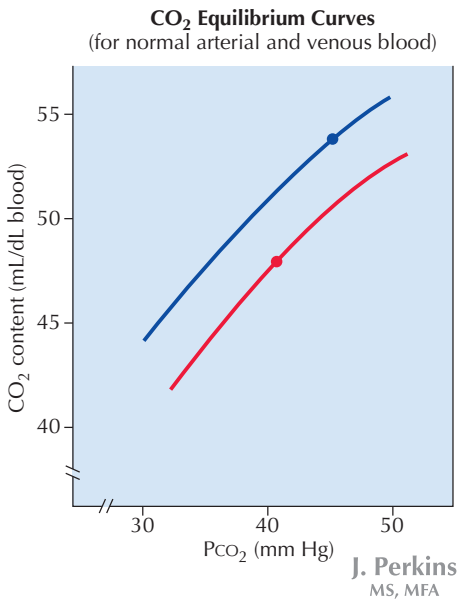
Comment: The dissociation curve for CO_2 in blood is linear and is shifted to the left when hemoglobin is in the form of deoxyhemoglobin, as in venous blood. Thus, the *left, upper line* in the figure is the curve for venous blood (the normal Pv_{O_2} marked), whereas the *right, lower line* represents the CO_2 dissociation curve for arterial blood (the point marked is the normal Pa_{O_2}. This shift is the Haldane effect. As a result of this effect, as hemoglobin is deoxygenated in systemic capillaries, its affinity for CO_2 is increased, facilitating CO_2 transport. In the lungs, as hemoglobin is oxygenated, its affinity for CO_2 is reduced, and as a result, transfer of CO_2 from blood to alveolar air is facilitated.

1. **Write the Henderson-Hasselbalch equation as it applies to the bicarbonate buffer system.**

2. **Write the equation in a form whereby pH can be calculated based on P_{CO_2} and plasma bicarbonate concentration.**

3. **Explain, in the context of this diagram, how the lungs act as a buffer for changes in blood pH.**

4. **Explain, in the context of this diagram, how changes in respiratory function can be a cause of acidosis or alkalosis.**

"Acid Load"

Volatile Acid (CO_2)

CO_2

$H^+ + HCO_3^- \longrightarrow H_2O + CO_2 \longrightarrow CO_2$

H^+ H^+ H^+ H^+ H^+ H^+ H^+ H^+ H^+ H^+ H^+

Body tissues

Nonvolatile Acid (HA)

$H^+ + A^- \longrightarrow HA$

CO_2
$+$
H_2O
$+$
NaA

NH_4^+

$NaHCO_3$

NaHCO$_3$
Replenish

NH_4A

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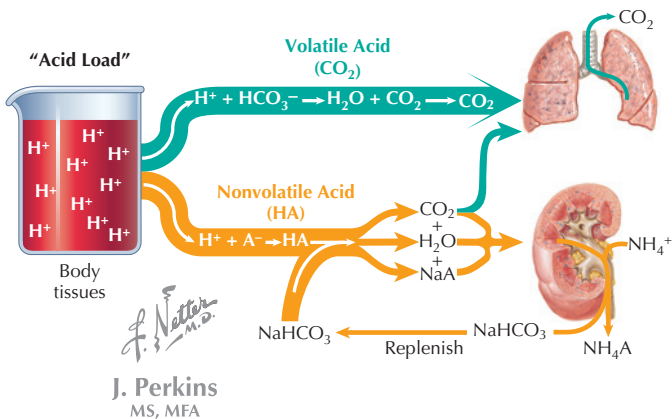
1.

$$pH = pK + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

2.

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03 \times Pco_2}$$

3. CO_2 formed during metabolism of lipids and carbohydrates is normally readily eliminated by the respiratory system. By adjusting respiration, the system can compensate for pH imbalances produced by metabolic disturbances. Thus, metabolic acidosis is compensated for in part by increased respiration, whereas reduced ventilation will occur in metabolic alkalosis.

4. Disturbances in respiration can result in acid–base imbalance because changes in CO_2 elimination will directly affect carbonic acid levels. Hypoventilation will cause respiratory acidosis, whereas hyperventilation will cause respiratory alkalosis. When a respiratory acid–base disturbance occurs, the compensation is primarily renal.

1. Explain the role of central chemoreceptors in the regulation of respiration. Discuss the relative importance of changes in arterial O_2, CO_2, and pH in this regulation.

2. Explain the role of arterial chemoreceptors in the regulation of respiration. Discuss the relative importance of changes in arterial O_2, CO_2, and pH in this regulation.
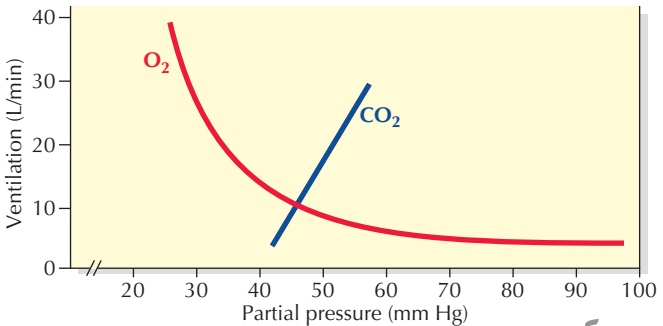
1. As illustrated, changes in arterial blood gas levels result in regulation of respiration. Central chemoreceptors respond primarily to changes in arterial P_{CO_2}, which diffuses into the CSF, altering its pH. The blood–brain barrier is largely impermeable to HCO_3^- and H^+. Brainstem respiratory centers adjust rate and depth of breathing, causing changes in Pa_{O_2} and Pa_{CO_2}, and thus blood pH.

2. Peripheral chemoreceptors in the carotid and aortic bodies respond to changes in arterial Pa_{O_2}, and also Pa_{CO_2} and pH. Impulses from these chemoreceptors reach the medullary respiratory center via the glossopharyngeal and vagus nerves, resulting in regulation of ventilation and normalization of Pa_{O_2} and Pa_{CO_2}.

Comment: Angiotensin II is a vasoconstrictor but does not play a role in the normal regulation of vascular smooth muscle tone in most vascular beds. However, in states such as hemorrhagic shock, the vasoconstriction by angiotensin may be important as one of the mechanisms that raise total peripheral resistance.

Note that in contrast to other vascular beds, in the kidney angiotensin II does have a physiological role in regulating the tone of afferent and efferent arterioles.

See Figure 15.5

1. **What are the factors that account for the initial, rapid adjustment of ventilation with the onset of exercise and the termination of exercise?**

2. **What are factors that play a role in the sustained elevation of respiration during exercise, and in the continued elevation in respiration during the recovery period?**
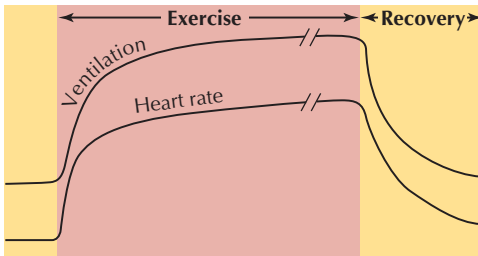
1. The rapid increase in respiration at the onset of exercise is through neural and reflexive mechanisms. Although not all of the mechanisms are known, one mechanism is that activation of motor pathways results in collateral activation of the respiratory center. Afferent signals from muscle and joint mechanoceptors result in further activation of respiration.

2. The slow responses that play a role in sustained elevation of respiration during exercise and during the recovery period are feedback responses. Chemoreceptor activation by changes in Pa_{O_2}, Pa_{CO_2}, and blood pH is important; the rise in core body temperature during exercise also has a role in stimulating respiration.

Renal Physiology

Identify each structure.

1. Renal artery
2. Renal vein
3. Renal pelvis
4. Ureter
5. Minor calyces
6. Major calyces
7. Renal pelvis
8. Cortex
9. Medulla
10. Papilla

Comment: The kidneys are bilateral retroperitoneal organs. Nephrons serve to filter the blood and process the ultrafiltrate. After the tubular fluid is processed, the remaining fluid (urine) flows through the medullary collecting ducts into the calyces: the calyces empty into the ureters that lead to the bladder where urine is stored until excreted.

Identify each structure.

Capsule

Cortex corticis

Cortex

Outer zone — Outer stripe

Outer zone — Inner stripe

Medulla (pyramid)

Inner zone

1

2

5

7

6

4

3
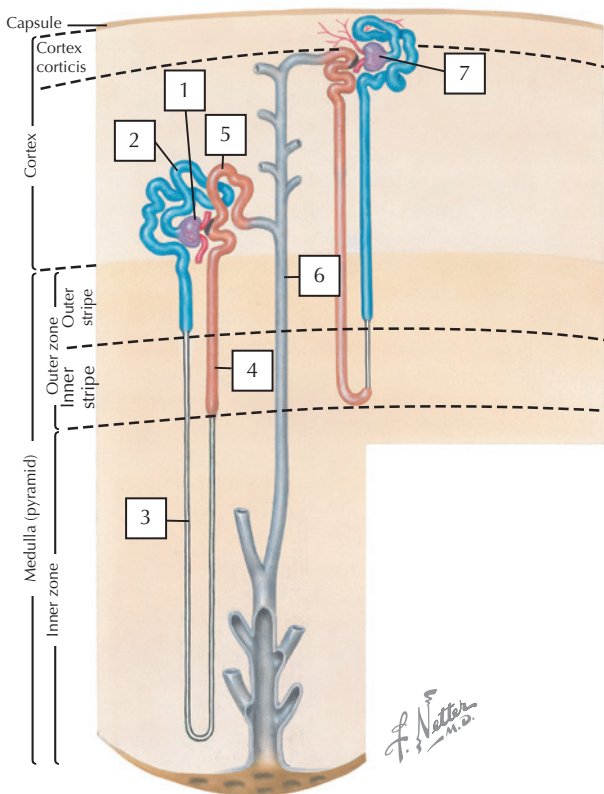
1. Juxtamedullary glomerulus
2. Proximal convoluted tubule
3. Thin descending limb of Henle
4. Thick ascending limb of Henle
5. Distal tubule
6. Collecting duct
7. Cortical glomerulus

Comment: The nephrons are the functional units of the kidneys. In humans, each kidney contains more than 1 million nephrons. Damage to, or loss of, up to 70% of the nephrons will not severely impair the ability of the kidneys to control fluid and electrolyte homeostasis.

Identify the two populations of nephrons and describe two characteristics of population 2 that are different than population 1.
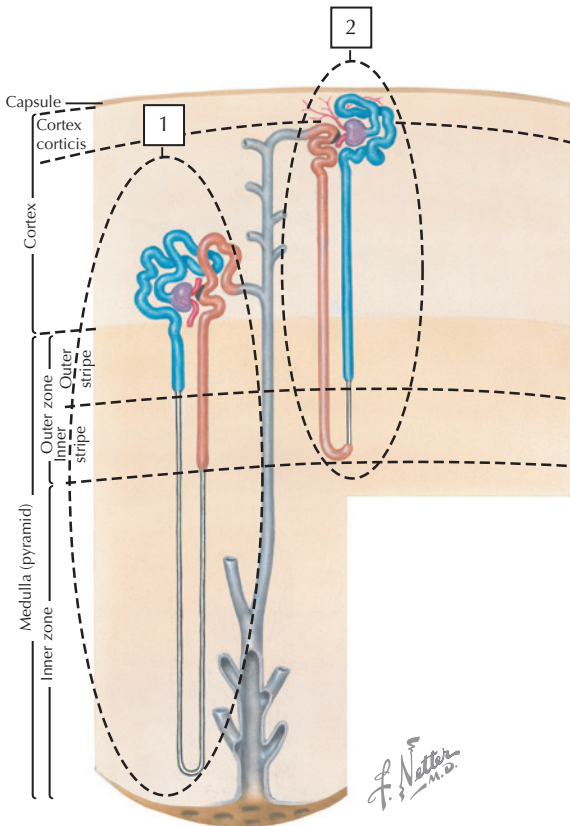
1. Cortical, or superficial, nephrons have glomeruli near the surface of the kidney and short loops of Henle that are found in the cortex and outer zone of the medulla. There are more than 1 million nephrons in each kidney, and 80% of the nephrons are cortical.

2. Juxtamedullary, or deep, nephrons have glomeruli in the cortex, but on the border of the medulla, with long loops of Henle, extending far into the medulla. Juxtamedullary nephrons have longer proximal convoluted tubules and loops of Henle than cortical nephrons. The longer proximal tubule contributes to greater proximal tubule bulk reabsorption of solutes, and the long loops of Henle establish and maintain a large interstitial osmotic gradient in the medulla, which is necessary for the concentration of urine.

Identify each structure.
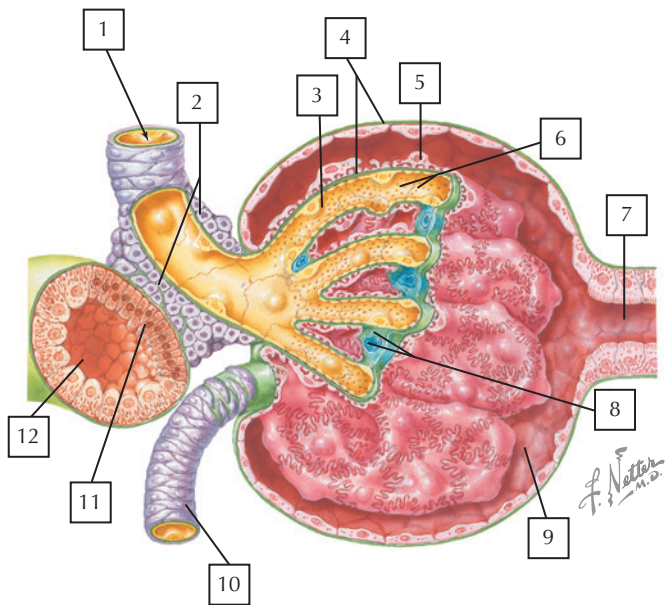
1. Afferent arteriole
2. Juxtaglomerular cells
3. Endothelium
4. Basement membrane
5. Podocytes
6. Fenestrated endothelium
7. Proximal tubule
8. Mesangial matrix
9. Bowman's space
10. Efferent arteriole
11. Macula densa
12. Distal tubule

Comment: The glomerulus is a capillary network from which an ultra-filtrate of plasma enters Bowman's space. Filtration depends on size and charge, and thus the capillary barrier prevents filtration of red blood cells and macromolecules (because of size) and most proteins (because of negative charge). Therefore, under normal conditions, urine will not contain red blood cells or protein.

1. Describe the effects of a selective increase in hydrostatic pressure (HP) in the afferent arteriole on glomerular filtration rate (GFR).

2. Describe the effect of an increase in tubular fluid flow rate through the macula densa on GFR.

3. Describe the effects of an increase in mesangial matrix on the GFR.
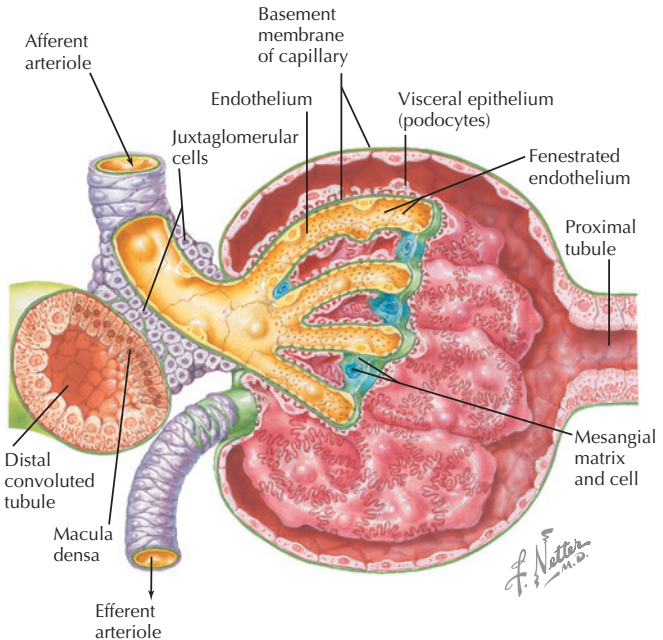
1. Increasing hydrostatic pressure (P) in the afferent arteriole will increase P_{GC} • P_{GC} is the major pressure forcing fluid out of the capillary and contributes to the GFR • GFR = Kf $\times$ [(P_{GC} + π_{BS}) − (P_{BS} + π_{GC})]. Thus, increasing P to the glomerulus will elevate GFR.

2. The juxtaglomerular apparatus (macula densa cells of the distal tubule and juxtaglomerular cells surrounding the afferent arteriole) are key factors in tubuloglomerular feedback control of GFR. Because of this association between the distal tubule and afferent arteriole, increasing tubular flow past the macula densa will increase afferent arteriolar resistance and reduce GFR. This mechanism allows regulation of GFR over a wide range of systemic blood pressures.

3. Increasing mesangial matrix increases the barrier to filtration and results in a reduction in GFR. Increased deposition of matrix can occur from pathologic processes involved in chronic renal failure and diabetes.

Glomerular Filtration   *See Figure 16.3*

If the urine flow rate ($\dot{V}$) is 2 mL/min, for the values given, determine:

1. Glomerular filtration rate (GFR)
2. Fractional excretion of x (FE_x)
3. Fractional reabsorption of x (FR_x)
4. Filtered load of y (FL_y)
5. Describe the net renal handling of substance Y.
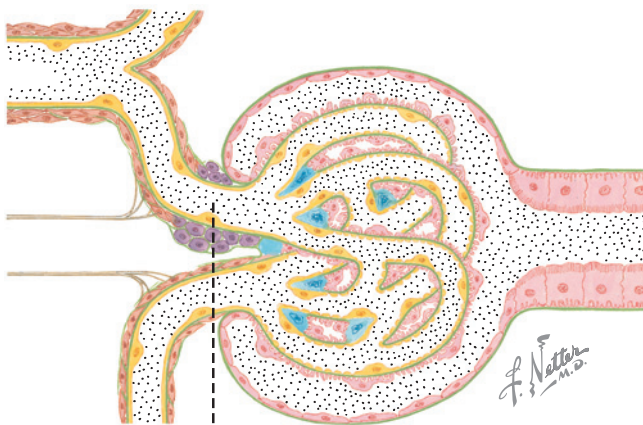
$P_{in} = 20$ mg%
$P_x = 1$ mg%
$P_y = 90$ mg%

$\dot{V} = 2$ mL/min

$U_{in} = 1000$ mg%
$U_x = 25$ mg%
$U_y = 0$ mg%

1. Glomerular filtration rate: $GFR = (U_{in}/P_{in}) \times \dot{V}$, thus $(1000 \text{ mg}\%/20 \text{ mg}\%) \times 2 \text{ mL/min} = 100 \text{ mL/min}$

2. Fractional excretion of x: $FE_x = [(U_x/P_x)/(U_{in}/P_{in})] \times 100$, thus $[(25 \text{ mg}\%/1 \text{ mg}\%)/(1000 \text{ mg}\%/20 \text{ mg}\%)] \times 100 = 50\%$

3. Fractional reabsorption of x: $FR_x = 100\% - FE_x$, thus $100\% - 50\% = 50\%$

4. Filtered load of y: $FL_y = GFR \times P_y$, thus because $90 \text{ mg}\% = 90 \text{ mg}/100 \text{ mL}$, $100 \text{ mL/min} \times 90 \text{ mg}/100 \text{ mL} = 90 \text{ mg/min}$

5. Net handling of a substance can be determined by comparing the clearance of the substance to the GFR (clearance of inulin). The clearance of substance Y is:

$$[(U_y/P_y)] \times \dot{V} = [(0 \text{ mg}\%/90 \text{ mg}\%)] \times 2 \text{ mL/min} = 0 \text{ mL/min}$$

Thus, the clearance of Y is less than the clearance of inulin, so net reabsorption occurred. Furthermore, in this particular case, substance Y was 100% reabsorbed because excretion was zero.

1. **Identify the sites where angiotensin II regulates glomerular filtration rate (GFR); does angiotensin II raise or lower GFR?**

2. **Describe the role of intrarenal prostaglandins on the GFR.**
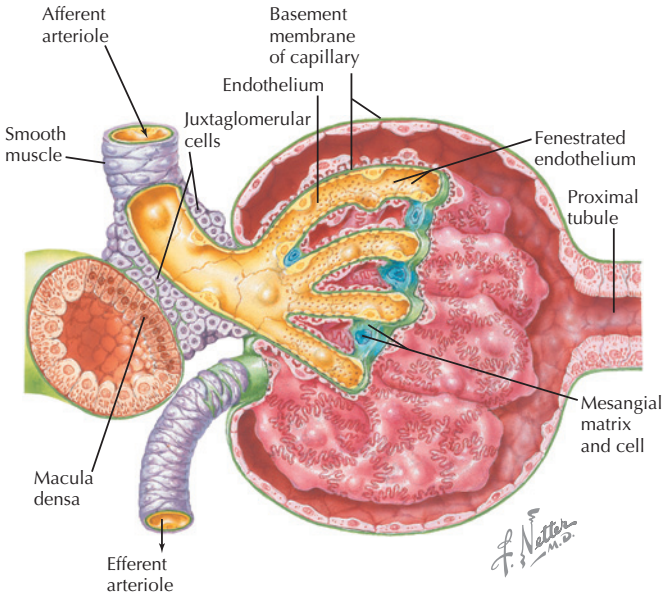
1. Angiotensin (Ang) II is a hormone that causes vasoconstriction of the renal arteries (not shown) and the renal arterioles, reducing glomerular capillary hydrostatic pressure. Ang II also constricts glomerular mesangial cells, and this, in addition to the decrease in capillary hydrostatic pressure, reduces GFR. Ang II is part of the renin-angiotensin-aldosterone system (RAAS).

2. Intrarenal prostaglandins (PGE_2 and PGI_2) are vasodilators and primarily serve to oppose the vasoconstrictor actions of Ang II on arterioles and mesangial cells.

1. Identify the sites where sympathetic nerves and catecholamines
   regulate glomerular filtration rate (GFR).

2. Does stimulation of sympathetic nerves and catecholamines raise
   or lower GFR?
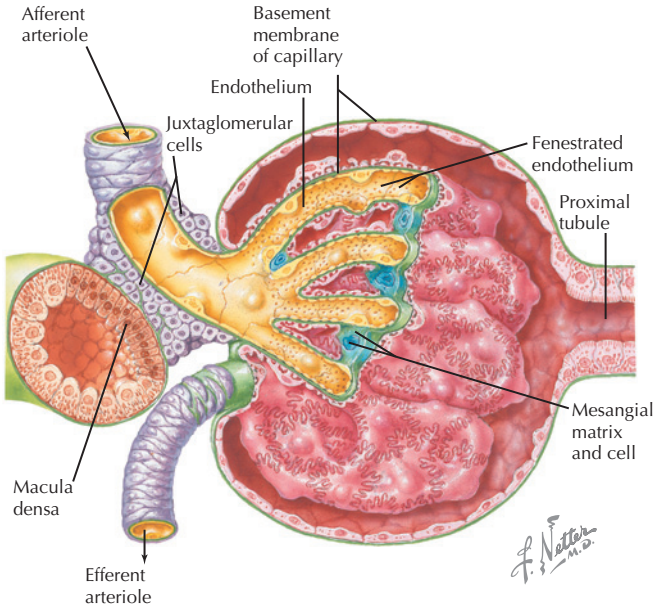
1. Sympathetic nerves and catecholamines are released in response to reductions in systemic blood pressure and cause constriction of renal arteries (not shown) and arterioles.
2. Decrease GFR.

1–6. Identify each site of the nephron.

7. Identify where sodium and chloride are reabsorbed.

8. Identify where water is reabsorbed.

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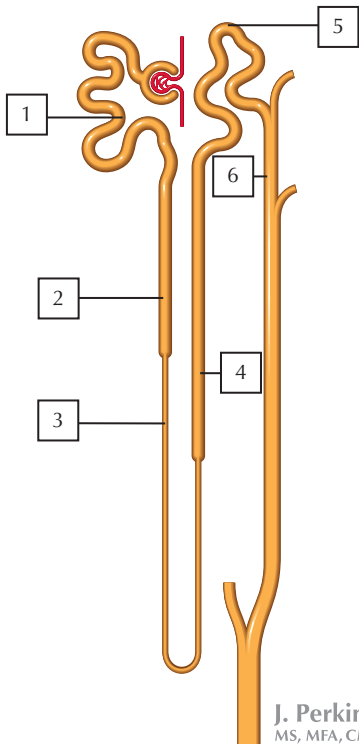
1. Proximal convoluted tube
2. Proximal straight tube
3. Thin descending limb of Henle
4. Thick ascending limb of Henle
5. Distal tubule
6. Collecting duct
7. Sodium is reabsorbed in the proximal convoluted tubule, proximal straight tubule, thick ascending limb of Henle, distal tubule, and collecting duct. Chloride follows sodium reabsorption in proximal convoluted tubule, proximal straight tubule, thick ascending limb of Henle, distal tubule, and collecting duct.
8. Water is reabsorbed with sodium movement in proximal convoluted tubule, proximal straight tubule, thick ascending limb of Henle, distal tubule, and collecting duct. In addition, *solute-free water* is reabsorbed in the thin descending limb of Henle, and in the presence of antidiuretic hormone (ADH), in the collecting ducts.

