

Chapter 1:

Functional Organization of the Human Body and Control of the “Internal Environment”

- *Human Physiology* attempt to explain the specific characteristics and mechanisms of the human body that make it a living being.
- *Anatomy* attempt to explain the structure of the body.

- Each type of life, from the simple virus to the largest tree or the complicated human being, has its own functional characteristics.



- The goal of physiology is to explain the physical and chemical factors that are responsible for the origin, development, and progression of life.
- Therefore, the vast field of physiology can be divided into:

- viral physiology*
- bacterial physiology*
- cellular physiology*
- plant physiology*
- human physiology*
-

The Human Body - A Complex Society of Differentiated Cells

- Cells: the basic structural and functional unit (~ 100 trillion)
- Each type of cell is specially adapted to perform one or a few particular functions.
 - For instance, the red blood cells, numbering 25 trillion in each human being, transport oxygen from the lungs to the tissues. 75 trillion additional cells of other types that perform functions different from those of the red cell.
- Although the many cells of the body often differ markedly from one another, all of them have certain basic characteristics that are alike.
 - For instance, in all cells, oxygen reacts with carbohydrate, fat, and protein to release the energy required for cell function. Further, the general chemical mechanisms for changing nutrients into energy are basically the same in all cells, and all cells deliver end products of their chemical reactions into the surrounding fluids.
- all cells also have the ability to reproduce additional cells of their own kind.

Extracellular Fluid—The “Internal Environment”

- About 60 per cent of the adult human body is fluid, mainly a water solution of ions and other substances.
- Most of this fluid is inside the cells and is called **intracellular fluid**, about one third is in the spaces outside the cells and is called **extracellular fluid**.
- Extracellular fluid is transported rapidly in the circulating blood and then mixed between the blood and the tissue fluids by diffusion through the capillary walls.
- The ions and nutrients that are in the extracellular fluid needed by the cells to maintain cell life. Thus, all cells live in essentially the same environment—the extracellular fluid. For this reason, the extracellular fluid is also called the internal environment of the body
- Cells are capable of living, growing, and performing their special functions as long as the proper concentrations of oxygen, glucose, different ions, amino acids, fatty substances, and other constituents are available in this internal environment.

Differences Between Extracellular and Intracellular Fluids.

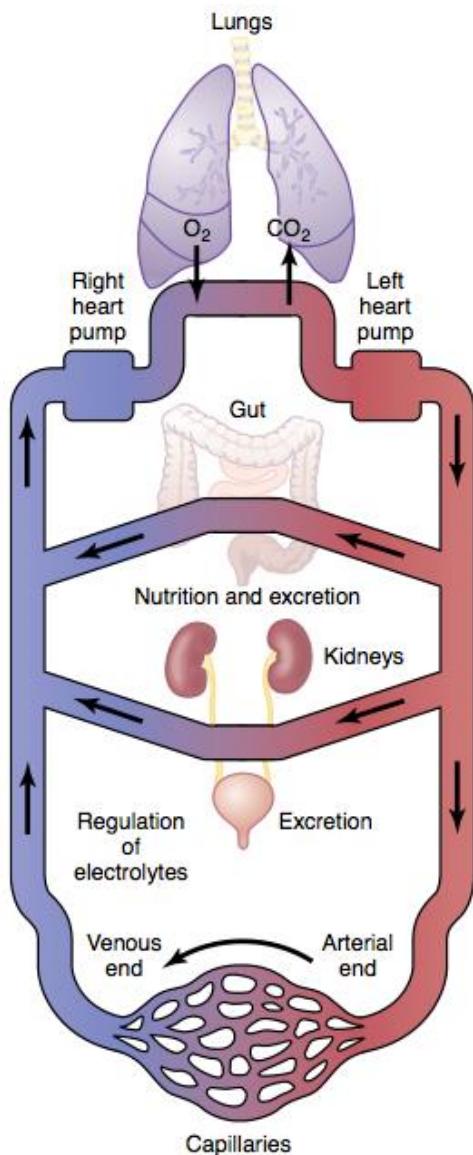
- The extracellular fluid contains large amounts of sodium, chloride, and bicarbonate ions plus nutrients for the cells, such as oxygen, glucose, fatty acids, and amino acids. It also contains carbon dioxide that is being transported from the cells to the lungs to be excreted, plus other cellular waste products that are being transported to the kidneys for excretion.
- The intracellular fluid differs significantly from the extracellular fluid; specifically, it contains large amounts of potassium, magnesium, and phosphate ions instead of the sodium and chloride ions found in the extracellular fluid. Special mechanisms for transporting ions through the cell membranes maintain the ion concentration differences between the extracellular and intracellular fluids.

“Homeostatic” Mechanisms of the Major Functional Systems

■ Homeostasis

- The term *homeostasis* is used by physiologists to mean *maintenance of nearly constant conditions in the internal environment*.
- Essentially all organs and tissues of the body perform functions that help maintain these constant conditions.
 - For instance, the lungs provide oxygen to the extracellular fluid to replenish the oxygen used by the cells, the kidneys maintain constant ion concentrations, and the gastrointestinal system provides nutrients.

- Different functional systems of the body and their contributions to homeostasis (briefly):
- Extracellular Fluid Transport and Mixing System—The Blood Circulatory System**



General organization of the circulatory system.

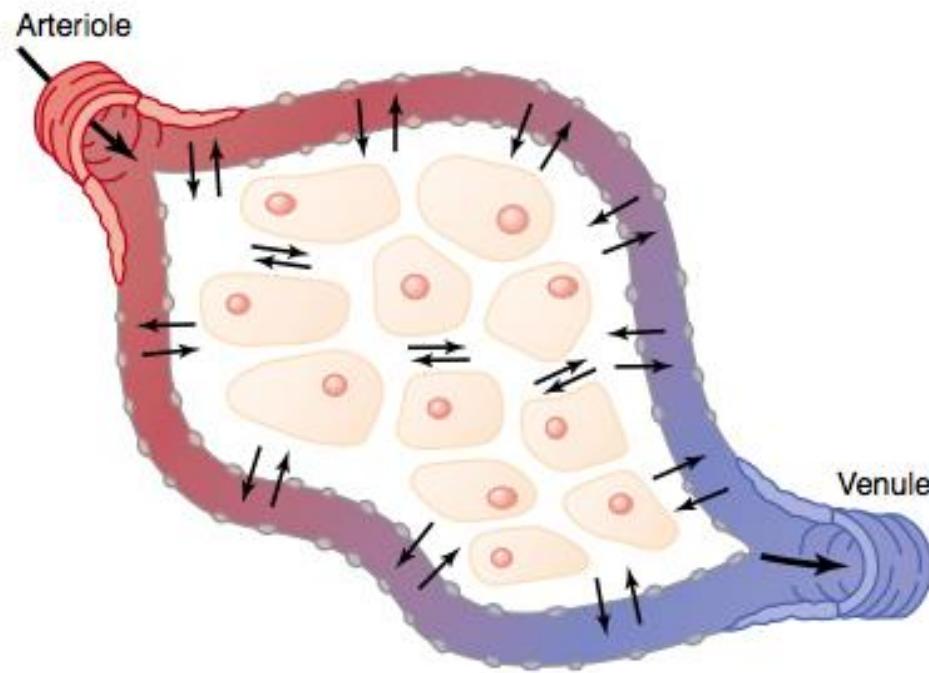


Figure 1-2

Diffusion of fluid and dissolved constituents through the capillary walls and through the interstitial spaces.

The walls of the capillaries are permeable to most molecules in the plasma of the blood, with the exception of the large plasma protein molecules. Therefore, large amounts of fluid and its dissolved constituents diffuse back and forth between the blood and the tissue spaces, as shown by the arrows. This process of diffusion is caused by kinetic motion of the molecules in both the plasma and the **interstitial fluid**.

- **Origin of Nutrients in the Extracellular Fluid**
- **Respiratory System** acquires the oxygen needed by the cells
- **Gastrointestinal Tract** absorbs different dissolved nutrients, including carbohydrates, fatty acids, and amino acids from the ingested food into the extracellular fluid of the blood
- **Liver and Other Organs That Perform Primarily Metabolic Functions:** Not all substances absorbed from the gastrointestinal tract can be used in their absorbed form by the cells. The liver changes the chemical compositions of many of these substances to more usable forms, and other tissues of the body—fat cells, gastrointestinal mucosa, kidneys, and endocrine glands—help modify the absorbed substances or store them until they are needed.
- **Musculoskeletal System** provides motility for protection against adverse surroundings, without which the entire body, along with its homeostatic mechanisms, could be destroyed instantaneously.

- **Removal of Metabolic End Products**
- **Removal of Carbon Dioxide by the Lungs:** At the same time that blood picks up oxygen in the lungs, carbon dioxide is released from the blood into the lung alveoli; the respiratory movement of air into and out of the lungs carries the carbon dioxide to the atmosphere.
- **Kidneys:** Passage of the blood through the kidneys removes from the plasma most of the other substances besides carbon dioxide that are not needed by the cells. These substances include different end products of cellular metabolism, such as urea and uric acid; they also include excesses of ions and water from the food that might have accumulated in the extracellular fluid.

- **Regulation of Body Functions**
- **Nervous System:** The nervous system is composed of three major parts:
 - ① sensory input portion: Sensory receptors detect the state of the body or the state of the surroundings
 - ② central nervous system (or integrative portion): The central nervous system is composed of the brain and spinal cord. The brain can store information, generate thoughts, create ambition, and determine reactions that the body performs in response to the sensations.
 - ③ motor output portion. Appropriate signals are then transmitted through the motor output portion of the nervous system to carry out one's desires.
- **Hormonal System of Regulation.** Located in the body are eight major *endocrine glands* that secrete chemical substances called hormones. Hormones help regulate cellular function.
 - For instance, thyroid hormone increases the rates of most chemical reactions in all cells, thus helping to set the tempo of bodily activity. Insulin controls glucose metabolism; adreno-cortical hormones control sodium ion, potassium ion, and protein metabolism; and parathyroid hormone controls bone calcium and phosphate.
- the hormones are a system of regulation that complements the nervous system. The nervous system regulates mainly muscular and secretory activities of the body, whereas the hormonal system regulates many metabolic functions.
- **Reproduction**
- It helps maintain homeostasis by generating new beings to take the place of those that are dying.

Control Systems of the Body

- The human body has thousands of control systems in it. The most intricate of these are the genetic control systems that operate in all cells to help control intracellular function as well as extracellular function.
- Many other control systems operate within the organs to control functions of the individual parts of the organs; others operate throughout the entire body to control the interrelations between the organs.

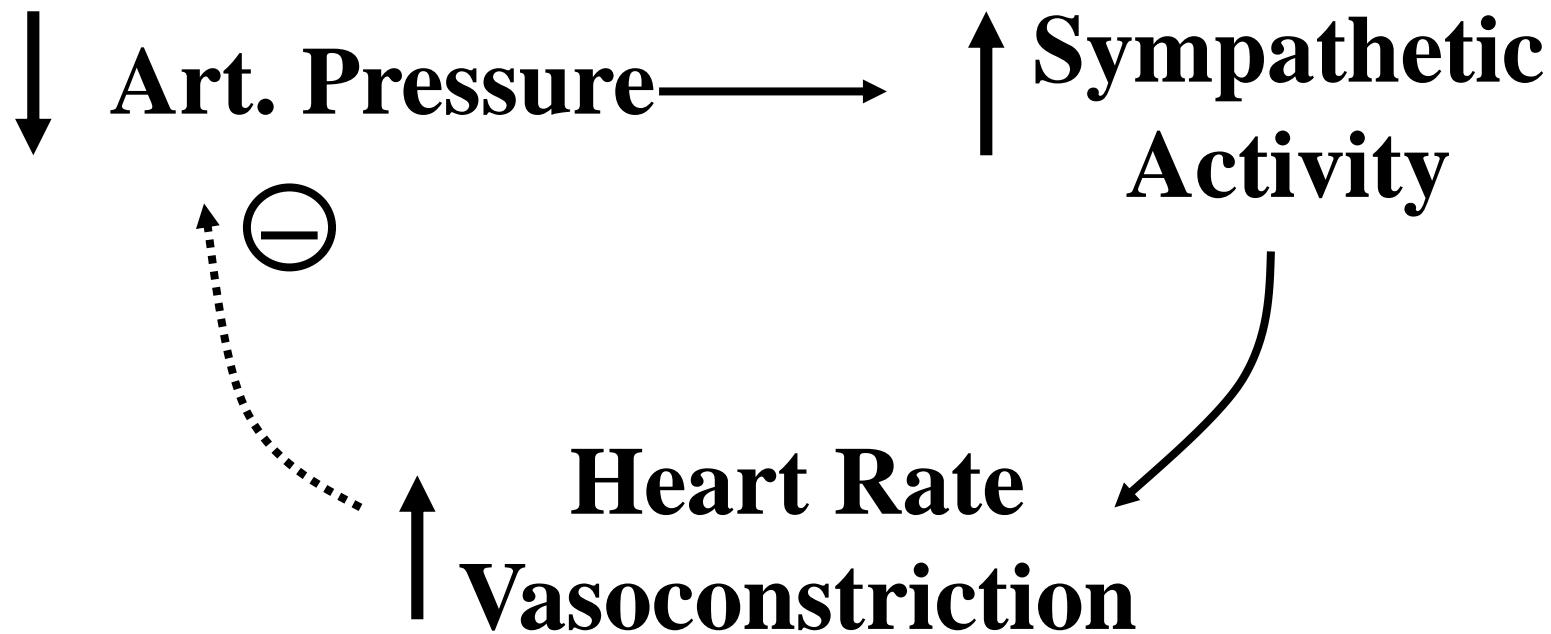
Examples of Control Mechanisms

- Regulation of Oxygen and Carbon Dioxide Concentrations in the Extracellular Fluid
 - *oxygen-buffering function of hemoglobin.*
 - Excitation of the respiratory center → causing a person to breathe rapidly and deeply.
- Regulation of Arterial Blood Pressure.
 - baroreceptor system → When the arterial pressure rises too high, the baroreceptors send barrages of nerve impulses to the medulla of the brain

Characteristics of Control Systems

- **Negative Feedback Nature of Most Control Systems**
- if some factor becomes excessive or deficient, a control system initiates negative feedback, which consists of a series of changes that return the factor toward a certain mean value, thus maintaining homeostasis.
 - For instance; In the arterial pressure-regulating mechanisms, a high pressure causes a series of reactions that promote a lowered pressure, or a low pressure causes a series of reactions that promote an elevated pressure. In both instances, these effects are negative with respect to the initiating stimulus.

Example: Negative Feedback Control of Arterial Pressure Promotes Stability



- Negative feedback: promotes stability

Positive Feedback Can Sometimes Cause Vicious Cycles and Death

- Positive feedback: promotes a change in one direction, often leading to instability, disease, and sometimes death.

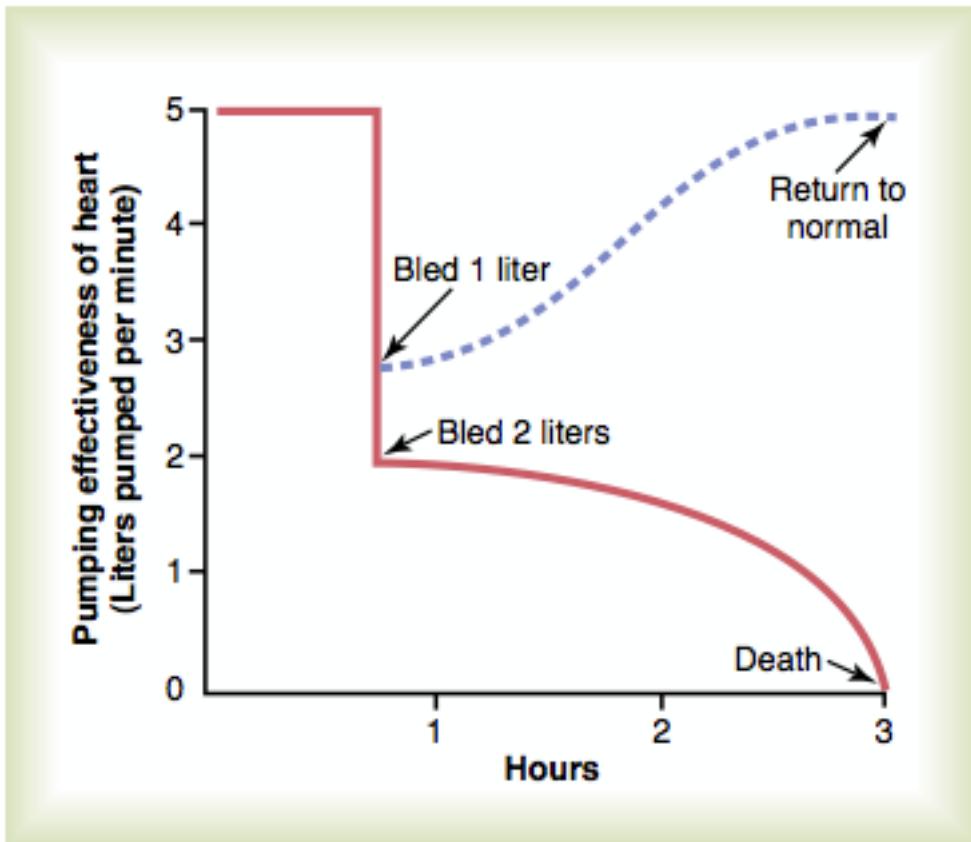
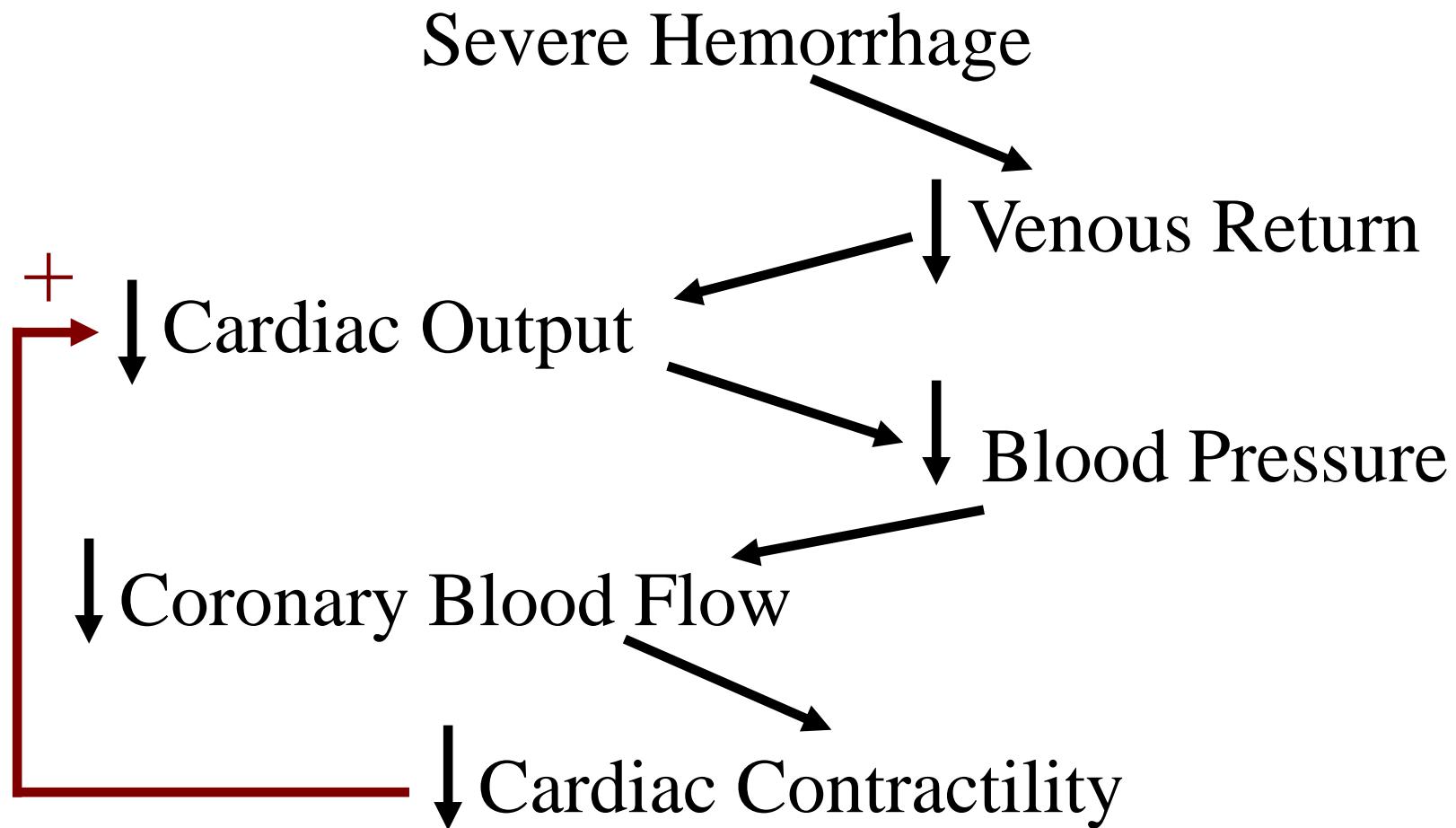


Figure 1–3

Recovery of heart pumping caused by *negative feedback* after 1 liter of blood is removed from the circulation. Death is caused by *positive feedback* when 2 liters of blood are removed.

- Positive feedback is better known as a “vicious cycle,” but a mild degree of positive feedback can be overcome by the negative feedback control mechanisms of the body, and the vicious cycle fails to develop.

Example: Hemorrhagic Shock: Positive Feedback



Chapter 2:

The Cell and its Functions

Organization of the Cell

Cell composition:

- **Water**----70-85% of cell mass
 - Many cellular chemicals are dissolved in the water and chemical reactions take place among the dissolved chemicals or at the surfaces of the suspended particles or membranes.
- **Ions**----potassium, magnesium, phosphate, sulfate, bicarbonate, and smaller quantities of sodium, chloride, and calcium. (do not contribute significantly to cell mass)
 - The ions provide inorganic chemicals for cellular reactions. Also, they are necessary for operation of some of the cellular control mechanisms.
- **Proteins**----10-20%
 - two types: structural proteins (microtubules→ cytoskeleton) and functional proteins (enzymes).

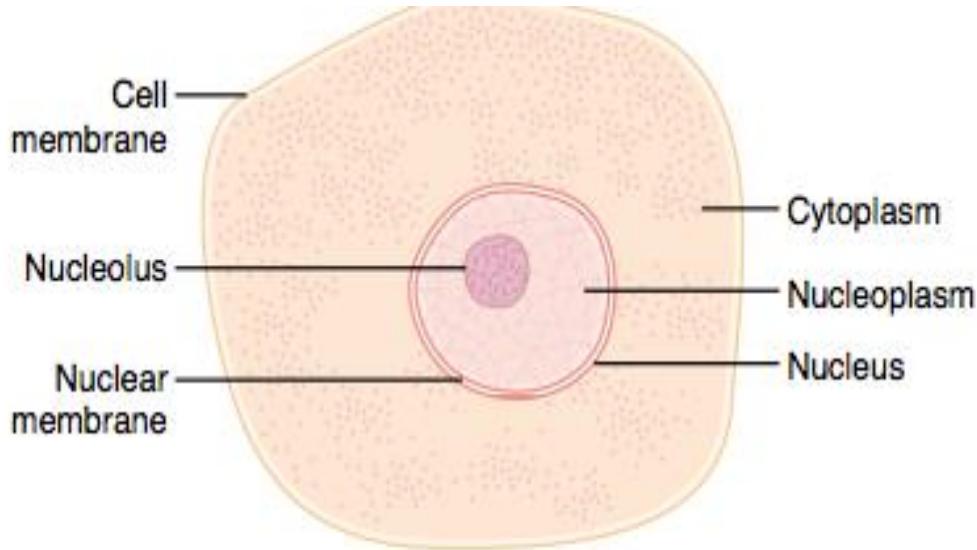


Figure 2-1

Structure of the cell as seen with the light microscope.

- **Lipids**----2-95%
 - important lipids are phospholipids and cholesterol. they are mainly insoluble in water and, therefore, are used to form the cell membrane and intracellular membrane barriers that separate the different cell compartments.
- **Carbohydrates**----1-6%
 - to supply the cells' energy needs.

Physical Structure of the Cell

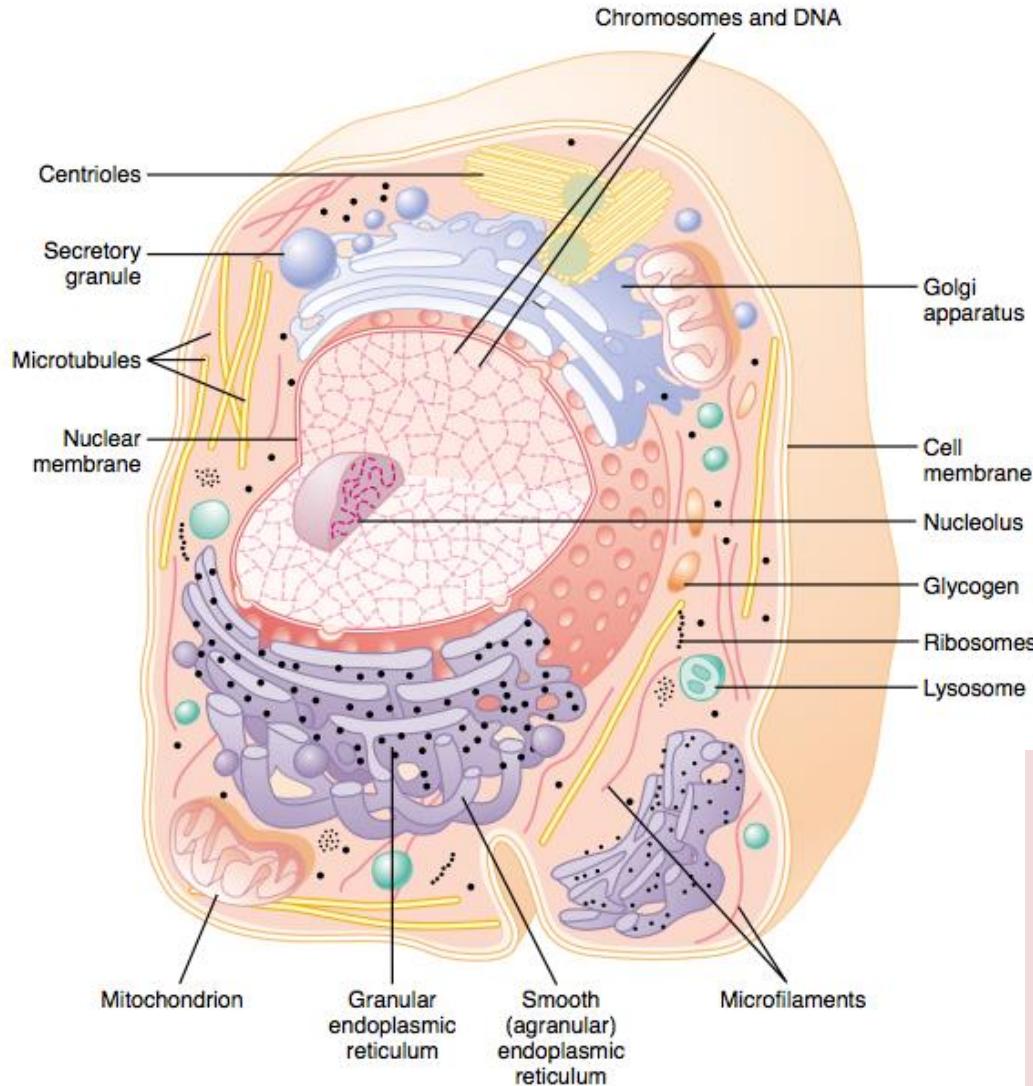


Figure 2-2

Reconstruction of a typical cell, showing the internal organelles in the cytoplasm and in the nucleus.

The cell is not merely a bag of fluid, enzymes, and chemicals; it also contains highly organized physical structures, called intracellular organelles.

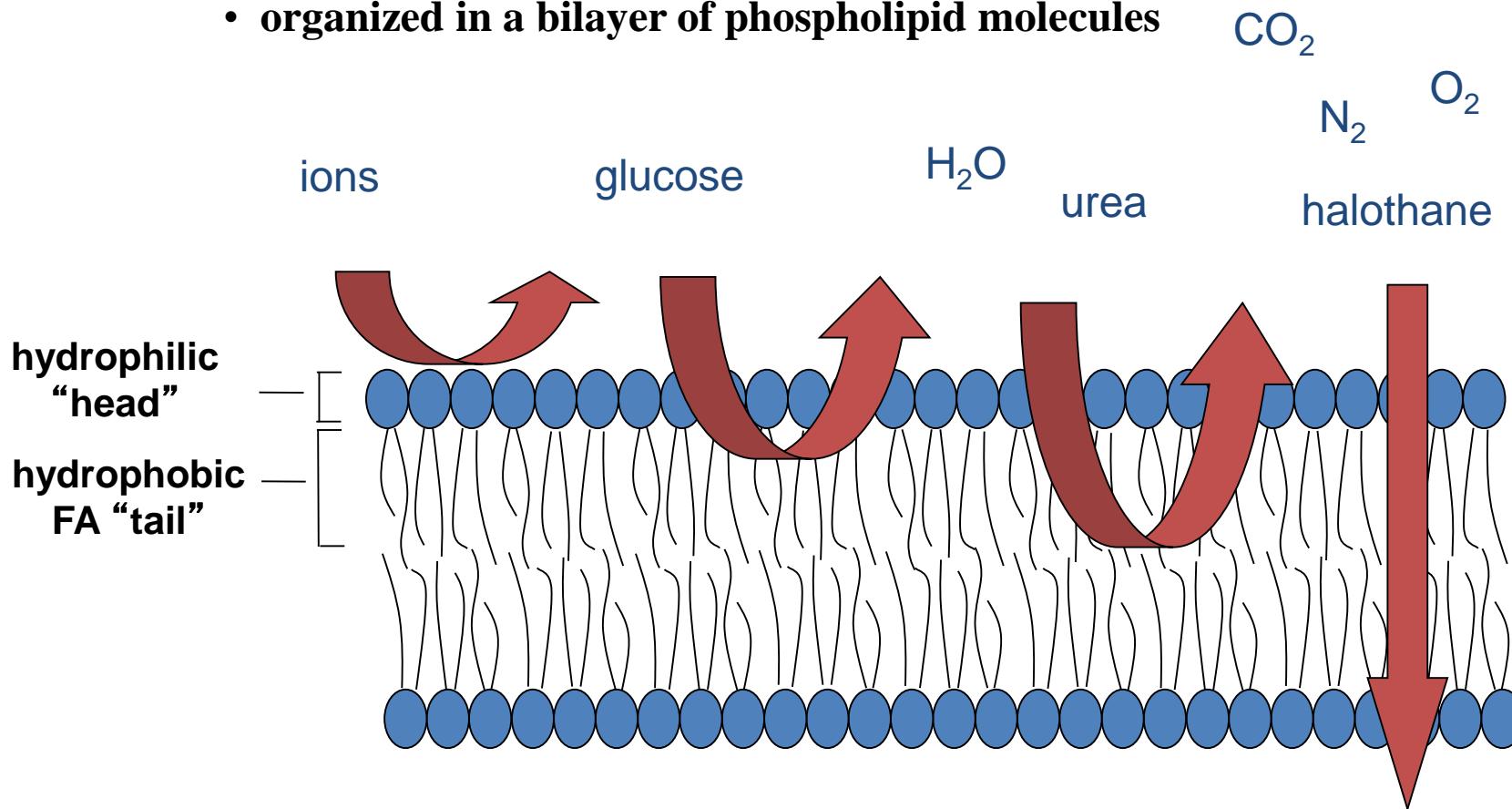
■ Membranous Structures of the Cell

- Most organelles of the cell are covered by membranes composed primarily of lipids and proteins. These membranes include *the cell membrane, nuclear membrane, membrane of the endoplasmic reticulum, and membranes of the mitochondria, lysosomes, and Golgi apparatus.*

Membrane Components:

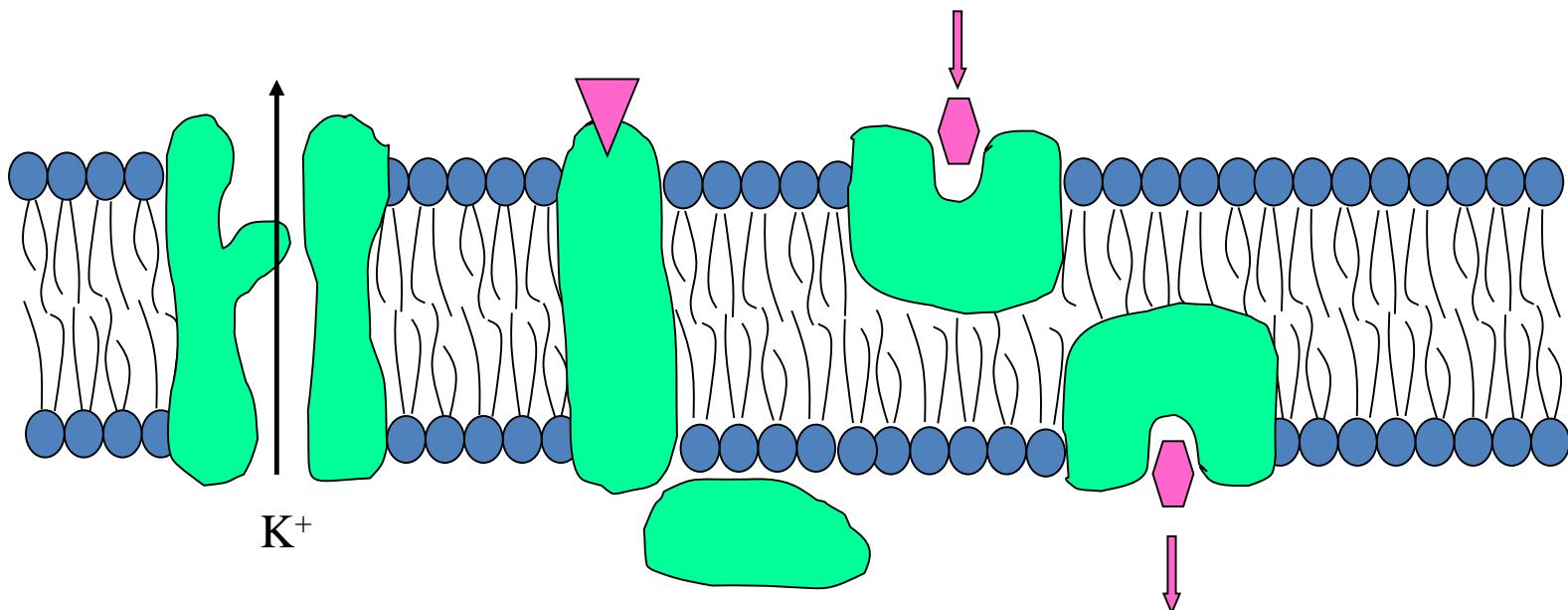
Lipids:

- ~42% of membrane
- barrier to water and water-soluble substances
- organized in a bilayer of phospholipid molecules



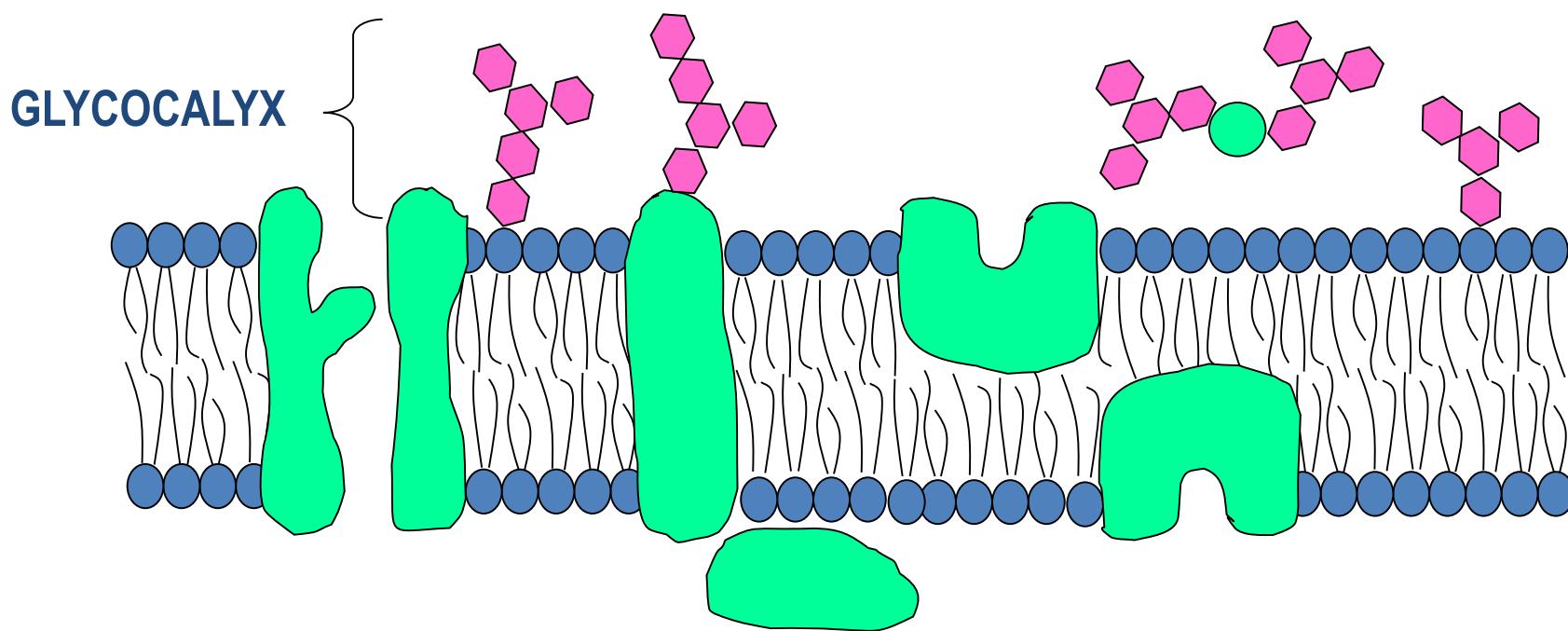
Proteins:

- ~55% of membrane
- provide “specificity” to a membrane
- defined by mode of association with the lipid bilayer
 - integral: protrude all the way through the membrane (channels, pores, carriers, enzymes, etc.)
 - peripheral: attached only to one surface of the membrane and do not penetrate all the way through (enzymes, intracellular signal mediators)



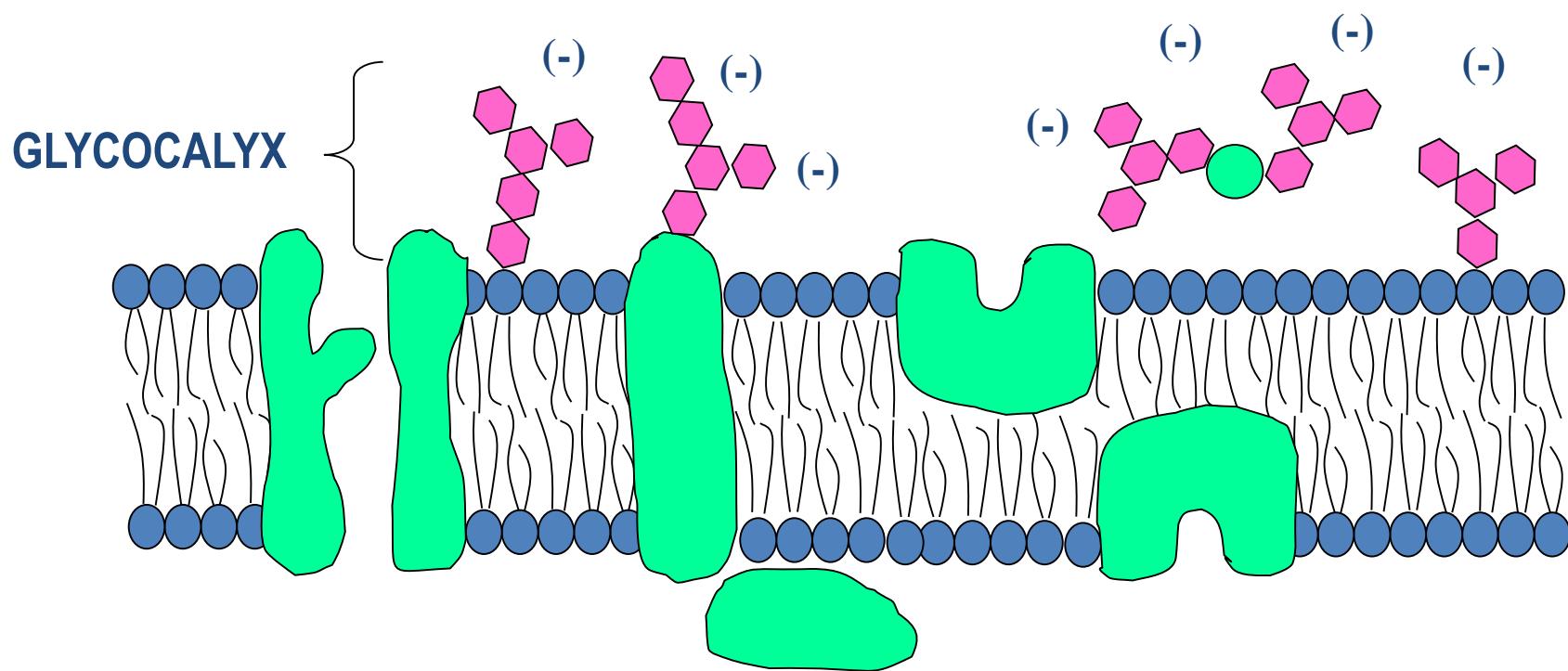
Carbohydrates:

- ~3% of membrane
- glycolipids (approx. 10% of membrane lipids)
- glycoproteins (majority of integral proteins)
- proteoglycans: mainly carbohydrate substances are loosely attached to the outer surface of the cell, and the entire outside surface of the cell often has a loose carbohydrate coat called the *glycocalyx*.



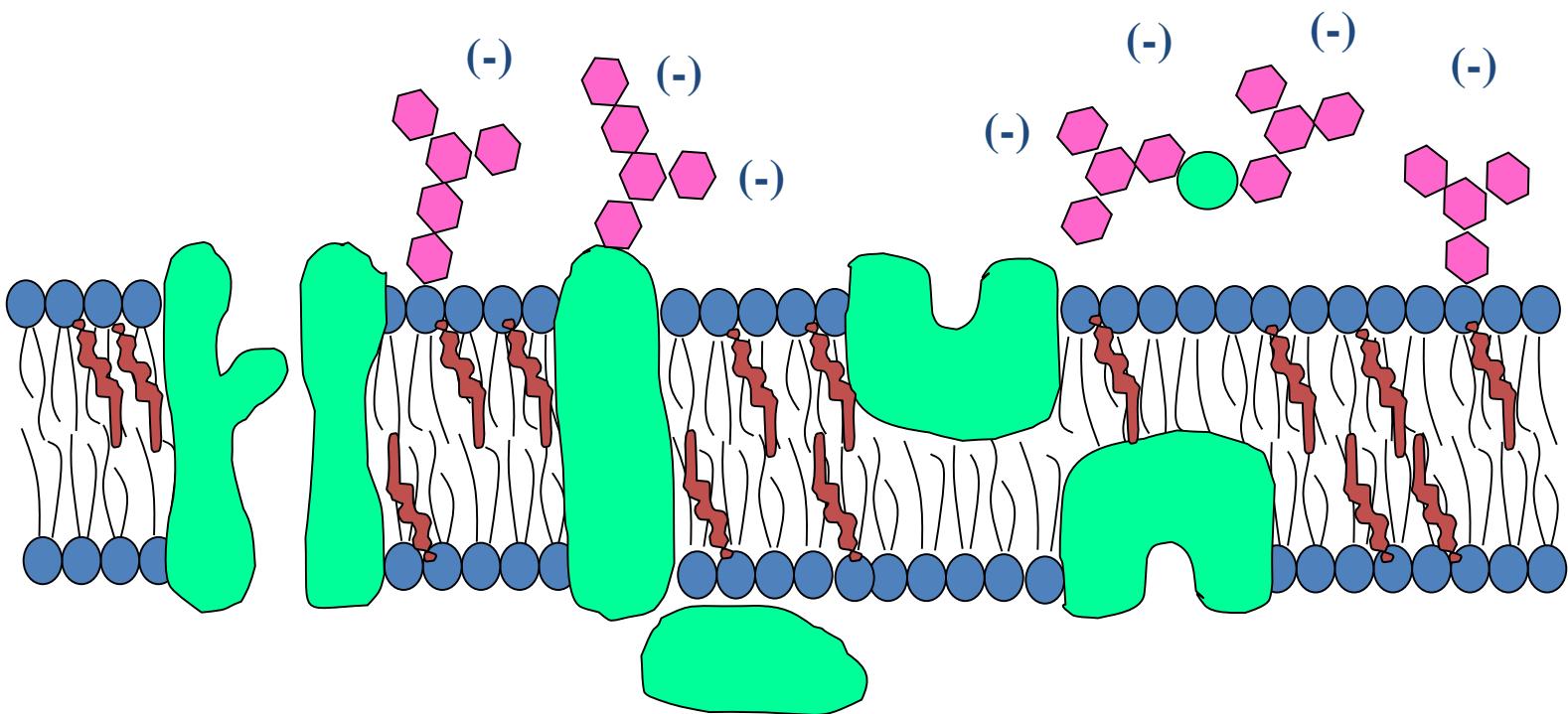
Carbohydrates (Cont.):

- negative charge of the carbo chains repels other negative charges
- The glycocalyx of some cells attaches to the glycocalyx of other cells, thus attaching cells to one another.
- act as receptor substances for binding hormones, such as insulin
- play a role in immune reactions



Cholesterol:

- present in membranes in varying amounts
- generally decreases membrane **FLUIDITY** and **PERMEABILITY**
- increases membrane **FLEXIBILITY** and **STABILITY**



■ Cytoplasm and Its Organelles

➤ Endoplasmic Reticulum

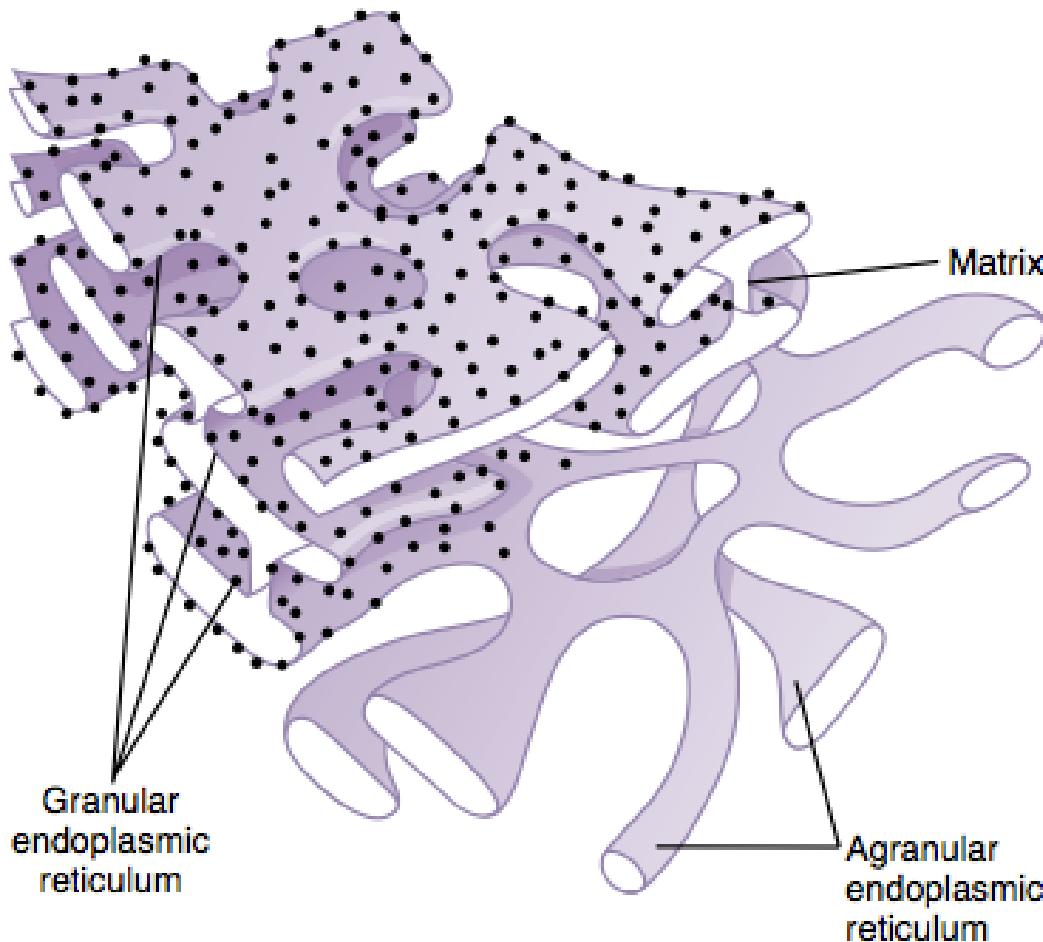
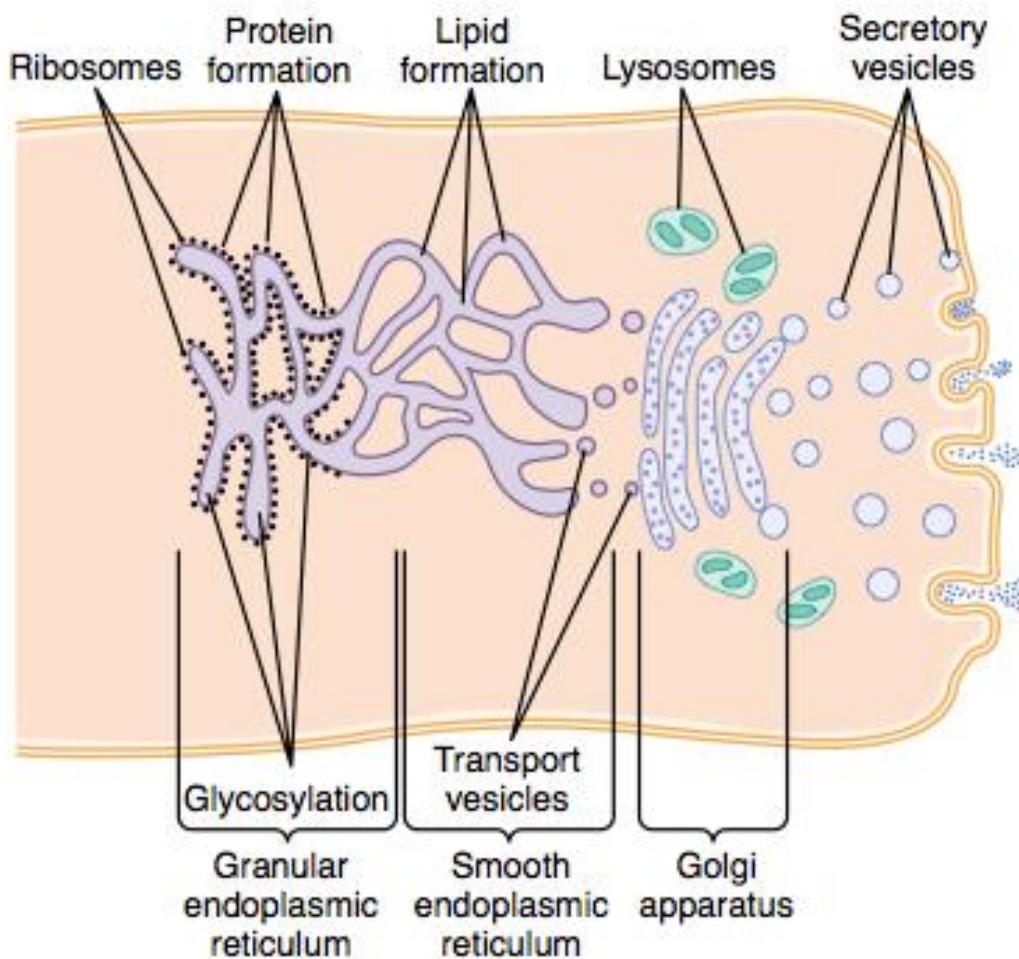


Figure 2-4

Structure of the endoplasmic reticulum. (Modified from DeRobertis EDP, Saez FA, DeRobertis EMF: Cell Biology, 6th ed. Philadelphia: WB Saunders, 1975.)

- Network of tubular and flat vesicular structures
- Space inside the tubules is called the endoplasmic matrix

➤ Ribosomes and the Granular Endoplasmic Reticulum.



- If outer surfaces of many parts of the endoplasmic is covered with ribosomes, the reticulum is called the **granular endoplasmic reticulum**.
- The *ribosomes* are composed of a mixture of RNA and proteins, and they function to synthesize new protein molecules in the cell.
- If the part of the endoplasmic reticulum has no attached ribosomes, this part is called the **agranular, or smooth, endoplasmic reticulum**.
- The agranular reticulum functions for the synthesis of lipid substances

➤ Golgi Apparatus

- Membrane composition similar to that of the smooth ER and plasma membrane
 - Composed of 4 or more stacked layers of flat vesicular structures
 - Receives transport vesicles from smooth ER
 - Substances formed in the ER are “processed”
 - phosphorylated
 - glycosylated
 - substances are concentrated, sorted and packaged for secretion.
- **secretory vesicles** containing proteins synthesized in the RER bud from the Golgi apparatus
- fuse with plasma membrane to release contents
 - constitutive secretion - happens randomly
 - stimulated secretion - requires trigger

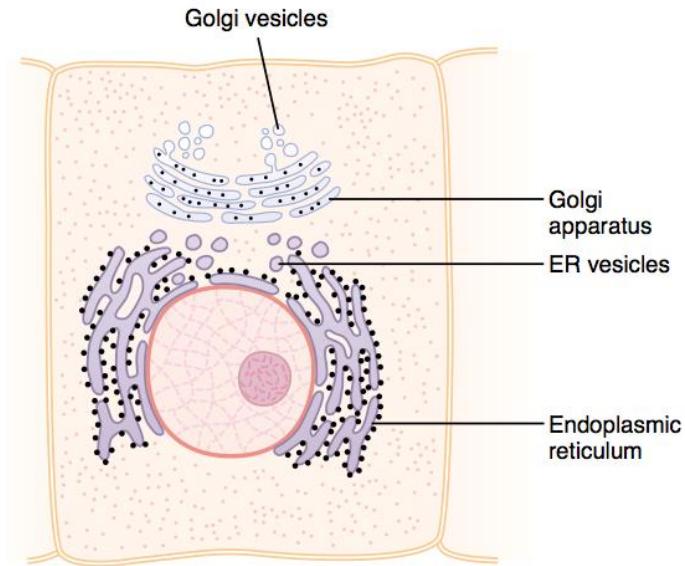
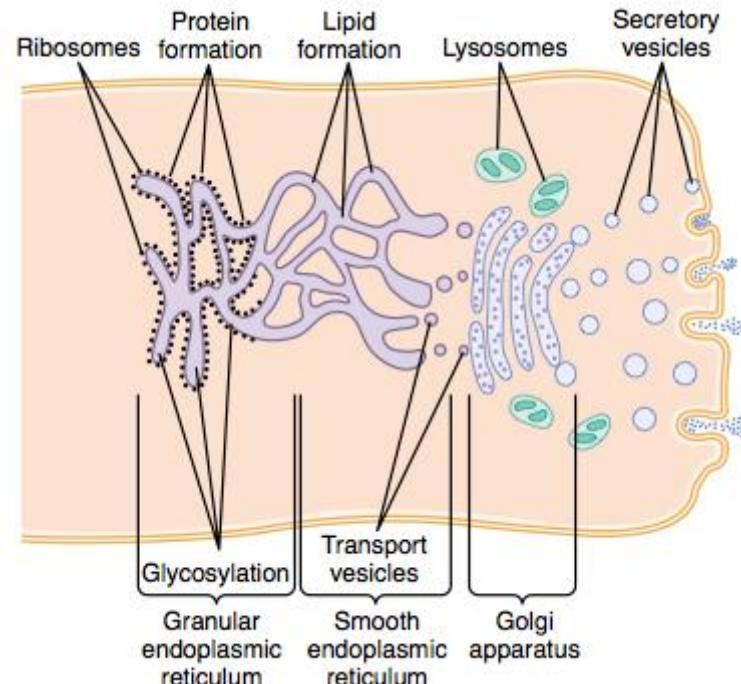


Figure 2-5

A typical Golgi apparatus and its relationship to the endoplasmic reticulum (ER) and the nucleus.



➤ Lysosomes

- vesicular organelle formed from budding Golgi
- contain hydrolytic enzymes (**acid hydrolases**)
 - phosphatases
 - nucleases
 - proteases
 - lipid-degrading enzymes
 - lysozymes digest bacteria
- fuse with pinocytotic or phagocytotic vesicles to form **digestive vesicles**

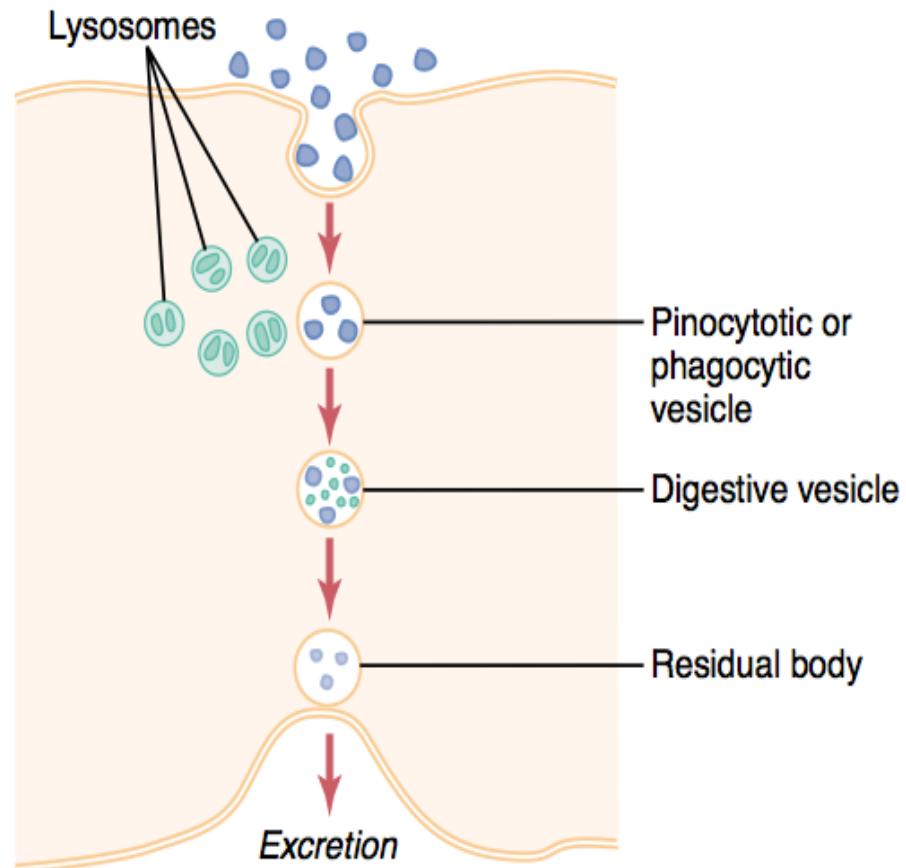


Figure 2-12

Digestion of substances in pinocytotic or phagocytotic vesicles by enzymes derived from lysosomes.

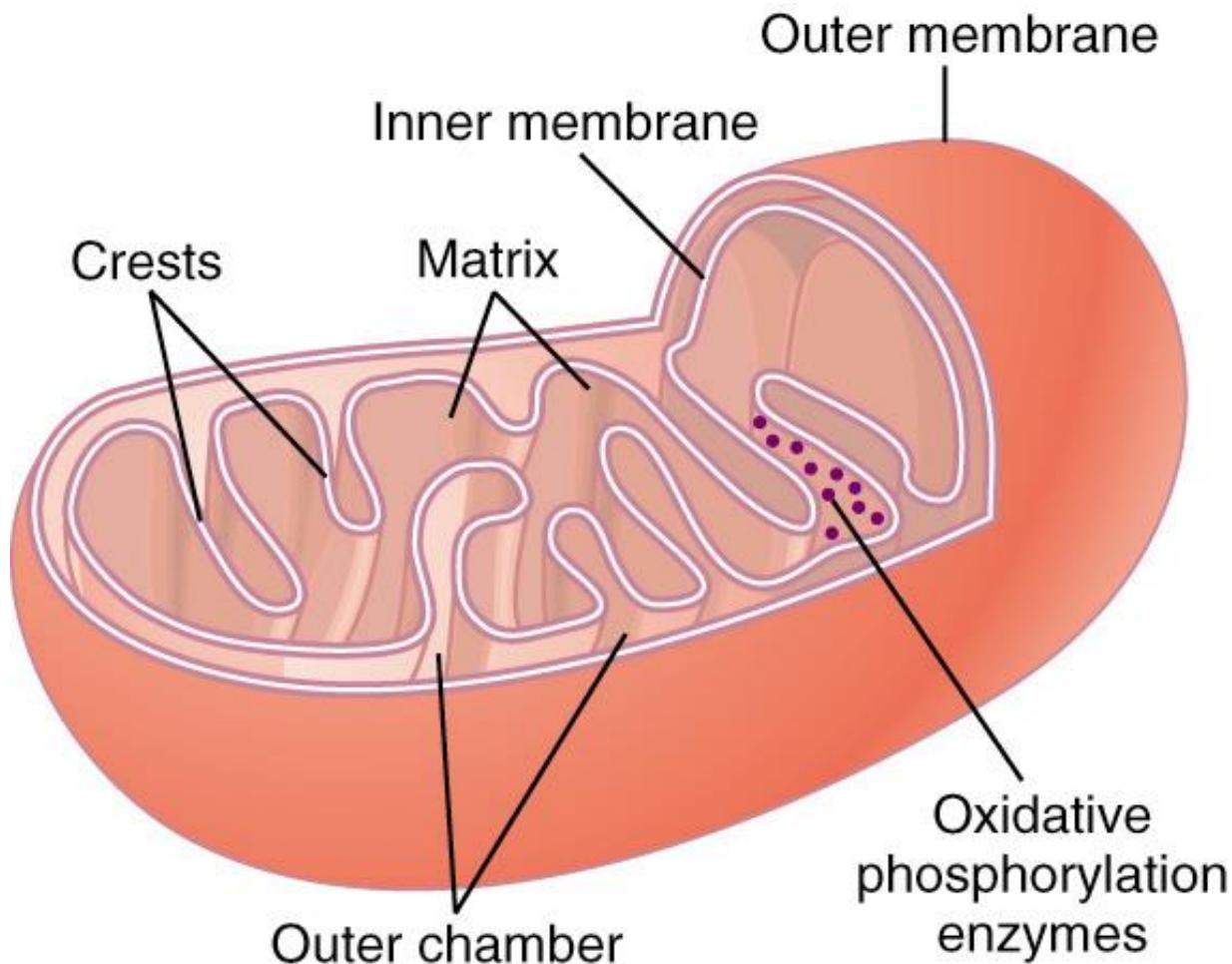
➤ Peroxisomes

- similar physically to lysosomes
- most commonly found in eukaryotic cells.
- two major differences:
 - formed by self-replication
 - they contain **oxidases**

Function: oxidize substances (e.g. alcohol) that may be otherwise poisonous

➤ Mitochondria

Primary function: extraction of **energy** from nutrients



ATP production

Step 1.

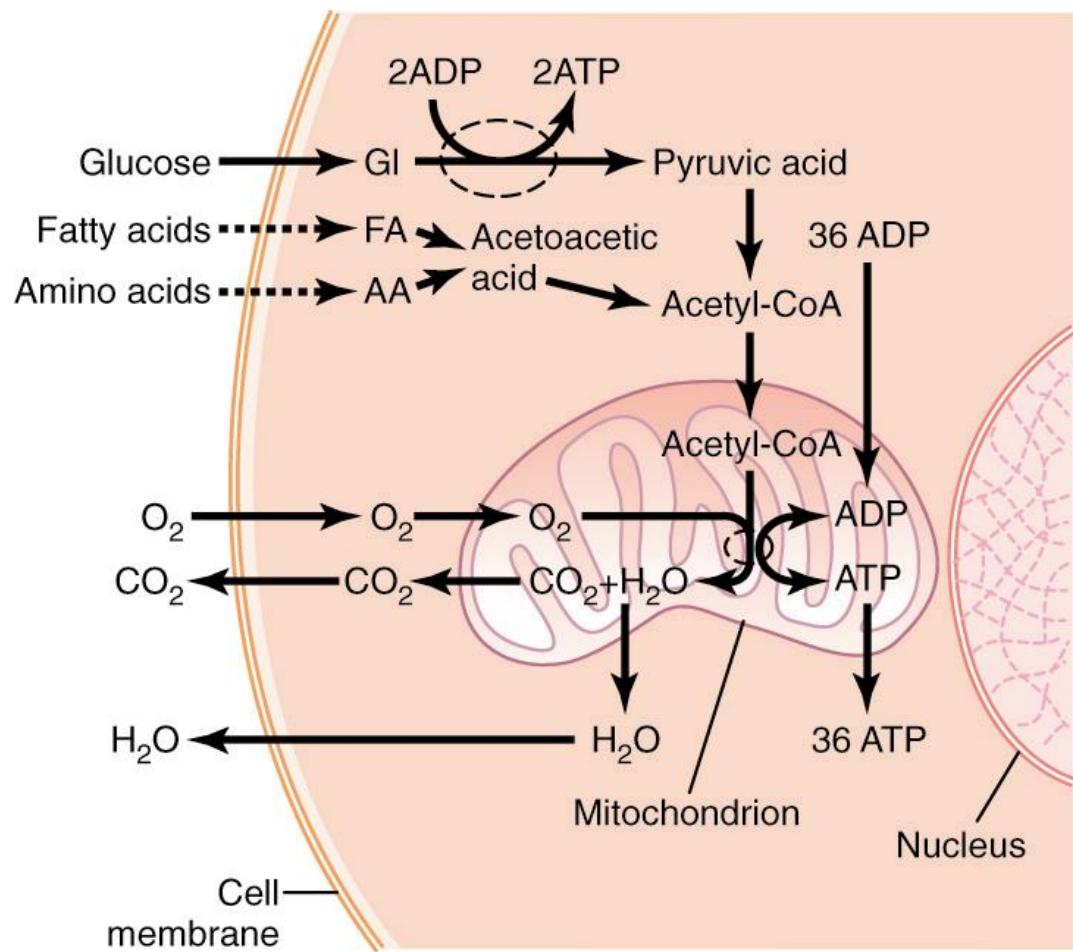
- Carbohydrates are converted into glucose
- Proteins are converted into amino acids
- Fats are converted into fatty acids

Step 2.

- Glucose, AA, and FA are processed into AcetylCoA

Step 3.

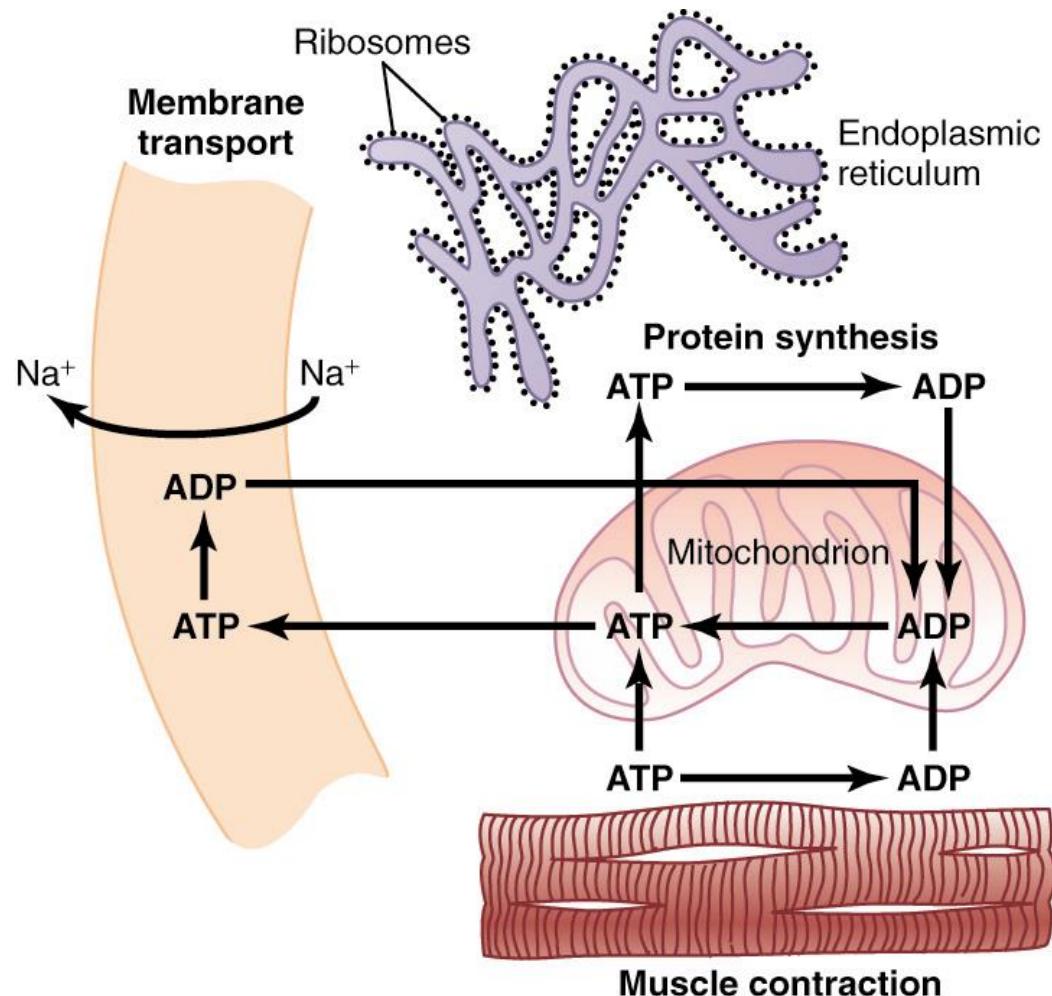
- AcetylCoA reacts with O₂ to produce ATP



A maximum of **38 molecules of ATP** are formed per molecule of **glucose** degraded.

The Use of ATP for Cellular Function

1. Membrane transport
2. Synthesis of chemical compounds
3. Mechanical work



- **Nucleus**
- The nucleus is the control center of the cell. Briefly, the nucleus contains large quantities of DNA, which are the genes. The genes determine the characteristics of the cell's proteins, including the structural proteins, as well as the intracellular enzymes that control cytoplasmic and nuclear activities.

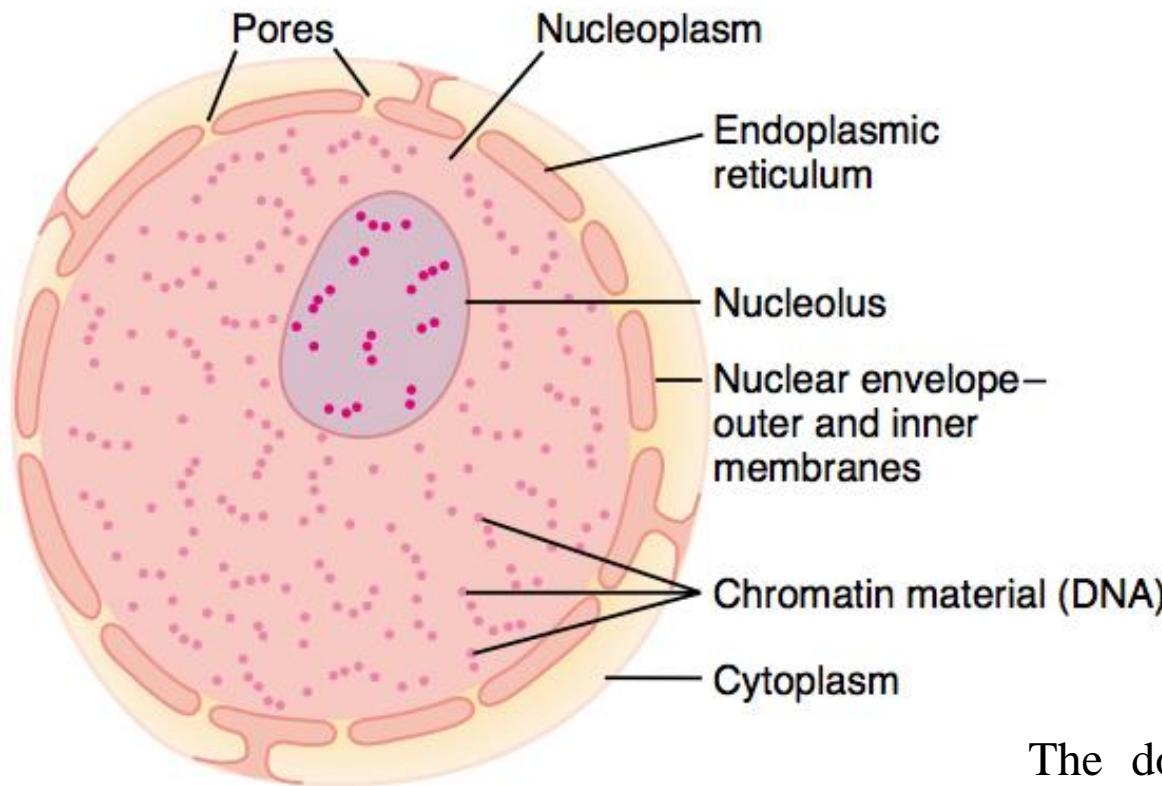


Figure 2–9

Structure of the nucleus.

The double **nuclear membrane** and matrix are contiguous with the endoplasmic reticulum

■ Nuclear Membrane

- The nuclear membrane is permeated by thousands of nuclear pores
 - 100 nm in diameter
 - (selectively) permeable to molecules of up to 44,000 MW

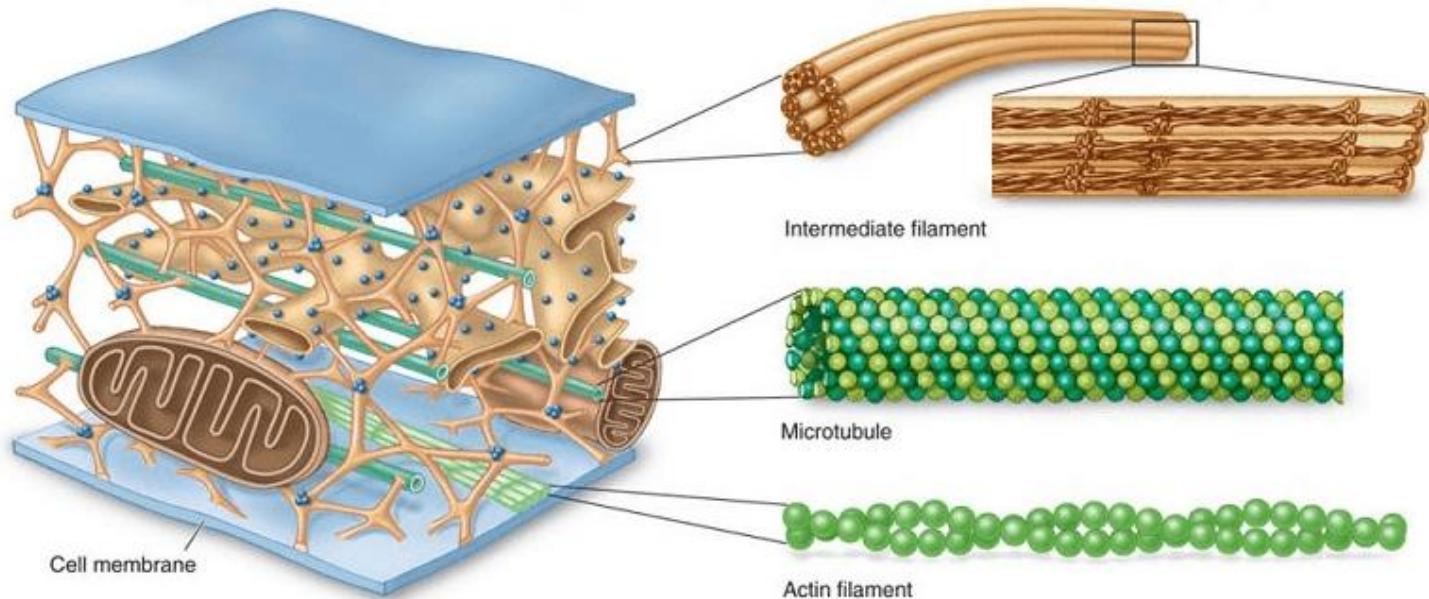
■ Nucleoli and Formation of Ribosomes

- Formation of the nucleoli (and of the ribosomes in the cytoplasm outside the nucleus) begins in the nucleus.
- First, specific DNA genes in the chromosomes cause RNA to be synthesized. Some of this is stored in the nucleoli, but most of it is transported outward through the nuclear pores into cytoplasm.
- Here, it is used in conjunction with specific proteins to assemble “mature” ribosomes that play an essential role in forming cytoplasmic proteins.

Locomotion of Cells

The Cytoskeleton

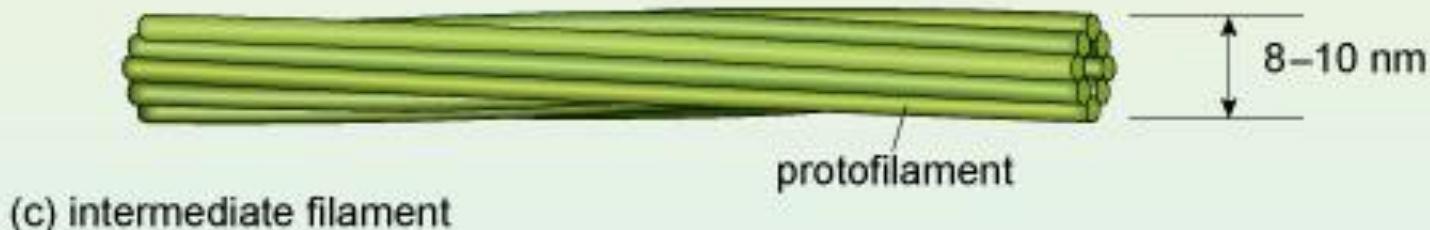
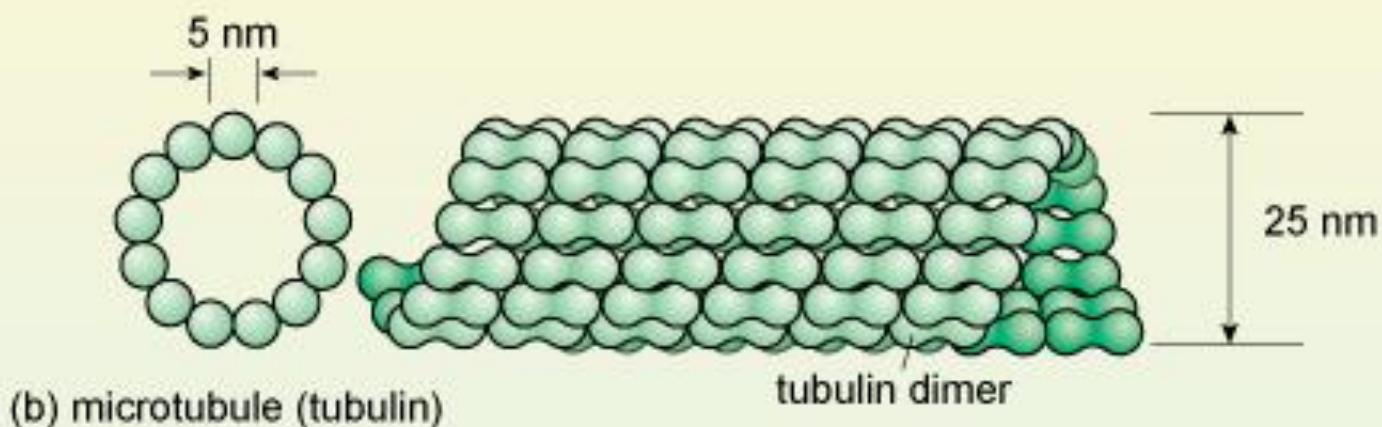
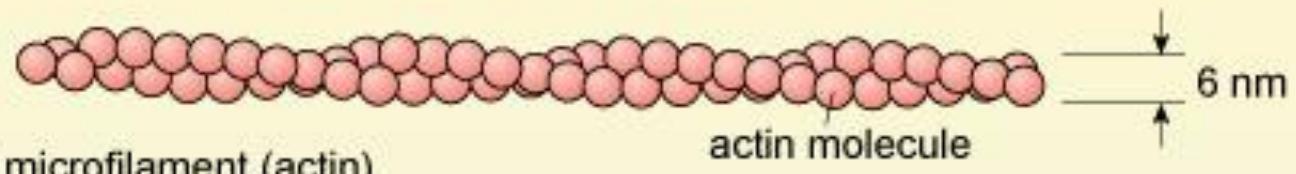
Cytoskeleton, a system of filaments or fibers that is present in the cytoplasm of eukaryotic cells.



Intermediate Filaments

Microtubules

Microfilaments



- **Microflaments**

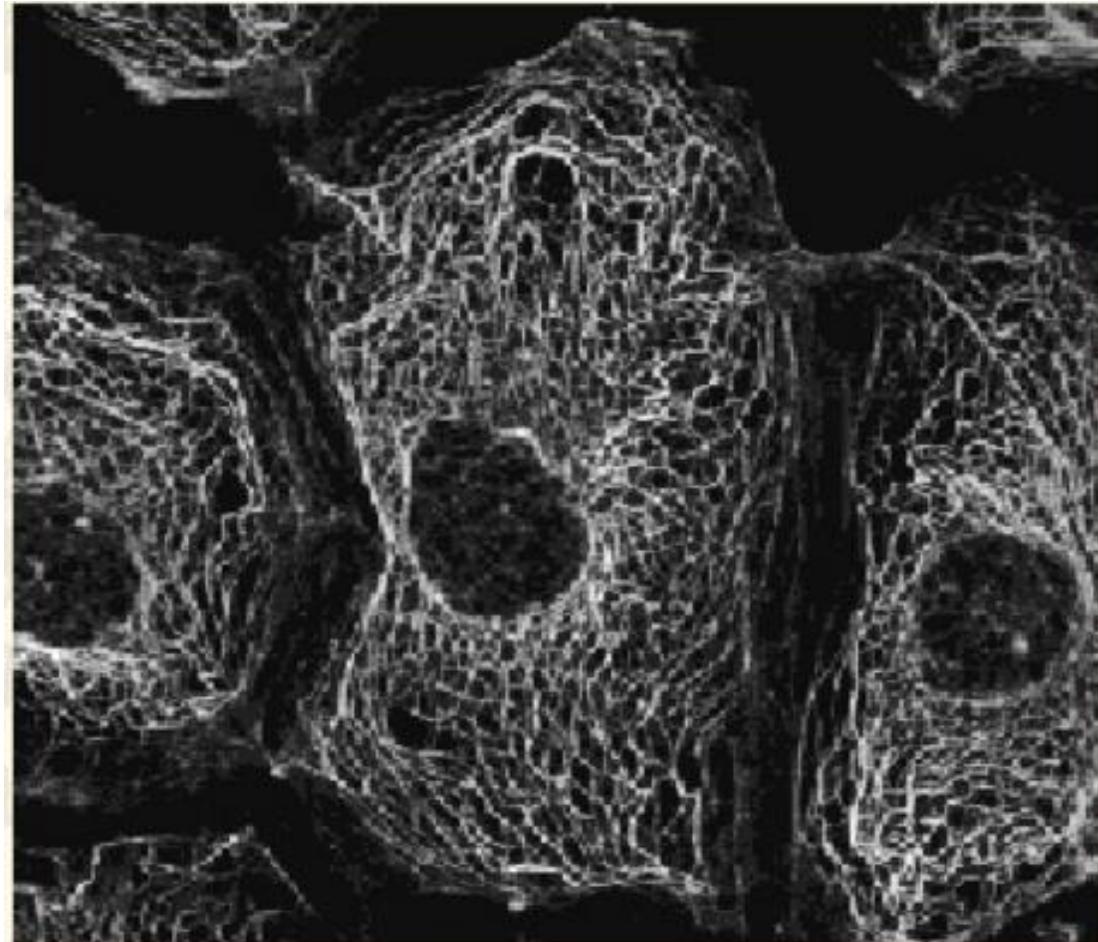
Important in cell contraction and cell movement.



Actin fibres in a cell stained with a fluorescent strain specific for actin

- **Intermediate Filaments**

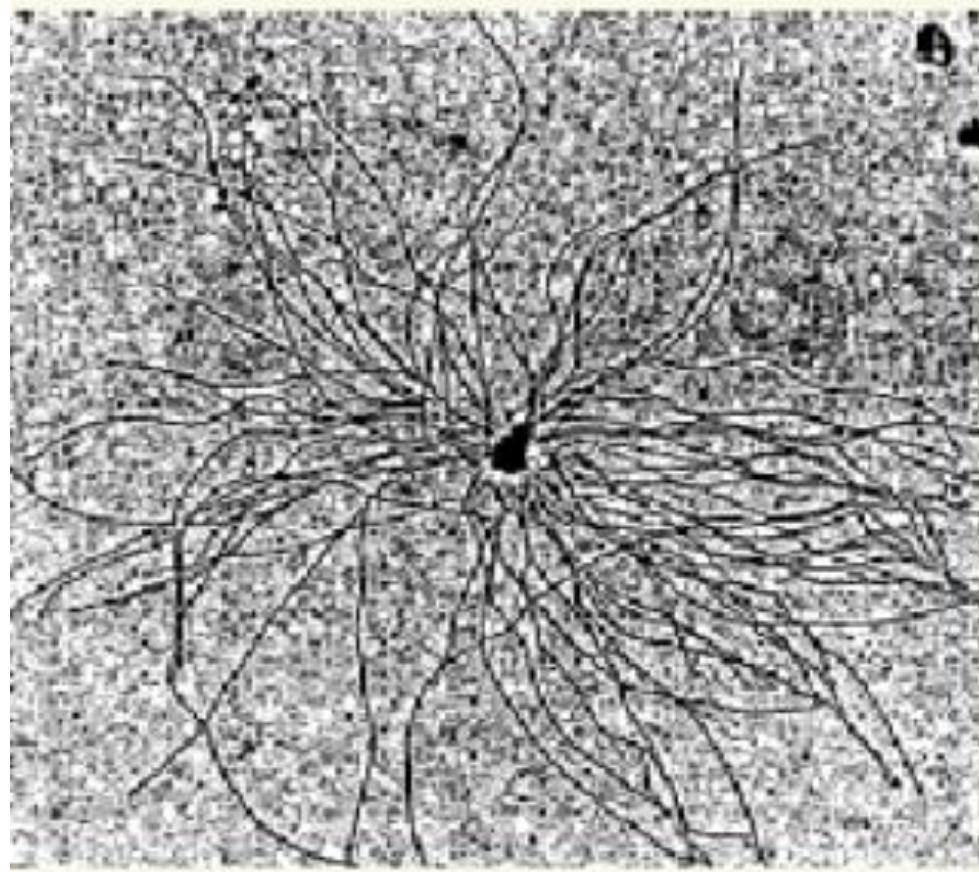
Provide mechanical strength to cells



The nucleus in epithelial cells is held within the cell by a basketlike network of intermediate filaments made of keratins which have been stained here using a fluorescent stain

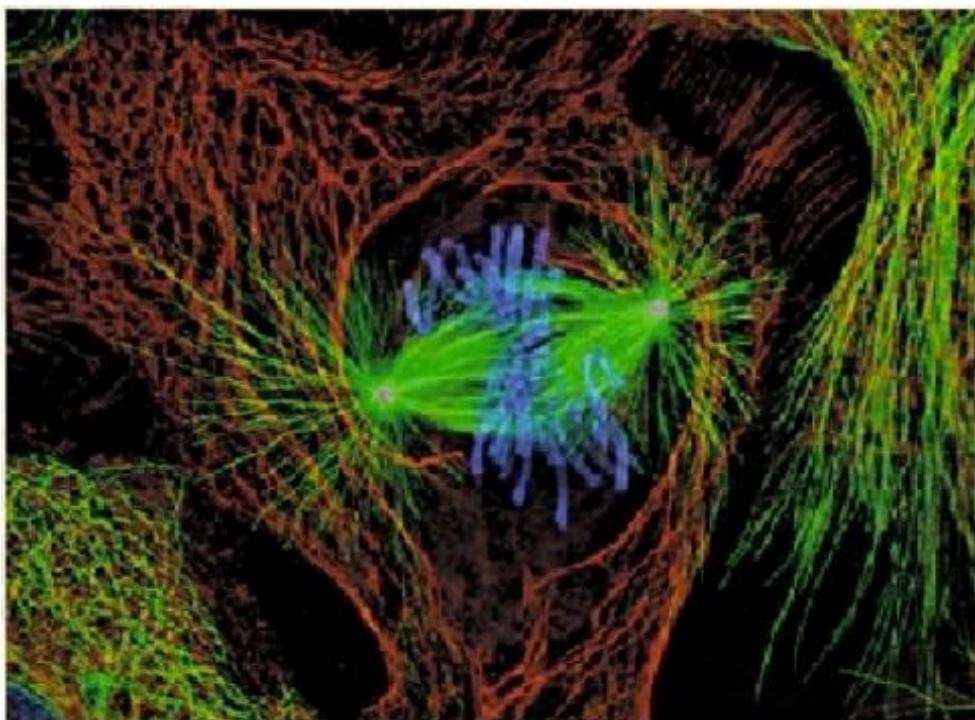
- **Microtubules**

- Microtubules only form around a centrosome (organising centre)
- The centrosome provides a “nucleus” from which the microtubule form. These are important in cell division as part of the spindle fibre network and can move components with the cell



Microtubules growing in vitro from an isolated centrosome

- **Functions**
- All these components give mechanical support and shape to the cell.
- Primary importance of the cytoskeleton is in cell mobility. Cytoskeleton extends throughout the cytoplasm and determines the internal movement of cell organelles as well as cell locomotion and muscle fiber contraction.



Chapter 3:

Genetic Control of Protein Synthesis, Cell Function, and Cell Reproduction

Central Dogma of Molecular Biology

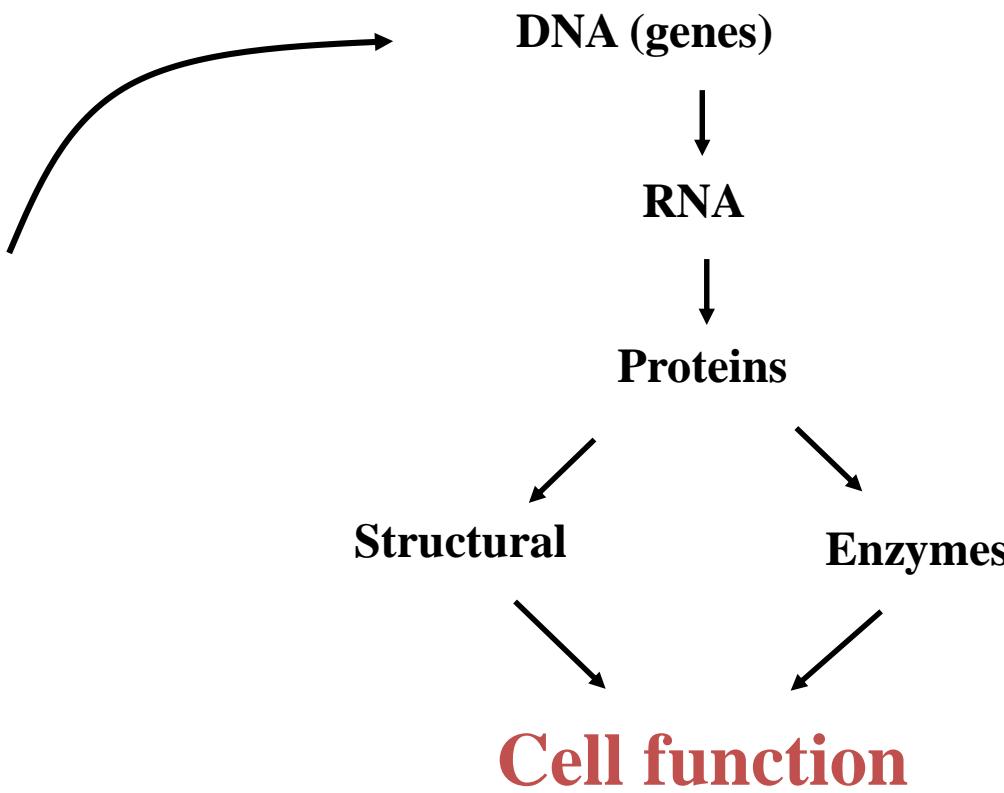
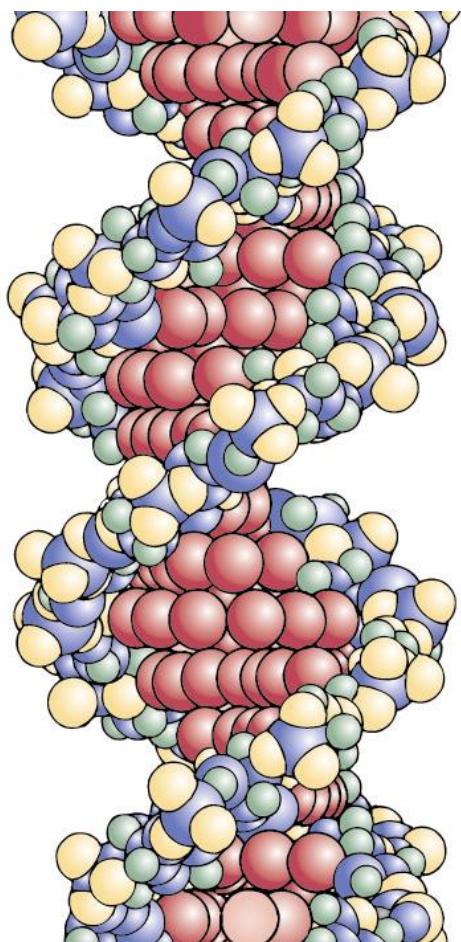


Figure 3-2 The helical, double-stranded structure of the gene. The outside strands are composed of phosphoric acid and the sugar deoxyribose. The internal molecules connecting the two strands of the helix are purine and pyrimidine bases; these determine the “code” of the gene.

➤ Transcription:

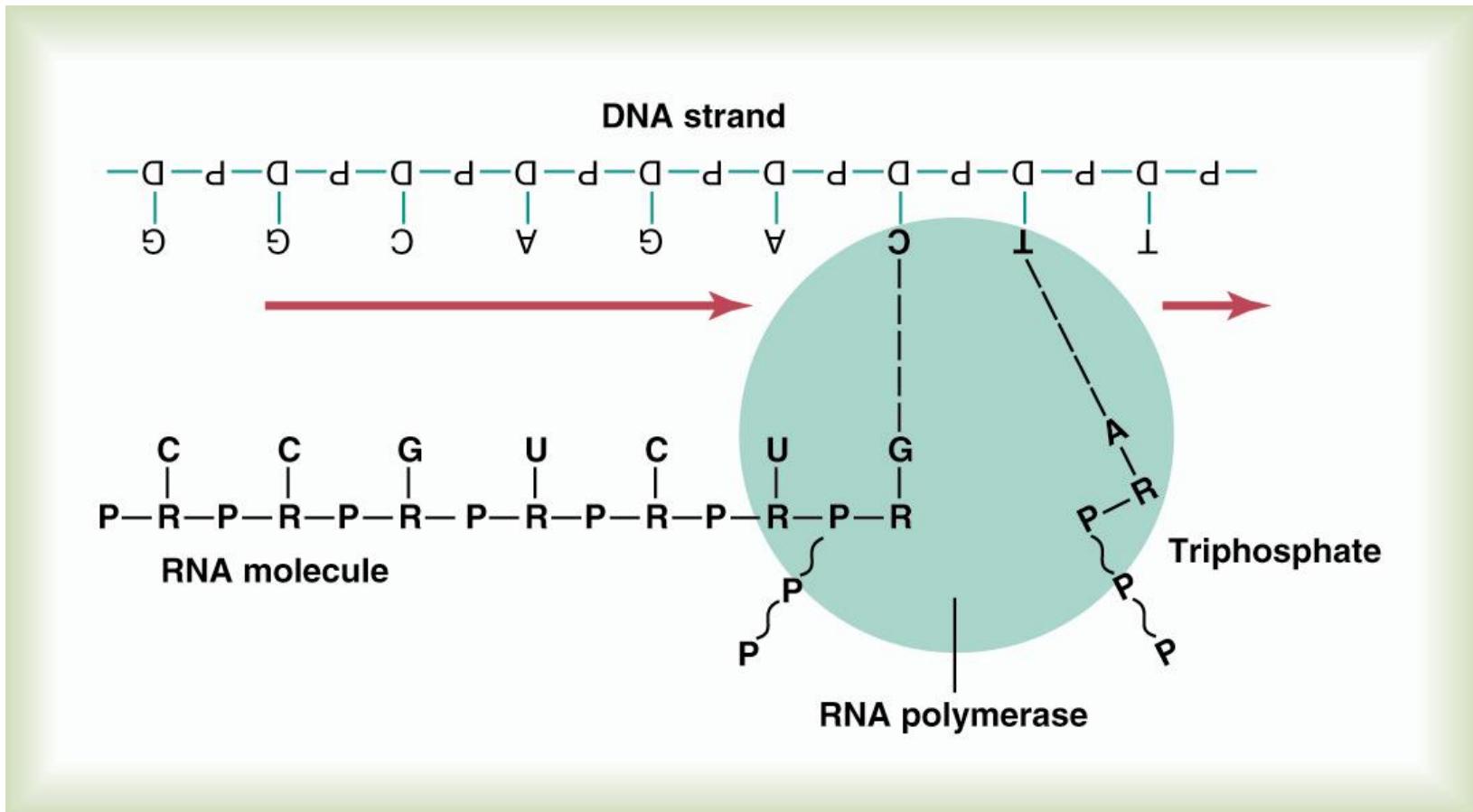


Figure 3-7 Combination of ribose nucleotides with a strand of DNA to form a molecule of RNA that carries the genetic code from the gene to the cytoplasm. The RNA polymerase enzyme moves along the DNA strand and builds the RNA molecule.

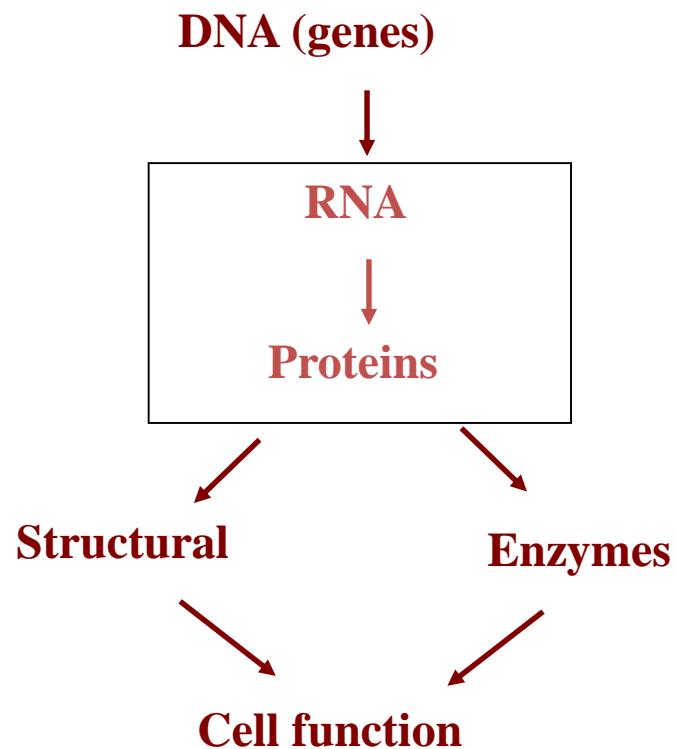
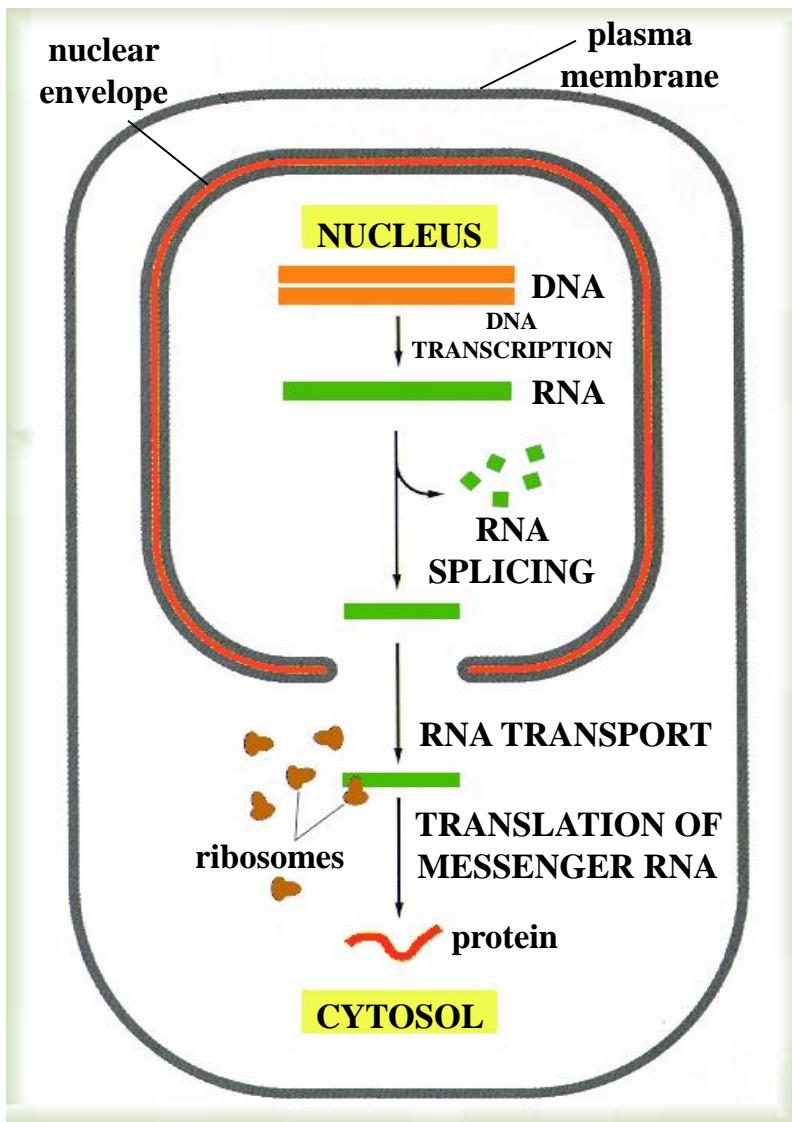
Overview

- ① RNA polymerase binds to the promoter sequence.
- ② The RNA polymerase temporarily “unwinds” the DNA double helix.
- ③ The polymerase “reads” the DNA strand and adds complementary RNA molecules to the DNA template.
- ④ “Activated” RNA molecules react with the growing end of the RNA strand and are added (3’ end).
- ⑤ Transcription ends when the RNA polymerase reaches a chain terminating sequence, releasing both the polymerase and the RNA strand.

Messenger RNA:

- complementary in sequence to the DNA coding strand
- 100's to 1000's of nucleotides per strand
- organized in **codons** - triplet bases
 - each codon “codes” for one **amino acid** (AA)
 - each AA - except **met**- is coded for by multiple codons
 - start codon: AUG (**specific for met**)
 - stop codons: UAA, UAG, UGA

➤ The Process of Translation



Transfer RNA

- acts as a **carrier molecule** during protein synthesis
- each transfer RNA (tRNA) combines with one AA
- each tRNA recognizes a specific codon by way of a complementary **anticodon** on the tRNA molecule

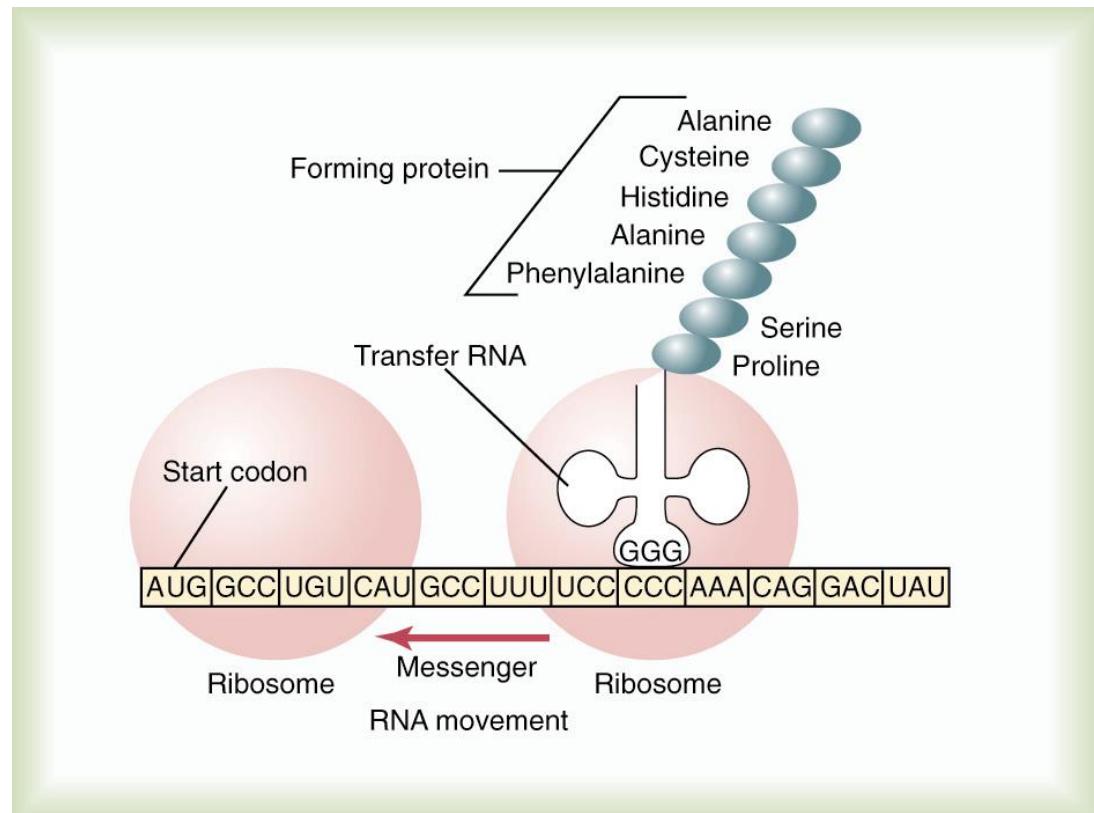


Figure 3-9 A messenger RNA strand is moving through two ribosomes. As each “codon” passes through, an amino acid is added to the growing protein chain, which is shown in the right-hand ribosome. The transfer RNA molecule transports each specific amino acid to the newly forming protein.

Ribosomes

Polyribosomes: multiple ribosomes can simultaneously translate a single mRNA

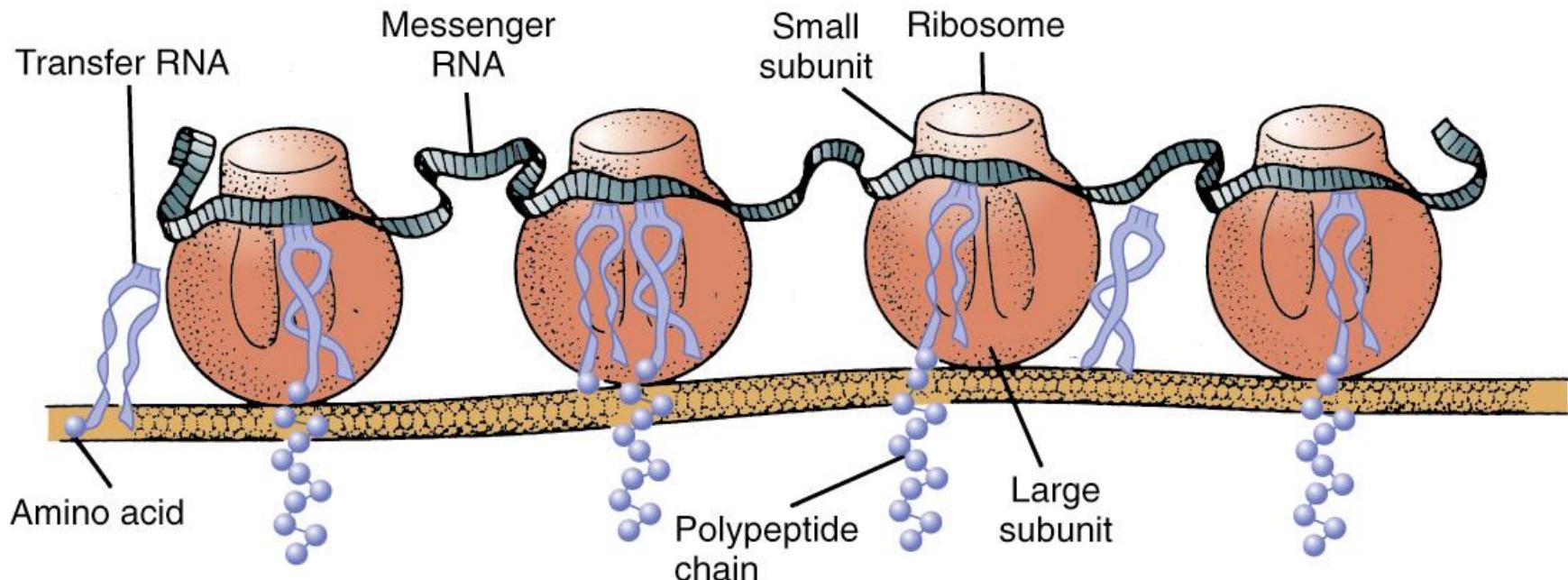


Figure 3-10 Physical structure of the ribosomes, as well as their functional relation to messenger RNA, transfer RNA, and the endoplasmic reticulum during the formation of protein molecules. (Courtesy of Dr. Don W. Fawcett, Montana.)

Overview :Protein Formation

Phase 1: Initiation

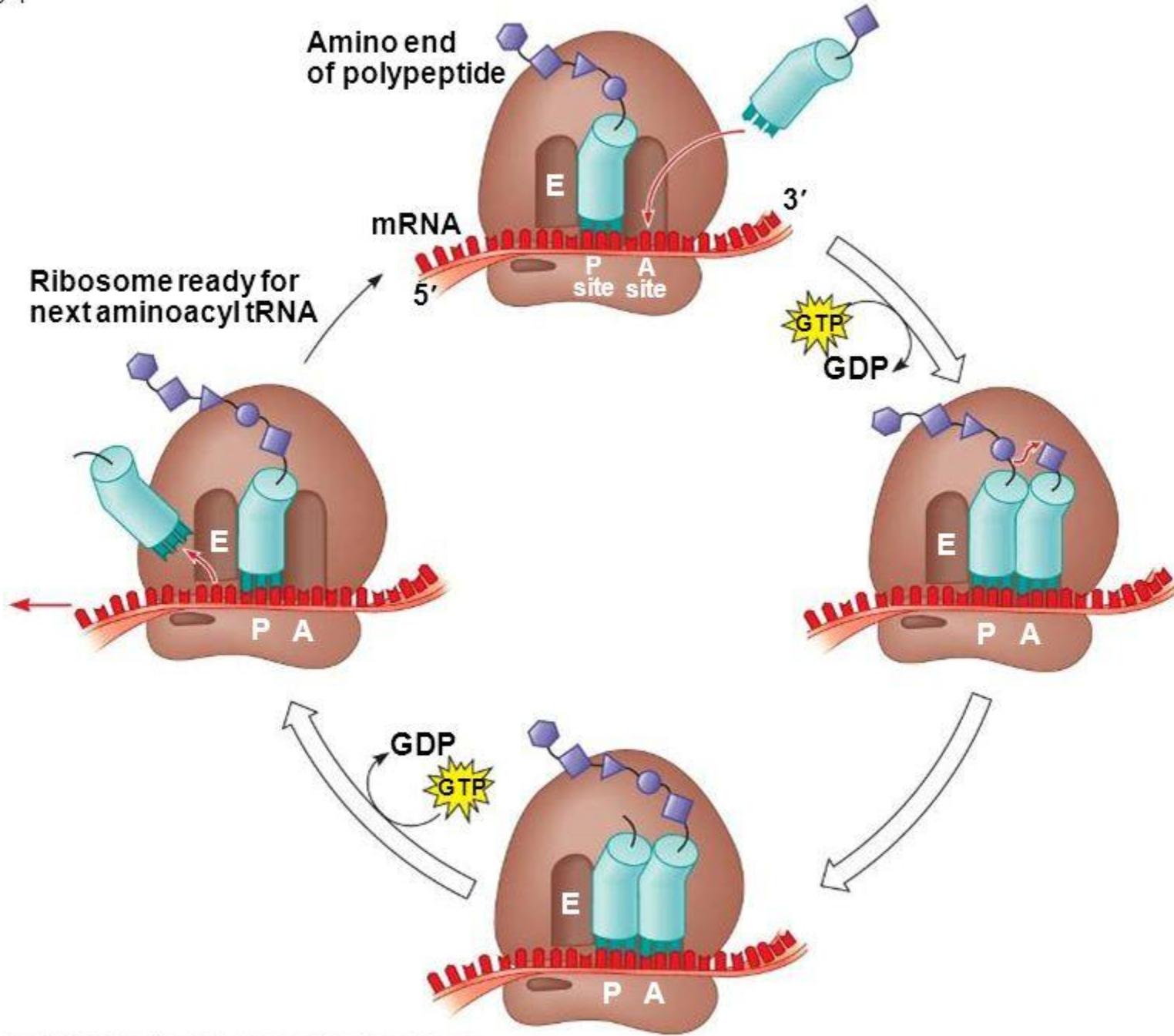
- small ribosomal subunit and initiator tRNA (Met) complex binds to 5' end of an mRNA chain
- this complex moves along mRNA molecule until it encounters a start codon (AUG)
- initiation factors dissociate and large ribosomal subunit binds

Overview :Protein Formation

Phase 2: Elongation

- AA-tRNA binds to the ribosomal A-site
- peptidyl transferase joins the tRNA at the P-site to the AA linked to the tRNA at the A-site with a peptide bond
- the new peptidyl-tRNA is translocated from the A-site to the P-site

Fig. 17-18-4

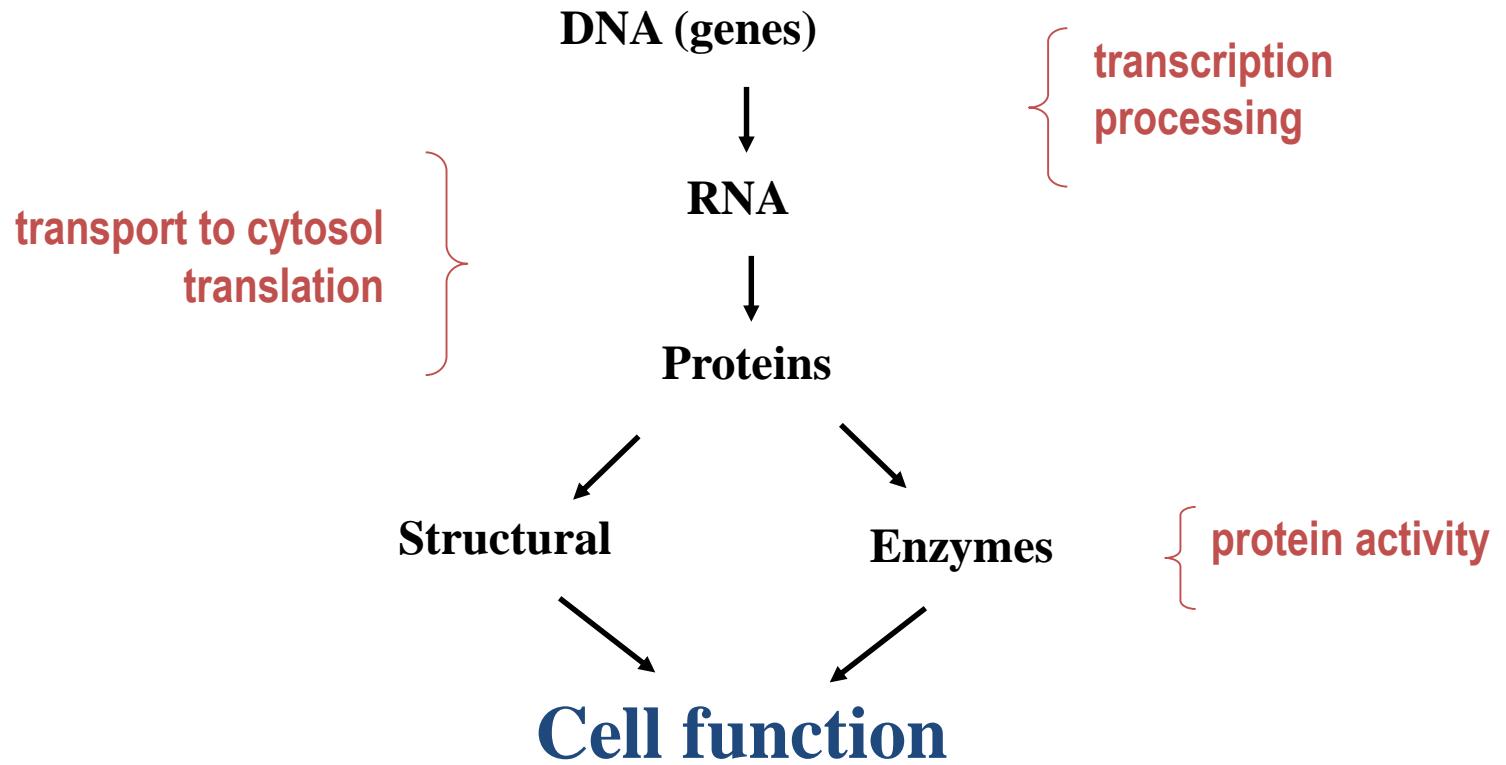


Overview :Protein Formation

Phase 3: Termination

- Release factor binds to the stop codon.
- Completed polypeptide is released.
- Ribosome dissociates into its 2 subunits.

Control of Genetic Function and Biochemical Activity



➤ Transcriptional Control:

The Operon: a prokaryote model

- series of genes and their shared regulatory elements

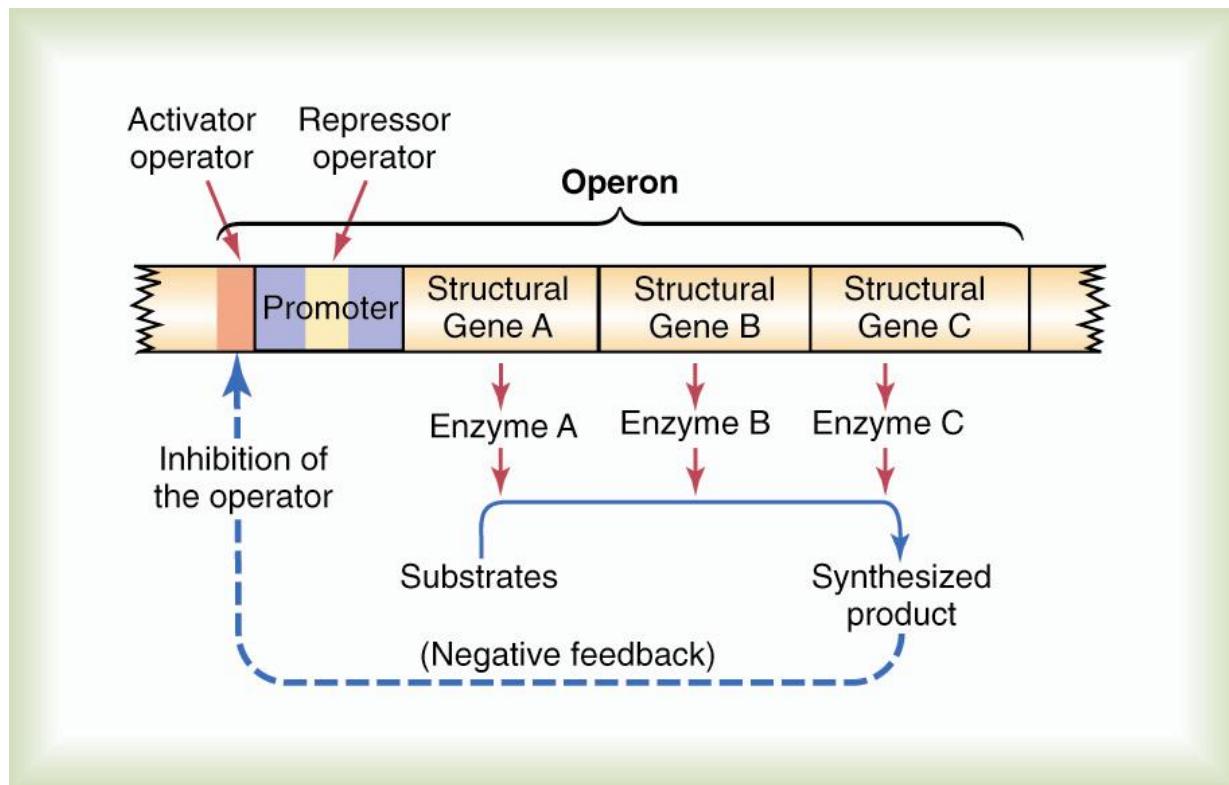


Figure 3-12 Function of an operon to control synthesis of a non protein intracellular product, such as an intracellular metabolic chemical. Note that the synthesized product exerts negative feedback to inhibit the function of the operon, in this way automatically controlling the concentration of the product itself.

Negative Regulation

- sequences called “repressor operators” bind repressor proteins
- binding interferes with the ability of the RNA polymerase to bind to the promoter

NO TRANSCRIPTION

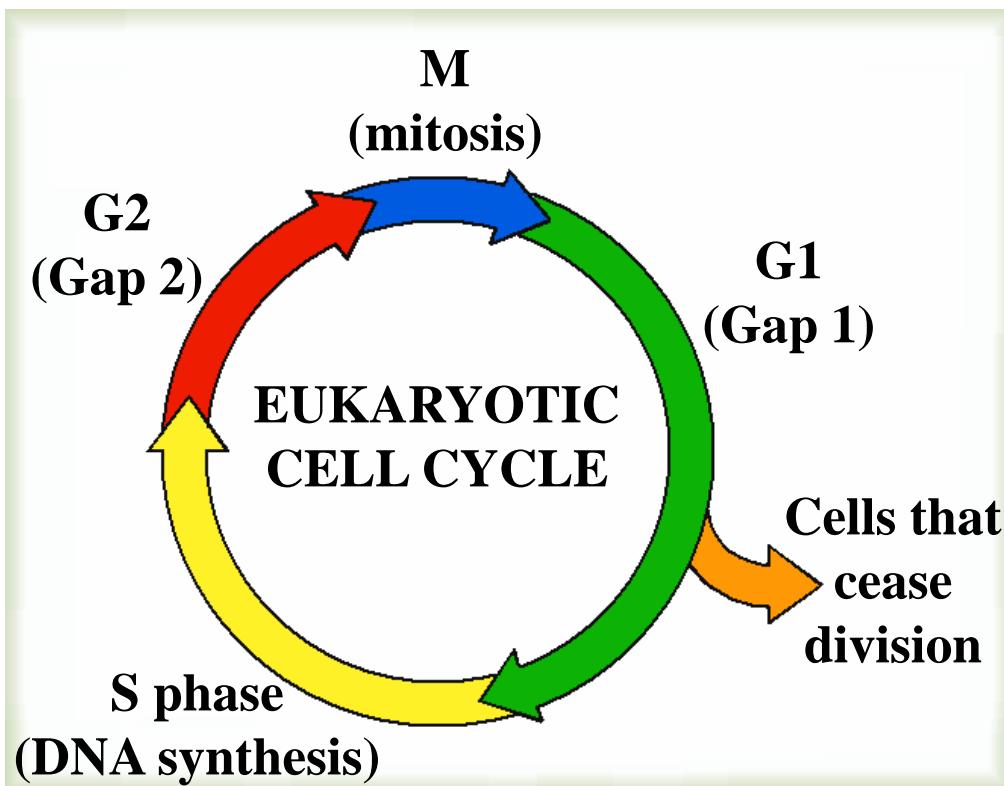
Positive Regulation

- so-called “activator operators” bind activator proteins
- binding facilitates the association of the RNA polymerase with the promoter

ENHANCED TRANSCRIPTION

➤ Genetic Control of Cell Reproduction

Life Cycle of the Cell:



M phase:

- cytokinesis

Interphase (>95%):

- G₁ phase (Growth)
- S phase (DNA synthesis)
- G₂ phase (Growth and preparation for mitosis)

DNA Repair, “Proofreading,” and “Mutations”

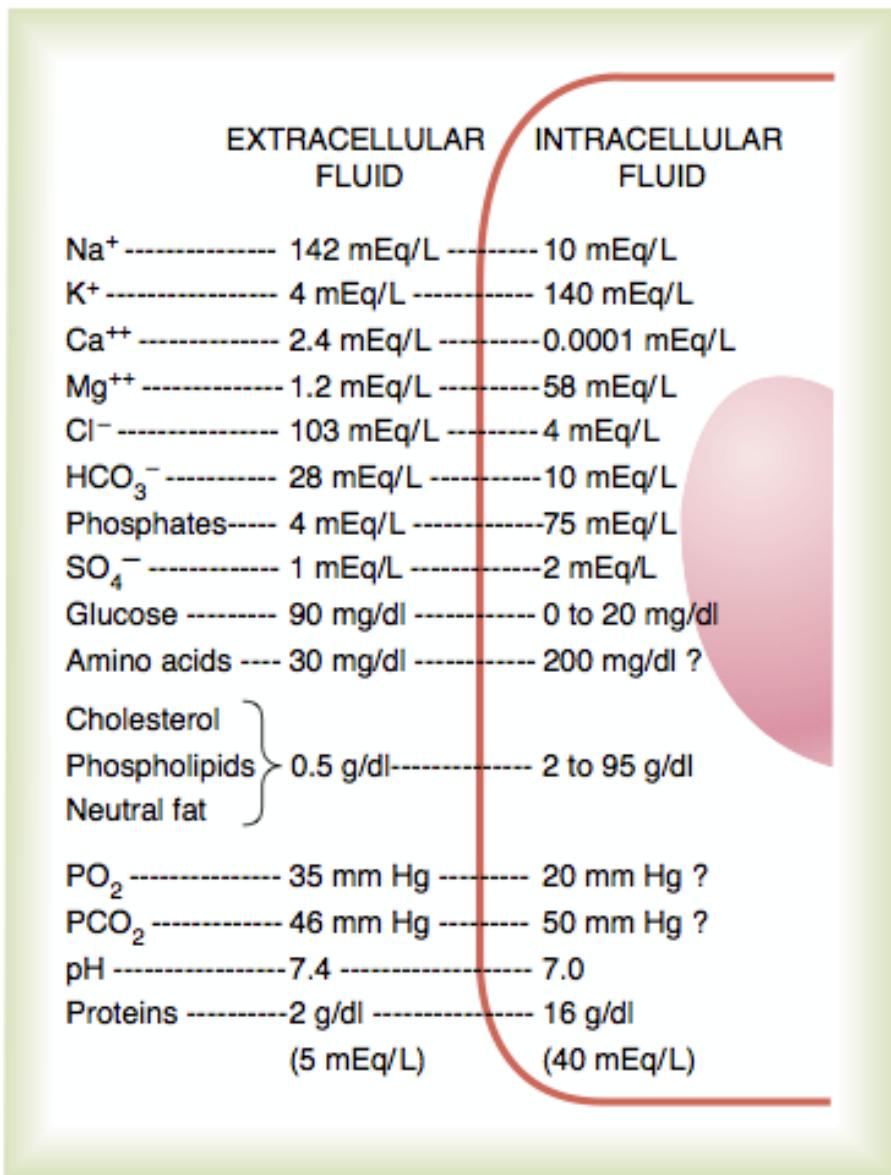
- Following replication and prior to mitosis, DNA polymerase “proofreads” the “new” DNA, and cuts out mismatches
- DNA ligase replaces the mismatches with complementary nucleotides
- A “mistake” during transcription results in a mutation causing the formation of an abnormal protein
- Approximately 10 DNA mutations are passed to the next generation, however two copies of each chromosome almost always ensures the presence of a functional gene

UNIT2

Membrane Physiology, Nerve, and Muscle

- 4. Transport of Substances Through the Cell Membrane
- 5. Membrane Potentials and Action Potentials
- 6. Contraction of Skeletal Muscle
- 7. Excitation of Skeletal Muscle: Neuromuscular Transmission and Excitation-Contraction Coupling
- 8. Contraction and Excitation of Smooth Muscle

➤ Transport of Substances Through the Cell Membrane



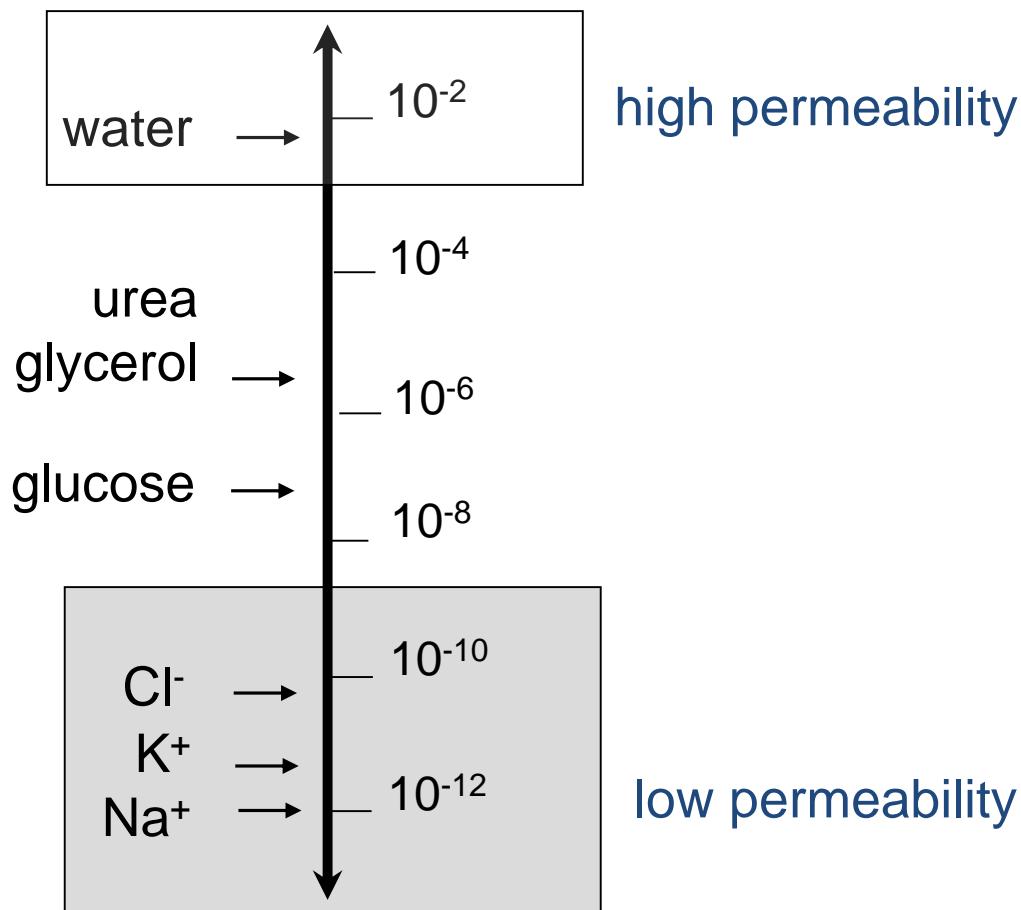
- the extracellular fluid contains a large amount of sodium but only a small amount of potassium.
- Exactly the opposite is true of the intracellular fluid.

Figure 4-1

Chemical compositions of extracellular and intracellular fluids.

Permeability coefficients (cm/sec)

(** across an artificial lipid bilayer)



The Lipid Barrier of the Cell Membrane, and Cell Membrane Transport Proteins

- *lipid bilayer barrier to water and water-soluble substances*

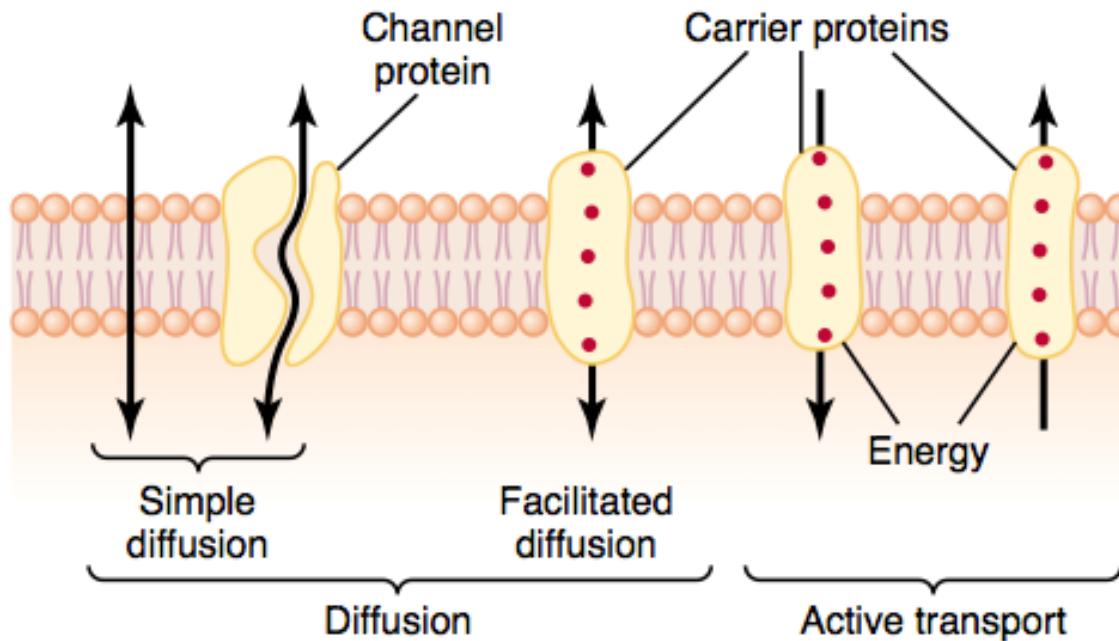


Figure 4-2

Transport pathways through the cell membrane, and the basic mechanisms of transport.

- **channel proteins** have watery spaces all the way through the molecule and allow free movement of water as well as selected ions or molecules
- **carrier proteins** bind with molecules or ions that are to be transported; conformational changes in the protein molecules then move the substances through the interstices of the protein to the other side of the membrane.

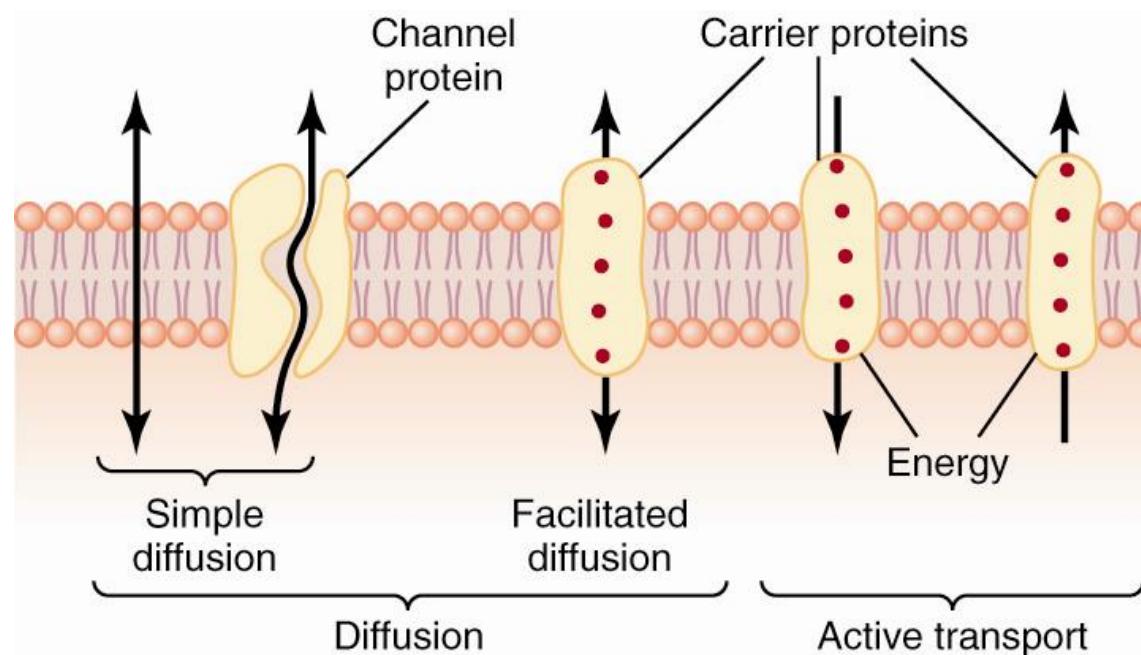
DIFFUSION

Diffusion

- occurs **down** a concn. gradient
- no mediator or involves a “**channel**” or “**carrier**”
- no additional energy

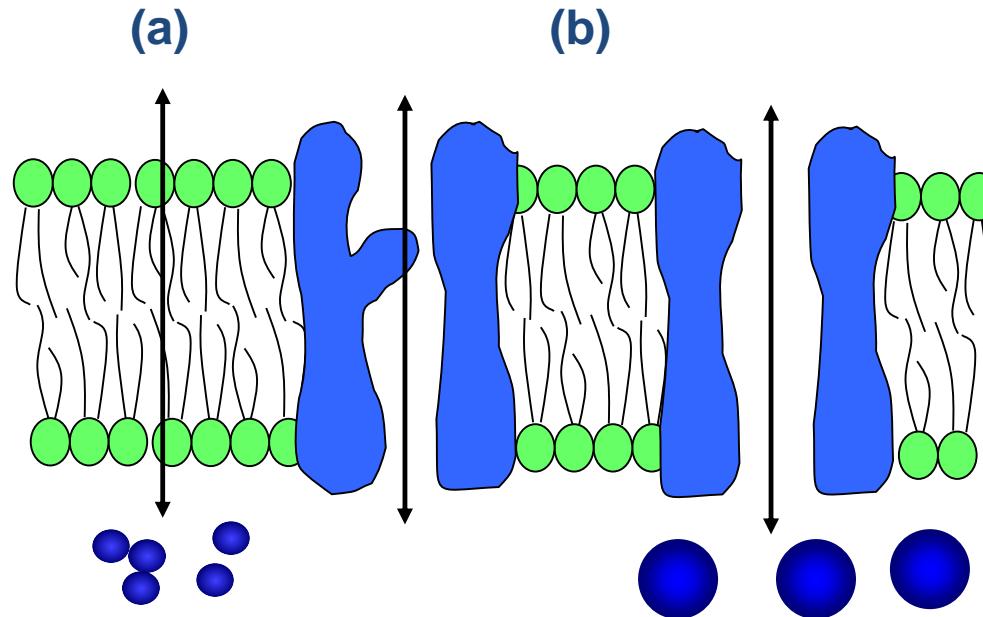
Active Transport

- occurs **against** a concn. gradient
- involves a “**carrier**”
- requires **ENERGY**



■ Simple Diffusion

- (a) lipid-soluble molecules move readily across the membrane
(rate depends on **lipid solubility**)
- (b) water-soluble molecules cross via channels or pores



■ Diffusion Through Protein Channels, and “Gating” of These Channels

- The protein channels are distinguished by two important characteristics: (1) they are often selectively permeable to certain substances, and (2) many of the channels can be opened or closed by gates.

Ion Channels

Characteristics:



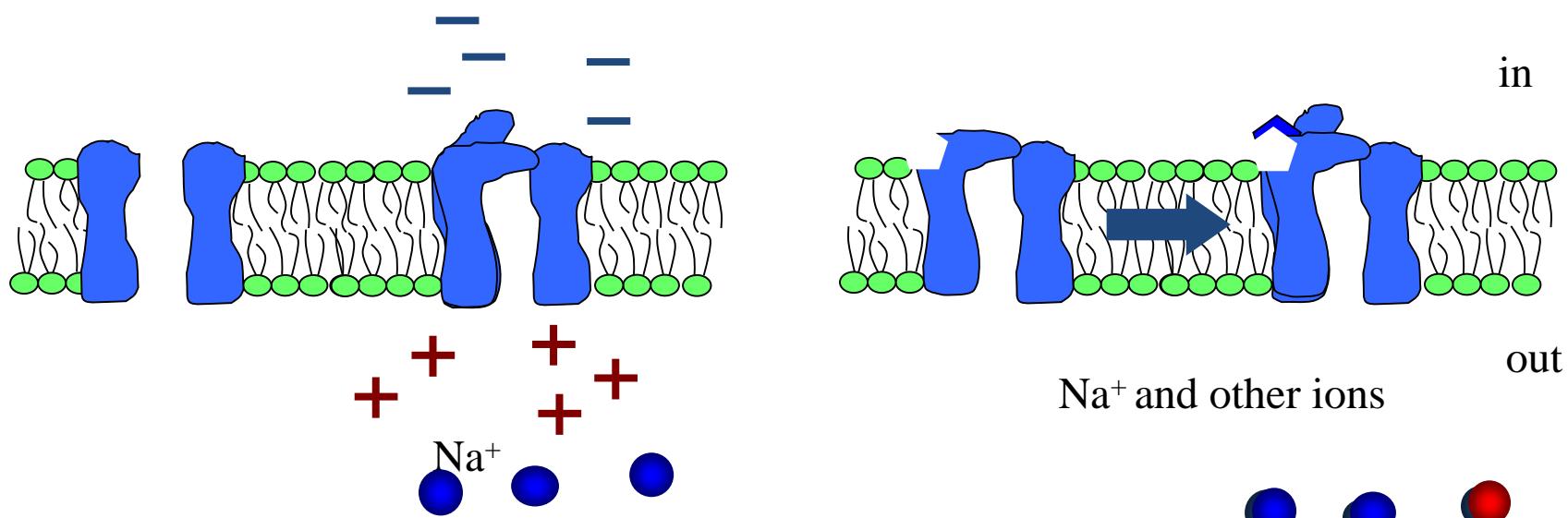
ungated

- determined by size, shape, distribution of charge, etc.

Gated

The opening and closing of gates are controlled in two principal ways:

- voltage (e.g. voltage-dependent Na^+ channels)
- chemically (e.g. nicotinic ACh receptor channels)



▪ Open-State Versus Closed-State of Gated Channels.

- “*Patch Clamp*: method for recording current flow through a single protein channel.”
- Nobel Prize in Physiology & Medicine -1991

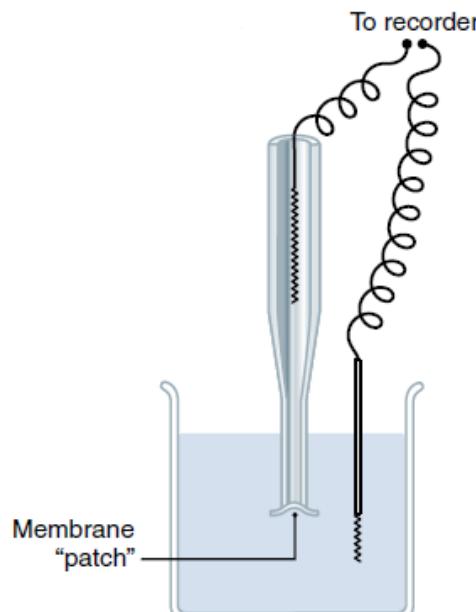
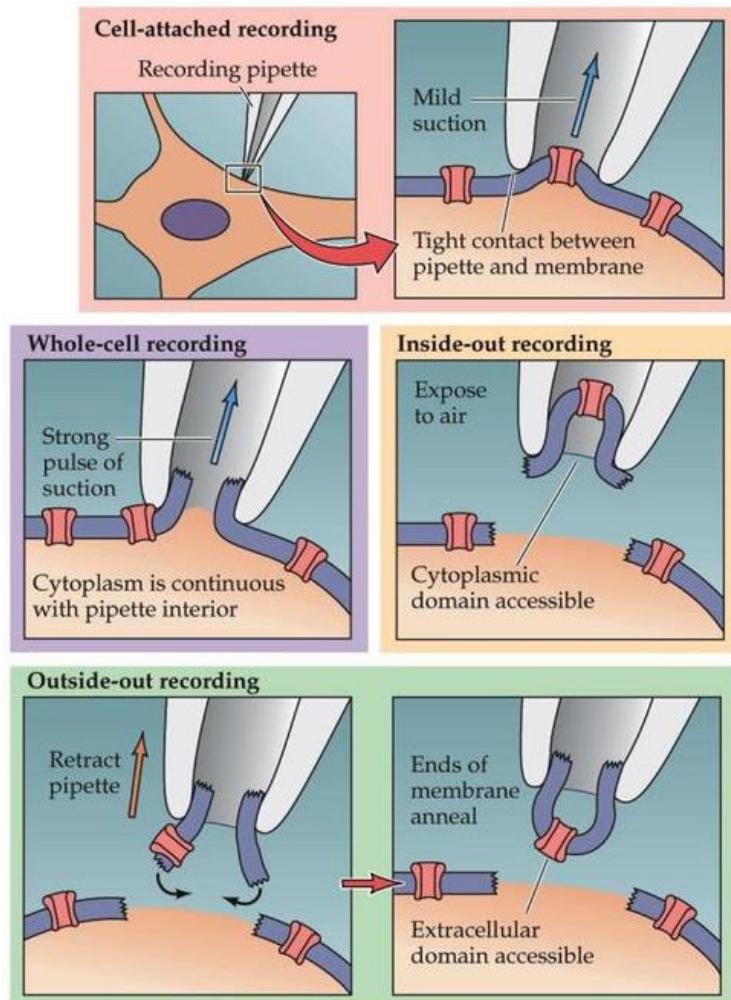
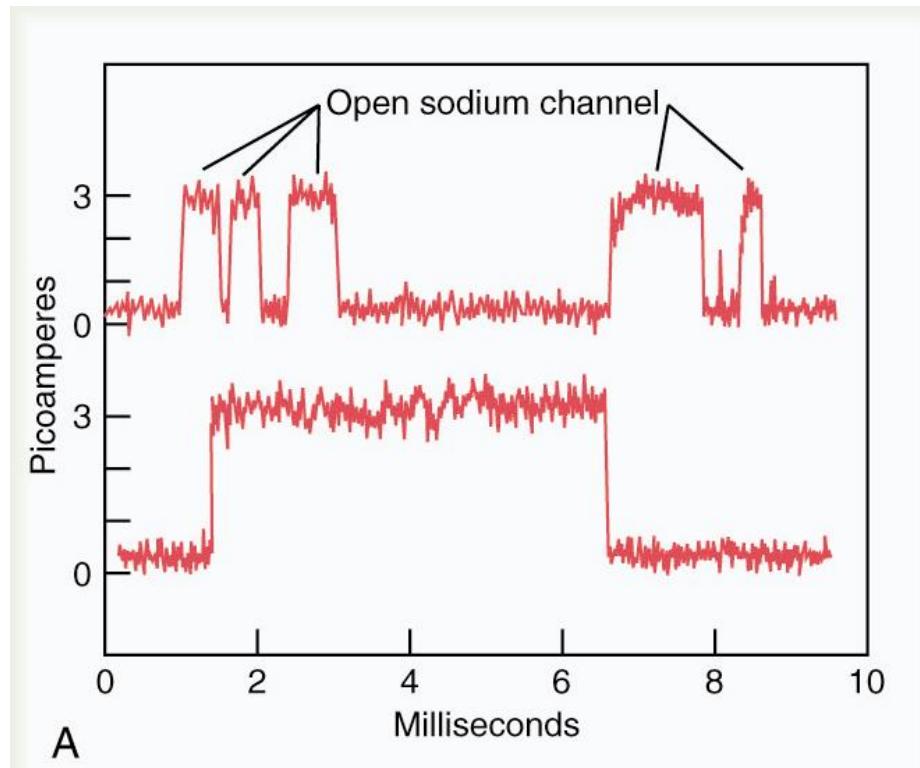
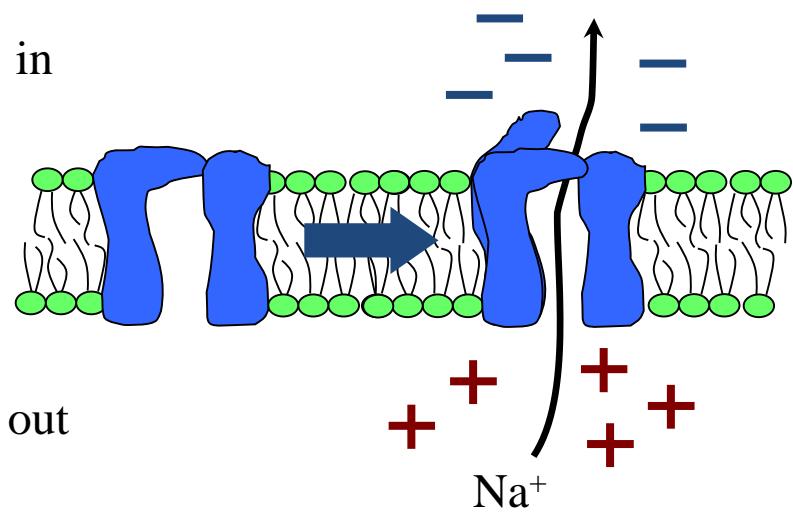


Figure 4-6 A, Record of current flow through a single voltage-gated sodium channel, demonstrating the “all or none” principle for opening and closing of the channel. B, The “patch-clamp” method for recording current flow through a single protein channel. To the left, recording is performed from a “patch” of a living cell membrane. To the right, recording is from a membrane patch that has been torn away from the cell.



Ion Channels

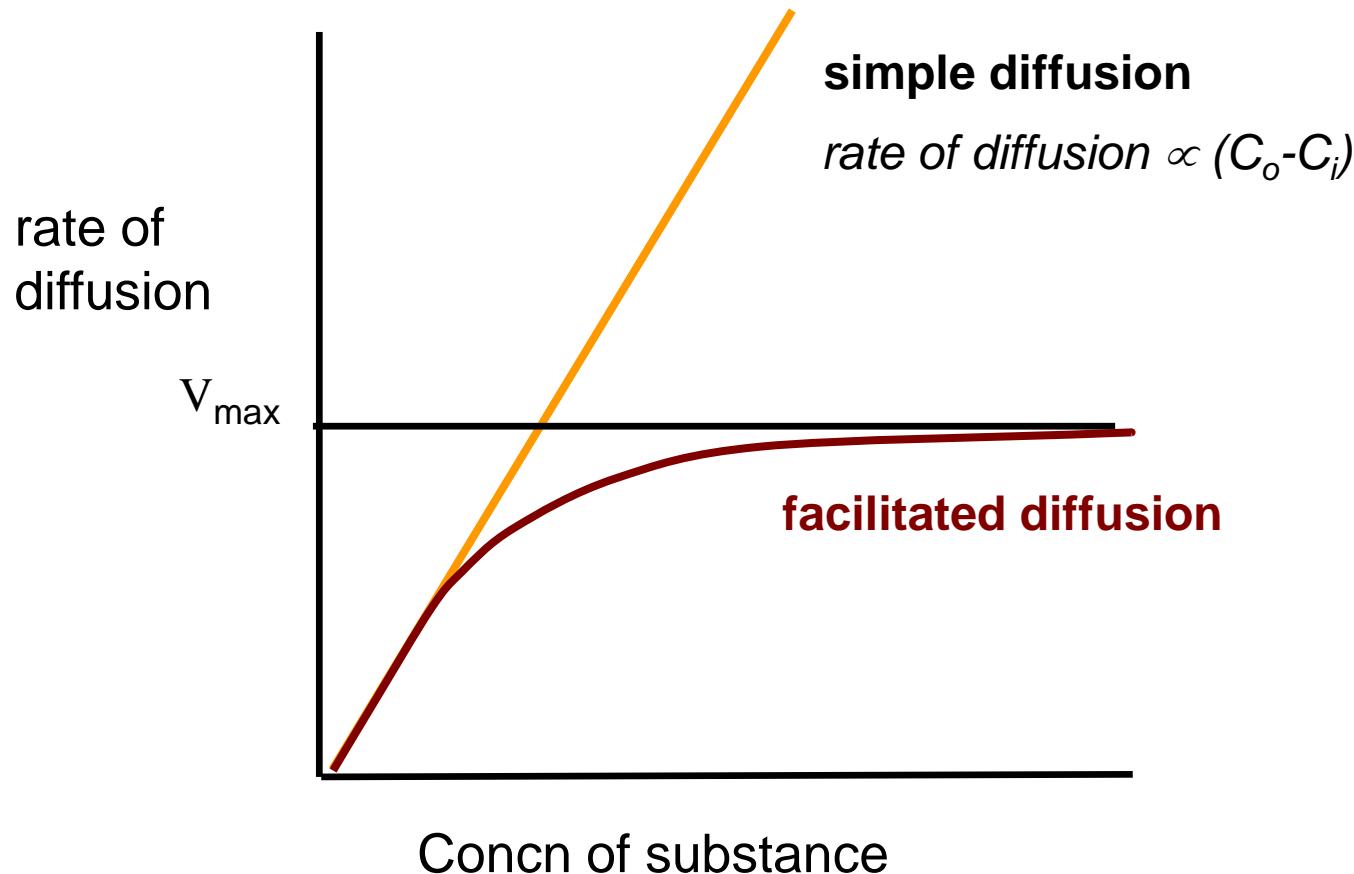


- This figure shows two recordings of electrical current flowing through a single sodium channel when there was an approximate 25-millivolt potential gradient across the membrane. Note that the channel conducts current either “all or none.”

