Veterinarian Licensure
Examination Review
Supplemental Materials

VETERINARY PHYSIOLOGY

VMLE
Review Systems

VETERINARY PHYSIOLOGY

REVIEW OUTLINE

I. Introduction to Physiology
- a. Definition of terms
- b. Control of Body Functions
- c. Properties of Water
- d. Henderson-Hasselbach Equation
- e. Buffers

II. Cellular Physiology
- a. Organelles
- b. Mitosis

III. Body Fluids
- a. Estimation of Fluid Compartments
- b. Measurement of Solute Concentrations
- c. Osmotic and Hydrostatic Pressure

IV. Membrane Transport Processes
- a. Simple Diffusion
- b. Restricted Diffusion
- c. Solvent Drag
- d. Facilitated Diffusion
- e. Active Transport
- f. Membrane Transport Proteins
- g. Osmosis
- h. Sodium Pump
- i. Chloride Ion transport
- j. Calcium Transport
- k. Non-electrolyte transport
- l. Transport of Macromolecules
- m. Movements of electrolytes across membranes

V. Membrane Potentials
- a. Resting Membrane Potential
- b. Action Potential
- c. Local Response
- d. Polarization
- e. Depolarization
- f. Hyperpolarization
- g. Generation of Action Potentials

VI. Nerve Cell Physiology
- a. Membrane Capacitance
- b. Electrical Resistance
- c. Time Element
- d. Membrane Resistance
- e. Myelination
- f. Saltatory Conduction
- g. Communication between Nerve and Muscle Cells

VII. Physiology of Muscle Contraction
- a. Skeletal muscles
- b. Steps in Skeletal Muscle Contraction
- c. Excitation and Contraction Coupling
- d. Smooth Muscles
- e. Action Potential of Smooth Muscles
- f. Shortening and Force Development
- g. Cardiac Muscles
- h. Cardiac Action Potential
- i. Excitation and Contraction Coupling

VIII. The Blood
- a. Functions of Blood
- b. Composition of Blood
- c. Plasma Proteins
- d. Formed Elements
- e. Formation of Blood Cells
- f. Blood Groups
- e. Hemostasis

IX. Physiology of the Cardiovascular System
- a. Initiation of Heartbeat
- b. Spread of Cardiac Impulse
- c. Control of Heart Rate
- d. Heart Sounds
- e. Factors Influencing Cardiac Output
- f. The Peripheral Circulation

X. Renal Physiology
- a. Kidneys: Vascular and Tubular Components
- b. Nephrons
- c. Glomerular Filtration
- d. Tubular Reabsorption
- e. Tubular Secretion
- f. Counter Current Multiplier
- g. Antidiuretic Hormones
- h. Renal Control of Salt Balance
- i. Renal Acid Base Imbalances
- j. Other Urinary Anatomy

XI. Respiratory Physiology
- a. Functions of the Respiratory System
- b. Physical Aspects and Mechanics of Breathing
- c. Gas Exchange in the Lungs
- d. Hemoglobin and Oxygen Transport
- e. CO_2 Transport
- f. Control of Respiration
- g. Regulation of Breathing
- h. Organization of Respiratory System

XII. The Nervous System
- a. General Design of the Nervous System
- b. Physiology of a Synapse
- c. Characteristics of Neurotransmitters
- d. Temporal and Spatial Summation
- e. Physiology of Receptors
- f. Parts of the Brain and Spinal Cord
- g. Autonomic Nervous System
- h. Cranial Nerves

XIII. Physiology of Special Senses
- a. Physiology of Eyesight
- b. Physiology of Hearing
- c. Physiology of Tastes
- d. Physiology of Smell

XIV. Gastrointestinal Physiology
- a. Process of Digestion
- b. Regulation of the GastroIntestinal Tract
- c. Parts of the Digestive System
- d. Digestion and Absorption of CHO, Proteins, and Lipids
- e. Ruminant Digestion
- f. Digestion in Fowls
- g. Bilirubin Formation and Excretion

XV. Metabolism
- a. ATP and energy Production
- b. Glycolysis
- c. Glycogenesis and Glycogenolysis
- d. Kreb Cycle
- e. ETS
- f. Pentose Phosphate Pathway
- g. Beta-Oxidation and Synthesis of Fats

XVI. Endocrinology
a. Routes of Delivery
b. Classification of Hormones
c. Mechanism of Hormone Secretion
d. Hypothalamic Hormones
e. Pituitary Hormones
f. Gastrointestinal Hormones
g. Thyroid and Parathyroid Hormones
h. Adrenal Gland Hormones
i. Pancreatic Hormone

XVII. Reproductive Physiology
a. Physiology of Male Reproductive Organs
b. Spermatogenesis
c. Primary and Secondary Sex Characteristics
d. Endocrinology of the Male Reproductive System
e. Endocrinology of the Female Reproductive System
f. Functions of the Ovary
g. Estrous cycle
h. Ovulation
i. Mechanism of Luteolysis
j. Placentation
k. Hormones that Regulate Pregnancy and Parturition
l. Development of Mammary Gland and Maintenance of Lactation
m. Zootechnics of Reproduction
n. Avian Reproductive Physiology

I. INTRODUCTION TO PHYSIOLOGY

Physiology
- ✓ the study of all the structures in the body and their functions
- ✓ divided into viral physiology, bacterial physiology, cellular physiology, systemic physiology, reproductive physiology, endocrinology and many more subdivisions

Organ
The functional units of the body

Cell
The structural unit of the body

Homeostasis
- ✓ The maintenance of steady state of non-equilibirum in internal environment despite variations in external conditions by coordinated physiologic mechanisms
- ✓ Maintenance of a constant internal environment despite variations in external conditions

Equilibrium
- ✓ A condition in which opposing forces are balanced in which any forward reaction is accompanied by a similar reaction in the reversed direction
- ✓ Remains stable if undisturbed. No energy is spent to maintain an equilibrium state

Steady State
- ✓ A condition that does not change
- ✓ Equilibrium and steady state are both stable conditions however energy expenditure is required to maintain a steady state

Homeorrhesis
- ✓ Refers to the steady flow of metabolites that results in partitioning of nutrients for muscle or adipose tissue growth or flow of dietary and body constituents into milk production

Negative feed back mechanism
- ✓ A series of changes that return a factor that has become excessive or deficient toward a certain normal or standard value, thus maintaining homeostasis
- ✓ Example: cortisol inhibiting the Anterior pituitary gland and Hypothalamus from secreting corticotrophin and CRH respectively

Positive feed back mechanism
- ✓ an initiating stimulus causes changes that bring about more of the same stimulus
- ✓ example: the contraction of uterus propels the fetus into the birth canal. The bulk of the fetus stretches the birth canal which stimulates more contraction

Extracellular fluid
- ✓ this is the liquid external environment of the cell
- ✓ when normal conditions are maintained in the extracellular fluid, the normal conditions of the intracellular fluid are maintained as well
- ✓ the external environment affects very little if at all the extracellular fluid because of homeostasis
- ✓ both the intracellular and extracellular fluid are made up of water and substances dissolved in them but respective compositions are different

Water
- ✓ Comprises over half of the body weight: 45-75% in humans and 55-75% in animals
- ✓ Can act as both an acid and a base (amphoteric)
- ✓ Ionization may form hydronium ions ($H3O^{+)}$ and a hydroxide ion (OH^{-})

Properties of Water

Freezing point	0º C
Boiling point	100º C
Maximal density	Occurs at 4º C
Specific Gravity	1.0
Specific Heat	High
pH	7
Number of molecules*	1 g of water contains $3.34x10^{22}$ molecules

*computed by multiplying the number of moles contained in 1 gram of water (0.056 moles) by Avogadros number ($6.022x10^{23}$ molecules/mole)

Specific Heat
The quantity of heat required to raise the temperature of 1gram of a substance by one degree Celsius

Calorie

A unit of energy defined as the amount of heat required to raise the temperature of 1 gram of water from 14.5ºC to 15.5ºC

Henderson-Hasselbach Equation

- ✓ provides an insight into the physiologic control of acid and base composition of the extracellular fluid
- ✓ the formula is: $pH = pK_a + \log [A^-]/[HA]$;
  A^- - conjugate base; HA^- conjugate acid; pKA- dissociation constant

Weak Acid and Weak Bases

- ✓ Physiologic substances may either be a weak acid or a weak bases
- ✓ Weak acids or weak bases, unlike strong acid and strong bases, do not dissociate completely in a solution
- ✓ For example HCl (a strong acid) dissociates into H^+ and Cl^-
- ✓ In the case of Acetic Acid (weak acid), it dissociates into three: the dissociated acetate ion (CH_3COO^-), the Hydrogen ion (H^+), and the undissociated acetic acid
- ✓ For **weak acids** the general reaction is:

HA	**H** ⟺	**A^-**
Protonated Undissociated Non-ionized **Lipid soluble**	Proton	Unprotonated Dissociated Ionized **Non-Lipid soluble**

HA – conjugate acid A^- – conjugate base

- ✓ For **Weak bases,** the general reaction is:

B+H ⟺	**BH**
Protonated Undissociated Non-ionized **Lipid soluble**	Proton Protonated Dissociated Ionized **Non-Lipid soluble**

B – conjugate base BH^+ - conjugate acid

Modified Henderson-Hasselbach Equation for Weak Acid and Weak Bases:

- ✓ From the original equation of
  $pH = pK_a + \log [A^-]/[HA]$
- ✓ since A^- is unprotonated and is HA protonated
  pH = pKa + log U/P or
  pH – pKa = log U/P

  where U = unprotonated and P = protonated

- ✓ In general, for a **weak acid**, when the pH is less than the pKa, the **protonated form (non-ionized)** predominates
- ✓ When the pH is greater than the pKa, the **unprotonated form (ionized)** predominates
- ✓ Conversely for a **weak base**, when the pH is less than the pKa, the **ionized form (protonated)** predominates
- ✓ When the pH is greater than the pKa, **non-ionized form (unprotonated)** predominates
- ✓ Application:
  - Given a drug X which is a weak acid and with a pKa of 4:

In the stomach (pH = 2);

2 -4 = log U/P
- 2 = log U/P
Antilog -2 = U/P
1/100 = U/P

- In the stomach, there will be 100 protonated for every unprotonated form of the drug
- Since the drug is a weak acid, the drug will be more absorbed in the stomach because in here it is protonated, undissociated, non-ionized and lipid soluble

In the duodenum (pH = 8);

8 -4 = log U/P
4 = log U/P
Antilog 4 = U/P
10000/1 = U/P

- In the duodenum, there are more unprotonated than protonated form of the drug
- Drug X is practically unabsorbable in the duodenum because most of it is non-lipid soluble form

Buffering

- ✓ The tendency of a solution to resist more effectively a change in pH following addition of acid or base than does an equal volume of water
- ✓ The important physiological buffers are:
  1. Bicarbonates (HCO_3^-/H_2CO_3)
  2. Inorganic orthophosphates($H_2PO_4^{-1}/HPO_4^{-2}$)
  3. Intracellular proteins
- ✓ The **bicarbonate system** accounts for most of the buffering capacity in blood
- ✓ Blood pH is 7.4

II. CELLULAR PHYSIOLOGY

Organelles

1. **Nucleus**- serves as the source of genetic materials like genes, DNA and chromosome.
- bounded by double lipid bilayer with opening called the nuclear pores, which are ubiquitously found in the surface of the nucleus and serve as means of transport between the nucleus and the rest of the cells.
- contains *nucleolus*, which consists of densely packed chromosome regions together with some proteins and RNA strands.

2. **Cytoplasm** - contains membrane-bound organelles, ribosome for synthesizing cytoplasmic proteins, cytoskeleton, and cytosol

Cytoskeleton - serves as the framework for the cells and provide basis of movement for the entire cells and its components; has three major types namely:
a. Microtubules - the largest
b. Intermediate filament - medium in size
c. actin filament - smallest

- Cytosol - fluid part of the cytoplasm that contains many enzymes

3. **Mitochondria** - the powerhouse of the cells
- site for the Krebs cycle and respiration

4. **Endoplasmic reticulum (ER)** - network of tubes and flattened sacs that formed a membrane distributed throughout the cytoplasm.

Rough ER - with granular appearance due to ribosome.
- responsible for synthesis of proteins for organelles, cell membrane or secretions to cell exterior (e.g. hormones).

Smooth ER - lacks attached ribosome
- participates in lipid metabolism, also serves in detoxification of drugs and deactivation of the steroid hormones.

5. **Golgi Apparatus**- sets of smooth membranes flattened and fluid filled sacs
- modify, sorts, package proteins for delivery to other organelles or to cell exterior.

6. **Endo and Exocytotic vesicles**- membrane-enclosed vesicles that travel on the cytoplasm of the cells.

- Exocytosis - these are actually secretion or movement of vesicles containing proteins from inside of the cells going out; vesicular membrane fuse with the plasma membrane.

- Endocytosis - movement of the materials from exterior of the cells going in; plasma membrane bud off.

a. **Phagocytosis** - when cells engulfed large molecules
b. **Pinocytosis** - when cells engulfed small molecules

7. **Lysosomes** - membrane bound vesicle that contains enzymes for digesting particles, damaged organelles, and bacteria that have access to cells via endocytosis.

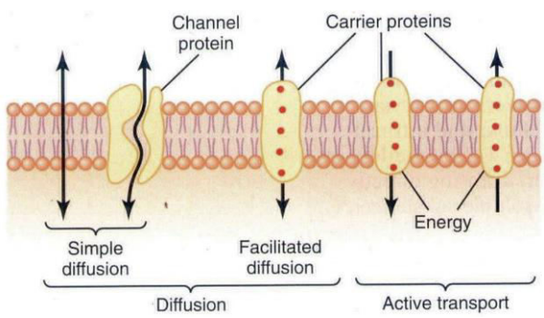
Cell membranes – Composed of lipid bilayer called *phospholipids.*

-Phospholipids have a dual structure, a hydrophilic head and a hydrophobic tail.
-Hydrophilic heads faces outside and inside the cells, while the hydrophobic tails are arranged in between these heads.
-Proteins are ubiquitously embedded on the surface of cells.
-Some proteins traverse the entire membrane, others are confined on one side and others are embedded in the external surface of the cells with carbohydrates chain attached (called *glycoprotein*).
-Proteins serve as filter, gates or others that control the movement of molecules inside and outside of the cells.

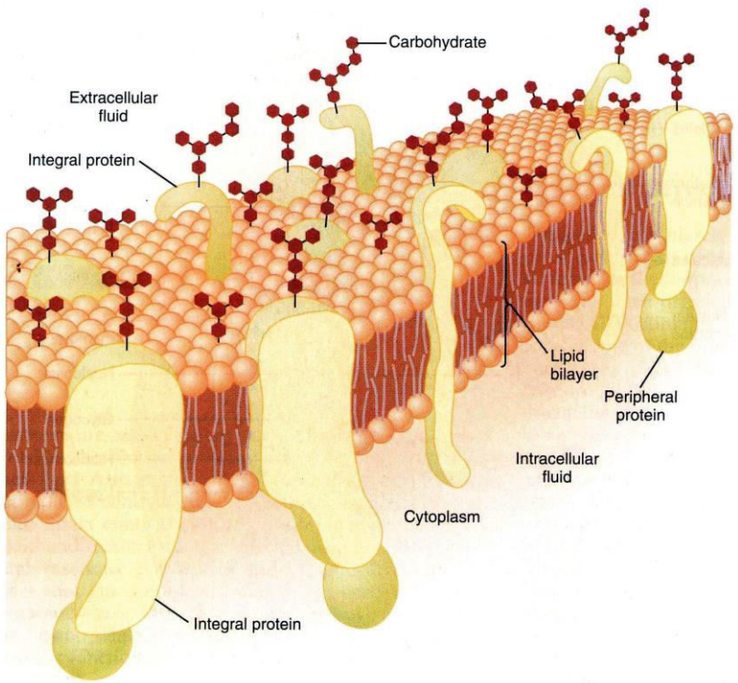
Epithelial cells
- commonly found lining a tubular or hollow structure thus it can be found on the skin, kidney, glands lining of the lungs, gastrointestinal tract, bladder and blood vessels.

Desmosomes - region of tight adhesion between cells that give cells structural integrity.
- concentrated in tissues like skin, that undergoes mechanical stress.

Types of desmosomes:
1. Belt desmosomes - continuous zone of attachment that encircles the cells.
2. Spot desmosomes - more localized attachments to small region of contacts.



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

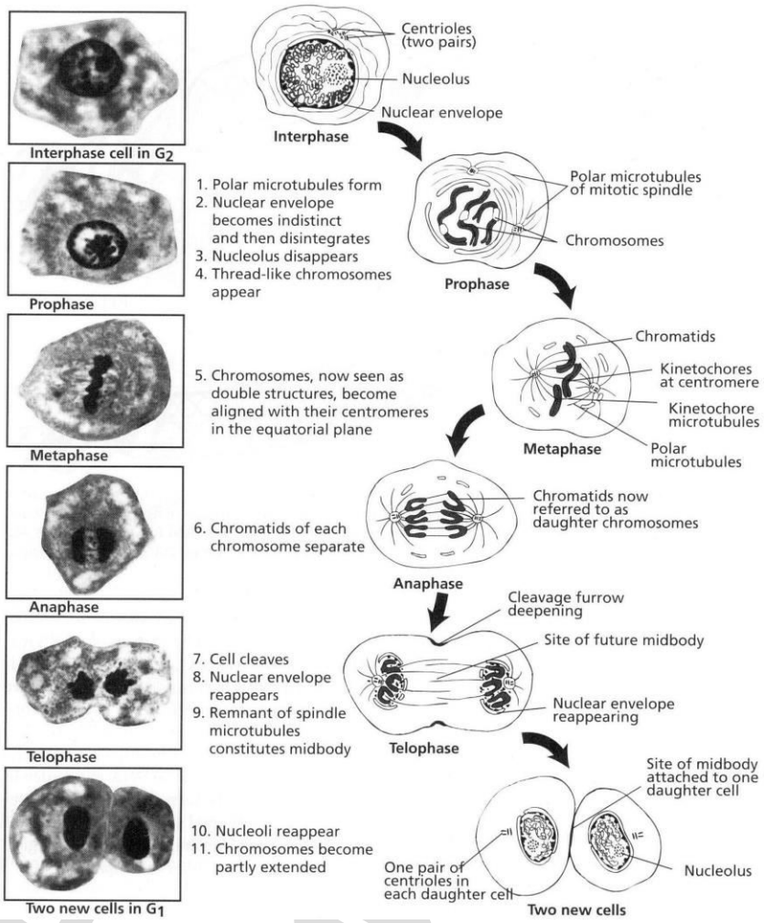


Structure of the cell membrane, showing that it is composed mainly of a lipid bilayer of phospholipids molecules, but with large numbers of protein molecules protruding through the layer. Also, carbohydrate moieties are attached to the protein molecules on the outside of the membrane and to additional protein molecules on the inside.

	EXTRACELLULAR FLUID	INTRACELLULAR FLUID
Na^+	142 mEq/L	10 mEq/L
K^+	4 mEq/L	140 mEq/L
Ca^{++}	2.4 mEq/L	0.0001 mEq/L
Mg^{++}	1.2 mEq/L	58 mEq/L
Cl^-	103 mEq/L	4 mEq/L
HCO_3^-	28 mEq/L	10 mEq/L
Phosphates	4 mEq/L	75 mEq/L
SO_4^-	1 mEq/L	2 mEq/L
Glucose	90 mg/dl	0 to 20 mg/dl
Amino acids	30 mg/dl	200 mg/dl ?
Cholesterol, Phospholipids, Neutral fat	0.5 g/dl	2 to 95 g/dl
PO_2	35 mm Hg	20 mm Hg ?
PCO_2	46 mm Hg	50 mm Hg ?
pH	7.4	7.0
Proteins	2 g/dl (5 mEq/L)	16 g/dl (40 mEq/L)

Chemical compositions of extracellular and intracellular fluids.

Mitosis



The stages of mitosis. Until anaphase, the two chromatids of a mitotic chromosome remain joined at a region known as the centromere of the chromosome. At this location, each chromatid has a microtubule attachment site called a kinetochore.

III. BODY FLUIDS

Total Body Water
- ✓ around 60% of adult body weight
- ✓ around 80% of body weight in young animals
- ✓ it is divided into
  1. ECF (40% of body weight) and
  2. ICF (20% of body weight)
- ✓ The ECF is further divided into
  1. plasma and the
  2. interstitial and transcellular compartments
- ✓ In summary

Intracellular Fluid	40% of BW
Extracellular Fluid	20% of BW
Interstital and Transcellular	15% of BW
Plasma	5% of BW

Estimation of Fluid Compartments

Total Body Fluid Volume
- ✓ The total body fluid volume is measured with any of the following:
  1. Deuterium oxide
  2. Tritium oxide
  3. Antipyrine solution

ECF Volume
- ✓ The ECF volume is measured with **inulin**

ICF Volume
- ✓ There is no substance that can be use to approximate the ICF volume
- ✓ It is measured mathematically by subtracting ECF volume from Total Body Fluid Volume
- ✓ **ICF = TBFV - ECF**

Plasma volume
- ✓ The volume of distribution of these compounds approximate the plasma volume
  1. Solution of Evans Blue (T-1824)
  2. ^{125}I-albumin

Interstitial Fluid Volume
- ✓ Measured by subtracting Plasma Volume for ECF volume
- ✓ **IFV = ECF – Plasma Volume**

Measurement of Body Fluid Volumes

Volume	Indicators
Total body water	$^{3}H_2O$, $^{2}H_2O$, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular fluid	(Calculated as Total body water – Extracellular fluid volume)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824)
Blood volume	^{51}Cr-labeled red blood cells, or calculated as Blood volume = Plasma volume/ (1 – Hematocrit)
Interstitial fluid	(Calculated as Extracellular fluid volume – Plasma volume)

Measurement of Solute Concentrations in the Body

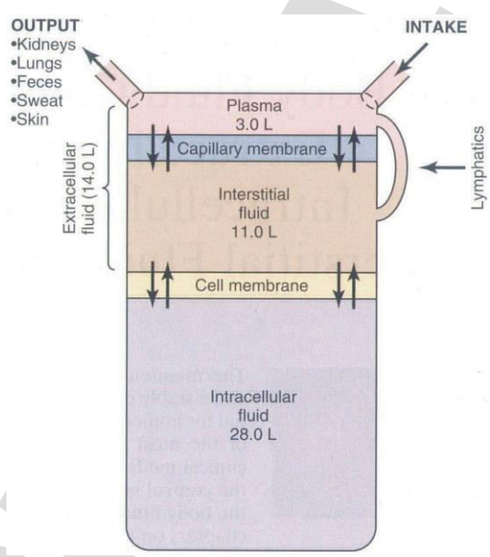
Equivalent
is a mole of an electrolyte divided by its valence

Normal Concentration (Normality)
it is expressed as Equivalent of an electrolyte/Liter of the solution

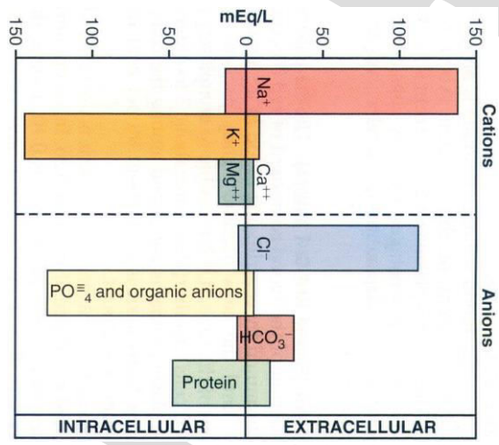
Molar Concentration(Molarity)
Expressed as mole of a substance /Liter of the solution

Molal Concentration (Molality)
Expresses as mole of a substance/ kg of solvent

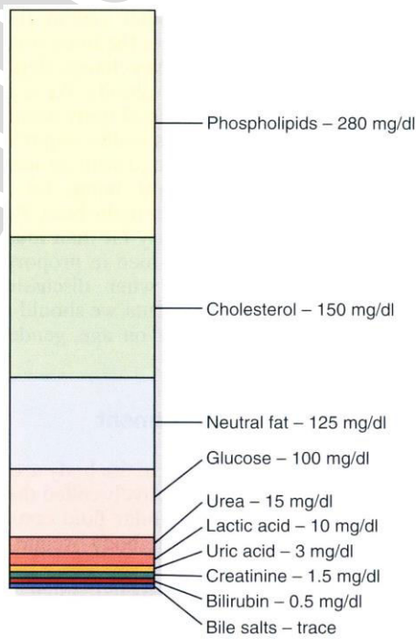
Osmolarity
- ✓ Measurement of solute concentration in terms of the number of dissolved particles
- ✓ For example: 1 mole of NaCl = 2 osmoles since NaCl dissociates into 2 particles
- ✓ 1 mole of $CaCl_2$ = 3 osmols because it dissociates into 3 particles
- ✓ For a substance that does not dissociate such as glucose, 1 mole of glucose is equal to 1 osmol
- ✓ the osmolarity of the blood is 300mosm



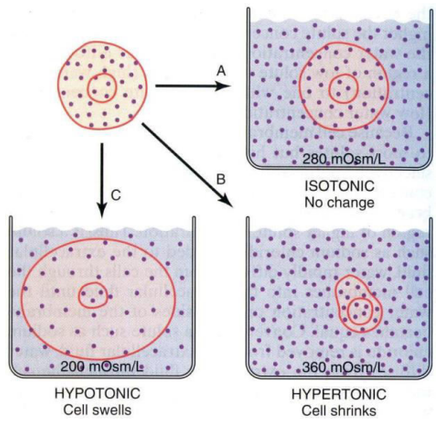
Summary of body fluid regulation, including the major body fluid compartments and the membranes that separate these compartments. The values shown are for an average 70-kilogram person.



Major cations and anions of the intracellular and extracellular fluids. The concentrations of Ca^{++} and Mg^{++} represent the sum of these two ions. The concentrations shown represent the total of free ions and complexed ions.



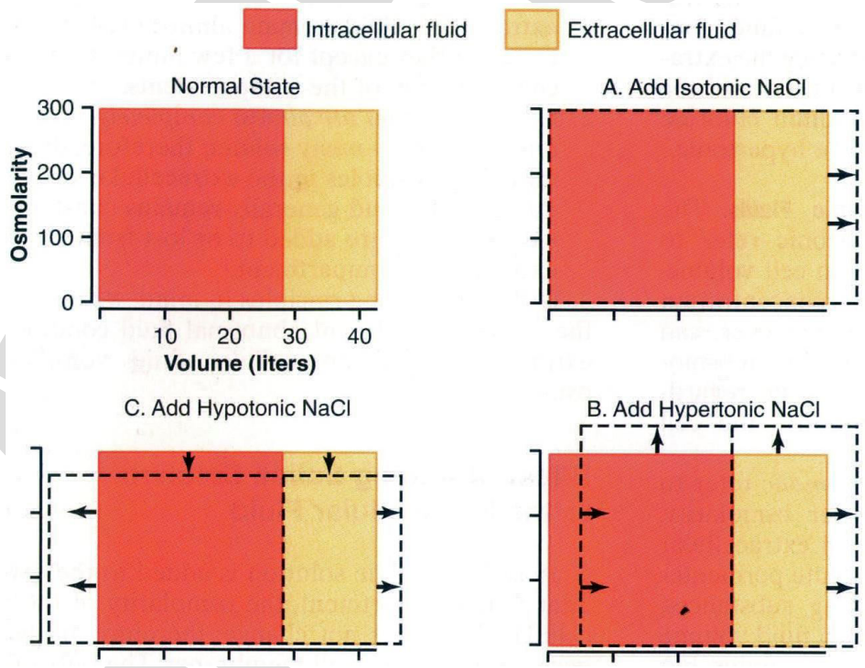
Nonelectrolytes of the plasma.



Effects of isotonic (A), hypertonic (B), and hypotonic (C) solutions on cell volume.

Osmolar Substances in Extracellular and Intracellular Fluids

	Plasma (mOsm/L H_2O)	Interstitial (mOsm/L H_2O)	Intracellular (mOsm/L H_2O)
Na^+	142	139	14
K^+	4.2	4.0	140
Ca^{++}	1.3	1.2	0
Mg^+	0.8	0.7	20
Cl^-	108	108	4
HCO_3^-	24	28.3	10
HPO_4^-, $H_2PO_4^-$	2	2	11
SO_4^-	0.5	0.5	1
Phosphocreatine			45
Carnosine			14
Amino acids	2	2	8
Creatine	0.2	0.2	9
Lactate	1.2	1.2	1.5
Adenosine triphosphate			5
Hexose monophosphate			3.7
Glucose	5.6	5.6	
Protein	1.2	0.2	4
Urea	4	4	4
Others	4.8	3.9	10
Total mOsm/L	301.8	300.8	301.2
Corrected osmolar activity (mOsm/L)	282.0	281.0	281.0
Total osmotic pressure at 37°C (mm Hg)	5443	5423	5423



Effect of adding isotonic, hypertonic, and hypotonic solutions to the extracellular fluid after osmotic equilibrium. The normal state is indicated by the solid lines, and the shifts from normal are shown by the shaded areas. The volumes of intracellular and extracellular fluid compartments are shown in the abscissa of each diagram, and the osmolarities of these compartments are shown on the ordinates.