1. Identify where amino acids and glucose are reabsorbed.

2. Identify where bicarbonate is reabsorbed.

Distal
tubule

Proximal
convoluted
tubule

Collecting
duct

Proximal
straight
tubule

Thick ascending
limb of Henle

Thin descending
limb of Henle
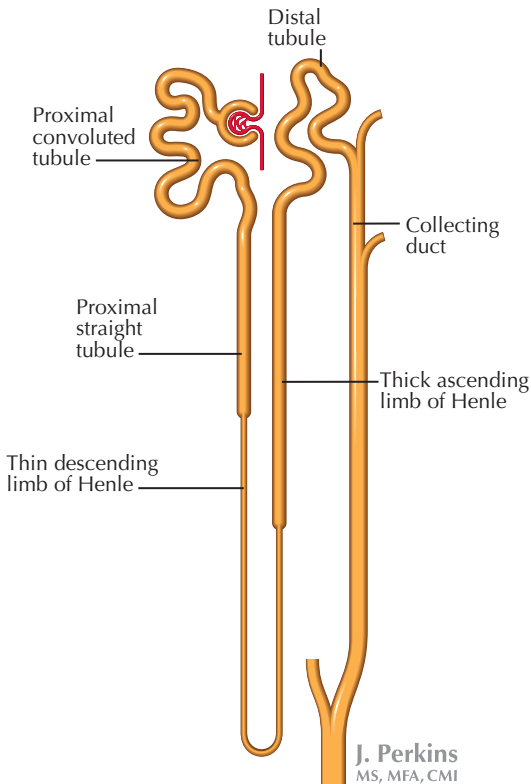
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1. Amino acids and glucose are reabsorbed (100%) in the proximal convoluted tubule.
2. Bicarbonate is reabsorbed in the proximal convoluted tubule, thick ascending limb of Henle, and collecting duct. Under most normal conditions, the filtered bicarbonate is 100% reabsorbed; however, if the person is alkalemic (higher then normal blood pH), bicarbonate will be secreted into the collecting ducts and excreted in the urine.

1. **Identify the site where bulk reabsorption of tubular fluid takes place.**
2. **State the approximate proportion of filtered water and (major) solutes reabsorbed by this process.**

THE NEPHRON:

KEY

	Glomerulus
	Afferent and efferent arterioles
	Proximal tubule Convoluted segment Straight segment
	Thin descending and ascending limbs of Henle's loop
	Distal segments Thick ascending limb of Henle's loop Distal convoluted tubule
	Macula densa Collecting duct
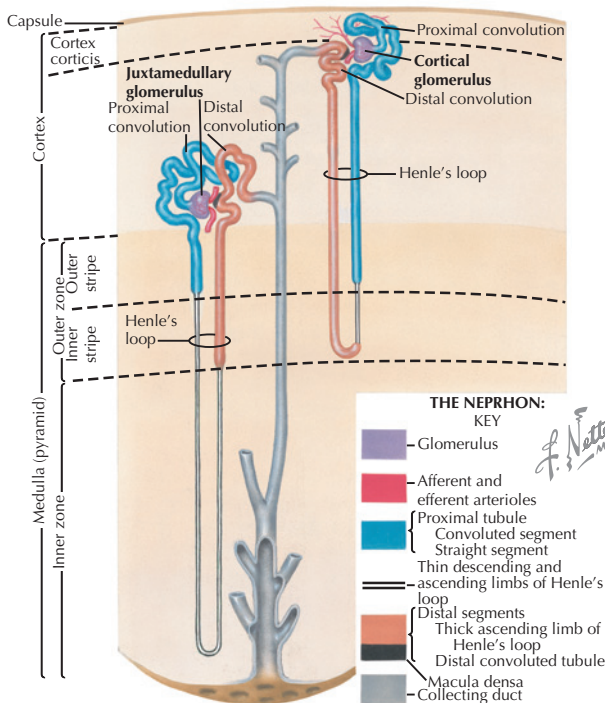
Renal blood flow	1–1.2 L/min	Number of nephrons	2.5 million
Glomerular filtration rate	100–125 mL/min 140–180 L/day	Cortical	2.1 million
Urine flow rate	0.5–18 L/day	Juxtamedullary	0.4 million

1. Bulk reabsorption of tubular fluid takes place in the proximal tubule.
2. About 60% to 70% of the sodium and water, 80% to 85% of K^+, 65% of Cl^-, and 100% of the glucose and amino acids in the tubular fluid are reabsorbed.

1. **Identify the site where the concentration of tubular fluid occurs, independent of antidiuretic hormone (ADH). Describe the mechanism.**
2. **Identify where the concentration of tubular fluid occurs in the presence of ADH.**
3. **Identify where the dilution of tubular fluid occurs.**

THE NEPHRON:
KEY
- Glomerulus
- Afferent and efferent arterioles
- Proximal tubule
  - Convoluted segment
  - Straight segment
- Thin descending and ascending limbs of Henle's loop
- Distal segments
  - Thick ascending limb of Henle's loop
  - Distal convoluted tubule
  - Macula densa
- Collecting duct

Renal blood flow	1–1.2 L/min	Number of nephons	2.5 million
Glomerular filtration rate	100–125 mL/min	Cortical	2.1 million
	140–180 L/day	Juxtamedullary	0.4 million
Urine flow rate	0.5–18 L/day		

1. ADH-independent concentration of tubular fluid occurs in the descending limb of Henle. This site is impermeable to solutes, but permeable to water, which serves to concentrate the tubular fluid at the bottom of the loop of Henle.

2. ADH increases water channels (aquaporins) in the collecting tubules and ducts. This allows solute-free water reabsorption, concentrating the urine.

3. Dilution of tubular fluid occurs in the thick ascending limb of Henle through the actions of the Na^+-K^+-$2Cl^-$ (NKCC) cotransporters. These transporters reabsorb solute while leaving fluid in the tubule, so that the distal tubule contains the most dilute tubular fluid in the nephron. This mechanism facilitates excretion of very dilute urine in volume-expanded states. It is also notable that the NKCC transporters contribute to the countercurrent multiplier system that sets up the interstitial osmotic gradient.

Describe the mechanisms by which sodium reabsorption occurs at each site.

Distal tubule

Proximal convoluted tubule

Collecting duct

Proximal straight tubule

Thick ascending limb of Henle

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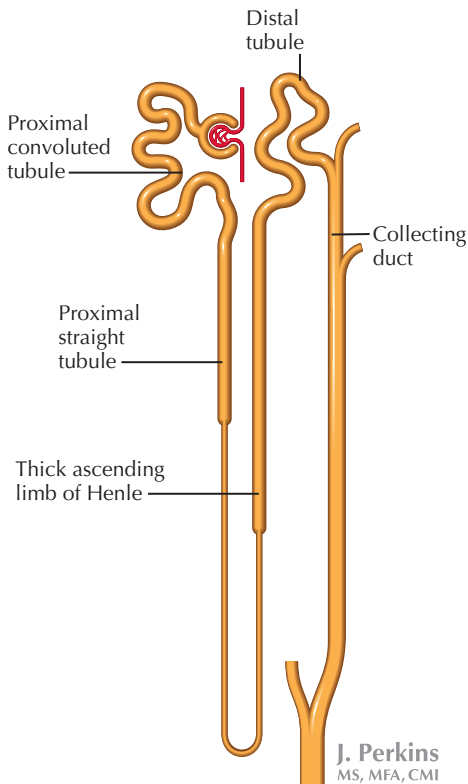
Nephron Sites of Sodium Handling

1. Proximal convoluted tubule: by cotransport (secondary active) with glucose, amino acids, phosphate, organic anions; antiport in exchange for H^+

2. Proximal straight tubule: by antiport in exchange for H^+

3. Thick ascending limb of Henle: by cotransport with K^+ and Cl^- (Na^+-K^+-$2Cl^-$ transporters), antiport in exchange for H^+

4. Distal tubule: by cotransport with Cl^-

5. Collecting duct: by aldosterone-sensitive Na^+ channels in principal cells

Comment: At each of these sites, the Na^+ gradient into the cells is generated by the basolateral Na^+/K^+ ATP.

Nephron Sites of Sodium Handling   *See Figure 17.1*
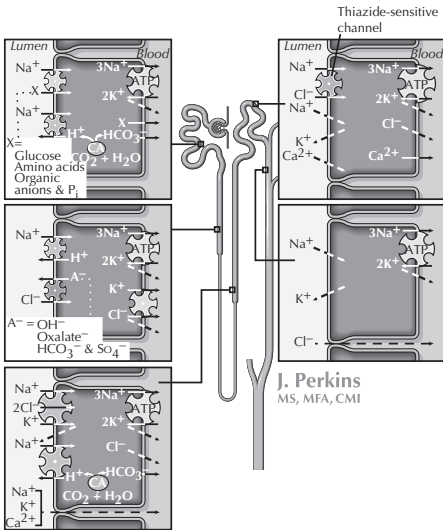
Angiotensin (Ang) II, aldosterone and atrial natriuretic peptide (ANP) all regulate renal sodium reabsorption. Identify how these substances affect sodium reabsorption at sites 1–3.
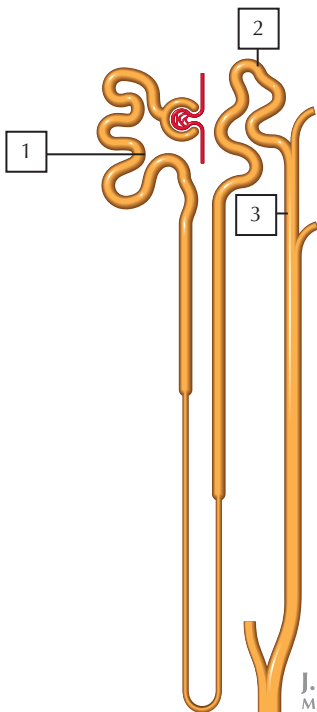
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Hormonal Control of Renal Sodium Reabsorption

1. At the proximal tubule, Ang II stimulates sodium reabsorption by increasing activity of the Na^+/H^+ antiporters.

2. Aldosterone is released from the adrenal cortex in response to elevated circulating Ang II concentrations. At the late distal tubules, aldosterone acts to increase apical Na^+ channels, thus increasing sodium (and Cl^- and water) reabsorption. Atrial natriuretic peptide (ANP) has indirect actions on distal sodium reabsorption by suppressing adrenal aldosterone release.

3. Aldosterone acts on collecting ducts to increase apical Na^+ channels, thus increasing sodium (and Cl^- and water) reabsorption. (Ang II has indirect actions to increase distal sodium reabsorption through its ability to reduce GFR and increase aldosterone release.) ANP is released from cardiac myocytes primarily in the right atrium in response to elevated volume. At the renal collecting ducts, ANP inhibits apical Na^+ channels, reducing Na^+ reabsorption and producing natriuresis and diuresis.

Hormonal Control of Renal Sodium Reabsorption

See Figure 17.1

1. Describe the site and mechanism of glucose reabsorption.

2–4. Describe the handling of glucose as represented at the three different filtered loads (glucose is depicted as *black dots*).
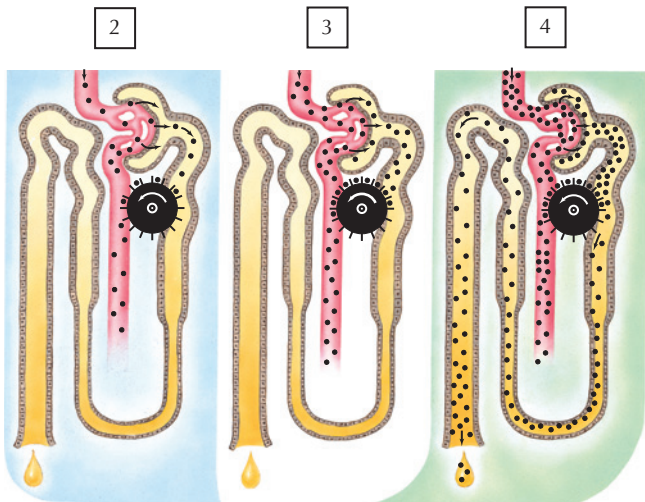
1. Renal glucose reabsorption occurs exclusively in the proximal convoluted tubules, via Na^+-glucose cotransporters. In normal individuals, glucose is 100% reabsorbed and does not appear in the urine. It can only appear in the urine if the transport maximum is exceeded.

2. Depicts when the filtered load of glucose is *under* the transport maximum. All of the glucose is reabsorbed, and none appears in the urine. This represents glucose handling under normal conditions.

3. Represents when the *transport maximum for glucose* is reached; *all of the transporters are saturated,* and all of the glucose that enters the renal tubules is reabsorbed (none is left in the tubule for excretion). Again, at this point, there is no glucose in the urine.

4. Depicts when the transport maximum for glucose is *exceeded*. If the filtered glucose enters the renal tubules at too high a rate, the transport maximum will be exceeded, and glucose will remain in the tubules. Because glucose transporters are only found in the proximal tubules, unabsorbed glucose will be excreted in the urine.

1. Identify the physiologic relevance of this point.

2. Explain what the *hatched area* depicts.

3. Give an example of when the transport maximum for glucose would be exceeded.
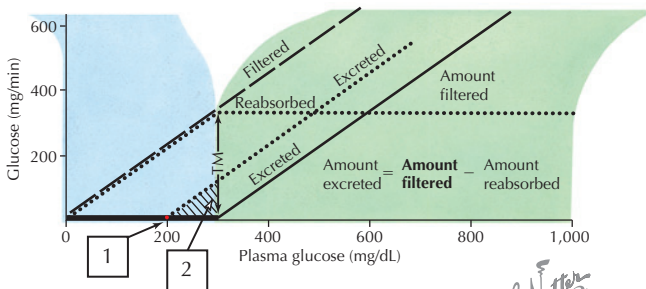
1. Plasma level above which glucose will start appearing in the urine.

2. The *hatched area* indicates splay. *Splay* refers to the phenomenon whereby glucose appears in the urine when plasma glucose is under the calculated plasma level at which the transport maximum (TM) (in this case for glucose) should be reached. The TM actually occurs at a plasma value that is less than the calculated value, because of nephron heterogeneity (whereby different nephron populations have different TMs).

3. The TM for glucose can be exceeded in poorly controlled diabetes: elevated plasma glucose concentrations will increase the filtered load of glucose above the renal threshold for reabsorption. The transporters will be saturated, and glucose will appear in the urine (*glucosuria*). Also, because glucose is an osmotic agent, the glucosuria will be accompanied by diuresis.

1–3. Give the percent of filtered bicarbonate (HCO_3^-) reabsorbed at each site.

4. From what cells of the nephron can HCO_3^- be secreted into the tubular fluid?

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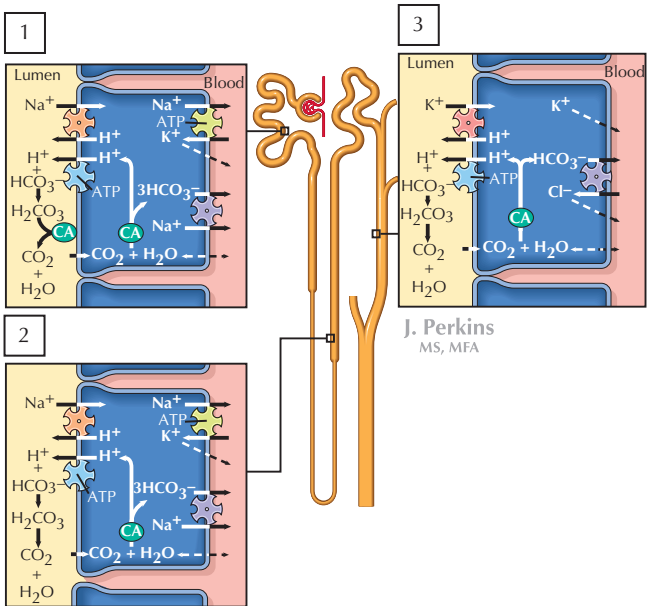
Renal Bicarbonate Handling

1. Proximal tubule: about 80% of bicarbonate
2. Thick ascending limb of Henle: 15%
3. Collecting ducts: 5%
4. Under normal conditions, 100% of the filtered bicarbonate is reabsorbed, and thus none is found in the urine. However, when HCO_3^- needs to be removed from the blood (as during alkalosis), HCO_3^-/Cl^- exchangers are inserted in the apical membranes of the *β-intercalated cells of the collecting ducts*. This allows HCO_3^- secretion into tubular fluid and excretion in urine.

Reabsorbs 80% of filtered load

Reabsorbs 5% of filtered load

Reabsorbs 15% of filtered load

J. Perkins
MS, MFA

1. Identify the nephron sites of potassium secretion.

2. Describe three physiologic factors or conditions that can stimulate potassium secretion into the renal tubule.

Proximal convoluted tubule

Distal tubule

Proximal straight tubule

Thick ascending limb of Henle
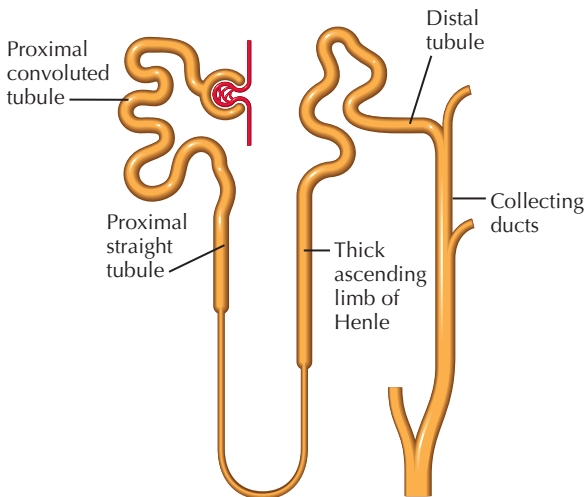
Collecting ducts

J. Perkins
MS, MFA

1. Potassium secretion can only occur distally, in late distal tubules, and collecting ducts. The principal cells of the collecting ducts have apical K^+ channels, which can transport potassium into the tubular fluid.

2. Potassium secretion can be stimulated by a diet high in potassium, which increases plasma potassium (hyperkalemia), aldosterone (which is elevated in response to hyperkalemia or stimulation of the RAAS), and acute and chronic alkalosis.
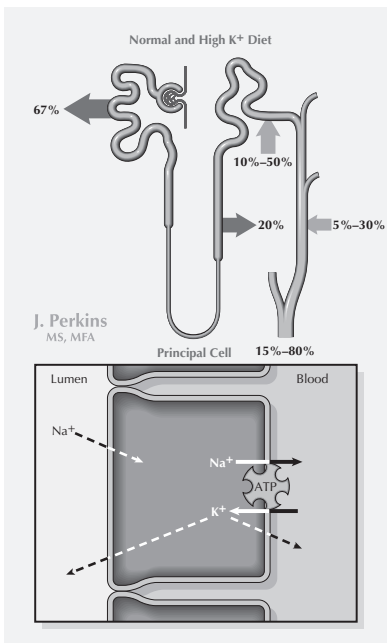
Normal and High K^+ Diet

67%

10%–50%

20%   5%–30%

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Principal Cell   15%–80%

Lumen   Blood

Na^+

Na^+

ATP

K^+

1. Identify the potential sites of K+ reabsorption.

2. Describe two physiologic factors/conditions that stimulate K+ reabsorption.
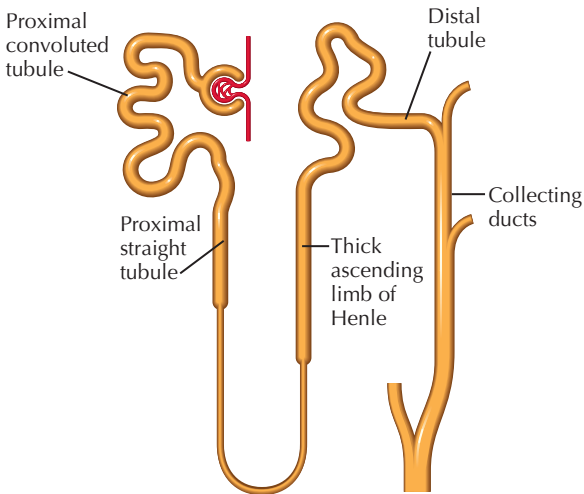
Proximal convoluted tubule

Distal tubule

Proximal straight tubule

Thick ascending limb of Henle

Collecting ducts

J. Perkins
MS, MFA

1. Proximal convoluted tubule, thick ascending limb of Henle, distal tubule, collecting ducts. Note: Under normal conditions reabsorption does not occur in the distal tubules and collecting ducts.

2. Potassium reabsorption can be increased when plasma potassium concentrations are low (hypokalemia, as from a diet low in potassium) or from acidosis. The α-intercalated cells of the collecting duct are an important site of distal K^+ reabsorption, with K^+ entering the cells via H^+/K^+ exchangers; this results in secretion of H^+ into the tubular fluid.
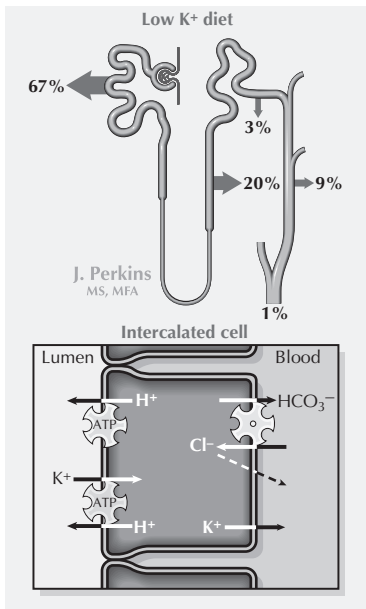
1. **Identify the nephron sites of calcium reabsorption.**

2. **Predict the effect of an increase in plasma PTH on calcium reabsorption.**
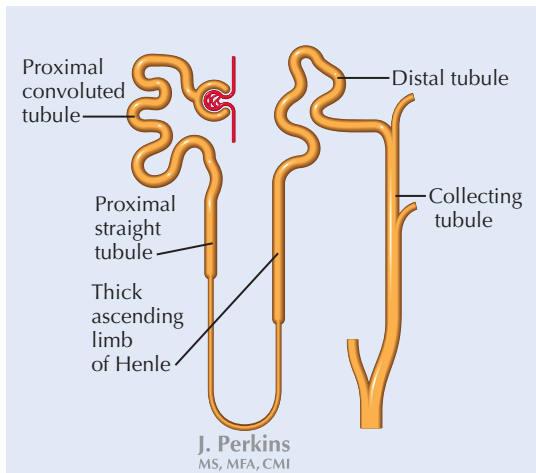
1. Proximal convoluted tubule, thick ascending limb of Henle, late distal tubules, collecting ducts. Under normal conditions, about 99% of filtered calcium is reabsorbed.
2. PTH will increase calcium channels in the apical membranes of cells in the distal tubules, ensuring efficient reabsorption of all calcium in the tubular fluid.