■ Facilitated Diffusion

- Facilitated diffusion is also called carrier-mediated diffusion because a substance transported in this manner diffuses through the membrane using a specific carrier protein to help. That is, the carrier facilitates diffusion of the substance to the other side.

Simple vs. Facilitated



What limits maximum rate of facilitated diffusion?

Rate of diffusion is limited by

- V_{max} of the carrier protein
- the density of carrier proteins in the membrane (i.e., number per unit area)

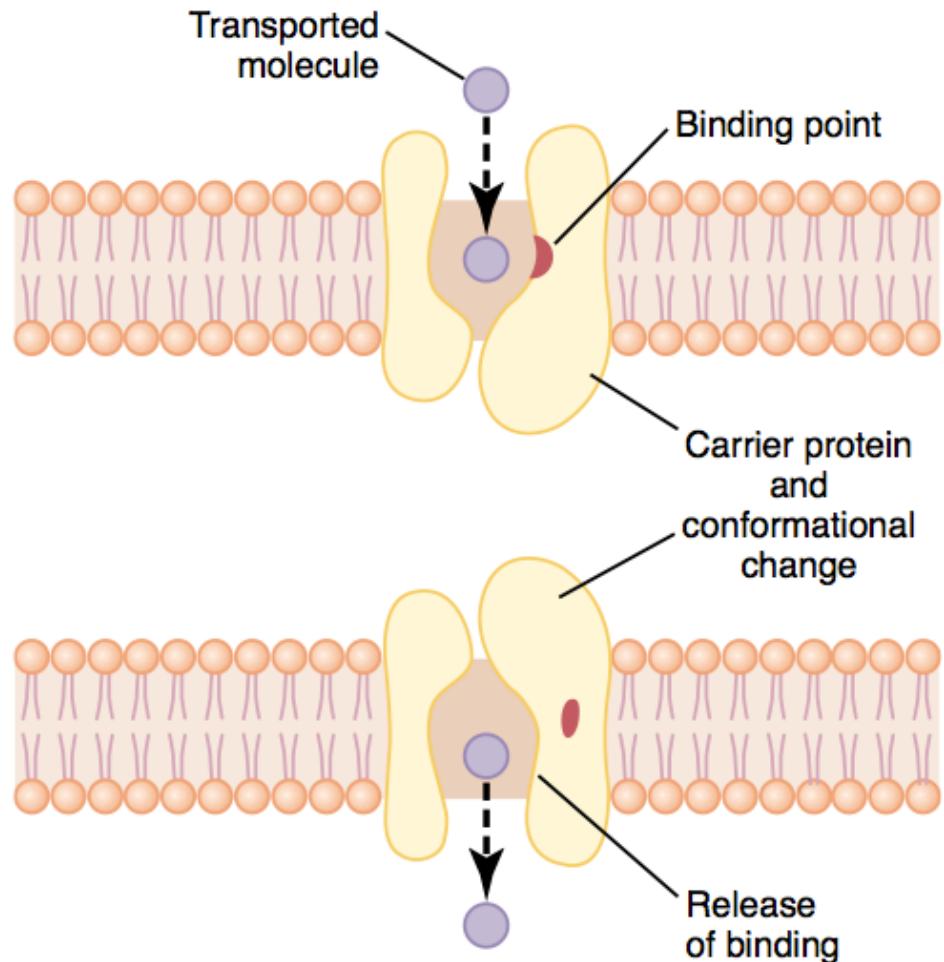


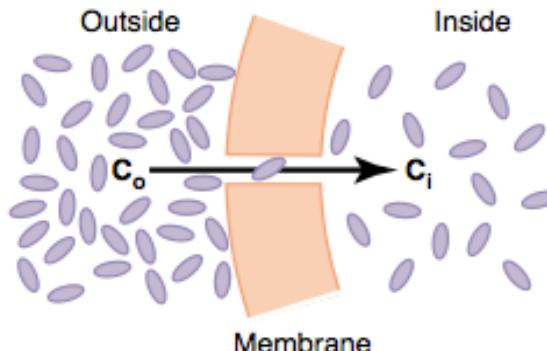
Figure 4–7

Postulated mechanism for facilitated diffusion.

■ Factors That Affect Net Rate of Diffusion

1. Concentration difference ($C_o - C_i$)

$$\text{net diffusion} \propto D (C_o - C_i)$$



2. Electrical potential (EMF)

The **Nernst potential** (*equilibrium potential*) is the theoretical intracellular electrical potential that would be equal in magnitude but opposite in direction to the concentration force.

$$EMF (mV) = \pm 61 \log (C_o / C_i)$$

3. Pressure difference

Higher pressure results in increased energy available to cause net movement from high to low pressure.

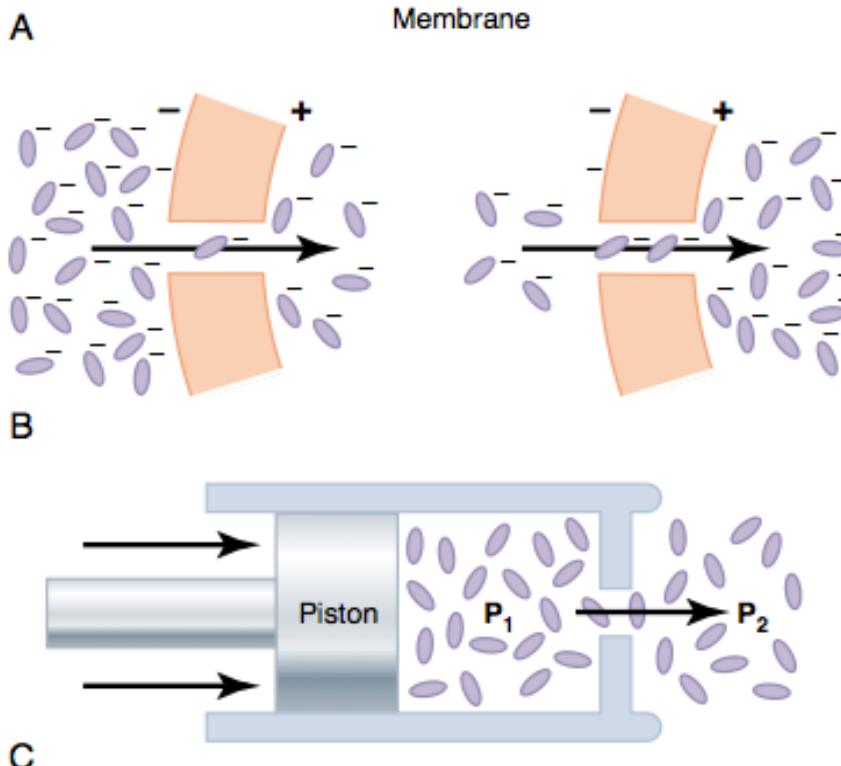


Figure 4–8

Effect of concentration difference (A), electrical potential difference affecting negative ions (B), and pressure difference (C) to cause diffusion of molecules and ions through a cell membrane.

OSMOSIS ACROSS SELECTIVELY PERMEABLE MEMBRANES—“NET DIFFUSION” OF WATER

- **Osmosis** occurs from pure water toward a water/salt solution. Water moves down its concn gradient.

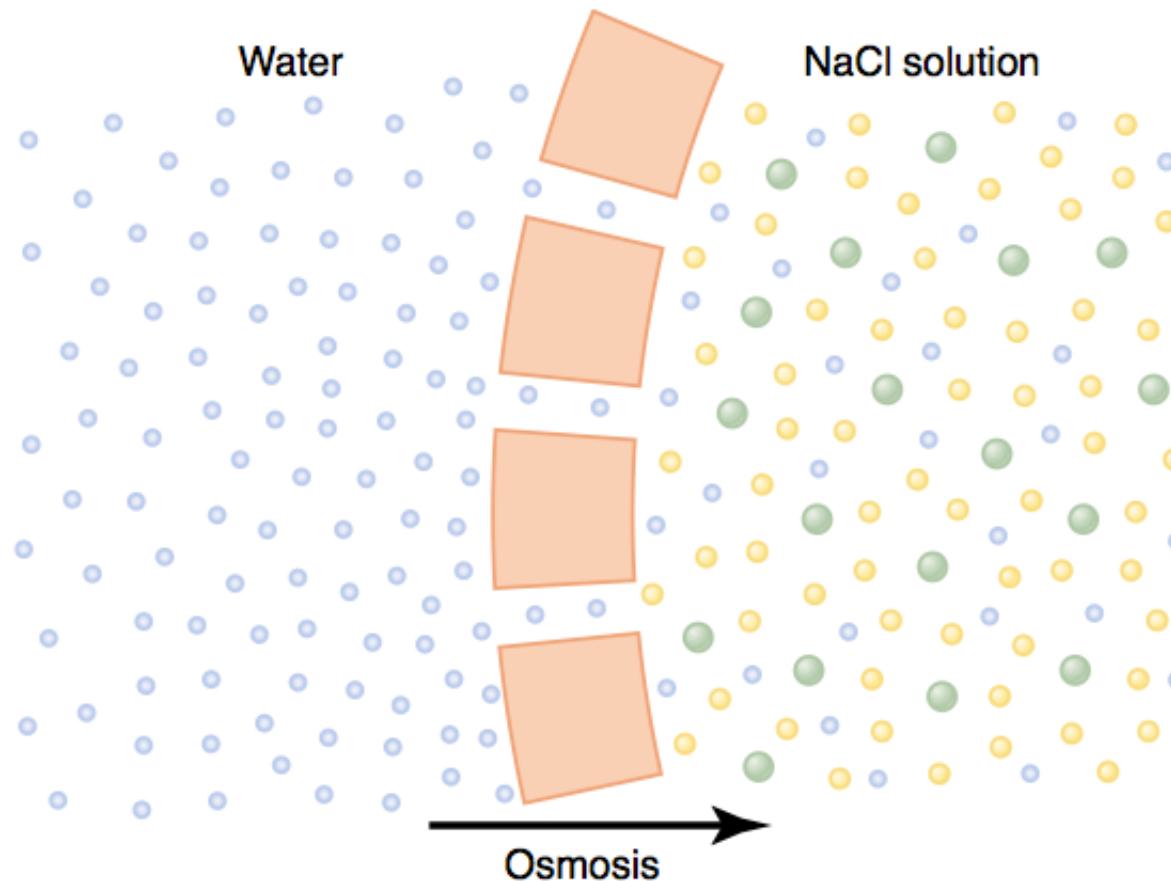


Figure 4–9

Osmosis at a cell membrane when a sodium chloride solution is placed on one side of the membrane and water is placed on the other side.

➤ Osmotic Pressure

- The exact amount of pressure required to stop osmosis is called the osmotic pressure of the sodium chloride solution.

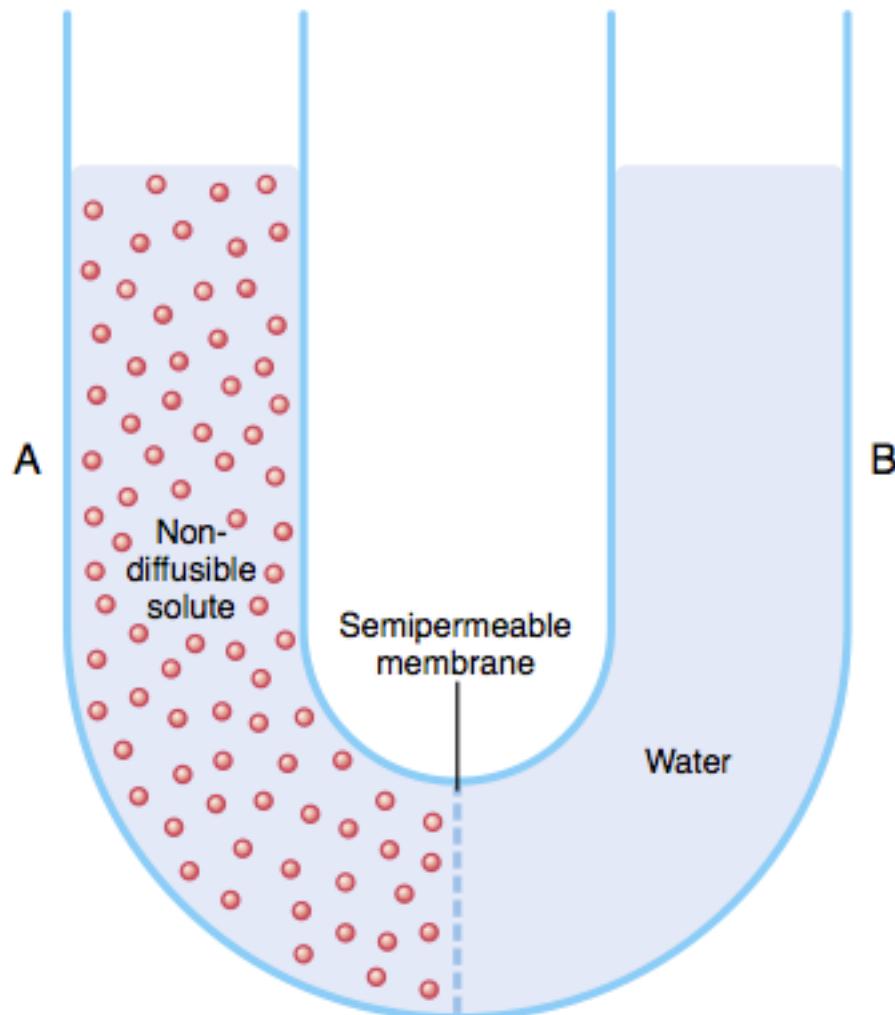


Figure 4-10

Demonstration of osmotic pressure caused by osmosis at a semi-permeable membrane.

Relation between osmolarity and molarity

mOsm (milliosmolar) = index of the concn
or mOsm/L of **particles** per liter soln

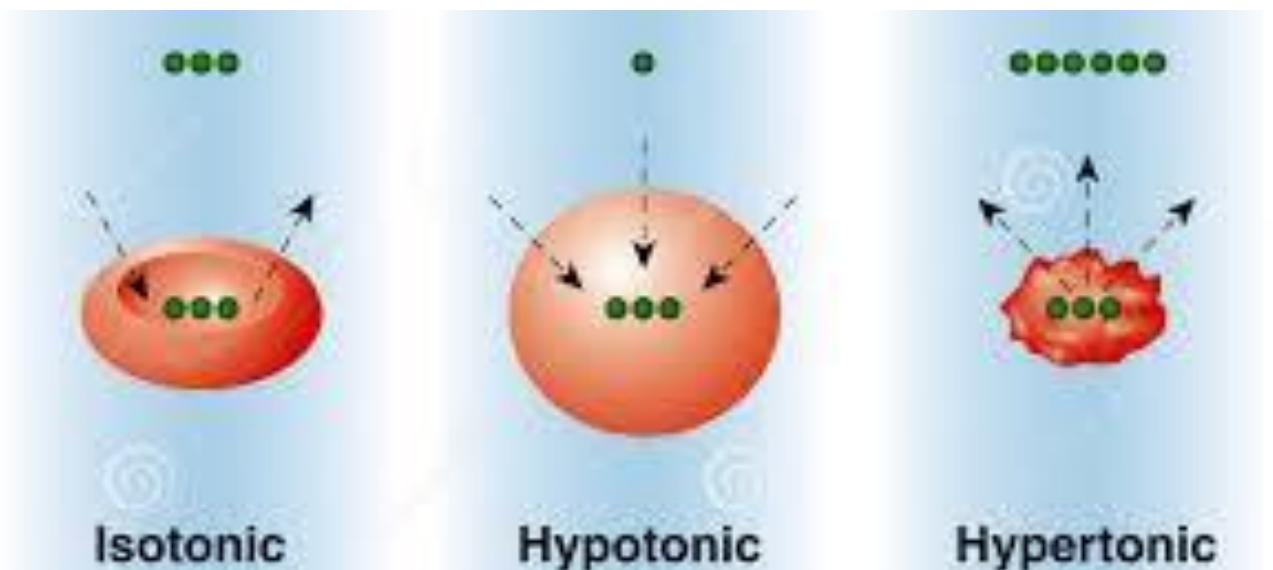
mM (millimolar) = index of concn of
or mM/L **molecules** per liter soln

150 mM NaCl = 300 mOsm

300 mM glucose = 300 mOsm

Isotonic, Hypotonic and Hypertonic

- The terms isotonic, hypotonic, and hypertonic refer to whether solutions will cause a change in cell volume.
- Solutions with an osmolarity the same as the cell are called isosmotic, regardless of whether the solute can penetrate the cell membrane.



Watch
video #1

● Relative salt concentration

→ Movement of water molecules

Clinical Abnormalities of Fluid Volume Regulation

Hypernatremia (increased plasma Na):

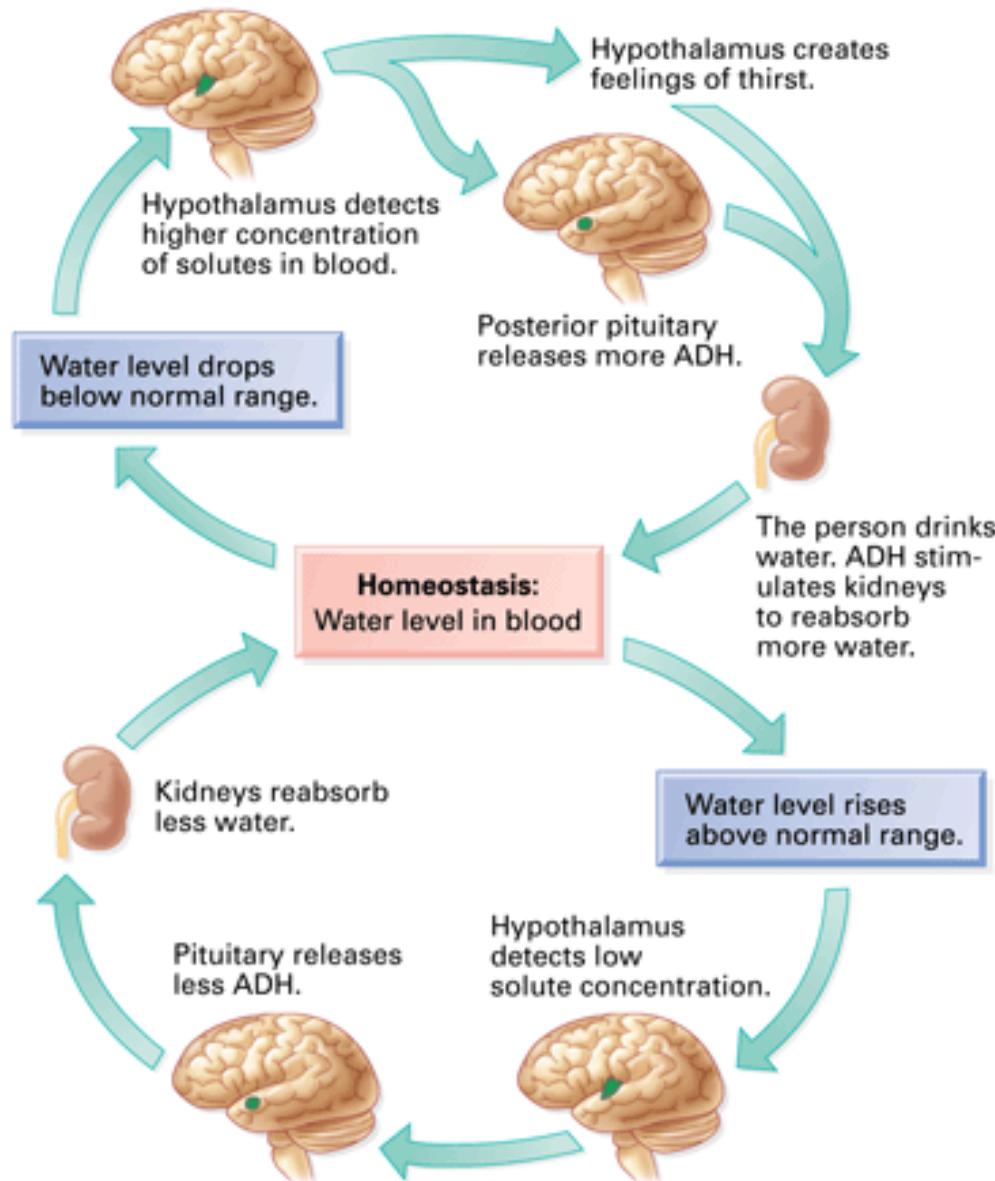
- increased water loss
- excessive sweat loss

**decreased ADH secretion or responsiveness to ADH

(Antidiuretic Hormone (ADH))

Hyponatremia (decreased plasma Na):

- large water ingestion
- **Syndrome of Inappropriate ADH Secretion (SIADH)** **too much ADH leads to water retention, hyponatremia, and excretion of concentrated urine.



“Active Transport” of Substances Through Membranes

Primary Active Transport

- molecules are “pumped” against a concentration gradient at the expense of energy (ATP)
 - *direct use of energy*

Secondary Active Transport

- transport is driven by the energy stored in the concentration gradient of another molecule (Na^+)
 - *indirect use of energy*

■ Primary Active Transport

1. Na^+/K^+ ATPase

- carrier protein located on the plasma membrane of all cells
- plays an important role in regulating osmotic balance by maintaining Na^+ and K^+ balance
- requires one to two thirds of cells **energy!**

α subunit

- 100,000 MW
- binds ATP, 3 Na^+ , and 2 K^+

β subunit

- 55,000 MW
- function ???

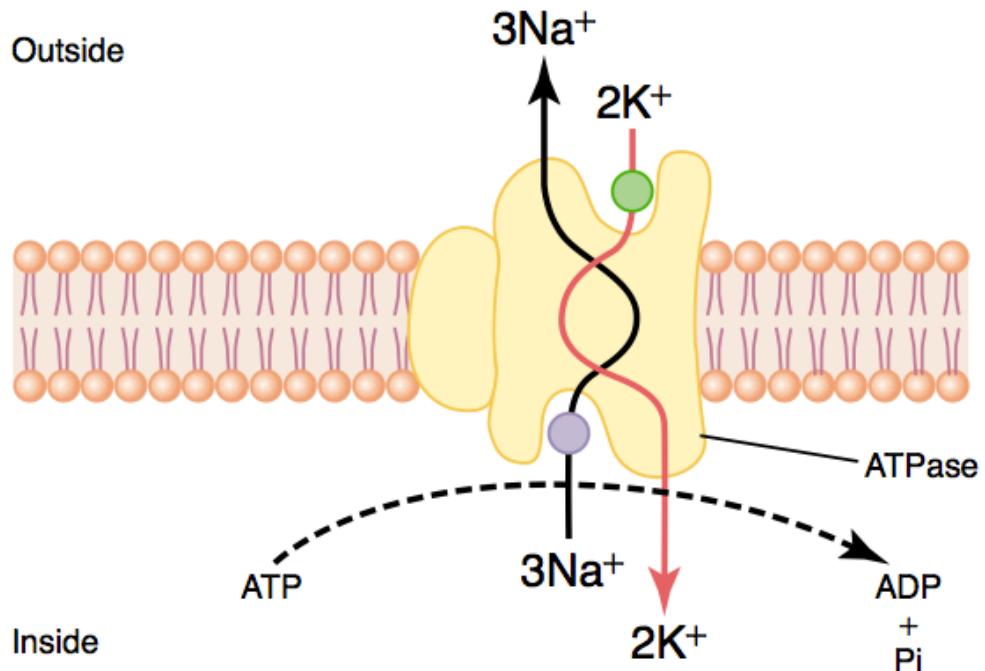


Figure 4-11

Postulated mechanism of the sodium-potassium pump. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Pi, phosphate ion.

2. Ca^{2+} ATPase

- present on the cell membrane and the sarcoplasmic reticulum
- maintains a low cytosolic Ca^{2+} concentration

3. H^+ ATPase

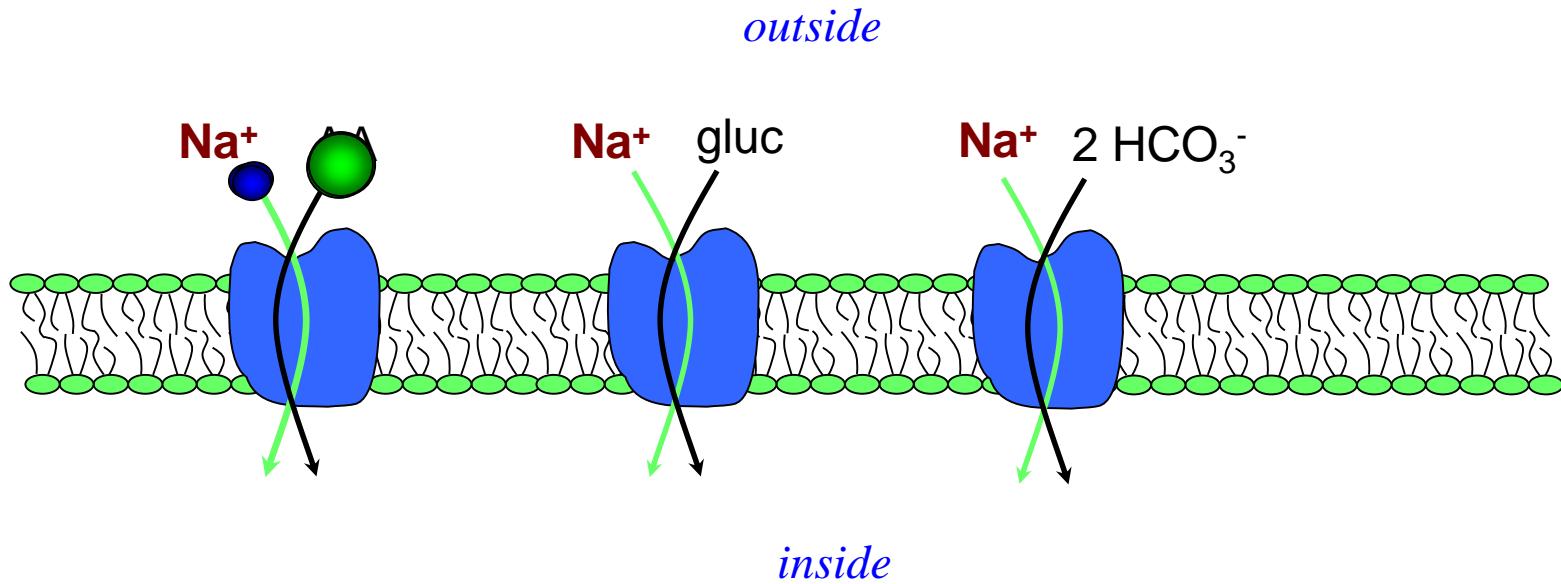
- found in parietal cells of gastric glands (HCl secretion) and intercalated cells of renal tubules (controls blood pH)
- concentrates H^+ ions up to 1 million-fold

- **Secondary Active Transport**

- *co-transport and counter-transport* -

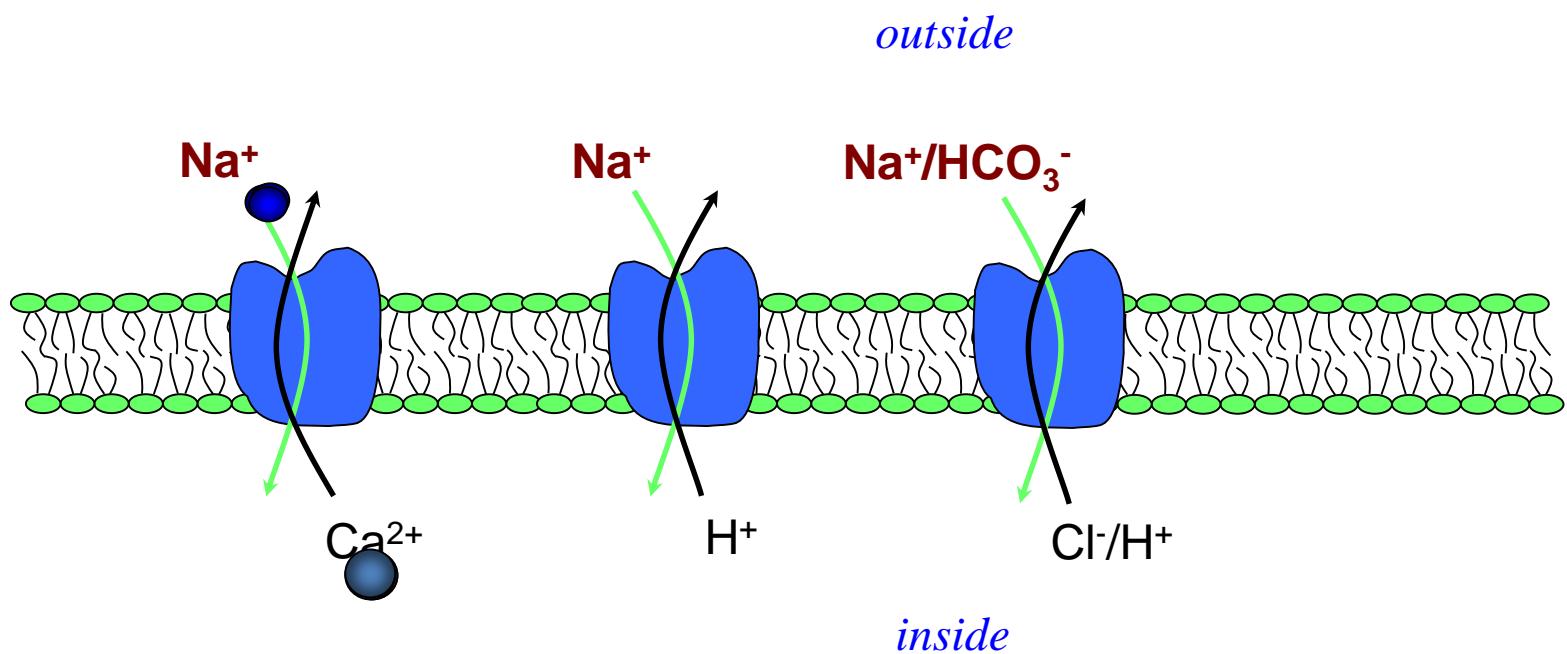
1. **Co-transport (*co-porters*):** substance is transported in the same direction as the “driver” ion (Na^+)

Examples:



2. Counter-transport (*anti-porters*): substance is transported in the opposite direction as the “driver” ion (Na^+)

Examples:

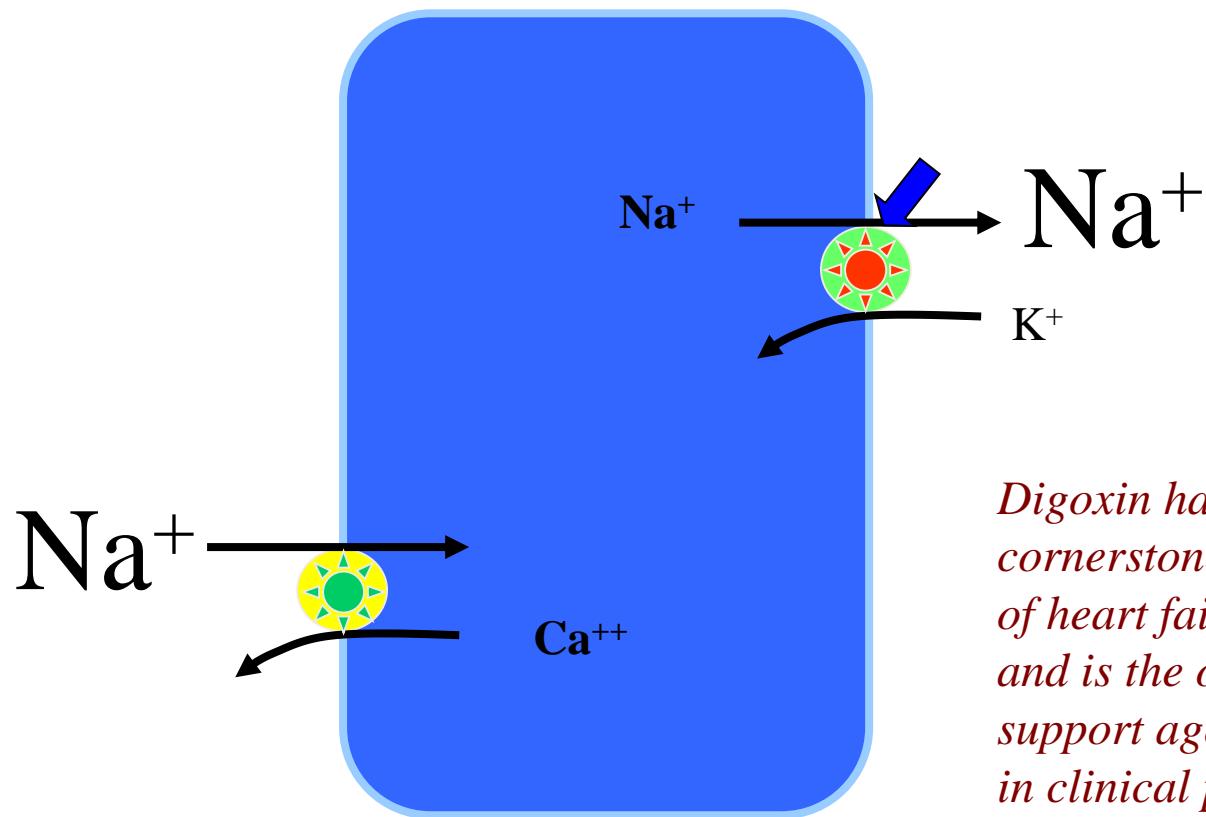


Q: How do cardiac glycosides increase cardiac contractility?

Glycosides (*eg. digoxin*) inhibit the **Na/K ATPase**...

- increase intracellular Na^+
- decrease Na^+ gradient
- decrease $\text{Na}^+/\text{Ca}^{2+}$ counter-transport
- **increase intracellular Ca^{2+}**

Q: How do cardiac glycosides increase cardiac contractility?

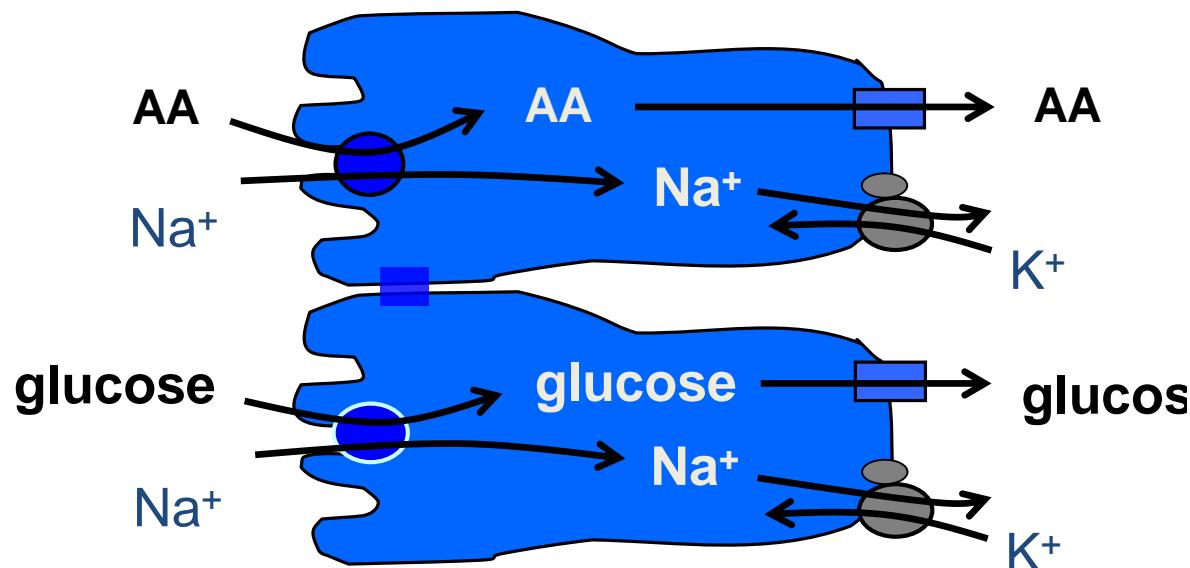


Digoxin has been a cornerstone for the treatment of heart failure for decades and is the only oral inotropic support agent currently used in clinical practice.

■ Active Transport Through Cellular Sheets

- At many places in the body, substances must be transported all the way through a cellular sheet instead of simply through the cell membrane.
- The basic mechanism for transport of a substance through a cellular sheet is (1) active transport through the cell membrane on one side of the transporting cells in the sheet, and then (2) either simple diffusion or facilitated diffusion through the membrane on the opposite side of the cell.

➤ Transcellular Transport of Glucose / AA



Examples:

1. Intestinal epithelium
2. Renal tubular epithelium
3. Epithelium of exocrine glands
4. Epithelium of gallbladder
5. Membrane of choroid plexus of brain etc.

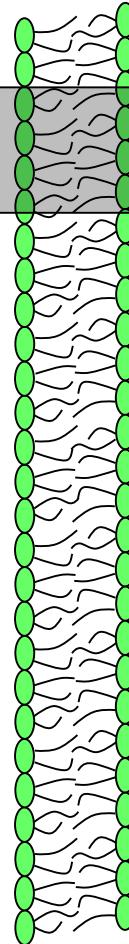
Chapter 5:

Membrane Potentials and Action Potentials

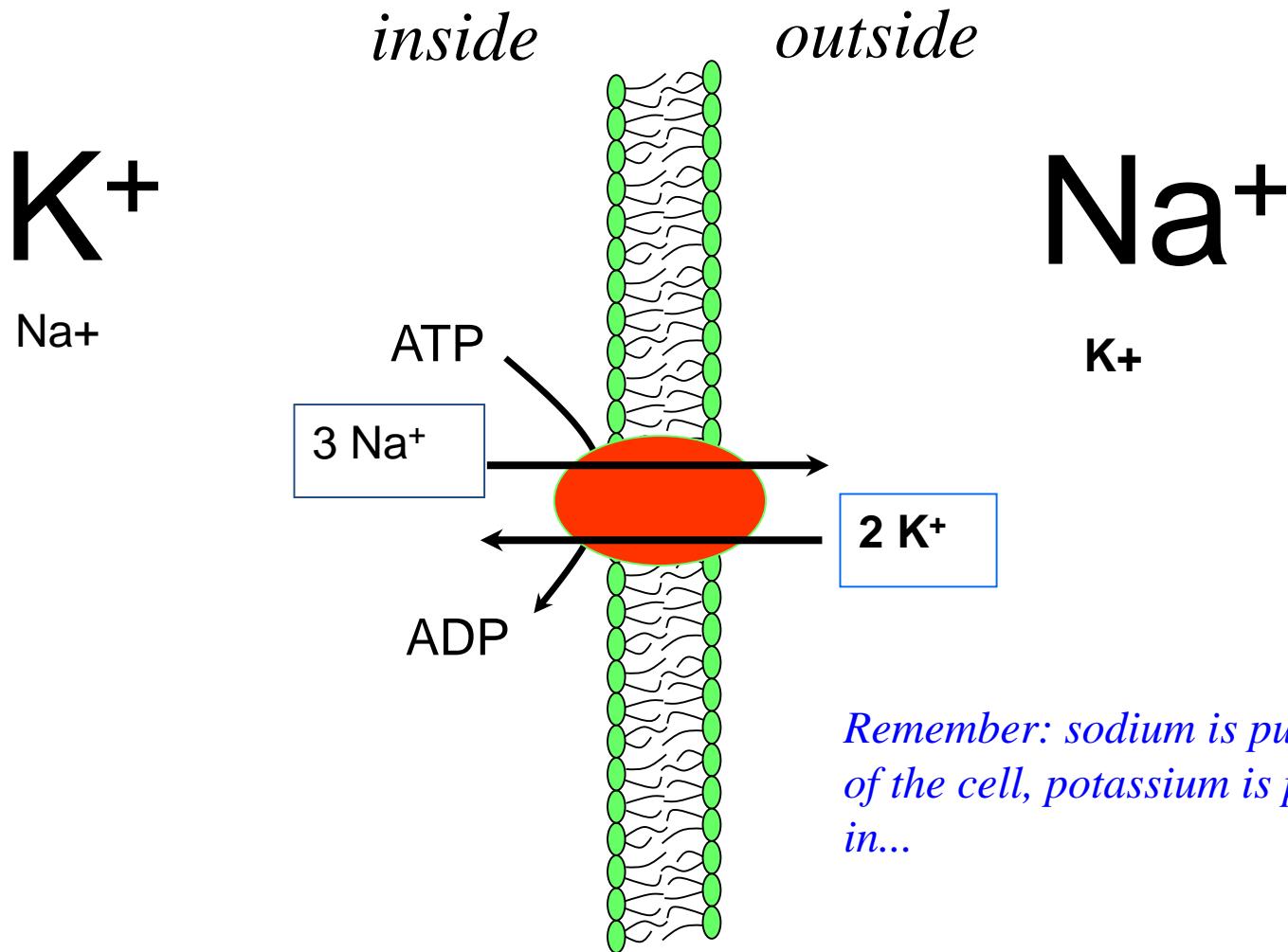
Basic Physics of Membrane Potentials

■ Molecular Gradients

	<i>inside (in mM)</i>	<i>outside (in mM)</i>
Na^+	14	142
K^+	140	4
Mg^{2+}	0.5	1-2
Ca^{2+}	10^{-4}	1-2
H^+	(pH 7.2)	(pH 7.4)
HCO_3^-	10	28
Cl^-	5-15	110
SO_4^{2-}	2	1
PO_4^{3-}	75	4
protein	40	5

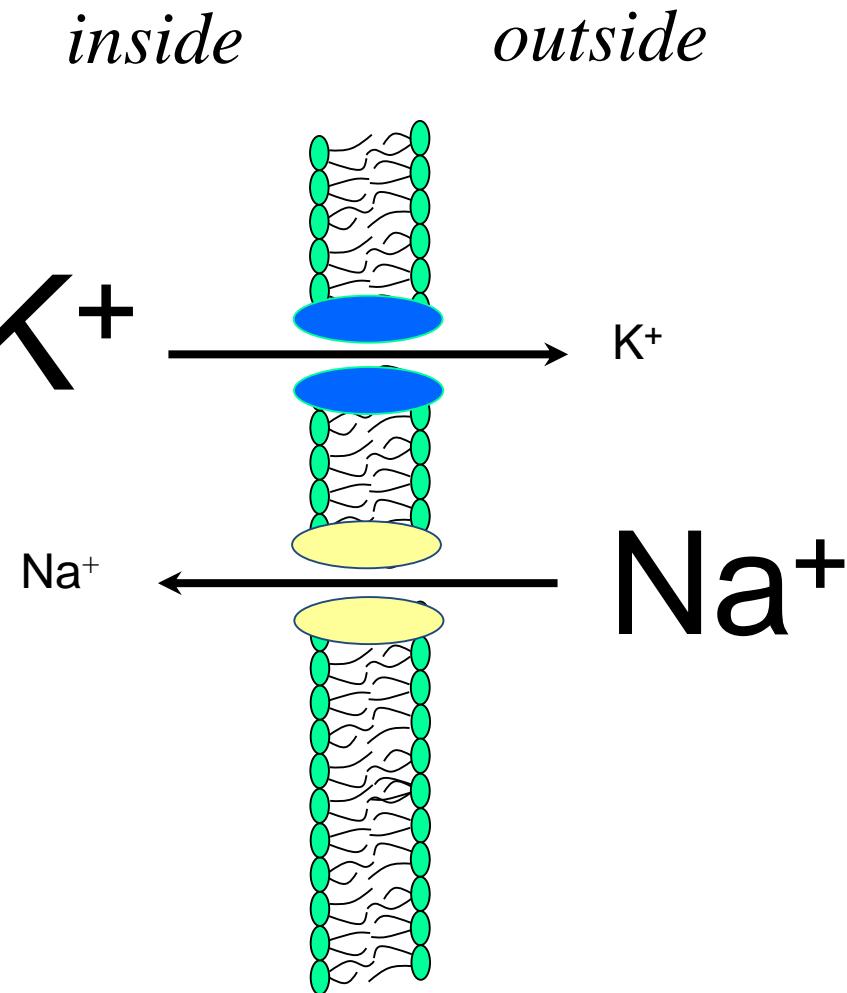


■ Active Transport

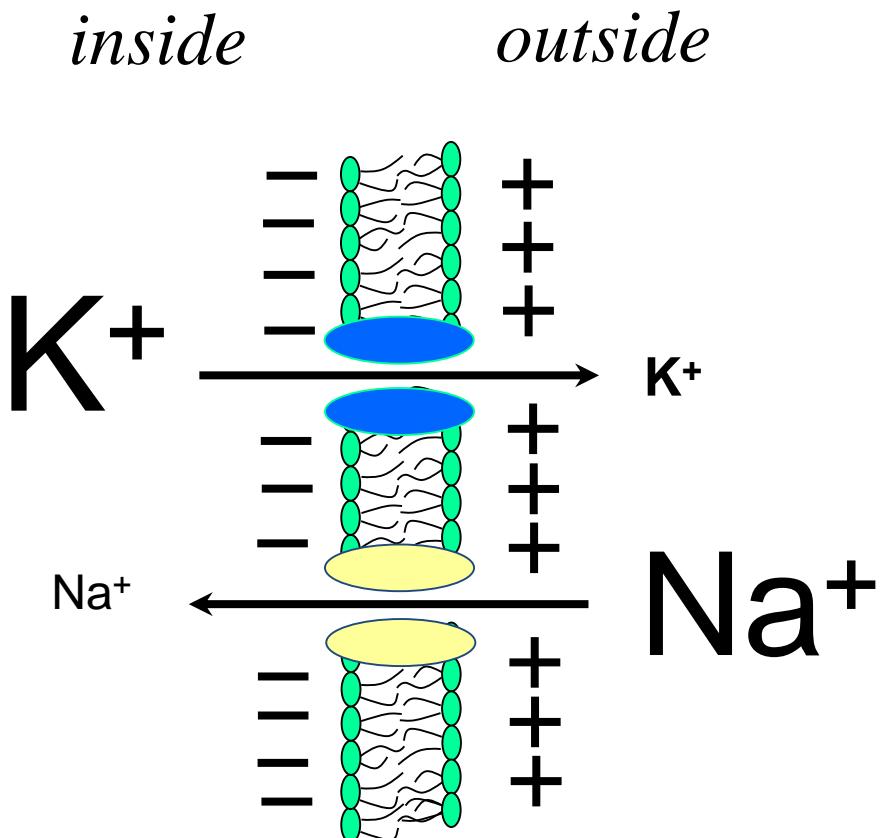


Remember: sodium is pumped out of the cell, potassium is pumped in...

■ Simple Diffusion



- **Membrane Potential (V_m):**
- charge difference across the membrane -

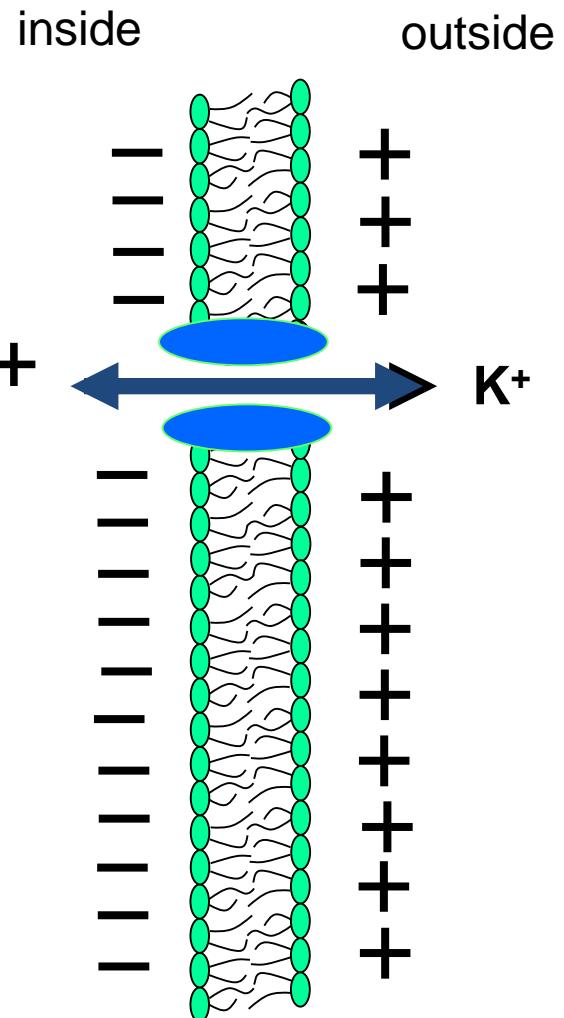


...how can passive diffusion of potassium and sodium lead to development of negative membrane potential?

➤ Simplest Case Scenario:

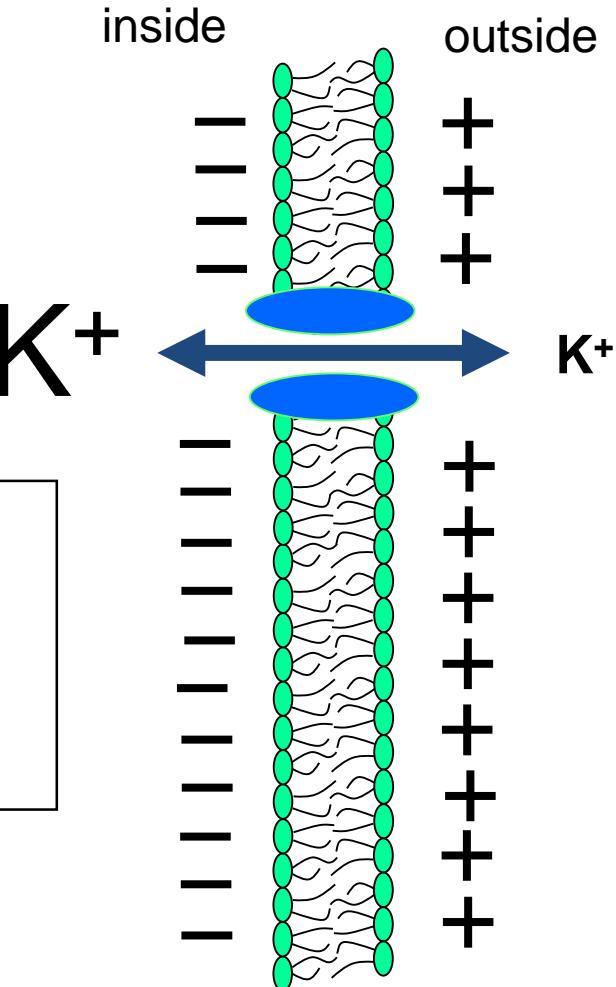
If a membrane were permeable to only K^+ then...

K^+ would diffuse down its concentration gradient until the electrical potential across the membrane countered diffusion.



➤ Simplest Case Scenario:

If a membrane were permeable to only K^+ then...



The electrical potential that counters net diffusion of K^+ is called the K^+ equilibrium potential (E_K).

■ The Potassium Nernst Potential

...also called the equilibrium potential

$$E_K = -61 \log \frac{K_i}{K_o}$$

Example: If $K_o = 5 \text{ mM}$ and $K_i = 140 \text{ mM}$

$$E_K = -61 \log(140/5)$$

$$E_K = -61 \log(28)$$

$$E_K = -94 \text{ mV}$$

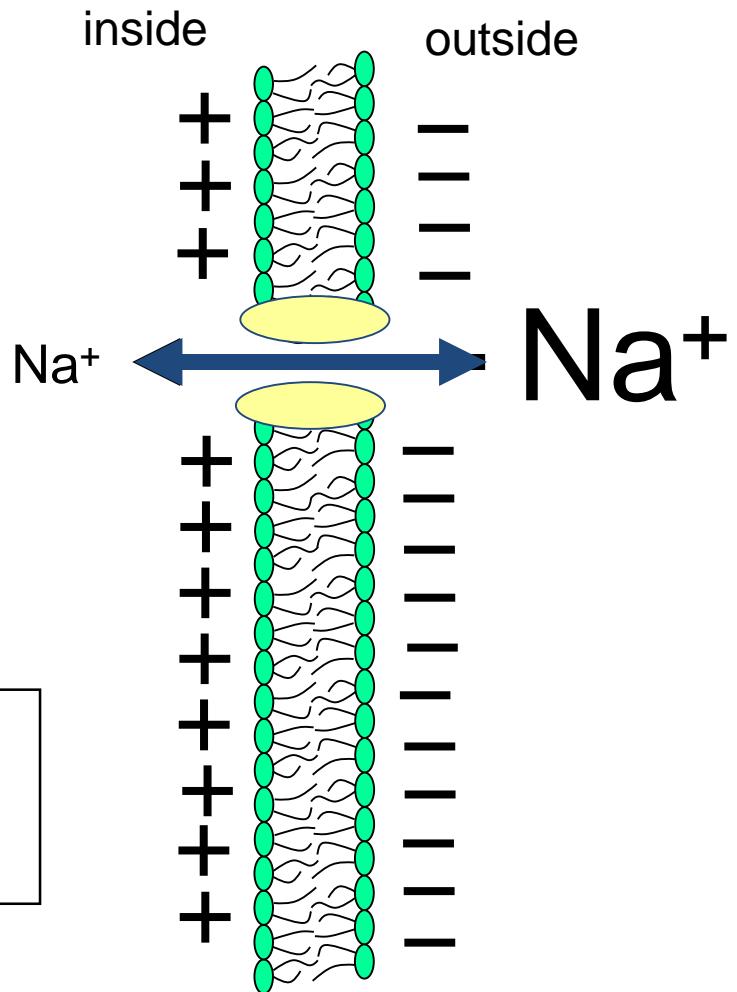
So, if the membrane were permeable only to K+, V_m would be -94 mV

➤ Simplest Case Scenario:

If a membrane were permeable to only Na^+ then...

Na^+ would diffuse down its concentration gradient until potential across the membrane countered diffusion.

The electrical potential that counters net diffusion of Na^+ is called the Na^+ equilibrium potential (E_{Na}).



■ The Sodium Nernst Potential

$$E_K = -61 \log \frac{N_{a_i}}{N_{a_o}}$$

Example: If $N_{a_o} = 142 \text{ mM}$ and $N_{a_i} = 14 \text{ mM}$

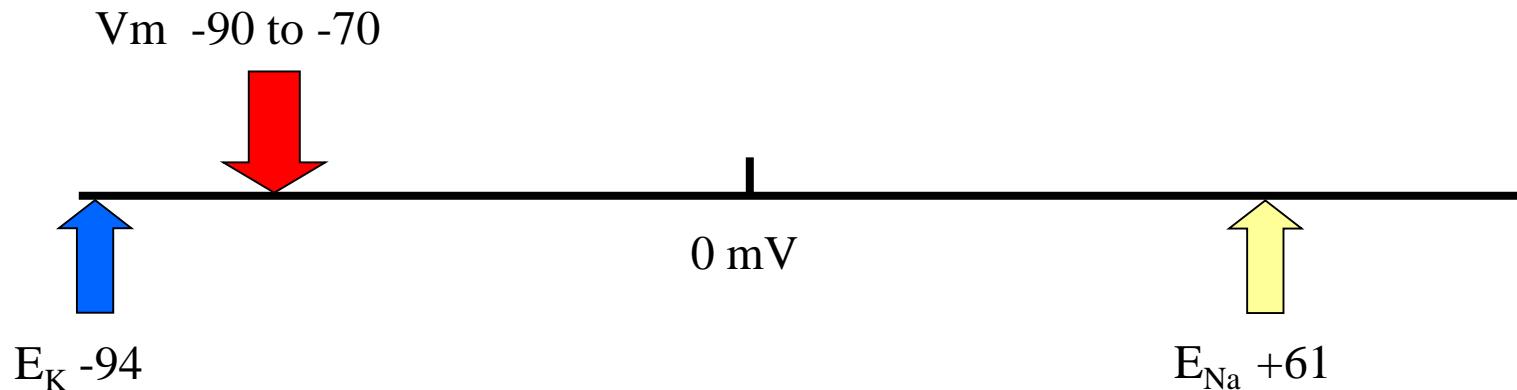
$$E_K = -61 \log(14/142)$$

$$E_K = -61 \log(0.1)$$

$$E_K = +61 \text{ mV}$$

So, if the membrane were permeable only to Na^+ , V_m would be +61 mV

▪ Resting Membrane Potential



Why is V_m so close to E_K?

Ans. The membrane is far more permeable to K than Na..

- **The Goldman-Hodgkin-Katz Equation**
(also called the Goldman Field Equation)

Calculates V_m when more than one ion is involved.

$$V_m = 61 \cdot \log \frac{p'_{K^+} [K^+]_o + p'_{Na^+} [Na^+]_o + p'_{Cl^-} [Cl^-]_i}{p'_{K^+} [K^+]_i + p'_{Na^+} [Na^+]_i + p'_{Cl^-} [Cl^-]_o}$$

or

$$V_m = -61 \cdot \log \frac{p'_{K^+} [K^+]_i + p'_{Na^+} [Na^+]_i + p'_{Cl^-} [Cl^-]_o}{p'_{K^+} [K^+]_o + p'_{Na^+} [Na^+]_o + p'_{Cl^-} [Cl^-]_i}$$

NOTE:
 P' = permeability

■ The Goldman-Hodgkin-Katz Equation

Take home message...

The resting membrane potential is closest to the equilibrium potential for the ion with the highest permeability!

Resting Membrane Potential Summary

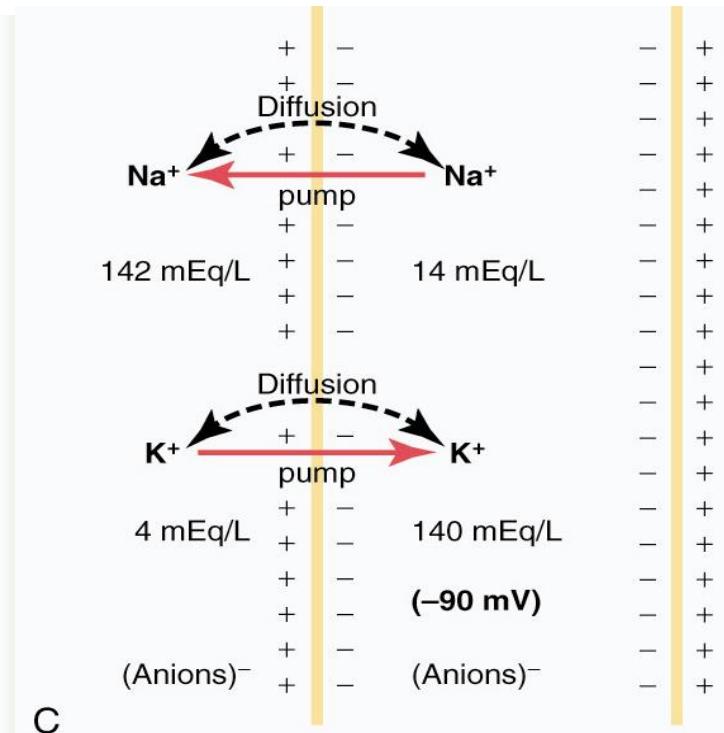
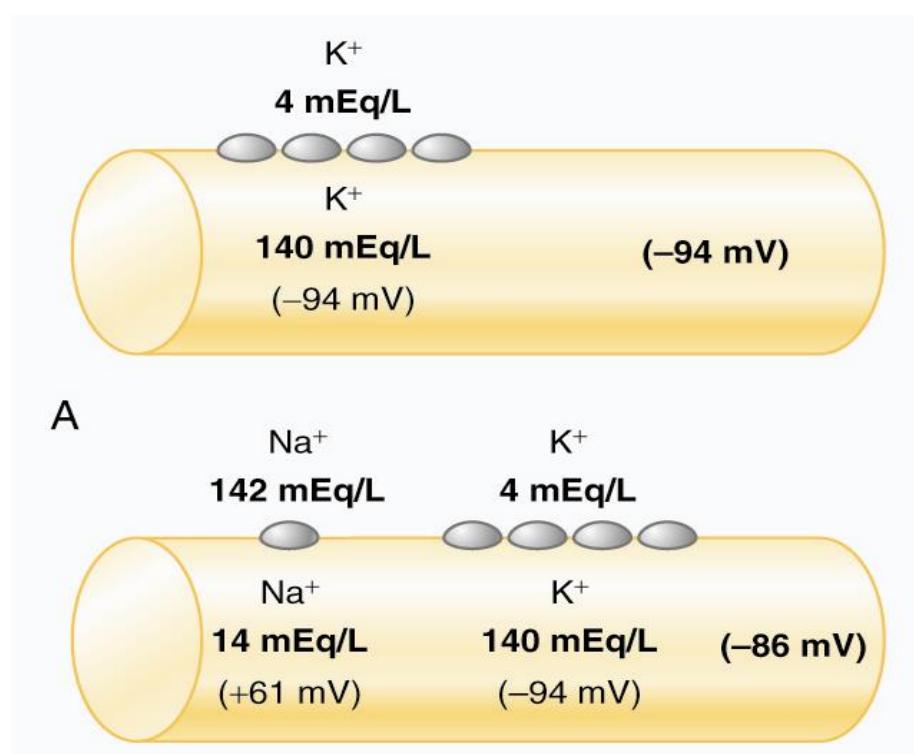
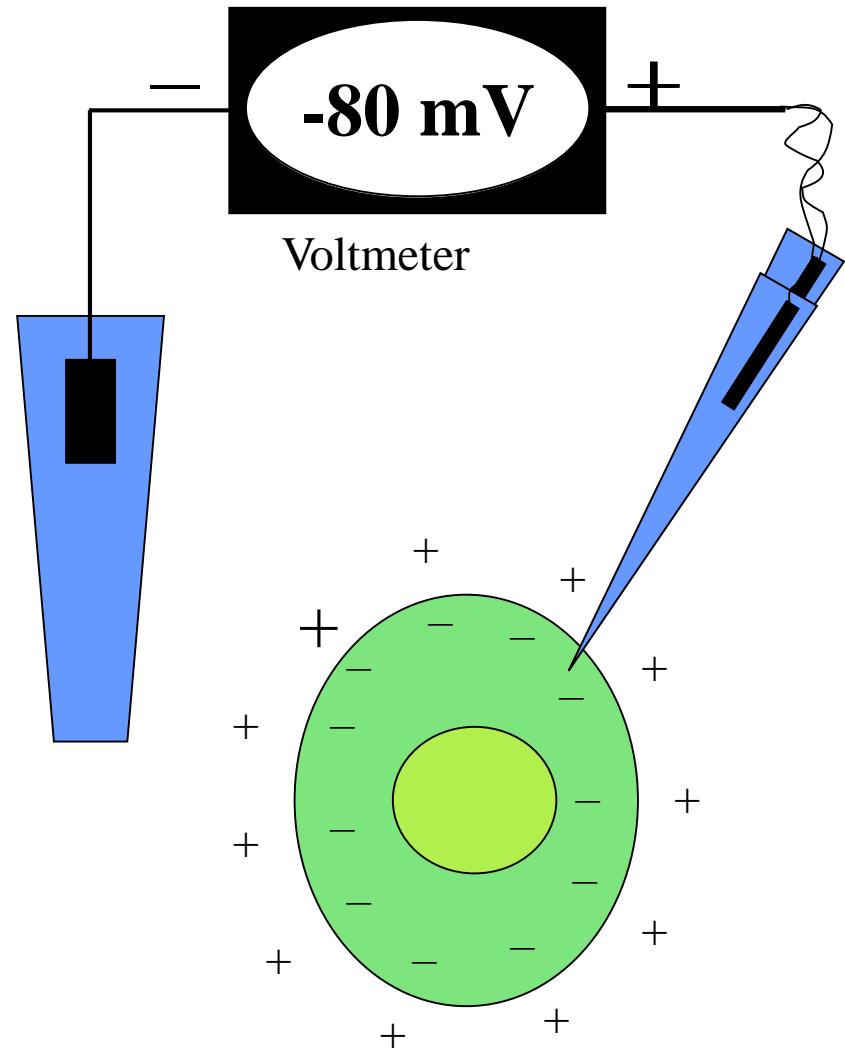


Figure 5-5: Establishment of resting membrane potentials in nerve fibers under three conditions: A, when the membrane potential is caused entirely by potassium diffusion alone; B, when the membrane potential is caused by diffusion of both sodium and potassium ions; and C, when the membrane potential is caused by diffusion of both sodium and potassium ions plus pumping of both these ions by the Na^+-K^+ pump.

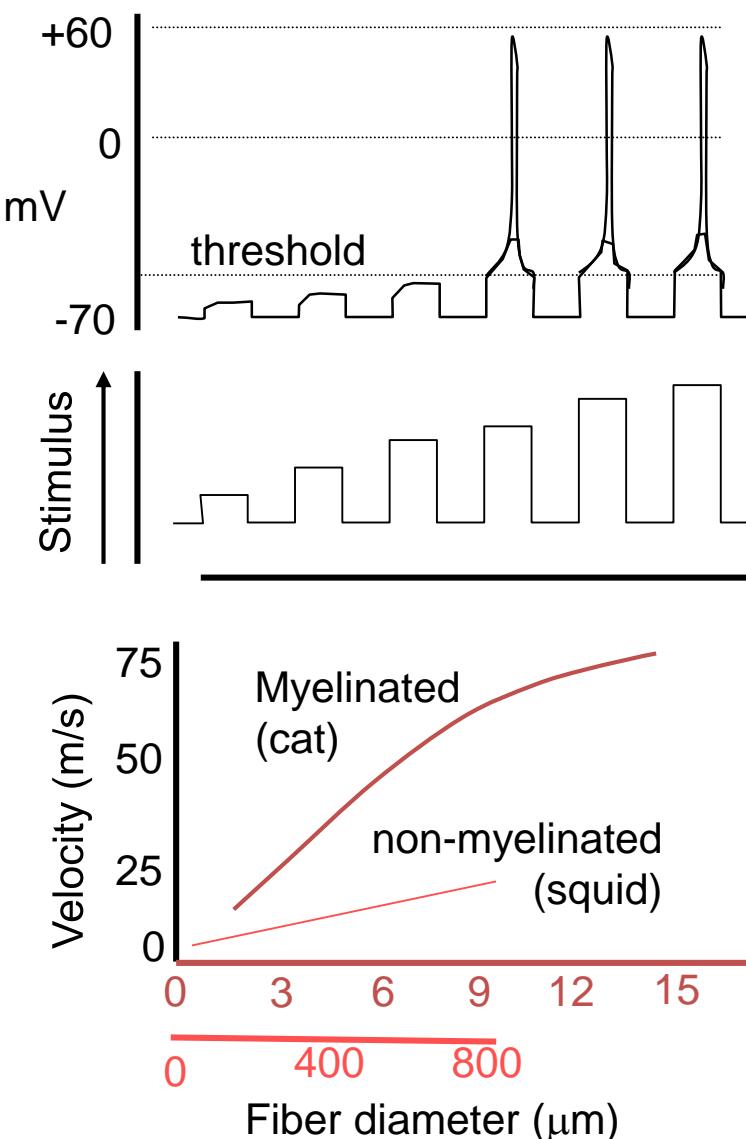
Resting and action potentials

- Recall that cells:
 - contain high a K^+ concentration
 - have membranes that are essentially permeable to K^+ at rest
- Membrane electrical potential difference (*membrane potential*) is generated by diffusion of K^+ ions and charge separation
 - measured in mV (=1/1000th of 1V)
 - typically resting membrane potentials in neurons are -70 to -90 mV



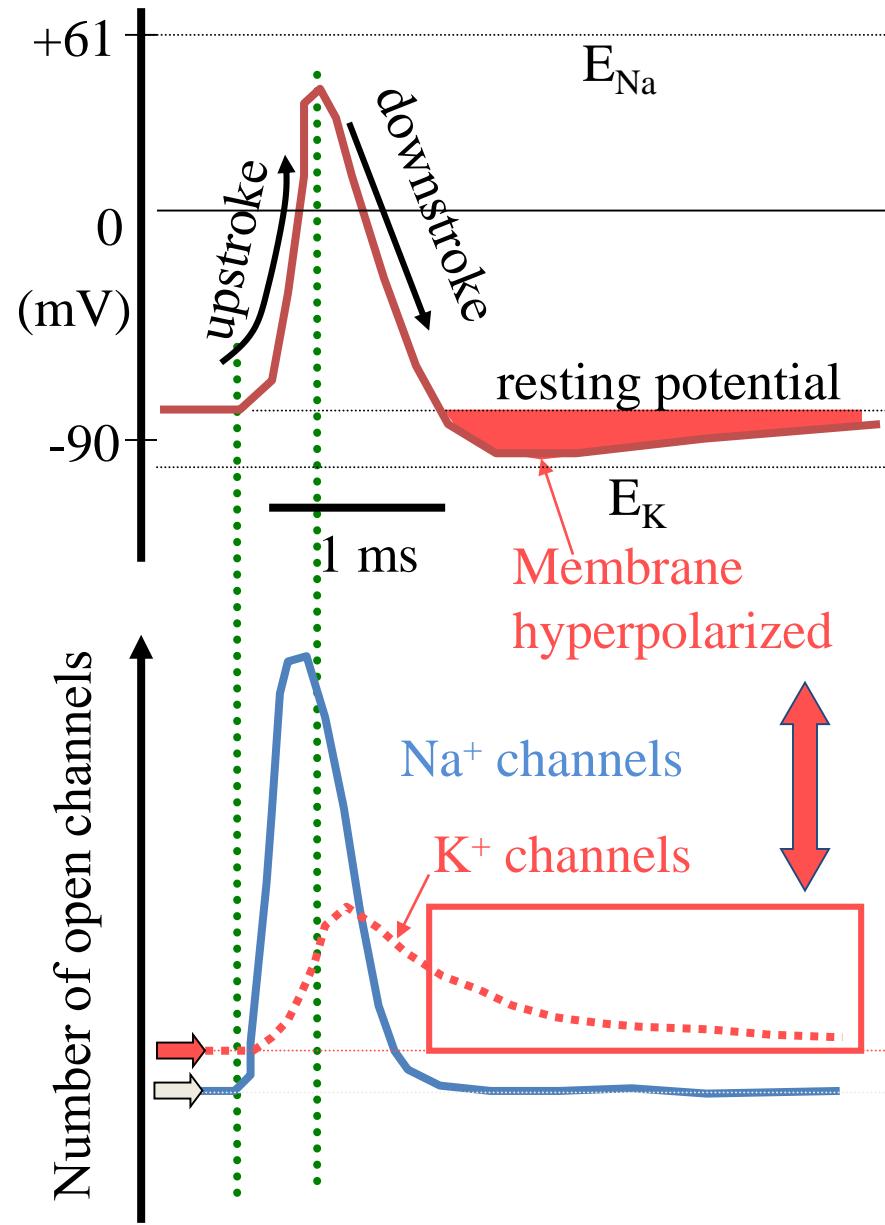
Properties of action potentials

- Action potentials:
 - are all-or-none events
 - threshold voltage (usually 15 mV positive to resting potential)
 - are initiated by depolarization
 - action potentials can be induced in nerve and muscle by extrinsic (percutaneous) stimulation
 - have constant amplitude
 - APs do not summate - information is coded by frequency not amplitude.
 - have constant conduction velocity
 - True for given fiber. Fibers with large diameter conduct faster than small fibers.



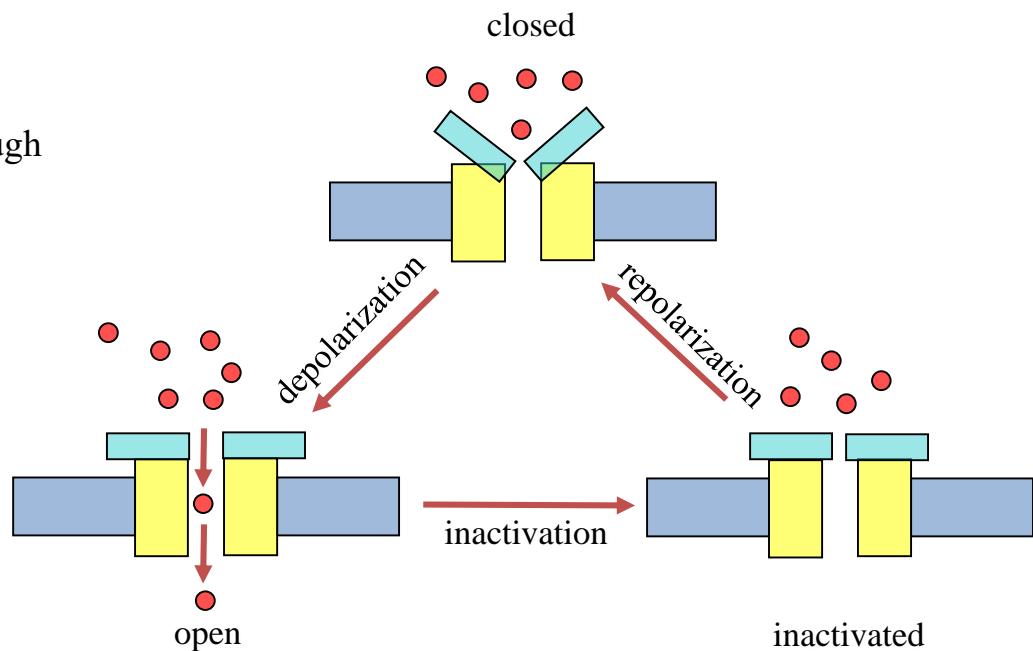
■ The AP - membrane permeability

- During the upstroke of an action potential:
 - Na permeability increases
 - due to opening of Na^+ channels
 - memb. potential approaches E_{Na}
- During the downstroke of an action potential:
 - Na permeability decreases
 - due to inactivation of Na^+ channels
 - K permeability increases
 - due to opening of K^+ channels
 - mem. potential approaches E_K
- After hyperpolarization of membrane following an action potential:
 - not always seen!
 - There is increased K^+ conductance
 - due to delayed closure of K^+ channels



➤ Ion channels

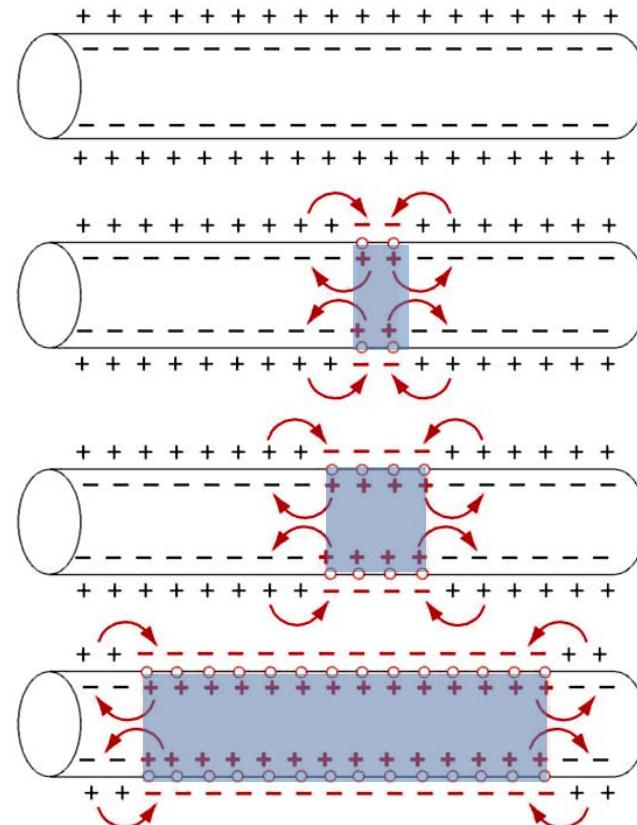
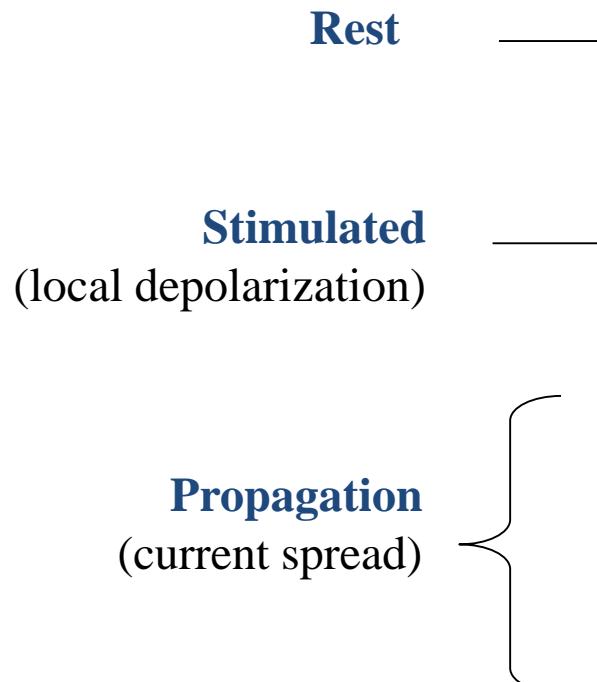
- Ion channels - structure
 - proteins that span the membrane
 - have water filled channel that runs through protein
- Ion channel - properties
 - Have conducting states and non-conducting states
 - transition between states = ‘gating’



- channels ‘gate’ in response to:
 - changes in membrane potential (usually depolarization)
 - voltage-gated channels. Action potential propagation relies on voltage-gated channels
 - occupation of receptor
 - ligand-gated or receptor operated channels (ROCs). These initiate action potentials

■ Propagation:

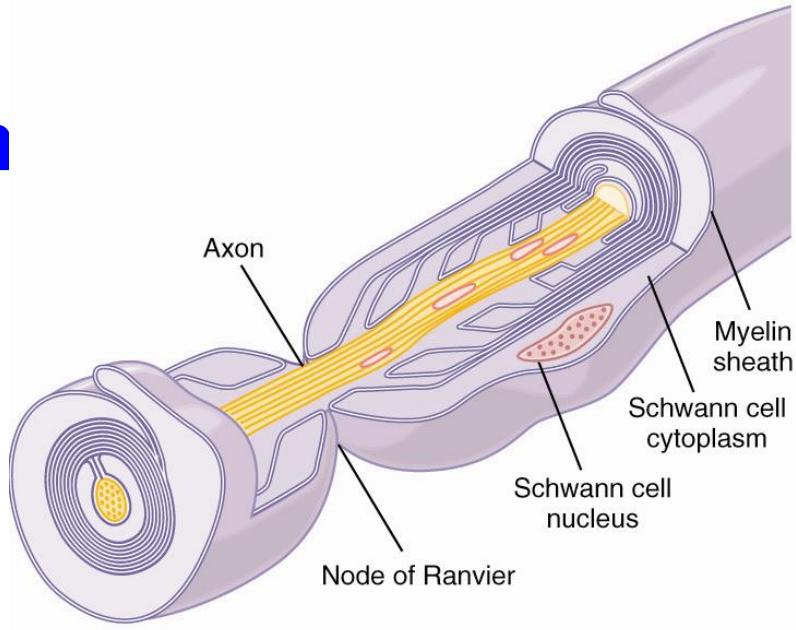
Opening of Na^+ channels generates local current circuit that depolarizes adjacent membrane, opening more Na^+ channels...



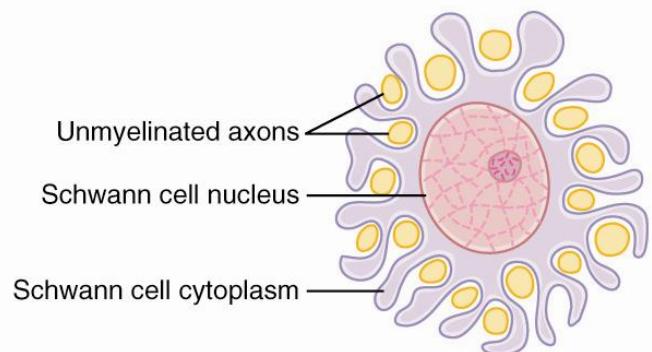
■ Signal Transmission

Myelination

- Schwann cells surround the nerve axon forming a myelin sheath
- Sphingomyelin decreases membrane capacitance and ion flow 5,000-fold
- Sheath is interrupted every 1-3 mm : **node of Ranvier**



A



B

Figure 5–16

Function of the Schwann cell to insulate nerve fibers. A, Wrapping of a Schwann cell membrane around a large axon to form the myelin sheath of the myelinated nerve fiber. B, Partial wrapping of the membrane and cytoplasm of a Schwann cell around multiple unmyelinated nerve fibers (shown in cross section). (A, Modified from Leeson TS, Leeson R: Histology. Philadelphia: WB Saunders, 1979.)

■ Saltatory Conduction

- AP's only occur at the nodes (*Na channels concentrated here!*)
- increased velocity
- energy conservation

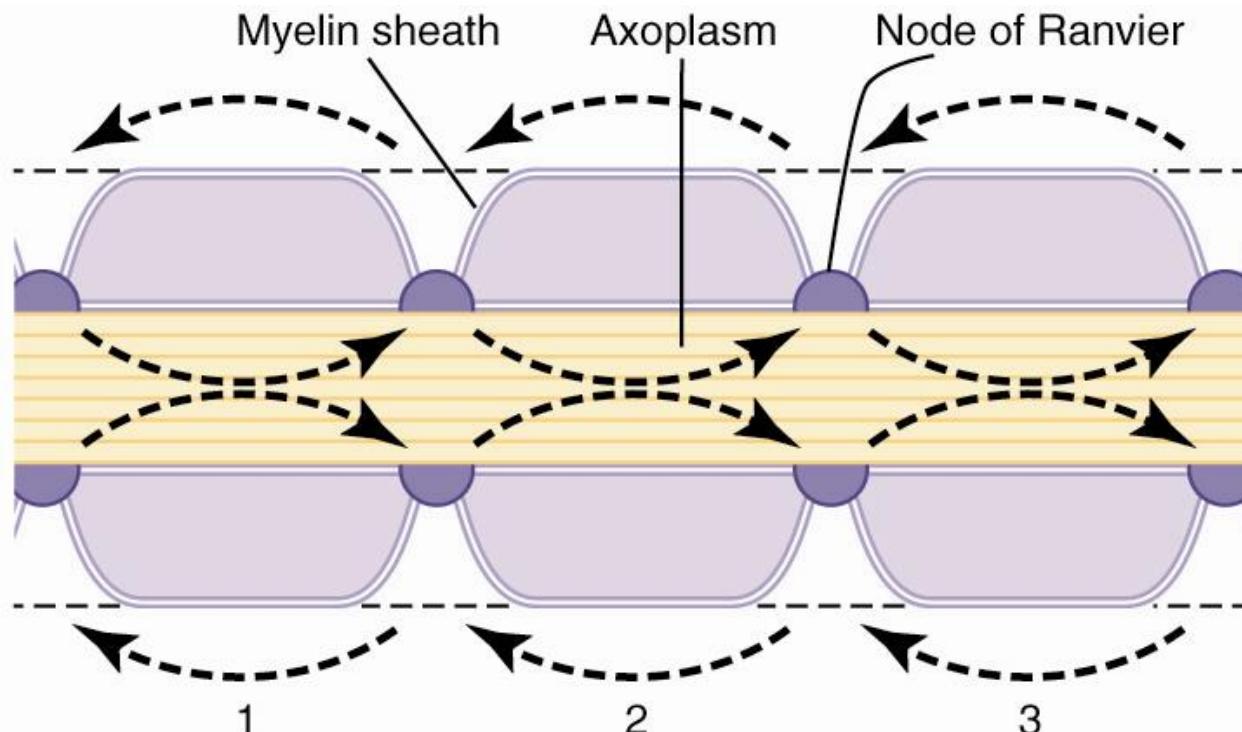
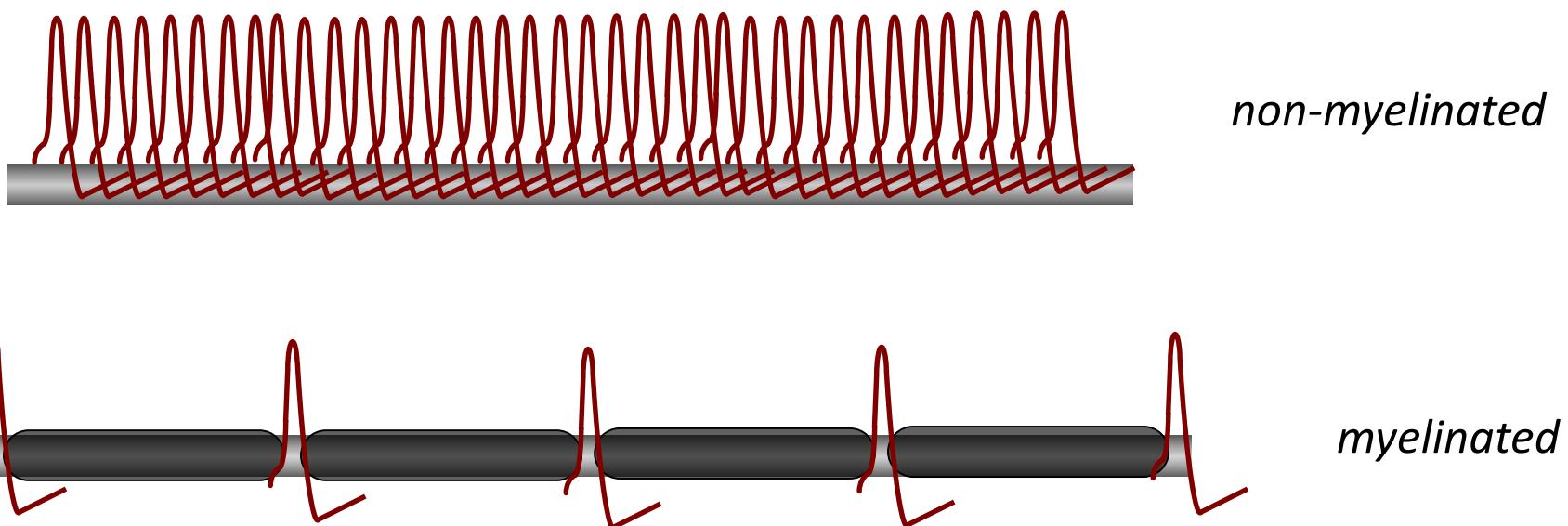


Figure 5-17; Saltatory conduction along a myelinated axon. Flow of electrical current from node to node is illustrated by the arrows.

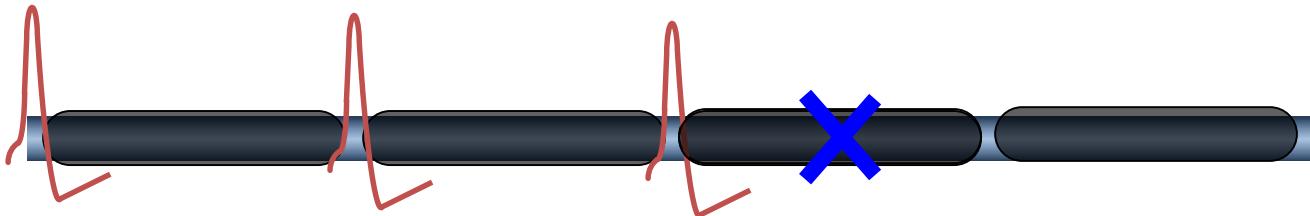
■ Conduction velocity

- *non-myelinated vs myelinated* -



- The velocity of conduction in nerve fibers varies from as little as 0.25 m/sec in very small unmyelinated fibers to as great as 100 m/ sec (the length of a football field in 1 second) in very large myelinated fibers.

Multiple Sclerosis



- MS is an immune-mediated inflammatory **demyelinating** disease of the CNS -

- About **1 person per 1000** in US is thought to have the disease - The female-to-male ratio is 2:1 - whites of northern European descent have the highest incidence

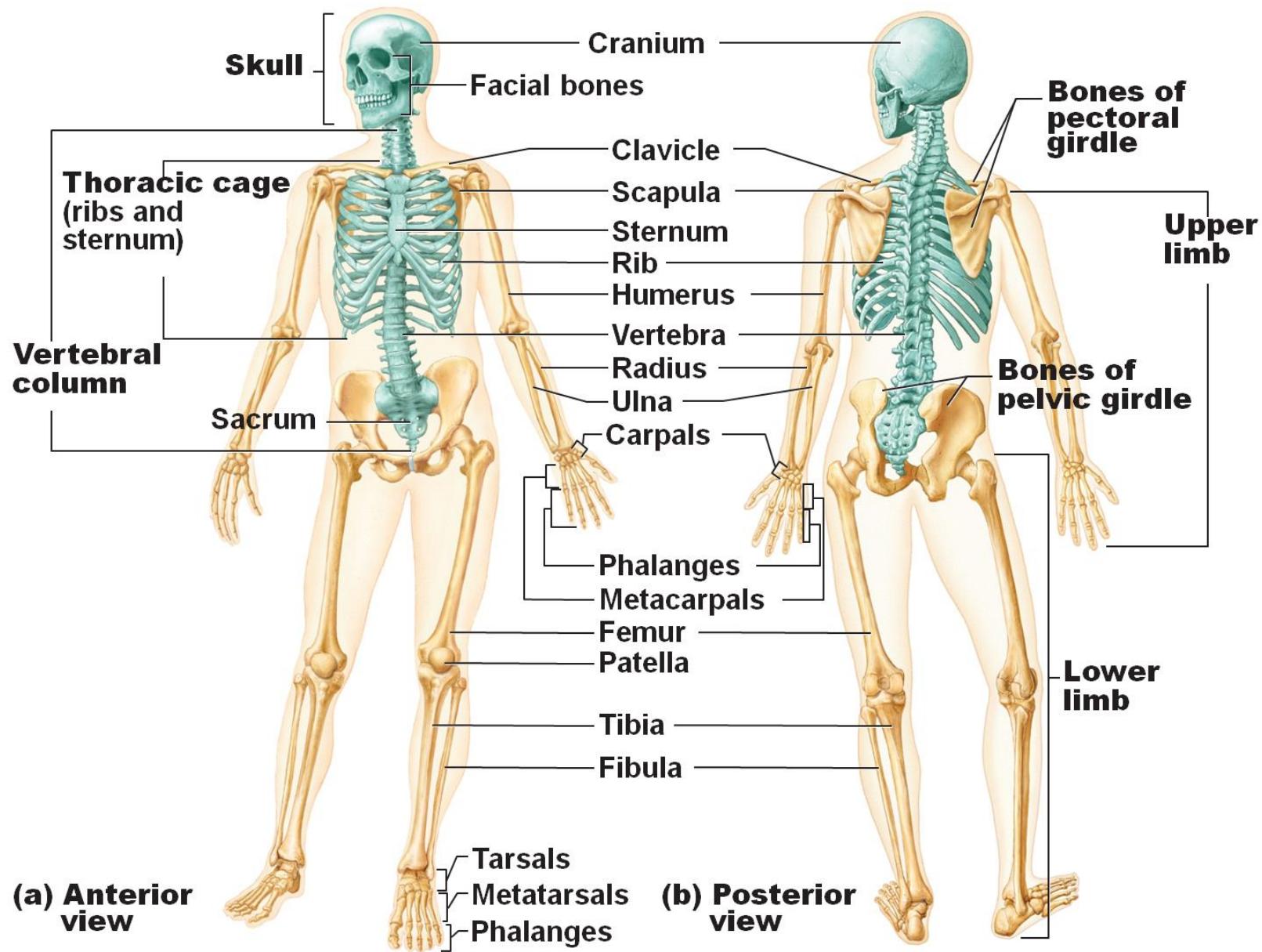
Patients have a difficult time describing their symptoms. Patients may present with paresthesias of a hand that resolves, followed in a couple of months by weakness in a leg or visual disturbances. Patients frequently do not bring these complaints to their doctors because they resolve. Eventually, the resolution of the neurologic deficits is incomplete or their occurrence is too frequent, and the diagnostic dilemma begins.



Chapter 6-7:

- Contraction of Skeletal Muscle
- Excitation of Skeletal Muscle: Neuromuscular Transmission and Excitation-Contraction Coupling

major bones in your body



- In clinical practice, directional terms are used to describe the **relative positions of various parts of the body**.

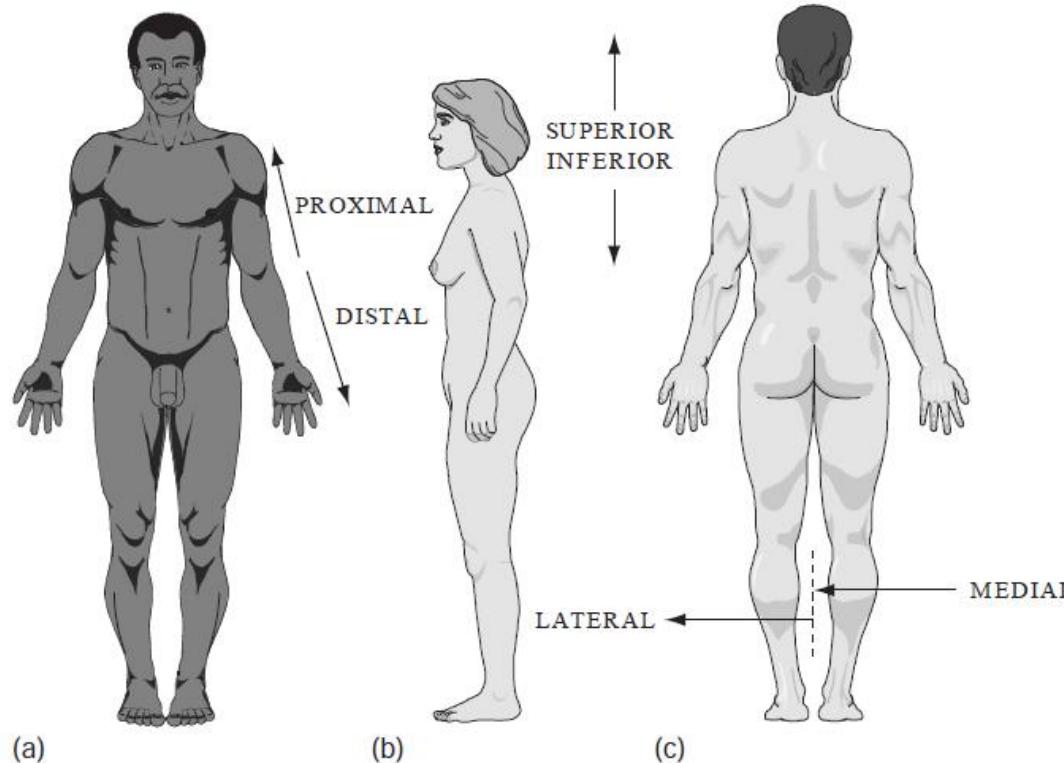


FIGURE 3.1 (a) Anterior view of male body in anatomical position. (b) Lateral view of female body. (c) Posterior view of male body in anatomical position. Relative directions (proximal and distal, superior and inferior, and medial and lateral) are also shown.

- Proximal parts** are nearer to the trunk of the body or to the attached end of a limb than are **distal parts** (Figure 3.1a).
- Parts of the body that are located closer to the head than other parts when the body is in anatomical position are said to be **superior** (Figure 3.1b), whereas those located closer to the feet than other parts are termed **inferior**.
- Medial** implies that a part is toward the midline of the body, whereas **lateral** means away from the midline (Figure 3.1c).

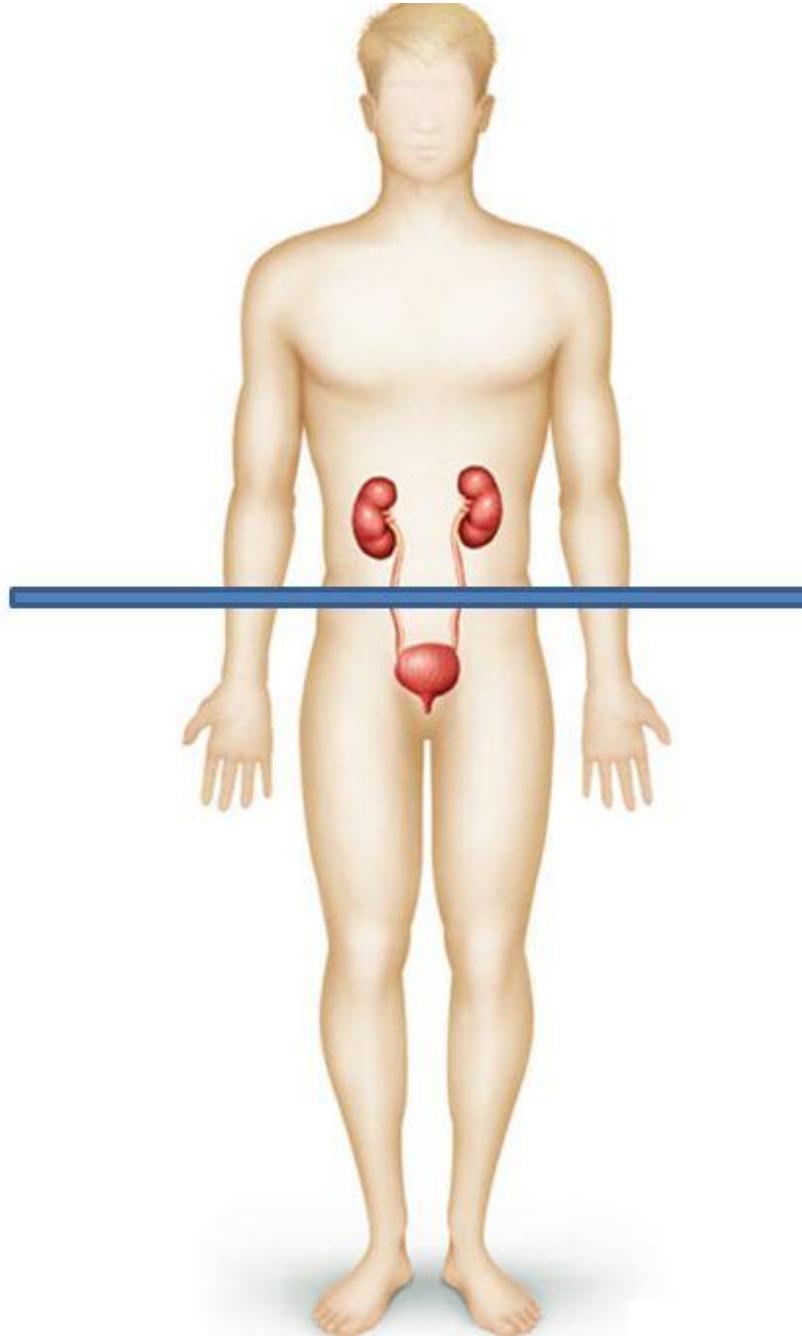
Superior vs. Inferior

Superior: Top. Or part that is above another part; closer to the head

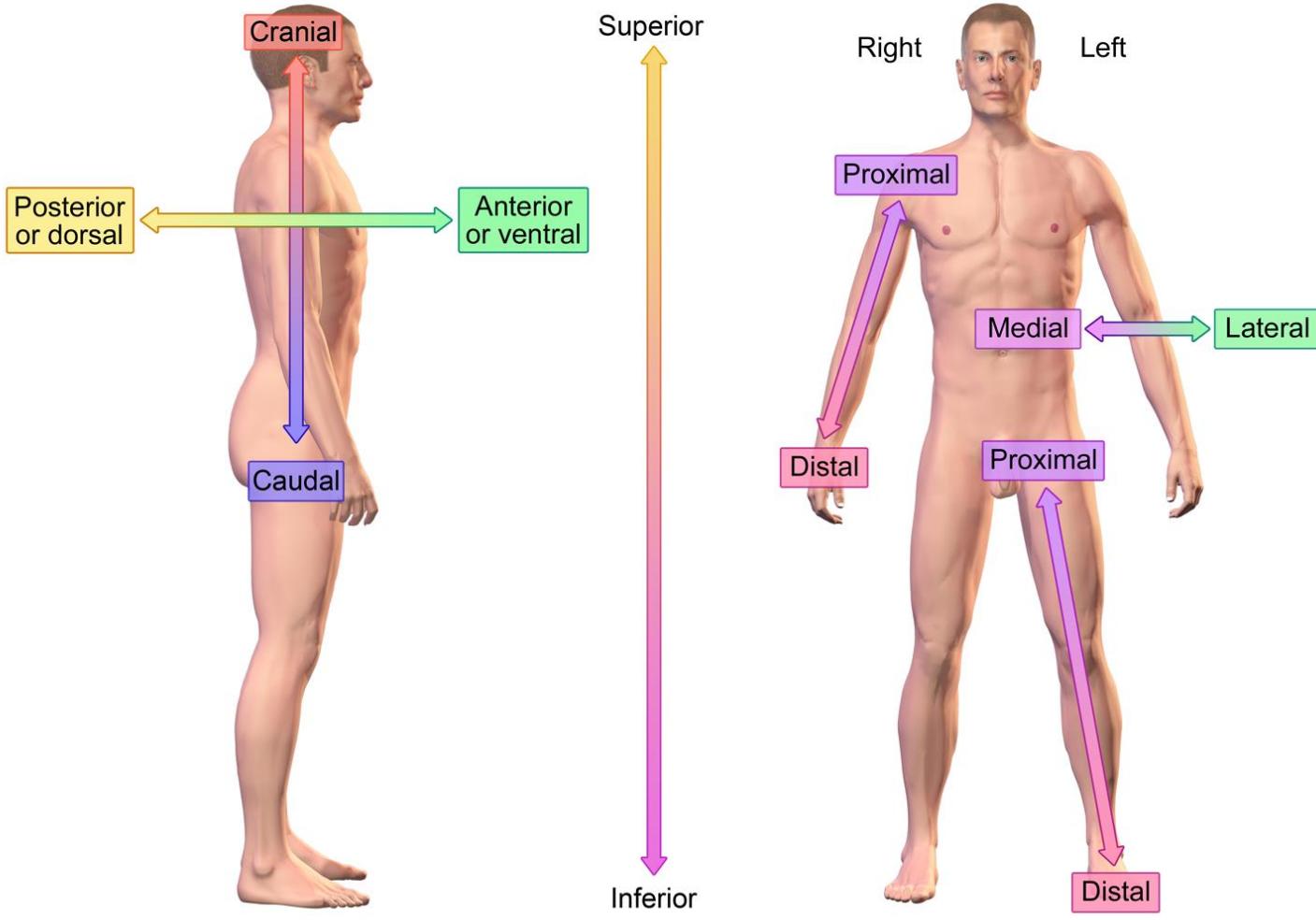
Ex: The Kidneys are **superior** to the bladder

Inferior: Bottom. Or part that is below another part; toward the feet

Ex: The bladder is **inferior** to the kidneys



Urinary system

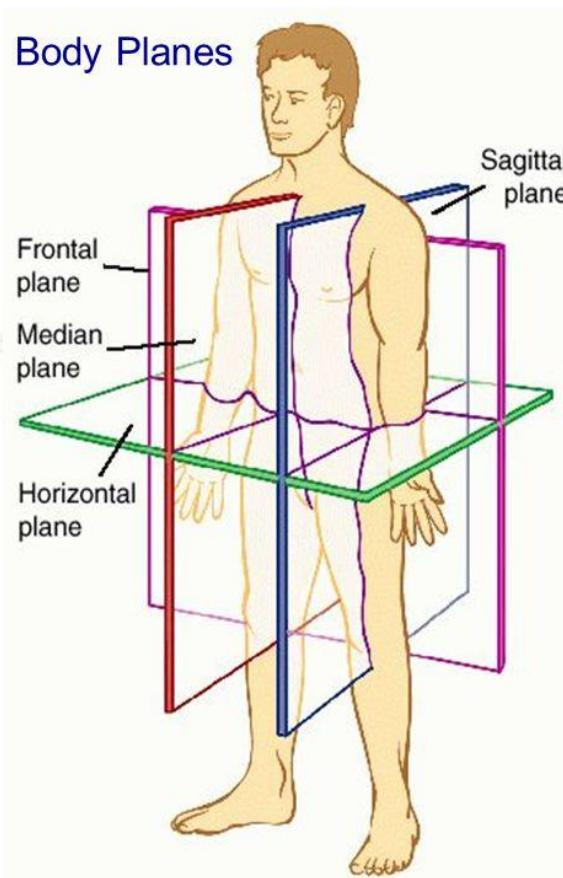
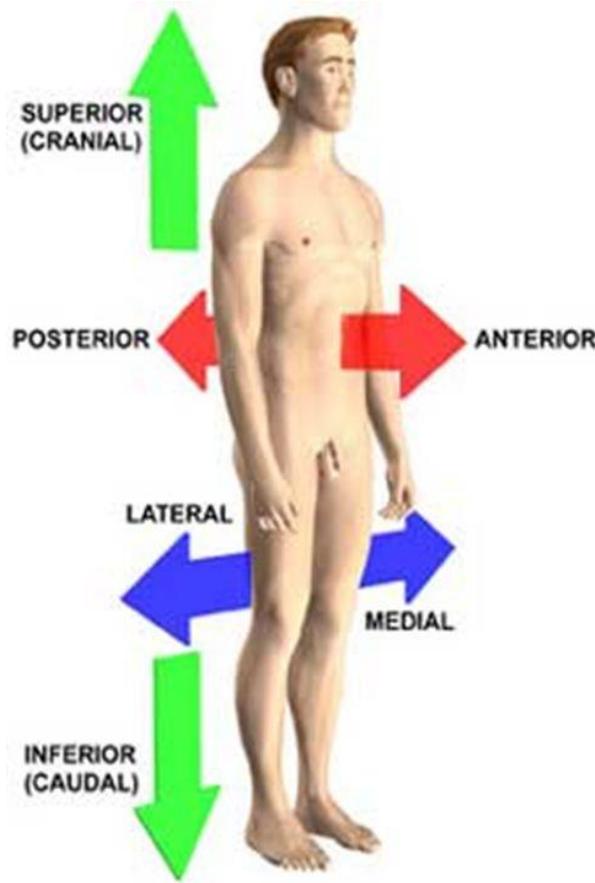


Lateral view

Anterior view

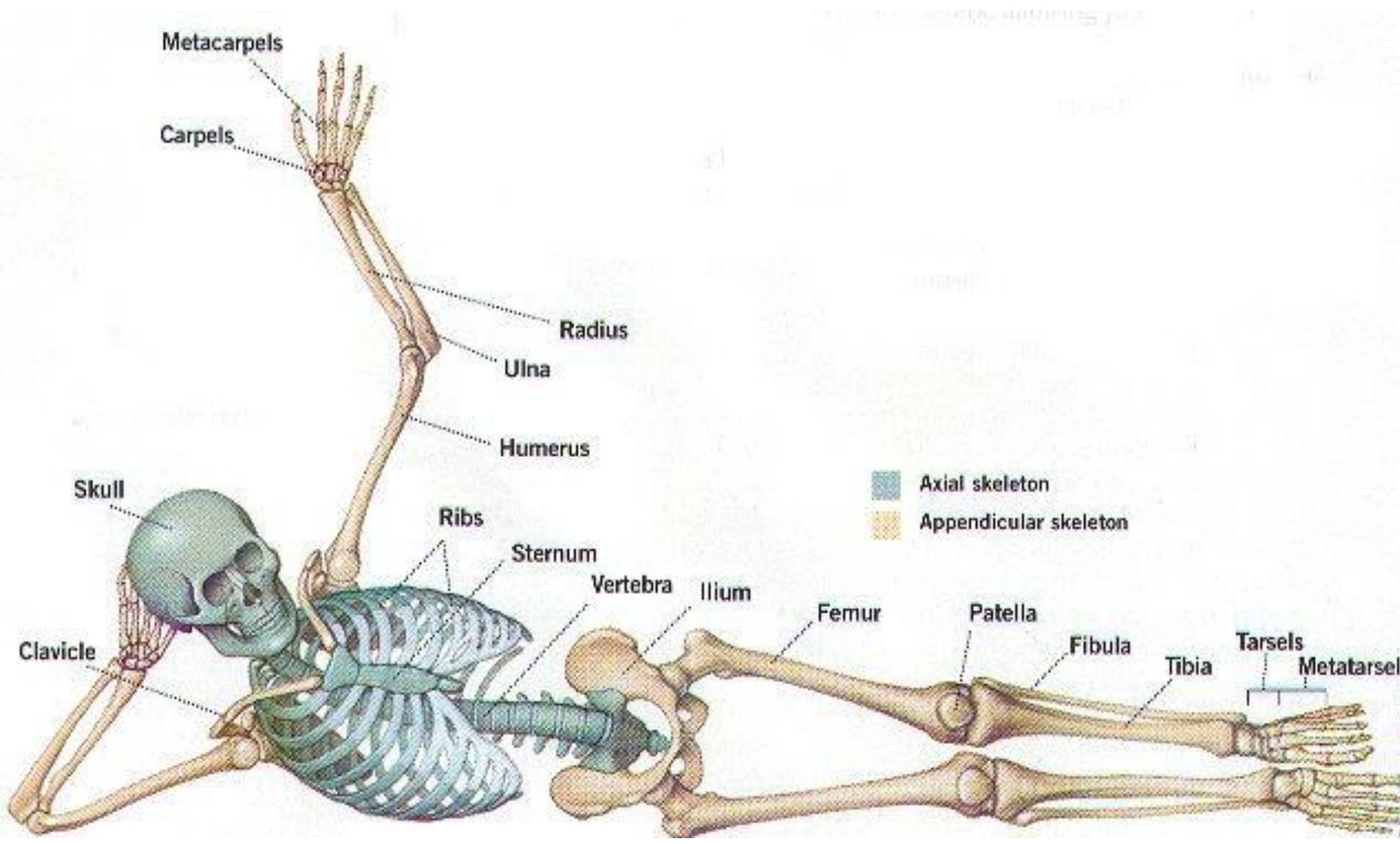
- Parts of the body that lie in the direction of the head are said to be in the **cranial direction**, whereas those parts that lie in the direction of the feet are said to be in the **caudal direction**

- Anatomical locations can also be described in terms of planes.



- The plane that divides the body into two symmetric halves along its midline is called the **midsaggital plane**
- Planes that are parallel to the midsaggital plane but do not divide the body into symmetric halves are called **sagittal planes**.
- The frontal plane** is perpendicular to the midsaggital plane and divides the body into asymmetric anterior and posterior portions.
- Planes that cut across the body and are perpendicular to the midsaggital and frontal planes are called **transverse planes**.

- Human bodies are divided into two main regions: **axial and appendicular**.
- The **axial part** consists of the head, neck, thorax (chest), abdomen, and pelvis
- The **appendicular part** consists of the upper and lower extremities.



“Walk-Along” Theory

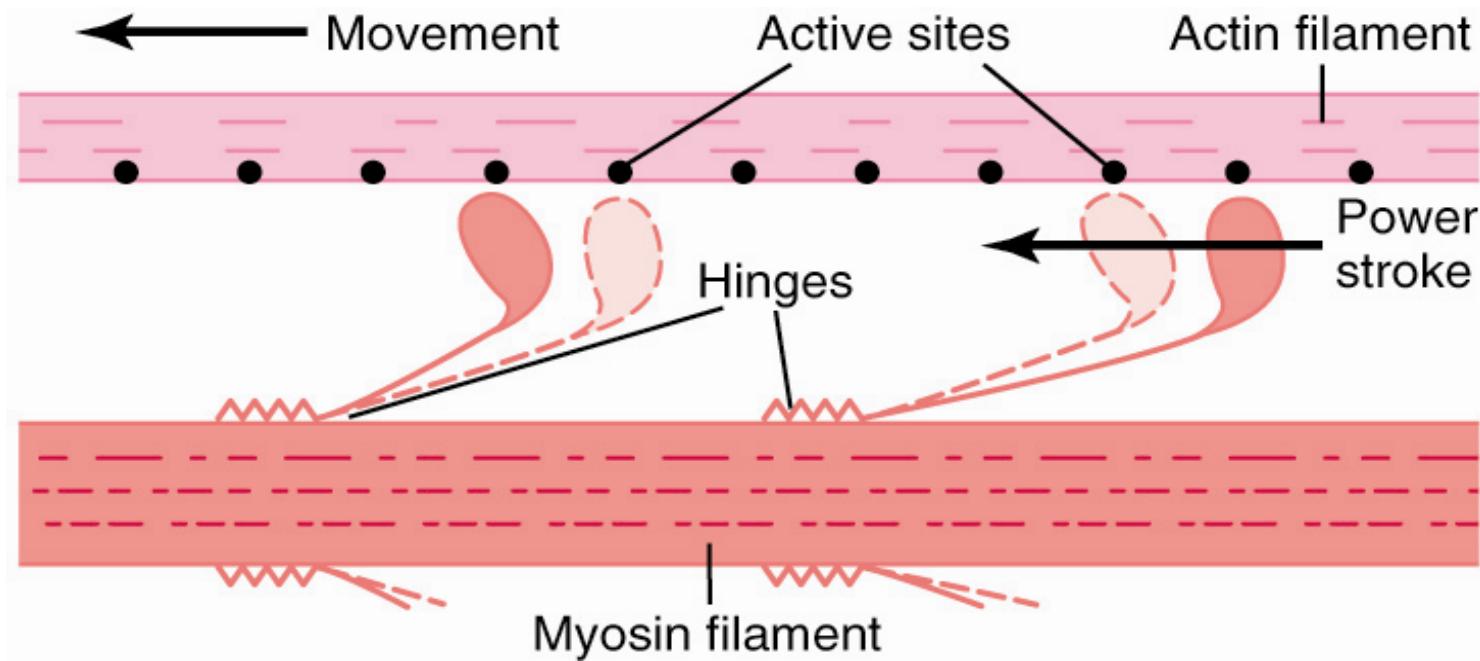


Figure 6-7; “Walk-along” mechanism for contraction of the muscle

Physiologic Anatomy of Skeletal Muscle

Gross organization:

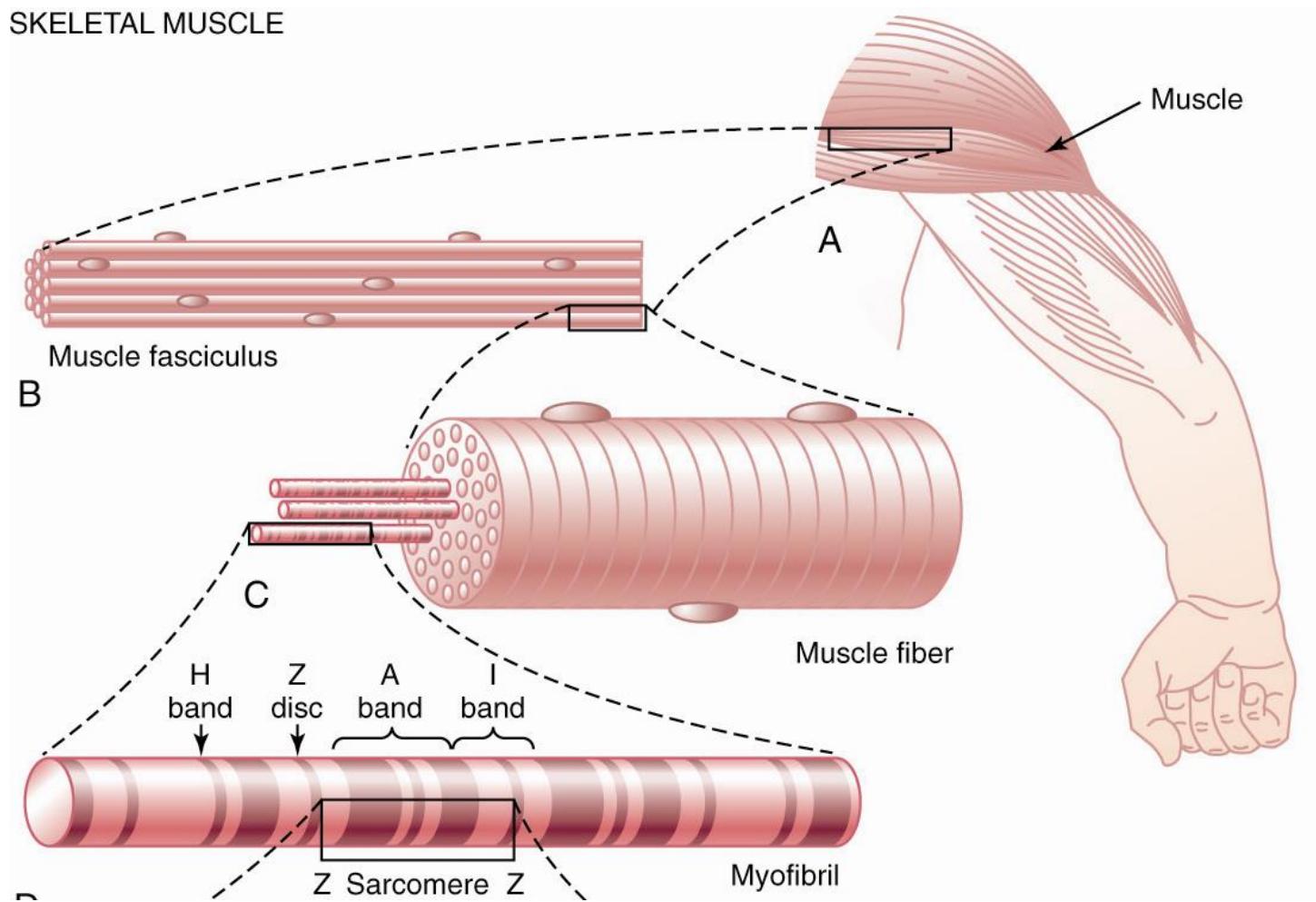


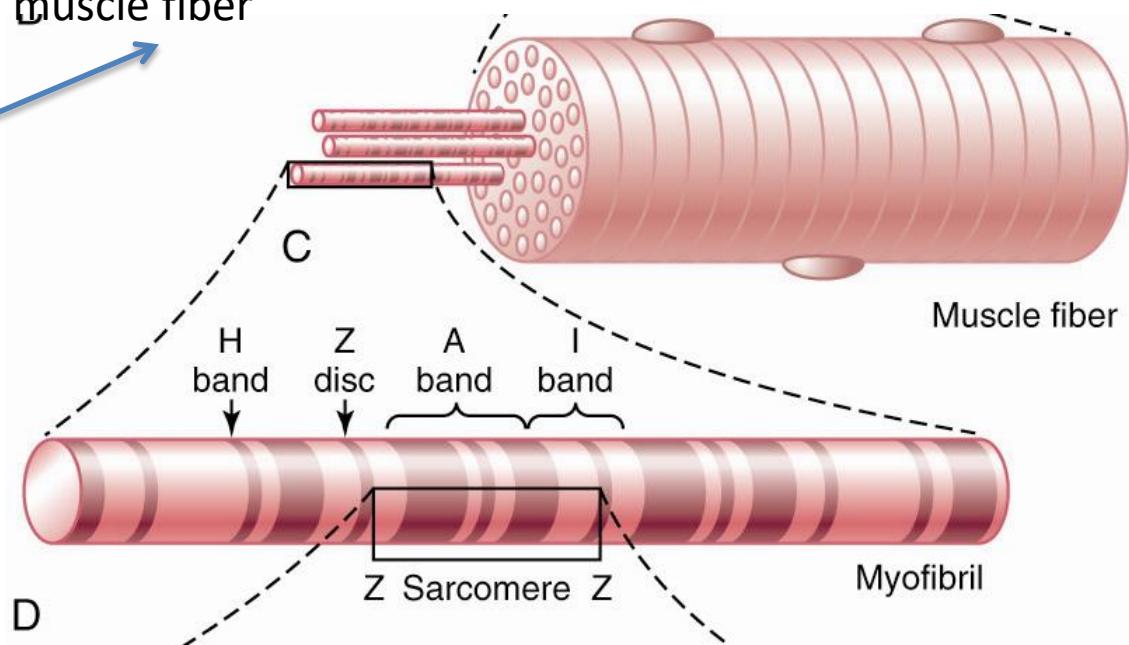
Figure 6-1; Organization of skeletal muscle, from the gross to the molecular level.

■ Cellular Organization

Muscle fibers

- single cells
- multinucleated
- surrounded by the sarcolemma

The sarcolemma is the cell membrane of the muscle fiber



Myofibrils

- contractile elements
- surrounded by the sarcoplasm

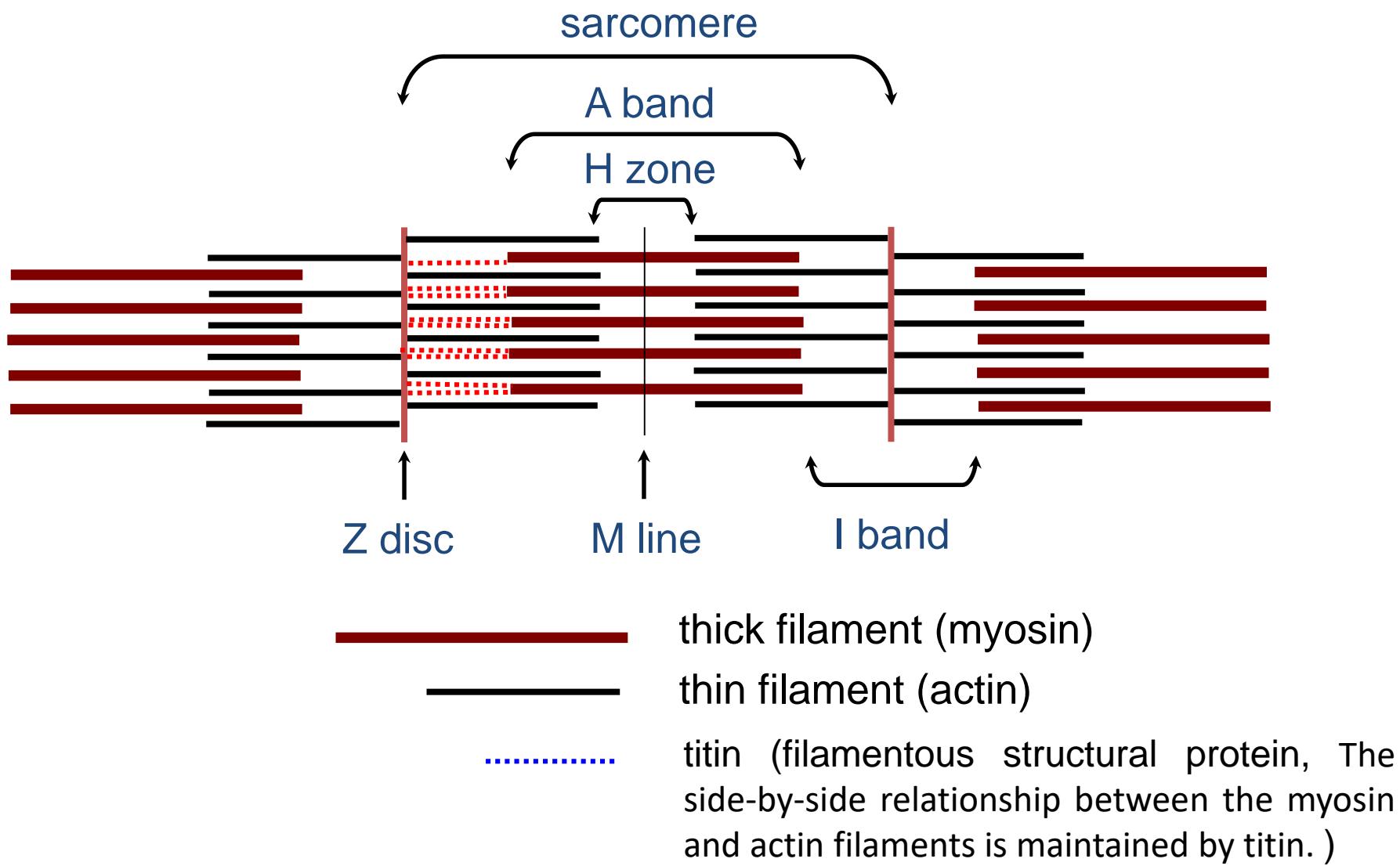
Cellular organelles - lie between myofibrils (mitochondria, sarcoplasmic reticulum etc.)

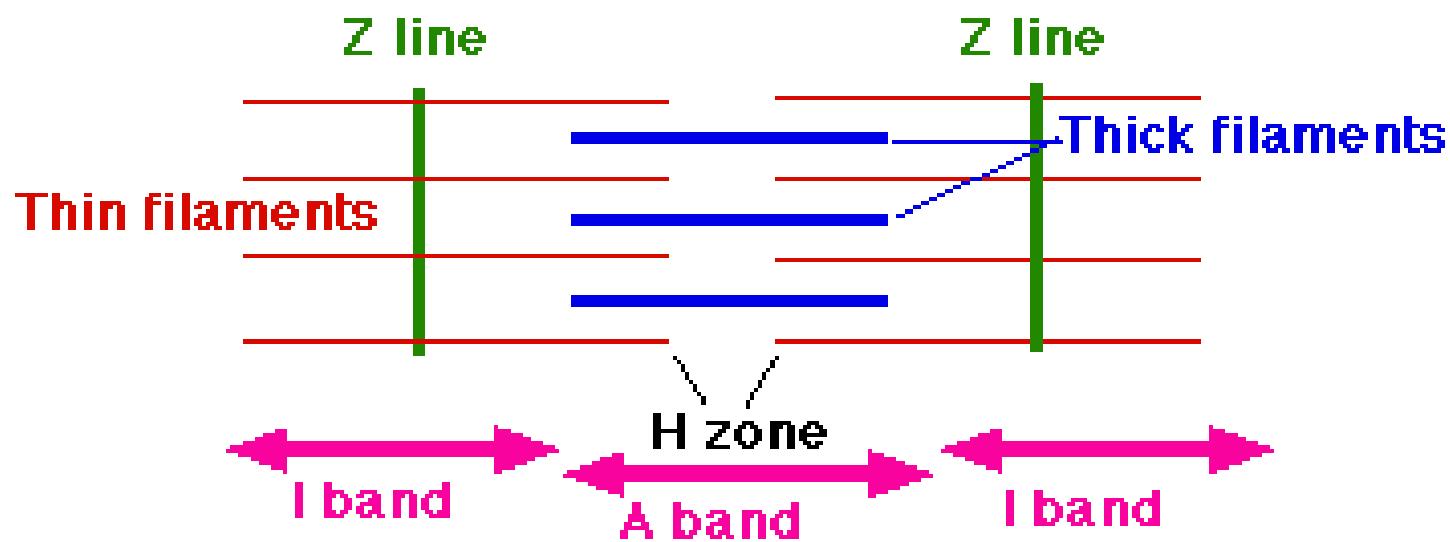
Figure 6-1; Organization of skeletal muscle, from the gross to the molecular level.

Sarcoplasm. The many myofibrils of each muscle fiber are suspended side by side in the muscle fiber. The spaces between the myofibrils are filled with intracellular fluid called sarcoplasm, containing large quantities of potassium, magnesium, and phosphate, plus multiple protein enzymes. Also present are tremendous numbers of mitochondria that lie parallel to the myofibrils. These supply the contracting myofibrils with large amounts of energy in the form of adenosine triphosphate (ATP) formed by the mitochondria.

The Sarcomere

- The portion of the myofibril (or of the whole muscle fiber) that lies between two successive Z discs is called a sarcomere.





Molecular Mechanism of Muscle Contraction

▪ Molecular Characteristics of the Contractile Filaments

➤ The Myosin Molecule:

- two **heavy chains** (MW 200,000)
- four **light chains** (MW 20,000)
- “head” region - site of **ATPase** activity

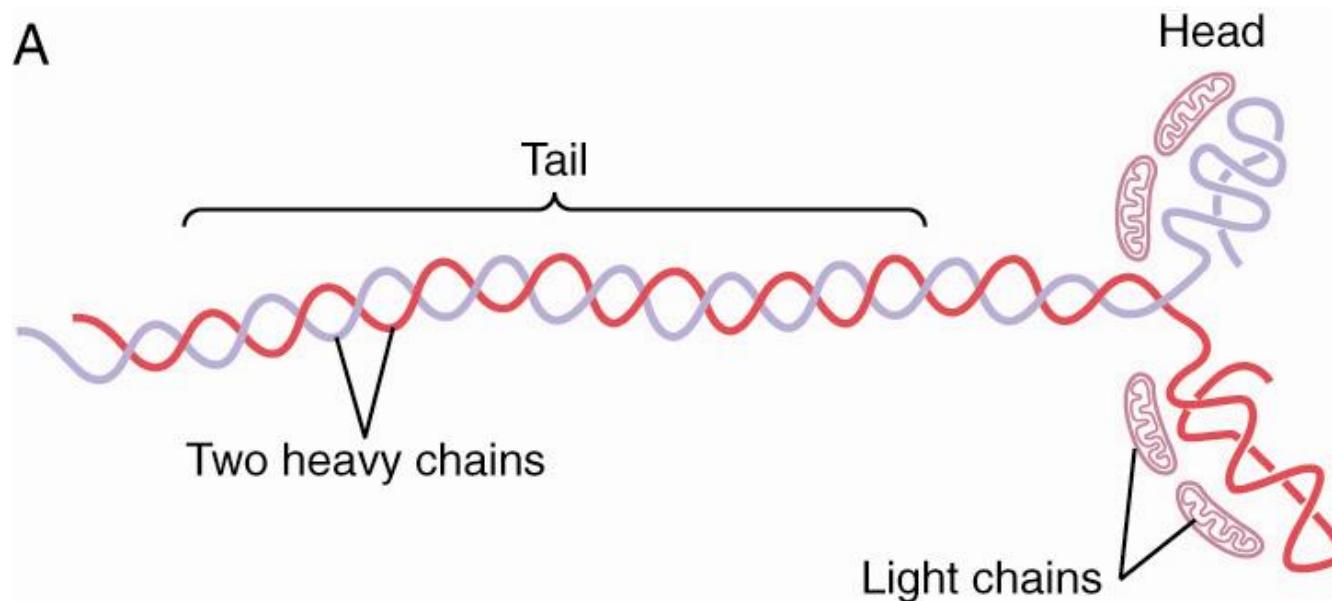


Figure 6-5: Myosin molecule

➤ The Actin Filament

- the I band filament
- tethered at one end at the Z disc
- 1 μm long

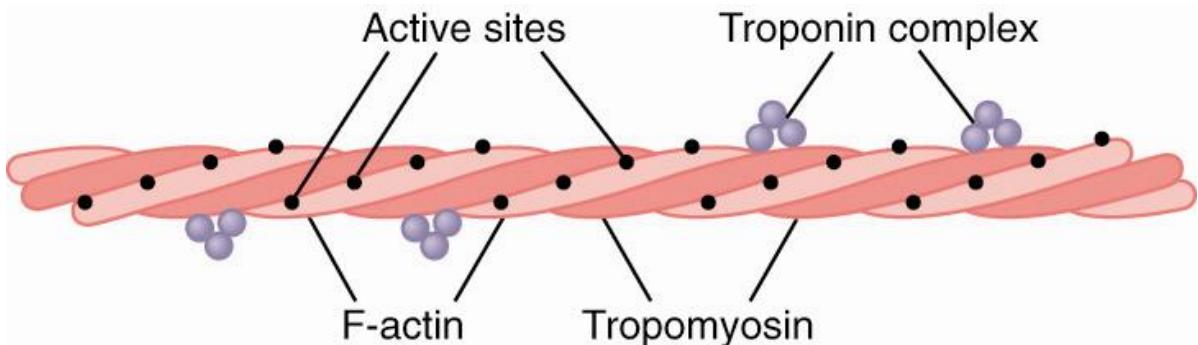


Figure 6-6; Actin filament, composed of two helical strands of F-actin molecules and two strands of tropomyosin molecules that fit in the grooves between the actin strands. Attached to one end of each tropomyosin molecule is a troponin complex that initiates contraction.

F-actin

- double-stranded helix
- composed of polymerized G-actin
- ADP bound to each G-actin (active sites)
- myosin heads bind to active sites

tropomyosin

- covers active sites
- prevents interaction with myosin at rest

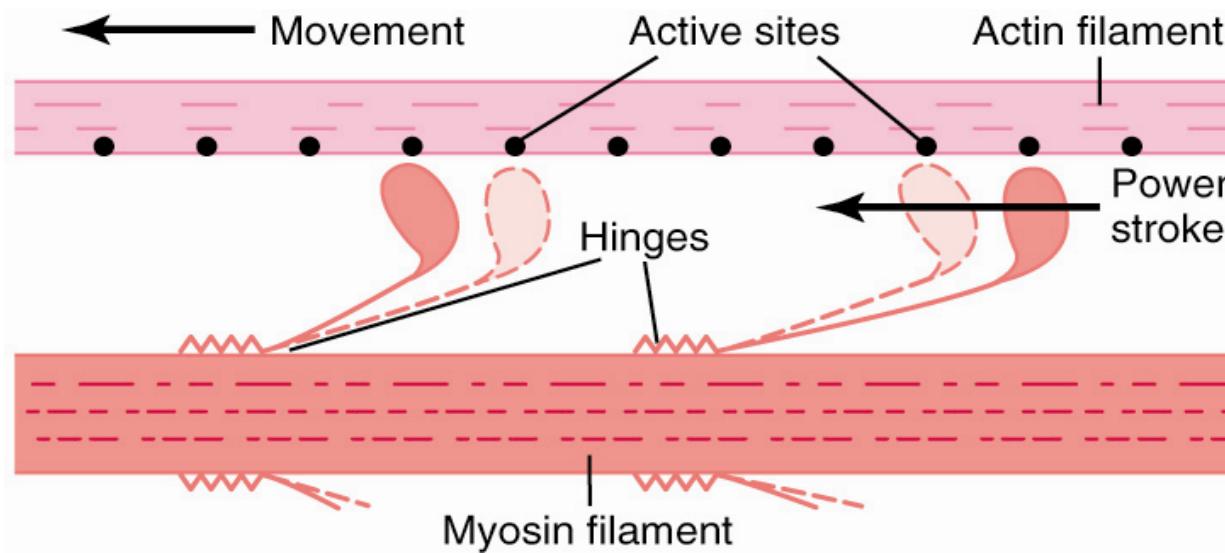
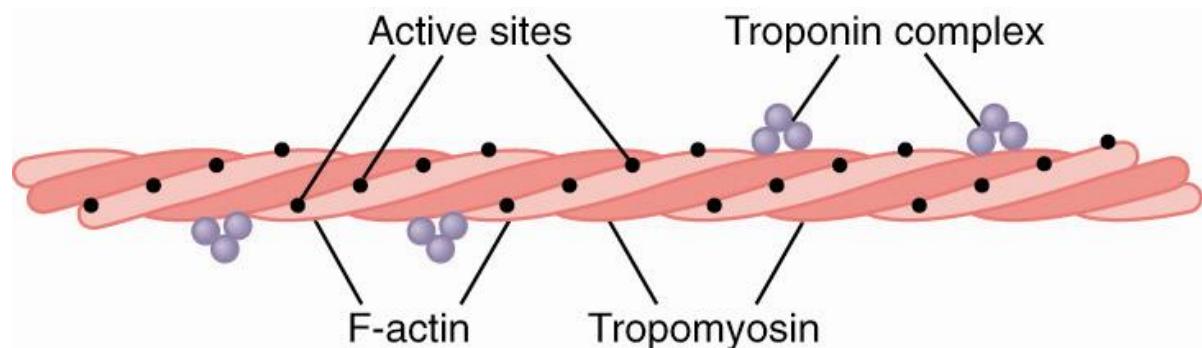
troponin

- I - binds actin
- T - binds tropomyosin
- C - binds Ca^{2+}

■ Mechanism of Muscle Contraction

Theory:

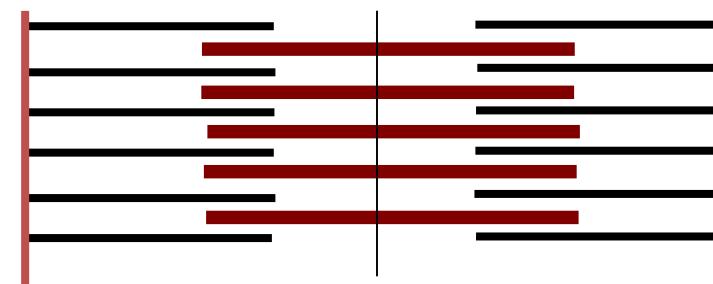
Binding of Ca^{2+} to **troponin** results in a conformational change in **tropomyosin** that “uncovers” the active sites on the actin molecule, allowing for myosin to bind.



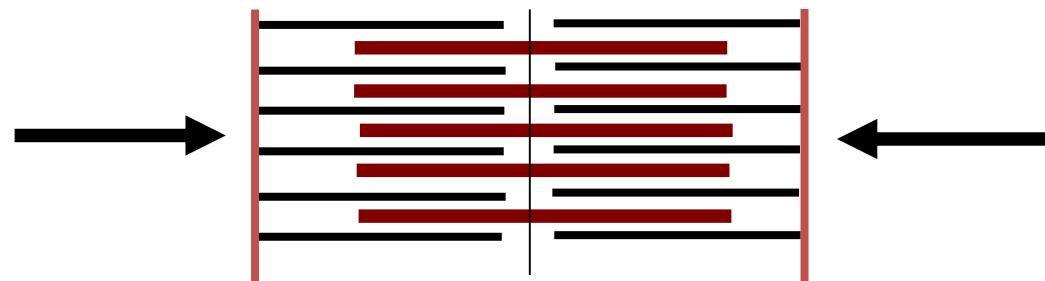
- “Sliding Filament” Mechanism

Contraction results from the sliding action of interdigitating actin and myosin filaments

RELAXED:



CONTRACTED:



Neuromuscular Transmission

- The Neuromuscular Junction -

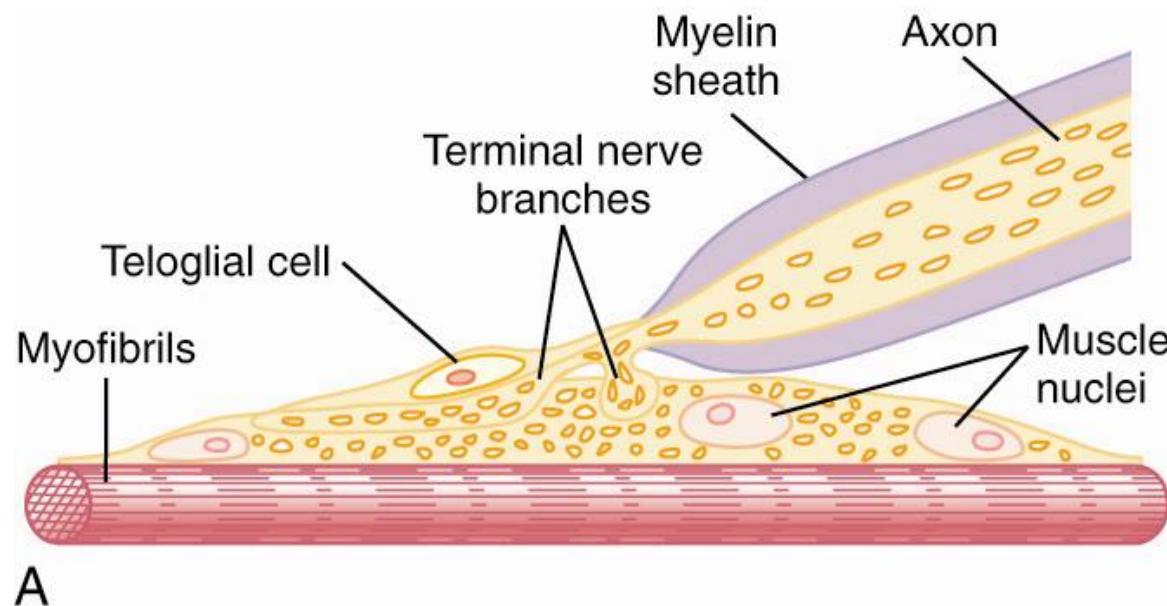
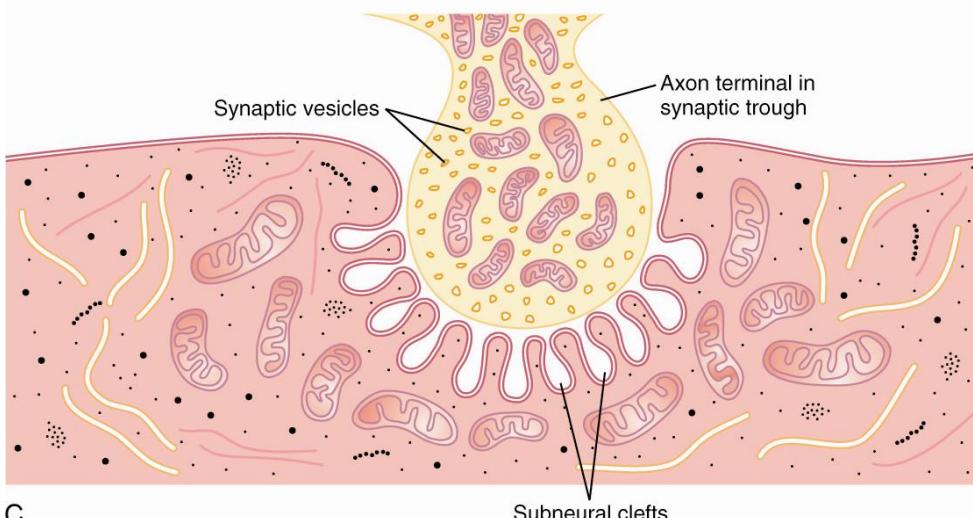


Figure 7-1; Longitudinal section through the end plate

- Specialized **synapse** between a **motoneuron** and a muscle fiber
- Occurs at a structure on the muscle fiber called the **motor end plate** (*usually only one per fiber*)

■ Neuromuscular Junction (*nmj*)

Synaptic trough: invagination in the motor endplate membrane



C

Figure 7-1: Electron micrographic appearance of the contact point between a single axon terminal and the muscle fiber membrane.

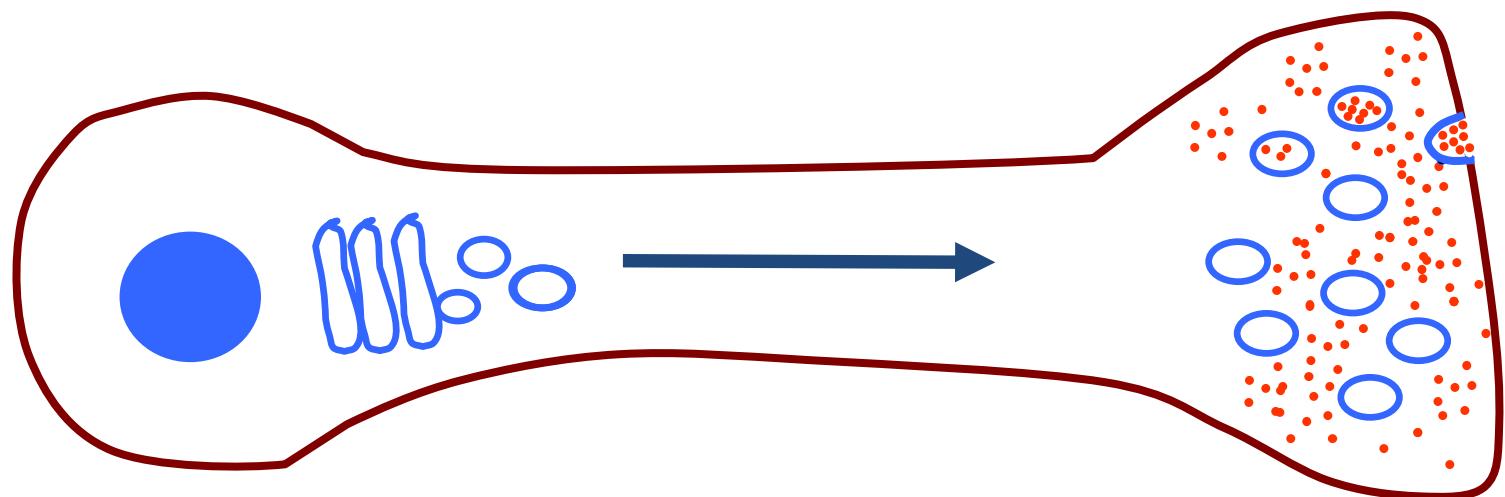
- **Synaptic cleft:**

- 20-30 nm wide
- contains large quantities of **acetylcholinesterase (AChE)**

- **Subneuronal clefts:**

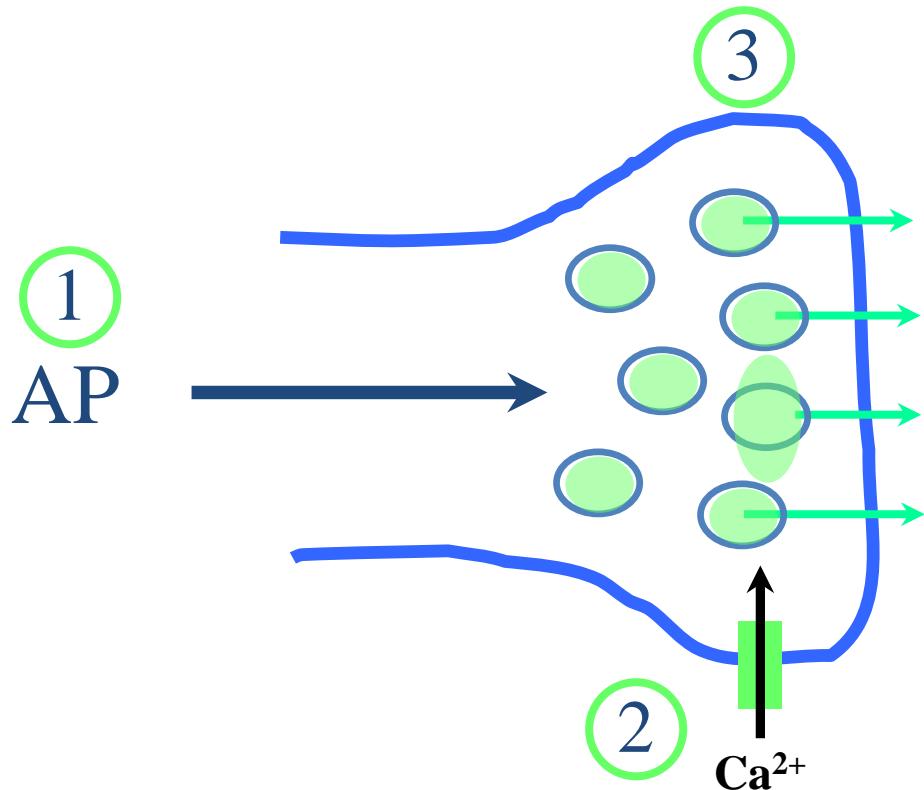
- increase the surface area of the post-synaptic membrane
- Ach gated channels at tops
- Voltage gated Na^+ channel in bottom half

■ The Motoneuron – *vesicle formation*



- **Synaptic vesicles:** are formed from budding Golgi and are transported to the terminal by axoplasm “streaming” (~300,000 per terminal)
- **Acetylcholine** (ACh) is formed in the cytoplasm and is transported into the vesicles (~10,000 per)
- Ach filled vesicles occasionally fuse with the post-synaptic membrane and release their contents. This causes **miniature end-plate potentials** in the post-synaptic membrane.

■ The Motoneuron - ACh Release



1. AP begins in the ventral horn of spinal cord.
2. Local depolarization opens voltage-gated Ca^{2+} channels.
3. An increase in cytosolic Ca^{2+} triggers the fusion of ~ 125 synaptic vesicles with the pre-synaptic membrane and release of ACh (*exocytosis*).

■ ACh Release - *details*

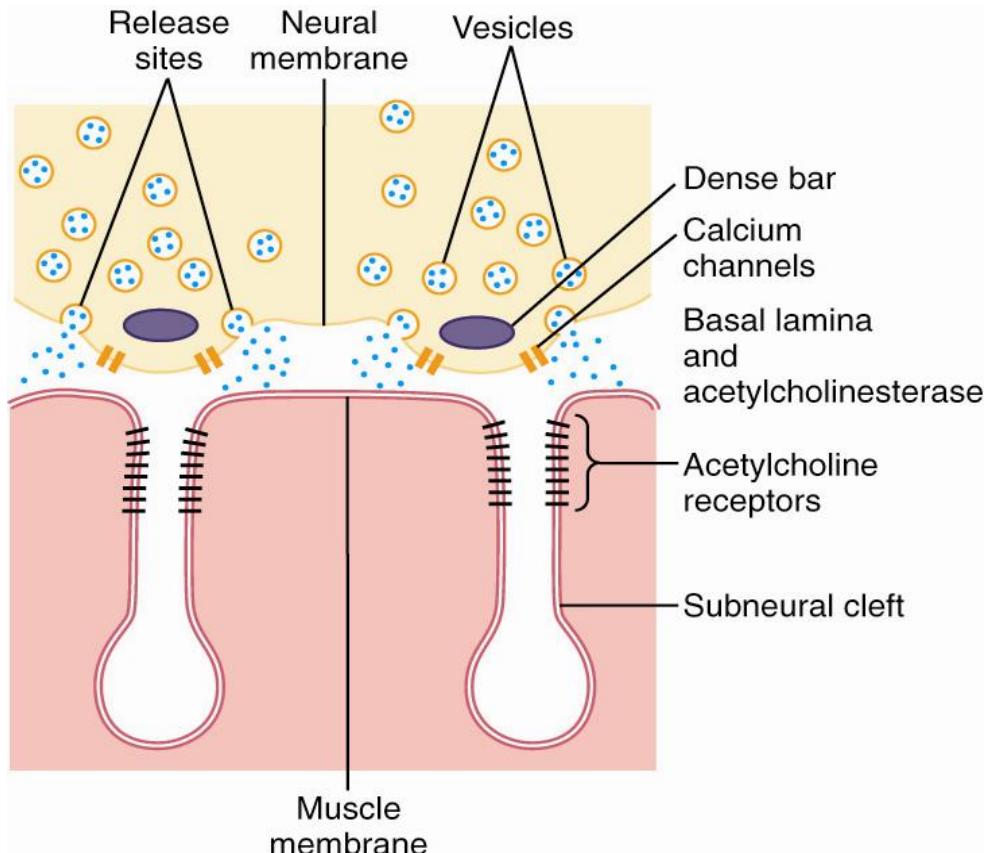


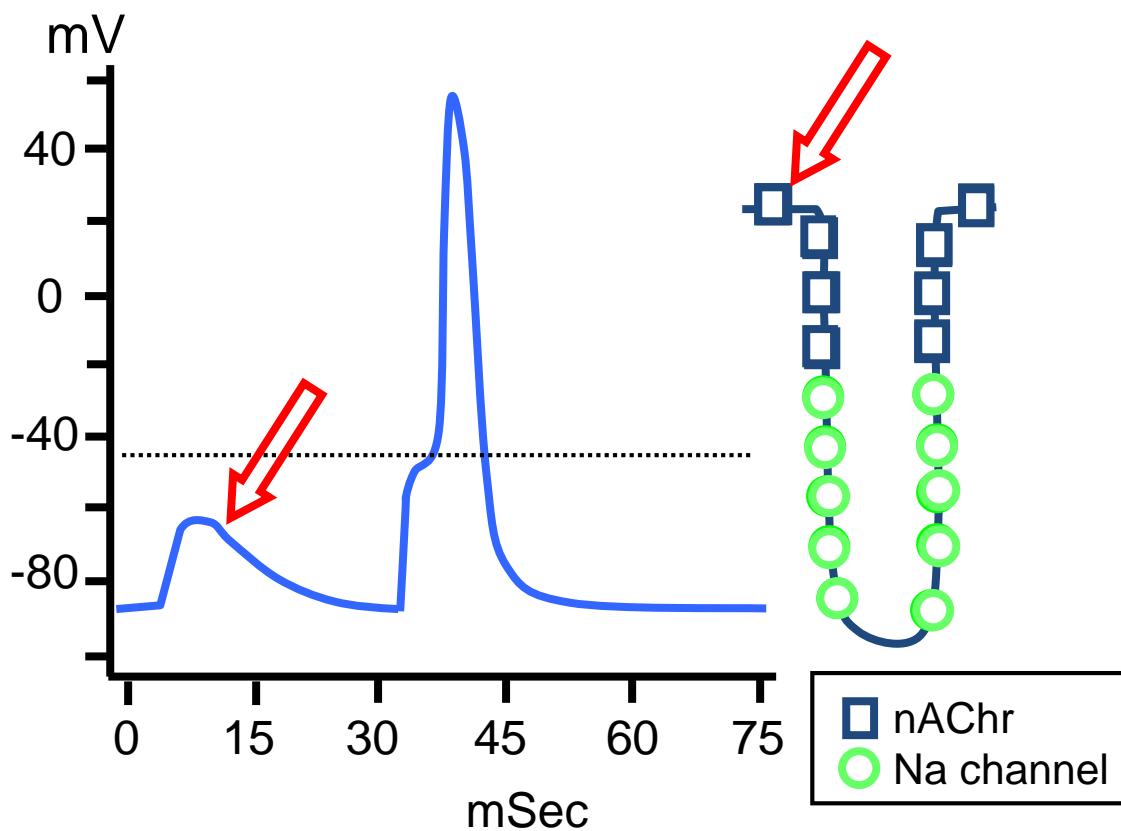
Figure 7-2; Guyton & Hall

- Ca^{2+} channels are localized around linear structures on the pre-synaptic membrane called **dense bars**.
- Vesicles fuse with the membrane in the region of the dense bars.
- Ach receptors located at top of subneuronal cleft.
- Voltage gated Na^+ channels in bottom half of subneuronal cleft.

■ End Plate Potential and Action Potential

- at the motor endplate -

- ACh released into the neuromuscular junction binds to, and opens, **nicotinic ACh receptor channels** on the muscle fiber membranes (Na^+ , K^+ , Ca^{2+}).