Osmotic and Hydrostatic Pressure

Hydrostatic pressure
The pressure exerted by water on a membrane that separates the 2 compartments

Osmotic pressure
- ✓ the pressure that would be needed to prevent the movement (diffusion) of water to the compartment with higher solute concentration through a semi-permeable membrane
- ✓ determination of osmotic pressure is done by **empirical means or theoretical means**
- ✓ **Empirical means** involve the estimation of **freezing point depression**
- ✓ **Theoretical means** involve the **van't Hoff Law:**

¶ = ΦiRTc where

¶ - osmotic pressure; Φ – osmotic coefficient; I – number of dissociated particles; R the molar gas constant; T – absolute temperature (in K), and c – molar concentration

IV. MEMBRANE TRANSPORT PROCESSES

Simple Diffusion

- ✓ Net transfer of molecule down an electrochemical gradient
- ✓ Molecules move from a place of greater concentration to areas of less concentration

Fick's Law

- ✓ the rate of diffusion of a solute in water depends on the **difference of concentration** between regions, the **size** of the molecules and the possible **interaction** of the diffusible substrate with water
- ✓ can be written as:

$$J = DA(C1-C2)/ \Delta X;$$

where J is the flow of solute from region 1 to region 2 in the solution, D is the diffusion coefficient of the solute; A is the cross sectional area through which the flow of the solute is measured, C is the concentration of solute at region 1 and 2 and ΔX is the distance between region 1 and 2

Restricted Diffusion

- ✓ Similar to simple diffusion but the rate of diffusion is altered by the 1) **structure** and 2) **composition** of the membrane through which diffusion occurs
  - *a.* **Pore** or channel in membrane
    - **Fixed charge in the inside lining of the pore**: if the charge is negative, cations are more rapidly translocated; if positive more anions are translocated
    - **Radius of the pore** excludes molecules with greater diameter than the radius
  - b. **chemical composition** of the membrane
    - the rate of diffusion is related to lipid solubility of the substrate

Solvent Drag

- ✓ Water moving in bulk can accelerate or impede solute transfer if both move through the same channel

Facilitated diffusion

- ✓ Is carrier mediated but **does not require energy**
- ✓ It involves a membrane carrier or specific transmembrane channel
- ✓ Rate of transfer is greater than simple diffusion
- ✓ Features of facilitated diffusion:
  1. It does not conform with the laws of simple diffusion
  2. It shows saturation kinetics
  3. There is competition between simultaneously penetrating substrate of similar chemical structure
  4. There is high structural specificity
     - i.e L-arabinose > D-arabinose

Active Transport

- ✓ The net movement of a substrate is **against its electrochemical gradient**
- ✓ Features of active transport
  1. There is a net transfer of substrate against an electrochemical gradient
  2. It **requires direct input of energy** and is inhibited by metabolic poisons, lack of oxygen and reduced temperature
  3. It shows saturation kinetics, competitive inhibition and substrate specificity
  4. It is temperature dependent
- ✓ Some active transport are **electrogenic**
- ✓ **Electrogenic pumps** are transport systems that pump a specific ionic species in preference to others, leading to a net charge transfer
- ✓ This contributes to the **transmembrane potential**

Membrane transport proteins

Uniports – transport one solute from one side of membrane to the other

Co-transports – transport two or more solutes across the cell membrane

Symports – transport two solutes to the same side
Antiports – transport one solute to one side and another to the other side

Osmosis

- ✓ the flow of water across a semi-permeable membrane from a compartment in which the solute concentration is lower to one in which the solute concentration is greater
- ✓ occurs because solute lowers the chemical potential of water and water tends to flow from where its **chemical potential is higher (low solute concentration) to where it is lower (high solute concentration)**

Some specific transport mechanisms

Sodium pump (Na-K-ATPase)

- ✓ this system is responsible for the asymmetrical distribution of **Na and K across the cell membrane** and represents a form of stored energy
- ✓ **3 Na ions are pump out in exchange for 2 K ions**
- ✓ Sodium pump is electrogenic
- ✓ It is important in:
  - Uphill transport of a number of non-electrolytes such as glucose by secondary active transport and of other ions such as chloride
  - Impulse transmission associated with nerve and muscle function
  - Maintenance of cell volume

Chloride ion transport

- ✓ Chloride ions translocate by at least 2 mechanisms:
  1. **Hamburger Effect**
     - Also known as **ion exchange or chloride shift**
     - Chloride is exchange with **bicarbonate**
  2. **Active transport** couple with sodium pump (a form of secondary active transport)
     - the energy derived for active chloride transport is the **Na^+ electrochemical gradient that is maintained by sodium pump**

- molecular model suggests that the carrier has two binding sites: one for Na^+ and one for Cl^- and these are transported as ternary complex

Calcium transport

- ✓ The Ca-pump is a Ca-ATPase pump that is analogous to the Na-K-ATPase
- ✓ During contraction, calcium concentration in the cytosol of skeletal muscles is increased to 10^{-3} M from 10^{-7} M
- ✓ The muscle relaxes only when the calcium is reduced to normal by the calcium pump
- ✓ Failure of the calcium pump to remove calcium in the cytosol results to **malignant hyperthermia**
- ✓ Among the animals, pigs are more susceptible to this condition
- ✓ **Dantrolene** is a drug that has been used to reverse this condition

Non-electrolyte transport

- ✓ The active transport of many non-electrolytes like sugars, amino acids is by **secondary active transport l**ike in chloride and is dependent on the maintenance of sodium gradient

Transport of Macromolecules

- ✓ **Transport proteins** can mediate the transport of small molecules but not the macromolecules such as proteins, carbohydrates or polysaccharides
- ✓ Yet most cells are able to eject and take in specific macromolecules across the cell membranes
- ✓ These are done through **Exocytosis and Endocytosis**

Exocytosis

- the process by which cells secrete materials from the cell interior

Endocytosis

- cells ingest macromolecules and particles
- the substance to be ingested is progressively enclosed by a small portion of the plasma membrane which first invaginates and then pinches off to form an intracellular vesicle containing the ingested material
- two types of endocytosis:
  - **1. Pinocytosis**
    - Involves ingestion of fluid and solutes and small molecules via small vesicle
  - **2. Phagocytosis**
    - involves the ingestion of large particles via large vesicles

Receptor Mediated Endocytosis

- ✓ Selectively internalize physiologically significant proteins
- ✓ Most cells contain specialized class of vesicles that vary in diameter and appear to be coated with bristle like structures on their cytoplasmic surface
- ✓ These are called **coated pits** and constitute about 2% of cell surface

Movements of Electrolytes Across Membranes

- ✓ Ions move across membranes in a manner quite different from non-electrolytes
- ✓ In the transport of ions, **chemical potential** (the concentration of the electrolyte) and the **electrical potential** (voltage difference across the membranes) are considered. Together, they are called **electrochemical potential**

Gibbs-Donnan equilibrium

- ✓ A special sort of ionic equilibrium that can be obtained when one of the ions involved cannot cross the membrane because the membrane is impermeable to that ion but is permeable to water and to other ions in the system

Nernst Equation

- ✓ Equation that defines **electrochemical equilibrium**
- ✓ Happens when the chemical potential and the electrical potential are the **same in magnitude but of different charges** so that the net force in the ion is zero
- ✓ Equation that permits calculation of an electrical potential difference that will create an electrical force that is equal but opposite in direction to the concentration force

V. MEMBRANE POTENTIALS

Resting Membrane Potential

- ✓ The undisturbed **polarized** (difference in voltage between the inside and outside of the cells) condition of the membrane of a cell
- ✓ Normal membrane potential is **-90mv** in the cardiac and skeletal muscle cells

Action Potential

- ✓ The rapid change in the membrane potential which is followed by a return to the resting membrane potential
- ✓ It is propagated in unchanged form and magnitude along the length of nerve axon or muscle fibers
- ✓ It is a standard event by which information is transmitted between distant points in the nervous system

Electrotonic response

- ✓ Also known as a **local response**
- ✓ Situation wherein the depolarizing response is observed only near the site of application of the stimulus
- ✓ Its magnitude declines exponentially as it travels some distance from the current application
- ✓ The distance by which the response declines to 37% of the maximum is called the **length constant**

Action Potential differs from Local response in 2 ways

1. action potential is a much larger response wherein the polarity reverses, the cell interior becomes more positive than the exterior
2. the action potential is propagated without decrement down the length of the fiber and does not decay exponentially with distance like the local response

Polarization

- ✓ Refers to the absolute magnitude of the difference in electrical potential between the cytoplasm and the extracellular fluid

Depolarization

- ✓ there is a reduction in the polarity of the membrane (the inside of the cell becomes less negative)

Hyperpolarization

- ✓ There is an increase in the polarity of the membrane (the inside becomes more negative)

Generation of Action Potential

1. When progressively larger inward current pulses are applied, a point is reached wherein instead of a local response, an action potential occurs
2. That point is called the **threshold potential**
3. Once the membrane is depolarized sufficiently to reach the threshold potential, an explosive depolarization occurs
4. This completely depolarizes the membrane, then it overshoots so that the membrane acquires a reversed polarity (from negative to positive)
5. The action potential peaks at about +50mV then it returns towards the normal resting membrane potential. This is called **repolarization.**
6. A transient hyperpolarization occurs after repolarization. It is called **hyperpolarizing afterpotential**
7. During most of the action potential, the membrane is refractory to further stimulation, this period is called the **absolute refractory period**
8. Toward the latter part of the action potential, the cell can be caused to fire a second action potential, but a stronger than normal stimulus is required. This period is called **relative refractory period.**

VI. NERVE CELL PHYSIOLOGY

- ✓ One of the functions of neurons that is carried out by their axons is the conduction of action potentials
- ✓ In a local response, 2 factors determine the speed of conduction along a nerve or muscle fiber. These are:
    1. **Membrane capacitance**
    2. **Electrical Resistance**

Membrane Capacitance

- ✓ It is the amount of charge that is stored per volt of potential differences across the membrane
- ✓ It determines **how much** charge must flow to depolarize the membrane

Electrical Resistance

- ✓ Determines **how rapid** the charge can flow along the fiber to depolarize the membrane
- ✓ Within the cell, the resistance is substantial because the current must flow through a small cross sectional area

Time constant

- ✓ The velocity of conduction of action potential along a nerve fiber is determined by **the time constant** which is a characteristic of the fiber
- ✓ The **product of membrane capacitance and electrical resistance** determines the time constant for conduction
- ✓ The larger the Membrane Capacitance (Cm), the more charge must flow in order to depolarize the membrane
- ✓ The larger the internal electrical resistance (Rin), the greater the impedance to current flow
- ✓ **The larger the product of RinCm, the slower is the spread of a localized depolarization**

- ✓ **Nerve impulse** is conducted faster along a **large diameter nerve fiber**
- ✓ The Cm depends on the nerve's insulating properties while Rm depends on the diameter of the nerve.
- ✓ As the nerve gets larger, the surface area and hence the capacitance per unit length of the fiber increases in proportion to the radius of the fiber
- ✓ The cross sectional area of a nerve increases with the square of the radius
- ✓ While membrane capacitance per unit length increases with increasing radius, the electrical resistance per unit length on the other hand, decreases with the square of the radius greater than the increase in membrane capacitance
- ✓ **The net effect is a decrease in time constant**

Membrane Resistance (Rm)

- ✓ the resistance offered by the cell membrane to the flow of the current from the inside of the fiber outward
- ✓ the higher the membrane resistance, the better as it prevents the escape of action potential from the fiber
- ✓ The ratio of the Membrane Resistance with the Internal Resistance describes the quality of a particular cell as a cable
- ✓ **Rm/Rin determines the length constant of a fiber which is defined as the distance over which a conducted signal falls 37% of its initial amount**
- ✓ one factor to improve membrane resistance is **myelination**

Myelination

- ✓ Improves substantially the Rm
- ✓ Hence, **Length constant which is defined as Rm/Rin** is substantially increased
- ✓ It also lowers the Membrane Capacitance

Saltatory Conduction

- ✓ Means the impulse that is conducted along myelinated fibers **"jump"** from node to node
- ✓ It occurs because action potentials are generated only at the **nodes of Ranvier**

Communication between Nerve and Muscle Cells

Motor End Plate

- ✓ the synapse that occur between axons of motor neurons and skeletal muscle fibers
- ✓ at the motor end plate, the motor nerve loses its myelin sheath and breaks up into fine terminal branches
- ✓ each of these fine terminal branches lies in a shallow groove called **synaptic through** on the surface of the muscle cell
- ✓ the ends of the axons in the throughs contain many smooth surface vesicles containing **acetylcholine**
- ✓ the sarcolemma of the muscle cell lining the trough is pleated to form numerous junctional folds. This is important for synchronized muscle contraction

Transmission at the Neuromuscular Junction

1. The action potential is conducted down the motor axon to the presynaptic axon terminals
2. The depolarization of the plasma membrane of the axon terminal causes a transient increase in the permeability to Ca
3. **Ca^{2+}** flows into the axon terminal and by a mechanism not completely understood, induces the **acetylcholine-filled synaptic vesicles to fuse with the plasma membrane** and empty their contents into the synaptic cleft by process of exocytosis
4. Acetylcholine diffuses across the synaptic cleft and combines with specific receptors that is embedded in the sarcolemma
5. The combination of **acetylcholine** with the receptor molecules **causes a transient increase in the permeability of the motor end plate to Na^+**. Na channels in the motor end plate are ligand gated Sodium channels, acetylcholine being the ligand. **The influx of Na results to a transient depolarization of the motor end plate known as the End Plate Potential (EPP).**
6. This will eventually lead to the formation of **Action potential**

Autonomic Nerve Endings

- ✓ Two types of unmyelinated autonomic nerves innervate cardiac and smooth muscles
- ✓ The **cholinergic nerves** contain agranular vesicles at their terminals and release acetylcholine
- ✓ The **adrenergic nerves** contain granular vesicles and release norepinephrine
- ✓ The synaptic vesicles are found in terminal expansions of the axons and in swellings termed **varicosities** which occur along the course of the axons in muscle tissues
- ✓ In **cardiac and smooth muscle**, the varicosities do not make the specialized contacts with muscle cells that occur in skeletal muscle and hence, there is no motor end plates

VII. PHYSIOLOGY OF MUSCLE CONTRACTION

Skeletal Muscles

- ✓ It is composed of myofibers which are made up of myofibrils which are arranged in parallel fashion along the axis of the cell
- ✓ Each myofibril is divided into thick and thin myofilaments
- ✓ The **myofilaments** are the contractile elements of the muscle and come into two types: thick filaments **(myosin)** and thin filaments **(actin)**
- ✓ These myofilaments interdigitate and are arranged in sarcomeres

Sarcomeres

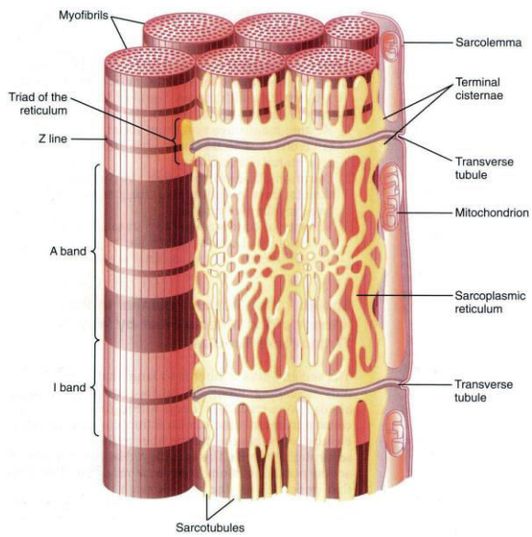
The fundamental contractile unit of muscle consisting of region between two Z-lines

Sarcolemma

- ✓ The outer covering of a myofibril
- ✓ Its main function is to spread the wave of depolarization originating at the motor end plate or the neuromuscular junction over the entire cell surface to initiate contraction

T-tubules

- ✓ Tubular extensions of the sarcolemma extending deep into the myofibrils at the level of the Z-line or at the junction of the A-I bands depending on the type of muscle and the species
- ✓ Allow the wave of depolarization to pass rapidly into the fiber so that deep lying myofibrils may be activated



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.

Sarcoplasmic Reticulum

- ✓ It is an elaborate anastomosing tubular network running parallel to the myofilaments
- ✓ The membrane of the sarcoplasmic reticulum contains a protein called ryanodine receptors that contain Ca^{2+}-release channels
- ✓ The functions of the SR are:
  1. Release of Calcium during muscle contraction
  2. To sequester and store of Ca^{2+} during muscle relaxation

Proteins of the Contractile Elements

- ✓ The thin filaments are composed of actin, tropomyosin and troponin
- ✓ **Actin** occurs in two forms:
  a) G-actin which is globular in form and the
  b) F-actin which is a polymer of G-actin monomers
- ✓ **Tropomyosin** is an elongated protein consisting of two α-helical chains which are wound around each other to form a coiled coil
- ✓ **Troponin** consists of a complex of three separate proteins, namely troponin T, troponin C and troponin I.
  - **Troponin T** binds the other 2 troponin units with tropomyosin
  - **Troponin C** is the Ca^{2+} acceptor protein
  - **Troponin I** is believed to induce inhibitory conformation of the actin-myosin filaments
- ✓ the thick filaments consist primarily of myosin
- ✓ the **myosin** is consists of 2 globular heads: (heavy meromyosin, HMM) which **hydrolyses ATP and interact with actin** and a rod like region (light meromyosin, LMM) which **confers stability to the molecule**

Steps in Skeletal Muscle Contraction

1. **ATP binds to myosin.** Initially, the complex between myosin and ATP has low affinity for actin
2. **ATP bound to myosin is split into ADP + Pi to form an activated complex**
3. The activated complex has a high affinity for actin and thus **activated myosin head promptly binds to a site on the adjacent thin filaments** forming a cross bridge between the filaments. The myosin binding site on actin must first be exposed by the binding of Ca^{2+} with troponin-C
4. The combination of the activated myosin head with actin is believed to promote two events:
   a. Liberation of ADP and Pi from the myosin head
   b. **Conformational change (or swiveling) of the myosin cross bridge** which pulls the bound thin filament toward the center of the sarcomere
5. The complex of actin and myosin that remains stable in the absence of ATP. The formation of such complexes in dead muscles when the intracellular ATP concentration falls to very low levels produces **rigor mortis**
6. In the presence of ATP in normal cells, each myosin head tends to bind an ATP, when it does so, it reverts to low affinity state which results in **detachment** of myosin from actin
7. The cycle is then repeated

Excitation-Contraction Coupling

- ✓ The term excitation-contraction coupling refers to the mechanism by which an action potential in the cell membrane causes the muscle cell to contract
- ✓ The steps are:

1. An action potential generated in the muscle cell plasma membrane is spread throughout the entire network of **T-tubules and sarcoplasmic reticulum**
2. The membrane of SR contains **Ca^{2+} pump** which is capable of accumulating Ca^{2+} in the SR against a large concentration gradient
3. The pumping action of Ca^{2+} pump maintains the concentration of **Ca^{2+} at less than 10^{-7} M** causing the contractile mechanism to remain inactive
4. When an action potential spreads throughout the T-tubules system, the sarcoplasmic reticulum releases Ca^{2+} in the sarcoplasm
5. When the Ca^{2+} in the sarcoplasm is high enough, the **Ca^{2+} binds with troponin C.** When the membranes of the T-tubular system return to their RMP, the SR membrane again becomes impermeable to Ca^{2+}
6. The action of a Ca^{2+} pump reaccumulates Ca^{2+} into the interior of the SR thus decreasing the Ca^{2+} concentration in the sarcoplasm
7. Ca^{2+} then dissociates from troponin and the muscle relaxes

Smooth Muscles

- ✓ Plays a major role in the physiological regulation of the respiratory tract, blood vessels and gastrointestinal tract. It is also found in the wall of the urogenital organs and other tissues
- ✓ Structures differs in skeletal muscles wherein:

1. Composed of elongated thin muscle fibers that contain a single nucleus
2. **Sarcomeres are absent**
3. Thin and thick myofibrils are dispersed throughout the cell
4. The thick filaments contain myosin and the thin filaments contain actin and tropomyosin. **Thin filaments lack troponin**
5. **T-tubules are absent** and unnecessary because the cell is small enough for a stimulus present on the cell surface to effectively activate the contractile machinery
6. Instead the smooth muscles contain **caveolae** which are small invaginations of the surface membrane that serve to increase the smooth muscle surface area and may function to couple membrane potential changes to the sarcoplasmic reticulum

Action Potential of Smooth Muscles

1. The RMP of smooth muscle varies from **-40 to -80mv**
2. The membrane potential may slowly vary in cyclical fashion or it may vary in non-cyclical way

in response to norepinephrine, acetylcholine, and other effector substance
3. Slow cyclical variations in membrane potential (slow waves) with duration of 5 to 7 seconds are typical of intestinal smooth muscle
4. Cross-bridge cycling is regulated by **Ca^{2+} induced phosphorylation of myosin**
5. Myosin cross bridges contain 4 light chains wherein 2 are associated with each head portions of the myosin
6. Myosin cannot bind with actin unless one of these light chains (LC20) is phosphorylated
7. The phosphorylation of LC20 is catalyzed by the enzyme **myosin light chain kinase which is activated by Calmodulin which in turn is activated by Ca^{2+}**
8. Calcium can enter the cell in a variety of ways:
   a. **by ligand gated Calcium channels**
   - when a smooth muscle is stimulated by a neurotransmitter, activated Ca channel may open allowing Ca^{2+} to enter the cell

   b. **by voltage gated Ca^{2+} channels**
   - Ca^{2+} may also enter the cell through **voltage gated channels** that may open during the action potential of smooth muscles

   c. **by release form SR**
   - Ca^{2+} may also be released from the SR
   - The Ca^{2+} release channels in SR are activated by inositol triphosphate (IP3) and is called the **IP3 receptor in contrast to the ryanodine receptors in skeletal muscles**
9. The light chains are dephosphorylated by the **enzyme myosin light chain phosphatase.**

Shortening and Force Development

1. The velocity of shortening is dependent on the phosphorylation of the myosin light chain
2. When the light chains are dephosphorylated by the phosphatase enzyme, the velocity of shortening decreases
3. The dephosphorylated cross-bridges remain attached to actin and are called **latch bridges**
4. **Latch bridges** provide smooth muscle with the ability to maintain tone with little energy consumption

Cardiac Muscles

Although cardiac muscles are striated, they differ somewhat from the skeletal muscles mainly by:

1. Cardiac fibers have single nucleus and are smaller than skeletal muscles
2. Each fiber is ribbon like rather than cylindrical
3. The T-tubule is larger in cardiac muscle than in skeletal muscles and is located at the Z-line rather than at the junction of the A and I bands.
4. The sarcoplasmic reticulum makes contact with the T-tubules and the cell membrane

Cardiac Action Potential

1. The **upstroke** of the cardiac action potential is due to **rapid inrush of Na^+** through the fast sodium channels which are apparently identical to the sodium channels involved in the skeletal muscle and nerve
2. During the **plateau phase, both sodium and calcium** enter the cell by way of the slow channels
3. **Repolarization** is caused by closing of the slow channels and a delayed increase in the **K+** conductance
4. **Slow spontaneous depolarization** is believed to be due to progressively decreasing **K+** conductance

Excitation-Contraction Coupling

1. The calcium released from SR is triggered by **Ca^{2+} itself**, not by membrane depolarization
2. The **Ca^{2+} responsible for Ca^{2+} induced Ca^{2+} release** enters the sarcoplasm from the ECF during the **plateau phase** of the cardiac action potential
3. The **T-tubule** of the cardiac muscle, unlike of the skeletal muscle, contains **Ca^{2+} channels** through which Ca^{2+} enter the cell from the ECF during action potential
4. The **SR ryanodine receptor** containing the Ca^{2+} release channel is opened by **influx of Ca^{2+} from the T-tubule**. In contrast, in skeletal muscles, Ca^{2+} release channel is opened by the voltage induced conformational change of the receptor
5. The amount of Ca^{2+} released from the SR is under physiologic control
6. The amount of Ca^{2+} entering the cell during the plateau phase can be **increased by norepinephrine and epinephrine.**
7. Increasing the amount of Ca^{2+} entering the cells increases the amount of Ca^{2+} released from the SR by Ca^{2+} induced Ca^{2+} release
8. The amount of intracellular Ca^{2+} is then regulated by the Na- Ca^{2+} exchanger, an antiport mechanism driven by Na^+ gradient that transports one Ca^{2+} out of the cell for every $3Na^+$ molecules that enter
9. In cases of low intracellular calcium, during the plateau phase of the cardiac action potential, the driving force for Na^+ is reduced. Because the exchange rate is proportional to the Na^+

concentration gradient, the amount of Ca^{2+} leaving the cell is also reduced

10. Drug induced inhibition of the Na-K-ATPase such as in the case of **digitalis glycosides**, causes Na^{+} to accumulate in the cell. The increase in intracellular Na^{+} reduces the driving force for Na^{+} to go inside the cell and thus reduces the ability of the Na^{+}- Ca^{2+} exchanger to remove Ca^{2+}
11. Under conditions of increased intracellular Calcium, the driving force for Ca^{2+} may exceed the driving force for Na^{+} entry.
12. Under these conditions, Ca^{2+} is pumped into the cell by the Na- Ca^{2+} exchanger wherein Ca^{2+} is pumped out of the cell and Na^{+} is pumped into the cell

VIII. THE BLOOD

Functions of Blood

1. For **transport** of substances to different parts of the body. Absorbed nutrients from the digestive tract and mobilized stored nutrients are transported by the circulating blood. Waste metabolic products from tissues are also carried by blood to organs of excretion.
2. For **homeostasis** or maintenance of constant internal environment. By flowing rapidly through tissues, blood ensures thorough mixing of the liquid elements of the body and keeps uniform the composition of body fluids
3. For **temperature regulation**. Blood warmed by internal organs can deliver heat if peripheral tissues become cold. Alternatively, the excess heat produced by active organs can be carried away by the blood and dissipated through the skin
4. As a convenient **pool of nutrients**. There are free sugars, amino acids, fatty acids and minerals in the plasma and extra amino acids can be obtained by breaking down plasma proteins.
5. For **protection**. If tissues or blood vessels are damaged, clotting process prevents excessive blood loss. Phagocytic cells and antibodies contained in blood help combat pathogens
6. Has **structural or supportive role.** Male penis has erectile tissue which is capable of being engorged with blood during sexual arousal

Composition of Blood

- ✓ Blood has 2 main components
  1. Plasma
  2. Formed elements
- ✓ **Plasma** consists mainly of water in which are dissolved electrolytes, sugars, proteins and other organic molecules and many important hormones as well as trace elements, metabolites and important gases
- ✓ **Formed elements (3 major types of cells)**
  1. **Red Blood Cells** whose primary function is to carry oxygen
  2. **White Blood Cells** whose main function is the protection of the body against invaders
  3. **Platelets** which are subcellular fragments important in the arrest of bleeding

Plasma Proteins

- ✓ Proteins are the most abundant colloid in the plasma
- ✓ Major plasma proteins are:
  1. **Albumin** – it is the most abundant plasma protein
  2. **Globulins** – round, compact molecules which are either an alpha, beta and gamma
  3. **Fibrinogen** – very long, thin molecules which are important in blood clotting

Functions of Plasma proteins

1. **Fibrinogen and other Clotting factors**- for protection from blood loss due to hemorrhage
2. **Gamma-globulins** are specific antibodies against infections and other foreign bodies
3. **Carrier molecules** which bind and transport hormones and other substances. Example: **ferritin** carries iron, **ceruplasmin** carries copper, **transcortin** carries glucocorticoids. Most drugs that are absorbed into the blood are bound and carried by albumin
4. **Buffers** – all blood proteins take part in maintain blood pH normal
5. **Pool of amino acids** – all plasma proteins, specially albumin serves as a pool of amino acids and when certain tissues need more amino acids, some plasma proteins become engulfed by the cells of the reticuloendothelial system (includes macrophages) and broken down into constituent amino acids which are then returned to circulation

Formed Elements

1. Red Blood Cells

- ✓ Most abundant in the blood
- ✓ Mature mammalian RBC's does not have nucleus, birds and lower animals have nucleated RBC
- ✓ Mammalian red blood cells appear as biconcave discs with diameter of approximately 7 micrometer and sufficiently deformable
- ✓ The transport function of RBC is due to hemoglobin
- ✓ **Hemoglobin**
  1. responsible for the red color of the blood
  2. changes color according to the maount of oxygen present in the blood: bright red when oxygenated, dark red when deoxygenated

Sahli's Method of Hb determination

- ✓ carbon monoxide (CO) is added to the blood sample
- ✓ CO binds irreversibly to Hb imparting bright red color
- ✓ The color of the sample is compared to a standard with known concentration

Haldane's method of Hb determination

- ✓ Acid is added to blood sample
- ✓ Hb changes irreversibly to acid hemtin
- ✓ resultant color is compared to a standard

- ✓ Knowing the Hb concentration, the RBC count and PCV, secondary blood indices such as Mean Corpuscular Volume (MCV), Mean Corpuscular

Concentration (MCHC) and Mean Corpuscular Hemoglobin (MCH) are calculated.

- ✓ **MCV** reflects the average volume of each red cells. Computed as MCV = PCV%/RBC count (x10/uL) x 10= fL

- ✓ **MCHC** provides an index of the average hemoglobin content in the mass of circulating red cells. MCHC = Hb (g/dl)/PCV (%) = g/dl

- ✓ **MCH** is an estimate of the average hemoglobin content of each red cell. Computed as MCH = Hb (g/dl)/RBC count (x10/uL) = pg

1. White Blood Cells

- ✓ divided into Granulocytes and Agranulocytes
- ✓ **Granulocytes**
  have granules in their cytoplasm and have multilobed nuclei which results in them being called polymorphonuclear cells
- ✓ **Agranulocytes**
  have no granules and have rather simple nuclei

- ✓ The **Granulocytes** are further divided into the following based on their histological staining:
  1. **Neutrophils** – do not bind either acidic or basic stains
  2. **Basophils** – stain deeply blue with basic stains and therefore have acidic material in their granules
  3. **Eosinophils** – granules take up the acidic red dye eosin and therefore contain basic or alkaline materials

The **Agranulocytes** are divided into:

1. **Lymphocytes** – have central densely staining nucleus and bluish cytoplasm and are slightly smaller than the monocytes.
2. **Monocytes –** look like large lymphocytes except that their nuclei are usually curved into a C or U shape.

Functions of the WBC

1. **Neutrophils:** non specific protective cells which migrate in large numbers to a site of injury, invasion or infection where they try to destroy the invading organisms by phagocytosis
2. **Basophils:** exert true effects when they reach the peripheral tissues where they are known as **Mast cells** which release the mediators of inflammation such as histamine
3. **Eosinophils**: attack parasites that are too large to be engulf by phagocytosis; also involved in allergic diseases
4. **Monocytes**: like basophils that exert effects in tissues where they are called **histiocytes or macrophages**. These cells contain lipase enzyme which can destroy fatty coats of many bacterial cell types. Aggregated macrophages are called **Giant Cells**
5. **Lymphocytes:** concerned with the body immune responses which are transformed in the lymph nodes and spleen into **plasma cells** (B-lymphocytes) which are producers of antibodies against antigens

3. Platelets: tiny fragments of cells that promote blood clotting

Formation of Blood Cells (Hematopoiesis)

Blood cell formation occurs at 3 sites:
1. **bone marrow** – major site in adults
2. **spleen and liver** – major site in fetus
3. **lymph nodes**

extramedullary hematopoiesis occurs only in some disease states such as leukemia

Bone Marrow are two types: **Red and Yellow**
1. Red Marrow: found in the flat bones such as the sternum and the pelvis in adults consisting of a network of trabeculae

2. Yellow or White marrow: found in the shafts of long bones, consists largely of fibrous tissues and fat which probably represents red marrow which ceased to function

Hematopoietic Cells in the Bone Marrow

1. **Pluripotential uncommitted stem cell** (Hemocytoblast)
   - ✓ primitive stem cells from which all blood cell types are derived. Differentiates into:
     a. Erythroid Stem cell
     b. Platelet Stem cells
     c. Phagocytic Stem cells
     d. Eosinophil Stem cells
     e. Basophil Stem cells
     f. Lymphoid Stem cells
   - ✓ promoted by hematopoietin and cytokines(interleukins 1, 6 and 3), these stem cells differentiate further that ultimately result in the formation of mature red blood cells

2. Erythroid Stem Cells

- ✓ in the influence of erythropoietin, develops into normoblasts then to reticulocyte and finally to mature red cells. RBC maturation requires **iron and vitamin B12**
- ✓ **Intrinsic factor** secreted from the stomach and is needed in the absorption of Vit B12. Deficiency of Vitamin B12 causes the development of **pernicious anemia; also known as megaloblastic anemia**
- ✓ **Erythropoietin,** a hormone produced by endothelial cells in peritubular capillaries in the renal cortex (85%) and by the Kupffer cells and hepatocytes in the liver (15%); it controls RBC formation

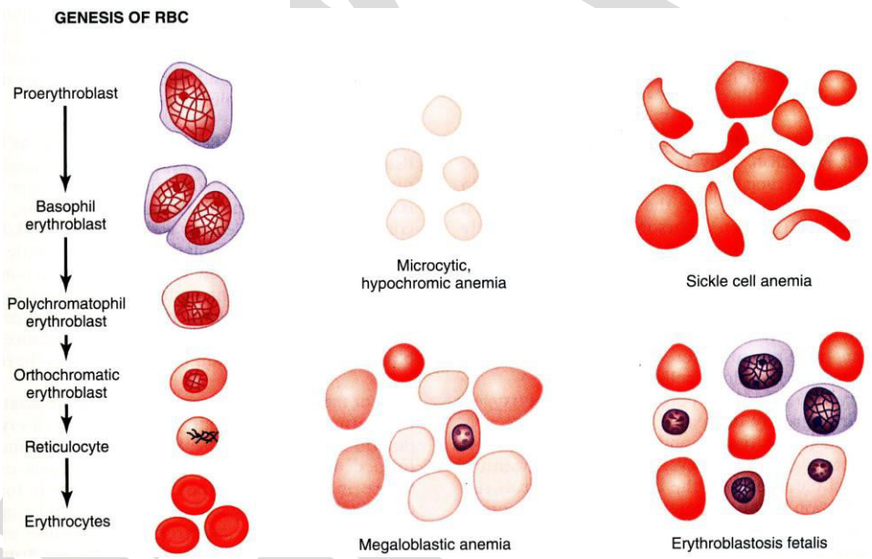
Platelet Stem Cells
- ✓ develop into **megakaryoblasts** then to **megakaryocytes** from which platelets bud off as tiny fragments

4. Phagocytic Stem Cells
- ✓ differentiate into **monocyte stem cell and granulocyte stem cells**
- ✓ **Monocyte stem cells** develop into **monoblasts** to **monocytes** and to **macrophages**
- ✓ **Granulocyte stem cells** develop into **myeloblasts** to **myelocytes** and then to **mature neutrophils**

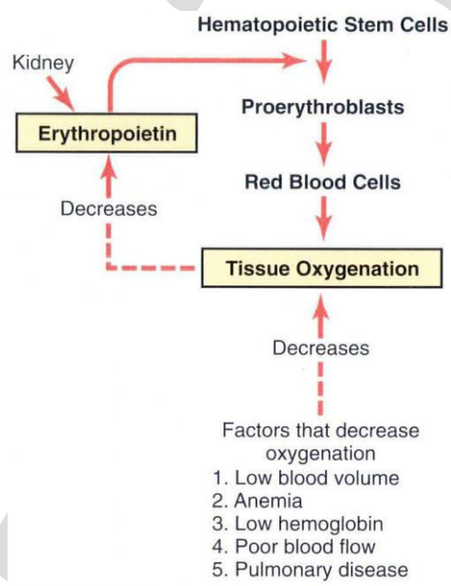
5. Eosinophil Stem Cells
- ✓ develop into **eosinophil myeloblasts** then to **eosinophil myelocytes** then to mature **eosinophils**

6. Basophil Stem Cells
- ✓ develop into **basophil myeloblasts** then to **basophil myelocytes** to **mature basophils**

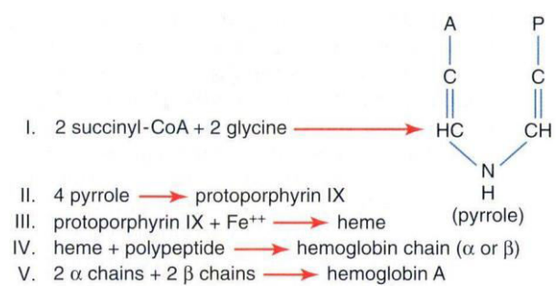
7. Lymphoid Stem Cells
- ✓ differentiate into **pre-B cells and pre-T cells**
- ✓ **pro-B cells** develop into **pre-B cells** to **early B cells to mature B cells** eventually giving rise to **plasma cells and memory cells**
- ✓ **pre-T cells** become **subcortical thymocytes** then to **medullary thymocytes** then to **blood/lymph node thymocytes** and eventually differentiate into **suppressor T cells, helper-cells and cytotoxic T cells.**



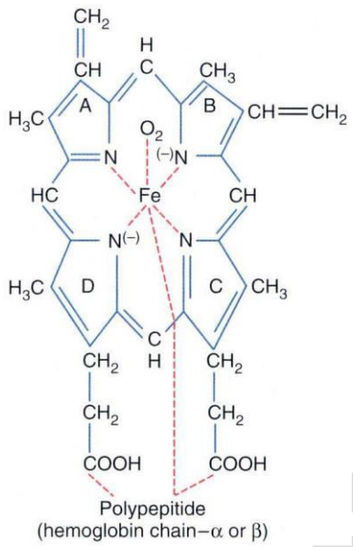
Genesis of normal red blood cells (RBC) and characteristics of RBCs in different types of anemias.



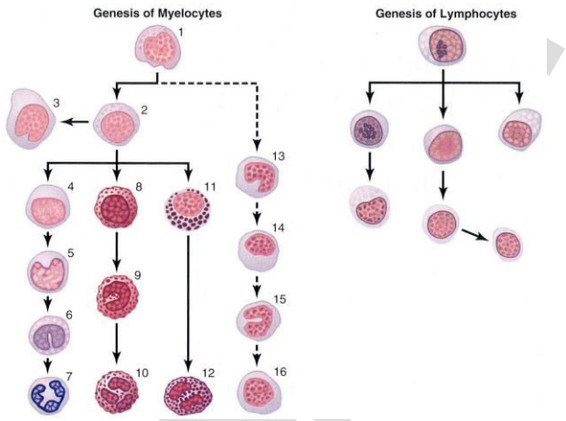
Function of the erythropoietin mechanism to increase production of red blood cells when tissue oxygenation decreases.