Calcium excretion

70%

~9%

20%   1%

1%

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Distal tubule

Lumen   Blood

Ca^{2+}

Ca^{2+}

Ca^{2+}

Ca^{2+}

3Na$^+$
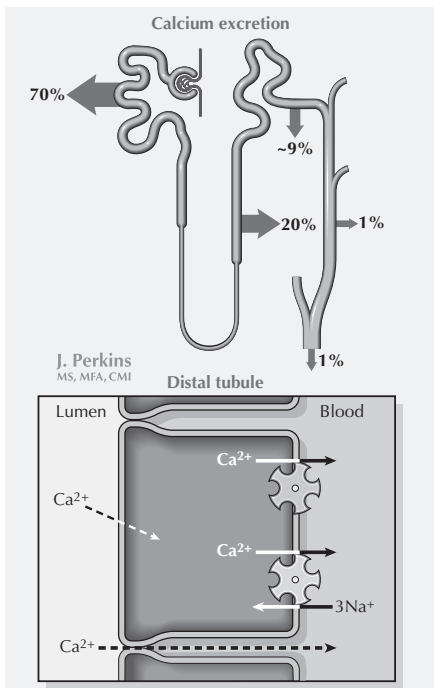
1. **Identify the nephron sites of phosphate reabsorption under normal conditions.**

2. **Predict the effect of an increase in PTH on phosphate reabsorption.**

3. **Predict the effect of a diet low in phosphate on phosphate reabsorption, and identify the nephron sites involved in this adaptation.**
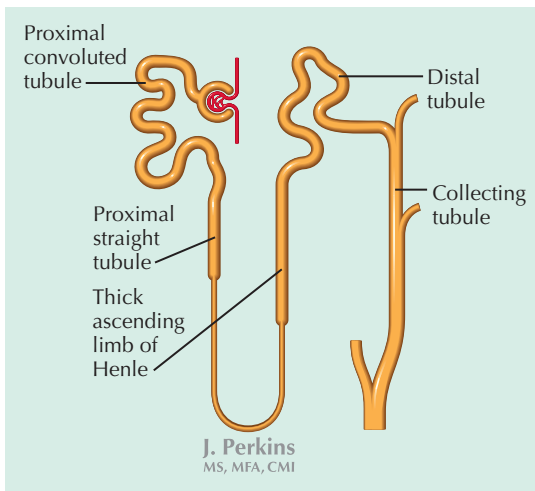
Renal Phosphate Handling

1. Under normal conditions, about 75% of the filtered phosphate is reabsorbed in the proximal convoluted tubule, and the remaining 25% is excreted in the urine.
2. PTH acts at the proximal tubule to inhibit sodium-phosphate co-transporters. This significantly increases phosphate excretion.
3. Diets low in phosphate will reduce plasma phosphate concentration, which is a main stimulus for phosphate reabsorption. Sodium-phosphate cotransporters will be inserted in membranes of the proximal convoluted, proximal straight, and distal tubules, reducing phosphate excretion.

Phosphate excretion

25%–75%

~5%

10%–15%

5%–25%

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Proximal tubule

Lumen | Blood

Na+

ATP

K+

Pi

II

2Na+

Pi

A−

P
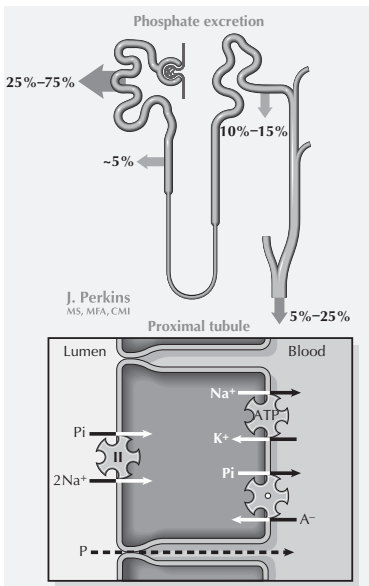
Renal Phosphate Handling   *See Figure 17.5*

1–5. Identify the mechanisms associated with establishing the renal medullary interstitial concentration gradient at each site during concentration of urine (values given below occur during urine dilution).

6. Identify the site of action of "loop" diuretics, and predict the effect of such a compound on the interstitial concentration gradient.

Note: Figures given are exemplary rather than specific
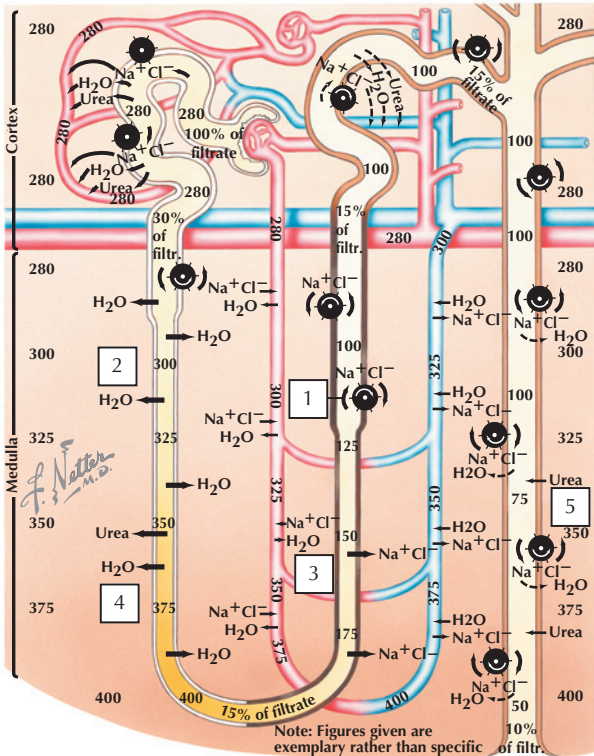
1. Concentrated tubular fluid facilitates solute transport out of tubule as it enters the thick ascending limb.

2. Solute-free water reabsorption in the descending limb of Henle concentrates tubular fluid.

3 and 5. Urea is "recycled" through ADH-dependent urea reabsorption in the collecting ducts (5) and thin descending loop of Henle (4), contributing to the interstitial concentration gradient.

4. Na^+-K^+ $2Cl^-$ cotransporters in the thick ascending limb of Henle dilute the tubular fluid and increase interstitial solutes.

6. Loop diuretics (such as furosemide and bumetanide) inhibit the Na^+-K^+ $2Cl^-$ cotransporters in the thick ascending limb of Henle (1). This increases the solute load to the distal tubule and collecting ducts, resulting in a natriuresis and diuresis. Because these transporters also help maintain the interstitial concentration gradient, inhibition by loop diuretics will disrupt the concentration gradient, reducing the ability to concentrate tubular fluid in the descending thin limb of Henle as well as the ability to concentrate urine in the collecting ducts. This results in continued diuresis.

1. **Identify the site of action of antidiuretic hormone (ADH) on water reabsorption.**
2. **Describe under what conditions ADH would be elevated, and predict the effect of increased plasma ADH on urine volume.**

Note: Figures given are exemplary rather than specific
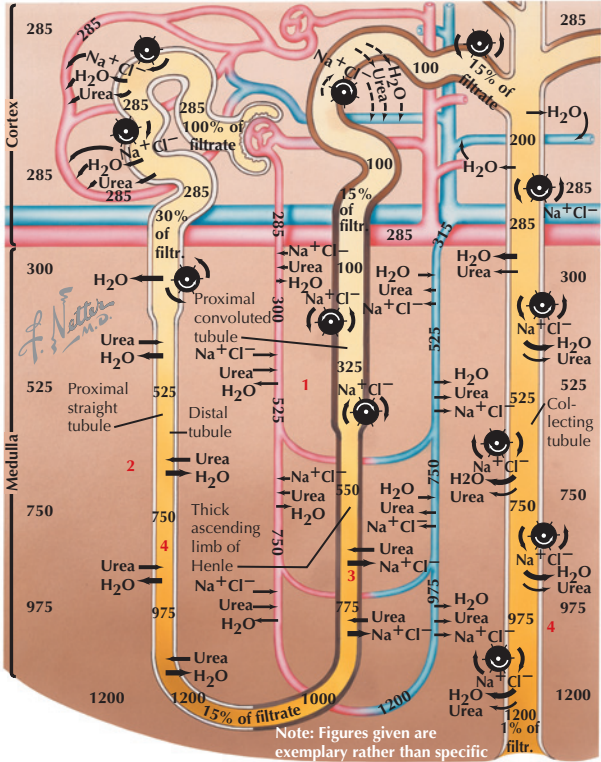
1. ADH acts at the principal cells of the collecting ducts to increase apical water channels (AQP2). This increases the reabsorption of water in cortical and medullary collecting ducts. ADH also promotes urea reabsorption in the medullary collecting ducts, an action that contributes to increasing the interstitial concentration gradient.

2. ADH secreted from the posterior pituitary gland in response to small increases (1% to 2%) in plasma osmolarity or significant reductions in blood volume (10% to 12% or greater loss). Thus, plasma ADH would typically be elevated as a person becomes dehydrated. ADH increases water channels in the collecting ducts, resulting in a small volume of concentrated urine.

1–4. Identify structures associated with the juxtoglomerular apparatus.

5. Define the components of the RAAS.
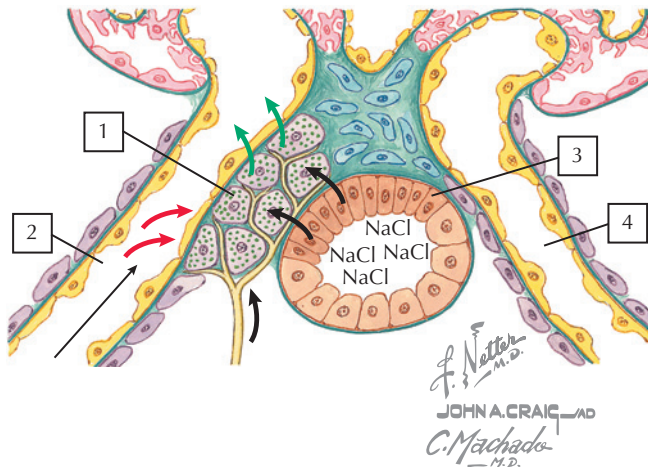
1. Juxtaglomerular (JG) cells
2. Afferent arteriole
3. Macula densa
4. Efferent arteriole
5. The components of the RAAS are: the enzyme **renin**, which cleaves the circulating protein **angiotensinogen** to **angiotensin I**; **angiotensin-converting enzyme (ACE)**, which acts on Ang I to produce **Ang II**; and the adrenal mineralocorticoid, **aldosterone**, the release of which is stimulated by Ang II. Ang II and aldosterone act primarily through the blood to regulate fluid homeostasis and blood pressure.

Mechanisms of Renin Release

Juxtaglomerular (JG) cells

Afferent arteriole

Macula densa

Efferent arteriole

NaCl
NaCl
NaCl
NaCl

F. Netter M.D.

JOHN A. CRAIG AD

C. Machado M.D.
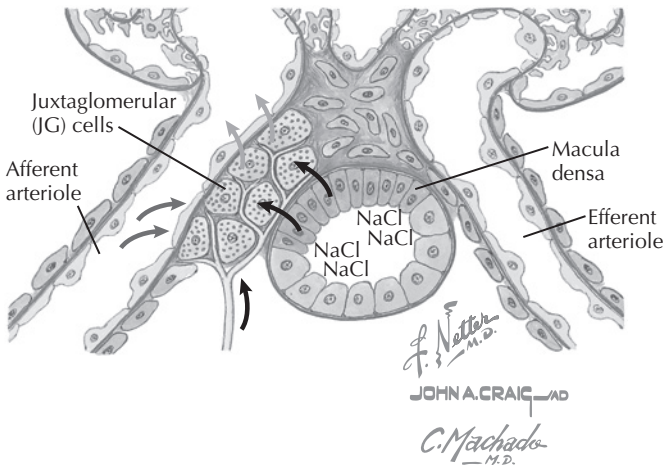
Renin-Angiotensin-Aldosterone System (RAAS) I

See Figure 19.1

1. Identify the site of renin production and secretion.

2. Identify the site of the intrarenal baroreceptor mechanism and describe how the mechanism works.

Mechanisms of Renin Release

Juxtaglomerular (JG) cells

Afferent arteriole

Macula densa

Efferent arteriole

NaCl NaCl
NaCl
NaCl
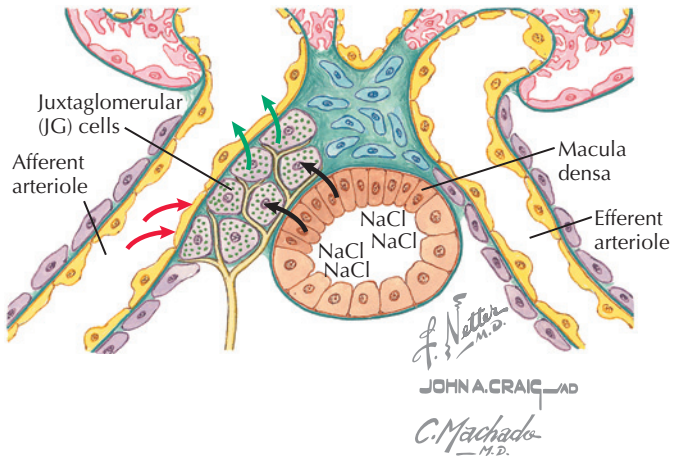
Renin-Angiotensin-Aldosterone System (RAAS) II

1. The juxtaglomerular cells produce and secrete renin into the afferent arteriole in response to low distal tubular sodium *or* increased distal tubular fluid flow rate.
2. The intrarenal baroreceptor mechanism responds to changes in pressure in the afferent arteriole. An increase in afferent arteriolar pressure will inhibit renin release from the juxtaglomerular cells; a decrease in pressure will stimulate renin release.

Predict the effect of a decrease in blood pressure and fluid volume, and an increase in β₁-adrenergic stimulation on:

1. Plasma angiotensin and aldosterone levels.

2. Renal sodium and fluid handling.

Angiotensinogen

↓ Blood pressure
↓ Fluid volume
↑ β₁-Sympathetic

? Renin

? Angiotensin I

ACE

? Angiotensin II

H₂O
NaCl

? NaCl/H₂O reabsorption

? Vasoconstriction
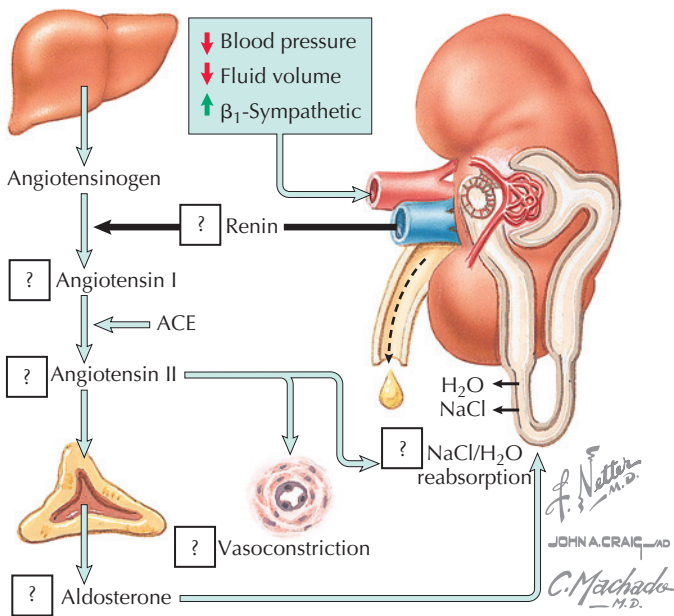
? Aldosterone

1. A reduction in blood pressure and fluid volume or β_1- adrenergic stimulation will increase the RAAS by elevating renin release from the juxtaglomerular cells. The increased renin secretion into the blood will facilitate conversion of angiotensinogen to Ang I, which will be converted to Ang II by ACE in the lungs and in other tissues. The Ang II will stimulate aldosterone secretion from the adrenal cortex.

2. At the kidney, Ang II acts to constrict afferent and efferent arterioles, with an overall effect of decreasing glomerular filtration rate, promoting sodium retention; Ang II also increases sodium reabsorption at the renal proximal tubule. Aldosterone acts at the late distal tubules and collecting tubules to stimulate sodium (and water) reabsorption. The overall effect is to increase renal sodium and water retention.
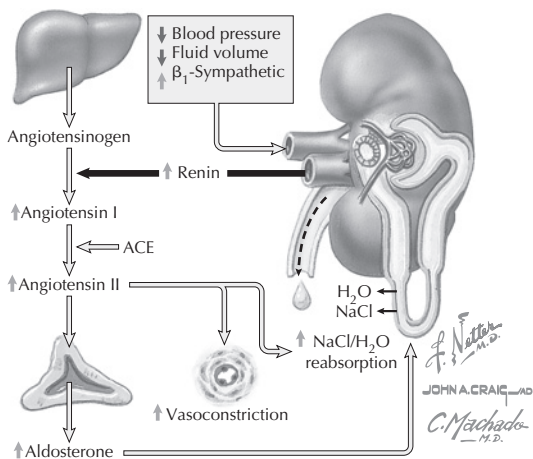
Predict the effect of an increase in blood pressure and fluid volume, and a decrease in β_1-adrenergic stimulation on:

1. Plasma angiotensin and aldosterone levels.

2. Renal sodium and fluid handling.

↑ Blood pressure
↑ Fluid volume
↓ β_1-Sympathetic
ANP

Angiotensinogen

? Renin

? Angiotensin I

ACE

? Angiotensin II

H_2O
NaCl

? NaCl/H_2O reabsorption

? Vasoconstriction
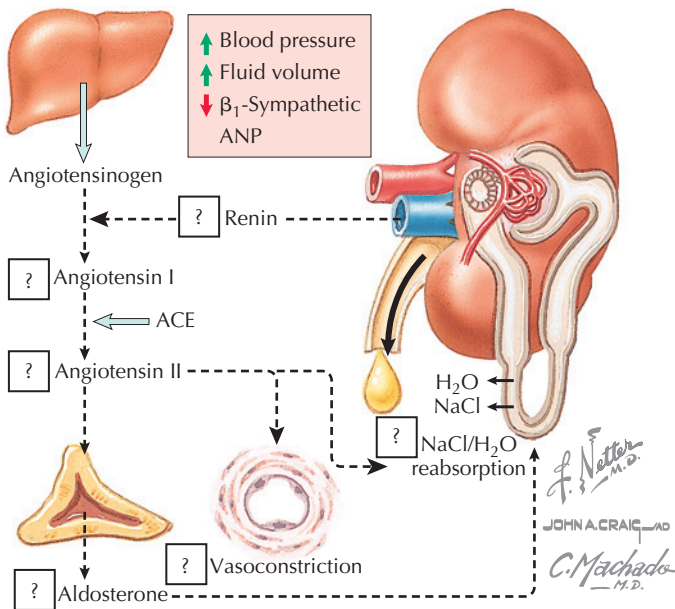
? Aldosterone

1. An increase in blood pressure or fluid volume or a decrease in β-adrenergic stimulation will reduce renin secretion, suppressing the RAAS. In addition, myocytes in the right cardiac atrium respond to the elevated blood volume and stretch by releasing ANP into the systemic circulation.

2. ANP increases sodium and fluid excretion and suppresses aldosterone, reducing volume load. Renal renin secretion into the blood decreases (due to the increased afferent arteriole pressure), reducing conversion of angiotensinogen to Ang I, and thus reducing circulating Ang II. The overall effect is to increase renal sodium and water excretion.

↑ Blood pressure
↑ Fluid volume
↓ β₁-Sympathetic
ANP

Angiotensinogen

↓ Renin

↓ Angiotensin I

⇐ ACE

↓ Angiotensin II

H_2O
NaCl

↓NaCl/H_2O
reabsorption

↓ Vasoconstriction

↓ Aldosterone

See Figure 19.1

1. **Predict the effect of volume contraction (eg, dehydration)
on changes in sympathetic activity and hormones listed.**

2. **Describe the overall effect of these changes on renal
sodium and water handling.**
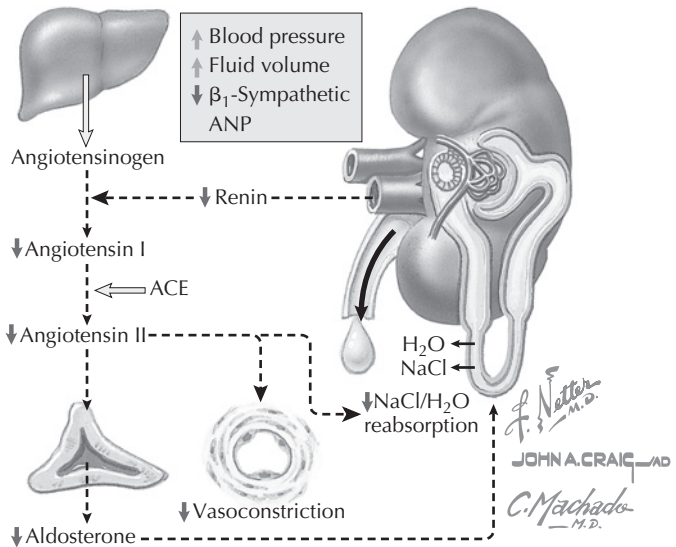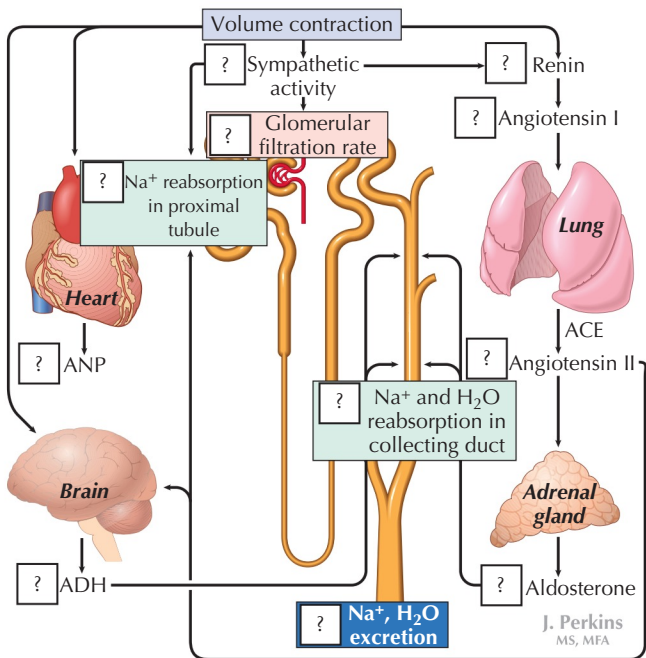
Volume Regulation I: Integrative Response to Volume Contraction

1. See diagram below.
2. The overall response to volume contraction is a *decrease* in renal sodium and water excretion.

See Figure 19.2

1. **Predict the effect of volume expansion (e.g., drinking an extra liter of fluid) on changes in sympathetic activity and hormones listed.**

2. **Describe the overall effect of these changes on renal sodium and water handling.**
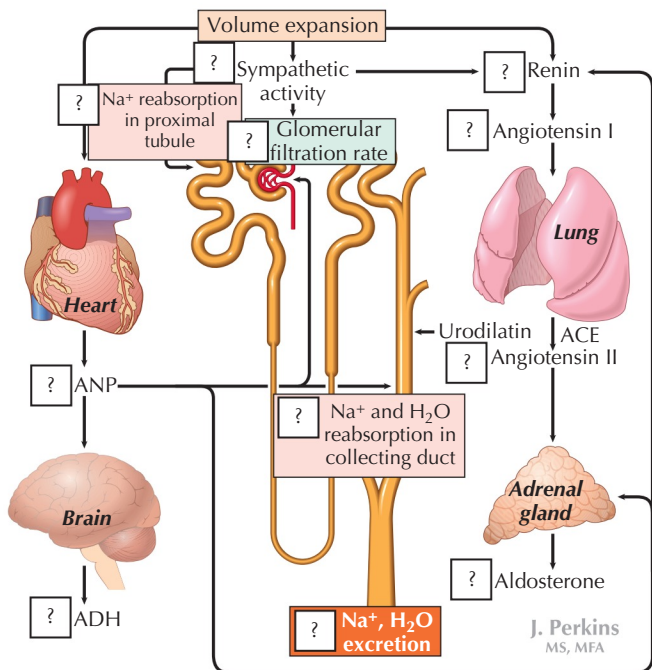
Volume Regulation II: Integrated Response to Volume Expansion

1. See diagram below for volume expansion.
2. The overall response to volume expansion is natriuresis and diuresis, reducing plasma volume.

1. Describe the renal mechanisms that contribute to excretion of H⁺.

2. Describe the renal mechanisms that allow excretion of HCO_3^-, and state under what conditions this would be likely to occur.

"Acid Load"

Acid intake → **Cell** → Nonvolatile acid (HA) → Lung buffering and renal acid excretion
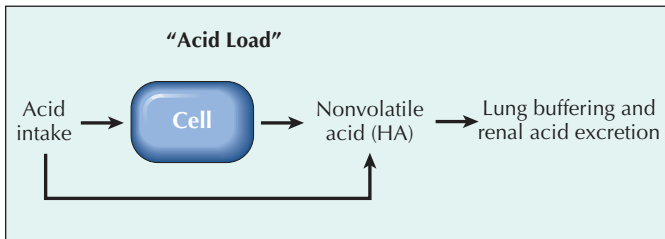
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MS, MFA

1. H^+ is buffered and excreted by the kidneys in the form of ammonium (NH_4^+) and titratable acids (TA) (primarily phosphoric acid, $H_2PO_4^-$).

2. The β-intercalated cells of the collecting ducts are the sites of apical HCO_3^-/Cl^- exchangers. These apical HCO_3^-/Cl^- transporters allow secretion of HCO_3^- into the tubular fluid and reabsorption of Cl^-. Under normal conditions, this antiporter is *not* active; however, the antiporter is increased during alkalosis, compensating for the elevated plasma pH by excreting HCO_3^- in the urine.