- Opening of nACh receptor channels produces an **end plate potential**, which will **normally** initiate an AP if the local spread of current is sufficient to open voltage sodium channels.

- *What terminates the process? acetylcholinesterase*

Drugs That Enhance or Block Transmission at the Neuromuscular Junction

Drug Effects on End Plate Potential

- Inhibitors -

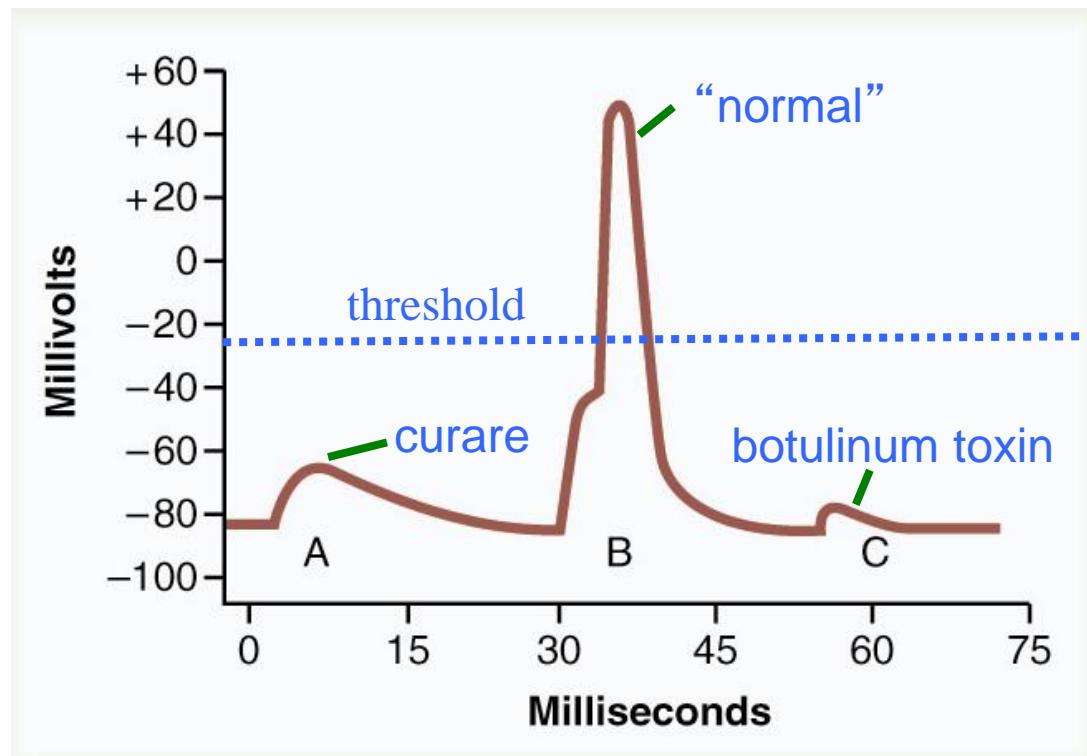


Figure 7-4; Guyton & Hall

Curariform drugs (D-turbocurarine)

- block nicotinic ACh channels by competing for ACh binding site
- reduces amplitude of end plate potential therefore, no AP

Botulinum toxin

- decreases the release of Ach from nerve terminals
- insufficient stimulus to initiate an AP

■ Drug Effects on End Plate Potential

- Stimulants -

ACh-like drugs (*methacholine, carbachol, nicotine*)

- bind and activate nicotinic ACh receptors
- not destroyed by AChE – prolonged effect

Anti-AChE (*neostigmine, physostigmine, diisopropyl fluorophosphate or “nerve gas”*)

- block the degradation of ACh
- prolong its effect

Excitation-Contraction Coupling

Transverse tubule / SR System

T-tubules:

- Invaginations of the **sarcolemma** filled with extracellular fluid
- Penetrate the muscle fiber, branch and form networks
- Transmit AP's deep into the muscle fiber

Sarcoplasmic Reticulum:

- terminal cisternae and longitudinal tubules
- **terminal cisternae** form junctional “feet” adjacent to the T-tubule membrane
- intracellular storage compartment for Ca^{2+}

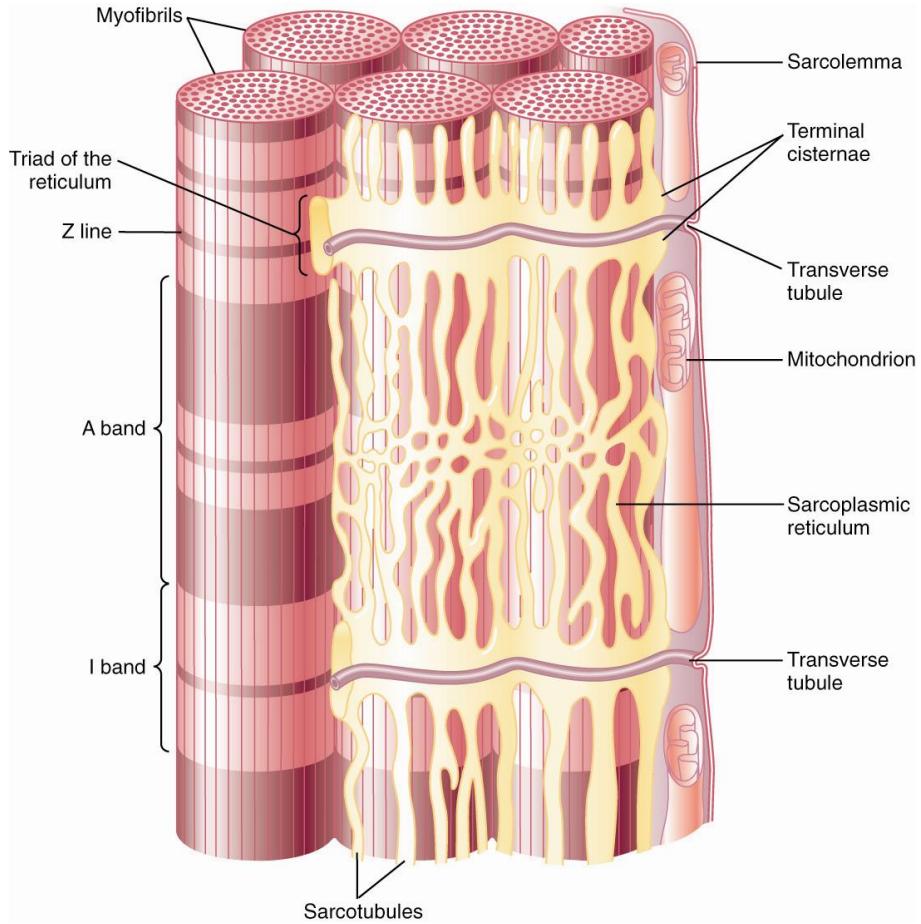


Figure 7-5; Guyton & Hall Transverse (T) tubule-sarcoplasmic reticulum system. Note that the T tubules communicate with the outside of the cell membrane, and deep in the muscle fiber, each T tubule lies adjacent to the ends of longitudinal sarcoplasmic reticulum tubules that surround all sides of the actual myofibrils that contract. This illustration was drawn from frog muscle, which has one T tubule per sarcomere, located at the Z line. A similar arrangement is found in mammalian heart muscle, but mammalian skeletal muscle has two T tubules per sarcomere, located at the A-I band junctions.

■ Arrangement of T-tubules to Myofibrils

- *Skeletal muscle vs cardiac muscle -*

Vertebrate skeletal muscle:

- Two T-tubule networks per sarcomere
- Located near the ends of the myosin filaments (zone of overlap)

Cardiac muscle (*and lower animals*):

- Single T-tubule network per sarcomere
- Located at the level of the Z disc

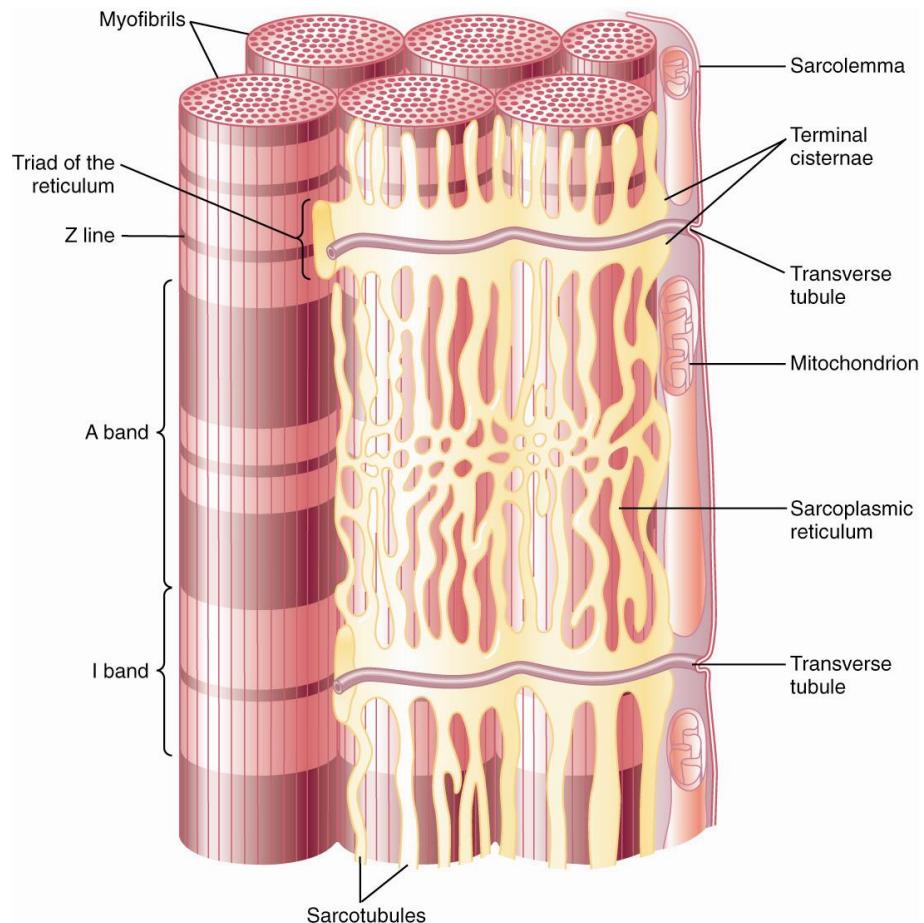
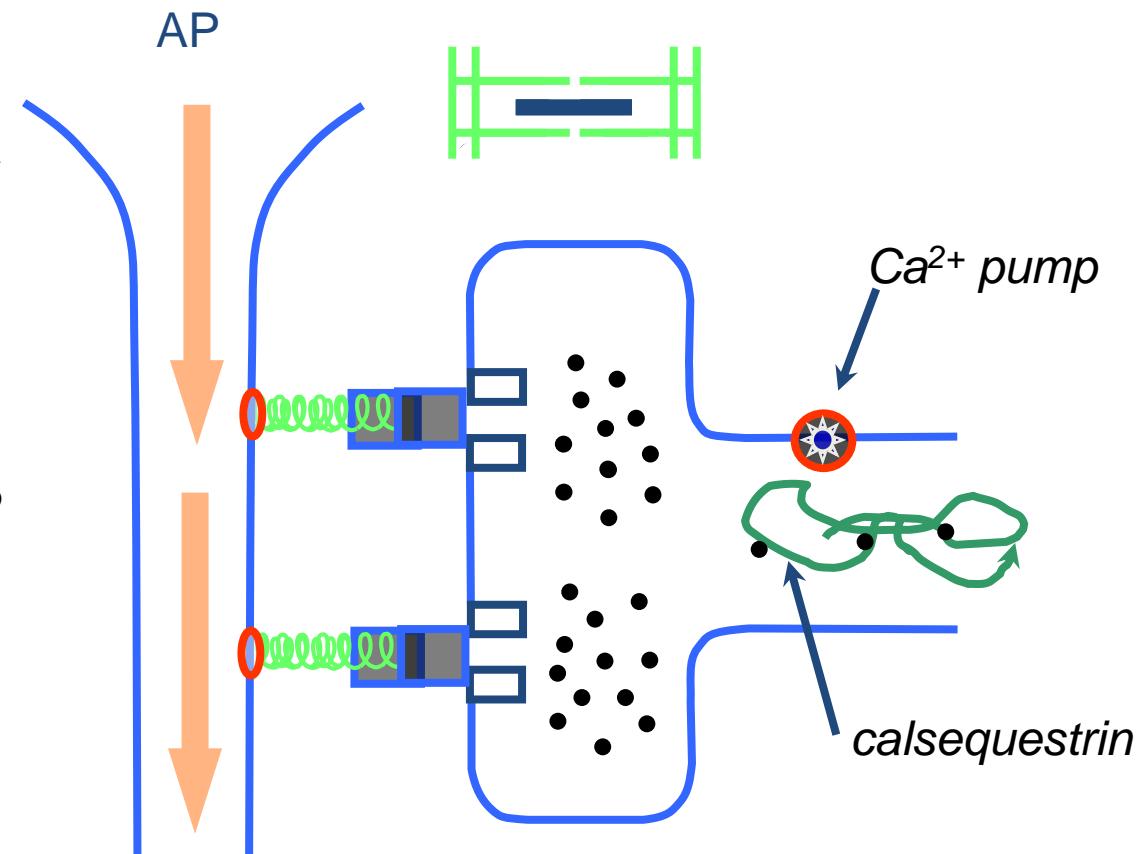


Figure 7-5; Guyton & Hall

■ EC Coupling – how it works (skeletal muscle)

Sequence of Events:

1. AP moves along T-tubule
2. The voltage change is sensed by the DHP receptor.
3. Is communicated to the ryanodine receptor which opens. (*VACR*)
4. Contraction occurs.
5. Calcium is pumped back into SR. Calcium binds to calsequestrin to facilitate storage.
6. Contraction is terminated.



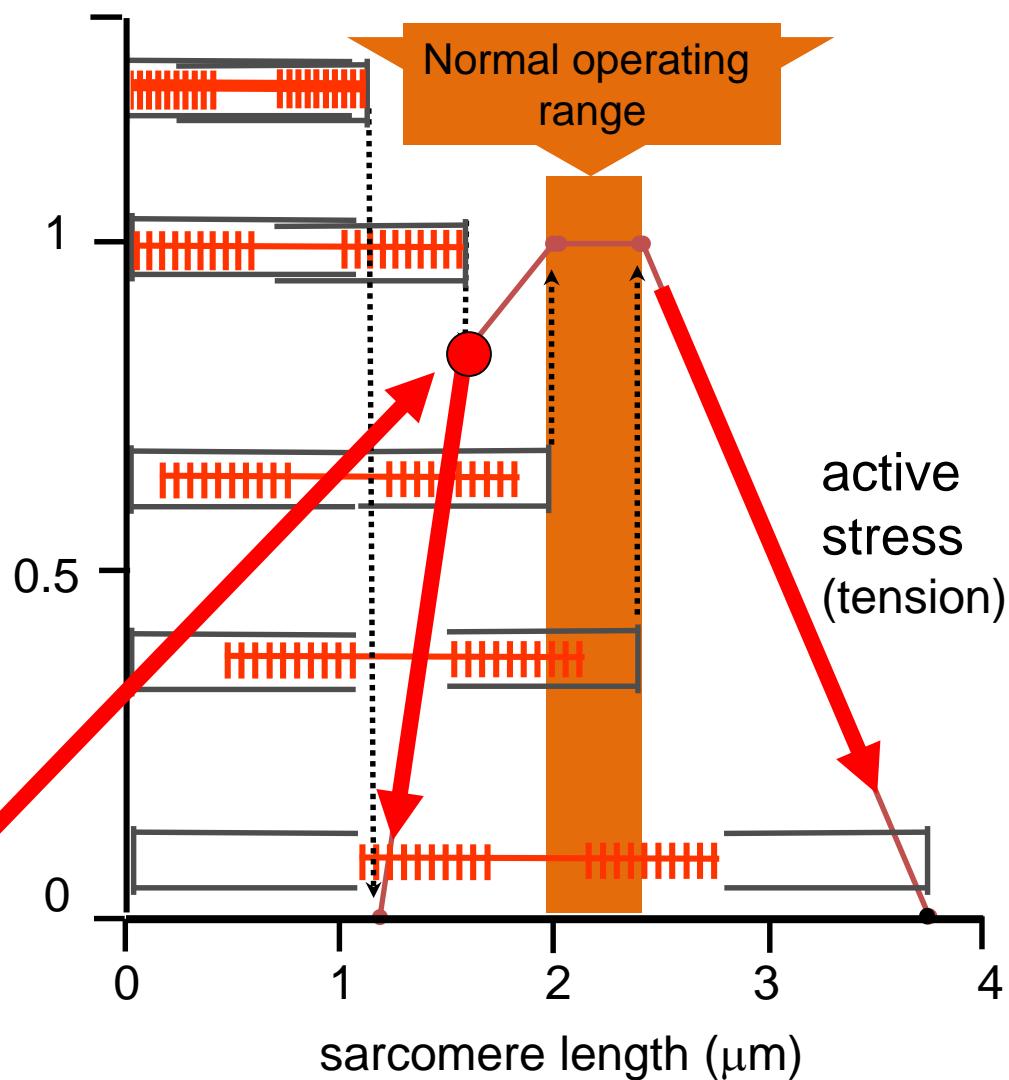


Watch video # 2!!

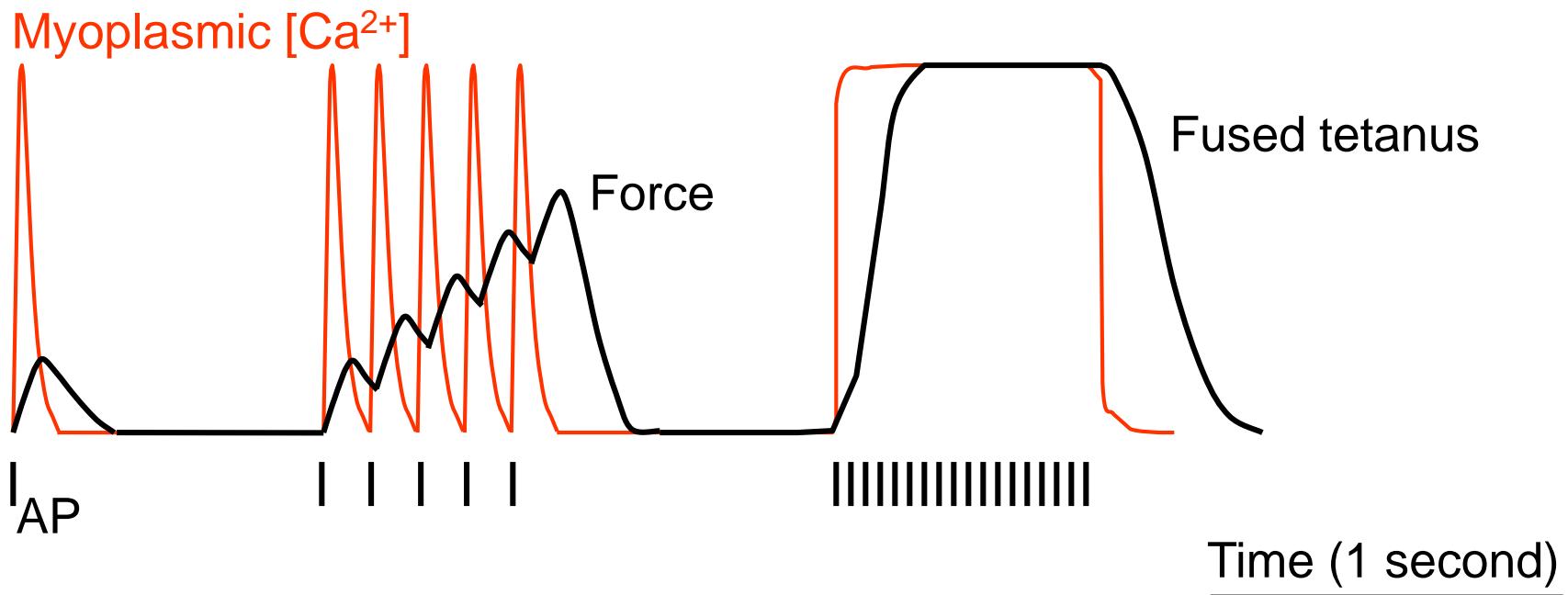
Muscle Mechanics

Tension as a Function of Sarcomere Length

- Stress is used to compare tension (force) generated by different sized muscles
 - $\text{stress} = \text{force}/\text{cross-sectional area of muscle}; \text{units } \text{kg}/\text{cm}^2$
- In skeletal muscle, maximal active stress is developed at normal resting length $\sim 2 \mu\text{m}$
- At longer lengths, stress declines -
- At shorter lengths stress also declines -
- Cardiac muscle normally operates at lengths below optimal length -



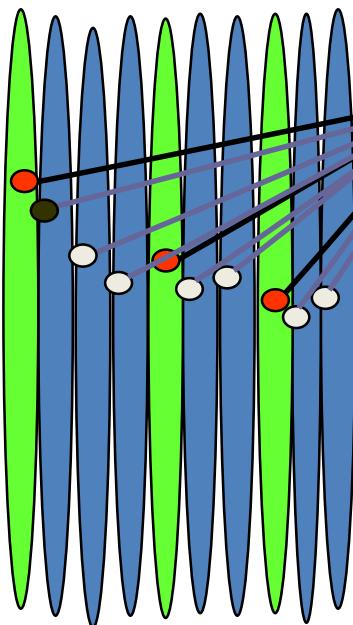
■ Frequency Summation of Twitches and Tetanus



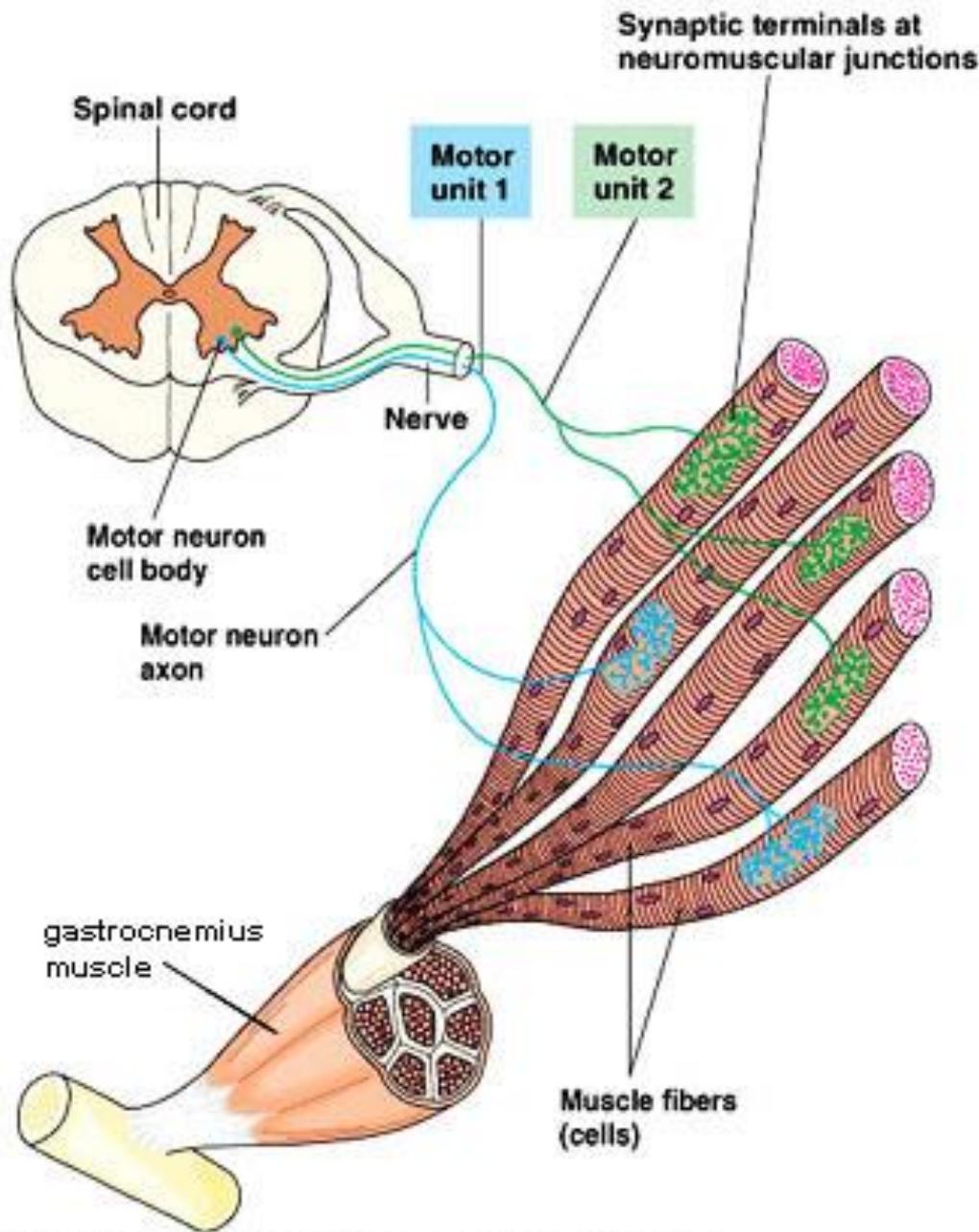
- Myoplasmic Ca^{2+} falls (initiating relaxation) before development of maximal contractile force
- If the muscle is stimulated before complete relaxation has occurred the new twitch will sum with the previous one etc.
- If action potential frequency is sufficiently high, the individual contractions are not resolved and a 'fused tetanus' contraction is recorded.

■ Motor Unit:

All the muscle fibers innervated by a single nerve fiber are called a motor unit.



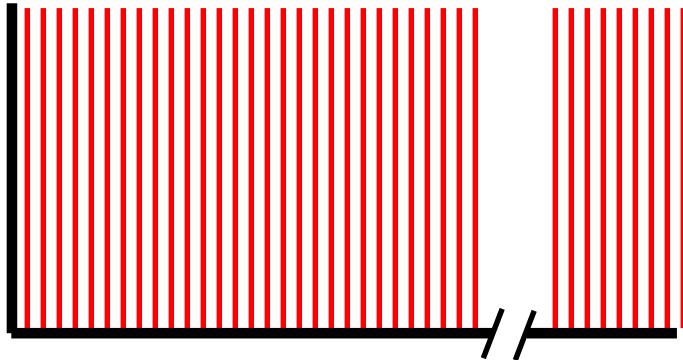
- All fibers are same type (*fast* or *slow*) in a given motor unit
- **Small motor units** (*e.g., larynx, extraocular*)
 - as few as 10 fibers/unit
 - precise control
 - rapid reacting
- **Large motor units** (*e.g., quadriceps muscles*)
 - as many as 1000 fibers/unit
 - coarse control
 - slower reacting



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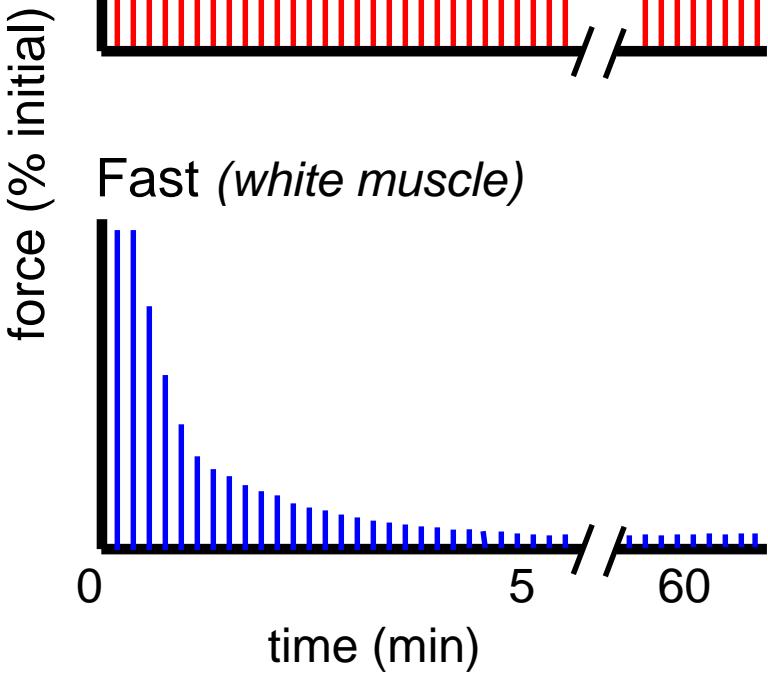
Types of Skeletal Muscle

Slow (*red muscle*)



- fast and slow fibers show different resistance to fatigue
- slow fibers
 - oxidative
 - small diameter
 - high myoglobin content
 - high capillary density
 - many mitochondria
 - low glycolytic enzyme content
- fast fibers
 - glycolytic

Fast (*white muscle*)



■ Types of Skeletal Muscle

- speed of twitch contraction -

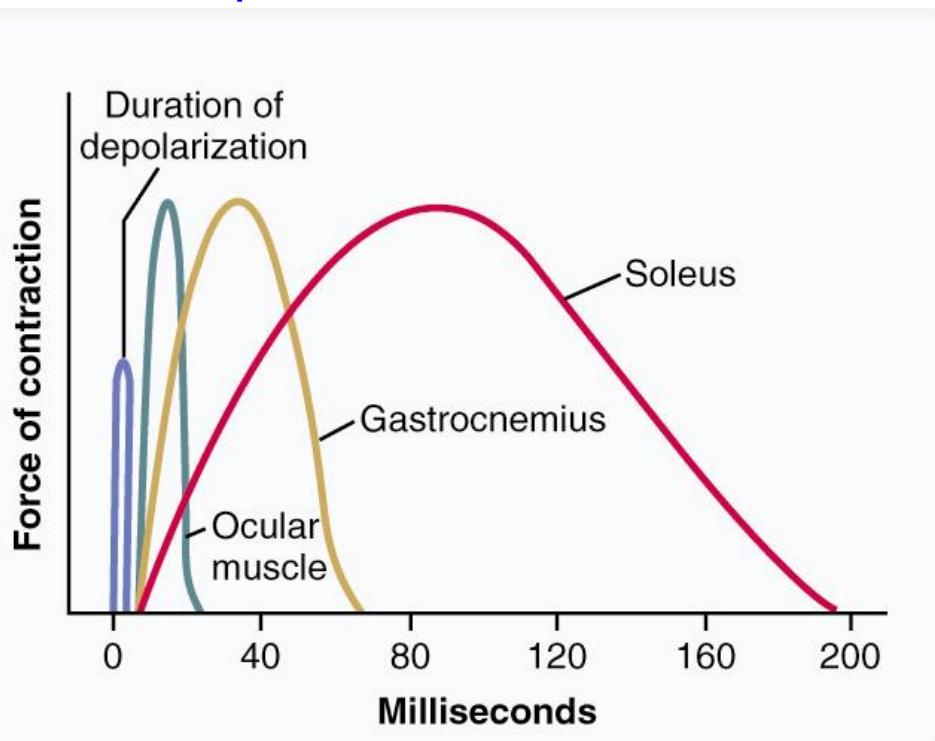
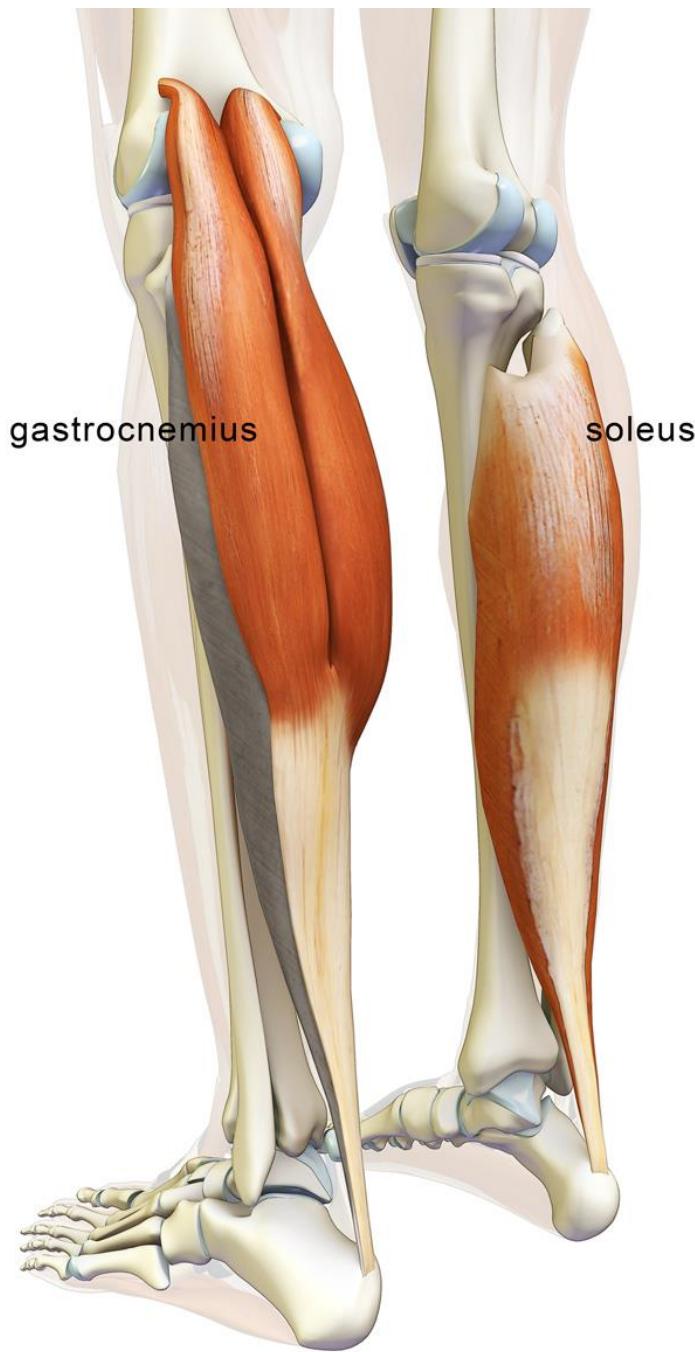


Figure 6-12; Duration of isometric contractions for different types of mammalian skeletal muscles, showing a latent period between the action potential (depolarization) and muscle contraction.

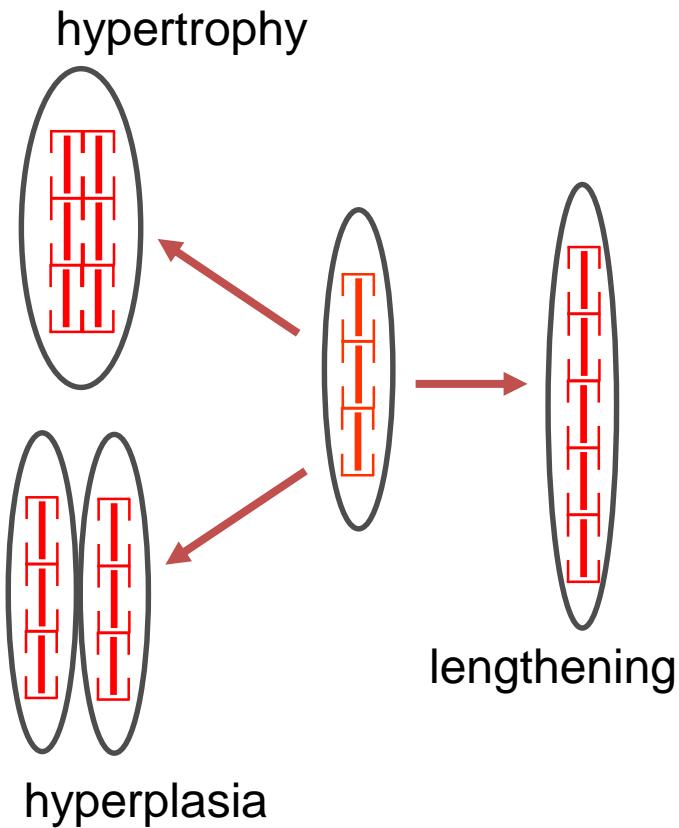
- Speed of contraction determined by V_{max} of myosin ATPase.
 - High V_{max} (*fast, white*)
 - rapid cross bridge cycling
 - *rapid rate of shortening (fast fiber)*
 - Low V_{max} (*slow, red*)
 - slow cross bridge cycling
 - slow rate of shortening (*slow fiber*)
- Most muscles contain both types of fiber but proportions differ
- All fibers in a particular motor unit will be of the same type i.e., fast or slow.

- **Ocular movements** must be extremely rapid to maintain fixation of the eyes on specific objects to provide accuracy of vision. **The gastrocnemius muscle** must contract moderately rapidly to provide sufficient velocity of limb movement for running and jumping, and the **soleus muscle** is concerned principally with slow contraction for continual, long-term support of the body against gravity.



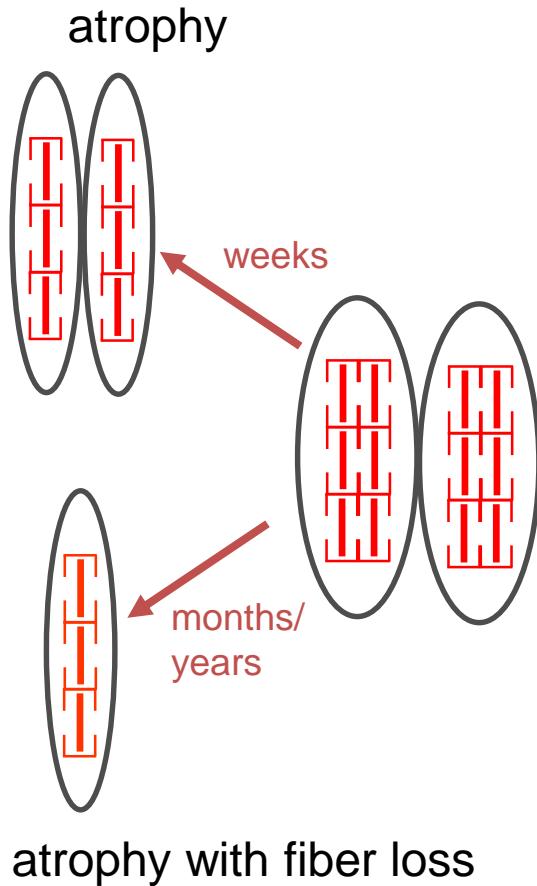
■ Muscle Remodeling - *growth*

- When the total mass of a muscle increases, this is called *muscle hypertrophy*. When it decreases, the process is called *muscle atrophy*.



- **Hypertrophy (common, weeks)**
 - Caused by near maximal force development (eg. weight lifting)
 - Increase in actin and myosin
 - Myofibrils split
- **Hyperplasia (rare)**
 - Formation of new muscle fibers
 - Can be caused by endurance training
- **Hypertrophy and hyperplasia**
 - Increased force generation
 - No change in shortening capacity or velocity of contraction
- **Lengthening (normal)**
 - Occurs with normal growth
 - No change in force development
 - Increased shortening capacity
 - Increased contraction velocity

■ Muscle Remodeling - *atrophy*



- Causes of atrophy
 - Denervation/neuropathy
 - Sedentary life style
 - Plaster cast
 - Space flight (zero gravity)
- Muscle performance
 - Decreased max force of contraction
 - Decreased velocity of contraction
- Atrophy with fiber loss
 - Disuse for 1-2 years
 - Very difficult to replace lost fibers

Chapter 8:

Contraction and Excitation of Smooth Muscle

Contraction of Smooth Muscle

Types of Smooth Muscle

- Mononucleate cells with no striations (*smooth in polarized light*).
- Form muscular walls of hollow organs - gut, airways, blood vessels & urogenital system
- 2 sorts of organization

↳ **Unitary:** sheets of electrically coupled cells which act in unison (a 'syncytium' e.g. gut and bladder)

↳ **Multiunit:** tissue made of discrete bundles of cells (no coupling) which are densely innervated and contract only in response to its innervation (e.g. iris)

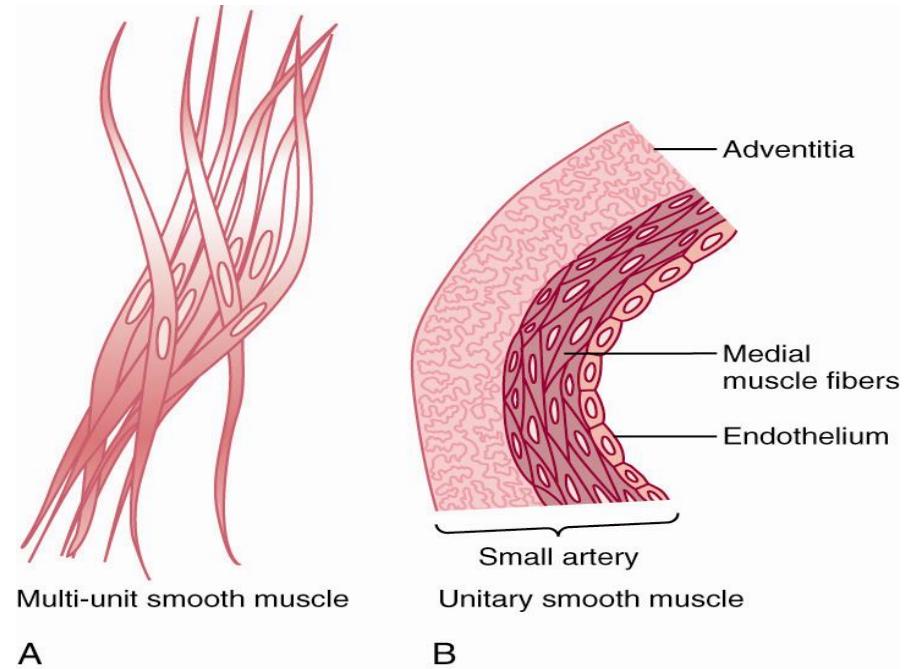
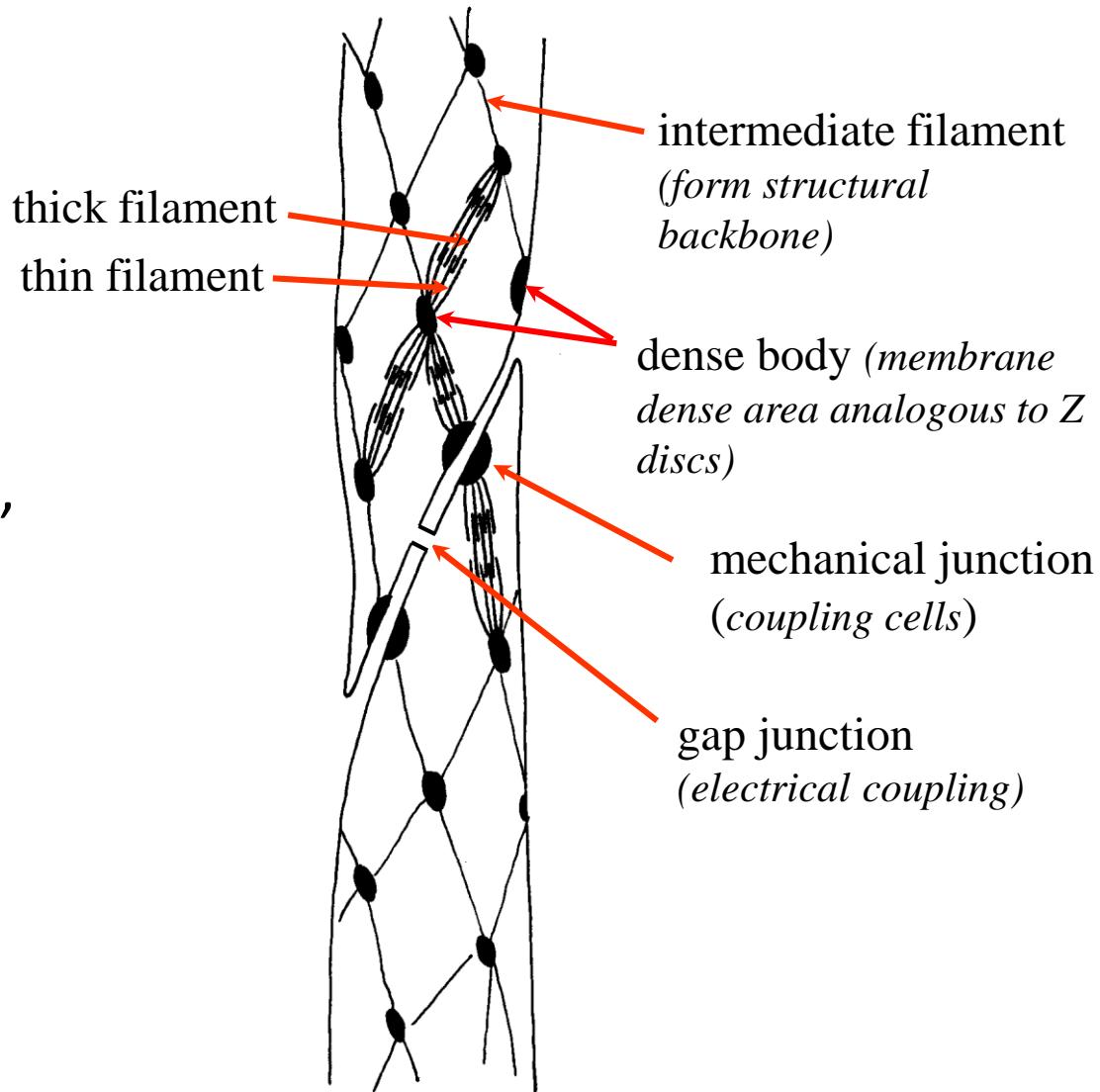


Figure 8-1; Multi-unit (A) and unitary (B) smooth muscle.

■ Special features of smooth muscle

Smooth muscle:

- Can operate over large range of lengths
- Is very energy efficient
- Can maintain force for long periods (hours, days, weeks) via latch state
- Can be myogenic (spontaneously active)
- Has Ca^{2+} action potentials. Ca entering through channels is a very important source of calcium
- Poorly developed SR



Neuromuscular Junction

Important points

- Autonomic nerve fibers branch and form “diffuse junctions” with underlying smooth muscle fibers.
- **Varicosities** in the terminal axons contain neurotransmitter.
- Excitation is transmitted by Ca action potential or simple diffusion of Ca into fiber.

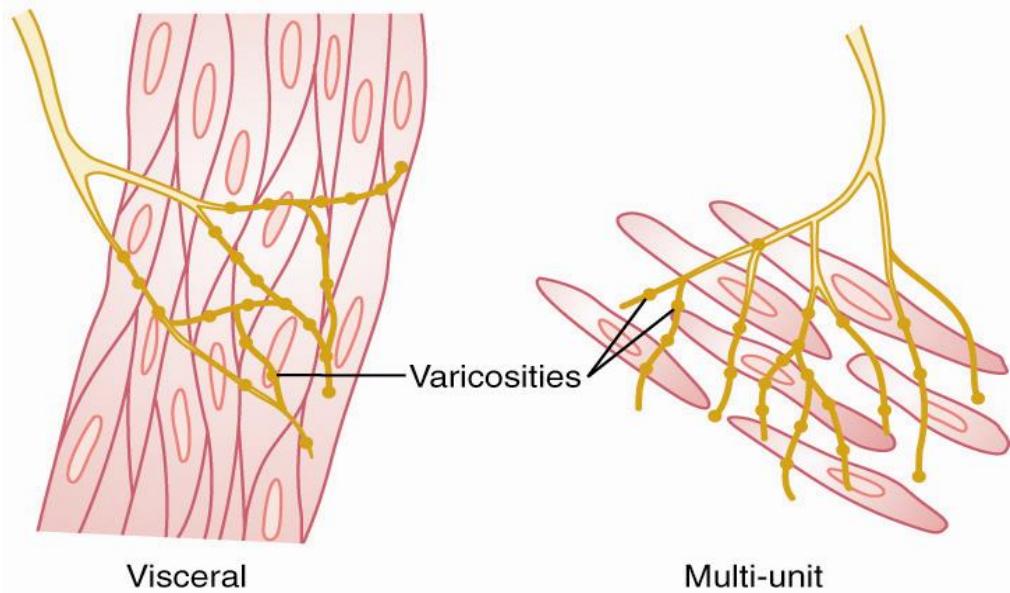
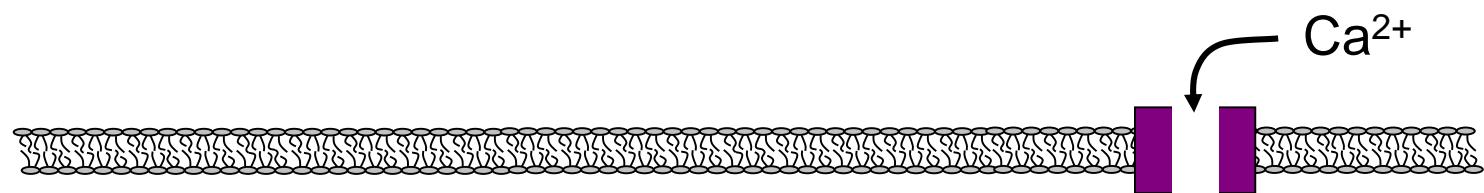


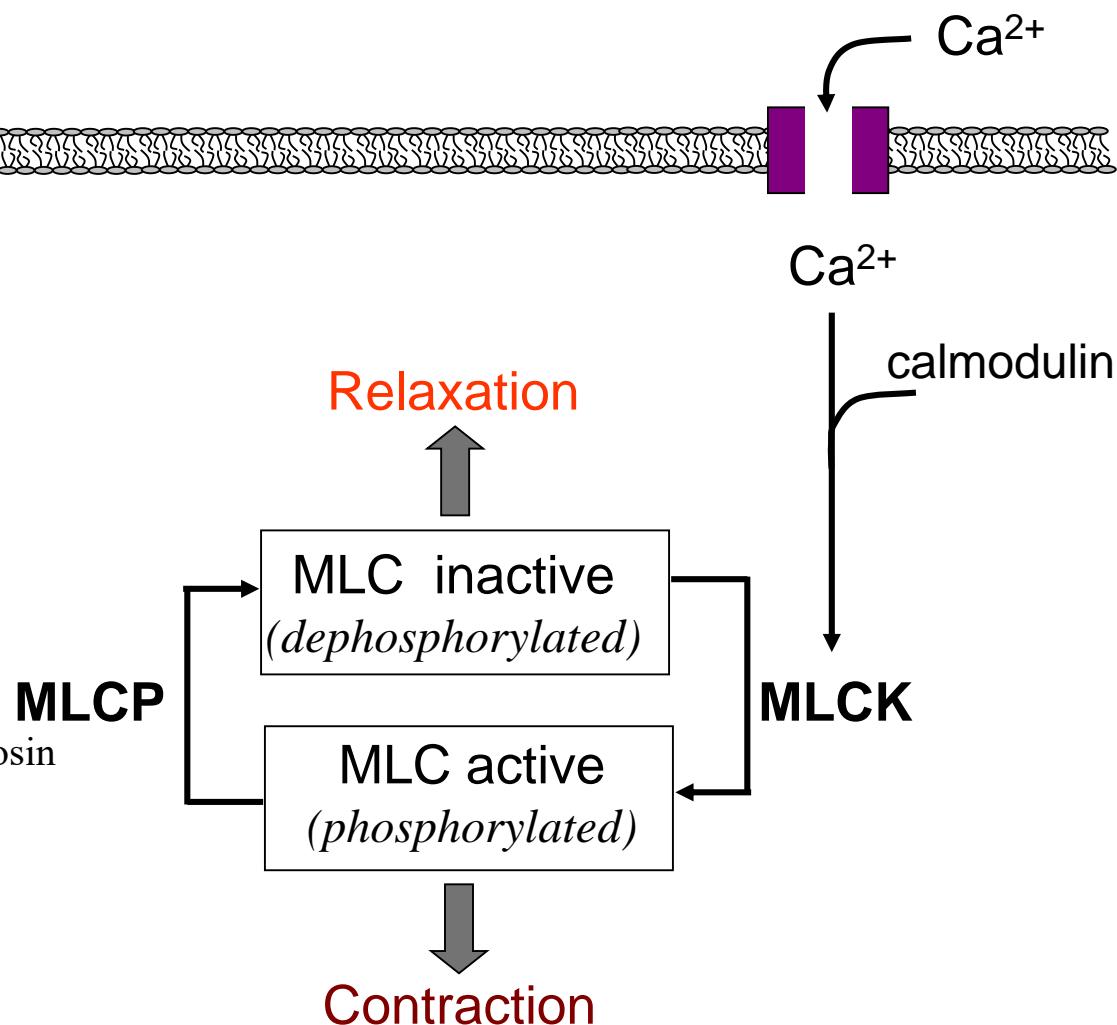
Figure 8-3; Guyton & Hall

■ Contraction-Relaxation – myosin based regulation



Important points:

1. Initiated by calcium
2. Calcium binds to calmodulin (instead of troponin as in skm)
3. Ca-calmodulin-MLCK complex leads to phosphorylation of MLC (requires 1 ATP)
4. MLC is part of myosin head
5. Phosphorylated myosin head binds to actin and power stroke occurs automatically
6. A second ATP is required to release myosin head from actin
7. Cross-bridge cycling requires both MLCK and MLCP



MLCK, myosin light chain kinase

MLCP, myosin light chain phosphatase

Muscle Metabolic Systems

- Phosphocreatine (also called creatine phosphate) has a high-energy phosphate bond and after decomposition to creatine and phosphate ion, large amounts of energy is released.
- The stored glycogen in muscle can be split into glucose and the glucose then used for energy.
- glucose, fatty acids, and amino acids from the foodstuffs—after some intermediate processing—combine with oxygen to release tremendous amounts of energy that are used to convert AMP and ADP into ATP

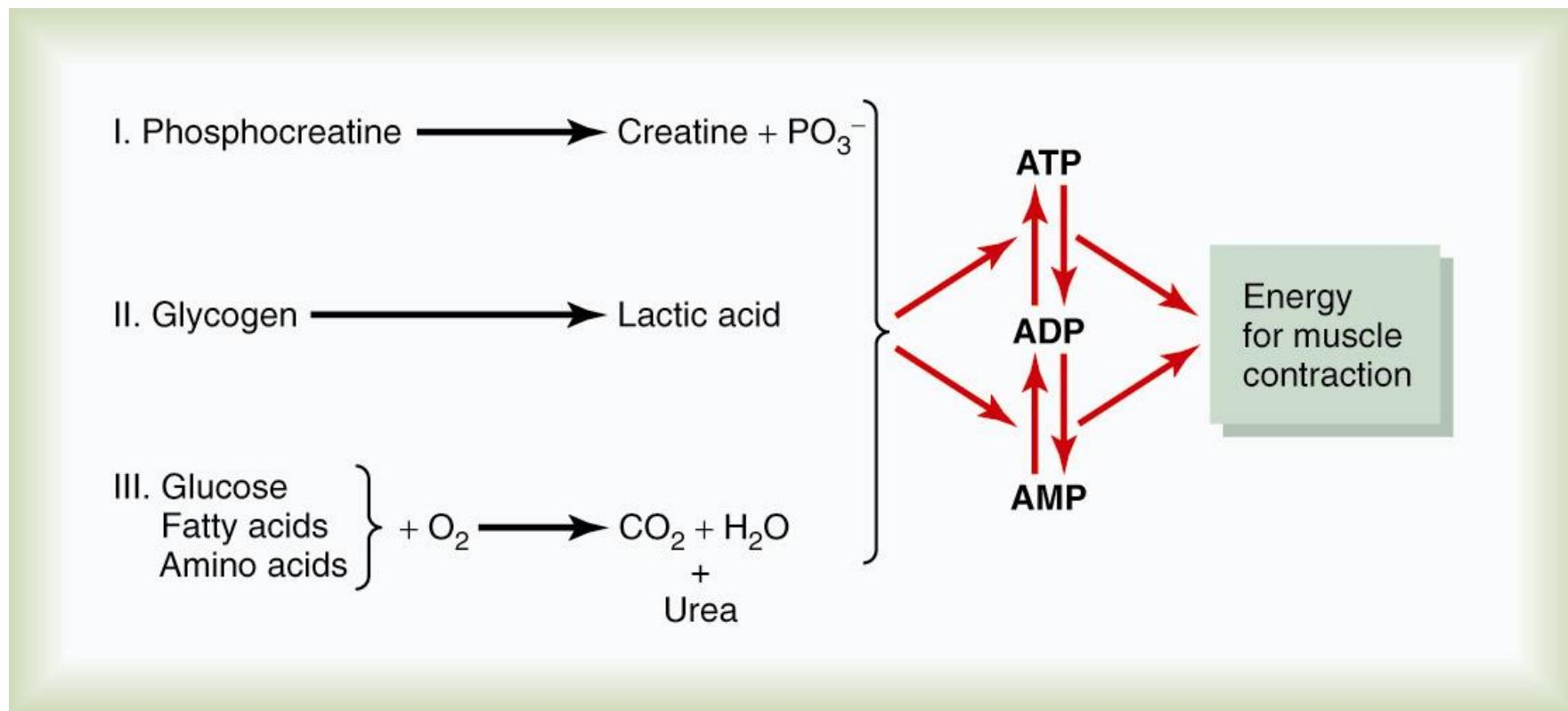


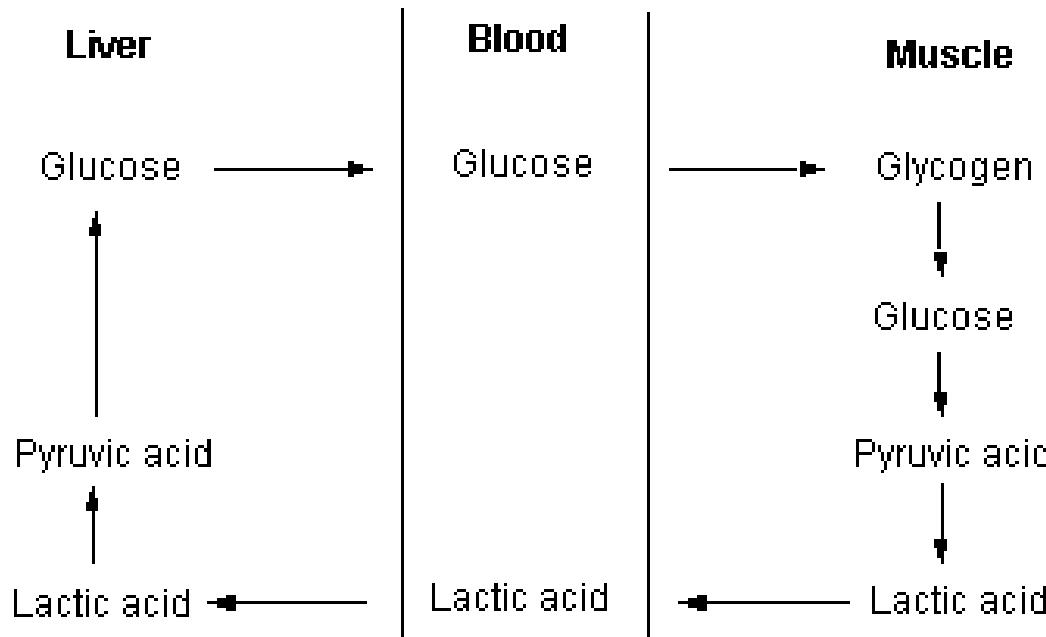
Figure 84-1; Important metabolic systems that supply energy for muscle contraction.

■ Muscle Metabolic Systems

- phosphate
 - enough stored for 8-10 sec max work
 - can supply 4x ATP/min as aerobic
- glycolysis
 - anaerobic
 - strongly inhibited by low pH
 - forms lactic acid
 - can supply 2.5x ATP/min as aerobic

■ Muscle Metabolic Systems

- aerobic can last indefinitely
- metabolic recovery



Nervous System overview

Nervous System

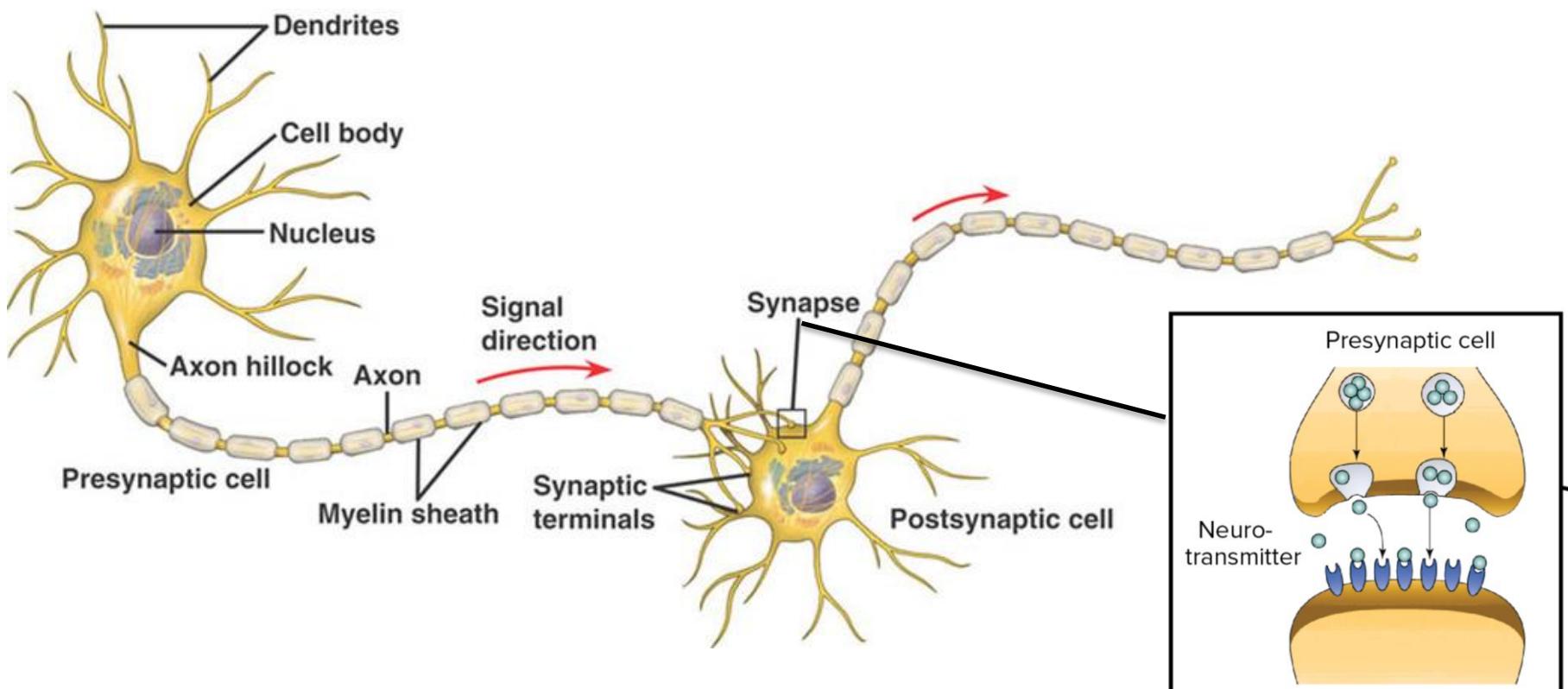
- is a rapid communication system using electrical signals.
- consists of a network of specialized cells called neurons.

Functions of the Nervous System:

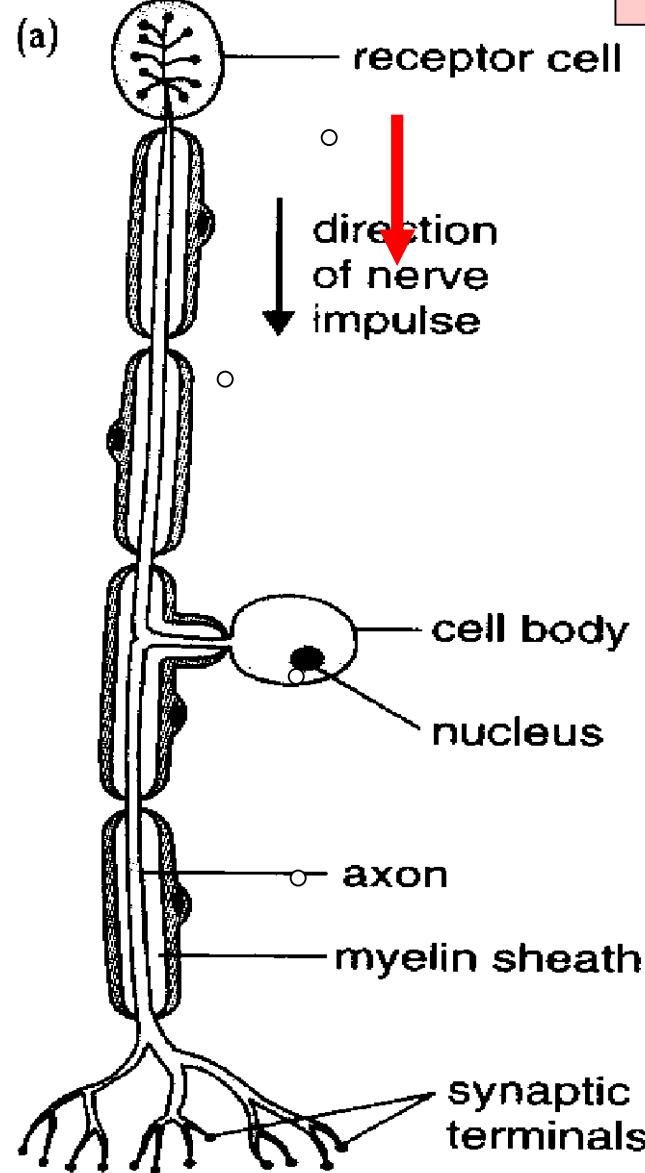
- Sensory input – gathering information
 - To monitor changes occurring inside and outside the body
 - Changes = stimuli
- Integration
 - To process and interpret sensory input and decide if action is needed
- Motor output
 - A response to integrated stimuli
 - The response activates muscles or glands

Structure of a neuron

- **Cell body:** central part of neuron, maintains cell function, relays signals from one part of cell to another.
- **Dendrites:** extend from cell body, receive information from other cells.
- **Axon:** long extension from the cell body, transmits signals to other neurons, ends in an axon terminal.
- **Synapse:** where the axon terminal connects with another neuron, separated by a gap called the synaptic cleft

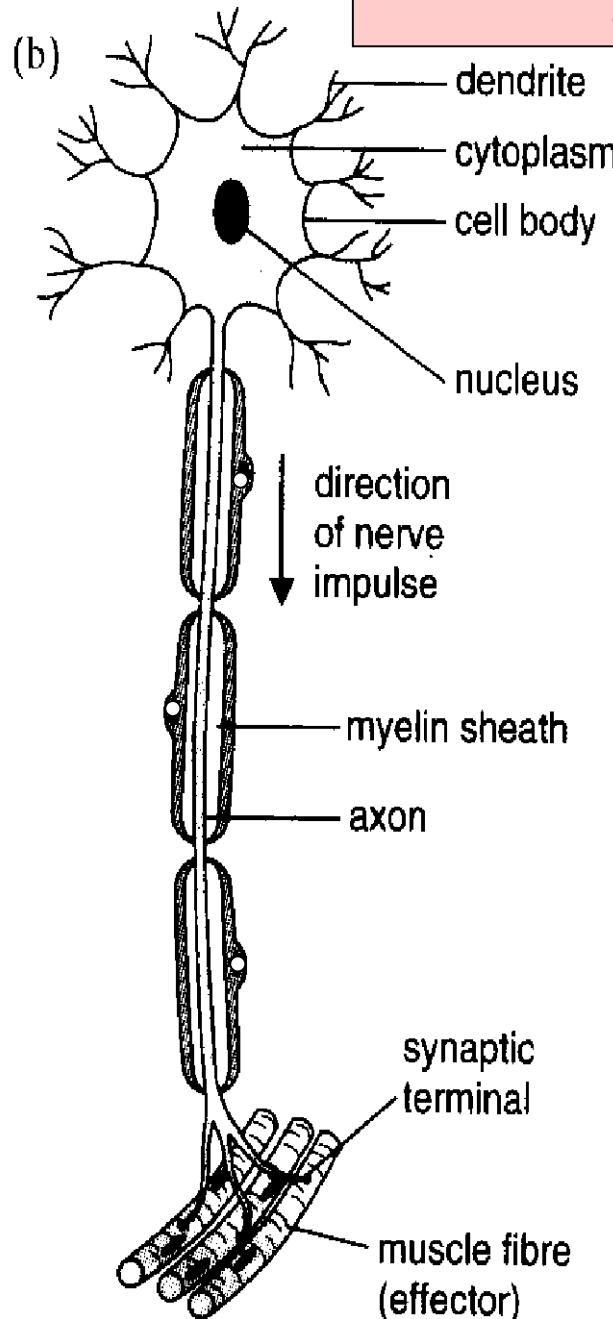


Kinds of Neurons



Structure of an afferent (sensory) neurone

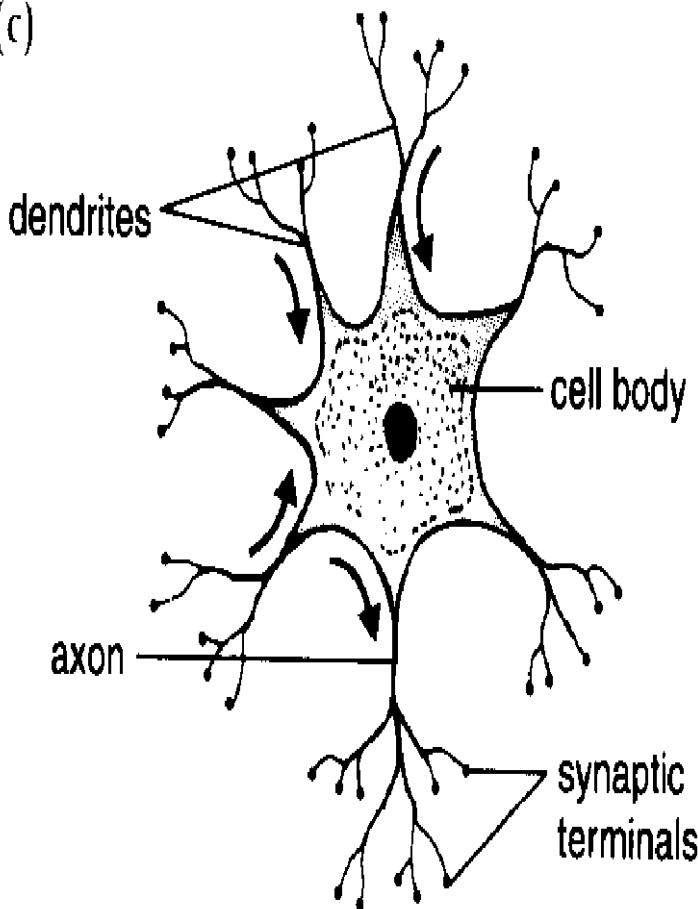
Carry sensory information from receptors cells to the brain & spinal cord



**Carry sensory information
from brain & spinal cord to
the effectors
[muscle / gland cells]**

Structure of an interneurone

(c)



- Convey nerve impulses between the various parts of the brain and spinal cord
- Transmit nerve impulses between the afferent neurones and efferent neurones
- Transmit nerve impulses from one side of the spinal cord to the other side, or from the brain to the spinal cord and vice versa

Watch
video # 3.1

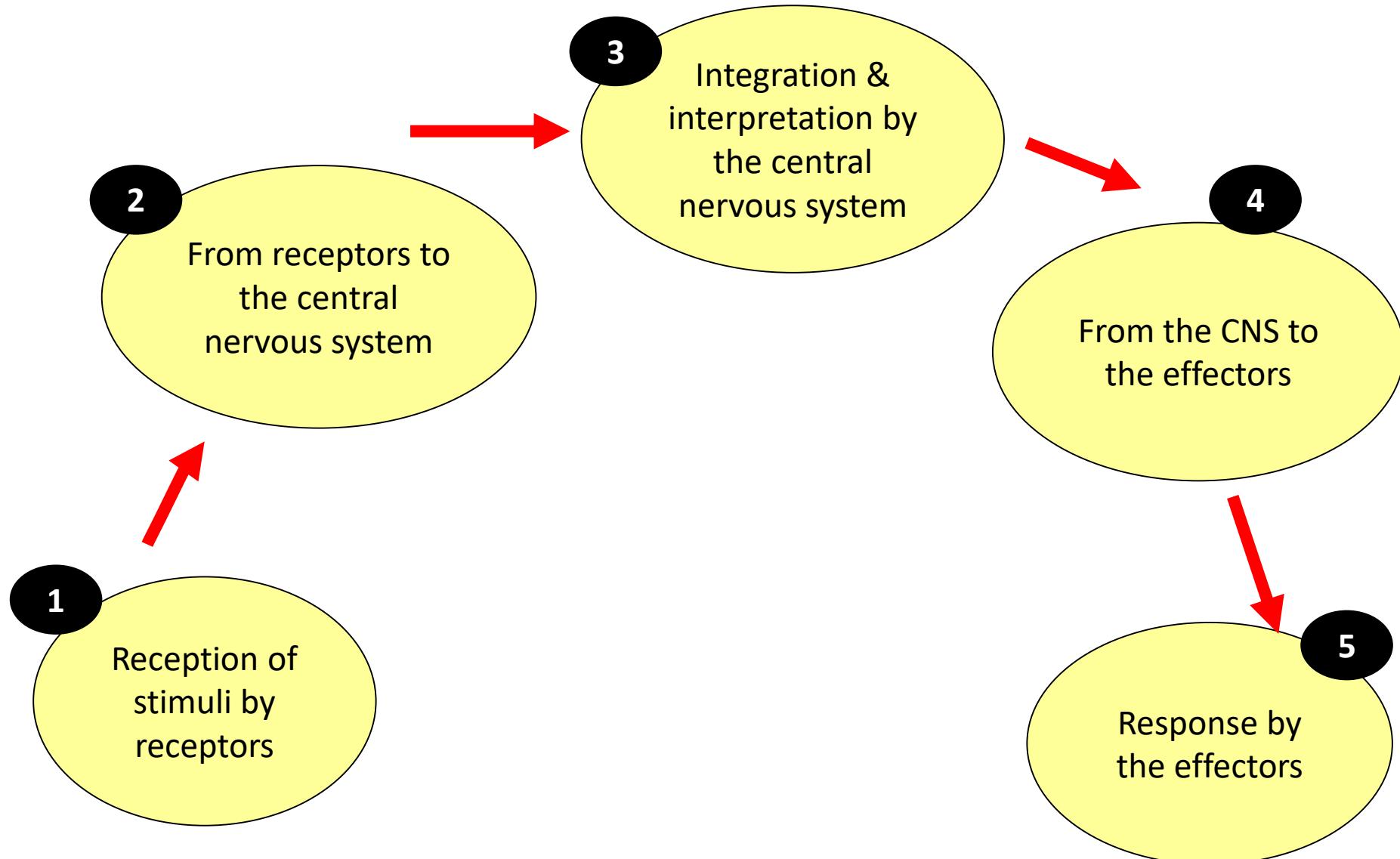
DIFFERENCE BETWEEN STRUCTURE OF AFFERENT NEURONE & EFFERENT NEURONE

AFFERENT NEURONE	EFFERENT NEURONE
Long dendrite, short axon	Short dendrite, long axon
Cell body at the side of the neurone [not at the end]	Cell body at the end of the neurone
Begins with receptor	Ends with effector

Path of a nerve impulse

- The transmission of information along the neurone is through **electrical signals** known as **nerve impulses**.
- An impulse is a wave of positive charges that travel along the axon to the synaptic terminal.
- A neurone will not transmit an impulse unless the stimulation is strong enough.
- Once the magnitude or size of the stimulation reaches a threshold level, a full-sized impulse is generated to travel the entire length of the axon.

The transmission pathway of information



The transmission pathway of information

3
The nerve impulses pass from the afferent neurones to the interneurones in the brain

2
The receptors trigger nerve impulses in the afferent neurones.

1
Receptors in the ear

Receptors in the ear pick up the ringing of the doorbell.

4

The brain interprets the nerve impulses from many interneurones that the doorbell is ringing. The brain also decides that the door should be opened

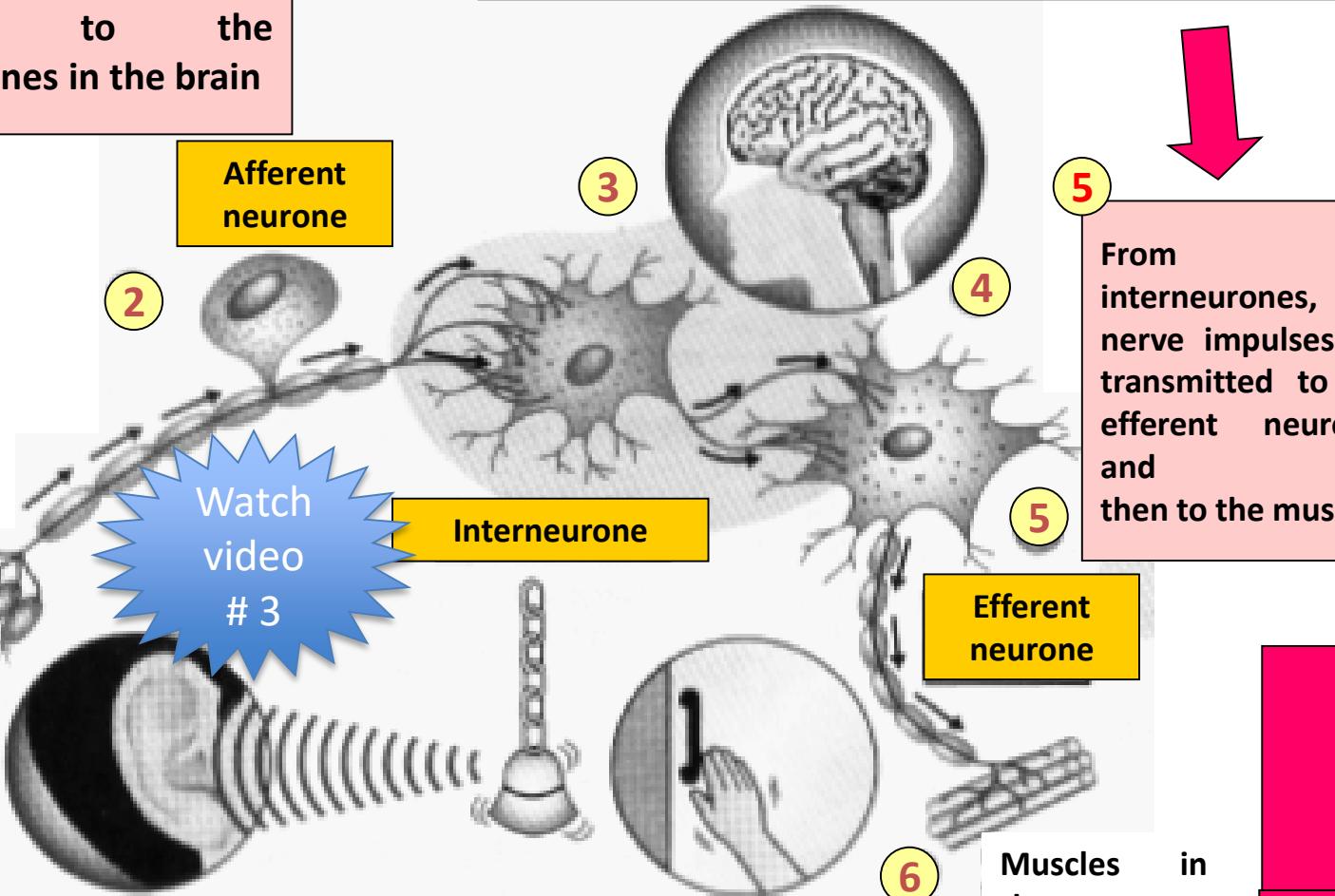
Afferent neurone

Interneurone

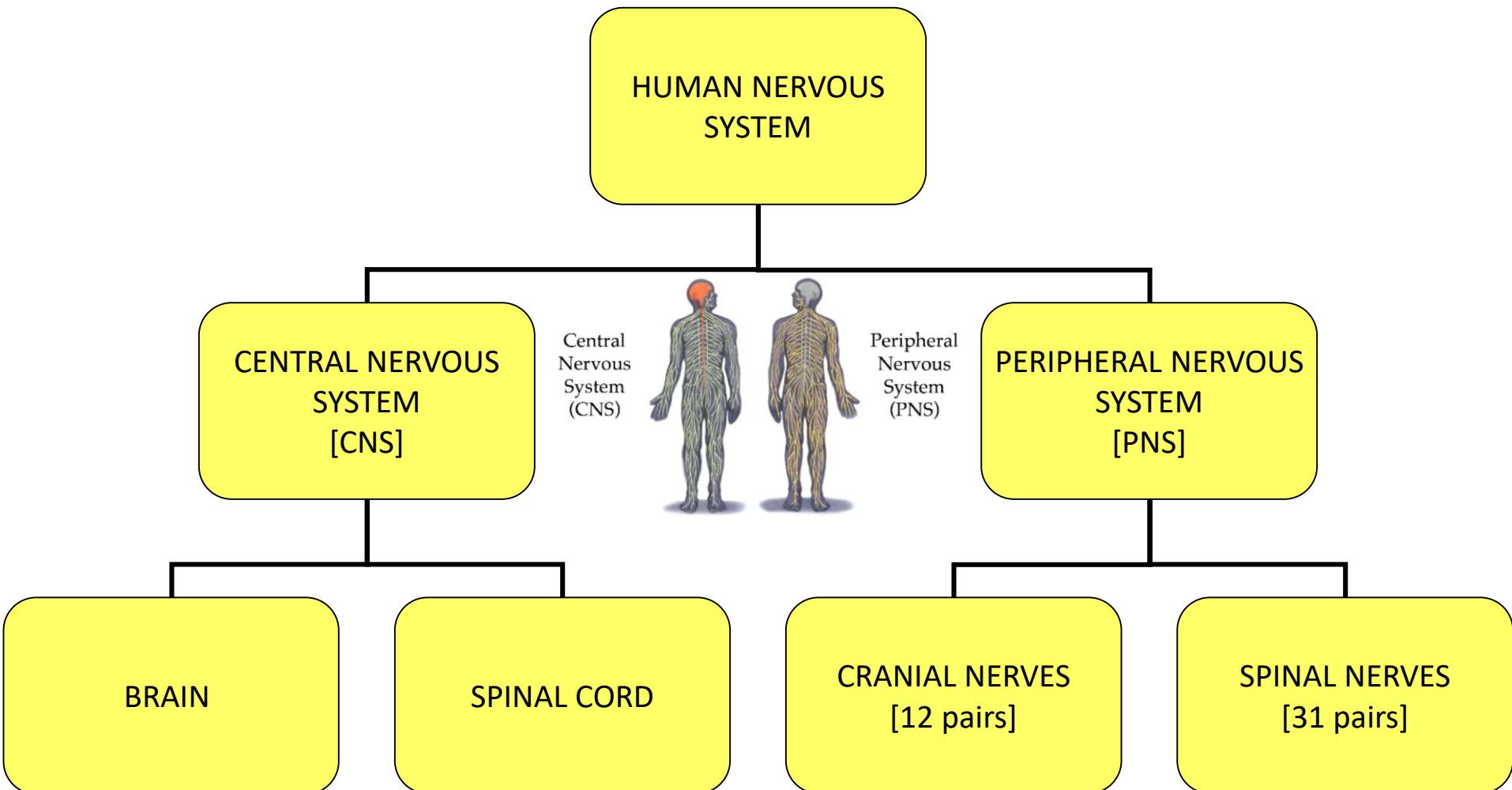
Efferent neurone

Muscles in the arm

6
The muscles in the arm carry out the response and open the door

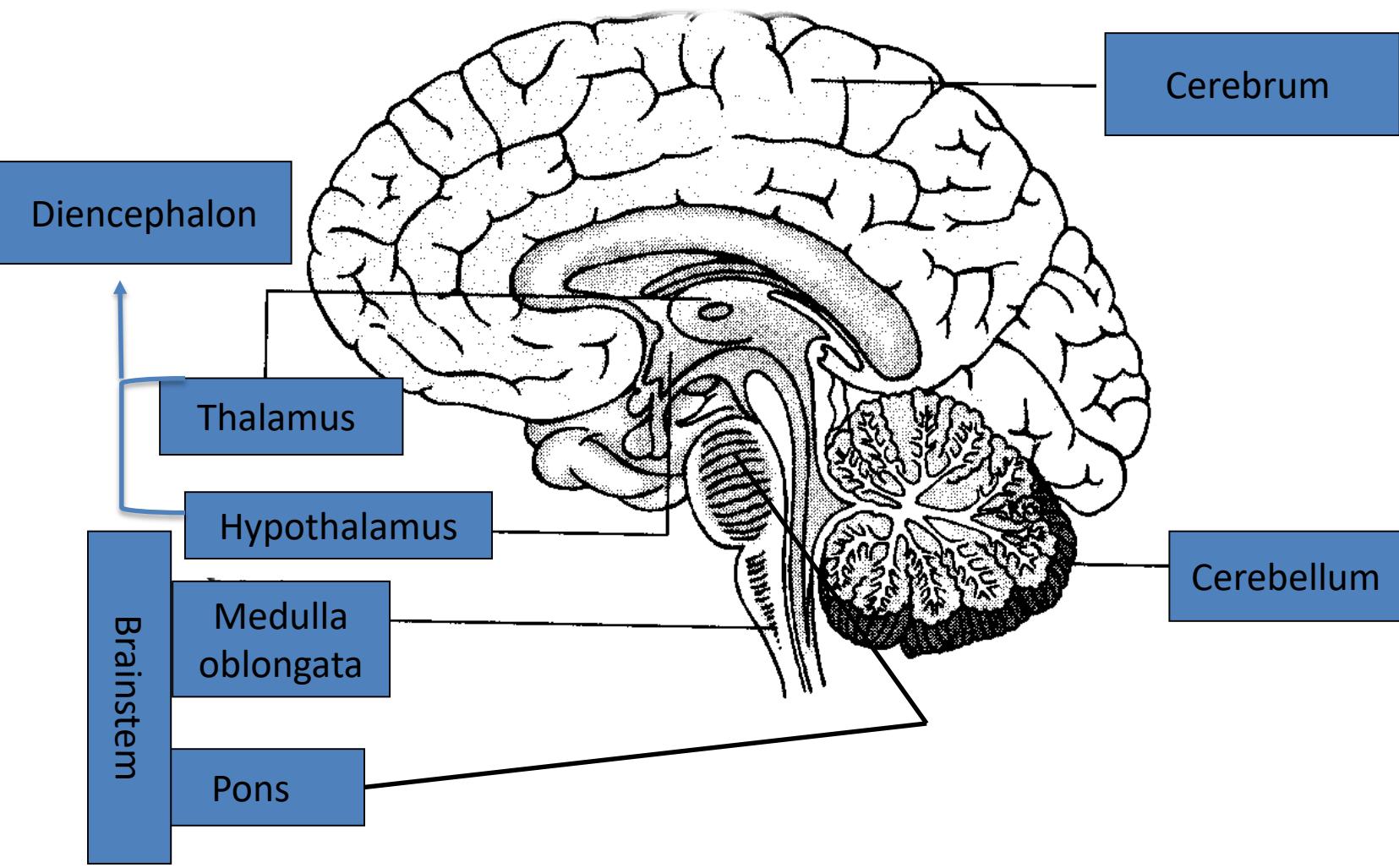


Divisions of the Nervous System

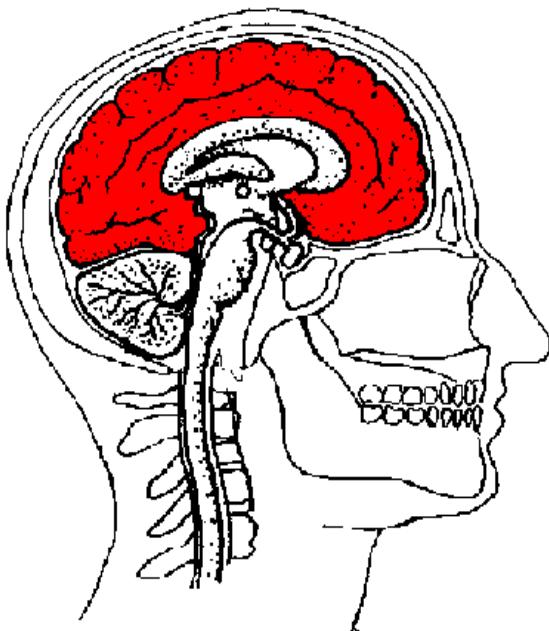


Central Nervous System

STRUCTURE OF THE BRAIN

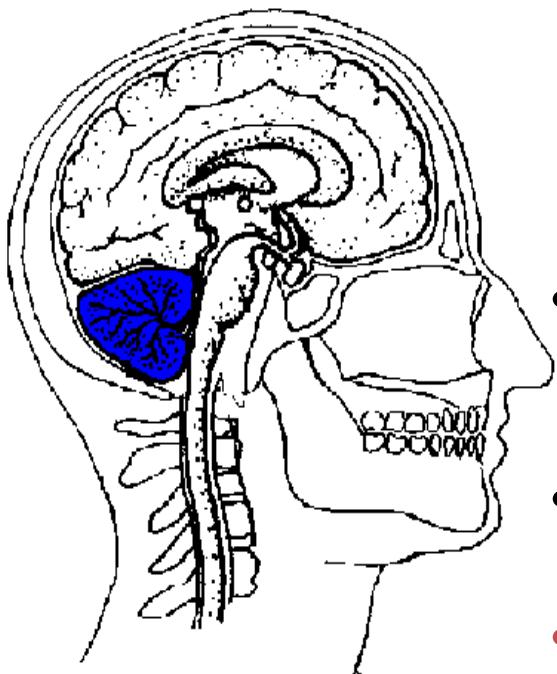


CEREBRUM



- The cerebrum is the largest and most complex part of the brain.
- It is divided into two halves called the **cerebral hemispheres**. These two halves are connected to each other by **corpus callosum**.
- The **left hemisphere** controls the movements on the right side of the body.
- The **right hemisphere** controls the movements on the left side of the body.
- The cerebrum is the centre which receives the sensory input and carries out integrative functions before initiating appropriate motor responses.
- It also coordinates the activities of the other parts of the brain.
- The outer region of the cerebrum is the **cerebral cortex**.
- The cerebral cortex is a structure with many folds which increases the surface area.
- The cerebral cortex directs **voluntary muscle movements**, which result in a **sensory perception** that is, when a person becomes aware of what he sees, hears, smells, tastes or touches.
- It is also responsible for many **mental abilities** such as learning, memorising, reasoning, language skills, speech, mathematical skills, imagination, artistic talent and personality traits.
- Brain damage from trauma, a stroke or a tumour can result in specific defects, such as speech impairment, reading difficulty, or the paralysis of certain parts of the body.

CEREBELLUM



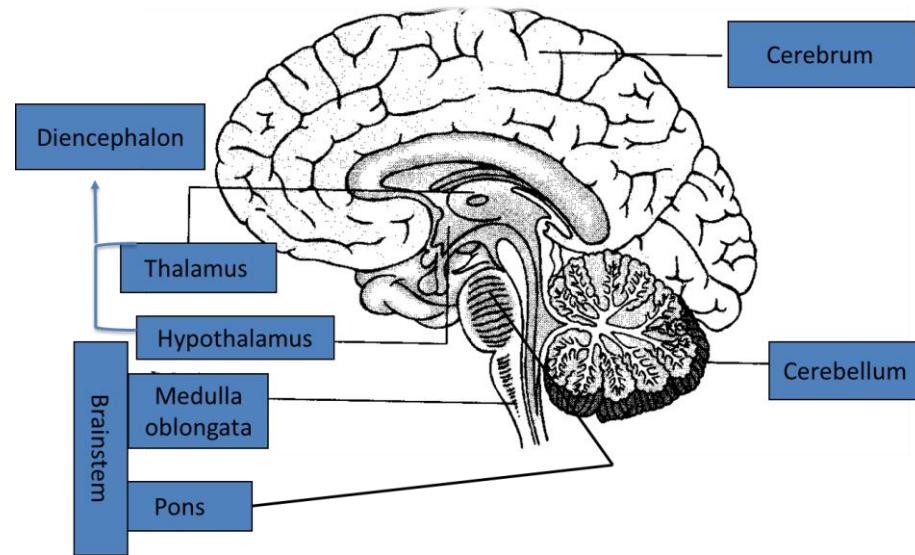
- The cerebellum is located below the cerebrum near the top of the spinal cord.
- The cerebellum is the coordinating centre for **body movement**
- The cerebellum receives information from the sensory receptors on the **positions** of different parts of the body; and, from the cerebrum, an indication of the **need to move**.
- The cerebellum evaluates the information and relays the need for **coordinated movements** back to the cerebrum.
- The cerebrum then sends appropriate commands to the **muscles**
- The cerebellum controls voluntary muscles, posture, balance and the coordination of walking, running and playing sports

Brainstem

MEDULLA OBLONGATA

- The medulla oblongata regulates the internal body processes that do not require conscious effort, that is, **automatic functions** such as the heartbeat, breathing and vasoconstriction
- It is also the **reflex centre** for vomiting, coughing, sneezing, hiccupping and swallowing.

STRUCTURE OF THE BRAIN



PONS

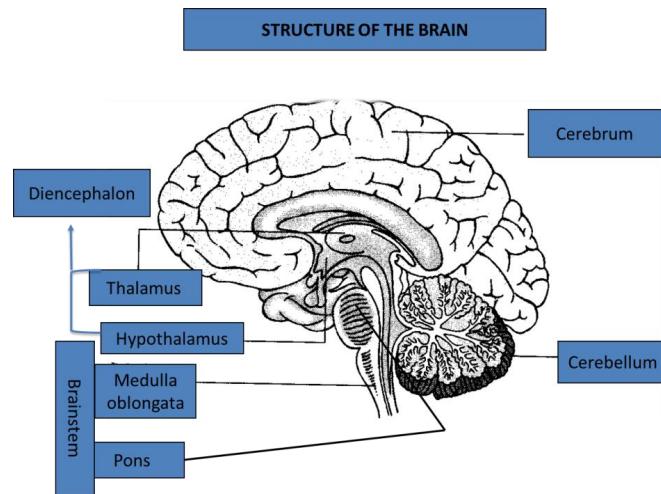
- Connects the medulla & midbrain
- Transmit information between spinal cord & higher brain regions via neural circuits
- Relay motor information between cerebral cortex & cerebellum

Diencephalon

HYPOTHALAMUS

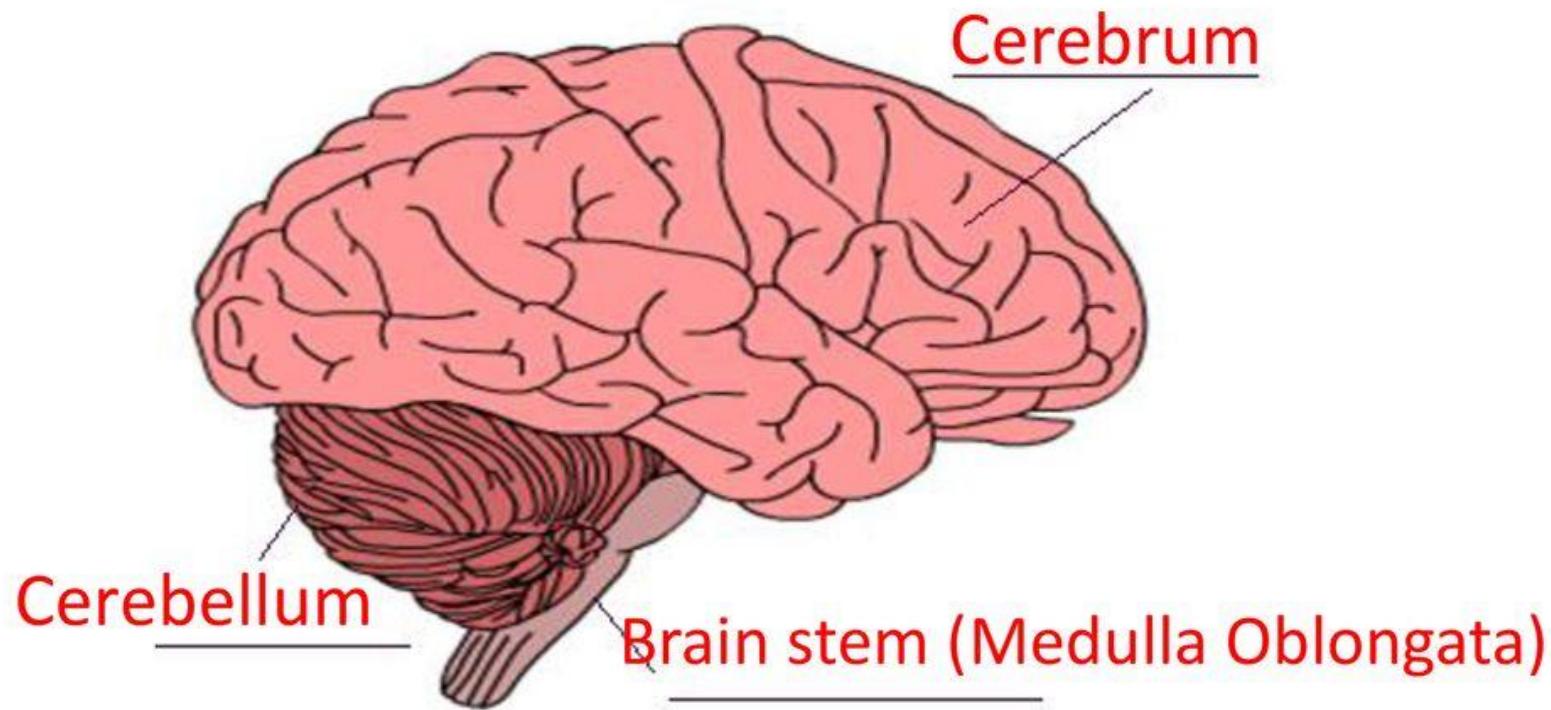
- The hypothalamus plays an important role in **homeostatic regulation**. It acts as a major coordinating centre for regulating sleep, hunger, thirst, body temperature, water balance and blood pressure.
- It is also the **control centre** of the endocrine system.

THALAMUS



- The thalamus is responsible for sorting the incoming and outgoing information in the cerebral cortex.
- It also integrates the information from the sensory receptors to the cerebrum by enhancing certain signals and blocking others.

In brief:



Brain stem

- Changes in heart rate
- Breathing, blood pressure, vomiting, swallowing
- Digestion

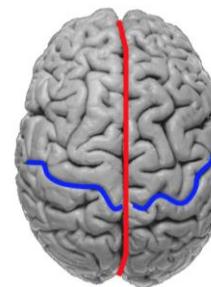
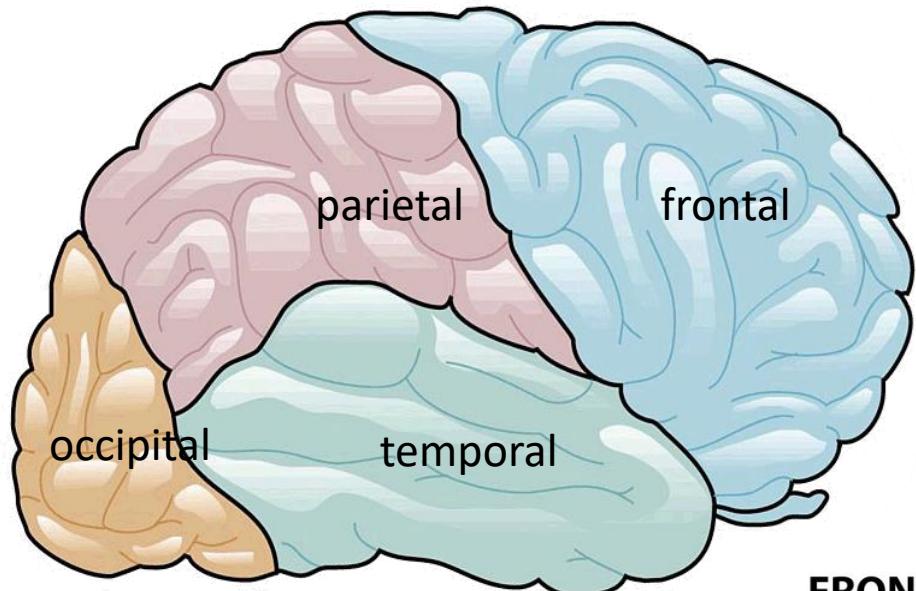
Cerebrum

- Intelligence, learning, judgment
- Speech and memory
- Sense of hearing, vision, taste and smell
- Skeletal muscle movements

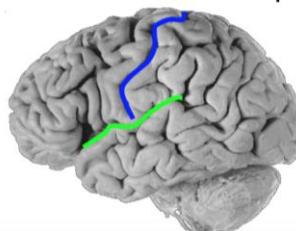
Cerebellum

- Balance and coordination
- Posture

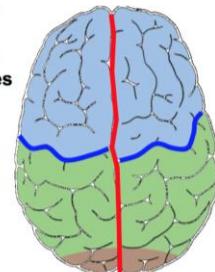
The lobes of the Crebrum



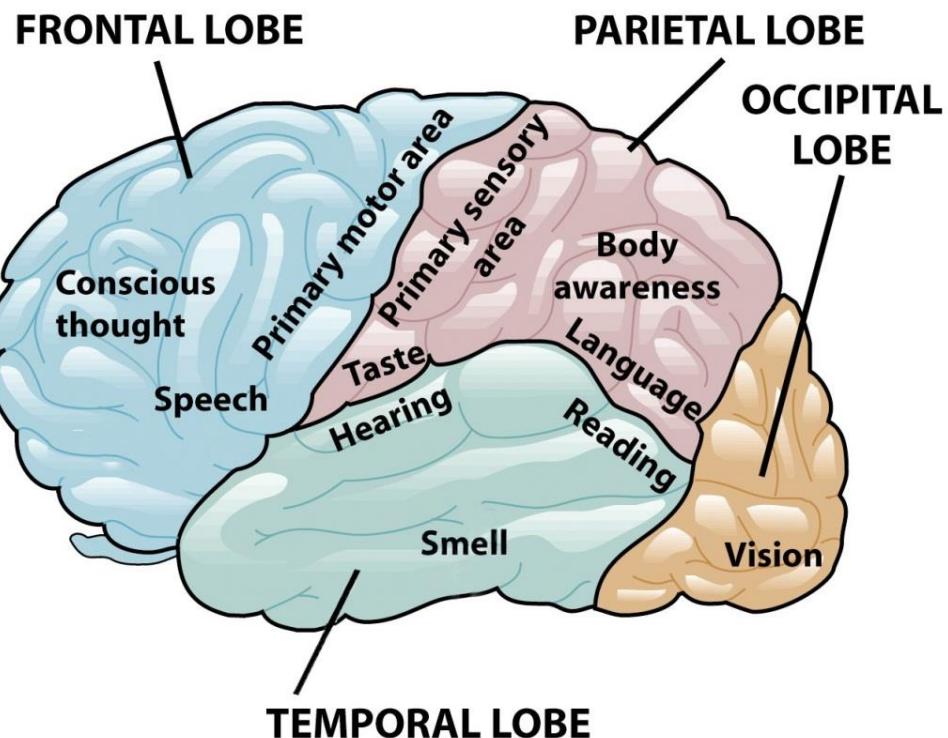
Longitudinal fissure
Divides the two cerebral hemispheres



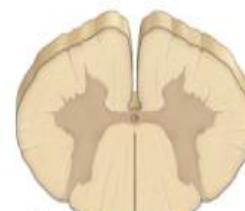
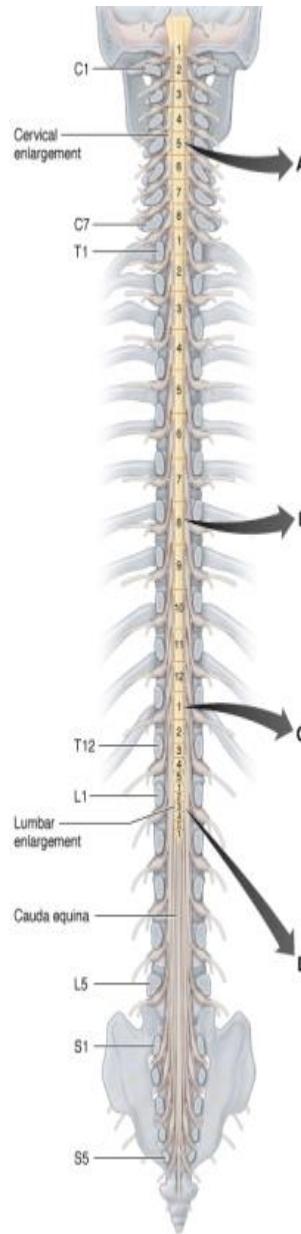
Lateral fissure
Separates the temporal lobe from the frontal & parietal lobes



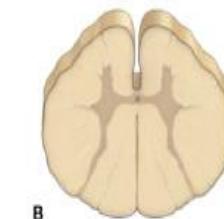
Central sulcus
Separates the frontal lobe from the parietal lobe



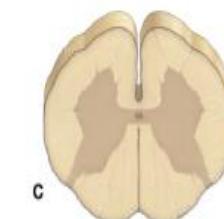
Spinal Cord



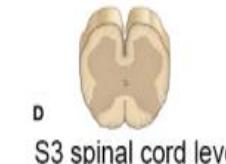
A
C5 spinal cord level



B
T8 spinal cord level

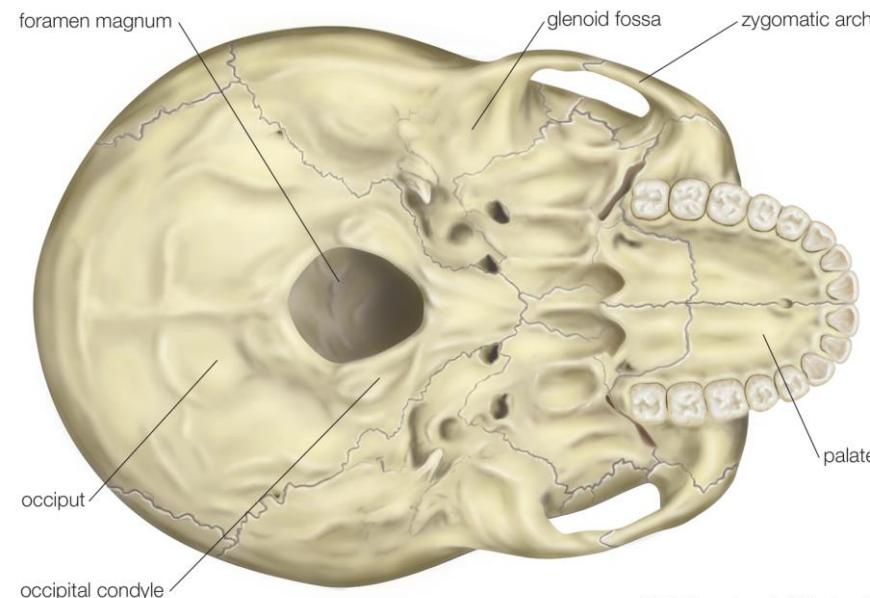


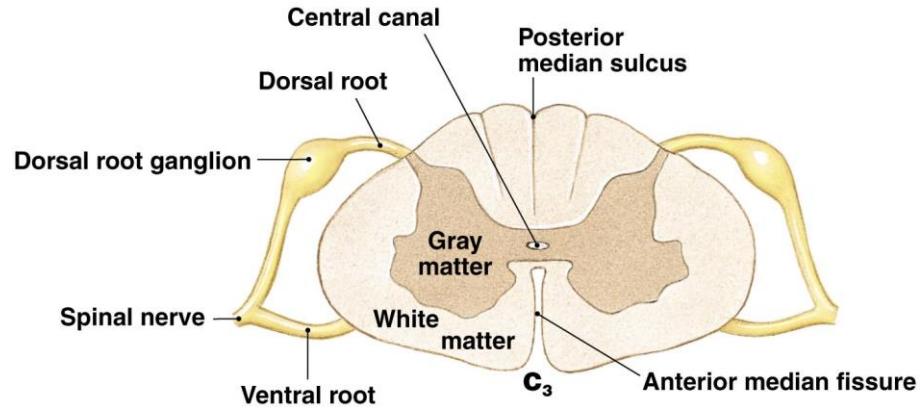
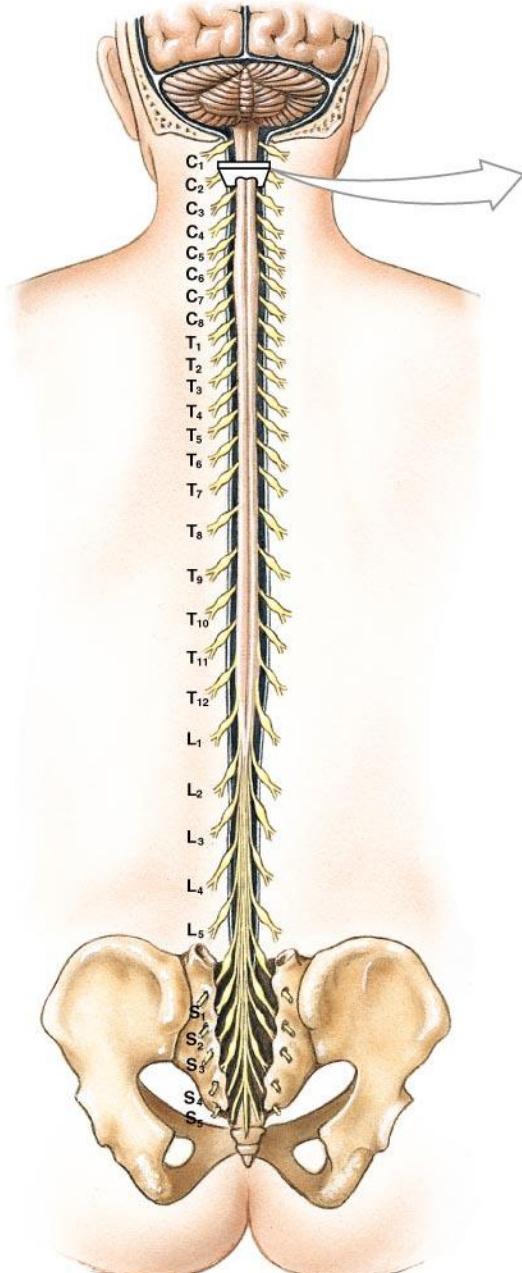
C
L1 spinal cord level



D
S3 spinal cord level

- Spinal cord is the pathway for messages sent by the brain to the body and from the body to the brain.
- Begins at foramen magnum & ends at L2 vertebral level
- Has 2 thickened areas-
 - cervical enlargement - supplies nerves to upper extremity
 - lumbar enlargement - supplies nerves to lower extremity
- Made up of 31 spinal cord segments





Each spinal cord segment has a pair of

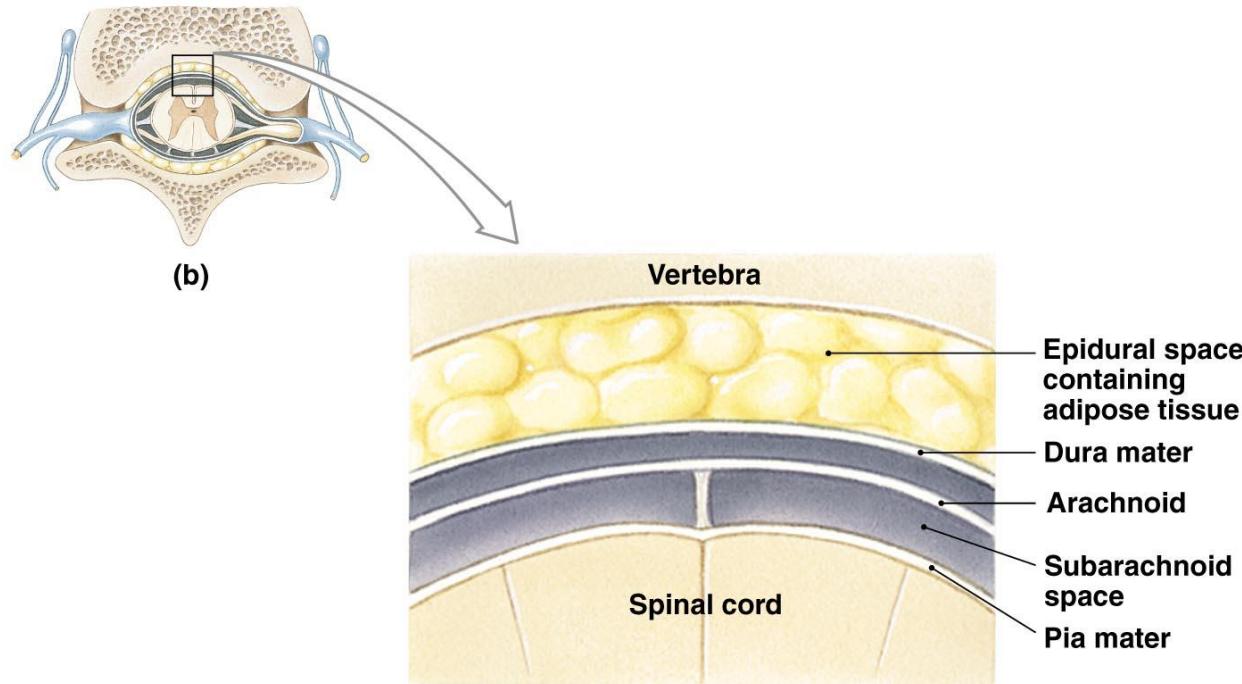
- *dorsal roots* with their associated *dorsal root ganglia (DRG)*
- *ventral roots*
- Each dorsal root contains the axons of sensory neurons
- Each dorsal root ganglion contains the cell bodies of these sensory neurons
- Each ventral root contains the axons of motor neurons
- The dorsal & ventral roots of each segment come together at the intervertebral foramen (IVF) to form a mixed spinal nerve

MENINGES – membranes that surround and protect the CNS. Three layers:

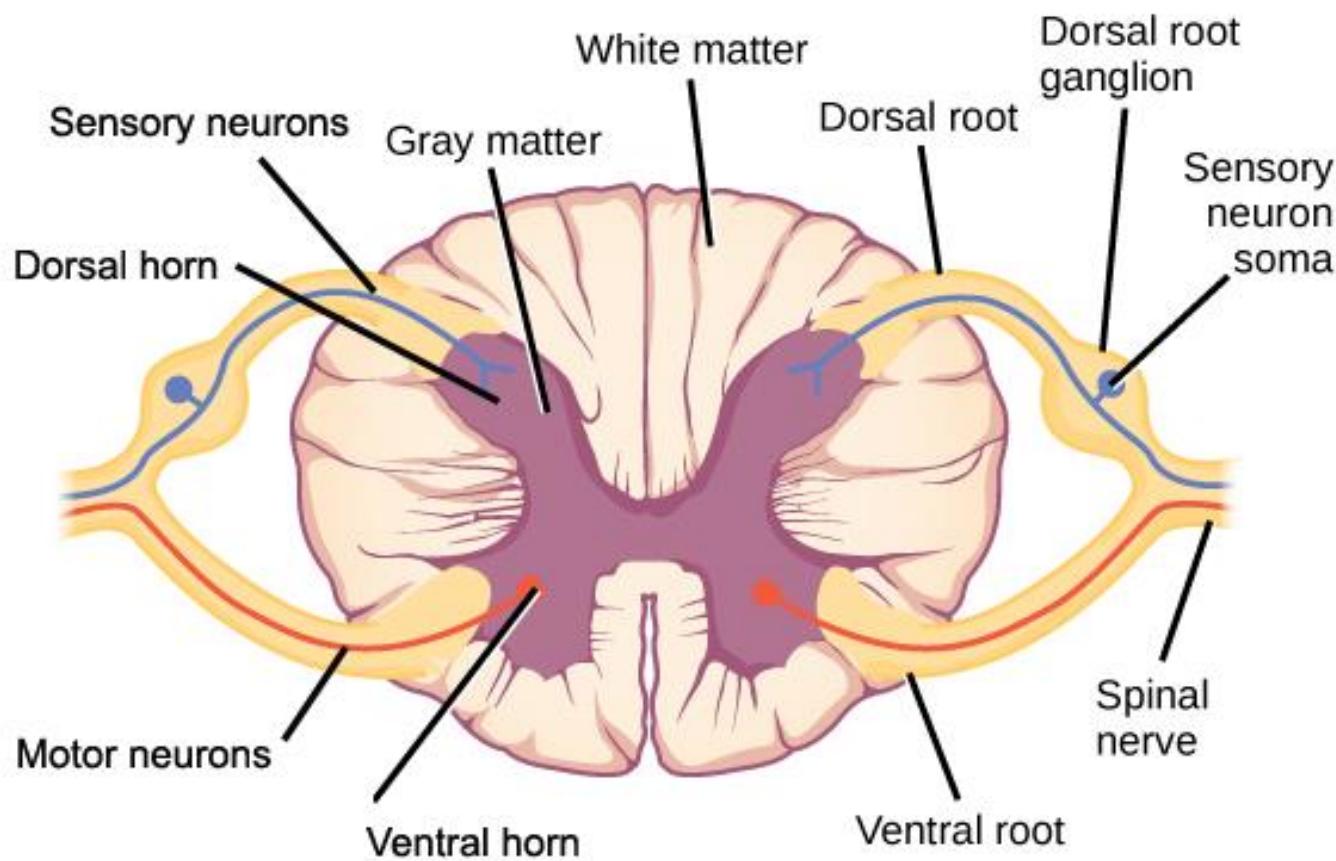
Dura Mater – tough, fibrous CT outer membrane; one layer thick around spinal cord with epidural space external

Arachnoid mater – “spidery” web-like middle layer

Pia Mater – delicate, thin inner layer



Subarachnoid space – between arachnoid & pia mater; contains **cerebrospinal fluid (CSF)**

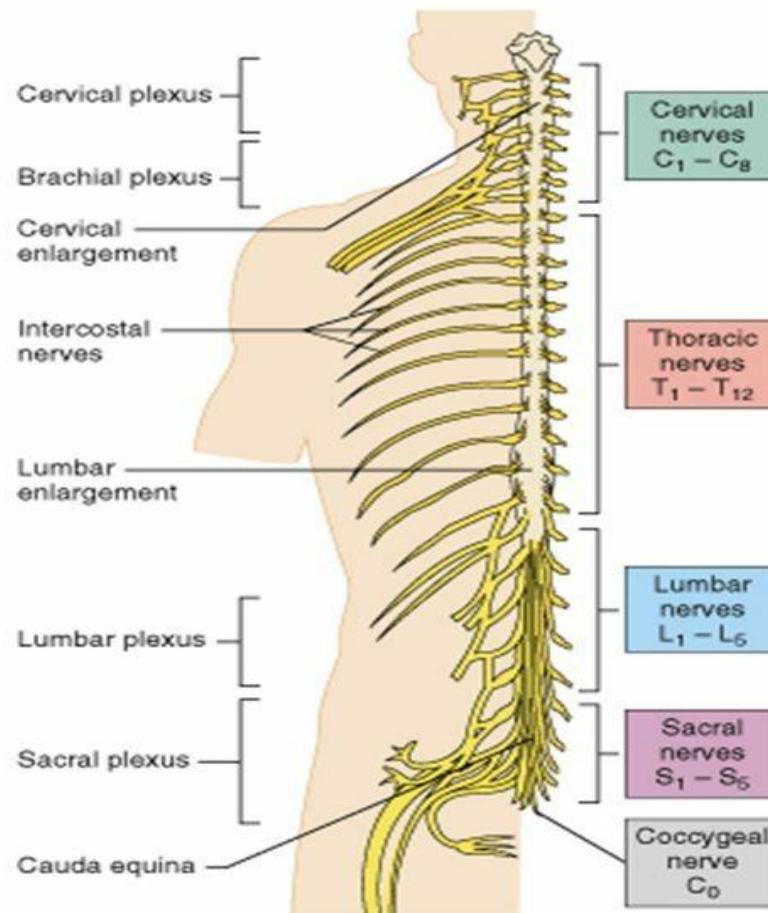


Cross Section of Spinal Cord

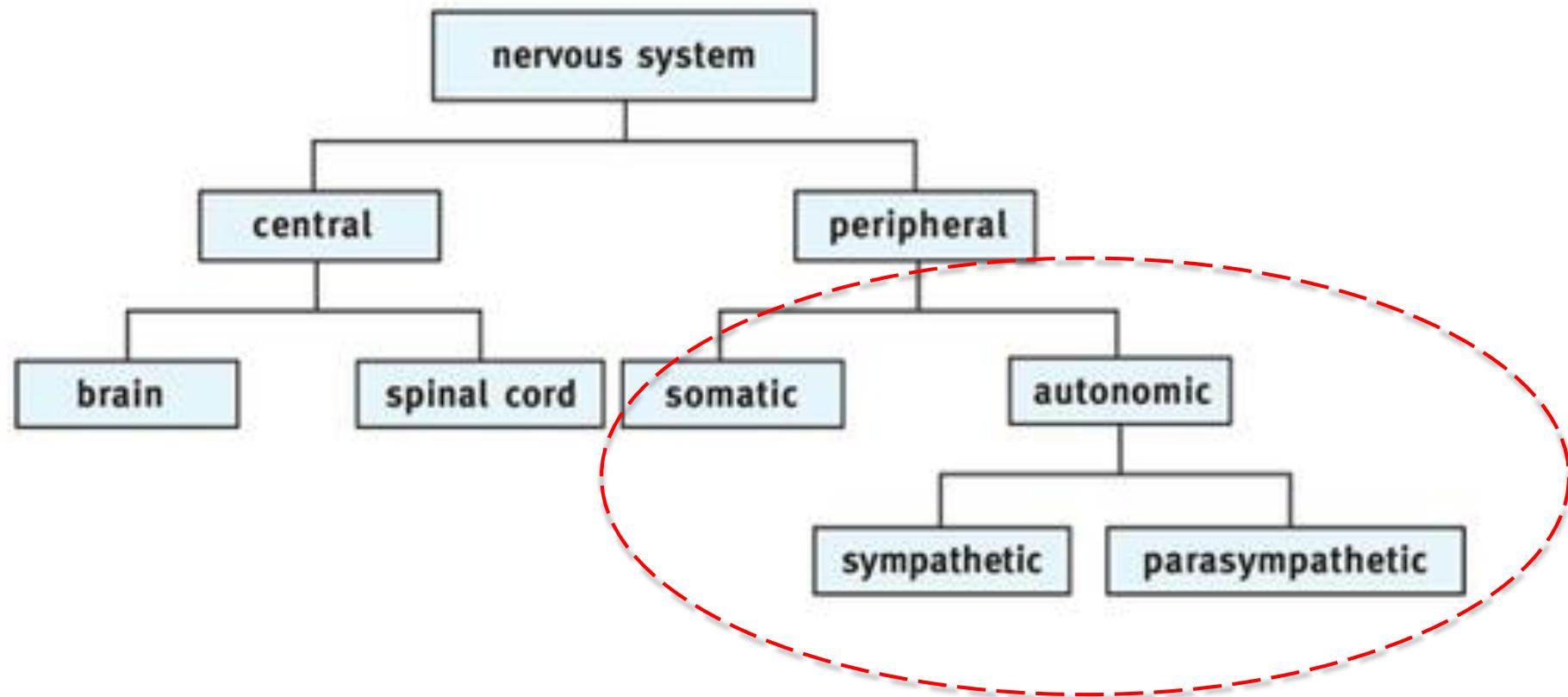
Peripheral Nervous System

Peripheral Nervous System (PNS) is composed of the sensory and motor neurons that connects the central nervous system (CNS) to the rest of the body:

- cranial nerves (12 pairs)
- spinal nerves (31 pairs)
- **31 nerves connecting the spinal cord and various body regions.**
 - 8 paired cervical nerves
 - 12 paired thoracic nerves
 - 5 paired lumbar nerves
 - 5 paired sacral nerves
 - 1 pair of coccygeal nerves

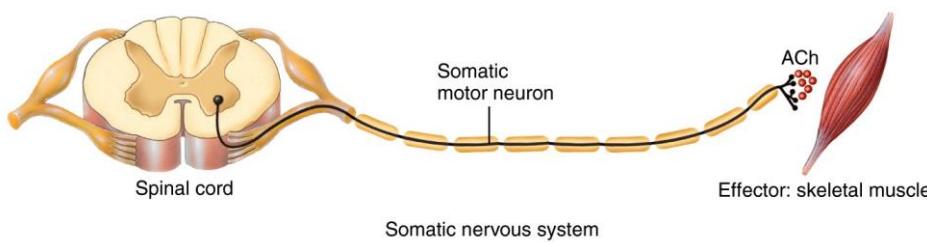


Peripheral Nervous System



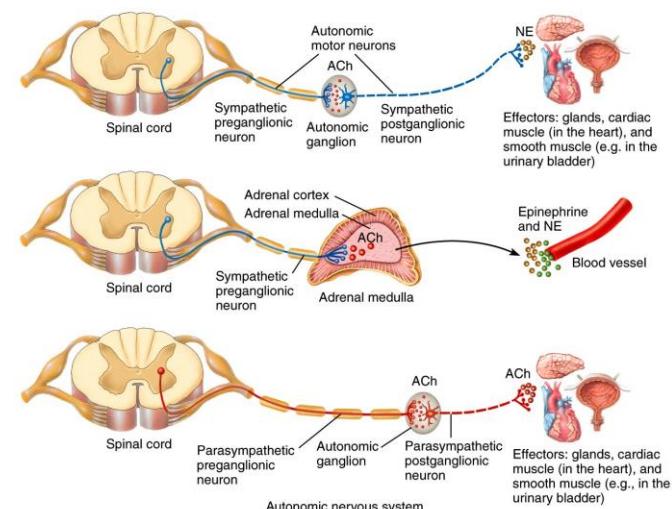
- SNS

- Controls skeletal muscle
- Conscious, voluntary control
- Motor pathway: one neuron from CNS to effector
- Does include sensory neurons (from skin, skeletal muscles, and special sense organs)
- All release the neurotransmitter ACh



- ANS

- Controls viscera: smooth and cardiac muscle, and glands
- Unconscious, involuntary
- Motor pathway: series of two neurons from CNS to effector
- Does include sensory neurons (monitors viscera)
- Release either ACh or NE
- Two divisions: sympathetic, parasympathetic

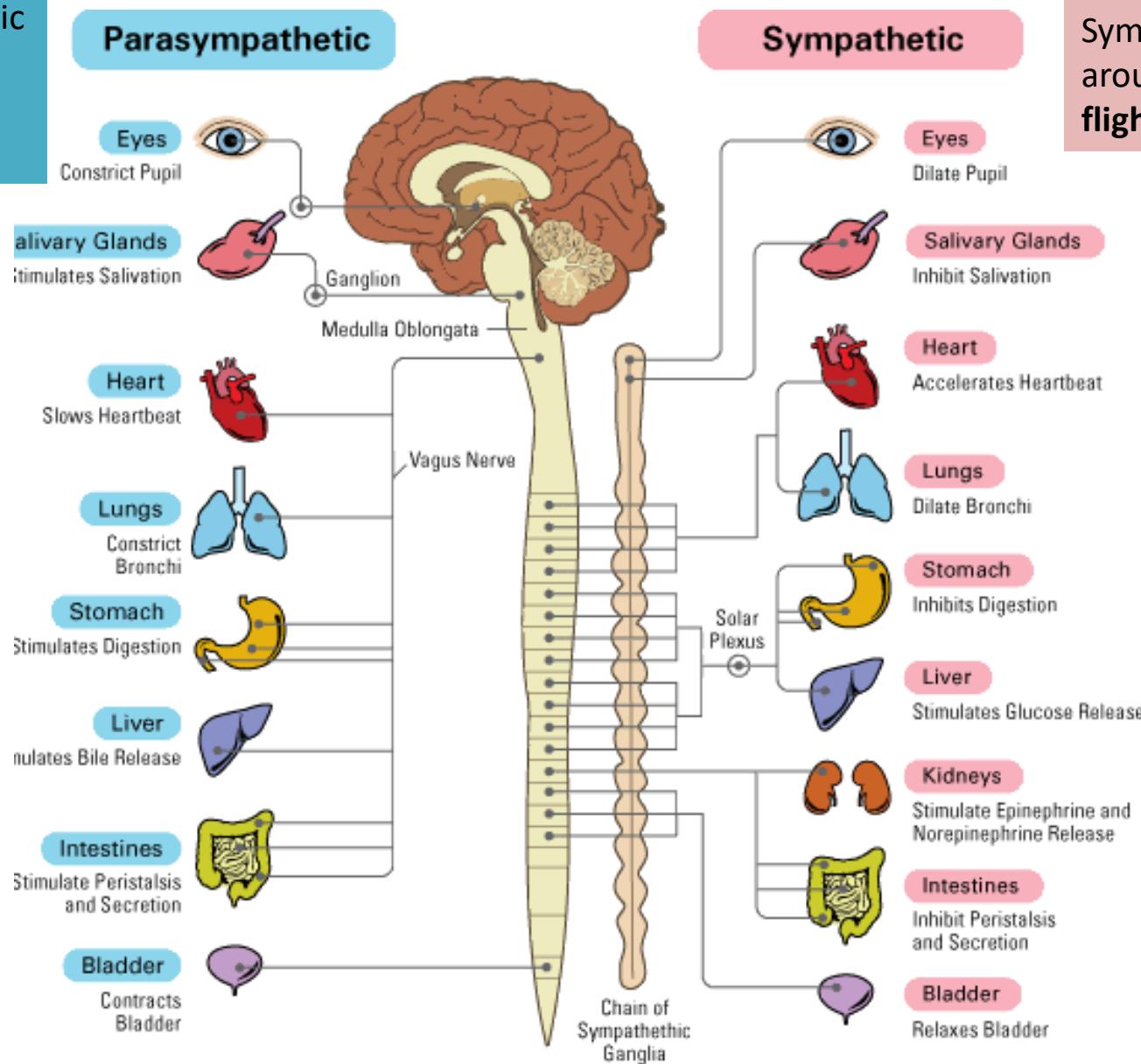


Sympathetic Nervous System: Divisions of the ANS that arouses the body, mobilizing its energy in stressful situations.

Parasympathetic Nervous System: Division of the ANS that calms the body, conserving its energy.

How sympathetic and parasympathetic nervous systems regulate functioning organs?

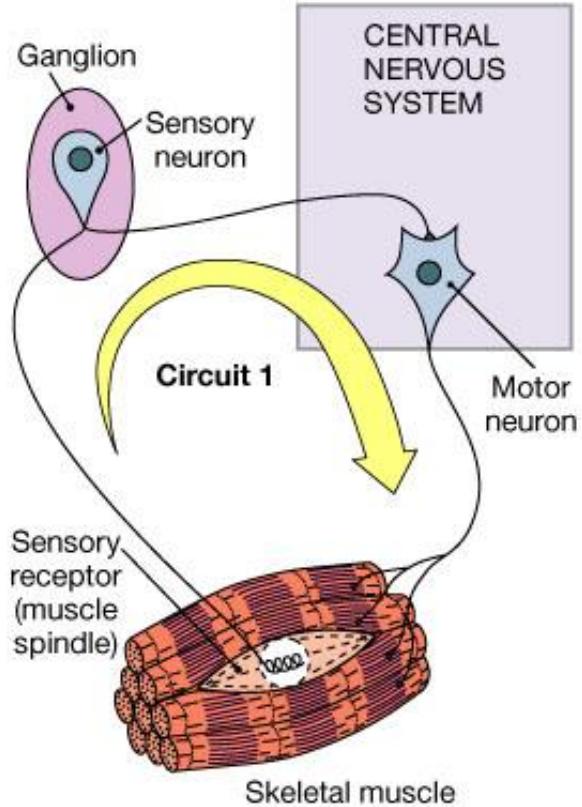
Parasympathetic NS calms (rest and digest activites)



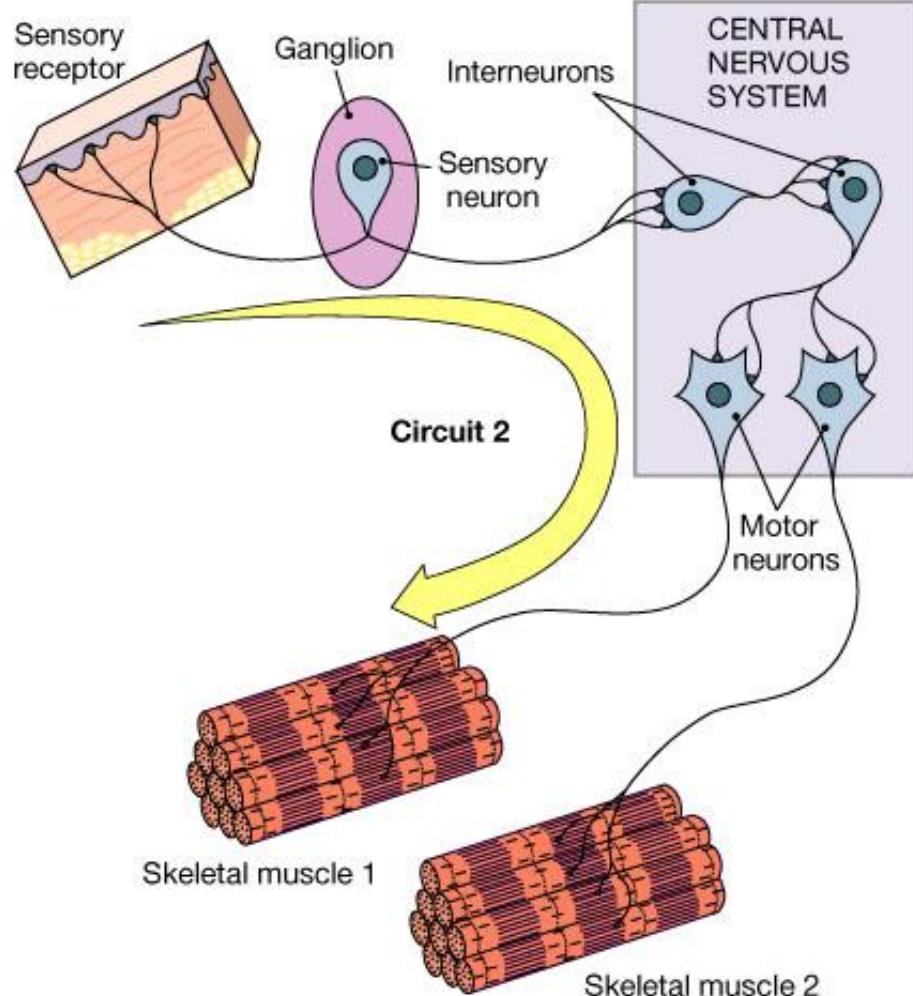
Sympathetic NS arouses (fight or flight activites)



Neural Organization and Simple Reflexes



(a) Monosynaptic reflex

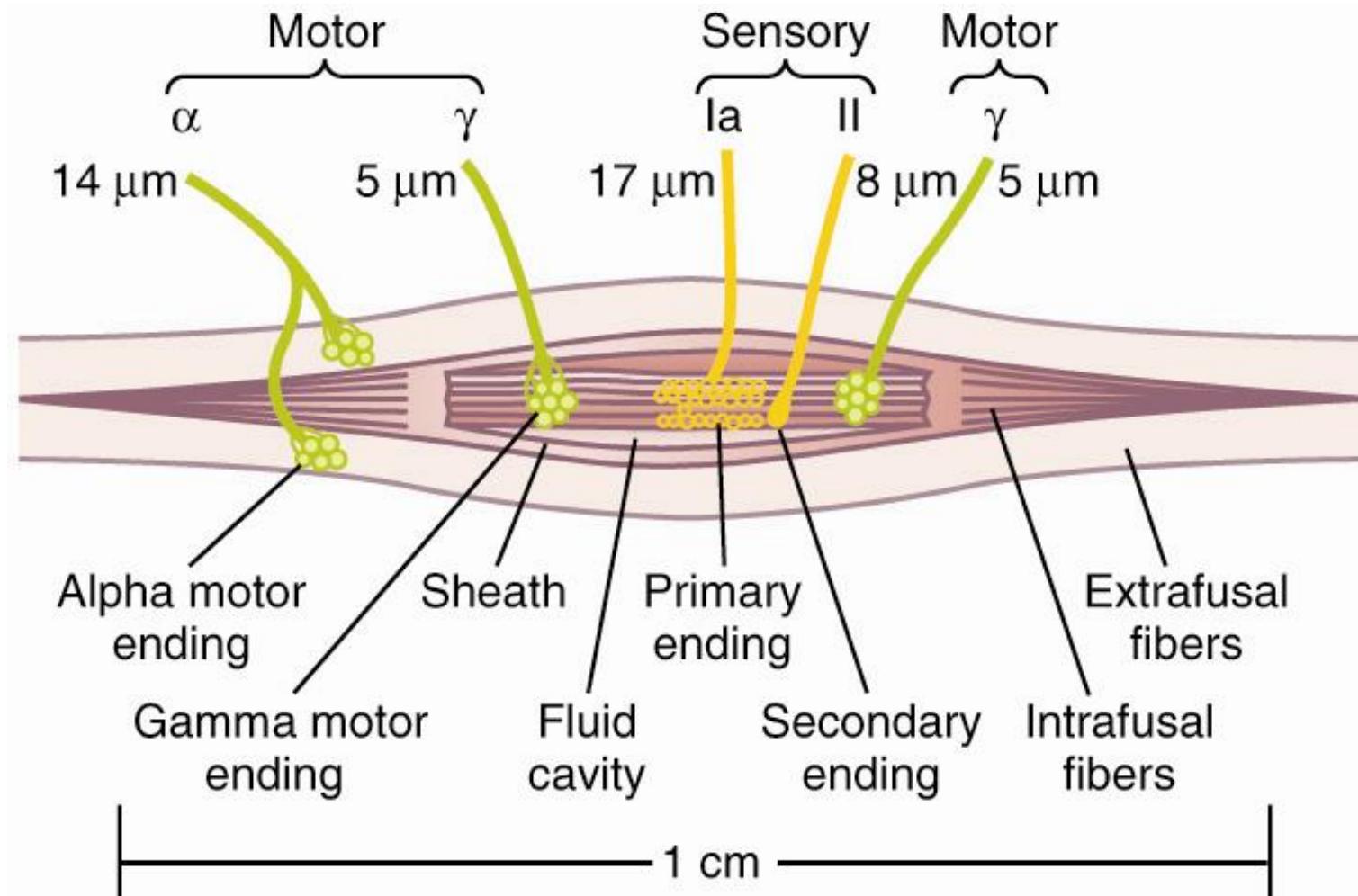


(b) Polysynaptic reflex

Anterior Motor Neurons

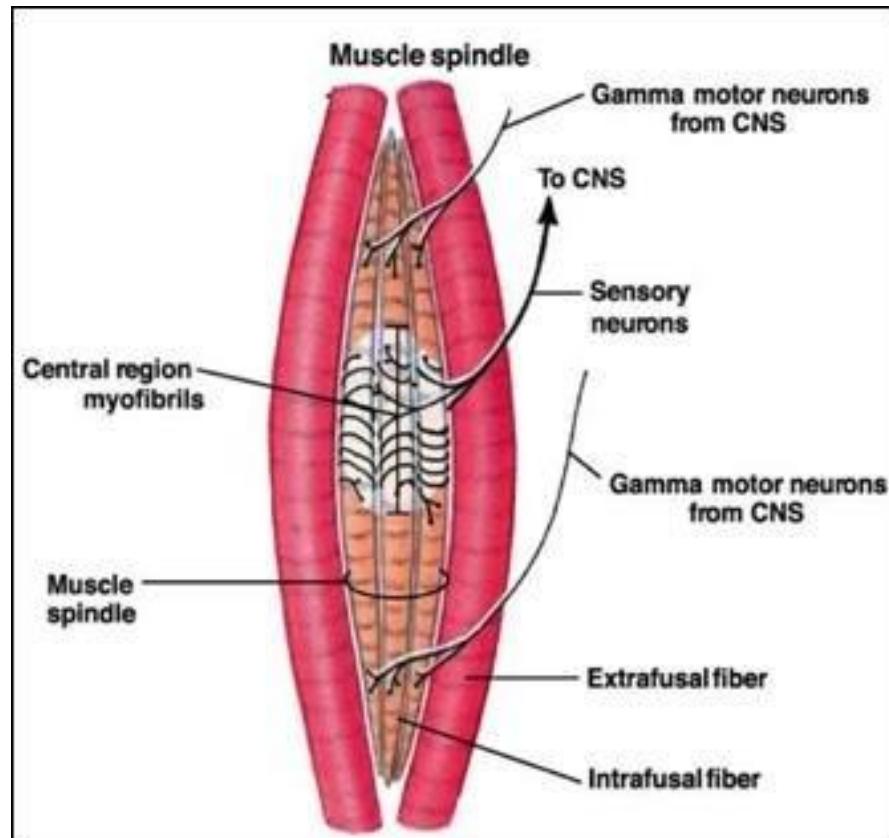
- Alpha motor neurons
 - give rise to large type A alpha fibers (~14 microns).
 - stimulation can excite 3 - 100 *extrafusal* muscle fibers collectively called a motor unit
- Gamma motor neurons
 - give rise to smaller type A gamma fibers (~5 microns)
 - stimulation excites *intrafusal fibers*, a special type of sensory receptor

- sense muscle length and change in length

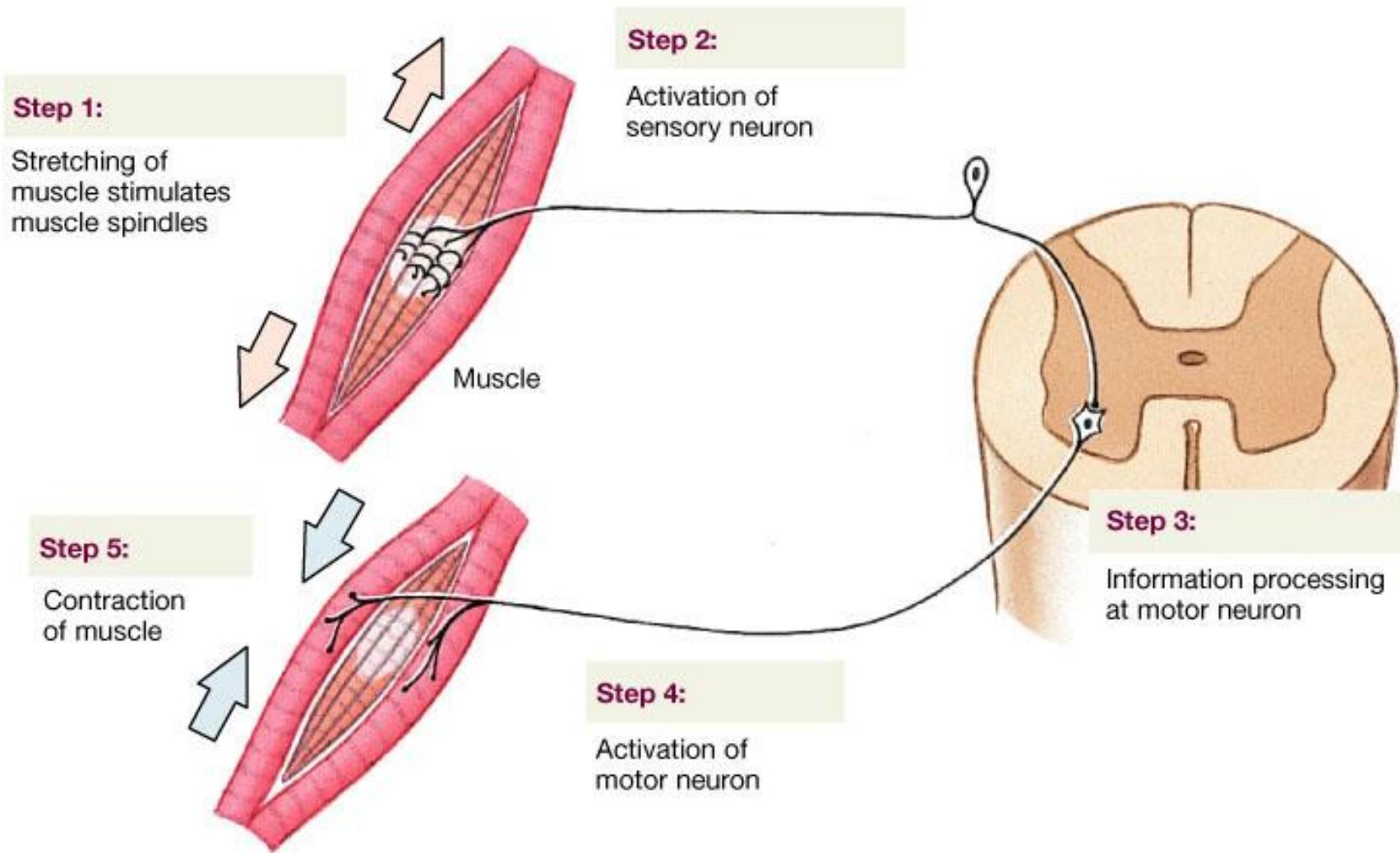


Physiologic Function of the Muscle Spindle

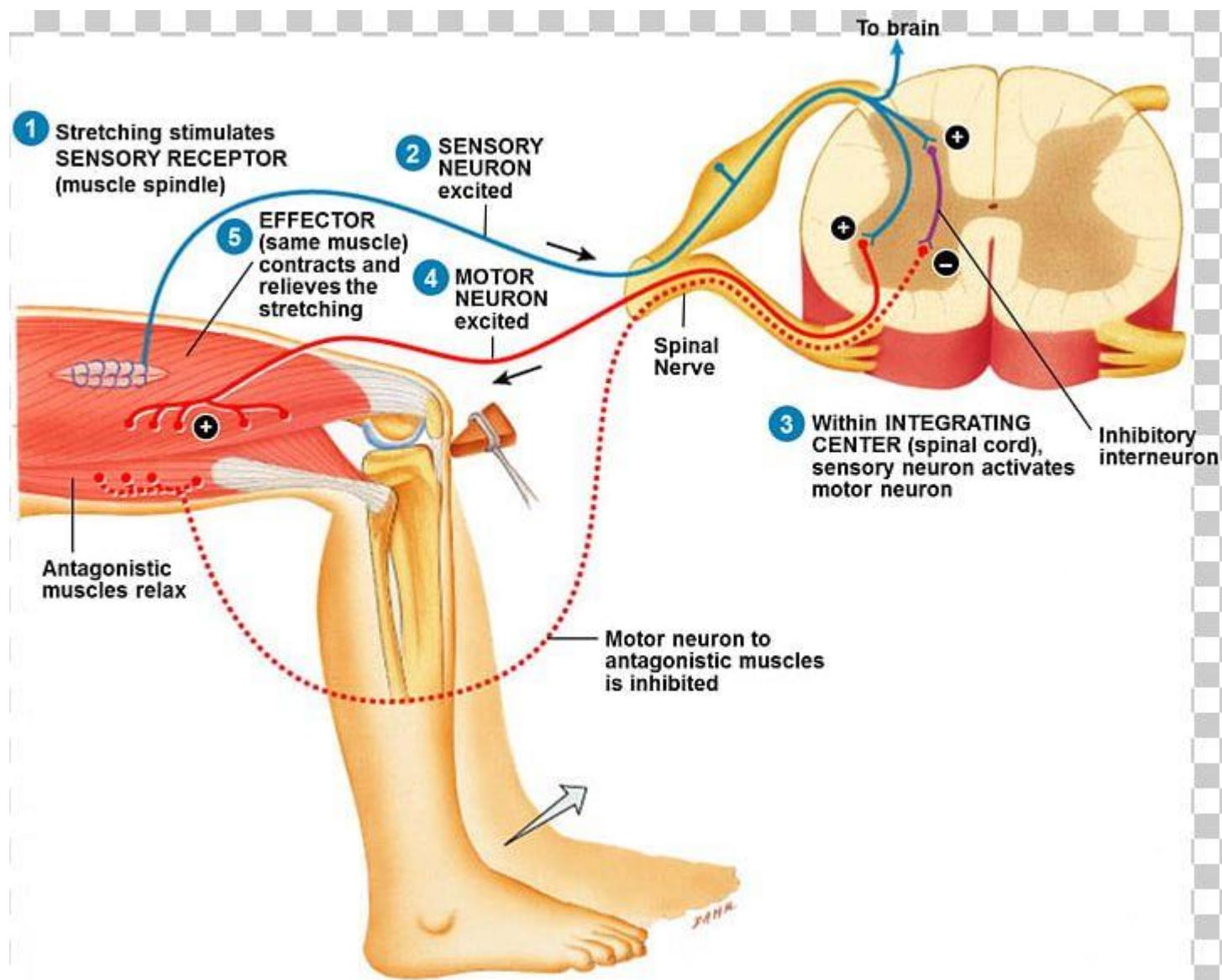
- **Muscle spindles** can be defined as small, spindle-shaped sensory receptors located in skeletal muscle tissue.
- Compares length between the intrafusal and extrafusal muscle fiber.
- Opposes a change in length of the muscle.
- When the muscle is stretched, the spindle returns it to its original length.
- Leads to the stretch reflex.



Components of the Stretch Reflex



The Patellar Reflex (knee-jerk reflex)



The Withdrawal Reflexes

- A painful stimulus causes the limb to automatically withdraw from the stimulus.
- Neural pathways for reflex:
 - nociceptor activation transmitted to the spinal cord
 - synapses with pool of interneurons that diverge to the muscles for withdrawal, inhibit antagonist muscles, and activate reverberating circuits to prolong muscle contraction
 - duration of the after discharge depends on strength of the stimulus

FLEXION vs EXTENSION

Flexion – forward movement that diminishes a joint angle and shortens the angle between two bones.

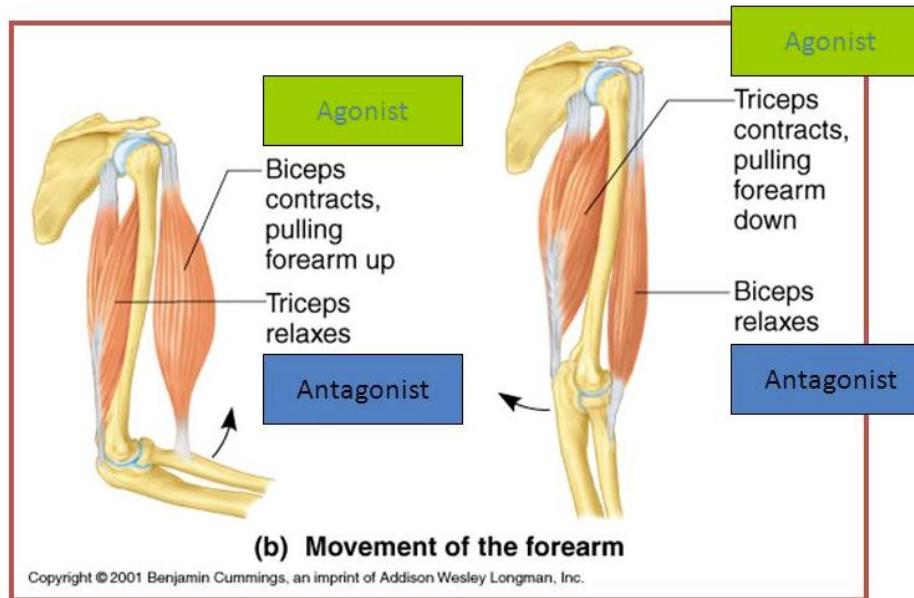
Extension – backward movement that increases a joint angle and lengthens the angle between two bones.

For example

- **Antagonist** and **agonist muscles** often occur in pairs, called **antagonistic pairs**. As one muscle contracts, the other relaxes.
- An example of an antagonistic pair is the biceps and triceps; to contract - the triceps relaxes while the biceps contracts to lift the arm.