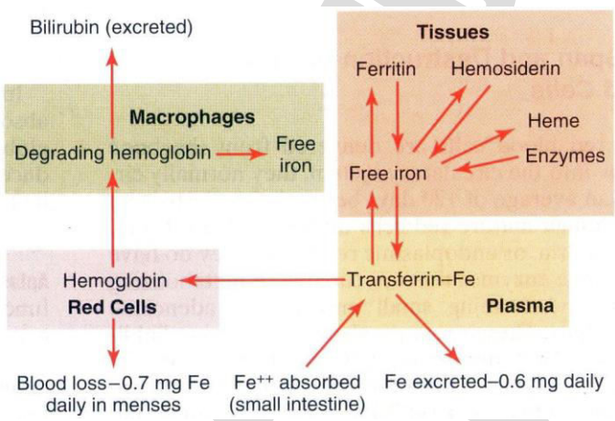
Formation of hemoglobin.



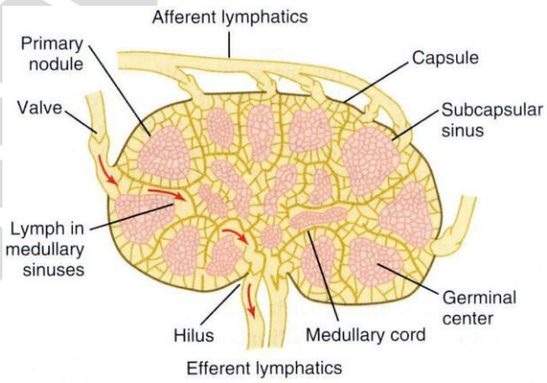
Basic structure of the hemoglobin molecule, showing one of the four heme chains that bind together to form the hemoglobin molecule.



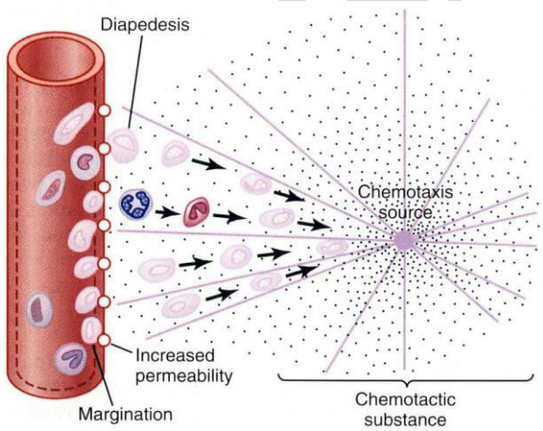
Genesis of white blood cells. The different cells of the myelocyte series are 1, myeloblast; 2, promyelocyte; 3, megakaryocyte; 4, neutrophil myelocyte; 5, young neutrophil metamyelocyte; 6, "band" neutrophil metamyelocyte; 7, polymorphonuclear neutrophil; 8, eosinophil myelocyte; 9, eosinophil metamyelocyte;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



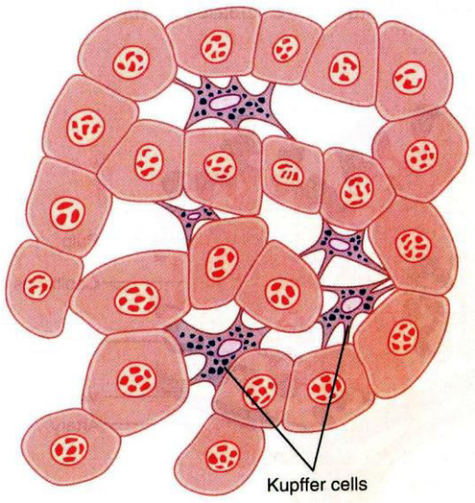
Iron transport and metabolism.



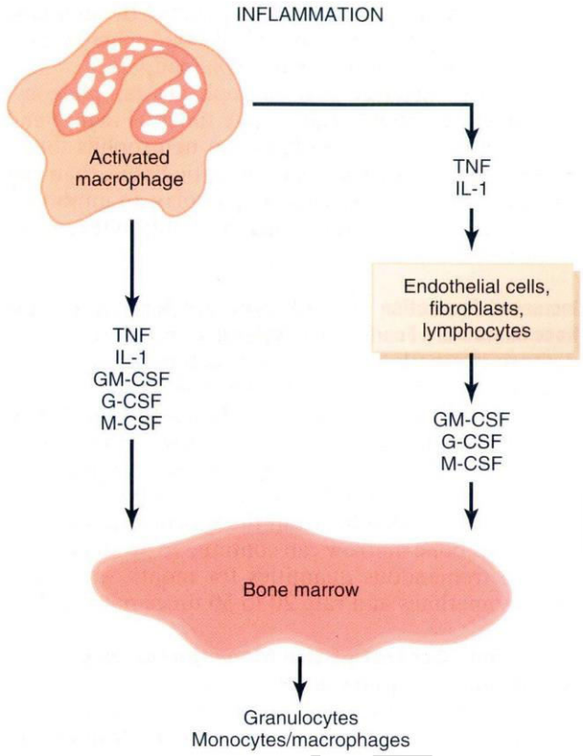
Functional diagram of a lymph node.



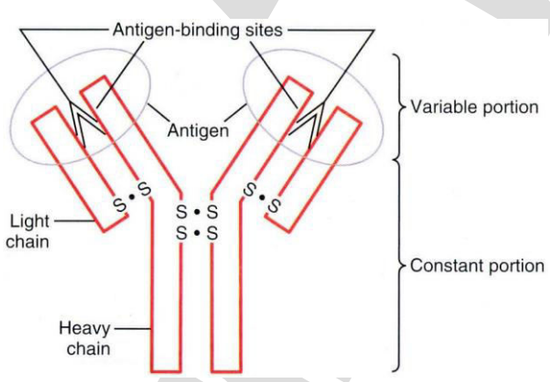
Movement of neutrophils by diapedesis through capillary pores and by chemotaxis toward an area of tissue damage.



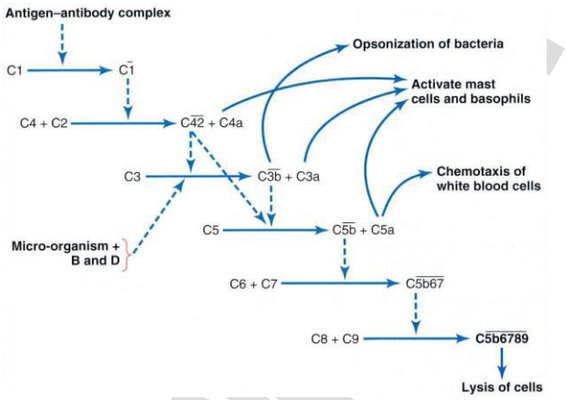
Kupffer cells lining the liver sinusoids, showing phagocytosis of India ink particles into the cytoplasm of the Kupffer cells.



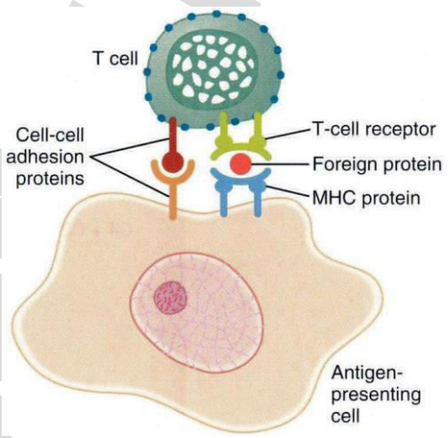
Control of bone marrow production of granulocytes and monocyte-macrophages in response to multiple growth factors released from activated macrophages in an inflamed tissue. G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-monocyte colony-stimulating factor; IL-1, interleukin-1; M-CSF, monocyte colony-stimulating factor; TNF, tumor necrosis factor.



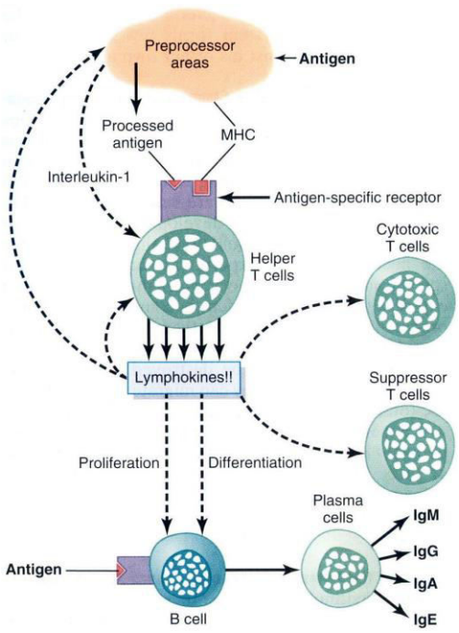
Structure of the typical IgG antibody showing it to be composed of two heavy polypeptide chains and two light polypeptide chains. The antigen binds at two different sites on the variable portions of the chains.



Cascade of reactions during activation of the classic pathway of complement.



Activation of T cells requires interaction of T-cell receptors with an antigen (foreign protein) that is transported to the surface of the antigen-presenting cell by a major histocompatibility complex (MHC) protein. Cell-to-cell adhesion proteins enable the T cell to bind to the antigen-presenting cell long enough to become activated.



Regulation of the immune system, emphasizing a pivotal role of the *helper T cells*. MHC, major histocompatibility complex.

Blood Groups

Major Blood Groups of Clinical Interest in Veterinary Medicine

Species	Blood Groups
Canine	DEA 1.1, 1.2 and 7
Feline	A, B
Equine	A,C,Q
Bovine	B,J
Ovine	B, R

Hemostasis

✓ refers to the mechanisms which prevent blood loss when the body is injured and prevent seepage of blood into the tissue in the leaky blood vessels

The mechanisms of hemostasis are:
1. **Vascular spasm** – constriction of arterioles to minimize blood loss
2. **Platelet Plugs** – platelet aggregate at the site of the break in blood vessels to prevent leakage
3. **Blood clotting** – reinforces the platelet plug

Bleeding Time
✓ is an indicator of the efficiency of the vascular reaction and is measured by pricking the fingers in humans with a needle and wiping the blood off at half minute intervals until the bleeding stops

Clotting Time
✓ is measured by taking a sample of blood into a glass tube, placing the tube in water bath at 37C and inverting the tube every 15 seconds until the blood no longer flows in the tube. It determines the efficiency of whole clotting process

Blood Clotting (Coagulation)
Two systems: the **intrinsic** and the **extrinsic**
1. Intrinsic System
- in the Intrinsic System, the formation of fibrin occurs in 3 steps
  1. Activation of Factor X
  2. Formation of thrombin
  3. Formation of fibrin

Activation of Factor X
1. Damage to blood vessels exposes the negatively charged collagen
2. **Factor XII** (Hageman Factor) by contact with **collagen and kallekrein** is activated to **Factor XIIa**. (XIIa can activate more Factor XII)
3. **Factor XIIa** activates **Factor XI** (Plasma Thromboplastin Antecedent) to **XIa**
4. **Factor XIa** in the presence of **Ca^{2+}** (Factor IV) activates **Factor IX** (Christmas Factor) to **IXa**
5. **Factor IXa** in the presence of **Factor VIII** (Antihemophilic Globulin), **Ca^{2+}** and phospholipids activate **Factor X** (Stuart-Power Factor) to **Xa**

Formation of Thrombin
1. **Factor Xa** with **Factor V** (proaccelerin), **Ca^{2+}** and phospholipids activates **Factor II** (Prothrombin) to **Factor IIa** (Thrombin)

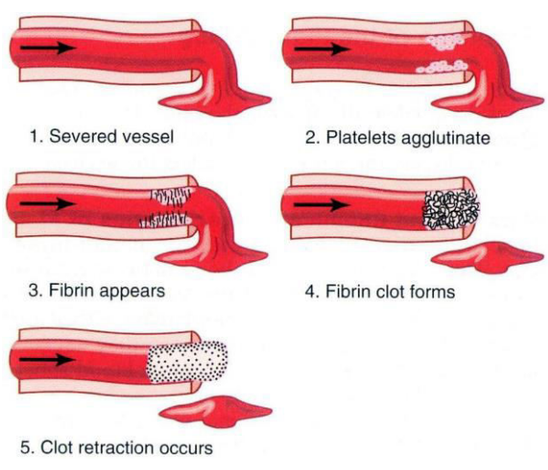
Formation of Fibrin
1. **Thrombin** activates **Factor I** (Fibrinogen) to soluble **fibrin** (Factor I')
2. **Thrombin** also activates **Factor XIII** (Fibrin Stabilizing Factors) to **Factor XIIIa**
3. **Factor XIIIa** stabilized **Factor I'** to **insoluble fibrin clot** (Factor I'')

2. The Extrinsic System of Blood Clotting
1. Blood is exposed to tissue factors during tissue damage
2. **Factor VII (Proconvertin)** is activated to **Factor VIIa** by **Factors XIIa, XIa** and the enzyme **kallikrein** (all from the intrinsic system)
3. **Factor VIIa** in the presence of **Factor III** (Tissue Thromboplastin) and **Ca2+** activate **Factor X to Xa.**
4. The rest of the steps is identical to the intrinsic system as described

Regulation of Blood Clotting
✓ Blood Clotting occurs all the time in the body and therefore should be regulated
✓ Regulation of clotting is accomplished in two ways:
1. Inhibition of Fibrin Formation
2. Fibrinolysis

1. Inhibition of Fibrin Formation
✓ this is mediated by **α-1 antitrypsin, α-2 macroglobulin, α-2 antiplasmin, antithrombin II or by thrombin**
✓ **thrombin** is modified by **thrombomodulin** leading to activation of **Protein C**
✓ **Protein C** in the presence of **Protein S** inactivates **VIIIa and Va**

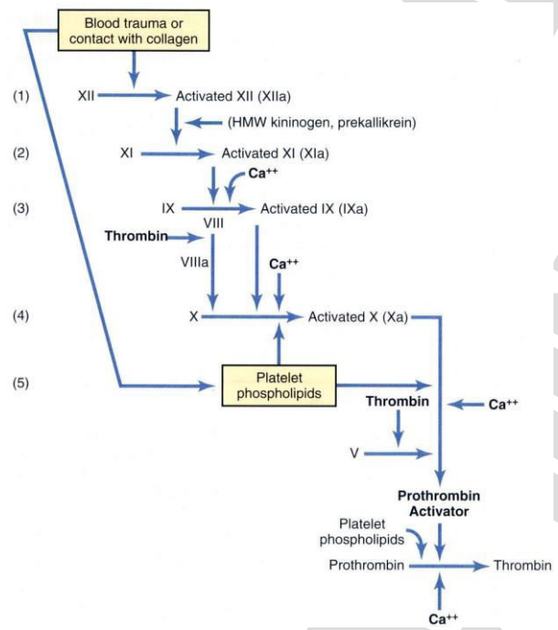
2. Fibrinolysis
✓ Plasmin can remove already formed fibrin clot



Clotting process in a traumatized blood vessel.

Clotting Factors in Blood and Their Synonyms

Clotting Factor	Synonyms
Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III; tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin; labile factor; Ac-globulin (Ac-G)
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B
Factor X	Stuart factor; Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
High-molecular-weight kininogen	Fitzgerald factor; HMWK (high-molecular-weight) kininogen
Platelets	



Intrinsic pathway for initiating blood clotting.

IX. PHYSIOLOGY OF THE CARDIOVASCULAR SYSTEM

Initiation of Heartbeat

1. the heart is composed of specialized striated muscle which contracts and relaxes in a rhythmic fashion
2. while it contracts (systole), it squeezes the blood out through the pulmonary and aortic valves
3. while it relaxes (diastole), it fills up again with blood from the veins
4. the rhythmic contraction and relaxation is brought about by the initiation and spread of electrical impulses throughout the heart muscle.
5. The electrical events occur independently of any intervention from the nervous system which is an intrinsic property of the heart itself
6. when any of the muscle cell is electrically excited above a certain threshold level, it discharge and electrical impulse or action potential
7. the impulse in one cell can spread to adjacent cells through the intercalated discs
8. the action potential in each myocardial cell causes contraction or systole
9. cessation of the action potential allows relaxation or diastole

Spread of Cardiac Impulse

1. different parts of the heart and different groups of myocardial cells **vary in the rate at which the membrane becomes depolarized** during diastole
2. the region of the heart which normally has the highest rate of spontaneous diastolic depolarization and hence acts as a pacemaker is the **sino-atrial node (SA node)**
3. cells in the SA node **reach threshold for depolarization earlier than** their neighbors and its action potential triggers off action potential in other cells
4. electrical impulses originating in the SA node are conducted from cell to cell through the atrial muscle via the **intercalated disk**
5. There is no direct pathway for spread of impulse from the atrial to ventricular muscle due to the **fibrous ring** which forms a supporting framework
6. A single site where it is possible for the impulse to cross from atria to ventricles is through the **AV node**
7. The electrical impulse is delayed for a short time in the AV node because the conduction velocity of this group of **specialized muscle is rather slower**
8. the impulse then passes to a group of rapidly conducting fibers called the **Bundle of His which lies in the intraventricular septum,** running down towards the apex of the heart and then splitting into bundles of **Purkinje fibers** which spread up to the **epicardial surfaces of the ventricles**

Control of Heart Rate

1. The action of the cardiac pacemaker and hence the heart rate can be influenced by certain **nerves and hormones**
2. The **vagus nerve** (parasymphathetic) when stimulated releases acetylcholine which **reduces the rate of diastolic depolarization** in the SA node thus slowing the heart rate
3. The **Sympathetic nerves** reaching the heart supply all parts of the myocardium particularly the nodes; impulses in these nerves release norepinephrine (noradrenaline) which **accelerates the rate of diastolic depolarization thus speed up the heart rate**
4. It is important to emphasize that the heart is not dependent on its nerves for initiation of heartbeat. A **denervated heart** will beat spontaneously as rhythmicity is its intrinsic property
5. Nerves are important in modifying, regulating and controlling the function of the heart

Heart Sounds

1. when a valve closes, turbulence is induced producing vibrations and sounds
2. the sounds are not caused by the leaflets of the valves slapping together
3. the **first heart sound** occurs at the time of closure of the AV valves and has a low pitched quality often describe as the "lub"
4. the **second heart sound** occurs at the time of closure of the aortic and pulmonary valves and has a higher pitch quality referred to as "dub"

Factors Influencing Cardiac Output

- ✓ **Cardiac Output** is the volume of blood flowing out of either left or right side of the heart per minute
- ✓ It is calculated by multiplying the **stroke volume** or volume ejected during each heart beat by the heart rate
- ✓ the **stroke volume** is influenced by

1. Venous return

- the heart can pump only the blood that comes into it
- if venous return increases, then the **stroke volume** increases; if it decreases, the stroke volume decreases

Frank-Starling Law of the Heart

- ✓ states that the **myocardium contracts more forcefully if the cells are stretched**
- ✓ however if the ventricles become over-filled so that the muscle fibers are over-stretched, then the force of contraction is reduced

Law of Laplace

- ✓ the pressure in a hollow sphere or cylinder is **inversely proportional to the radius**
- ✓ **Pressure = Tension/Radius**
- ✓ hence, as the radius increases, the ability to develop pressure decreases
- ✓ an over-filled heart which is unable to eject all of the blood entering it is said to be in cardiac failure

2. Contractility of the Myocardium

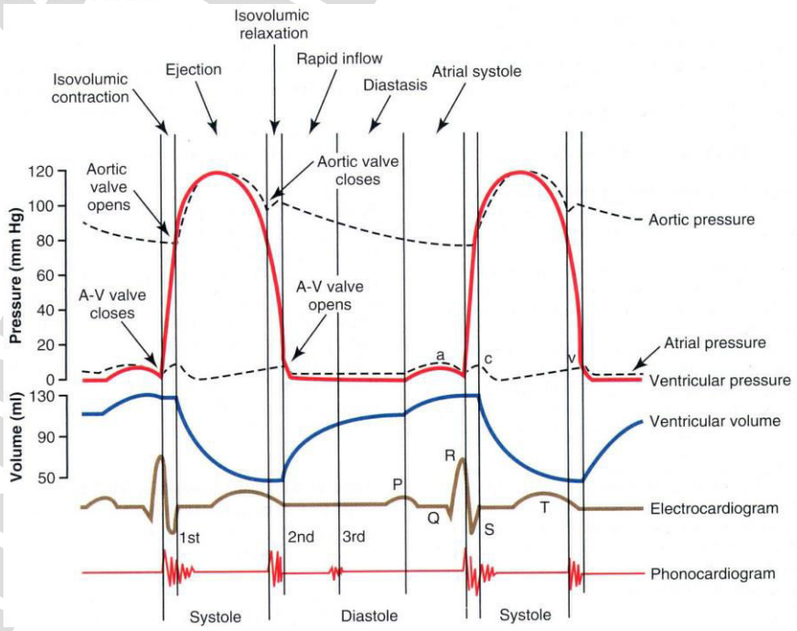
- influenced by nerves and hormones
- example: the Sympathetic stimulation increases both the rate and force of contraction

The Peripheral Circulation

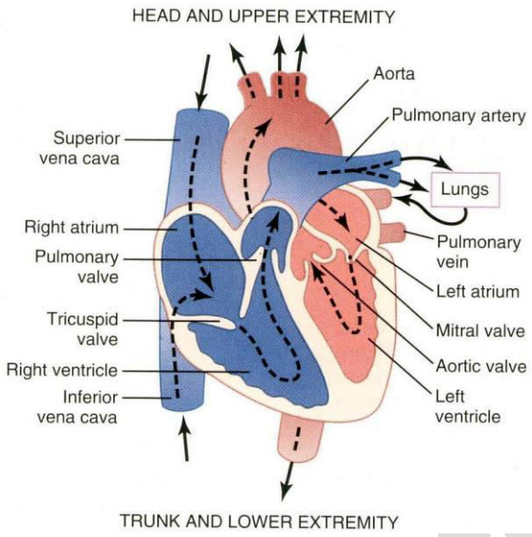
- ✓ Blood flows in the body through a series of tubes
- ✓ factors which regulate the flow of fluid through a tube include:
  1. the **pressure difference (**ΔP) between the two ends of the tubes
  2. the **resistance** to fluid flow
- ✓ the **resistance to fluid flow** depends on:
  1. **viscosity** (ή) of the fluid (more viscous the more resistance)
  2. the **length** (L) of the tube (a long tube has more resistance than a short one)
  3. the **radius of the tube (**r) (a narrow tube has more resistance than a wide one; resistance is inversely proportional to the fourth power radius)
- ✓ According to **Poisseille's Law,**
  Fluid Flow = ΔP ¶ r^4 / 8 ήL

Pulse Pressure
the difference between systolic and diastolic pressure

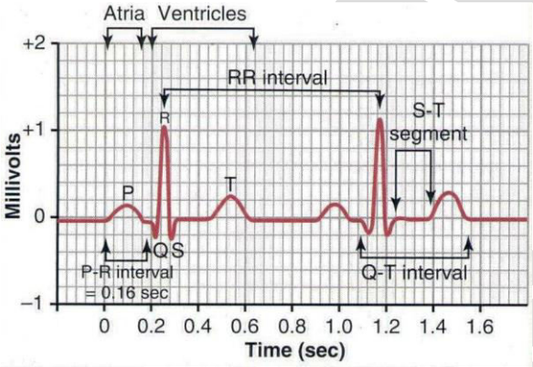
Perfusion pressure
the mean arterial pressure minus the venous pressure



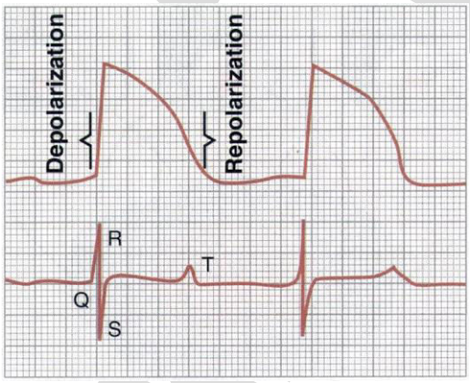
Events of the cardiac cycle for left ventricular function, showing changes in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonocardiogram.



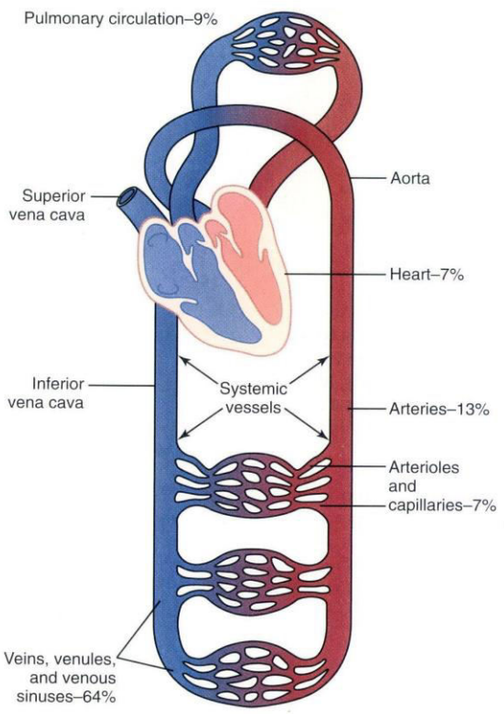
Structure of the heart and course of blood flow through the heart chambers and heart valves.



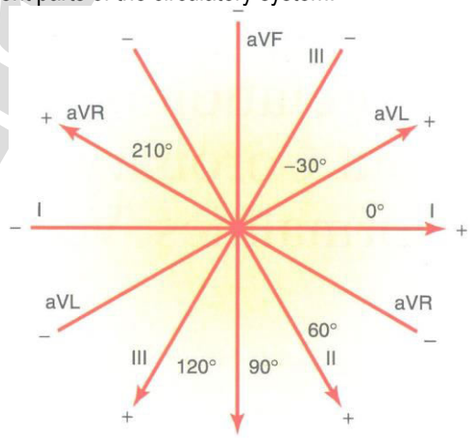
Normal electrocardiogram.



Above, Monophasic action potential from a ventricular muscle fiber during normal cardiac function, showing rapid depolarization and then repolarization occurring slowly during the plateau stage but rapidly toward the end. Below, Electrocardiogram recorded simultaneously.



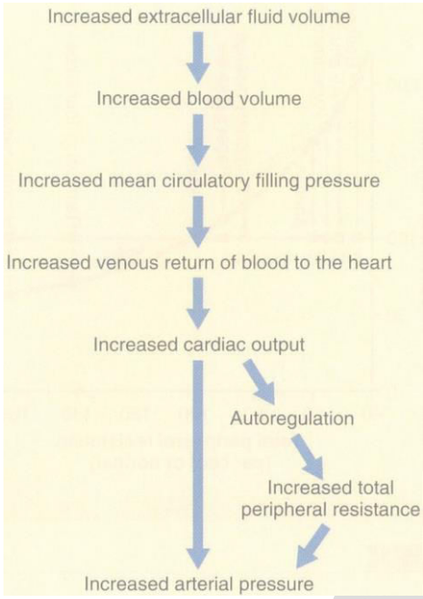
Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.



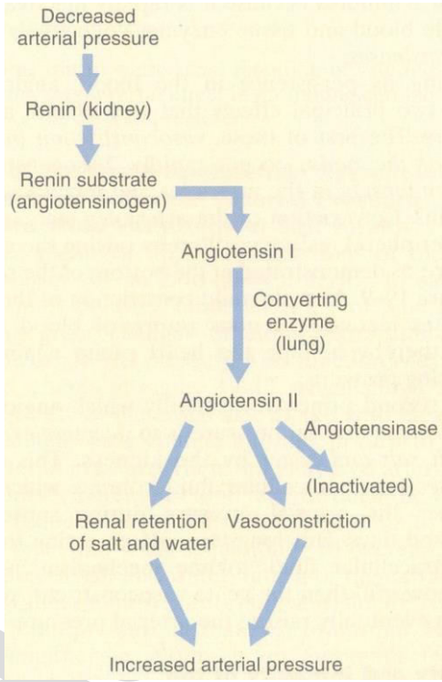
Axes of the three bipolar and three unipolar leads.

Blood Flow to Different Organs and Tissues Under Basal Conditions

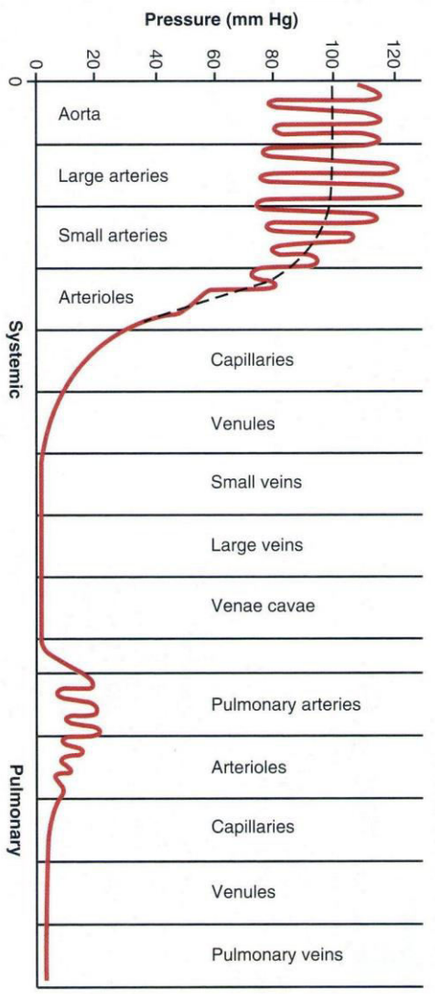
	Per cent	ml/min	ml/min/100 g
Brain	14	700	50
Heart	4	200	70
Bronchi	2	100	25
Kidneys	22	1100	360
Liver	27	1350	95
Portal	(21)	1050	
Arterial	(6)	300	
Muscle (inactive state)	15	750	4
Bone	5	250	3
Skin (cool weather)	6	300	3
Thyroid gland	1	50	160
Adrenal glands	0.5	25	300
Other tissues	3.5	175	1.3
Total	100.0	5000	



Sequential steps by which increased extracellular fluid volume increase the arterial pressure. Note especially that increased cardiac output has both a direct effect to increase arterial pressure and an indirect effect by first increasing the total peripheral resistance.



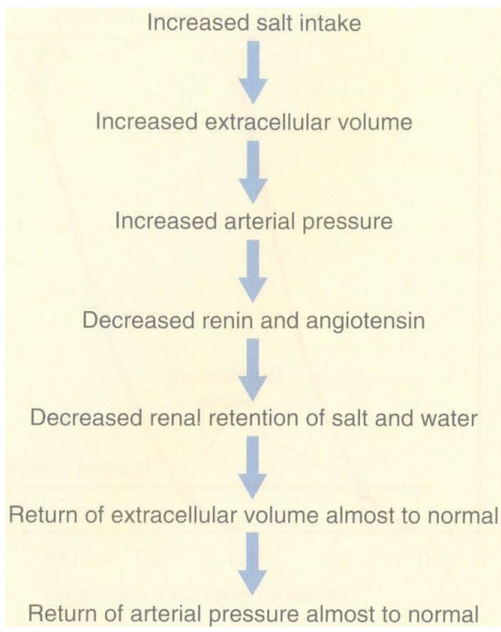
Renin-angiotensin vasoconstrictor mechanism for arterial pressure control.



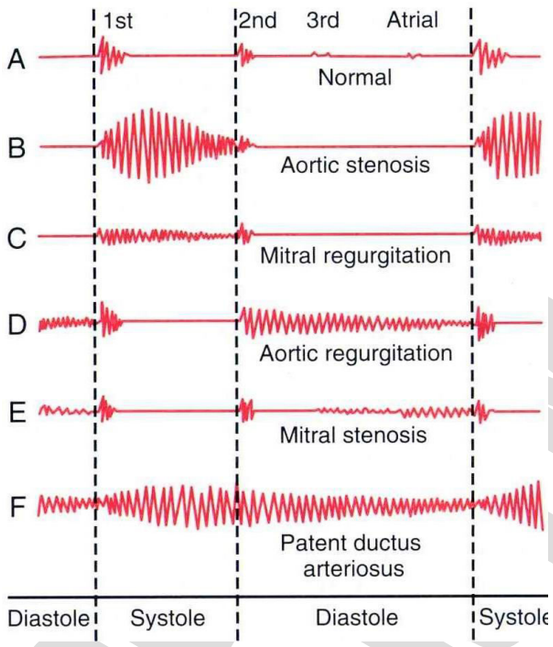
Normal blood pressures in the different portions of the circulatory system when a person is lying in the horizontal position.