Comment: Although there is secretion of H^+ in many segments of the nephron, the α-intercalated cell of the collecting ducts is a key site contributing to H^+ secretion. In this late segment of the nephron the H^+ that is secreted will be buffered (as NH_4^+ or TA) and excreted in the urine.

1. **Identify the site of renal ammonia (NH₃) production, and describe the mechanism for ammonia generation.**

2. **Predict the effect of systemic acidosis on urinary ammonium excretion.**

Distal tubule

Proximal convoluted tubule

Collecting duct

Proximal straight tubule

Thick ascending limb of Henle

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Acid–Base II: Ammonia Synthesis
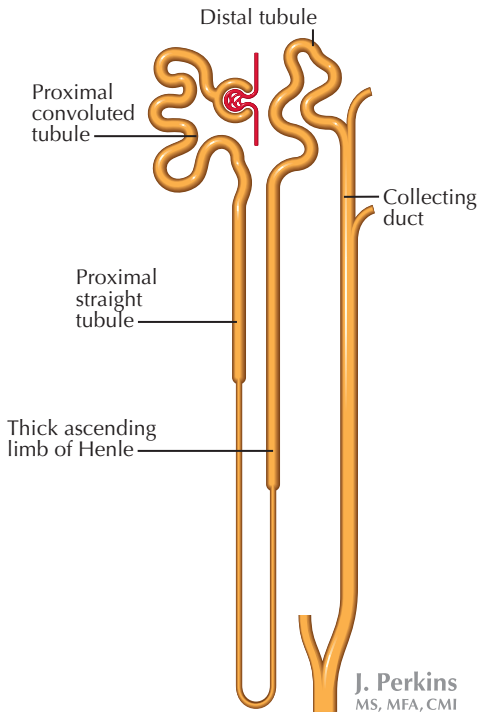
1. Renal ammoniagenesis occurs in the proximal tubule. The tubular cells can synthesize glutamine, which is the substrate for ammonia. The glutamine is hydrolyzed to produce glutamate and one NH_3. The glutamate is further metabolized to α-ketoglutarate and an additional NH_3. The α-ketoglutarate metabolism yields two HCO_3^-, which is reabsorbed as *new* bicarbonate. Thus, the reaction yields two NH_3 and two HCO_3^-. The NH_3 is secreted into the tubule, immediately binding free H^+, forming NH_4^+ (ammonium).

2. To compensate for acidosis, the kidneys will increase ammoniagenesis and increase secretion of H^+ from the α-intercalated cells of the collecting ducts, resulting in *increased* urinary excretion of NH_4^+.

Production and Excretion of Ammonium

Acid–Base II: Ammonia Synthesis   *See Figure 17.1*
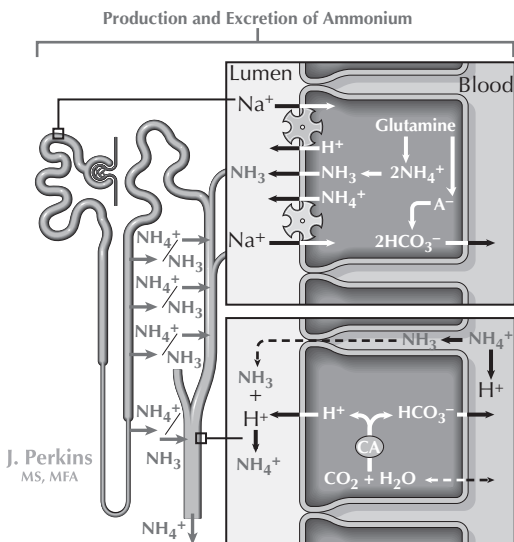
1. Complete the equation shown.

2. Predict daily NAE if a person is in acid–base balance and they ingest 40 μmol of H⁺ in food and drink each day.

Net acid excretion=?

1. $NAE = U_{TA} + U_{NH4+} - U_{HCO3-}$
2. If a person is in balance, intake will equal urine output (40 μmol H^+).

1. State the primary form of urinary titratable acids.

2. Predict the effect of systemic acidosis on urinary TA excretion, and identify the main site of H+ secretion during acidosis.

Distal tubule

Proximal convoluted tubule

Collecting duct

Proximal straight tubule

Thick ascending limb of Henle

J. Perkins
MS, MFA, CMI
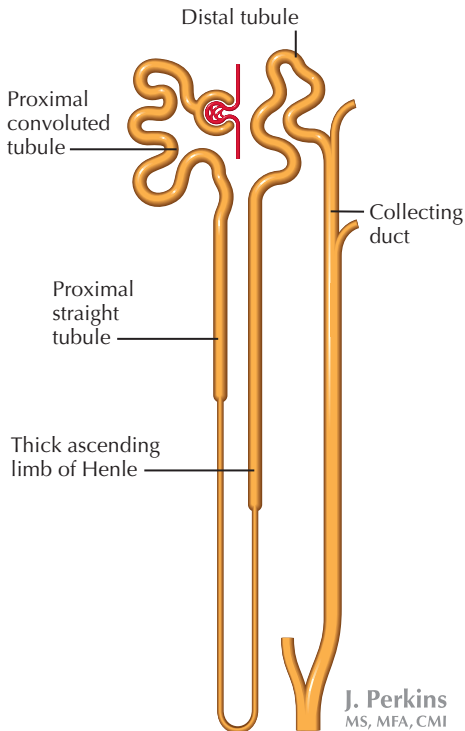
1. Phosphoric acid ($H_2PO_4^-$) is the primary urinary titratable acid.
2. The renal compensation for acidosis will result in increased secretion of H^+ into the tubular lumen, from the α-intercalated cells of the collecting ducts. Any HPO_4^{2-} present in the collecting ducts will bind the H^+ and be excreted as $H_2PO_4^-$.

1–3. Describe the anion gap (AG) presented in each panel and what the electrolyte concentrations indicate.

4. Predict urinary HCO_3^- excretion in a person with values depicted in panel 3.
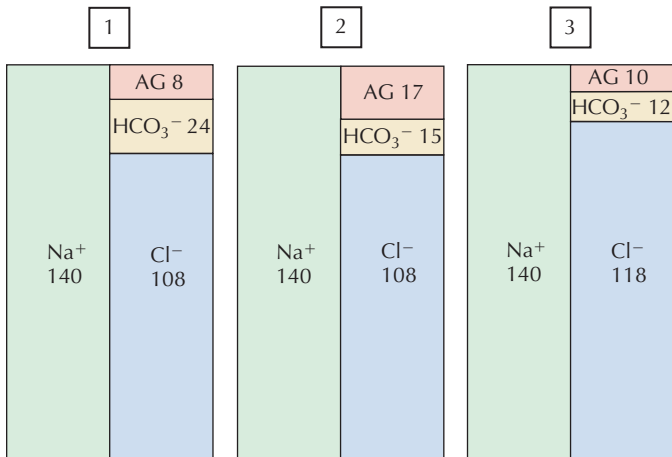
1. **Normal anion gap (**AG) (typically 8–12 mEq/L) and normal electrolyte levels
2. **Acidosis from acid loading**. In this case, *AG increases from the acid load*, and HCO_3^- values decrease as the acid is buffered by plasma bicarbonate. Chloride remains at normal values.
3. **Acidosis from base loss**. In this case, *AG is within normal values*: the plasma HCO_3^- (base) loss is offset by an increase in plasma chloride. The HCO_3^- losses (e.g., in feces) are caused by HCO_3^-/Cl^- exchangers, which secrete HCO_3^- and reabsorb Cl^-.
4. In normal (panel 1) and acidotic (panel 3) individuals, HCO_3^- excretion will be zero.

The following blood values were obtained from a patient being assessed for renal insufficiency:

pH	P_{CO_2}	HCO_3^-	Na^+	K^+	Cl^-
7.28	26 mm Hg	14 mEq/L	136 mEq/L	5.0 mEq/L	100 mEq/L

1. Using the values above, determine the acid–base imbalance, and state whether or not compensation has occurred.

2. In general terms, describe the cause of the imbalance.

1. A pH of 7.28 indicates **acidosis** (pH < 7.4). When the pH is compared with the status of the plasma Pco_2 and HCO_3^- values, the value that matches the state of the pH determines whether the primary imbalance is respiratory (Pco_2) or metabolic (HCO_3^-). In this case, the Pco_2 is "alkaline" (<40 mm Hg), and the HCO_3^- is "acid" (<24 mEq/L), indicating *metabolic* acidosis. It is **compensated** because the Pco_2 is lower than normal, reflecting the attempt to blow off volatile CO_2 and reduce the acid load.

2. The AG is used to determine whether the acidosis is caused by acid loading or base loss: $AG = Na^+ - (Cl^- + HCO_3^-) = 136 - (100 + 14) = 22$. A normal AG is 8 to 12, and an increased AG indicates *acid loading* (AG would be in normal range with base loss). Potential causes of acid loading include diabetic ketoacidosis, chronic renal failure, and lactic acidosis. In this case, because the patient has renal insufficiency, the acidosis is most likely from chronic renal failure.

A 30-year-old man had persistent vomiting for 2 days, during which time he was unable to keep fluids down. Upon examination he was found to be severely dehydrated, with blood values shown below:

pH	P_{CO_2}	HCO_3^-	Na^+	K^+	Cl^-
7.55	48 mm Hg	45 mEq/L	136 mEq/L	3.0 mEq/L	85 mEq/L

1. Using the values above, determine the acid–base imbalance, and state whether or not compensation has occurred.

2. In general terms, describe the cause of the imbalance.

◯

1. The high pH (>7.4) indicates **alkalosis,** which is matched by the alkaline HCO_3^- value of 45 mEq/L. Thus, the imbalance is *metabolic alkalosis*. The elevated Pco_2 levels indicate respiratory **compensation**.

2. The chronic vomiting resulted in a large loss of stomach acid (HCl) that initiated the alkalosis. The normal compensation for alkalosis would be for the β-intercalated cells of the collecting duct to secrete HCO_3^- for excretion in urine; however, this is not able to occur owing to the person's volume-contracted state. Dehydration due to chronic vomiting stimulates vasoconstrictor and fluid-retaining mechanisms (sympathetic nerve activity, ADH [also called *vasopressin*], and the renin-angiotensin-aldosterone system), which serve to retain fluids and electrolytes and limit urinary losses. Because of this, almost all of the sodium, chloride, and water are reabsorbed by the late distal tubule, and there is not enough chloride present in the lumen of the collecting ducts to "run" the HCO_3^-/Cl^- exchangers and allow secretion of HCO_3^-. Therefore, the plasma HCO_3^- remains high, and respiratory compensation must occur. This condition is *contraction alkalosis*.

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Identify each structure.

1. Liver
2. Pancreas
3. Gallbladder
4. Colon (large intestine)
5. Small intestine
6. Stomach
7. Esophagus
8. Salivary glands

1. Liver
Secretion of bile (important for lipid digestion), storage of nutrients, production of cellular fuels, plasma proteins, clotting factors, and detoxification and phagocytosis

8. Salivary glands
Secretion of lubricating fluid containing enzymes that initiate digestion

7. Esophagus
Transport of food into the stomach

2. Pancreas
Secretion of buffers and digestive enzymes by exocrine cells; secretion of hormones by endocrine cells to regulate digestion

6. Stomach
Chemical breakdown of food by acid and enzymes; mechanical breakdown via muscular contractions

3. Gallbladder
Storage and concentration of bile

4. Large intestine
Dehydration and compaction of indigestible materials for elimination; resorption of water and electrolytes; host defense

5. Small intestine
Enzymatic digestion and absorption of water, organic substrates, vitamins, and ions; host defense

C.Machado
_M.D._

Identify site of Meissner's (submucosal) and Auerbach's (myenteric) plexuses and describe their general functions.

Identify site of Meissner's (submucosal) and Auerbach's (myenteric) plexuses and describe their general functions.

1. The myenteric nerve plexus is located between the longitudinal and circular muscle layers of the gastrointestinal tract, from the esophagus to the anus. Stimulation of the myenteric nerves initiates contraction of muscles.

2. The submucosal nerve plexus is located between the circular muscle and the submucosa. Stimulation of the submucosal plexus increases secretion of buffers and mucus into the gastrointestinal tract.

Comment: The enteric nerves are singular, in that they are intrinsic to the gastrointestinal tract, and if necessary, they can function without input from the autonomic nervous system. Under normal conditions, the enteric nerves receive input from the autonomic nerves, hormones, and chemoreceptors, osmoreceptors, and mechanoreceptors located in the lumen of the GI tract.

1−5. Identify the main vessels in the portal system.
   6. Explain the "first pass" effect.
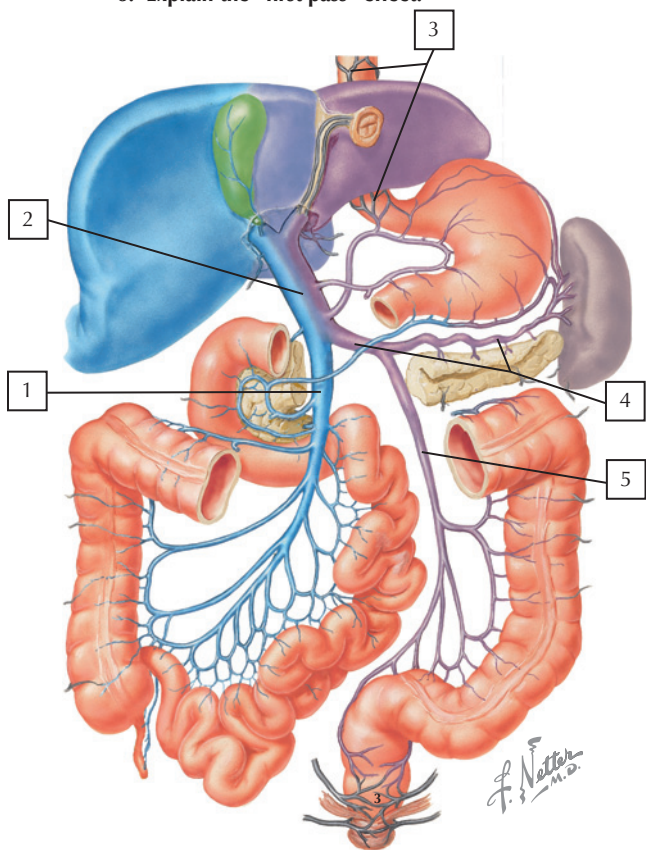
1. Superior mesenteric vein
2. Portal vein
3. Esophageal veins
4. Splenic vein
5. Inferior mesenteric vein
6. The portal system includes the veins that drain blood from the circulation surrounding the esophagus, intestines, and anus. All substances absorbed into capillaries in the small and large intestines flow through the portal vein and into the liver, where processing occurs. Flow of blood through the liver before entry into systemic circulation is termed the *first-pass effect*.

The thirst response can be mediated by several different mechanisms 1−4. State what effect the changes in factors 1−4 will have on thirst.

5. Describe how the thirst response contributes to fluid homeostasis.
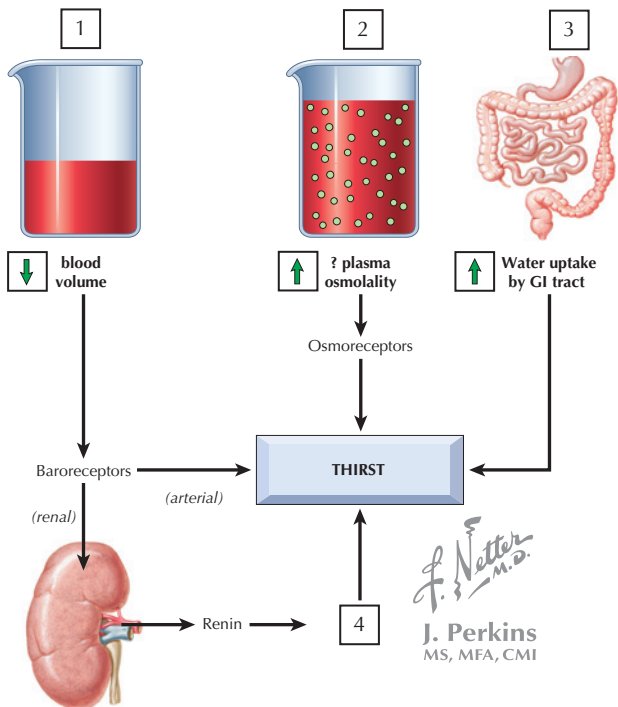
The Thirst Response

1. Decreased blood volume
2. Increased plasma osmolarity
3. Increased water intake by the GI tract
4. Increased angiotensin II
5. Because small increases in plasma osmolarity rapidly stimulate thirst, fluid usually enters the GI tract before dehydration has deleterious effects on cells. Once the fluid enters the body, any oversupply will be handled by the kidneys and excreted. Thus, thirst helps provide a supply of fluid to maintain proper extracellular volume.
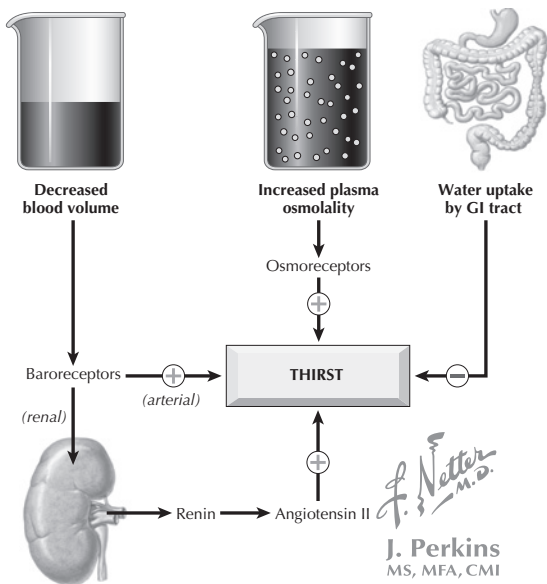
The Thirst Response

The autonomic nerves help fine-tune motility and secretion through the GI tract.

1. Name the parasympathetic nerves from the brainstem that innervate the enteric nervous system.
2. Name the parasympathetic nerves from the sacral spinal cord that innervate the enteric nervous system.
3. Which branch of the autonomic nervous system stimulates, and which inhibits motility and secretion?

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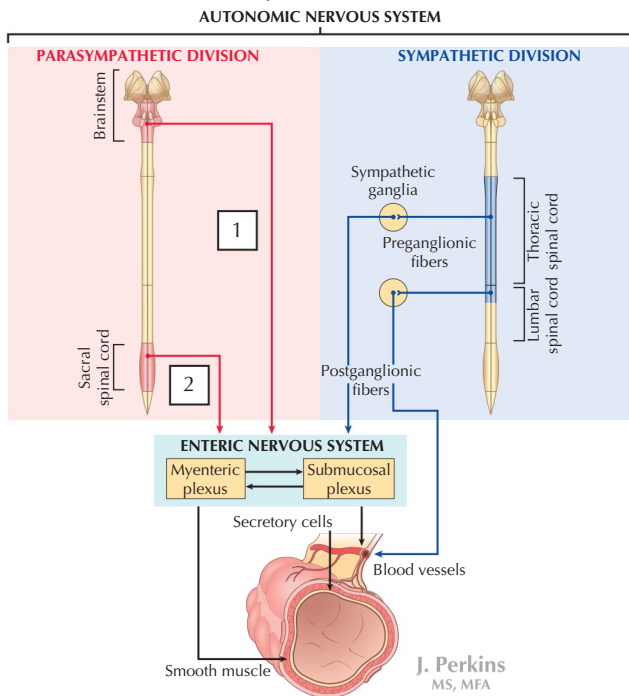
1. Parasympathetic vagus nerves innervate the GI tract down to the transverse colon.
2. Pelvic nerves innervate the GI tract from transverse colon to the anus.
3. In general, the parasympathetic nerves promote motility and secretion in the GI tract, whereas the sympathetic nerves slow or stop motility and secretion.

Both mechanical and chemical stimulation can elicit motility in the GI tract. Identify the major neurotransmitters that are released during peristalsis from excitatory motor neurons (1) and inhibitory motor neurons (2). Describe whether stimulation of the respective motor neuron populations results in smooth muscle contraction or relaxation.
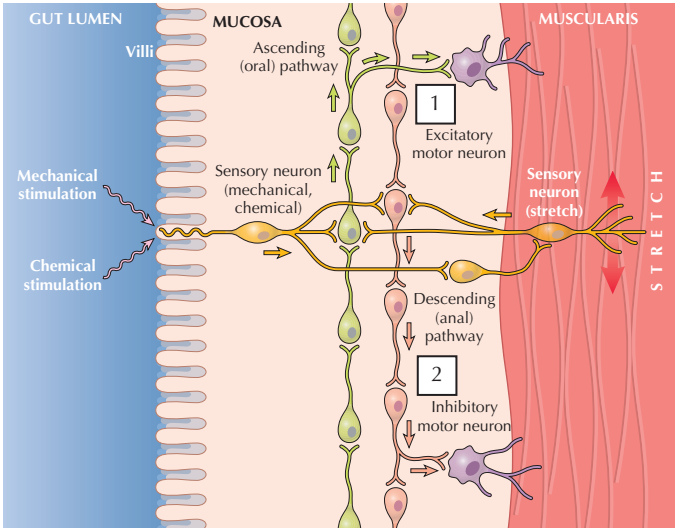
J. Perkins
MS, MFA

1. Excitatory motor neurons in the GI tract can release acetylcholine (ACh) and substance P (tachykinin); these substances cause contraction of the smooth muscle.
2. Inhibitory motor neurons release vasoactive intestinal peptide (VIP) or nitric oxide (NO); these substances cause relaxation of the smooth muscle.

Comment: The oral constriction and aboral relaxation are the hallmark of peristalsis, allowing aboral movement of the chyme.

1. **Identify and define the waveform depicted.**

2. **Identify and define the spikes on the top of the wave.**
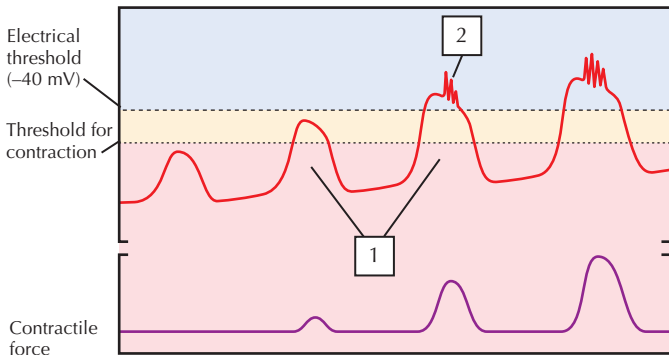
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1. Slow waves are the resting membrane potential found in the smooth muscle of the GI tract. The undulating waves occur at regular intervals, and they are called the *basic electrical rhythm* (BER). Depolarization of the slow waves above threshold (-40 mV) stimulates action potentials, which cause contractions.

2. Action or spike potentials are generated on the peaks of slow waves, when slow waves are depolarized above the electrical threshold (-40 mV). The action potential results from entry of calcium into the cells via voltage-gated channels; calcium binds to calmodulin, which initiates cellular events leading to contraction.

Comment: Depolarization of slow waves can be caused by stretch, ACh, or parasympathetic stimulation, for example. The force of contraction increases with the number of action potentials generated. Thus, the stronger the stimulus (e.g., local stretch due to presence of chyme), the greater the depolarization and number of action potentials, and the stronger the contraction.

Duodenal hormones respond to the constituents in chyme and reduce gastric emptying. Identify the hormones that respond to acid (1), fats (2), and amino acids/peptides (3) and decrease gastric emptying.
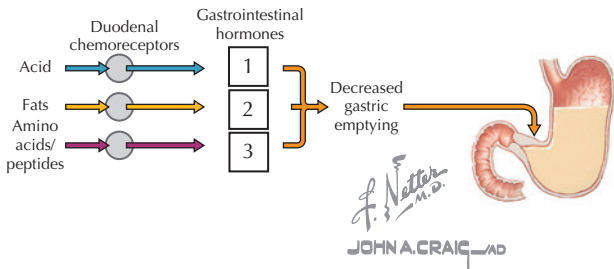
Control of Gastric Emptying

1. Secretin is released in response to acidic chyme.
2. Cholecystokinin (CCK) and gastric inhibitory peptide (GIP) are released in response to fats in the chyme.
3. Gastrin is released in response to peptides and amino acids in the chyme.