Agonist and Antagonist

Watch
video # 7

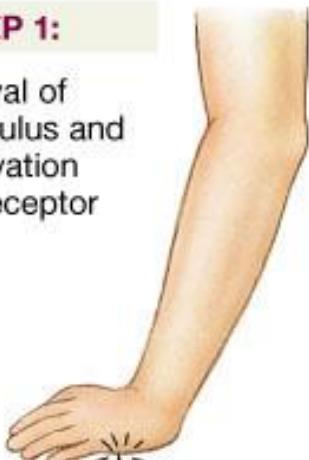


Components of a Flexor Withdrawal Reflex

Watch
video # 8

STEP 1:

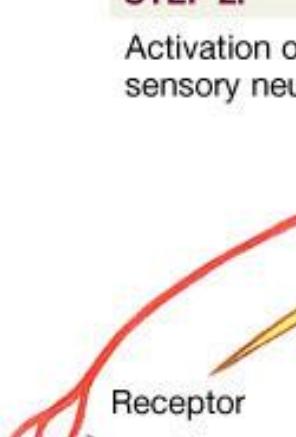
Arrival of stimulus and activation of receptor



Stimulus

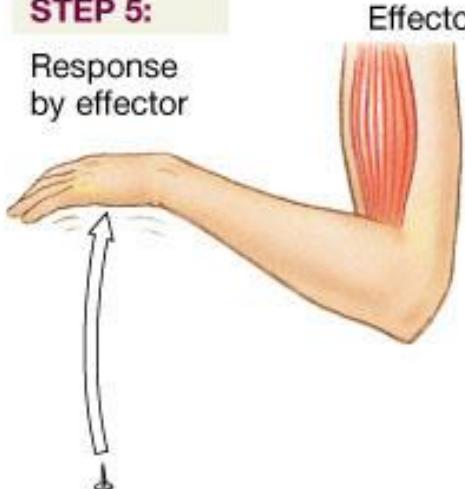
STEP 2:

Activation of a sensory neuron



STEP 5:

Response by effector



Effector

STEP 4:

Activation of a motor neuron



Dorsal root

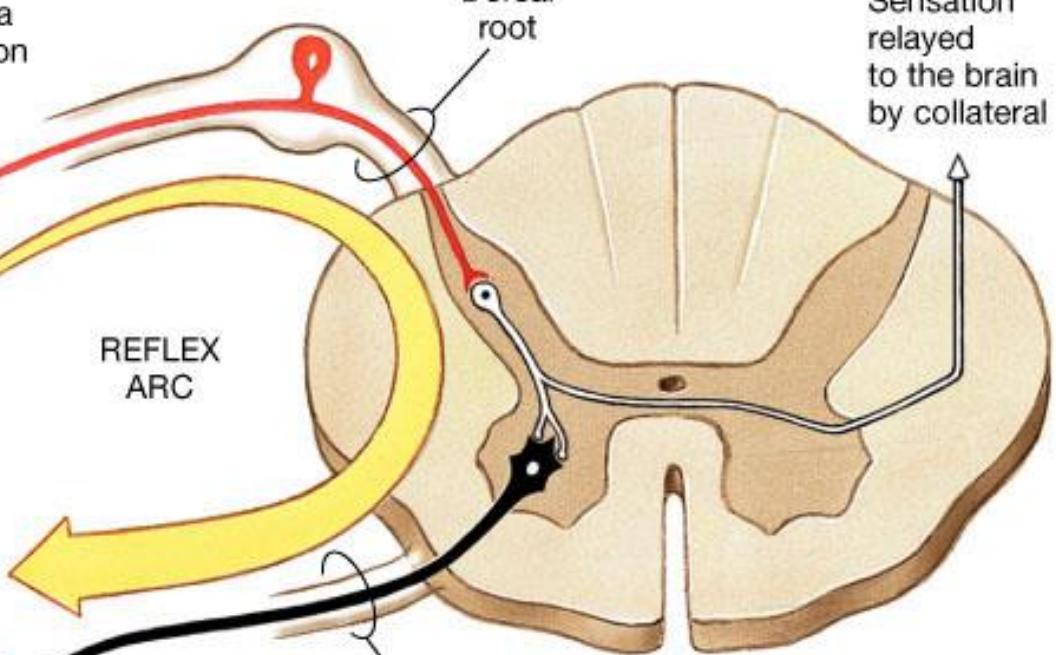
REFLEX ARC

Ventral root

Sensation relayed to the brain by collateral

STEP 3:

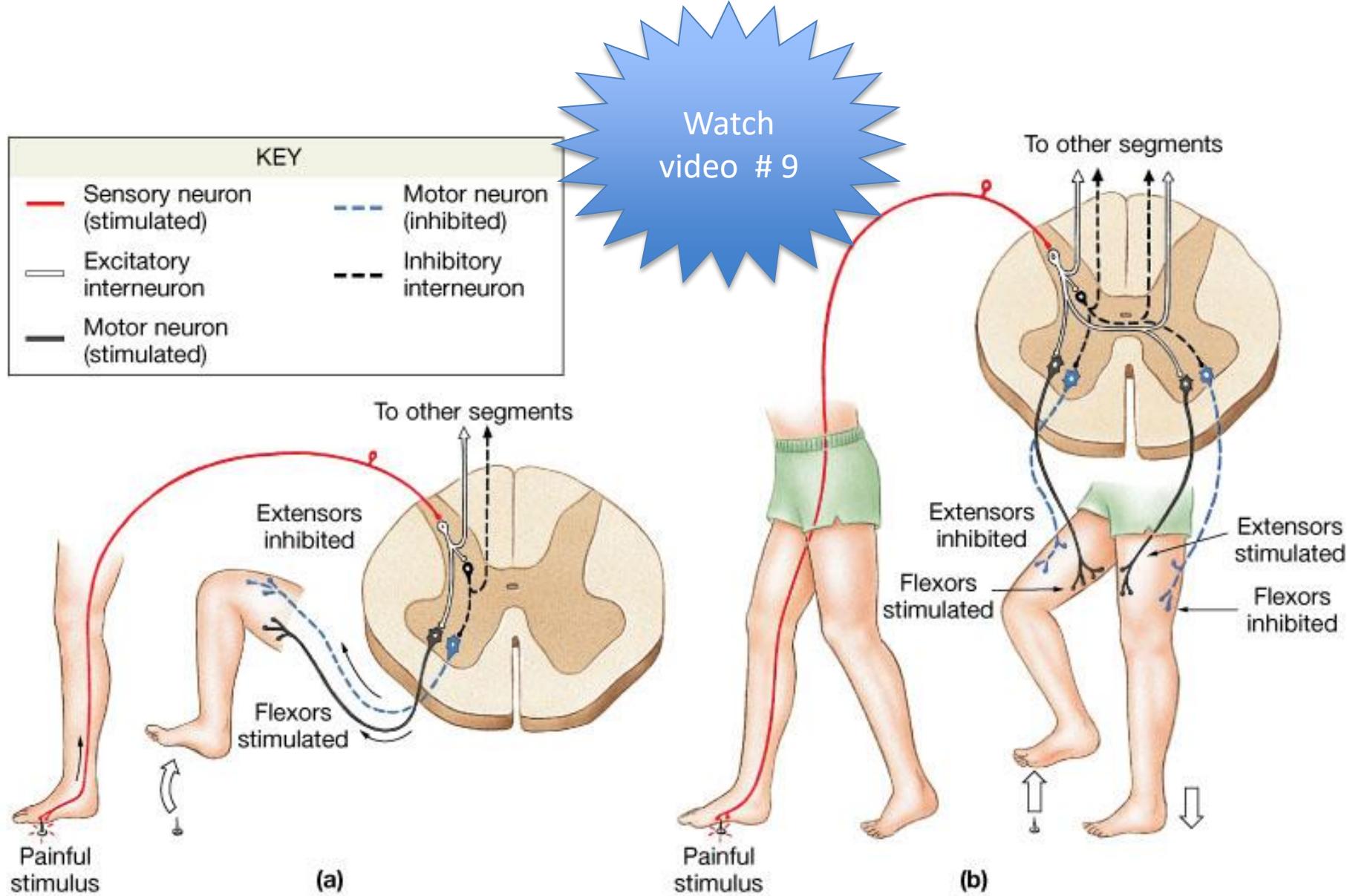
Information processing in CNS



Crossed Extensor Reflex

- Painful stimulus elicits a flexor reflex in affected limb and an extensor reflex in the opposite limb.
- Extensor reflex begins 0.2 - 0.5 seconds after the painful stimulus.
- Serves to push body away from the stimulus, also to shift weight to the opposite limb.

The Flexor Withdrawal/Crossed Extensor Reflexes

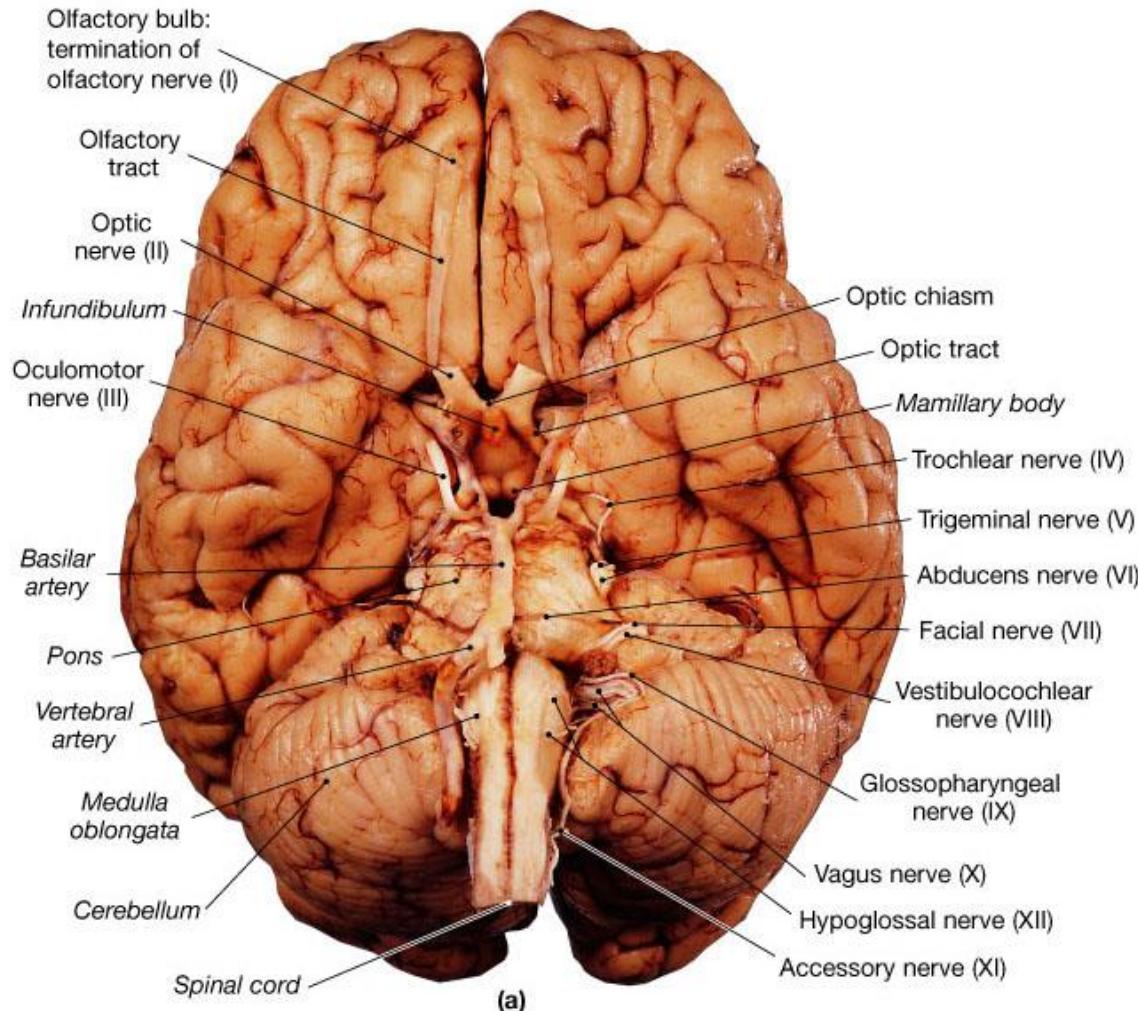


Reflexes that Cause Muscle Spasm

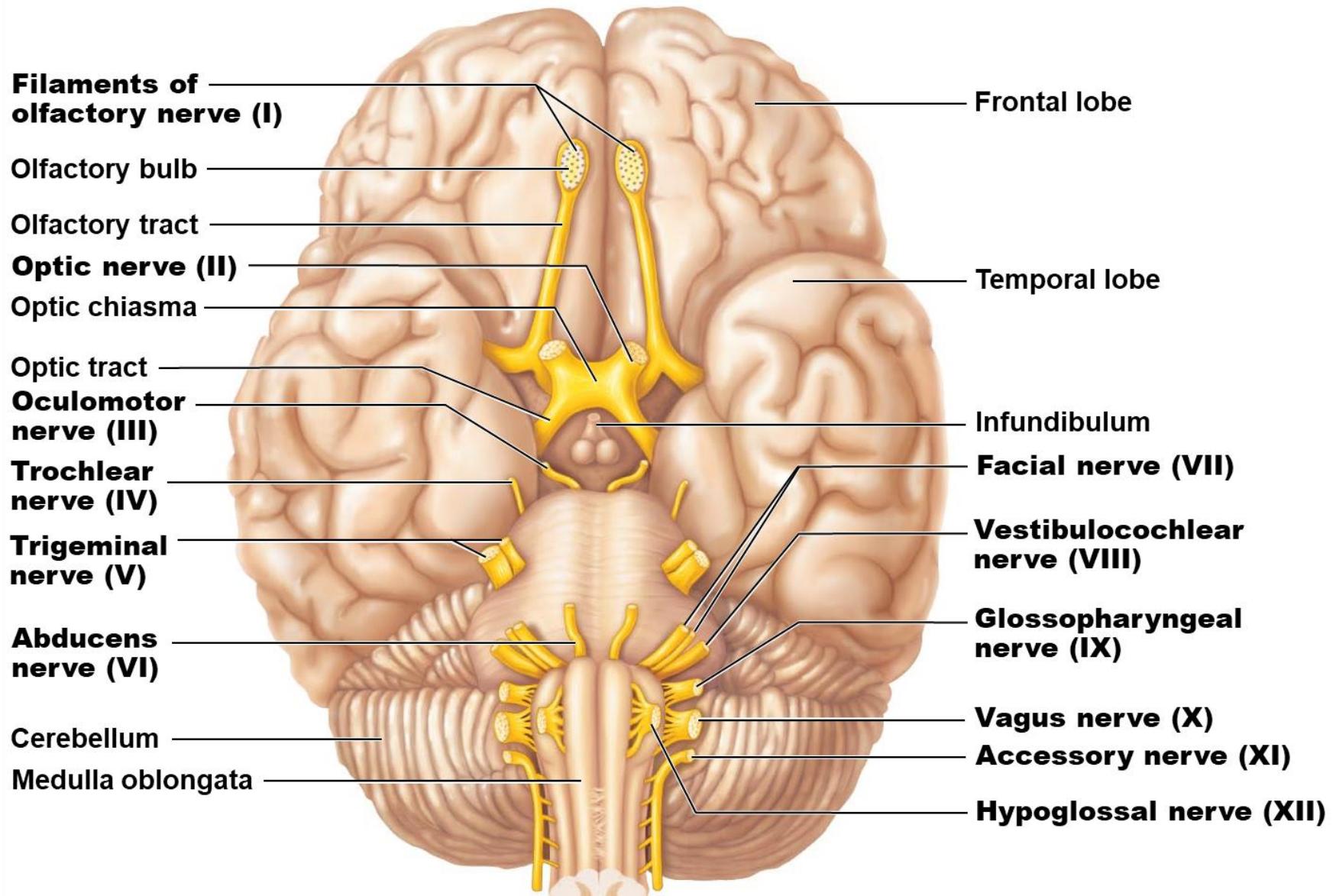
- Pain signals can cause reflex activation and spasm of local muscles.
- Inflammation of peritoneum can cause abdominal muscle spasm.
- Muscle cramps caused by painful stimulus in muscle:
 - can be due to cold, ischemia, or overactivity
 - reflex contraction increases painful stimulus and causes more muscle contraction

Origins of the Cranial Nerves

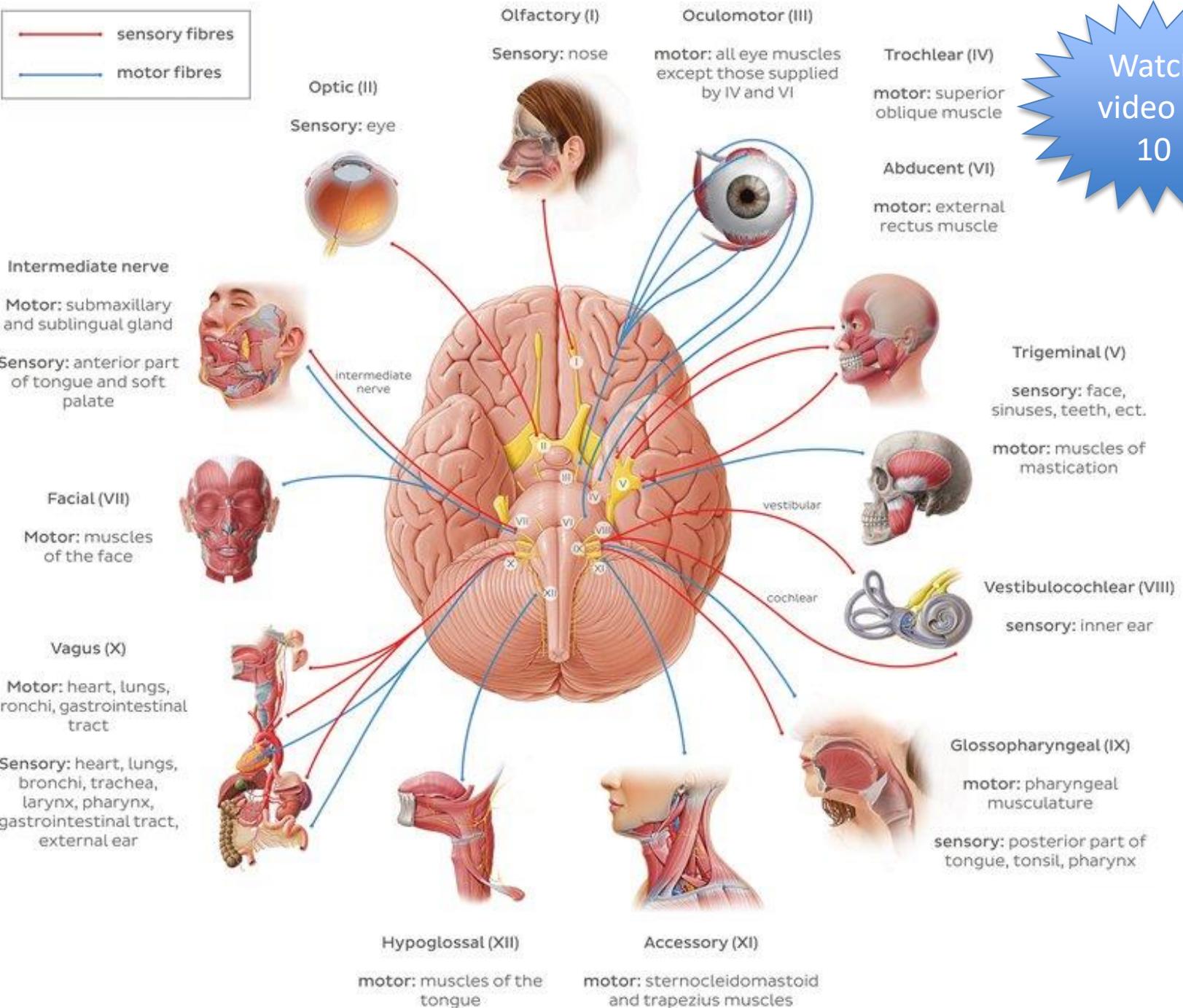
The **cranial nerves** are a set of 12 paired **nerves** that arise directly from the brain. The first two **nerves** (olfactory and optic) arise from the cerebrum, whereas the remaining ten emerge from the brain stem.



Origins of the Cranial Nerves



sensory fibres
 motor fibres



Watch video #
10

Heart

Cardiac Muscle Cells
Hearth Anatomy
Excitation of the Hearth
ECG,Cardiac Cycle
Cardiac Arrythmias

Cardiac Muscle Cells
Chapter 9

Heart function as syncytium

- “ Cardiac muscle cells are mechanically, chemically, and electrically connected to one another, thus, the entire tissue resembles a single, enormous muscle cell. For this reason, cardiac muscle has been called a functional syncytium. ”
- when one cardiac cell undergoes an action potential, the electrical impulse spreads to all other cells that are joined by gap junctions so they become excited and contract as a single functional syncytium.

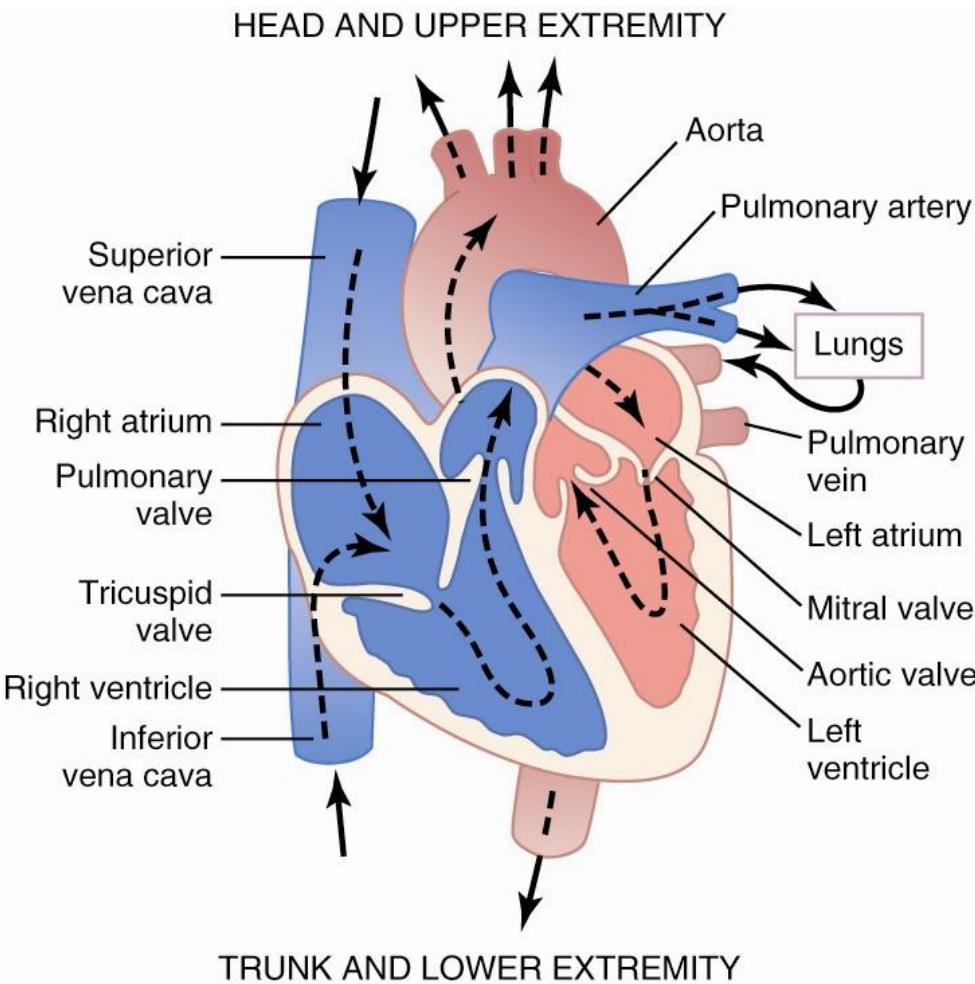


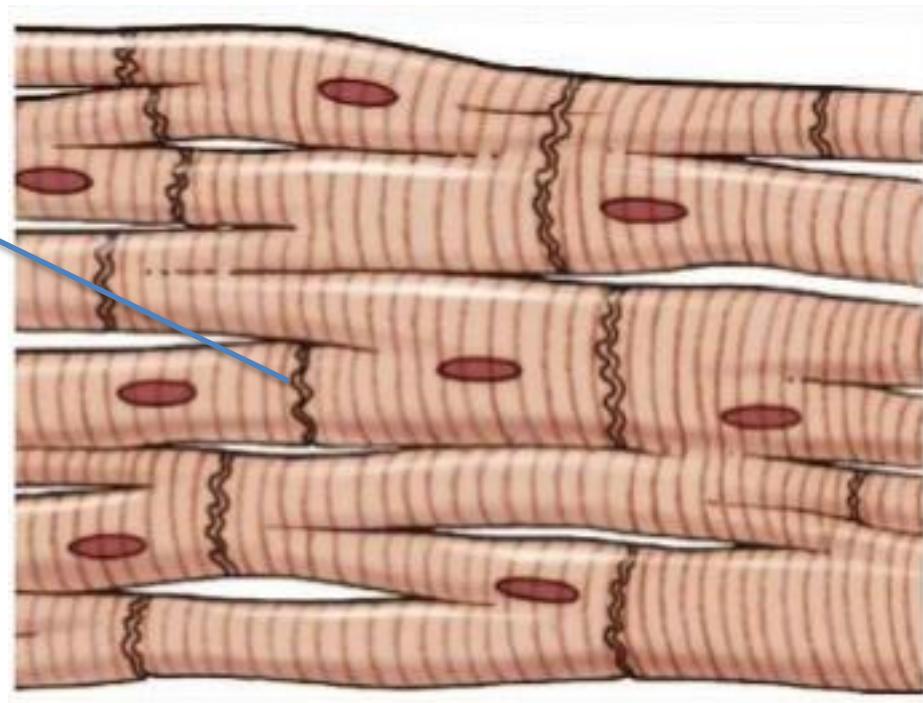
Figure 9-1; Structure of the heart, and course of blood flow through the heart chambers and heart valves.

The heart actually is composed of two syncytiums:

- **Atrial syncytium**
 - constitutes the walls of the two atria
- **Ventricular syncytium**
 - constitutes the walls of the two ventricles
- **Fibrous insulator**
 - exists between atrium and ventricle
 - potentials are not conducted from the atrial syncytium into the ventricular syncytium directly through this fibrous tissue. Instead, they are conducted only by way of a specialized conductive system

■ Cardiac Muscle

The dark areas crossing the cardiac muscle fibers in Figure 9–2 are called *intercalated discs*; they are actually cell membranes that separate individual cardiac muscle cells from one another.

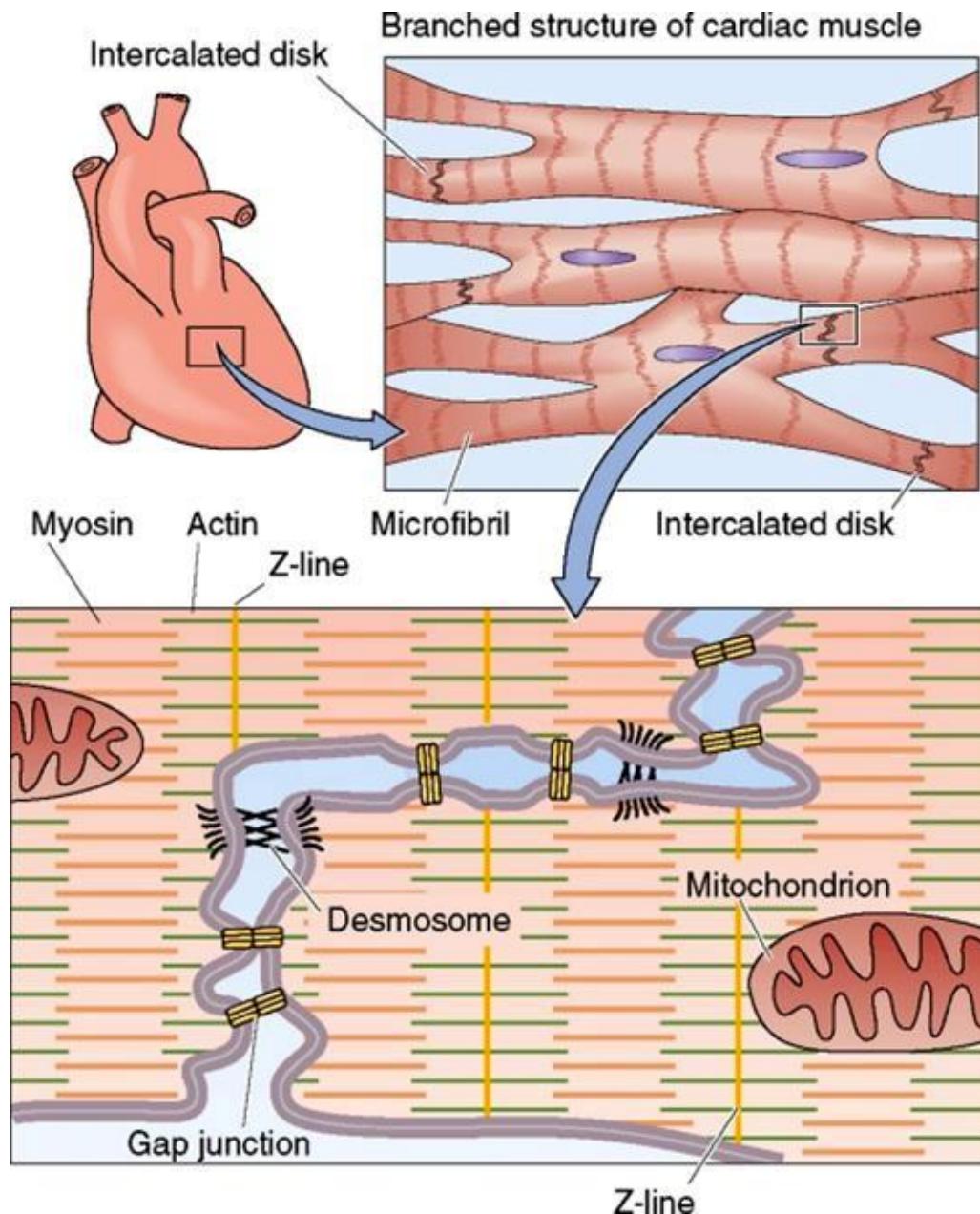


“Syncytial,”
interconnecting
nature of cardiac
muscle fibers.

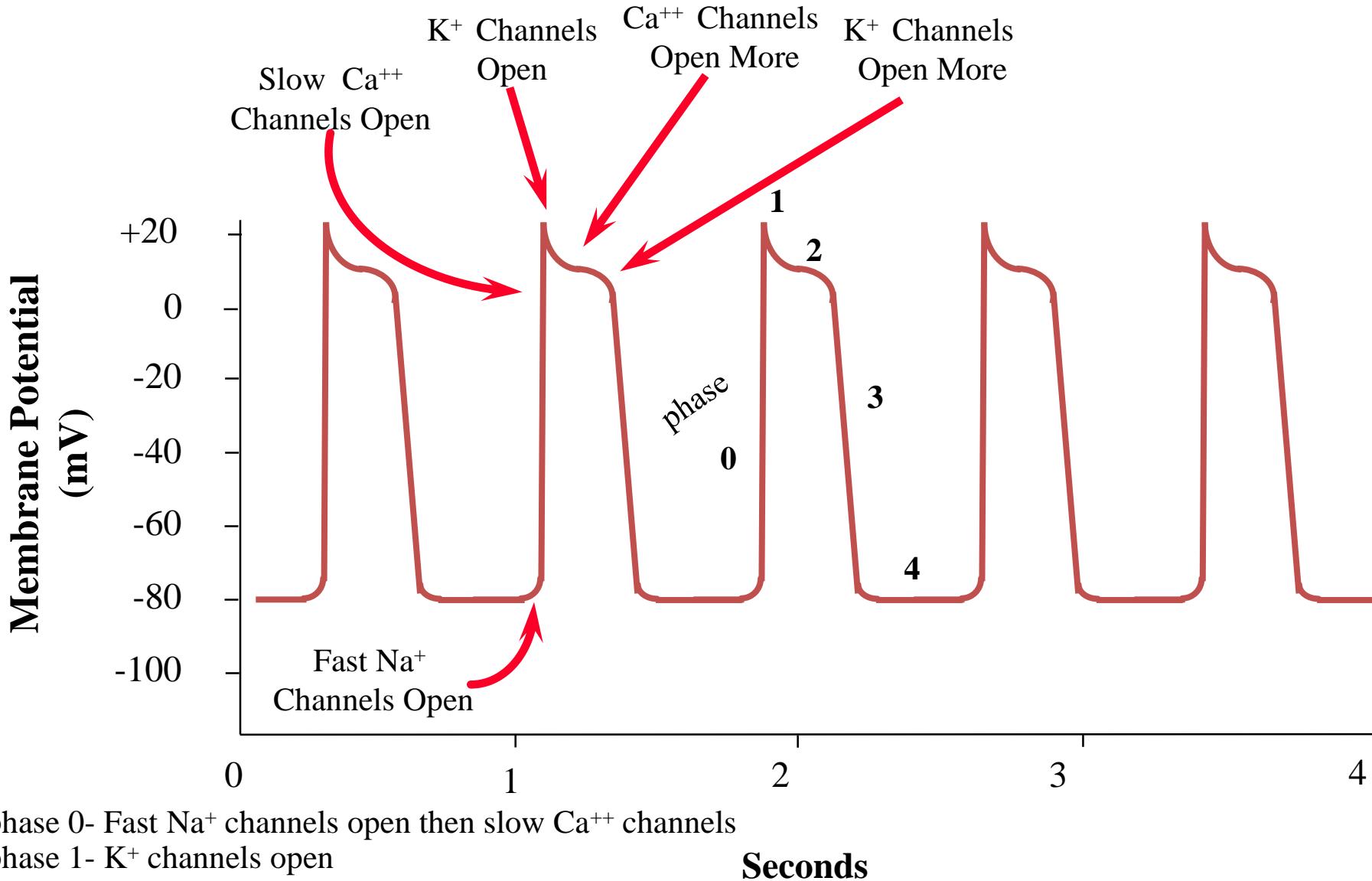
- cardiac muscle fibers arranged in a latticework, with the fibers dividing, recombining, and then spreading again

- cardiac muscle has typical myofibrils that contain actin and myosin filaments almost identical to those found in skeletal muscle
- cardiac muscle fibers are made up of many individual cells connected in series and in parallel with one another. Thus, cardiac muscle is a syncytium of many heart muscle cells in which the cardiac cells are so interconnected that when one of these cells becomes excited, the action potential spreads to all of them, spreading from cell to cell throughout the latticework interconnections.

- **gap junctions** couple the cardiac muscle cells electrically.
- **desmosomes** hold the cardiac muscle cells together during contraction



■ Ventricular Muscle Action Potential



phase 0- Fast Na^+ channels open then slow Ca^{++} channels

phase 1- K^+ channels open

phase 2- Ca^{++} channels open more

phase 3- K^+ channels open more

phase 4- Resting membrane potential

Seconds

Why is the action potential of cardiac muscle so long, and why does it have a plateau, whereas that of skeletal muscle does not?

Skeletal Muscle

- i. the action potential is caused almost entirely by sudden opening of large numbers of
 1. fast sodium channels that allow tremendous numbers of sodium ions to enter the skeletal muscle fiber from the extra-cellular fluid.

Cardiac Muscle

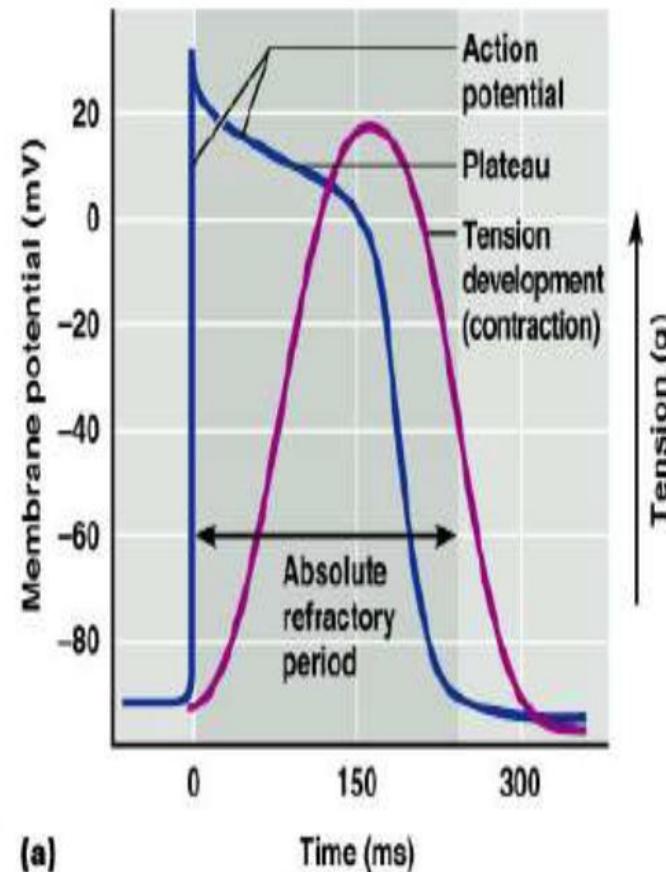
- i. the action potential is caused by opening of two types of channels:
 1. fast sodium channels as those in skeletal muscle
 2. slow calcium channels, which are also called calcium-sodium channels.
- slow calcium channels differs from the fast sodium channels in that they are slower to open and, even more important, remain open for several tenths of a second. During this time, a large quantity of both calcium and sodium ions flows through these channels to the interior of the cardiac muscle fiber, and this maintains a prolonged period of depolarization, causing the plateau in the action potential.

! the calcium ions that enter during plateau phase activate the muscle contractile process, while the calcium ions that cause skeletal muscle contraction are derived from the intracellular sarcoplasmic reticulum

- ii. Immediately after the onset of the action potential, the permeability of the cardiac muscle membrane for potassium ions decreases about fivefold, an effect that does not occur in skeletal muscle

■ Refractory Period

- It is that period during which a second stimulus fails to evoke a response.
- Absolute Refractory Period : It is that period during which a second stimulus however high it is fails to evoke a response.
- Relative Refractory Period : It is that period during which a second stimulus evokes a response if it is sufficiently high.
 - Long refractory period (250 msec) compared to skeletal muscle (3msec)
 - During this period membrane is refractory to further stimulation until contraction is over.
 - It lasts longer than muscle contraction, prevents tetanus
 - Gives time to heart to relax after each contraction, prevent fatigue
 - It allows time for the heart chambers to fill during diastole before next contraction

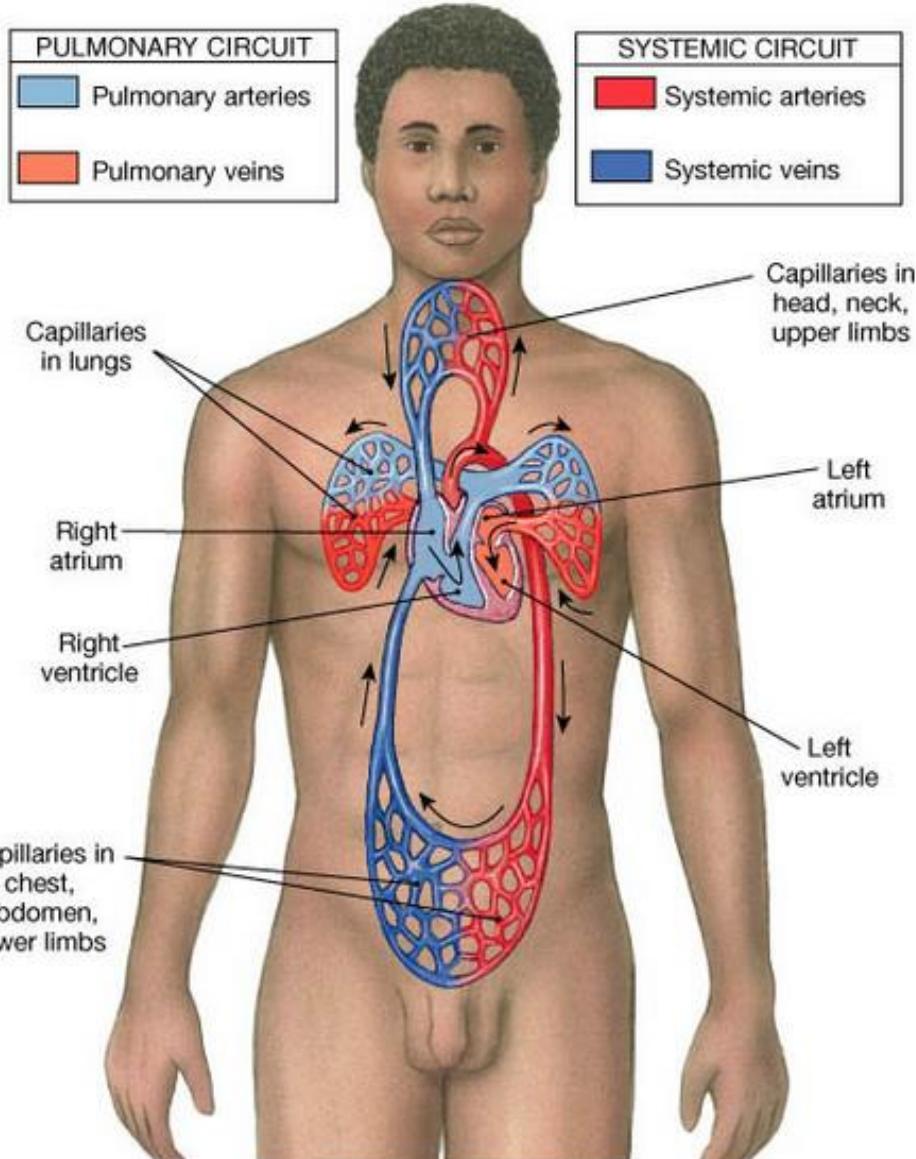


Hearth Anatomy

- The heart is the pump that maintains the circulation of blood. This circulation of blood can be divided into two circuits:

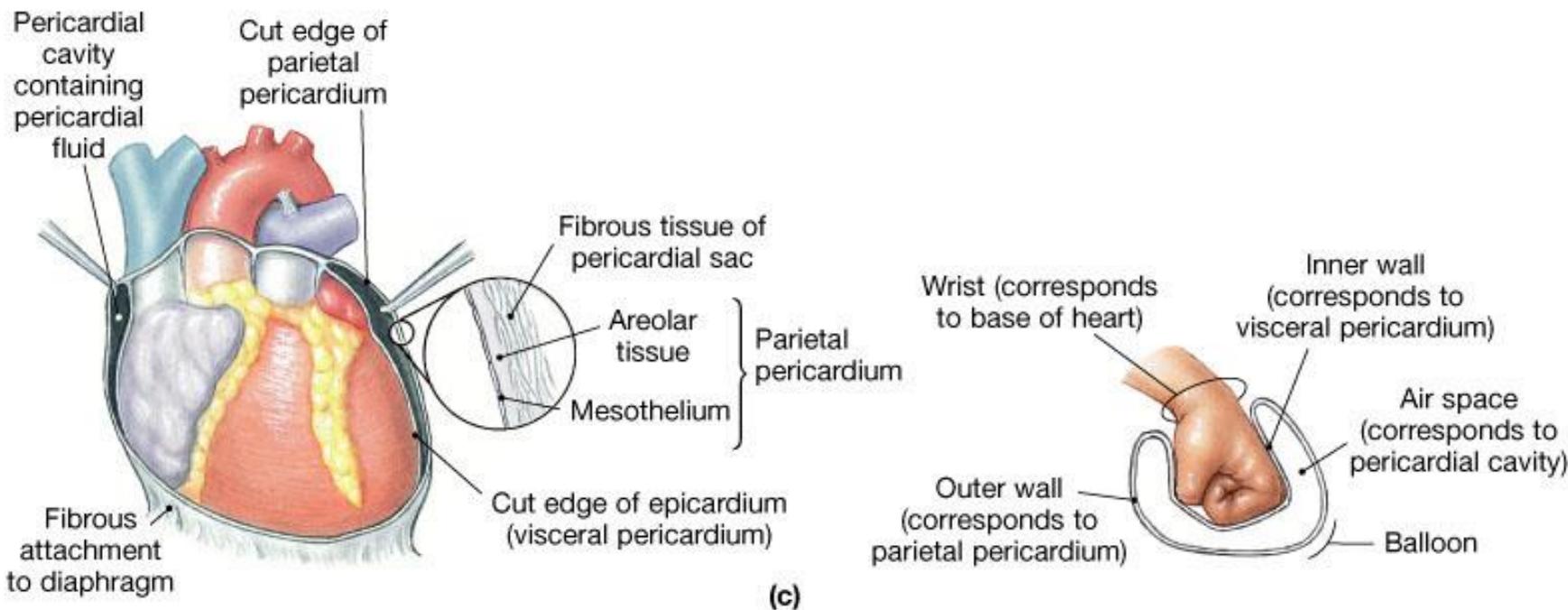
- Pulmonary circuit** carries deoxygenated blood from the heart to the lungs and back to the heart.
- Systemic circuit** carries oxygenated blood from the heart to all the other peripheral tissues and back to the heart.

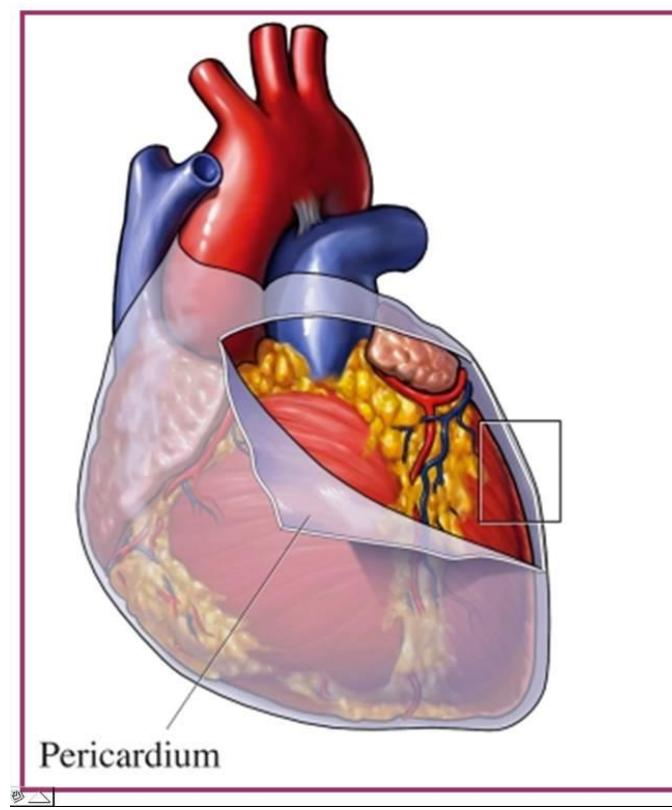
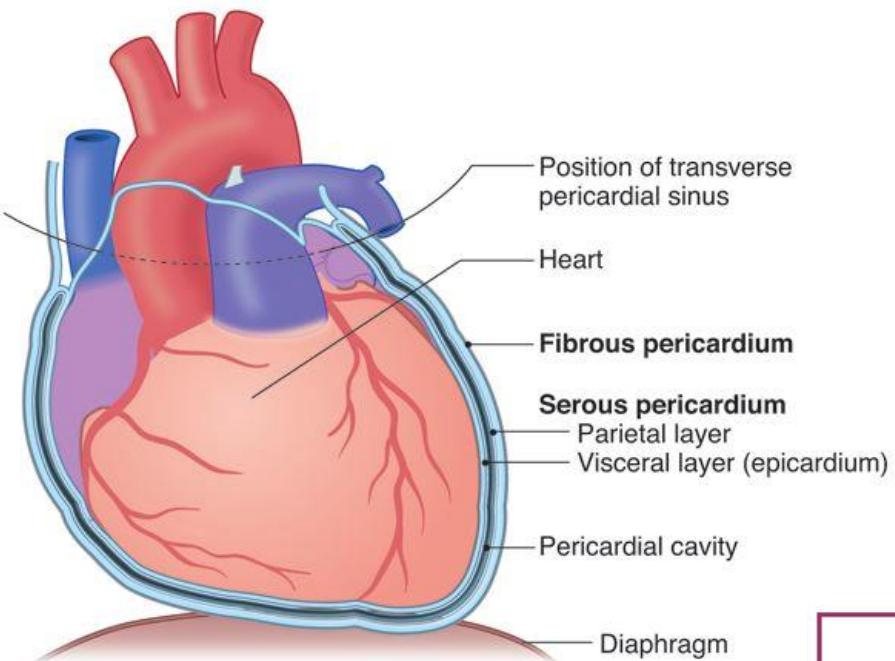
Blood flows through each of these circuits in sequence.



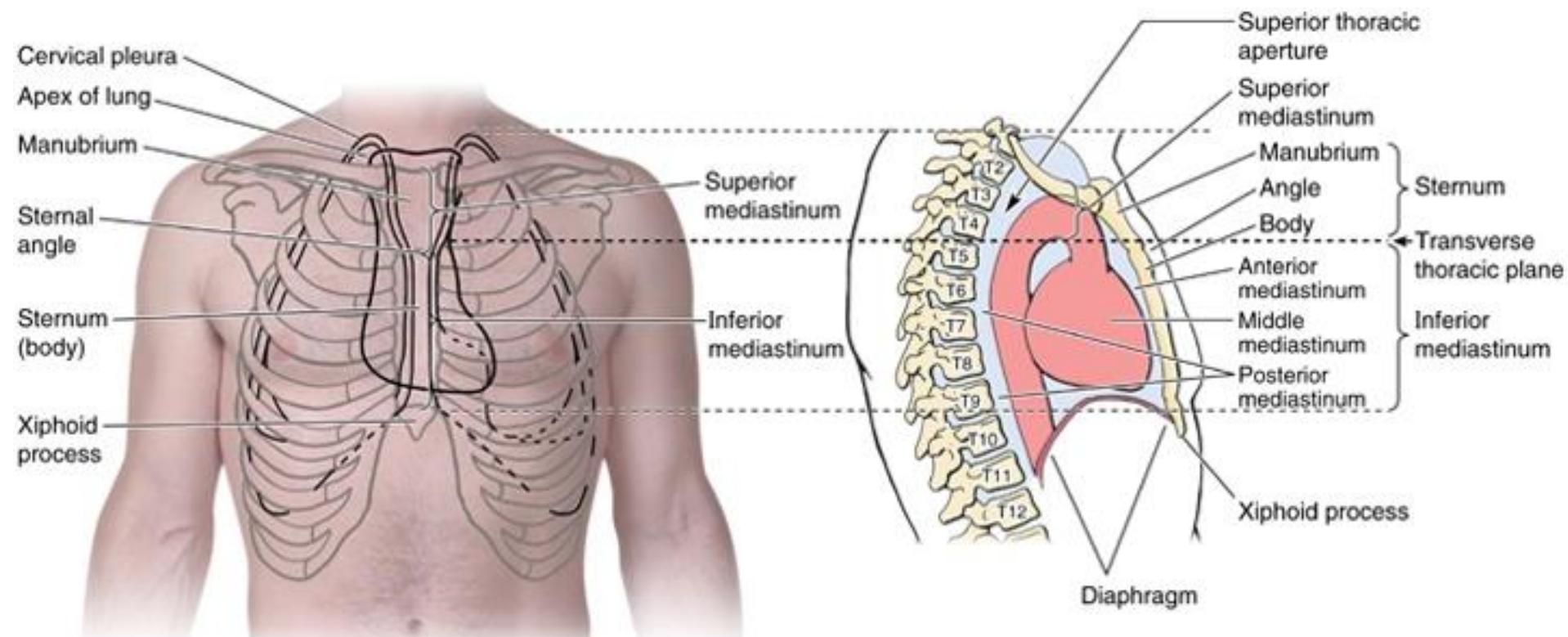
Pericardium

- The heart is located in the **mediastinum** in a cavity called the **pericardial cavity**.
- The **pericardium** is the serous membrane lining the cavity. The pericardium is a continuous membrane but the part that attaches to the surface of the heart is the **visceral pericardium (epicardium)** and the part that lines the outer wall of the cavity is the **parietal pericardium**.
- The outer surface of the parietal pericardium is reinforced by a layer of dense, irregular connective tissue called the **fibrous pericardium**.
- A small amount of **pericardial fluid** (10 to 20 ml) within the pericardial cavity reduces friction

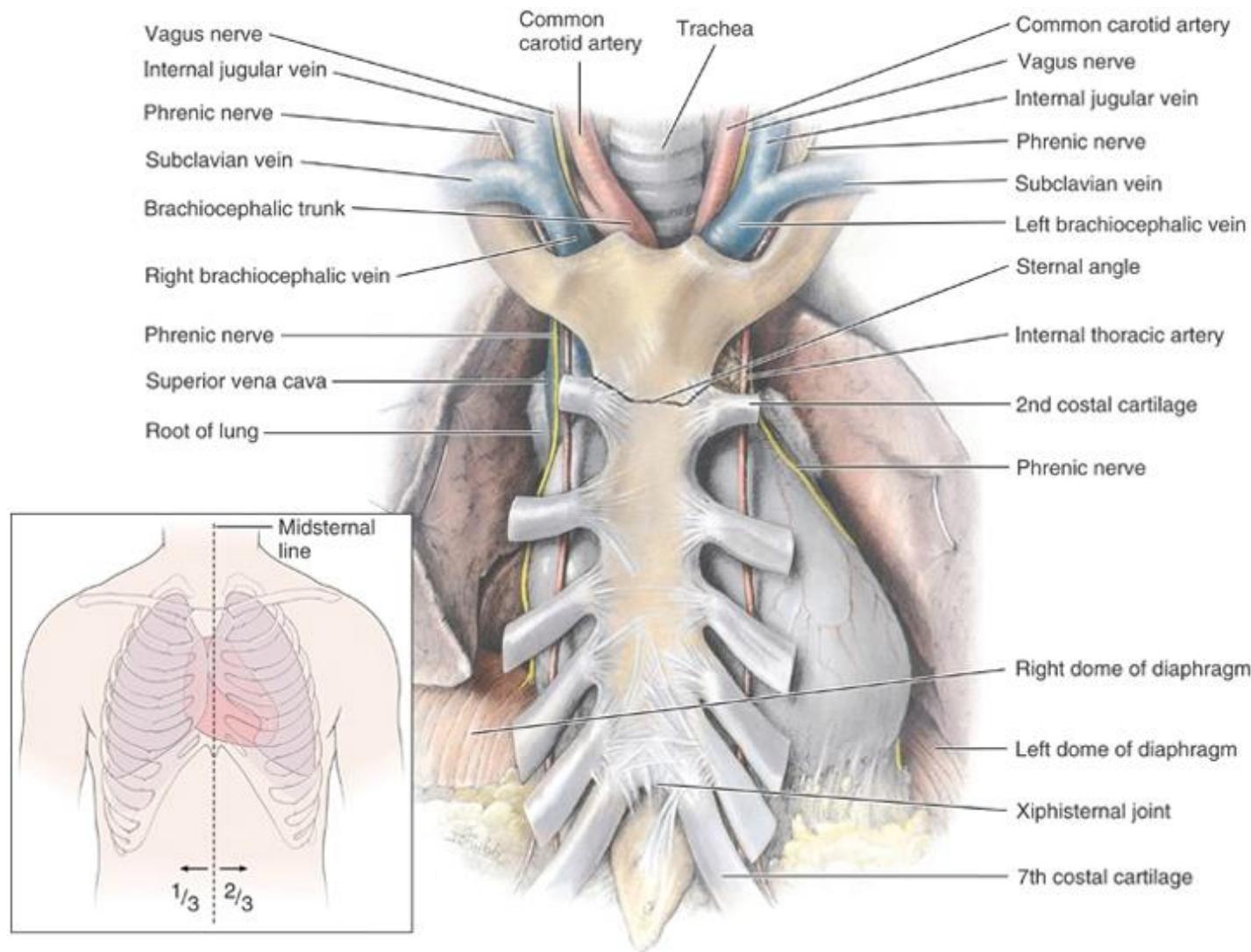




The Mediastinum

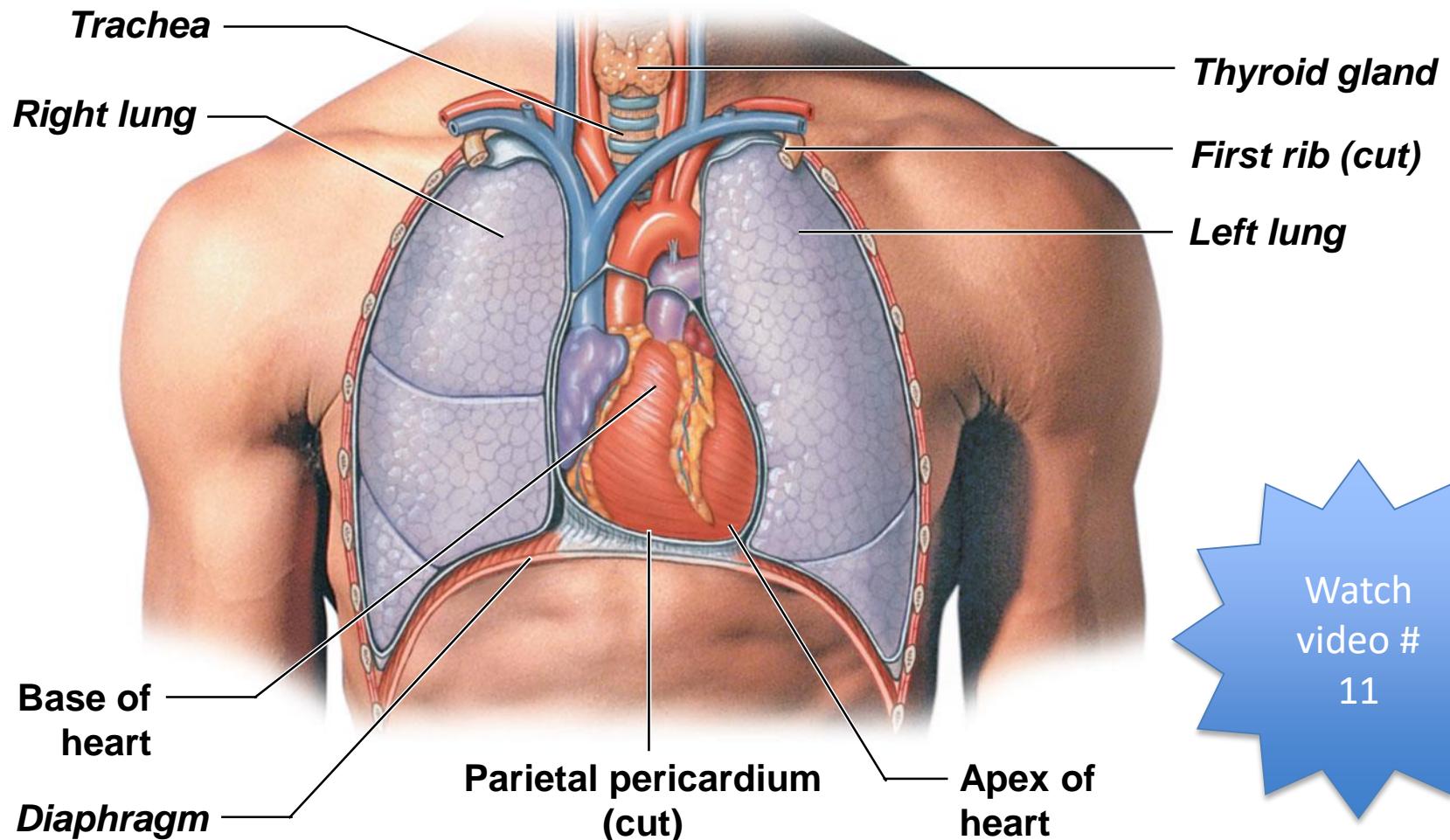


Heart Position in Thoracic Cavity



Anterior views

Figure 21.2a Location of the Heart in the Thoracic Cavity

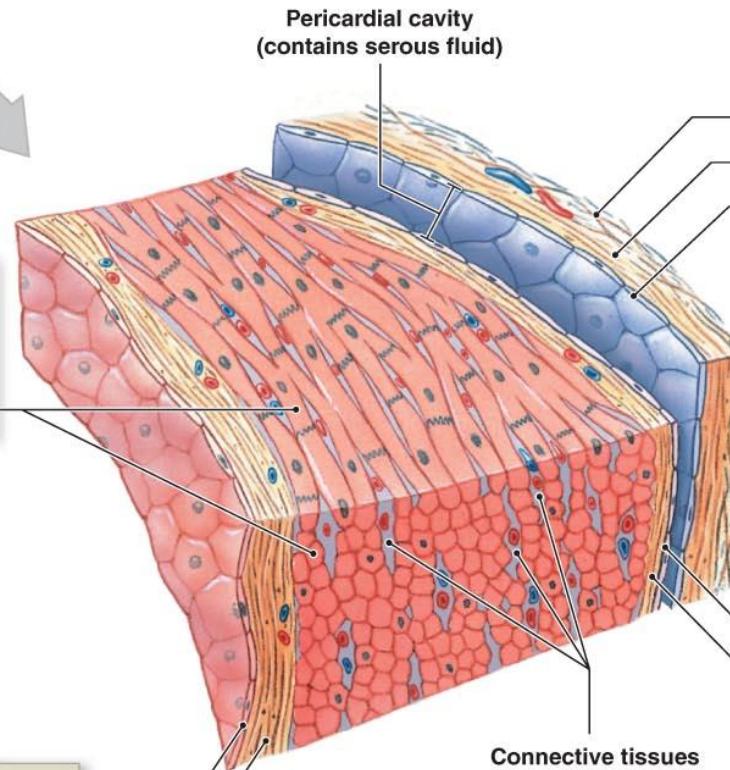
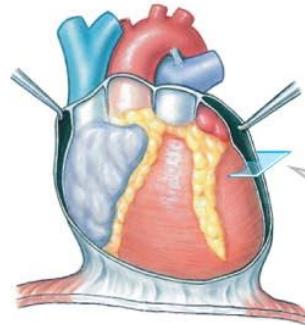


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11

Anterior view of the open chest cavity showing the position of the heart and major vessels relative to the lungs.

The Heart Wall

A section of the heart showing its three layers: epicardium, myocardium, and endocardium



Myocardium

Muscular wall of the heart consisting primarily of cardiac muscle cells

Parietal Pericardium

The serous membrane that forms the outer wall of the pericardial cavity; it and a dense fibrous layer form the pericardial sac surrounding the heart

Dense fibrous layer

Areolar tissue

Mesothelium

Epicardium

Covers the outer surface of the heart; also called the visceral pericardium

Mesothelium

Areolar tissue

Endocardium

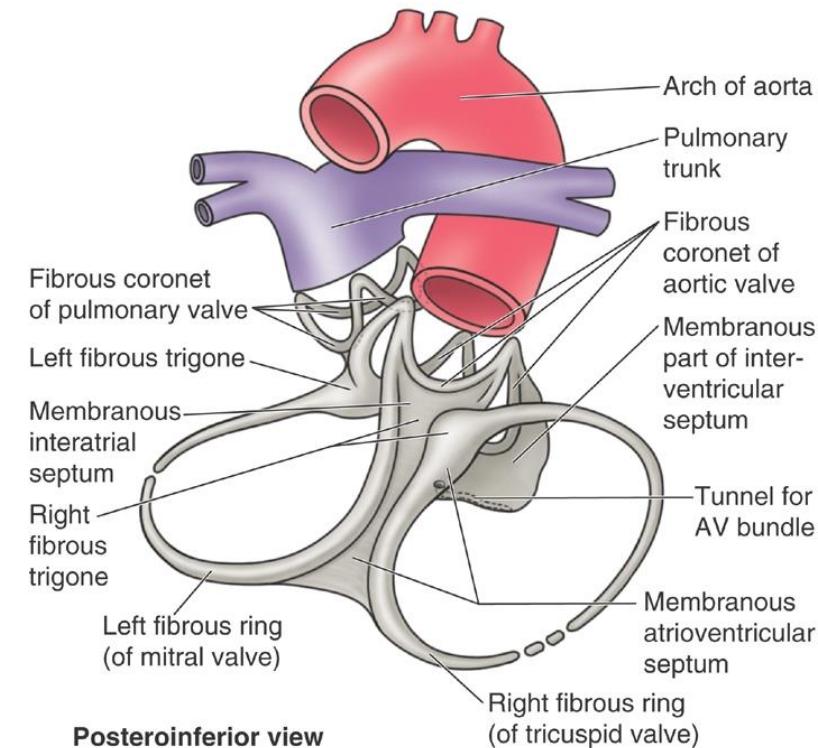
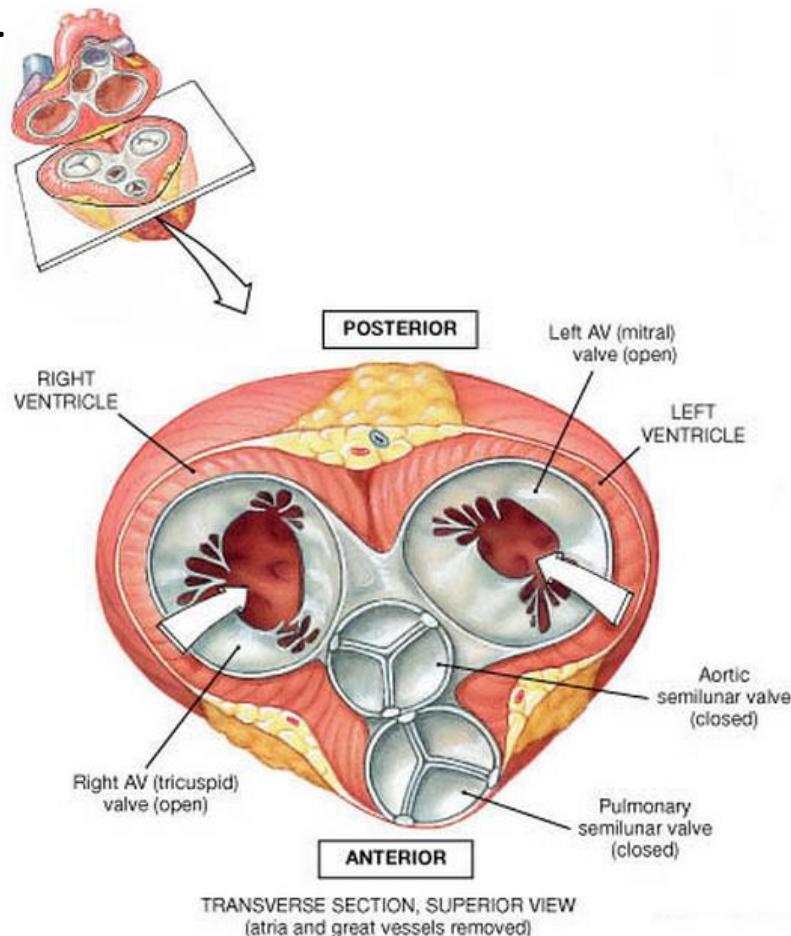
Covers the inner surfaces of the heart

Endothelium

Areolar tissue

Fibrous Skeleton of Heart

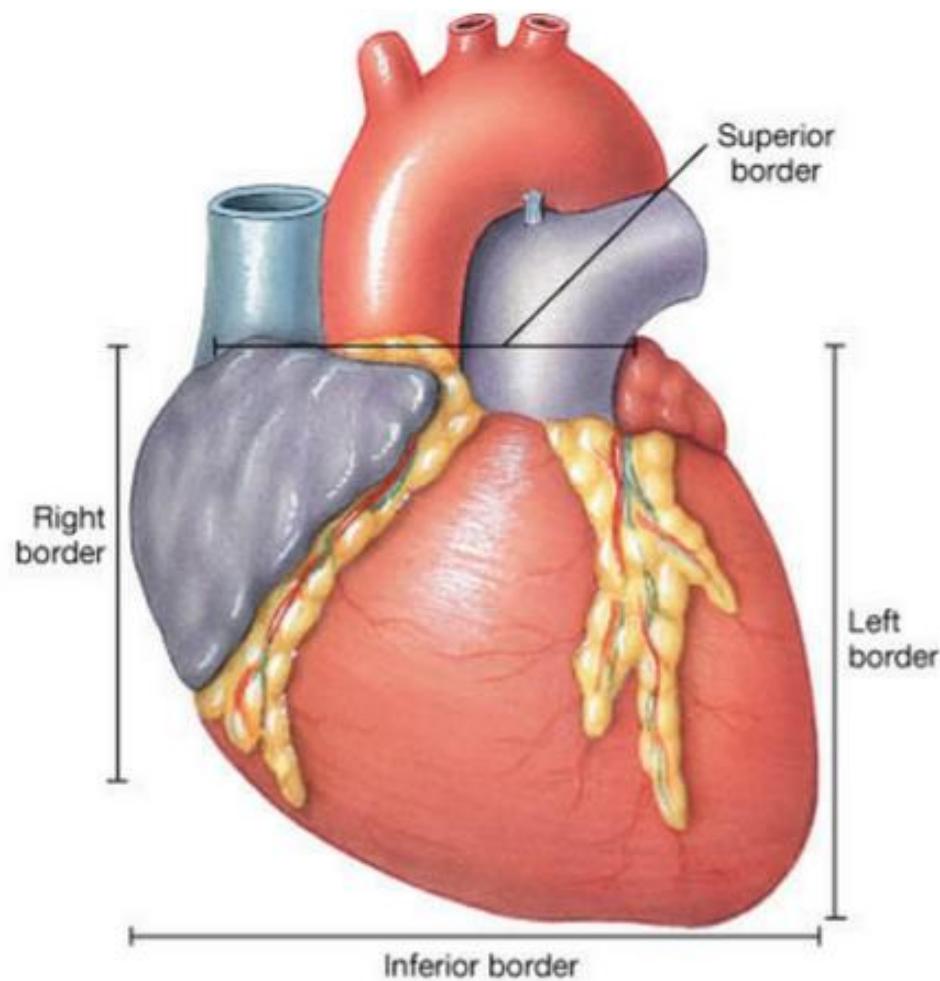
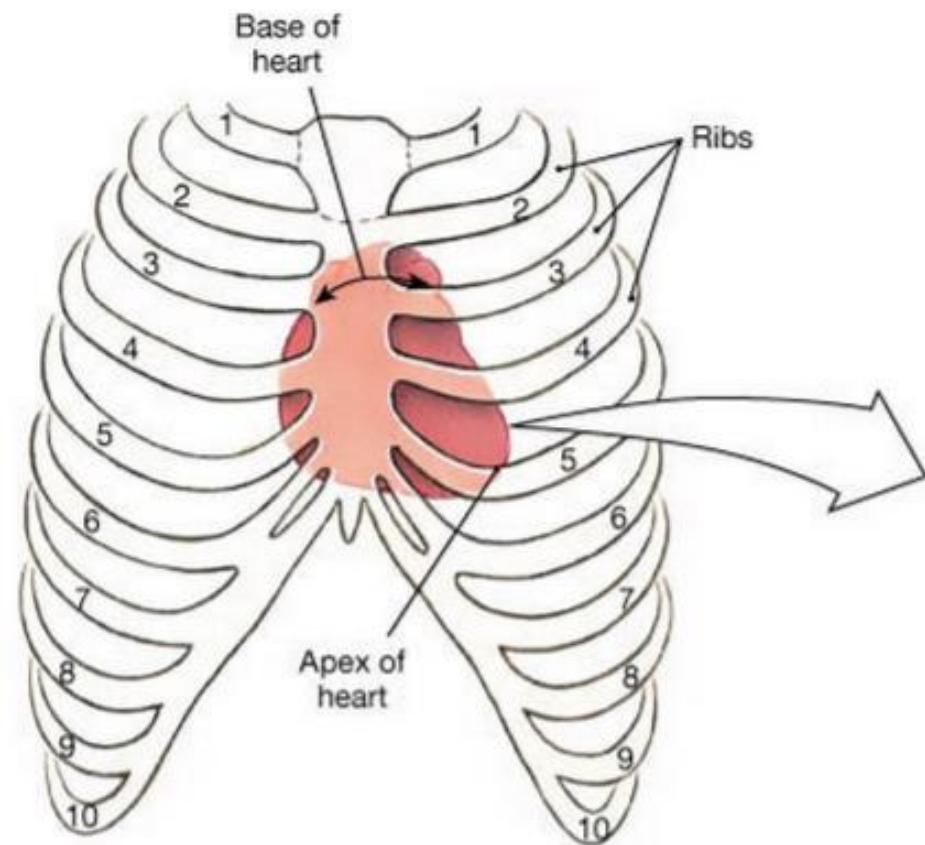
- The fibrous skeleton of the heart consists of four fibrous rings that surround the valve orifices and two triangular fibrous connections between these rings, the right and left fibrous **trigones**. The valves include the aortic and pulmonary semilunar valves and the right and left atrioventricular valves.
- The fibrous skeleton physically supports the valves, provides independent attachment for the atrial and ventricular myocardium, and acts an electrical insulator between the atria and ventricles.



Orientation and Superficial Anatomy of Heart

1. The heart lies slightly to left of midline.

The **base** of the heart is formed mainly by the left atrium, and, to a small extent, by the back part of the right atrium. The **apex** is the inferior rounded tip.

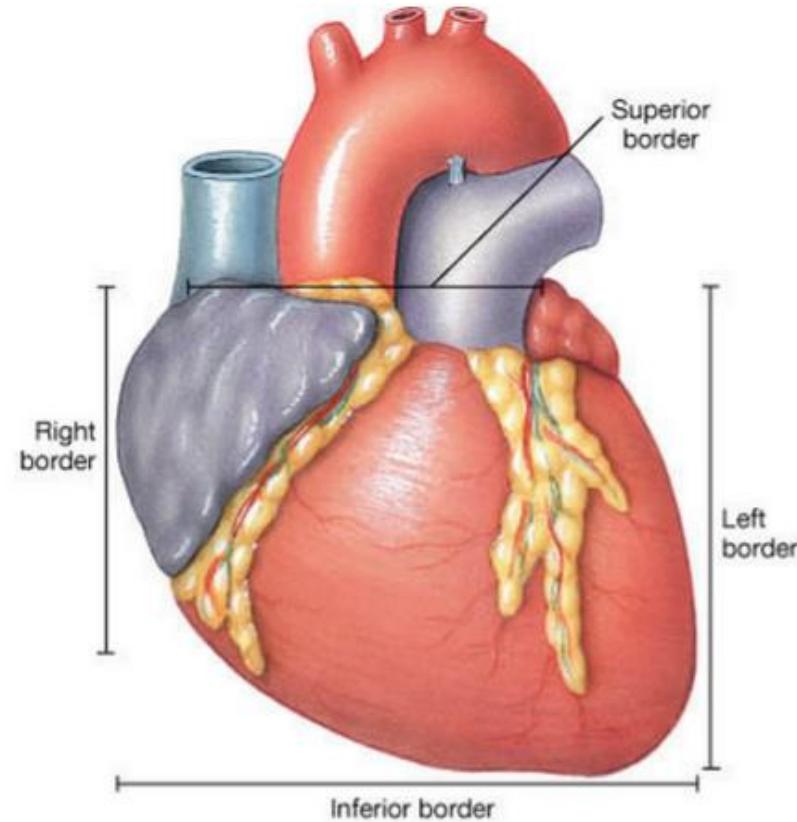
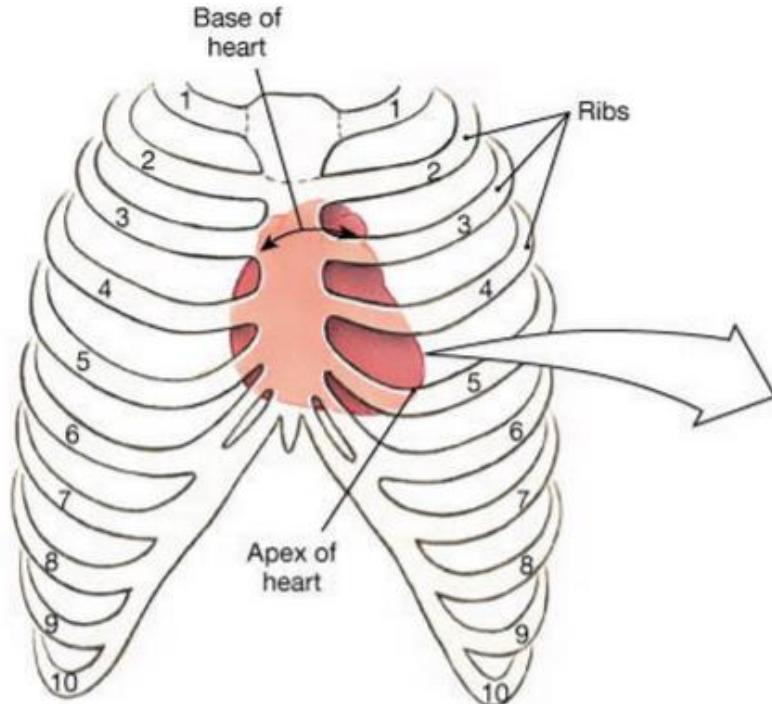


2. The heart at oblique angle to longitudinal axis.

Because of this tilt, the apex points obliquely toward the left.

This tilt in the orientation of the heart also causes the horizontal and vertical borders of the heart to be as follows:

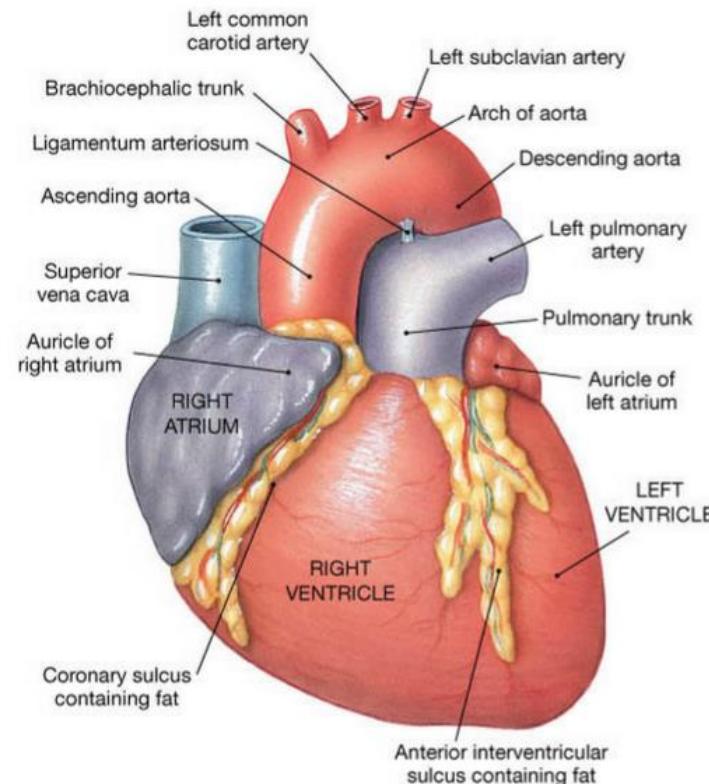
1. The superior border is formed by the base.
2. The right border is formed by the right atrium.
3. The inferior border is formed by the inferior wall of the right ventricle.
4. The left border is formed by the left ventricle and a small portion of the left atrium.



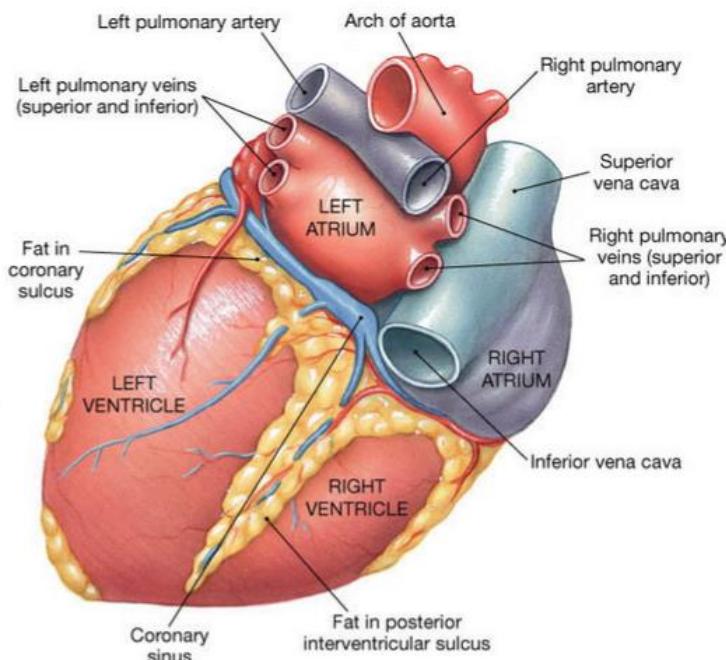
3. The heart rotated slightly toward left.

Because of this rotation:

- The surface of the heart underneath the sternum and the ribs on the left side, the **sternocostal** surface, is that of the right atrium and ventricle.
- The surface of the heart that rests on the diaphragm, which curves directly behind the heart, is called the **diaphragmatic surface**, and is formed by the posterior walls of the right and left ventricles

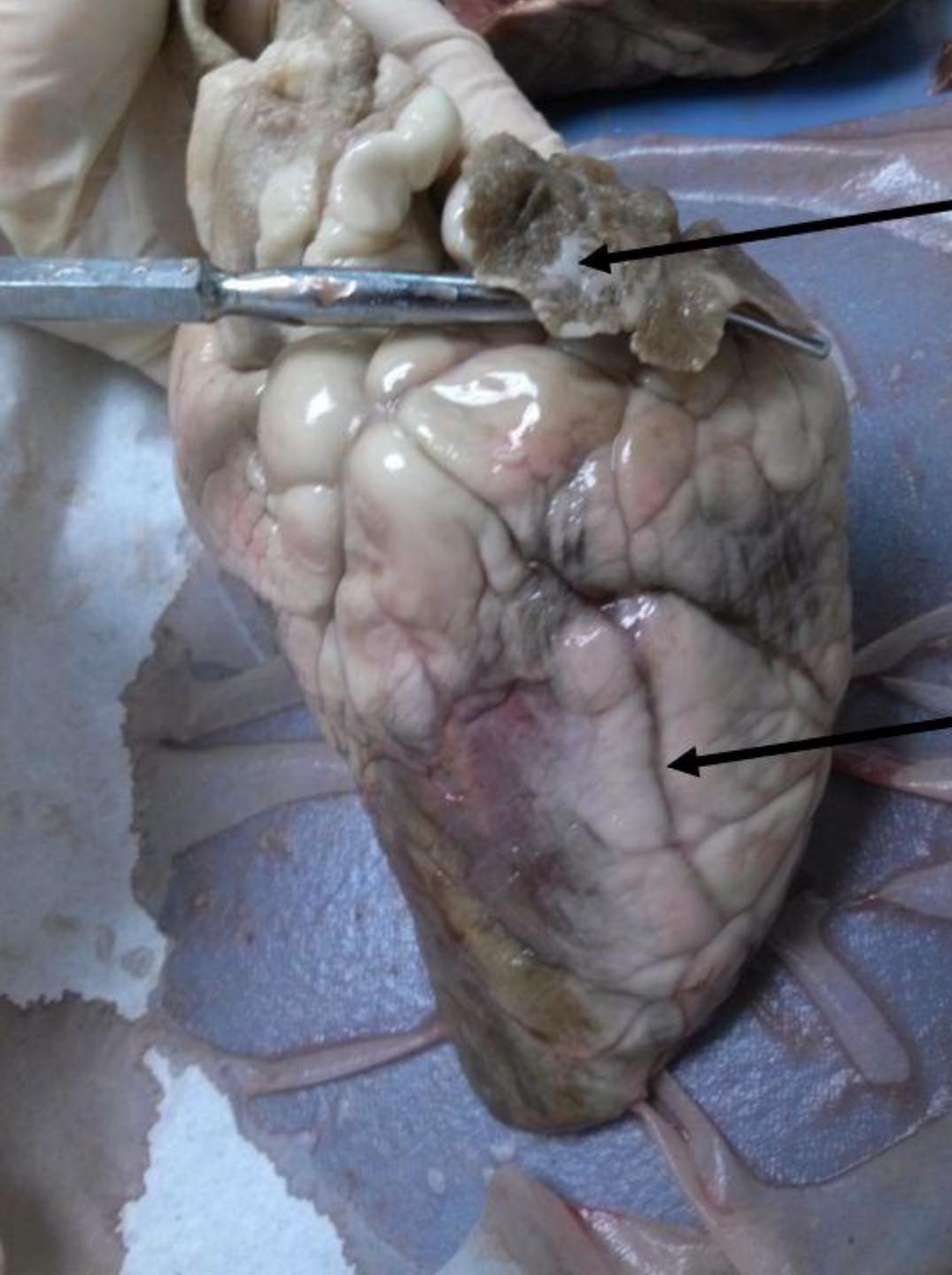


(a) Anterior (sternocostal) surface



(b) Posterior (diaphragmatic) surface

- The atria have thin muscular walls that are distended as they receive blood. When contracted, the anterior walls form flaps that are called **auricles**. A deep groove between the atria and ventricles is called the **coronary sulcus**. The boundary between the right and left ventricles is indicated externally by a shallow groove on the anterior surface, the **anterior interventricular sulcus**, and the posterior surface, the **posterior interventricular sulcus**.



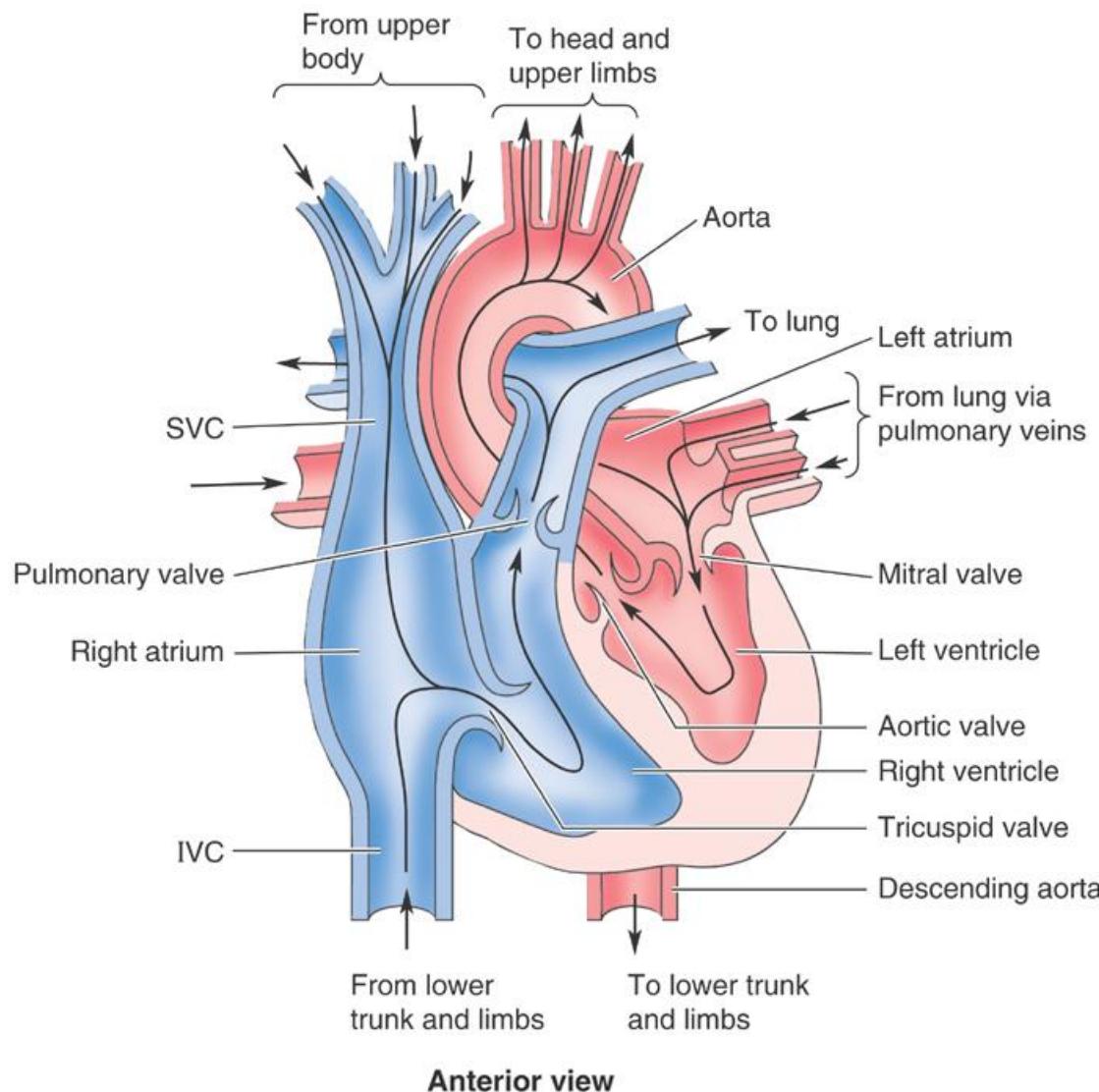
Left Auricle

Auricle (atrial appendage) increases the blood holding capacity of the atrium

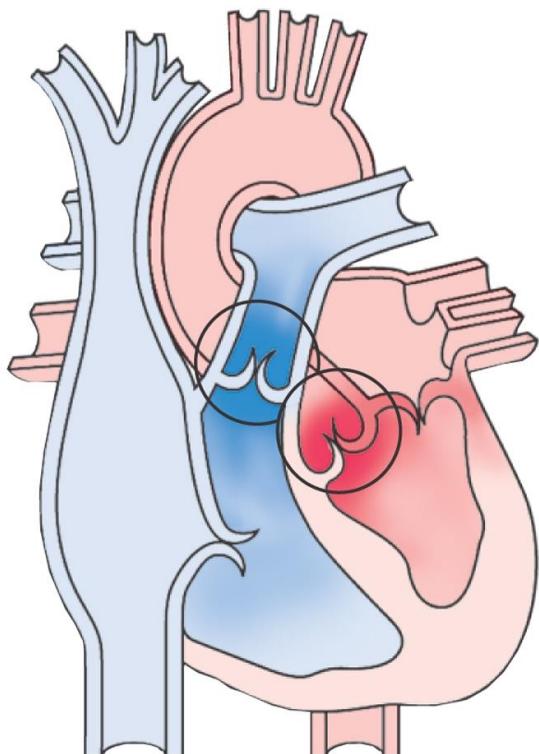
**Anterior
longitudinal
sulcus**

You can find the anterior side of the heart by finding the auricle that you can see completely; it is the left auricle. The anterior longitudinal sulcus is on that side and the coronary sinus is on the posterior side.

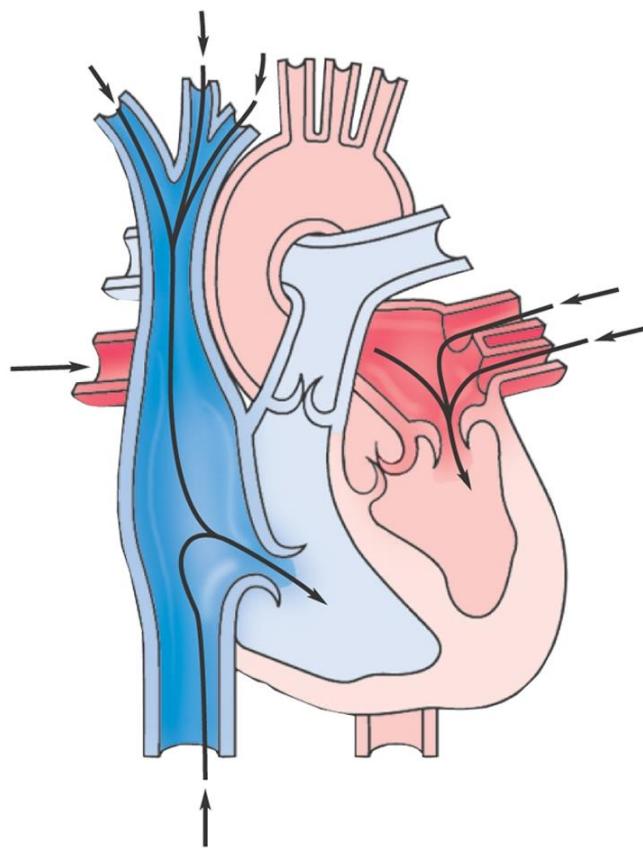
Bloodflow Through Heart



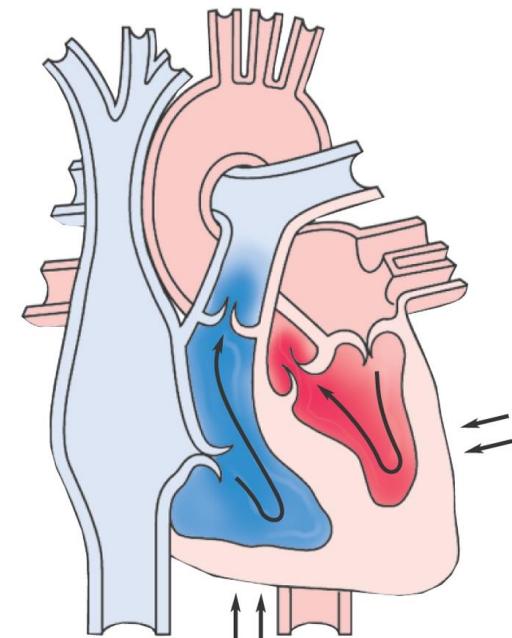
Valves of Heart



Beginning of diastole
upon closure of aortic
and pulmonary valves



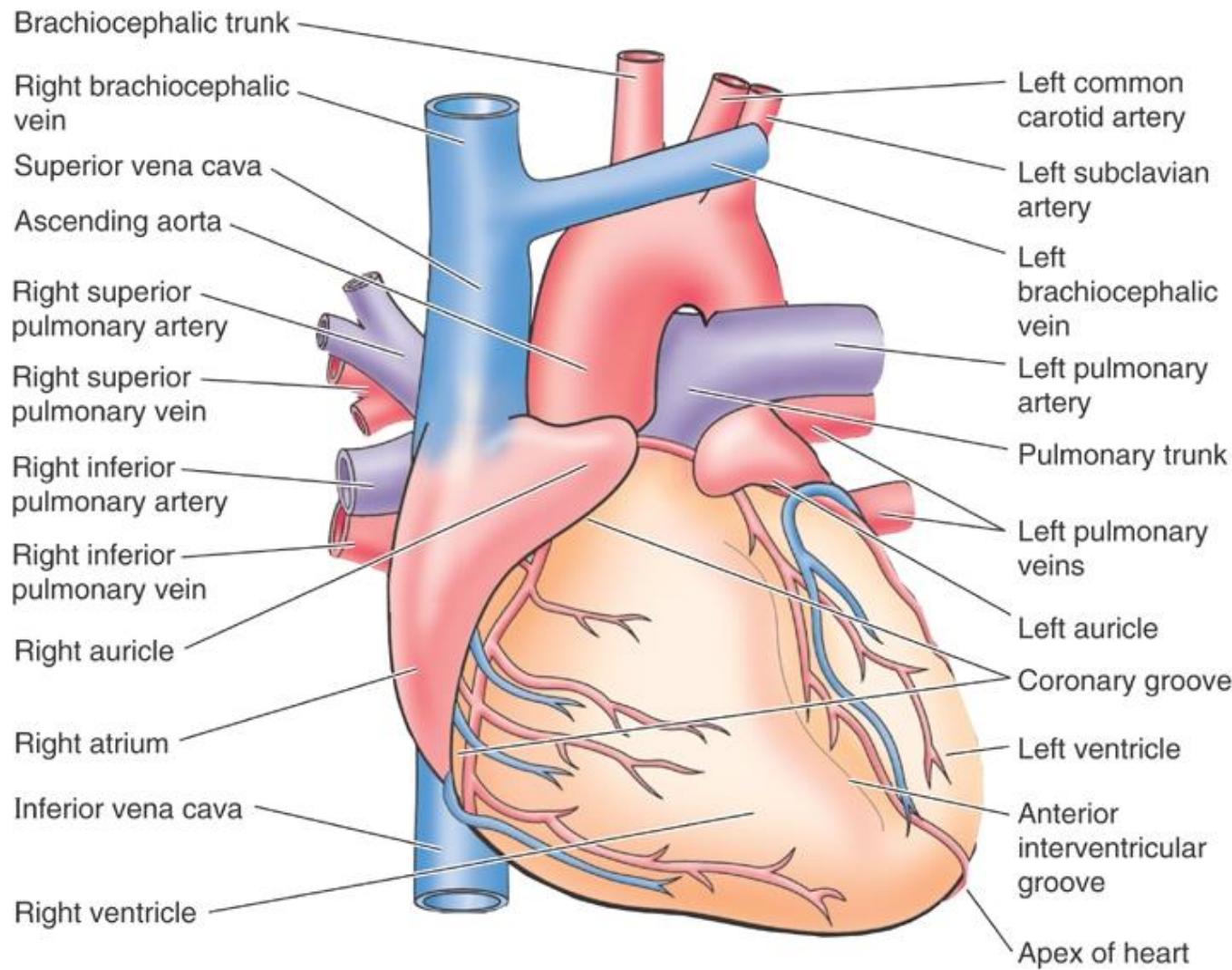
Opening of atrio-
ventricular valves
during early
moments of diastole



Closure of
atrioventricular valves
(tricuspid and mitral)
very soon after
systole begins

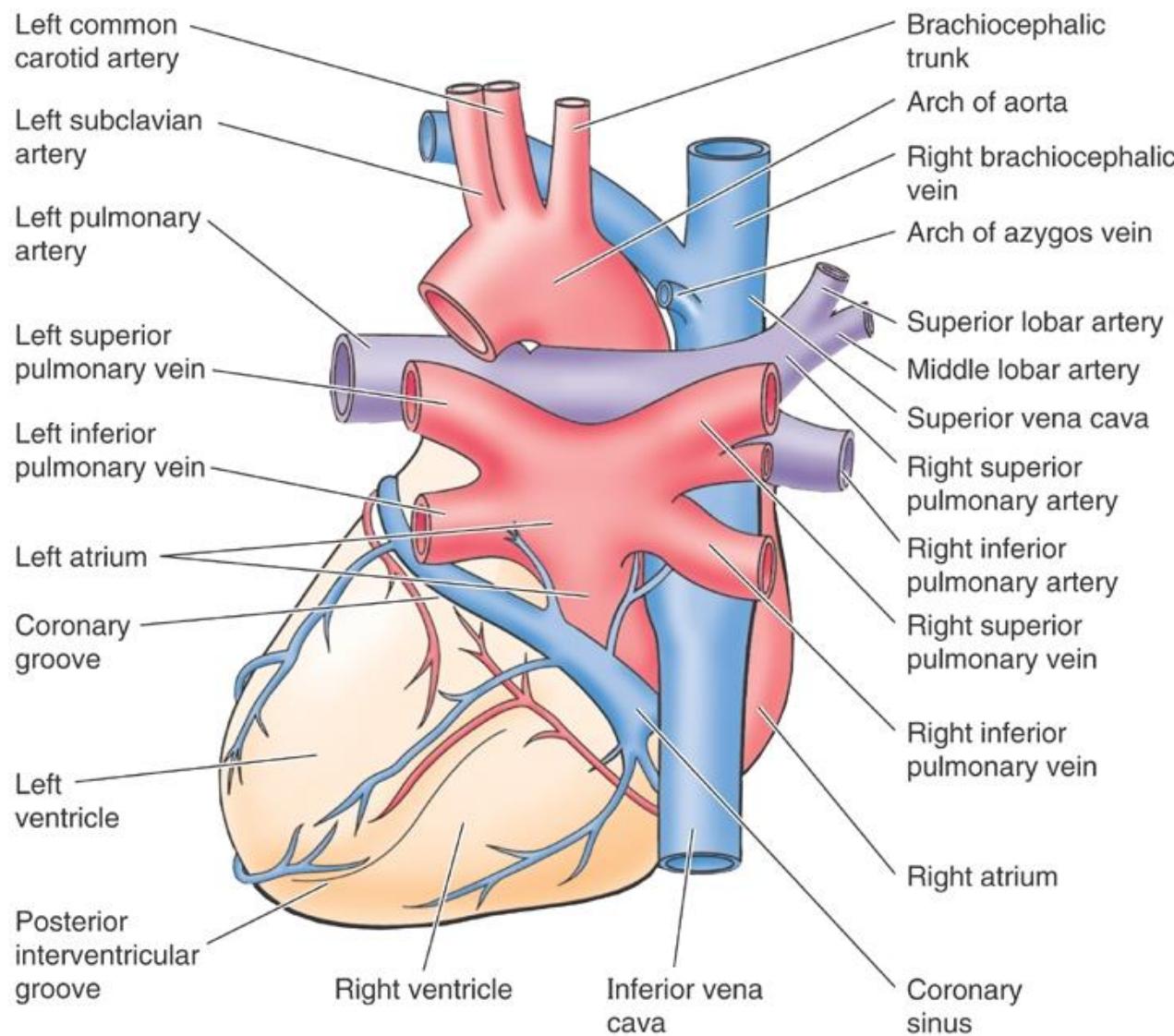
Anterior views

Anterior Heart



Anterior views

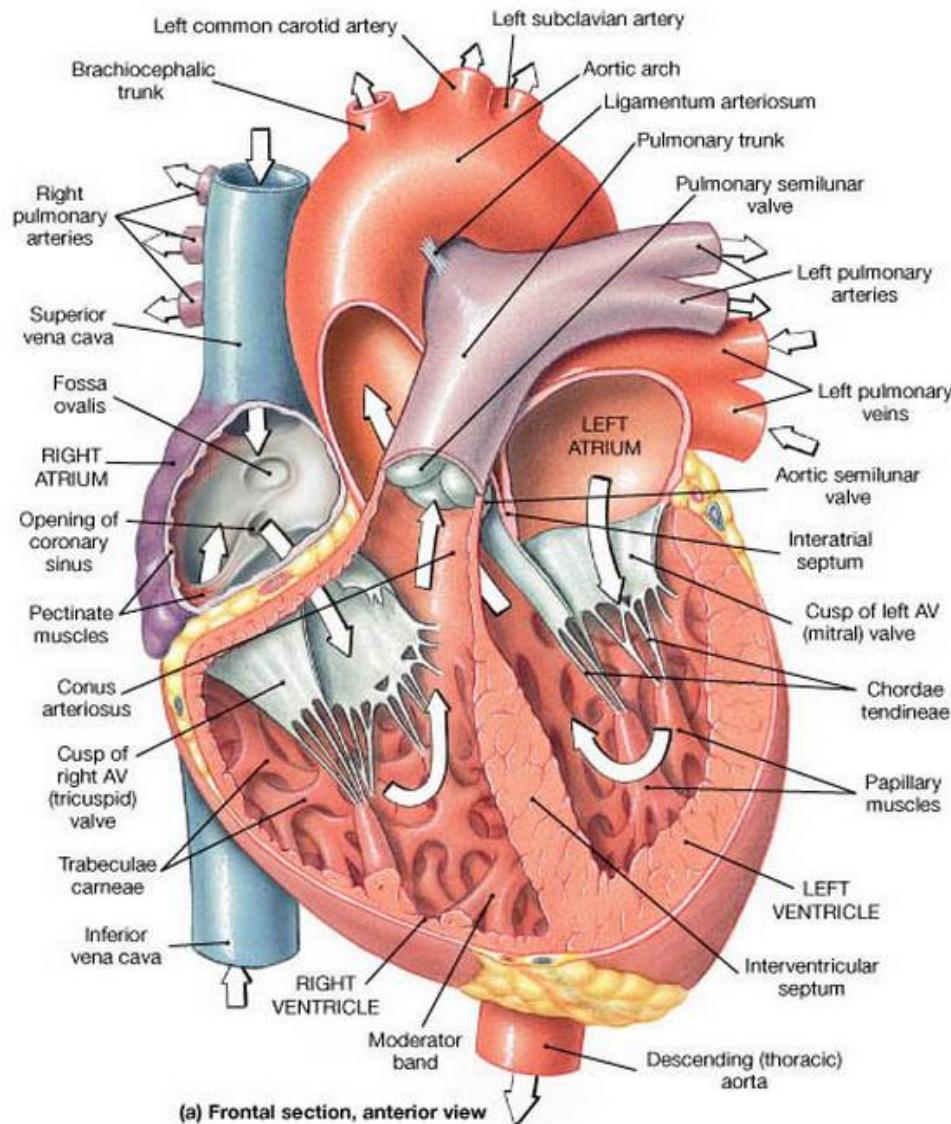
Posterior Heart



Right atrium

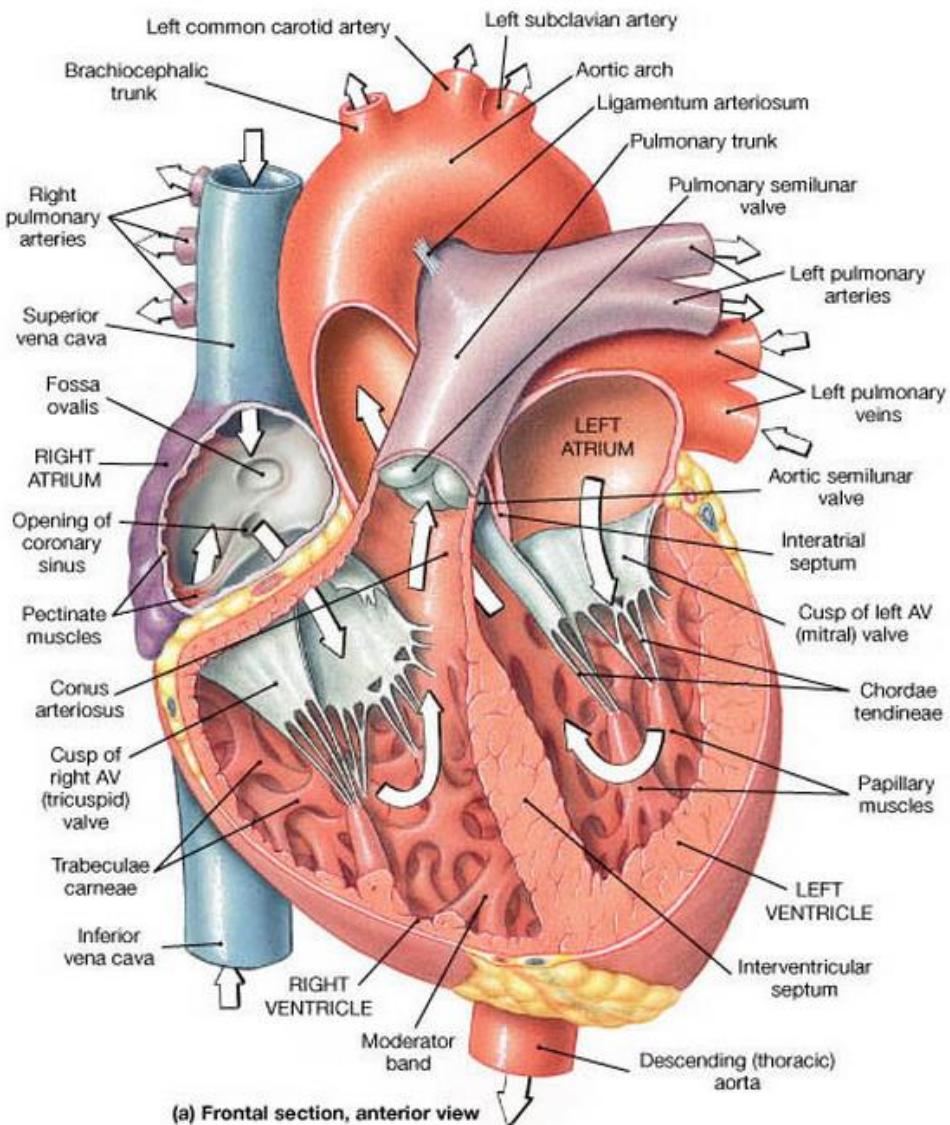
The right atrium receives deoxygenated blood from **superior vena cava**, **inferior vena cava** and **coronary sinus**.

Parallel ridges of muscle called **pectinate muscles** are found in the interior of the right auricle.



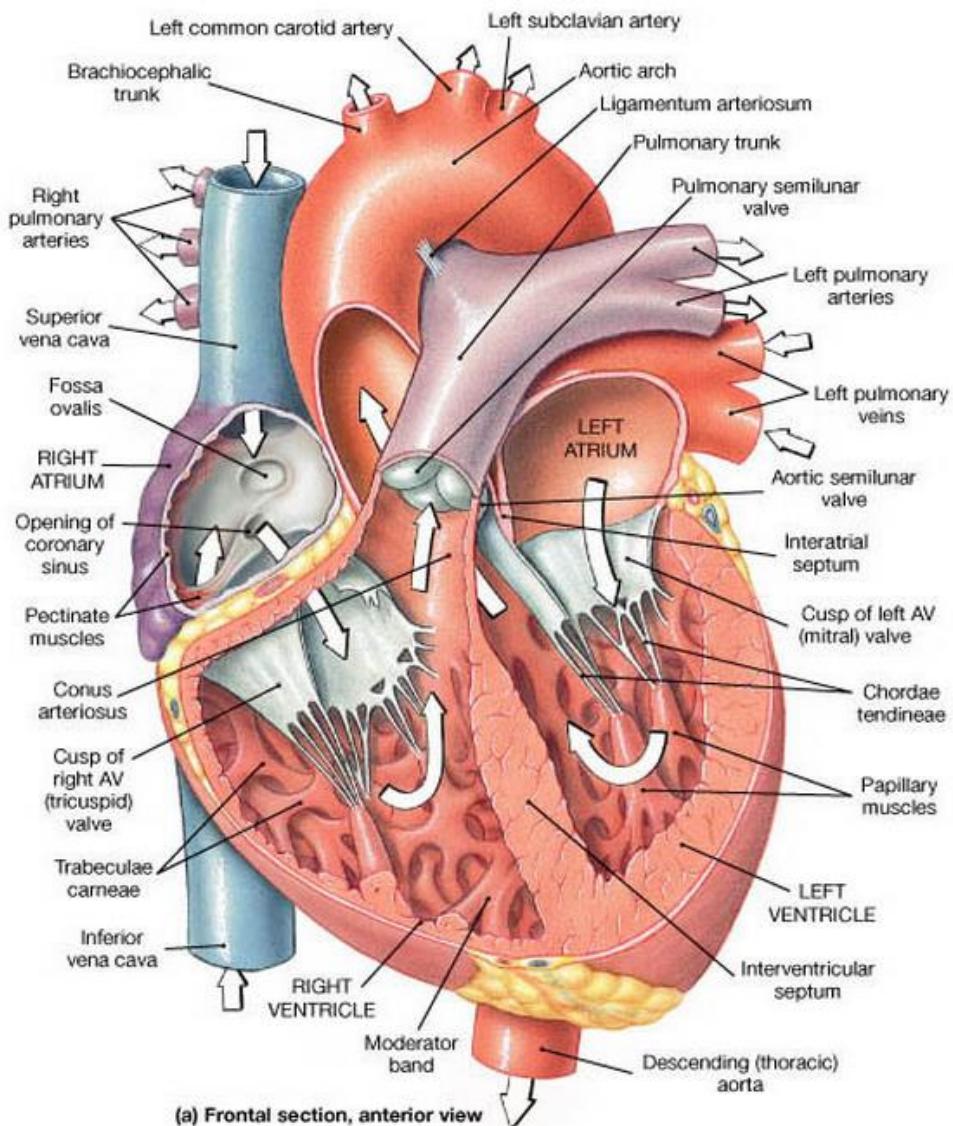
Right ventricle

- The deoxygenated blood from right atrium enters the right ventricle through an opening bounded by three flaps, or cusps, of the right **atrioventricular (tricuspid) valve**.
- The inner surface of the right ventricle has irregular, muscular folds called **trabeculae carneae**.
- The pulmonary trunk branches into the **right and left pulmonary arteries**.
- Backflow of blood is prevented by three half-moon flaps attached to the base of the pulmonary trunk that forms the **pulmonary semilunar valve**



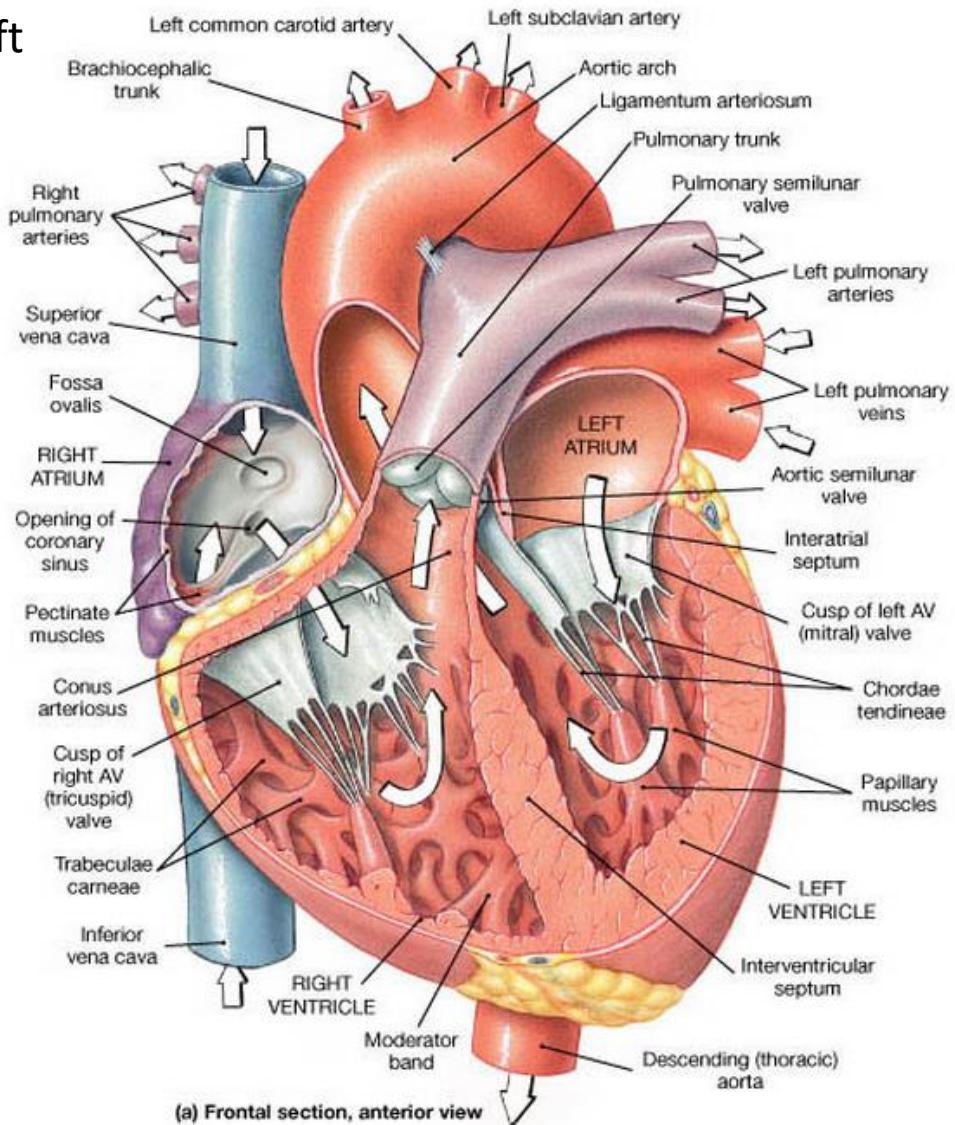
Left atrium

- The left (2) and right (2) pulmonary veins drain oxygenated blood from the lungs into the left atrium.
- The auricle of the left atrium lacks **pectinate** muscles.
- The oxygenated blood enters the left ventricle through a valve with two flaps, the **left atrioventricular (bicuspid, mitral) valve**.

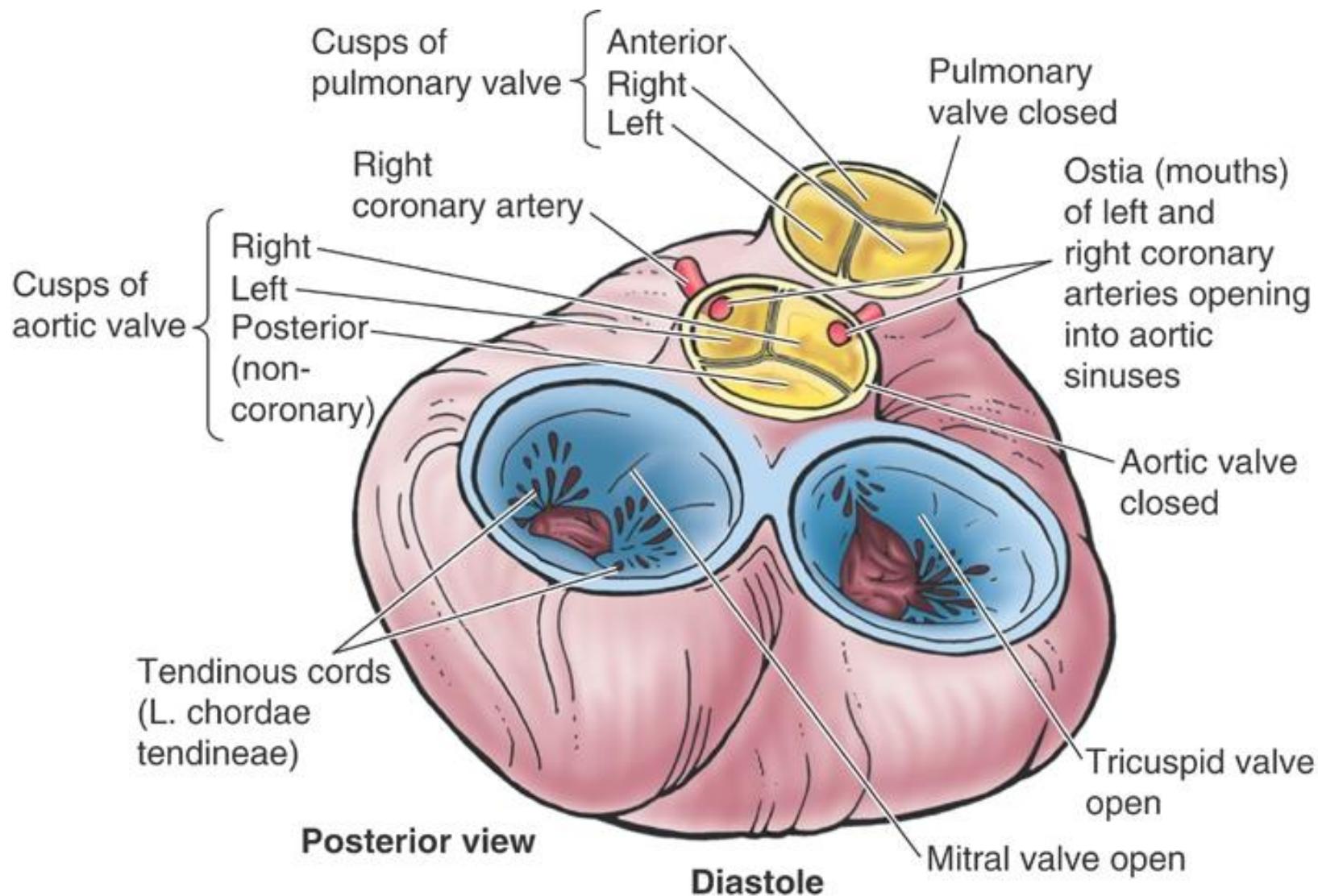


Left ventricle

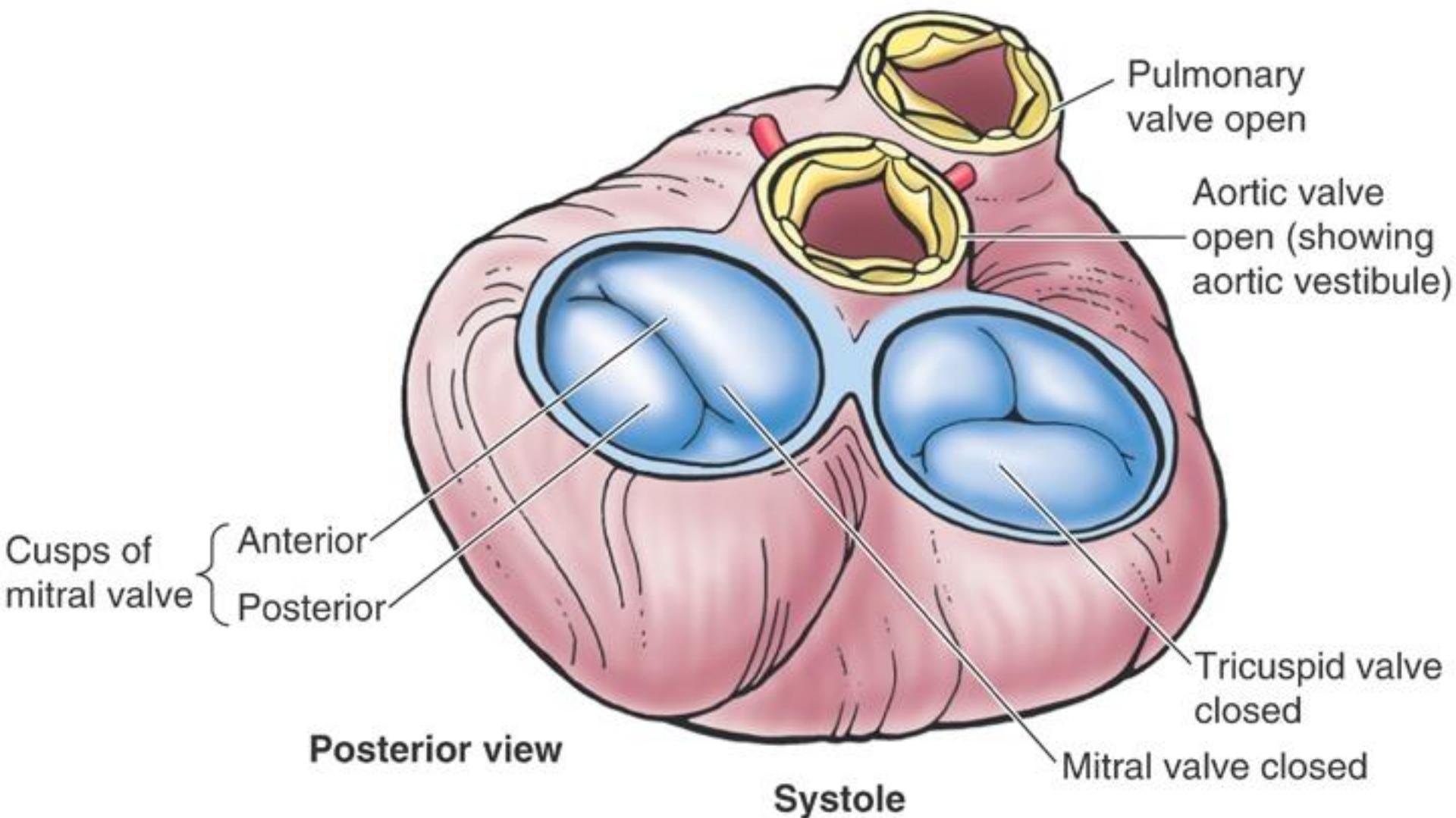
- As oxygenated blood is ejected from the left ventricle it passes through the **aortic semilunar valve** and enters the **ascending aorta**.
- The left ventricle, has a thicker wall than the right. It also has more prominent **trabeculae carneae**.



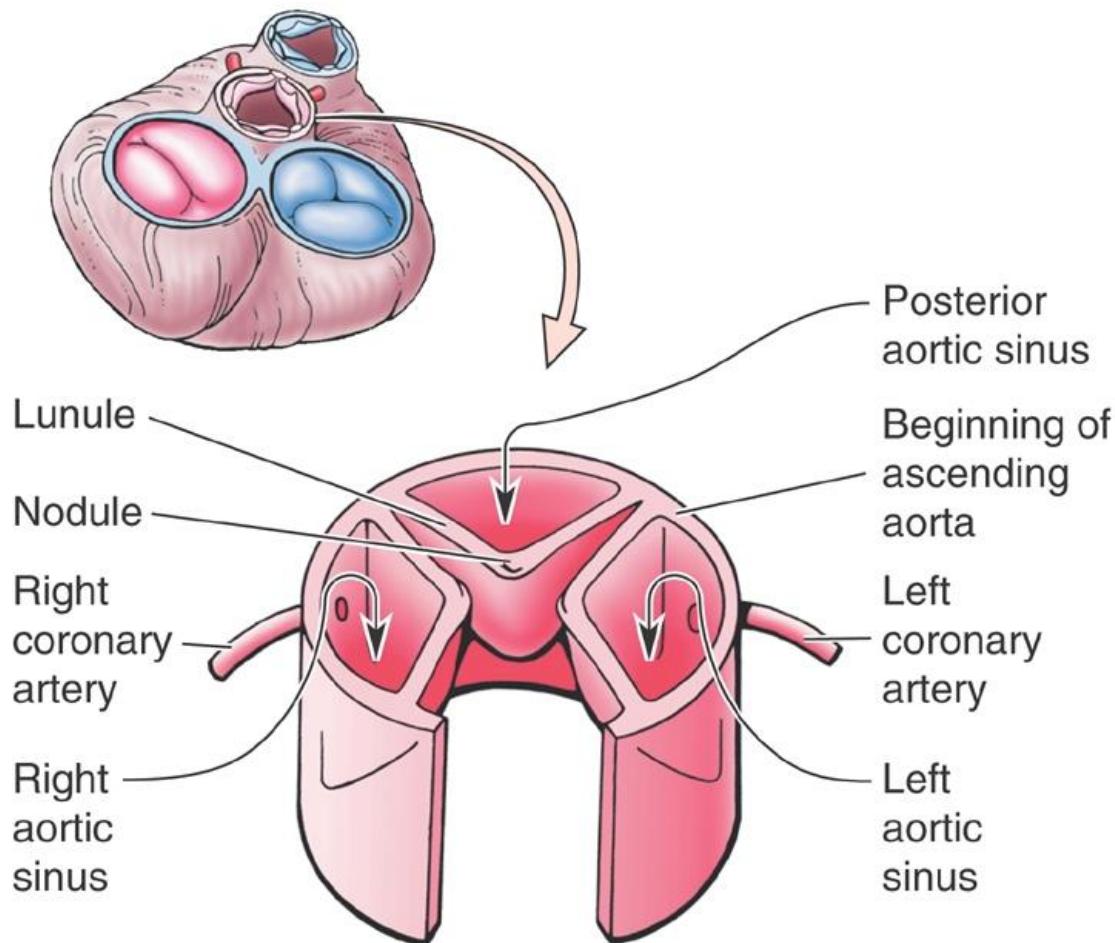
Valves during ventricular diastole



Valves during ventricular systole



Aortic Semilunar Valve



Anterior view of aortic valve

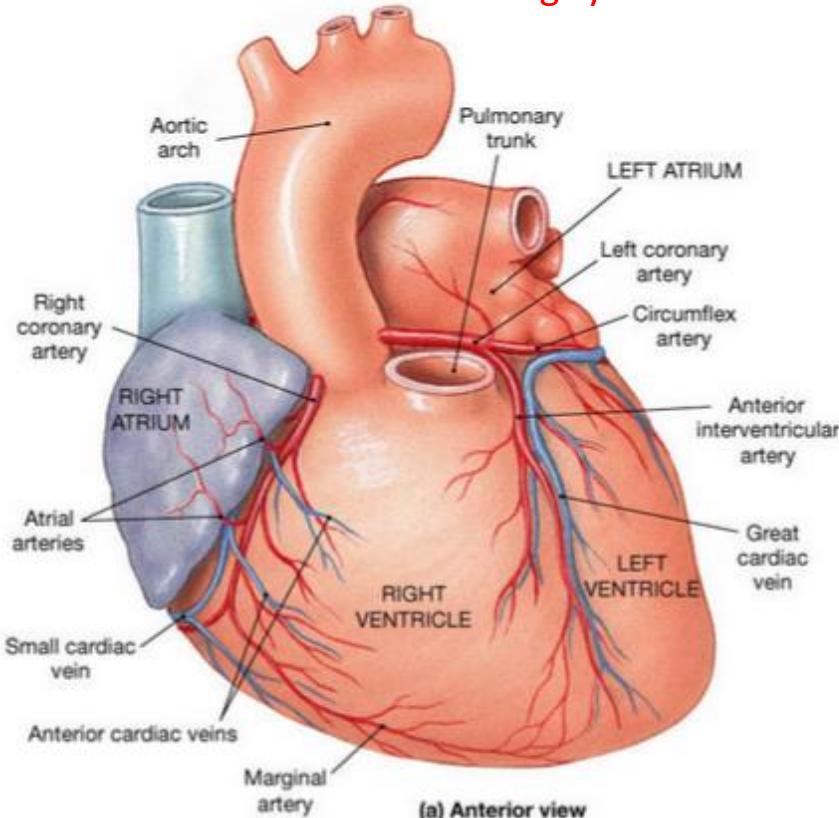
Coronary Blood Vessels

- The coronary circulation supplies blood to heart tissue.
- The right and left coronary arteries come off ascending aorta at the aortic sinuses

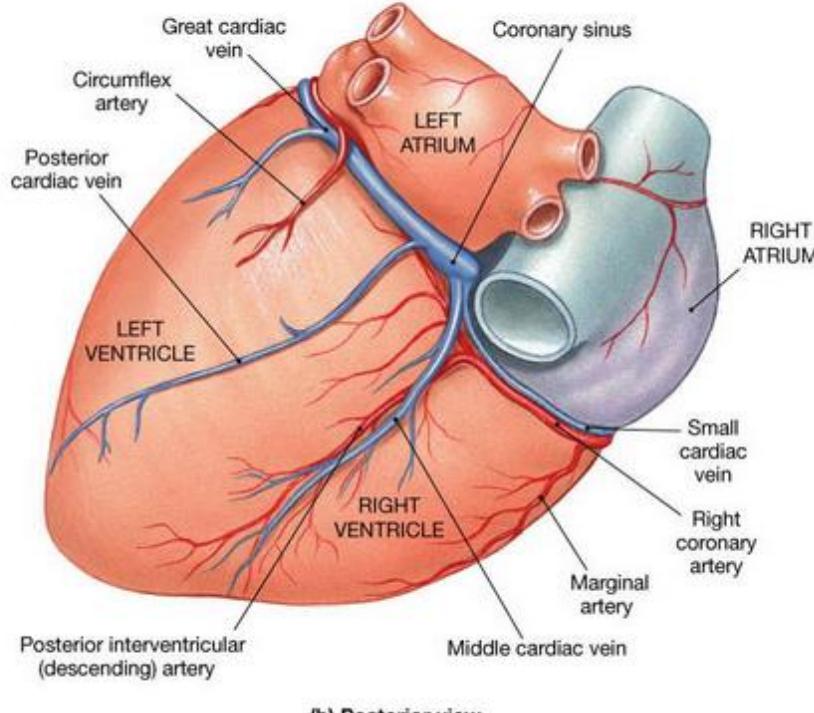
right coronary artery

The right coronary artery branches include:

1. Atrial branches that supply the myocardium of the right atrium.
2. Ventricular branches include the right marginal branch that extends toward the apex along the anterior surface of the right ventricle, and the posterior interventricular branch that descends toward the apex along the posterior interventricular sulcus.
3. Branches to the conducting system include branches to the sinoatrial and atrioventricular nodes.



(a) Anterior view

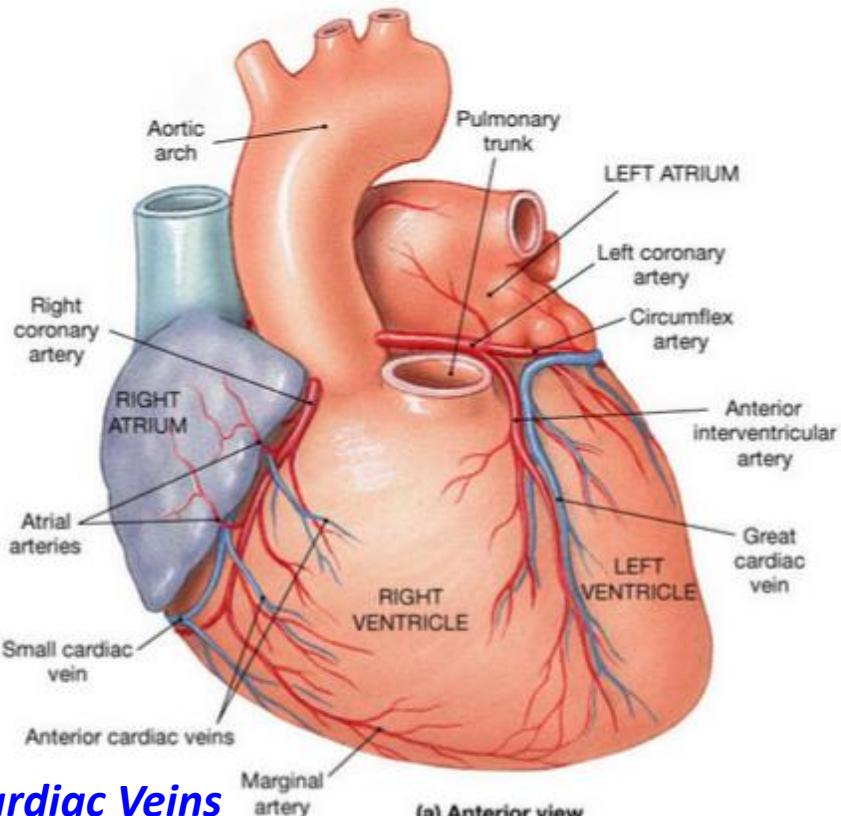


(b) Posterior view

left coronary artery

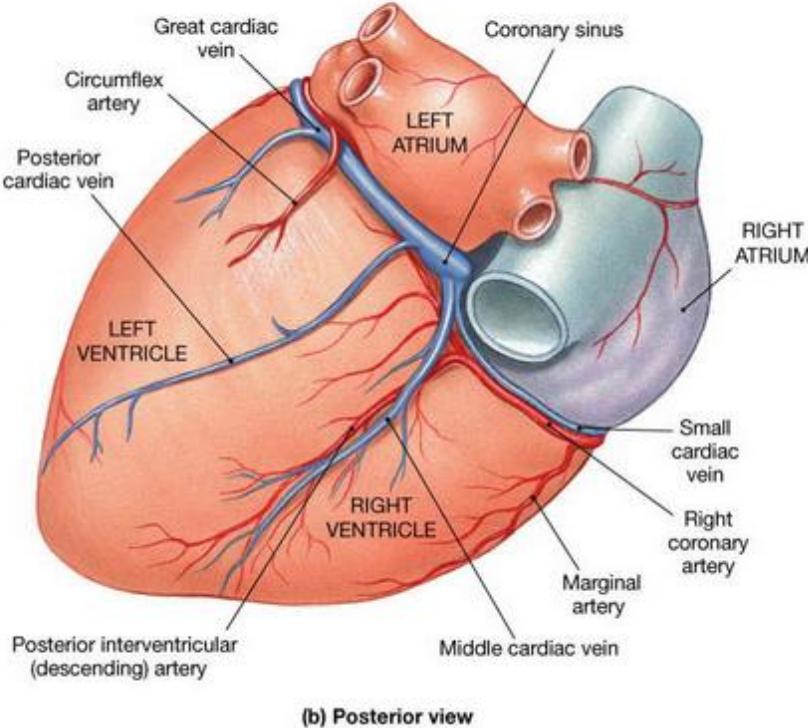
The left coronary artery supplies the left atrium and ventricle and contributes to the supply to the interventricular septum. As it reaches the anterior surface it divides into two branches:

1. **The circumflex branch** curves to left in coronary sulcus.
2. **The anterior interventricular branch** descends along anterior interventricular sulcus.



Cardiac Veins

(a) Anterior view



(b) Posterior view

The great cardiac vein and middle cardiac vein are found in the anterior interventricular sulcus and posterior interventricular sulcus, respectively. Both veins drain blood into the coronary sinus that is a thin-walled vein that lies in the posterior coronary sulcus.

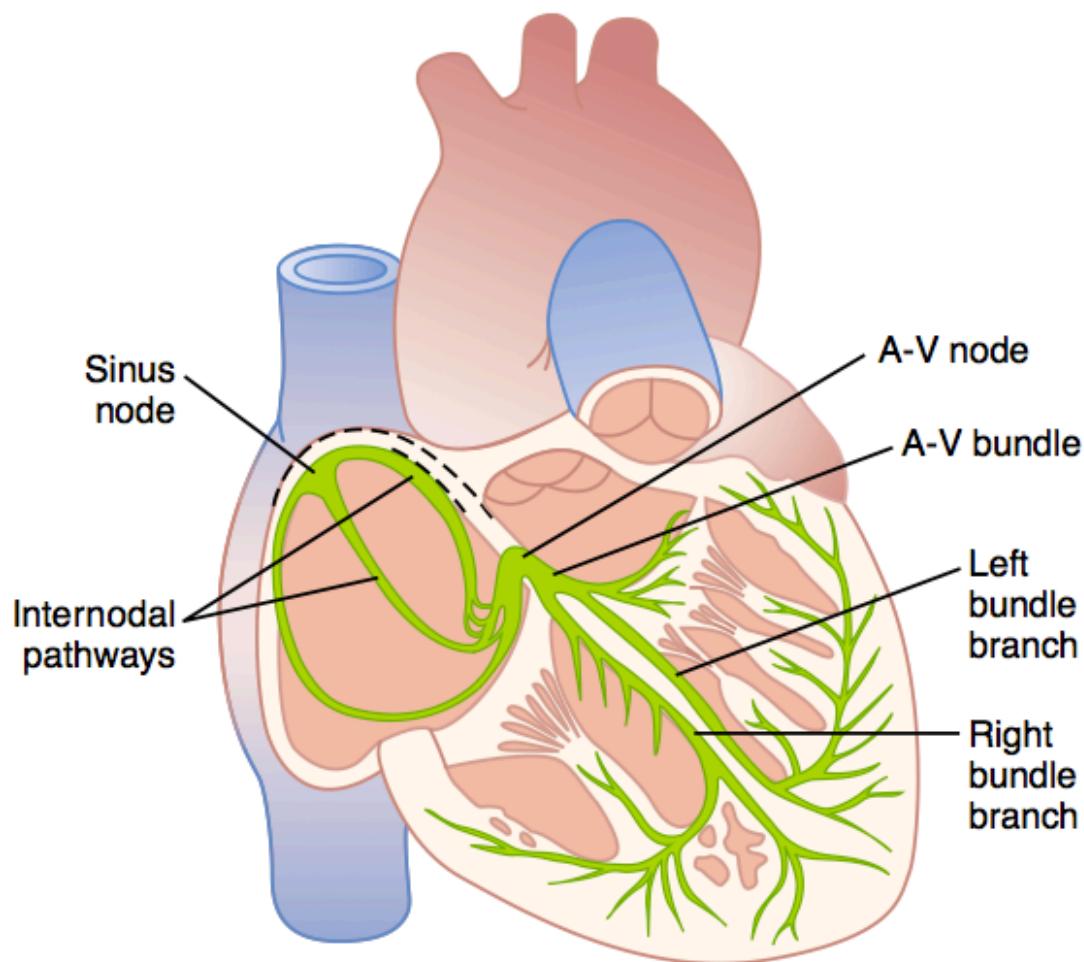


Watch video
12 and # 13

Excitation of the Heart

Chapter 10

Excitatory and Conductive System of The Heart



sinoatrial or S-A node: normal rhythmical impulse is generated

internodal pathways : conduct the impulse from the sinus node to the atrioventricular (A-V) node

A-V node: the impulse from the atria is delayed before passing into the ventricles

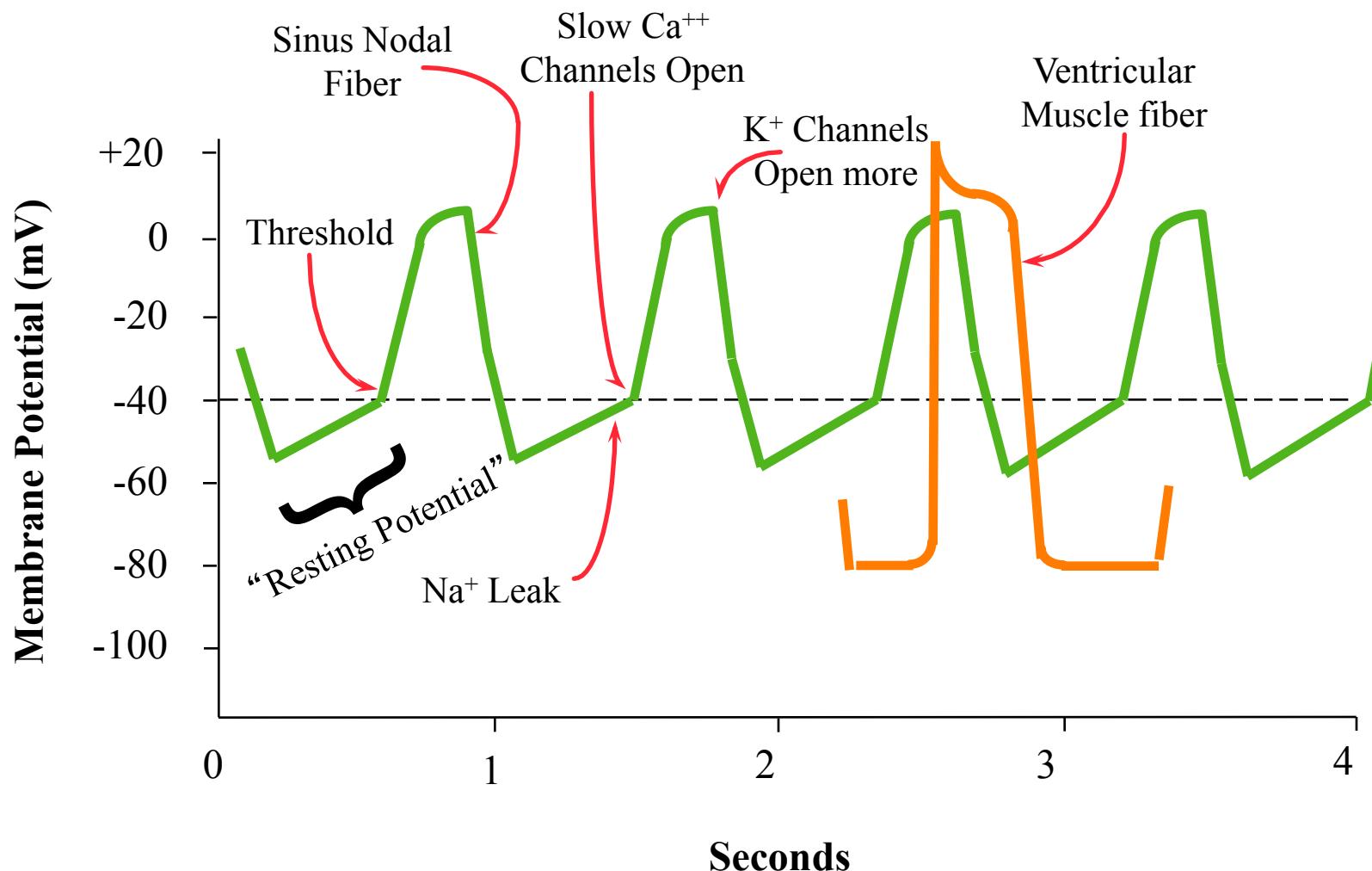
the A-V bundle (His bundle): conducts the impulse from the atria into the ventricles

the left and right bundle branche of Purkinje fibers : conduct the cardiac impulse to all parts of the ventricles

the sinus node ordinarily controls the rate of beat of the entire heart

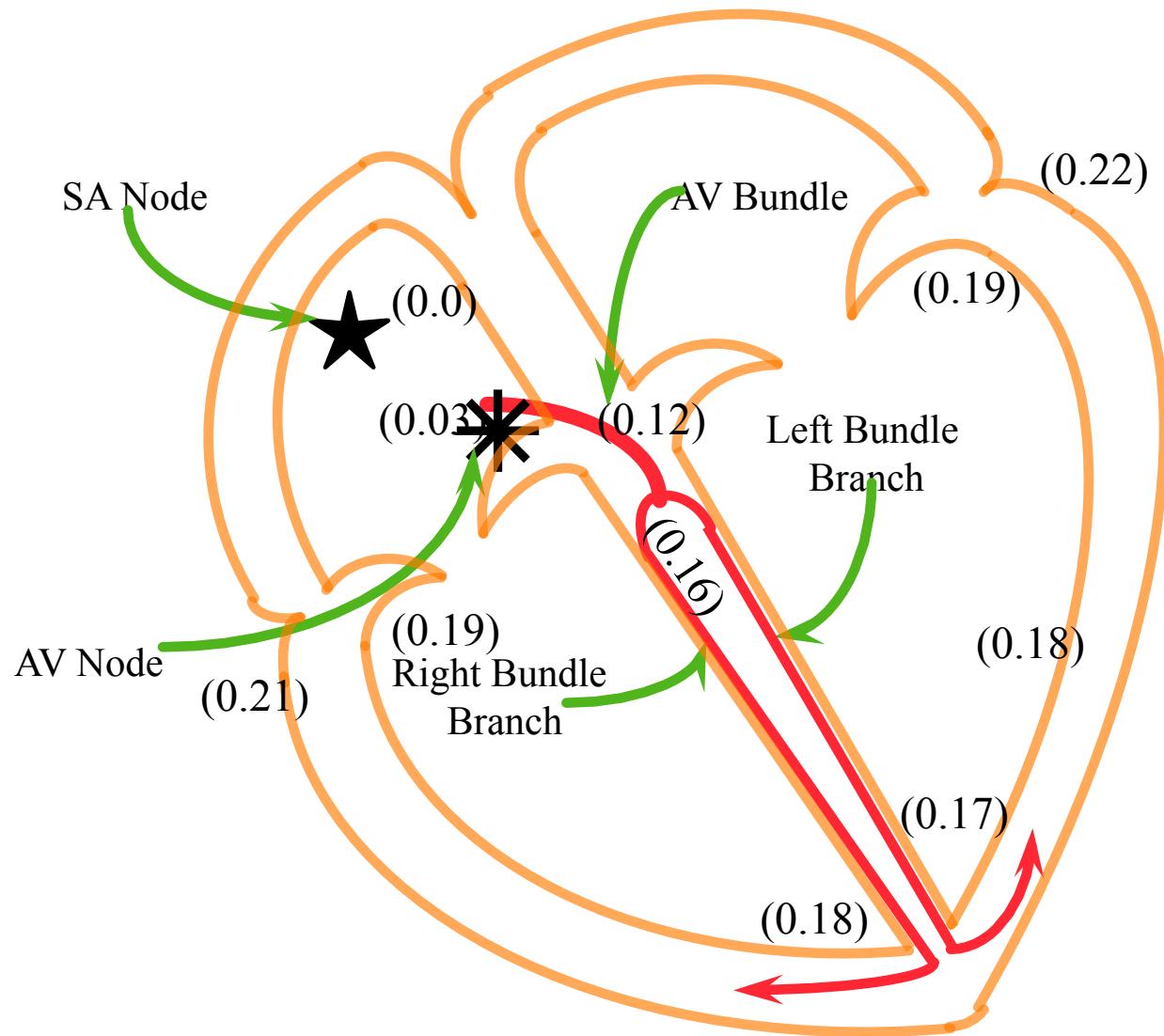
Figure 10–1
Sinus node, and the Purkinje system of the heart,
showing also the A-V node, atrial internodal
pathways, and ventricular bundle branches.

■ Rhythmic Discharge of Sinus Nodal Fiber



- “resting membrane potential” of the sinus nodal fiber between discharges has a negativity of about -55 to -60 millivolts, in comparison with -85 to -90 millivolts for the ventricular muscle fiber.
- The cause of this lesser negativity is that the cell membranes of the sinus fibers are naturally leaky to sodium and calcium ions, and positive charges of the entering sodium and calcium ions neutralize much of the intracellular negativity.

■ Time of Arrival of Cardiac Impulse



Note that the impulse spreads at moderate velocity through the atria but is delayed more than 0.1 second in the A-V nodal region before appearing in the ventricular septal A-V bundle. Once it has entered this bundle, it spreads very rapidly through the Purkinje fibers to the entire endocardial surfaces of the ventricles. Then the impulse once again spreads slightly less rapidly through the ventricular muscle to the epicardial surfaces.

Main Arrival Times

S-A Node	0.00 sec
A-V Node	0.03 sec
A-V Bundle	0.12 sec
Ventricular Septum	0.16 sec

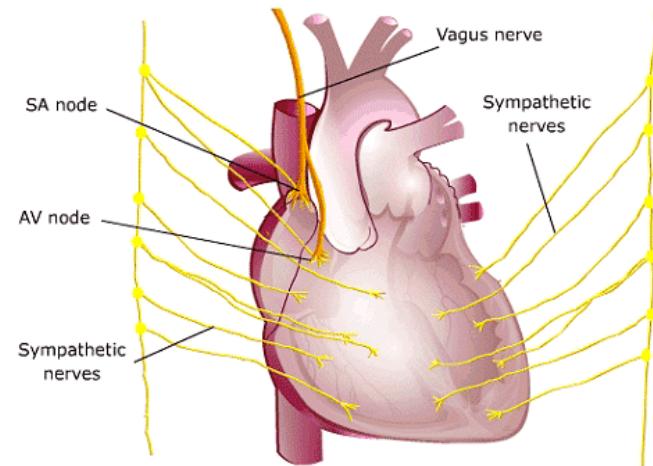
Control of Excitation and Conduction in the Heart

- Sinus Node is Cardiac Pacemaker
 - Normal rate of discharge in sinus node is 70-80/min.; A-V node - 40-60/min.; Purkinje fibers - 15-40/min.
 - Sinus node is pacemaker because of its faster discharge rate

- **Ectopic Pacemaker**
- A pacemaker elsewhere than the sinus node is called an “ectopic” pacemaker.
- This is a portion of the heart with a more rapid discharge than the sinus node.
- Also occurs when transmission from sinus node to A-V node is blocked (A-V block).
 - For instance, this sometimes occurs in the A-V node or in the Purkinje fibers.

- **Control of Heart Rhythmicity and Impulse Conduction by the Cardiac Nerves: The Sympathetic and Parasympathetic Nerves**

- **Parasympathetic Effects on Heart Rate**



- Parasympathetic (vagal) nerves, which release acetylcholine at their endings, innervate S-A node and A-V junctional fibers proximal to A-V node.
- Causes hyperpolarization because of increased K^+ permeability in response to acetylcholine.
- This causes decreased transmission of impulses maybe temporarily stopping heart rate.

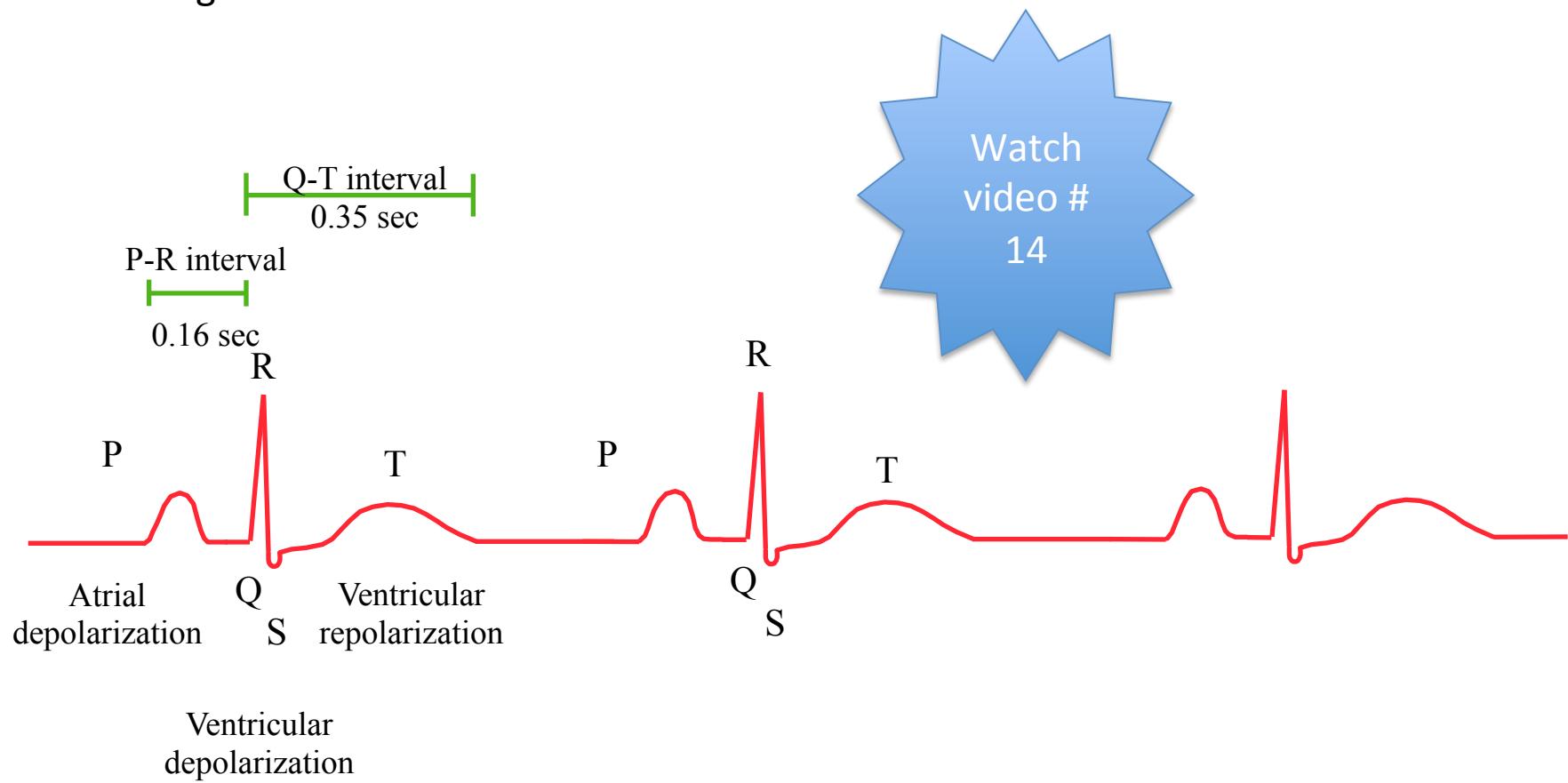
➤ Sympathetic Effects on Heart Rate

- Releases norepinephrine at sympathetic ending
- Causes increased sinus node discharge
- Increases rate of conduction of impulse
- Increases force of contraction in atria and ventricles

- Electrocardiogram (ECG)
 - Cardiac Cycle
(chapter 11)

Characteristics of the Normal Electrocardiogram

- **Normal ECG**
- When the cardiac impulse passes through the heart, electrical current also spreads from the heart into the adjacent tissues surrounding the heart. If electrodes are placed on the skin, electrical potentials generated by the current can be recorded; the recording is known as an electrocardiogram.