Relative Permeability of Skeletal Muscle Capillary Pores to Different-Sized Molecules

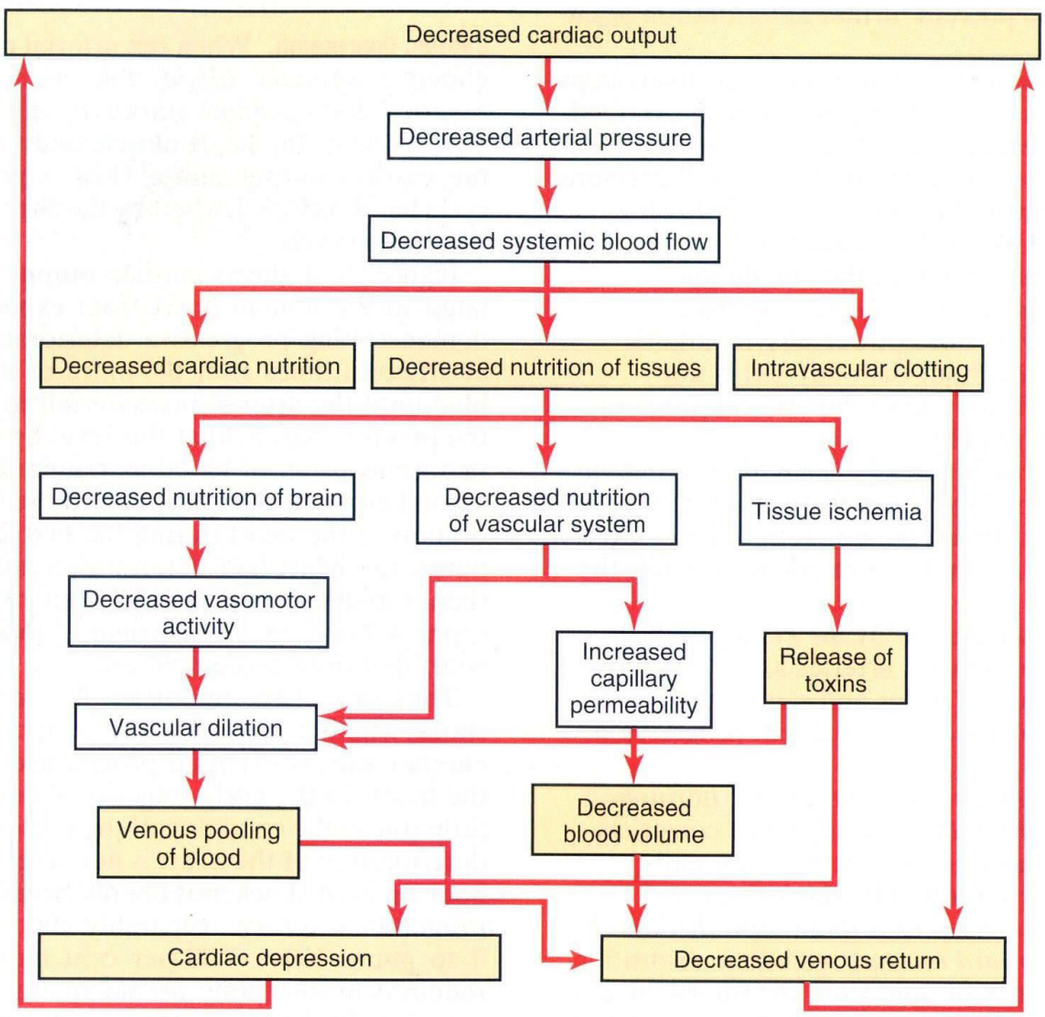
Substance	Molecular Weight	Permeability
Water	18	1.00
NaCl	58.5	0.96
Urea	60	0.8
Glucose	180	0.6
Sucrose	342	0.4
Inulin	5,000	0.2
Myoglobin	17,600	0.03
Hemoglobin	68,000	0.01
Albumin	69,000	0.001



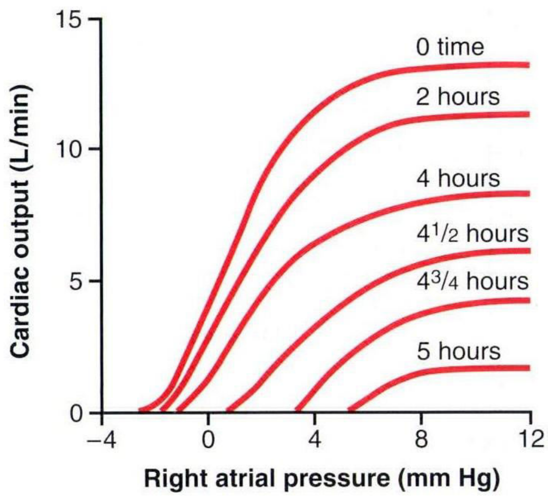
Sequential events by which increased salt intake increases the arterial pressure, but feedback decrease in activity of the rennin angiotensin system returns the arterial pressure almost to the normal level.



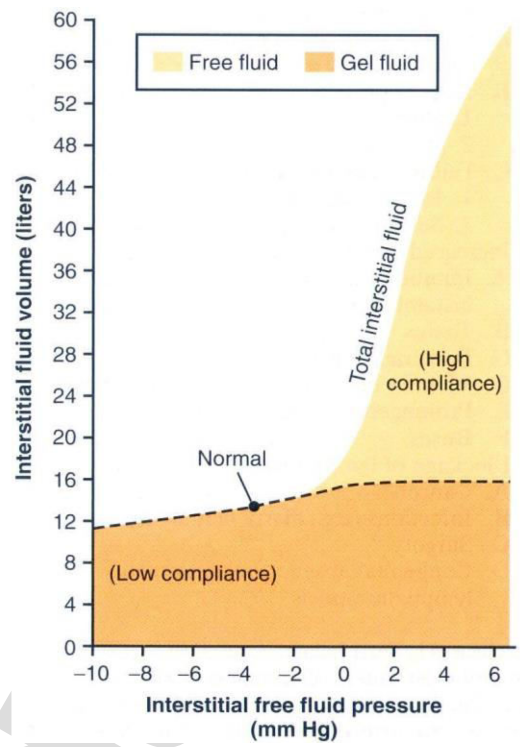
Phonocardiograms from normal and abnormal hearts.



Different types of "positive feedback" that can lead to progression on shock.



Cardiac output curves of the heart at different times after hemorrhagic shock begins. (These curves are extrapolated to the human heart from data obtained in dog experiments.)



Relation between interstitial fluid hydrostatic pressure and interstitial fluid volumes, including total volume, free fluid volume, and gel fluid volume, for loose tissues such as skin. Note that significant amounts of free fluid occur only when the interstitial fluid pressure becomes positive.

X. RENAL PHYSIOLOGY

Kidneys

- Paired, bean-shaped organs
- Receive 20-25% of the cardiac output.
- Has an outer **cortex** and an inner **medulla**.
- The **functional unit** of the kidneys is the **nephron**.
- Each nephron has a **vascular** and **tubular** component.

Some key vascular components

- **Afferent arterioles** - Carry blood to the glomerulus
- **Glomeruli** - Capillaries which filter plasma
- **Efferent arterioles** - Carry blood away from the glomerulus
- **Peritubular capillaries** - Supply renal tissue w/ blood

Key tubular components

- **Bowman's capsule** - Collects glomerular filtrate.
- **Proximal convoluted tubule, Loop of Henle (descending and ascending limbs), Distal convoluted tubule, Collecting duct**
- **Renal corpuscle** = Bowman's capsule + glomerulus

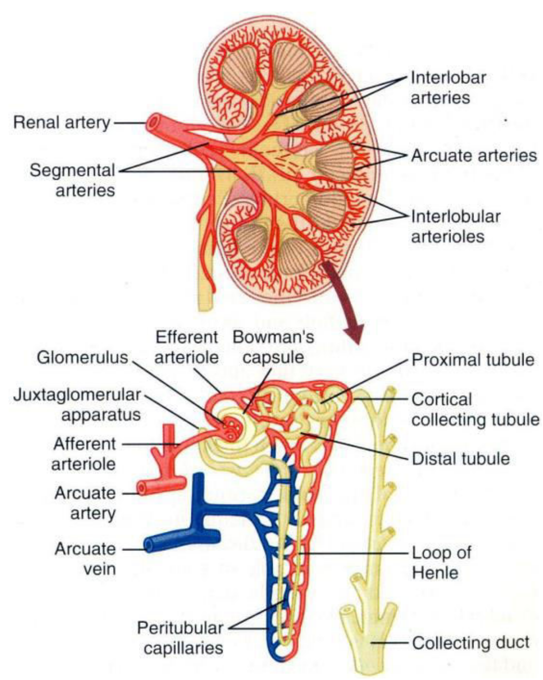
Nephrons

Cortical

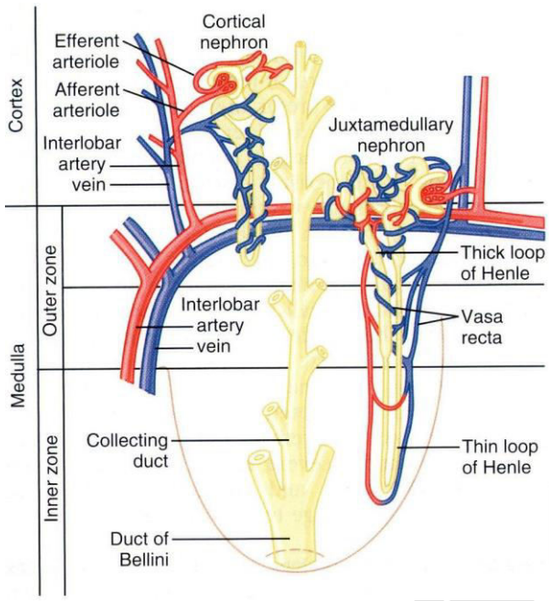
- More numerous, glomeruli lie in outer cortex, have short loops of Henle that barely dip into the medulla

Juxtamedullary

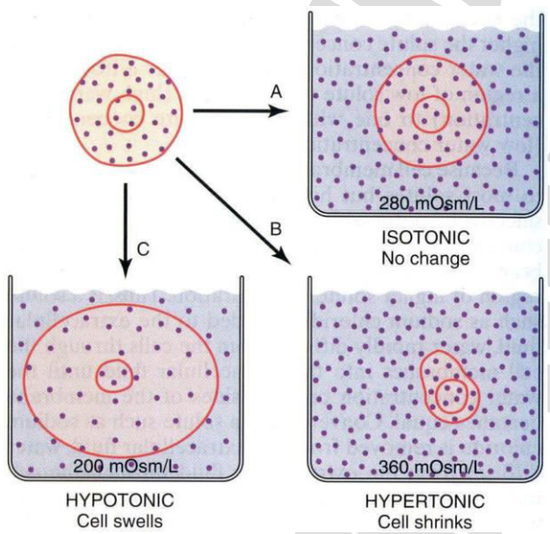
- Less numerous, glomeruli lie in inner cortex, have long loops of Henle that plunge deep into the medulla, vascular system has hairpin loops called the **vasa recta**



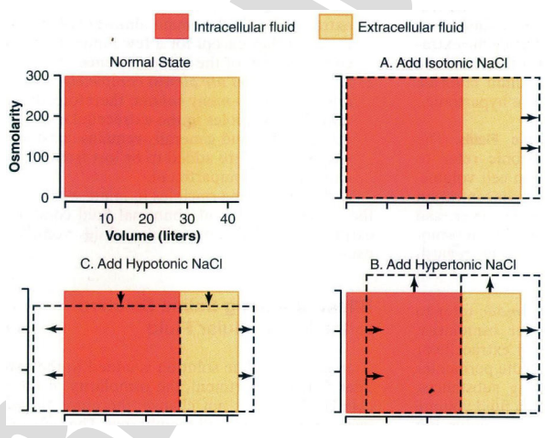
Section of the human kidney showing the major vessels that supply the blood flow to the kidney and schematic of the microcirculation of each nephron.



Schematic of relations between blood vessels and tubular structures and differences between cortical and juxtamedullary nephrons.

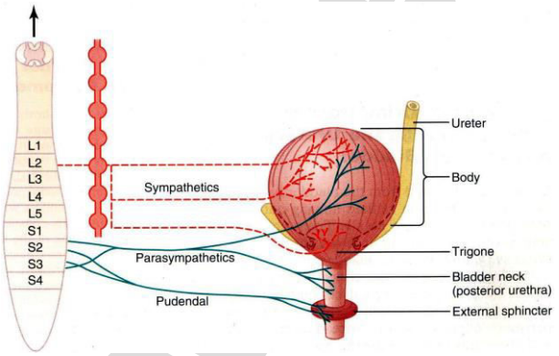


Effects of isotonic (A), hypertonic (B), and hypotonic (C) solutions on cell volume.

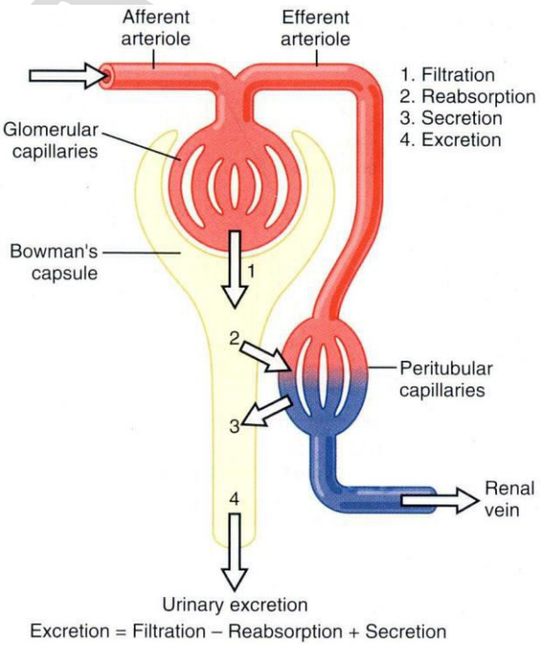


Effect of adding isotonic, hypertonic, and hypotonic solutions to the extracellular fluid after osmotic equilibrium.

The normal state is indicated by the solid lines, and the shifts from normal are shown by the shaded areas. The volumes of intracellular and extracellular fluid compartments are shown in the abscissa of each diagram, and the osmolarities of these compartments are shown on the ordinates.



Urinary bladder and its innervation.



Basic kidney processes that determine the composition of the urine. Urinary excretion rate of a substance is equal to the rate at which the substance is filtered minus its reabsorption rate plus the rate at which it is excreted from the peritubular capillary blood into the tubules.

3 basic processes are involved in the formation of urine:

- **Glomerular filtration** - Filtration of a protein free plasma from the glomerulus into Bowman's capsule. (Referred to as an **ultrafiltrate** once in Bowman's capsule).
- **Tubular reabsorption** - Selective movement of filtered substances from the tubule into the capillaries.

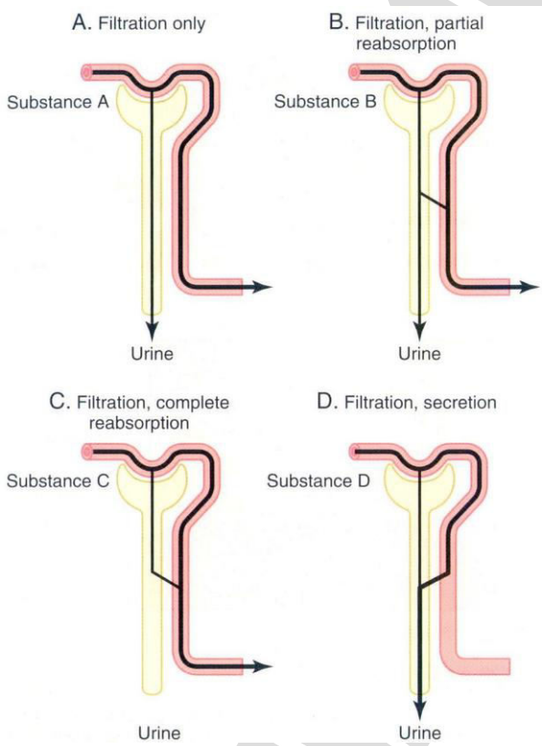
- **Tubular secretion** - Selective movement of nonfiltered substances from the capillaries into the tubule.

- **Excretion** - Elimination of substances from the body in the urine. It is the result of the first 3 processes.
- Do not confuse secretion with excretion.

- Glomerular filtration - Initial stage of urine formation

- Process depends on several factors:

- **Glomerular Capillary Blood Pressure (GCBP)** - (Favors filtration)
- **Plasma Colloid Osmotic Pressure (PCOP)** - (Opposes filtration)



Renal handling of four hypothetical substances. A, The substance is freely filtered but not reabsorbed. B, The substance is freely filtered, but part of the filtered load is reabsorbed back in the blood. C, The substance is freely filtered but is not excreted in the urine because all the filtered substance is reabsorbed from the tubules into the blood. D, The substance is freely filtered and is not reabsorbed but is secreted from the peritubular capillary blood into the renal tubules.

Bowman's Capsule Hydrostatic Pressure (BCHP) - (Opposes filtration)

- **Net filtration pressure (NFP)** - Net difference favoring filtration.
- NFP = GCBP - (PCOP + BCHP)
- NFP = 55 mm Hg - (30 + 15) mm Hg = 10 mm Hg
- NFP favors filtration if value > 0 and opposes filtration if value < 0.

- Permeable nature of glomerular capillaries contributes to glomerular filtration. The glomerular capillaries are about 100X more permeable than the systemic capillaries because walls contain numerous pores.

- **Glomerular filtration rate (GFR)** - Volume of filtrate formed by both kidneys each minute.

Rate of glomerular filtration is about 115-125 ml/min, or about 160-180 L/day. Unless most of this is reabsorbed into the bloodstream, the body would quickly dehydrate.

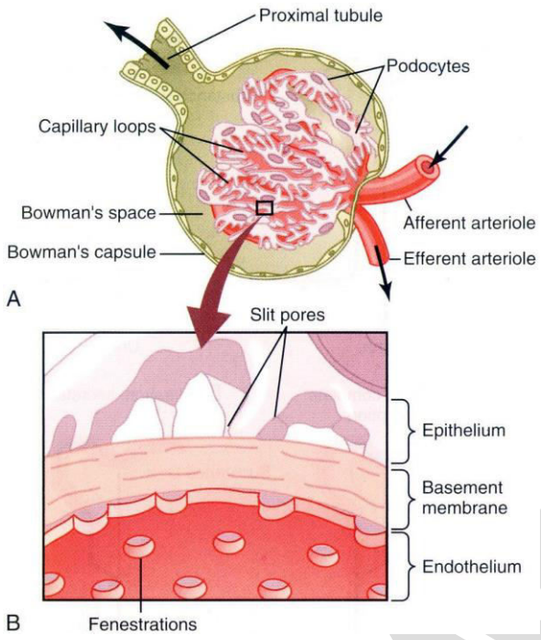
Regulation of GFR

- **Extrinsic** control of GFR occurs through the sympathetic N.S. control of vasoconstriction of afferent arterioles and a subsequent decrease in blood flow. This decreases GFR and, therefore, diverts blood flow elsewhere.
- **Renal autoregulation** - **Intrinsic** regulatory changes designed to maintain a relatively constant GFR in the face of fluctuating blood pressures. One way in which it occurs is via locally produced chemicals that affect the afferent arterioles.
- If GFR increases:

- Vasoconstriction → ↓Blood flow → ↓Glom. Cap. B.P. → ↓Filtration P → ↓GFR

- If GFR decreases:

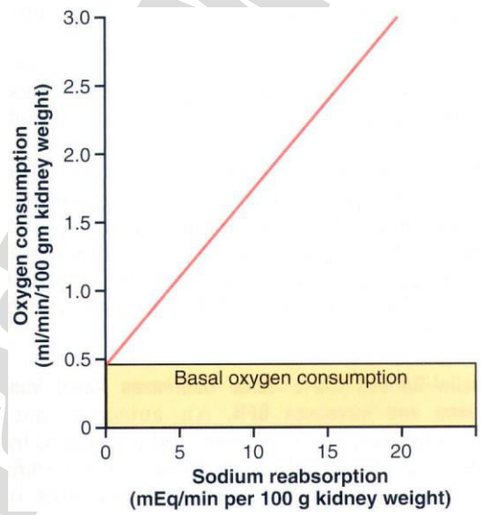
- Vasodilation → ↑Blood flow → ↑Glom. Cap. B.P. → ↑Filtration P → ↑GFR



A, Basic ultrastructure of the glomerualr capillaries. B, Cross-section of the glomerular capillary membrane and its major components: capillary endothelium, basement membrane, and epithelium (podocytes).

Filterability of Substances by Glomerular Capillaries Based on Molecular Weight

Substance	Molecular Weight	Filterability
Water	18	1.0
Sodium	23	1.0
Glucose	180	1.0
Inulin	5,500	1.0
Myoglobin	17,000	0.75
Albumin	69,000	0.005



Relationship between oxygen consumption and sodium reabsorption in dog kidneys.

Tubular Reabsorption

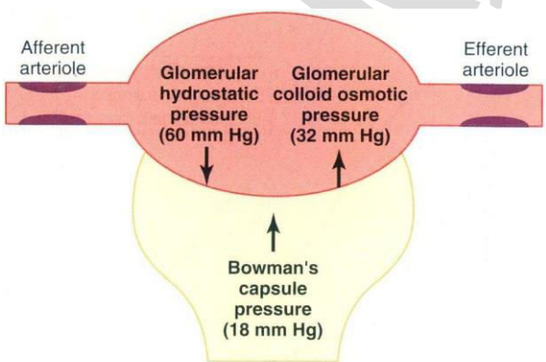
- **Proximal tubule (PT)** initiates the process of concentrating the ultrafiltrate.
- About 65% of salt and water is reabsorbed before it can reach the loop of Henle.
- Other substances reabsorbed include: glucose, bicarbonate, amino acids, and **urea** (waste product of protein metabolism).

- **Descending limb of Loop of Henle**

Highly permeable to water.

Hormones and Autacoids That Influence Glomerular Filtration Rate (GFR)

Hormone or Autacoid	Effect on GFR
Norepinephrine	↓
Epinephrine	↓
Endothelin	↓
Angiotensin II	⟷ (prevents ↓)
Endothelial-derived nitric oxide	↑
Prostaglandins	↑



Net filtration pressure (10 mm Hg) = Glomerular hydrostatic pressure (60 mm Hg) − Bowman's capsule pressure (18 mm Hg) − Glomerular oncotic pressure (32 mm Hg)

Summary of forces causing filtration by the glomerular capillaries. The values shown are estimates for healthy humans.

Thin segment of ascending limb of Loop of Henle

- Passive transport of NaCl and urea.

Thick segment of ascending limb of Loop of Henle

- Active transport of Na^+, passive transport of Cl^-

Distal tubule

- Secretes K^+, H^+, and ammonia (NH_3) into the tubule.
- Transports Na^+, Cl^-, and HCO_{3-} out of the tubule.

Collecting duct

- Passive transport of water (ADH influenced) and urea.

Countercurrent Multiplier System

- The ability to excrete urine of varying concentrations depends on the **countercurrent multiplier system** and ADH.
- Components of countercurrent multiplier system:

- Loops of Henle of juxtamedullary nephrons establish vertical osmotic gradient (VOG).
- Vasa recta prevent loss of the VOG by maintaining hypertonicity of renal medulla by **countercurrent exchange** (passive exchange of solutes and water between the two limbs of the vasa recta and ISF).
- Collecting ducts - Use gradient (along with ADH) to produce urine of varying concentrations.

- VOG is maintained in the ISF of medulla of each kidney and increases from the cortical boundary to the depths of the medulla.
- Presence of the large VOG enables the kidneys to produce urine that ranges in concentration from ~ 100-1400 milliosmolar (mOsm).
- **Countercurrent multiplication** - Process by which the descending and ascending limbs interact to produce a concentrated interstitial fluid (ISF) in the renal medulla.

- Why concentrate the fluid in the descending limb, only to dilute it in the ascending limb?

- Doing so creates the VOG.
- It ensures that a hypotonic fluid will enter the distal tubule and ultimately enable the kidneys to excrete a concentrated urine.

- Medullary VOG permits excretion of urine of differing concentrations by means of ADH-controlled, variable water reabsorption from the final tubular segments.
- The kidney's ability to concentrate urine and to minimize water loss is possible only because of the presence of the medullary VOG.
- If there wasn't a VOG, then a urine no more concentrated than the body fluids could be produced.

- **Urea recycling** contributes to medullary ISF hypertonicity.

- Thin ascending limb of L of H and the lower collecting duct (CD) are permeable to urea.
- Urea can diffuse down its concentration gradient from CD to ascending limb.

Antidiuretic hormone (ADH; Vasopressin)

+ water reabsorption by increasing the permeability of the collecting duct to water after insertion of water channels (**aquaporins**) in the membrane. The CD is relatively impermeable in the absence of the channels.

Response of the CD to ADH is graded; as ADH increases, more water channels are inserted into the membrane and the permeability to water increases.

ADH is inhibited in response to alcohol and an excess fluid intake.

Glucose and amino acids are completely reabsorbed by sodium-dependent secondary active transport and exhibit a **transport (tubular) maximum**.

- Unwanted waste products are not reabsorbed.

Secretion

- Serves to hasten the elimination of substances (including potentially dangerous substances) in the urine.
- Some important substances secreted into the tubules are K^+, H^+, and ammonia (NH_3).

Renal Control of Salt Balance

- Sodium transport is <u>not</u> under hormonal control in the proximal tubule.
- Hormonal control of sodium reabsorption occurs in the late distal tubule (some) and **cortical collecting duct** (most). ~ 8-10% of filtered Na^+ is dependent upon hormones.

- Occurs via the **Renin-Angiotensin-Aldosterone system** (R-A-A system) in response to decreased NaCl, decreased fluid volume, or decreased MAP.

Sensors are located in the **juxtaglomerular apparatus (JGA)** = **granular cells** (located within afferent arteriole and secrete **renin**) + **macula densa** (located in walls of distal tubule)

- AII stimulates ADH, thirst to increase fluid intake, and arteriolar vasoconstriction.

Aldosterone

- Stimulates Na^+ reabsorption and stimulates K^+ and H^+ secretion.
- Stimulated directly by increased blood K^+ (**hyperkalemia**) and indirectly by decreased blood Na^+ (**hyponatremia**) .
- **Atrial natriuretic peptide**

+ sodium and water excretion (or inhibits reabsorption). Inhibits R-A-A system.

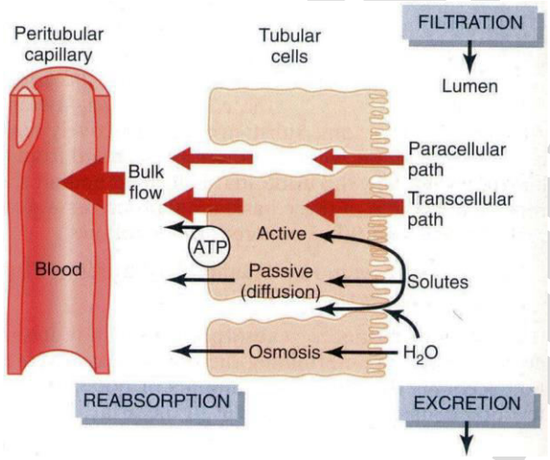
+ by increased fluid volume, NaCl, and MAP. These are opposite to the factors which stimulate the R-A-A system.

Approximate Pressures and Vascular Resistances in the Circulation of a Normal Kidney

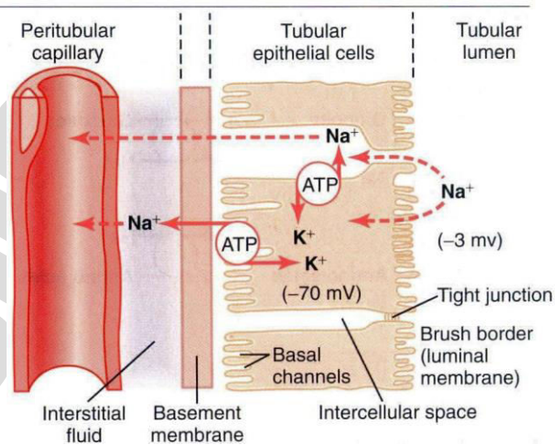
Vessel	Pressure in Vessel (mm Hg) *Beginning*	*End*	Per Cent of Total Renal Vascular Resistance
Renal artery	100	100	~0
Interlobar, arcuate, and interlobular arteries	~100	85	~16
Afferent arteriole	85	60	~26
Glomerular capillaries	60	59	~1
Efferent arteriole	59	18	~43
Peritubular capillaries	18	8	~10
Interlobar, interlobular, and arcuate veins	8	4	~4
Renal vein	4	~4	~0

Filtration, Reabsorption, and Excretion Rates of Different Substances by the Kidneys

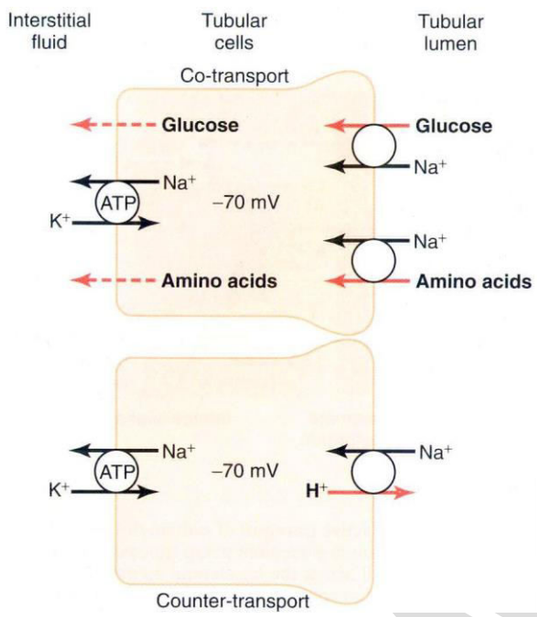
	Amount Filtered	Amount Reabsorbed	Amount Excreted	% of Filtered Load Reabsorbed
Glucose (g/day)	180	180	0	100
Bicarbonate (mEq/day)	4,320	4,318	2	>99.9
Sodium (mEq/day)	25,560	25,410	150	99.4
Chloride (mEq/day)	19,440	19,260	180	99.1
Potassium (mEq/day)	756	664	92	87.8
Urea (g/day)	46.8	23.4	23.4	50
Creatinine (g/day)	1.8	0	1.8	0



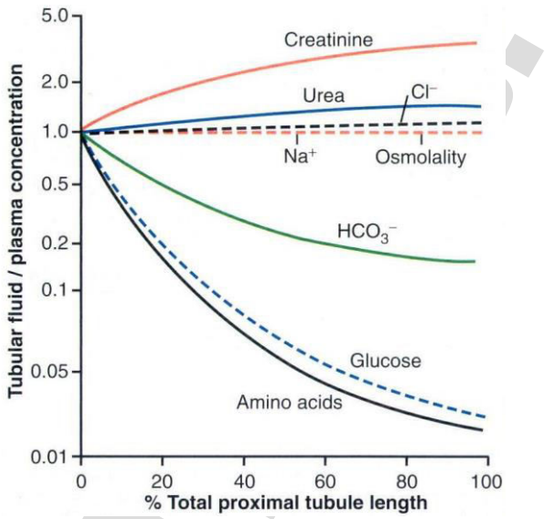
Reabsorption of filtered water and solutes from the tubular lumen across the tubular epithelial cells, through the renal interstitium, and back into the blood. Solutes are transported through the cells (transcellular route) by passive diffusion or active transport, or between the cells (paracellular route) by diffusion. Water is transported through the cells and between the tubular cells by osmosis. Transport of water and solutes from the interstitial fluid into the peritubular capillaries occurs by ultrafiltration (bulk flow).



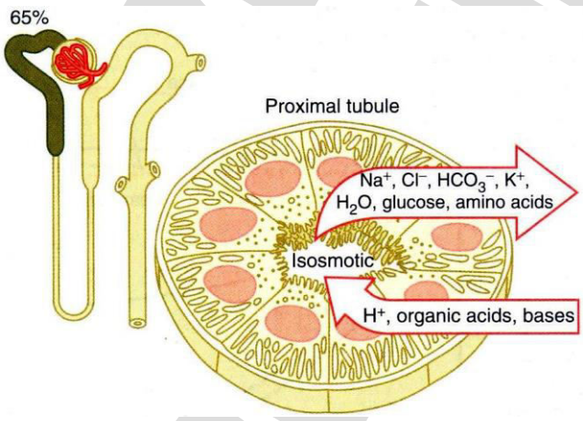
Basic mechanism for active transport of sodium through the tubular epithelial cell. The sodium-potassium pump transports sodium from the interior of the cell across the basolateral membrane, creating a low intracellular sodium concentration and a negative intracellular electrical potential. The low intracellular sodium concentration and the negative electrical potential cause sodium ions to diffuse from the tubular lumen into the cell through the brush border.



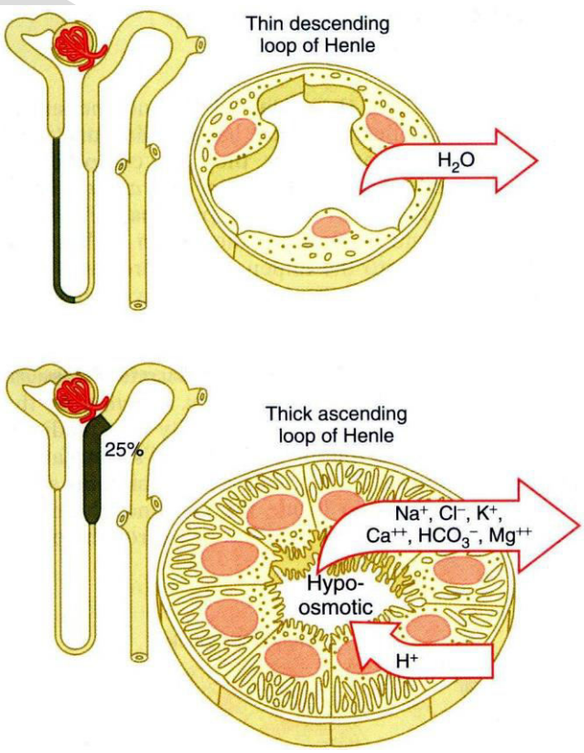
Mechanisms of secondary active transport. The upper cells shows the co-transport of glucose and amino acids along with sodium ions through the apical side of the tubular epithelial cells, followed by facilitated diffusion through the basolateral membranes. The lower cell shows the counter-transport of hydrogen ions from the interior of the cell across the apical membrane and into the tubular lumen; movement of sodium ions into the cell, down and electrochemical gradient established by the sodium-potassium pump on the basolateral membrane, provides the energy for transport of the hydrogen ions from inside the cell into the tubular lumen.



Changes in concentrations of different substances in tubular fluid along the proximal convoluted tubule relative to the concentrations of these substances in the plasma and in the glomerular filtrate. A value of 1.0 indicates that the concentration of the substance in the tubular fluid is the same as the concentration in the plasma. Values below 1.0 indicate that the substance is reabsorbed more avidly than water, whereas values above 1.0 indicate that the substance is reabsorbed to a lesser extent than water or is secreted into the tubules.

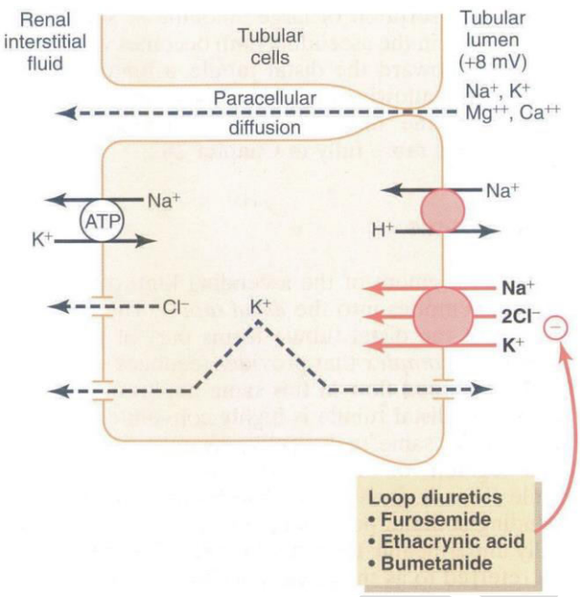


Cellular ultrastructure and primary transport characteristics of the proximal tubule. The proximal tubules reabsorb about 65% of the filtered sodium, chloride, bicarbonate, and potassium and essentially all the filtered glucose and amino acids. The proximal tubules also secrete organic acids, and hydrogen ions into the tubular lumen.