1. Name the type of slow movement depicted by "haustra" formation at this site.

2. Name the type of rapid propulsive movement depicted at this site.

3. Explain the defecation (or rectosphincteric) reflex.
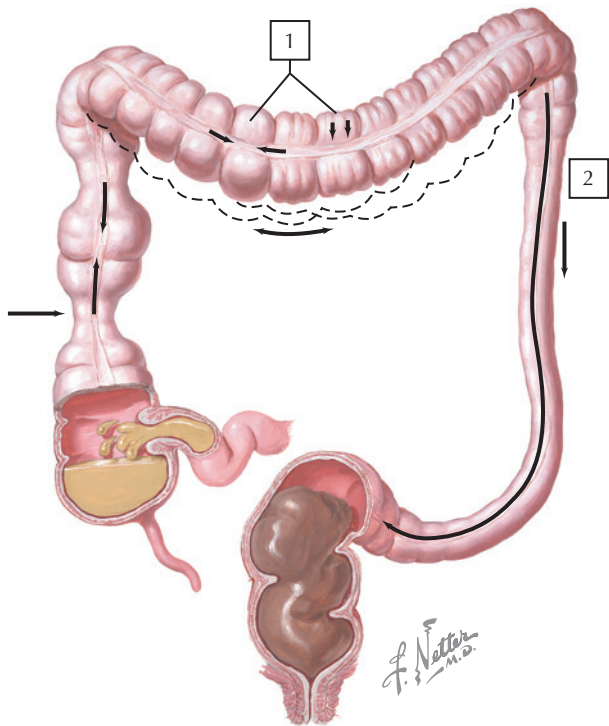
1. Depicts segmental propulsion, which forms sacs (haustra) for long periods of time. This very slow movement allows final absorption of sodium and water, forming feces in the descending colon.
2. Depicts mass movements, which occur several times daily; strong peristaltic contractions move chyme and feces through the transverse and descending colon to the rectum.
3. The defecation reflex occurs when feces enter the rectum. Mechanoreceptors sense rectal stretch and signal the myenteric plexus, which causes the internal anal sphincter to relax, and initiates a central urge to defecate. This stimulates the voluntary contraction of the external anal sphincter.

Describe the main action(s) elicited in response to the reflexes listed below:

1. Vomiting reflex
2. Gastrocolic reflex
3. Ileogastric reflex
4. Enteroenteric reflex
5. Defecation (rectosphincteric) reflex

1. The vomiting reflex causes expulsion of upper intestinal and gastric contents via reverse peristalsis.
2. The gastrocolic reflex stimulates colonic mass movements in response to food or chyme in the stomach.
3. The ileogastric reflex reduces gastric emptying when there is chyme in the ileum.
4. The enteroenteric reflex will relax an area of the intestines when an adjacent area is distended.
5. The defecation reflex is initiated by feces entering and stretching the rectum. This elicits the relaxation of the internal anal sphincter (IAS) and the urge to defecate.

Comment: These reflexes do not occur in an all-or-nothing manner, and many act in concert to promote efficient movement of the chyme. These represent only a few of the reflex actions present in the GI tract.

In the salivary gland shown:
1. State the general components of the primary secretion.

2. State the general components of the saliva.

3. Describe the effects of autonomic stimulation on salivary gland secretion.

Na^+ K^+

Cl^- HCO_3^-

Saliva

2
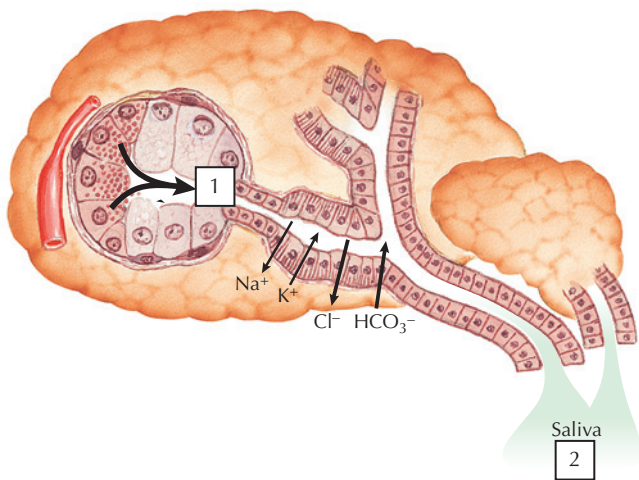
J. Perkins
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1. Primary secretion contains electrolyte concentrations similar to plasma (Na^+, K^+, Cl^-, HCO_3^-) as well as the enzyme salivary α-amylase, which initiates starch digestion, and R proteins (R binders) that bind vitamin B_{12}.

2. Saliva is always hypotonic to plasma, at any flow rate, primarily due to reabsorption of Na^+ and Cl^- in the striated ducts. In the mouth, the saliva also contains lingual lipase (secreted from glands in the tongue), which has a small role in initial hydrolysis of lipids.

3. The facial and glossopharyngeal parasympathetic nerves innervate the salivary glands and stimulate salivation. Sympathetic nerves constrict blood supply and reduce salivation. The main control of salivation is through the parasympathetic nerves: if they are severed, the glands will atrophy.

Name the secretions from the chief, parietal, and mucous cells of the gastric pit.
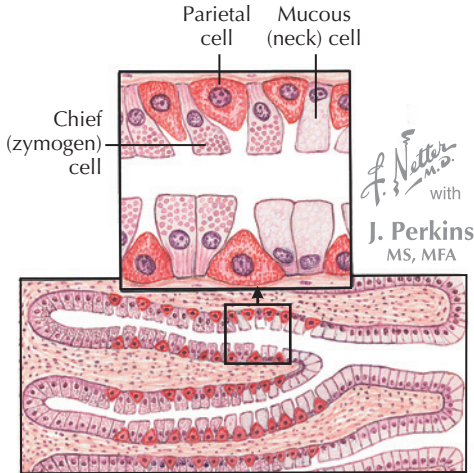
1. **Chief cells** release the zymogen form of pepsins. The pepsinogens are cleaved to active pepsins (proteolytic enzymes) in the acid lumen of the stomach. Chief cells also release lipase, which hydrolyzes lipids.
2. **Parietal cells** secrete HCl (and to a lesser extent, KCl) as well as intrinsic factor (IF), which is required for vitamin B_{12} absorption in the terminal ileum.
3. **Mucous (neck) cells** secrete mucus, which sequesters HCO_3^- and serves to protect the gastric mucosa from damage by acid and enzymes.

1–2. In the gastric parietal cell, identify the transporters at each site, which are important in production of HCl.

3. State the source of the H⁺ at this site.

Capillary   Parietal cell
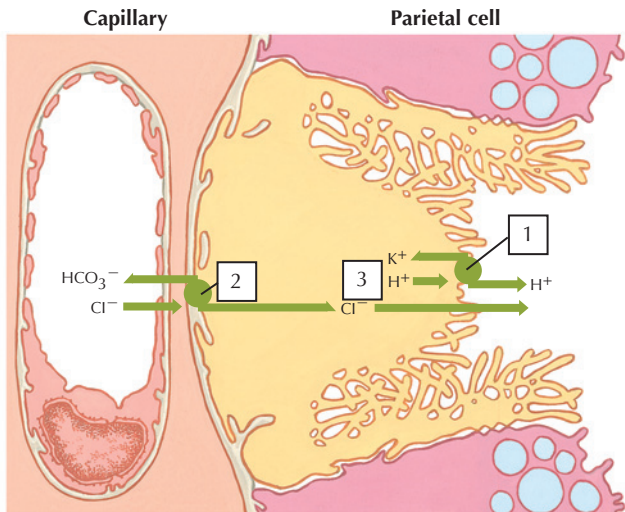
JOHN A.CRAIG—AD

1. The H^+/K^+-ATPase pump, or "proton pump." This uses energy to transport H^+ into the lumen of the gastric pits against a million-fold concentration gradient.
2. The HCO_3^-/Cl^- exchanger on the basolateral membranes. This is an electroneutral antiporter that transports Cl^- into the parietal cells.
3. In the cell, the H^+ is a product of carbonic anhydrase action on CO_2, producing H^+ and HCO_3^-. This H^+ is then transported into the lumen by the proton pump (1).

1–3. Identify the substances, which stimulate the proton pump.

4. In this parietal cell, what is the rate-limiting step for hydrochloric acid production?
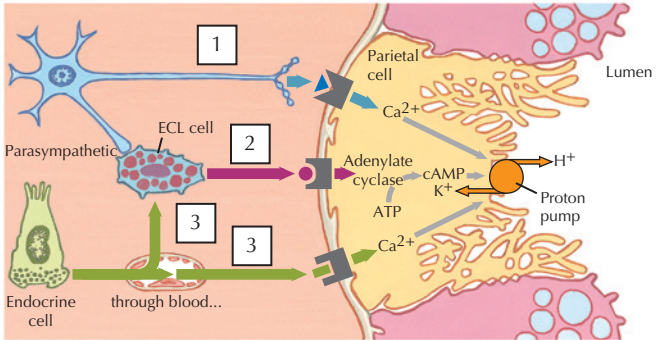
Stimulation of Gastric Acid Secretion

1. Acetylcholine, from parasympathetic nerve terminals
2. Histamine, from enterochromaffin-like cells in the gastric pits
3. Gastrin, from endocrine G-cells in the stomach (antrum), and duodenum
4. The rate-limiting step in hydrochloric acid production is the proton pump. Stimulation of acid secretion results in insertion of more pumps in the luminal membrane. This is also the site of pharmacologic suppression of gastric acid: PPI (proton pump inhibitors) such as omeprazole act at this site.

Secretions from the pancreas, liver, and gallbladder are necessary for the efficient digestion and absorption of nutrients. Name the structures labeled 1–5, related to the ductal systems of these organs.
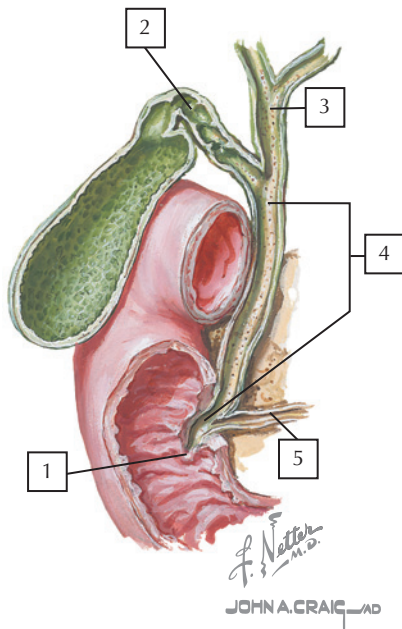
1. Papilla of Vater
2. Cystic duct
3. Common hepatic duct
4. Common bile duct
5. Pancreatic duct

Several hormones are produced in cells of the GI tract, are released into the blood, and facilitate GI secretion and/or motility at different sites. Complete the table for the five GI hormones listed.

Major GI hormones			
GI hormones	**Site of secretion**	**Primary stimuli**	**General actions**
Gastrin	?	?	?
Secretin	?	?	?
Cholecystokinin (CCK)	?	?	?
Gastric inhibitory peptide, *aka* glucose insulinotropic peptide (GIP)	?	?	?
Motilin	?	?	?

MAJOR GI HORMONES

GI HORMONES	SITE OF SECRETION	PRIMARY STIMULI	GENERAL ACTIONS
Gastrin	G cells in antrum of stomach and duodenum	Stretch, peptides and amino acids, vagus (through GRP)	↑ **Gastric H^+** ↑ Gastric mixing ↑ Lower GI tract motility
Secretin	S cells of the duodenum	Acidic chyme	↑ **Pancreatic buffer (HCO_3^-) secretion** ↑ **Biliary and small intestine buffer secretion** ↓ Gastric H^+ (by ↓gastrin) ↓ Gastric emptying
Cholecystokinin (CCK)	I cells of the duodenum and jejunum	Small peptides and amino acids, fats	↑ **Pancreatic enzyme secretion** contracts gallbladder and relaxes sphincter of Oddi ↑ Pancreatic and biliary buffer secretion ↓ Gastric emptying ↑ Lower GI tract motility
Gastric inhibitory peptide, *aka* glucose insulinotropic peptide	Duodenum and jejunum	Fatty acids, glucose, amino acids	↓ **Gastric H^+ secretion** ↑ **Pancreatic insulin secretion** ↓ Gastric emptying
Motilin	Mo cells of the duodenum	Fasting	↑ **Phase III contractions of the MMC**

GRP, gastrin-releasing peptide; MMC, migrating myoelectric complex.
Reprinted with permission from Hansen J: Netter's Atlas of Human Physiology. Philadelphia, Elsevier, 2002.

Identify each structure.
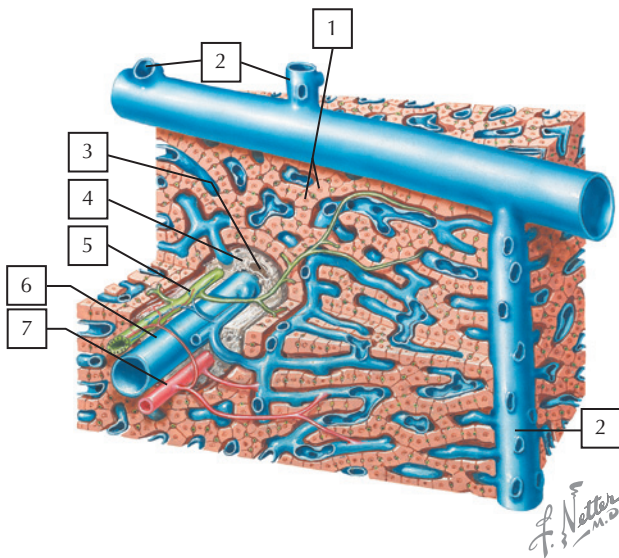
1. Hepatocytes
2. Central veins
3. Lymph vessel
4. Connective tissue
5. Bile duct
6. Portal vein branch
7. Hepatic artery branch

Comment: The liver has metabolic, vascular, and secretory functions, much of which are carried out by the hepatocytes. The hepatocytes are surrounded by capillary sinusoids, which perfuse the tissues: the ability of the liver to sequester blood ("sponge" function) helps to regulate systemic blood volume. Under normal conditions, the liver contains about 450 mL of blood.

Hepatocytes metabolize many of the nutrients absorbed by the GI tract. Complete the table.

Major nutrients occurring	Constituents entering the liver	Metabolic processes
Carbohydrates	?	?
Proteins	?	?
Lipids	?	?

MAJOR NUTRIENTS OCCURRING	CONSTITUENTS ENTERING THE LIVER	MAIN LIVER PROCESSES
Carbohydrates	Glucose, galactose, fructose	Glycogen synthesis and storage Gluconeogenesis Metabolism to other compounds
Proteins	Amino acids	Deamination Urea production Synthesis of plasma proteins
Lipids	Triglycerides, fatty acids, cholesterol esters	β-Oxidation of fatty acids Formation of lipoproteins Synthesis of cholesterol and phospholipids

1. **Name the neural and hormonal mechanisms that stimulate production of primary bile acids by the hepatocytes.**

2. **Identify the structure where modification of bile "juice" occurs.**

3. **Through which vessel does bile recycling occur?**
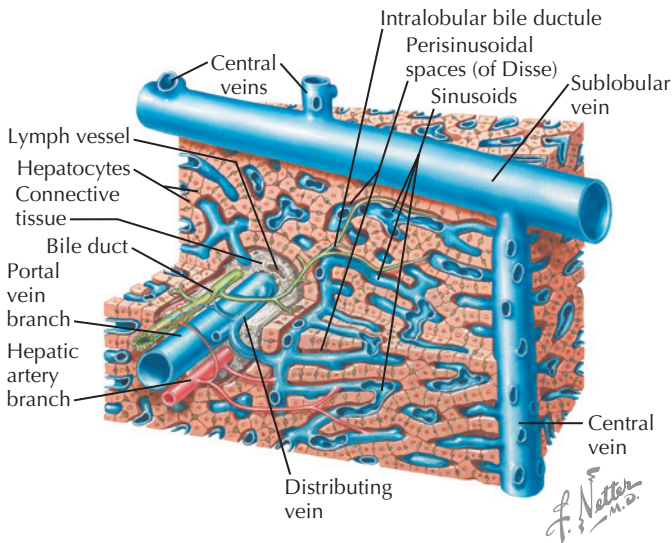
1. Production of primary bile acids is stimulated through vagal afferent nerves as well as by the hormone cholecystokinin (CCK), which is released into blood in response to chyme entering the duodenum.
2. Modification of bile occurs in the bile ducts. Bile is an osmotic agent, and when bile acids are secreted from the hepatocytes into the bile ducts they draw water, and electrolytes (sodium chloride, bicarbonate) follow. Thus, bile also provides buffering in the relatively acidic early duodenum.
3. Bile recycling occurs through the portal vein. Primary bile is reabsorbed in the terminal ileum and flows back to the liver, where it can be secreted again through the bile ducts. In a typical meal, bile will be recycled three to five times, before it is stored in the gallbladder when chyme leaves the upper GI tract.

1. Explain how **suprahepatic pathology** (such as hepatic vein thrombosis, tricuspid incompetence, and constrictive pericarditis) can increase portal vein pressure.
2. Explain how a **cirrhotic liver** can cause portal hypertension.
3. Explain how **infrahepatic pathology** (such as portal vein thrombosis) can cause portal hypertension.
4. Explain why the **esophagus** is sensitive to developing varices during portal hypertension associated with cirrhosis or infrahepatic causes.

Suprahepatic causes

Tricuspid incompetence

Thrombosis of hepatic veins (Chiari syndrome)

Constrictive pericarditis

No or few esophageal varices

Spleen moderately enlarged

Intrahepatic causes

Esophageal varices

Spleen markedly enlarged

Liver enlarged

Liver cirrhosis (or schistosomiasis)

Infrahepatic causes

Esophageal varices

Spleen decidedly enlarged

Portal vein thrombosis

1. With suprahepatic causes, the pressure in the hepatic veins is elevated, causing pooling of blood in the liver and increasing pressure in the portal and splenic veins.
2. With cirrhotic livers (intrahepatic cause), blood flow through the liver is dramatically reduced because of the scarring. Thus, while the hepatic vein pressure is normal (low), the portal and splenic vein pressures are high.
3. With infrahepatic causes of portal hypertension, blockage in some of the portal veins will increase blood flow and pressure in the other veins.
4. Portal hypertension can result in a backup of pressure in the veins coming from the stomach and esophagus. The increased pressure causes enlargement and thinning of the vessel walls and can make them prone to rupture. Because of the superficial nature of the vessels serving the esophagus, the vessels are sensitive to forming varices and rupturing and bleeding into the esophagus. Esophageal varices occur more often from intrahepatic and infra-hepatic causes, which directly affect pressure in the portal system and the vessels serving the esophagus.

Comment: Normal hepatic vein pressure is less than 1 mm Hg, which allows the unimpeded flow of blood out of the liver. If hepatic vein pressure increases, blood pools in the liver, and the portal vein pressure can also become elevated.

As nutrients enter the small intestine, hormones are secreted from the duodenum and stimulate pancreatic secretions. Name the two hormones involved and the pancreatic secretions that they stimulate.

Stimulation of Digestive Enzymes
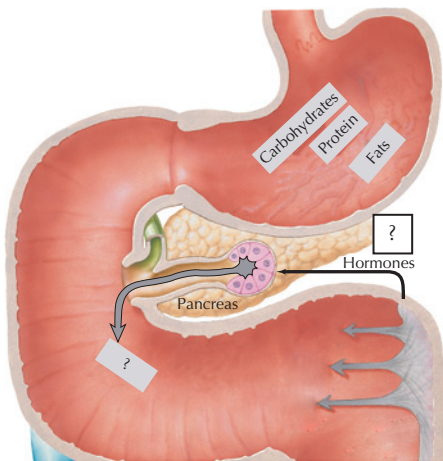
1. Entry of acidic chyme into the duodenum stimulates the release of **secretin** into the blood. At the pancreas, secretin stimulates secretion of buffers, which enter the duodenum through the papilla of Vater. The buffers serve to neutralize the acidic chyme and bring the pH up to about 7.

2. In response to carbohydrates, fats, and proteins, **cholecystokinin** (CCK) is secreted into the blood. At the pancreas, CCK stimulates secretion of pancreatic proenzymes, including:
   - Pancreatic proteases (e.g., trypsinogen, chymotrypsinogen, procarboxypeptidase, proelastase) (protein digestion)
   - Pancreatic α-amylase (starch digestion)
   - Pancreatic lipase and colipase (lipid digestion)

Name the major dietary carbohydrates and identify the carbohydrate-specific digestive enzymes, their site of secretion, their substrates, and their products.

C.Machado
M.D.
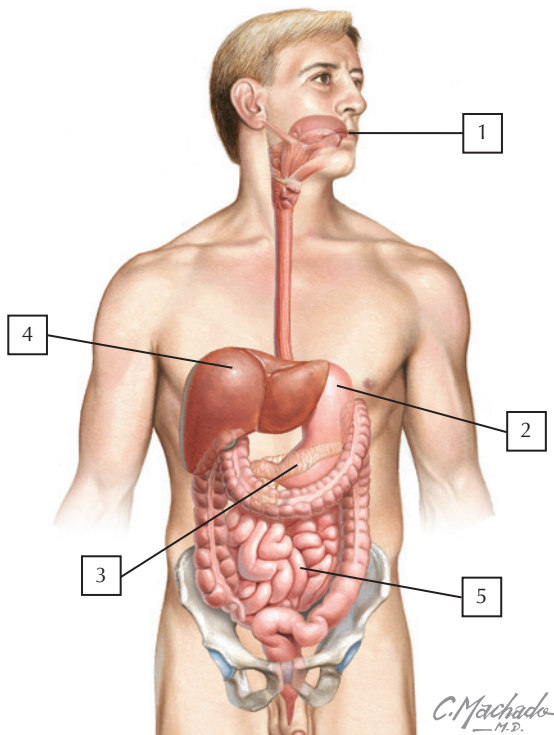
The major dietary carbohydrates are starches (which are polymers of glucose) and simple sugars, such as the disaccharides, sucrose, and lactose, and the monosaccharide fructose.

1. Mouth secretes salivary α-amylase, which digests starch to glucose polymers
2. Stomach (none)
3. Pancreas secretes α-amylase, which digests starch to glucose polymers
4. Liver (none)
5. Small intestine: brush-border enzymes; maltase digests maltose to glucose, isomaltase digests isomaltose to glucose, sucrase digests sucrose to glucose, and fructose, lactase digests lactose to glucose and galactose

Comment: Final digestion of carbohydrates is at the intestinal brush border. The enzymes maltase, isomaltase, sucrase, and lactase are fixed in the brush-border membrane and serve to digest the disaccharides and polysaccharides to the constitutive monosaccharides glucose, galactose, and fructose.

Name the cellular processes used to transport monosaccharides at sites 1 and 2.
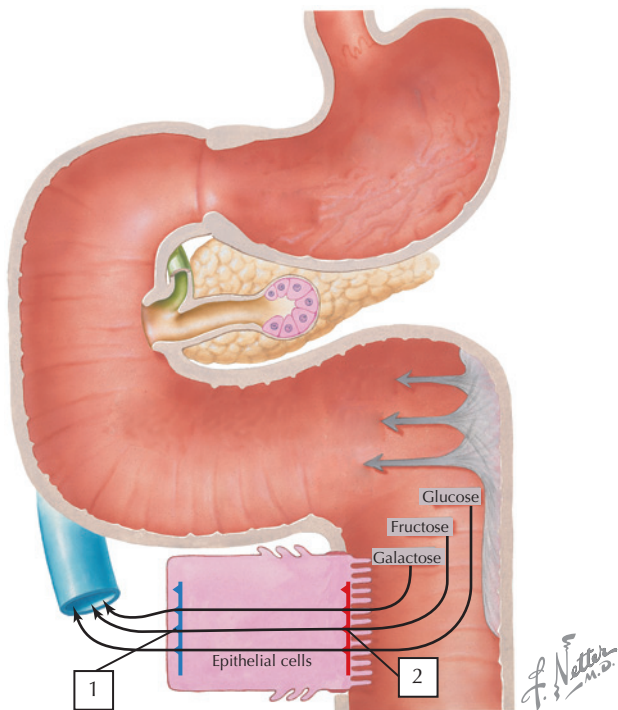
1. Basolateral transport of all monosaccharides is through facilitated transport and diffusion through the interstitium and into the capillaries.
2. Luminal absorption of glucose and galactose is via Na^+-cotransporters; the two monosaccharides share this transporter. Fructose enters the cells via facilitated transport (special transport protein).