- **Standardized ECGs**

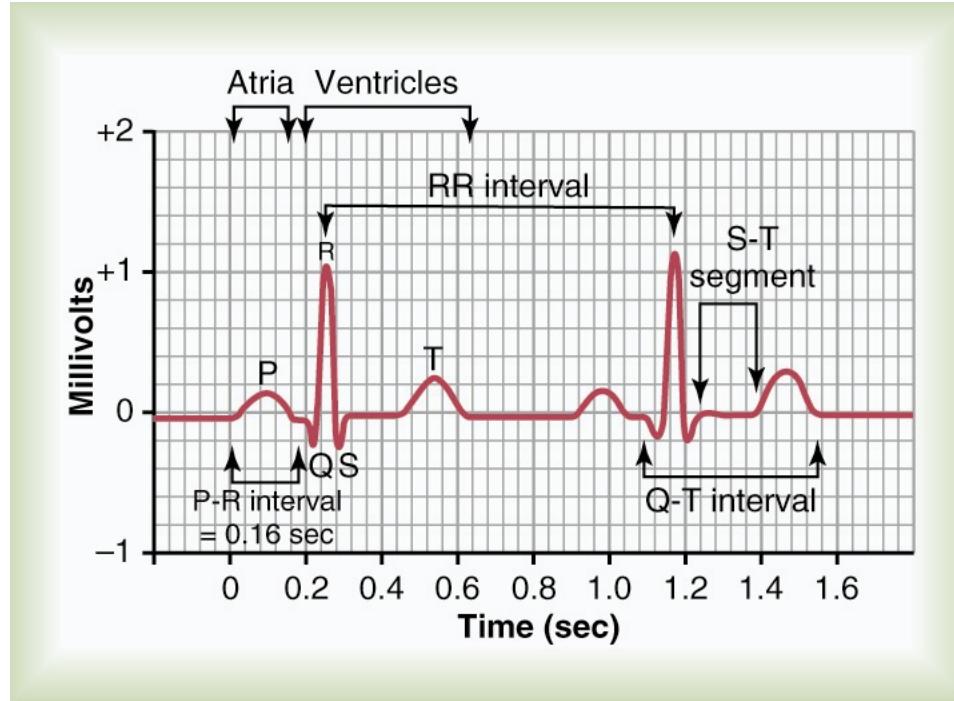
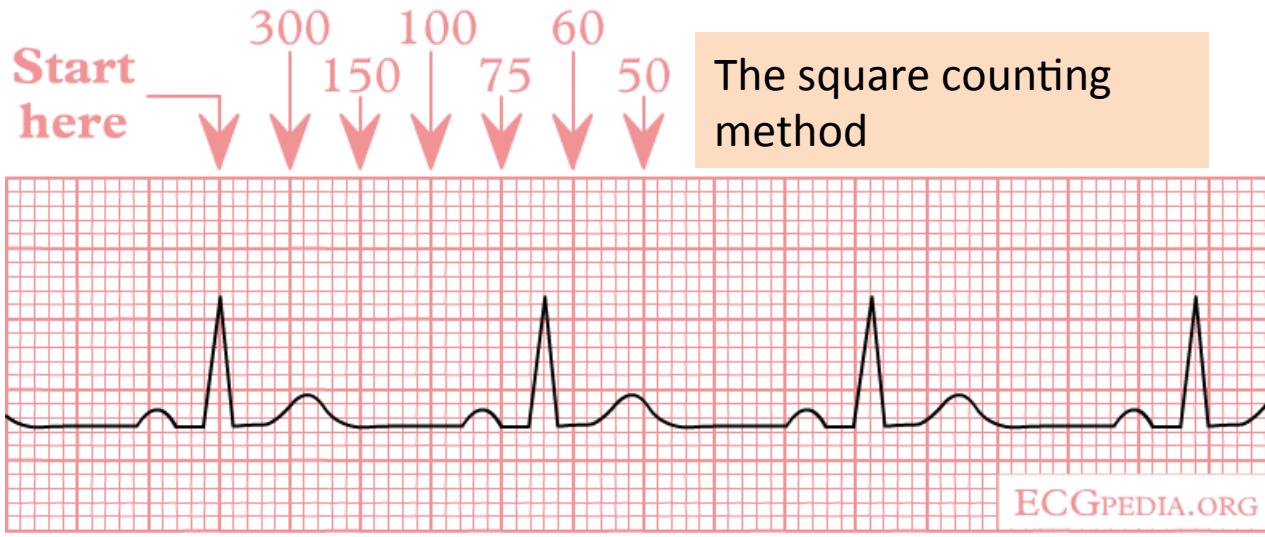


Figure 11-1; Guyton & Hall

- Time and voltage calibrations are standardized as shown on figure 11-1.

■ Heart Rate Calculation

- The rate of heartbeat can be determined easily from an electrocardiogram because the heart rate is the reciprocal of the time interval between two successive heartbeats. If the interval between two beats as determined from the time calibration lines is 1 second, the heart rate is 60 beats per minute. The normal interval between two successive QRS complexes in the adult person is about 0.83 second. This is a heart rate of $60/0.83$ times per minute, or 72 beats per minute.
- R-R interval = 0.83 sec
- Heart rate = $(\underline{60 \text{ sec}})/(\underline{0.83 \text{ sec}}) = 72 \text{ beats/min}$



The count method to determine the heart frequency. The second QRS complex is between 75 and 60 beat per minute. This heartbeat is between that, around 65 beats per minute.

Flow of Current Around the Heart During the Cardiac Cycle

- Recording Electrical Potentials from a Partially Depolarized Mass of Syncytial Cardiac Muscle

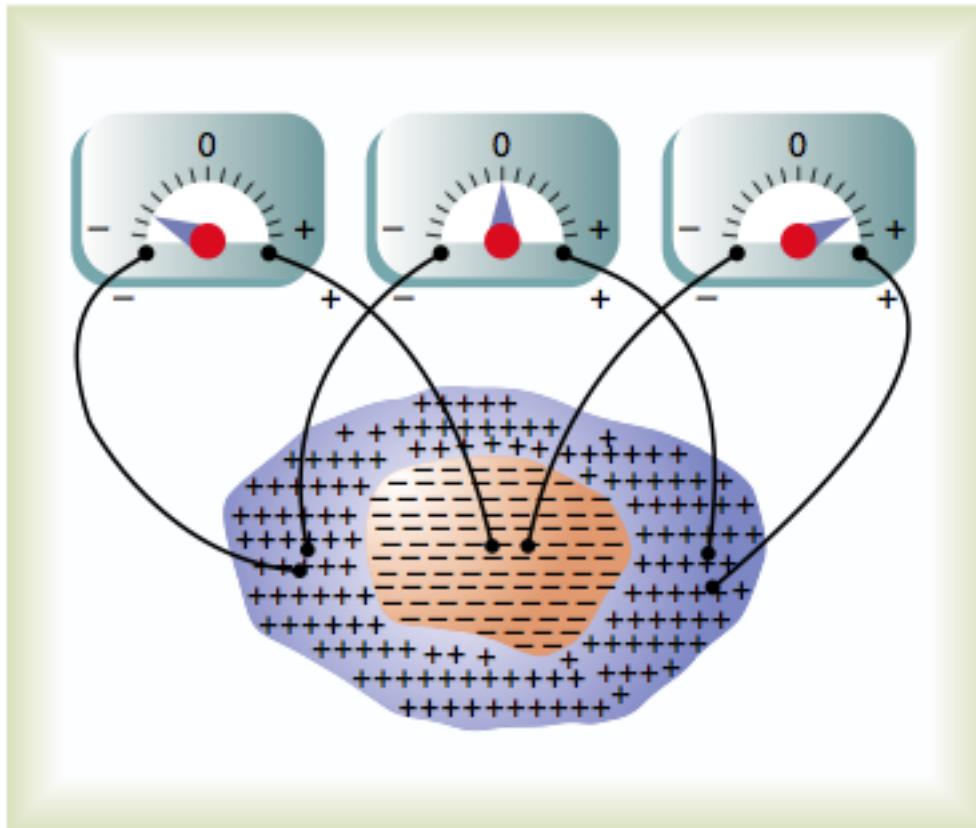


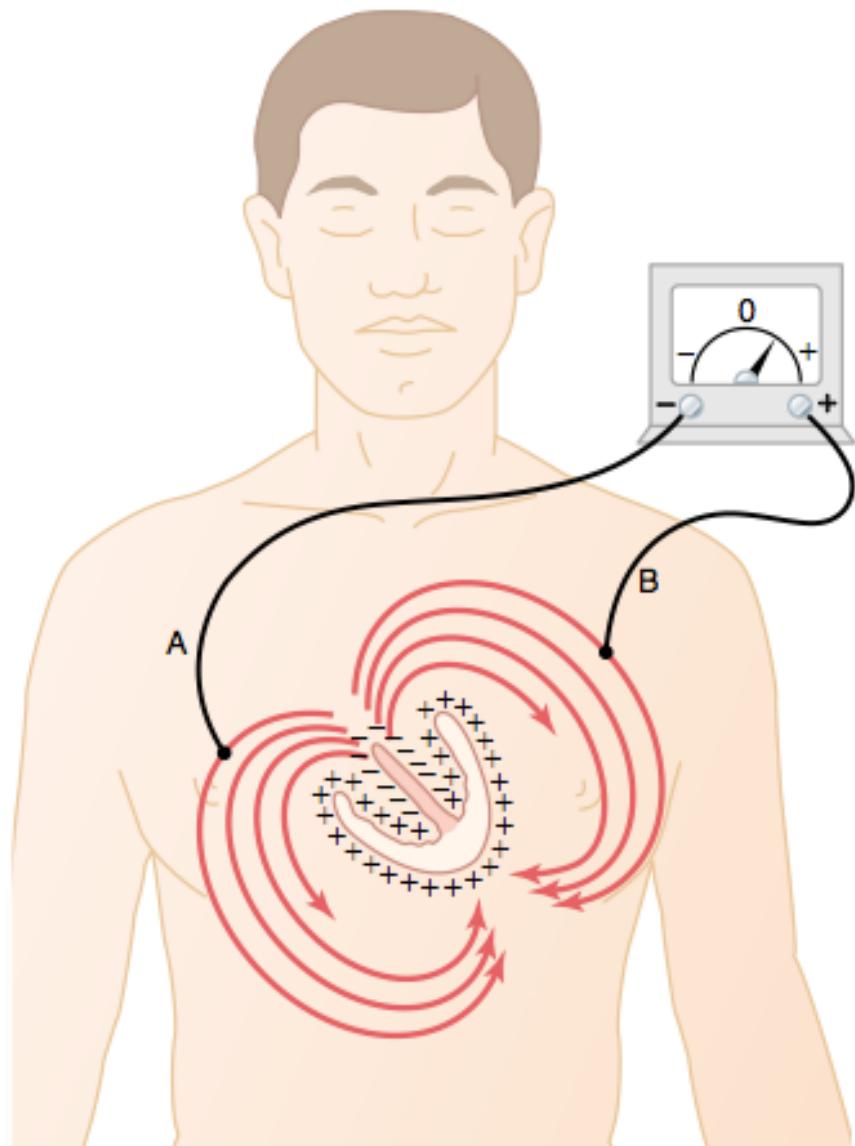
Figure 11–4

Instantaneous potentials develop on the surface of a cardiac muscle mass that has been depolarized in its center.

a meter connected with its negative terminal on the area of depolarization and its positive terminal on one of the still-polarized areas, as shown to the right in the figure, records positively.

Two other electrode placements and meter readings are also demonstrated in Figure 11–4.

■ Flow of Electrical Currents in the Chest Around the Heart



- the heart is actually suspended in a conductive medium
- When one portion of the ventricles depolarizes and therefore becomes electronegative with respect to the remainder, electrical current flows from the depolarized area to the polarized area in large circuitous routes, as noted in the figure

Figure 11–5

Flow of current in the chest around partially depolarized ventricles.

■ Flow of Electrical Currents in the Chest Around the Heart

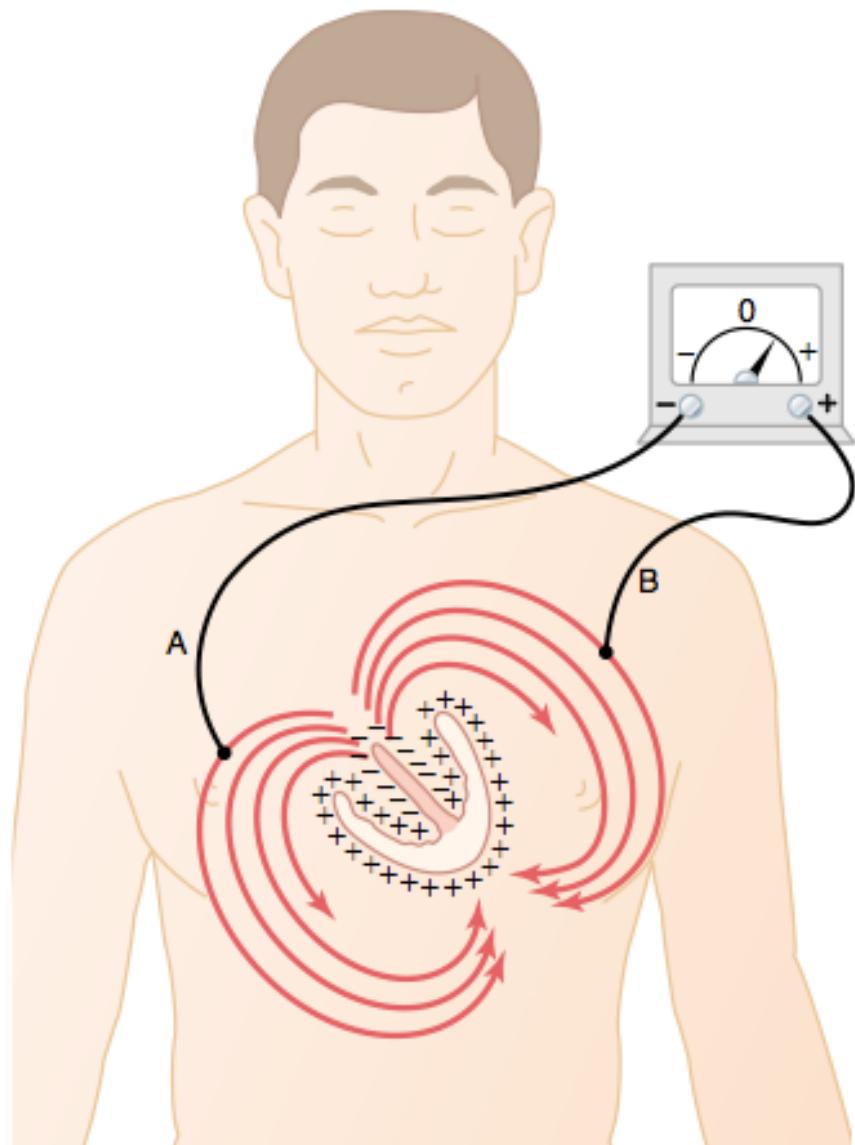
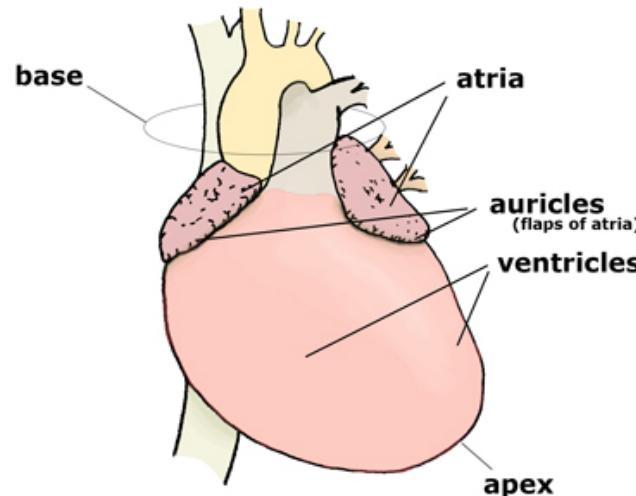


Figure 11–5

Flow of current in the chest around partially depolarized ventricles.



- in normal heart ventricles, current flows from negative to positive primarily in the direction from the base of the heart toward the apex during almost the entire cycle of depolarization, except at the very end. And if a meter is connected to electrodes on the surface of the body as shown in Figure 11–5, the electrode nearer the base will be negative, whereas the electrode nearer the apex will be positive, and the recording meter will show positive recording in the electrocardiogram.

Electrocardiographic Leads

■ Bipolar Limb Leads

- Bipolar means that the ECG is recorded from two electrodes on the body.

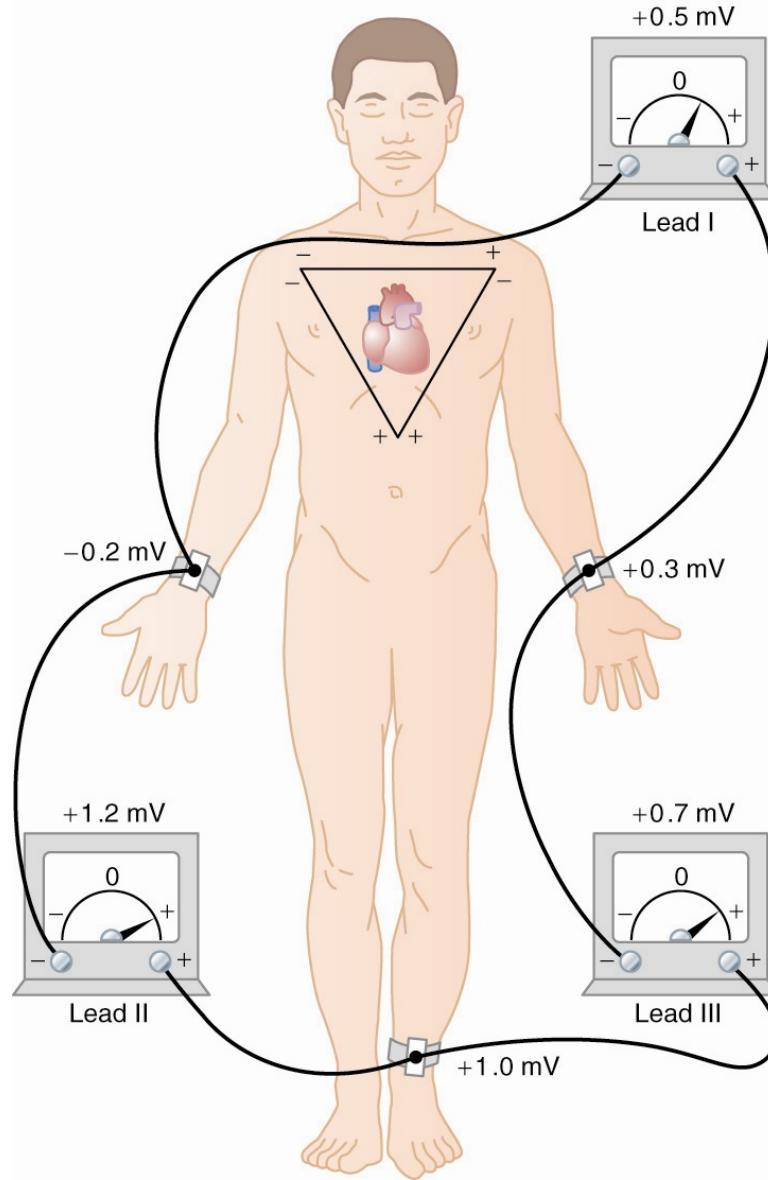


Figure 11-6; Guyton & Hall

- **Lead I.** In recording limb lead I, the negative terminal of the electrocardiograph is connected to the right arm and the positive terminal to the left arm. Therefore, when the point where the right arm connects to the chest is electronegative with respect to the point where the left arm connects, the electrocardiograph records positively, that is, above the zero voltage line in the electrocardiogram. When the opposite is true, the electrocardiograph records below the line.
- **Lead II.** To record limb lead II, the negative terminal of the electrocardiograph is connected to the right arm and the positive terminal to the left leg. Therefore, when the right arm is negative with respect to the left leg, the electrocardiograph records positively.
- **Lead III.** To record limb lead III, the negative terminal of the electrocardiograph is connected to the left arm and the positive terminal to the left leg. This means that the electrocardiograph records positively when the left arm is negative with respect to the left leg.

Einthoven's Triangle. In Figure 11–6, the triangle, called Einthoven's triangle, is drawn around the area of the heart. This illustrates that the two arms and the left leg form apices of a triangle surrounding the heart. The two apices at the upper part of the triangle represent the points at which the two arms connect electrically with the fluids around the heart, and the lower apex is the point at which the left leg connects with the fluids.

Einthoven's Law. Einthoven's law states that if the electrical potentials of any two of the three bipolar limb electrocardiographic leads are known at any given instant, the third one can be determined mathematically by simply summing the first two (but note that the positive and negative signs of the different leads must be observed when making this summation).

- the sum of the voltages in leads I and III equals the voltage in lead II. Mathematically, this principle, called Einthoven's law, holds true at any given instant while the three “standard” bipolar electrocardiograms are being recorded.

- Bipolar Limb Leads (cont'd)

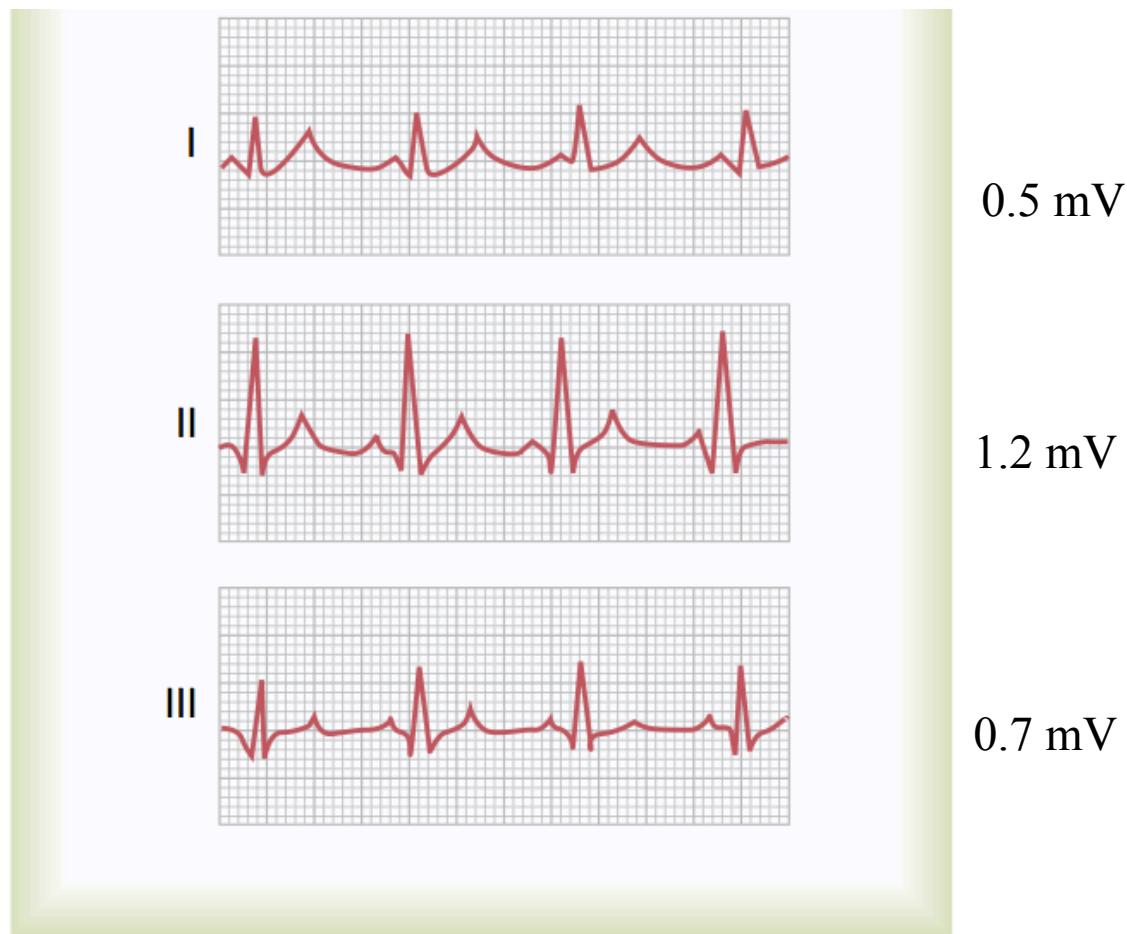


Figure 11–7

Normal electrocardiograms recorded from the three *standard* electrocardiographic leads.

■ Other ECG Leads

Unipolar Limb Leads

Unipolar means that the ECG is recorded from an electrode on the body with respect to the indifferent electrode.

- Often electrocardiograms are recorded with one electrode placed on the anterior surface of the chest directly over the heart at one of the points shown in Figure 11–8.
- This electrode is connected to the positive terminal of the electrocardiograph, and the negative electrode, called the *indifferent electrode*, is connected through equal electrical resistances to the right arm, left arm, and left leg all at the same time, as also shown in the figure.

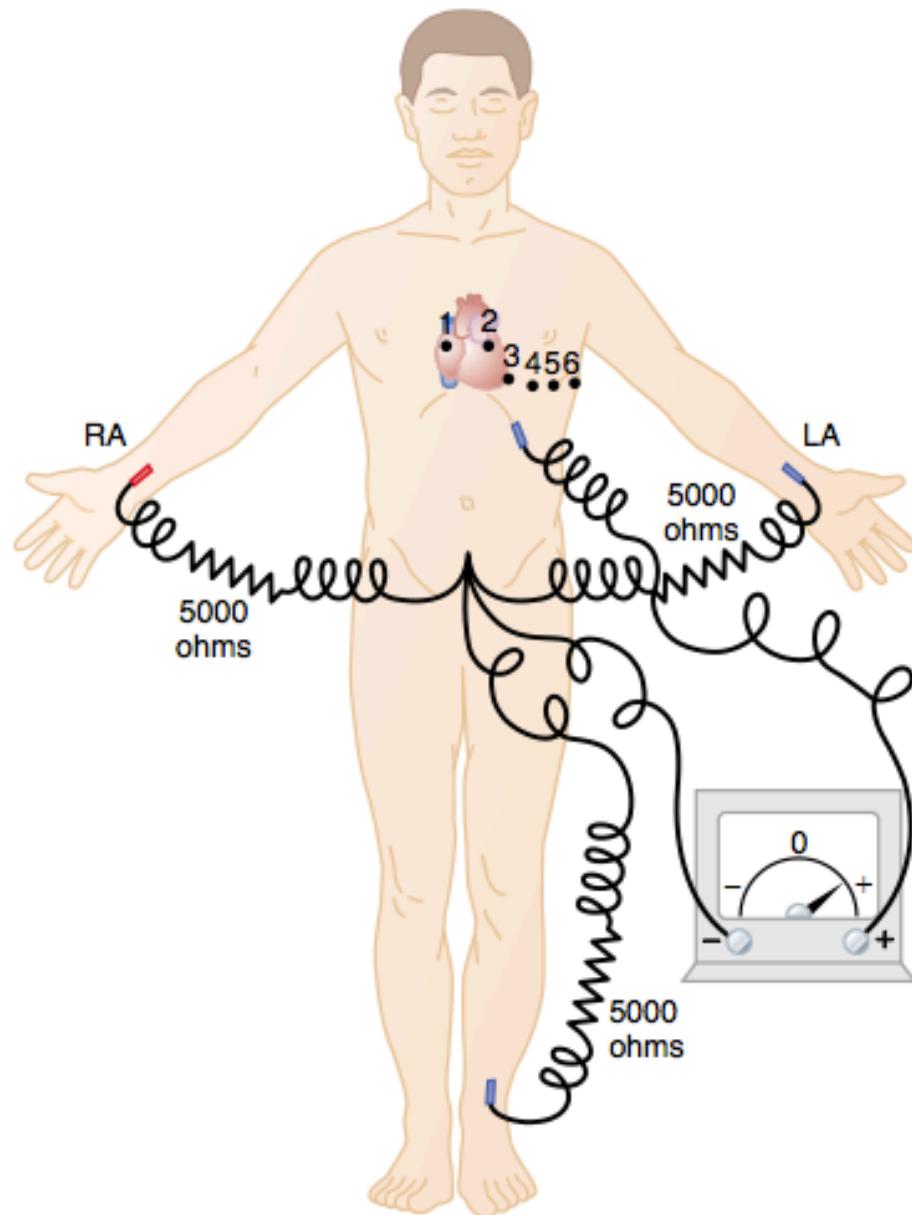


Figure 11–8

Connections of the body with the electrocardiograph for recording *chest leads*. LA, left arm; RA, right arm.

- Chest Leads (Precordial Leads) known as V_1 - V_6 are very sensitive to electrical potential changes underneath the electrode.

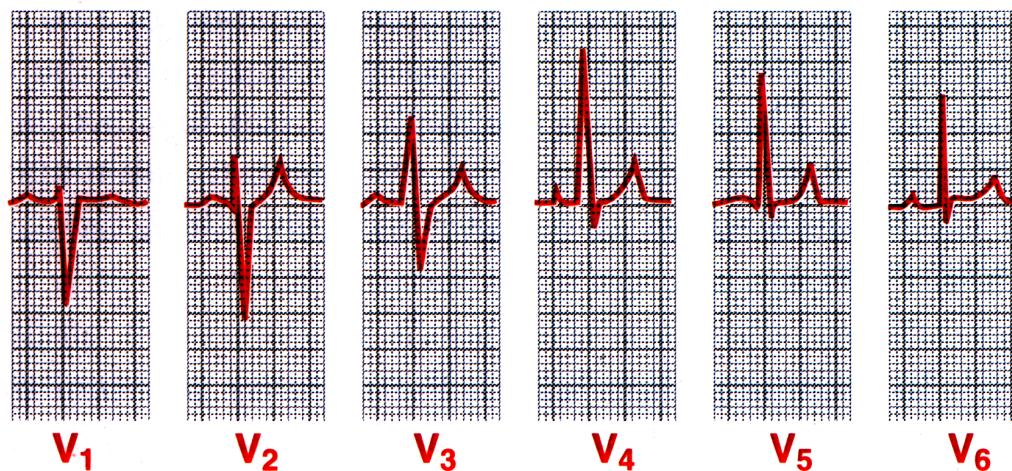
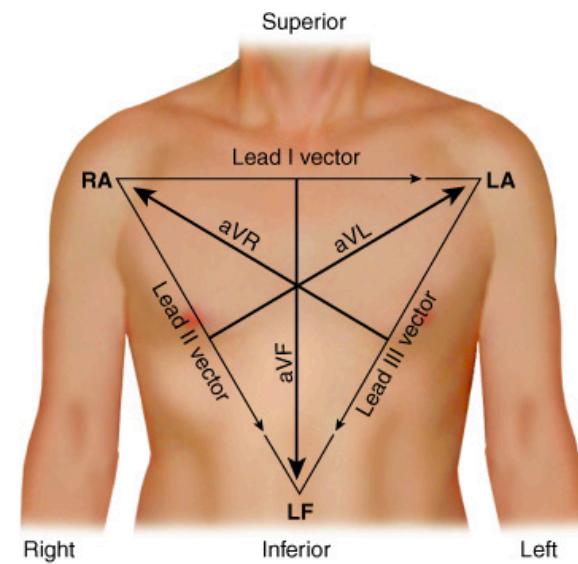
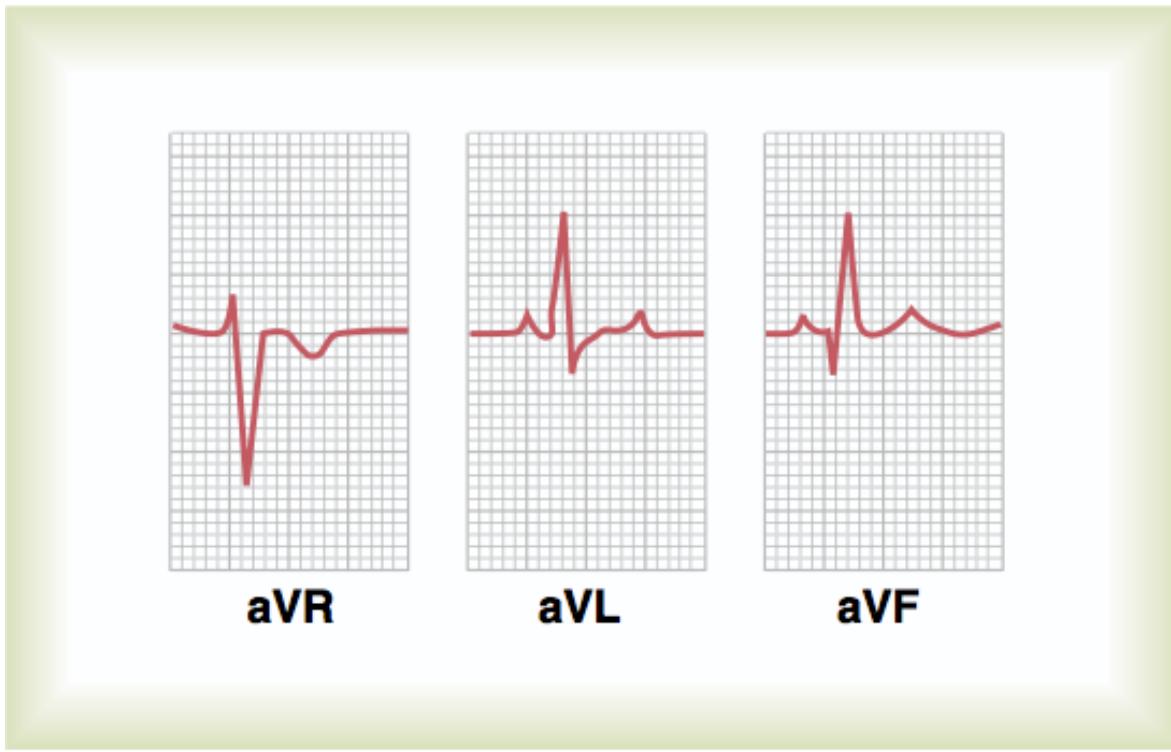


Figure 11-9; Normal electrocardiograms recorded from the six standard chest leads.

■ Augmented Unipolar Limb Leads



Copyright ©

Figure 11–10

Normal electrocardiograms recorded from the three augmented unipolar limb leads.

Cardiac Cycle

- The cardiac events that occur from the beginning of one heartbeat to the beginning of the next are called the *cardiac cycle*.

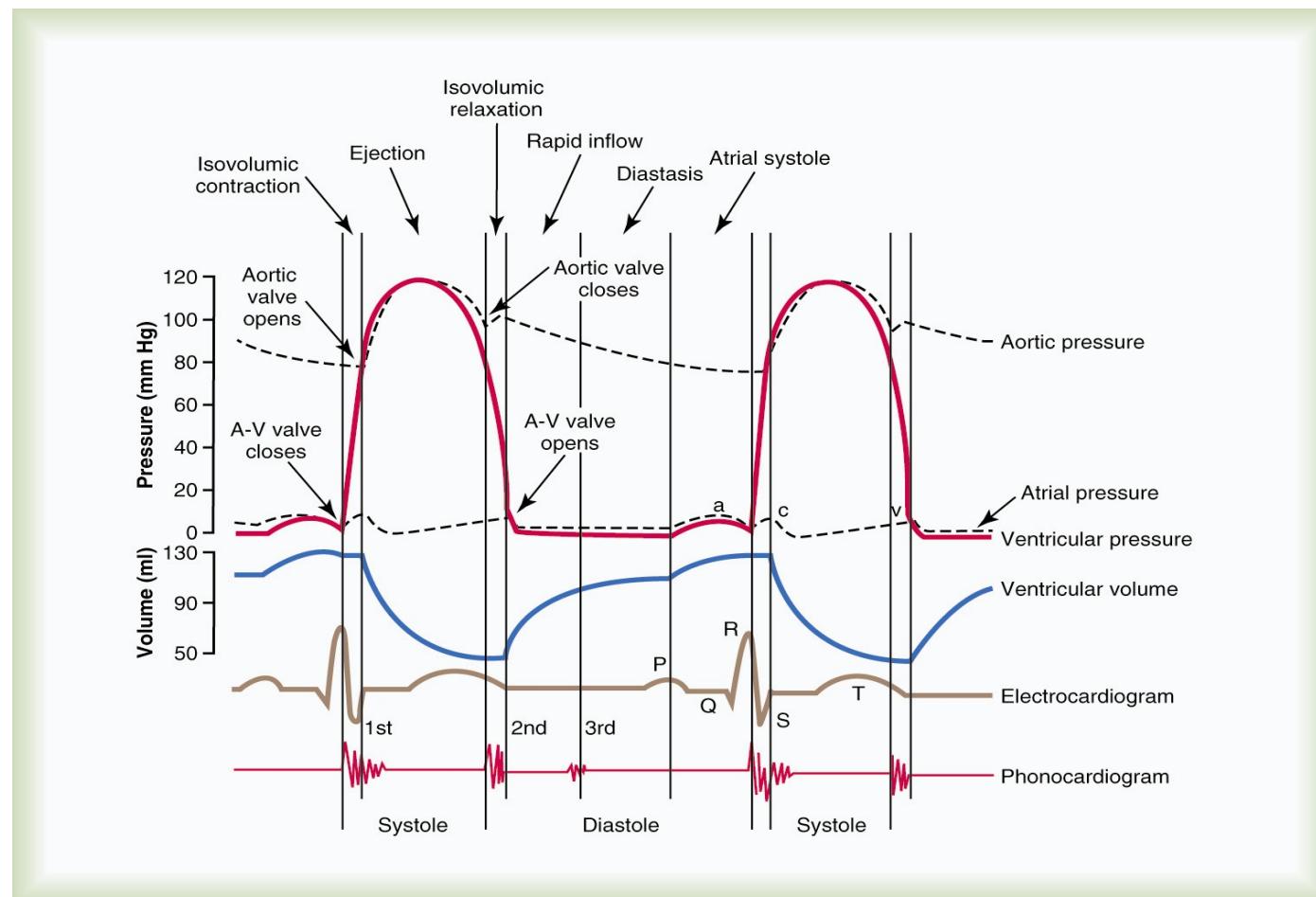
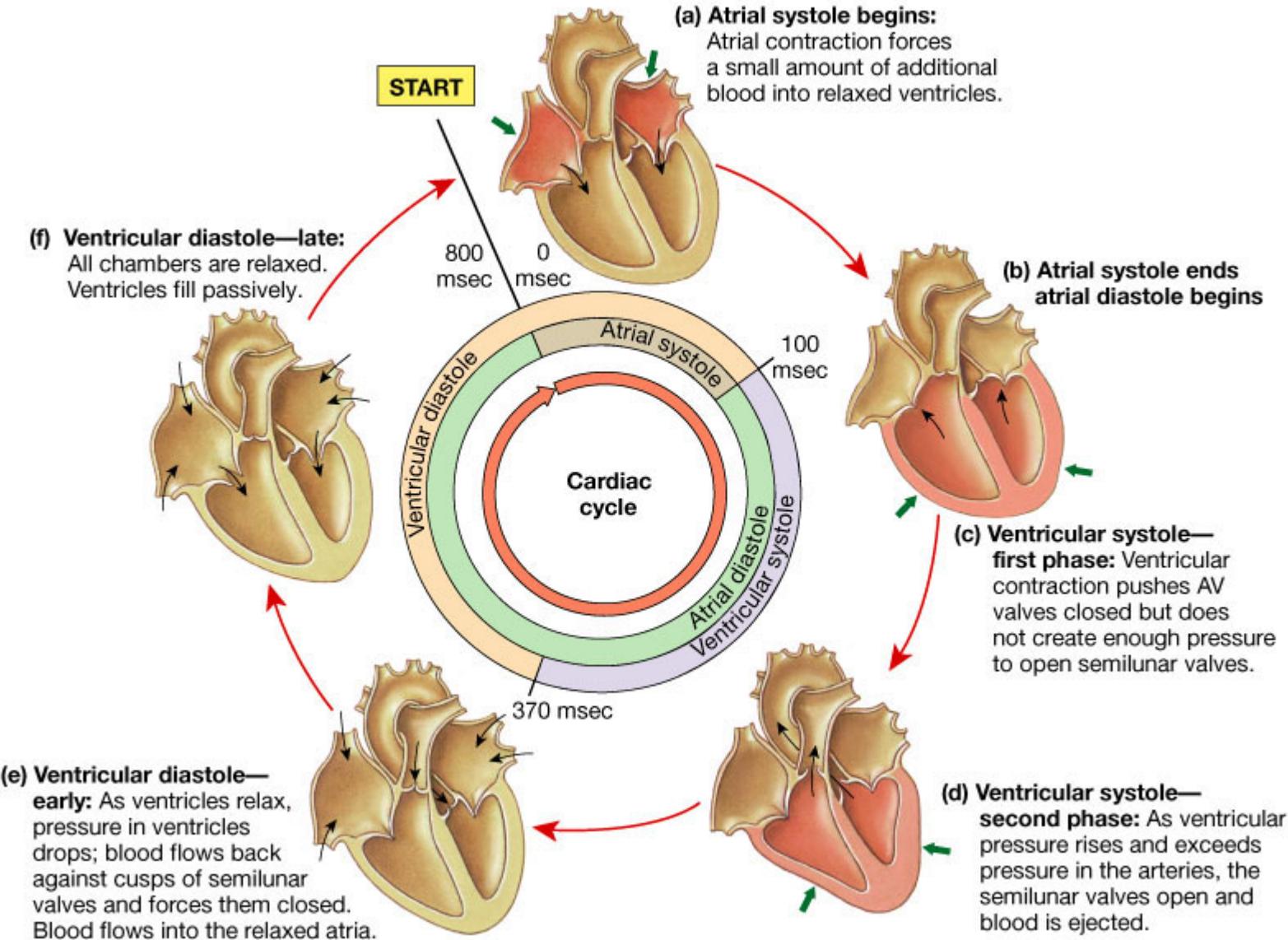


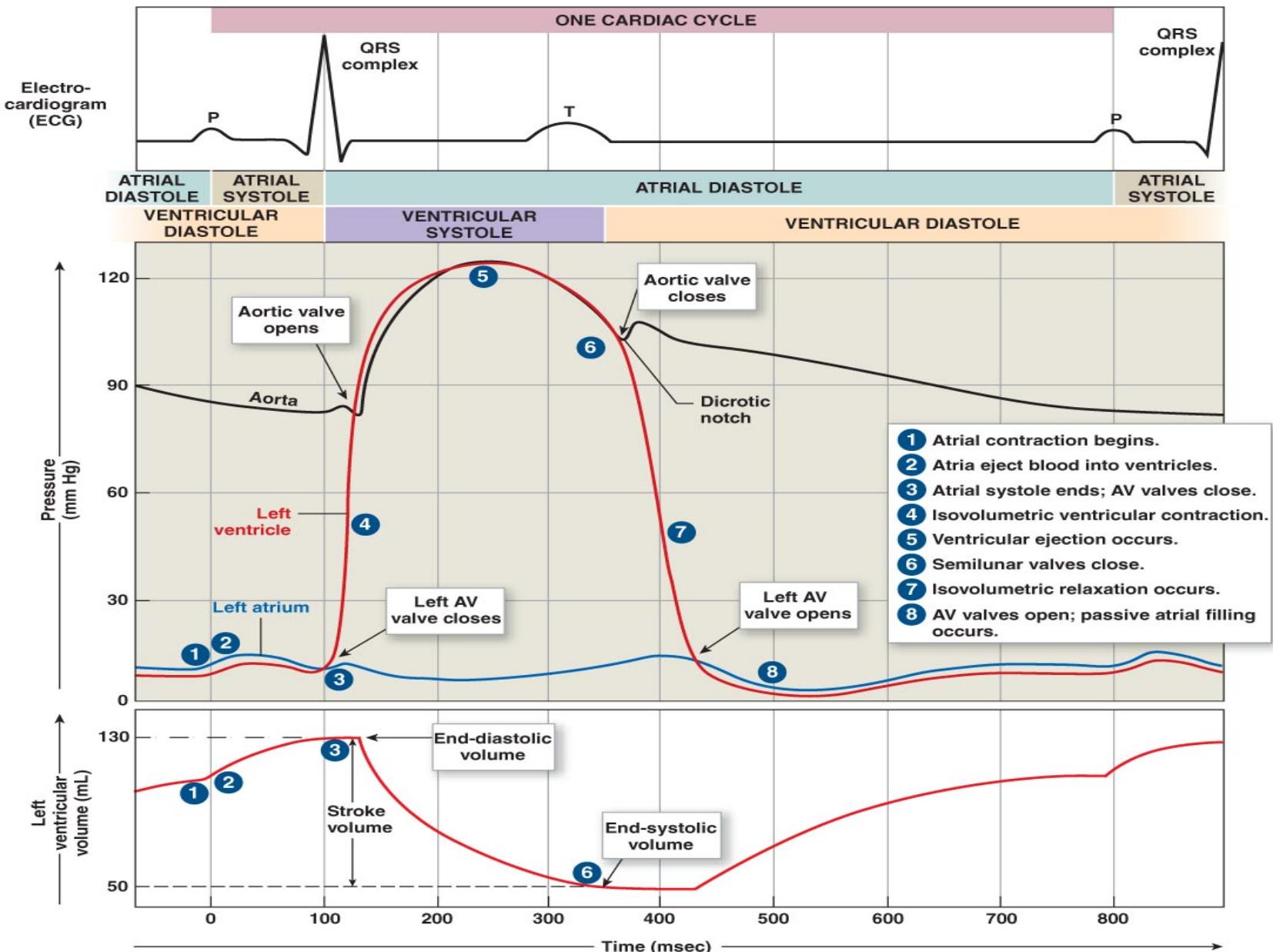
Figure 9–5

Events of the cardiac cycle for left ventricular function, showing changes in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonocardiogram.

■ Phases of the Cardiac Cycle



Pressure and Volume Relationships in the Cardiac Cycle

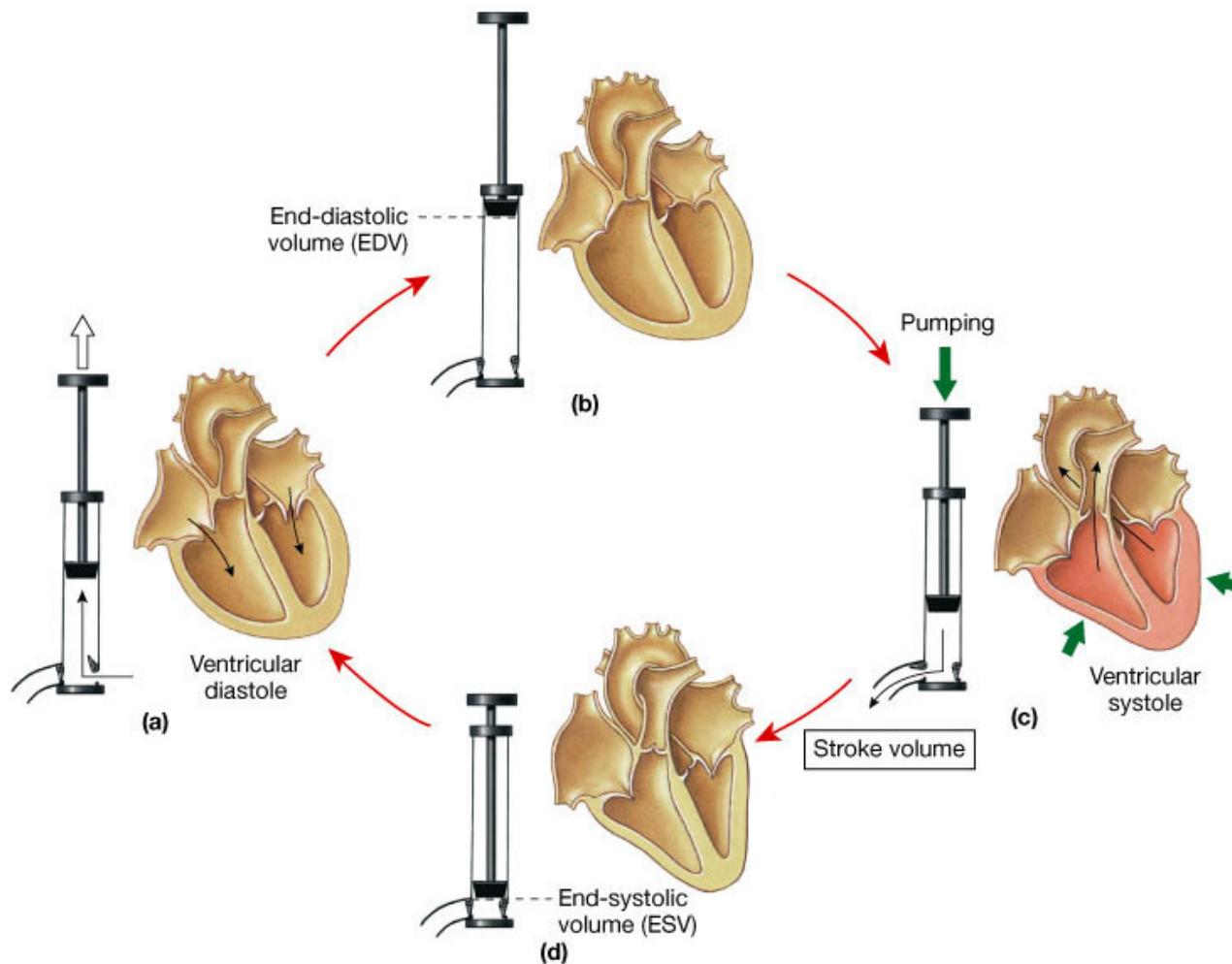


- **Stroke Volume and Cardiac Output**
- Cardiac output – the amount of blood pumped by each ventricle in one minute
 - Cardiac output equals heart rate times stroke volume

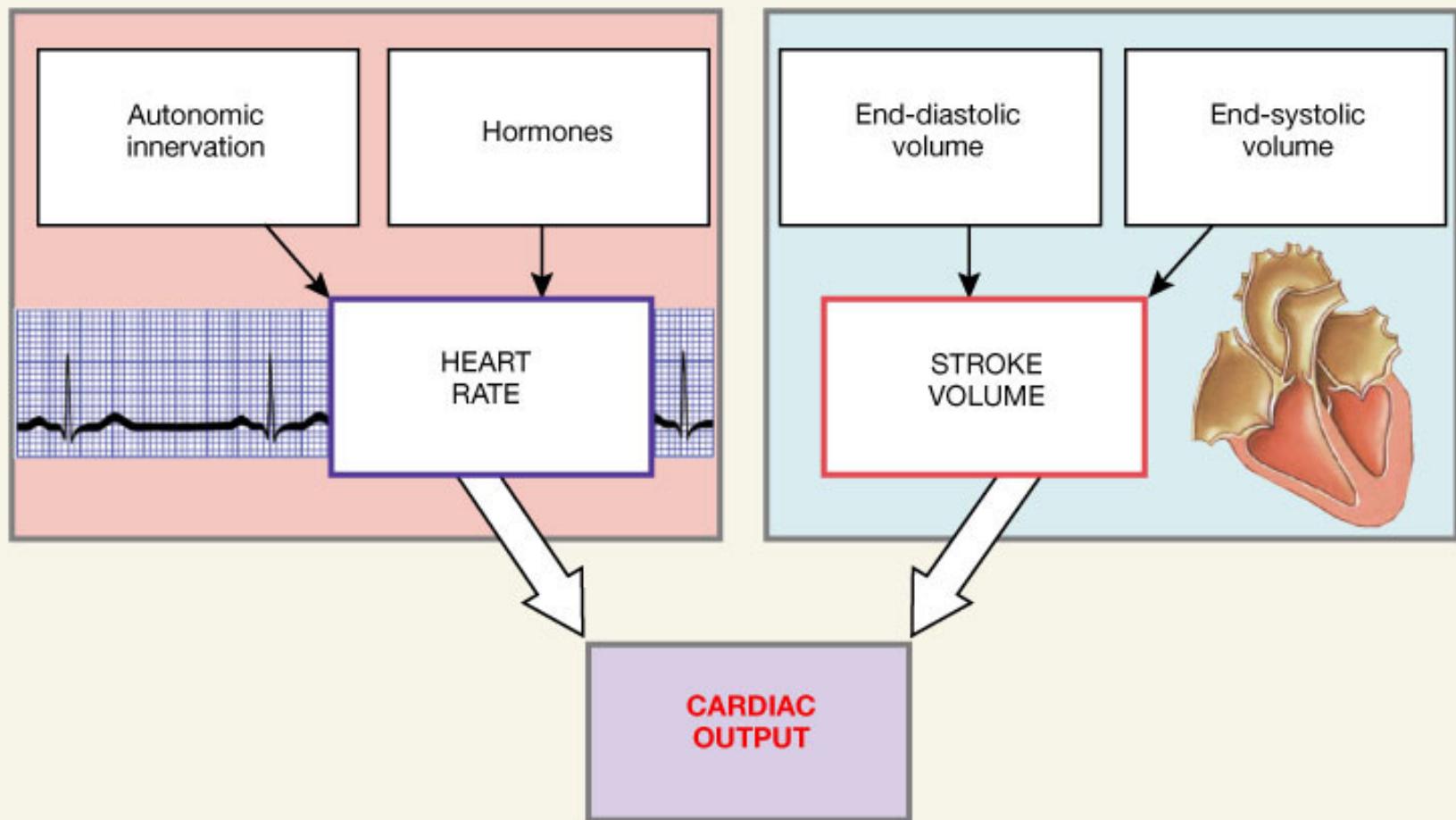
CO Cardiac output (ml/min)	=	HR Heart rate (beats/min)	X	SV Stroke volume (ml/beat)
----------------------------------	---	---------------------------------	---	----------------------------------

■ A Simple Model of Stroke Volume

During diastole, normal filling of the ventricles increases the volume of each ventricle to about 110 to 120 milliliters. This volume is called the *end-diastolic volume*. Then, as the ventricles empty during systole, the volume decreases about 70 milliliters, which is called the *stroke volume output*. The remaining volume in each ventricle, about 40 to 50 milliliters, is called the *end-systolic volume*.



Factors Affecting Cardiac Output



Cardiac Arrhythmias (chapter 13)

Abnormal Sinus Rhythms

- Tachycardia means a fast heart rate usually greater than 100 beats /min.

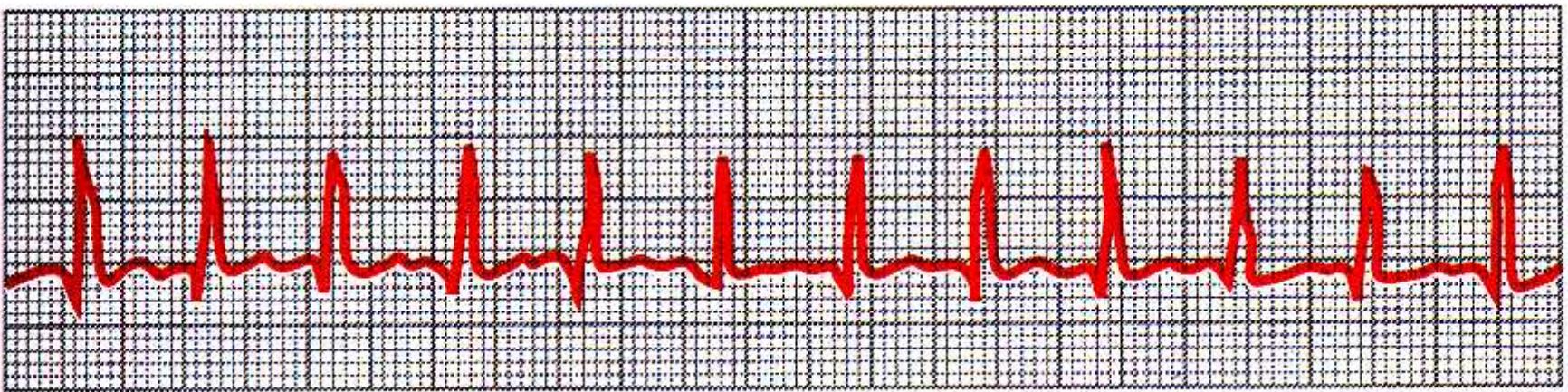


Figure 13-1; Sinus tachycardia (lead I).

- Bradycardia means a slow heart rate usually less than 60 beats /min

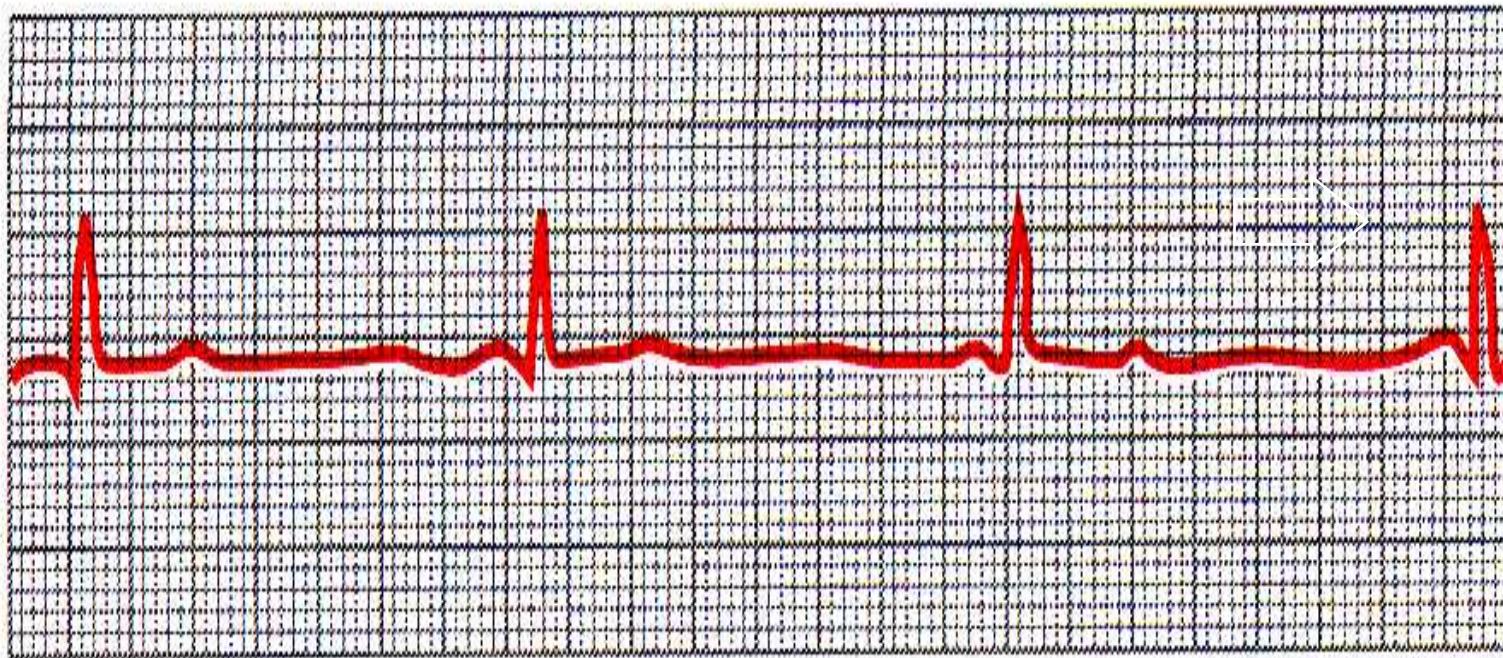
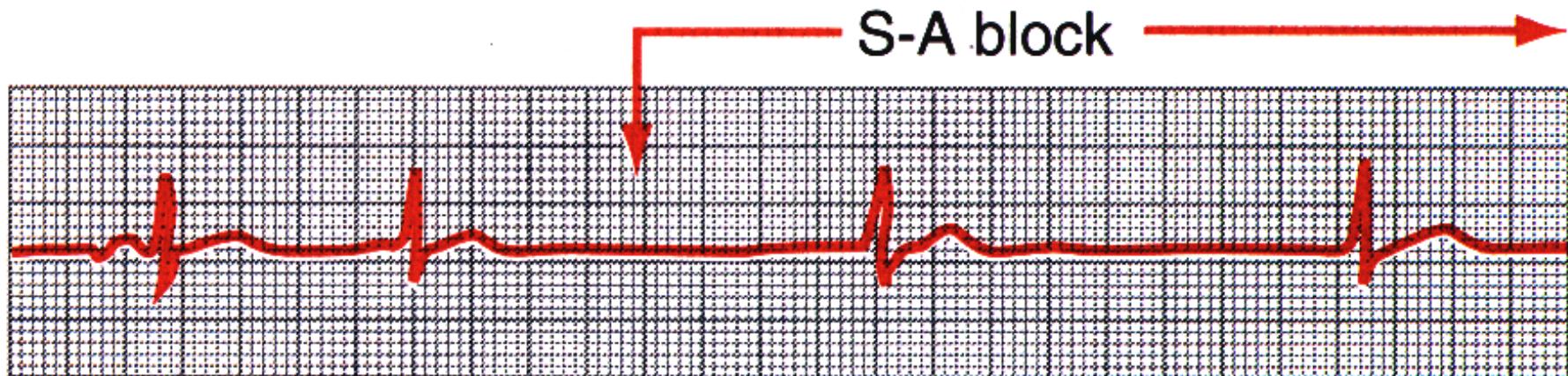


Figure 13-2: Sinus bradycardia (lead III).

Abnormal Rhythms That Result from Block of Heart Signals Within the Intracardiac Conduction Pathways

Sinoatrial Block

- In rare instances impulses from S-A node are blocked.
- New pacemaker is region of heart with the fastest discharge rate, usually the A-V node.



Note: no P waves and slow rate

Figure 13-4; Sinoatrial nodal block, with A-V nodal rhythm during the block period (lead III).

■ Atrioventricular Block

- Impulses ordinarily can pass from the atria into the ventricles through the A-V bundle, also known as *the bundle of His*. Conditions that can either decrease the rate of impulse conduction in this bundle or block the impulse entirely are :
- 1. **Ischemia of the A-V node or A-V bundle fibers** often delays or blocks conduction from the atria to the ventricles. Coronary insufficiency can cause ischemia of the A-V node and bundle in the same way that it can cause ischemia of the myocardium.
- 2. **Compression of the A-V bundle by scar tissue** or by calcified portions of the heart can depress or block conduction from the atria to the ventricles.
- 3. **Inflammation of the A-V node or A-V bundle** can depress conductivity from the atria to the ventricles. Inflammation results frequently from different types of myocarditis, caused, for example, by diphtheria or rheumatic fever.
- 4. **Extreme stimulation of the heart by the vagus nerves in rare instances blocks impulse conduction through the A-V node.** Such vagal excitation occasionally results from strong stimulation of the baroreceptors in people with carotid sinus syndrome, discussed earlier in relation to bradycardia.

■ Incomplete Atrioventricular Heart Block

➤ Prolonged P-R (or P-Q) Interval—First Degree Heart Block

- The usual lapse of time of the QRS complex is about 0.16 second when the heart is beating at a normal rate.
- P-R interval usually decreases in length with faster heartbeat and increases with slower heartbeat
- Figure 13–5 shows an electrocardiogram with prolonged P-R interval; the interval in this instance is about 0.30 second instead of the normal 0.20 or less.



Figure 13–5

Prolonged P-R interval caused by first degree A-V heart block (lead II).

■ Second Degree Heart Block

- When conduction through the A-V bundle is slowed enough to increase the P-R interval to 0.25 to 0.45 second, the action potential sometimes is strong enough to pass through the bundle into the ventricles and sometimes is not strong enough. In this instance, there will be an atrial P wave but no QRS-T wave, and it is said that there are “dropped beats” of the ventricles. This condition is called second degree heart block.

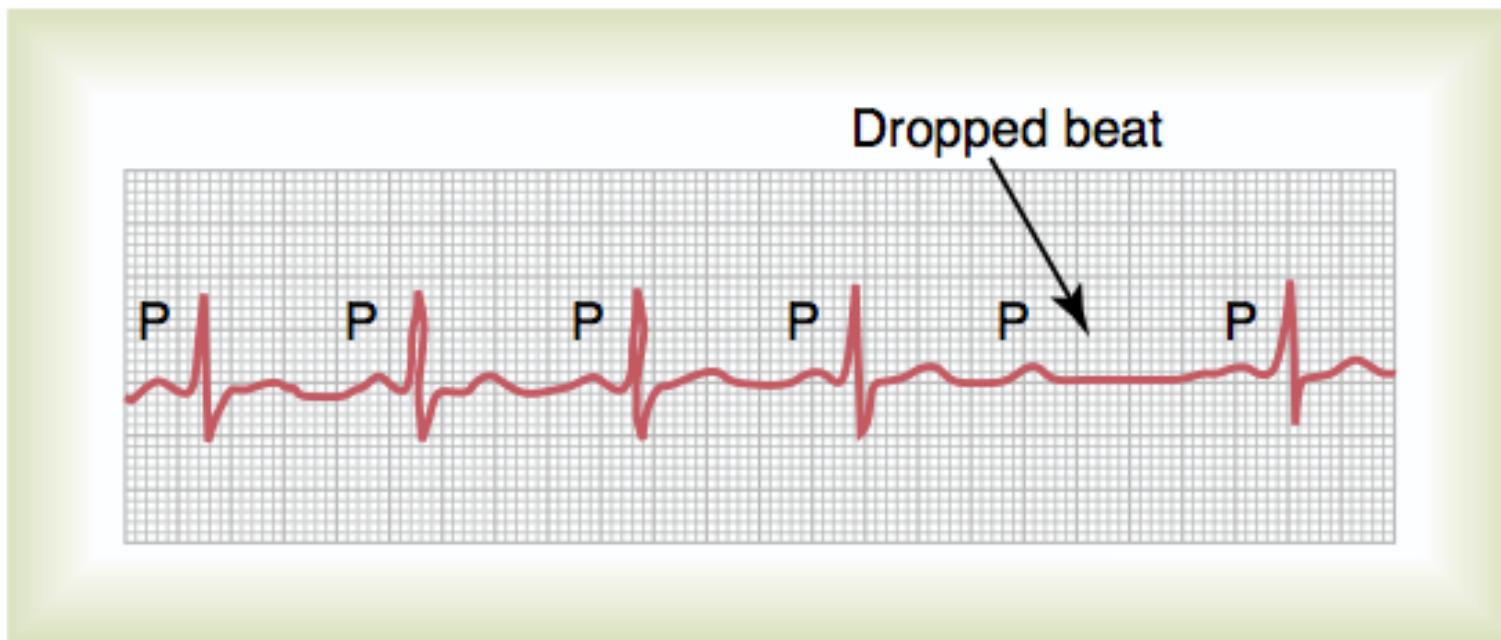


Figure 13–6

Second degree A-V block, showing occasional failure of the ventricles to receive the excitatory signals (lead V₃).

■ Third Degree Complete Block

- Total block through the A-V node or A-V bundle
- P waves are completely dissociated from QRST complexes

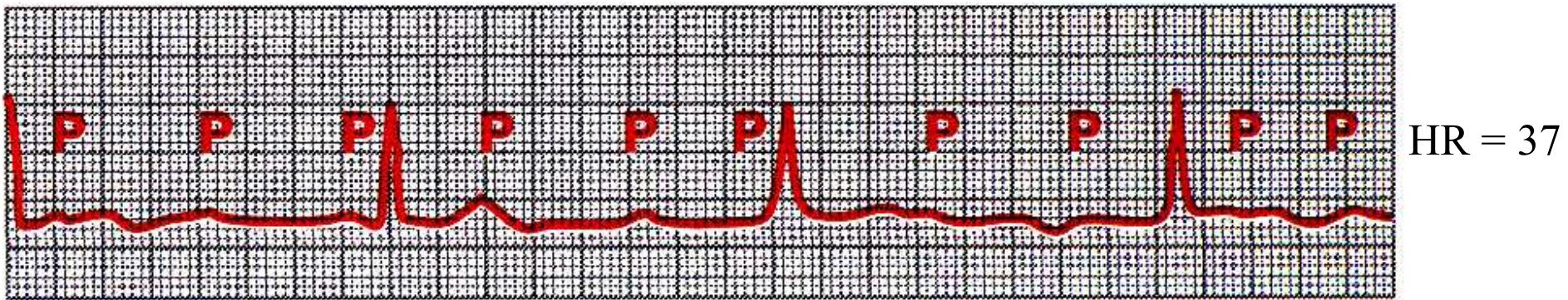


Figure 13-7; Complete A-V block (lead II).

Premature Contractions

- A premature contraction is a contraction of the heart before the time that normal contraction would have been expected. This condition is also called extrasystole, premature beat, or ectopic beat.
- **Premature Atrial Contractions**
- The P wave of this beat occurred too soon in the heart cycle; the P-R interval is shortened, indicating that the ectopic origin of the beat is in the atria near the A-V node.

Premature beat



Figure 13-9 Atrial premature beat (lead I).

■ A-V Nodal or A-V Bundle Premature Contractions

- P wave is superimposed onto the QRS-T complex because the cardiac impulse traveled backward into the atria at the same time that it traveled forward into the ventricles; this P wave slightly distorts the QRS-T complex.

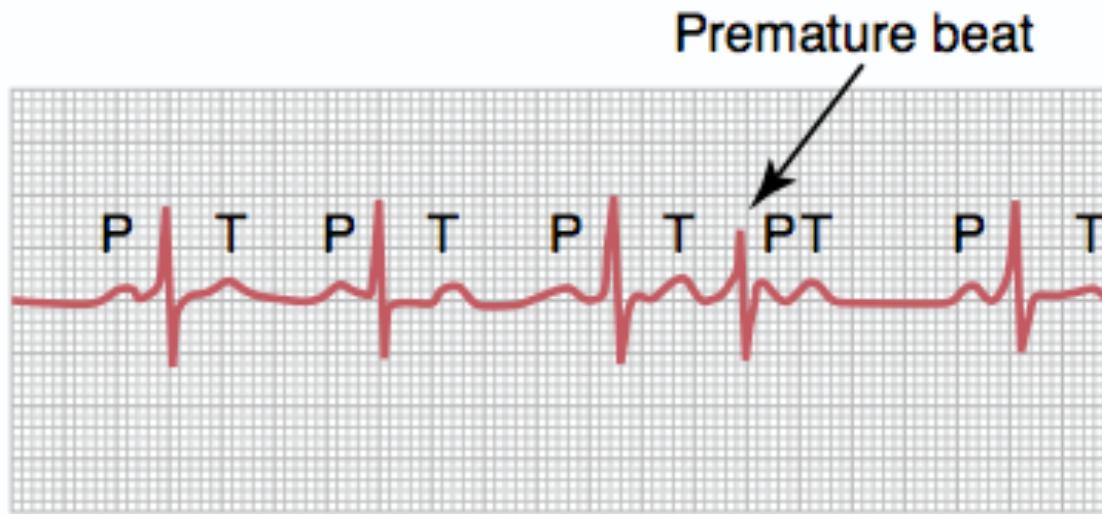


Figure 13–10 A-V nodal premature contraction (lead III).

■ Premature Ventricular Contractions (PVC's)



Figure 13–11
Premature ventricular contractions (PVCs) demonstrated by the **large abnormal QRS-T complexes** (leads II and III).

Paroxysmal Tachycardia

- Atrial Paroxysmal Tachycardia
- Paroxysmal means a series of rapid heart beats suddenly start and then suddenly stop.
- P wave is inverted if origin is near A-V node

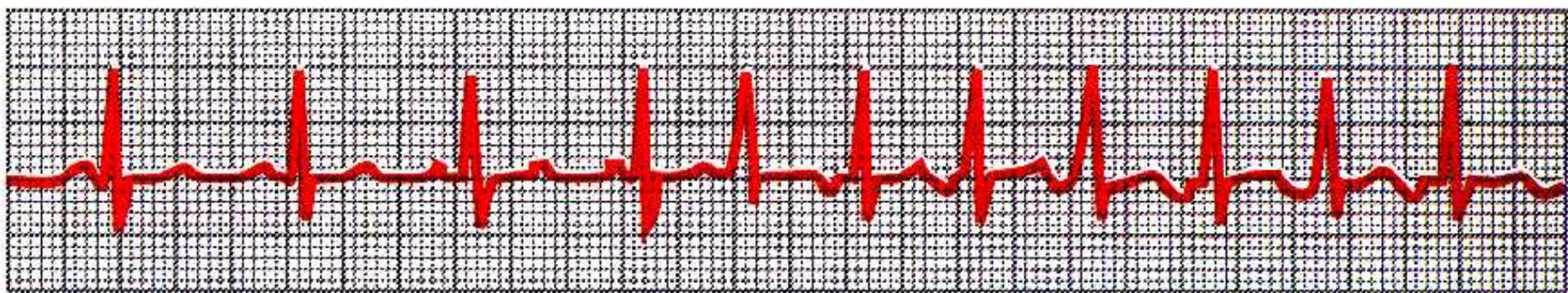


Figure 13-12; Atrial paroxysmal tachycardia—onset in middle of record (lead I).

■ Ventricular Paroxysmal Tachycardia

- Usually does not occur unless there has been ischemic damage

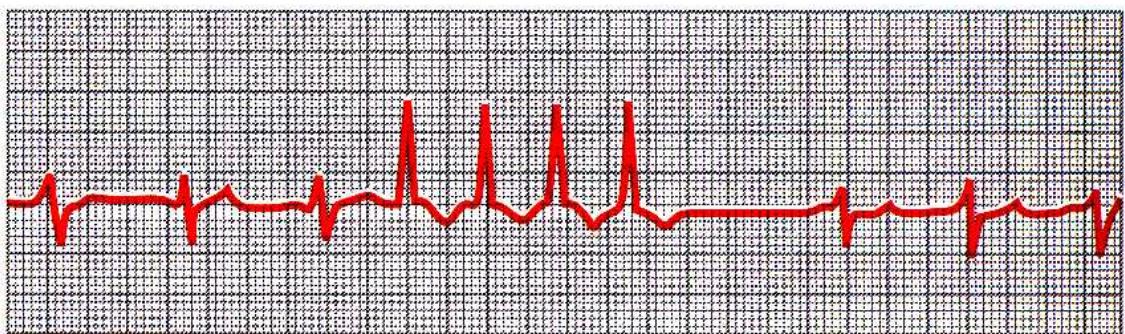


Figure 13-13 Ventricular paroxysmal tachycardia (lead III).

Atrial Fibrillation

- no P waves from the atria

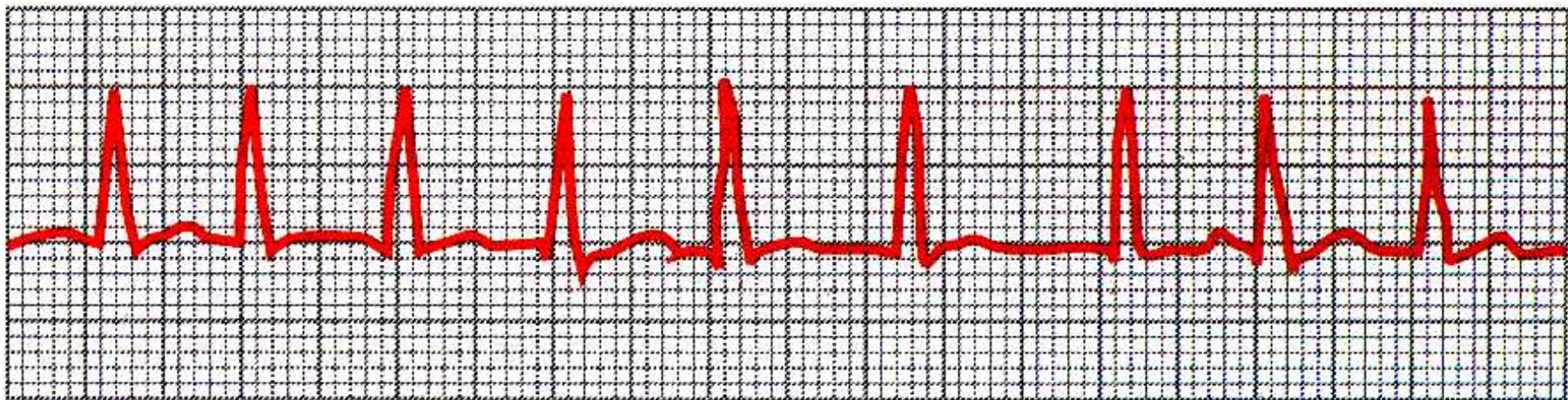


Figure 13-19; Atrial fibrillation (lead I). The waves that can be seen are ventricular QRS and T waves.

Ventricular Fibrillation

- The most serious of all cardiac arrhythmias is ventricular fibrillation, which, if not stopped within 1 to 3 minutes, is almost invariably fatal.

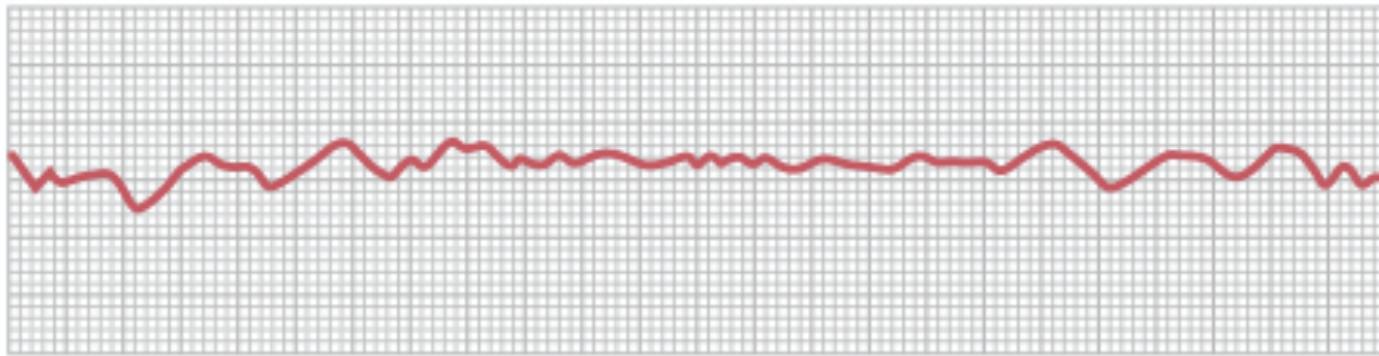


Figure 13–16 Ventricular fibrillation (lead II).

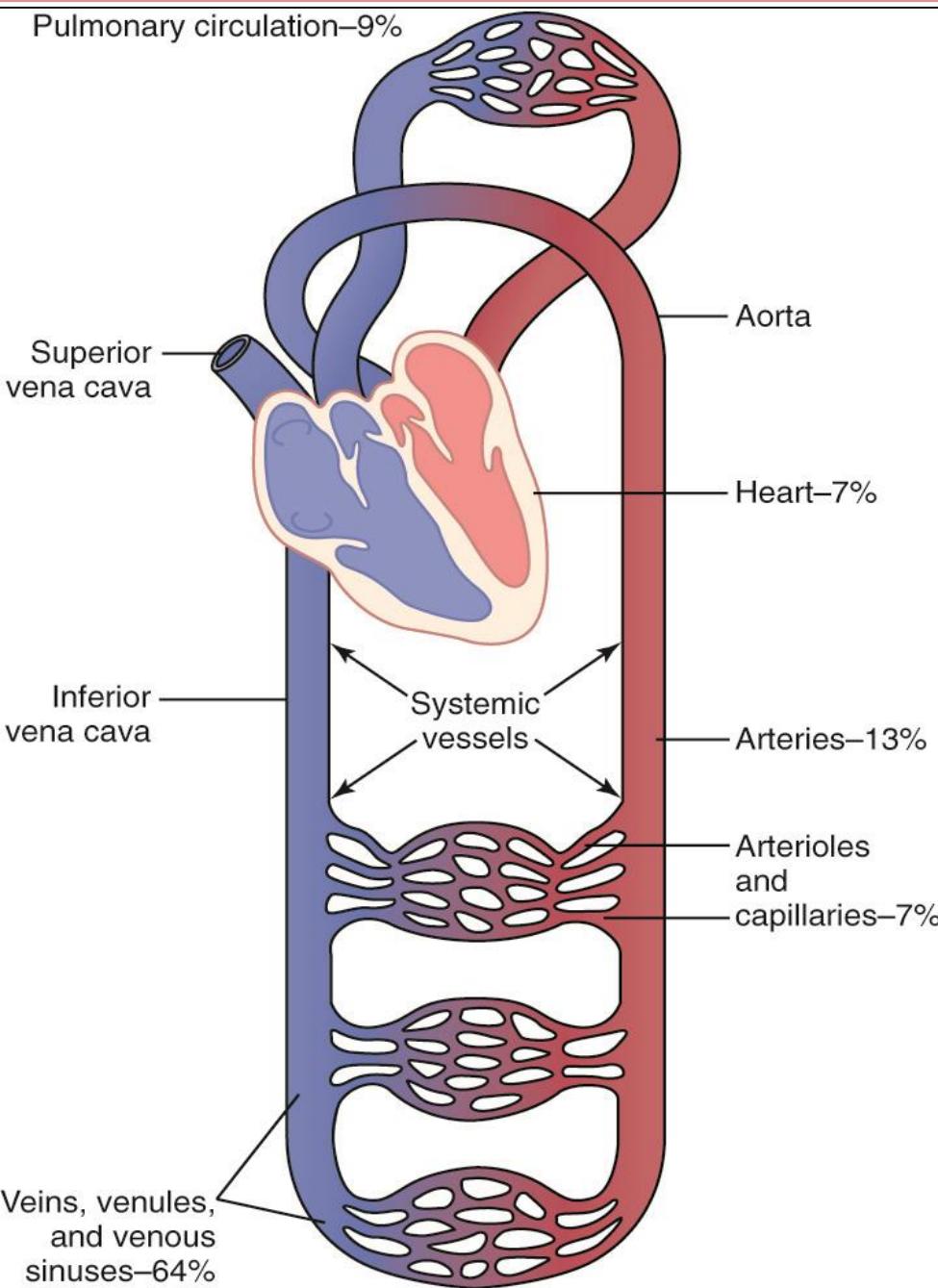
Circulatory

- 14. Overview of the Circulation; Medical Physics of Pressure, Flow, and Resistance
- 15. Vascular Distensibility and Functions of the Arterial and Venous Systems
- 16. The Microcirculation and the Lymphatic System: Capillary Fluid Exchange, Interstitial Fluid, and Lymph Flow
- 18. Nervous Regulation of the Circulation, and Rapid Control of Arterial Pressure
- 20. Cardiac Output, Venous Return, and Their Regulation

14. Overview of the Circulation; Medical Physics of Pressure,
Flow, and Resistance

15. Vascular Distensibility and Functions of the Arterial and
Venous Systems

Physical Characteristics of the Circulation



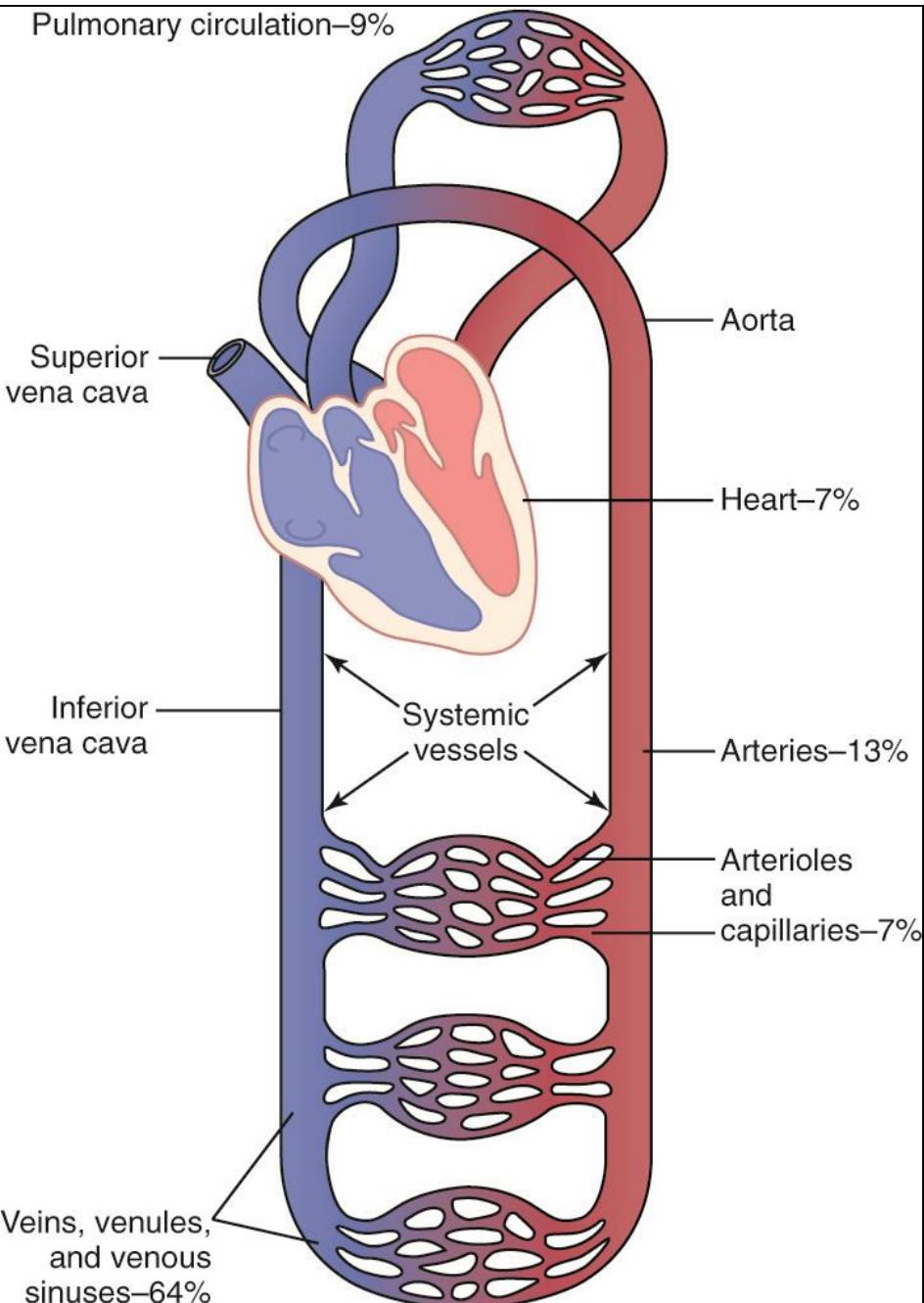
The circulation, shown in Figure 14–1, is divided into the *systemic circulation* and the *pulmonary circulation*.

- **systemic circulation** is the part of the cardiovascular system which carries oxygenated blood away from the heart to the body, and returns deoxygenated blood back to the heart
- **Pulmonary circulation** is the portion of the cardiovascular system which carries deoxygenated blood away from the heart, to the lungs, and returns oxygenated (oxygen-rich) blood back to the heart

Figure

14-1;
Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.

Pulmonary circulation—9%



- The function of the arteries is to transport blood under high pressure to the tissues. For this reason, the arteries have strong vascular walls, and blood flows at a high velocity in the arteries.
- The arterioles are the last small branches of the arterial system; they act as control conduits through which blood is released into the capillaries.
- The function of the capillaries is to exchange fluid, nutrients, electrolytes, hormones, and other substances between the blood and the interstitial fluid. To serve this role, the capillary walls are very thin and have numerous minute capillary pores permeable to water and other small molecular substances.
- The venules collect blood from the capillaries, and they gradually coalesce into progressively larger veins.
- The veins function as conduits for transport of blood from the venules back to the heart; equally important, they serve as a major reservoir of extra blood.

- The Capillaries Have the Largest Total Cross-sectional Area of the Circulation

	<i>cm²</i>
Aorta	2.5
Small Arteries	20
Arterioles	40
Capillaries	2500
Venules	250
Small Veins	80
Venae Cavae	8

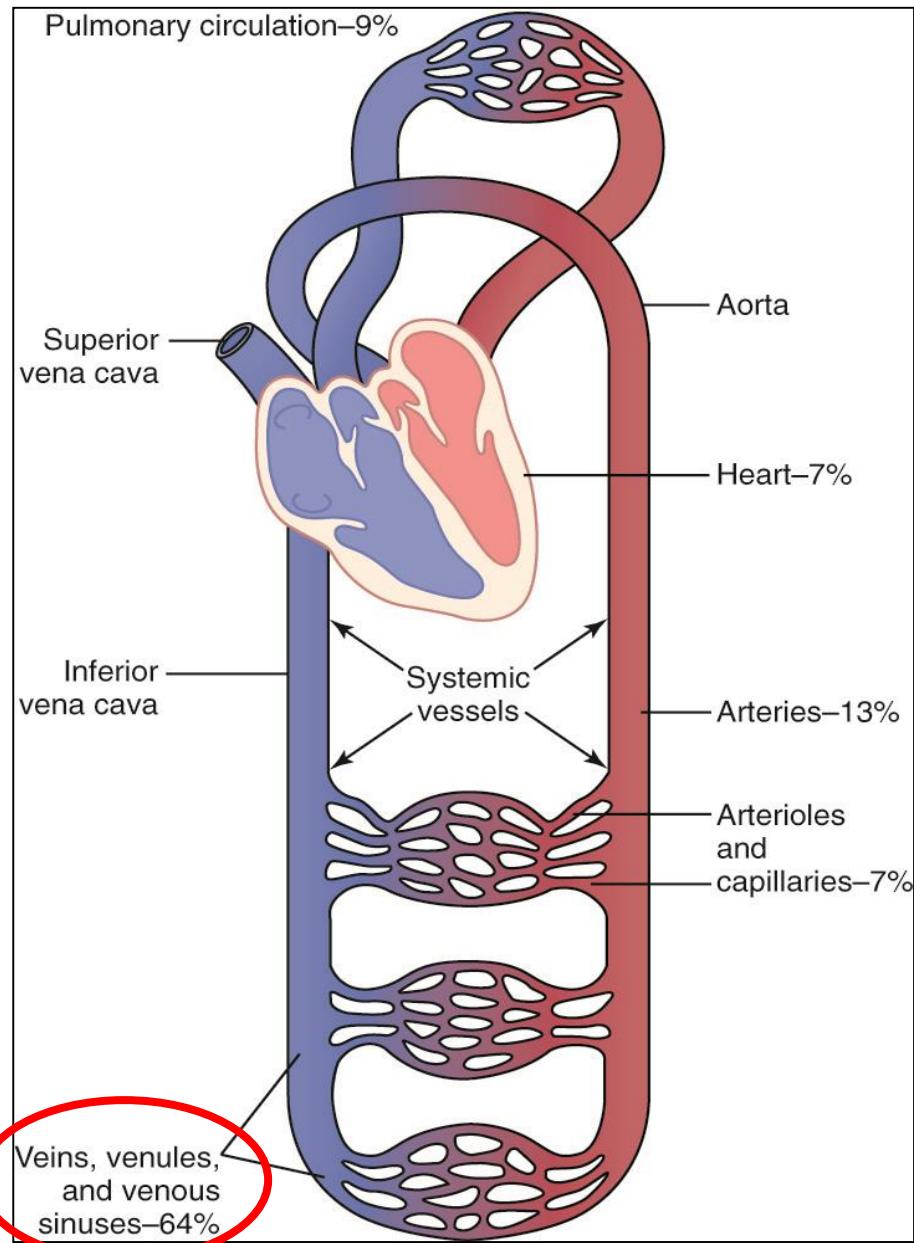
- **Velocity of Blood Flow is Greatest in the Aorta**
- Because the same volume of blood must flow through each segment of the circulation each minute, the velocity of blood flow is inversely proportional to vascular cross-sectional area.

$$\text{Velocity of Blood Flow} = \frac{\text{Blood Flow}}{\text{Cross sectional area}}$$

Aorta >Arterioles> Small veins >Capillaries

under resting conditions, the velocity averages about 33 cm/sec in the aorta and 0.3 mm/sec in the capillaries.

The Majority of Blood Volume is in the Veins



Note particularly the much larger cross-sectional areas of the veins than of the arteries, averaging about four times those of the corresponding arteries. This explains the large storage of blood in the venous system in comparison with the arterial system.

Blood Pressure Profile in the Circulatory System

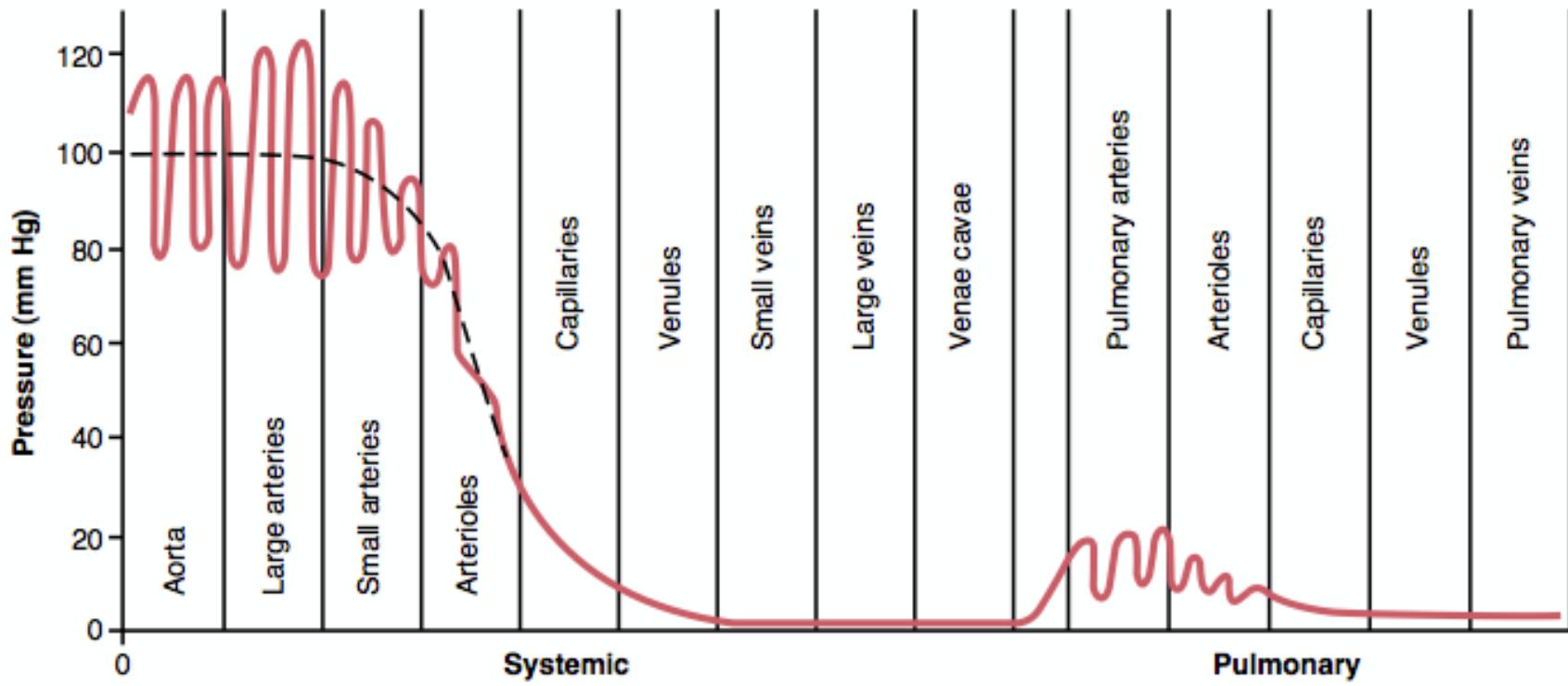


Figure 14-2: Normal blood pressures in the different portions of the circulatory system when a person is lying in the horizontal position.

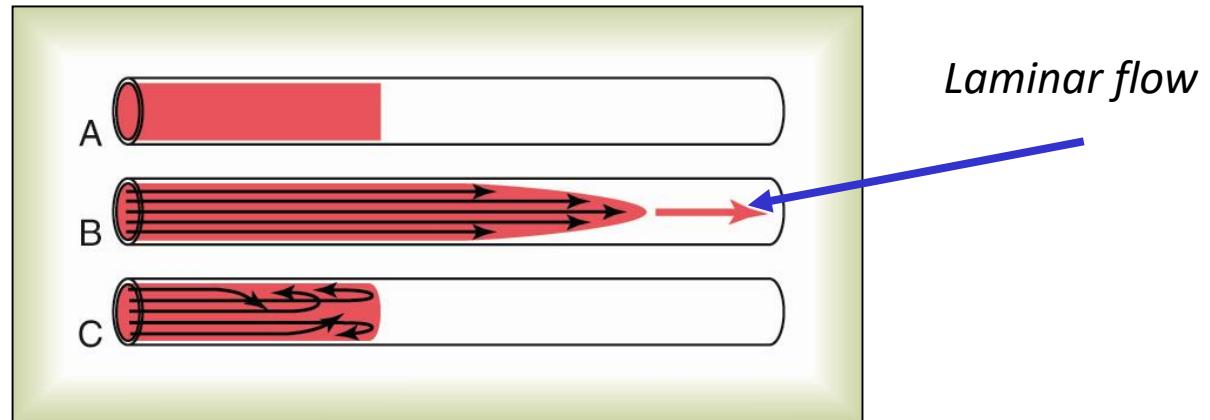
- High pressures in the arterial tree
- Low pressures in the venous side of the circulation
- Large pressure drop across the arteriolar-capillary junction

■ Variations in Tissue Blood Flow

	Percent	ml/min
Brain	14	700
Heart	4	200
Bronchi	2	100
Kidneys	22	1100
Liver	27	1350
Portal	(21)	(1050)
Arterial	(6)	(300)
Muscle (inactive state)	15	750
Bone	5	250
Skin (cool weather)	6	300
Thyroid gland	1	50
Adrenal glands	0.5	25
Other tissues	3.5	175
Total	100.0	5000

Characteristics of Blood Flow

- A, Two fluids (one dyed red, and the other clear) before flow begins;
B, the same fluids 1 second after flow begins;
C, turbulent flow, with elements of the fluid moving in a disorderly pattern

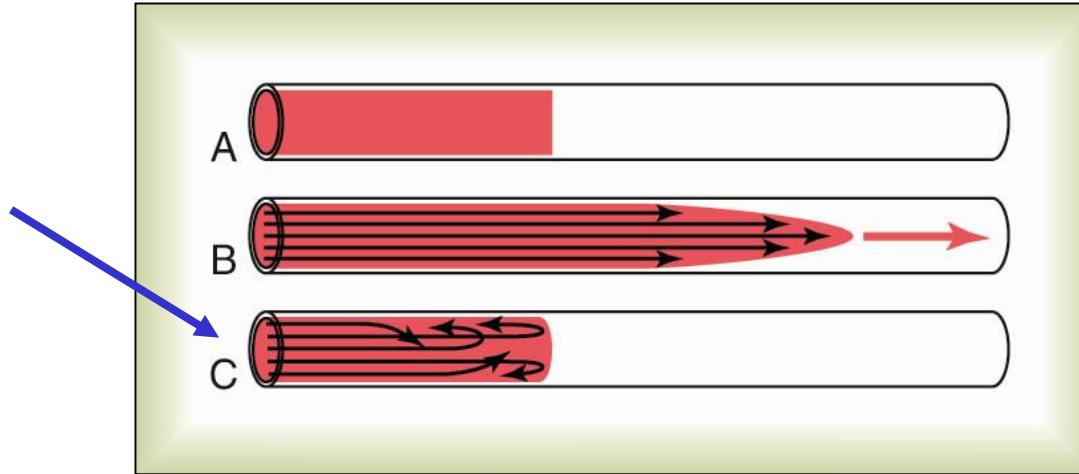


Blood Vessel

- When laminar flow occurs, the velocity of blood in the center of the vessel is greater than that toward the outer edge creating a parabolic profile.

■ Laminar vs. Turbulent Blood Flow

Turbulent flow

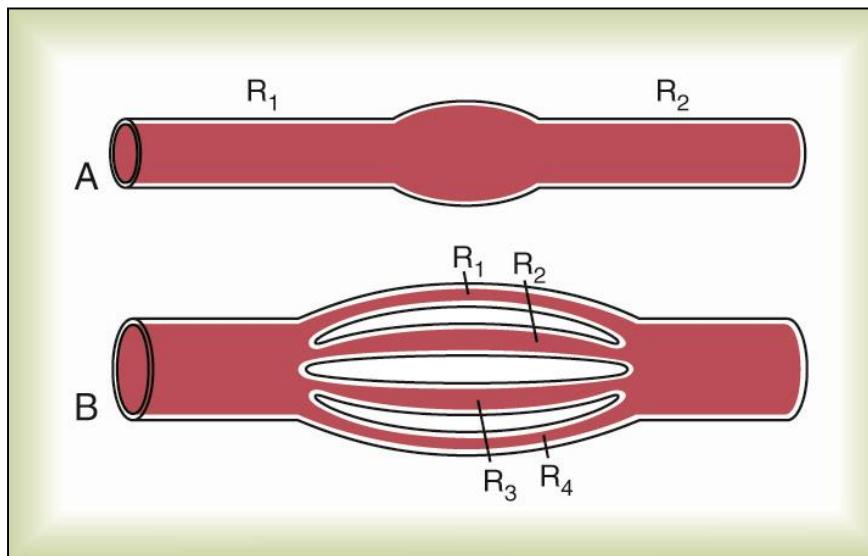


- Laminar flow is silent, whereas turbulent flow tend to cause *murmurs*.
- Murmurs are important in diagnosing vessels stenosis, vessel shunts, and cardiac valvular lesions.

■ Parallel and Serial Resistance Sites in the Circulation

The arteries, arterioles, capillaries, venules, and veins are collectively arranged in series. When blood vessels are arranged in series, flow through each blood vessel is the same and the total resistance to blood flow

$$R_{\text{total}} = R_1 + R_2 + R_3 + R_4 \dots$$



Vascular resistances: A, in series and B, in parallel.

Blood vessels branch extensively to form parallel circuits that supply blood to the many organs and tissues of the body. This parallel arrangement permits each tissue to regulate its own blood flow, to a great extent, independently of flow to other tissues. Total resistance to blood flow is expressed

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

■ Effect of Vessel Diameter on Blood Flow

- Conductance is very sensitive to change in *diameter* of vessel.
- The conductance of a vessel increases in proportion to the *fourth power of the radius*.

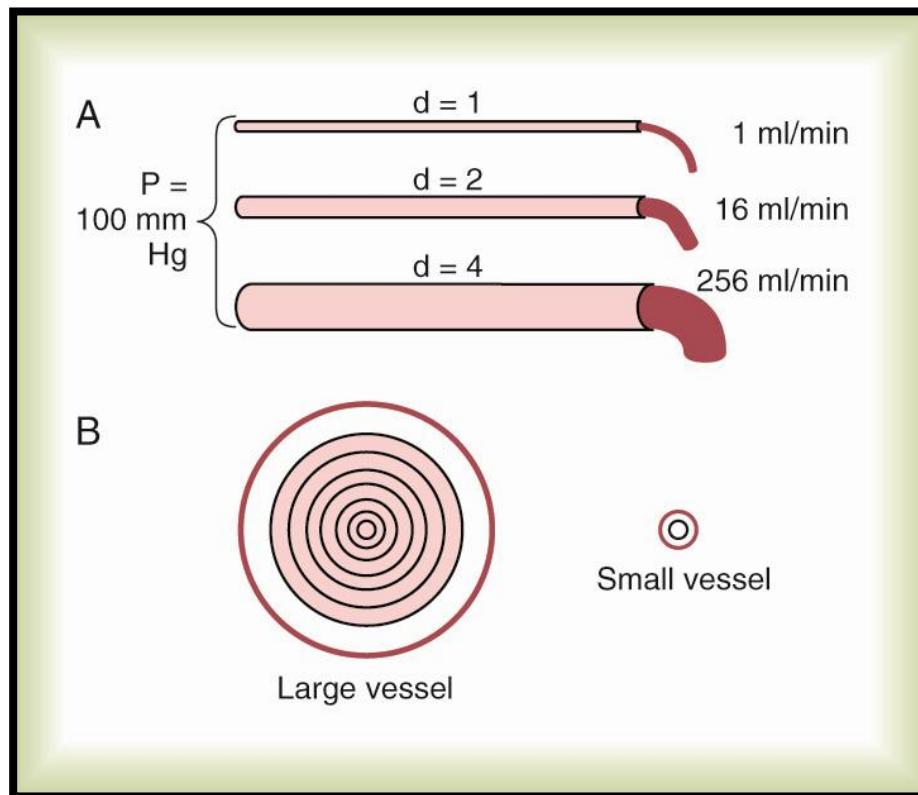
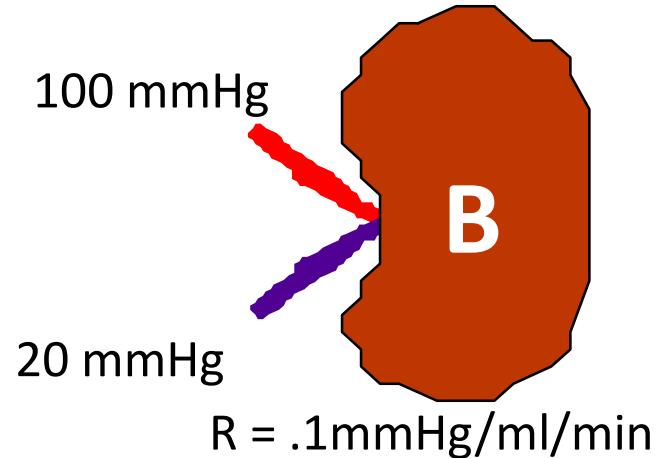
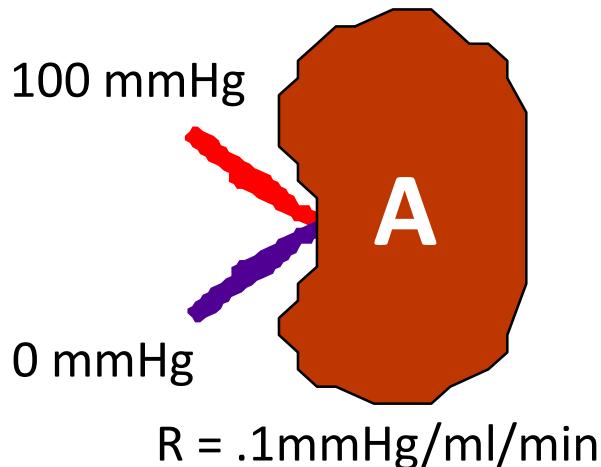


Figure 14-9;
A, Demonstration of the effect of vessel diameter on blood flow. B, Concentric rings of blood flowing at different velocities; the farther away from the vessel wall, the faster the flow.

- Determinants of Blood Flow

$$\text{FLOW} = \frac{\text{arterial pressure} - \text{venous pressure } (\Delta P)}{\text{resistance } (R)}$$



$$\text{FLOW} = \frac{100 - 0 \text{ mmHg}}{.1 \text{ mmHg/ml/min}}$$

$$\text{FLOW} = 1000 \text{ ml/min}$$

$$\text{FLOW} = \frac{100 - 20 \text{ mmHg}}{.1 \text{ mmHg/ml/min}}$$

$$\text{FLOW} = 800 \text{ ml/min}$$

- How Would a Decrease in Vascular Resistance Affect Blood Flow?

Vascular resistance refers to the resistance that must be overcome to push blood through the circulatory system and create flow.

$$\uparrow \text{FLOW} = \frac{\Delta P}{\downarrow \text{RESISTANCE}}$$

Conversely,

$$\downarrow \text{FLOW} = \frac{\Delta P}{\uparrow \text{RESISTANCE}}$$

Hematocrit and Viscosity Effects on Blood Flow

- The percentage of the blood that is cells is called the hematocrit. Thus, if a person has a hematocrit of 40, this means that 40 per cent of the blood volume is cells and the remainder is plasma. The hematocrit of men averages about 42, while that of women averages about 38.

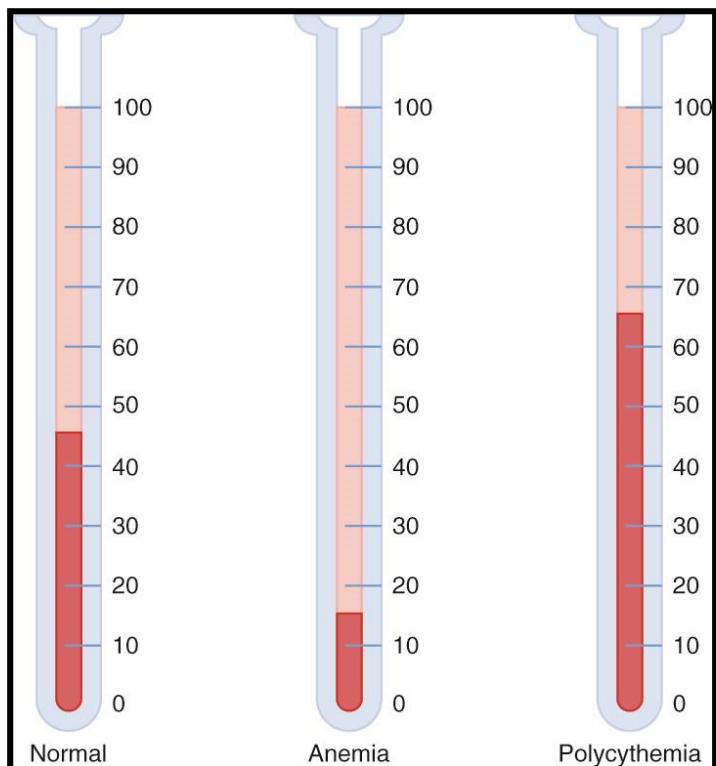


Figure 14-11; Hematocrits in a healthy (normal) person and in patients with anemia and polycythemia.

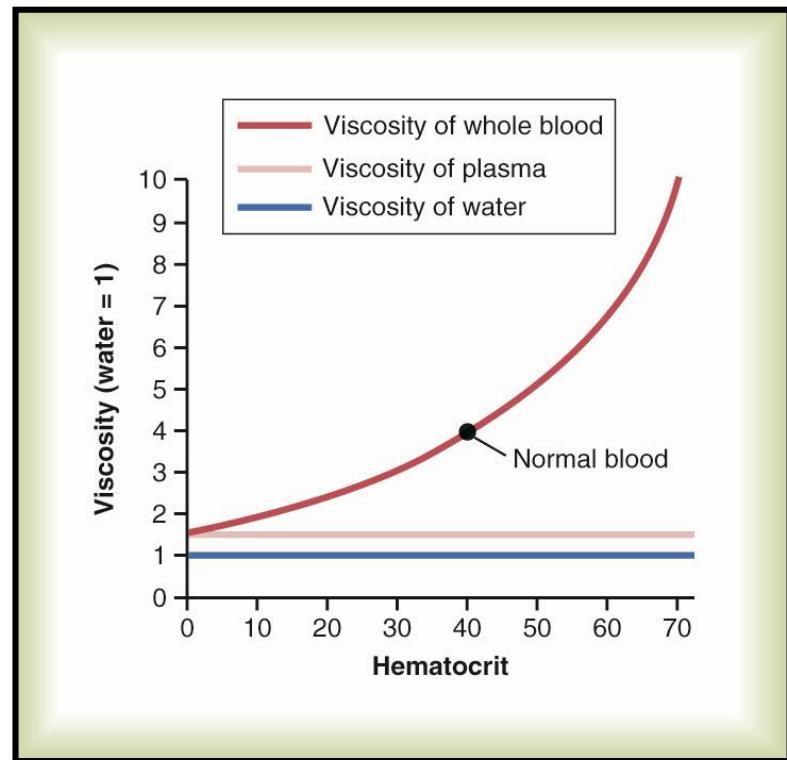
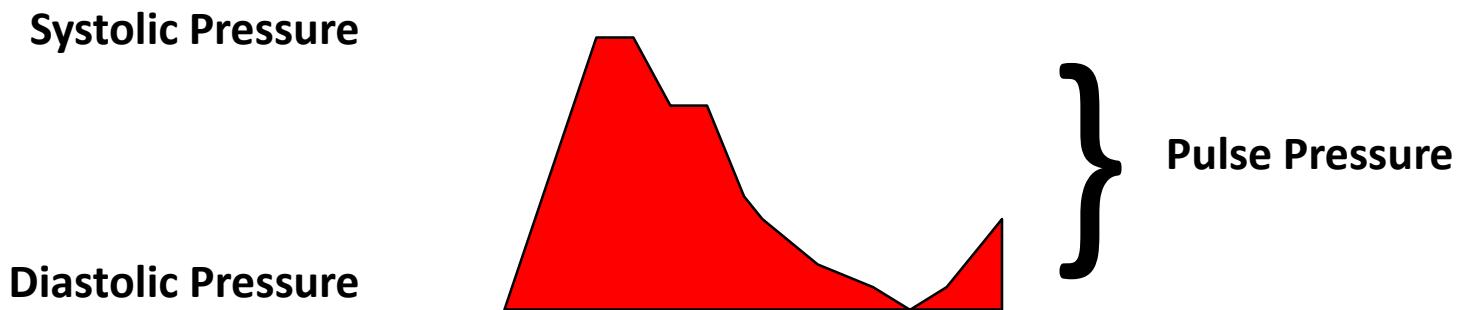


Figure 14-12; Effect of hematocrit on blood viscosity. (Water viscosity = 1.)

- The viscosity of whole blood at normal hematocrit is about 3; this means that three times as much pressure is required to force whole blood as to force water through the same blood vessel.

■ Arterial Pulsations

- The height of the pressure pulse is the *systolic pressure* (120mmHg), while the lowest point is the *diastolic pressure* (80mmHg).
- The difference between *systolic* and *diastolic pressure* is called the *pulse pressure* (40mmHg).



➤ Factors Affecting Pulse Pressure

- *Stroke volume* —increases in stroke volume increase pulse pressure, conversely decreases in stroke volume decrease pulse pressure.
- *Arterial compliance* —decreases in compliance increases pulse pressure; increases in compliance decrease pulse pressure.

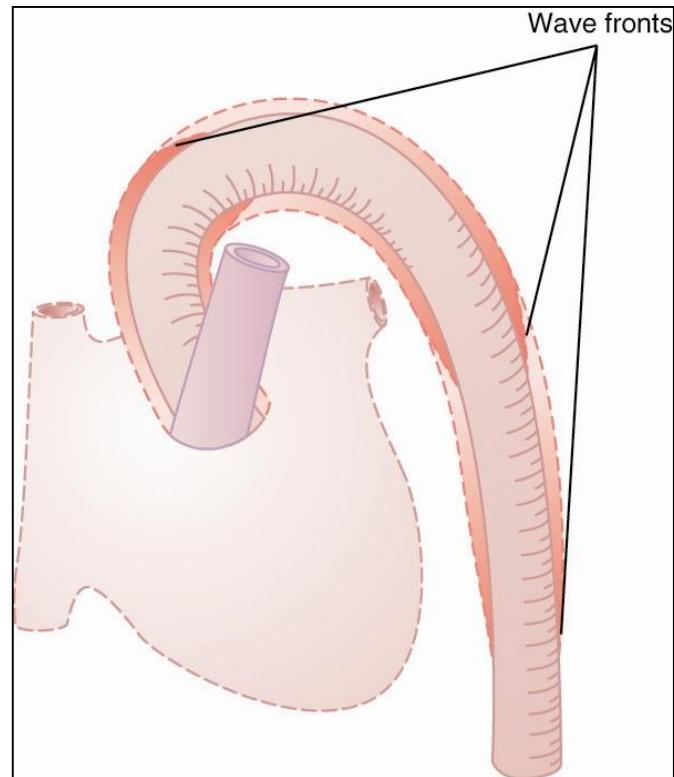
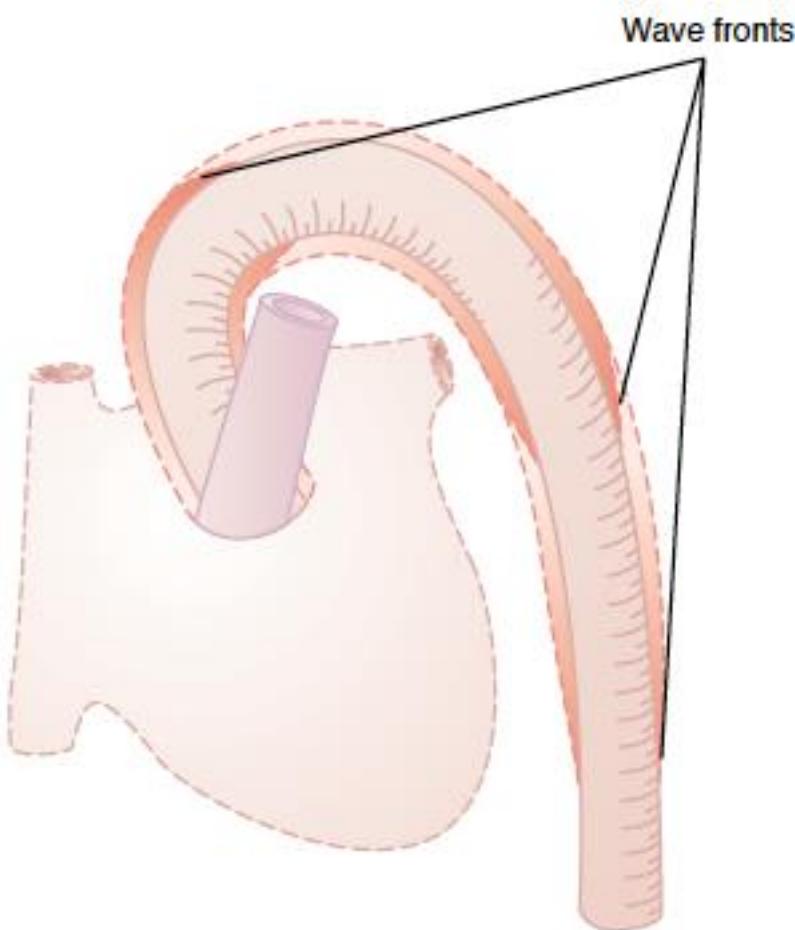


Figure 15-5; Guyton and Hall

• Transmission of Pressure Pulses to the Peripheral Arteries

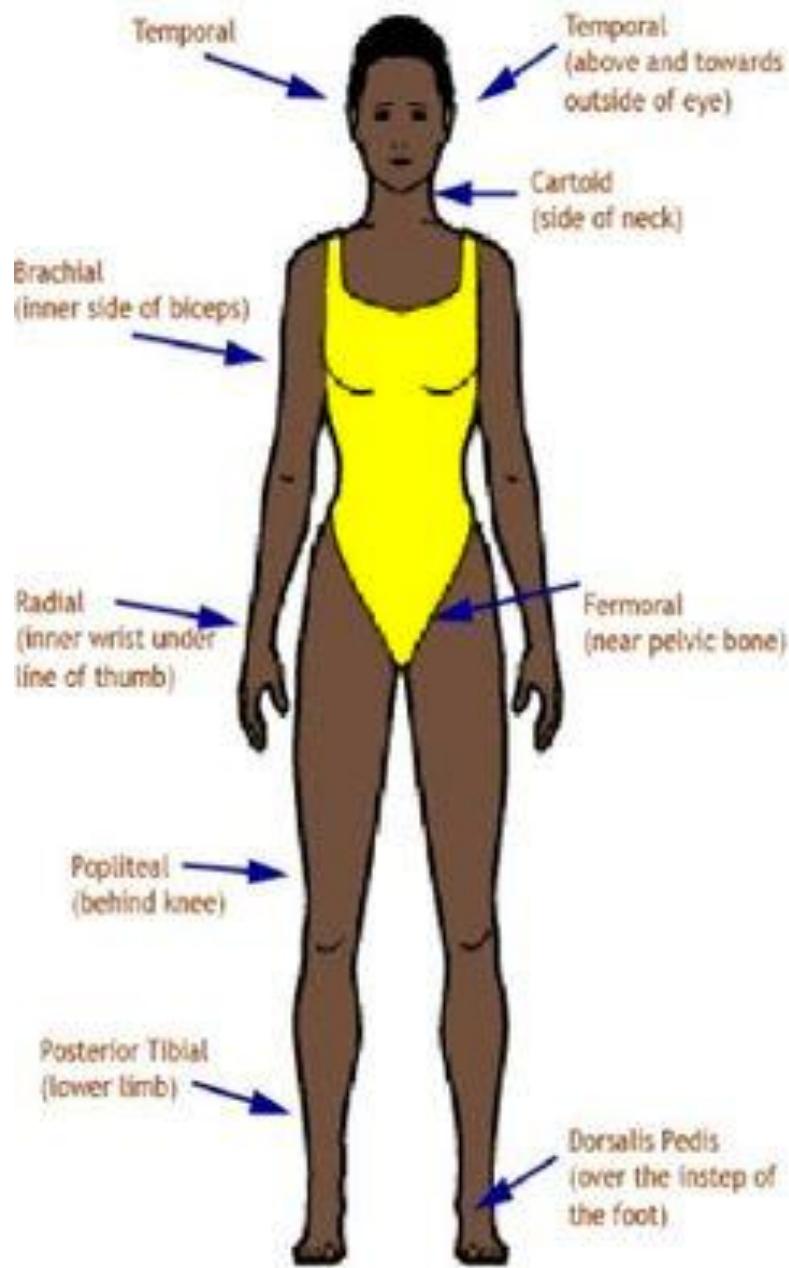


- When the heart ejects blood into the aorta during systole, at first only the proximal portion of the aorta becomes distended because the inertia of the blood prevents sudden blood movement all the way to the periphery. However, the rising pressure in the proximal aorta rapidly overcomes this inertia, and the wave front of distention spreads farther and farther along the aorta, as shown in **Figure 15–5**. This is called transmission of the pressure pulse in the arteries.

Figure 15–5

Progressive stages in transmission of the pressure pulse along the aorta.

Pulse Points and Pressure Points



External Maxillary

Posterior Tibial

Dorsalis Pedis

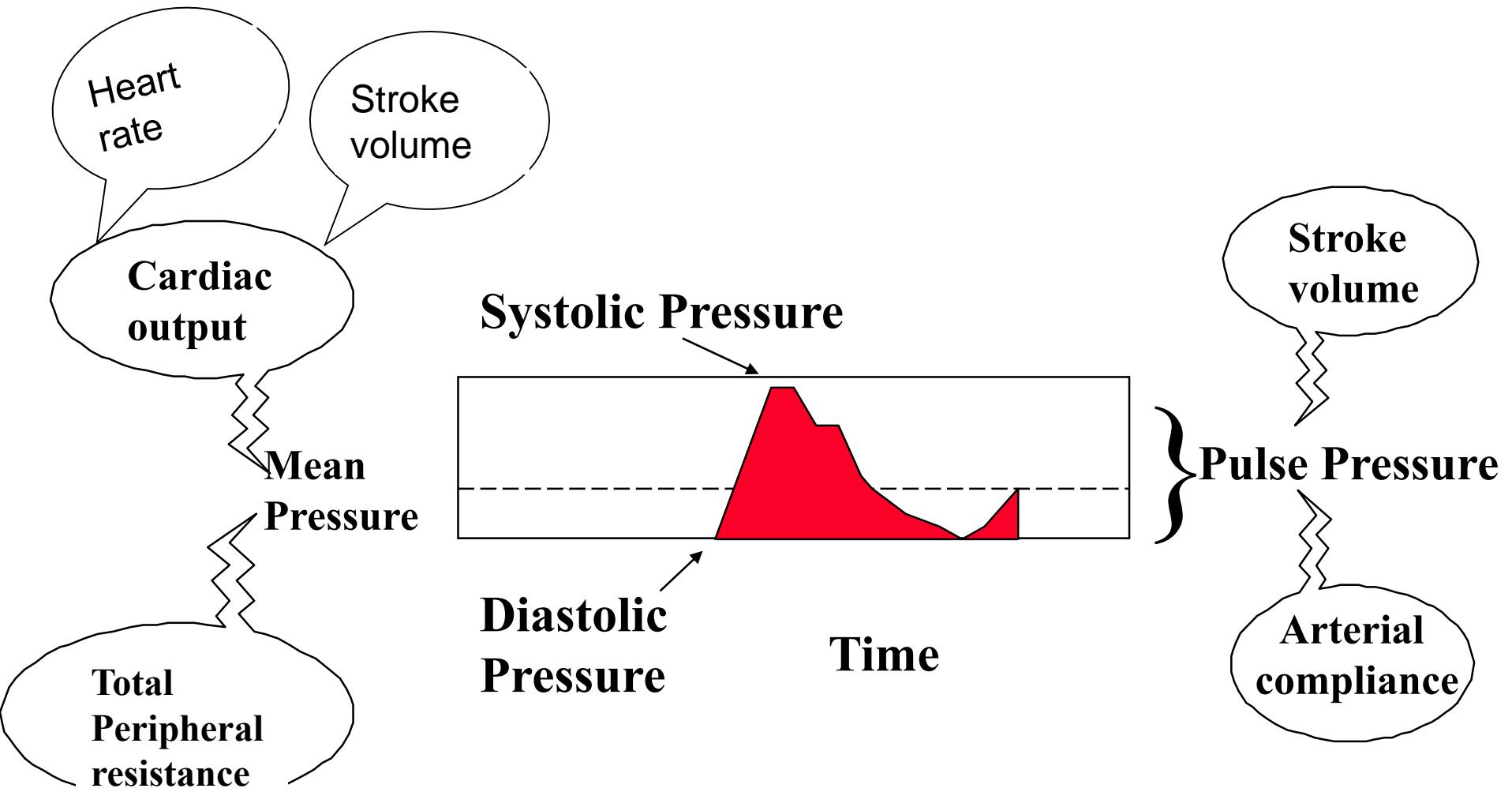
Brachial

Ulnar
Radial

Femoral
Popliteal

Carotid

Superficial
Temporal



$$HR \times SV = CO = MAP / TPR$$

$$MAP = (0.4 SP) + (0.6 DP)$$

$$PP = SP - DP$$

Damping of Pulse Pressures in the Peripheral Arteries

Some of the major arteries and veins in the human body.

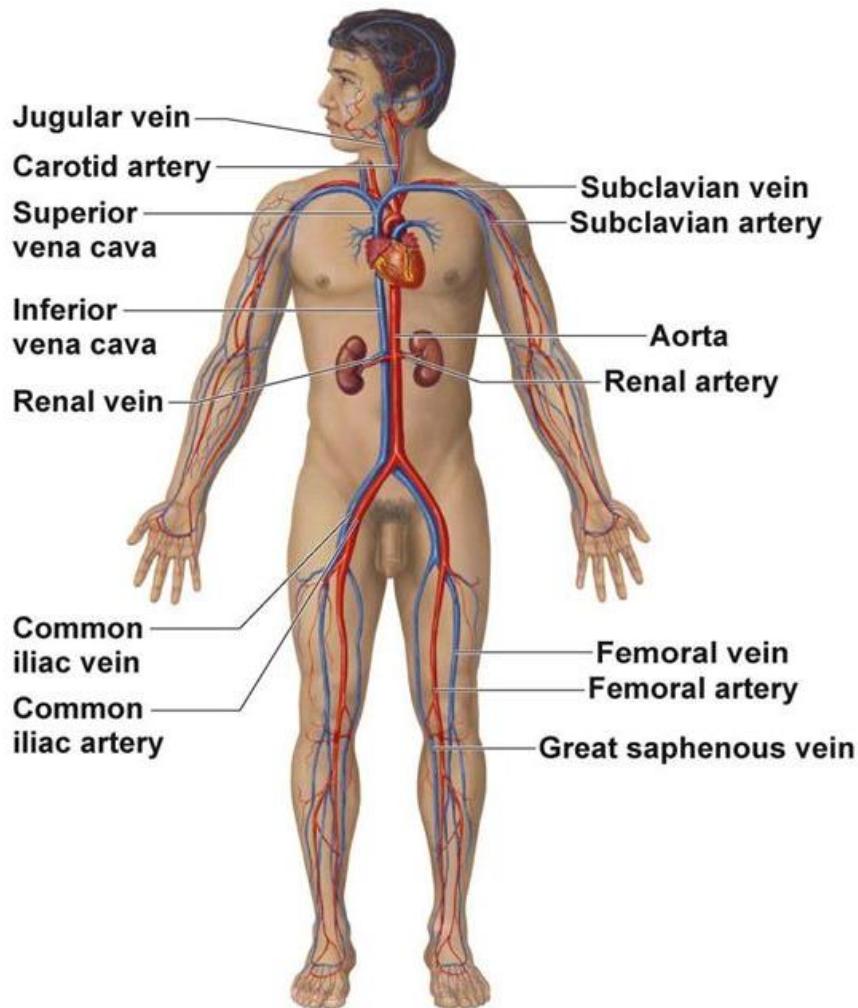
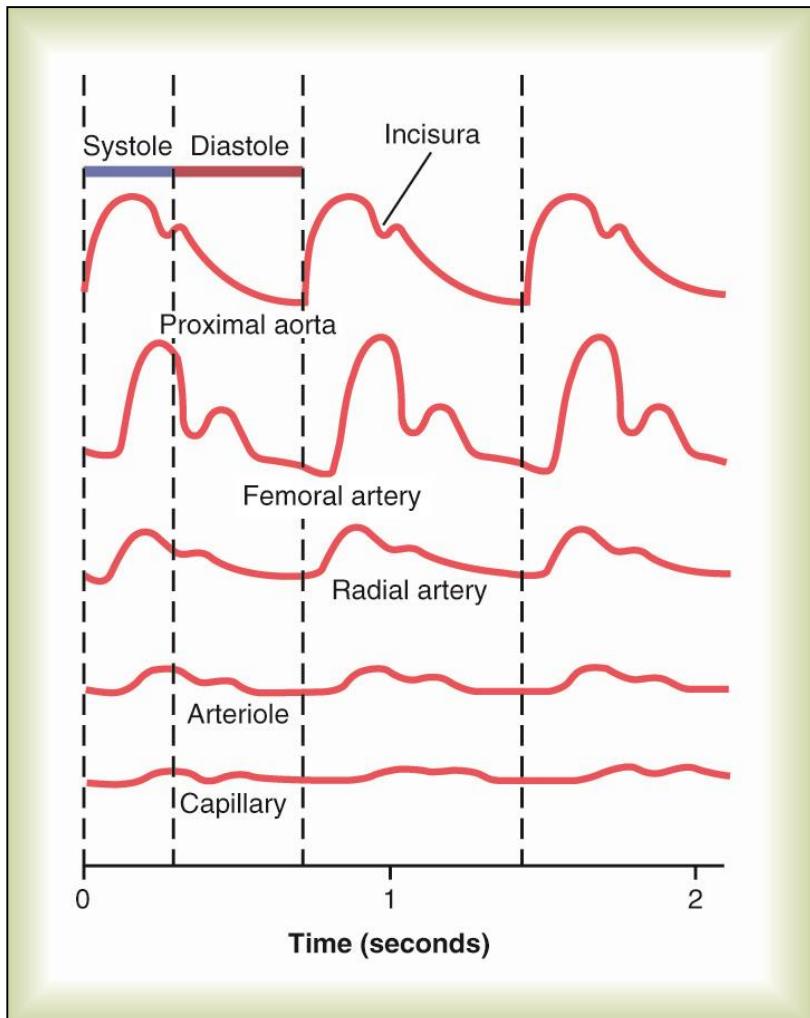
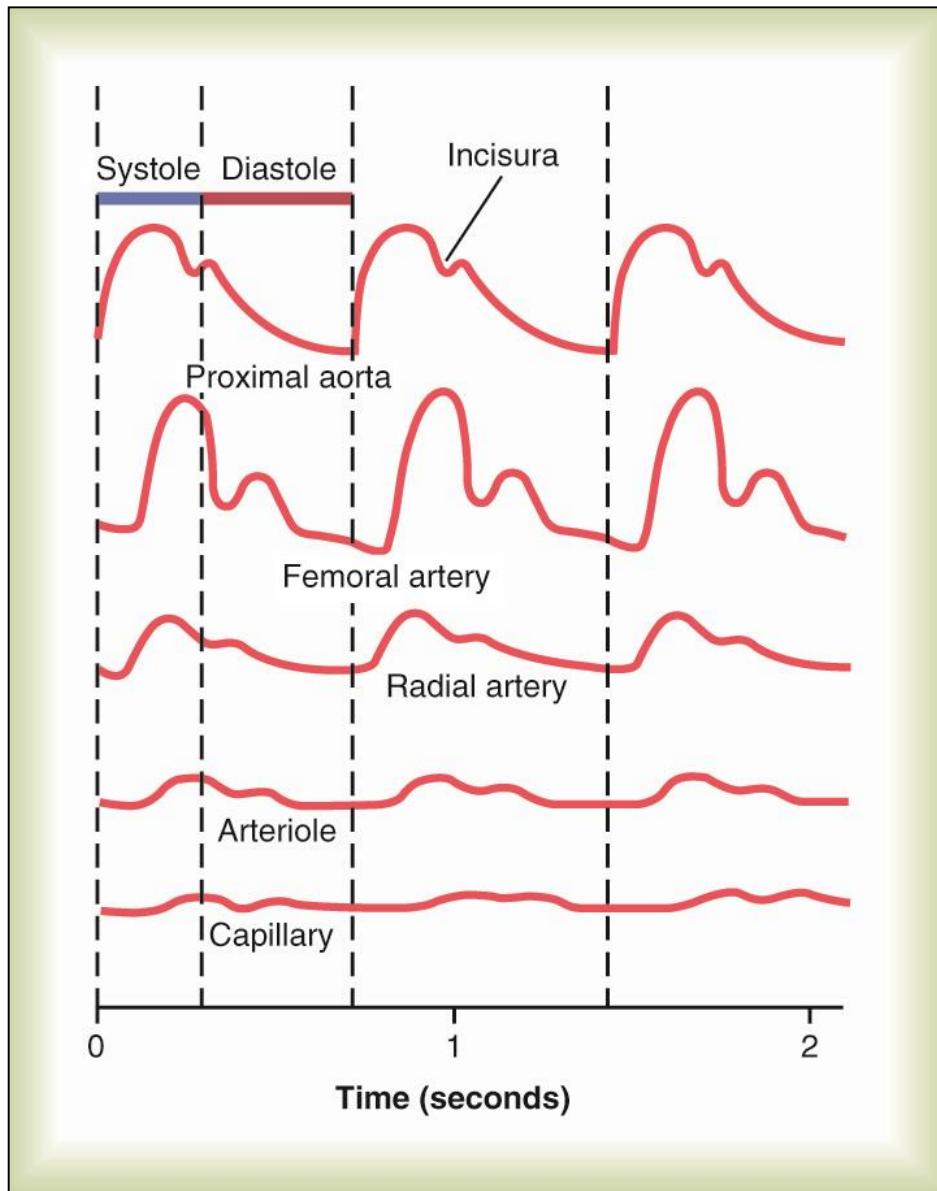


Figure 15-6; Changes in the pulse pressure contour as the pulse wave travels toward the smaller vessels.

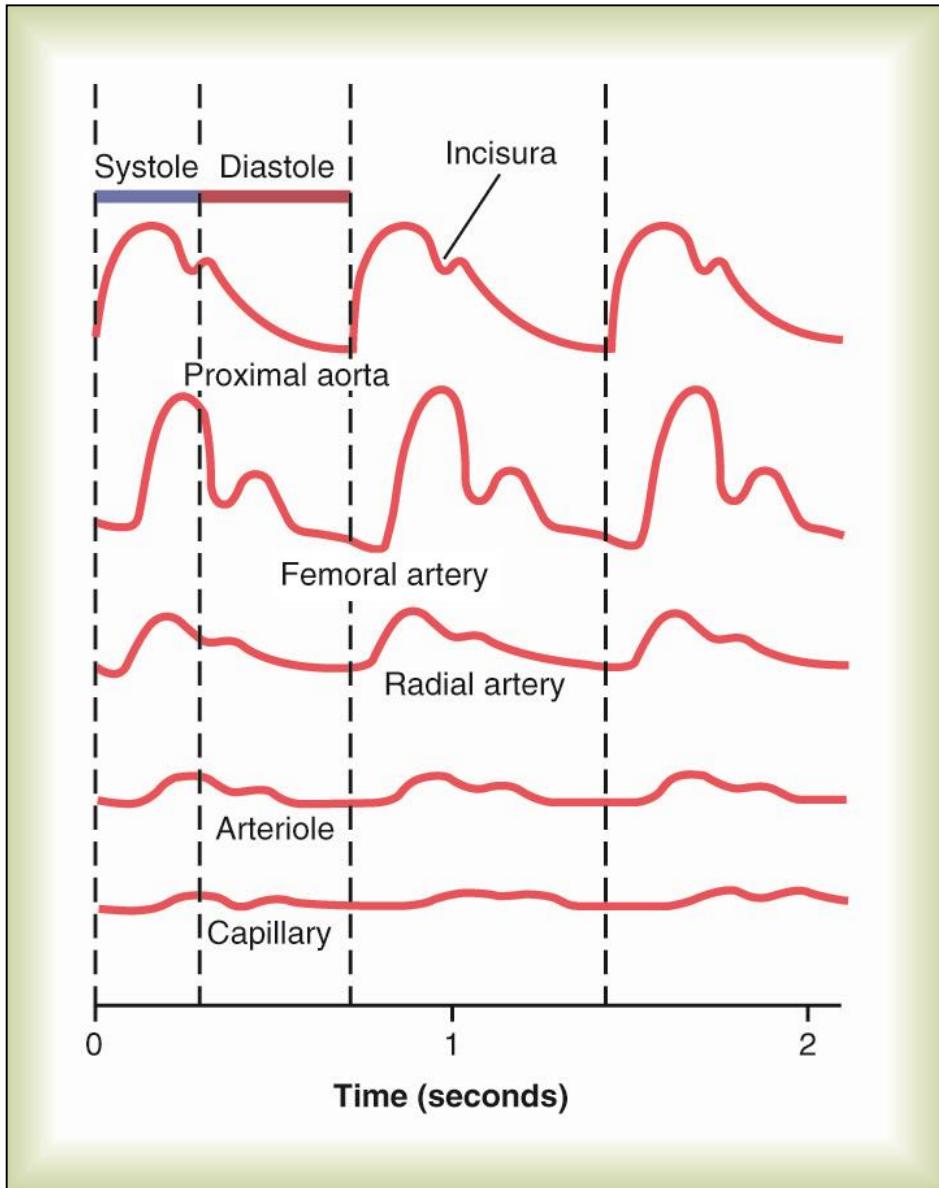
Damping of Pulse Pressures in the Peripheral Arteries



- progressive diminution of the pulsations in the periphery is called damping of the pressure pulses. The cause of this is twofold:
 - (1) resistance to blood movement in the vessels
 - The resistance damps the pulsations because a small amount of blood must flow forward at the pulse wave front to distend the next segment of the vessel; the greater the resistance, the more difficult it is for this to occur

Figure 15-6; Changes in the pulse pressure contour as the pulse wave travels toward the smaller vessels.

Damping of Pulse Pressures in the Peripheral Arteries



(2) compliance of the vessels.

- The compliance damps the pulsations because the more compliant a vessel, the greater the quantity of blood required at the pulse wave front to cause an increase in pressure.

the degree of damping is almost directly proportional to the product of resistance times compliance.

Figure 15-6; Changes in the pulse pressure contour as the pulse wave travels toward the smaller vessels.

■ Abnormal Pressure Pulse Contours ??

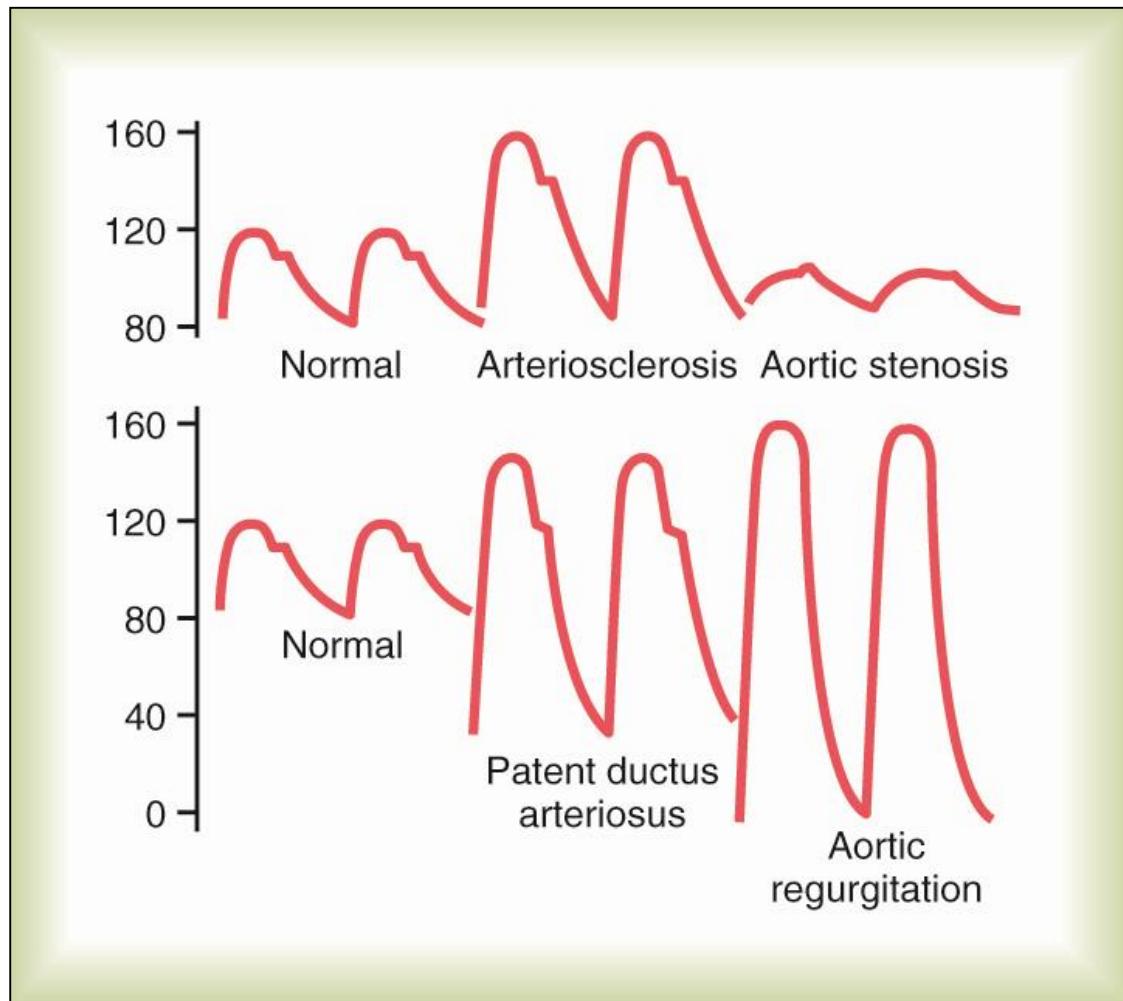


Figure 15–4, the pulse pressure in old age sometimes rises to as much as twice normal, because the arteries have become hardened with arteriosclerosis and therefore are relatively noncompliant.

Figure 15-4; aortic pressure pulse contours in arteriosclerosis, aortic stenosis, patent ductus arteriosus, and aortic regurgitation.

- Pulse Pressure and Age

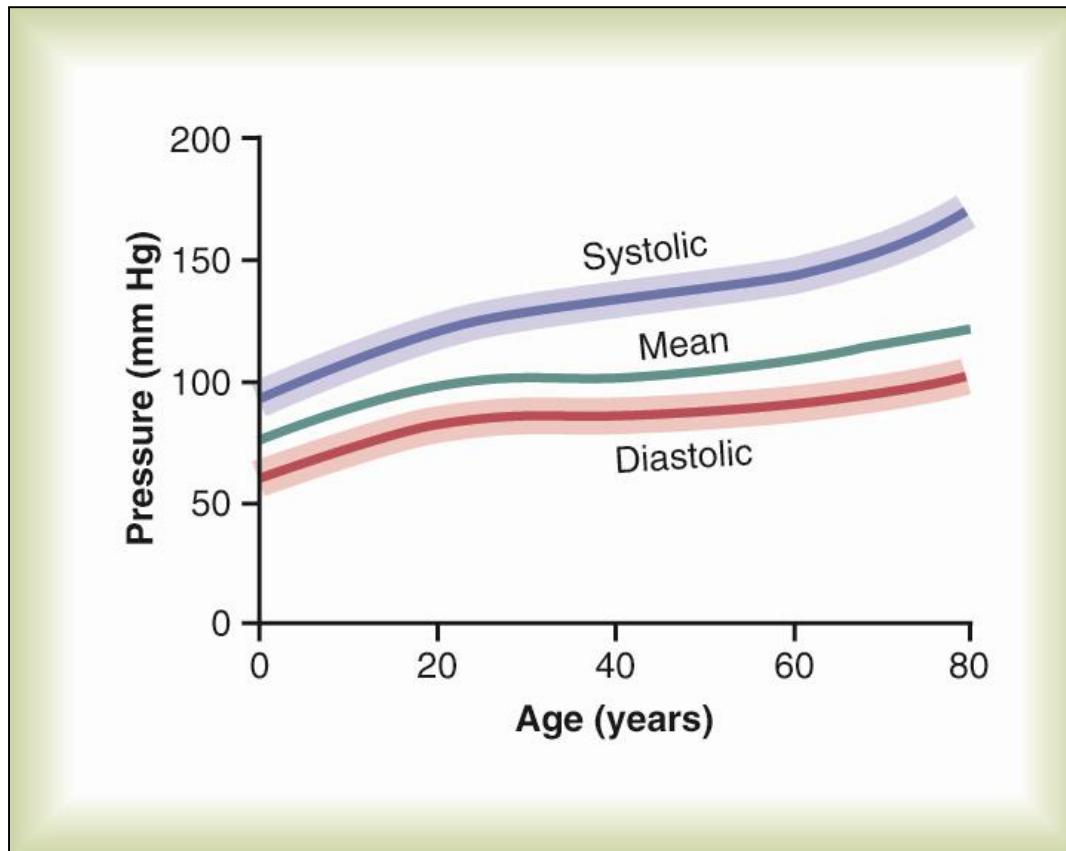
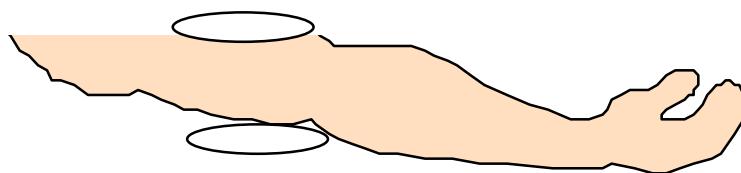


Figure 15-8;

Changes in systolic, diastolic, and mean arterial pressures with age. The shaded areas show the approximate normal ranges.

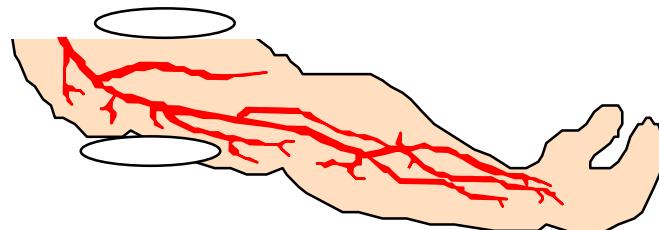
- Effect of Cuff Pressure on Brachial Blood Flow

Cuff Pressure > 120



NO FLOW

Cuff Pressure < 80



FREE FLOW

■ Measurement of Blood Pressure

Use of Korotkoff Sounds

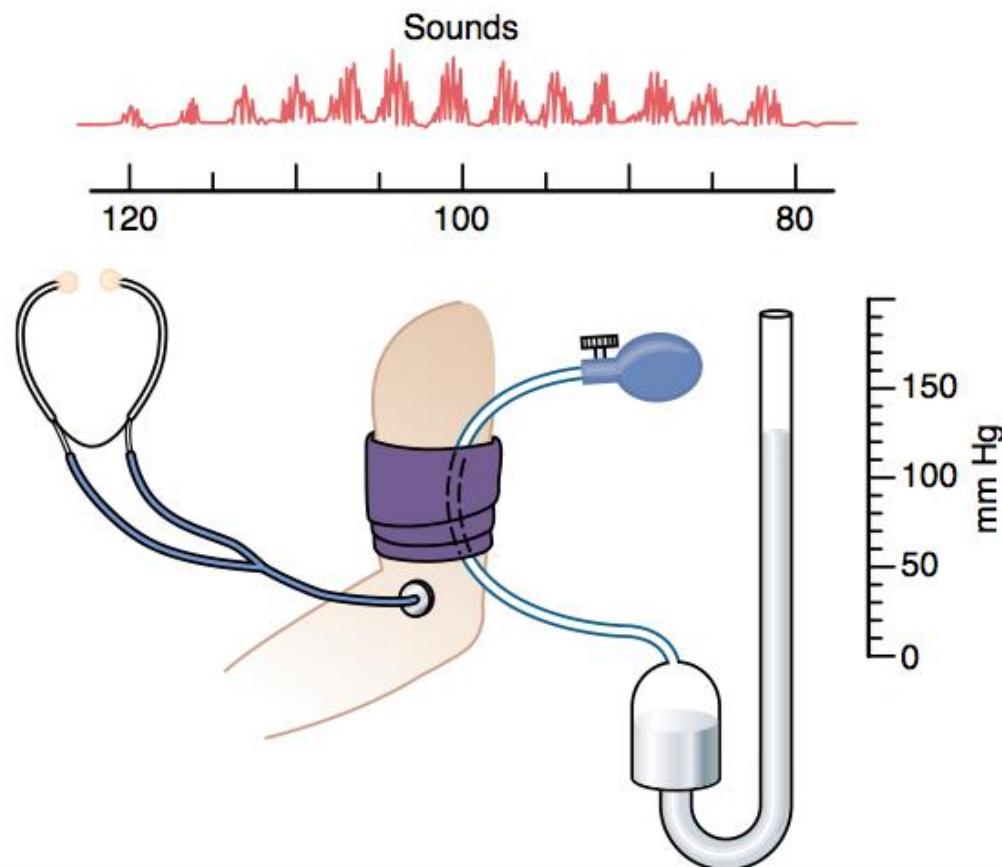


Figure 15–7

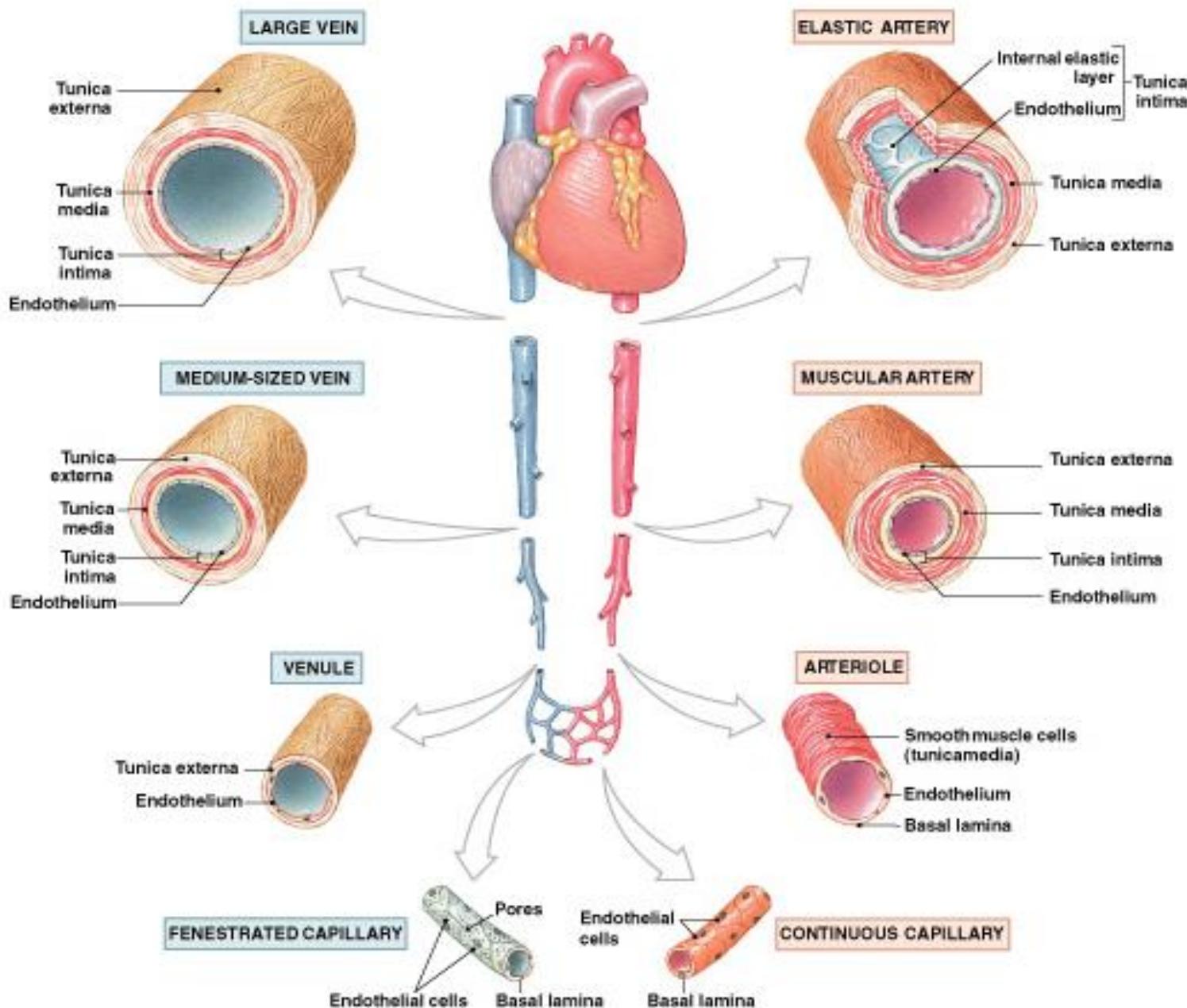
Auscultatory method for measuring systolic and diastolic arterial pressures.