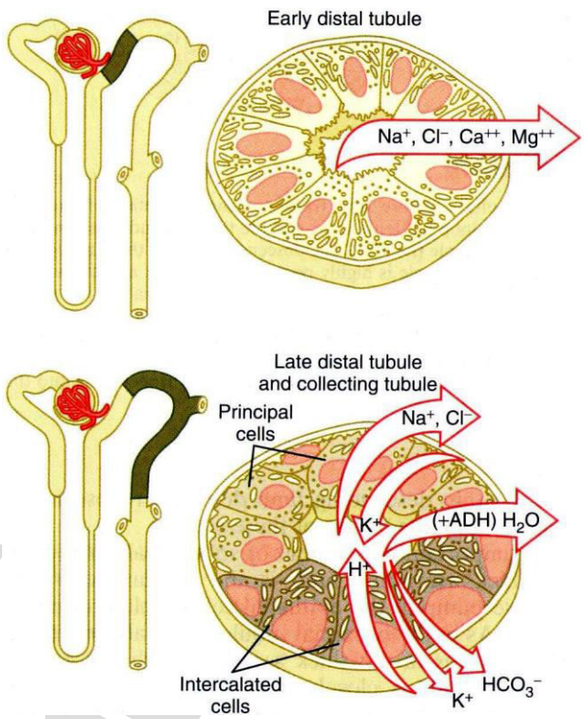


Cellular ultrastructure and transport characteristics of the thin descending loop of Henle (top) and the thick ascending segment of the loop of Henle (bottom). The descending part of the thin segment of the loop of Henle is highly permeable to water and moderately permeable to most solutes but has few mitochondria and little or no active reabsorption. The thick ascending limb of the loop of Henle reabsorbs about 25% of the filtered loads of sodium, chloride, and potassium, as well as large amounts of

calcium, bicarbonate, and magnesium. This segment also secretes hydrogen ions into the tubular lumen.



Mechanism of sodium, chloride, and potassium transport in the thick ascending loop of Henle. The sodium-potassium ATPase pump in the basolateral cell membrane maintains a low intracellular sodium concentration and a negative electrical potential in the cell. The 1-sodium,, 2-chloride, 1-potassium co-transporter in the luminal membrane transports these three ions from the tubular lumen into the cells, using the potential energy released by diffusion of sodium down an electrochemical gradient into the cells. Sodium is also transported into the tubular cell by sodium-hydrogen counter-transport. The positive charge (+8 mV) of the tubular lumen relative to the interstitial fluid forces cations such as Mg^{++} and Ca^{++} to diffuse from the lumen to the interstitial fluid via the paracellular pathway.

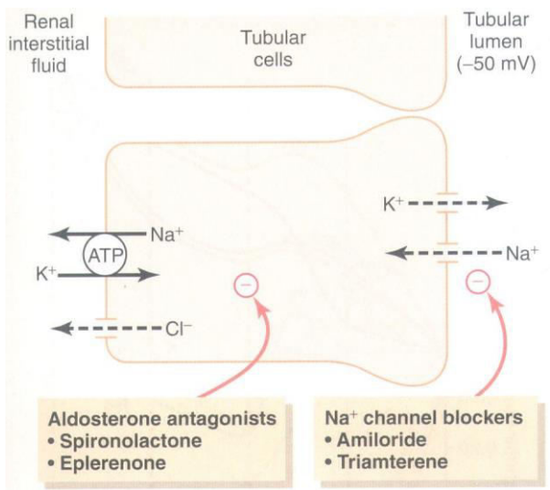


Cellular ultrastructure and transport characteristics of the early distal tubule and collecting tubule. The early distal tubule and the late distal tubule has many of the same characteristics as the thick ascending loop of Henle and reabsorbs sodium,, chloride, calcium, and magnesium but is virtually impermeable to water and urea. The late distal tubules and cortical collecting tubules are composed of two distinct cell types, the *principal cells* and the *intercalated cells*. The principal cells reabsorb sodium from the lumen and secrete potassium ions into the lumen. The intercalated cells reabsorb potassium and bicarbonate ions from the lumen and secrete hydrogen ions into the lumen. The reabsorption of water from this tubular segment is controlled by the concentration of *antidiuretic hormone*.

Summary of Tubule Characteristics—Urine Concentration

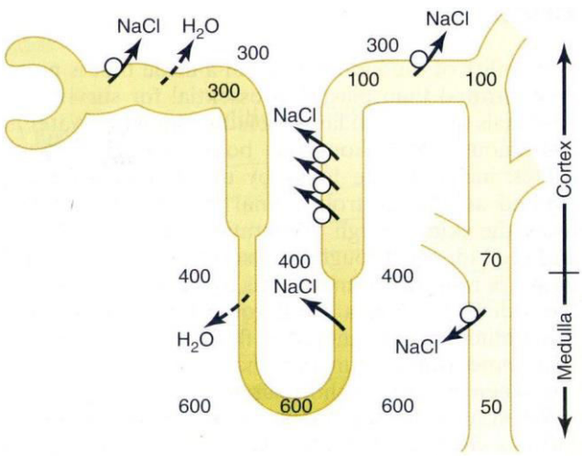
	Active NaCl Transport	Permeability		
		H_2O	*NaCl*	*Urea*
Proximal tubule	++	++	+	+
Thin descending limb	0	++	+	+
Thin ascending limb	0	0	+	+
Thick ascending limb	++	0	0	0
Distal tubule	+	+ADH	0	0
Cortical collecting tubule	+	+ADH	0	0
Inner medullary collecting duct	+	+ADH	0	++ADH

0, minimal level of active transport or permeability; +, moderate level of active transport or permeability; ++, high level of active transport or permeability; +ADH, permeability to water or urea is increased by ADH.

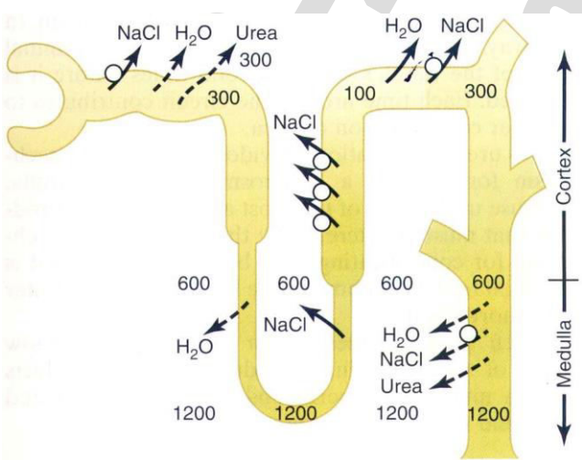


Mechanism of sodium chloride reabsorption and potassium secretion in the late distal tubules and cortical collecting tubules. Sodium enters the cell through special channels and is transported out of the cell by the sodium-potassium ATPase pump. Aldosterone antagonists compete with aldosterone for binding sites in the cell and therefore inhibit

the effects of aldosterone to stimulate sodium reabsorption and potassium secretion. Sodium channel blockers directly inhibit the entry of sodium into the sodium channels.



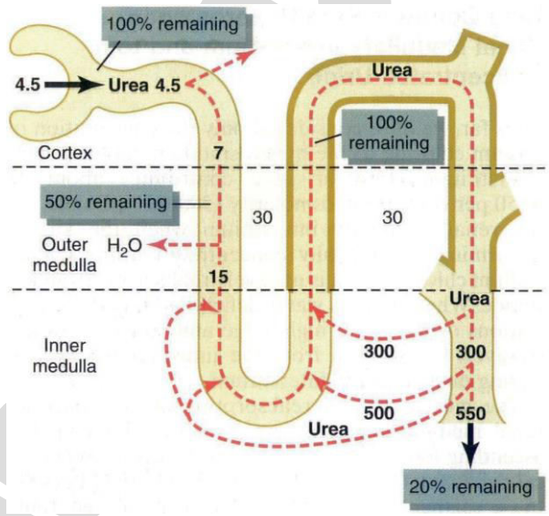
Formation of a dilute urine when antidiuretic hormone (ADH) levels are very low. Note than in the ascending loop of Henle, the tubular fluid becomes very dilute. In the distal tubules and collecting tubules,, the tubular fluid is further diluted by the reabsorption of sodium chloride and the failure to reabsorb water and continued reabsorption of solutes lead to a large volume of dilute urine. (Numerical values are in milliosmoles per liter.)



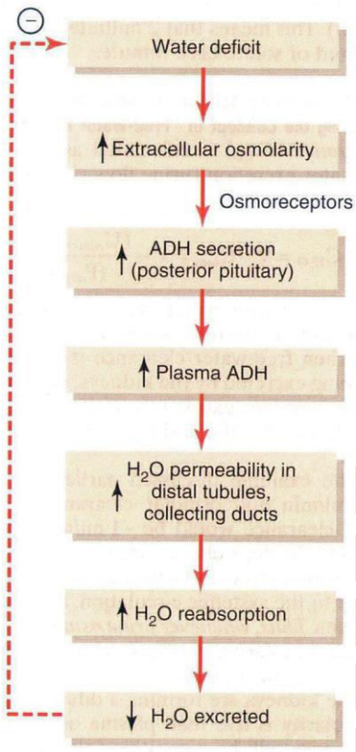
Formation of a concentrated urine when ADH levels are high. Note that the fluid leaving the loop of Henle is dilute but becomes concentrated as water is absorbed from the distal tubules and collecting tubules. With high ADH levels, the osmolarity of the urine is about the same as the osmolarity of the renal medullary interstitial fluid in the pailla, which is about 1200 mOsm/L. (Numerical values are in miiliosmoles per liter.)

Control of Thirst

Increase Thirst	Decrease Thirst
↑ Osmolarity	↓ Osmolarity
↓ Blood volume	↑ Blood volume
↓ Blood pressure	↑ Blood pressure
↑ Angiotensin	↓ Angiotensin II
Dryness of mouth	Gastric distention



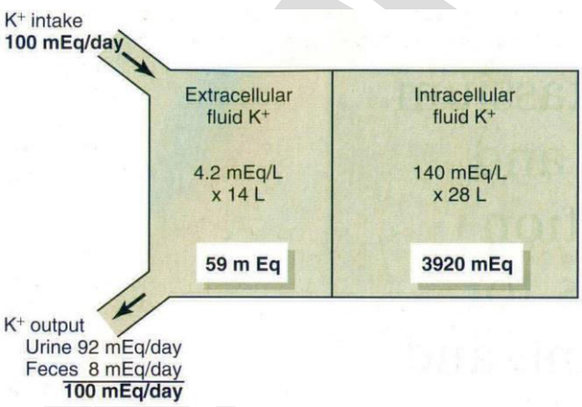
Recirculation of urea absorbed from the medullary collecting duct into the interstitial fluid. This urea diffuses into the thin loop of Henle, and then passes through the distal tubules, and finally passes back into the collecting duct. The recirculation of urea helps to trap urea in the renal medulla and contributes to the hyperosmolarity of the renal medulla. The heavy dark lines, from the thick ascending loop of Henle to the medullary collecting ducts, indicate that these segments are not very permeable to urea. (Numerical values are in milliosmoles per liter of urea during antidiuresis,, when large amounts of ADH are present. Percentages of the filtered load of urea that remain in the tubules are indicated in the boxes.)



Osmoreceptor-antidiuretic hormone (ADH) feedback mechanism for regulating extracellular fluid osmolarity in response to a water deficit.

Regulation of ADH Secretion

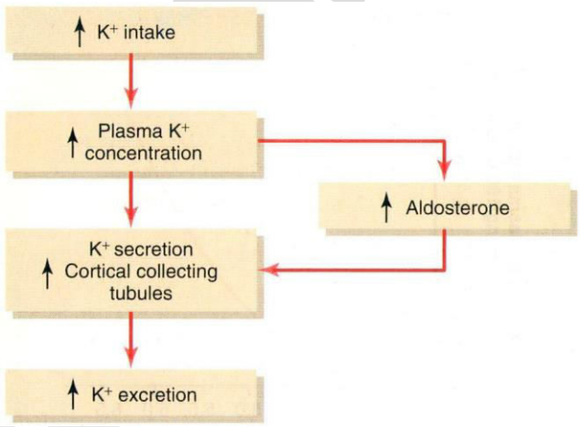
Increase ADH	Decrease ADH
↑ Plasma osmolarity	↓ Plasma osmolarity
↓ Blood volume	↑ Blood volume
↓ Blood pressure	↑ Blood pressure
Nausea	
Hypoxia	
Drugs:	Drugs:
Morphine	Alcohol
Nicotine	Clonidine (antihypertensive drug)
Cyclophosphamide	Haloperidol (dopamine blocker)



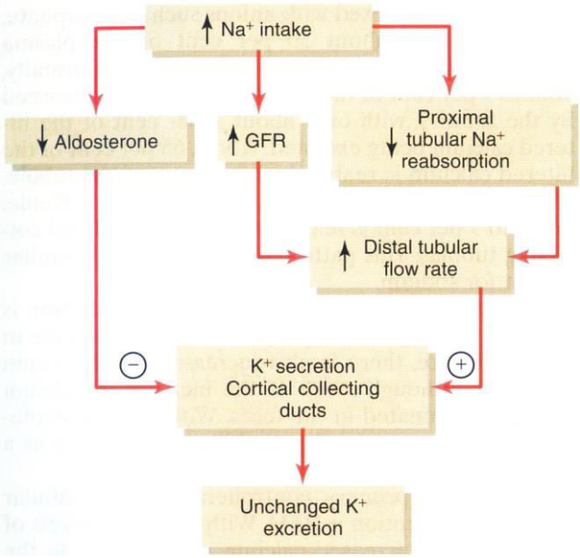
Normal potassium intake, distribution of potassium in the body fluids, and potassium output from the body.

Factors That Can Alter Potassium Distribution Between the Intra- and Extracellular Fluid

Factors That Shift K^+ into Cells (Decrease Extracellular $[K^+]$)	Factors That Shift K^+ Out of Cells (Increase Extracellular $[K^+]$)
• Insulin	• Insulin deficiency (diabetes mellitus)
• Aldosterone	• Aldosterone deficiency (Addison's disease)
• β-adrenergic stimulation	• β-adrenergic blockade
• Alkalosis	• Acidosis
	• Cell lysis
	• Strenuous exercise
	• Increased extracellular fluid osmolarity



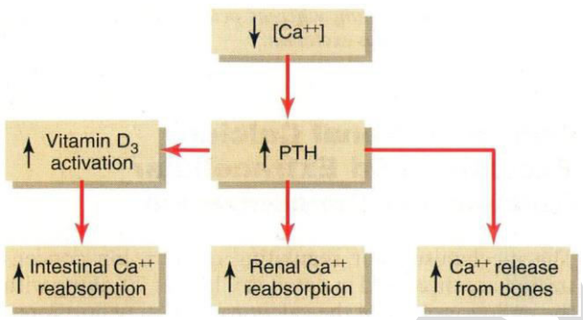
Primary mechanisms by which high potassium intake raises potassium excretion. Note that increased plasma potassium concentration directly raises potassium secretion by the cortical collecting tubules and indirectly increases potassium secretion by raising plasma aldosterone concentration.



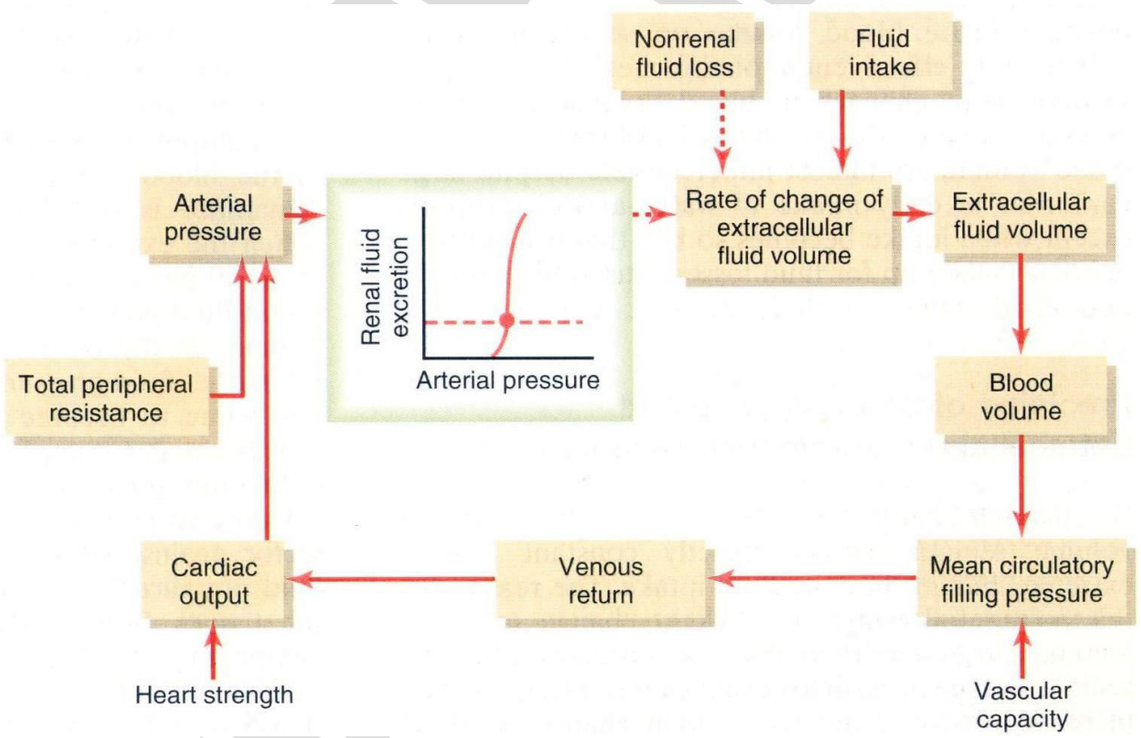
Effect of high sodium intake on renal excretion of potassium. Note that a high-sodium diet decreases plasma aldosterone, which tends to decrease potassium secretion by the cortical collecting tubules. However, the high-sodium diet simultaneously increases fluid delivery to the cortical collecting duct, which tends to increase potassium secretion. The opposing effects of a high-sodium diet counterbalance each other, so that there is little change in potassium excretion.

Factors That Alter Renal Calcium Excretion

↓ Calcium Excretion	↑ Calcium Excretion
↑ Parathyroid hormone (PTH)	↓ PTH
↓ Extracellular fluid volume	↑ Extracellular fluid volume
↓ Blood pressure	↑ Blood pressure
↑ Plasma phosphate	↓ Plasma phosphate
Metabolic acidosis	Metabolic alkalosis
Vitamin D_3	



Compensatory responses to decreased plasma ionized calcium concentration mediated by parathyroid hormone (PTH) and vitamin D.



Basic renal-body fluid feedback mechanism for control of blood volume, extracellular fluid volume, and arterial pressure. Solid lines indicate positive effects, and dashed lines indicate negative effects.

Acid-Base Balance

- (refers to the regulation of free [H^+] in body fluids)
- **Acids** - Substances that release H^+ when in solution.
- **Bases** - Substances that accept H^+ when in solution.
- **pH** - Measure of the hydrogen ion concentration in a solution.
- Concentration of hydrogen ions and pH are inversely related.
- Every unit change of pH represents a 10-fold change (increase or decrease) in hydrogen ions.
- **Acidic (pH < 7) vs neutral (pH = 7) vs basic (pH > 7) solutions**.

Acidosis vs alkalosis

- Blood pH is regulated at ~ 7.4 to prevent profound effects on the chemistry of the body.
- Hydrogen ions are continually being added to body fluids as a result of metabolic activities.

3 ways to resist changes in hydrogen ion concentration:

- **Buffers** - Molecules that act to minimize pH changes.
- Respiratory control of pH
- Renal control of pH
- Examples of buffers: HCO_3^-(plasma buffer), proteins and hemoglobin (intracellular buffers), phosphate and ammonia (urinary buffers).
- In the urine, H^+ binds with NH_3 (secreted by tubule) to form an **ammonium (NH_4^+)** ion. NH_4^+ cannot be reabsorbed by tubule.
- Kidneys regulate blood pH by adjusting:
- Hydrogen ion excretion
- Bicarbonate reabsorption and excretion

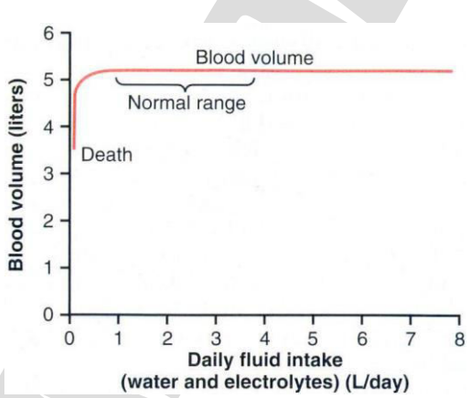
Renal Acid-Base Imbalances

- **Metabolic acidosis** - Acidosis characterized by a reduction in plasma bicarbonate or an increase in hydrogen ions.
- Can be caused by:
  - Diarrhea, increased fatty acids, exercise-generated lactic acid production, ketone bodies from uncontrolled diabetes

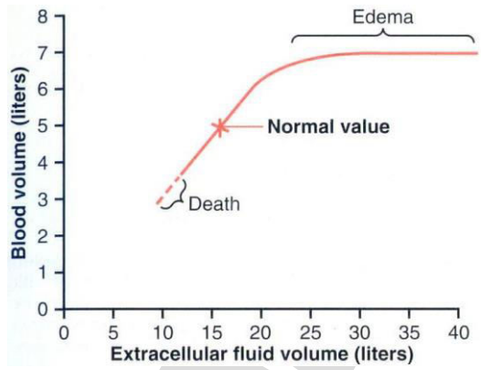
- **Metabolic alkalosis** - Alkalosis characterized by an increase in plasma bicarbonate or a decrease in hydrogen ions.
- Can be caused by:
  - Vomiting, ingestion of alkaline substances ($NaHCO_3$)

pH and H^+ Concentration of Body Fluids

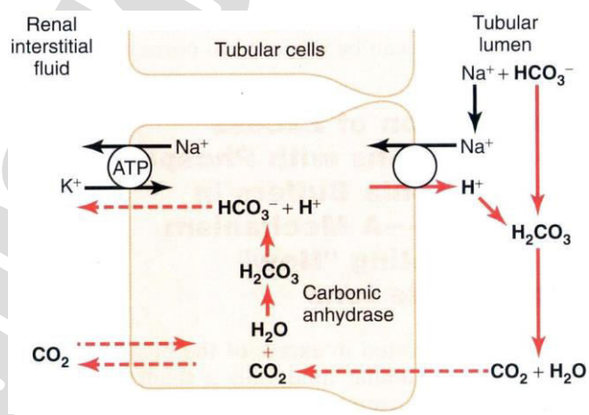
	H^+ Concentration (mEq/L)	pH
Extracellular fluid		
Arterial blood	4.0×10^{-5}	7.40
Venous blood	4.5×10^{-5}	7.35
Interstitial fluid	4.5×10^{-5}	7.35
Intracellular fluid	1×10^{-3} to 4×10^{-5}	6.0 to 7.4
Urine	3×10^{-2} to 1×10^{-5}	4.5 to 8.0
Gastric HCl	160	0.8



Approximate effect of changes in daily fluid intake on blood volume. Note that blood volume remains relatively constant in the normal range of daily fluid intakes.



Approximate relation between extracellular fluid volume and blood volume, showing a nearly linear relation in the normal range but also showing the failure of blood volume to continue rising when the extracellular fluid volume becomes excessive. When this occurs, the additional extracellular fluid volume resides on the interstitial spaces, and edema results.



Cellular mechanisms for (1) active secretion of hydrogen ions into the renal tubule; (2) tubular reabsorption of bicarbonate ions by combination with hydrogen ions to form carbonic acid, which dissociates to form carbon dioxide and water; and (3) sodium ion reabsorption in exchange of hydrogen ions secreted. This pattern of hydrogen ion secretion occurs in the proximal tubule, the thick ascending segment of the loop of Henle, and the early distal tubule.

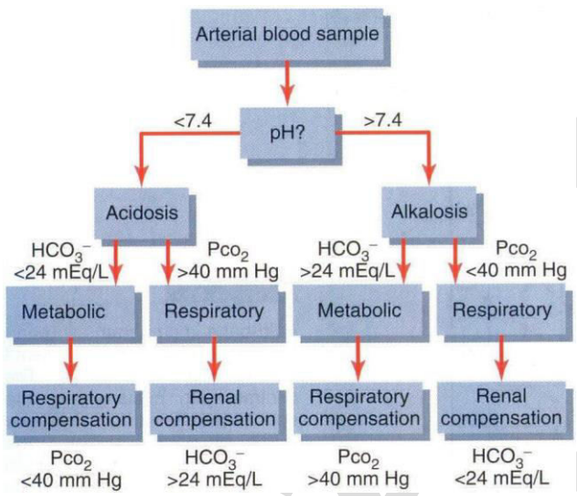
Factors That Increase or Decrease H^+ Secretion and HCO_3^- Reabsorption by the Renal Tubules

Increase H^+ Secretion and HCO_3^- Reabsorption	Decrease H^+ Secretion and HCO_3^- Reabsorption
↑ P_{CO_2}	↓ P_{CO_2}
↑ H^+, ↓ HCO_3^-	↓ H^+, ↑ HCO_3^-
↓ Extracellular fluid volume	↑ Extracellular fluid volume
↑ Angiotensin II	↓ Angiotensin II
↑ Aldosterone	↓ Aldosterone
Hypokalemia	Hyperkalemia

Characteristics of Primary Acid-Base Disturbances

	pH	H^+	P_{CO_2}	HCO_3^-
Normal	7.4	40 mEq/L	40 mm Hg	24 mEq/L
Respiratory acidosis	↓	↑	↑↑	↑
Respiratory alkalosis	↑	↓	↓↓	↓
Metabolic acidosis	↓	↑	↓	↓↓
Metabolic alkalosis	↑	↓	↑	↑↑

The primary event is indicated by the double arrows (↑↑ or ↓↓). Note that respiratory acid-base disorders are initiated by an increase or decrease in P_{CO_2}, whereas metabolic disorders are initiated by an increase or decrease in HCO_3^-.



Analysis of simple acid-base disorders. If the compensatory responses are markedly different from those shown at the bottom of the figure, one should suspect a mixed acid-base disorder.

Metabolic Acidosis Associated with Normal or Increased Plasma Anion Gap

Increased Anion Gap (Normochloremia)	Normal Anion Gap (Hyperchloremia)
Diabetes mellitus (ketoacidosis)	Diarrhea
Lactic acidosis	Renal tubular acidosis
Chronic renal failure	Carbonic anhydrase inhibitors
Aspirin (acetylsalicylic acid) poisoning	Addison's disease
Methanol poisoning	
Ethylene glycol poisoning	
Starvation	

Some Causes of Prerenal Acute Renal Failure

Intravascular volume depletion
- Hemorrhage (trauma, surgery, postpartum, gastrointestinal)
- Diarrhea or vomiting
- Burns

Cardiac failure
- Myocardial infarction
- Valvular damage

Peripheral vasodilation and resultant hypotension
- Anaphylactic shock
- Anesthesia
- Sepsis, severe infections

Primary renal hemodynamic abnormalities
- Renal artery stenosis, embolism, or thrombosis of renal artery or vein

Some Causes of Intrarenal Acute Renal Failure

Small vessel and/or glomerular injury
- Vasculitis (polyarteritis nodosa)
- Cholesterol emboli
- Malignant hypertension
- Acute glomerulonephritis

Tubular epithelial injury (tubular necrosis)
- Acute tubular necrosis due to ischemia
- Acute tubular necrosis due to toxins (heavy metals, ethylene glycol, insecticides, poison mushrooms, carbon tetrachloride)

Renal interstitial injury
- Acute pyelonephritis
- Acute allergic interstitial nephritis

Total Kidney Excretion and Excretion per Nephron in Renal Failure

	Normal	75% Loss of Nephrons
Number of nephrons	2,000,000	500,000
Total GFR (ml/min)	125	40
Single nephron GFR (nl/min)	62.5	80
Volume excreted for all nephrons (ml/min)	1.5	1.5
Volume excreted per nephron (nl/min)	0.75	3.0

GFR, glomerular filtration rate.

Classes of Diuretics, Their Mechanisms of Action, and Tubular Sites of Action

Class of Diuretic	Mechanism of Action	Tubular Site of Action
Osmotic diuretics (mannitol)	Inhibit water and solute reabsorption by increasing osmolarity of tubular fluid	Mainly proximal tubules
Loop diuretics (furosemide, bumetanide)	Inhibit Na^+-K^+-Cl^- co-transport in luminal membrane	Thick ascending loop of Henle
Thiazide diuretics (hydrochlorothiazide, chlorthalidone)	Inhibit Na^+-Cl^- co-transport in luminal membrane	Early distal tubules
Carbonic anhydrase inhibitors (acetazolamide)	Inhibit H^+ secretion and HCO_3^- reabsorption, which reduces Na^+ reabsorption	Proximal tubules
Aldosterone antagonists (spironolactone, eplerenone)	Inhibit action of aldosterone on tubular receptor, decrease Na^+ reabsorption, and decrease K^+ secretion	Collecting tubules
Sodium channel blockers (triamterene, amiloride)	Block entry of Na^+ into Na^+ channels of luminal membrane, decrease Na^+ reabsorption, and decrease K^+ secretion	Collecting tubules

Some Causes of Chronic Renal Failure

Metabolic disorders
- Diabetes mellitus
- Obesity
- Amyloidosis

Hypertension

Renal vascular disorders
- Atherosclerosis
- Nephrosclerosis-hypertension

Immunologic disorders
- Glomerulonephritis
- Polyarteritis nodosa
- Lupus erythematosus

Infections
- Pyelonephritis
- Tuberculosis

Primary tubular disorders
- Nephrotoxins (analgesics, heavy metals)

Urinary tract obstruction
- Renal calculi
- Hypertrophy of prostate
- Urethral constriction

Congenital disorders
- Polycystic disease
- Congenital absence of kidney tissue (renal hypoplasia)

Other Urinary Anatomy

Ureter
- Carries urine from kidney to bladder

Bladder
- Temporarily stores urine
- Capable of tremendous expansion
- Parasympathetic nervous system stimulates bladder contraction.
- Exit of urine from bladder is guarded by 2 sphincters (one smooth muscle and one skeletal muscle).
- **Micturition** = urination
- Micturition is under reflex control from the sacral spinal cord; there is also voluntary control.
- **Incontinence** - Inability to prevent urine discharge.

Urethra
- Carries urine from bladder to the outside.
- Shorter in females (4 cm) than in males (20 cm)
- In males, passes through the prostate and penis; provides a route for discharge of urine and semen

XI. RESPIRATORY PHYSIOLOGY

Some functions of the respiratory system:

- Exchange of O_2 and CO_2 between lungs and blood.
- Humidification and warming of inspired air.
- Enhancement of venous return via the respiratory pump.
- Alteration of acid-base balance by affecting amount of CO_2 exhaled.

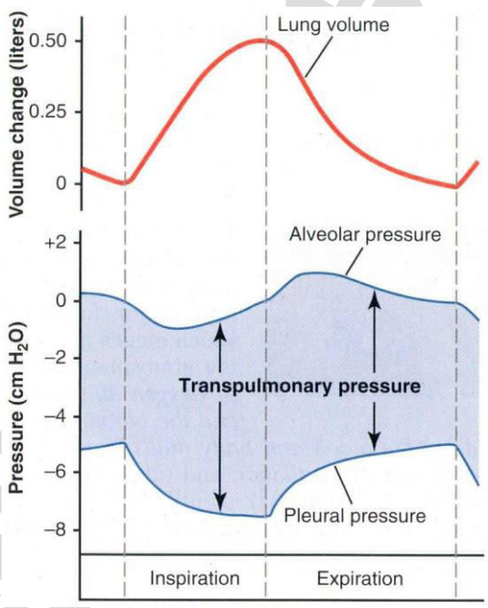
Physical Aspects of Breathing (Ventilation) and Mechanics of Breathing

- Air moves down a pressure gradient from a region of high pressure to a region of low pressure due to changes in lung volumes.
- Relevant pressures:
- **Atmospheric** - Pressure exerted by gases in the atmosphere.
- **Intrapulmonary (intra-alveolar)** - Pressure within the alveoli.
- **Intrapleural** - Pressure within the pleural cavity.
- **Transmural** (**Transpulmonary**) - Pressure difference across the lung wall. It is equal to intrapulmonary minus intrapleural pressure. Keeps lungs against the chest wall during respiratory movements.
- If chest wall gets punctured and changes the pressure difference across the chest wall, then a **pneumothorax** can result. This can cause the lung to collapse away from the chest wall and **atelectasis** occurs.
- Pulmonary ventilation requires **inspiration** (inhalation) = breathing in and **expiration** (exhalation) = breathing out.
- For air to flow into the lungs, intrapulmonary pressure must be lower than atmospheric pressure. This follows from **Boyle's Law** in which pressure decreases as the volume (of the chest cavity) increases.
- Lung expansion is not caused by movement of air into the lungs; it's due to the fall in pressure that allows air to flow into the lungs.
- The lungs exhibit: **compliance** (a measure of the ease at which the lung expands under pressure) and **elasticity** (the tendency of a structure to return to its initial size after being stretched).
- To accomplish lung expansion, the **diaphragm** and **external intercostals** contract at the onset of inspiration, resulting in the enlargement of the thoracic cavity.
- Diaphragm descends downward.
- External intercostals elevate the ribs and subsequently the sternum upward and outward.
- Deeper inspirations require more forceful contractions of the diaphragm and external intercostals and the involvement of some neck and thoracic muscles.
- Inspiration is always an **active** process; it requires contraction of inspiratory muscles and energy utilization.
- During expiration
- Diaphragm and external intercostals relax.
- Lungs recoil due to their elasticity.
- Intrapulmonary pressure increases and air leaves the lungs down its partial pressure gradient.
- Expiration is considered a **passive** process during quiet breathing since it is accomplished by elastic recoil of the lungs on relaxation of the inspiratory muscles, with no muscular exertion or energy expenditure required.
- Forced expiration (now an active event) requires contraction of the expiratory muscles (the **internal intercostals** and, importantly, the abdominal muscles).