Identify the enzymes facilitating protein digestion at each labeled site. Describe how the pancreatic proteases are activated at site 2.
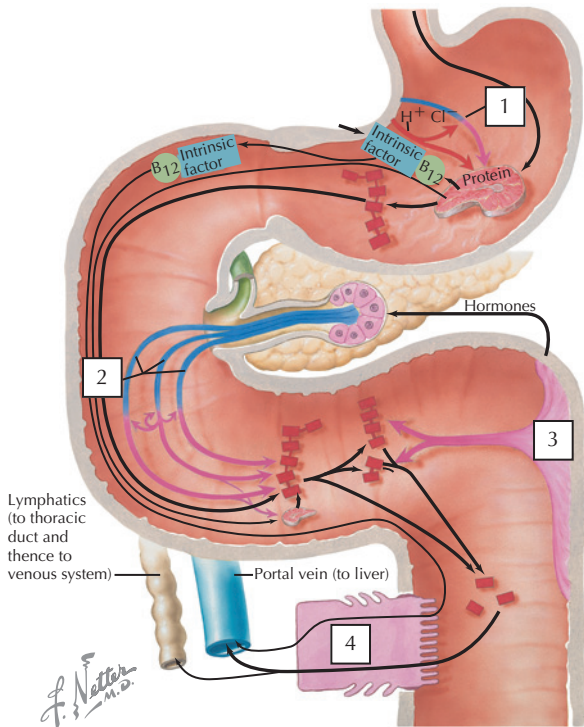
1. In the stomach, pepsinogens are released from the chief cells and activated to pepsins (proteases) by the acid environment. The hormone gastrin is released early in the digestive process and stimulates release of stomach acid and pepsinogens.

2. The pancreatic proteases (stimulated by cholecystokinin) are released into the duodenum as inactive proenzymes. The enzyme enterokinase is secreted from the intestinal epithelial cells into the gut lumen and activates trypsin. Trypsin activates itself as well as the other proteases (chymotrypsin, carboxypeptidases, elastase), and digestion to smaller oligopeptides proceeds.

3. Final digestion of proteins to amino acids and dipeptides and tripeptides occurs at the brush border of the small intestine, where enzymes are fixed in the membrane.

4. In the enterocytes (intestinal epithelial cells), any dipeptides and tripeptides that are absorbed are digested to amino acids by cytoplasmic proteases.

**Describe the transport processes used for peptides
and amino acids at sites 1 and 2.**

Lymphatics
(to thoracic
duct and
thence to
venous system)

Portal vein (to liver)

Peptides

Amino
acids

1 │ Epithelial
│ cells

2

f. Netter
M.D.
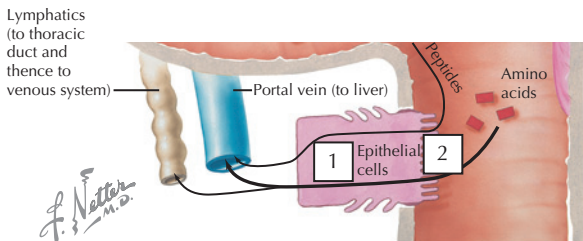
1. At the basolateral membrane, amino acids exit the cells by facilitated transport and diffuse into capillaries.
2. At the luminal membrane, amino acids are absorbed using separate Na^+-dependent cotransporters for basic, acidic, neutral, and imino acids. Dipeptides and tripeptides enter the cells by H^+-cotransport.

Identify the lipid-specific digestive enzymes secreted (if any) at each site and their substrates and products.

Mouth

| 1 |

Liver

| 4 |

Stomach

| 2 |

Pancreas

| 3 |

Small intestine

| 5 |

C. Machado
—M.D.
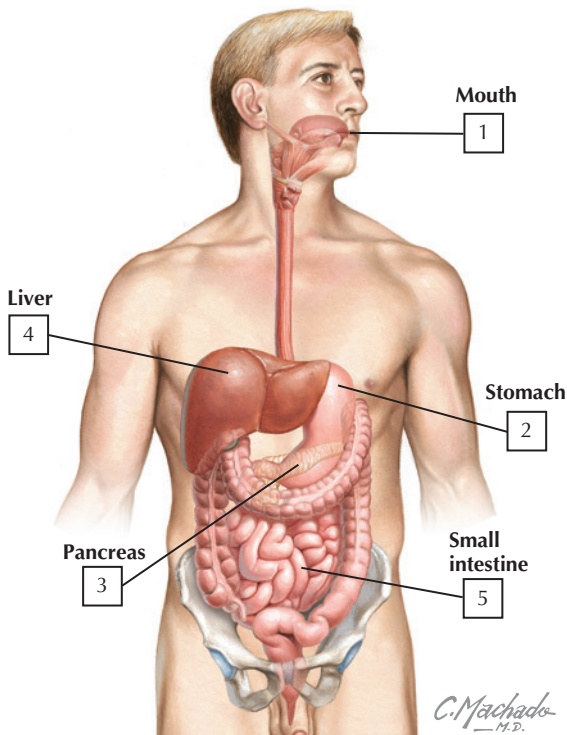
1. In the mouth, **lingual lipase** is secreted into saliva from Von Ebner's glands in the tongue. It has a minor role in lipid digestion in humans but can digest triglycerides (TG) to diglycerides and free fatty acids (FFA).

2. In the stomach, **gastric lipase** is secreted from chief cells and hydrolyzes TG to diglycerides and FFA. Like lingual lipase, this enzyme plays a minor role in lipid digestion.
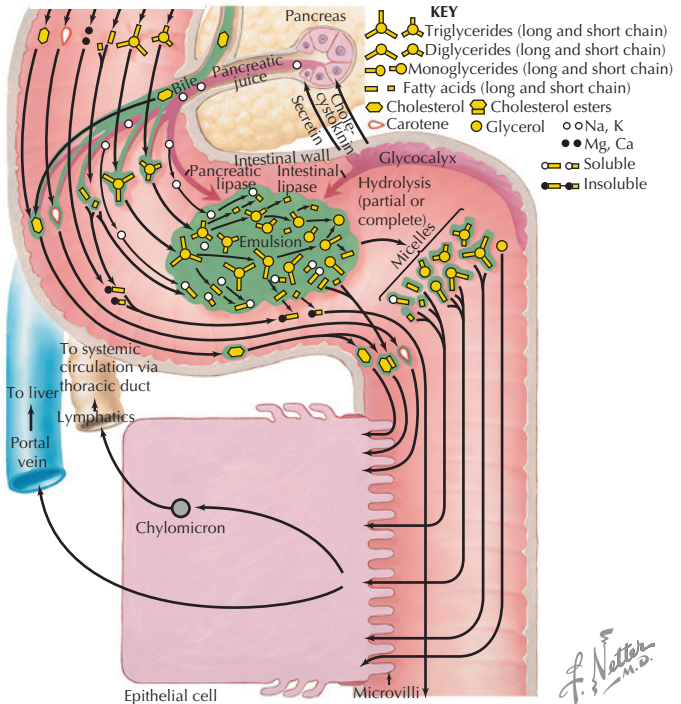
3. Pancreatic secretions (stimulated by cholecystokinin) include various lipases: **pancreatic lipase** hydrolyzes TG to monoglycerides and FFA; **phospholipase A$_2$** hydrolyzes phospholipids to lysophospholipids and FFA; **cholesterol ester hydrolase** hydrolyzes cholesterol esters to cholesterol and FFA.

4. **Liver** (none)

5. Whereas no lipases are secreted by the small intestine, **pancreatic lipase** acts in the small intestine to perform the major hydrolysis of lipids. However, because of the presence of bile, the pancreatic lipase cannot readily access the lipids. To overcome this obstacle, procolipase is also secreted by the pancreas and is activated to **colipase** in the gut lumen by trypsin. The colipase displaces the bile from the lipids, binds with the lipase, and lipid hydrolysis ensues.

Comment: Triglycerides constitute the majority (98%) of dietary lipids, with the remainder primarily cholesterol esters and phospholipids. In the small intestine, the hydrolysis products combine with bile to form micelles. The hydrophilic sides of the bile are oriented outward, allowing the micelle to traverse the unstirred water layer near the enterocytes. At the cells, the lipids are released from the micelle and diffuse into the enterocytes.

1. **Micelles are shown in the small intestine; what purpose do micelles serve?**

2. **Describe the process of micelle formation.**

KEY

Triglycerides (long and short chain)
Diglycerides (long and short chain)
Monoglycerides (long and short chain)
Fatty acids (long and short chain)
Cholesterol   Cholesterol esters
Carotene   Glycerol   Na, K
Mg, Ca
Soluble
Insoluble

Pancreas
Bile
Pancreatic juice
Cholecystokinin
Secretin
Intestinal wall
Pancreatic lipase
Intestinal lipase
Glycocalyx
Hydrolysis (partial or complete)
Emulsion
Micelles
To systemic circulation via thoracic duct
To liver
Lymphatics
Portal vein
Chylomicron
Epithelial cell
Microvilli

1. Micelles are "taxis" that carry lipids across the unstirred water layer adjacent to the intestinal epithelial cells. Because lipids are hydrophobic, they cannot traverse this water layer, and thus absorption would be very inefficient. The micelles are digested lipids surrounded by bile salts, which can readily move through the water layer and "drop off" the fats at the enterocytes, where they can diffuse into the cells.

2. Bile is secreted early in the digestive process, in response to stimulation of the gallbladder and liver by the vagus nerves and cholecystokinin. Bile salts and pancreatic enzymes (including lipase and colipase) are released into the duodenum. Primary bile salts are detergents that are amphipathic (hydrophilic and lipophilic sides); their detergent action emulsifies lipids. This does not digest the lipids; it only reduces the size of the lipid droplets. Digestion is by *pancreatic lipase*; however, the lipase cannot access the lipids through the hydrophilic ends of the bile. The *colipase* displaces the bile and binds to the lipase, allowing hydrolysis of the lipids. When there is a critical mass of bile along with, for example, monoglycerides, free fatty acids, and cholesterol, micelles are formed, with the lipophilic ends inside, surrounding the fats, and the hydrophilic ends on the outside, allowing movement through the water layer.

Comment: When the micelle "taxi' drops the fats off at the villi, the bile stays in the lumen of the gut, where most is absorbed in the terminal ileum by sodium-dependent cotransport.

The diagram illustrates uptake of lipids by the small intestine and intracellular processing to chylomicrons.

1. After lipids are absorbed, in what organelle does re-esterification occur?
2. Name the products of the re-esterification process.
3. What are chylomicrons, and how do they exit the cells?
4. How do chylomicrons enter the systemic circulation?

Intracellular processing

Chylomicron

Epithelial cell

Microvilli

Intracellular Lipid Processing
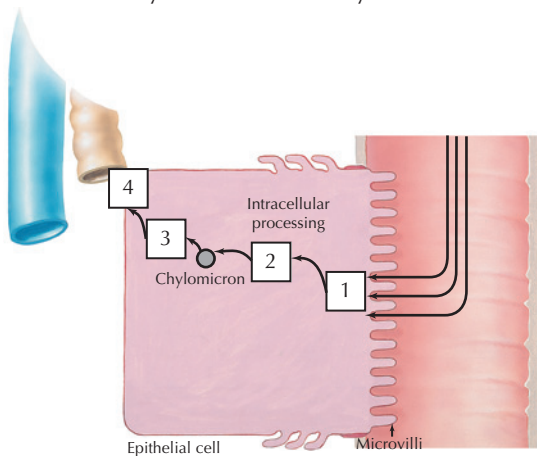
1. Re-esterification takes place in the smooth endoplasmic reticulum.
2. Re-esterification adds FFA back to the monoglycerides, lysophospholipids, and cholesterol to produce TG, phospholipids (PL), and cholesterol esters (CE), respectively.
3. Chylomicrons are large groups of TG (and to a much lesser extent, PL and CE) surrounded by a β-lipoprotein coat. These large globs of lipid exit the cells by exocytosis.
4. The chylomicrons are too large to enter the capillaries and portal blood. Instead, they enter the lymph lacteals and access the systemic circulation in the large vessels in the thorax. Once in the systemic circulation, they enter the liver through the hepatic artery.
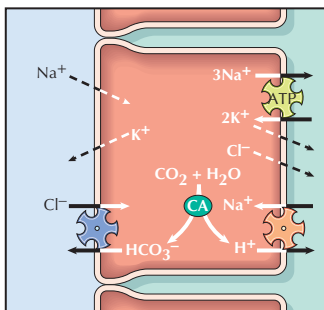
1. **Which area (jejunum, ileum, or colon) is the site of the greatest bulk absorption of fluid and electrolytes?**

2. **What transporter creates the main gradient for sodium reabsorption?**
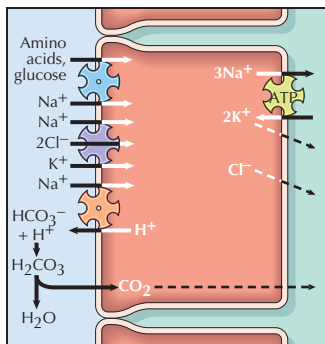

Jejunum
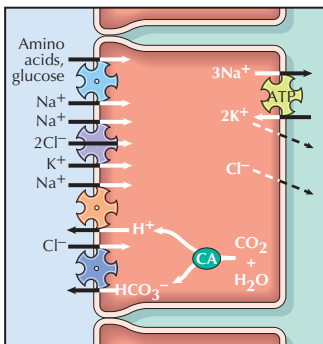
Ileum

Colon

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1. The jejunum is the major site of bulk reabsorption of fluids and electrolytes. Much of the absorption occurs via cotransport with glucose, amino acids, and other nutrients.

2. As in all cells, the basolateral Na^+,K^+-ATPase pump (seen in all sites) maintains a low intracellular concentration of sodium, which creates a large gradient for sodium absorption. As sodium is absorbed, other electrolytes and water follow. There is a great deal of electrolyte and water absorption in the ileum, although most is absorbed by the jejunum.

1. **In this intestinal cell, name two mechanisms by which calcium exits the enterocytes on the basolateral membrane.**

2. **Name the hormone that increases the intracellular calcium-binding protein, calbindin.**
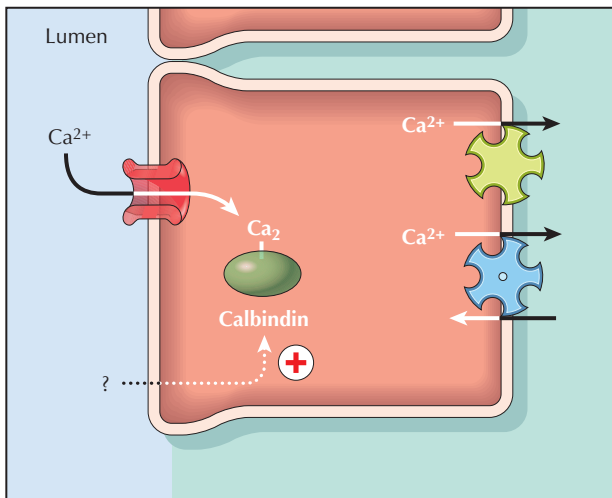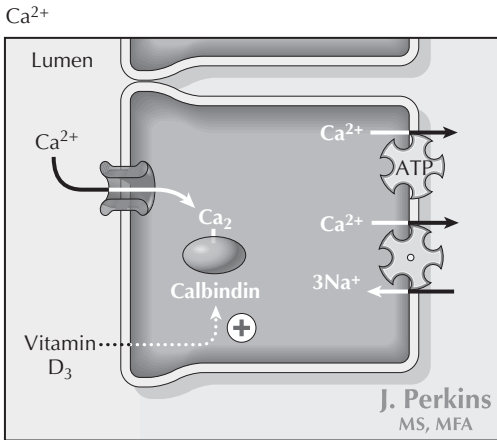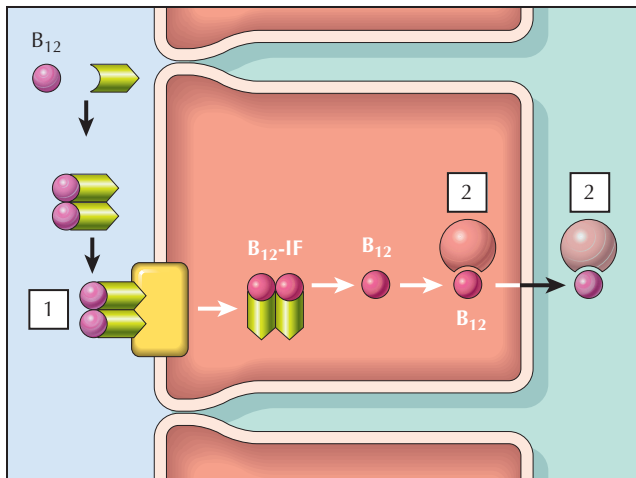

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1. Calcium leaves the cells by active transport via Ca^{2+}-ATPase pumps and through secondary active transport by Na^+,Ca^{2+} antiporters.

2. Vitamin D stimulates addition of calcium channels (TRPV-6) and synthesis of calbindin in the enterocytes, allowing increased calcium absorption. The calbindin is necessary for calcium transport through the cell because intracellular free calcium concentrations must be maintained at very low levels.

Ca^{2+}

Lumen

Ca^{2+}

Ca^{2+}

ATP

Ca^{2+}

Ca_2

Ca^{2+}

Calbindin

$3Na^+$

Vitamin D_3

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1. **Vitamin B$_{12}$ binds to enterocytes in the form of a complex (1). Name this complex.**

2. **What binding protein (2) binds B$_{12}$ in the enterocytes and blood?**
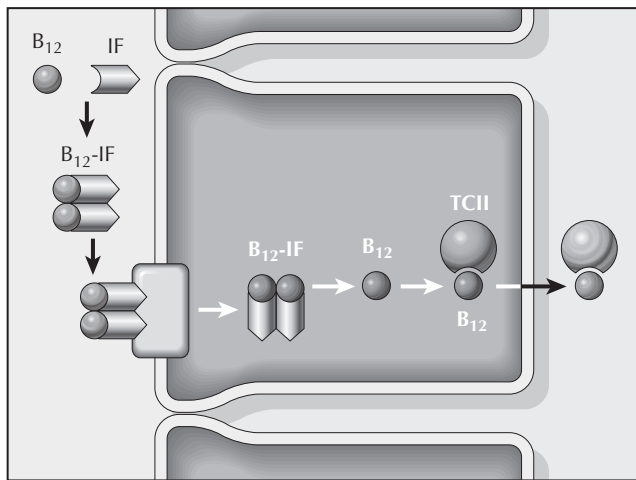

Vitamin B$_{12}$

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Vitamin B$_{12}$ Absorption

1. Receptors recognize B$_{12}$/intrinsic factor (B$_{12}$/IF) dimers.
2. Receptors for the B$_{12}$/IF dimers are located in the terminal ileum.

Comment: B$_{12}$ binds with transcobalamin II (TCII; labeled 2) in the cytosol, exits the cell, and is transported to bone marrow (for use) or is stored in the liver.
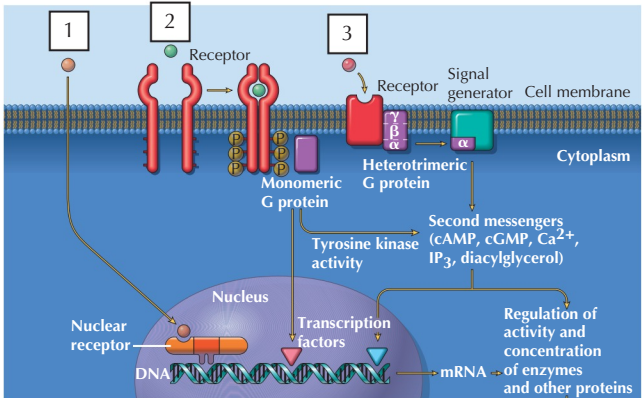

Vitamin B$_{12}$

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Identify the hormones that work through receptor mechanisms 1−3.

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1. Nuclear receptors: steroid hormones, thyroid hormones, and vitamin D
2. Monomeric G-protein receptors: growth hormones (growth hormone, insulin-like growth factors)
3. Heteromeric G-protein receptors: peptide hormones, catecholamine hormones

Identify the types of hormonal actions depicted.
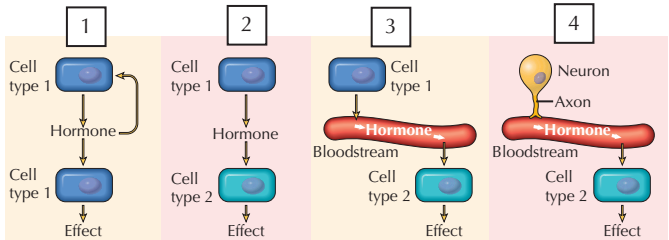
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1. Autocrine: feeds back to same cells
2. Paracrine: affects adjacent cells
3. Endocrine: secreted into bloodstream
4. Neuroendocrine: secreted from neurons into bloodstream

Comment: True hormones are produced by ductless glands and are carried through the blood to target tissues. As noted above, various secretions have been shown to act both locally (autocrine, paracrine) and through the bloodstream (endocrine, neuroendocrine).

Identify each structure.

Thalamus

Interventricular foramen

Hypothalamic sulcus

1

2

3

Hypothalamohypophyseal tract

Mamillary body

Optic chiasm

5

Neural stalk

4

Infundibular stem

Pars tuberalis

Neurohypophysis

6

Adenohypophysis

Infundibular process

Pars distalis

Cleft

Connective tissue (trabecula)

8

7
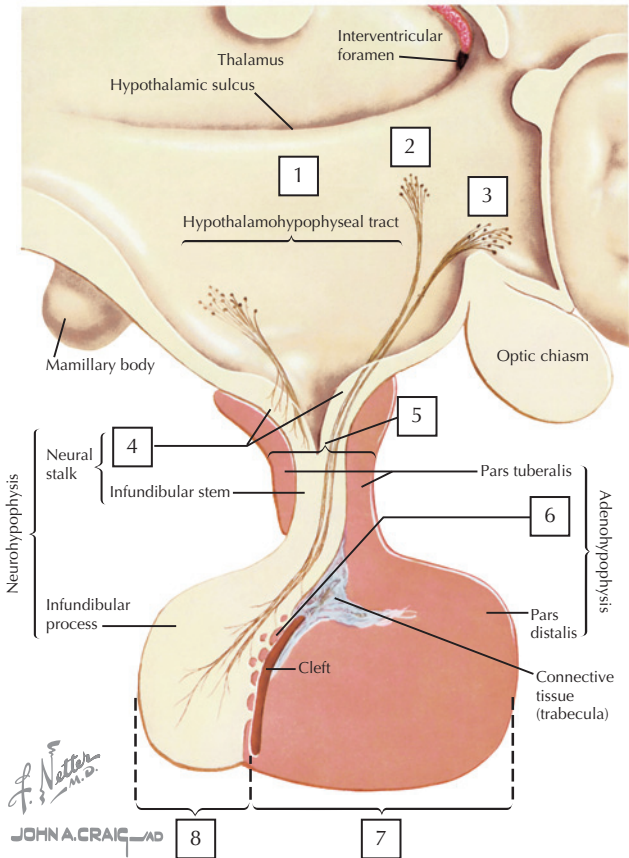
1. Hypothalamic area
2. Paraventricular nucleus (PVN)
3. Supraoptic nucleus (SON)
4. Median eminence
5. Hypophyseal stalk
6. Pars intermedia
7. Anterior pituitary (adenohypophysis)
8. Posterior pituitary (neurohypophysis)

Comment: Nuclei in the hypothalamus (PVN and SON) synthesize the posterior pituitary hormones vasopressin (antidiuretic hormone) and oxytocin; axons carry the hormones from the hypothalamus to the posterior pituitary (hence the name, *neurohypophysis*). The vasopressin and oxytocin are stored in the posterior pituitary until release.

The anterior pituitary gland secretes hormones that target different organs. Identify the hormones (1–6) that act on these organs. Identify the hormones (7–10) that are released from the target organs after stimulation by the pituitary hormone.