16. The Microcirculation and the Lymphatic System: Capillary Fluid Exchange, Interstitial Fluid, and Lymph Flow

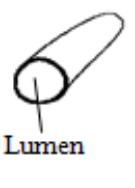
■ Blood Vessels

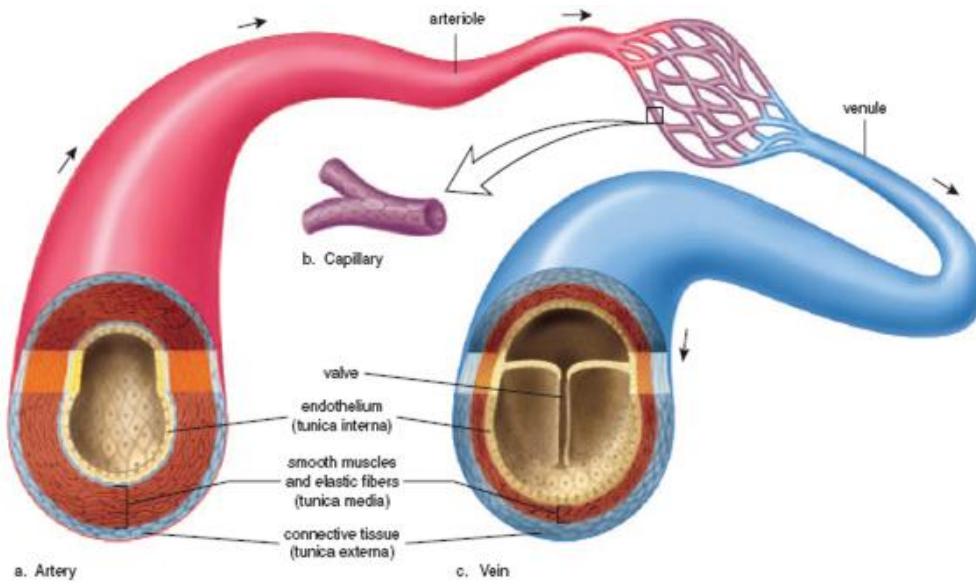
- Blood is carried in a closed system of vessels that begins and ends at the heart
- The three major types of vessels are arteries, capillaries, and veins
- Arteries carry blood away from the heart, veins carry blood toward the heart
- Capillaries contact tissue cells and directly serve cellular needs

- **Generalized Structure of Blood Vessels**
- Arteries and veins are composed of three tunics – tunica interna, tunica media, and tunica externa
- Lumen – central blood-containing space surrounded by tunics
- Capillaries are composed of endothelium with sparse basal lamina



Generalized Structure of Blood Vessels

Aspect	Artery	Vein	Capillary
Cross section	 Lumen	 Lumen	 Lumen
Function	To carry blood away from the heart to other parts of the body	To carry blood to the heart	To connect the artery and the vein
Size of lumen	Small	Large	Very small
Wall thickness	Thick, elastic and muscular	Thinner and less elastic	Very thin (one-cell thick)
Blood flow	Very fast, high pressure	Slow, low pressure	Very slow, very low pressure
Type of blood carried	Oxygenated blood (except pulmonary artery)	Deoxygenated blood (except pulmonary vein)	Carries oxygenated blood to cell body; bring deoxygenated blood out of cell body
Presence of valve	✗ (except pulmonary artery)	✓ (except pulmonary vein)	✗



Structure of the Microcirculation and Capillary System

- **The Microcirculation**
- The microcirculation of each organ is organized specifically to serve that organ's needs.
- In general, each nutrient artery entering an organ branches six to eight times before the arteries become small enough to be called arterioles, which generally have internal diameters of only 10 to 15 micrometers.
- Then the arterioles themselves branch two to five times, reaching diameters of 5 to 9 micrometers at their ends where they supply blood to the capillaries.

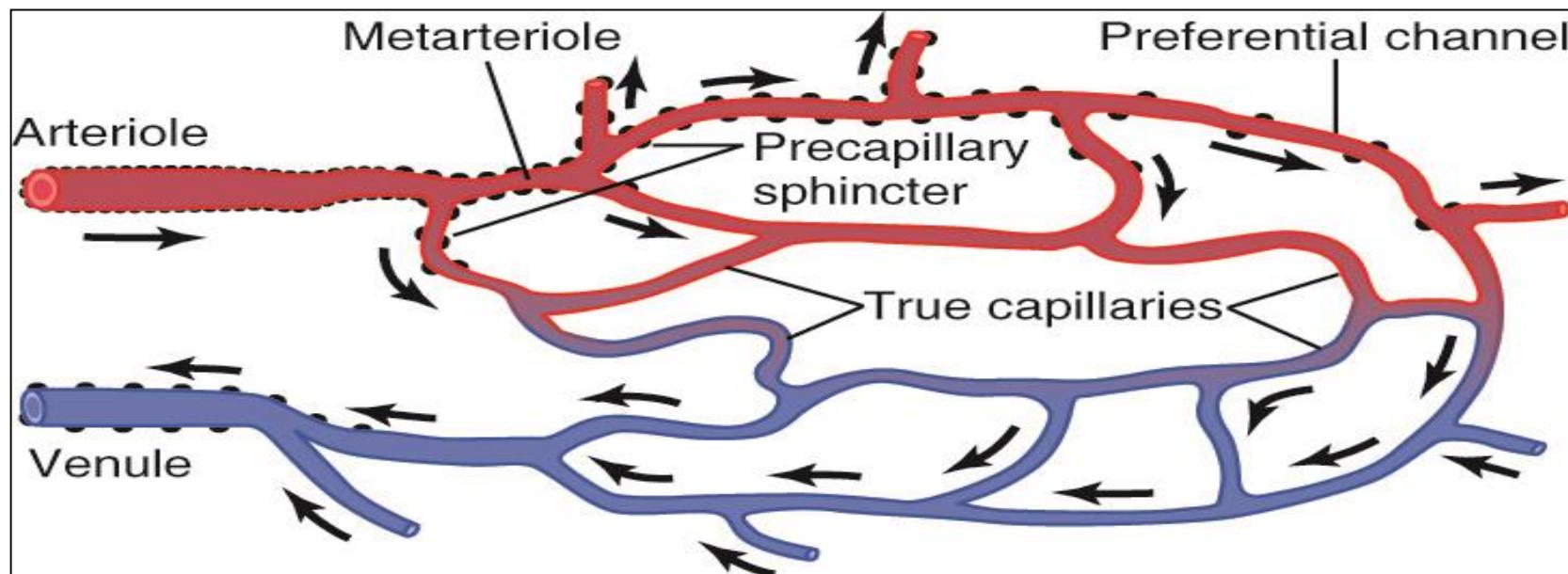


Figure 16-1;
Structure of the mesenteric capillary bed. (Redrawn from Zweifach BW: Factors Regulating Blood Pressure. New York: Josiah Macy, Jr., Foundation, 1950.)

The Microcirculation

- The arterioles are highly muscular. The metarterioles (the terminal arterioles) do not have a continuous muscular coat, but smooth muscle fibers encircle the vessel at intermittent points (black dots).
- At the point where each true capillary originates from a metarteriole, a smooth muscle fiber usually encircles the capillary. This is called the precapillary sphincter. This sphincter can open and close the entrance to the capillary.
- The venules are larger than the arterioles and have a much weaker muscular coat and remember that the pressure in the venules is much less than that in the arterioles

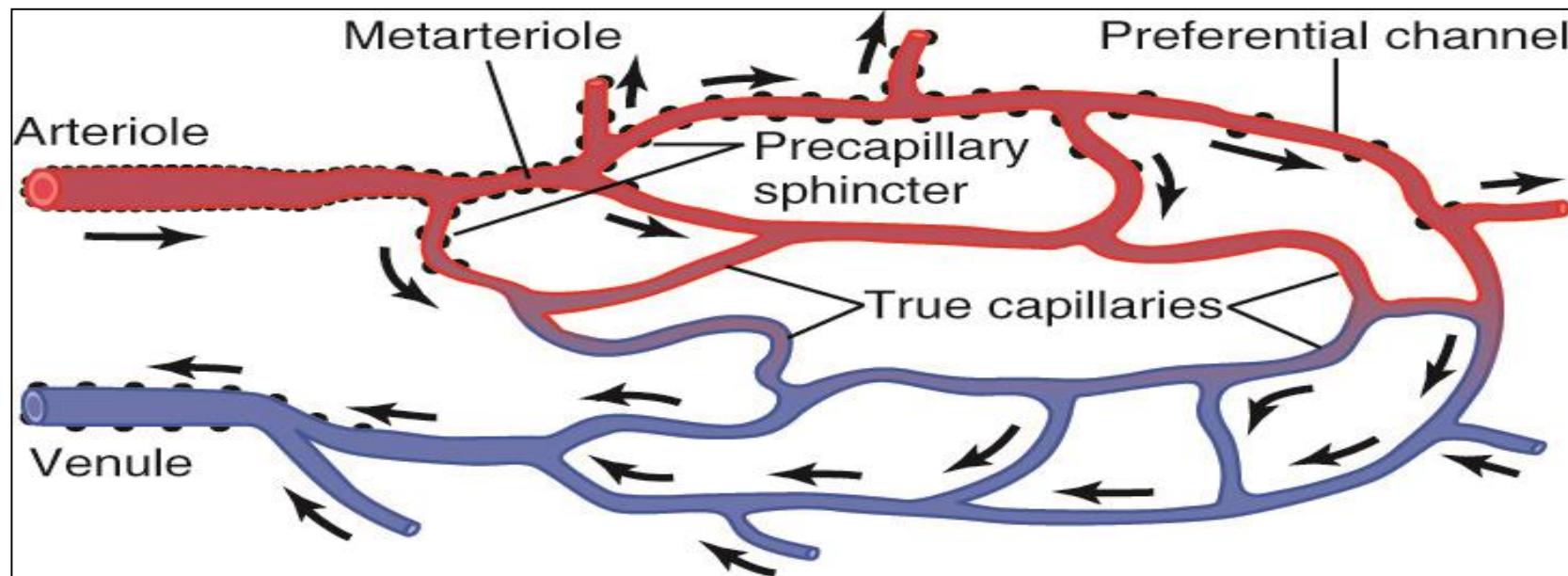
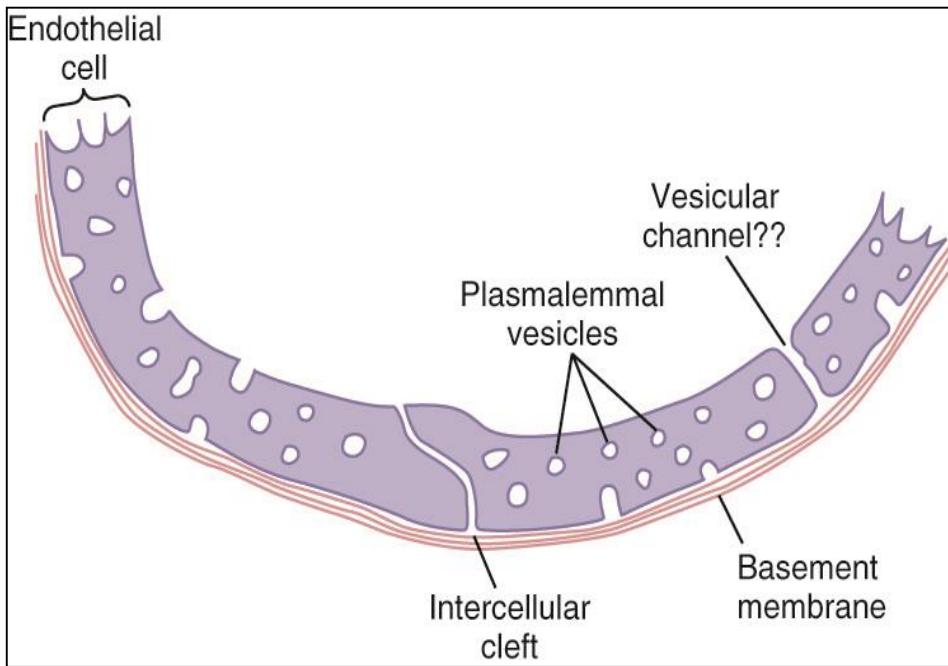


Figure 16-1;
Structure of the mesenteric capillary bed. (Redrawn from Zweifach BW: Factors Regulating Blood Pressure. New York: Josiah Macy, Jr., Foundation, 1950.)

- Structure of Capillary Wall
- Composed of unicellular layer of endothelial cells surrounded by a basement membrane.
- Diameter of capillaries is 4 to 9 microns.
- Solute and water move across capillary wall via *intercellular cleft* (space between cells) or by *plasmalemma vesicles*.



Structure of the capillary wall. Note especially the intercellular cleft at the junction between adjacent endothelial cells; it is believed that most water-soluble substances diffuse through the capillary membrane along the clefts.

■ Effect of Molecular Size on Passage Through Capillary Pores

- The *width of capillary intercellular slit pores* is 6 to 7 nanometers.
- The *permeability* of the capillary pores for different substances varies according to their *molecular diameters*.
- The capillaries in different tissues have *extreme differences* in their permeabilities.

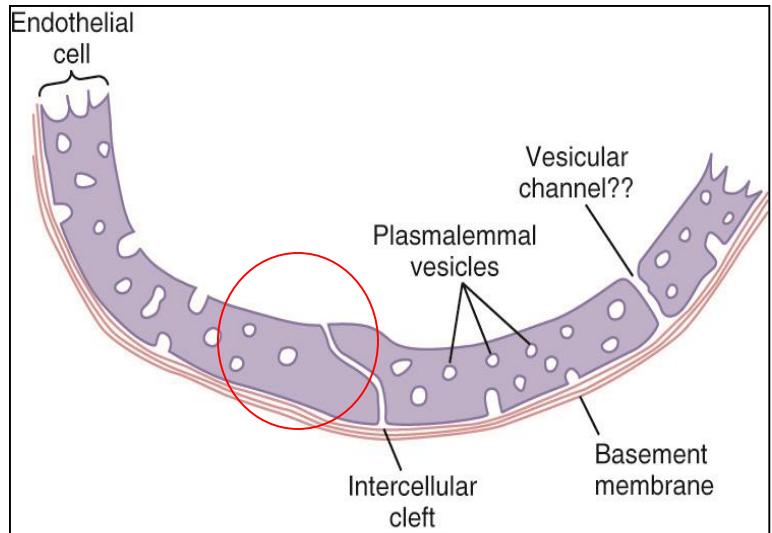
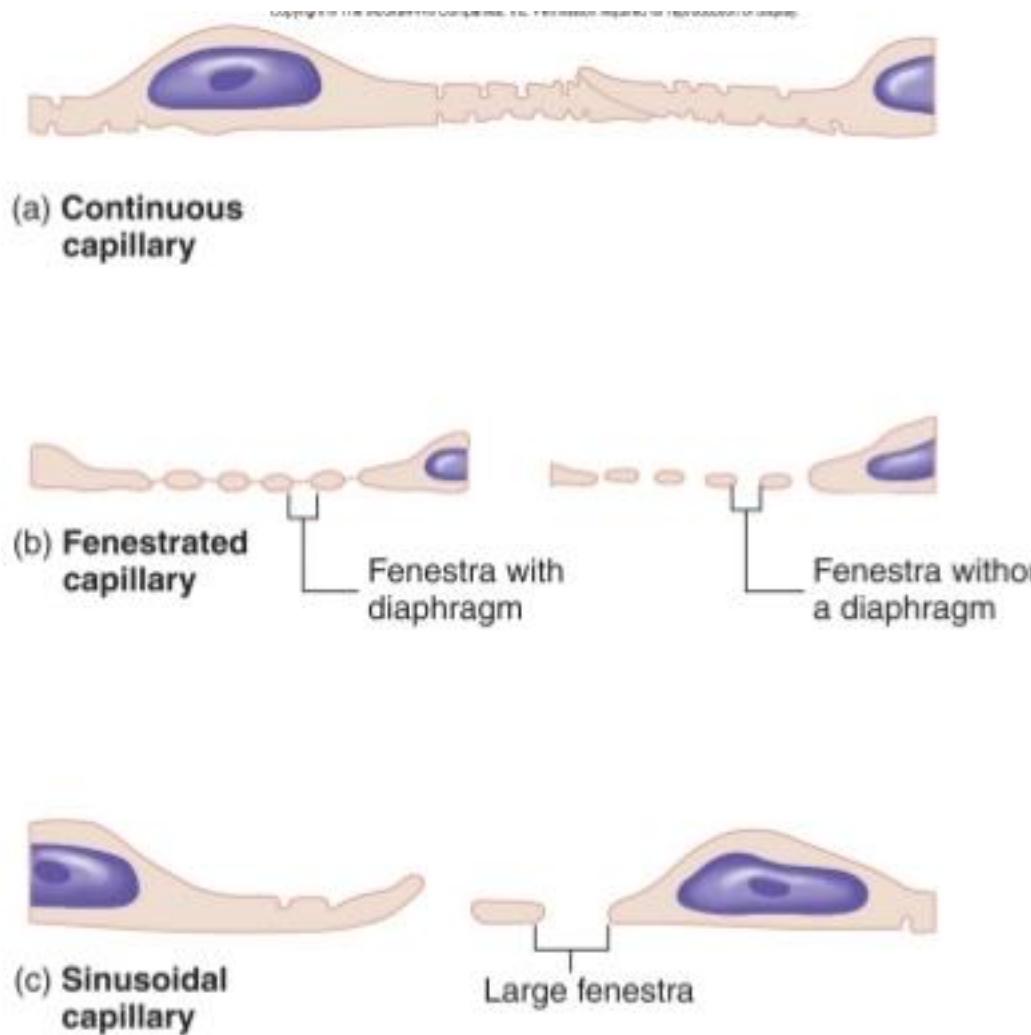


Figure 16-2; Guyton and Hall

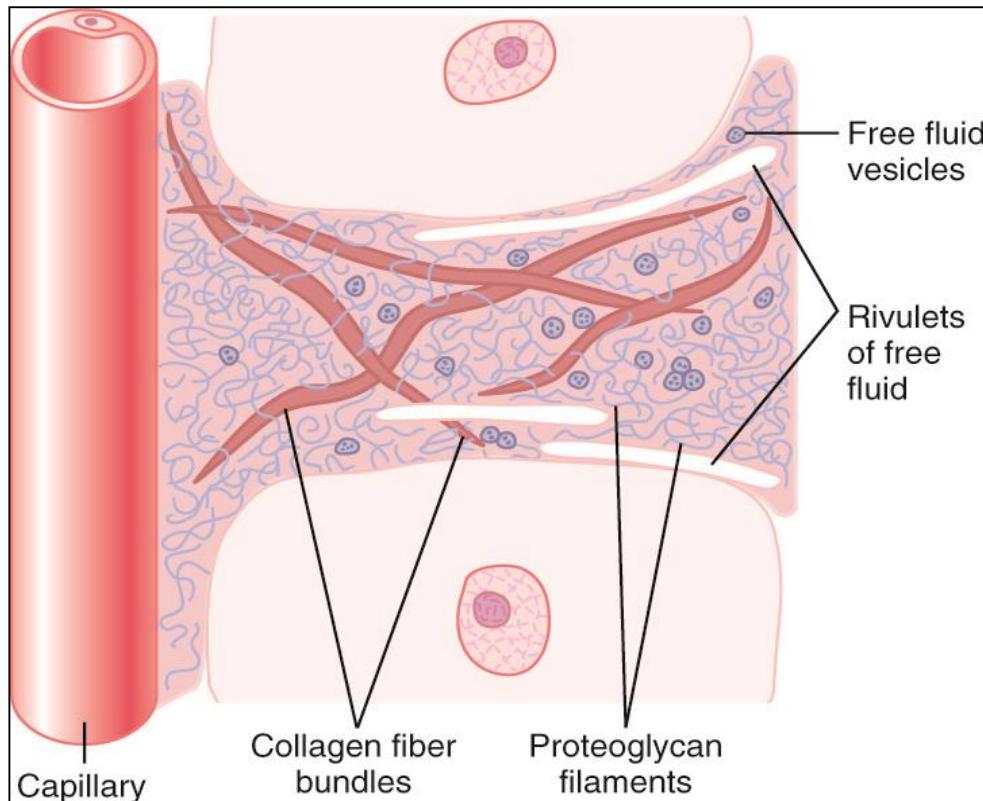
Types of Capillaries

- **Continuous.** No gaps between endothelial cells. No fenestrae. Less permeable to large molecules than other capillary types. E.g., muscle, nervous tissue.
- **Fenestrated.** Fenestrae are areas where cytoplasm is absent and plasma membrane is made of a thin, porous diaphragm. Endothelial cells have numerous fenestrae. Highly permeable. E.g., intestinal villi, ciliary process of eye, choroid plexus, glomeruli of kidney
- **Sinusoidal.** Large diameter with large fenestrae. Less basement membrane. E.g., endocrine glands (large molecules cross their walls).



Interstitium and Interstitial Fluid

- About one sixth of the total volume of the body consists of spaces between cells, which collectively are called the *interstitium*. The fluid in these spaces is the *interstitial fluid*.



- **two major types of solid structures: (1) collagen fiber bundles and (2) proteoglycan filaments.**
- The collagen fiber bundles extend long distances in the interstitium. They are extremely strong and therefore provide most of the tensional strength of the tissues.
- The proteoglycan filaments form a mat of very fine reticular filaments aptly described as a “brush pile.”

Figure 16-4; Structure of the interstitium. Proteoglycan filaments are every where in the spaces between the collagen fiber bundles. Free fluid vesicles and small amounts of free fluid in the form of rivulets occasionally also occur.

Determinants of Net Fluid Movement across Capillaries

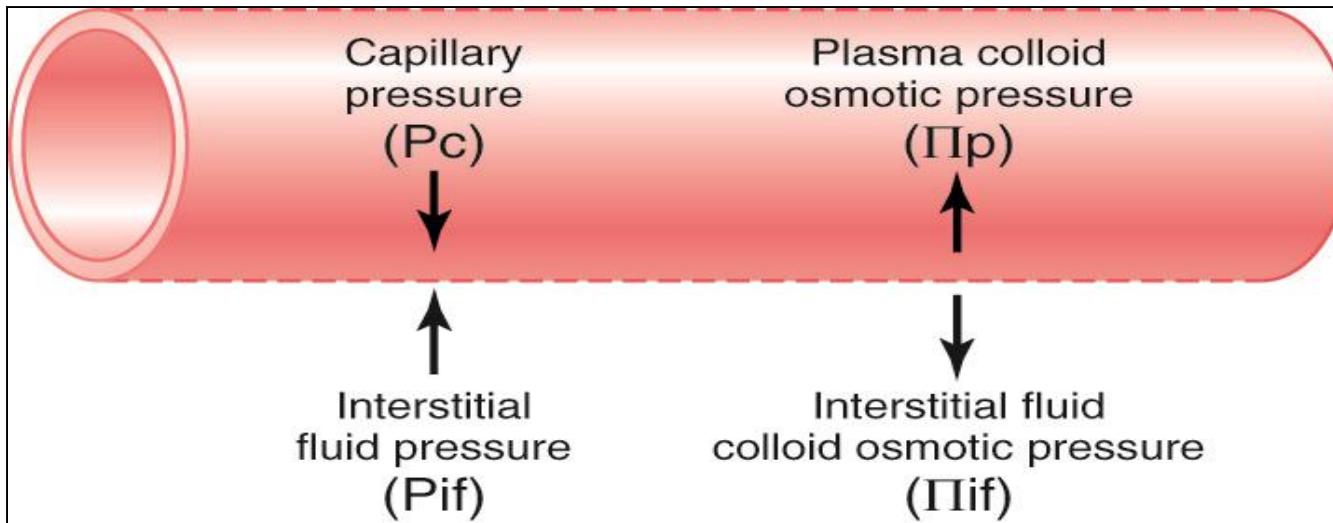


Figure 16-5; Fluid pressure and colloid osmotic pressure forces operate at the capillary membrane, tending to move fluid either outward or inward through the membrane pores.

- *Capillary hydrostatic pressure (Pc)*-tends to force fluid outward through the capillary membrane.
- *Interstitial fluid pressure (Pif)*- opposes filtration when value is positive.

Determinants of Net Fluid Movement across Capillaries- (cont.)

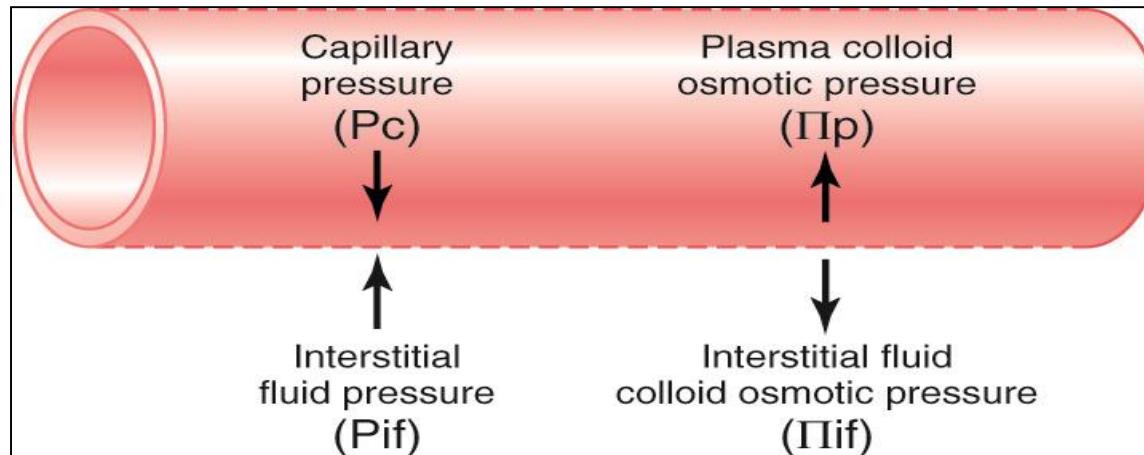


Figure 16-5; Guyton and Hall

- *Plasma colloid osmotic pressure by the plasma proteins (π_p)*- opposes filtration causing osmosis of water inward through the membrane
- *Interstitial fluid colloid osmotic pressure (π_{if})* promotes filtration of fluid outward through the membrane

If the sum of these forces, the net filtration pressure, is positive, there will be a net fluid filtration across the capillaries. If the sum of the Starling forces is negative, there will be a net fluid absorption from the interstitial spaces into the capillaries.

■ Forces Causing Filtration at the Arterial End of the Capillary

	mm Hg
Forces tending to move fluid outward:	
Capillary pressure (arterial end of capillary)	30
Negative interstitial free fluid pressure	3
Interstitial fluid colloid osmotic pressure	<u>8</u>
TOTAL OUTWARD FORCE	41
Forces tending to move fluid inward:	
Plasma colloid osmotic pressure	28
TOTAL INWARD FORCE	28
Summation of forces:	
Outward	41
Inward	<u>28</u>
NET OUTWARD FORCE (AT ARTERIAL END)	13

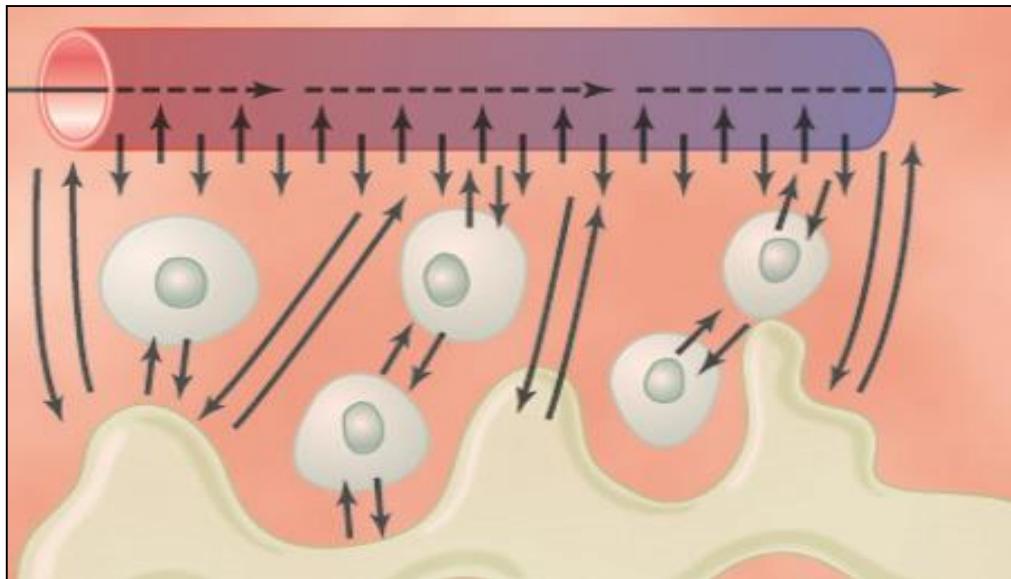
■ Forces Causing Reabsorption at the Venous End of the Capillary

	mm Hg
<i>Forces tending to move fluid inward:</i>	
Plasma colloid osmotic pressure	<u>28</u>
TOTAL INWARD FORCE	<u>28</u>
<i>Forces tending to move fluid outward:</i>	
Capillary pressure (venous end of capillary)	10
Negative interstitial free fluid pressure	3
Interstitial fluid colloid osmotic pressure	<u>8</u>
TOTAL OUTWARD FORCE	<u>21</u>
<i>Summation of forces:</i>	
Inward	28
Outward	<u>21</u>
NET INWARD FORCE	<u>7</u>

Net Starling Forces in Capillaries

	mm Hg
<i>Mean forces tending to move fluid outward:</i>	
Mean capillary pressure	17.3
Negative interstitial free fluid pressure	3.0
Interstitial fluid colloid osmotic pressure	<u>8.0</u>
TOTAL OUTWARD FORCE	28.3
<i>Mean force tending to move fluid inward:</i>	
Plasma colloid osmotic pressure	<u>28.0</u>
TOTAL INWARD FORCE	28.0
<i>Summation of mean forces:</i>	
Outward	28.3
Inward	<u>28.0</u>
NET OUTWARD FORCE	0.3

- Net Starling Forces in Capillaries



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video #15

Figure 16–3 Diffusion of fluid molecules and dissolved substances between the capillary and interstitial fluid spaces.

- *Net filtration pressure* of .3 mmHg which causes a net filtration rate of 2ml/min for entire body.

Lymphatic System

- The lymphatic system represents an accessory route through which fluid can flow from the interstitial spaces into the blood. Most important, the lymphatics can carry proteins and large particulate matter away from the tissue spaces, neither of which can be removed by absorption directly into the blood capillaries.

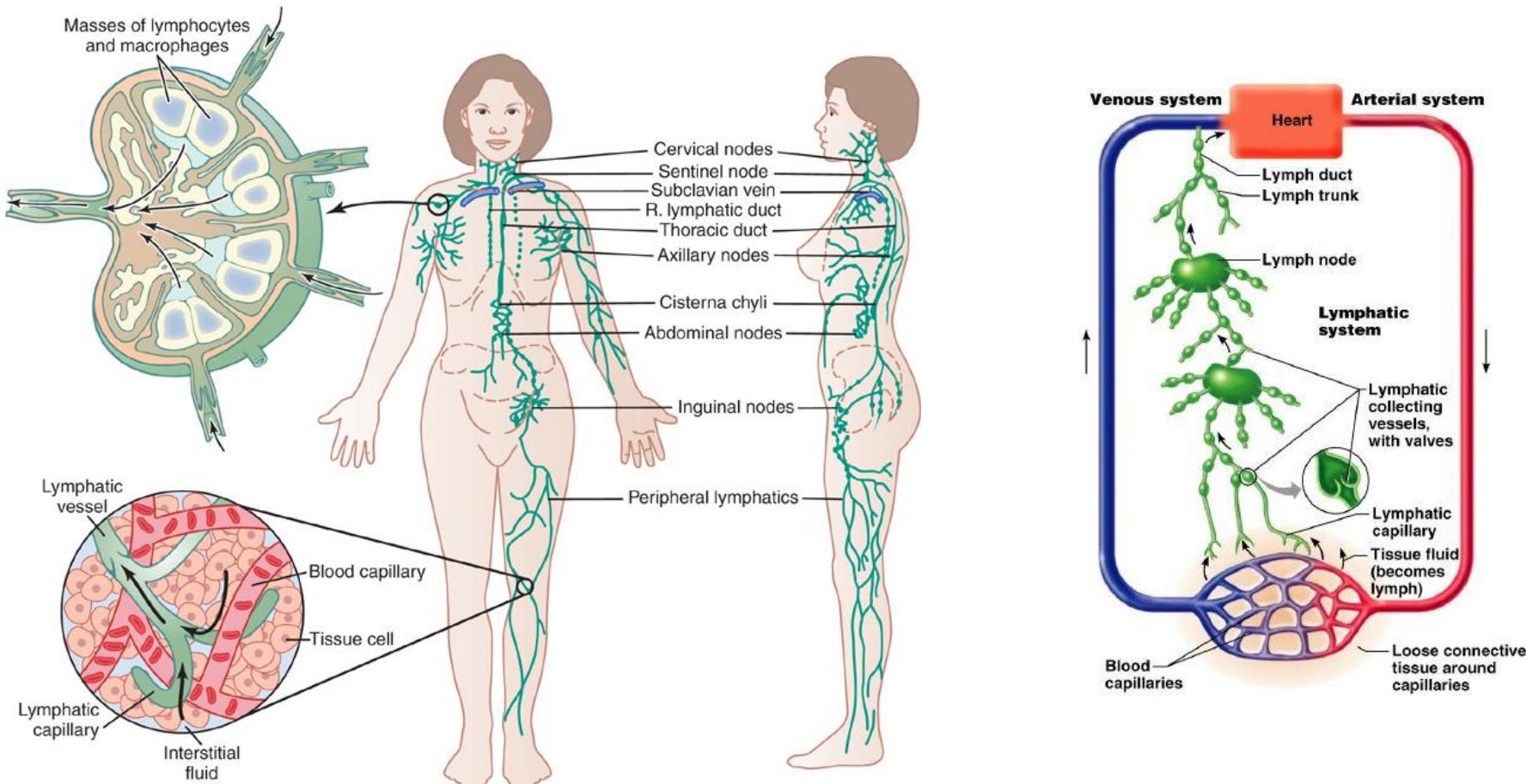


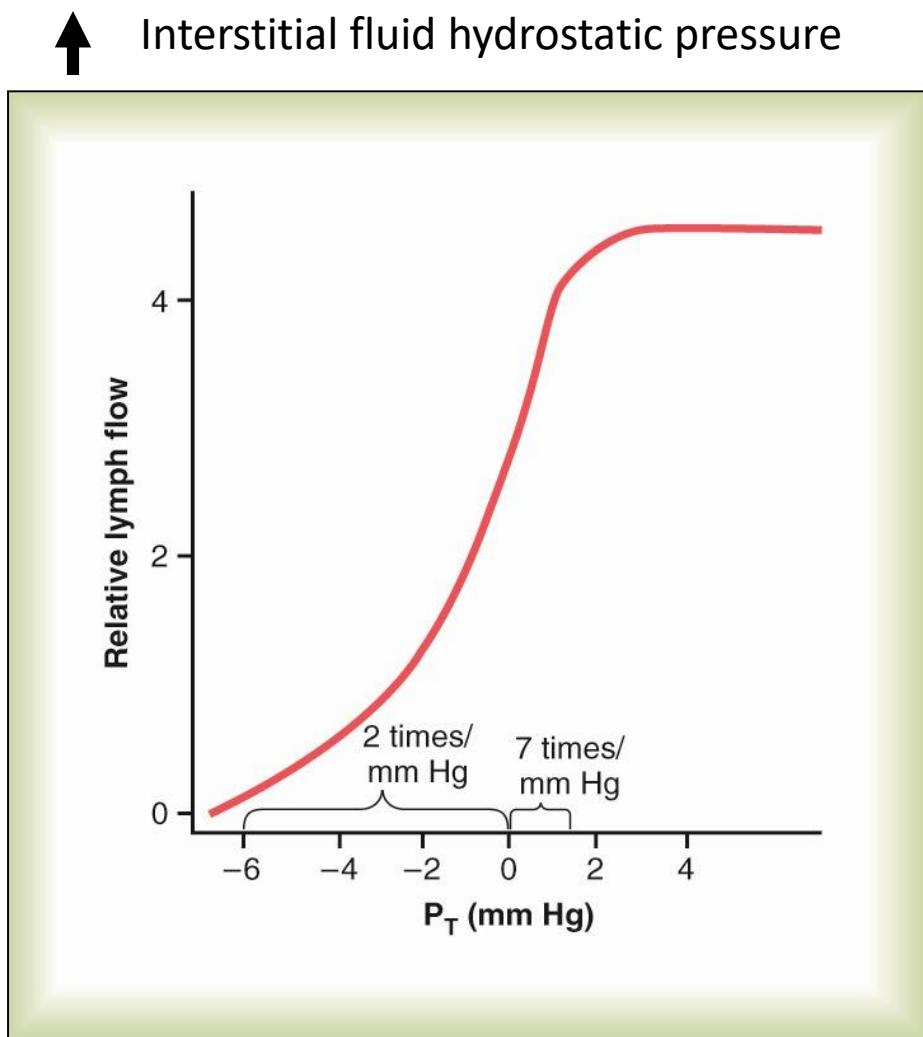
FIGURE 16–8
Lymphatic system.

■ FUNCTIONS OF THE LYMPHATIC SYSTEM:

1. It carries excess of interstitial fluid from interstitium into the blood. Rate of lymph flow is more than 3 liters/day. So this amount is drained by lymphatic system.
2. It drains proteins and electrolytes from Interstitial space into lymphatic system. Lymphatic system drain 195 grams of blood proteins from interstitium back into the blood.
3. It provides lymphocytes and antibodies into the circulation
4. Removes bacteria and other microorganisms from the tissues.
5. Lacteals (lymphatic vessels of the small intestine) are involved in the absorption and transport of lipids.
6. Many large enzymes which are produced in the tissues get entry into the circulation through lymphatic system like histaminases and lipase.
7. It maintains the negative interstitial fluid hydrostatic pressure.

Watch
video
#16

Determinants of Lymph Flow



→ ↑ Lymph Flow

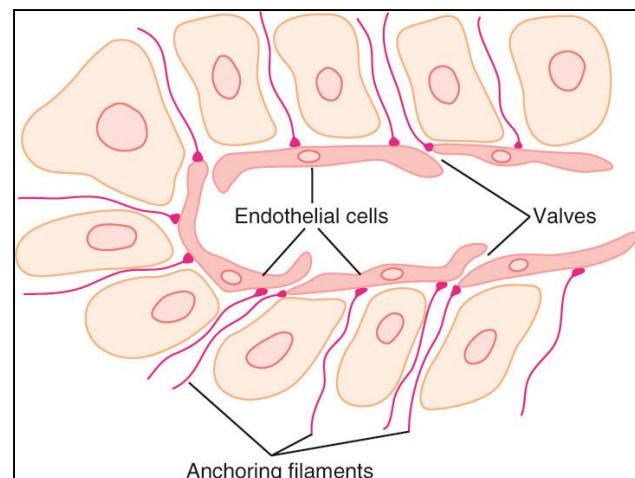


Figure 16-9; Special structure of the lymphatic capillaries that permits passage of substances of high molecular weight into the lymph.

Figure 16-10; Relation between interstitial fluid pressure and lymph flow in the leg of a dog. Note that lymph flow reaches a maximum when the interstitial pressure, P_T , rises slightly above atmospheric pressure (0 mm Hg). (Courtesy Drs. Harry Gibson and Aubrey Taylor.)

Venous System

• Veins and Their Functions

- 60% of blood is in veins
- The veins are capable of constricting and enlarging and thereby storing either small or large quantities of blood
- The spleen, liver, large abdominal veins, and the venous plexus also serve as reservoirs

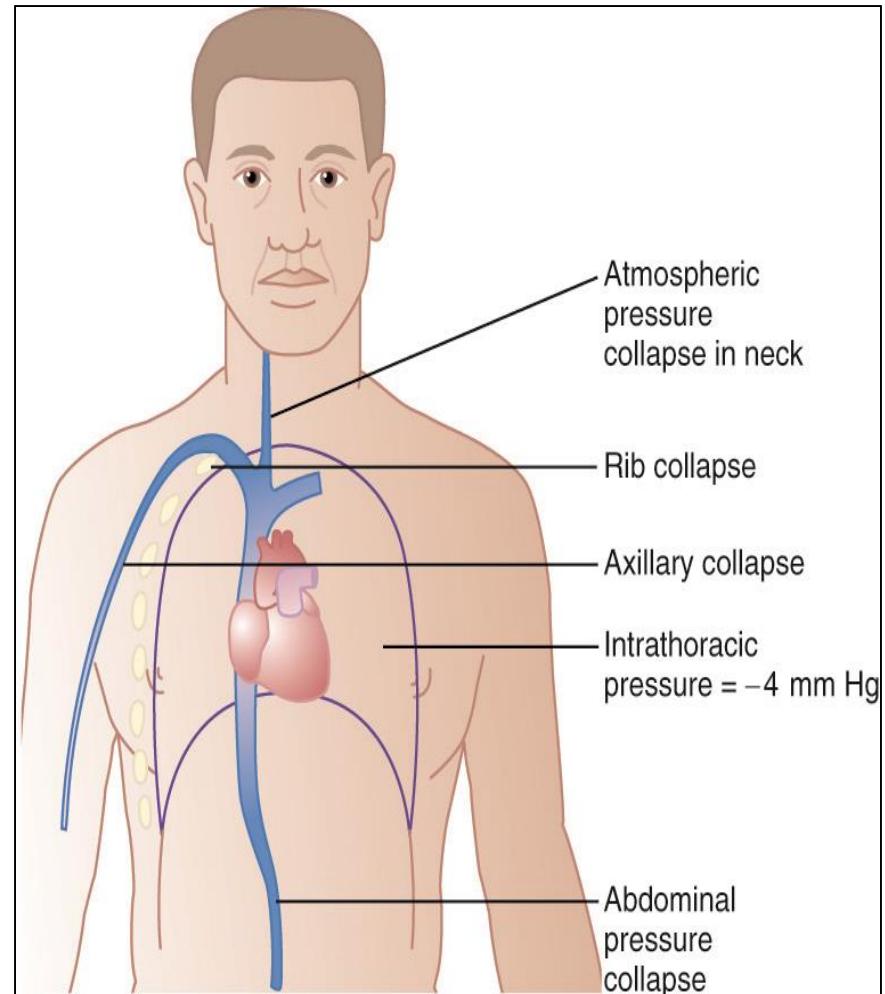
- **Venous Pressures**-Right Atrial Pressure (Central Venous Pressure) and Peripheral Venous Pressures

- Blood from all the systemic veins flows into the right atrium of the heart; therefore, the pressure in the right atrium is called the **central venous pressure**
- **Right atrial pressure** is regulated by a balance between (1) the ability of the heart to pump blood out of the right atrium and ventricle into the lungs and (2) the tendency for blood to flow from the peripheral veins into the right atrium

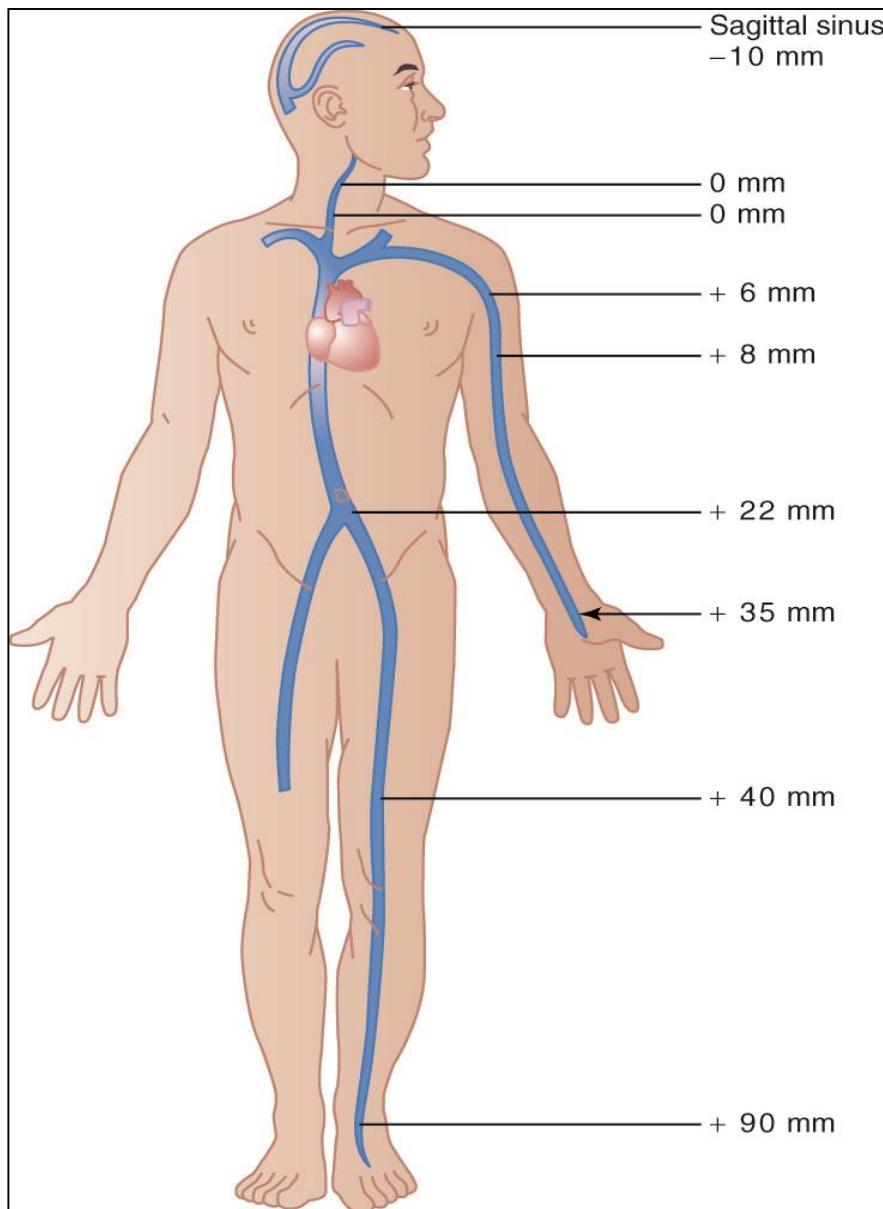
- **Normal right atrial pressure ~ 0 mm Hg**
 - Right arterial pressure can increase to 20-30 mm Hg due to heart failure or after massive transfusion of blood
- **Venous return is increased by:**
 - increased blood volume
 - increased large vessel tone and peripheral vessel tone
 - dilatation of arterioles which decreases peripheral resistance and increases blood flow

■ Venous resistance and peripheral venous pressure

- Large veins have virtually little resistance to blood flow as they are distended
- Many large veins that enter the thorax are compressed at many points by the surrounding tissue
- Venous pressure is slightly higher (4-6 mm Hg) compared with PRA (**Right atrial pressure**) since otherwise it may collapse.

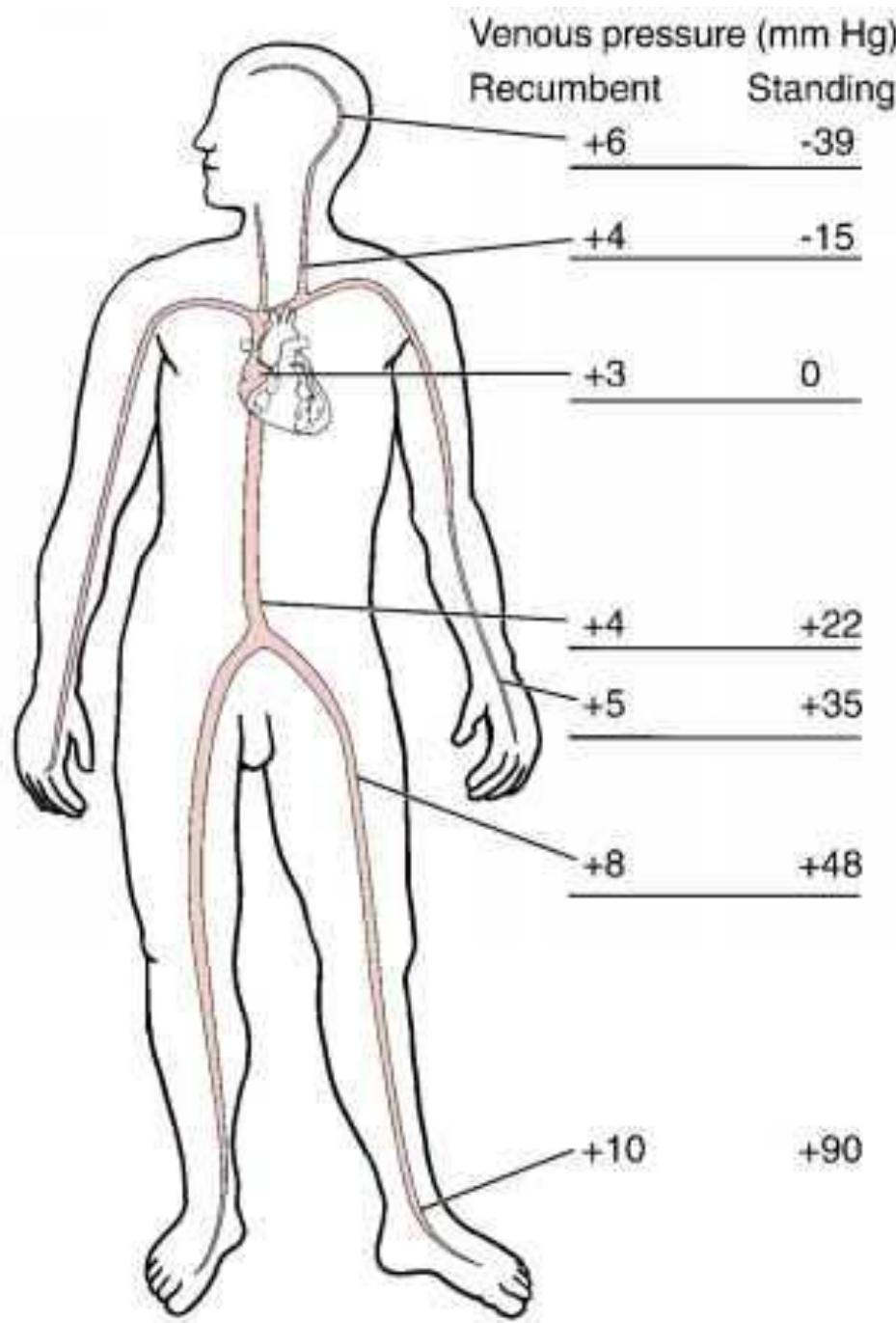


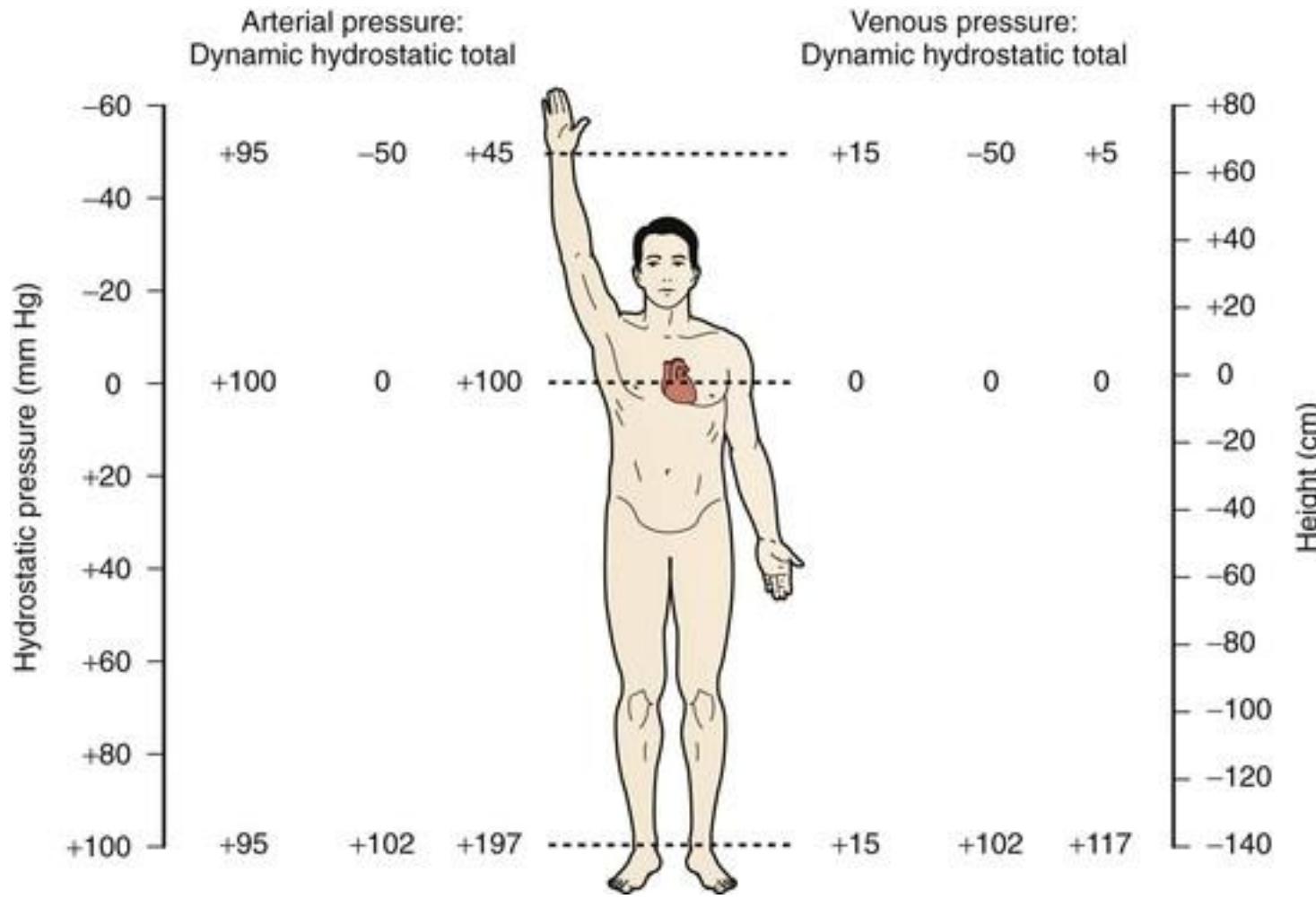
Effect of Gravitational Pressure on Venous Pressure



- Gravitational pressure occurs in the vascular system of the human being because of weight of the blood in the vessels
- When a person is standing, the pressure in the right atrium remains about 0 mm Hg because the heart pumps into the arteries any excess blood that attempts to accumulate at this point.
- The venous pressures at other levels of the body are proportionately between 0 and 90 mm Hg.

Figure 15-10; Effect of gravitational pressure on the venous pressures throughout the body in the standing person.



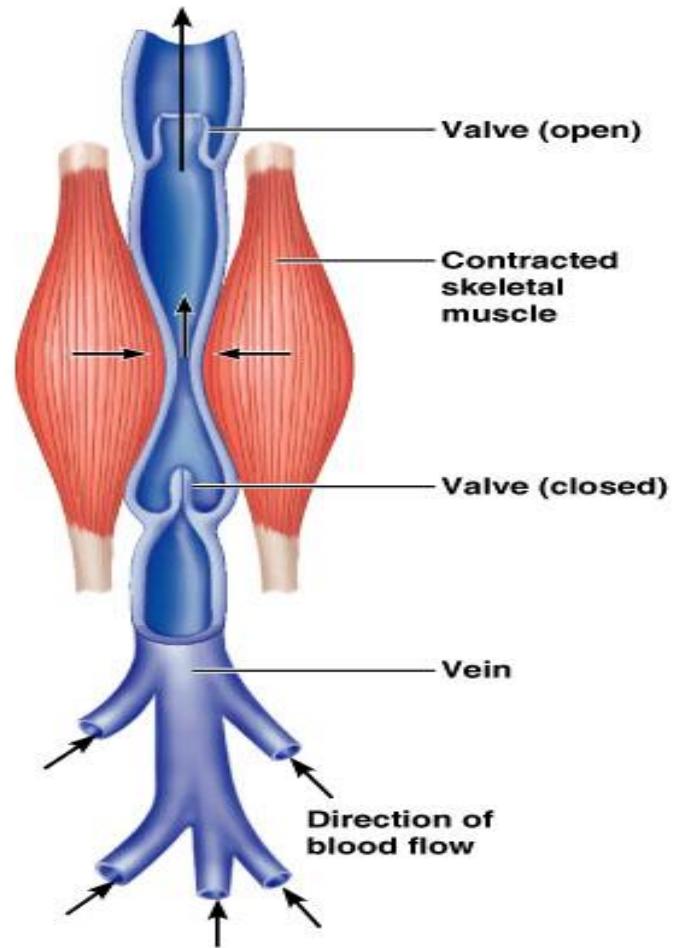


Effect of upright position on venous and arterial pressure. Pressure at the right atrial level is 0. In the supine position, hydrostatic pressure is essentially 0, so total intravascular pressure closely approximates dynamic pressure.

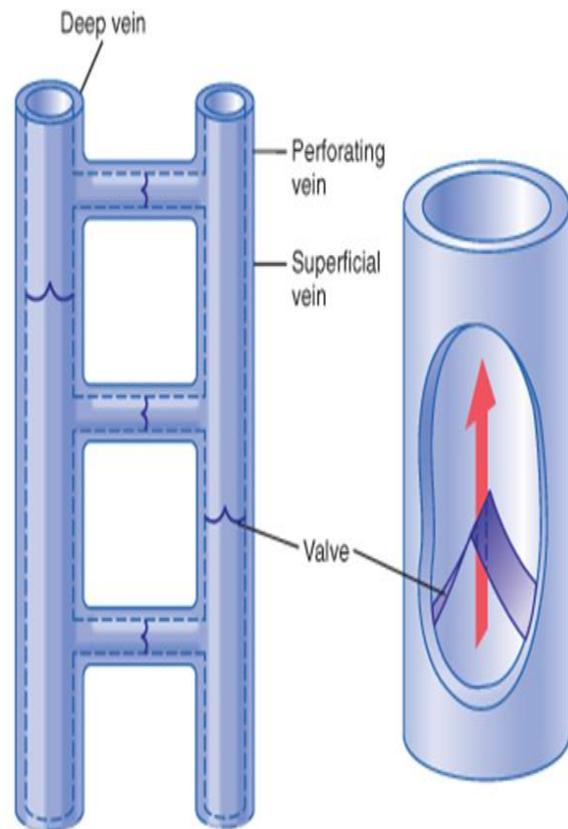
- Effect of Intra-abdominal Pressure on Venous Pressures of the Leg
- The pressure in the abdominal cavity normally averages about **6 mm Hg**,
- It can rise to 15 to 30 mm Hg as a result of **pregnancy, large tumors, or excessive fluid** in the abdominal cavity
- When the intra-abdominal pressure rises, the pressure in the veins of the legs must rise *above* the abdominal pressure before the abdominal veins will open and allow the blood to flow from the legs to the heart

■ Venous Valves and the "Venous Pump": Their Effects on Venous Pressure

- Leg muscle contractions squeezes veins and pumps blood toward the heart, lowering venous pressure to less than 20 mm Hg in a walking person
- Valves prevent backflow during venous return
- This pumping system is known as the "*venous pump*" or "*muscle pump*,"



- In a person standing or sitting for long period of time “venous pump” does not work, pressure rises to full gravitational values of up to +90 mm Hg.
- Fluid leaks from the circulation system to tissues spaces, the legs swell, and blood volume diminishes, risk of blood clots develops
- Thus, the person develops **“varicose veins,”** which are characterized by large protrusions of the veins beneath the skin of the entire leg, particularly the lower leg.

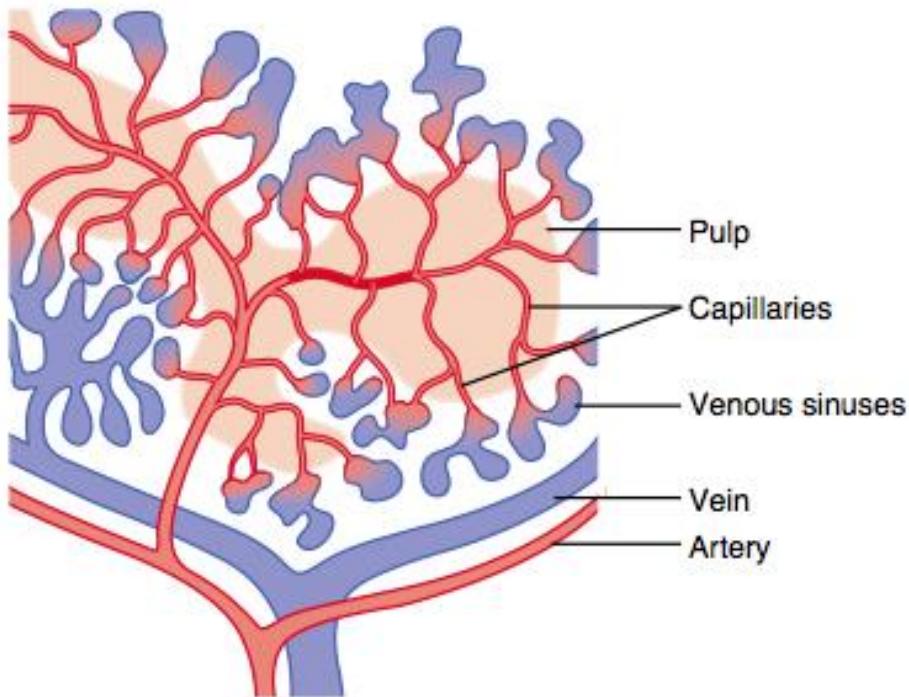


■ Blood Reservoir Function of the Veins

- more than 60 per cent of all the blood in the circulatory system is usually in the veins. For this reason and also because the veins are so compliant, it is said that the venous system serves as a blood reservoir for the circulation.

Specific Blood Reservoirs.

- ① spleen which sometimes can decrease in size sufficiently to release as much as 100 milliliters of blood into other areas of the circulation;



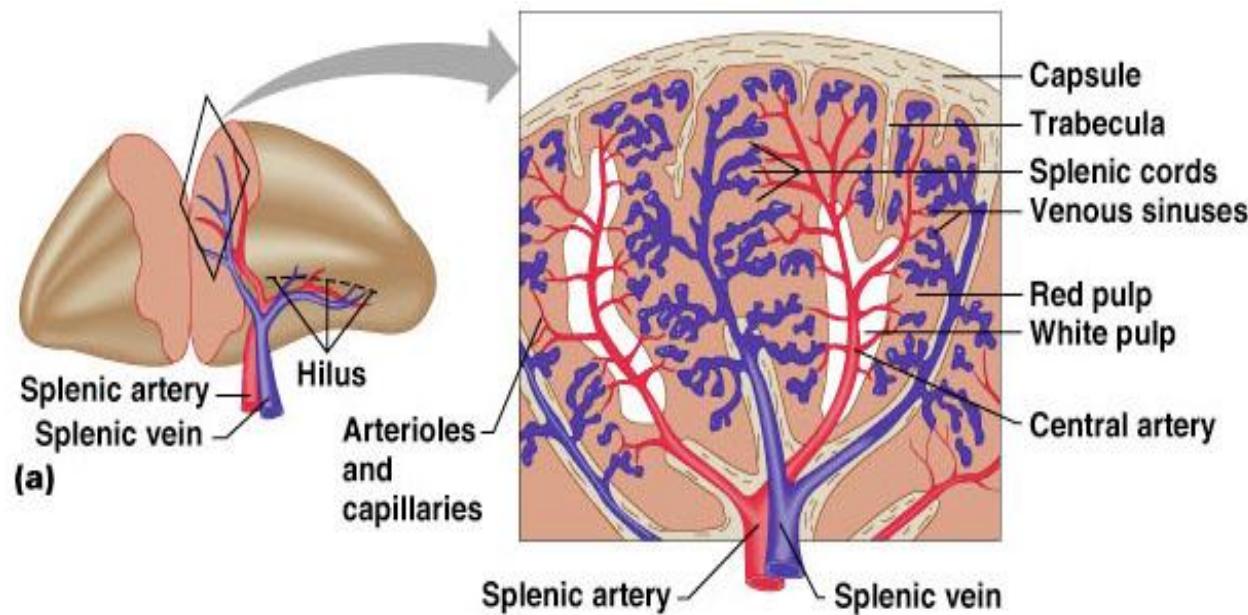
- ② the liver, the sinuses of which can release several hundred milliliters of blood into the remainder of the circulation
- ③ the large abdominal veins, which can contribute as much as 300 milliliters
- ④ the venous plexus beneath the skin, which also can contribute several hundred milliliters

Figure 15–13

Functional structures of the spleen. (Courtesy of Dr. Don W. Fawcett, Montana.)

- **The Spleen as a Reservoir for Storing Red Blood Cells**

- the spleen has two separate areas for storing blood:
 1. the *venous sinuses*
 2. the *pulp*
- The sinuses can swell the same as any other part of the venous system and store whole blood
- In the splenic pulp, the capillaries are so permeable that whole blood, oozes through the capillary walls into a trabecular mesh, forming the *red pulp*
- The red cells are trapped by the trabeculae, while the plasma flows on into the venous sinuses and then into the general circulation.



- The red pulp of the spleen is a *special reservoir that contains large quantities of concentrated red blood cells*
- These can then be expelled into the general circulation whenever the sympathetic nervous system becomes excited and causes the spleen and its vessels to contract
- In other areas of the splenic pulp are islands of white blood cells, which collectively are called the *white pulp*
- Lymphoid cells are manufactured , they are part of the body's immune system.

- Blood-Cleansing Function of the Spleen-Removal of Old Cells
 - Many of the red blood cells destroyed in the body have their final demise in the spleen.
 - After the cells rupture, the released hemoglobin and the cell stroma are digested by the reticuloendothelial cells of the spleen
 - the products of digestion are mainly reused by the body as nutrients, often for making new blood cells

- **Reticuloendothelial Cells of the Spleen**

- Reticuloendothelial cells function as part of a cleansing system for the blood
- When the blood is invaded by infectious agents, the reticuloendothelial cells of the spleen rapidly remove debris, bacteria, parasites, and so forth.
- Also, in many chronic infectious processes, the spleen enlarges in the same manner that lymph nodes enlarge and then performs its cleansing function even more avidly.

Spleen function

- Reservoir of blood in the venous sinuses
- Filtration of the blood
- Reservoir of red and white cells in the red and white pulp
- Immunity for the body
- Blood cleanser
- Iron recycling

Cardiac Output

- Cardiac output is the quantity of blood pumped into the aorta each minute by the heart. This is also the quantity of blood that flows through the circulation.
- Venous return is the quantity of blood flowing from the veins into the right atrium each minute.

The venous return and the cardiac output must equal each other except for a few heartbeats at a time when blood is temporarily stored in or removed from the heart and lungs.

factors directly affect cardiac output:

- (1) the basic level of body metabolism,
- (2) whether the person is exercising,
- (3) the person's age,
- (4) size of the body.

■ Effect of Age on Cardiac Output.

Cardiac Index

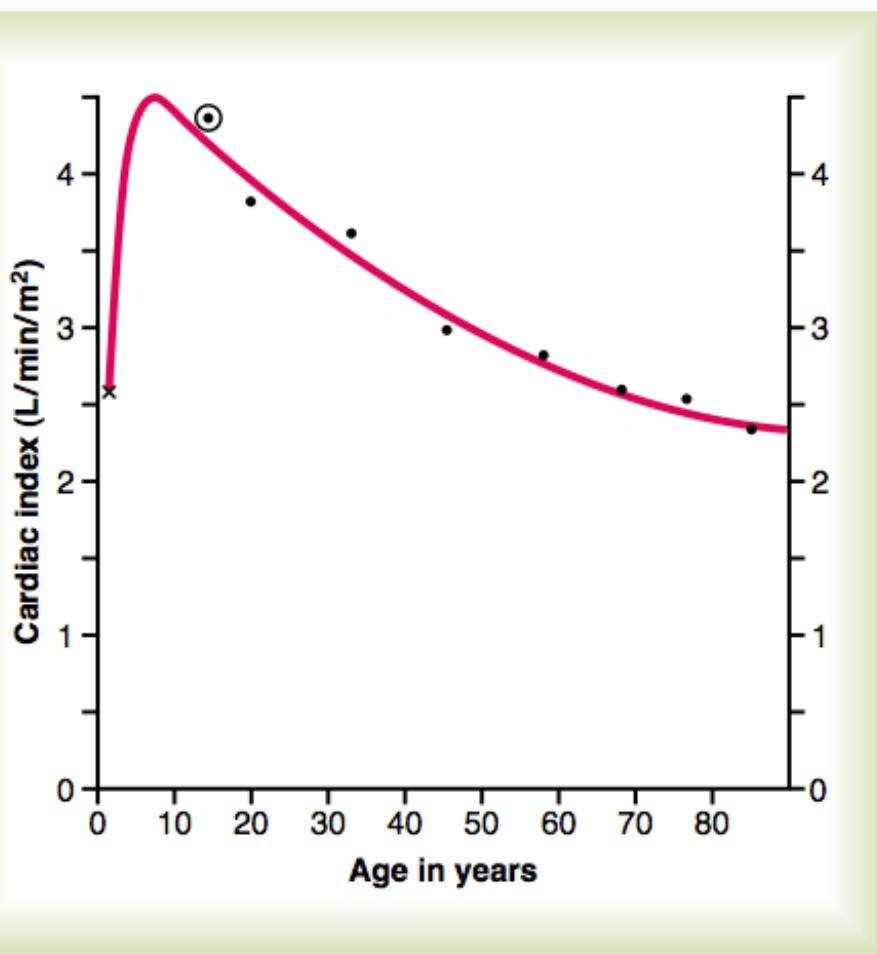


Figure 20-1

Cardiac index for the human being (cardiac output per square meter of surface area) at different ages. (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation. 2nd ed. Philadelphia: WB Saunders Co, 1973.)

- cardiac output increases approximately in proportion to the surface area of the body. Therefore, cardiac output is frequently stated in terms of the cardiac index, which is the cardiac output per square meter of body surface area.
- The normal human being weighing 70 kilograms has a body surface area of about 1.7 square meters, which means that the normal average cardiac index for adults is about 3 L/min/m² of body surface area.

$$CI = \frac{CO}{BSA} = \frac{SV \times HR}{BSA}$$

■ Effect of Exercising on Cardiac Output.

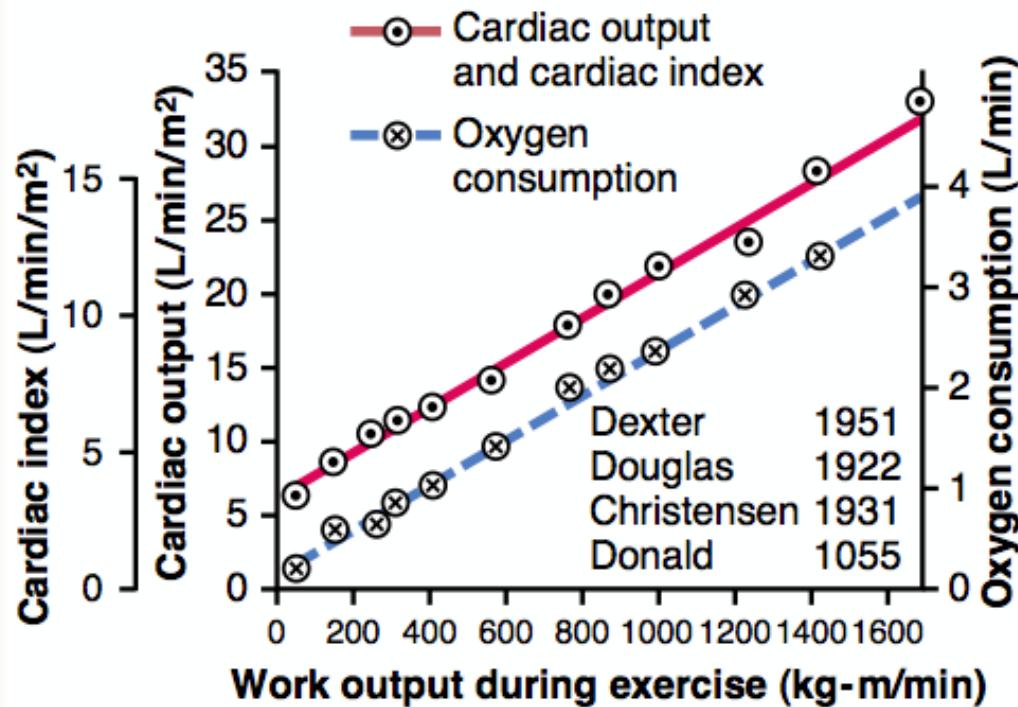


Figure 20–2

Effect of increasing levels of exercise to increase cardiac output (*red solid line*) and oxygen consumption (*blue dashed line*). (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation. 2nd ed. Philadelphia: WB Saunders Co, 1973.)

- local blood flow almost always increases when tissue oxygen consumption increases
- each peripheral tissue of the body controls its own local blood flow, and all the local tissue flows combine and return by way of the veins to the right atrium. The heart, in turn, automatically pumps this incoming blood into the arteries, so that it can flow around the circuit again.
- **intrinsic ability** of the heart to adapt to increasing volumes of inflowing blood is called the ***Frank- Starling mechanism*** of the heart.

■ Effect of Total Peripheral Resistance on the Long-Term Cardiac Output

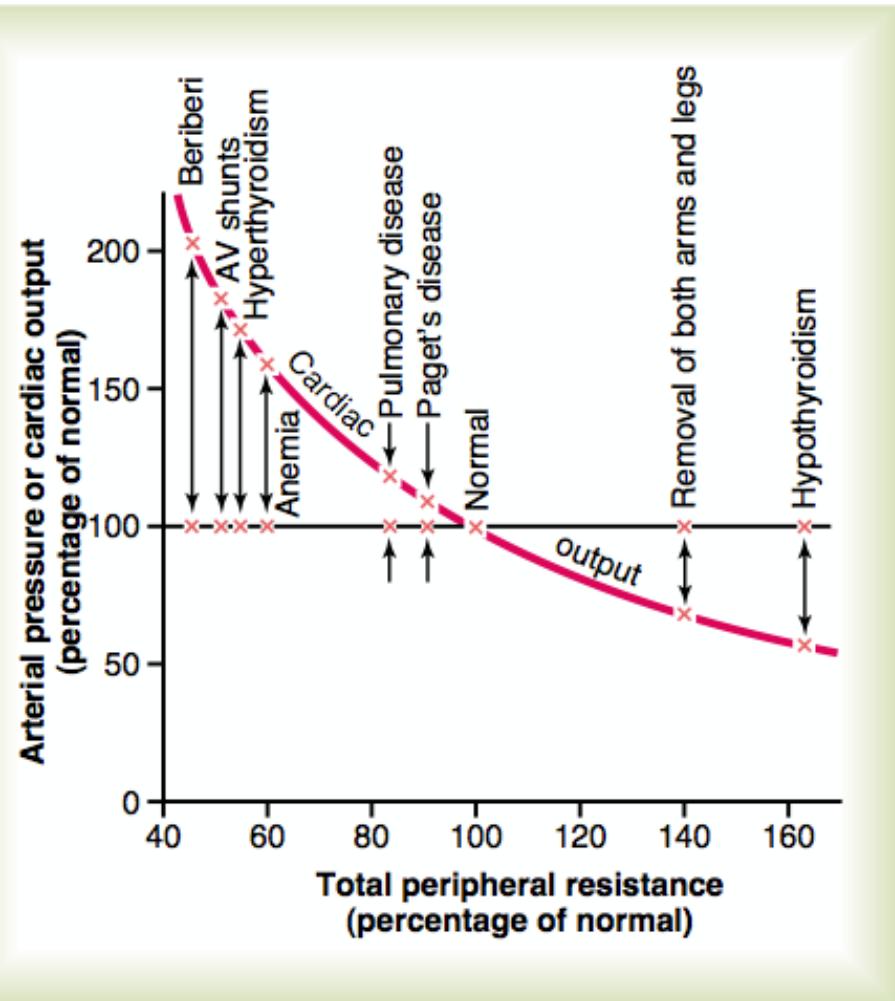


Figure 20-3

Chronic effect of different levels of total peripheral resistance on cardiac output, showing a reciprocal relationship between total peripheral resistance and cardiac output. (Redrawn from Guyton AC: Arterial Pressure and Hypertension. Philadelphia: WB Saunders Co, 1980.)

- when the total peripheral resistance is exactly normal (at the 100 per cent mark in the figure), the cardiac output is also normal. Then, when the total peripheral resistance increases above normal, the cardiac output falls; conversely, when the total peripheral resistance decreases, the cardiac output increases.

$$\text{Cardiac Output} = \frac{\text{Arterial Pressure}}{\text{Total Peripheral Resistance}}$$

Cardiac Output Curves

- There are definite limits to the amount of blood that the heart can pump, which can be expressed quantitatively in the form of *cardiac output curves*.

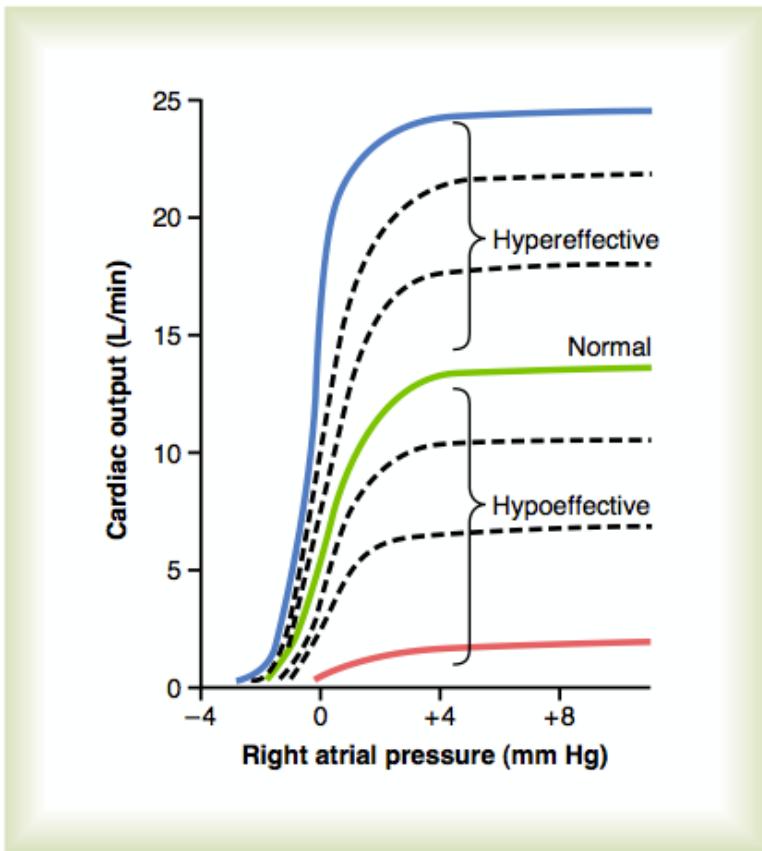


Figure 20-4

Cardiac output curves for the normal heart and for hypoeffective and hypereffective hearts. (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation. 2nd ed. Philadelphia: WB Saunders Co, 1973.)

- Note that the plateau level of this normal cardiac output curve is about 13 L/min, 2.5 times the normal cardiac output of about 5 L/min.
- This means that the normal human heart, functioning without any special stimulation, can pump an amount of venous return up to about 2.5 times the normal venous return before the heart becomes a limiting factor in the control of cardiac output.

■ Factors causing Hypereffective Heart

- (1) nervous stimulation
- (2) hypertrophy of the heart muscle

- nervous stimulation

- For given levels of input atrial pressure, the amount of blood pumped each minute (cardiac output) often can be increased more than 100 per cent by **sympathetic stimulation**. By contrast, the output can be decreased to as low as zero or almost zero by **vagal (parasympathetic)** stimulation.

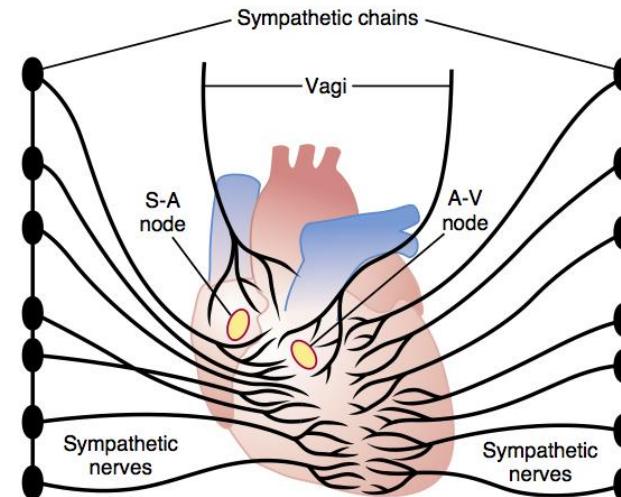


Figure 9-10

Cardiac sympathetic and parasympathetic nerves. (The vagus nerves to the heart are parasympathetic nerves.)

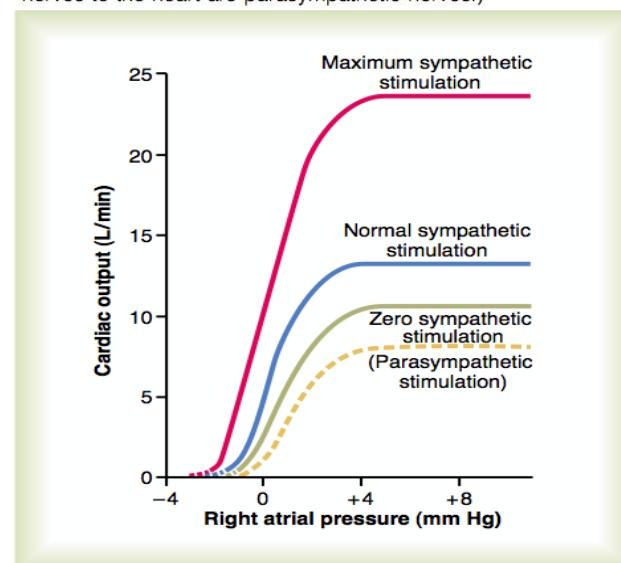


Figure 9-11

Effect on the cardiac output curve of different degrees of sympathetic or parasympathetic stimulation.

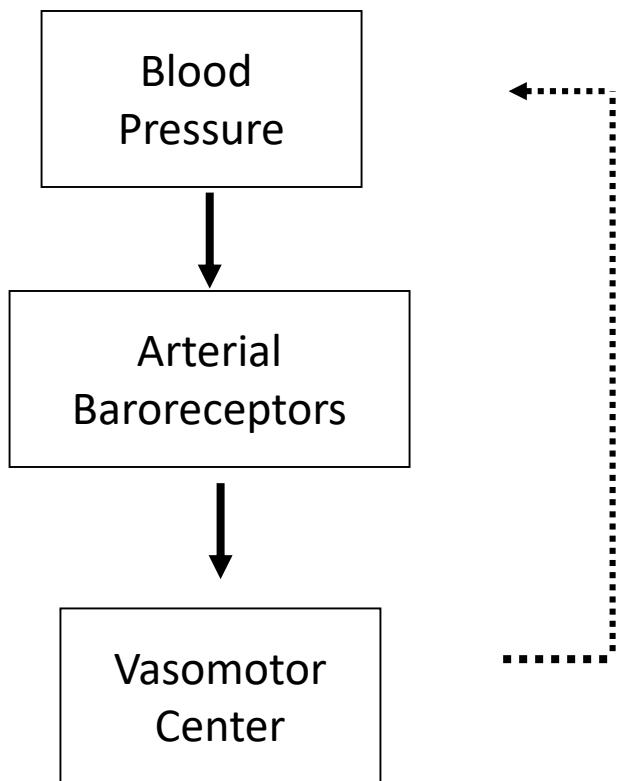
➤ hypertrophy of the heart muscle

A long-term increased workload, but not so much excess load that it damages the heart, causes the heart muscle to increase in mass and contractile strength in the same way that heavy exercise causes skeletal muscles to hypertrophy.

■ Factors That Cause a Hypoffective Heart

- Any factor that decreases the heart's ability to pump blood causes hypoeffectivity. Some of the factors that can do this are :
 - Coronary artery blockage, causing a "heart attack"
 - Inhibition of nervous excitation of the heart
 - Pathological factors that cause abnormal heart rhythm or rate of heartbeat
 - Valvular heart disease
 - Congenital heart disease

■ Arterial Baroreceptor Reflex



- A rise in arterial pressure stretches the baroreceptors and causes them to transmit signals into the central nervous system. “Feedback” signals are then sent back through the autonomic nervous system to the circulation to reduce arterial pressure downward toward the normal level.

■ Anatomy of the Baroreceptors

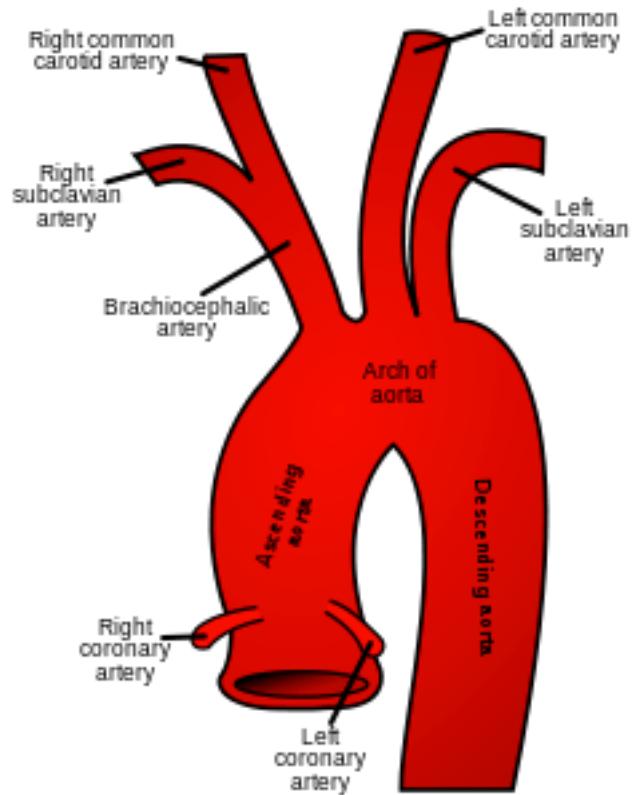
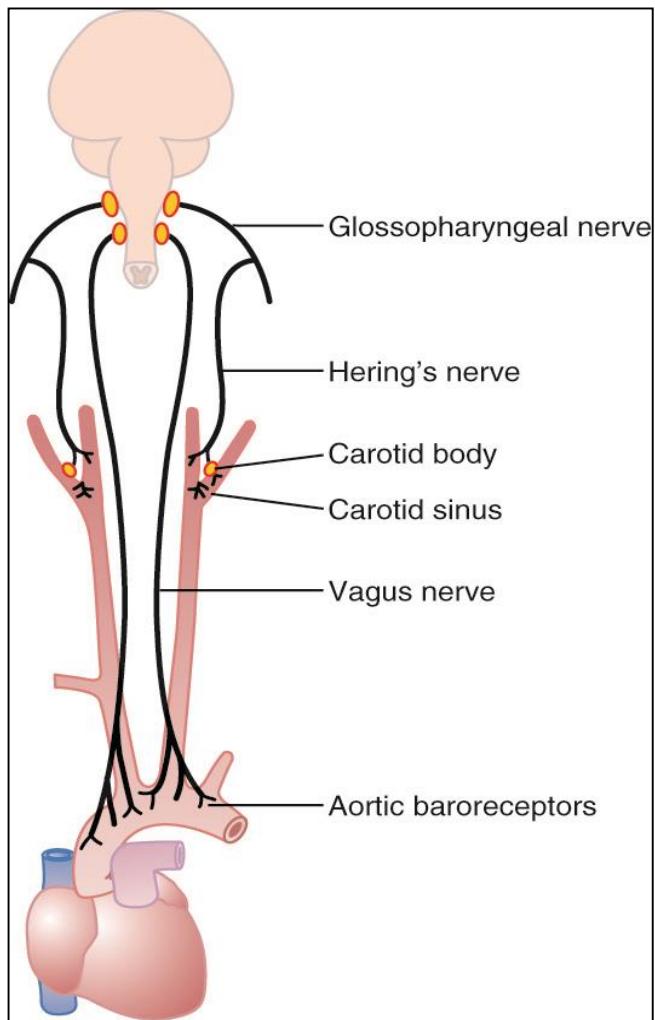
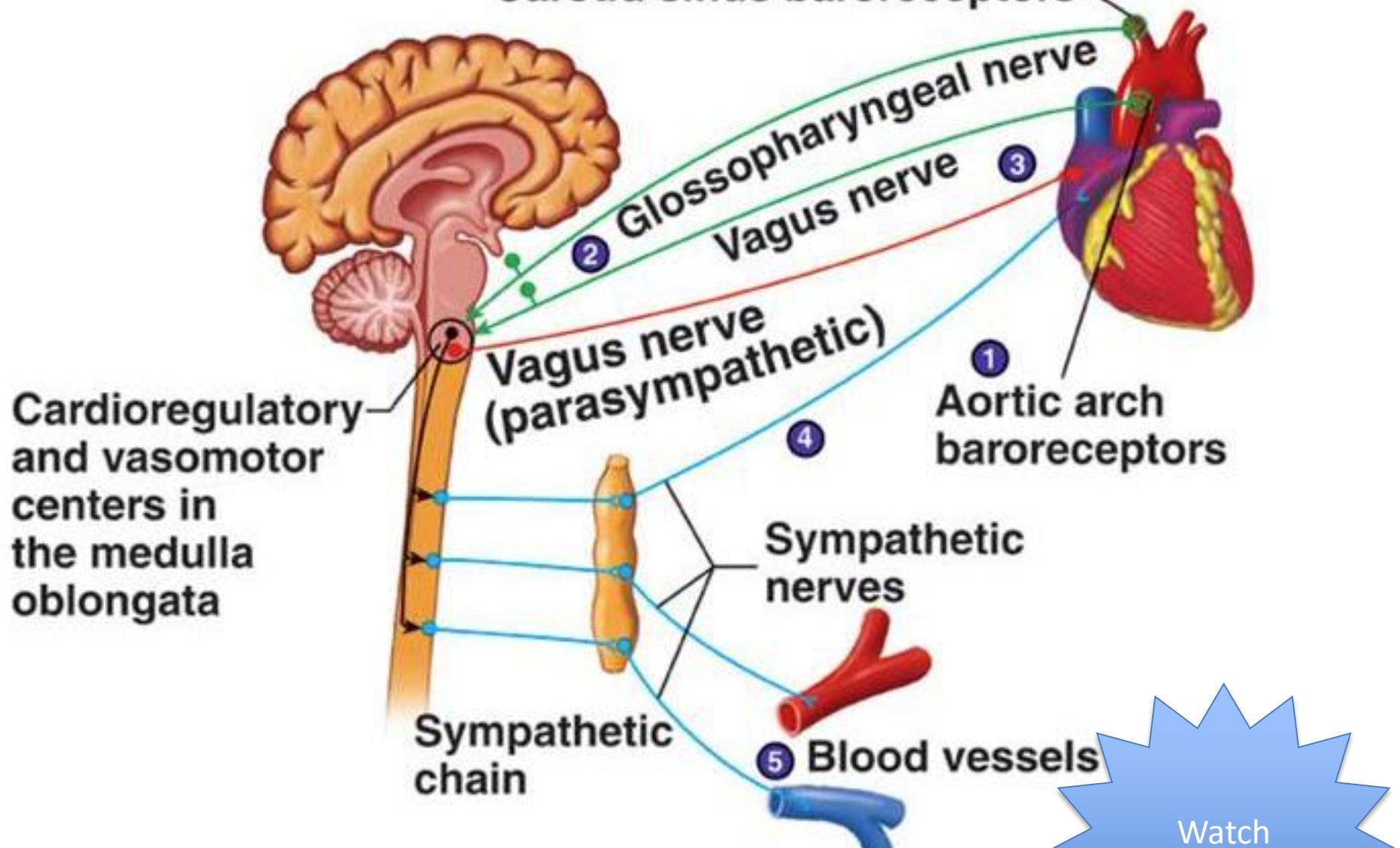


Figure 18-5; The baroreceptor system for controlling arterial pressure.

Carotid sinus baroreceptors



Watch
video #17

Response of the Baroreceptors to Arterial Pressure- (cont.)

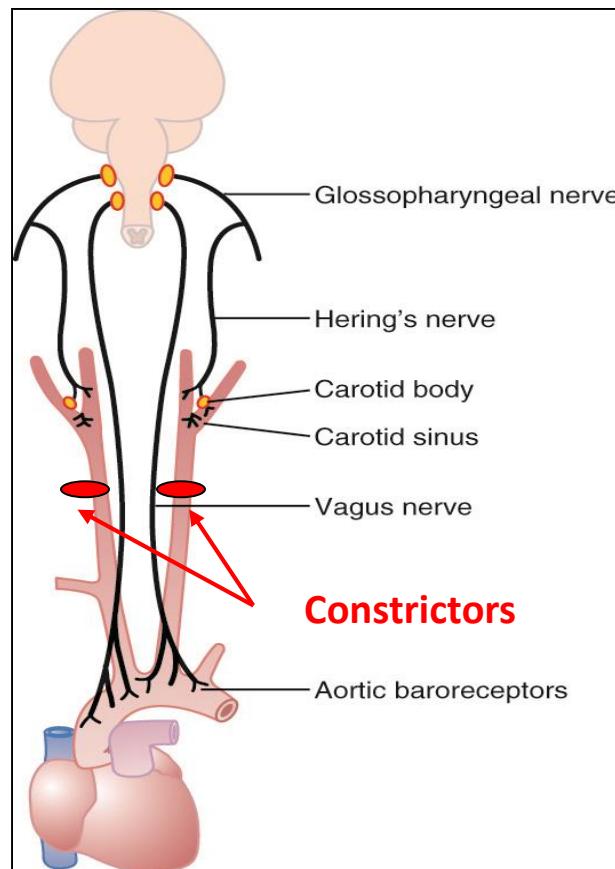


Figure 18-5; Guyton and Hall

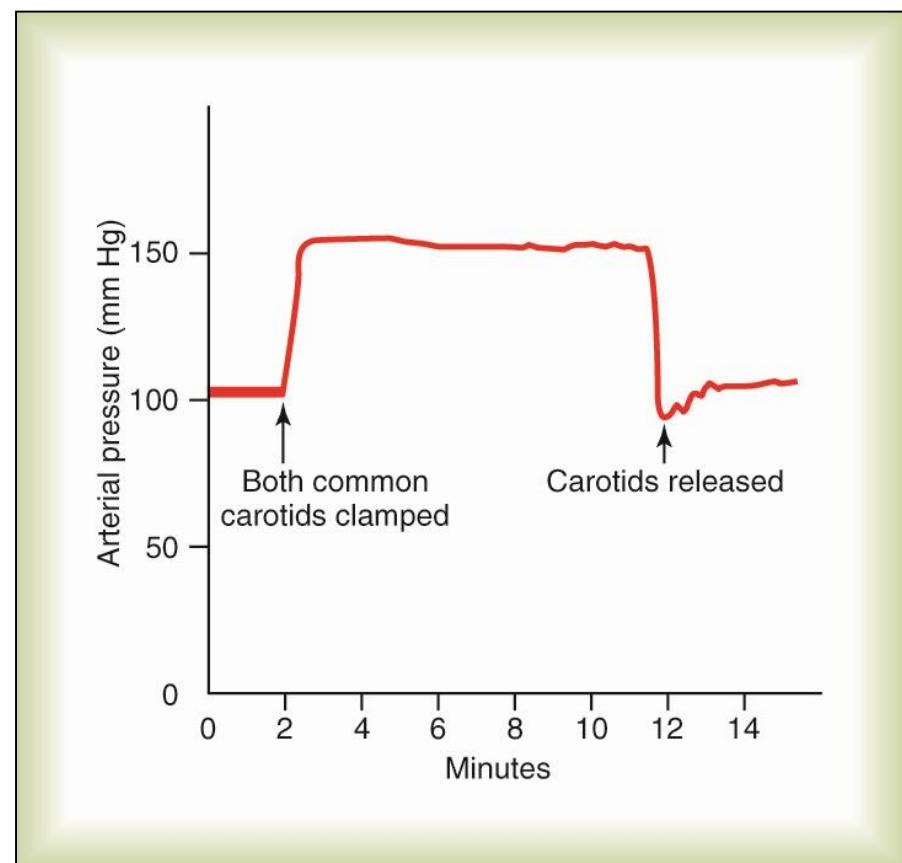
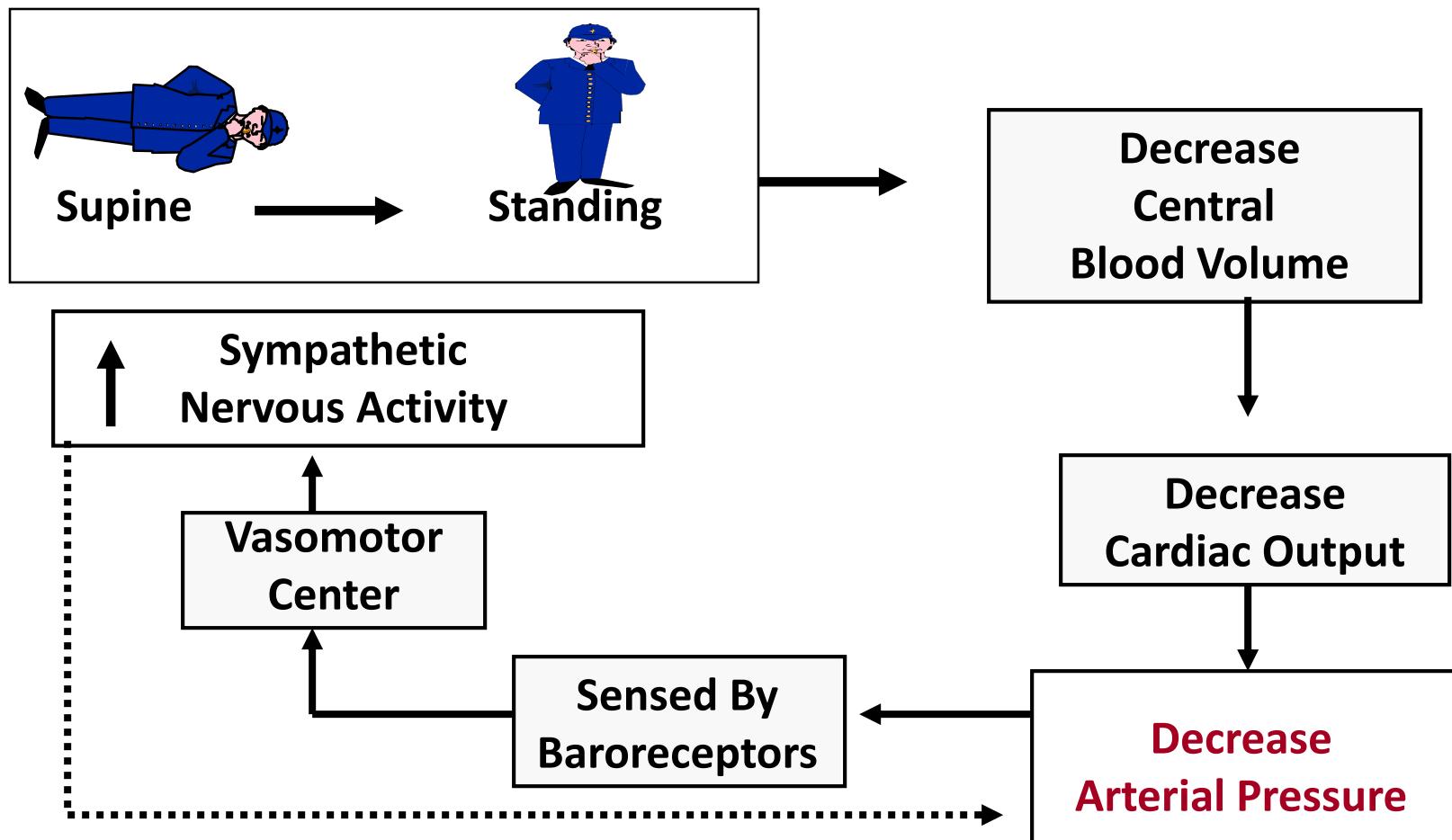


Figure 18-7; Typical carotid sinus reflex effect on aortic arterial pressure caused by clamping both common carotids (after the two vagus nerves have been cut).

■ Functions of the Baroreceptors

- Maintains relatively constant pressure despite changes in body posture.



■ Carotid and Aortic Chemoreceptors

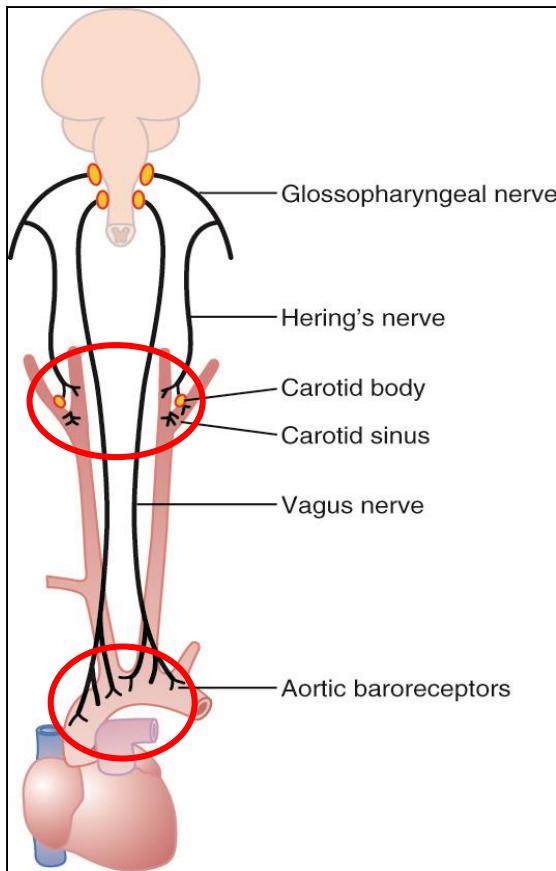
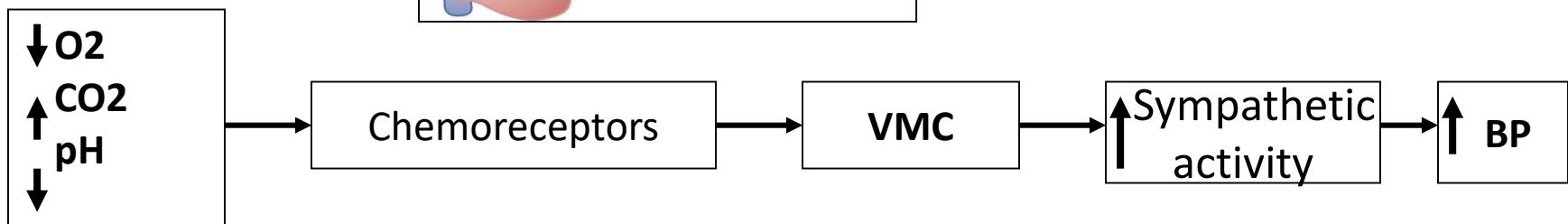


Figure 18-5; Guyton and Hall



Red Blood Cells (Erythrocytes)

- The major function of red blood cells, also known as erythrocytes, is to transport hemoglobin, which in turn carries oxygen from the lungs to the tissues.

➤ Concentration of Red Blood Cells in the Blood

In normal men, the average number of red blood cells per cubic millimeter is 5,200,000 ($\pm 300,000$); in normal women, it is 4,700,000 ($\pm 300,000$).

➤ Quantity of Hemoglobin in the Cells.

Red blood cells have the ability to concentrate hemoglobin in the cell fluid up to about 34 grams in each 100 milliliters of cells.

- in a normal man, a maximum of about 20 milliliters of oxygen can be carried in combination with hemoglobin in each 100 milliliters of blood, and in a normal woman, 19 milliliters of oxygen can be carried.

■ Production of Red Blood Cells

In the early weeks of embryonic life, primitive, nucleated red blood cells are produced in the *yolk sac*. During the middle trimester of gestation, the *liver* is the main organ for production of red blood cells, but reasonable numbers are also produced in the *spleen* and *lymph nodes*. Then, during the last month or so of gestation and after birth, red blood cells are produced exclusively in the *bone marrow*

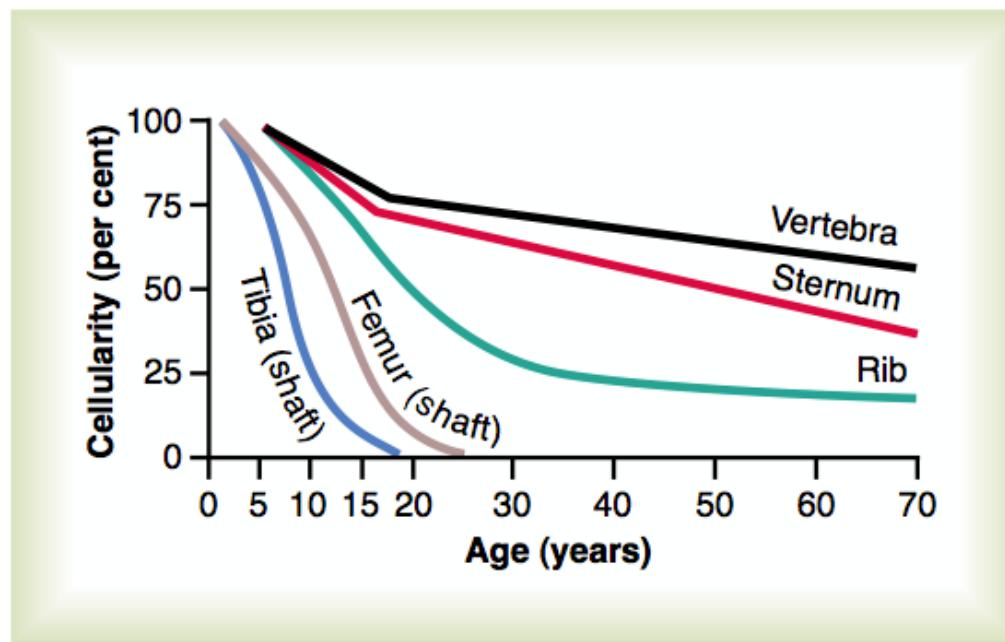


Figure 32-1

Relative rates of red blood cell production in the bone marrow of different bones at different ages.

- the bone marrow of essentially all bones produces red blood cells until a person is 5 years old

■ Genesis of Blood Cells

The blood cells begin their lives in the bone marrow from a single type of cell called the *pluripotential hematopoietic stem cell*, from which all the cells of the circulating blood are eventually derived.

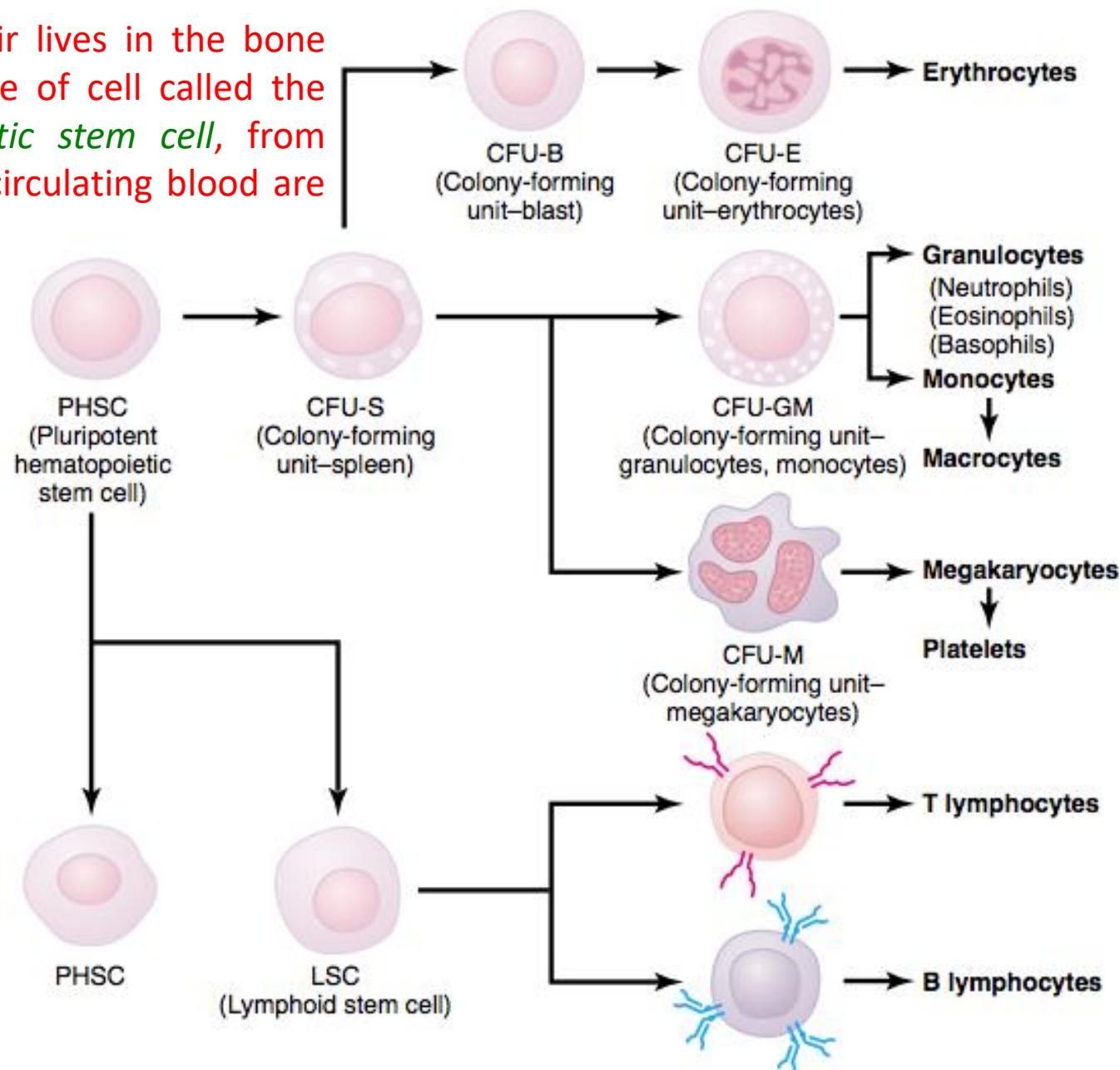


Figure 32-2

Formation of the multiple different blood cells from the original *pluripotent hematopoietic stem cell* (PHSC) in the bone marrow.

Formation of Hemoglobin

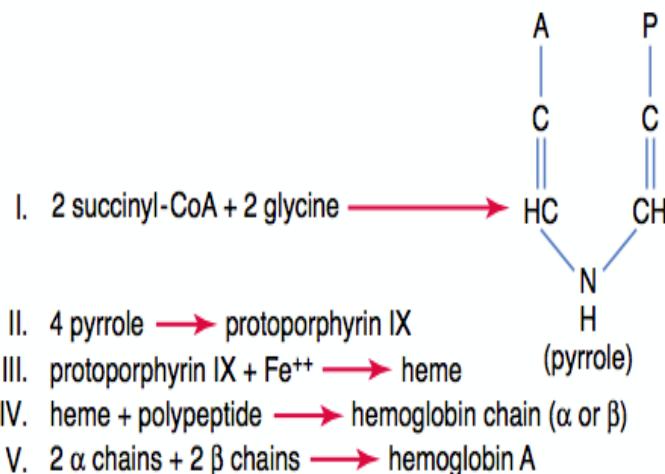


Figure 32–5
Formation of hemoglobin.

The most important feature of the hemoglobin molecule is its ability to combine loosely and reversibly with oxygen.

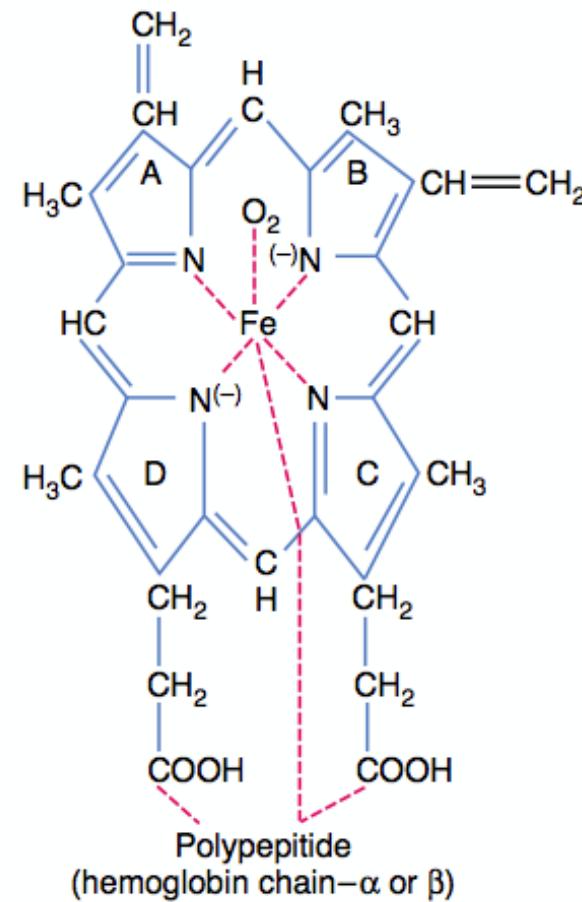


Figure 32–6

Basic structure of the hemoglobin molecule, showing one of the four heme chains that bind together to form the hemoglobin molecule.

■ Iron

The total quantity of iron in the body averages 4 to 5 grams, about 65 per cent of which is in the form of hemoglobin.

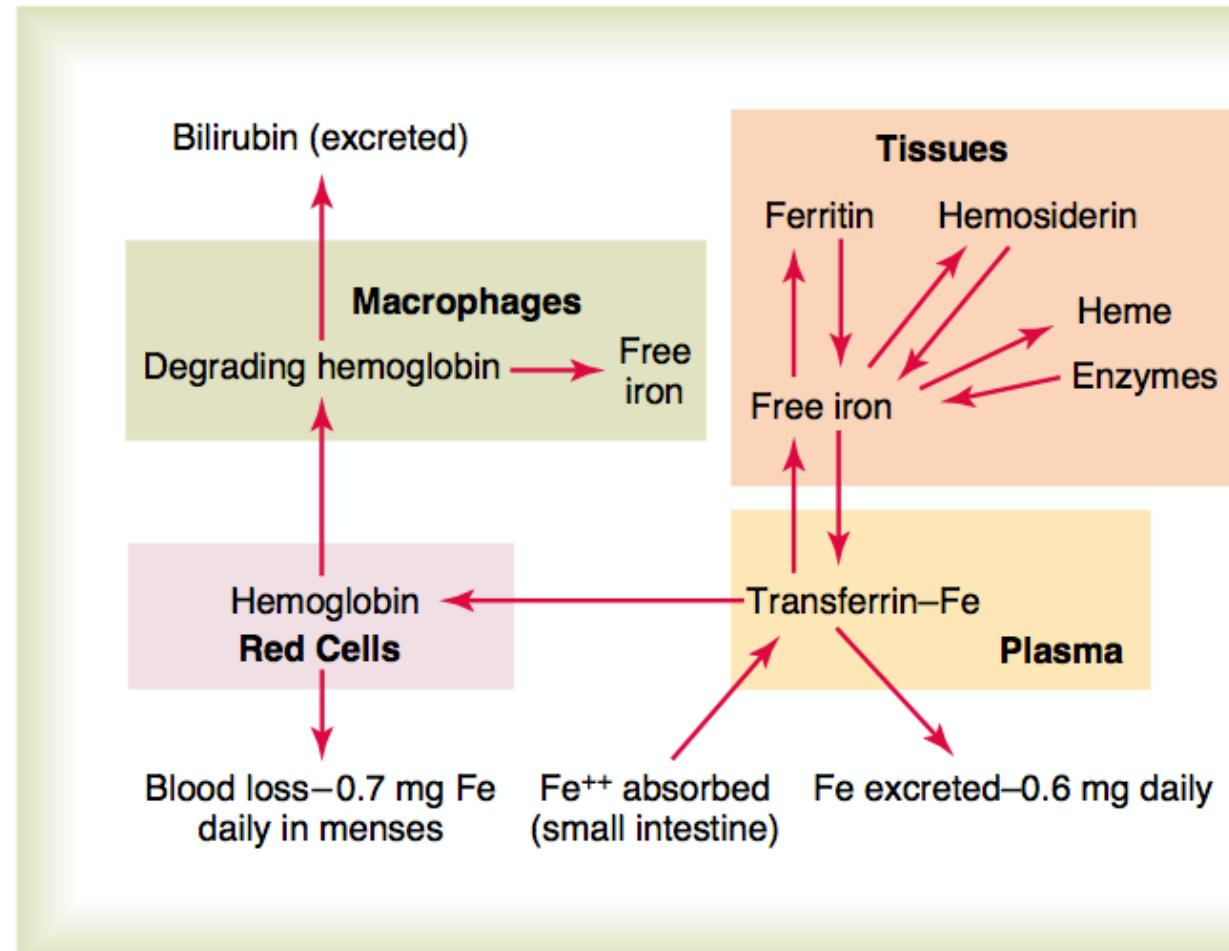


Figure 32–7

Iron transport and metabolism.

Resistance of the Body to Infection

- Our bodies have a special system for combating the different infectious and toxic agents. This is comprised of blood **leukocytes** (white blood cells) and **tissue cells** derived from leukocytes. These cells work together in two ways to prevent disease:
 - (1)destroying invading bacteria or viruses by phagocytosis
 - (2)forming antibodies and sensitized lymphocytes

■ Leukocytes (White Blood Cells)

The leukocytes, also called white blood cells, are the mobile units of the body's protective system. They are formed partially in the bone marrow (granulocytes and monocytes and a few lymphocytes) and partially in the lymph tissue (lymphocytes and plasma cells). After formation, they are transported in the blood to different parts of the body where they are needed.

➤ Types of White Blood Cells.

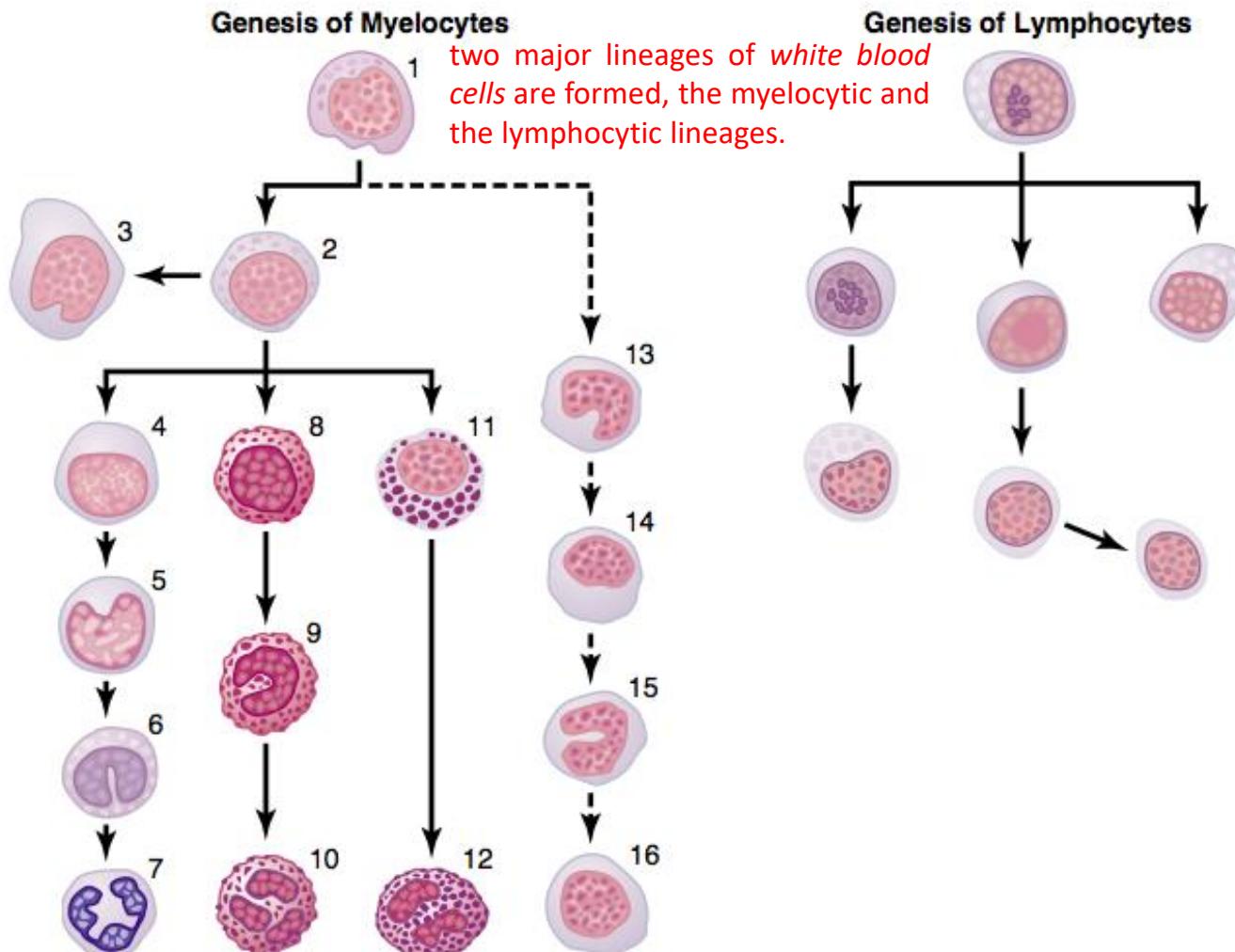
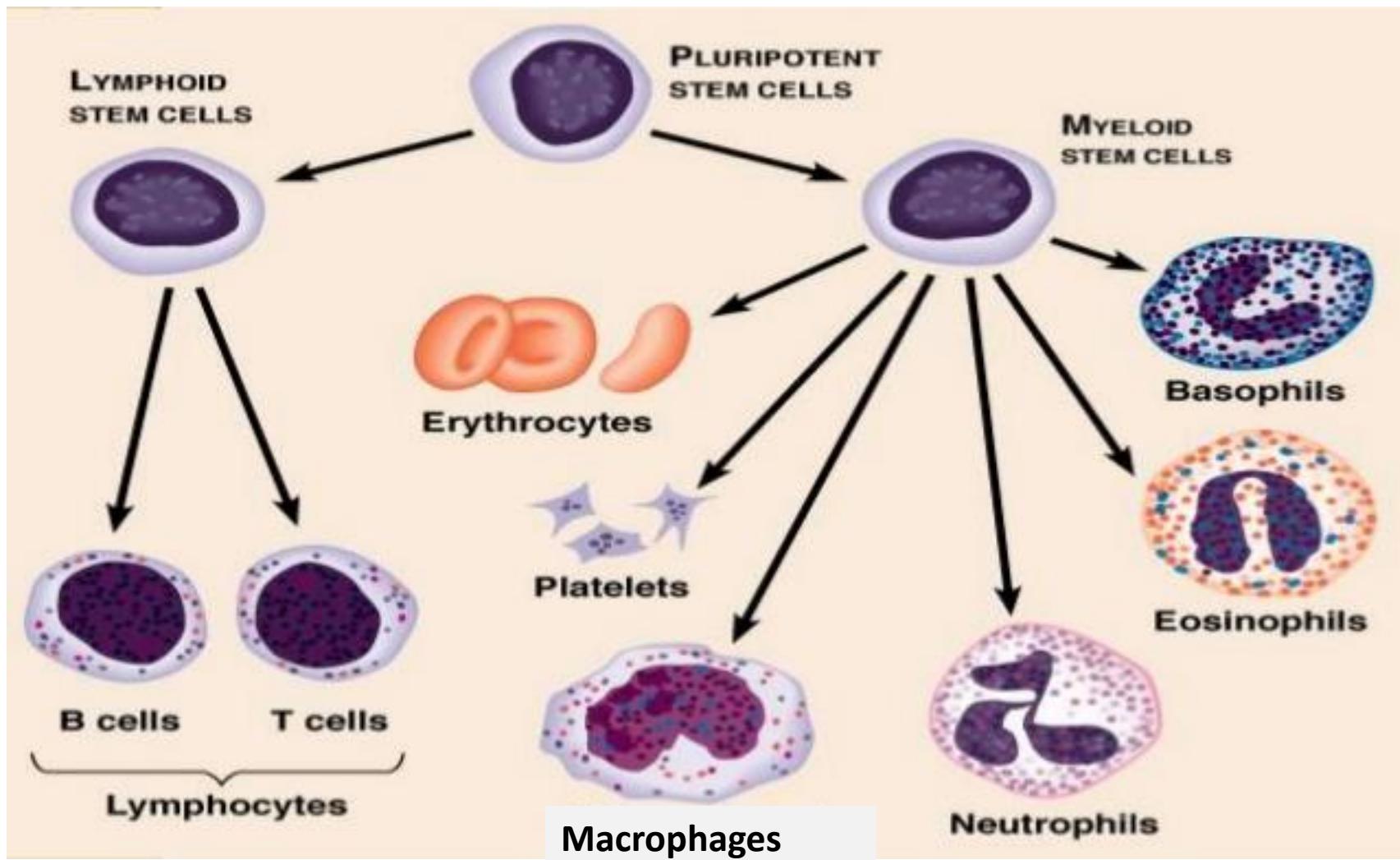


Figure 33–1

Genesis of white blood cells. The different cells of the myelocyte series are 1, myeloblast; 2, promyelocyte; 3, megakaryocyte; 4, neutrophil myelocyte; 5, young neutrophil metamyelocyte; 6, "band" neutrophil metamyelocyte; 7, polymorphonuclear neutrophil; 8, eosinophil myelocyte; 9, eosinophil metamyelocyte; 10, polymorphonuclear eosinophil; 11, basophil myelocyte; 12, polymorphonuclear basophil; 13–16, stages of monocyte formation.



➤ Neutrophils and Macrophages Defend Against Infections

- White Blood Cells Enter the Tissue Spaces by Diapedesis.
- White Blood Cells Are Attracted to Inflamed Tissue Areas by Chemotaxis.

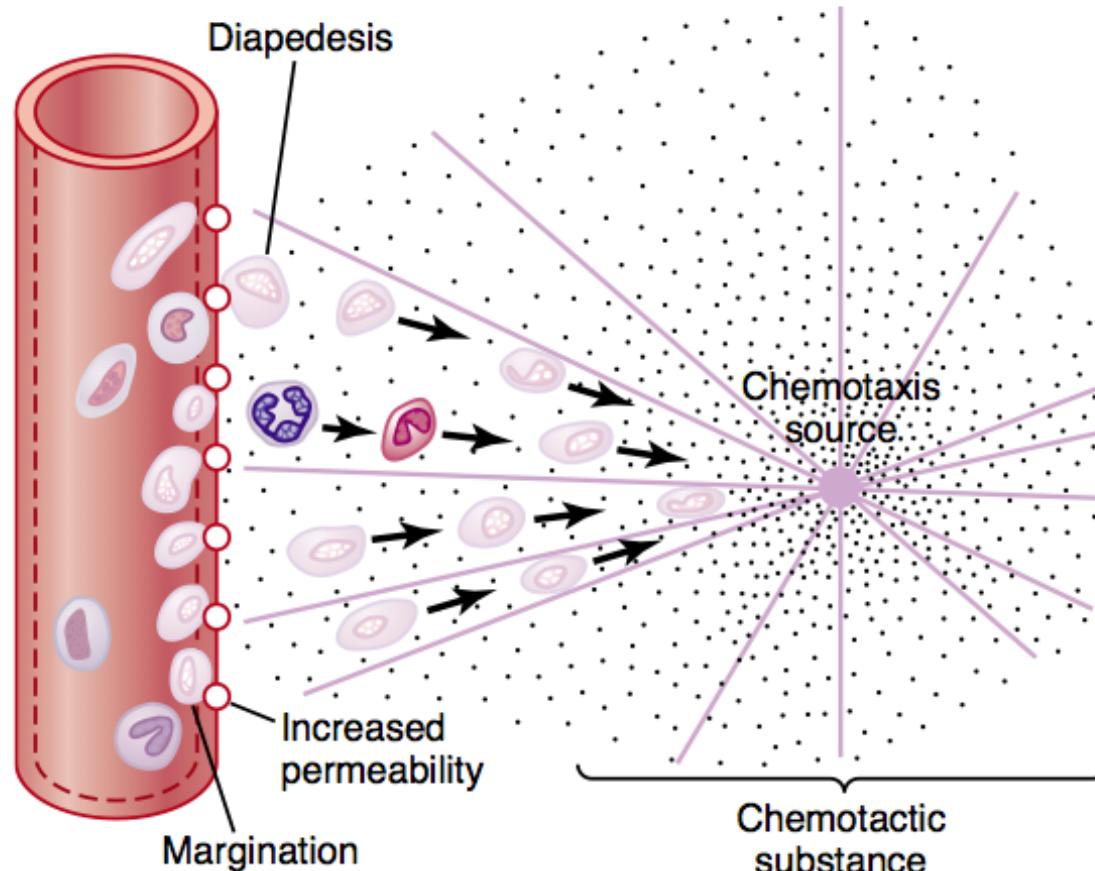


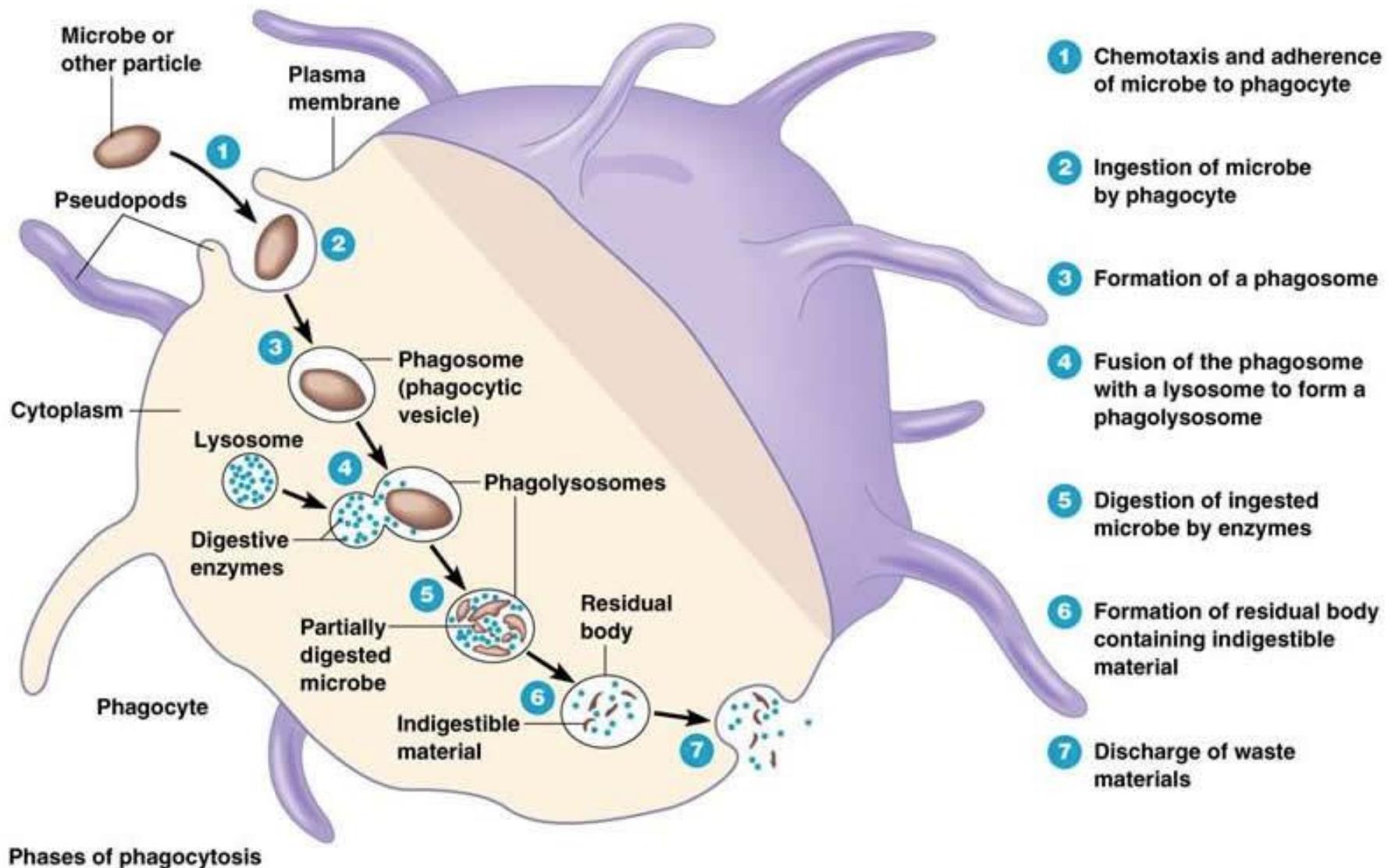
Figure 33–2

Movement of neutrophils by *diapedesis* through capillary pores and by *chemotaxis* toward an area of tissue damage.

- **NEUTROPHILS AND MACROPHAGES**
- It is mainly the ***neutrophils and tissue macrophages*** that attack and destroy invading bacteria, viruses, and other injurious agents
- The **neutrophils are mature cells** that can attack and destroy bacteria even in the circulating blood.
- the tissue macrophages **begin life as blood monocytes**, which are ***immature cells*** while still in the blood and have little ability to fight infectious agents
- once they enter the tissues, they **begin to swell** – sometimes increasing their diameters as much as fivefold – ***macrophages*** -extremely capable of combating intratissue disease agents.

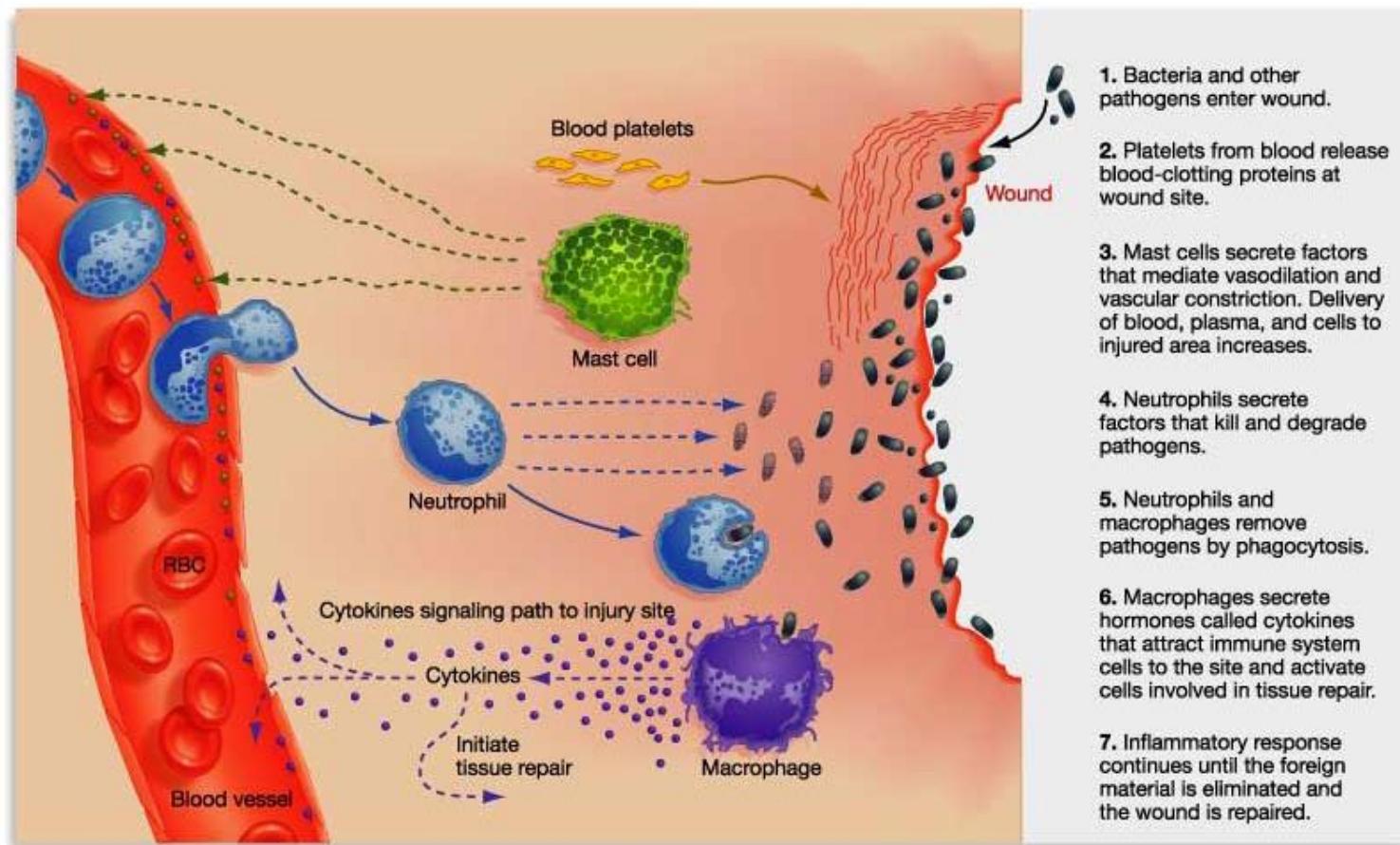
■ Phagocytosis

- The most important function of the neutrophils and macrophages is phagocytosis, which means cellular ingestion of the offending agent. Phagocytes must be selective of the material that is phagocytized; otherwise, normal cells and structures of the body might be ingested.



■ Inflammation

- When tissue injury occurs, whether caused by bacteria, trauma, chemicals, heat, or any other phenomenon, multiple substances are released by the injured tissues and cause dramatic secondary changes in the surrounding uninjured tissues. This entire complex of tissue changes is called inflammation.



■ The Leukemias

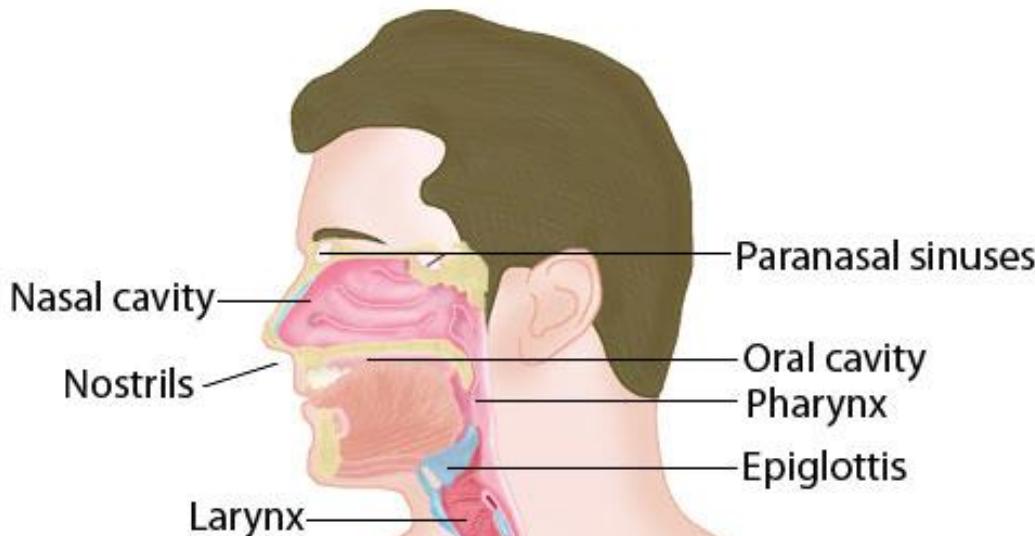
- Uncontrolled production of white blood cells can be caused by cancerous mutation of a myelogenous or lymphogenous cell. This causes leukemia, which is usually characterized by greatly increased numbers of abnormal white blood cells in the circulating blood.
- Leukemias are divided into two general types: lymphocytic leukemias and myelogenous leukemias.
- The lymphocytic leukemias are caused by cancerous production of lymphoid cells, usually beginning in a lymph node or other lymphocytic tissue and spreading to other areas of the body.
- Myelogenous leukemia, begins by cancerous production of young myelogenous cells in the bone marrow and then spreads throughout the body so that white blood cells are produced in many extramedullary tissues—especially in the lymph nodes, spleen, and liver.

Respiratory Anatomy
37. Pulmonary Ventilation
Gas Exchange
Gas Transport

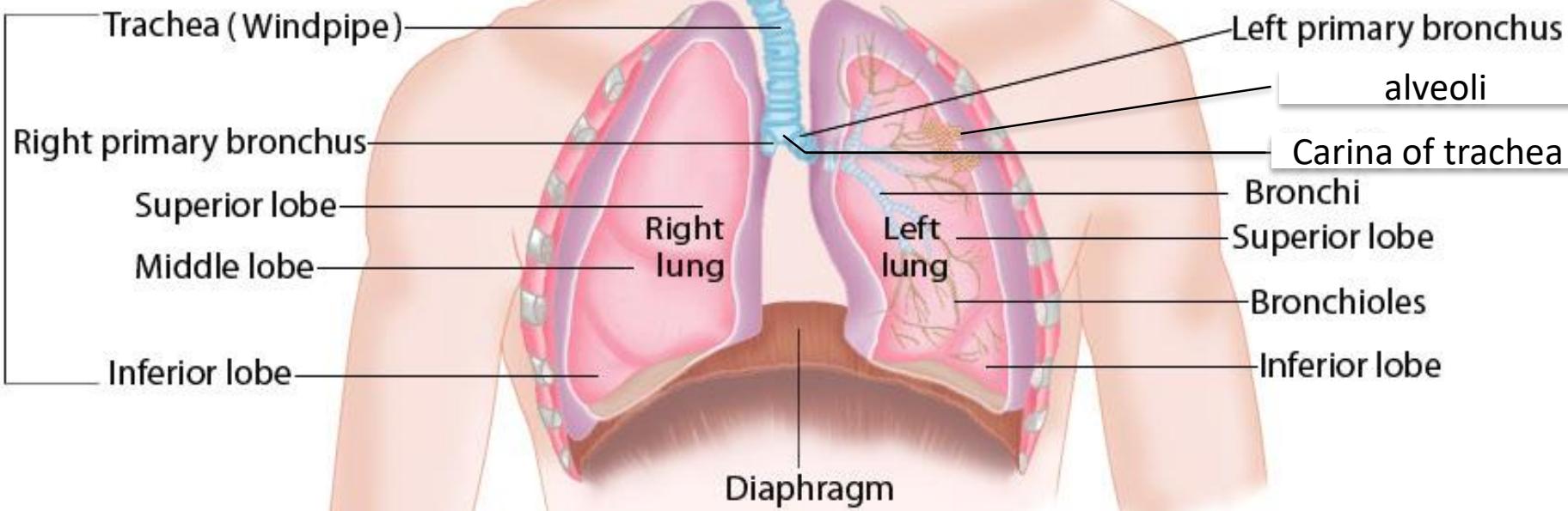
- Respiratory system is responsible for inhaling oxygen and carrying out the exchange of oxygen and carbon dioxide in the human body
- It has specific respiratory organs, blood vessels and muscles.
- Main functions of the respiratory system:
 - ✓ Providing oxygen and removing carbondioxide for metabolism in tissues
 - ✓ Protecting respiratory surfaces from dehydration, temperature changes
 - ✓ Defending the respiratory system and other tissues from invasion by pathogenic microorganisms
 - ✓ Producing sounds involved in speaking, singing, or nonverbal communication
 - ✓ Assisting in the regulation of blood volume, blood pressure, and the control of body fluid pH

Airway Anatomy

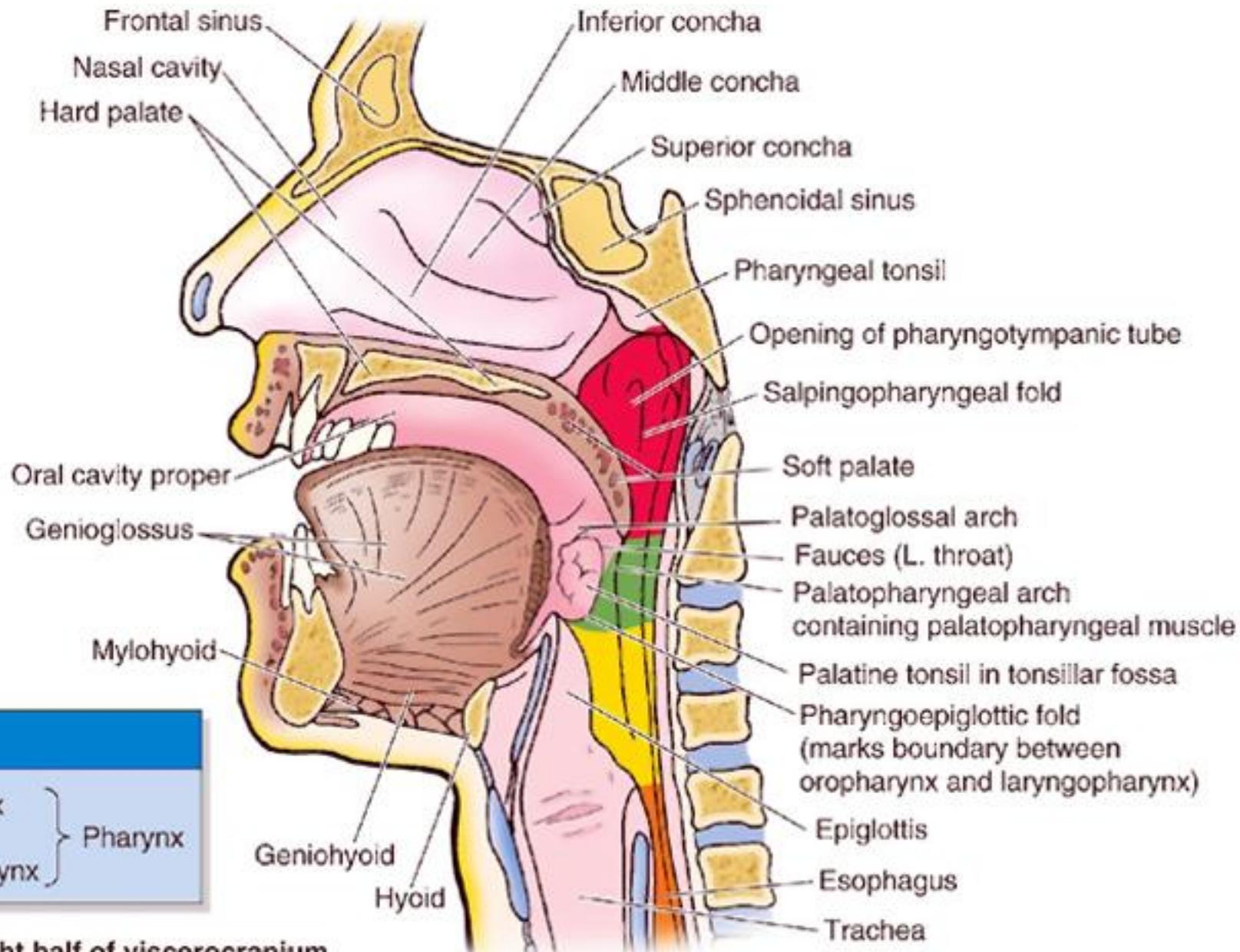
Upper Respiratory Tract



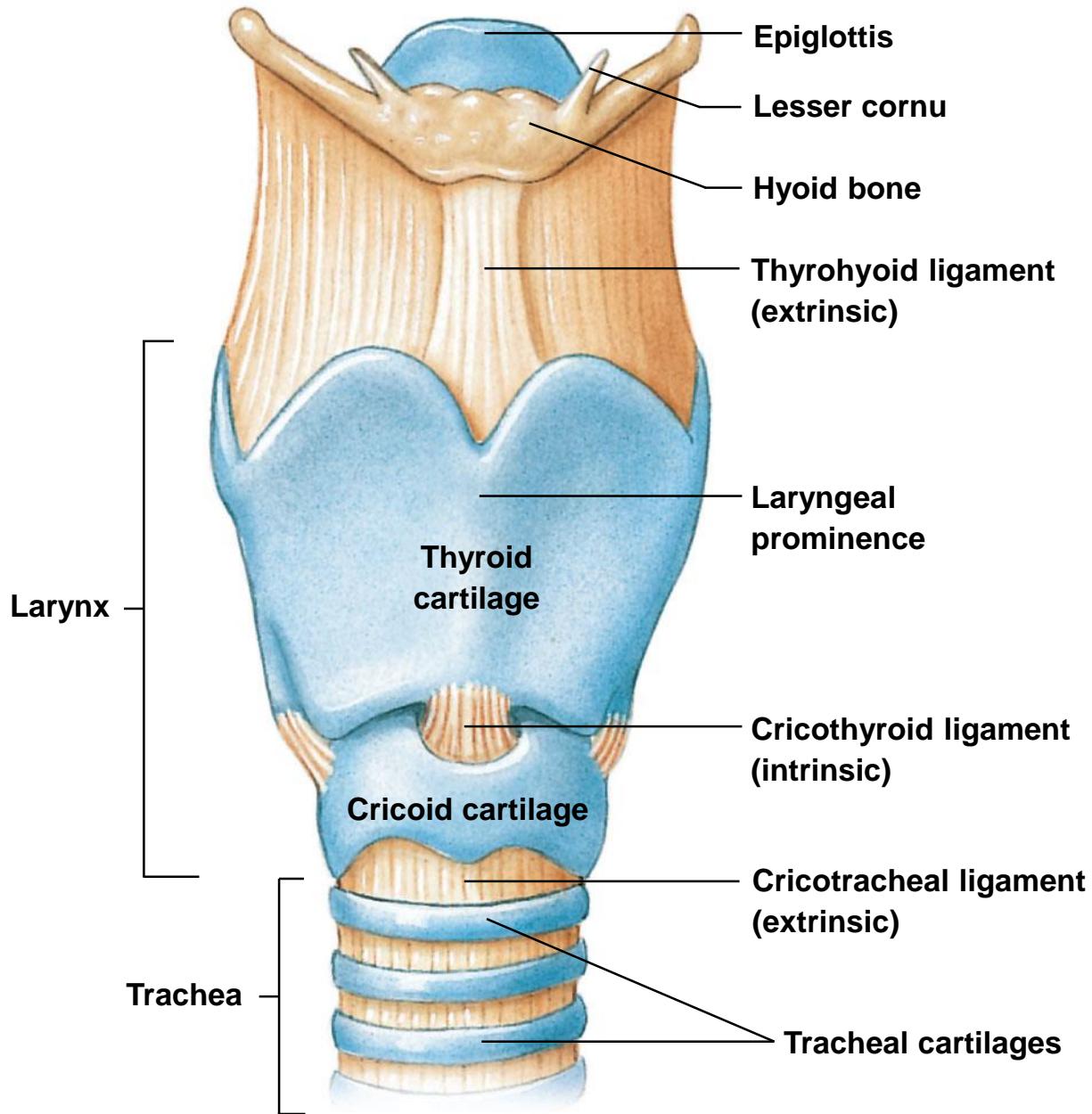
Lower Respiratory Tract



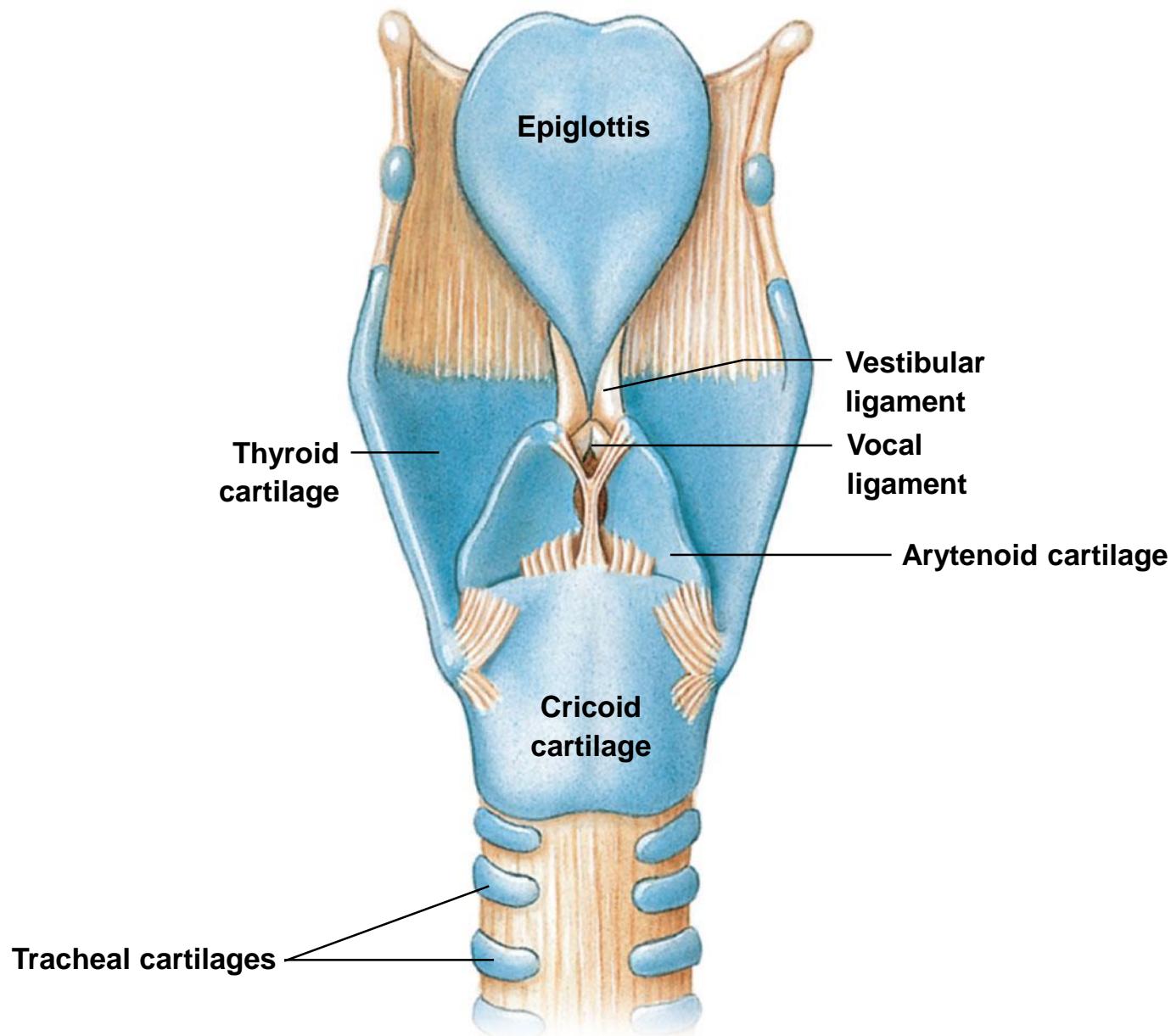
➤ anatomy of upper respiratory system



Medial view of right half of viscerocranum

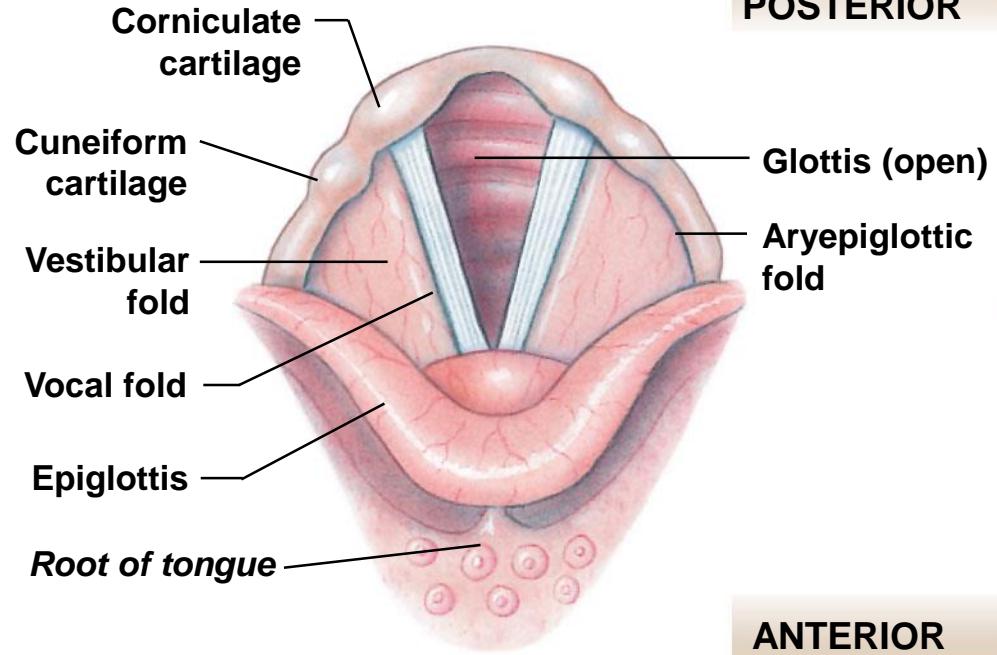


Anterior view of the intact larynx

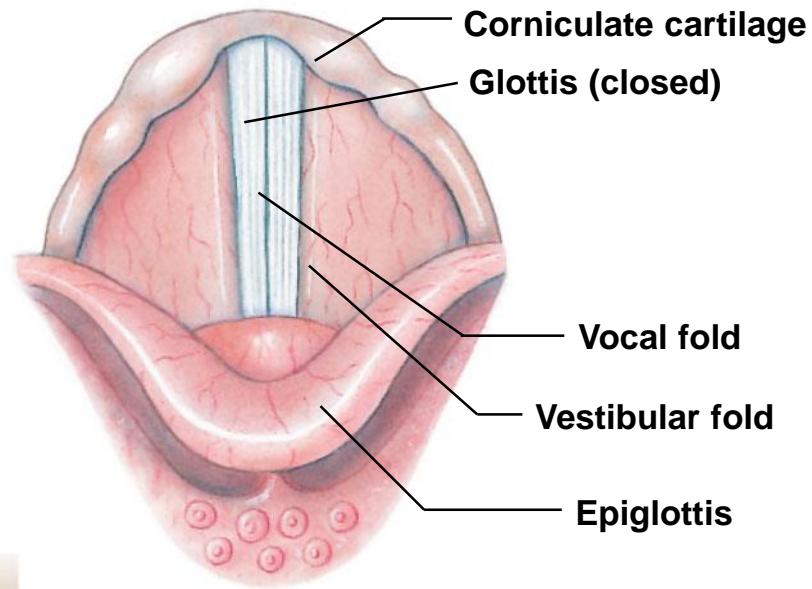


Posterior view of the intact larynx

The Vocal Cords



Glottis in the open position

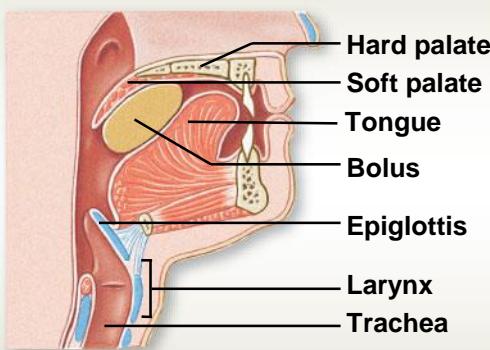


Glottis in the closed position

Movements of the Larynx during Swallowing

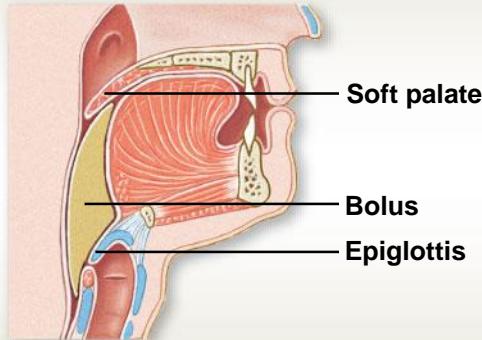
1

Tongue forces compacted bolus into oropharynx.