Gas Exchange in the Lungs

- Gases move down partial pressure gradients.
- **Partial pressure** - The pressure exerted by a gas within a mixture of gases.
- Atmospheric pressure at sea level is = 760 mmHg.
- **Dalton's Law** - The total pressure of a gas mixture is equal to the sum of the pressures that each gas independently exerts.
- O_2 constitutes 21% and N_2 78% of the atmosphere.
- O_2 and CO_2 enter and leave the blood down partial pressure gradients.
- Rate of gas transfer between blood and alveoli is dependent on such factors as the:
- Partial pressure gradient of gases
- Solubility of gas (For example, CO_2 is 20X more soluble than O_2 in body tissues and can diffuse 20X more rapidly.)
- Temperature of solution (more gas can be dissolved in cold water than in warm water)
- Surface area of alveolar membrane - Normally constant, but can change under abnormal physiological conditions such as emphysema.
- Thickness of barrier separating air and blood across alveolar membrane- Normally constant, but can change under abnormal physiological conditions such as pulmonary edema and pneumonia.

- In addition to proper ventilation of the lungs, blood flow (**perfusion**) in the lungs must be adequate and matched to air flow (**ventilation**) in order for adequate gas exchange to occur. This is referred to as **ventilation-perfusion matching**.



Changes in lung volume, alveolar pressure, pleural pressure, and transpulmonary pressure during normal breathing.

Abbreviations and Symbols for Pulmonary Function

V_T	tidal volume	P_B	atmospheric pressure
FRC	functional residual capacity	Palv	alveolar pressure
ERV	expiratory reserve volume	Ppl	pleural pressure
RV	residual volume	P_{O_2}	partial pressure of oxygen
IC	inspiratory capacity	P_{CO_2}	partial pressure of carbon dioxide
IRV	inspiratory reserve volume	P_{N_2}	partial pressure of nitrogen
TLC	total lung capacity	P_{aO_2}	partial pressure of oxygen in arterial blood
VC	vital capacity	P_{aCO_2}	partial pressure of carbon dioxide in arterial blood
Raw	resistance of the airways to flow of air into the lung	P_{AO_2}	partial pressure of oxygen in alveolar gas
C	compliance	P_{ACO_2}	partial pressure of carbon dioxide in alveolar gas
V_D	volume of dead space gas	P_{AH_2O}	partial pressure of water in alveolar gas
V_A	volume of alveolar gas	R	respiratory exchange ratio
$\dot{V}_I$	inspired volume of ventilation per minute	$\dot{Q}$	cardiac output
$\dot{V}_E$	expired volume of ventilation per minute		
$\dot{V}_S$	shunt flow		
$\dot{V}_A$	alveolar ventilation per minute	Ca_{O_2}	concentration of oxygen in arterial blood
$\dot{V}_{O_2}$	rate of oxygen uptake per minute	$C\bar{v}_{O_2}$	concentration of oxygen in mixed venous blood
$\dot{V}_{CO_2}$	amount of carbon dioxide eliminated per minute	S_{O_2}	percentage saturation of hemoglobin with oxygen
$\dot{V}_{CO}$	rate of carbon monoxide uptake per minute	Sa_{O_2}	percentage saturation of hemoglobin with oxygen in arterial blood
D_{LO_2}	diffusing capacity of the lungs for oxygen		
D_{LCO}	diffusing capacity of the lungs for carbon monoxide		

Partial Pressures of Respiratory Gases as They Enter and Leave the Lungs (at Sea Level)

	Atmospheric Air* (mm Hg)		Humidified Air (mm Hg)		Alveolar Air (mm Hg)		Expired Air (mm Hg)	
N_2	597.0	(78.62%)	563.4	(74.09%)	569.0	(74.9%)	566.0	(74.5%)
O_2	159.0	(20.84%)	149.3	(19.67%)	104.0	(13.6%)	120.0	(15.7%)
CO_2	0.3	(0.04%)	0.3	(0.04%)	40.0	(5.3%)	27.0	(3.6%)
H_2O	3.7	(0.50%)	47.0	(6.20%)	47.0	(6.2%)	47.0	(6.2%)
TOTAL	760.0	(100.0%)	760.0	(100.0%)	760.0	(100.0%)	760.0	(100.0%)

* On an average cool, clear day.

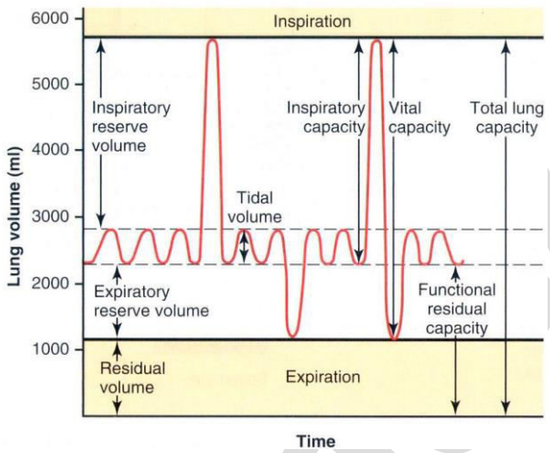
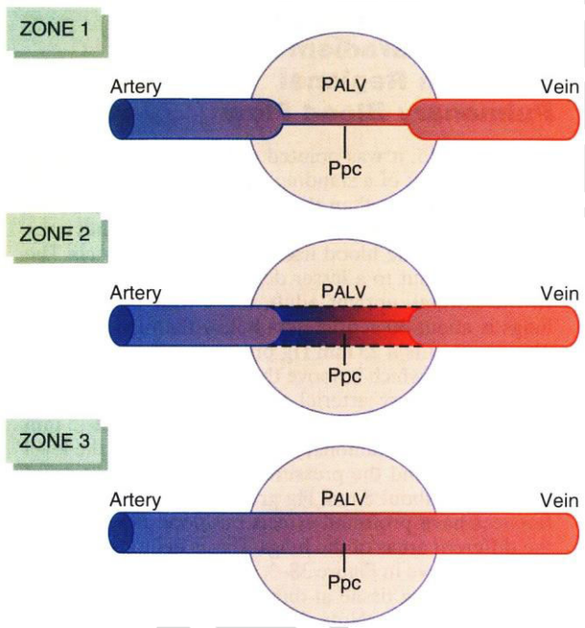


Diagram showing respiratory excursions during normal breathing and during maximal inspiration and maximal expiration.



Mechanics of blood flow in the three blood flow zones of the lung: zone 1, no flow – alveolar air pressure (P_{ALV}) is greater than arterial pressure; zone 2, intermittent flow – systolic arterial pressure rises higher than alveolar air pressure, but diastolic arterial pressure falls below alveolar air pressure; and zone 3, continuous flow – arterial pressure and pulmonary capillary pressure (Ppc) remain greater than alveolar air pressure at all times.

- Most O_2(98-99%) in blood is bound to **hemoglobin** in RBC's. The rest is dissolved in the plasma.
- Adult hemoglobin contains 4 polypeptide chains (2 **alpha** and 2 **beta**), each with a **heme** group that contains a central **Fe^{2+}** atom.
- **Fetal Hb** has 2 alpha and 2 **gamma** chains.

Each heme binds 1 O_2 molecule. Therefore, each Hb molecule binds 4 O_2 molecules.

- **Oxyhemoglobin** - Occurs when oxygen is bound.
- **Deoxyhemoglobin** (**reduced** Hb) - Occurs when oxygen is unbound.
- **Methemoglobin** - Hb in which the iron atom is in the **Fe^{3+}** form. It cannot bind O_2.
- DeoxyHb + O_2 ⇌ OxyHb **Loading** and **Unloading** Reactions
- Which way the reaction proceeds depends on the partial pressure of oxygen and the **affinity** (bond strength) between Hb and oxygen.
- High P_{O2} favors the **loading reaction** in lungs.
- Low P_{O2} favors the **unloading reaction** in the tissues.
- About 97% of Hb leaving the lungs is oxyhemoglobin.
- About 22% of O_2 is unloaded at the tissues at rest. (More during exercise).
- **Oxyhemoglobin Dissociation (Saturation) Curve**
- Curve is **sigmoidal (S-shaped)**. Small changes in P_{O2} produce large differences in % saturation on the steep part of the curve.
- Hb exhibits **subunit cooperativity** in which the binding of 1 O_2 facilitates the binding of subsequent O_2's.
- Several factors shift the curve to the right to decrease affinity. These include:
- Increased H^+ (decreased pH) = **Bohr effect**
- Increased P_{CO2}
- Increased temperature (during metabolism and fever)
- Increased **2,3-diphosphoglyceric acid (2,3-DPG)**

Hemoglobin (Hb) and Oxygen Transport

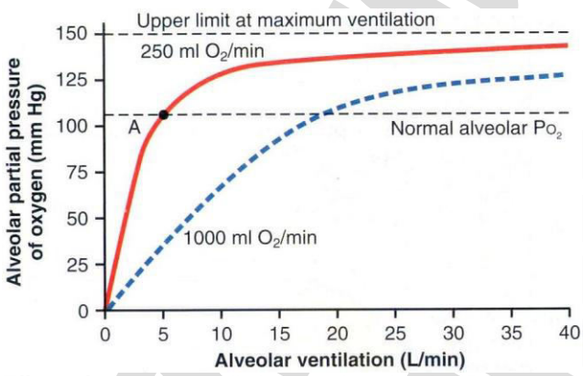
The product of a side reaction in RBC's.

- Inhibited by oxyHb.
- Increased during anemia or at high altitudes.
- **Carbon monoxide (CO)** out competes (has a much greater affinity for) oxygen for binding to Hb = **carboxyhemoglobin**. This shifts the curve to the left.
- **Myoglobin**
- Found in striated muscle (skeletal and cardiac).
- Has 1 heme; binds 1 O_2 molecule.
- Doesn't unload O_2 until the P_{O2} gets very low.

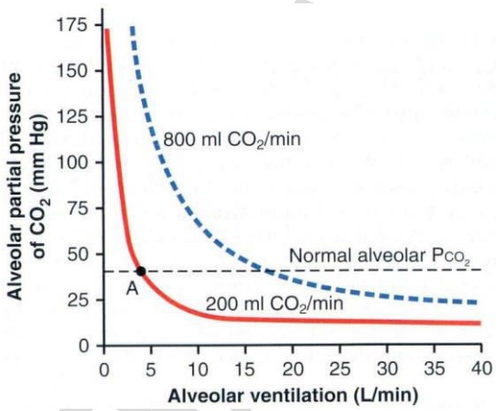
CO_2 Transport

- CO_2 is carried by the blood in 3 forms:
- Dissolved in plasma = ~ 10% of total.
- Bound to Hb (**carbaminohemoglobin**) = ~ 20% of total
- As **bicarbonate (HCO_{3-})** = **~** 70% of total

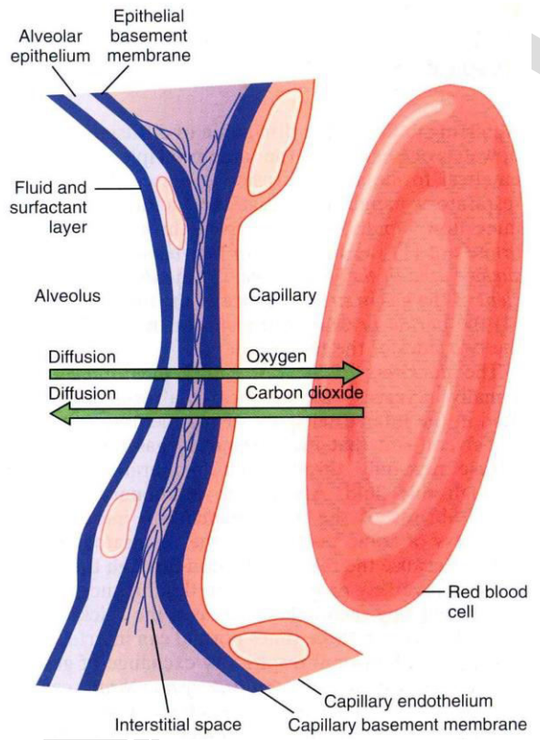
Reverse chloride shift occurs in pulmonary capillaries.



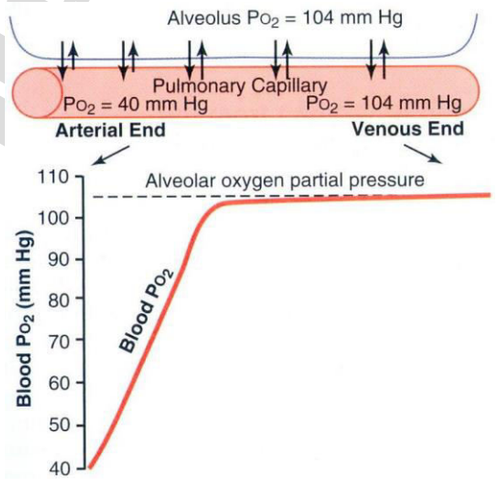
Effect of alveolar ventilation on the alveolar PO_2 at two rates of oxygen absorption from the alveoli – 250 ml/min and 1000 ml/min. Point A is the normal operating point.



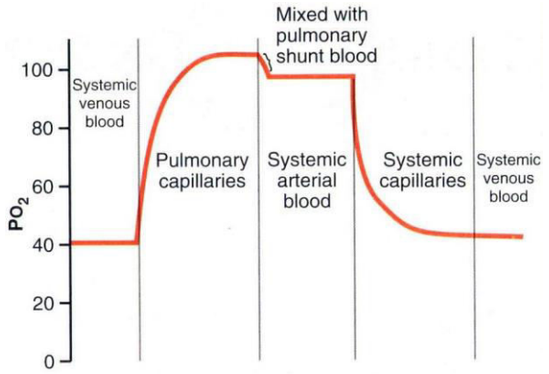
Effect of alveolar ventilation on the alveolar PCO_2 at two rates of carbon dioxide excretion from the blood – 800 ml/min and 20 ml/min. Point A is the normal operating point.



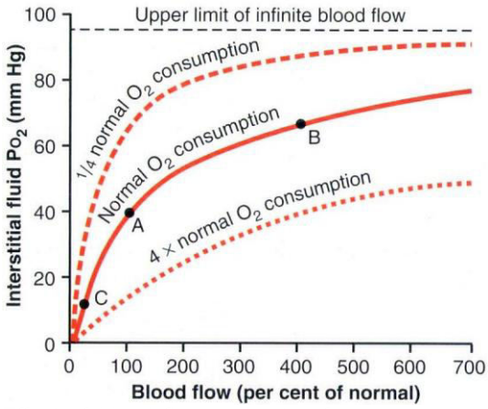
Ultrastructure of the alveolar respiratory membrane, shown in cross section.



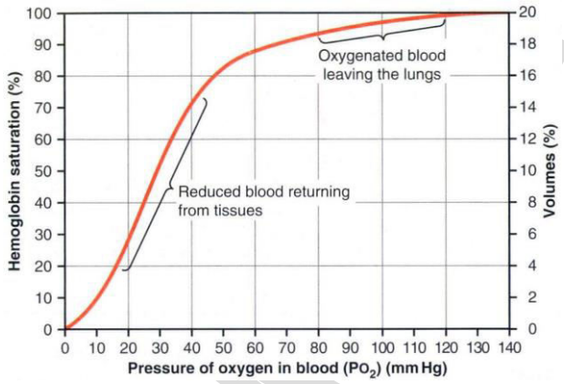
Uptake of oxygen by the pulmonary capillary blood.



Changes in PO_2 in the pulmonary capillary blood, systemic arterial blood, and systemic capillary blood, demonstrating the effect of "venous admixture."



Effect of blood flow and rate of oxygen consumption on tissue PO_2.



Oxygen-hemoglobin dissociation curve.

Ventilation and Acid-Base Balance of the Blood

- Normal arterial blood pH (a measure of H^+ concentration) averages ~ 7.40 with a range of 7.35-7.45.
- **Acidosis** - Decreased pH (< 7.35) relative to the normal pH.
- **Alkalosis** - Increased pH (> 7.45) relative to the normal pH.

Elimination of acids is accomplished by:

- Lungs - Via exhalation of CO_2.
- Kidneys - Via excretion of H^+.
- Ventilation is normally adjusted to keep pace with metabolism so that arterial P_{CO2} remains in the normal range.
- **Hypoventilation**, resulting from abnormal retention of CO_2, causes **respiratory acidosis**.
- **Hyperventilation**, resulting from excessive loss of CO_2, causes **respiratory alkalosis**.
- Why do individuals who are hyperventilating breathe into a paper bag?

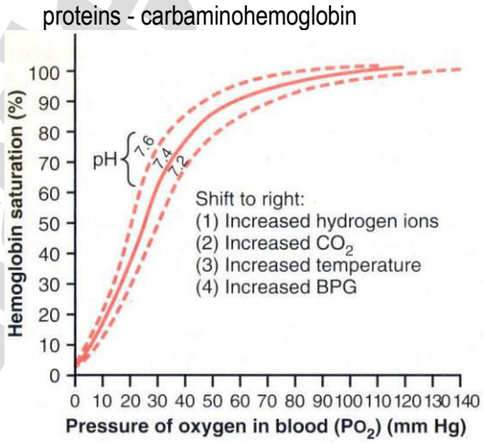
Control of Respiration

- Respiratory centers in the brain stem establish a rhythmic (automatic) breathing pattern.
- Since respiratory muscles are skeletal muscles, they require nervous stimulation to contract.
- Primary respiratory **rhythmicity center** is in the **medulla**.
- Medulla contains **dorsal** and **ventral respiratory groups** which directly control the diaphragm and internal intercostals.
- **Pons** contains the **pneumotaxic** and **apneustic centers** which influence the medullary respiratory center.

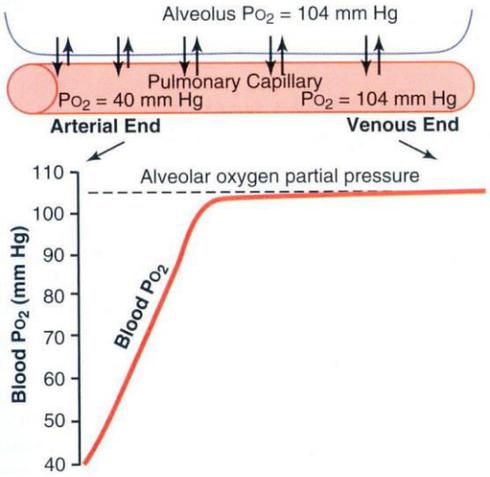
An additional level of control is via the **Hering-Breuer reflex** which is a reflex designed to prevent overinflation of the lungs when pulmonary stretch receptors sense that the lungs are being overstretched as inspiration occurs. This results in the inhibition of inspiration.

Chemical forms in which carbon dioxide is transported:

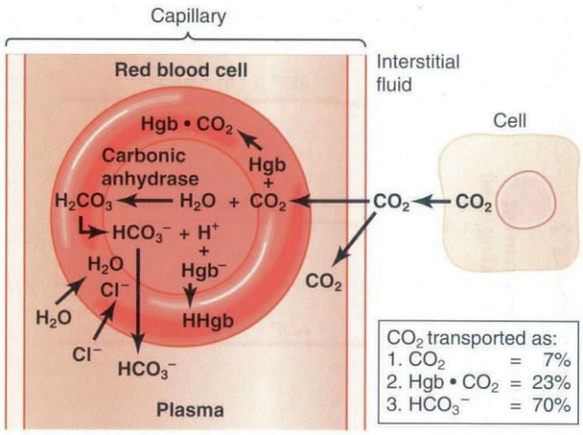
- Dissolved state
- In the form of bicarbonate ion
- In combination with hemoglobin and plasma proteins - carbaminohemoglobin



Shift of the oxygen-hemoglobin dissociation curve to the right caused by an increase in hydrogen ion concentration (decrease in pH). BPG, 2-3-biphosphoglycerate.



Effect of intracellular ADP and PO_2 on rate of oxygen usage by the cells. Note that as long as the intracellular PO_2 remains above 1 mm Hg, the controlling factor for the rate of oxygen usage is the intracellular concentration of ADP.

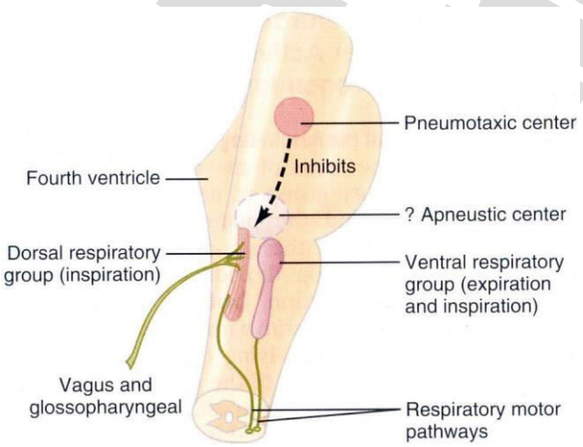


Transport of carbon dioxide in the blood.

Respiratory exchange ratio – the ratio of carbon dioxide output to oxygen uptake

Regulation of Breathing

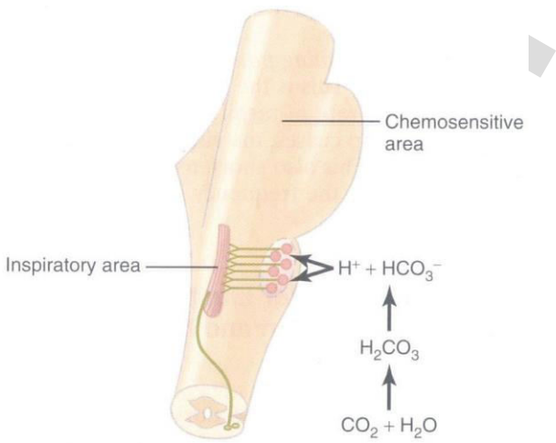
- Breathing is affected by chemoreceptors sensitive to the P_{CO2}, pH, and P_{O2} of the blood.
- **Central chemoreceptors** - Located in medulla.
- **Peripheral chemoreceptors** - Include the **aortic bodies** (in the aortic arch) and **carotid bodies** (in the common carotid artery)..
- P_{CO2} and consequent changes in pH are of greater importance than P_{O2} in regulating breathing.
- Decreases in blood P_{O2} (**hypoxemia**) directly stimulate breathing only when the blood P_{O2} is < 50 mmHg.



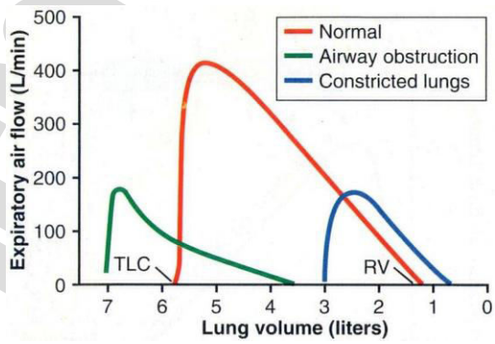
Organization of the respiratory center

There are two qualities of the inspiratory ramp (a steady increase in the volume of the lungs during inspiration, rather than inspiratory gasps) that are controlled:

- Control of the rate of increase of the ramp signal
- Control of the limiting point at which the ramp suddenly ceases



Stimulation of the brain stem respiratory area by signals from the chemosensitive area located bilaterally in the medulla, lying only a fraction of a millimeter beneath the ventral medullary surface. Note also that hydrogen ions stimulate the chemosensitive area, but carbon dioxide in the fluid gives rise to most of the hydrogen ions.



Effect of two respiratory abnormalities – constricted lungs and airway obstruction – on the maximum expiratory flow-volume curve. TLC, total lung capacity; RV, residual volume.

XII. THE NERVOUS SYSTEM

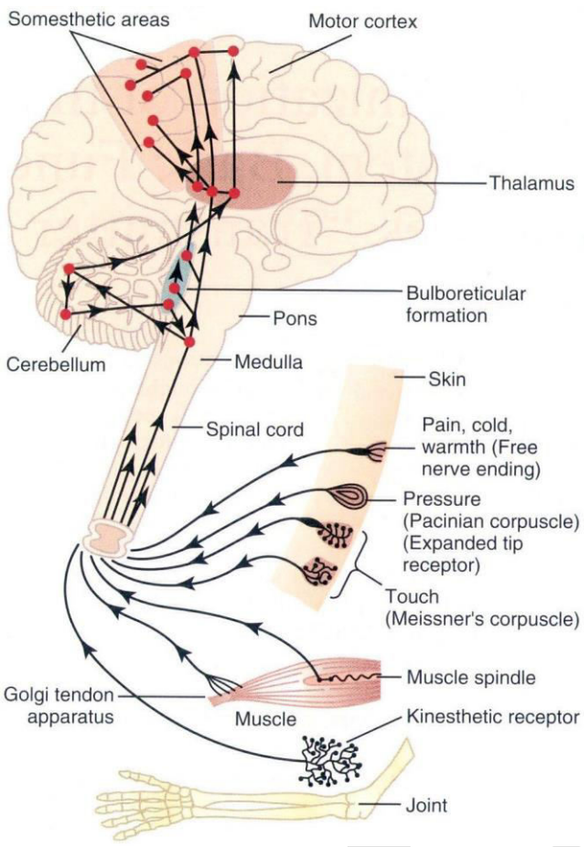
General Design of the Nervous System

- Central nervous system neuron: the basic functional unit
- Sensory part of the nervous system – sensory receptors
- Motor part of the nervous system – effectors
- Processing of information – "integrative" function of the nervous system
- Storage of information - memory

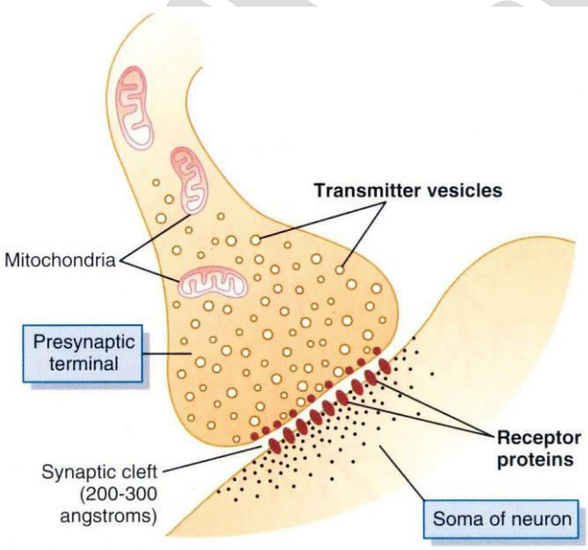
Three major levels of CNS function:

- The spinal cord level
- The lower brain or subcortical level
- The higher brain or cortical level

Physiology of a Synapse



Somatosensory axis of the nervous system.



Physiologic anatomy of the synapse.

Two major types of synapses:

- Chemical synapse – the first neuron secretes at its nerve ending synapse a chemical substance called a neurotransmitter
- Electrical synapse – characterized by direct open fluid channels that conduct electricity from one cell to the next.

Presynaptic terminals – have varied anatomical forms, but most resemble small round or oval knobs and, therefore, are sometimes called terminal knobs, boutons, end-feet, or synaptic knobs.

Excitatory or inhibitory receptors in the postsynaptic membrane: The different molecular and membrane mechanisms used by he different receptors to cause excitation or inhibition include the following:

Excitation:

1. Opening of sodium channels to allow large numbers of positive electrical charges to flow to the interior of the postsynaptic cell.
2. Depressed conduction through chloride or potassium channels, or both.
3. Various changes in the internal metabolism of the postsynaptic neuron.

Inhibition:

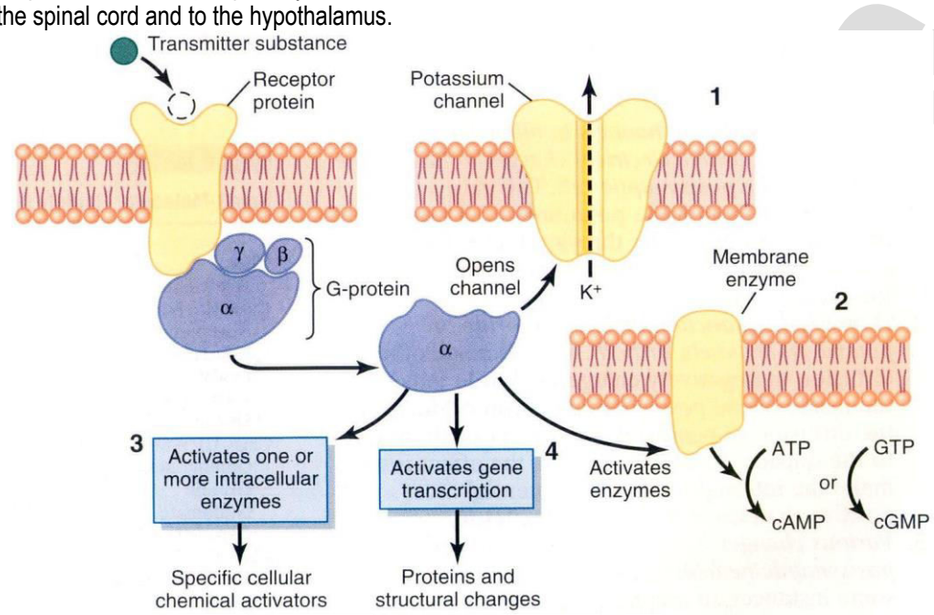
1. Opening of chloride ion channels through the postsynaptic neuronal membrane.
2. Increase in conductance of potassium ions out of the neuron.
3. Activation of receptor enzymes that inhibit cellular metabolic functions that increase the number of inhibitory synaptic receptors or decrease the number of excitatory receptors.

Characteristics of Neurotransmitters

- Acetylcholine – secreted by neurons in many areas of the nervous system but specifically by:
  - Terminals of the large pyramidal cells from the motor cortex
  - Several different types of neurons in the basal ganglia
  - The motor neurons that innervate the skeletal muscles
  - The preganglionic neurons of the autonomic nervous system
  - The postganglionic neurons of the parasympathetic nervous system
  - Some of the postganglionic neurons of the sympathetic nervous system
- Norepinephrine – secreted by the terminals of many neurons whose cell bodies are located in the brain stem and hypothalamus. Specifically, norepinephrine-secreting neurons located in the locus ceruleus in the pons send nerve fibers to widespread areas of the brain to help control overall activity and mood of the mind, such as increasing the level of wakefulness
- Dopamine – secreted by neurons that originate in the substantia nigra.
- Glycine – secreted mainly at synapses in the spinal cord.
- GABA – secreted by nerve terminals in the spinal cord, cerebellum, basal ganglia, and many areas of the cortex.
- Glutamate – secreted by the presynaptic terminals in many of the sensory pathways entering the central

nervous system, as well as in many areas of the cerebral cortex.

- Serotonin – secreted by nuclei that originate in the median raphe of the brain stem and project to many brain and spinal cord areas, especially to the dorsal horns of the spinal cord and to the hypothalamus.
- Nitric oxide – especially secreted by nerve terminals in areas of the brain responsible for long-term behavior and memory.



"Second messenger" system by which a transmitter substance from an initial neuron can activate a second neuron by first releasing a "G-protein" into the second neuron's cytoplasm. Four subsequent possible effects of the G-protein are shown, including 1, opening an ion channel in the membrane of the second neuron; 2, activating an enzyme system in the neuron's membrane; 3, activating an intracellular enzyme system; and/or 4, causing gene transcription in the second neuron.

Neuropeptides

- An entirely different class of transmitters that are synthesized differently and whose actions are usually slow and in other ways quite different from those of the small-molecule transmitters.
- Not synthesized in the cytosol of the presynaptic terminals.
- Synthesized as integral parts of large-protein molecules by ribosomes in the neuronal cell body.

Small-Molecule, Rapidly Acting Transmitters

Class I
Acetylcholine
Class II: The Amines
Norepinephrine
Epinephrine
Dopamine
Serotonin
Histamine
Class III: Amino Acids
Gamma-aminobutyric acid (GABA)
Glycine
Glutamate
Aspartate
Class IV
Nitric oxide (NO)

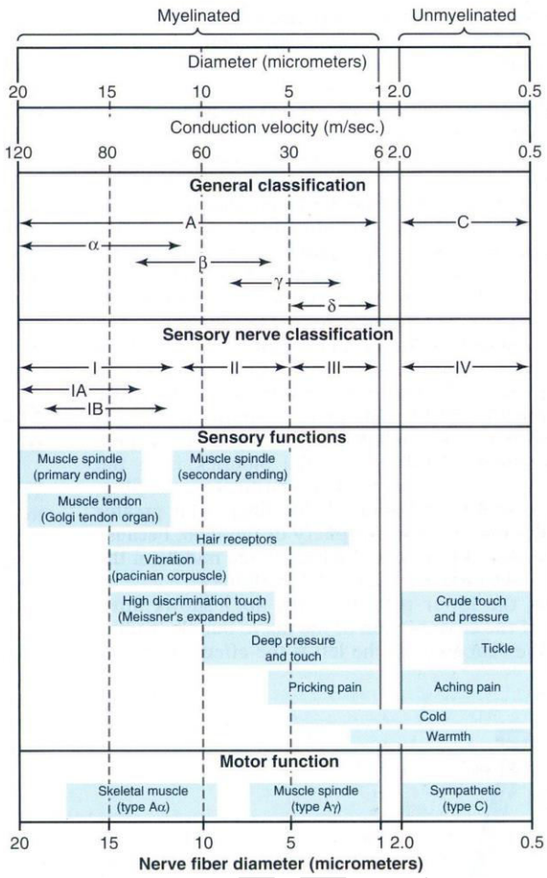
Temporal and Spatial Summation

- "Temporal summation" – successive discharges from a single presynaptic terminal, if they occur rapidly enough, can add to one another; that is, they can "summate."

Spatial summation – the effect of summing simultaneous postsynaptic potentials by activating multiple terminals on widely spaced areas of the neuronal membrane.