Emotional and exteroceptive influences via afferent nerves

Paraventricular nucleus

Supraoptic nucleus

Hypothetical site for TSH stimulation

Hypothalamic artery

Neurosecretions from hypothalamus released into primary plexus of hypophyseal portal circulation after passing down nerve fibers

Superior hypophyseal artery

Hypophyseal portal veins carry neurosecretions to adenohypophysis

Neurohypophysis

Specific secretory cells of adenohypophysis influenced by neurosecretions from hypothalamus

Blood levels—regulatory influence

1

2

3

4

5

6

IGFs

Thyroid gland

Adrenal cortex

Testis

Ovary

Breast (milk production)

Muscle

Fat tissue

Bone, muscle, organs (growth)

7

8

9

10

1. Thyroid-stimulating hormone (TSH)
2. Adrenocorticotropic hormone (ACTH)
3. Follicle-stimulating hormone (FSH) (works at both testes and ovaries)
4. Luteinizing hormone (LH) (works at both testes and ovaries)
5. Prolactin
6. Growth hormone (GH)
7. Thyroid hormones
8. Cortical hormones (cortisol)
9. Testosterone
10. Estrogen and progesterone

State the general actions of the pituitary hormones:

1. Growth hormone
2. Prolactin
3. Thyroid-stimulating hormone
4. Adrenocorticotropic hormone
5. Follicle-stimulating hormone
6. Luteinizing hormone
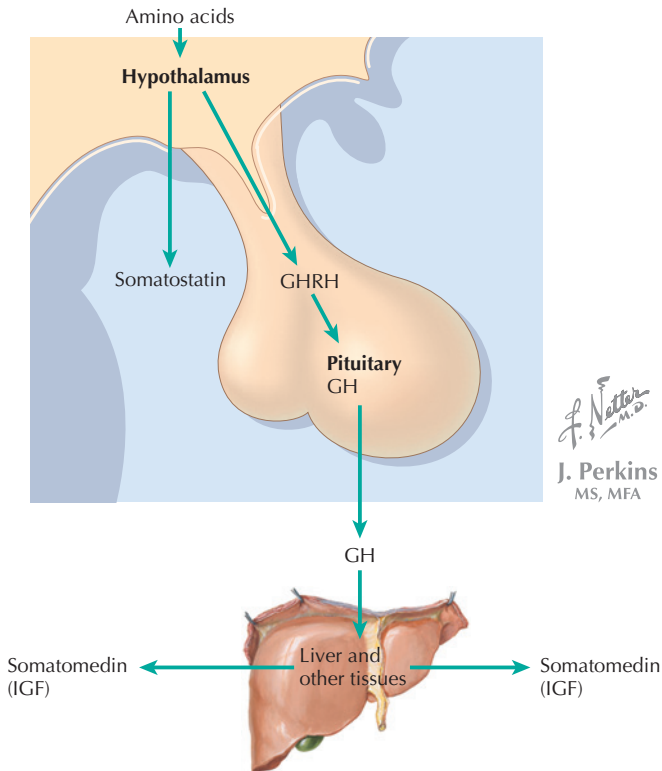7. Oxytocin
8. Vasopressin
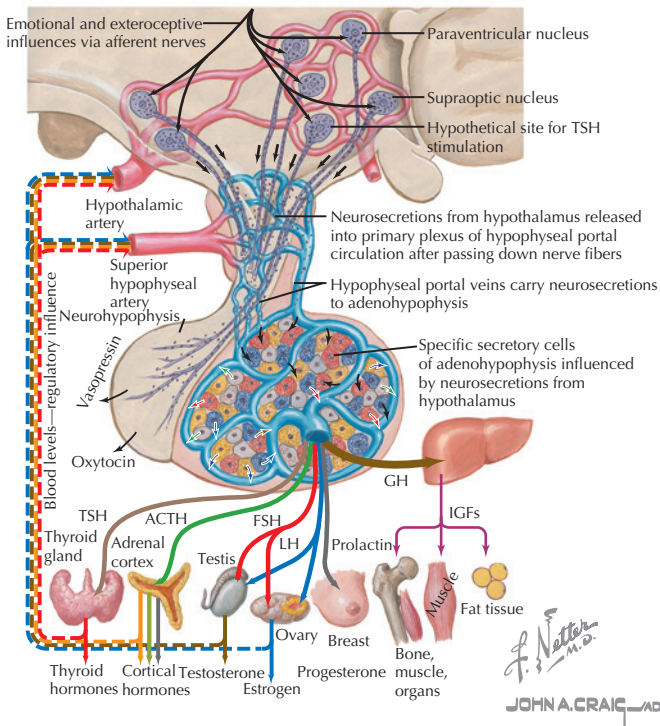
1. Growth hormone promotes the synthesis of insulin-like growth factors; has growth-promoting and anabolic effects.
2. Prolactin stimulates production of breast milk.
3. Thyroid-stimulating hormone stimulates thyroid hormone production by the thyroid gland. Thyroid hormones affect virtually all systems and generally act to increase metabolism and growth processes.
4. Adrenocorticotropic hormone (ACTH) stimulates synthesis of adrenocortical steroids. In the adrenal cortex, ACTH stimulates cortisol synthesis; ACTH also can stimulate adrenal androgen synthesis and has permissive effects on aldosterone production.
5. Follicle-stimulating hormone promotes development of primordial ovarian follicles in the first half of the menstrual cycle. In the male, FSH promotes spermatogenesis, in conjunction with testosterone.
6. Luteinizing hormone promotes ovulation during the ovulatory phase of menstruation. In the male, LH stimulates Leydig cell testosterone synthesis.
7. Oxytocin stimulates milk let-down and uterine contraction.
8. Vasopressin acts on the renal collecting ducts to insert water channels (aquaporins) in the lumenal membranes, increasing solute-free water reabsorption. These effects help conserve fluid and maintain blood pressure during dehydration or volume loss. It is also a potent vasoconstrictor.

1. Identify the substances that contribute to negative feedback regulation of growth hormone.
2. Predict the effect of uncontrolled elevation in circulating growth hormone in an adult.

Amino acids

Hypothalamus

Somatostatin

GHRH

Pituitary
GH

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MS, MFA

GH

Somatomedin
(IGF)

Liver and
other tissues

Somatomedin
(IGF)

1. Circulating insulin-like growth factor-1 (IGF-1) and growth hormone will down-regulate hypothalamic GHRH secretion, reducing pituitary GH secretion. In addition, increases in glucose and free fatty acids (FFA), as well as GHRH itself, will also exert negative feedback on GHRH.

2. Uncontrolled hypersecretion of GH in adulthood results in acromegaly, which is characterized by thickening of the bones of the jaw and brow ridges, enlargement of the tongue, cardiovascular and renal complications, diabetes, and other effects. This condition is usually caused by a pituitary tumor (adenoma).
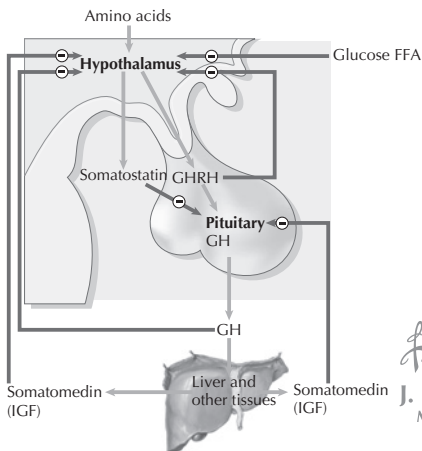
1. **Name the hypothalamic and anterior pituitary hormones controlling the release of testosterone from the testes.**

2. **Name the targets for the negative feedback effects of testosterone.**

Negative Feedback
Hypothalamus

(+)

Anterior pituitary

(+)

Testes
(+)
Testosterone
(+)
Target tissue
(e.g., muscle)

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M.D.
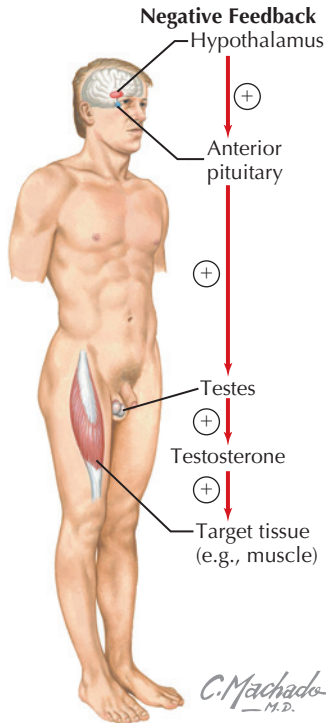
1. Hypothalamic gonadotropin-releasing hormone (GnRH) stimulates LH and FSH from the anterior pituitary gland. LH stimulates testosterone synthesis.
2. Testosterone exerts negative feedback on both the hypothalamus and pituitary.

1. Name the hypothalamic and anterior pituitary hormones controlling estrogen secretion.
2. Name the hormonal targets for the negative feedback effects of estrogen.
3. Name the hormonal targets for the positive feedback effects of estrogen. When does this occur?

Hypothalamus

$\oplus$

Anterior pituitary

$\oplus$

Ovary

$\oplus$

Estradiol

$\oplus$

Target tissue (e.g., breast, uterine endometrium)

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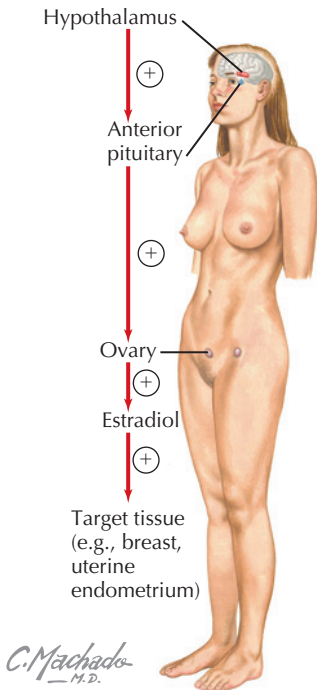
1. Hypothalamic GnRH stimulates LH and FSH from the anterior pituitary gland. LH stimulates androgen production by theca interna cells; FSH stimulates the conversion of these androgens to estradiol in the granulosa cells of the ovarian follicles.
2. Estrogen (mainly estradiol) exerts negative feedback on GnRH, LH, and FSH.
3. High levels of estradiol can exert positive effects on both LH and FSH. This occurs near midcycle of the menstrual cycle and stimulates a surge in LH and FSH resulting in ovulation.

1. Name the hypothalamic releasing hormone indicated.
2. Name the pituitary trophic hormone indicated in this axis.
3. Describe the effect of increased circulating T_4 and T_3 on the hypothalamic releasing hormone and the pituitary trophic hormone in this axis.
4. Describe the effect of decreased circulating T_4 and T_3 on the hypothalamic releasing hormone and the pituitary trophic hormone in this axis.
5. Describe the effect of increased cortisol or growth hormone on the pituitary trophic hormone in this axis.

Hypothalamus

1

Pituitary

2

Thyroid

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1. Thyrotropin-releasing hormone (TRH)
2. TSH
3. Increased circulating triiodothyronine (T_3) and thyroxine (T_4; through conversion to T_3) exert negative feedback at both hypothalamic TRH and pituitary TSH.
4. Decreased circulating T_3 and T_4 will stimulate TRH and TSH production and secretion; the elevated TSH will stimulate release of thyroid hormones.
5. In addition to T_3 and T_4, cortisol and growth hormone can also inhibit TSH and thus inhibit thyroid hormone release.
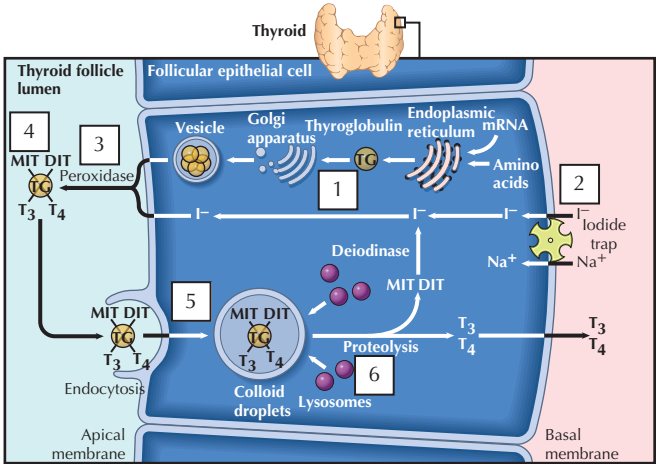
Thyroid hormone synthesis is illustrated in this thyroid follicular cell. Describe the events outlined in 1–6.

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1. Thyroglobulin molecules are produced in the endoplasmic reticulum and exocytosed into the follicular lumen.
2. Iodide enters the cell through the iodide trap and exits the cell into the lumen of the follicle.
3. Iodide is oxidized by thyroid peroxidase to iodine and substituted for the H^+ on the benzene ring of tyrosine residues of thyroglobulin.
4. Binding of one iodine forms monoiodotyrosine (MIT), and binding of two iodine moieties forms diiodotyrosine (DIT). The thyroid peroxidase catalyzes the binding of DIT to DIT, forming T_4, and DIT to MIT, forming T_3.
5. The mature thyroglobulin (containing DIT, MIT, T_4, and T_3) is endocytosed and can be stored as colloid.
6. TSH stimulates lysosomal proteolysis of the colloid, release of T_4 and T_3 into the blood, and reentry of the DIT and MIT into the synthetic pool.

The diagram illustrates binding of thyroid hormone (TH) to its nuclear receptor and subsequent intracellular actions.

1. What is the major form of circulating thyroid hormone?
2. What is the active form of TH?
3. What are the effects of thyroid hormone on the processes within the cell listed in the inset box?

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1. T_4 is the major circulating form of thyroid hormone. There is about 20 times the amount of plasma T_4 compared with T_3.

2. T_3 is the active form of thyroid hormone, which binds to the nuclear receptors. T_4 enters the cells and is deiodinated by 5'-deiodinase to active T_3.

3. Thyroid hormone increases all the processes listed in the *inset box* and thereby produces an increase in cellular metabolism.
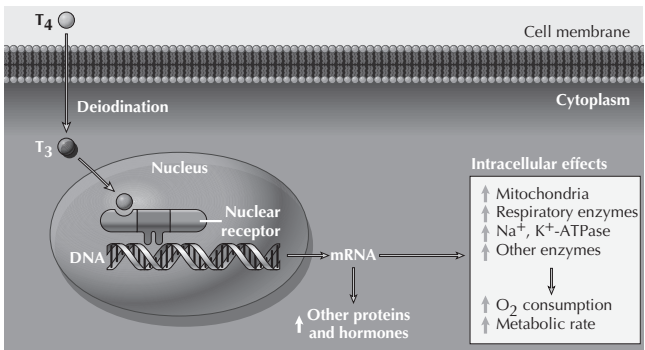
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Thyroid hormone has effects on all organ systems. Describe:

**1. The general effects on growth and development of the central
nervous system and bone.**

**2. The effects of thyroid hormone on the parameters listed below
for the lungs, heart, and kidneys.**

Whole body effects

Normal growth
and development

Bones

Central
nervous system

CO_2
Ventilation

Cardiac
output

Urea
Renal
function

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1. Thyroid hormone (TH) promotes normal growth and development of the central nervous system and bone. Typically, it acts in a synergistic manner with growth factors.
2. TH increases CO_2 production and increases ventilation and cardiac output. TH also increases renal function and urea production.

Comment: Remember, although T_4 is the predominant circulating thyroid hormone, once in tissues, T_4 is converted to active T_3 by 5´-deiodinase. In general, TH increases cellular metabolism and thus will promote hormone production, Na^+/K^+-ATPase activity, and O_2 consumption.

Referring to this adrenal gland structure, name the sites of production of:

1. Cortisol
2. Aldosterone
3. Androgens
4. Epinephrine
5. Norepinephrine

Suprarenal artery (one of many)
Capsular plexus
Capsule
Glomerulosa
Cortical capillaries
Fasciculata
Medullary arteriole
Reticularis
Medullary capillaries
Medulla
Central vein
Muscle veins

Schematic stereogram of intrinsic suprarenal circulation
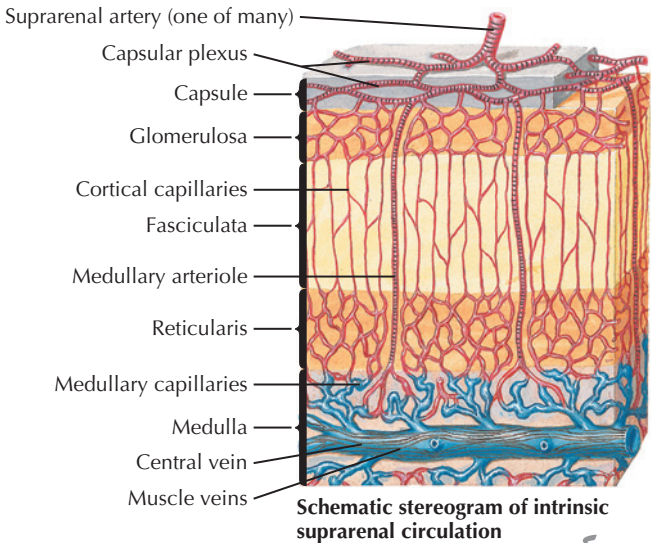
1. Zona fasciculata
2. Zona glomerulosa
3. Zona reticularis
4. Medullary chromaffin cells
5. Medullary chromaffin cells

Comment: The adrenal steroids (cortisol, aldosterone, and the androgens dehydroepiandrosterone and androstenedione) are synthesized in cells of the adrenal cortex. Small amounts of testosterone and estradiol are also produced. The medullary cells synthesize catecholamines, primarily epinephrine.

1−2. Identify the major elements in the biosynthetic pathway found in the adrenal cortex.

3. Predict the effect of chronically elevated cortisol as observed in Cushing's syndrome on blood pressure, blood glucose, and bone density.
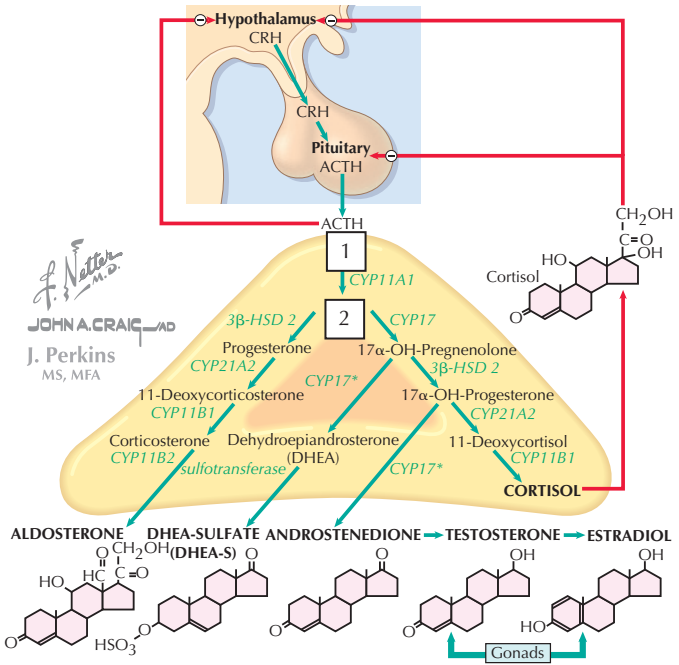
1. Cholesterol
2. Δ5-Pregnenolone
3. Symptoms of Cushing's syndrome include increased blood pressure (hypertension), hyperglycemia and insulin resistance, and decreased bone density and osteoporosis.

Comment: In addition, Cushing's syndrome is also commonly associated with:
- "Moon face"
- Centripetal obesity, with muscle wasting in the extremities
- Thinning and bruising of the skin

Other important actions of the glucocorticoids include anti-inflammatory, immunosuppressive, and vascular effects.

Identify the structure labeled 1, and describe its function.

Identify the structure labeled 2, and name the cell types in this structure and identify their products.
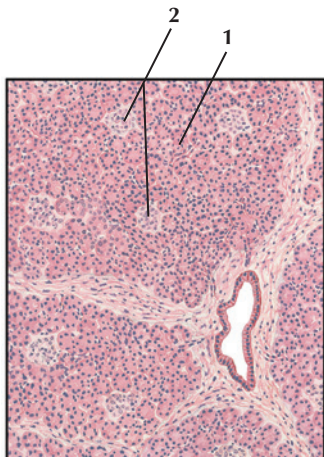
Low-power section of pancreas

High-power section of pancreas
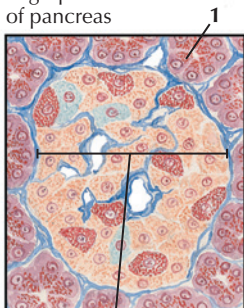
1. Acinar cells produce exocrine buffers and enzymes that are secreted through ducts into the small intestine.
2. The islet cells produce hormones that are released into systemic blood:

   Insulin is produced by the β cells.

   Glucagon is produced by the α cells.

   Somatostatin is produced by the δ cells.

Illustration depicts the proinsulin molecule.

1. Cleavage of the connecting peptide (C-peptide) occurs in what organelle?
2. Name the insulin-sensitive glucose transporters (GLUT) that are on skeletal and cardiac muscle and adipose tissue.
3. When is C-peptide useful in determining insulin secretion?
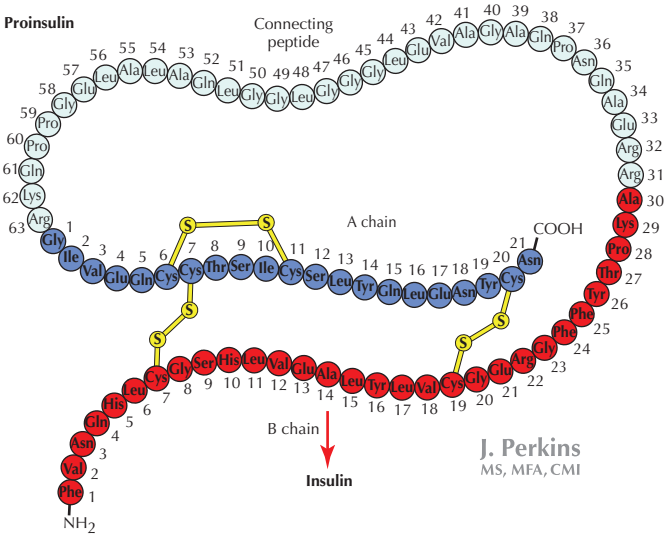
1. C-peptide is cleaved from proinsulin in the Golgi apparatus, forming insulin. Both insulin and C-peptide are secreted.
2. GLUT4 transporters are the insulin-sensitive transporters on these tissues.
3. C-peptide is used to determine endogenous insulin secretion in diabetic patients who receive insulin injections. Because C-peptide is secreted with insulin, the amount of C-peptide reflects endogenous insulin production.

Insulin is a hypoglycemic, or "fuel storage" hormone.
Describe the actions of insulin on each site.

Amino acids

1

Muscle

Glucose

Glycogen

Liver

Glucose-P

2

Glucose

Pyruvate
CO_2

Free fatty acids

Keto acids

Insulin
Stimulates

Inhibits

3

**Adipose
tissue**

C. Machado
_M.D._
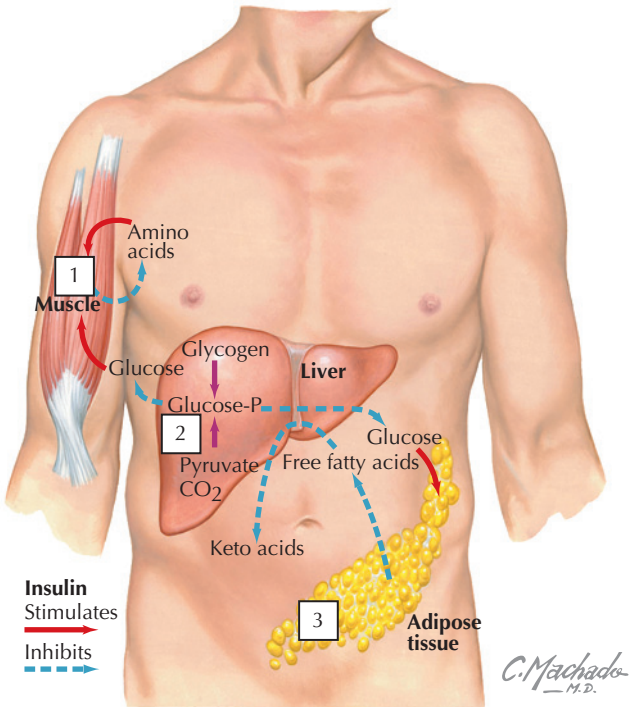
1. In muscle, insulin increases GLUT4 transporters in membranes, promoting efficient glucose entry into cells. Insulin also stimulates glycogen production and inhibits glycogenolysis.
2. In the liver, insulin increases glycogen production and inhibits glycogenolysis and gluconeogenesis. This inhibits glucose release into the blood. In addition, insulin inhibits oxidation of fatty acids, reducing formation of keto acids.
3. In adipose tissue, insulin inhibits lipolysis, reducing circulating free fatty acids. Insulin also inhibits oxidation of fatty acids, reducing formation of keto acids.

Glucagon is a hyperglycemic, or "fuel mobilization" hormone. Describe the actions of glucagon at each site.

1. In muscle, glucagon inhibits protein synthesis, releasing amino acids into the circulation for use in gluconeogenesis in the liver.
2. In the liver, glucagon inhibits glycolysis and stimulates glycogenolysis and gluconeogenesis; this releases glucose into the blood.
3. In adipose tissue, glucagon stimulates lipolysis and increases β-oxidation of fatty acids. Circulating free fatty acids and keto acids are increased.

Active vitamin D (1,25-dihydroxycholecalciferol) is a major calcium regulatory hormone. Describe the products in the pathway for active vitamin D synthesis by the organs:

1. Skin
2. Liver
3. Kidneys
4. State under what conditions vitamin D would be stimulated.

Ca^{2+} and P_i in food

Vit. D

Sun

Ultraviolet light

Skin

Liver

?