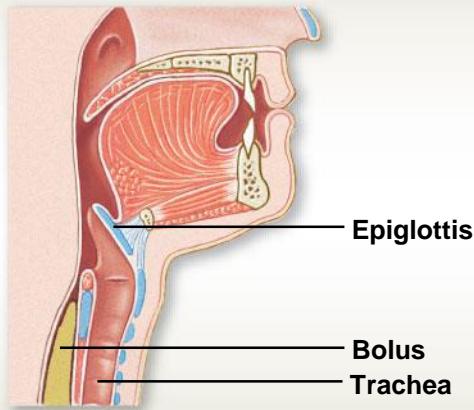
2

Laryngeal movement folds epiglottis; pharyngeal muscles push bolus into esophagus.

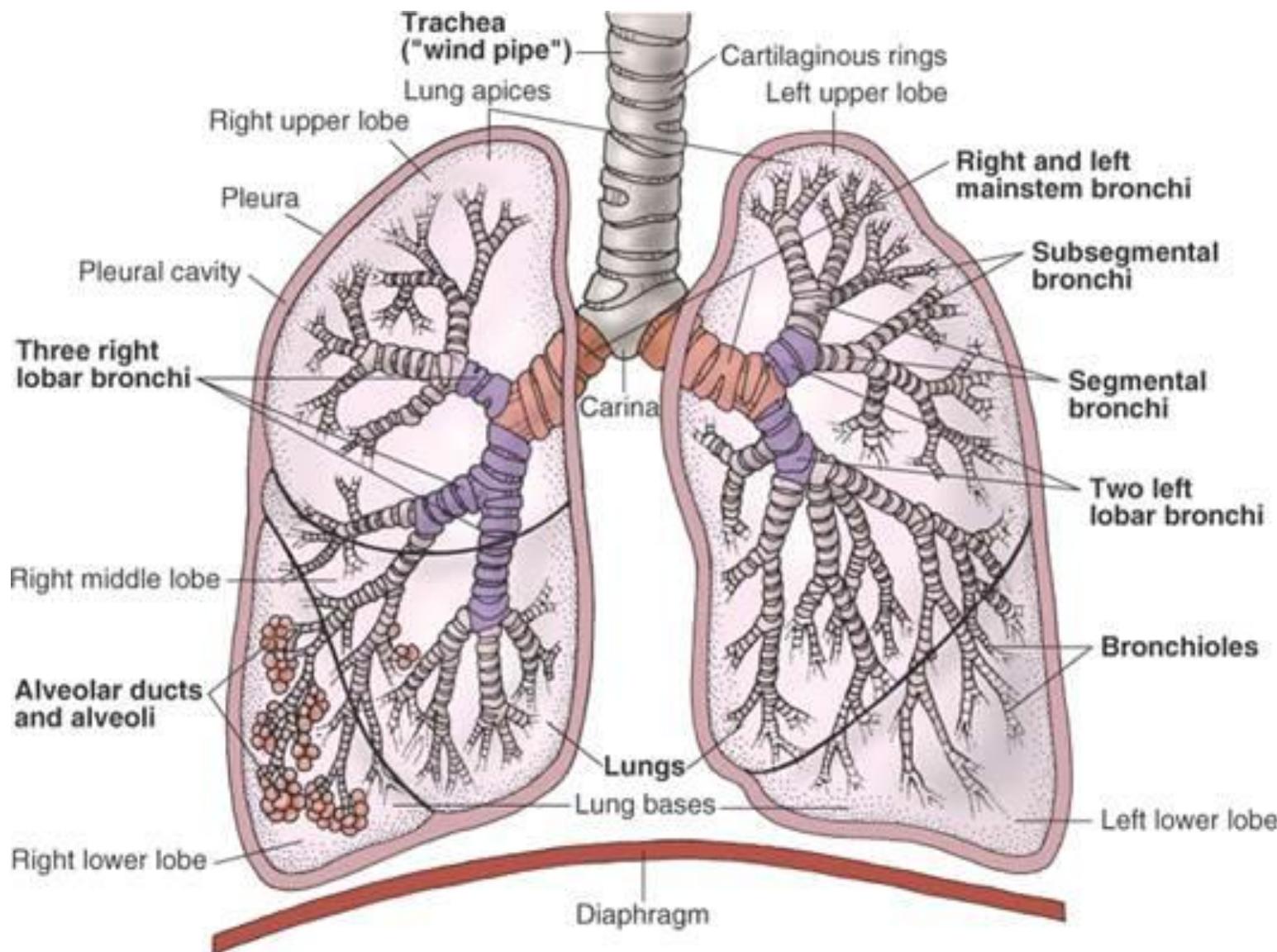


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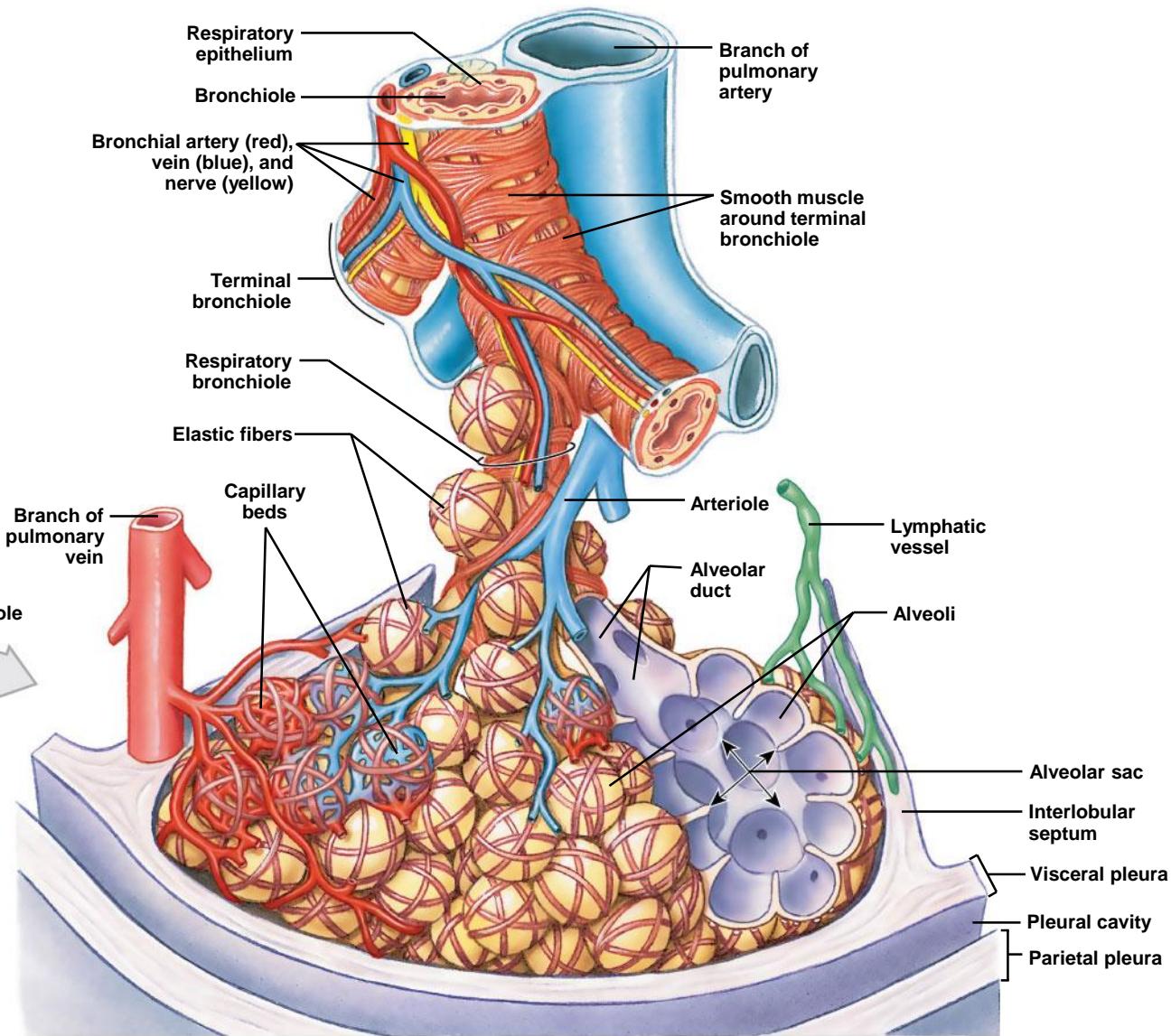
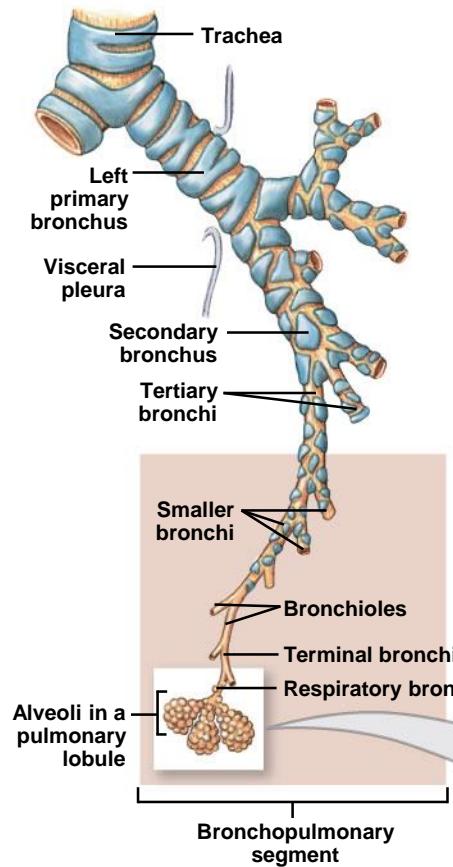
Bolus moves along esophagus; larynx returns to normal position.



➤ anatomy of lower respiratory system



Bronchi and Bronchioles

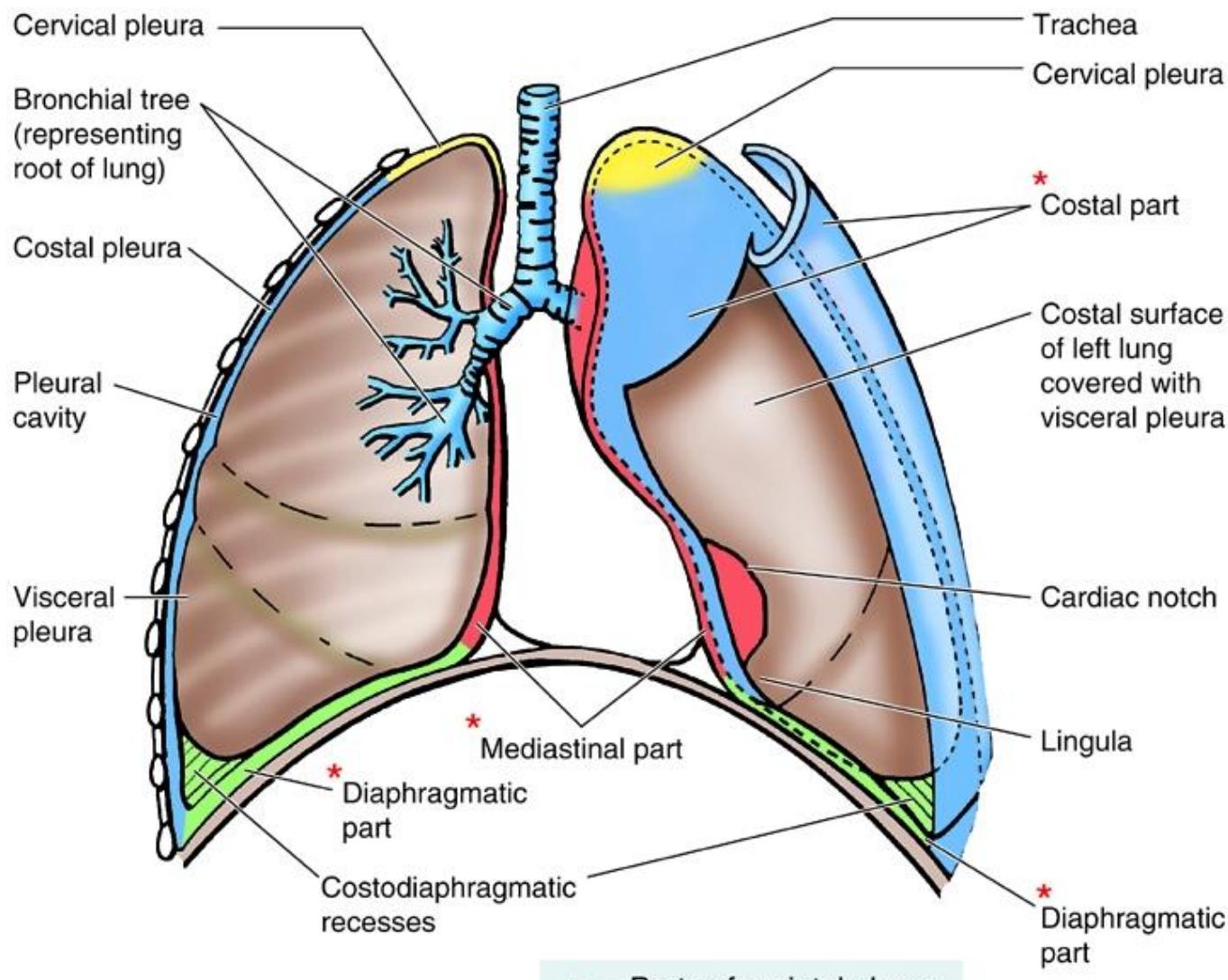


a The structure of one portion of a single pulmonary lobule

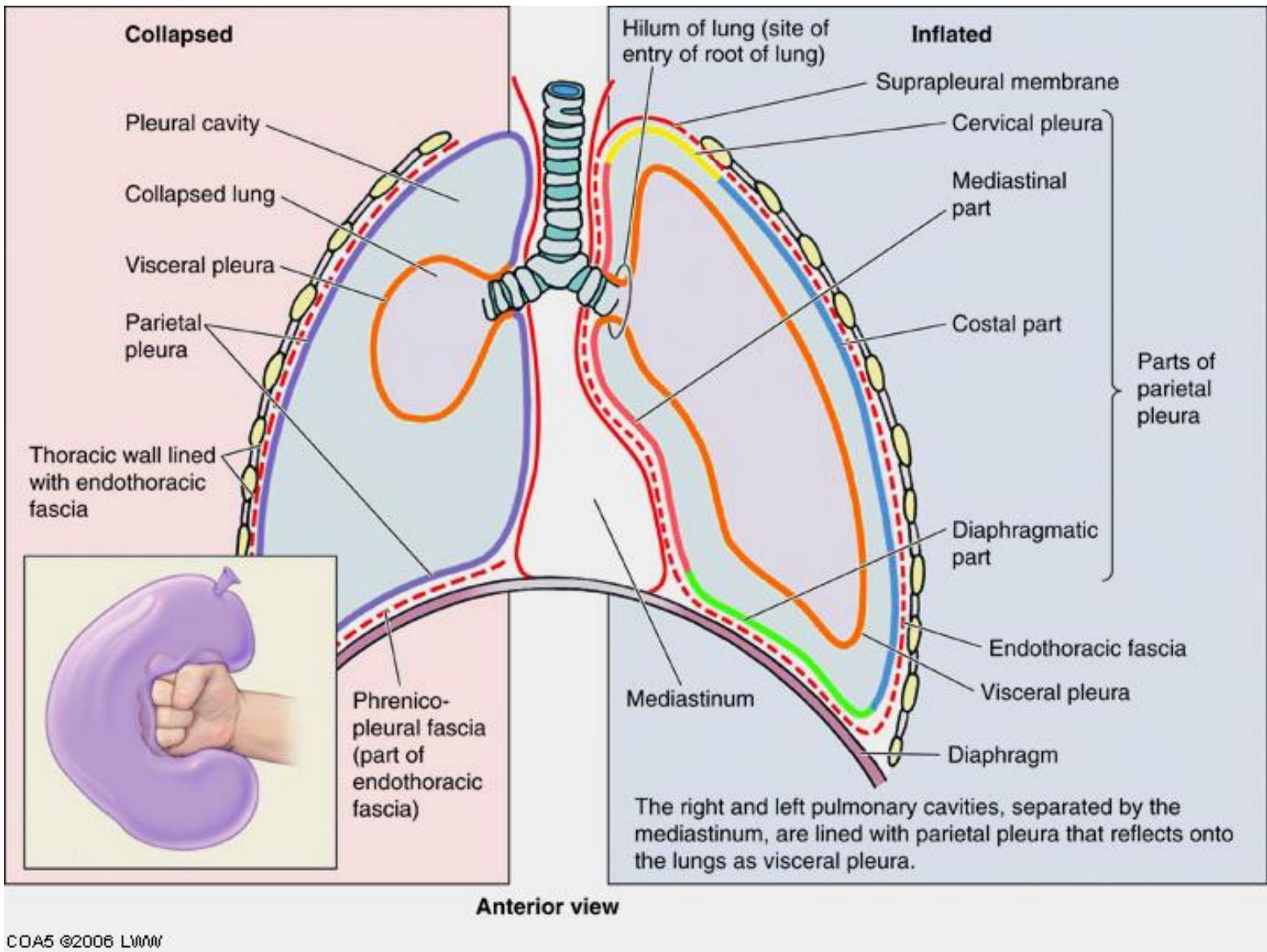
Table 22.1 Principal Organs of the Respiratory System

STRUCTURE	DESCRIPTION, GENERAL AND DISTINCTIVE FEATURES	FUNCTION
Nose (external nose and nasal cavity)	Jutting external portion is supported by bone and cartilage. Internal nasal cavity is divided by midline nasal septum and lined with mucosa. Roof of nasal cavity contains olfactory epithelium.	Produces mucus; filters, warms, and moistens incoming air; resonance chamber for speech Receptors for sense of smell
Paranasal sinuses	Mucosa-lined, air-filled cavities in cranial bones surrounding nasal cavity.	Same as for nasal cavity except no receptors for smell; also lighten skull
Pharynx	Passageway connecting nasal cavity to larynx and oral cavity to esophagus. Three subdivisions: nasopharynx, oropharynx, and laryngopharynx. Houses tonsils (lymphoid tissue masses involved in protection against pathogens).	Passageway for air and food Facilitates exposure of immune system to inhaled antigens
Larynx	Connects pharynx to trachea. Has framework of cartilage and dense connective tissue. Opening (glottis) can be closed by epiglottis or vocal folds. Houses vocal folds (true vocal cords).	Air passageway; prevents food from entering lower respiratory tract Voice production
Trachea	Flexible tube running from larynx and dividing inferiorly into two main bronchi. Walls contain C-shaped cartilages that are incomplete posteriorly where connected by trachealis.	Air passageway; cleans, warms, and moistens incoming air
Bronchial tree	Consists of right and left main bronchi, which subdivide within the lungs to form lobar and segmental bronchi and bronchioles. Bronchiolar walls lack cartilage but contain complete layer of smooth muscle. Constriction of this muscle impedes expiration.	Air passageways connecting trachea with alveoli; cleans, warms, and moistens incoming air
Alveoli	Microscopic chambers at termini of bronchial tree. Walls of simple squamous epithelium overlie thin basement membrane. External surfaces are intimately associated with pulmonary capillaries. Special alveolar cells produce surfactant.	Main sites of gas exchange Reduces surface tension; helps prevent lung collapse
Lungs	Paired composite organs that flank mediastinum in thorax. Composed primarily of alveoli and respiratory passageways. Stroma is fibrous elastic connective tissue, allowing lungs to recoil passively during expiration.	House respiratory passages smaller than the main bronchi
Pleurae	Serous membranes. Parietal pleura lines thoracic cavity; visceral pleura covers external lung surfaces.	Produce lubricating fluid and compartmentalize lungs

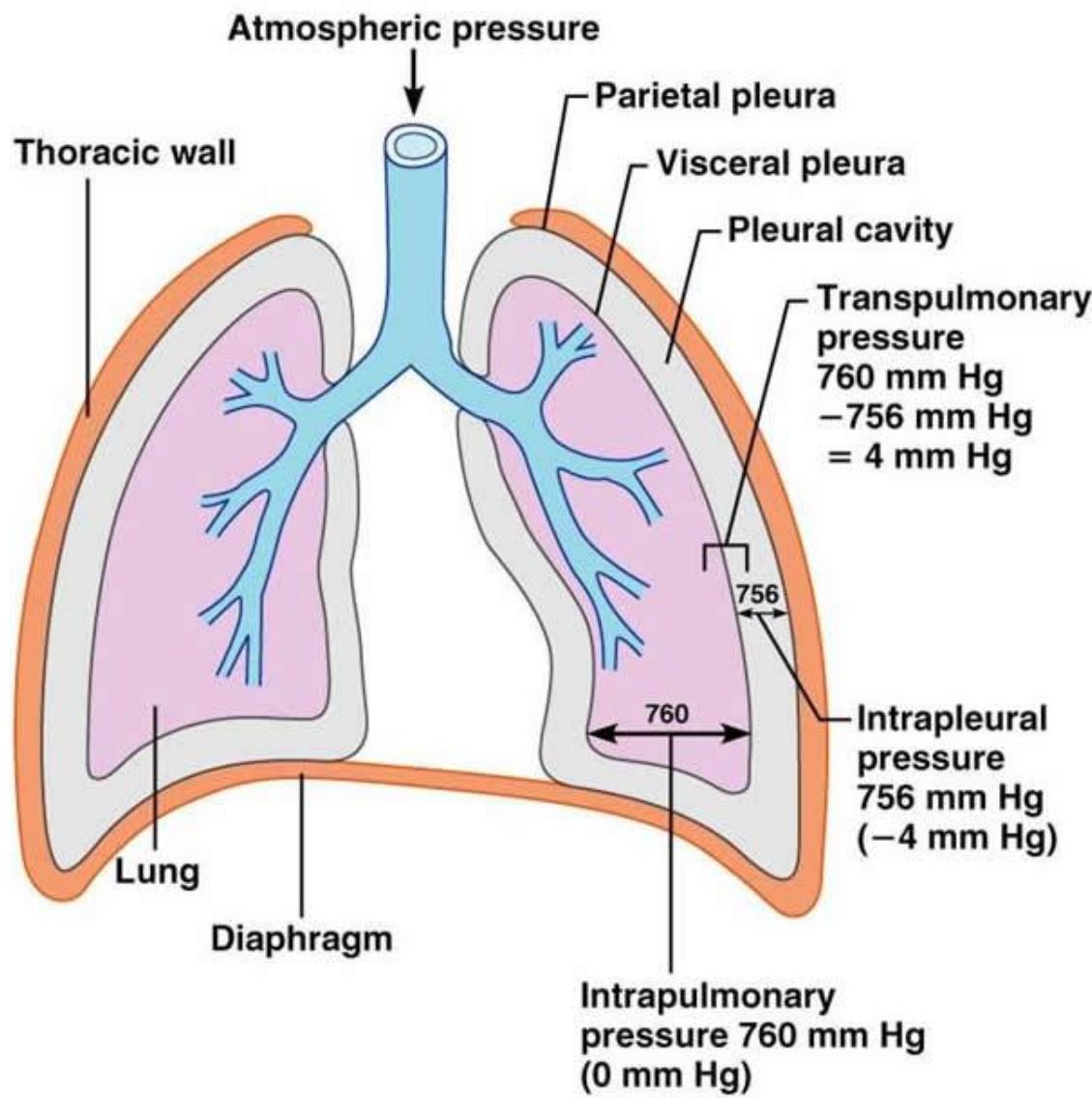
➤ pleura



Anterior view



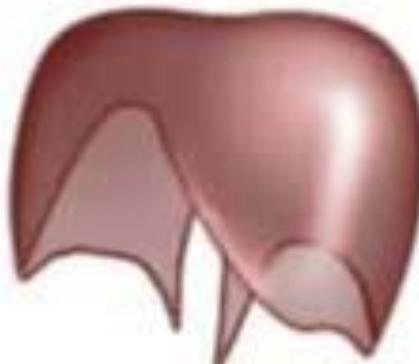
- **Intrapleural pressure** is the pressure in the pleural cavity. It also rises and falls during respiration, but is always about 4 mm Hg less than **intrapulmonary pressure**.



➤ Diaphragm

- acts as a separating sheath between the chest cavity and the abdominal cavity.
- composed of both muscle and tendon

Watch
video
#19,20,21



The diaphragm
is shaped
like a parachute



- # Respiratory Muscles

- **Inspiratory muscles**
 - Diaphragm
 - External intercostal muscles
- **Expiratory muscles**
 - Usually not needed due to elastic recoil of lungs and thoracic cavity
- **Accessory respiratory muscles**
 - Inspiration
 - Sternocleidomastoid, serratus anterior, pectoralis minor, and scalene muscles
 - Expiration
 - Transversus thoracis, oblique, and rectus abdominis muscles
 - Internal intercostal muscles

Accessory Muscles of Inspiration

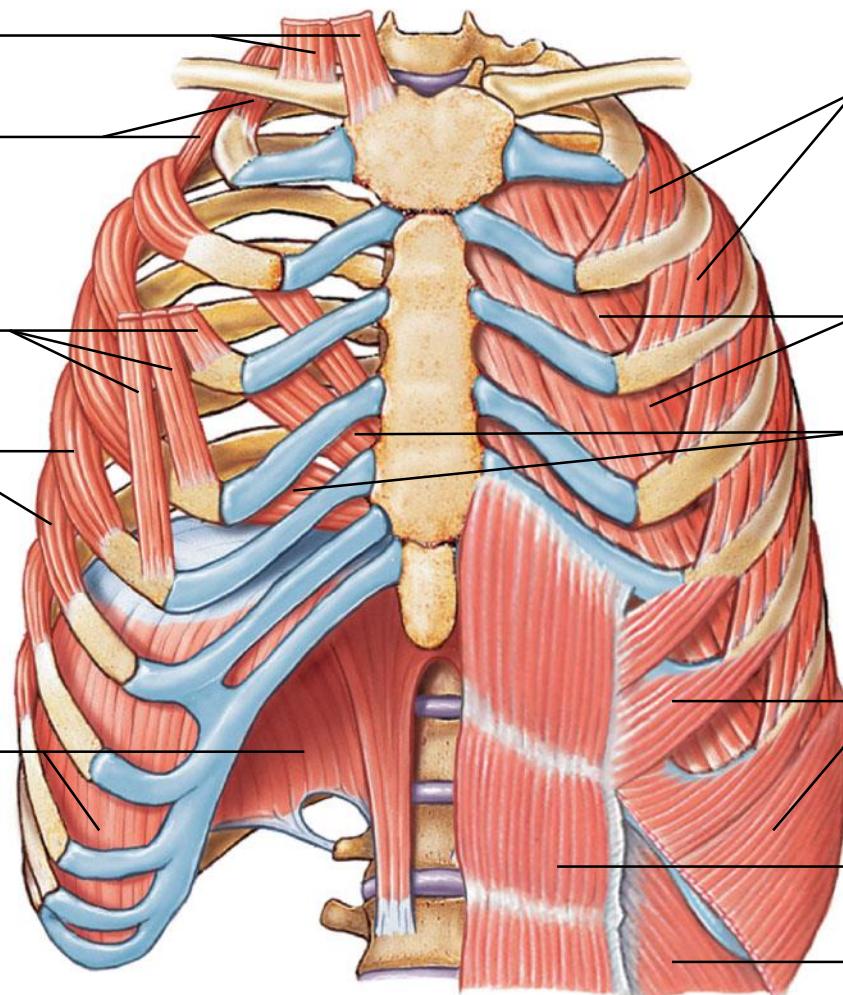
Sternocleidomastoid muscle

Scalene muscles

Pectoralis minor muscle

Serratus anterior muscle

Diaphragm



Accessory Muscles of Exhalation

Internal intercostal muscles

Transversus thoracis muscle

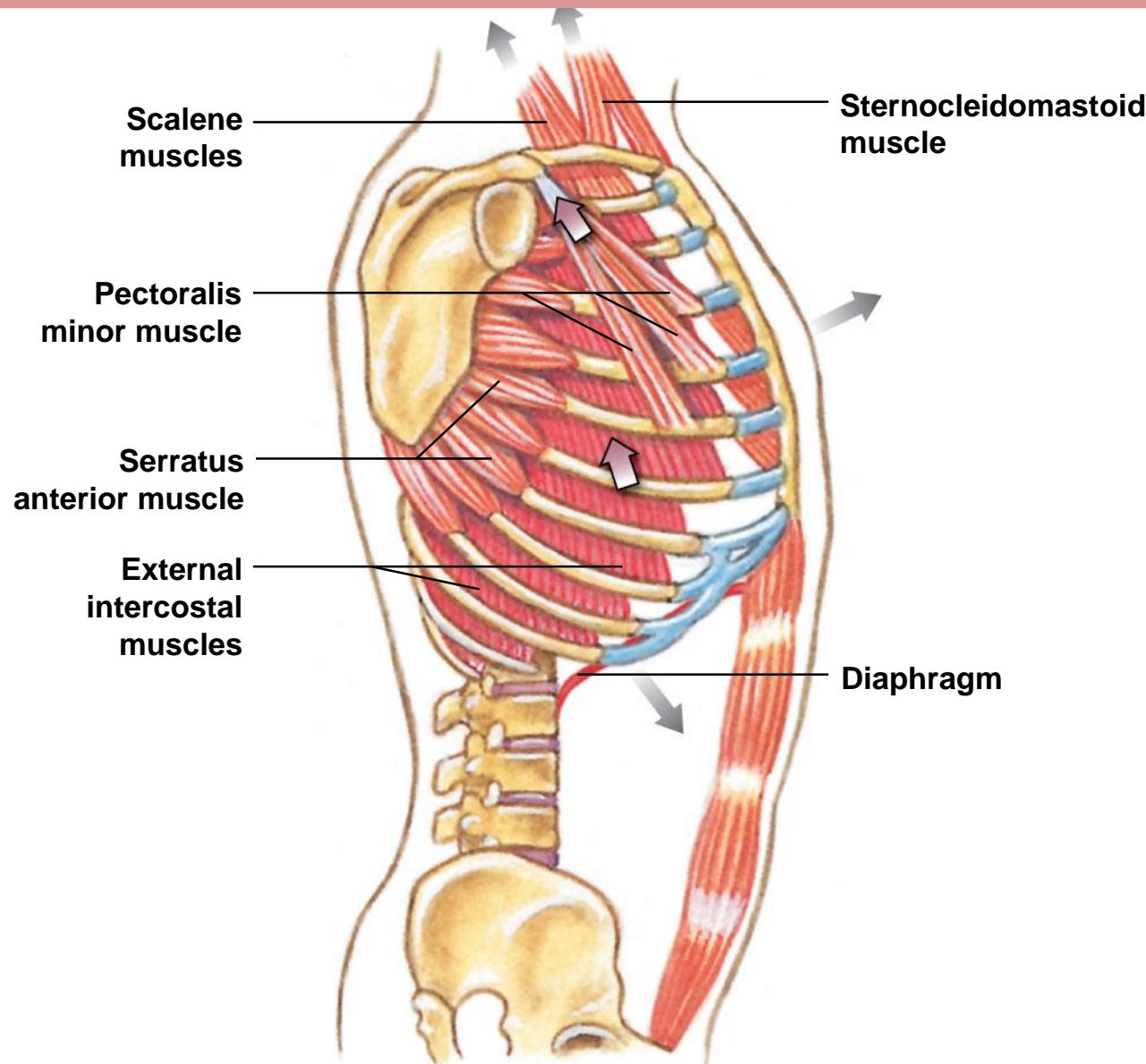
External oblique muscle

Rectus abdominus

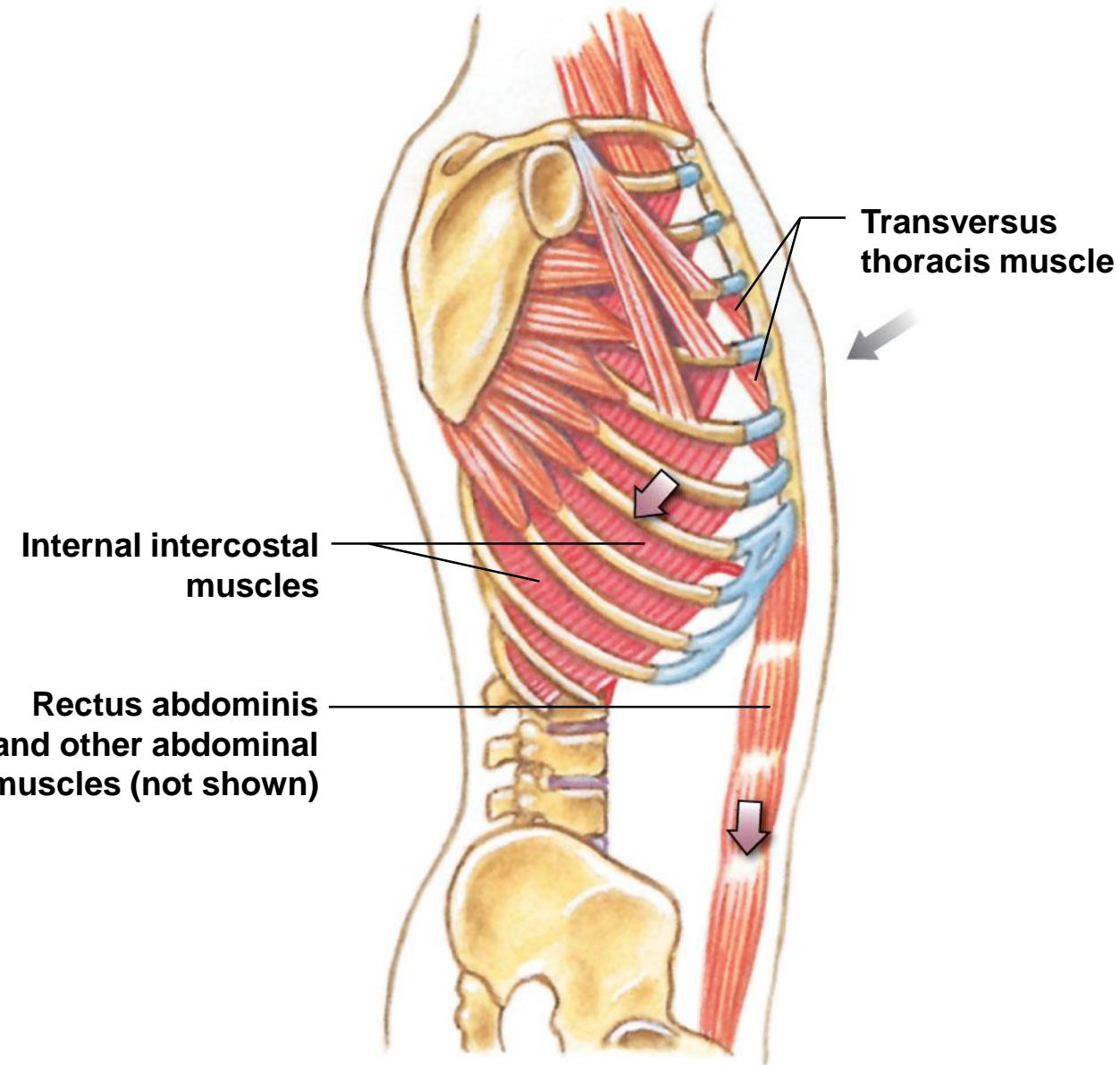
Internal oblique muscle

b The primary and accessory muscles of respiration

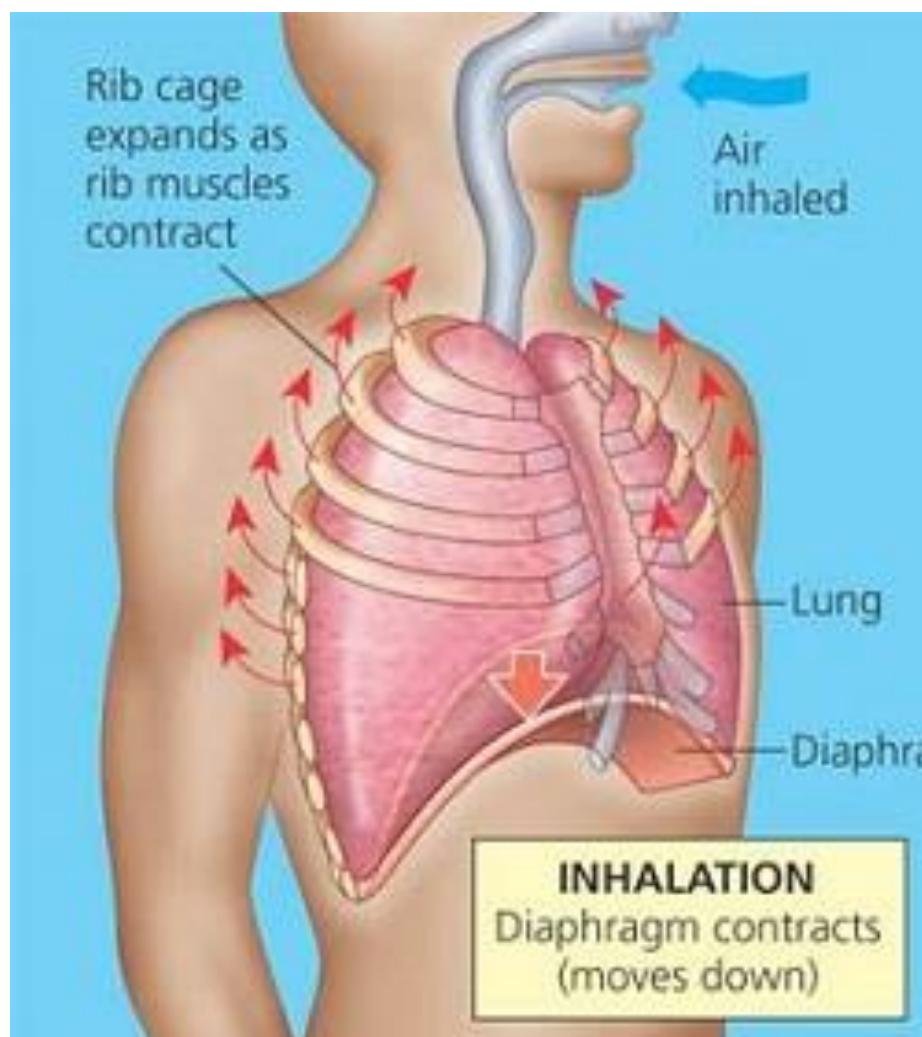
Mechanics of Respiration



Inhalation, showing the primary and accessory respiratory muscles that elevate the ribs and flatten the diaphragm.

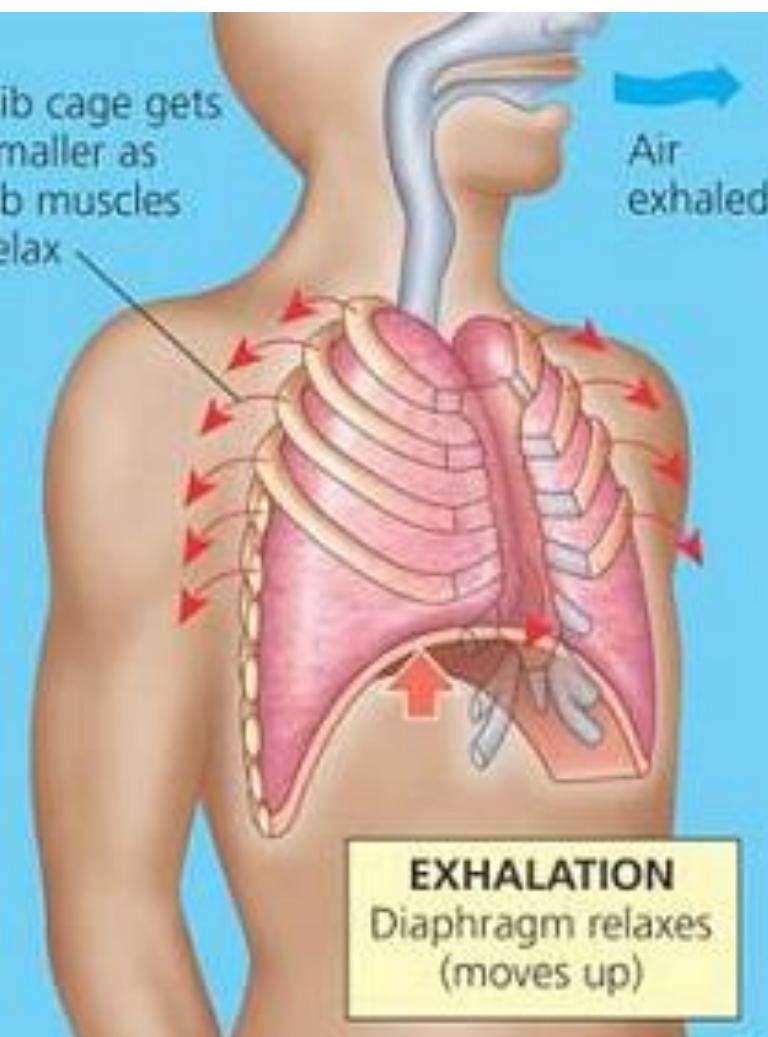


Exhalation, showing the primary and accessory respiratory muscles that depress the ribs and elevate the diaphragm.



Rib cage expands as rib muscles contract

Air inhaled



Rib cage gets smaller as rib muscles relax

Air exhaled

Lung

Diaphragm

INHALATION
Diaphragm contracts
(moves down)

EXHALATION
Diaphragm relaxes
(moves up)

Mechanics of Respiration- (cont.)

➤ MVPA Process



M
Muscle &
Movement

V
Volume

P
Pressure (relative to
atmosphere)

A
Air flow (H to L)

Mechanics of Respiration- (cont.)

➤ Inspiration at REST

- **Diaphragm muscle**

contracts-flattens,
lowering dome when
contracted

- **External intercostal
Muscles**

contract to move ribs
up & out

When thorax
expands.

So do parietal and
visceral pleurae.

**Lung Volume
increases**

**Alveolar Pressure
drops**

(lower than the
atmospheric
pressure)

Air moves IN

From atmosphere
to alveoli

Inspiration at REST → active

Mechanics of Respiration- (cont.)

➤ Expiration at REST

- Respiratory muscles relax

When thorax returns to resting volume.

Lung Volume decreases

Alveolar Pressure increases

(higher than atmospheric pressure)

Air moves OUT

From alveoli to atmosphere

Inspiration at REST → passive

Mechanics of Respiration- (cont.)

Inspiration During Exercise

- Accessory muscles help deeper breathing and increase TV
- External intercostal muscles & diaphragm contract

Larger Volume
Increase in lungs

Larger pressure reduction
(relative to atmosphere)

**More Air flows
(sucked faster)
into lungs**

Inspiration at EXERCISE → active

Mechanics of Respiration- (cont.)

Expiration During Exercise

- Accessory muscles makes expiration **FORCED**
- External intercostal muscles & diaphragm relax
- Internal intercostal contract to force ribs to normal position

Volume is forcibly reduced.

Pressure quickly increase (relative to atmosphere)

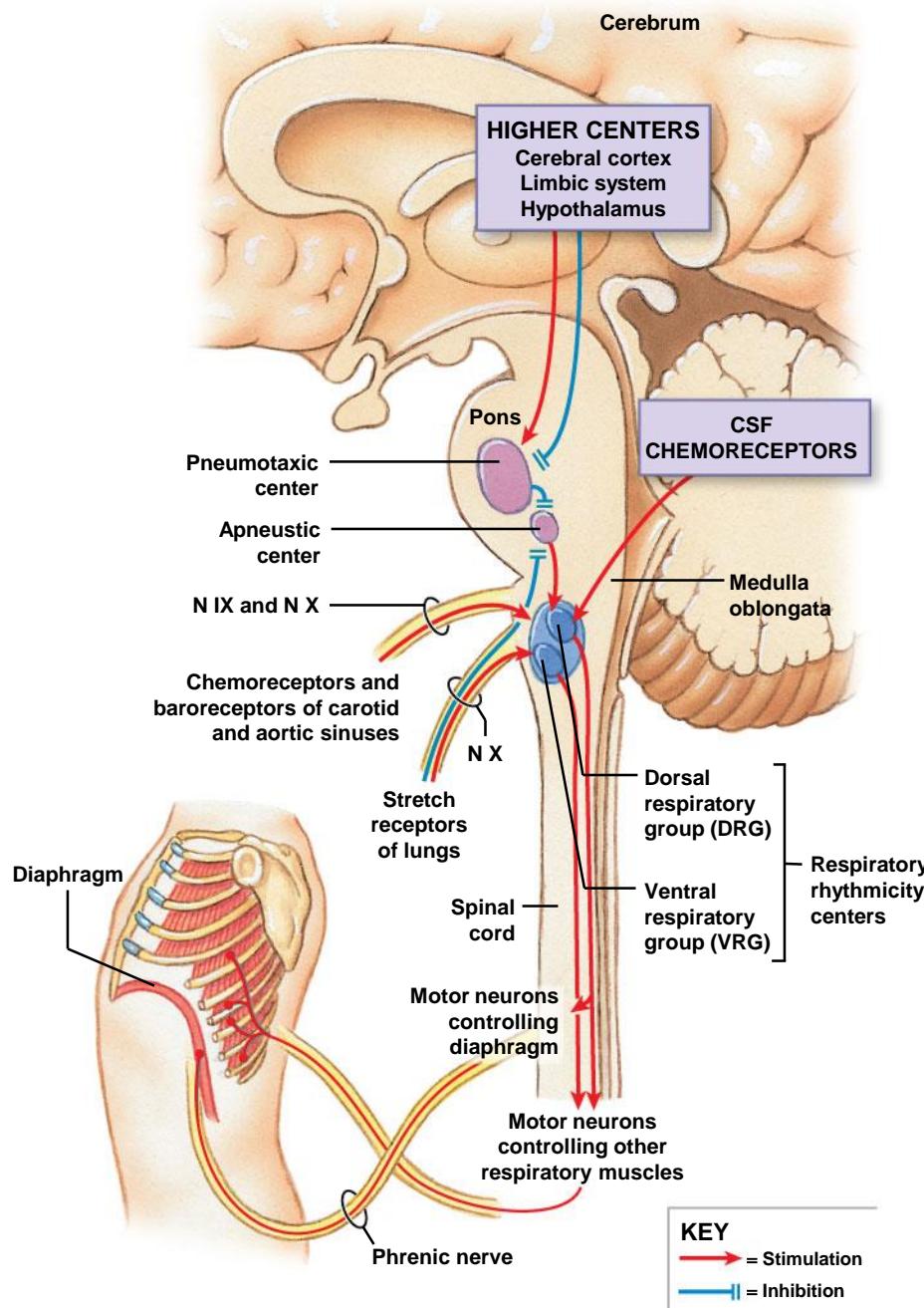
More Air is forced out faster

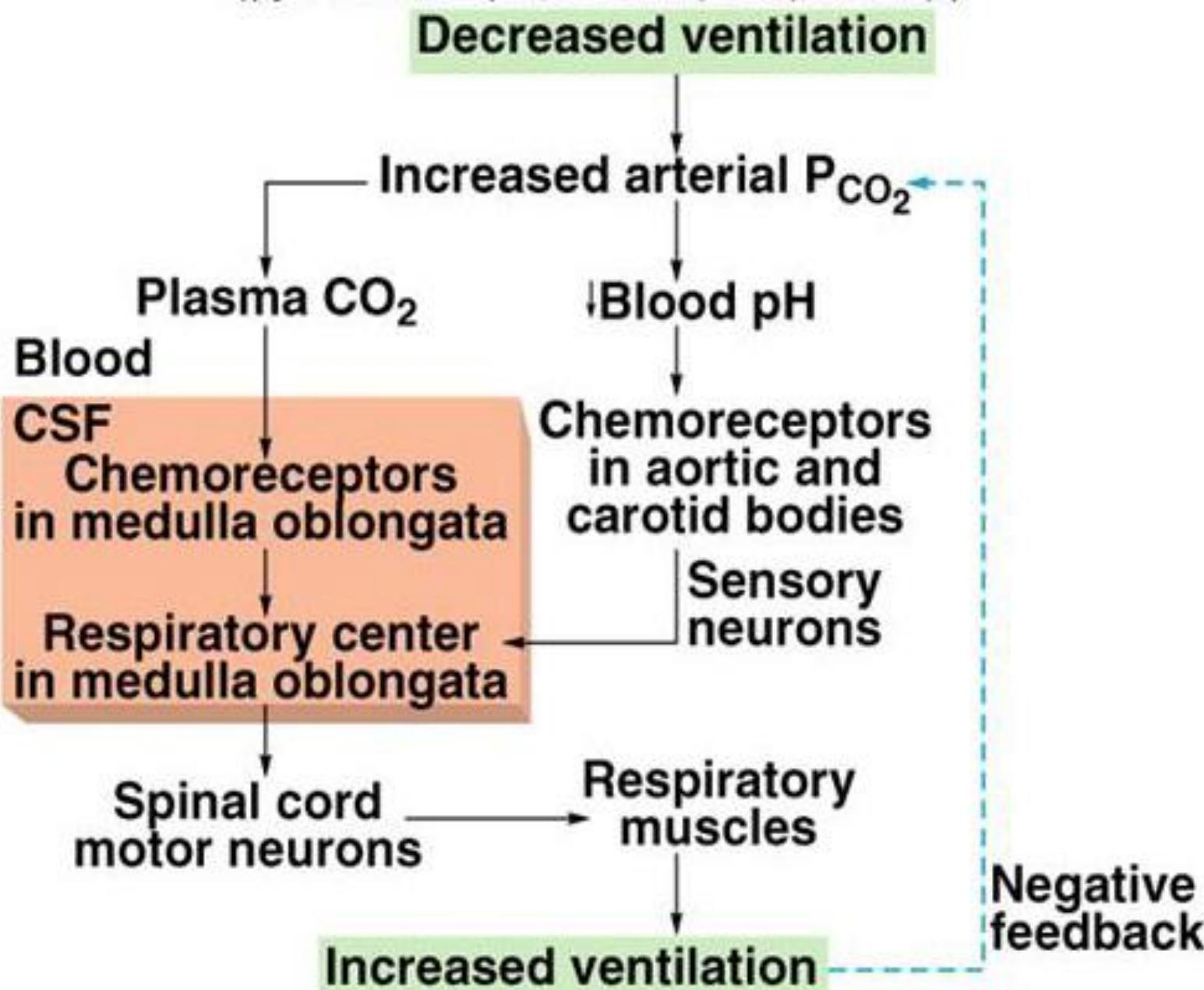
Inspiration at EXERCISE → active

Mechanics of Respiration- (cont.)

SUMMARY	REST		DURING EXERCISE	
	INSPIRATION	EXPIRATION	INSPIRATION	EXPIRATION
(M) Muscles	External intercostal muscles & diaphragm CONTRACT (Active)	External intercostal muscles & diaphragm RELAX (Passive)	External intercostals & diaphragm CONTRACT (Active) Sternocleidomastoid, Scalenes and Pectoralis minor contract to exaggerate action (Active)	External IC and diaphragm relax (Passive) Internal intercostals & diaphragm CONTRACT to force ribs to normal position Rectus abdominus and Lat Dorsi contract to exaggerate action (Active)
(M) Movement	Rib cage pulled up and out and diaphragm flattens	D – dome-shaped and ribs in and down	Greater expansion of thoracic cavity	More forceful reduction in cavity
(V) Volume	INCREASES	DECREASES	Greater and faster Increase in volume	Greater and faster decrease in volume
(P) Pressure	LOW (in comparison to atmospheric air outside body)	HIGH	VV LOW	VV HIGH
(A) Air movement	AIR SUCKED IN – HIGH TO LOW PRESSURE	AIR MOVES OUT – HIGH TO LOW PRESSURE	MORE AIR FORCED IN – high to low	MORE AIR FORCED OUT – HIGH TO LOW PRESSURE

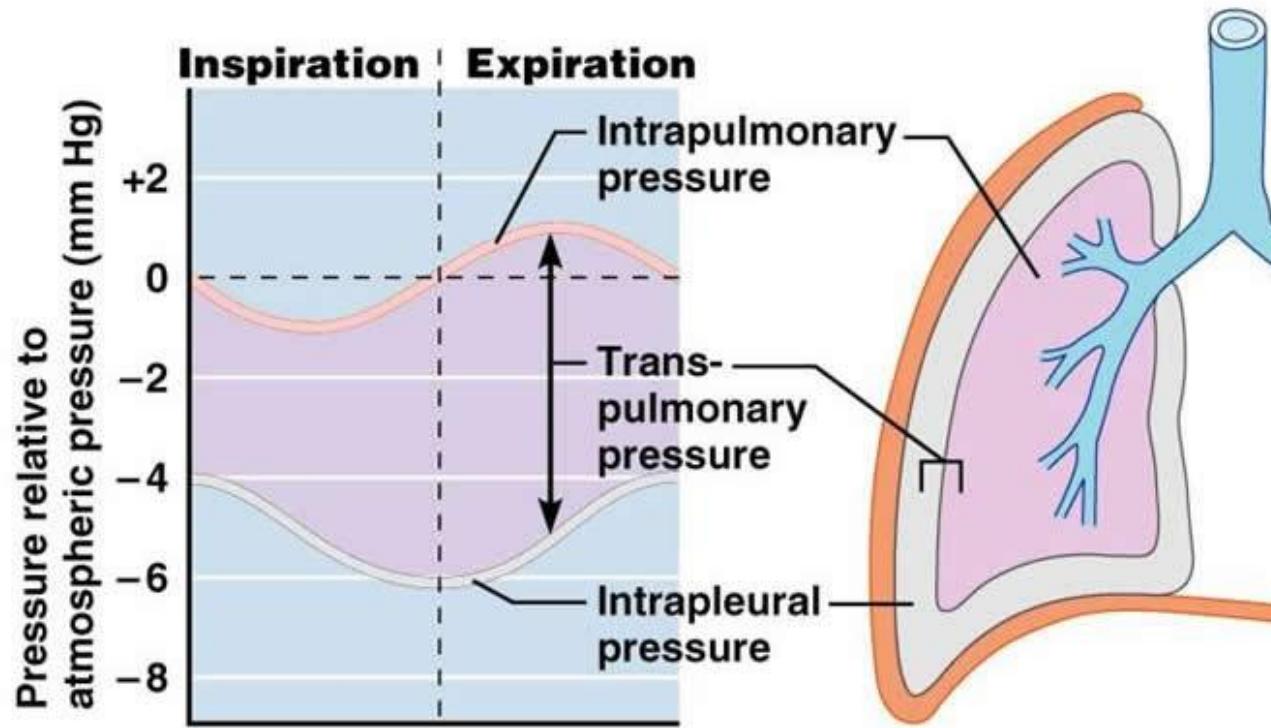
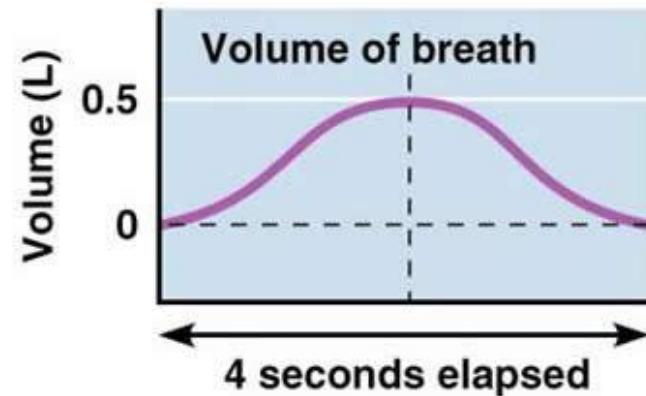
• Respiratory Centers and Reflex Controls





Mechanics of Respiration- (cont.)

➤ Pressure and Volume Changes During Breathing



Pulmonary Volumes and Capacities

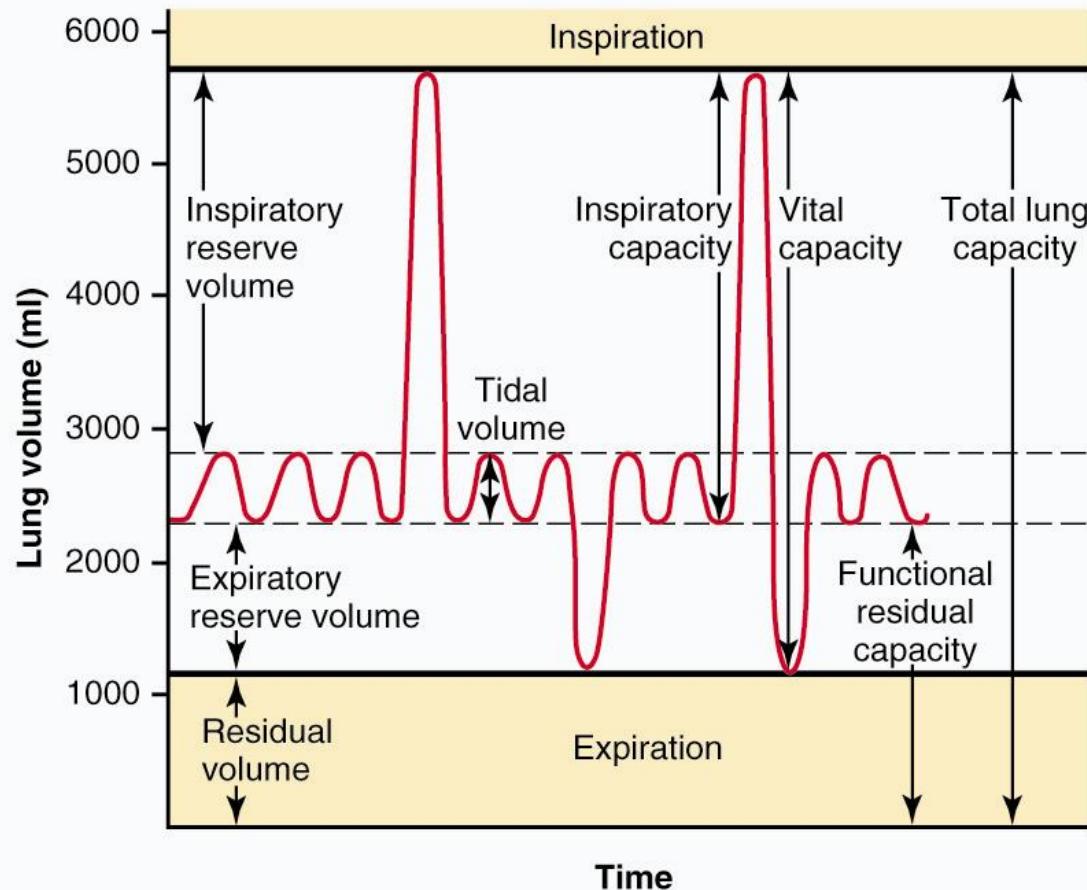
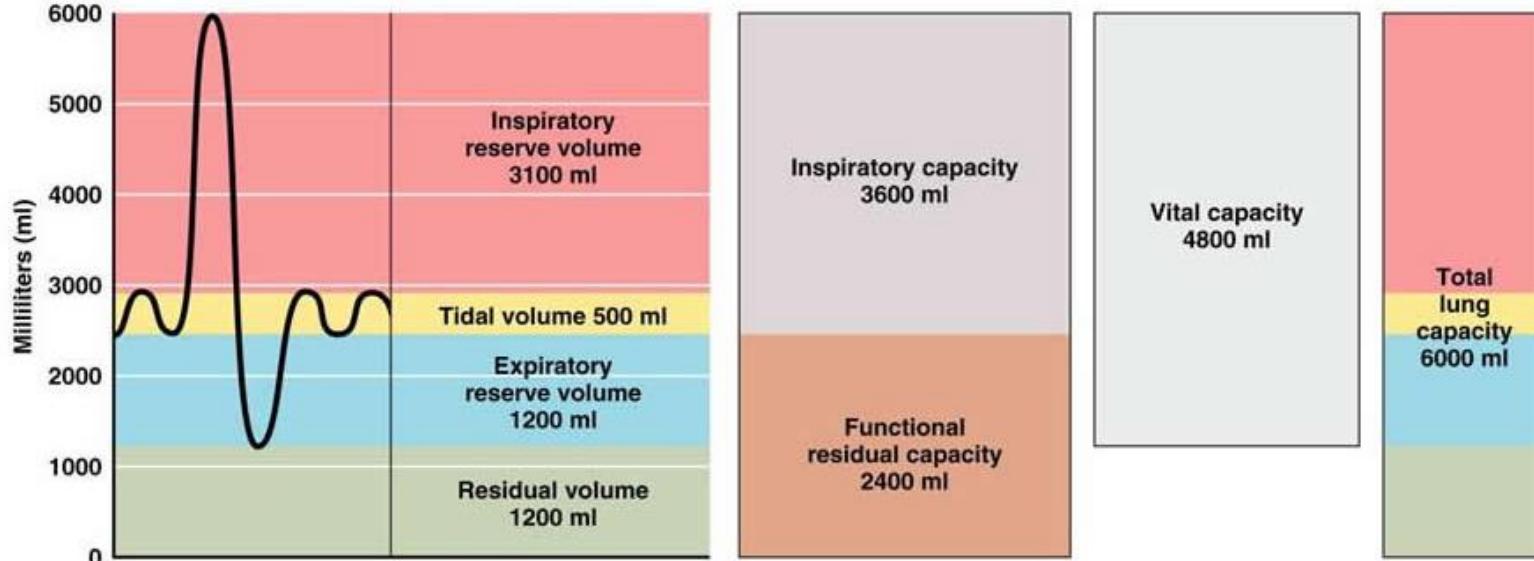


Figure 37-6; Diagram showing respiratory excursions during normal breathing and during maximal inspiration and maximal expiration.



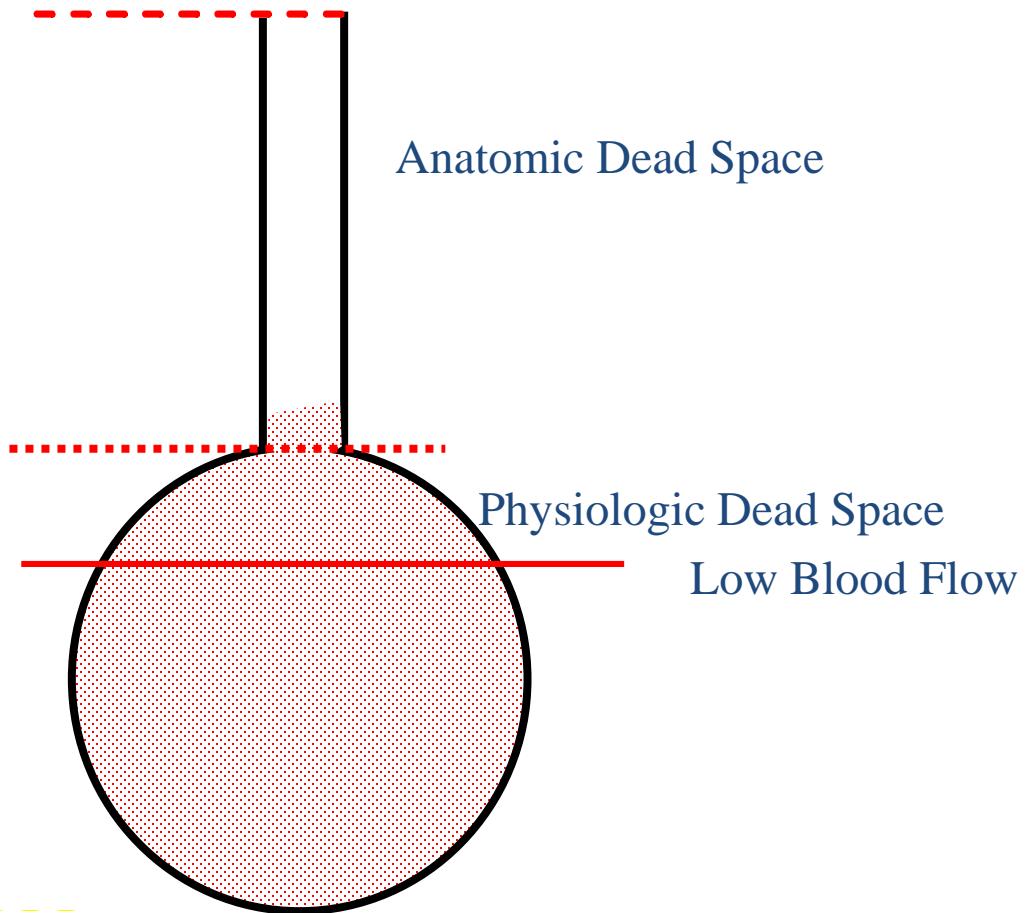
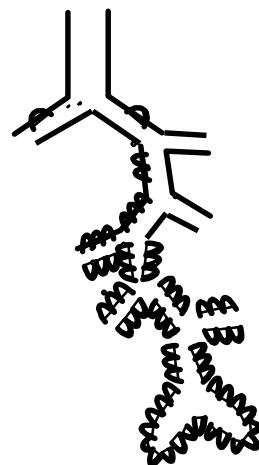
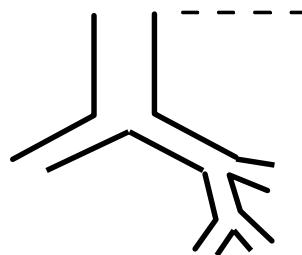
(a) Spirographic record for a male

	Measurement	Adult male average value	Adult female average value	Description
Respiratory volumes	Tidal volume (TV)	500 ml	500 ml	Amount of air inhaled or exhaled with each breath under resting conditions
	Inspiratory reserve volume (IRV)	3100 ml	1900 ml	Amount of air that can be forcefully inhaled after a normal tidal volume inhalation
	Expiratory reserve volume (ERV)	1200 ml	700 ml	Amount of air that can be forcefully exhaled after a normal tidal volume exhalation
	Residual volume (RV)	1200 ml	1100 ml	Amount of air remaining in the lungs after a forced exhalation
Respiratory capacities	Total lung capacity (TLC)	6000 ml	4200 ml	Maximum amount of air contained in lungs after a maximum inspiratory effort: $TLC = TV + IRV + ERV + RV$
	Vital capacity (VC)	4800 ml	3100 ml	Maximum amount of air that can be expired after a maximum inspiratory effort: $VC = TV + IRV + ERV$ (should be 80% TLC)
	Inspiratory capacity (IC)	3600 ml	2400 ml	Maximum amount of air that can be inspired after a normal exhalation: $IC = TV + IRV$
	Functional residual capacity (FRC)	2400 ml	1800 ml	Volume of air remaining in the lungs after a normal tidal volume exhalation: $FRC = ERV + RV$

(b) Summary of respiratory volumes and capacities for males and females

Definitions of Dead Space

- Dead space is the total volume of the conducting airways from the nose or mouth down to the level of the terminal bronchioles which does not participate in the gas exchange.
- **Anatomical dead space:** portions where there is no possibility of gas exchange
- **Physiological dead space:** portions where there is possibility of gas exchange but is just not happening



Compliance of Lungs

- The extent to which the lungs will expand for each unit increase in transpulmonary pressure is called the lung compliance.
- Compliance describes the elasticity or distensibility of the respiratory structures (alveoli, chest wall, and pulmonary parenchyma)

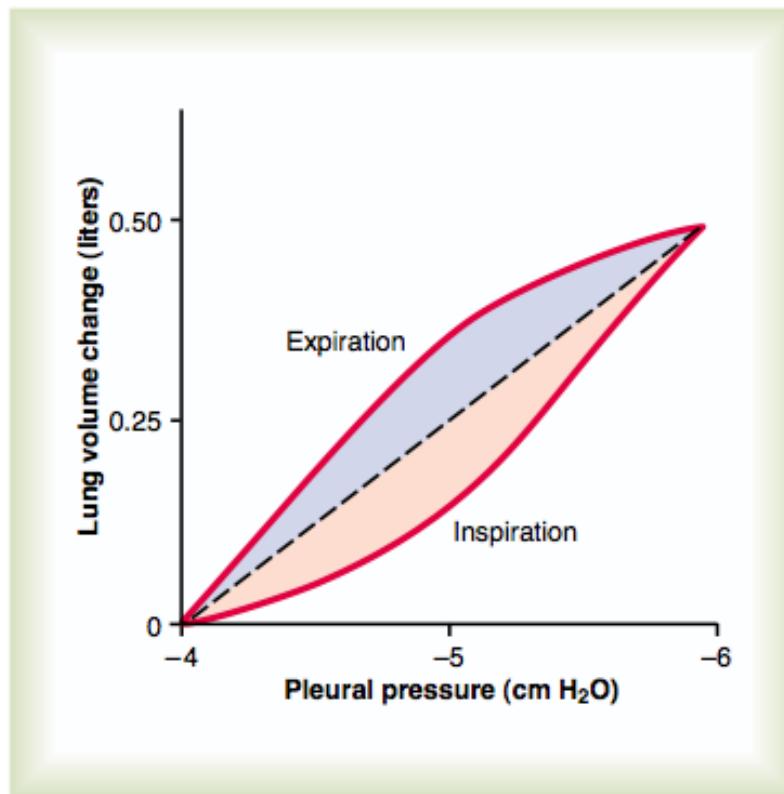


Figure 37-3

Compliance diagram in a healthy person. This diagram shows compliance of the lungs alone.

Control of Bronchiolar Diameter

- Nervous
 - Sympathetics
 - β_2 receptors dilate
 - Parasympathetics
 - Acetylcholine constrict
- Humoral
 - Histamine, acetylcholine » Constrict
 - Adrenergic (β agonists) » Relax

Airway Resistance during Forced Exhalation

- Airway resistance is the opposition to gas flow.
- Airway resistance depends on:

- Radii of the airways (total cross-sectional area)
- Lengths of the airways
- Flow Type: Laminar or Turbulent
- Density and viscosity of gas

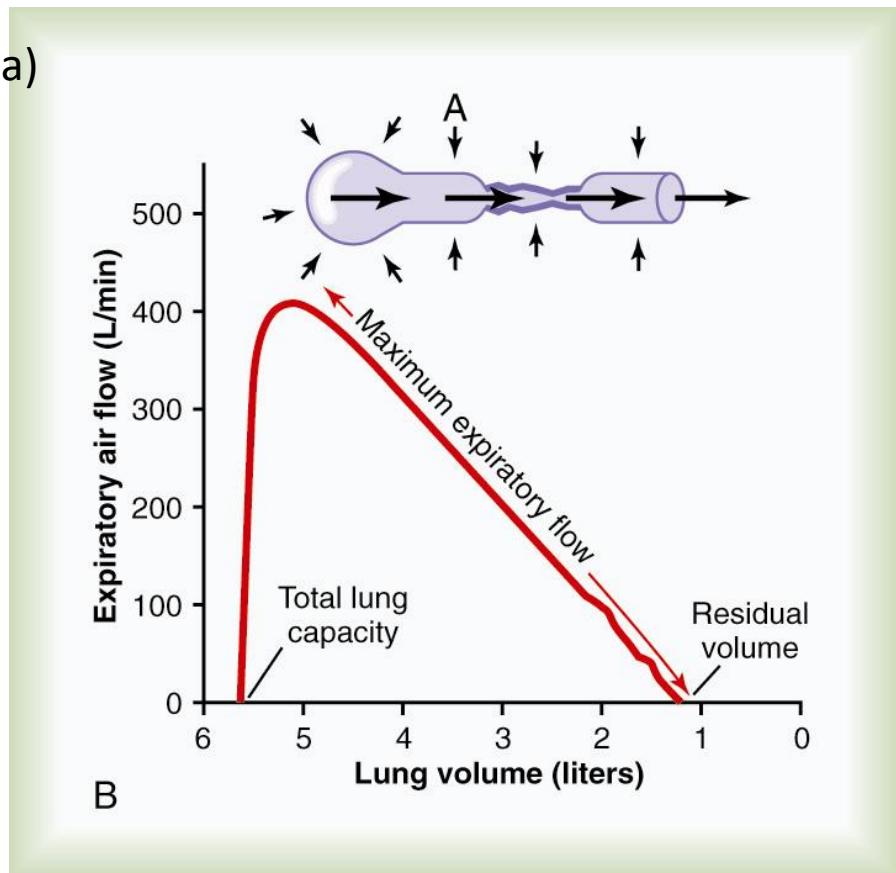


Figure 42–1; A, Collapse of the respiratory passageway during maximum expiratory effort, an effect that limits expiratory flow rate. B, Effect of lung volume on the maximum expiratory air flow, showing decreasing maximum expiratory air flow as the lung volume becomes smaller.

Determinants of Diffusion

➤ factors that affect the rate of gas diffusion

- Pressure Gradient
- Area (cross-sectional area of the fluid)
- Distance (the distance through which the gas must diffuse)
- Solubility (solubility of the gas in the fluid) and MW (the molecular weight of the gas)

$$\text{Rate of Diffusion} = (P_1 - P_2) * \text{Area} * \text{Solubility}$$

$$\frac{\text{Distance} * \sqrt{\text{MW}}}{}$$

■ Changes in Alveolar Gas Composition

- *functional residual capacity* : the volume of air remaining in the lungs at the end of normal expiration

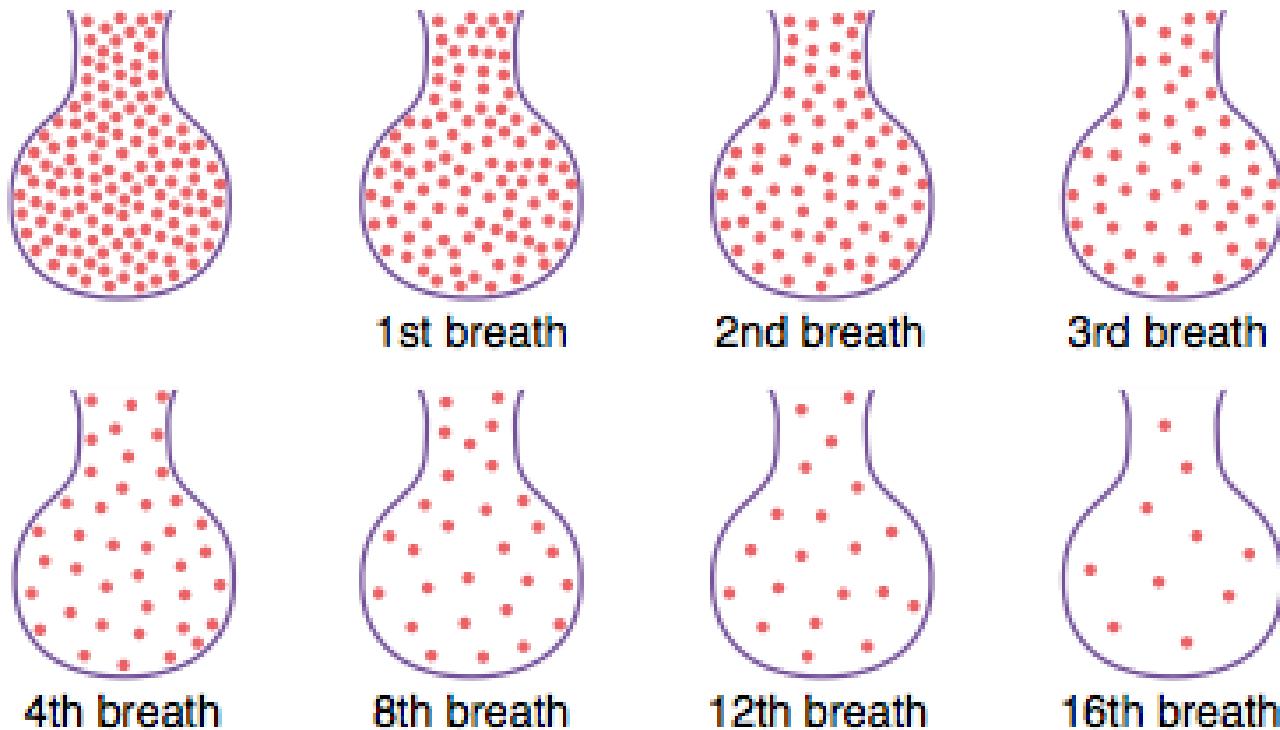


Figure 39–2

Expiration of a gas from an alveolus with successive breaths.

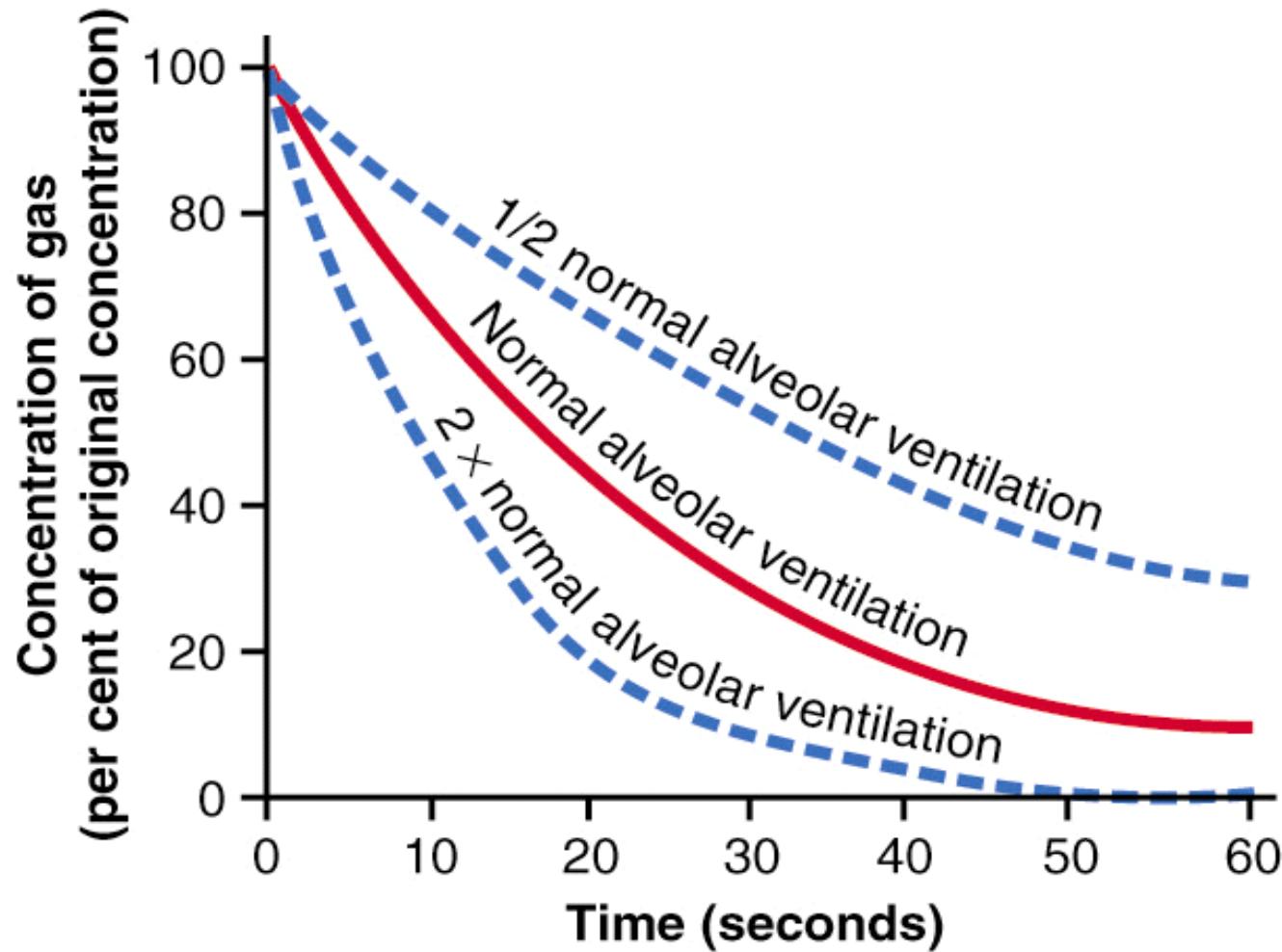
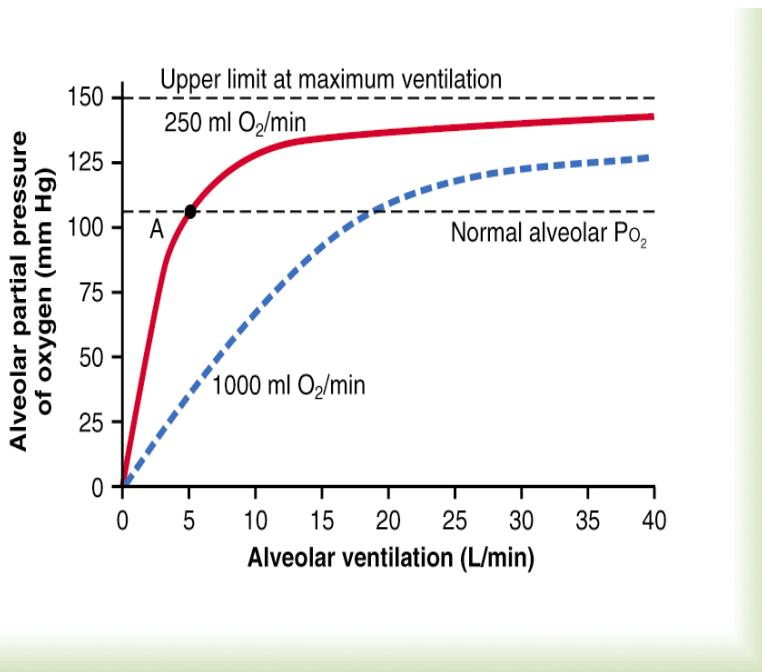


Figure 39-3; Rate of removal of excess gas from alveoli.

■ Partial Pressure of Oxygen in Alveoli

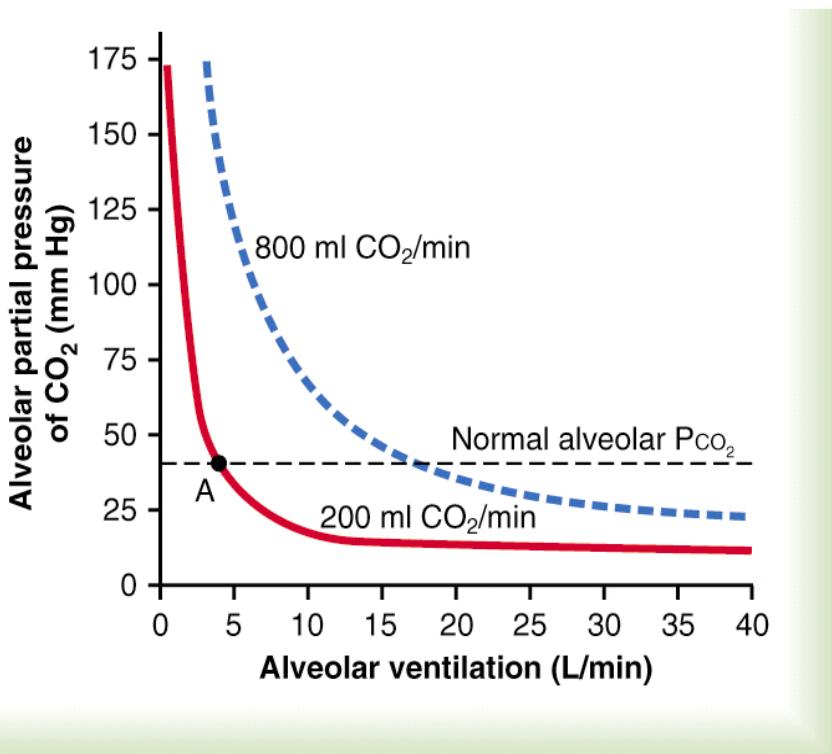


- oxygen concentration in the alveoli, and its partial pressure as well, is controlled by (1) the rate of absorption of oxygen into the blood and (2) the rate of entry of new oxygen into the lungs by the ventilatory process.
- At a normal ventilatory rate of 4.2 L/min and an oxygen consumption of 250 ml/min, the normal operating point in Figure 39–4 is point A. The figure also shows that when 1000 milliliters of oxygen is being absorbed each minute, as occurs during moderate exercise, the rate of alveolar ventilation must increase fourfold to maintain the alveolar PO_2 at the normal value of 104 mm Hg.



Figure 39-4: Effect of alveolar ventilation on the alveolar PO_2 at two rates of oxygen absorption from the alveoli—250 ml/min and 1000 ml/min. Point A is the normal operating point.

■ Partial Pressure of CO₂ in Alveoli



- Carbon dioxide is continually being formed in the body and then carried in the blood to the alveoli; it is continually being removed from the alveoli by ventilation.
- Figure 39–5 shows the effects on the alveolar partial pressure of carbon dioxide (PCO₂) of both alveolar ventilation and two rates of carbon dioxide excretion, 200 and 800 ml/min. One curve represents a normal rate of carbon dioxide excretion of 200 ml/min. At the normal rate of alveolar ventilation of 4.2 L/min, the operating point for alveolar PCO₂ is , at point A, 40 mm Hg.



Figure 39-5; Effect of alveolar ventilation on the alveolar PCO₂ at two rates of carbon dioxide excretion from the blood—800 ml/min and 200 ml/ min. Point A is the normal operating point.

■ Diffusion of Oxygen and Carbon dioxide

- Oxygen
- The PO_2 of the gaseous oxygen in the alveolus averages 104 mm Hg, whereas the PO_2 of the venous blood entering the pulmonary capillary at its arterial end averages only 40 mm Hg because a large amount of oxygen was removed from this blood as it passed through the peripheral tissues
- 230 ml/min diffusion of oxygen

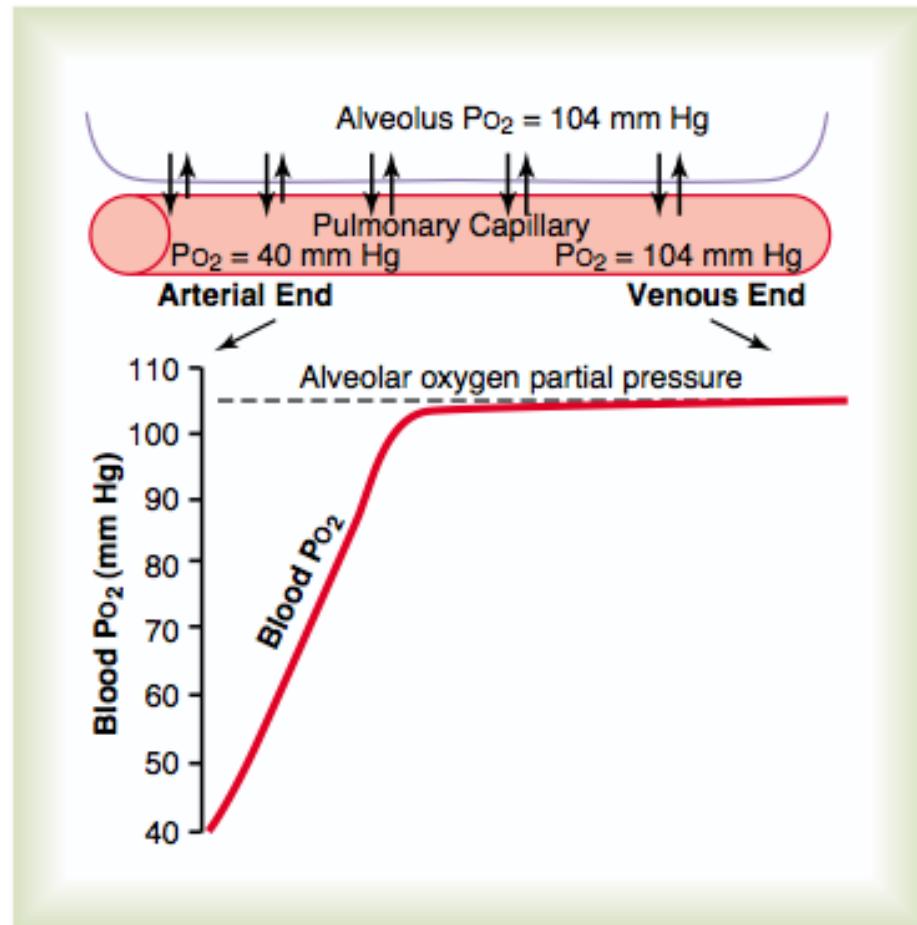


Figure 40-1

Uptake of oxygen by the pulmonary capillary blood. (The curve in this figure was constructed from data in Milhorn HT Jr, Pulley PE Jr: A theoretical study of pulmonary capillary gas exchange and venous admixture. *Biophys J* 8:337, 1968.)

- Carbon Dioxide

- 200 ml/min diffusion of carbon dioxide

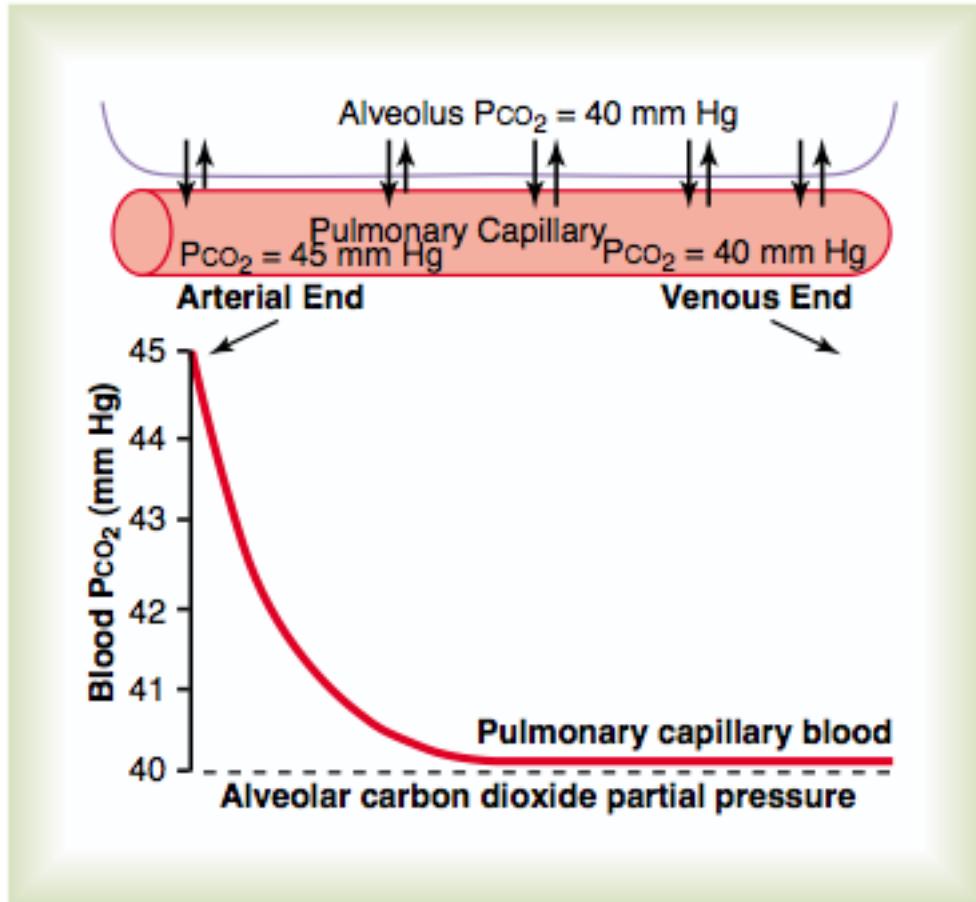
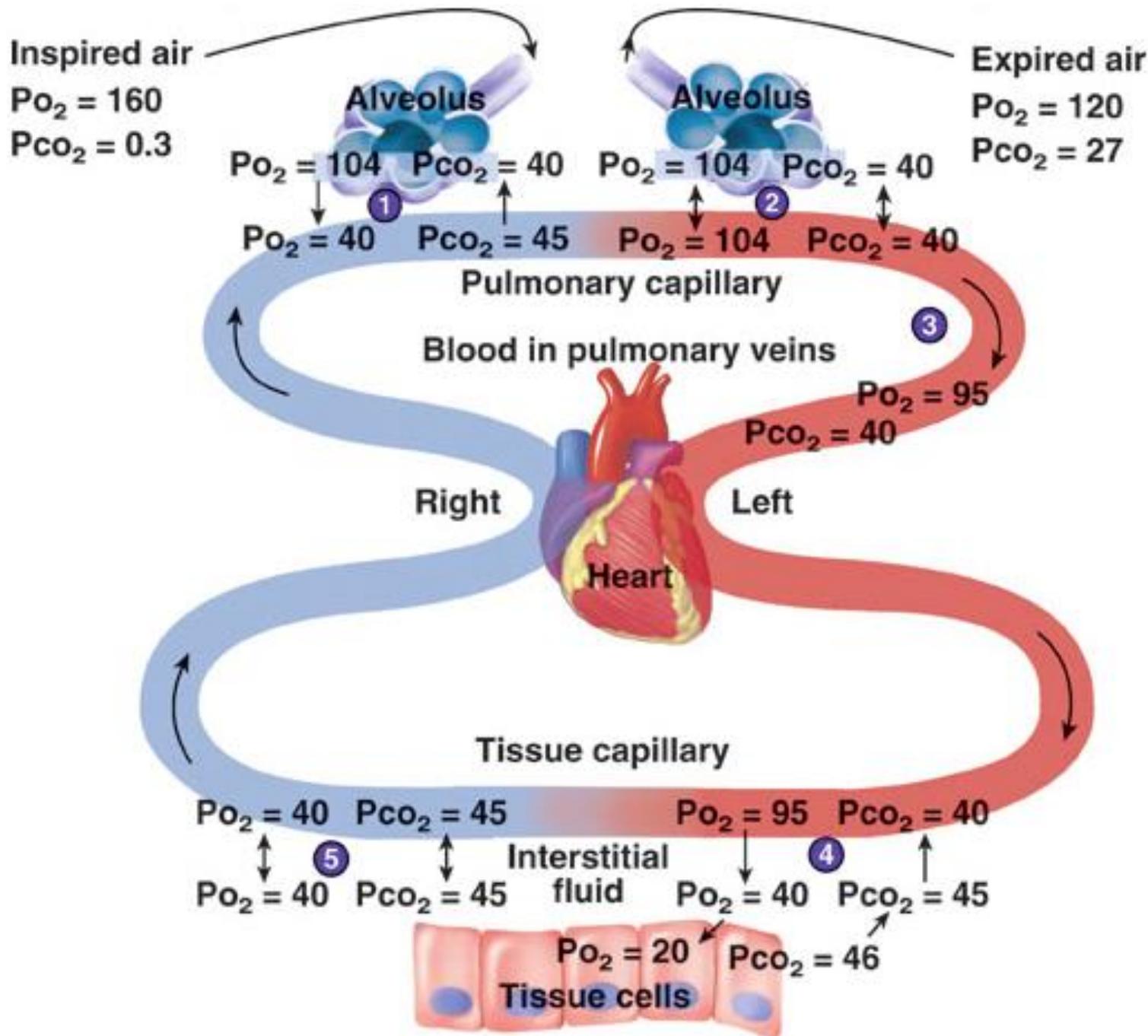


Figure 40-6

Diffusion of carbon dioxide from the pulmonary blood into the alveolus. (This curve was constructed from data in Milhorn HT Jr, Pulley PE Jr: A theoretical study of pulmonary capillary gas exchange and venous admixture. *Biophys J* 8:337, 1968.)



■ Ventilation/Perfusion

- quantitative concept has been developed to help us understand respiratory exchange when there is imbalance between alveolar ventilation and alveolar blood flow is called the ventilation-perfusion ratio.
- Defined as V/Q
- $V/Q = (4 \text{ L/min}) / (5 \text{ L/min}) = 0.8$

Ventilation/Perfusion – (cont.)

- Whenever V_a/Q is below normal, there is inadequate ventilation to provide the oxygen needed to fully oxygenate the blood flowing through the alveolar capillaries. Therefore, a certain fraction of the venous blood passing through the pulmonary capillaries does not become oxygenated. This fraction is called shunted blood.
- When ventilation of some of the alveoli is great but alveolar blood flow is low, there is far more available oxygen in the alveoli than can be transported away from the alveoli by the flowing blood. Thus, the ventilation of these alveoli is said to be wasted. The ventilation of the anatomical dead space areas of the respiratory passageways is also wasted. The sum of these two types of wasted ventilation is called the physiologic dead space.

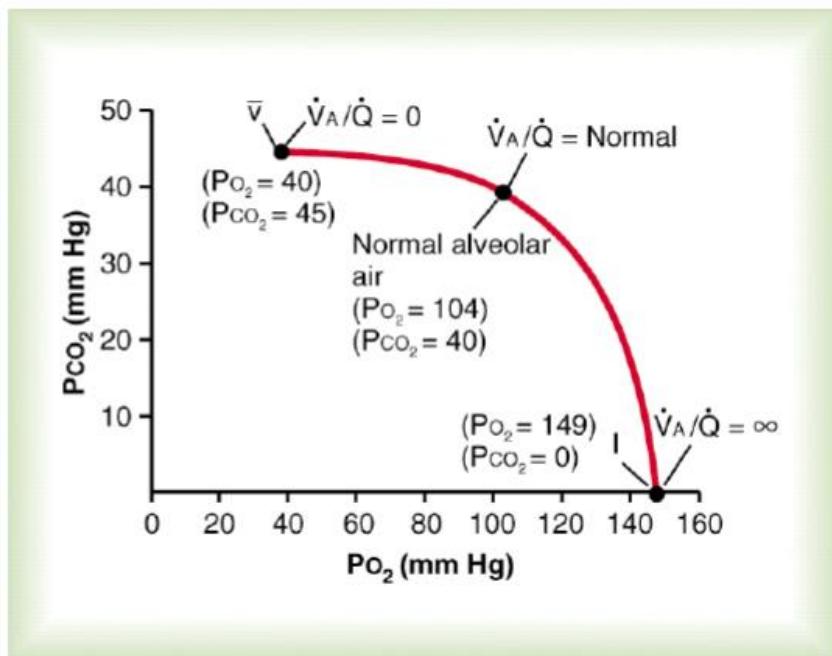
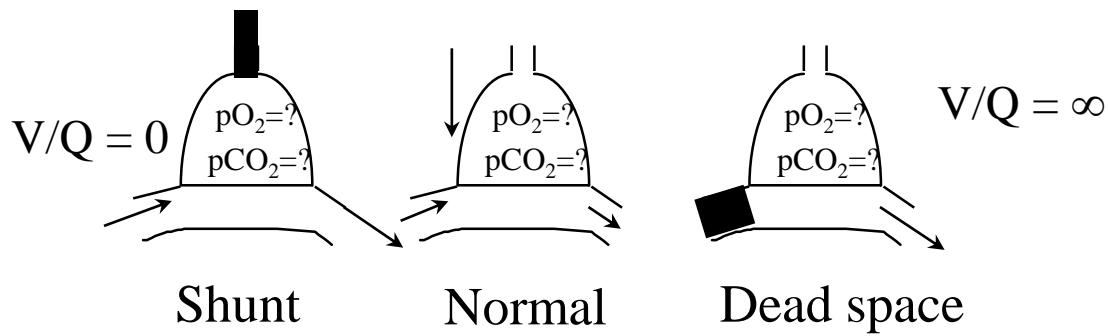


Figure 39-11; Normal PO_2-PCO_2 , VA/Q diagram.

Ventilation/Perfusion – (cont.)

- Physiologic shunt
 - $V_a/Q < \text{normal}$
 - low ventilation
- Physiologic dead space
 - $V_a/Q > \text{normal}$
 - wasted ventilation
- Abnormalities
 - Upper lung $V_a/Q \sim 2.5$
 - Lower lung $V_a/Q \sim .5$

Uptake of Oxygen During Exercise

- Increased cardiac output
- Decreased transit time
- Increased diffusing capacity
 - Opening up of additional capillaries
 - Better ventilation/perfusion match
- Equilibration even with shorter time

Oxygen Transport

- Normally, about 97 per cent of the oxygen transported from the lungs to the tissues is carried in chemical combination with hemoglobin in the red blood cells.
- The remaining 3 per cent is transported in the dissolved state in the water of the plasma and blood cells. Thus, under normal conditions, oxygen is carried to the tissues almost entirely by hemoglobin.
- oxygen molecule combines loosely and reversibly with the heme portion of hemoglobin. When PO_2 is high, as in the pulmonary capillaries, oxygen binds with the hemoglobin, but when PO_2 is low, as in the tissue capillaries, oxygen is released from the hemoglobin. This is the basis for almost all oxygen transport from the lungs to the tissues.

■ Hemoglobin Dissociation Curve

- from the dissociation curve that the usual oxygen saturation of systemic arterial blood averages 97 %. Conversely, in normal venous blood returning from the peripheral tissues, the PO_2 is about 40 mm Hg, and the saturation of hemoglobin averages 75 %.

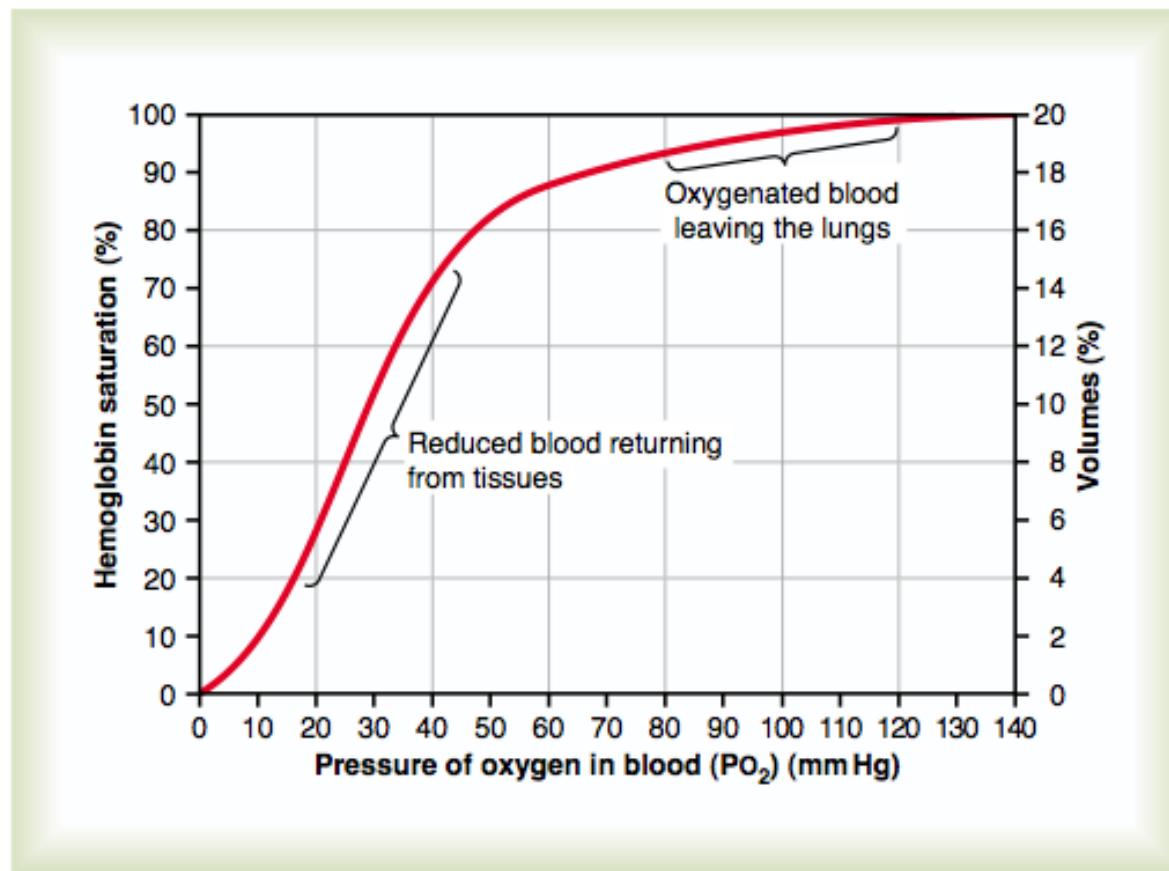
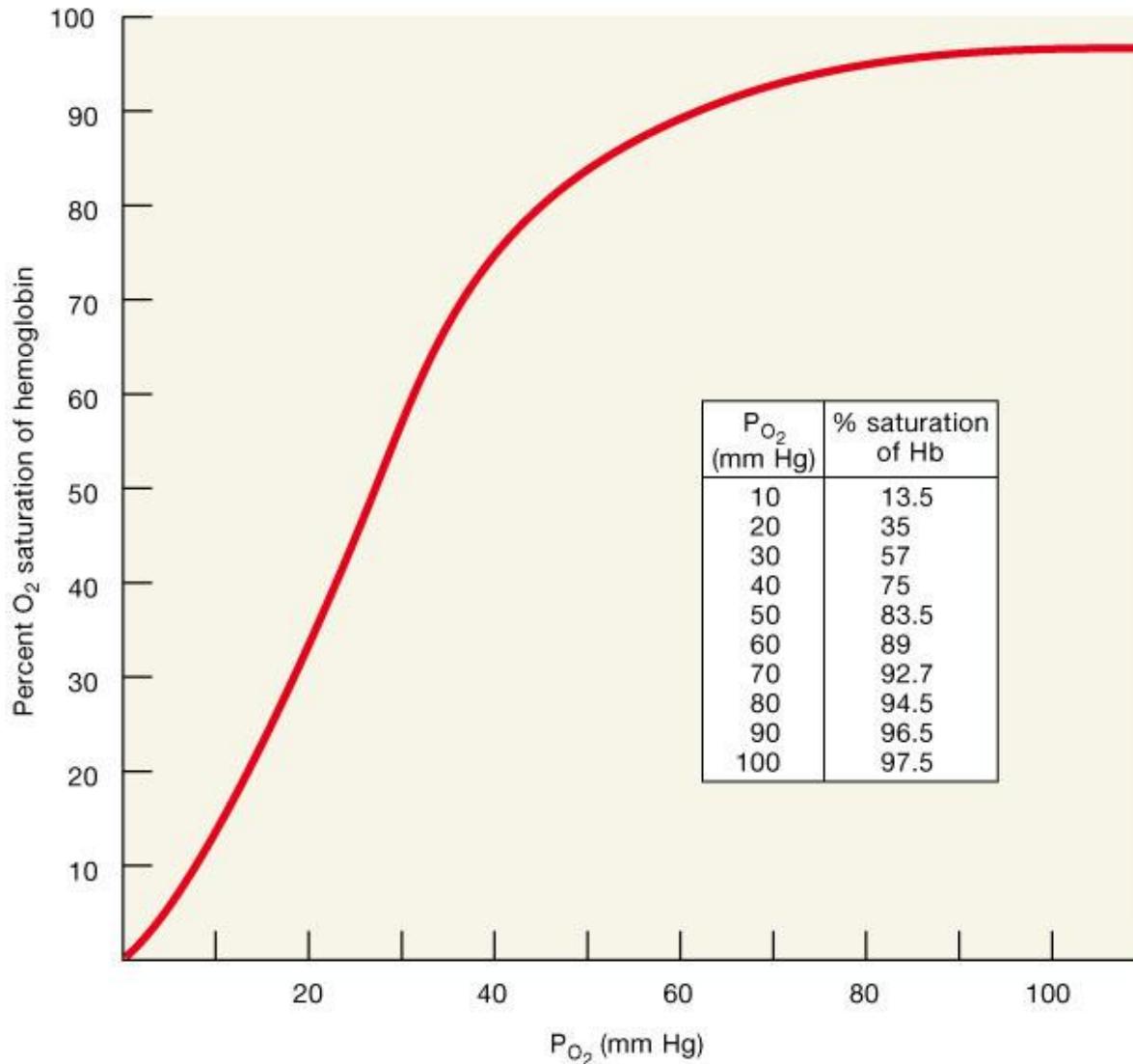
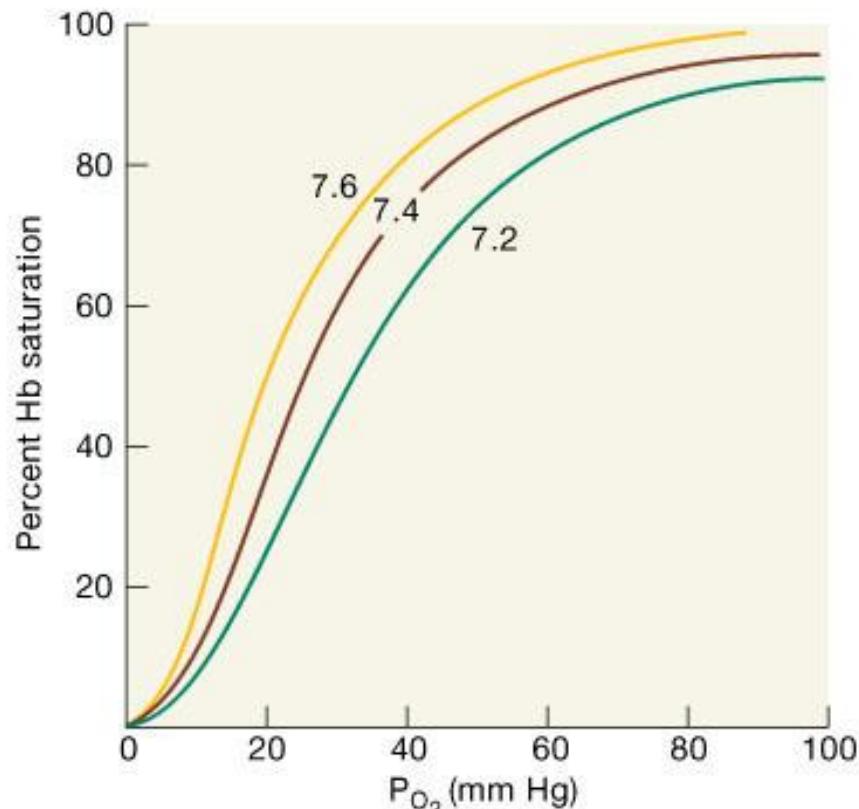


Figure 40–8
Oxygen-hemoglobin dissociation curve.

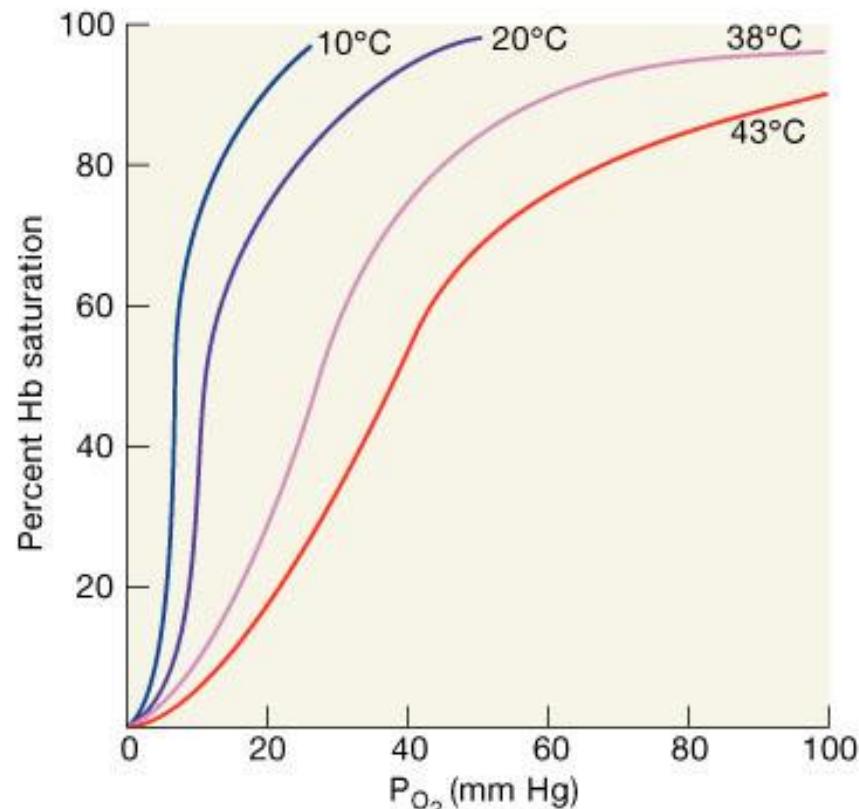
■ The Oxygen-Hemoglobin Saturation Curve



■ The Effect of pH and Temperature on Hemoglobin Saturation



(a) Effect of pH



(b) Effect of temperature

Transport of Carbon Dioxide from Tissue

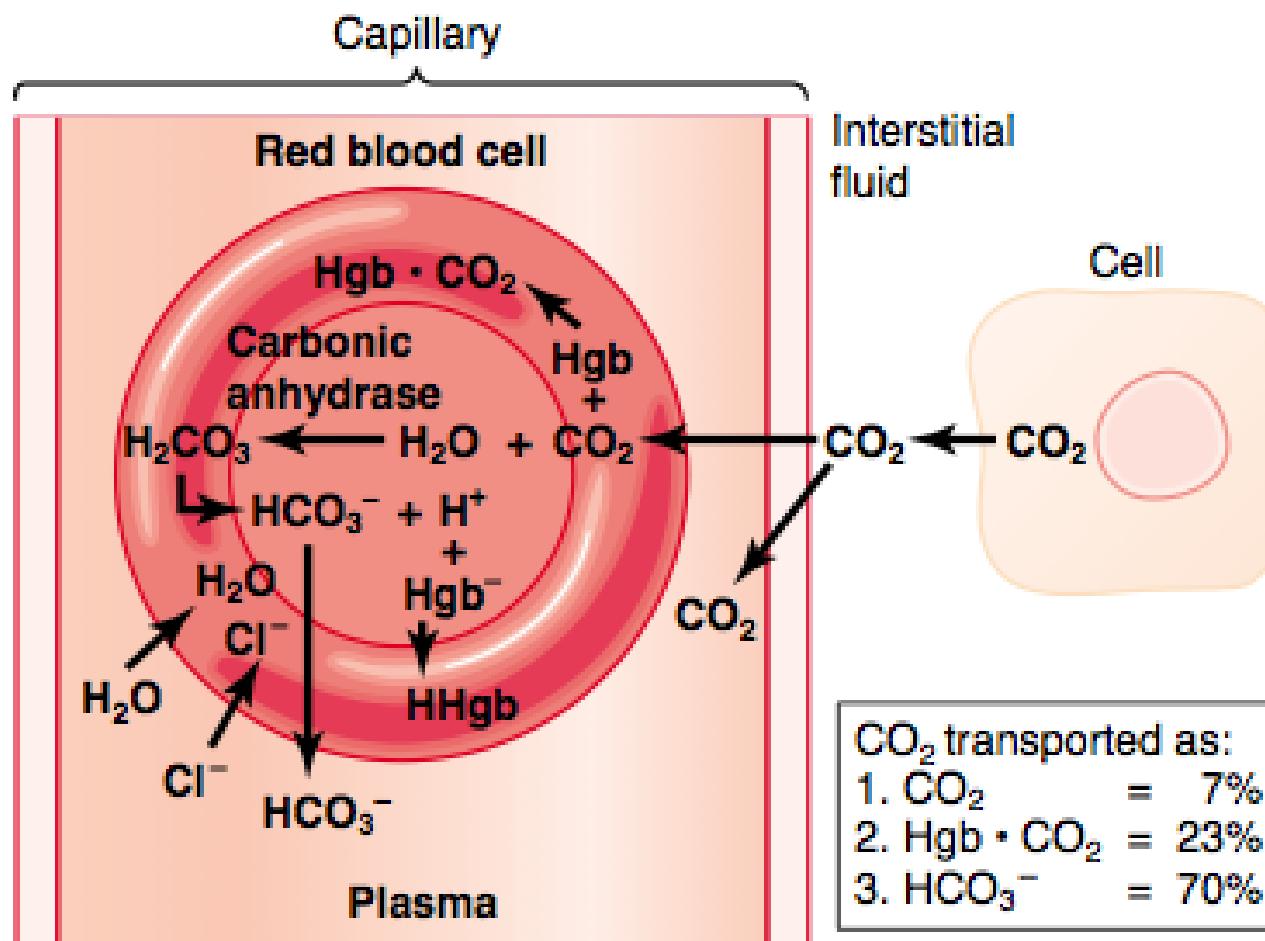


Figure 40–13

Transport of carbon dioxide in the blood.

Digestive System

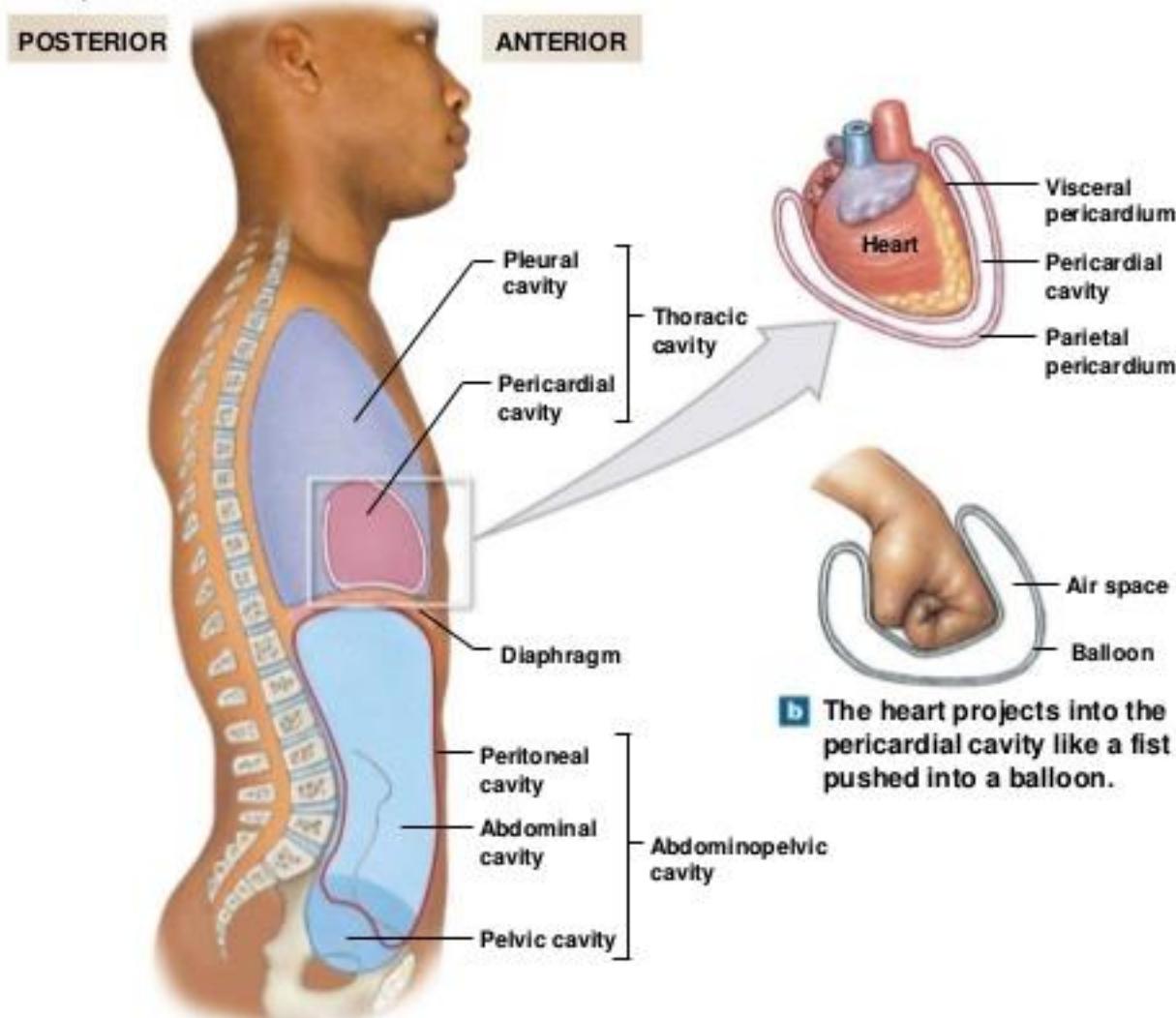
- The alimentary canal or gastrointestinal (GI) tract **digests and absorbs food**
- **Alimentary canal** – mouth, esophagus, stomach, small intestine, and large intestine
- **Accessory digestive organs** – teeth, tongue, gallbladder, salivary glands, liver, and pancreas

Gastrointestinal Tract Activities

- **Ingestion** – taking food into the digestive tract
- **Propulsion** – swallowing and peristalsis
 - Peristalsis – waves of contraction and relaxation of muscles in the organ walls
- **Mechanical digestion** – chewing, mixing, and churning food
- **Chemical digestion** – catabolic breakdown of food
- **Absorption** – movement of nutrients from the GI tract to the blood or lymph
- **Defecation** – elimination of indigestible solid wastes

Peritoneal Cavity – lateral view

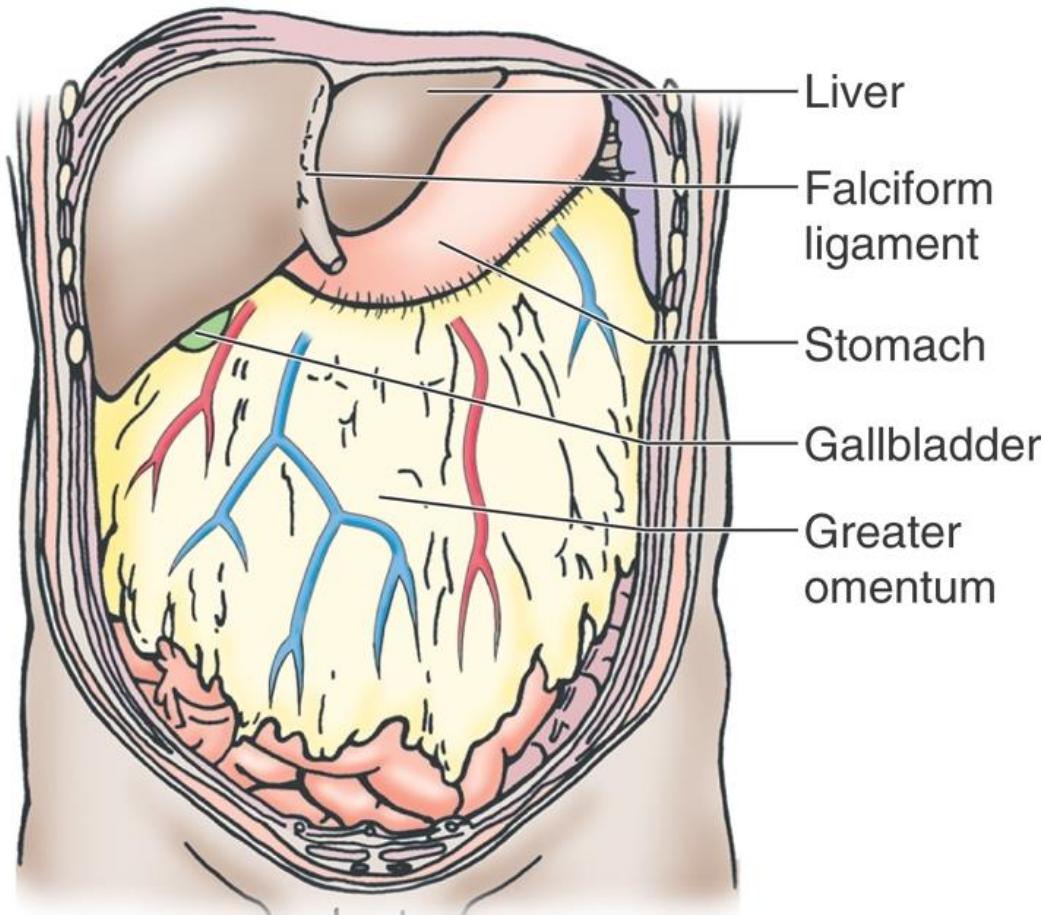
Figure 1.13ab Body Cavities



a Lateral view of the subdivisions of the ventral body cavities.
The muscular diaphragm separates the superior thoracic (chest) cavity and the inferior abdominopelvic cavity.

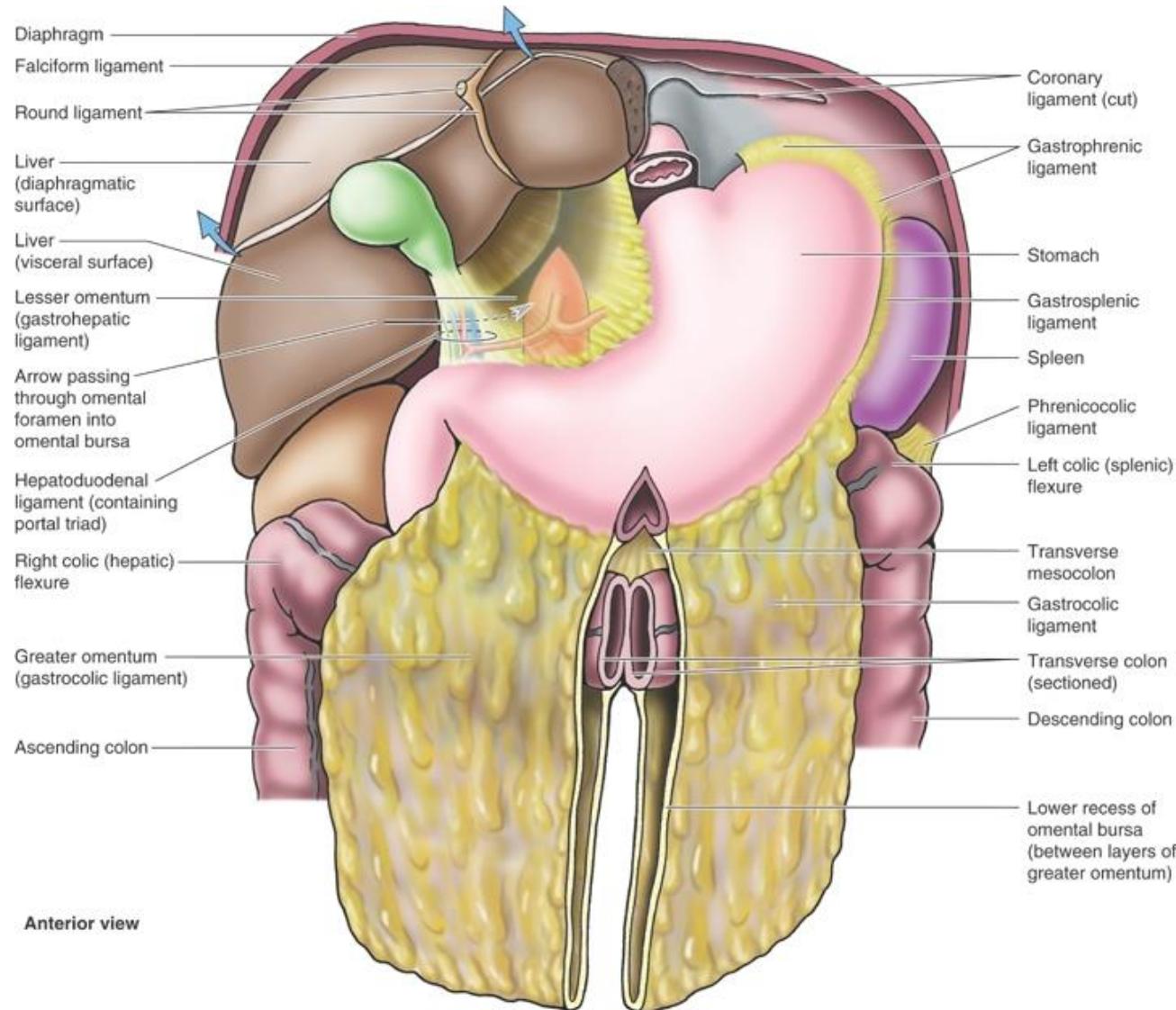
b The heart projects into the pericardial cavity like a fist pushed into a balloon.