Modality of sensation – each of the principal types of sensation that we can experience – pain, touch, sight, sound, and so forth.

Labeled line principle – the specificity of nerve fibers for transmitting only one modality of sensation.



Spatial summation – phenomenon whereby increasing signal strength is transmitted by using progressively greater numbers of fibers.

Mechanisms of receptor potentials:

1. By mechanical deformation of the receptor, which stretches the receptor membrane and opens ion channels.
2. By application of a chemical to the membrane, which also opens ion channels.
3. By change of the temperature of the membrane, which alters the permeability of the membrane.
4. By the effects of electromagnetic radiation, such as light on a retinal visual receptor, which either directly or indirectly changes the receptor membrane characteristics and allows ions to flow through membrane channels.

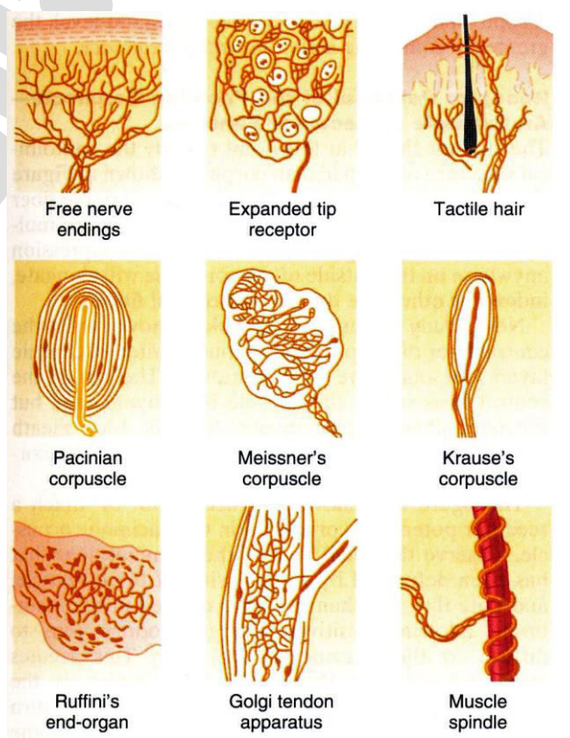
Neuropeptide, Slowly Acting Transmitters or Growth Factors

Hypothalamic-releasing hormones
- Thyrotropin-releasing hormone
- Luteinizing hormone–releasing hormone
- Somatostatin (growth hormone inhibitory factor)

Pituitary peptides
- Adrenocorticotropic hormone (ACTH)
- β-Endorphin
- α-Melanocyte-stimulating hormone
- Prolactin
- Luteinizing hormone
- Thyrotropin
- Growth hormone
- Vasopressin
- Oxytocin

Peptides that act on gut and brain
- Leucine enkephalin
- Methionine enkephalin
- Substance P
- Gastrin
- Cholecystokinin
- Vasoactive intestinal polypeptide (VIP)
- Nerve growth factor
- Brain-derived neurotropic factor
- Neurotensin
- Insulin
- Glucagon

From other tissues
- Angiotensin II
- Bradykinin
- Carnosine
- Sleep peptides
- Calcitonin



Several types of somatic sensory nerve endings.

The "excitatory state" of a neuron is defined as the summated degree of excitatory drive to the neuron. If there is a higher degree of excitation than inhibition of the neuron at any given instant, then it is said that there is an excitatory state. Conversely, if there is more inhibition than excitation, then it is said that there is an inhibitory state.

Physiology of Receptors

Physiologic classifications and functions of nerve fibers.

The following classification is frequently used by sensory physiologists:

Group Ia
Fibers from the annulospiral endings of muscle spindles.
Group Ib
Fibers from the Golgi tendon organs.
Group II
Fibers from most discrete cutaneous tactile receptors and from the flower-spray endings of the muscle spindles.
Group III
Fibers carrying temperature, crude touch, and pricking pain sensations.
Group IV
Unmyelinated fibers carrying pain, itch, temperature, and crude touch sensations.

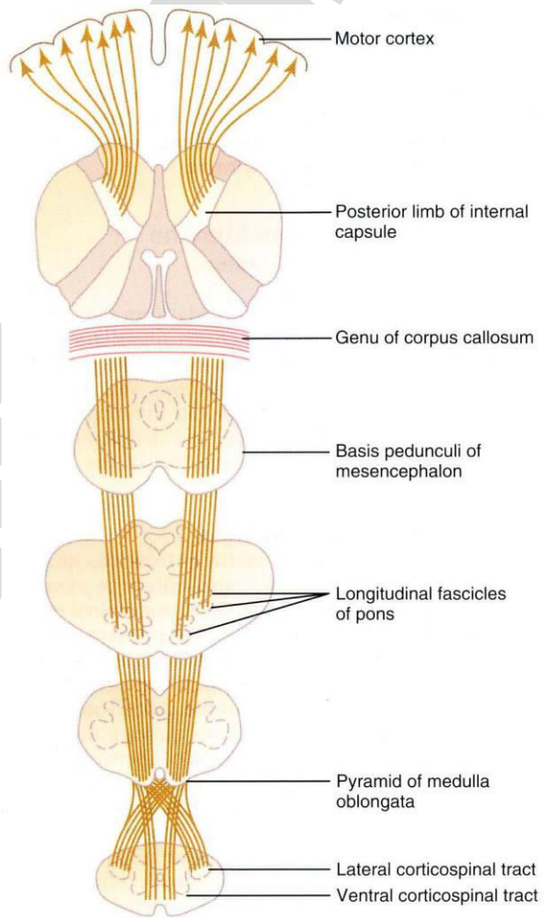
Classification of Sensory Receptors

- **I. Mechanoreceptors**
  - Skin tactile sensibilities (epidermis and dermis)
    - Free nerve endings
    - Expanded tip endings
      - Merkel's discs
      - Plus several other variants
    - Spray endings
    - Ruffini's endings
    - Encapsulated endings
      - Meissner's corpuscles
      - Krause's corpuscles
    - Hair end-organs
  - Deep tissue sensibilities
    - Free nerve endings
    - Expanded tip endings
    - Spray endings
      - Ruffini's endings
    - Encapsulated endings
      - Pacinian corpuscles
      - Plus a few other variants
    - Muscle endings
      - Muscle spindles
      - Golgi tendon receptors
  - Hearing
    - Sound receptors of cochlea
  - Equilibrium
    - Vestibular receptors
  - Arterial pressure
    - Baroreceptors of carotid sinuses and aorta
- **II. Thermoreceptors**
  - Cold
    - Cold receptors
  - Warmth
    - Warm receptors
- **III. Nociceptors**
  - Pain
    - Free nerve endings
- **IV. Electromagnetic receptors**
  - Vision
    - Rods
    - Cones
- **V. Chemoreceptors**
  - Taste
    - Receptors of taste buds
  - Smell
    - Receptors of olfactory epithelium
  - Arterial oxygen
    - Receptors of aortic and carotid bodies
  - Osmolality
    - Neurons in or near supraoptic nuclei
  - Blood CO_2
    - Receptors in or on surface of medulla and in aortic and carotid bodies
  - Blood glucose, amino acids, fatty acids
    - Receptors in hypothalamus

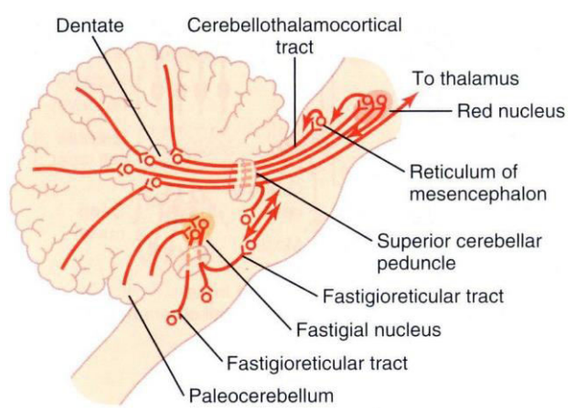
Adrenergic Receptors and Function

Alpha Receptor	Beta Receptor
Vasoconstriction	Vasodilation (β_2)
Iris dilation	Cardioacceleration (β_1)
Intestinal relaxation	Increased myocardial strength (β_1)
Intestinal sphincter contraction	Intestinal relaxation (β_2)
	Uterus relaxation (β_2)
Pilomotor contraction	Bronchodilation (β_2)
Bladder sphincter contraction	Calorigenesis (β_2)
	Glycogenolysis (β_2)
	Lipolysis (β_1)
	Bladder wall relaxation (β_2)

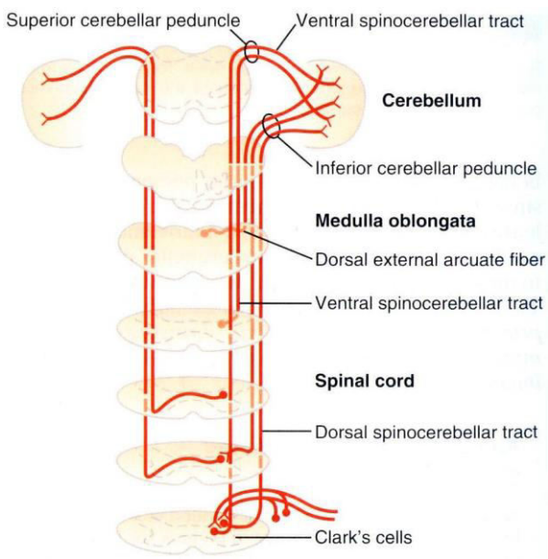
Parts of the Brain and Spinal Cord



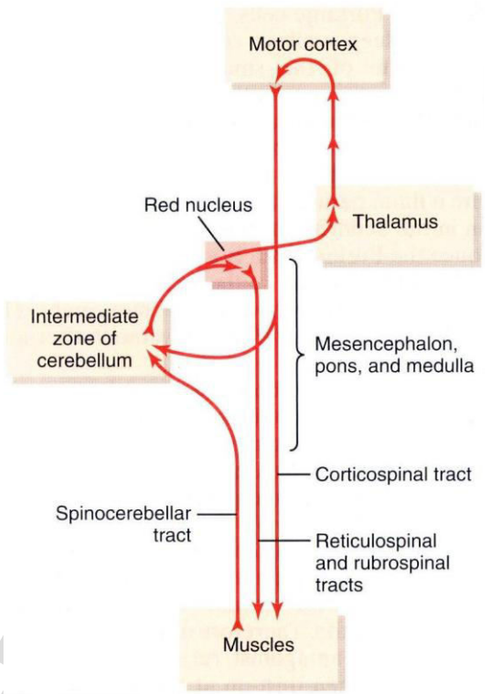
Pyramidal tract.



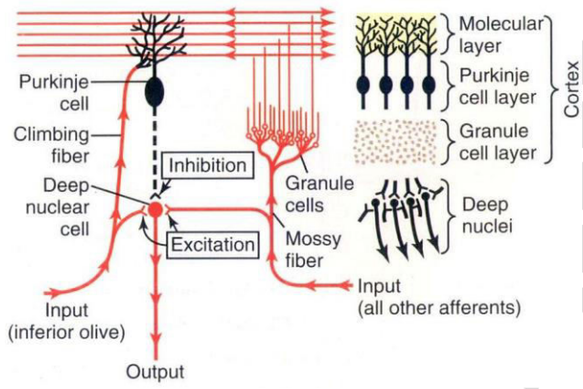
Principal *efferent* tracts from the cerebellum.



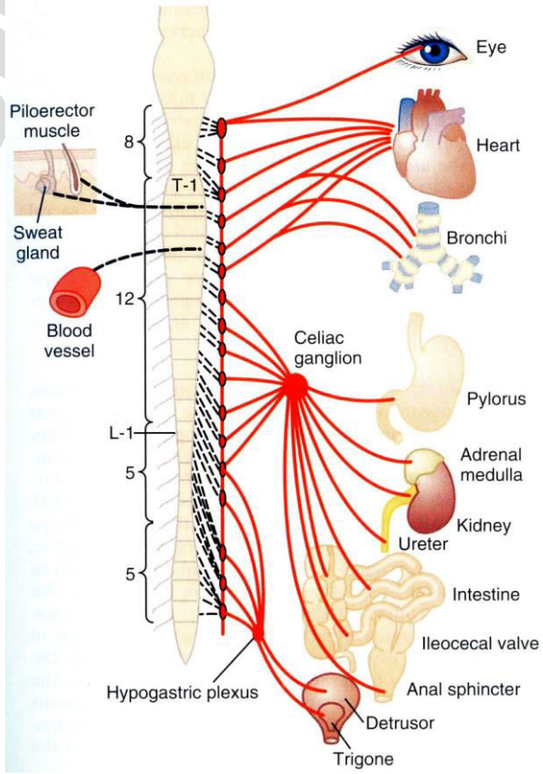
Spinocerebellar tracts.



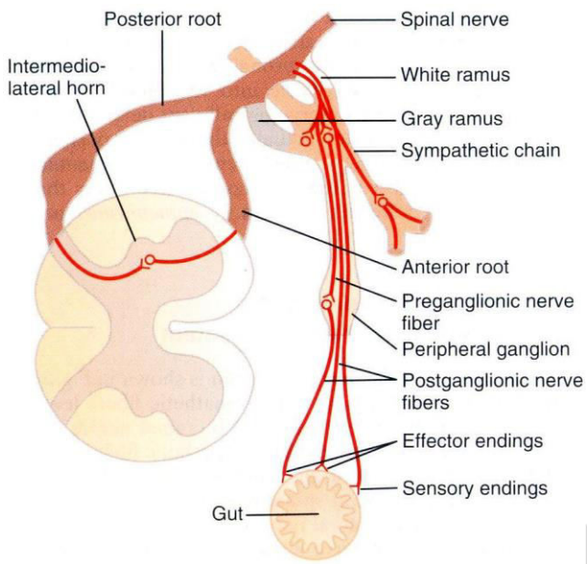
Cerebral and cerebellar control of voluntary movements, involving especially the intermediate zone of the cerebellum.



The left side of this figure shows the basic neuronal circuit of the cerebellum, with excitatory neurons shown in lighter color and the Purkinje cell (an inhibitory neuron) shown in black. To the right is shown the physical relationship of the deep cerebellar nuclei to the cerebellar cortex with its three layers.



Sympathetic nervous system. The black dashed lines represent postganglionic fibers in the gray rami leading from the sympathetic chains into spinal nerves for distribution to blood vessels, sweat glands, and piloerector muscles.



Nerve connections between the spinal cord, spinal nerves, sympathetic chain, and peripheral sympathetic nerves.

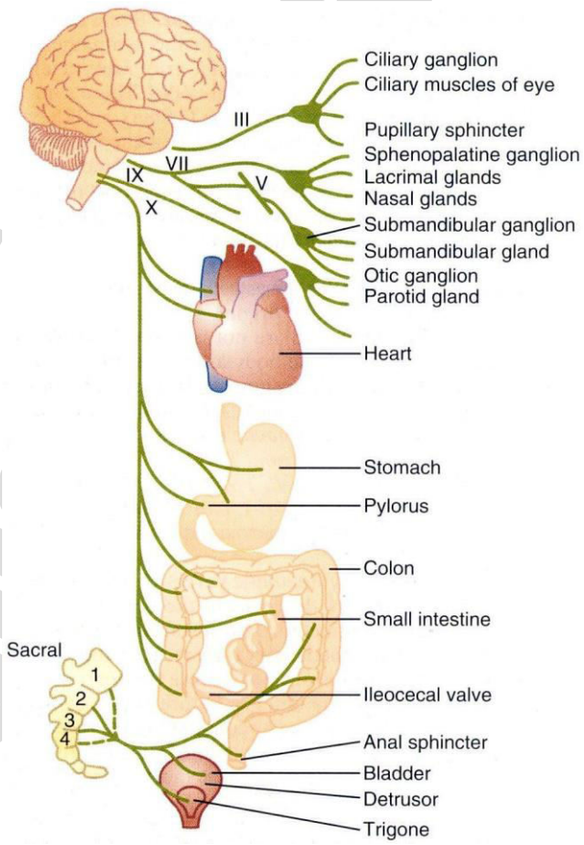
Integration of the many parts of the total motor control system: synopsis of the different levels of control

Spinal level
Programmed in the spinal cord are local patterns of movement for all muscle areas of the body – for instance, programmed withdrawal reflexes that pull any part of the body away from a source of pain. The cord is the locus also of complex patterns of rhythmical motions such as to-and-fro movement of the limbs for walking, plus reciprocal motions on opposite sides of the body or of the hindlimbs versus the forelimbs in four-legged animals.

Hindbrain level
The hindbrain provides two major functions for general motor control of the body:

- Maintenance of axial tone of the body for the purpose of standing
- Continuous modification of the degrees of tone in the different muscles in response to information from the vestibular apparatuses for the purpose of maintaining body equilibrium.

Motor cortex level
The motor cortex system provides most of the activating motor signals to the spinal cord. It functions partly by issuing sequential and parallel commands that set into motion various cord patterns of motor action.



Parasympathetic nervous system.

Autonomic Effects on Various Organs of the Body

Organ	Effect of Sympathetic Stimulation	Effect of Parasympathetic Stimulation
Eye		
Pupil	Dilated	Constricted
Ciliary muscle	Slight relaxation (far vision)	Constricted (near vision)
Glands	Vasoconstriction and slight secretion	Stimulation of copious secretion (containing many enzymes for enzyme-secreting glands)
Nasal		
Lacrimal		
Parotid		
Submandibular		
Gastric		
Pancreatic		
Sweat glands	Copious sweating (cholinergic)	Sweating on palms of hands
Apocrine glands	Thick, odoriferous secretion	None
Blood vessels	Most often constricted	Most often little or no effect
Heart		
Muscle	Increased rate Increased force of contraction	Slowed rate Decreased force of contraction (especially of atria)
Coronaries	Dilated (β_2); constricted (α)	Dilated
Lungs		
Bronchi	Dilated	Constricted
Blood vessels	Mildly constricted	? Dilated
Gut		
Lumen	Decreased peristalsis and tone	Increased peristalsis and tone
Sphincter	Increased tone (most times)	Relaxed (most times)
Liver	Glucose released	Slight glycogen synthesis
Gallbladder and bile ducts	Relaxed	Contracted
Kidney	Decreased output and renin secretion	None
Bladder		
Detrusor	Relaxed (slight)	Contracted
Trigone	Contracted	Relaxed
Penis	Ejaculation	Erection
Systemic arterioles		
Abdominal viscera	Constricted	None
Muscle	Constricted (adrenergic α) Dilated (adrenergic β_2) Dilated (cholinergic)	None
Skin	Constricted	None
Blood		
Coagulation	Increased	None
Glucose	Increased	None
Lipids	Increased	None
Basal metabolism	Increased up to 100%	None
Adrenal medullary secretion	Increased	None
Mental activity	Increased	None
Piloerector muscles	Contracted	None
Skeletal muscle	Increased glycogenolysis Increased strength	None
Fat cells	Lipolysis	None

ACTIONS OF AUTONOMIC STIMULATION

ORGAN/STRUCTURE	SYMPATHETIC ACTION	PARASYMPATHETIC ACTION
Eye		
Muscles of iris	Contraction of radial muscle (dilates pupil)	Contraction of circular muscle (contracts pupil)
Heart		
S-A node	Increase in heart rate	Decrease in heart rate
A-V node	Increase in conduction velocity	Decrease in conduction velocity
Muscle	Increase in force of contraction	Decrease in force of contraction
Intestines		
Muscle	Decreased	Increased
Secretions	Decreased	Increased
Lungs		
Bronchi	Dilation	Constriction
Kidney	Afferent arteriole constriction and renin secretion	None
Urinary bladder		
Bladder wall	None	Contraction
Sphincter	Contraction	Relaxation
Penis	Ejaculation	Erection
Piloerector muscles	Contraction	None
Salivary glands	Mucus secretion	Serous secretion

Cranial Nerves

Functions of 12 Cranial Nerves

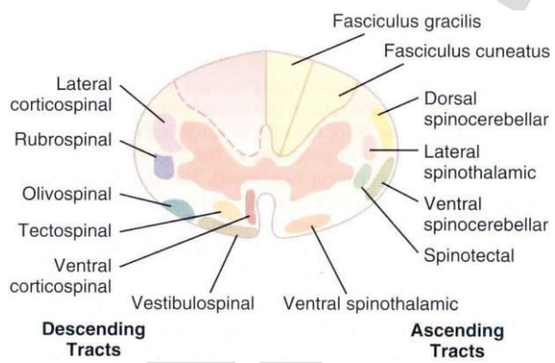
Number	Name	Type	Key Functions
I	Olfactory	Sensory	Smell
II	Optic	Sensory	Vision
III	Oculomotor	Motor	Eye movement, pupil size, focusing lens
IV	Trochlear	Motor	Eye movement
V	Trigeminal	Both sensory and motor	Sensations from the head and teeth, chewing
VI	Abducent	Motor	Eye movement
VII	Facial	Both sensory and motor	Face and scalp movement, salivation, tears, taste
VIII	Vestibulocochlear	Sensory	Balance, hearing
IX	Glossopharyngeal	Both sensory and motor	Tongue movement, swallowing, salivation, taste
X	Vagus ("wanderer")	Both sensory and motor	Sensory from gastrointestinal tract and respiratory tree, motor to the larynx, pharynx, parasympathetic motor to the abdominal and thoracic organs
XI	Accessory	Motor	Head movement, accessory motor with vagus
XII	Hypoglossal	Motor	Tongue movement

Mnemonic Devices for Cranial Nerve Names and Functions

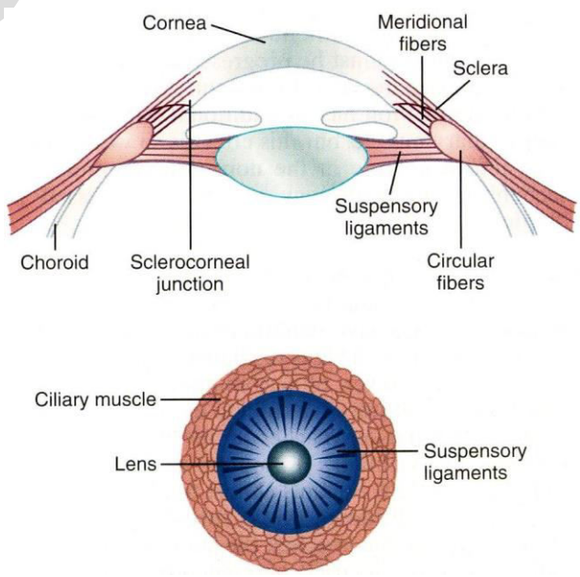
Cranial Nerve	Nerve Name	Word of the Saying	Type of Nerve	Word of the Saying
I	Olfactory	On	Sensory	Six
II	Optic	old	Sensory	sailors
III	Oculomotor	Olympus'	Motor	made
IV	Trochlear	towering	Motor	merry,
V	Trigeminal	top,	Both sensory and motor	but
VI	Abducent	a	Motor	my
VII	Facial	fine,	Both sensory and motor	brother
VIII	Vestibulocochlear	vocal	Sensory	said,
IX	Glossopharyngeal	German	Both sensory and motor	"Bad
X	Vagus	viewed	Both sensory and motor	business,
XI	Spinal accessory	some	Motor	my
XII	Hypoglossal	hops.	Motor	man."

XIII. PHYSIOLOGY OF THE SPECIAL SENSES

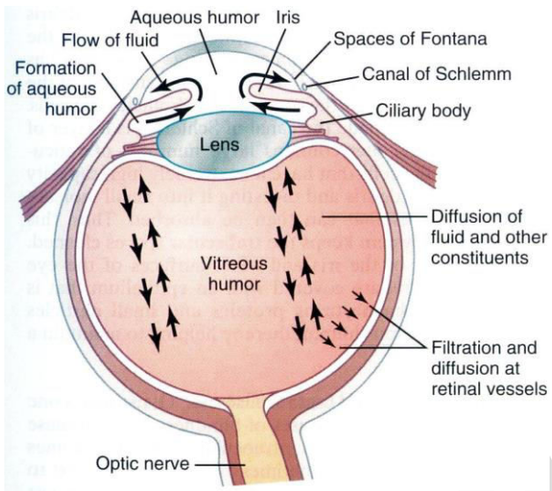
Physiology of Eyesight



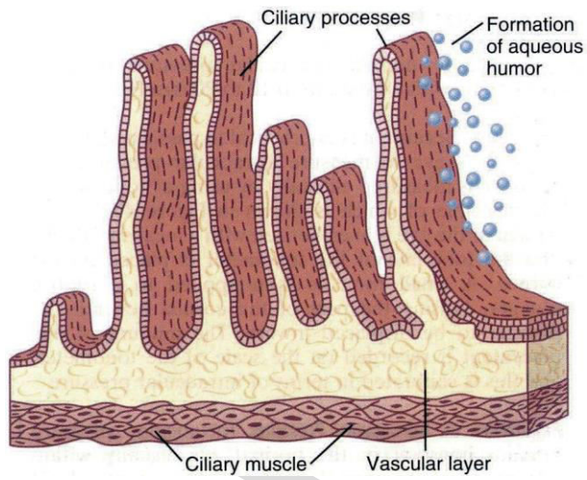
Cross section of the spinal cord, showing principal ascending tracts on the right and principal descending tracts on the left.



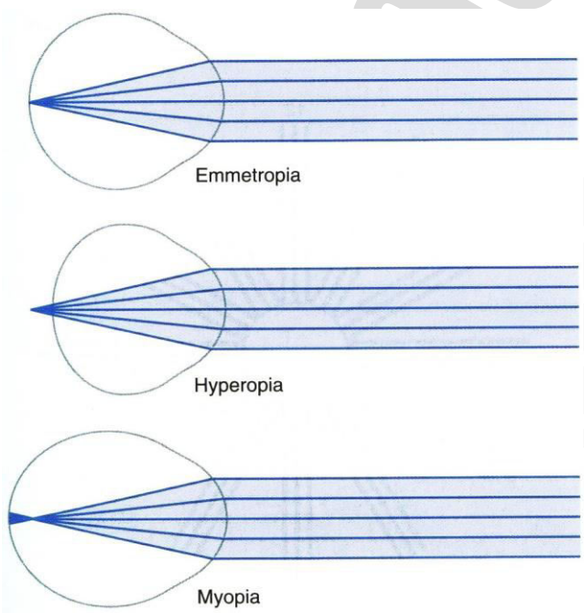
Mechanism of accommodation (focusing).



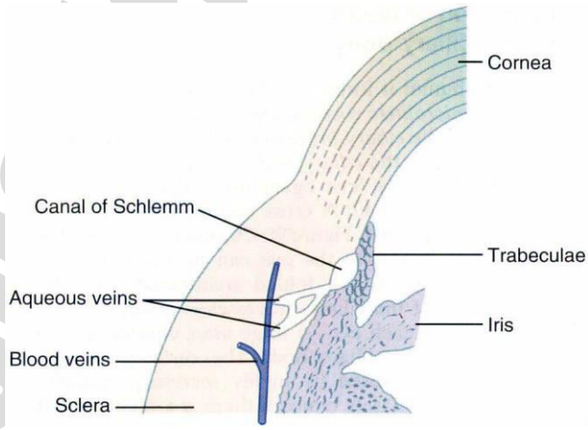
Formation and flow of fluid in the eye.



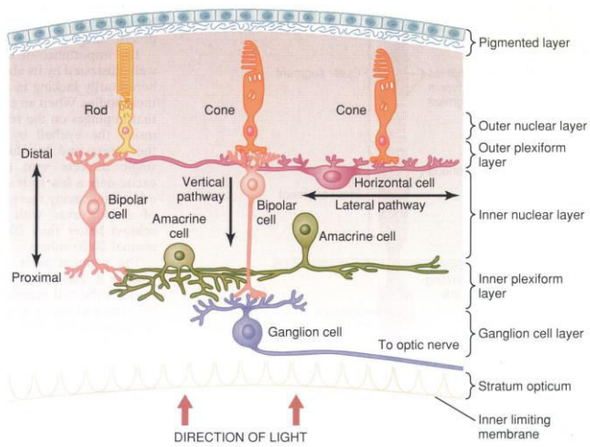
Anatomy of the ciliary processes. Aqueous humor is formed in surfaces.



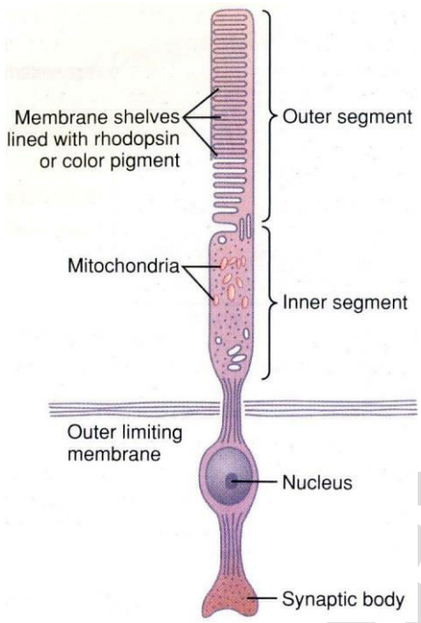
Parallel light rays focus on the retina in emmetropia, behind the retina in hyperopia, and in front of the retina in myopia.



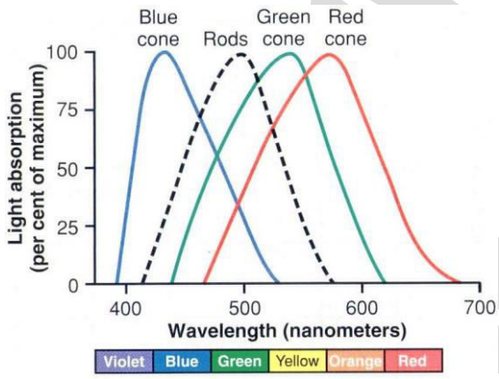
Anatomy of the iridocorneal angle, showing the system for outflow of aqueous humor from the eyeball into the conjunctival veins.



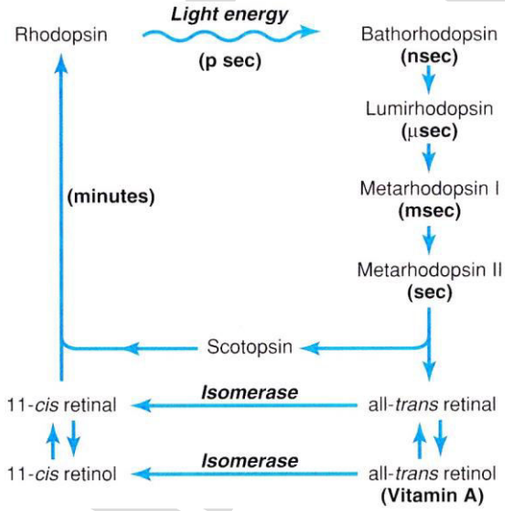
Layers of retina.



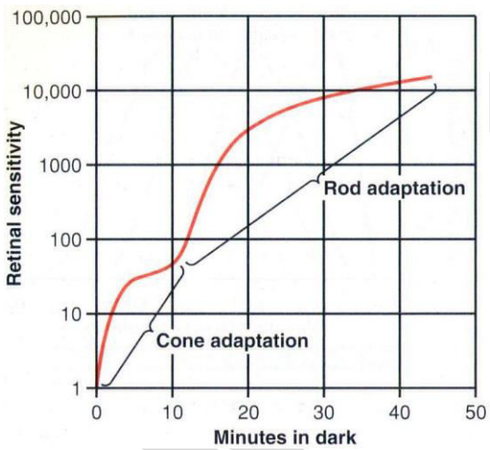
Schematic drawing of the functional parts of the rods and cones.



Light absorption by the pigment of the rods and by the pigments of the three color-receptive cones of the human retina.



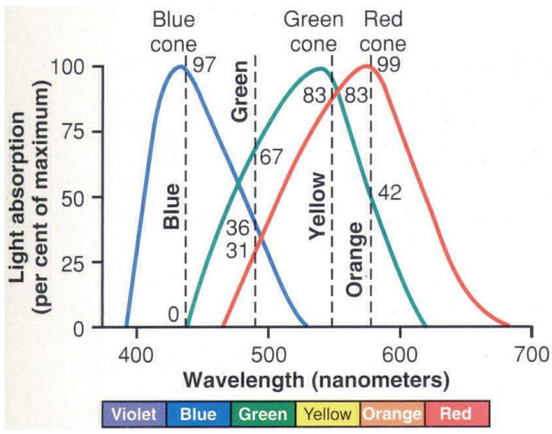
Rhodopsin-retinal visual cycle in the rod, showing decomposition of rhodopsin during exposure to light and subsequent slow reformation of rhodopsin by the chemical processes.



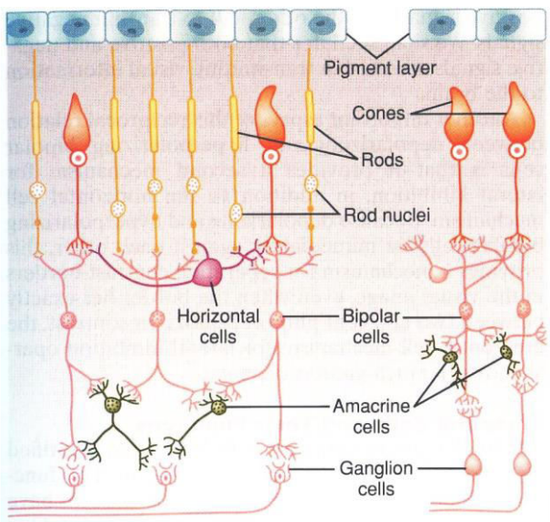
Dark adaptation, demonstrating the relation of cone adaptation to rod adaptation.