?

?

Kidney
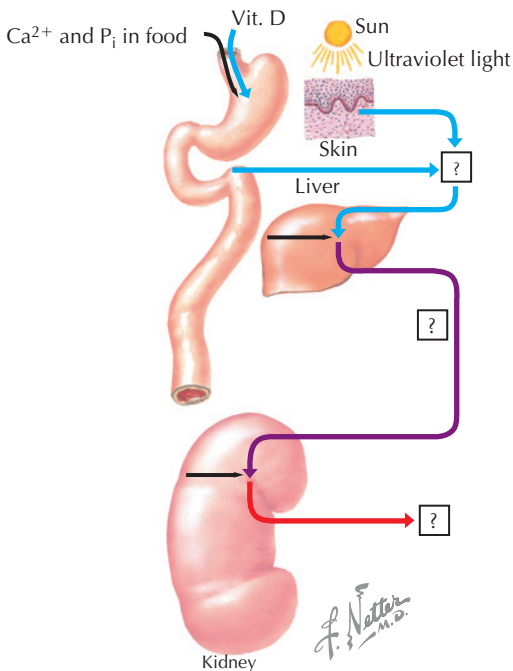
1. **Skin:** Exposure to ultraviolet light can produce vitamin D (cholecalciferol) from 7-dehydroxycholesterol in skin cells.
2. **Liver**: Cholecalciferol from the skin (and from dietary intake) is hydroxylated in the liver to 25-hydroxycholecaliferol.
3. **Kidneys**: Circulating 25-hydroxycholecalciferol is further hydroxylated to 1, 25-dihydroxycholecalciferol in the kidneys. This is the active form of vitamin D.
4. Active vitamin D production is *stimulated* when plasma calcium level is low. Parathyroid hormone (PTH) secretion is stimulated when plasma calcium falls; the PTH stimulates renal $1\text{-}\alpha\text{-hydroxylase}$ to increase formation of active vitamin D.

Describe the actions of vitamin D on each site.

1. In the small intestine, active vitamin D (1,25-dihydroxycholecalciferol) stimulates absorption of calcium by increasing apical calbindin proteins and basolateral Ca^{2+}-ATPases.
2. In the bone, active vitamin D promotes mineralization and remodeling (affects both osteoblastic and osteoclastic activity).

Describe the actions of parathyroid hormone (PTH) on each site.

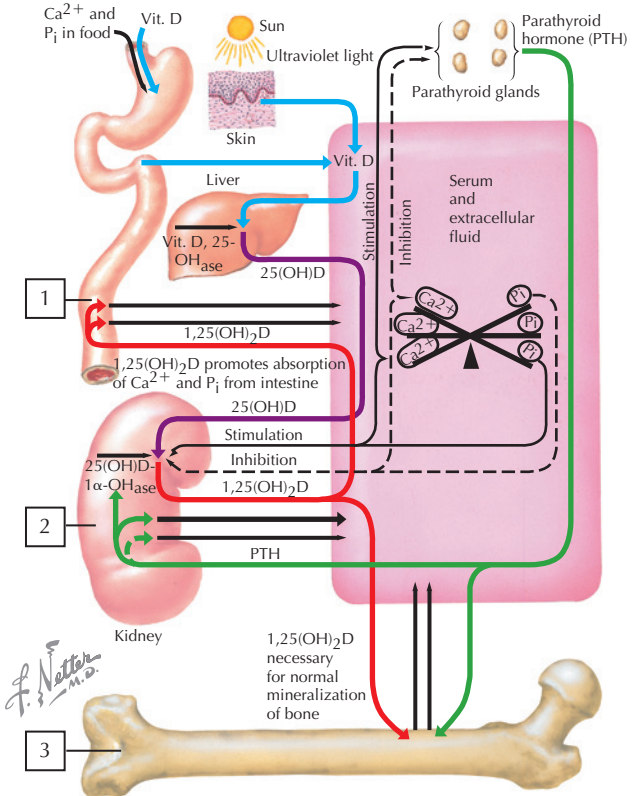1. **Small Intestine:** PTH *indirectly* promotes intestinal calcium absorption by increasing the formation of active vitamin D by the kidneys. This is a slow mechanism for adjusting plasma calcium level because it is dependent on calcium intake.

2. **Kidneys:** PTH *directly* increases calcium reabsorption in the distal tubule; decreases phosphate reabsorption in the proximal tubule; and increases the formation of active vitamin D. These actions are rapid and are the primary pathway for restoration of plasma calcium levels.

3. **Bone:** PTH promotes the osteoclastic resorption of bone matrix, which adds both calcium and phosphate to the plasma. The actions of PTH also contribute to normal bone remodeling.

Comment: PTH responds rapidly to decreased plasma calcium levels and acts to increase intestinal absorption and bone resorption of both calcium *and* phosphate, and renal reabsorption of only calcium. PTH also reduces renal phosphate reabsorption, so surplus phosphate in the plasma is eliminated in the urine.

Describe the effects of hyperparathyroidism on calcium handling at each site.

Adenoma (~85% of cases)

Hyperplasia (~15% of cases)

Carcinoma (rare)

1

Skin

Vit. D

Ca^{2+}
P_i
Gut
Liver

25(OH)D

Ca^{2+}
P_i

High $1,25(OH)_2D$ promotes absorption of Ca^{2+} from gut

Renal tubule

Ca^{2+}

Ca^{2+} filtration

P_i

25(OH)D normal
$1,25(OH)_2D$ elevated

2

Ca^{2+}
P_i
?

Ca^{2+}
P_i
Ca^{2+}
P_i

Parathyroid hormone (PTH) elevated

Serum and extracellular fluid Serum Ca^{2+} increased; fails to suppress PTH secretion

Ca^{2+}
P_i
P_i

Serum P_i low or normal
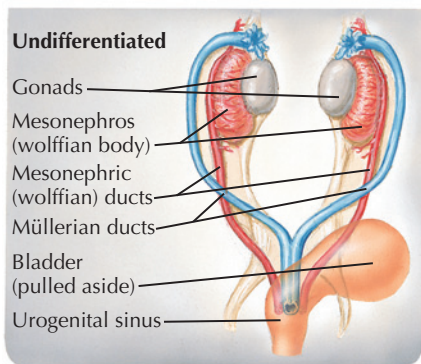
PTH

3

Urine Ca^{2+}
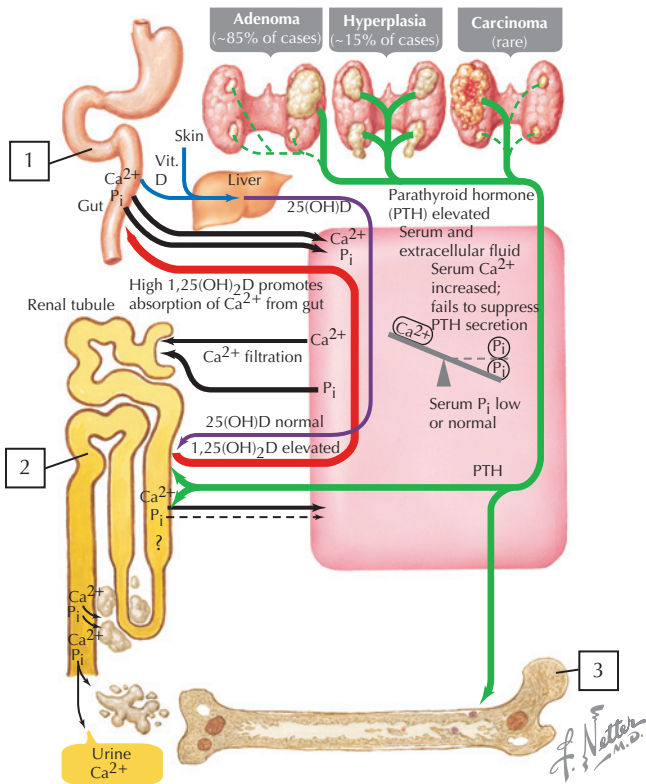
1. **Small intestine:** Intestinal calcium and phosphate absorption is stimulated by the high plasma vitamin D levels.

2. **Kidneys:** Elevated PTH will increase the formation of active vitamin D, increase calcium reabsorption in the distal tubules, and decrease phosphate reabsorption in the proximal tubules. The continual elevation of PTH in hyperparathyroidism will result in abnormally high plasma calcium and low plasma phosphate levels. The normal feedback regulation of PTH by high plasma calcium is not operant in hyperparathyroidism.

3. **Bone:** High PTH levels will increase osteoclastic resorption of bone; however, there can be a compensatory increase in osteoblastic activity (stimulated by vitamin D); thus, although remodeling is increased, reduction in bone density is not always observed.

Comment: The abnormally high filtered load of calcium results in hypercalciuria. The high concentration of calcium in the tubular fluid may result in the formation of calculi (kidney stones). The primary cause of hyperparathyroidism is adenoma.

1. Name the main genital structure that persists in the developing genitalia of males and the hormone that accounts for persistence and differentiation of this structure.

2. Name the main genital structure that persists in the developing genitalia of females and the hormone that accounts for this differentiation.

Undifferentiated
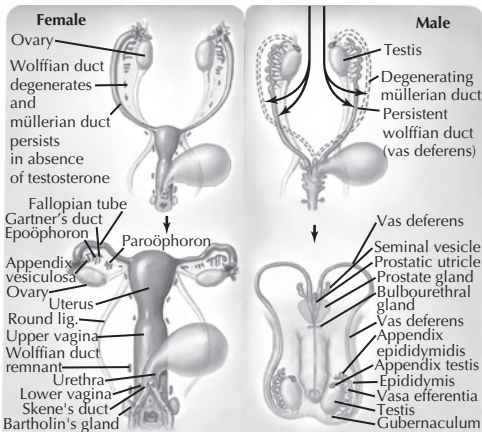
Gonads

Mesonephros (wolffian body)

Mesonephric (wolffian) ducts

Müllerian ducts

Bladder (pulled aside)

Urogenital sinus

1. The wolffian ducts persist in the male fetus and become the vas deferens. Testosterone, secreted from the fetal testes, induces this differentiation. The testes also secrete müllerian-inhibiting factor, which causes degeneration of the müllerian ducts.
2. In the female fetus, the absence of testosterone allows the persistence of the müllerian ducts and degeneration of the wolffian ducts. The müllerian ducts become the fallopian tubes.

Comment: Differentiation in the early embryo depends on the products encoded by the X and Y chromosomes. Importantly, the *SRY* gene on the Y chromosome results in the differentiation of the gonads into testes. By 8 to 9 weeks of development, the Leydig cells of the fetal testes begin to secrete testosterone.

Female
Ovary
Wolffian duct degenerates and müllerian duct persists in absence of testosterone
Fallopian tube
Gartner's duct
Epoöphoron
Paraöphoron
Appendix vesiculosa
Ovary
Uterus
Round lig.
Upper vagina
Wolffian duct remnant
Urethra
Lower vagina
Skene's duct
Bartholin's gland

Male
Testis
Degenerating müllerian duct
Persistent wolffian duct (vas deferens)
Vas deferens
Seminal vesicle
Prostatic utricle
Prostate gland
Bulbourethral gland
Vas deferens
Appendix epididymidis
Appendix testis
Epididymis
Vasa efferentia
Testis
Gubernaculum

Reproductive Hormones I:
Development of Genital Sex

See Figure 31.1

Secondary sex characteristics appearing during or after puberty are depicted. Name the hormones responsible for characteristics shown.

1
Hair loss

2 Libido

3
Muscle
mass

7
Libido

8
Breast
development

9
Axial and
pubic hair

4
Axial and
pubic hair

Penis/scrotal
growth 5

6
Long bone
growth

10
Long
bone
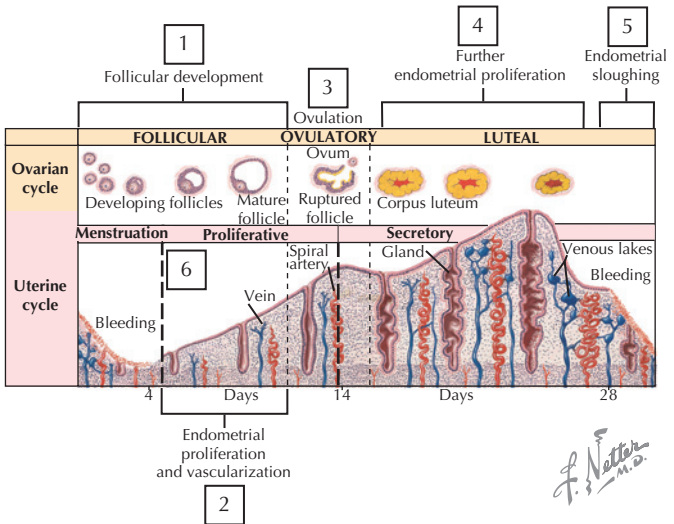growth

11
Skin
texture

C. Machado
M.D.

1. Testosterone (and genetic profile)—hair loss in adulthood is caused by a combination of genetic factors and the presence of testosterone
2. Testosterone—male libido
3. Testosterone—increased muscle mass in males
4. Testosterone—growth of male axillary, pubic, and body hair
5. Testosterone—penis and scrotal growth
6. Estrogen—long bone growth in males
7. Adrenal androgens—female libido
8. Estrogen—breast development
9. Adrenal androgens—female axillary and pubic hair
10. Estrogen—long bone growth in females
11. Estrogen—smooth skin texture

Comment: Testosterone actions occur primarily after conversion to dihydrotestosterone (DHT) in the target tissues by the enzyme 5α-reductase. In female breast development, although estrogen is the primary pubertal stimulus, complete development of the lobules and alveoli during pregnancy is stimulated by estrogen, progesterone, and prolactin.

**Identify the hormones primarily responsible
for changes in the ovary and uterus.**

1. Follicular development—FSH
2. Endometrial proliferation and vascularity—estrogen
3. Ovulation—LH, stimulated by surge in estrogen
4. Further endometrial proliferation—progesterone
5. Endometrial sloughing—reduction in progesterone (with absence of implantation of fertilized egg)

1. Name the hormone that produces positive feedback effects on the hypothalamus and pituitary during the late follicular and ovulatory phases.
2. Name the precursor of this hormone (1) produced by the theca interna cells.
3. Name the hormones produced by the granulosa cells of the corpus luteum that produce negative feedback on both the pituitary and hypothalamus.
4. Name the hormone produced by the granulosa cells that exerts negative feedback on pituitary FSH secretion.

A. Late follicular and ovulatory phases
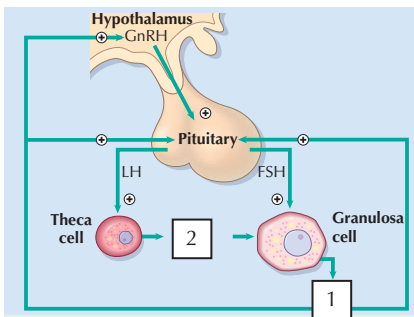
B. Luteal phase
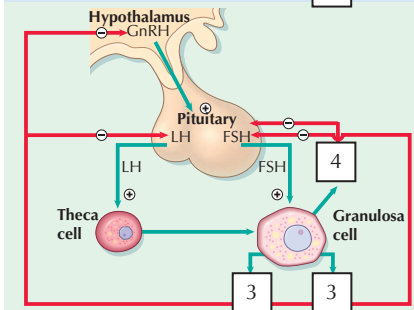
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MS, MFA

1. Estrogen
2. Androgens
3. Estrogen and progesterone
4. Inhibin

Identify each structure.
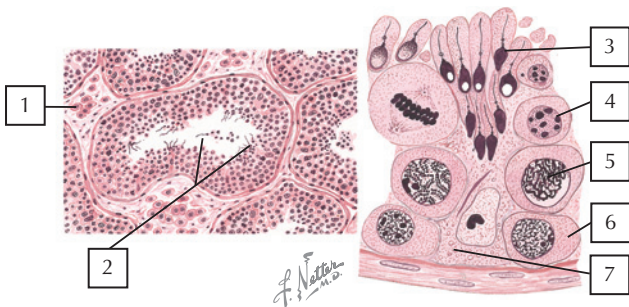
1. Leydig cells
2. Seminiferous tubules
3. Spermatid
4. Secondary spermatocyte
5. Primary spermatocyte
6. Spermatogonium
7. Sertoli cell

1. Name the hormone secreted from Leydig cells that has positive effects on spermatogenesis and Sertoli cells and exerts negative feedback on the hypothalamic GnRH and pituitary FSH secretion.
2. Name the pituitary hormone that stimulates Leydig cell secretion of hormone 1.
3. Name the pituitary hormone that acts with hormone 1 to stimulate spermatogenesis.
4. Name the hormone produced by the Sertoli cells that has negative effects on pituitary FSH secretion.

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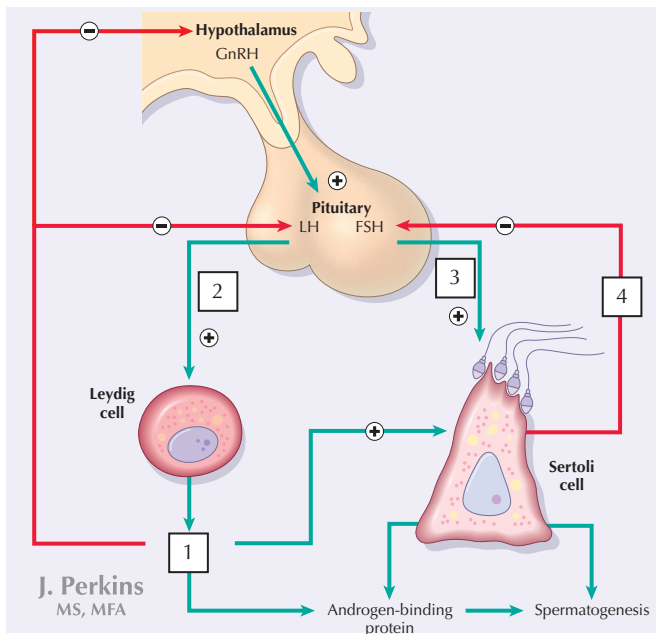
1. Testosterone
2. LH
3. FSH
4. Inhibin

Fluid Homeostasis

Net filtration $= K_f [(HP_c + \pi_i) - (P_i + \pi_c)]$

Starling's equation, where K_f is the filtration coefficent, HP_c is capillary hydrostatic pressure, π_i is interstitial oncotic pressure, P_i is interstitial hydrostatic pressure and π_c is capillary oncotic pressure.

Nerve and Muscle Physiology

$$E_X = \frac{61\ mV}{z} * \log \frac{[X]_o}{[X]_i}$$

Simplified Nernst equation, where E_X is the equilibrium potential, z is charge of ion x, $[X]_o$ is its concentration outside the cell and $[X]_i$ is its concentration inside the cell.

$$V_m = 61\ mV * \log \frac{P_{K+}[K^+_o] + P_{Na+}[Na^+_o] + P_{Cl-}[Cl^-_i]}{P_{K+}[K^+_i] + P_{Na+}[Na^+_i] + P_{Cl-}[Cl^-_o]}$$

Simplified Goldman-Hodgkin-Katz equation, where V_m is resting membrane potential, and P_x is membrane permeability to ion x.

$V = IR$
Ohm's law, where V is potential difference (voltage), I is current and R is resistance.

$G = 1/R$
Where G is conductance.

$I_x = G(V_m - E_x)$
Where I_x is current for ion x and E_x is the Nernst potential of the ion.

$\tau = R_m C_m$
Where τ is the time constant, R_m is membrane resistance and C_m is membrane capacitance.

$\lambda = \sqrt{(R_m/R_i)}$
Where λ is the space constant and R_i is internal resistance.

Cardiovascular Physiology

$Q = \Delta P/R$, where Q is flow, ΔP is the pressure gradient, and R is resistance to flow.

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

Poiseuille's law, where Q is flow, ΔP is the pressure gradient, r is radius, η is viscosity and L is the length.

$$CO = HR \times SV$$

Cardiac output formula, where CO is cardiac output, HR is heart rate and SV is stroke volume.

$$TPR = P_{MAP}/CO$$

Total peripheral resistance (TPR) is approximated as mean arterial pressure (P_{MAP}) divided by cardiac output (CO).

$$Q = vA$$

where Q is blood flow, A is cross-sectional area and v is velocity.

$$Re = \frac{vD\partial}{\eta}$$

where R_e is Reynold's Number, v is velocity, D is the diameter, ∂ is the density, and η is viscosity.

$$T = P_t r$$

Laplace's Law, where T is wall tension, P_t is transmural pressure (the difference between pressure inside and outside the vessel), and r is radius.

Respiratory Physiology

$TLC = RV + ERV + V_T + IRV = RV + VC,$
where **TLC** is total lung capacity, **RV** is residual volume, **ERV** is expiratory reserve volume, V_T is tidal volume, **IRV** is inspiratory reserve volume, and **VC** is vital capacity.

$FRC = ERV + RV,$ where **FRC** is functional residual capacity, **ERV** is expiratory reserve volume and **RV** is residual volume.

$\dot{V}_E = R \times V_T,$ where $\dot{V}_E$ is minute ventilation, **R** is the respiratory rate and V_T is the tidal volume.

$\dot{V}_A = R(V_T - V_D),$ where $\dot{V}_A$ is alveolar ventilation, **R** is respiratory rate, V_T is tidal volume and V_D is dead space volume.

$P_{A_{O_2}} = P_{I_{O_2}} - P_{A_{CO_2}}/R,$
the alveolar gas equation, where $P_{A_{O_2}}$ is partial pressure of oxygen in alveolar air, $P_{I_{O_2}}$ is partial pressure of oxygen in inspired air, $P_{A_{CO_2}}$ is partial pressure of CO_2 in alveolar air, and **R** is the respiratory quotient.

$$\dot{V}_{gas} = \frac{A \cdot D \cdot (P_1 - P_2)}{T}$$
Fick's law, where $\dot{V}_{gas}$ is diffusion of gas between two compartments, **A** is the area of a membrane separating the compartments, **T** is thickness, **D** is the diffusion constant and P_1 and P_2 are gas concentrations in the two compartments.

$D_{LCO} = \dot{V}_{CO}/P_{ACO},$ where D_{LCO} is diffusion capacity of the lung for **CO**, $\dot{V}_{CO}$ is diffusion of **CO** and P_{ACO} is alveolar partial pressure of **CO**.

Rate of airflow $= (P_A - P_{ATM})/R_{aw},$ where P_A is alveolar pressure, P_{ATM} is atmospheric pressure and R_{aw} is airway resistance.

$Q = \frac{\Delta P \pi\ r^4}{\eta 8 L}$ **Poiseuille's law**, where **Q** is airflow, ΔP is the pressure gradient, **r** is radius, η is viscosity and **L** is the length.

O_2 binding capacity $= (1.34$ ml $O_2/$g Hb$) \times ($g Hb$/100$ ml blood$).$

O_2 content $= \%$ Saturation $\times O_2$ binding capacity $+$ dissolved $O_2.$

O_2 consumption $= [a - v]_{O_2} \times$ Cardiac Output.

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03 \cdot P_{CO_2}}$$
Henderson-Hasselbalch equation for bicarbonate buffering system in blood.

Renal Physiology

$C_x = (U_x * \dot{V})/P_x$
where C_x is the clearance of substance **x**, U_x is its urine concentration, $\dot{V}$ is urine flow rate and P_x is plasma concentration of substance **x**.

$GFR = C_{in} = (U_{in} * \dot{V})/P_{in}$
where **GFR** is glomerular filtration rate, which is equal to clearance of inulin (C_{in}).

$eRPF = C_{PAH} = (U_{PAH} * \dot{V})/P_{PAH}$
where **eRPF** is effective renal plasma flow, which is equal to clearance of **PAH** (paraminohippurate).

$eRBF = (eRPF)/(1-HCT)$
where **eRBF** is effective renal blood flow and HCT is hematocrit.

$FF = GFR/RPF$
where **FF** is the filtration fraction, the fraction of the renal plasma flow that is filtered.

$FL_x = P_x * GFR$
where FL_x is the filtered load of substance **x**, and P_x is plasma concentration of substance **x**.

$E_x = U_x \dot{V}$
where E_x is urinary excretion rate of substance **x**, U_x is its urine concentration and $\dot{V}$ is urine flow rate.

$R_x = FL_x - U_x \dot{V}$
where R_x is the reabsorption rate of substance **x**.

$FE_x = [(U/P)_x /(U/P)_{in}]*100$
where FE_x is fractional excretion of substance **x**, $(U/P)_x$ is the ratio of urinary to plasma concentration of **x**, and $(U/P)_{in}$ is the ratio of urinary to plasma concentration of inulin.

$FR_x = [1- (E_x/FL_x)]*100$
where FR_x is fractional reabsorption of substance **x**.