Peritoneal Cavity – Anterior View

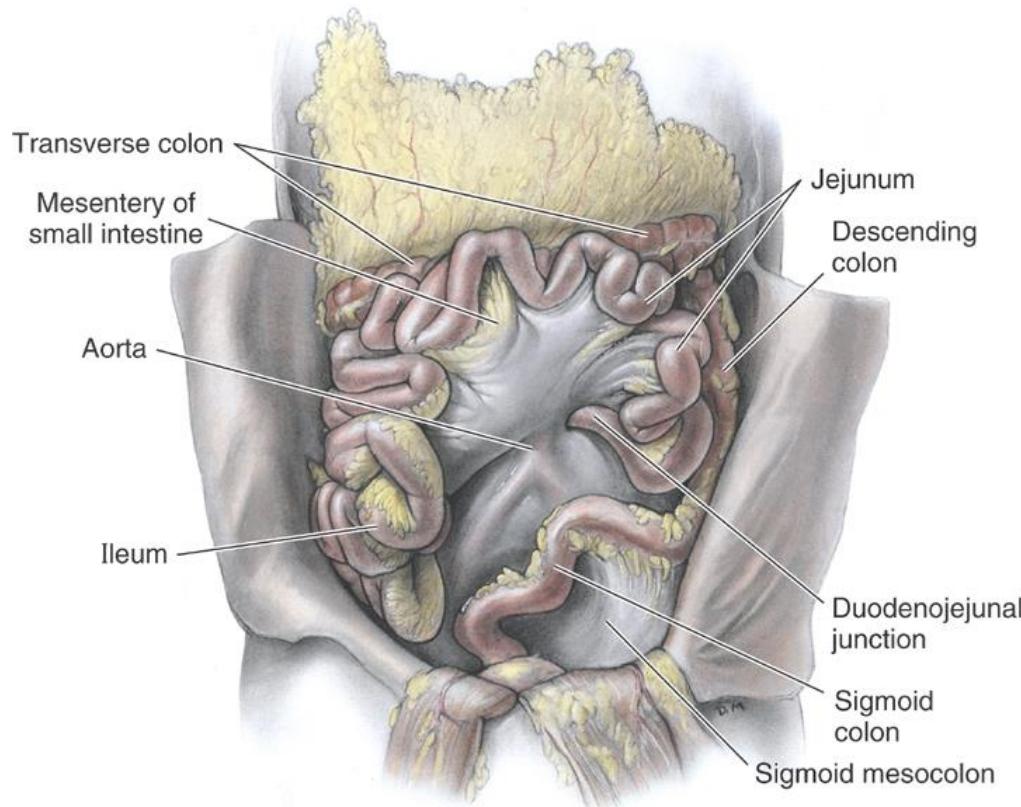


Anterior view

Greater and Lesser Omentum



Mesentery



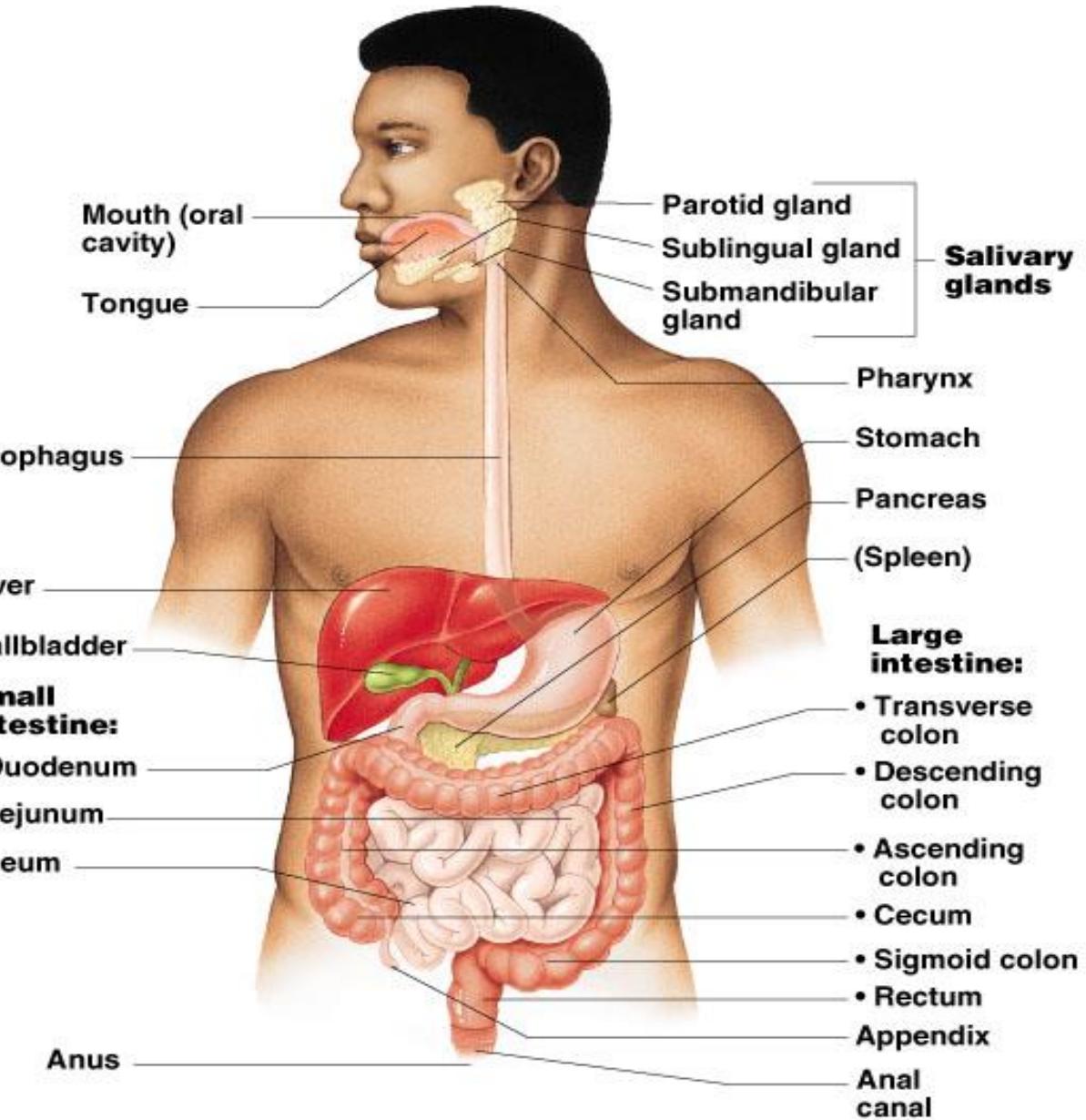
Anterior view

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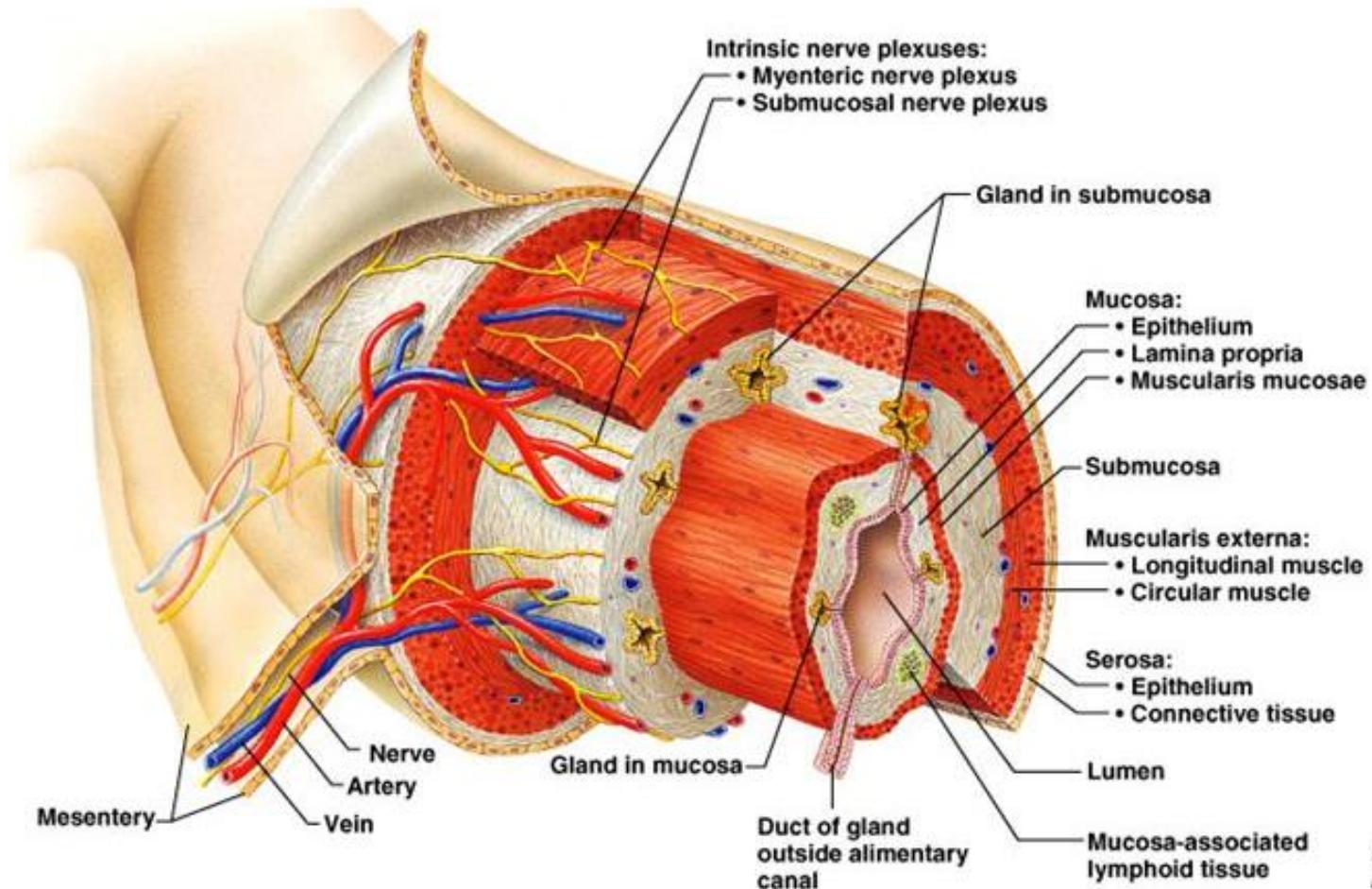
The **mesentery** is an organ that attaches the intestines to the posterior abdominal wall in humans

Organs of the Digestive System

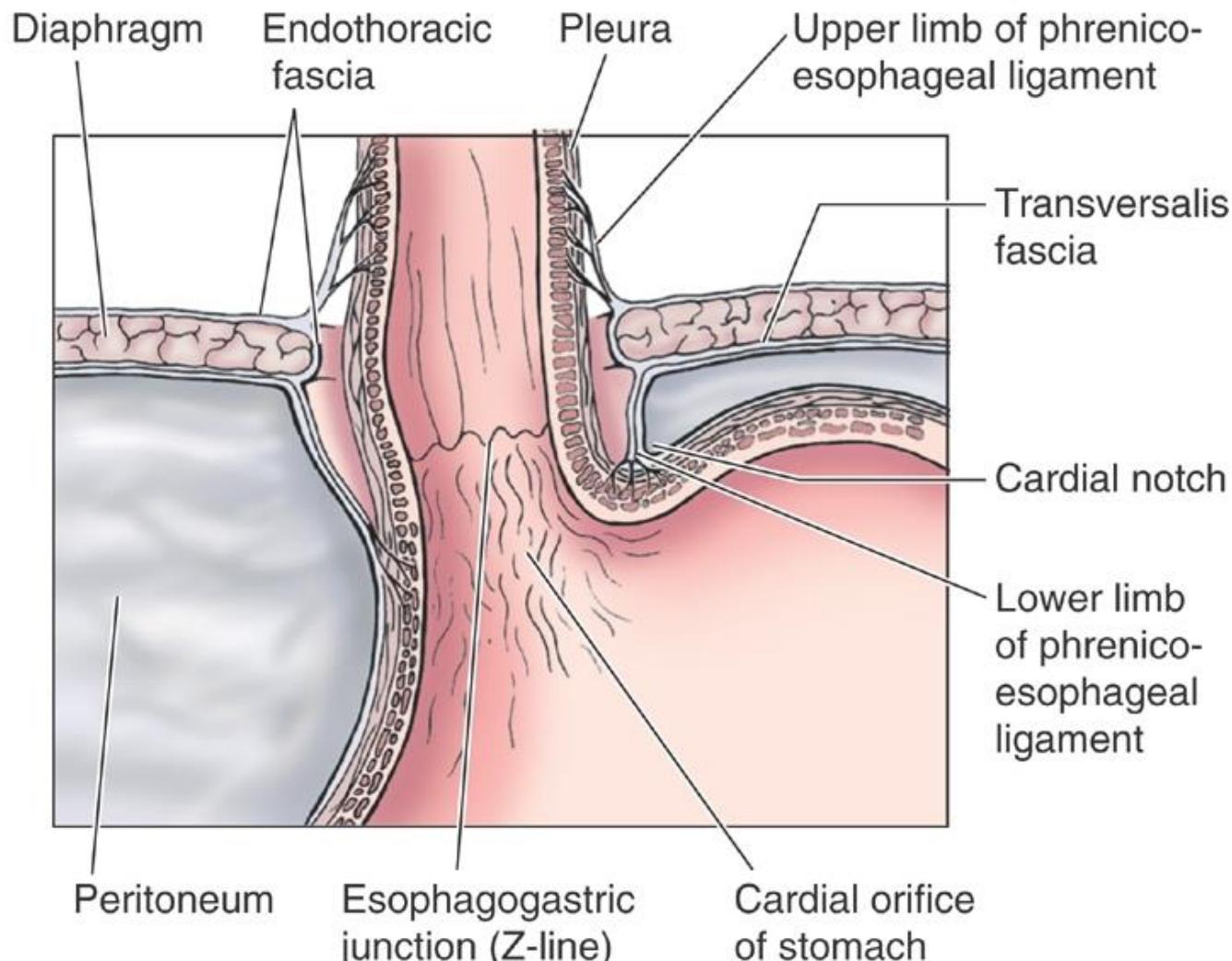
- Mouth
- teeth
- Salivary glands
- Pharynx
- Esophagus
- Stomach
- Liver
- Gallbladder (GB)
- Pancreas
- Small intestine
- Large intestine
- Rectum
- Anus



- From esophagus to the anal canal the walls of the GI tract have the same four tunics
- From the lumen to outward they are the:
 - Mucosa
 - Sub Mucosa
 - Muscularis externa
 - Serosa

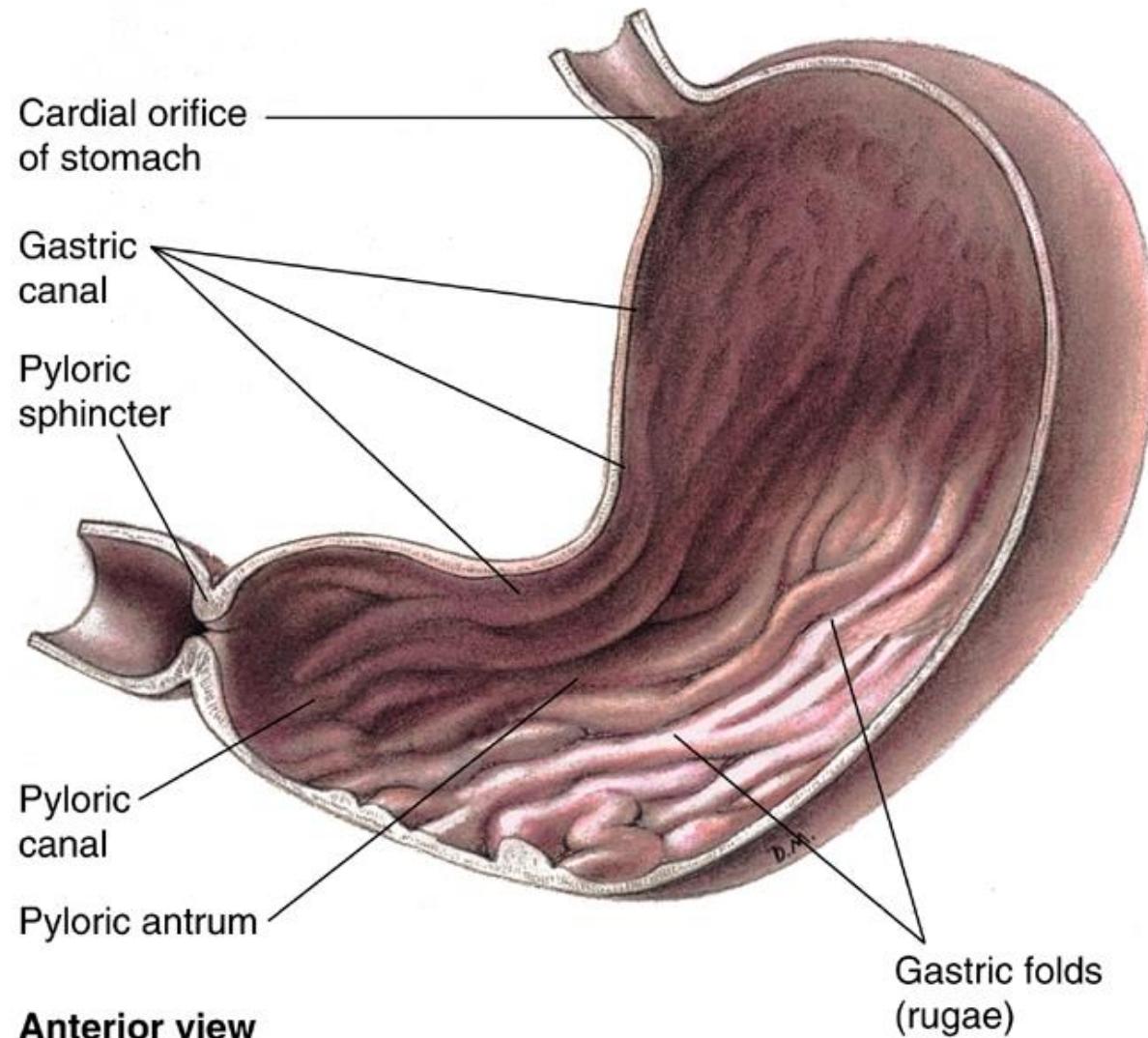


Entrance to Stomach (Cardiac Sphincter)

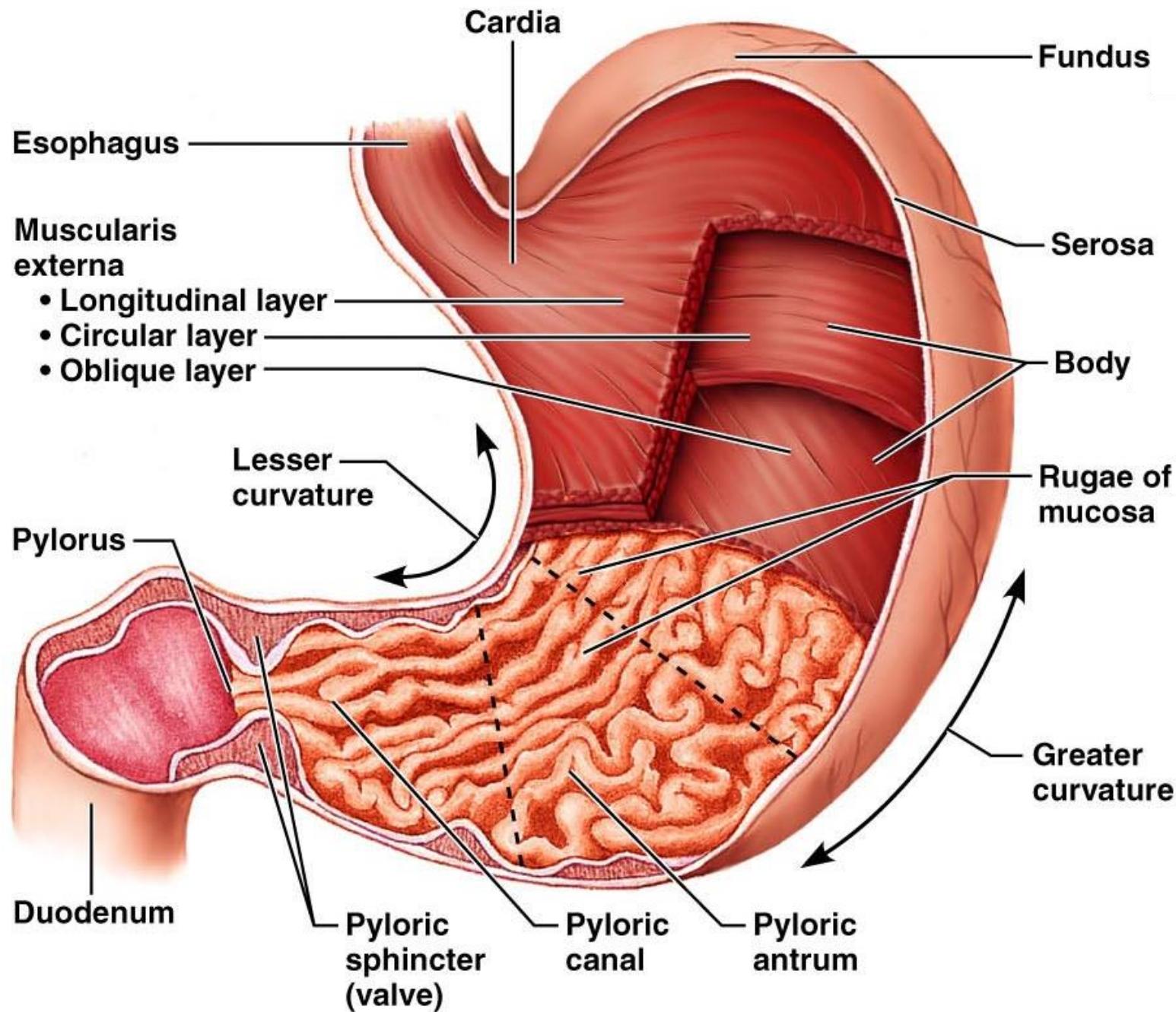


Anterior view

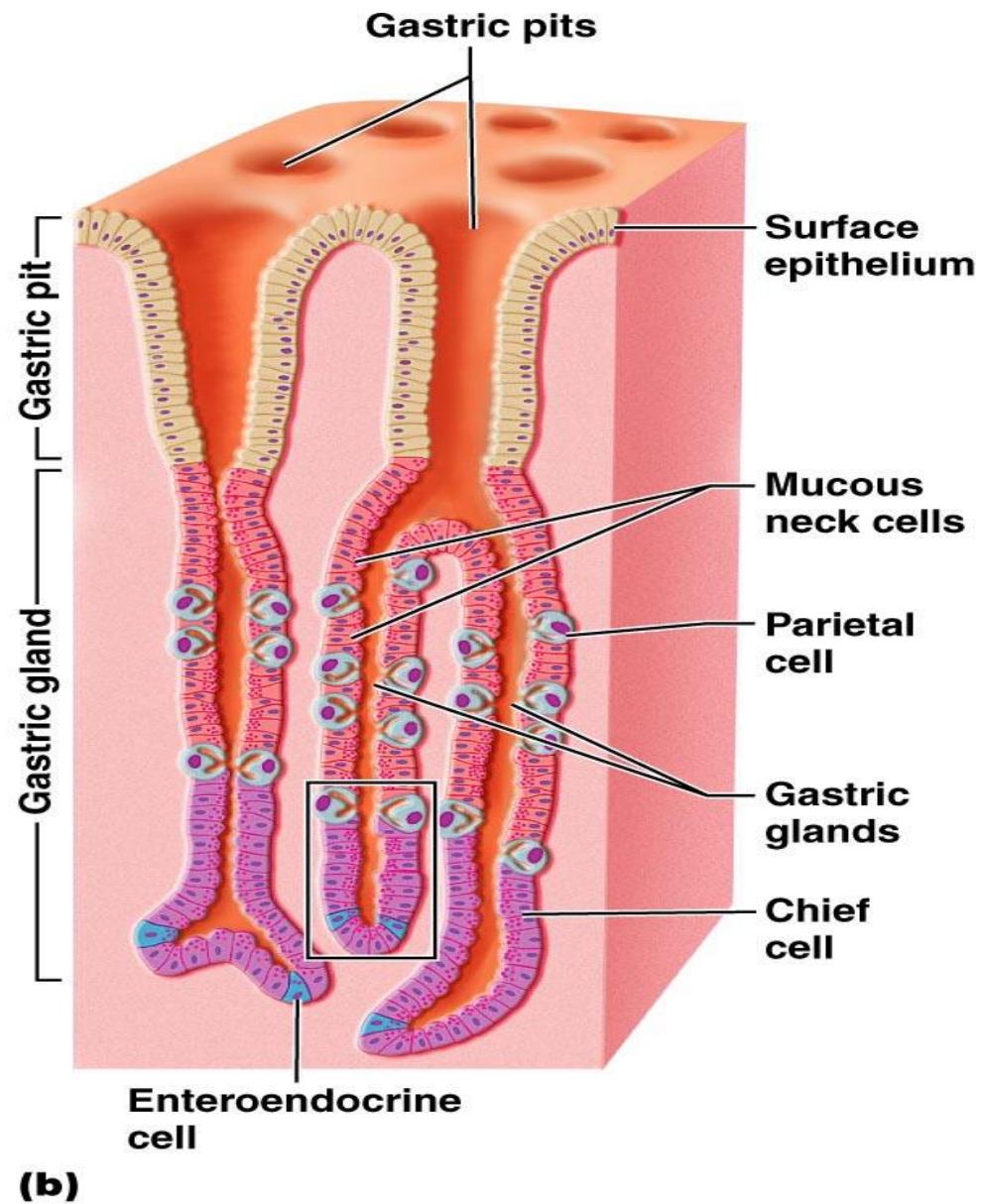
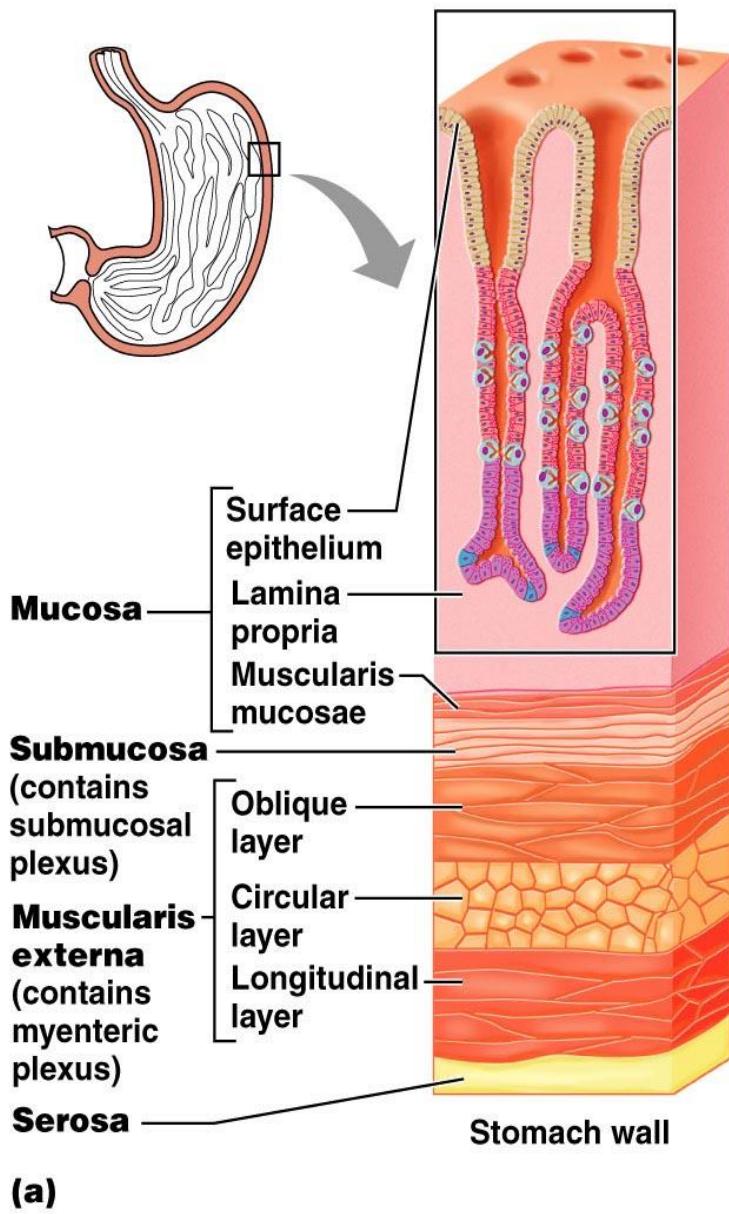
Anatomy of the Stomach



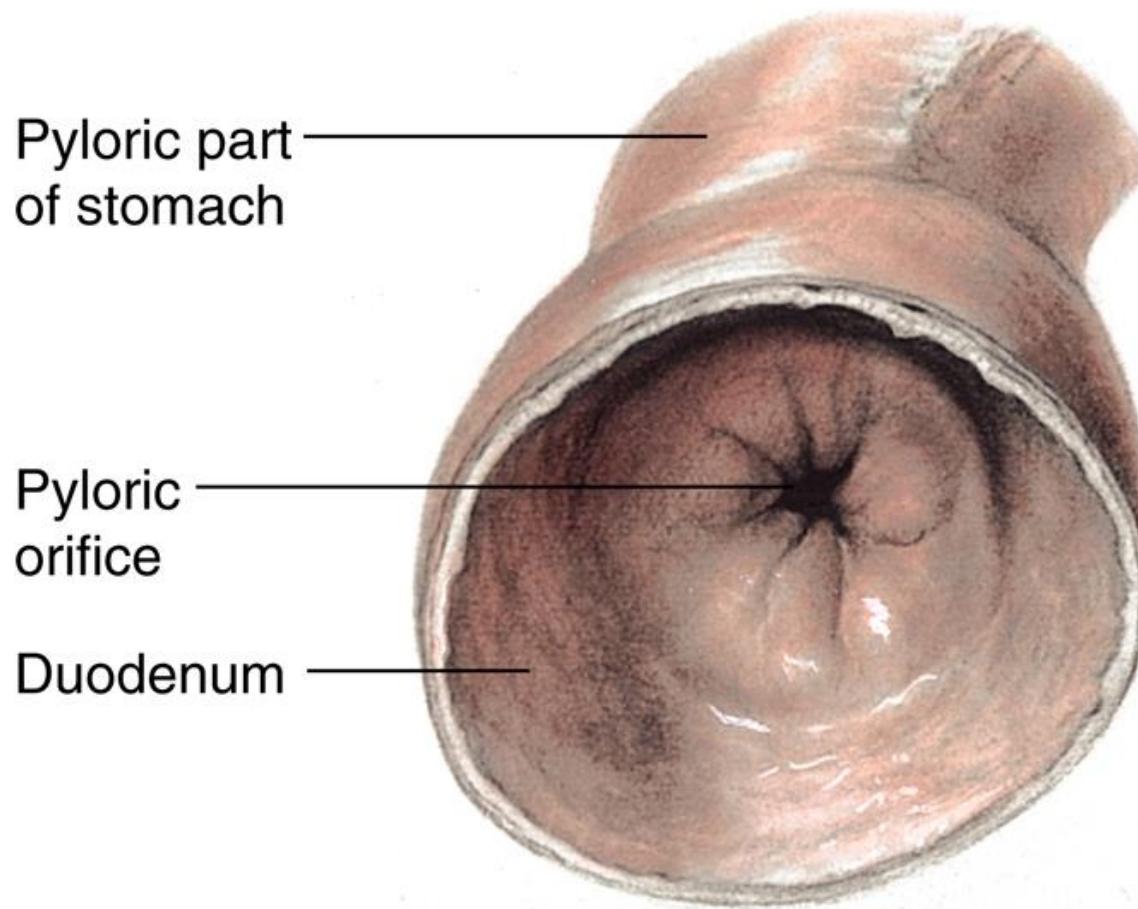
Anterior view



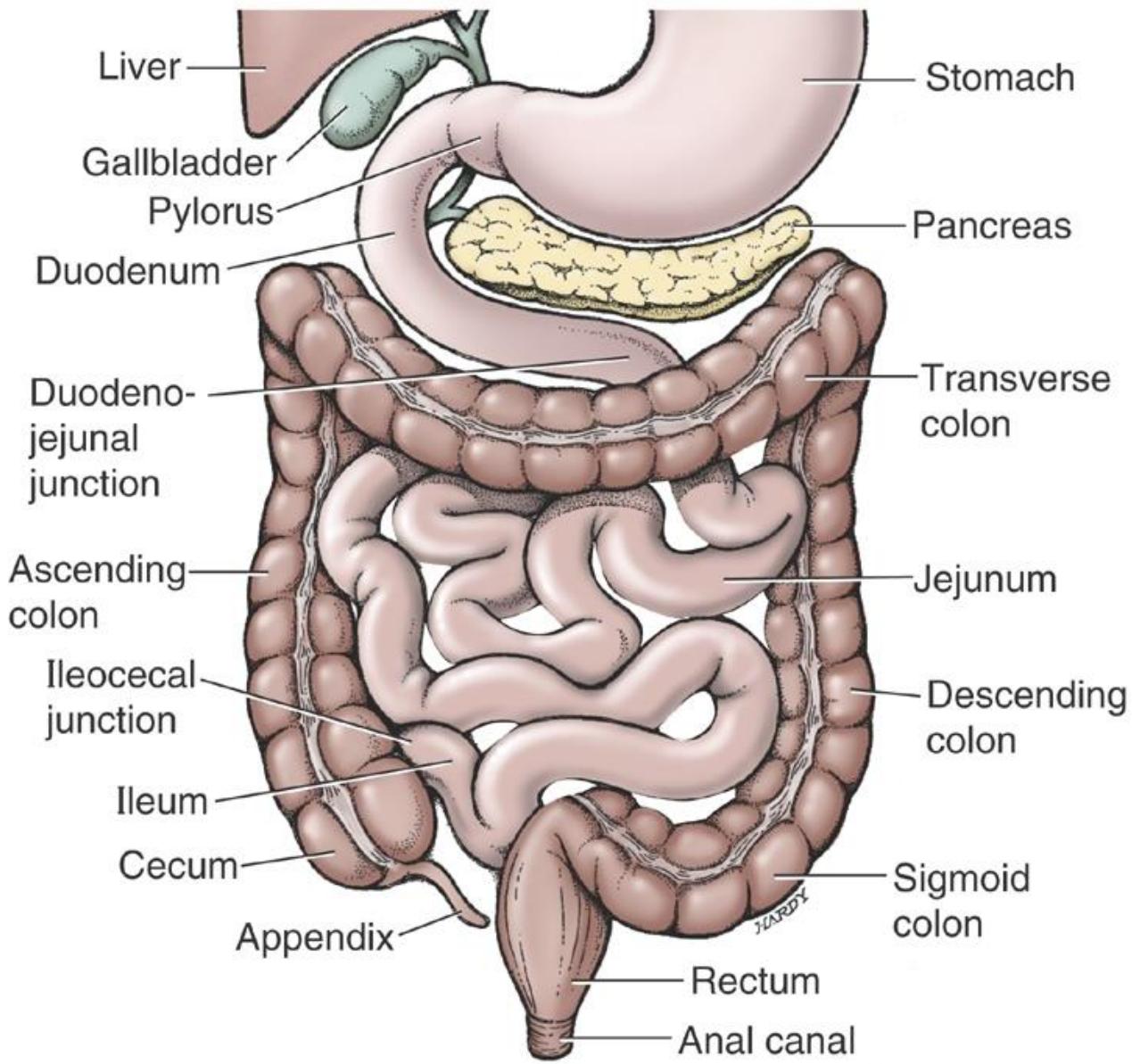
Microscopic Anatomy of the Stomach



Pyloric Sphincter

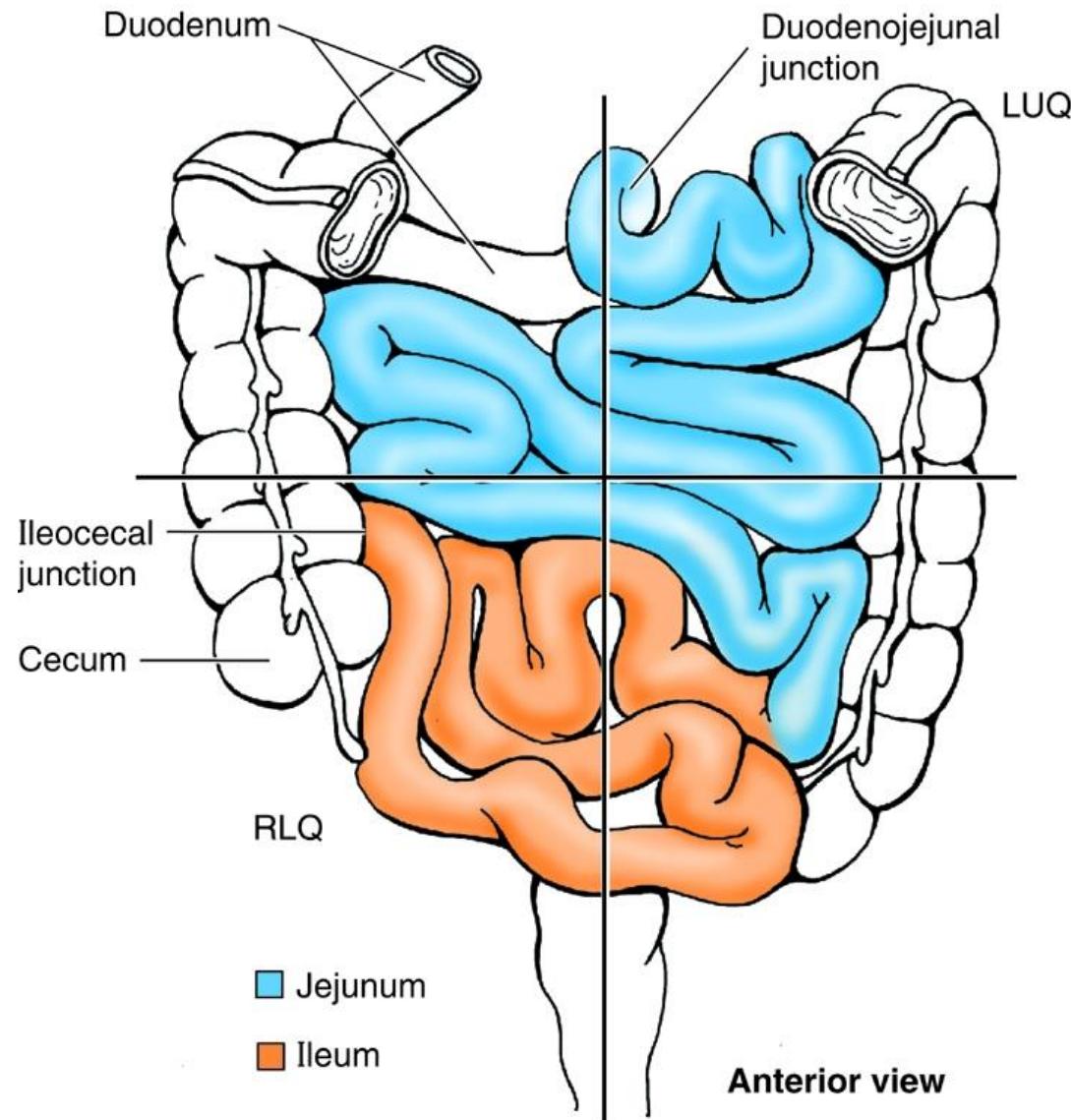


Internal (lateral) view from duodenum

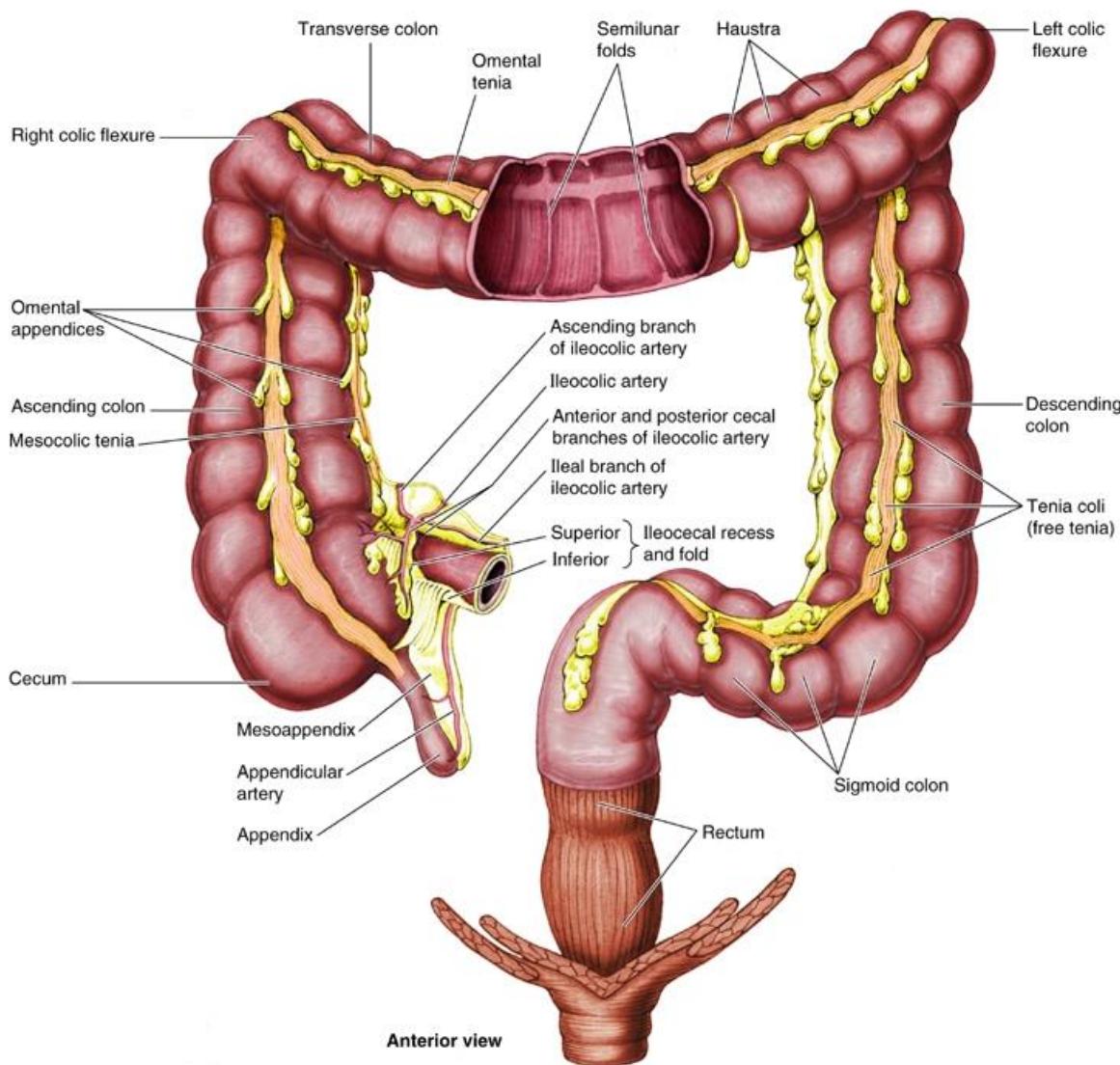


Anterior view

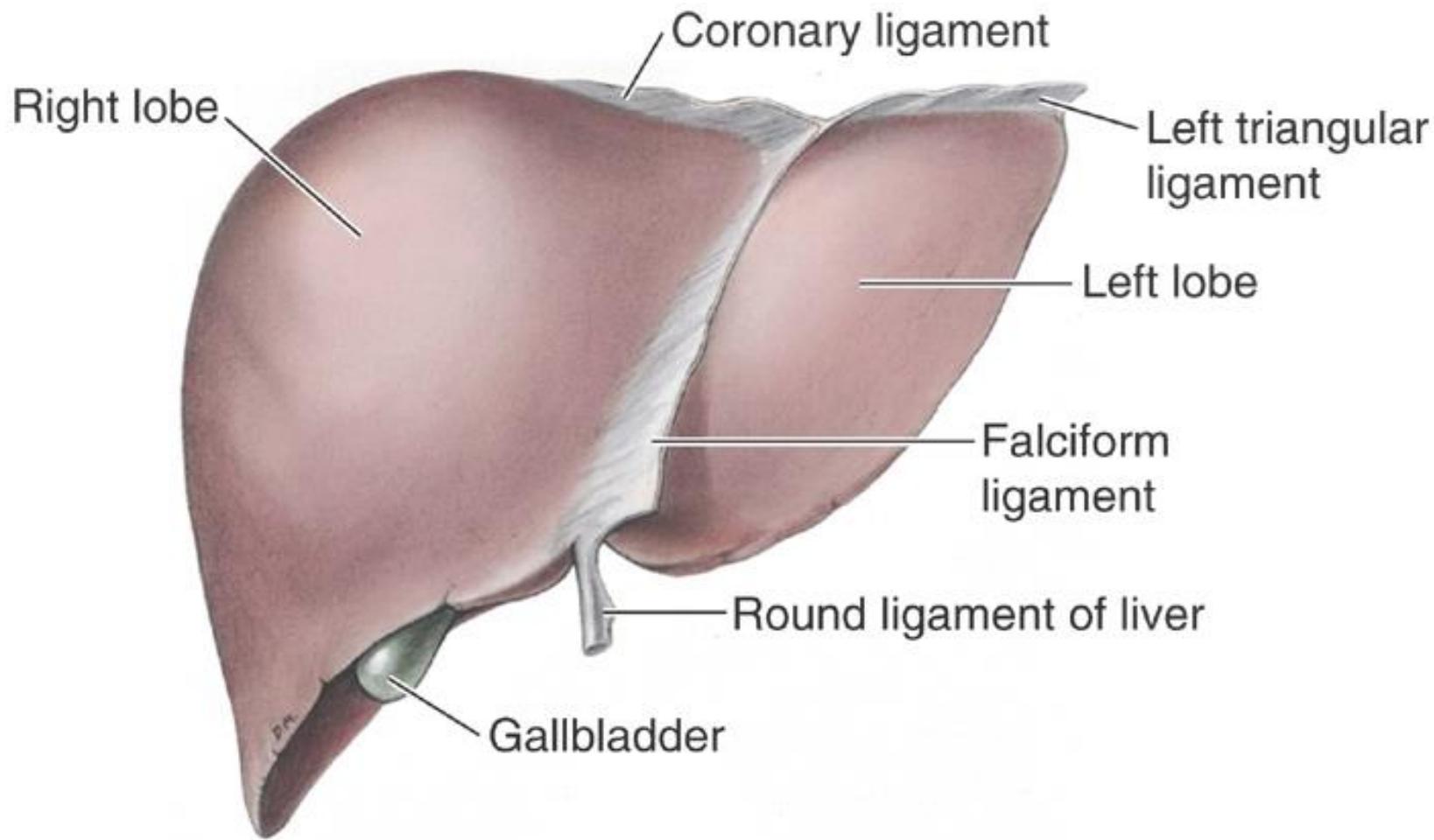
Ileum/Jejunum



Large Intestine

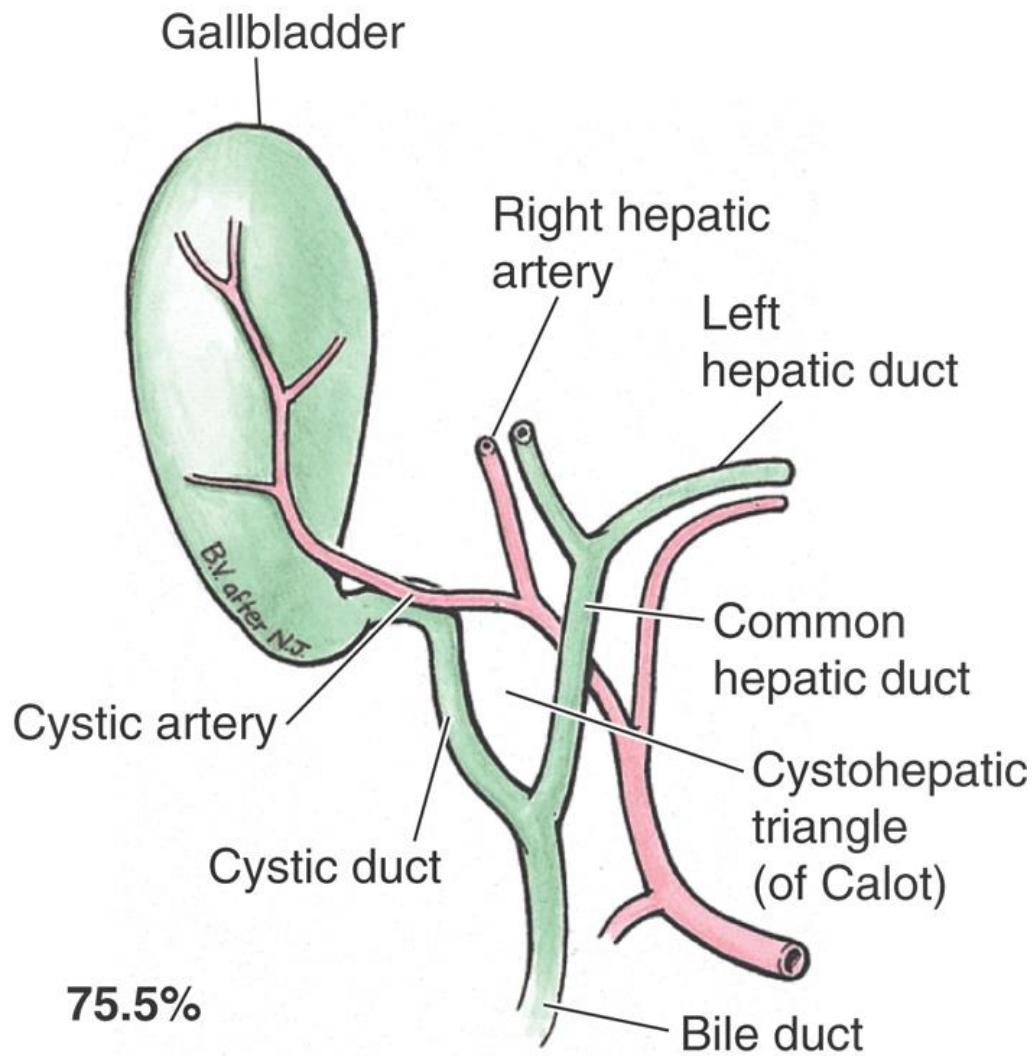


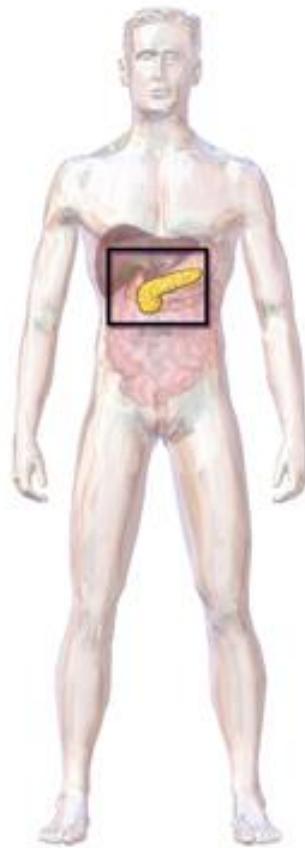
Liver - anterior



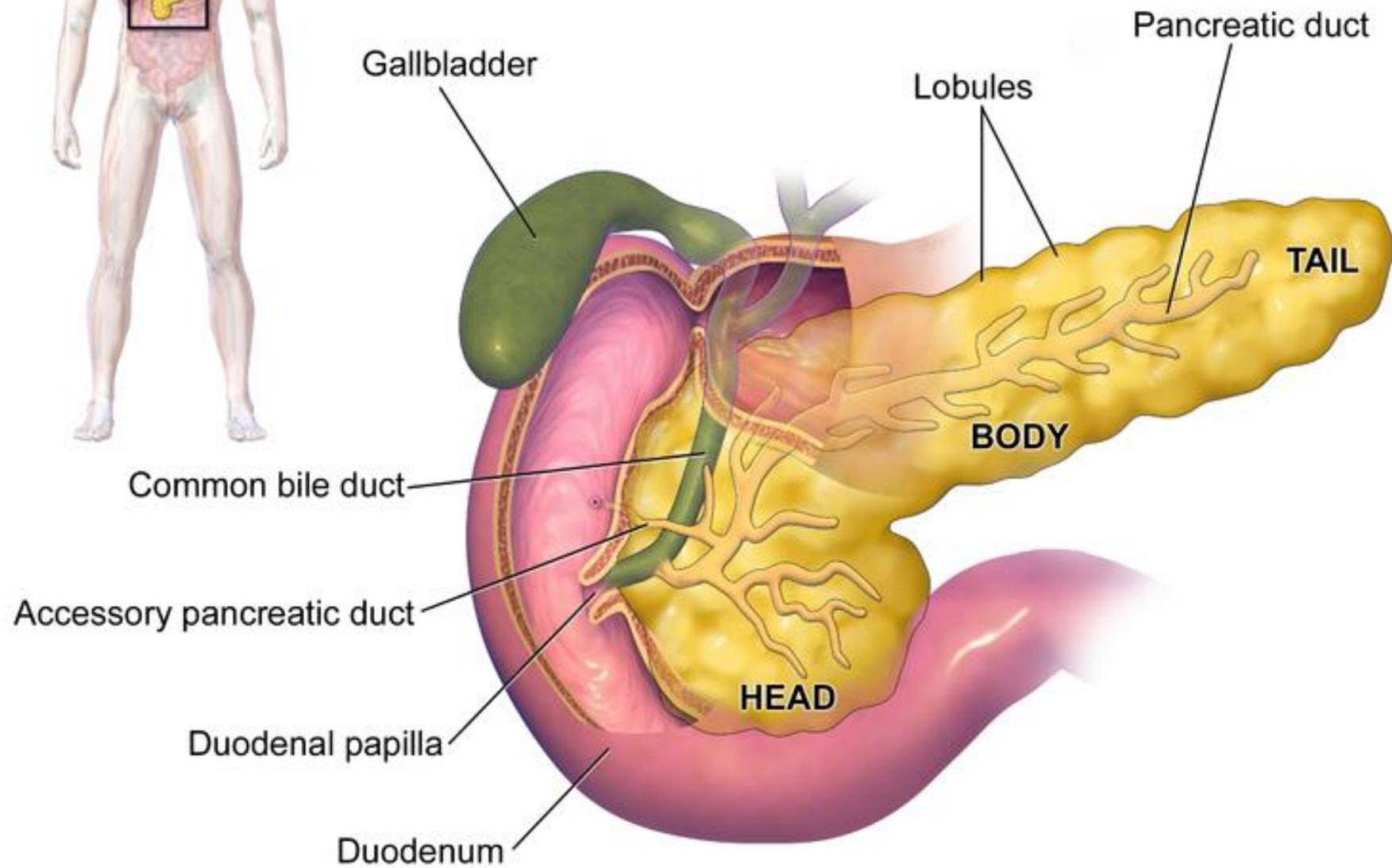
Diaphragmatic surface (Anterior view)

Biliary tree





pancreas





Watch video #
D1-D4

Digestive Physiology (chapter 64)

Types of Secretory Glands

- Single Cell - mucous cells or goblet cells
- Simple - indentations in epithelium
(crypts of Lieberkühn)
- Tubular - acid secreting oxyntic gland
- Complex - salivary, pancreas

Control of Secretions

- Local - tactile, distention, irritation
- Reflex- nervous input
- Hormonal - gastrointestinal (G.I.) hormones

Digestive Enzymes

Salivary glands

α -amylase

ptyalin

lingual lipase

Pancreas

amylase

trypsin

chymotrypsin

carboxypeptidase

elastase

lipase-colipase

phospholipase A₂

cholesterol

esterase

Stomach

pepsin

Intestinal Mucosa

enterokinase

sucrase

maltase

lactase

α -dextrinase

(isomaltase)

amino-

oligopeptidase

dipeptidase

■ Daily Secretion of Intestinal Juices

	Daily Volume (ml)	pH
Saliva	1000	6.0-7.0
Gastric secretion	1500	1.0-3.5
Pancreatic secretion	1000	8.0-8.3
Bile	1000	7.8
Small intestinal secretion	1800	7.5-8.0
Brunner's gland secretion	200	8.0-8.9
Large intestinal secretion	200	7.5-8.0
Total	6700	

Saliva

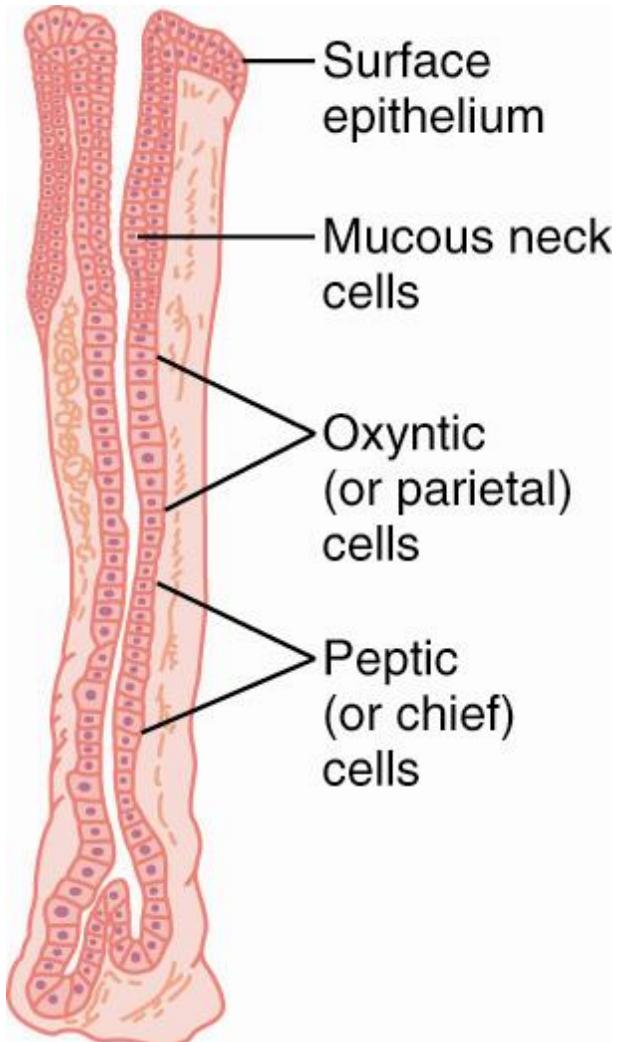
- Two types of secretion -
 - Serous - watery secretion, contains α -amylase (and ptyalin)
 - Mucous - contains mucin - lubrication
- Secrete 800-1500 ml/day of saliva
- Maximum rate of secretion: 4 ml/min

Salivary Glands

Watch video
#D6

Gland	Type of saliva	% of total Secreted
Parotid	Serous	90%
Submandibular	Mucous/ Serous	
Sublingual	Mucous/ Serous	10%
Buccal	Mucous	<1%

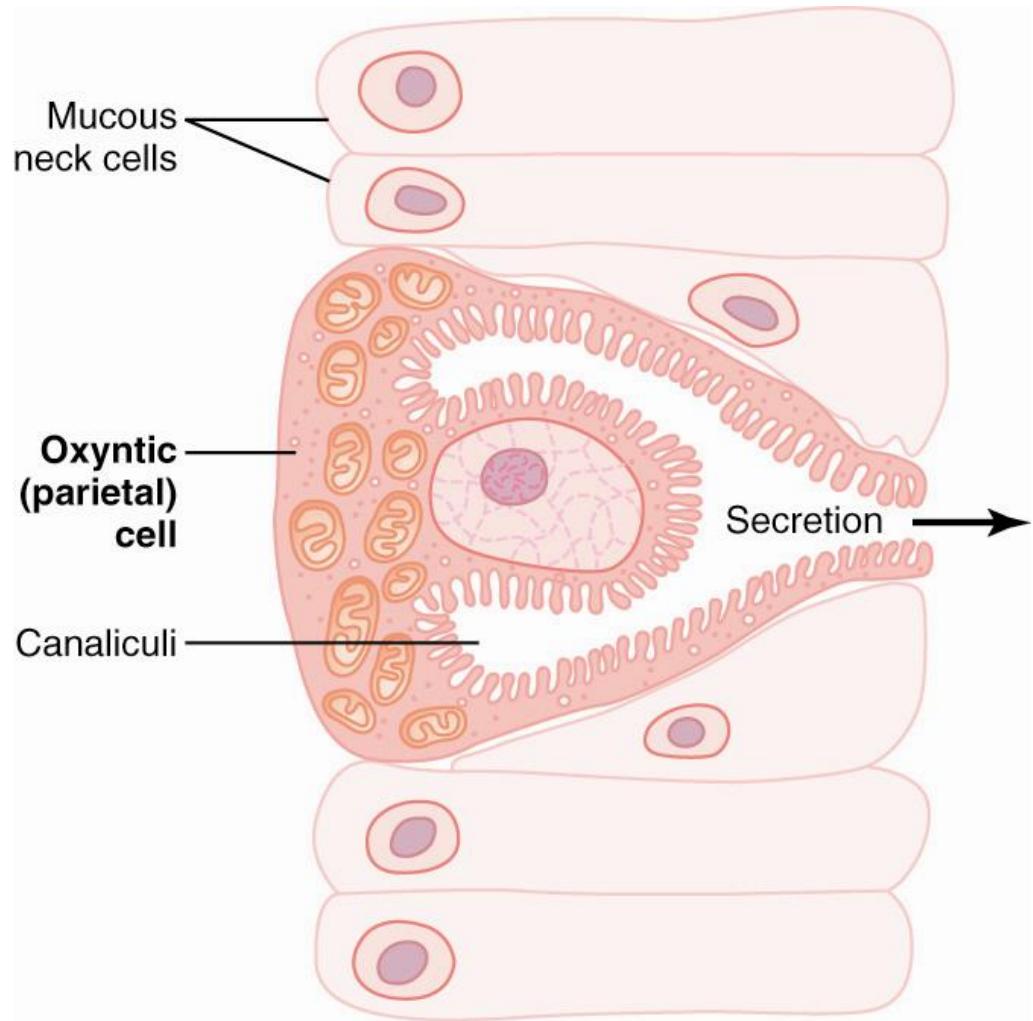
Gastric Secretion



Oxyntic gland from the body of the stomach

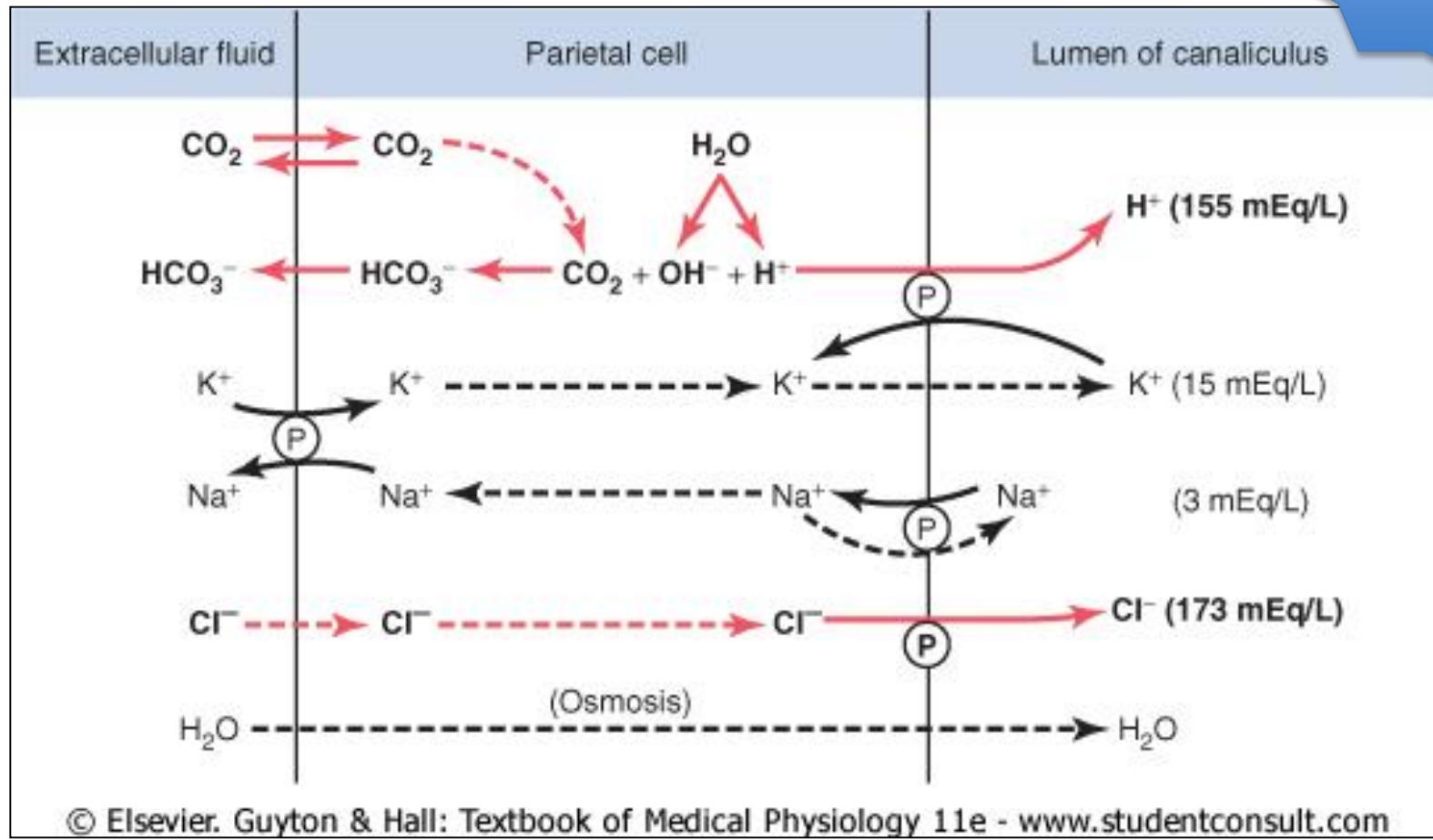
Oxyntic gland composed of three types of cells: (1) mucous neck cells, which secrete mainly mucus; (2) peptic (or chief) cells, which secrete large quantities of pepsinogen; and (3) parietal (or oxyntic) cells, which secrete hydrochloric acid and intrinsic factor.

Figure 64-4 :Oxyntic gland from the body of the stomach.



Oxytic gland
from the body of
the stomach

Figure 64-5; Schematic anatomy of the canaliculi in a parietal (oxytic) cell



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Figure 64–6

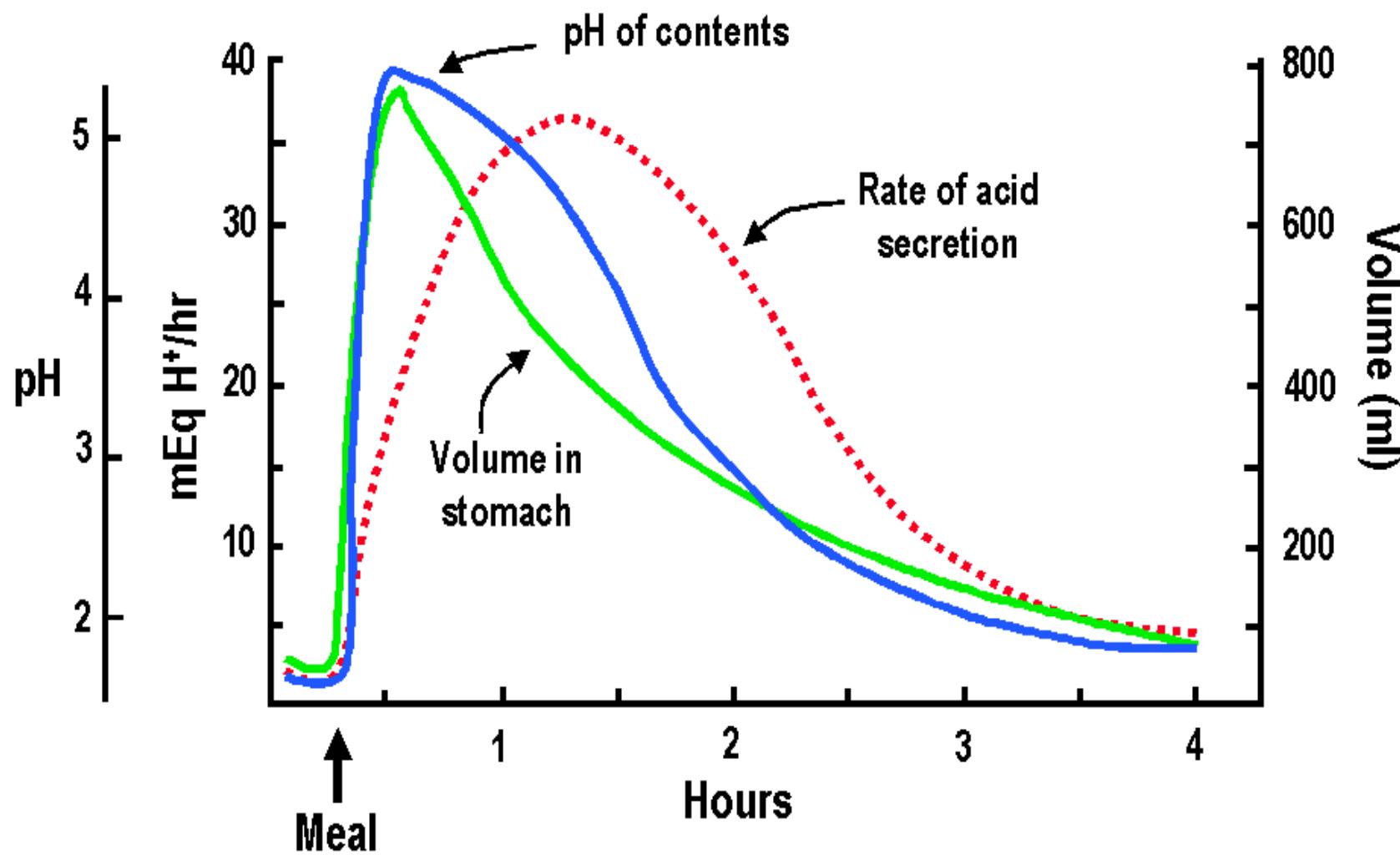
Postulated mechanism for secretion of hydrochloric acid. (The points labeled “P” indicate active pumps, and the dashed lines represent free diffusion and osmosis.)

Gastric Acid

- Three major functions -
 - Bacteriostatic
 - Converts pepsinogen to pepsin
 - Begins protein digestion (with pepsin)

■ Pepsinogen

- Pepsinogen is an inactive, secreted form of pepsin -
 - Acid converts pepsinogen to pepsin
 - Pepsin (35 kDa) converts more pepsinogen to pepsin
 - proteolytic enzyme
 - optimal pH 1.8 - 3.5
 - reversibly inactivated > pH 5.0
 - irreversibly inactivated > pH 7-8



➤ Peptic Ulcers

- Peptic ulcers occur when damaging effects of acid and pepsin overcome ability of mucosa to protect itself
 - Gastric ulcers - main problem is decreased ability of mucosa to protect itself
 - Duodenal ulcers - main problem is exposure to increased amounts of acid and pepsin

Pancreas

- As chyme floods into small intestine two things must happen:
 - Acid must be neutralized to prevent damage to duodenal mucosa
 - Macromolecular nutrients - proteins, fats and starch must be broken down much further so their constituents can be absorbed

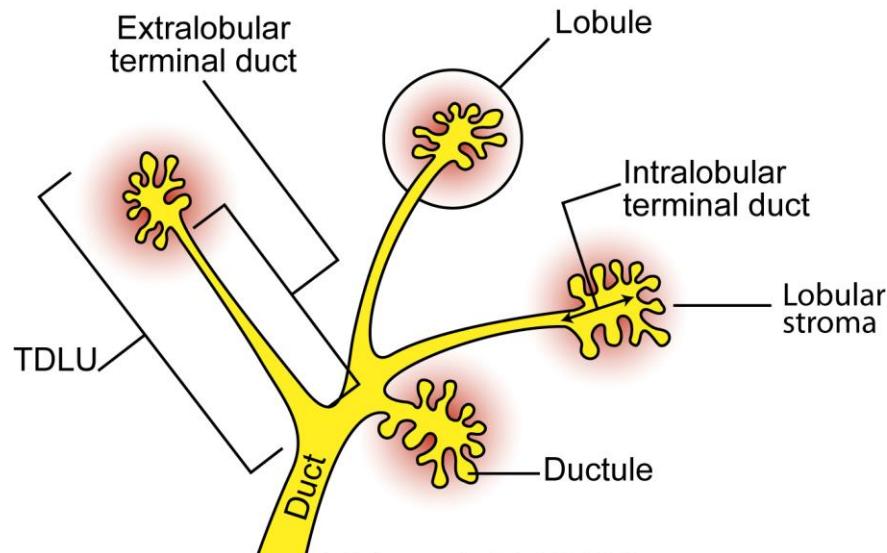
Pancreas – (cont.)

- Pancreas plays vital role in accomplishing both objectives
 - Digestive enzymes for all food types
 - Bicarbonate solution to neutralize acid chyme

Internal Structure of Pancreas

Watch video
#D9-D10

- Compound gland with structure similar to salivary gland
- Acini - grape-like clusters of cells that store and secrete digestive enzymes
- Ducts - secrete bicarbonate
 - Intercalated ducts - receive secretions from acini
 - Intralobular ducts - receive fluid from intercalated ducts



■ Enzymes for Protein Digestion

- Proteolytic enzymes
 - Trypsin
 - Chymotrypsin
 - Carboxypeptidase
- } Cleaves proteins to polypeptides
- } Cleaves polypeptides to AA

■ Enzymes for Carbohydrate Digestion

- Pancreatic amylase
 - starches
 - glycogen } to disaccharides

■ Enzymes for Fat Digestion

- Pancreatic lipase -
 - fat → fatty acids +monoglycerides
- Phospholipase -
 - phospholipids → fatty acid
- Cholesterol esterase -
 - cholesterol esters → fatty acid

Why Doesn't the Pancreas Digest Itself?

- Pancreatic proteolytic enzymes are stored and secreted in an inactive form - (also, a trypsin inhibitor is present in cells)
 - trypsinogen → trypsin
 - chymotrypsinogen → chymotrypsin
 - procarboxypeptidase → carboxypeptidase

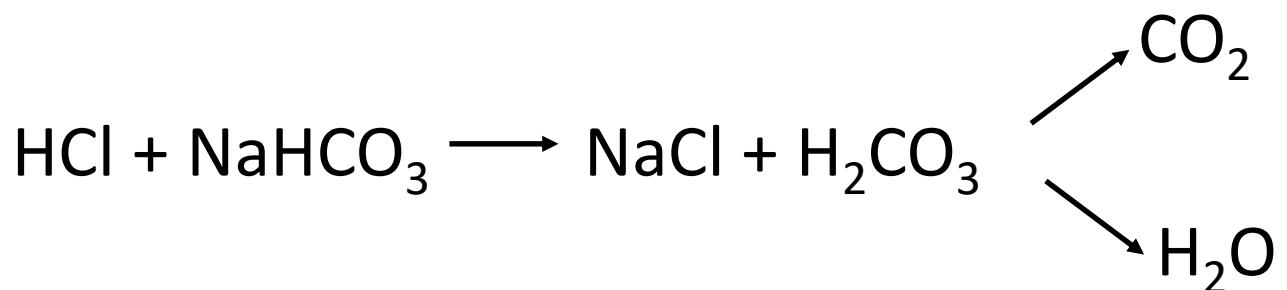
■ Activation of Proteolytic Enzymes



- Enterokinase - located on intestinal mucosal cells
- Trypsin - autocatalytic activation
 - activates → chymotrypsinogen,
 - procarboxypeptidase
 - trypsinogen

- Bicarbonate Neutralizes Acid Chyme

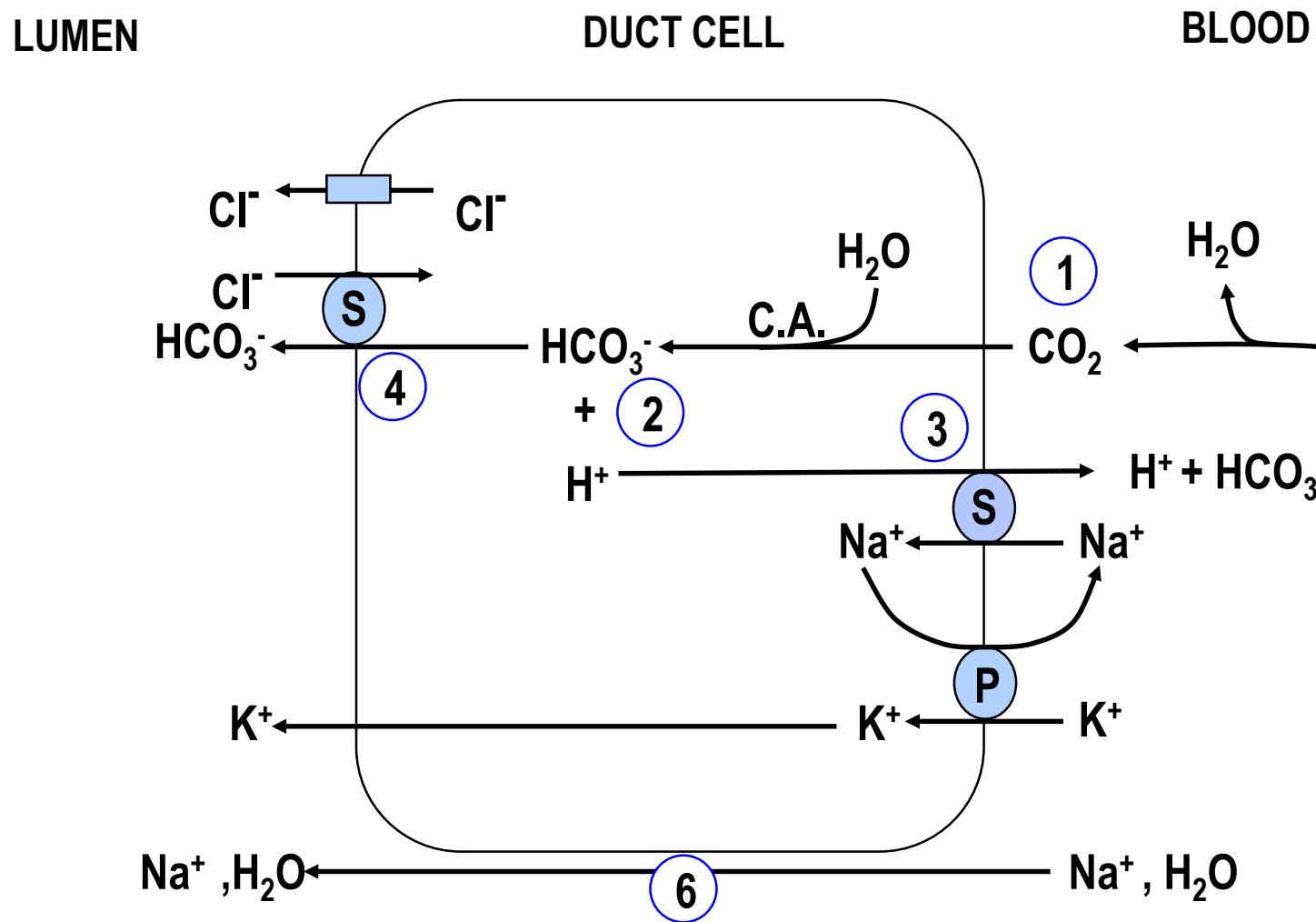
- Secretin induced bicarbonate secretion neutralizes acid chyme creating optimal conditions (pH = 7-8) for digestive enzymes -



Secretin is nature's antiacid

■ Model of Bicarbonate Secretion

1. CO_2 combines with H_2O in presence of C.A. in cell
2. Carbonic acid dissociates into HCO_3^- and H^+ ions
3. H^+ ions are transported through apical membrane by secondary transport mechanism that requires Na^+ gradient. Na^+ gradient is established by usual $\text{Na}^+ - \text{K}^+$ ATPase pump.
4. HCO_3^- moves out of cell in exchange for Cl^- .



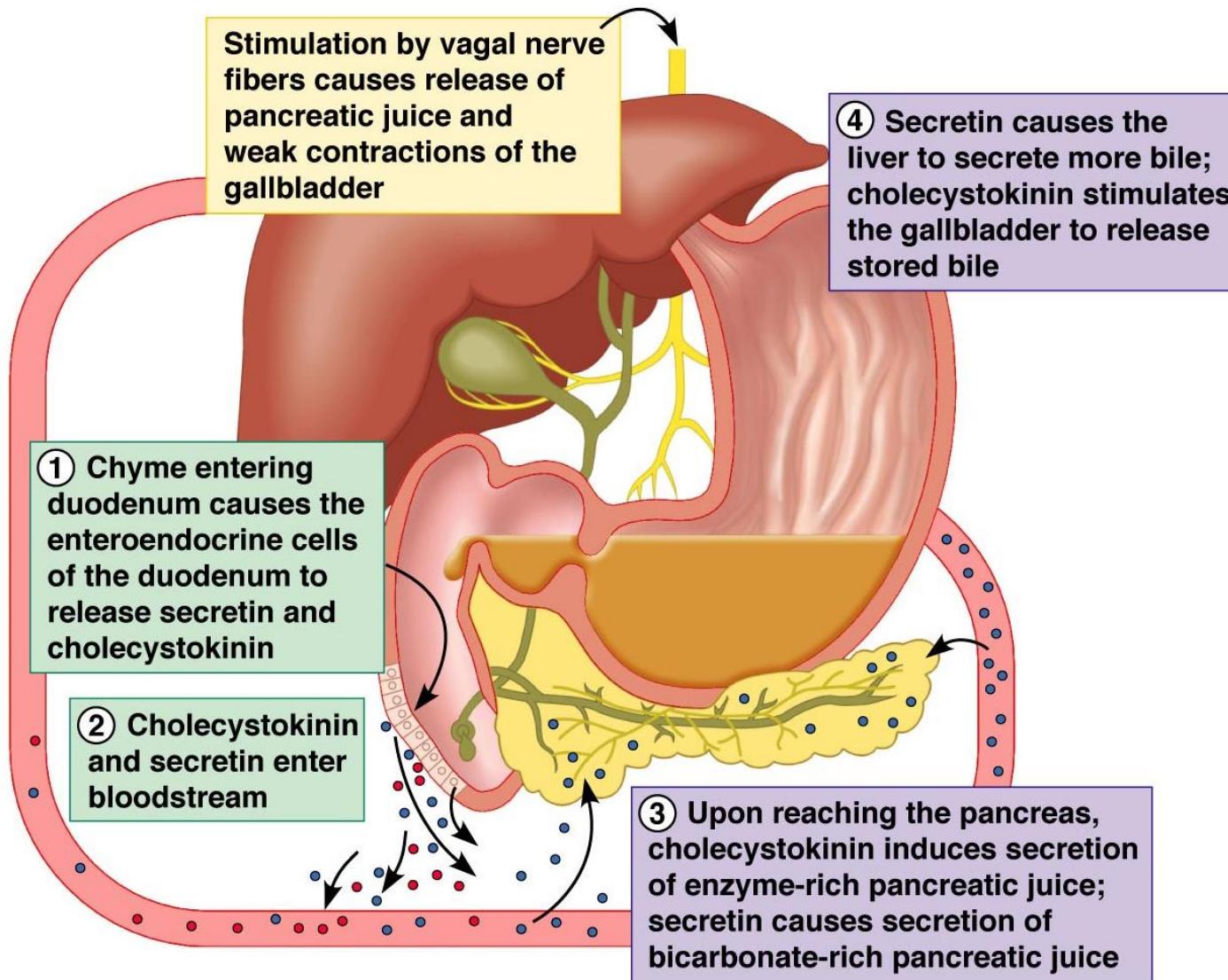
Model of Bicarbonate Secretion - (cont)

5. Rate of HCO_3^- secretion is dependent upon luminal Cl^- concentration.
6. Na^+ moves down electrochemical gradient. Water moves into lumen establishing osmotic equilibrium.

Secretin - acts to open Cl^- channels and thus increase secretion of bicarbonate.

- Effect of Secretion Rate on Ionic Composition of Pancreatic Juice
 - Low secretion rates -
 - bicarbonate concentration is low
 - chloride concentration is high
 - High secretion rates -
 - bicarbonate concentration is high
 - chloride concentration is low
 - Sodium and potassium concentrations always same as plasma

■ Regulation of pancreatic secretion



Hormones & Hormonelike Products that Act in Digestion

TABLE 14.1 **Hormones and Hormonelike Products That Act in Digestion**

Hormone	Source	Stimulus for secretion	Action
Gastrin	Stomach	Food in stomach (chemical stimulus); ACH released by nerve fibers	<ul style="list-style-type: none">• Stimulates release of gastric juice• Stimulates stomach emptying
Intestinal gastrin	Duodenum	Acidic food in stomach	<ul style="list-style-type: none">• Stimulates gastric secretion and emptying
Histamine	Stomach	Food in stomach	<ul style="list-style-type: none">• Activates parietal cells to secrete hydrochloric acid.
Somatostatin	Stomach and duodenum	Food in stomach; stimulated by sympathetic nerve fibers	<ul style="list-style-type: none">• Inhibits secretion of gastric juice and pancreatic juice• Inhibits emptying of stomach and gallbladder.

Hormones & Hormonelike Products that Act in Digestion

TABLE 14.1**Hormones and Hormonelike Products That Act in Digestion (continued)**

Hormone	Source	Stimulus for secretion	Action
Secretin	Duodenum	Acidic chyme and partially digested foods in duodenum	<ul style="list-style-type: none">• Increases output of pancreatic juice rich in bicarbonate ions• Increases bile output by liver• Inhibits gastric mobility and gastric gland secretion.
Cholecystokinin (CCK)	Duodenum	Fatty chyme and partially digested proteins in duodenum	<ul style="list-style-type: none">• Increases output of enzyme-rich pancreatic juice• Stimulates gallbladder to expel stored bile• Relaxes sphincter of duodenal papilla to allow bile and pancreatic juice to enter the duodenum.
Gastric inhibitory peptide (GIP)	Duodenum	Fatty chyme in duodenum	<ul style="list-style-type: none">• Inhibits secretion of gastric juice.

Distribution of GI Hormones

- Digestive products are equally effective in releasing secretin when applied to any part of duodenum or jejunum.

Fundus | Antrum | Duo | Jejun | Ileum | Colon

Secretin



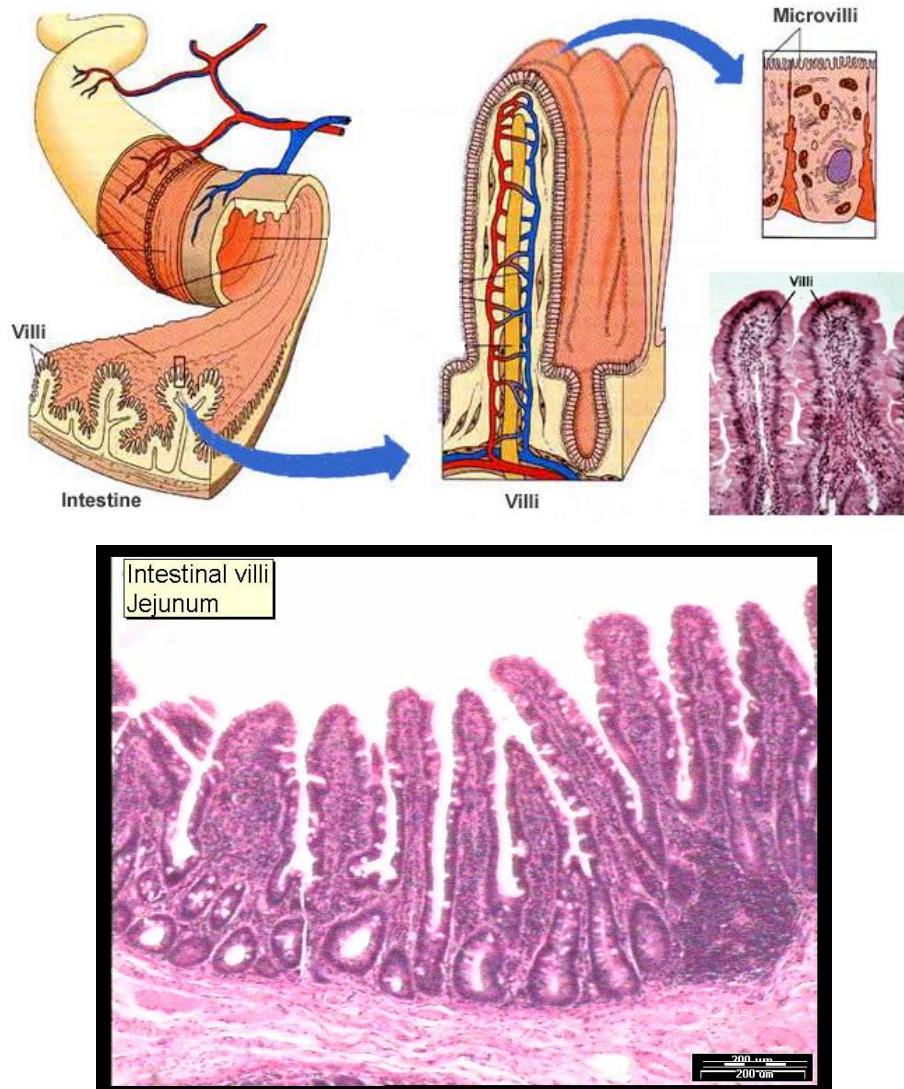
Pancreatic Failure

- Digestion is abnormal when pancreas fails to secrete normal amounts of enzymes.
- Without pancreatic enzymes -
 - 60% fat not absorbed
 - 30-40% protein and carbohydrates not absorbed

Absorption and Neural Control of Digestion

Absorption in the Small Intestine

- The small intestine is specially adapted for absorption of nutrients.
 - The folded surfaces of the small intestine are covered with fingerlike projections called villi.
 - Villi increases the surface area for absorption of nutrients



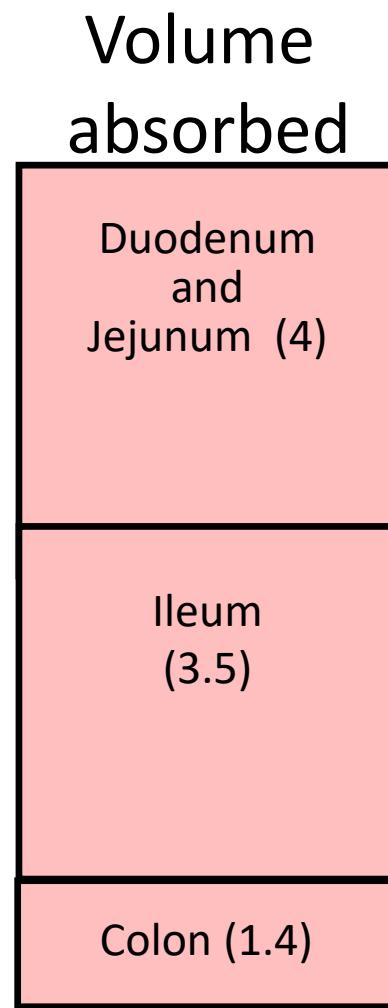
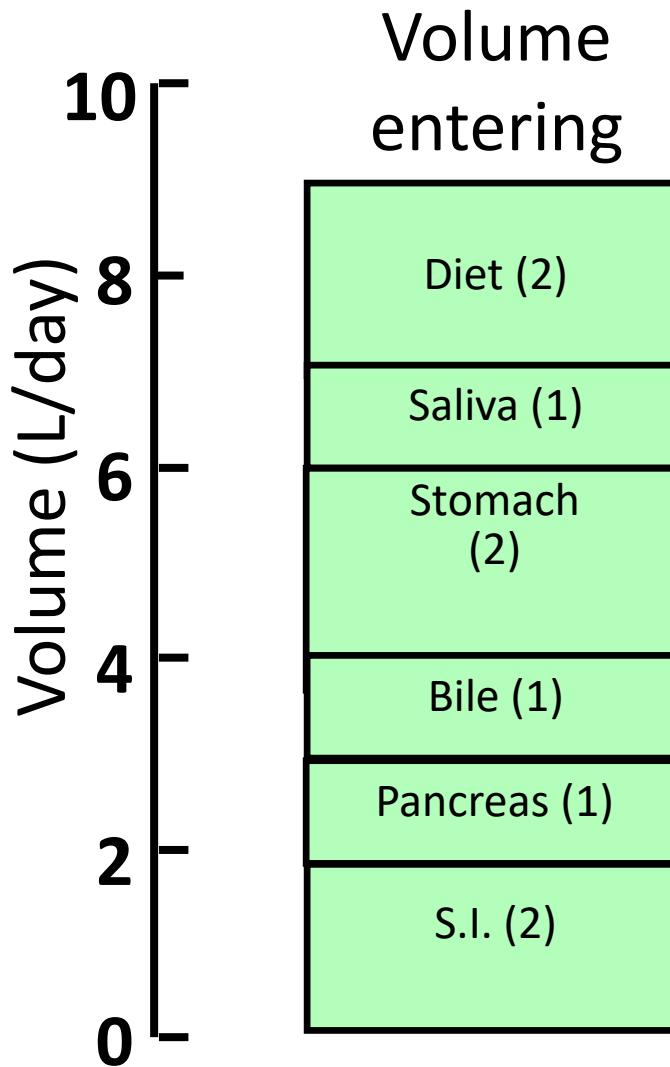
Absorption in the Small Intestine

- By the time food is ready to leave the small intestine, it is basically nutrient-free.
 - The complex organic molecules have been digested and absorbed, leaving only water, cellulose, and other undigestible substances behind.

Mechanisms of Absorption

- Four mechanisms are important in transport of substances across intestinal cell membrane
 - Active Transport -
 - primary
 - secondary (co-transport, counter-transport)
 - Passive Diffusion
 - Facilitated Diffusion - carrier mediated
 - Endocytosis

Fluid Entering and Exiting the Gut



Volume Excreted
100-200 ml

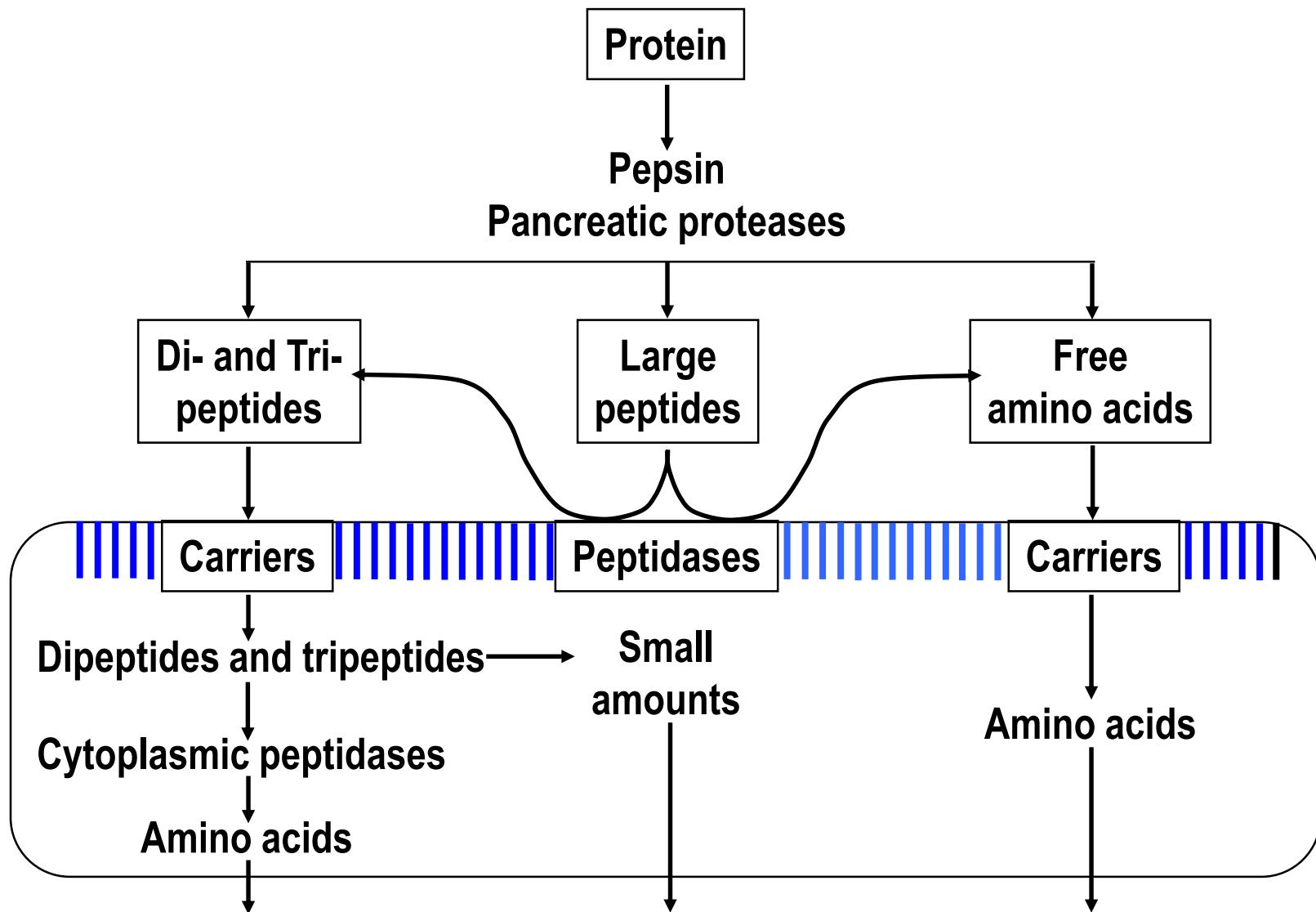
A horizontal bar chart showing the volume of fluid excreted per day. The Y-axis represents Volume in liters per day (L/day), ranging from 0 to 10. The X-axis represents the volume excreted. The total length of the bar is approximately 100-200 ml.

Excretion	Volume (ml)
Excreted	100-200

Carbohydrate Digestion and Assimilation

- Begins in the mouth via our saliva, with help from an enzyme - salivary amylase
- Digestive enzymes released by the pancreas into the small intestine (in response to eating carbohydrates) allows the absorption of carbohydrates throughout the small intestine

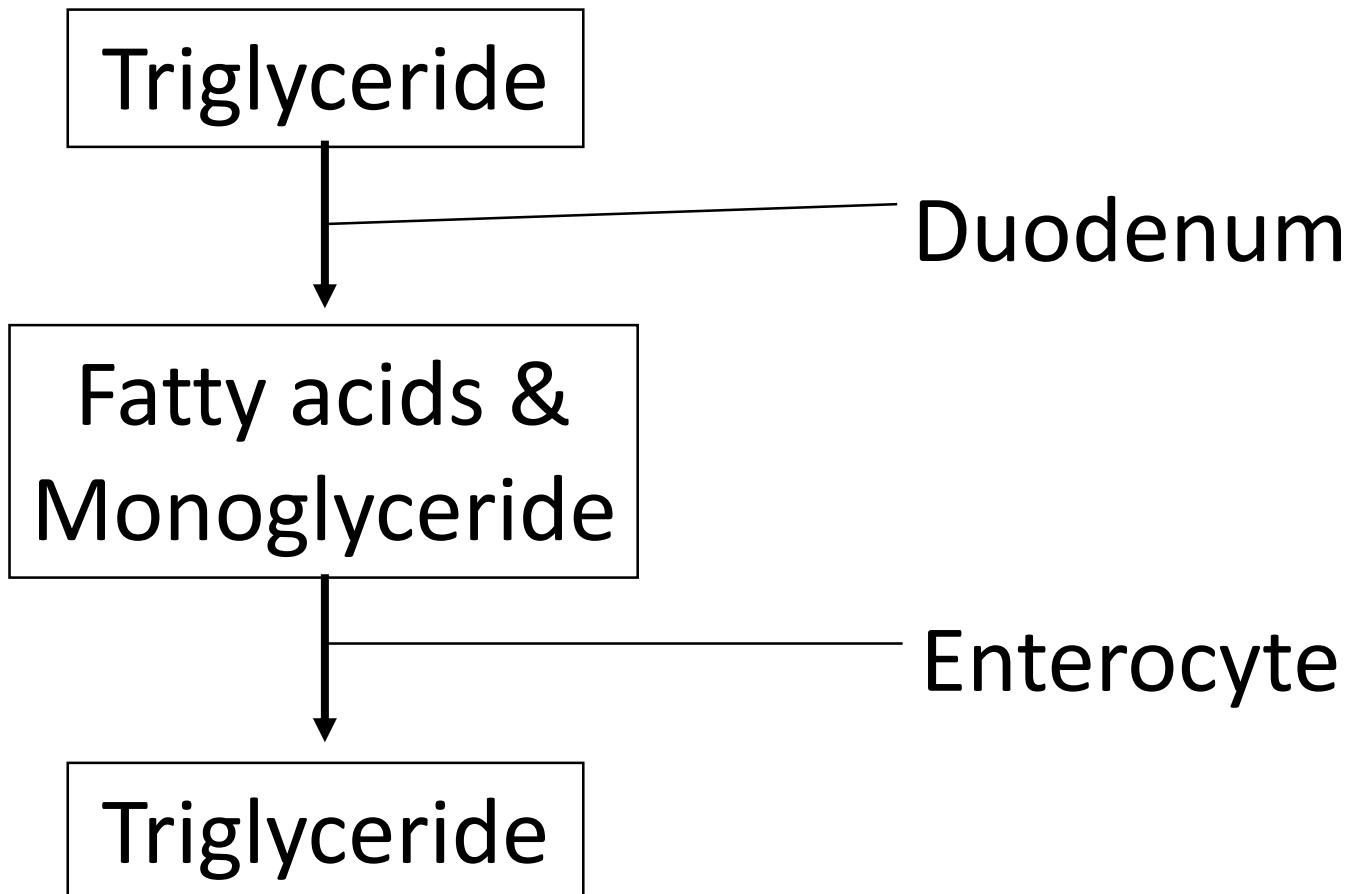
Protein Digestion and Absorption



Basic Steps of Lipid Assimilation

- Most dietary lipid is neutral fat or triglyceride. Three main processes must occur for triglyceride to be absorbed into blood:
 - Emulsification - large aggregates of dietary triglyceride are broken down.
 - Enzymatic digestion - to yield monoglyceride and fatty acids. Both can diffuse into enterocyte.
 - Reconstitution of triglyceride and chylomicron formation

Assimilation of Lipids – Overall Scheme



Neural Control of GI Tract

- Intrinsic Control - Enteric nervous system
 - Myenteric (Auerbach's) plexus
 - Submucosal (Meissner's) plexus
- Extrinsic Control - Autonomic nervous system
 - Parasympathetic - mainly stimulates (Ach)
 - Sympathetic - mainly inhibits (NE)

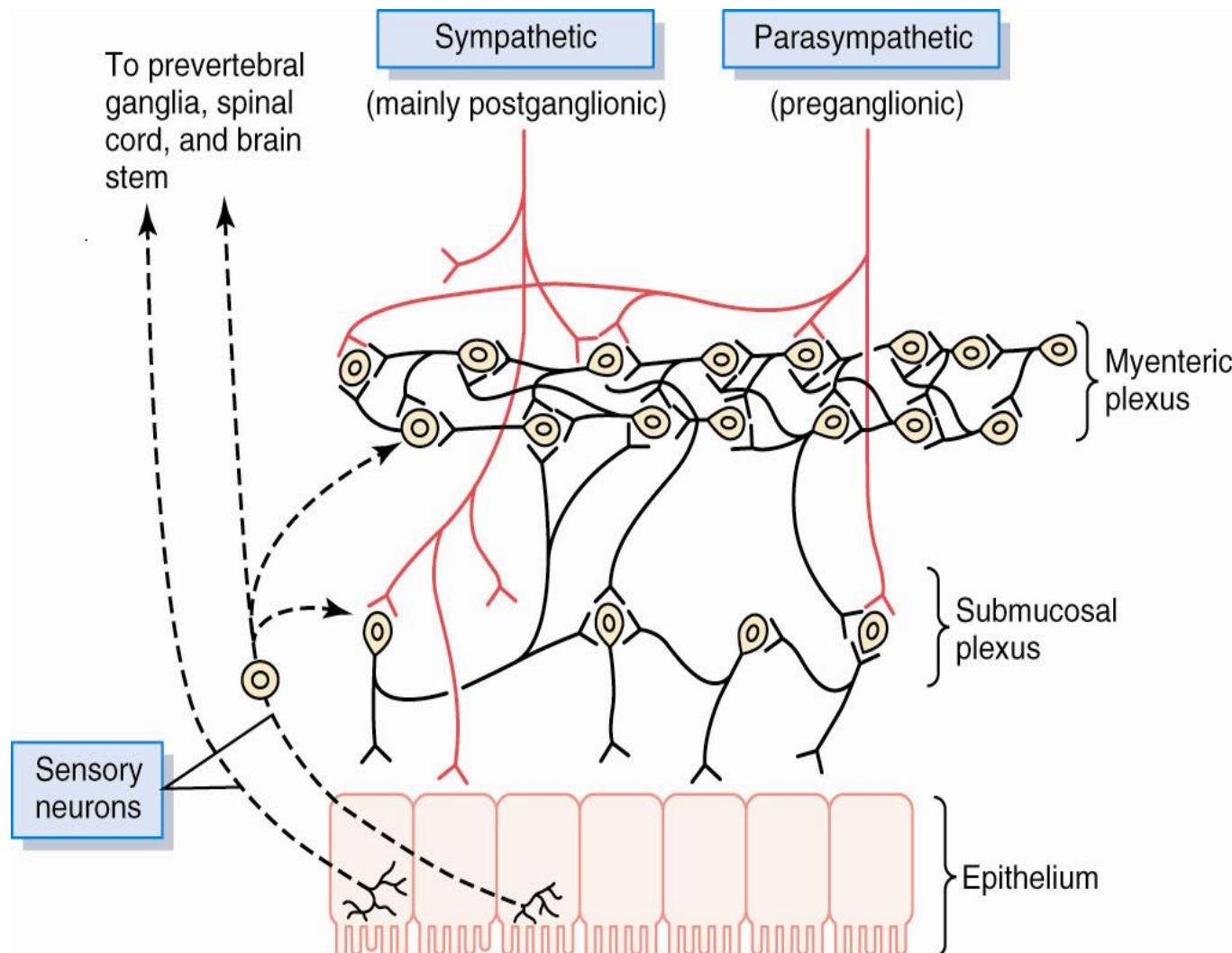


Figure 62-4 Neural control of the gut wall, showing (1) the myenteric and submucosal plexuses (black fibers); (2) extrinsic control of these plexuses by the sympathetic and parasympathetic nervous systems (red fibers); and (3) sensory fibers passing from the luminal epithelium and gut wall to the enteric plexuses, then to the prevertebral ganglia of the spinal cord and directly to the spinal cord and brain stem (dashed fibers)

Metabolism

67. Metabolism of Carbohydrates, and
Formation of Adenosine Triphosphate

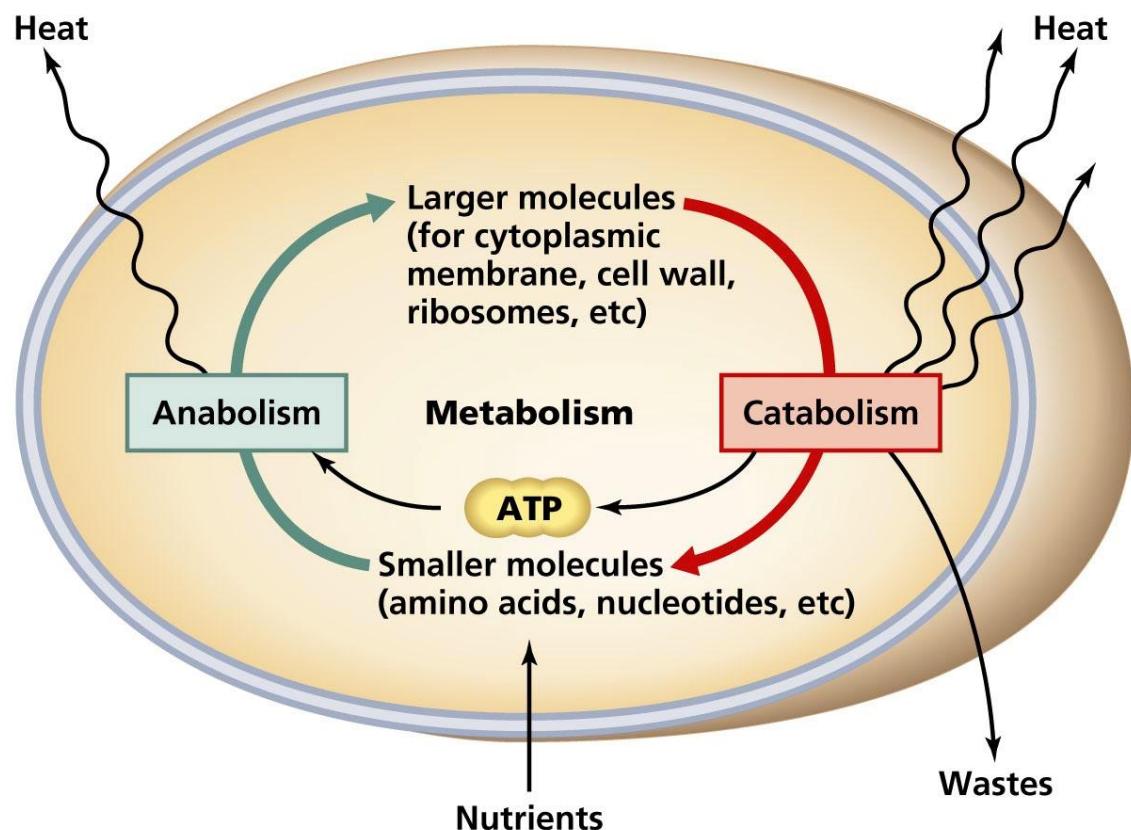
68. Lipid Metabolism

69. Protein Metabolism

□ Metabolism

- **Metabolism** is the sum of all of the chemical activities cells undergo throughout their lives. It is composed of two main subdivisions:

- Anabolism
- Catabolism



➤ Anabolism and Catabolism

- **Anabolism**
 - Buildup or synthesis of larger organic macromolecules from small organic subunits
 - Reactions usually require ATP energy
 - Reactions result in
 - Manufacture of materials needed by the cell
 - Storage of excess ingested nutrients not immediately needed for energy production or needed as cellular building blocks
- **Catabolism**
 - Breakdown or degradation of large, energy-rich organic molecules within cells
 - Two levels of breakdown
 - Hydrolysis of large cellular molecules into smaller subunits
 - Oxidation of smaller subunits to yield energy for ATP production
- Both types of reactions occur through a series of enzyme-mediated steps called **metabolic pathways**

□ Cells and Mitochondria

- cells provide small organic molecules for their mitochondria
- Mitochondria produce ATP used to perform cellular functions

Role of Adenosine Triphosphate in Metabolism

- Adenosine triphosphate (ATP) - the central link between energy-producing and energy-using systems of the body

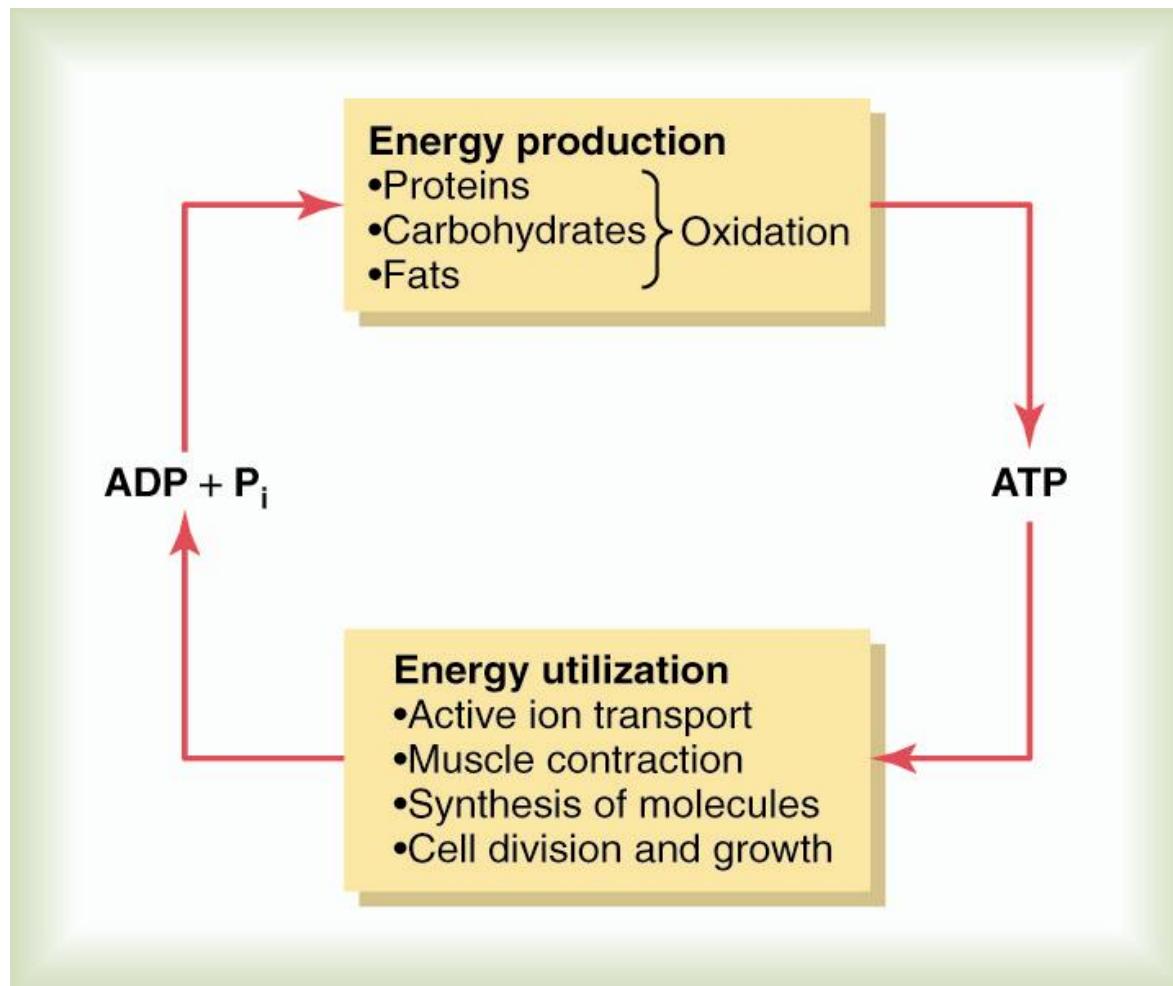
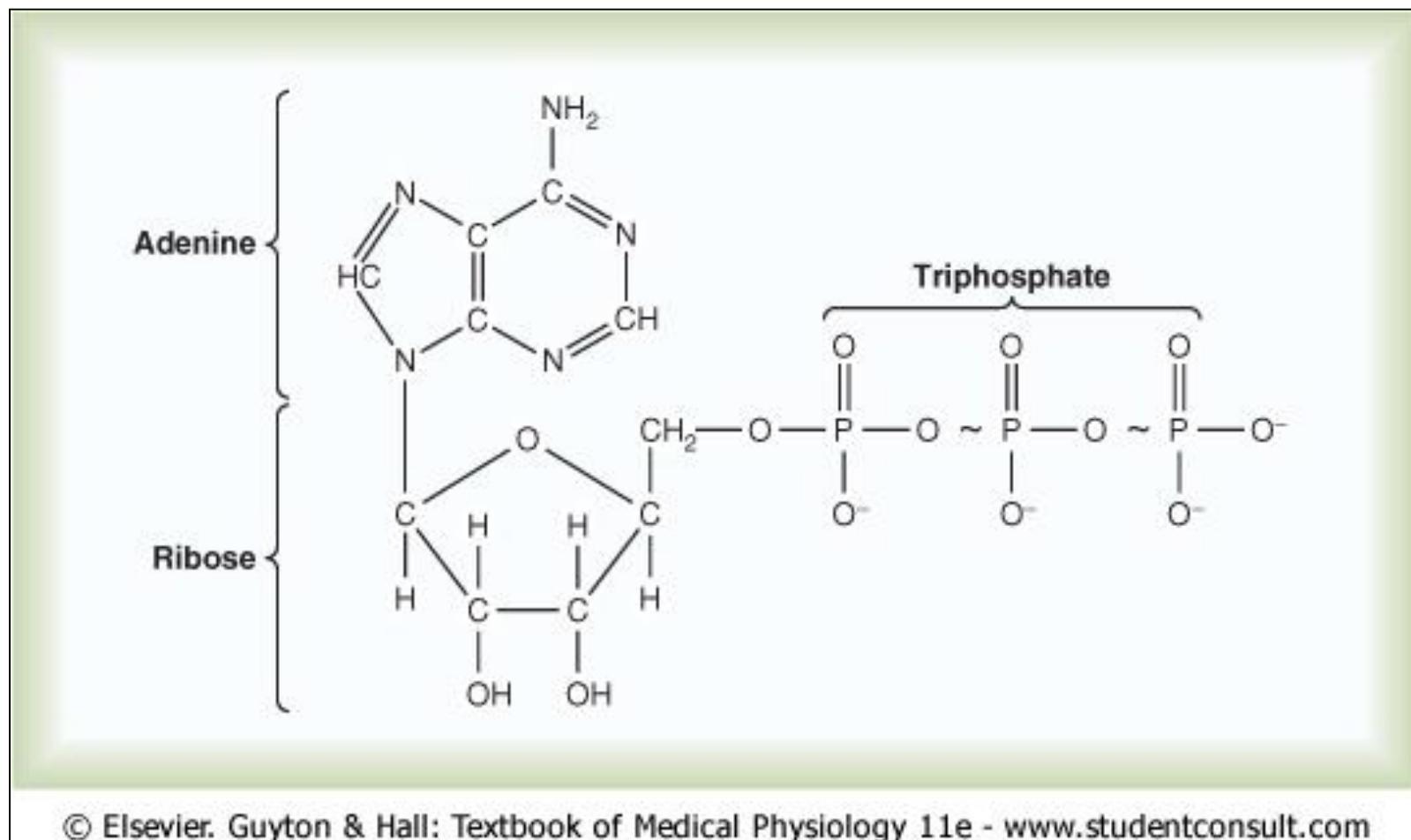


Figure 67-1; Adenosine triphosphate (ATP) as the central link between energy- producing and energy-utilizing systems of the body. ADP, adenosine diphosphate; Pi, inorganic phosphate.

■ ATP Structure

- ATP is a combination of adenine, ribose, and three phosphate radicals. The last two phosphate radicals are connected with the remainder of the molecule by high-energy bonds, which are indicated by the symbol ~.



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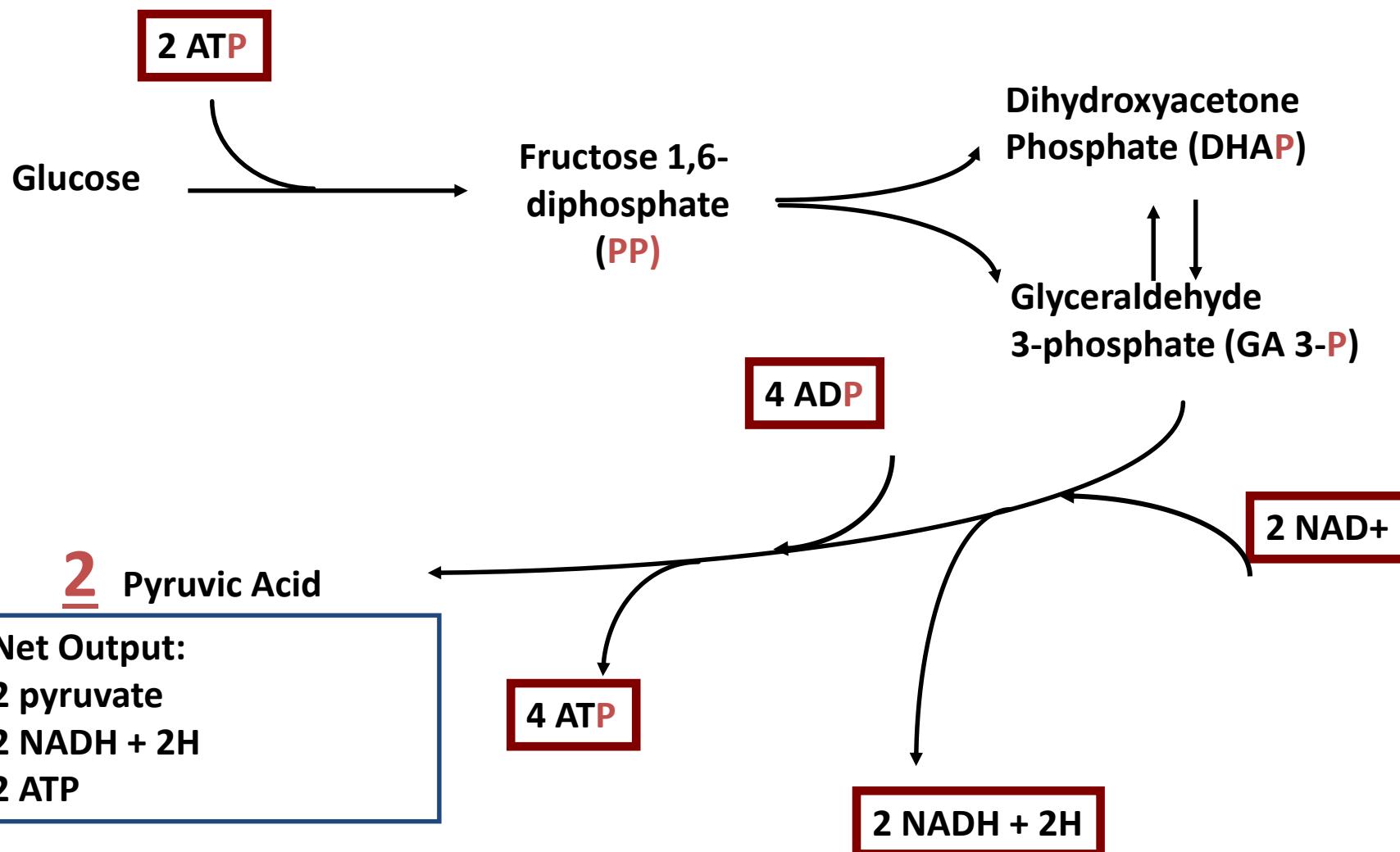
Figure 67–2
Chemical structure of adenosine triphosphate (ATP).

Glucose Transport Into Most Cells

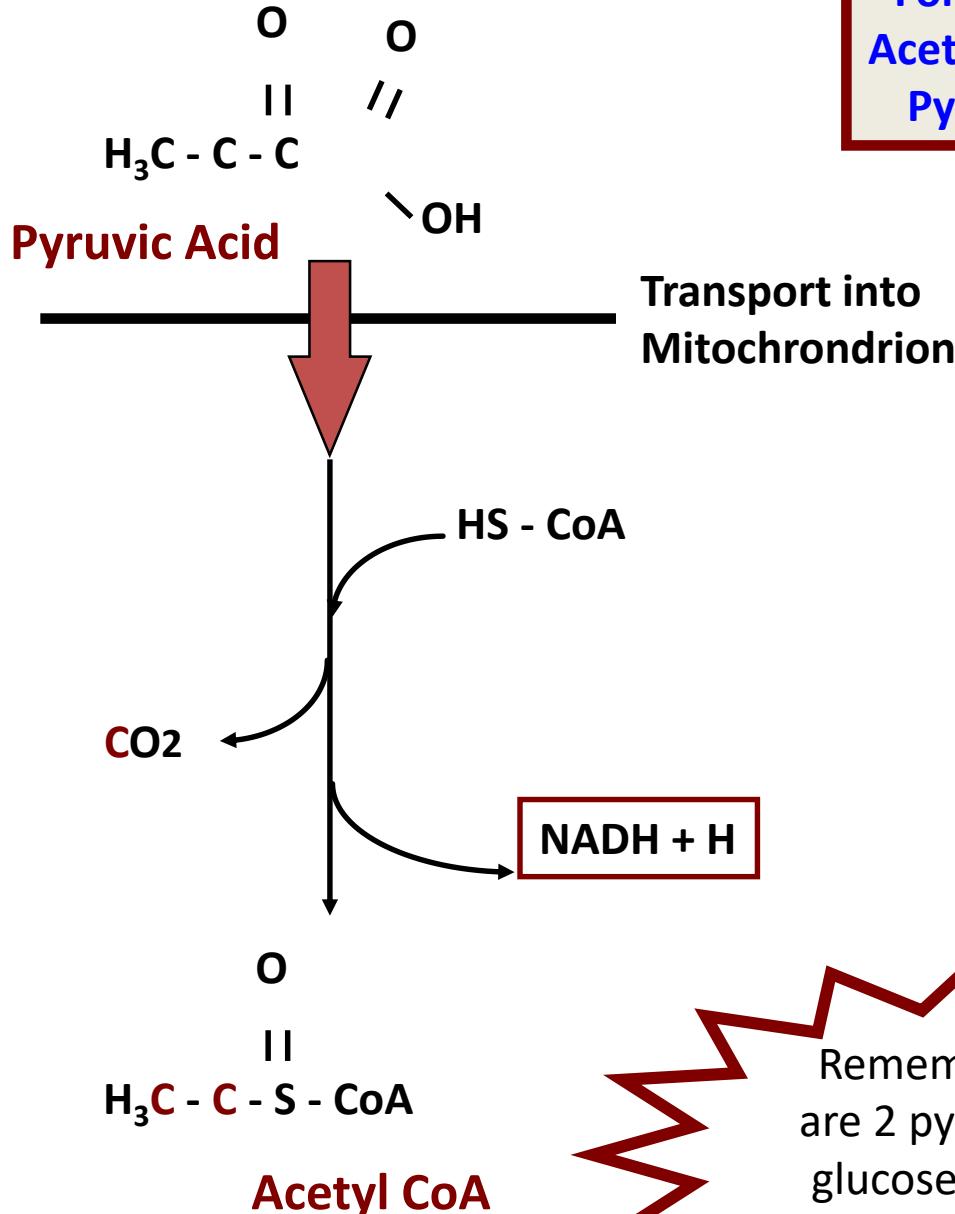
- Down a concentration gradient by facilitated diffusion,
 - i.e. a carrier is required but energy is not
- There are many different carriers. The most important and commonly studied are
 - GLUT-1, does not require insulin
 - GLUT-4, insulin dependent

Release of Energy from the Glucose Molecule by the Glycolytic Pathway

Glycolysis



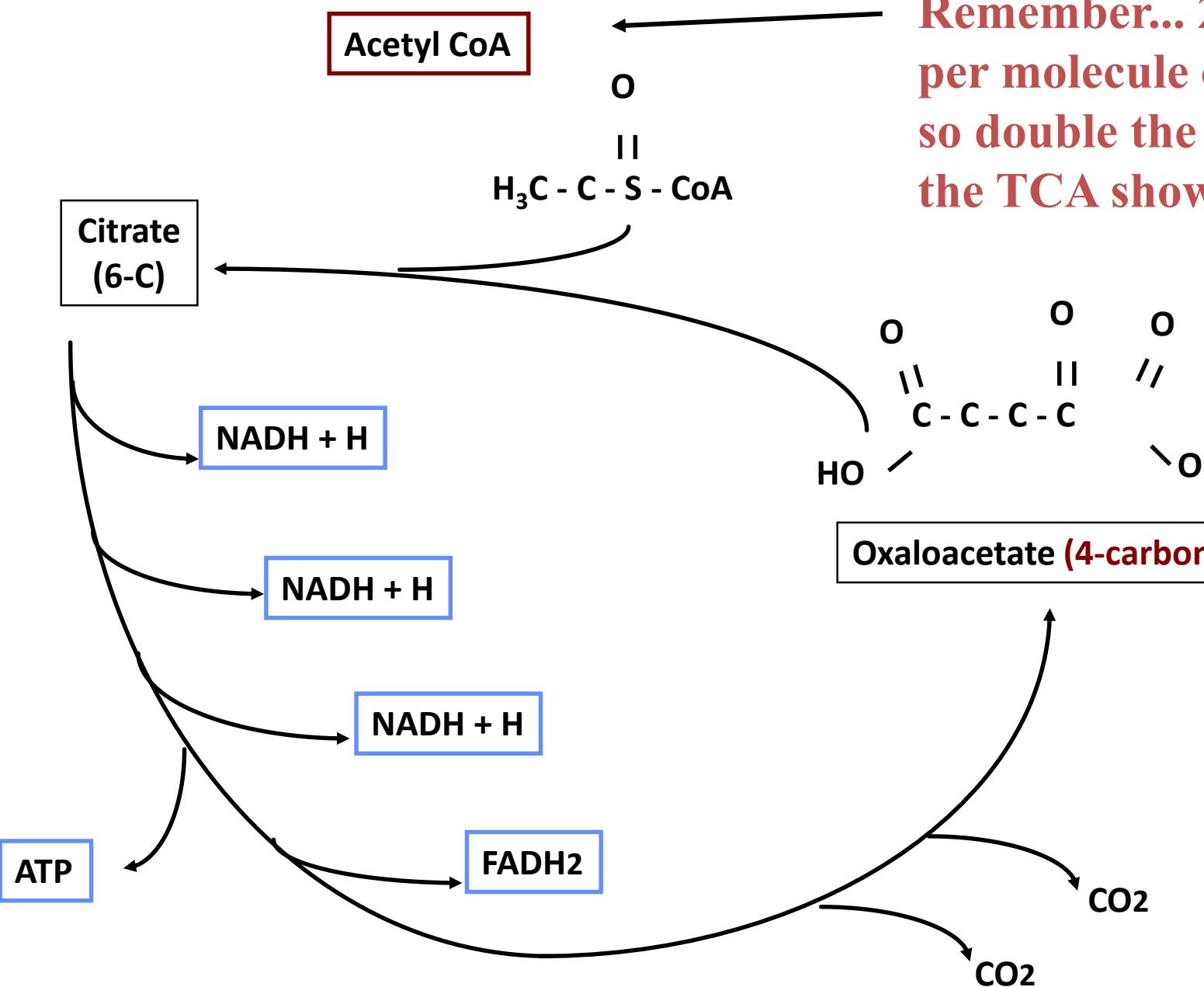
Go from 3-C
pyruvate to ...



... a 2-C
Acetyl CoA

Remember, there
are 2 pyruvates per
glucose molecule!

Remember... 2 of these per molecule of glucose, so double the outputs of the TCA shown here.



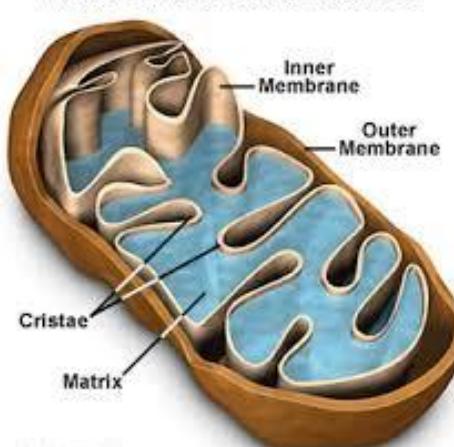
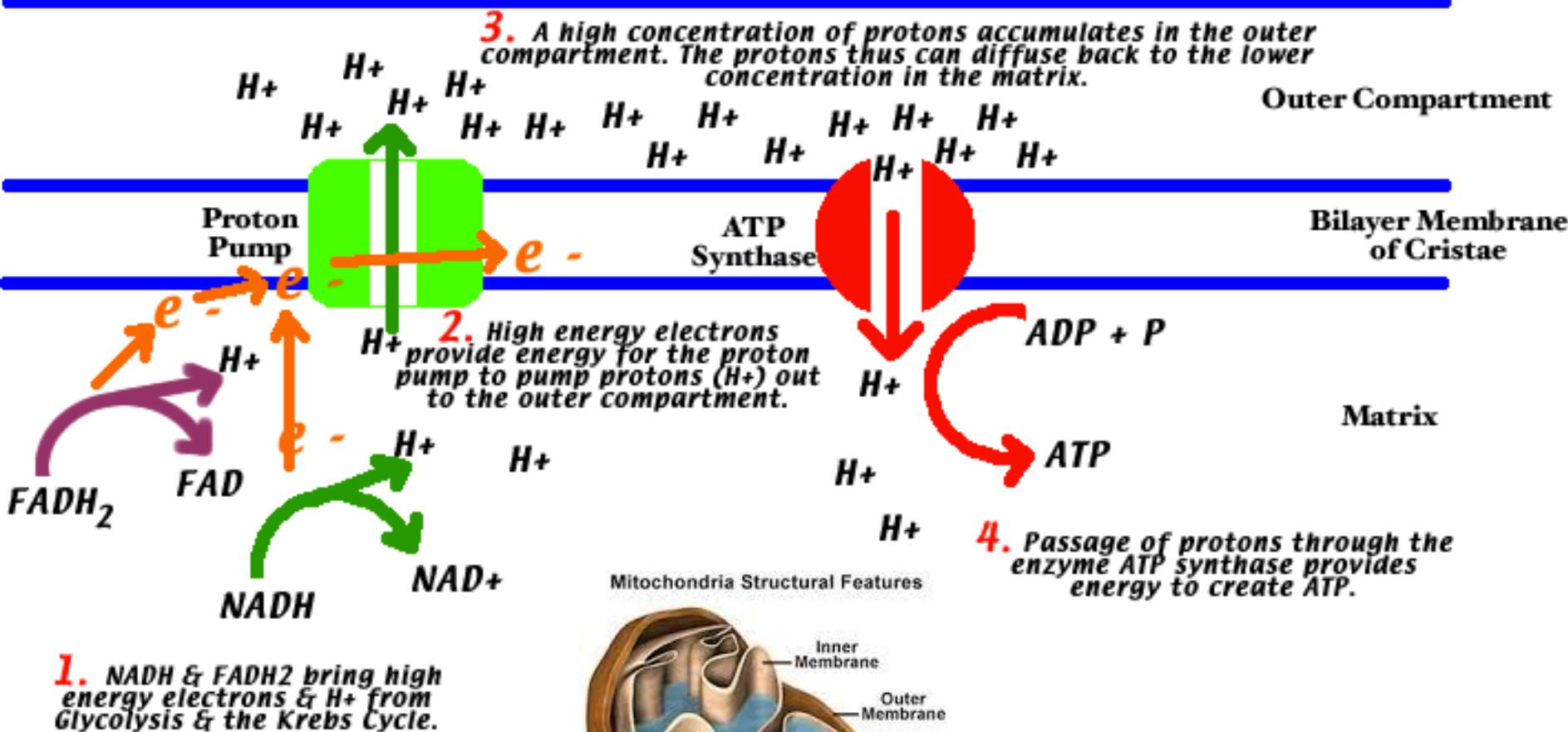
- One molecule of glucose yields...
 - Glycolysis
 - 2 NADH
 - 2 ATP
 - Pyruvate to Acetyl CoA conversion
 - 2 NADH (because there are 2 pyruvates)
 - Citric Acid cycle (numbers are for 2 pyruvates going through)
 - 6 NADH
 - 2 FADH₂
 - 2 ATP
 - Total: 10 NADH, 2 FADH₂, and 4 ATP

■ Electron Transport, Making ATP

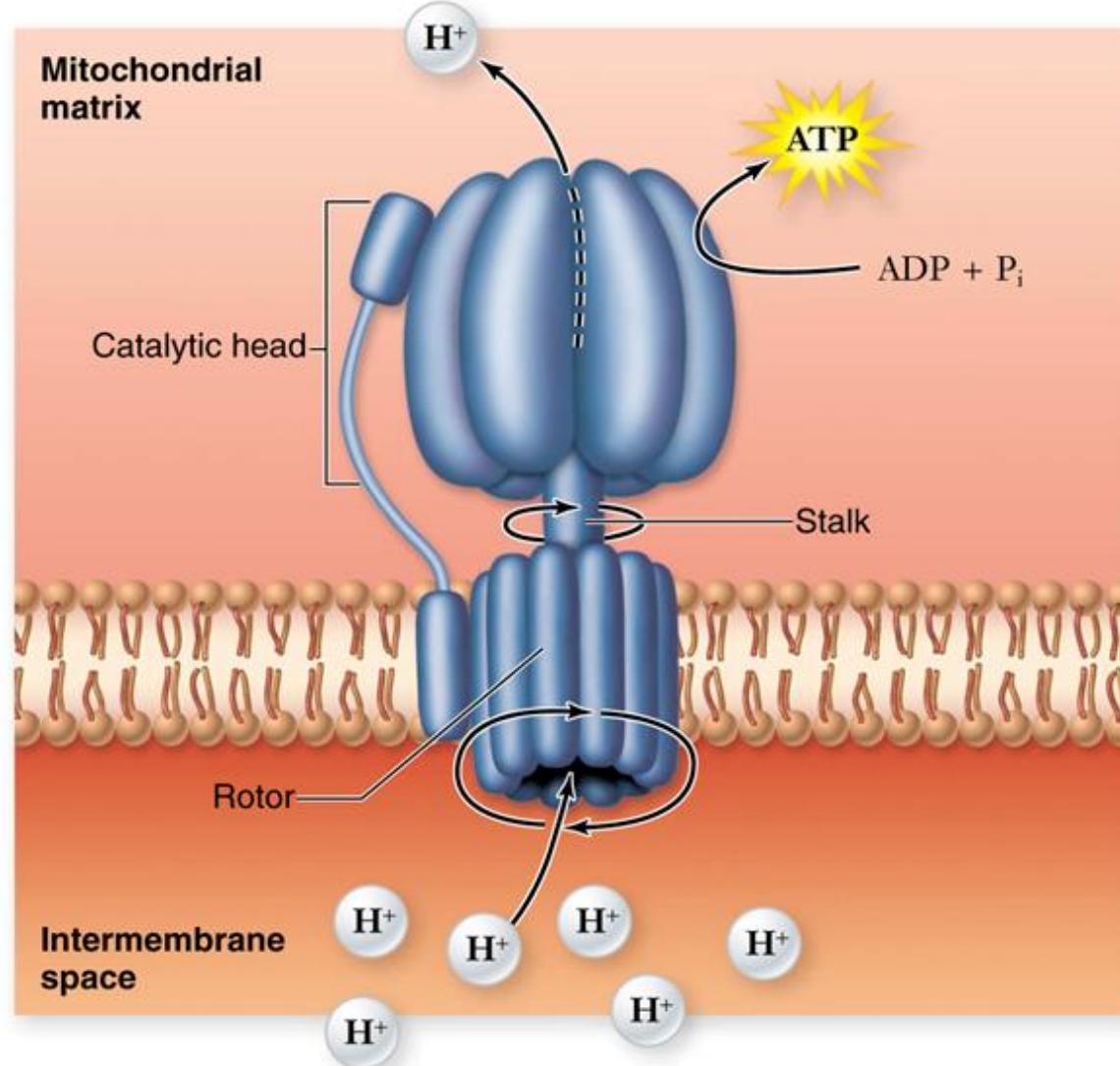
- Each NADH + H yields 2 electrons
 - Electron transport along the cytochrome chain enables establishment of an electrochemical H⁺ gradient along the inner mitochondrial membrane.
- Hydrogen movement down this gradient, through the ATP synthetase, provides the energy for conversion of ADP to ATP.
- Each electron pair from each NADH + H can provide enough energy for production of 3 ATP
 - electron pair from FADH₂ yield 2 ATP

Chemiosmosis

Outer Bilayer Membrane of Mitochondria

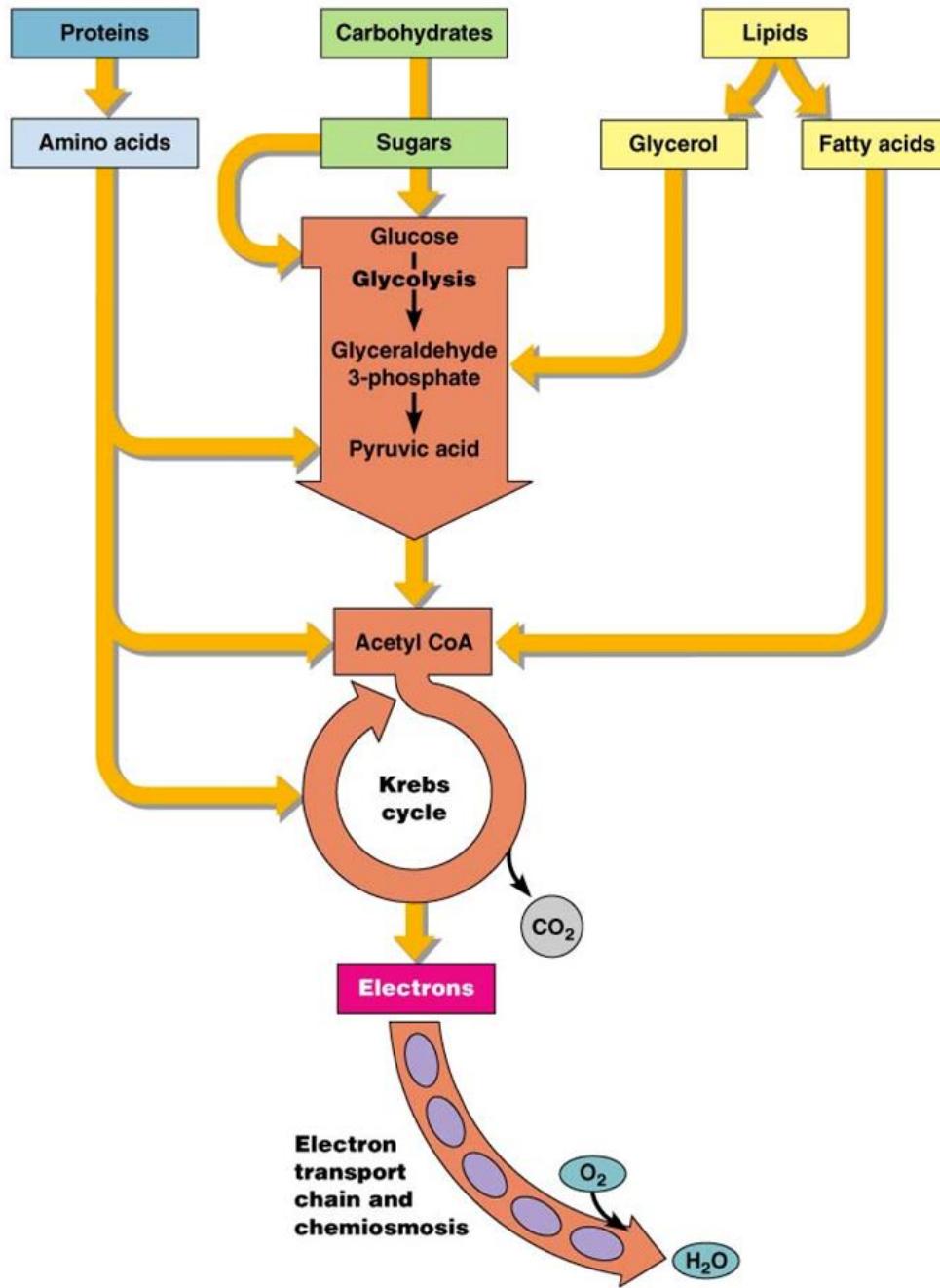


ATP Synthase



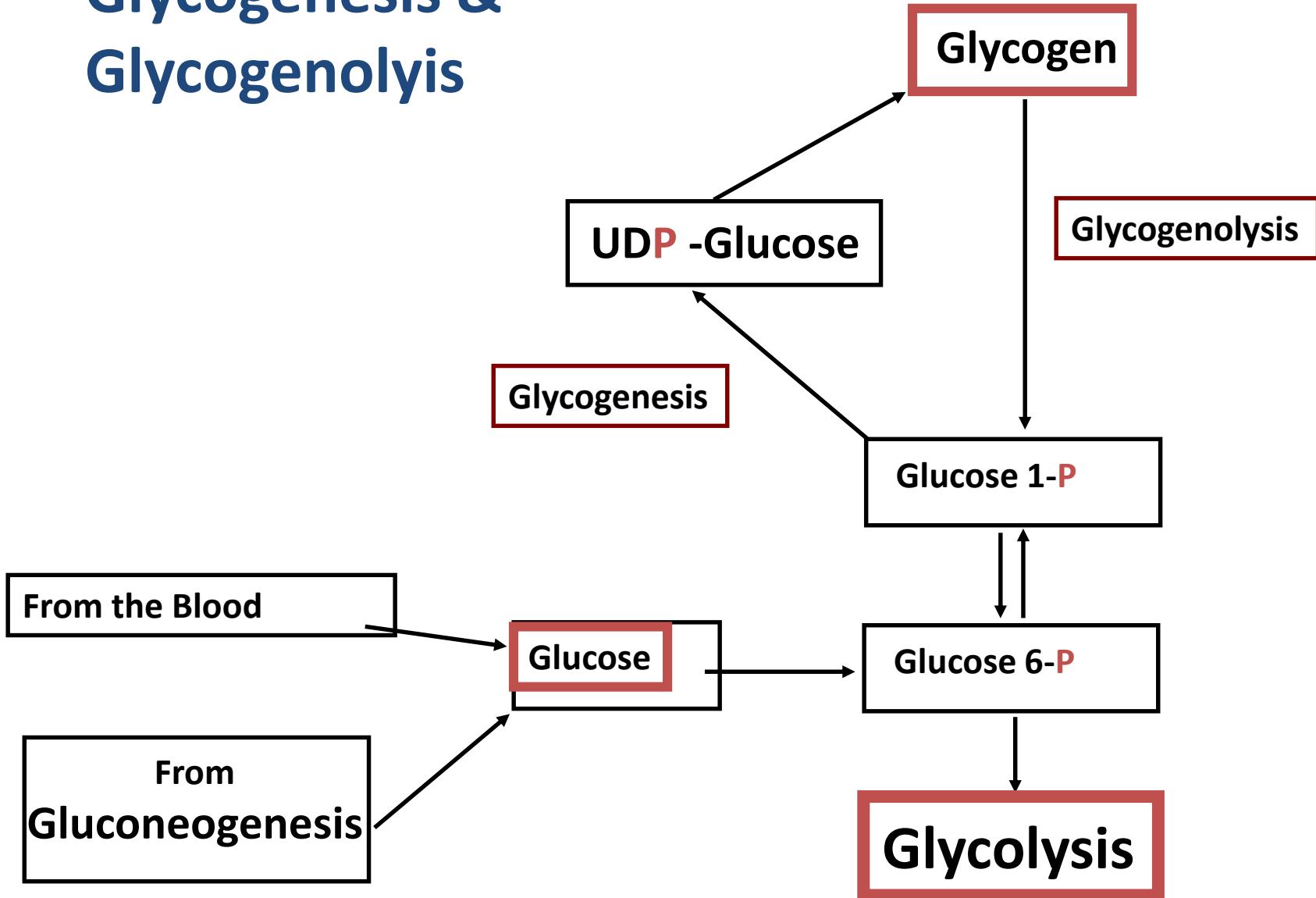
➤ One molecule of glucose yields...

- Glycolysis
 - 2 NADH + 2H **6 ATP**
 - 2 **ATP**
- Pyruvate to Acetyl CoA conversion
 - 2 NADH + 2H **6 ATP**
- Citric Acid cycle
 - 6 NADH + 6H **18 ATP**
 - 2 FADH₂ **4 ATP**
 - 2 **ATP**
- Total: 38 ATP, which yields ~ 456 kcal



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video #
M3

Glycogenesis & Glycogenolysis



Glycogenesis & Glycogenolysis

- Glycogenesis is the formation of glycogen from glucose. Glycogen is synthesized depending on the demand for glucose and ATP (energy). If both are present in relatively high amounts, then the excess of insulin promotes the glucose conversion into glycogen for storage in liver and muscle cells.
- In glycogenolysis, glycogen stored in the liver and muscles, is converted first to glucose-1-phosphate and then into glucose-6-phosphate. Two hormones which control glycogenolysis are a peptide, glucagon from the pancreas and epinephrine from the adrenal glands. Glucagon is released from the pancreas in response to low blood glucose and epinephrine is released in response to a threat or stress. Both hormones act upon enzymes to stimulate glycogen phosphorylase to begin glycogenolysis and inhibit glycogen synthetase (to stop glycogenesis).

Gluconeogenesis

- The biosynthesis of new glucose
- Substrates for gluconeogenesis include lactate, pyruvate, glycerol and glucogenic amino acids
- Under normal circumstances, the liver is responsible for 85%-95% of the glucose that is made
 - **during starvation or metabolic acidosis, the kidney is capable of making glucose and may contribute up to 50% of the glucose formed
 - ** the only other tissue capable of gluconeogenesis is the epithelial cell of the small intestine, which contributes $\leq 5\%$ of total glucose formation

■ The Lactate Story

- The NADH formed from oxidizing glucose eventually gets oxidized back to NAD⁺ in the mitochondria.
 - (the result of giving the electrons to electron transport chain)
- NAD⁺ is needed to keep oxidizing glucose.
- In exercise (once the anaerobic threshold is crossed), NAD⁺ isn't re-formed fast enough, so low levels threaten to stop glycolysis and ATP production.
- The main reason to form **lactate** is to regenerate the NAD⁺ needed to continue oxidizing glucose.

Lactate:

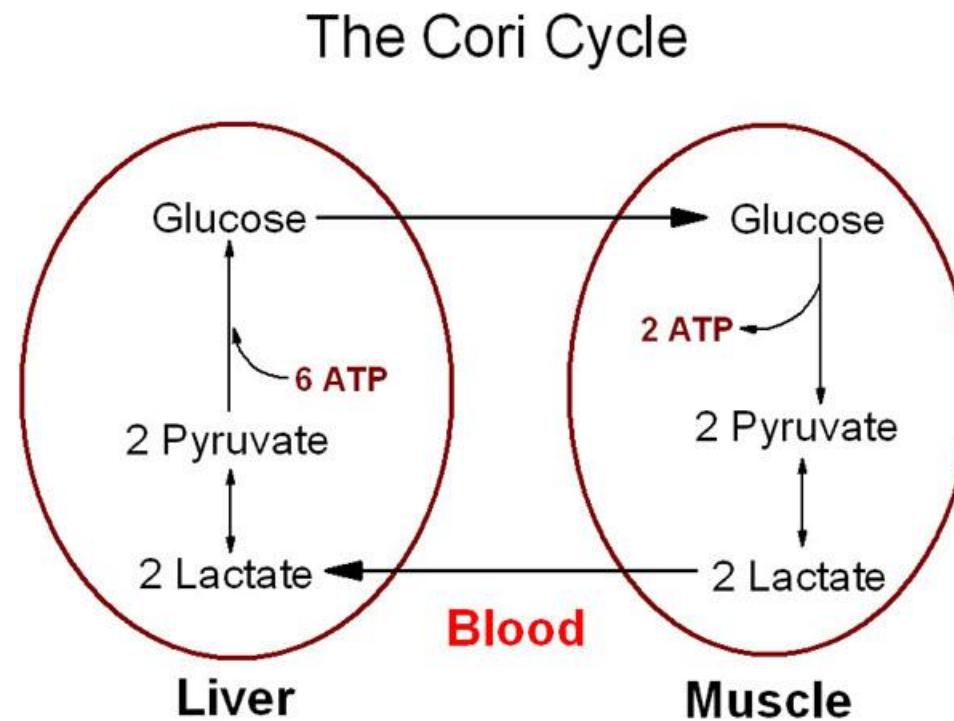
- interconversion of lactate and pyruvate is catalyzed by lactate dehydrogenase (LDH), an oxidized NAD⁺- dependent enzyme



- a. In gluconeogenic tissues (liver), LDH usually runs this reaction in the direction of pyruvate formation
- b. In muscle cells and erythrocytes, LDH usually runs this reaction in the direction of lactate formation

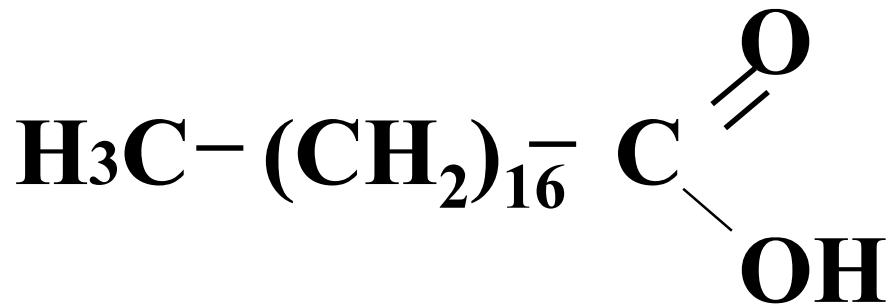
Cori cycle

- a. Pyruvate formed from glucose by glycolysis in the muscle cells and erythrocytes is converted to lactate by LDH
- b. Lactate is released into the blood, taken up by the liver, and converted to pyruvate by LDH
- c. Pyruvate is converted to glucose via gluconeogenesis in the liver and is released into the blood where it can be used as an energy source for muscle as well as other tissues

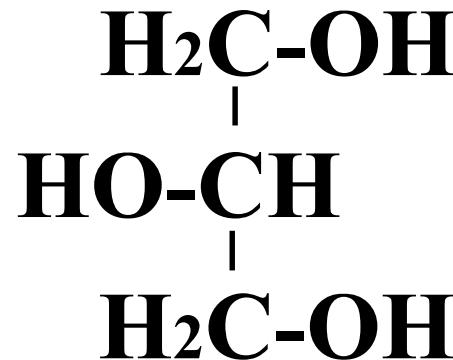


Lipids

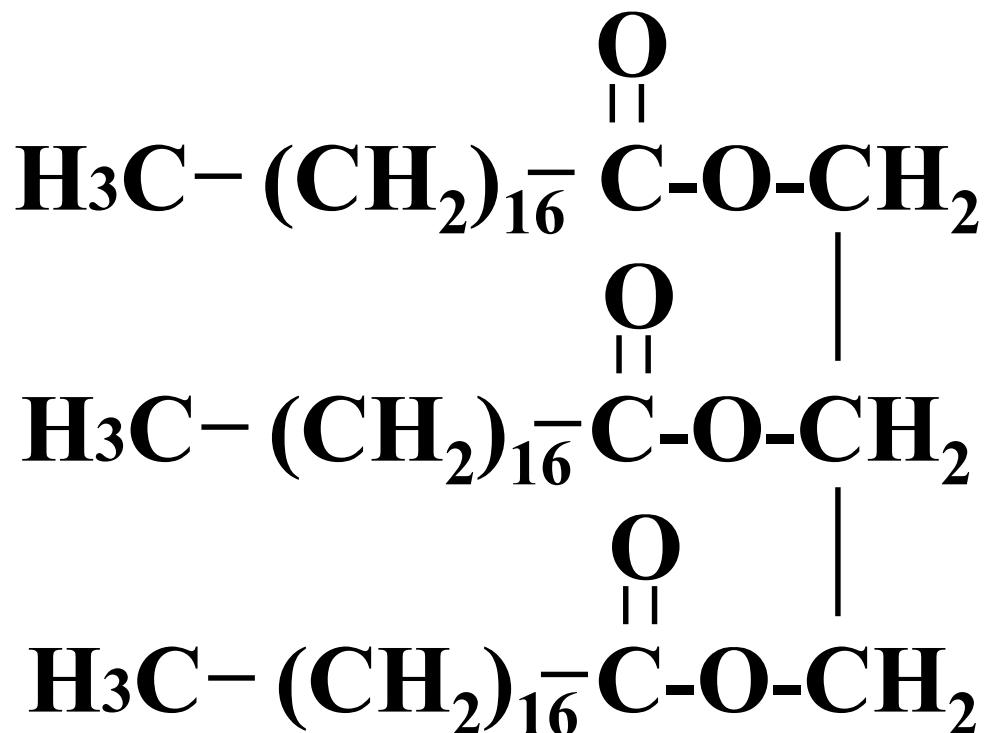
- Fatty Acids (FA) and Triglycerides (TG)
 - high density energy store
- Phospholipids
 - major components of membranes
 - contain precursors of many biologically active substances
 - modulate the activities of membrane enzymes and transporters
- Cholesterol (not really a lipid, but lipid soluble and lipid derived)
 - prominent part of membranes, control fluidity and protein function
 - precursor for bile acids and steroid hormones
 - most cells can synthesize it from Acetyl CoA; liver makes most of it



3 of these fatty acids (stearic acid)



Glycerol



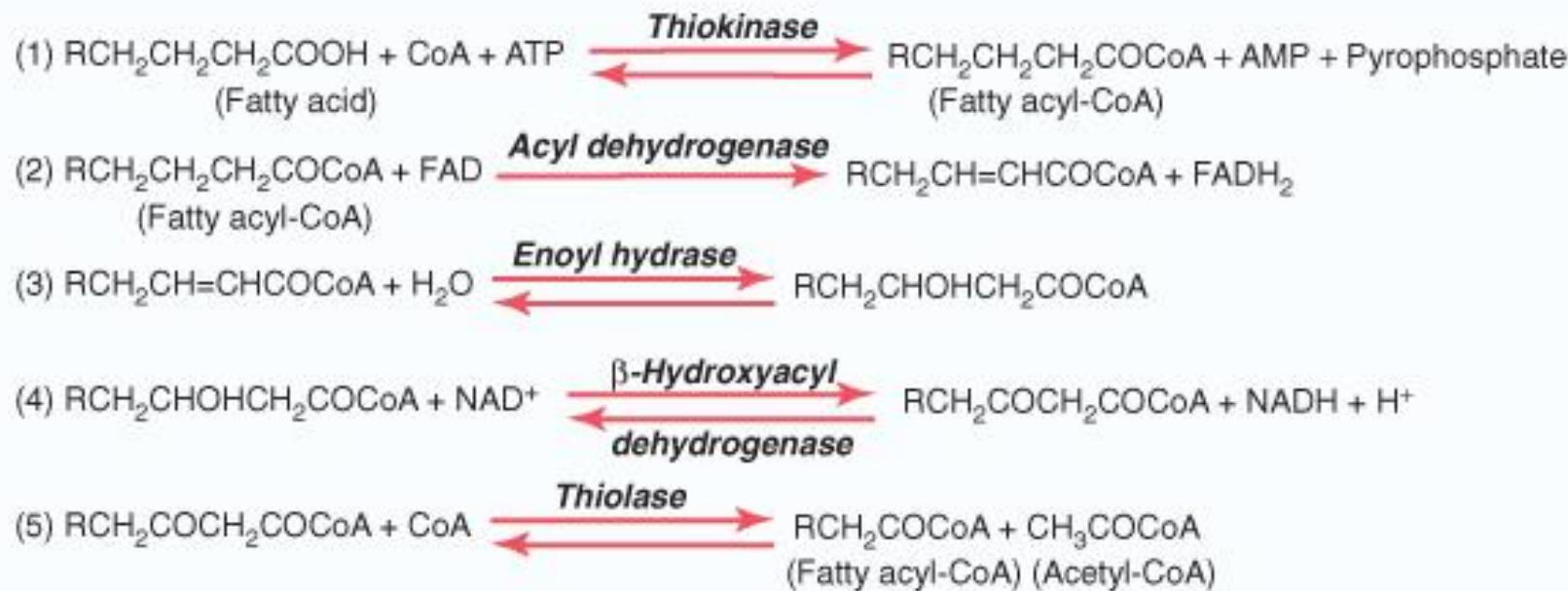
a triglyceride
(tristearin, p. 840)

The Liver & Lipids

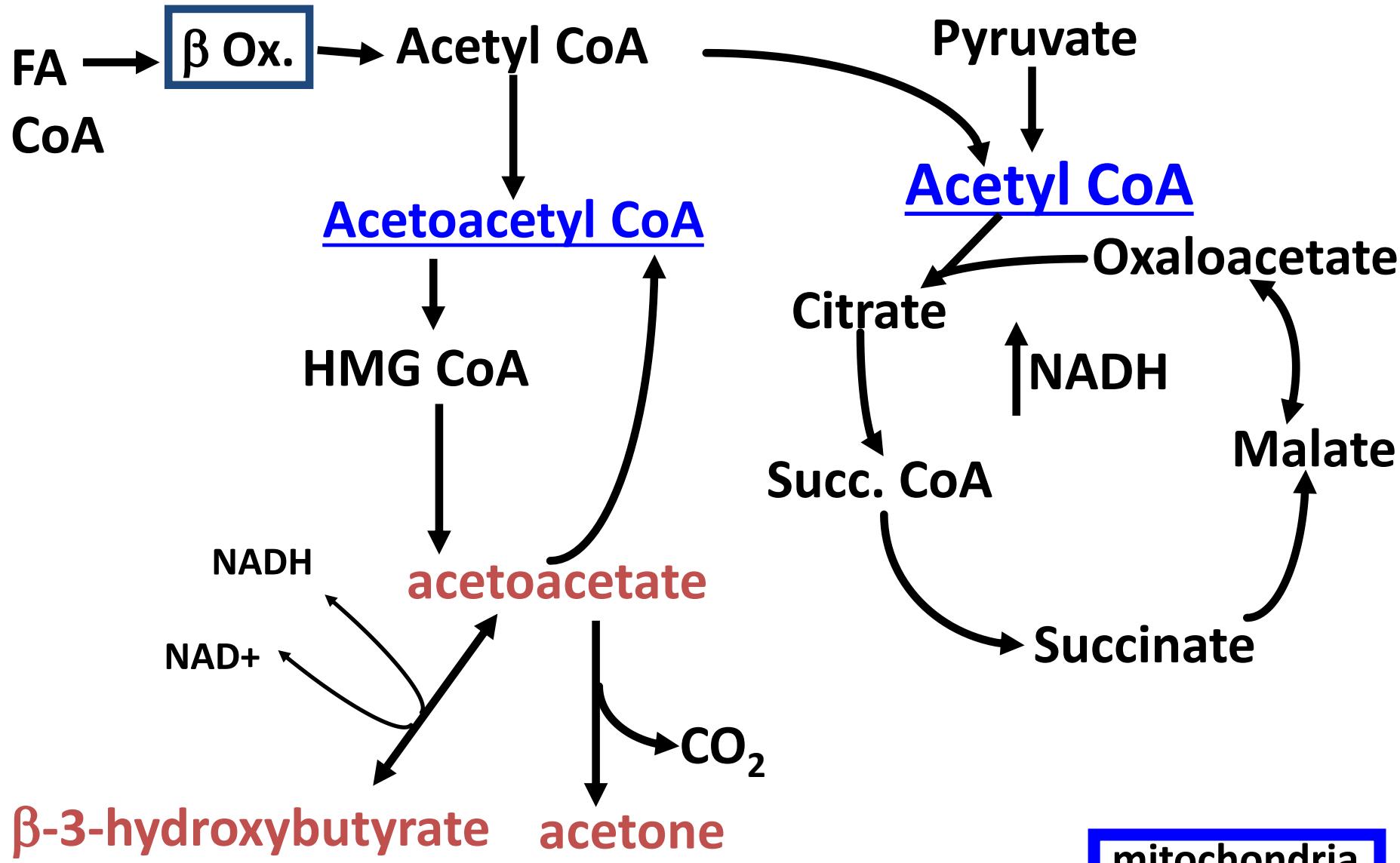
- oxidize triglycerides (fatty acids) for energy
- production of ketone bodies from triglycerides (FA)
 - exported to other cells as energy source (Acetyl CoA)
- synthesize triglycerides, mainly from glucose
 - some from amino acids as well
- synthesize other lipids, mainly phospholipids and cholesterol, from fatty acids
- de-saturate fatty acids (most FA in TG's in adipose tissue are saturated)
 - saturated means no double bonds

Beta Oxidation of Fatty Acids

The fatty acid molecule is degraded in the mitochondria by progressive release of two-carbon segments in the form of acetyl coenzyme A (acetyl-CoA). This process, which is shown in Figure 68-1, is called the beta-oxidation process for degradation of fatty acids.



Ketone Bodies



- **Ketone bodies**: acetone, β -hydroxybutyrate, and acetoacetate;
 - are formed principally in liver mitochondria.
 - can be used as a fuel in most tissues and organs.
- Formation occurs when the amount of acetyl CoA produced is excessive compared to the amount of oxaloacetate available to react with it and take it into the TCA

Problem Solving...

- What would be the net ATP gain from a triglyceride consisting of three palmitic acid chains (these are 16-C fatty acids...)?

- Glycerol enters glycolysis as glyceraldehyde-3-phosphate – worth ~ 36 ATP
- Palmitic acid – 16 carbons = 8 acetyl-CoA, 7 NADH, & 7 FADH₂
- 8 acetyl-CoA = 12 ATP each = 96 ATP
- 7 NADH = 3 ATP each = 21 ATP
- 7 FADH₂ = 2 ATP each = 14 ATP
- Palmitic acid then worth 131 ATP – but 2 ATP equivalent required to start beta-oxidation, so actually worth approximately 129 ATP.
- Three palmitic acid chains in a triglyceride – $129 \times 3 = \sim 387$ ATP, plus ~ 36 ATP from glycerol = ~ 423 ATP

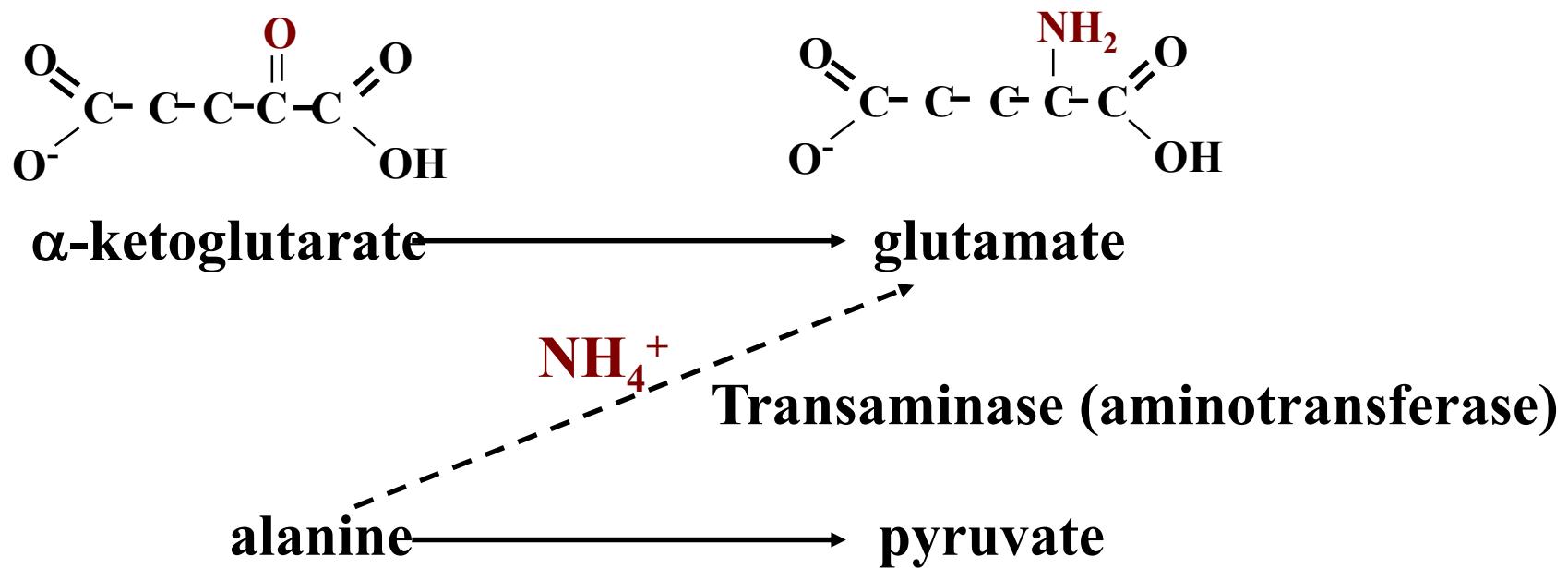
Protein Metabolism

Amino Acid Transport and Storage

- ionized AA's circulate in the plasma, ~ 35-65 mg/dl
 - control is not known, but even after a meal, plasma levels return to normal very rapidly
 - also, when plasma [AA] decreases, cell protein catabolism compensates
- transport of AA's into cells is carrier-mediated
- very little free AA's in cells, rapidly used for proteins
- proteins in different tissue cells are linked via reversible exchange with plasma amino acids
 - plasma proteins (e.g. albumin) are another important AA source (degraded by tissue macrophages and AA's released)

- Removing the amino group; deamination

Basically, α -ketoglutarate takes the NH_3^+ from an amino acid



Continuing the amino acid breakdown

- The first step in this example was turning the AA alanine into pyruvate
 - This involved production of glutamate (i.e. glutamic acid)
- The second step is breakdown of glutamate



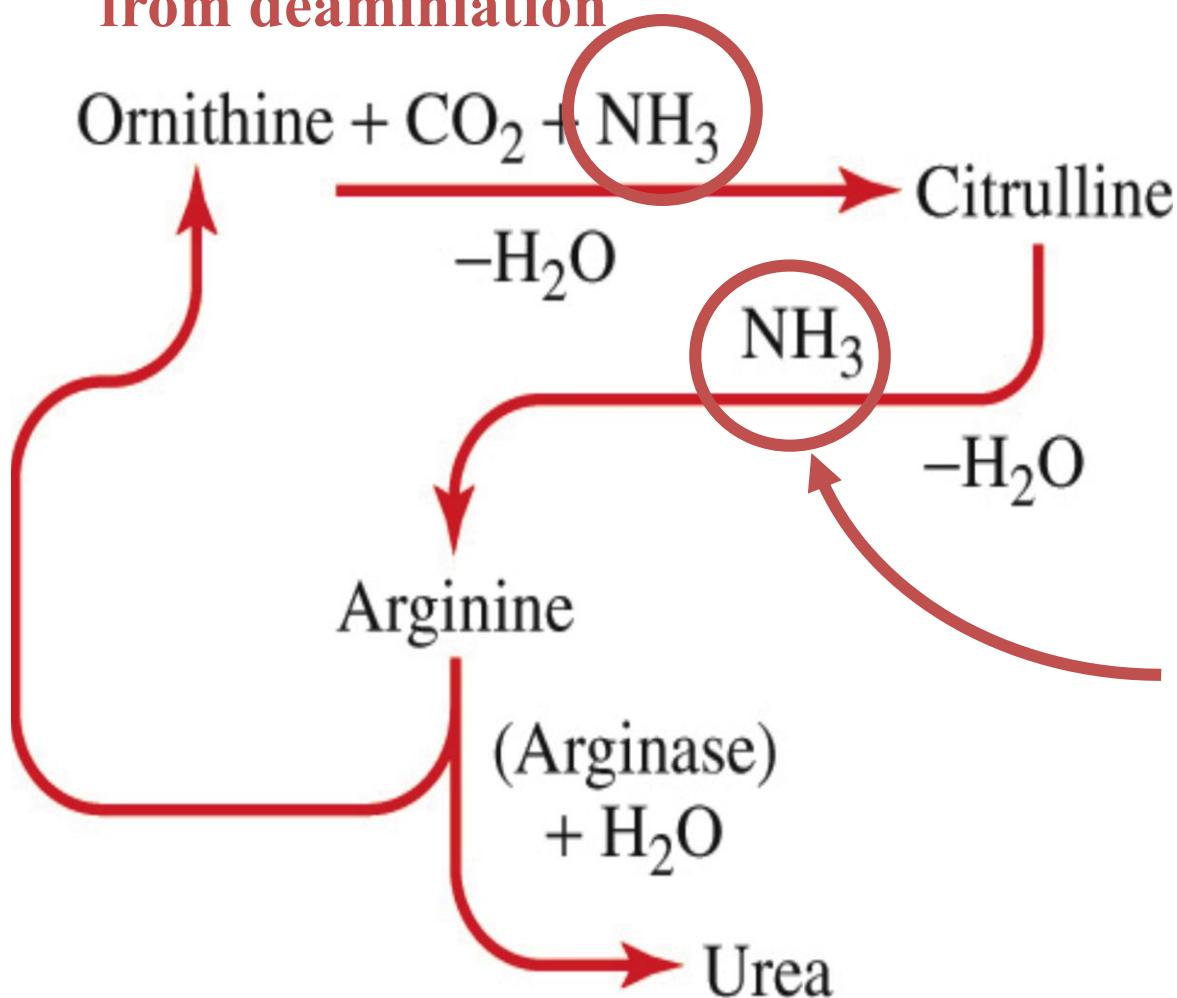
- NOTE: This rxn needs NAD^+ , which is high in a low-energy state. So, energy is low and we catabolize proteins for energy. Glutamate breakdown yields NADH; plus, the pyruvate from step one also can be used for energy. We also generated α -ketoglutarate.

■ Fate of the ammonia, role of urea

- The ammonia generated from the breakdown of glutamate can go towards generating other AA's, or
- The ammonia can be excreted
 - excretion occurs mainly as urea (2 ammonia molecules plus a carbon dioxide)
 - urea formation occurs essentially only in the liver

■ Main Urea Cycle Steps

The ammonia
from deamination



This ammonia comes
from “step 2”, i.e. the
conversion of glutamate
back to α -ketoglutarate,
which is tied directly
to the running of the
TCA cycle.

■ Strategy of Amino Acid Degradation

- AA degradation occurs in the liver, mainly with protein excess.
- Goal is to form major metabolic intermediates that can be converted into glucose or be oxidized by the TCA cycle
 - AA's that are degraded to Acetyl CoA or acetoacetyl CoA are ketogenic because they give rise to ketone bodies
 - AA's that form glucose or progress through the TCA cycle are termed glucogenic