General and Special Senses

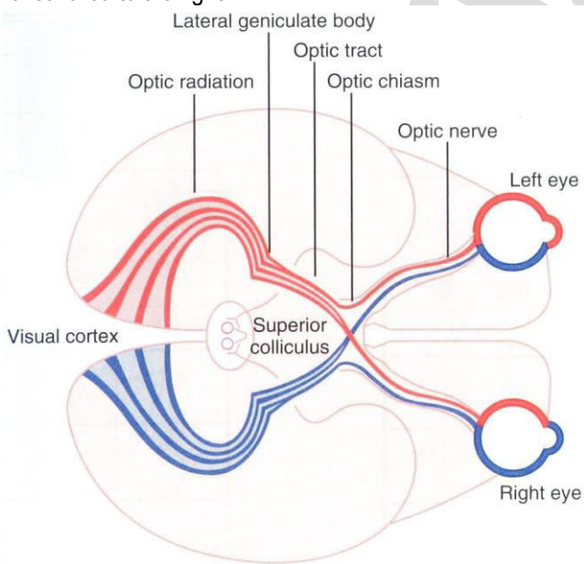
Sense	What Is Sensed	Type of Stimulus
General Senses		
Visceral sensations	Hunger, thirst, hollow-organ fullness	Chemical, mechanical
Touch	Touch and pressure	Mechanical
Temperature	Heat and cold	Thermal
Pain	Intense stimuli of any type	Mechanical, chemical, or thermal
Proprioception	Body position and movement	Mechanical
Special Senses		
Taste	Tastes	Chemical
Smell	Odors	Chemical
Hearing	Sounds	Mechanical
Equilibrium	Balance and head position	Mechanical
Vision	Light	Electromagnetic



Demonstration of the degree of stimulation of the different color-sensitive cones by monochromatic lights of four colors: blue, green, yellow, and orange.



Neural organization of the retina: peripheral area to the left, foveal area to the right.

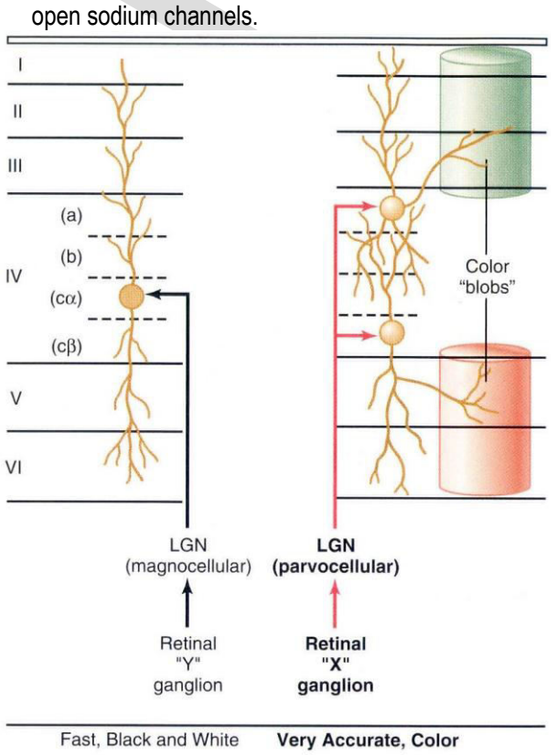


Principal visual pathways from the eyes to the visual cortex.

Cataracts – a cloudy or opaque area or areas in the lens. In the early stage of cataract formation, the proteins in some of the lens fibers become denatured. Later, these same proteins coagulate to form opaque areas in place of the normal transparent protein fibers.

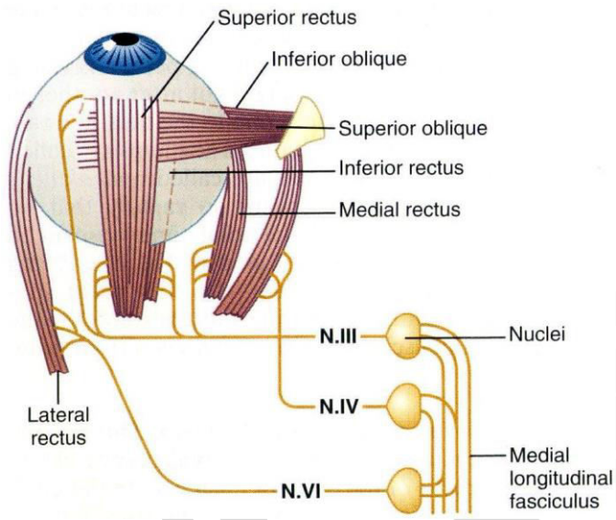
Mechanism by which rhodopsin decomposition decreases membrane sodium conductance – the excitation "cascade": The photoreceptors have an extremely sensitive chemical cascade that amplifies the stimulatory effects about a millionfold, as follows:

1. The photon activates an electron in the 11-cis retinal portion of the rhodopsin; this lead to the formation of metarhodopsin II, which is the active form of rhodopsin.
2. The activated rhodopsin functions as an enzyme to activate many molecules of transducin, a protein present in an inactive form in the membranes of the discs and cell membrane of the rod.
3. The activated transducin activates many more molecules of phosphodiesterase.
4. Activated phosphodiesterase is another enzyme; it immediately hydrolyzes many molecules of cyclic guanosine monophosphate (cGMP), thus destroying it. Before being destroyed, the cGMP had been bound with the sodium channel protein of the rod's outer membrane in a way that "splints" it in the open state. But in light, when phosphodiesterase hydrolyzes the cGMP, this removes the splinting and allows the sodium channels to close. Several hundred channels close for each originally activated molecule of rhodopsin.
5. Within about a second, another enzyme, rhodopsin kinase, which is always present in the rod, inactivates the activated rhodopsin (the metarhodopsin II), and the entire cascade reverses back to the normal state with open sodium channels.

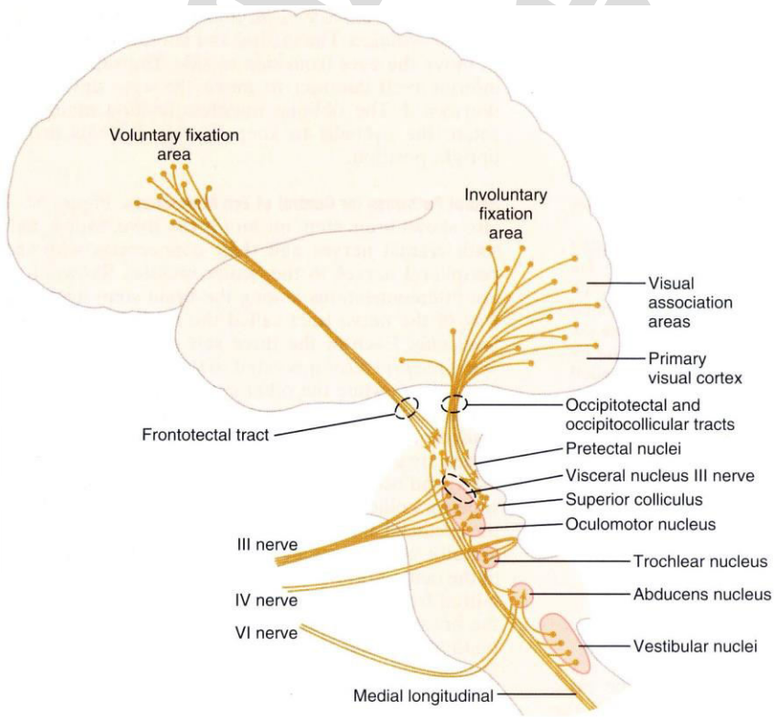


Six layers of the primary visual cortex. The connections shown on the left side of the figure originate in the magnocellular layers of the lateral geniculate nucleus (LGN) and transmit rapidly changing black-an-white visual signals. The pathways to the right originate in the parvocellular layers (layers III through VI) of the LGN; they transmit signals that depict accurate spatial detail as well as color. Note especially the areas of the visual cortex called "color blobs," which are necessary for detection of color.

Tricolor mechanism of color detection: all theories of color vision are based on the well-known observation that the human eye can detect almost all gradations of color when only **red**, **green**, and **blue** monochromatic lights are appropriately mixed in different combinations.



Extraocular muscles of the eye and their innervation.



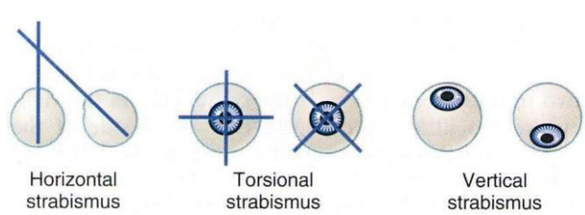
Neural pathways for control of conjugate movement of the eyes.

The eyes normally have three types of continuous but almost imperceptible movements:

1. A continuous tremor at a rate of 30 to 90 cycles per second caused by successive contractions of the motor units in the ocular muscles.
2. A slow drift of the eyeballs in one direction or another.
3. Sudden flicking movements that are controlled by the involuntary fixation mechanism.

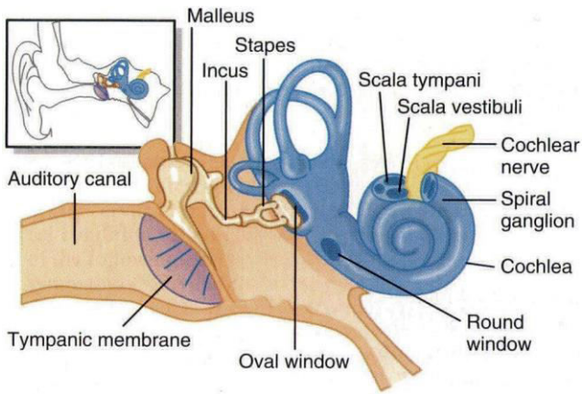
Strabismus

- Also called squint or cross-eye, means lack of fusion of the eyes in one or more of the visual coordinates: horizontal, vertical, or rotational.
- Often caused by abnormal "set" of the fusion mechanism of the visual system. That is, in a young animal's early efforts to fixate the two eyes on the same object, one of the eyes fixates satisfactorily while the other fails to do so, or they both fixate satisfactorily but never simultaneously.

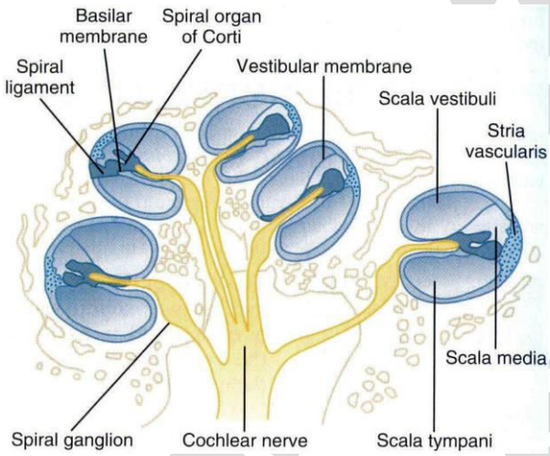


Basic types of strabismus. Combinations of two or even all three often occur in humans.

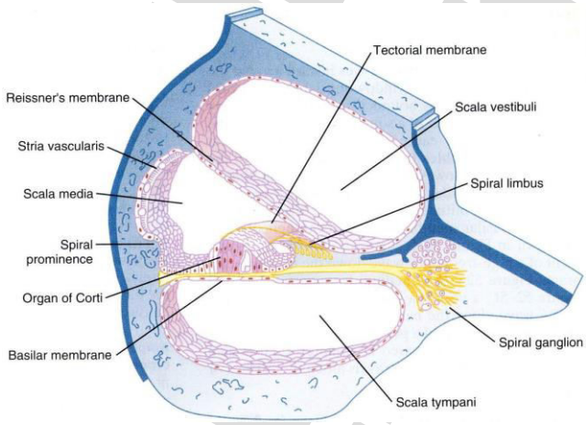
Physiology of Hearing



Tympanic membrane, ossicular system of the middle ear, and inner ear.



Cochlea.



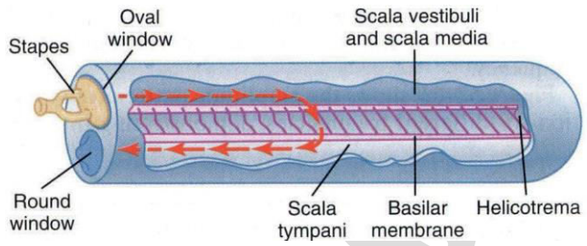
Section through one of the turns of the cochlea.

Attenuation of sound: by contraction of the

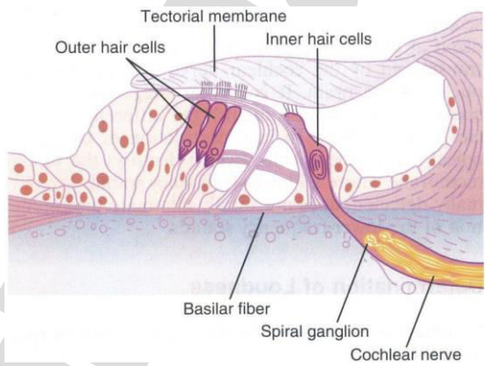
- tensor tympani and
- stapedius muscles

Functions of the attenuation reflex:

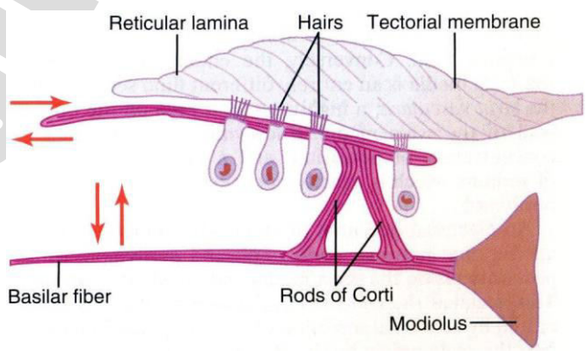
- to protect the cochlea from damaging vibrations caused by excessively loud sound.
- To mask low-frequency sounds in loud environments.



Movement of fluid in the cochlea after forward thrust of the stapes.



Organ of Corti, showing especially the hair cells and the tectorial membrane pressing against the projecting hairs.
Organ of Corti – the receptor organ that generates nervfe impulses in response to vibration of the basilar membrane.



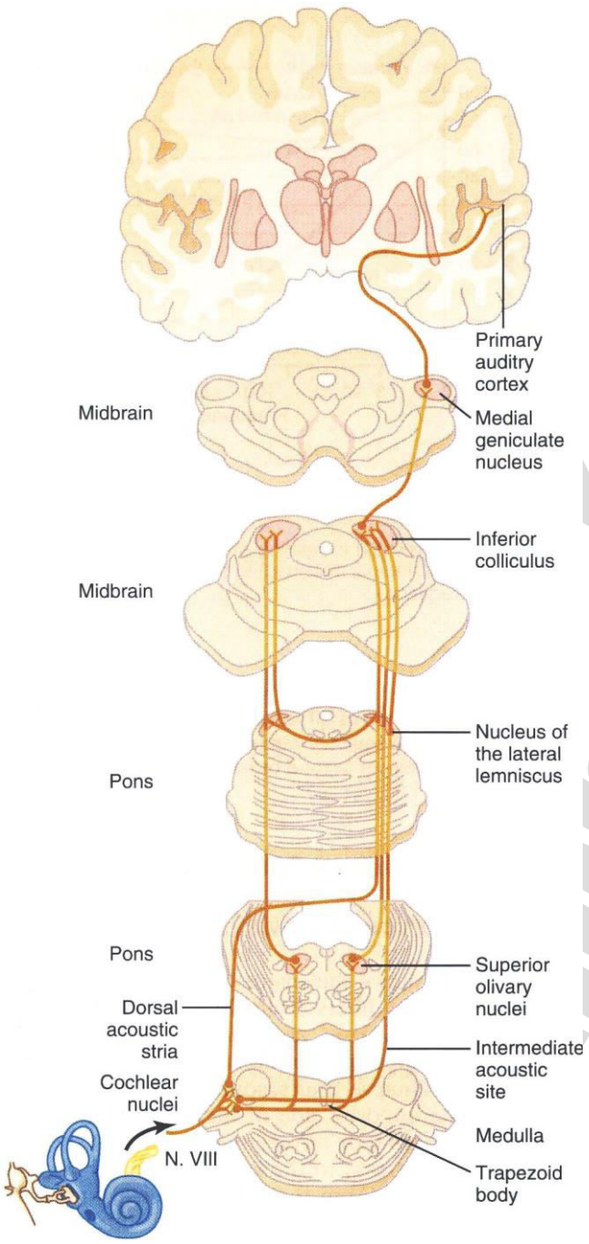
Stimulation of the hair cells by to-and-fro movement of the hairs projecting into the gel coating of the tectorial membrane.

Determination of loudness

Loudness is determined by the auditory system in at least three ways:

1. As the sound becomes louder, the amplitude of the vibration of the basilar membrane and hair cells also increases, so that the hair cells excite the nerve endings at more rapid rates.
2. As the amplitude of vibration increases, it causes more and more of the hair cells on the fringes of the resonating portion of the basilar membrane to become stimulated, thus causing spatial summation of impulses – that is, transmission through many nerve fibers rather than through only a few.
3. The outer hair cells do not become stimulated significantly until vibration of the basilar membrane reaches high intensity, and stimulation of these cells

presumably appraises the nervous system that the sound is loud.



Auditory nervous pathways.

In at least three places in the brain stem, crossing over occurs between the two pathways in:

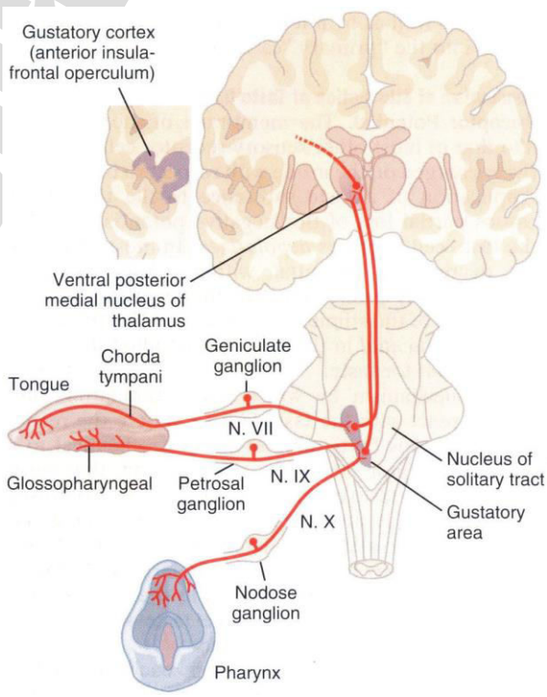
1. The trapezoid body
2. The commissure between the two nuclei of the lateral menisci
3. The commissure connecting the two inferior colliculi

The auditory cortex lies principally on the supratemporal plane of the superior temporal gyrus but also extends onto the lateral side of the temporal lobe, over much of the insular cortex, and even onto the lateral portion of the parietal operculum.

Physiology of Tastes

Primary sensations of taste:

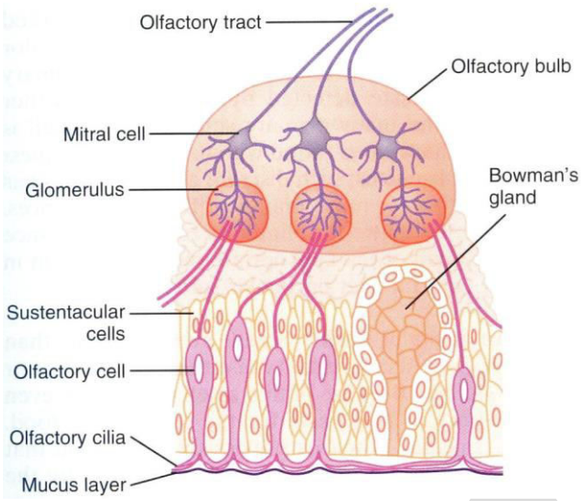
- Sour taste – caused by acids
- Salty taste – elicited by ionized salts, mainly by the sodium ion concentration
- Sweet taste – not caused by any single class of chemicals. Some of the types of chemicals that cause this taste include sugars, glycols, alcohols, aldehydes, ketones, amides, esters, some amino acids, some small proteins, sulfonic acids, halogenated acids, and inorganic salts of lead and beryllium. Note specifically that most of the substances that cause a sweet taste are organic chemicals.
- Bitter taste – not also caused by any single type of chemical agent. Here again, the substances that give the bitter taste are almost entirely organic substances. Two particular classes of substances are especially likely to cause bitter taste:
    - Long-chain organic substances that contain nitrogen
    - Alkaloids
- Umami (Japanese word meaning “delicious”) taste – a pleasant taste sensation that is qualitatively different from sour, salty, sweet, or bitter. Umami is the dominant taste of food containing L-glutamate, such as meat extracts and aging cheese, and some physiologists consider it to be a separate, fifth category of primary taste stimuli.



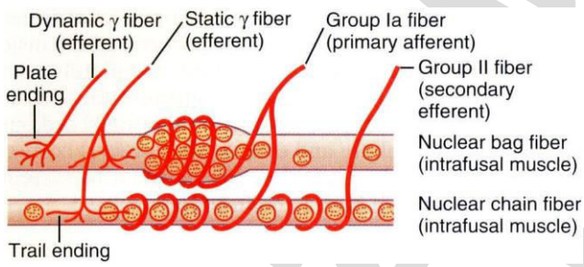
Transmission of taste signals into the central nervous system.

Microelectrode studies from single taste buds show that each taste bud usually responds mostly to one of the five primary taste stimuli when the taste substance is in low concentration. But at high concentration, most buds can be excited by two or more of the primary taste stimuli, as well by a few other taste stimuli that do not fit into the “primary” categories.

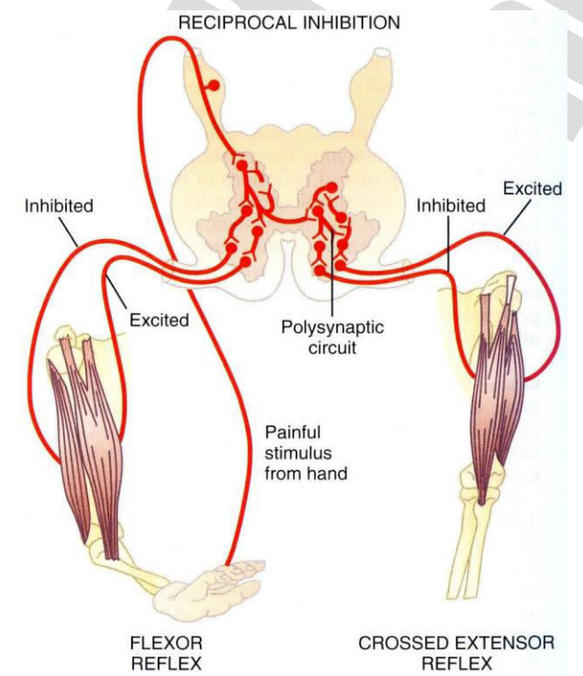
Physiology of Smell



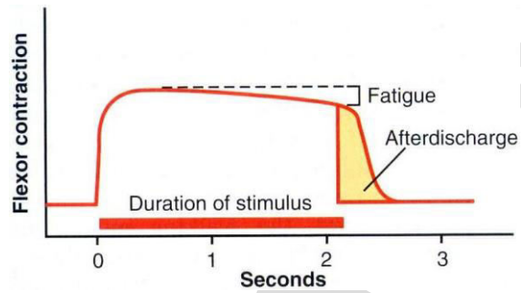
Organization of the olfactory membrane and olfactory bulb, and connections to the olfactory tract.



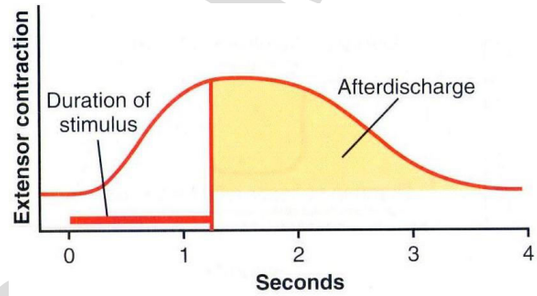
Details of nerve connections from the nuclear bag and nuclear chain muscle spindle fibers.



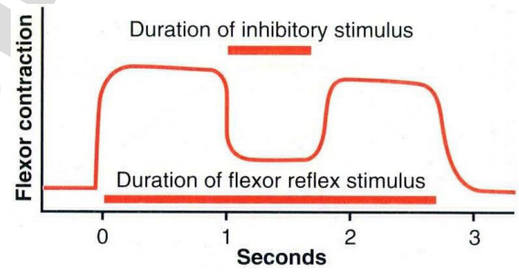
Flexor reflex, crossed extensor reflex, and reciprocal inhibition.



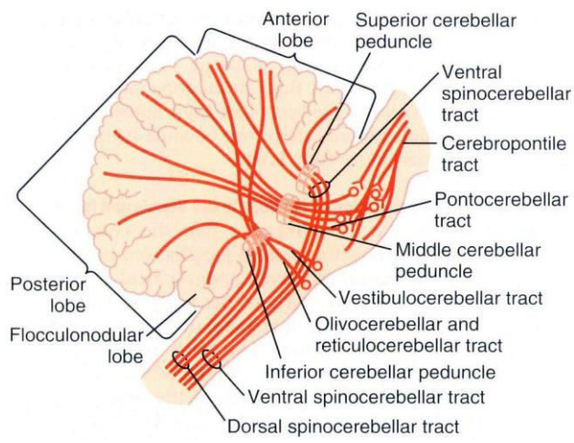
Myogram of the flexor reflex showing rapid onset of the reflex, an interval of fatigue, and, finally, afterdischarge after the input stimulus is over.



Myogram of a crossed extensor reflex showing slow onset but prolonged afterdischarge.



Myogram of a flexor reflex showing reciprocal inhibition caused by an inhibitory stimulus from a stronger flexor reflex on the opposite side of the body.

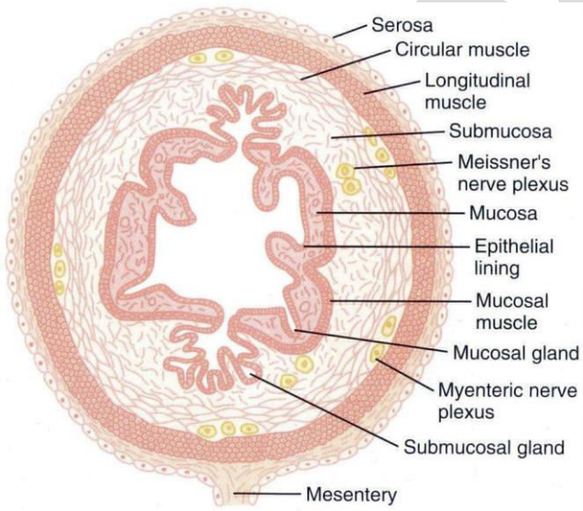


Principal *afferent* tracts to the cerebellum.

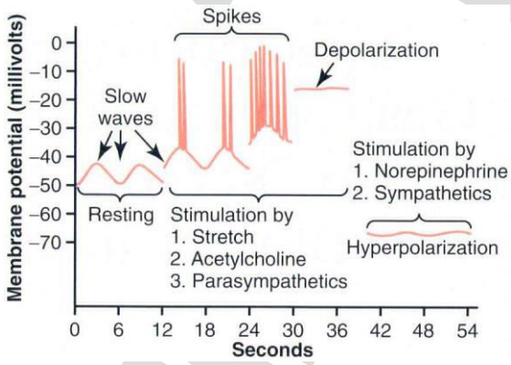
XIV. GASTROINTESTINAL PHYSIOLOGY

Process of Digestion

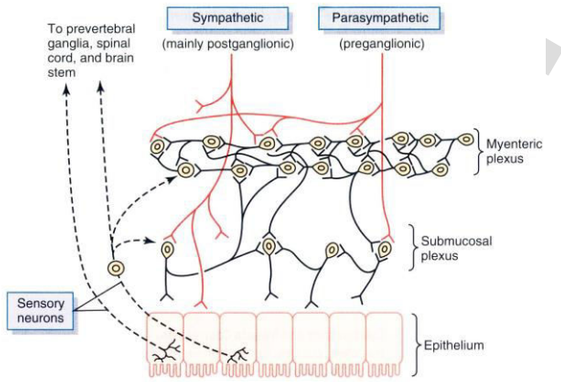
1. **Motility** - Movement of food through the digestive tract.
2. **Secretion -** Release of substances to the outside of a cell via an exocrine or endocrine route. Examples include enzymes, HCl, bile salts, mucus, hormones
3. **Digestion** - Breakdown of complex food molecules to smaller subunits, which can be absorbed.
   Carbohydrates ⟶ Simple sugars
   Proteins ⟶ Amino acids, small peptides
   Fats ⟶ Glycerol + fatty acids
4. **Absorption** - Movement of molecules from lumen of digestive tract into the blood or lymph.
5. **Storage and elimination** of indigestible food molecules.



Typical cross section of the gut.



Membrane potentials in intestinal smooth muscle. Note the slow waves, the spike potentials, total depolarization, and hyperpolarization, all of which occur under different physiologic conditions of the intestine.



Neural control of the gut wall, showing (1) the myenteric and submucosal plexuses (dark fibers); (2) extrinsic control of these plexuses by the sympathetic and parasympathetic nervous systems (light 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).

Layers of GI Tract - **Mucosa, submucosa, muscularis, serosa**

Regulation of the GastroIntestinal Tract

Autonomous Cells

Some cells are capable of generating spontaneous graded **slow wave potentials** that, if brought to threshold, will initiate A.P.'s and smooth muscle contraction.

Intrinsic sensory neurons

Myenteric + submucosal plexuses = enteric nervous system

Located in walls of digestive tract
Coordinate local activity in tract by, for example, regulating peristalsis and intestinal reflexes.

Extrinsic nerves - Nerves from the ANS that regulate the activity of the GI tract.

Gastrointestinal hormones (Gastrin, Ghrelin, Secretin, CCK, GIP)

Parts of the Digestive System

Mouth

Responsible for taste (**gustation**)
Chewing (**mastication**) - Process that grinds, breaks up, and mixes food with saliva. Saliva has many functions.
Saliva is secreted by 3 pairs of **salivary glands**.
Salivary enzymes (**amylases**) begin process of carbohydrate digestion. Digestion in mouth is minimal and involves no absorption.

Substrate	Enzyme	Product
Starch	Salivary α-amylase (ptyalin)	hydrolyzes 1:4α linkages producing α-limit dextrins, maltotriose and maltose
Triglycerides	Lingual lipase	fatty acids + 1,2-diacylglycerols

Tongue -responsible for maneuvering food mass within the mouth; assist in moving food into the esophagus; used as a structure for prehension (seizing and bringing food to the mouth) in ruminants

Salivary glands and saliva
functions of saliva include:
a) facilitates swallowing (*mucin*, glycoproteins that lubricates food and protects oral mucosa; responsible for saliva's viscosity)
b) keeps mouth moist
c) serves as solvent for molecules that stimulate taste buds
d) antimicrobial factors (*IgA*, the first immunologic defense against bacteria and viruses; *lysozyme*, which attacks walls of bacteria; *lactoferrin*, which binds iron and bacteriostatic) in saliva keeps mouth and teeth protected against infections
e) digestive function

Salivary secretion can be either unconditioned (occurs when food is in the mouth) or conditioned (occurs without oral stimulation).

Swallowing (**deglutition**) - Involves sequentially programmed events under the control of a **swallowing center** in the medulla..

Pharynx and Esophagus

Propels mass of food (**bolus**) forward by **peristalsis** (contractions of the circular smooth muscle that push the bolus ahead of the contraction.)

Gastroesophageal sphincter regulates passage of food into stomach and prevents reflux out of the stomach.
Sphincters prevent large volumes of air from entering and regurgitation. Excessive gas can lead to burping (**eructation**).
No digestion in esophagus.

Stomach

Capable of filling, storing, mixing, and emptying.
Mixing and emptying occur by peristalsis.
Main factor affecting gastric emptying is the amount of **chyme** (mixture of food and digestive juices) in the stomach.

Factors in the duodenum can also affect gastric emptying. These include presence of fat and acid, and distension of duodenum.

Emotion and pain can influence gastric function.
Secretes **mucus, HCl, pepsinogen, intrinsic factor (IF).** IF facilitates the absorption of **vitamin B_{12}** which is necessary for normal RBC maturation). Deficiency of IF leads to **pernicious anemia**.

Ghrelin is a newly discovered hormone that may play a role in regulating hunger.

Control of gastric secretion involves 3 phases:
- **Cephalic, gastric, intestinal phases**

Does not absorb food, but can absorb alcohol and aspirin

Small intestine (SI)
3 segments - **Duodenum, jejunum, ileum**
Most digestion and absorption occur in the duodenum and jejunum.

Most contractile activity of the SI occurs by **segmentation** = simultaneous contractions and relaxations of smooth muscle that propel chyme along the length of the SI.

Weak peristaltic waves also occur in the SI.

Digestion in the SI lumen is accomplished by pancreatic enzymes.

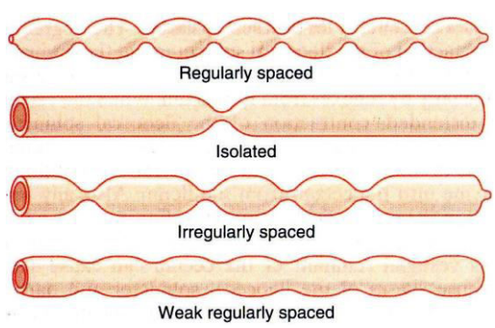
SI is remarkably well adapted for its role in absorption. Has modifications which dramatically increase the surface area for absorption.

Plicae circularis (large folds) - 3-fold increase

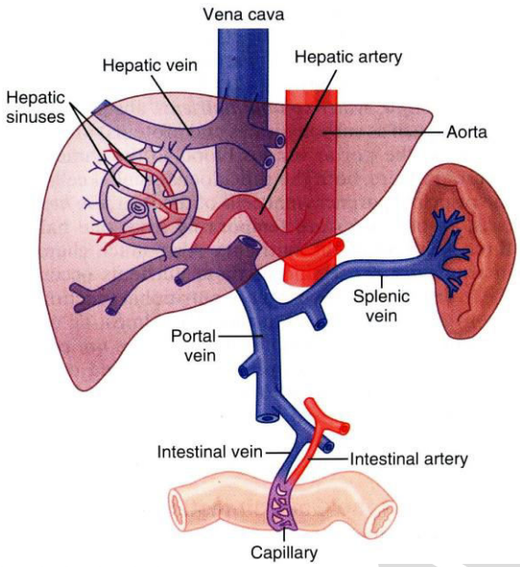
Villi (finger-like projections) - 10-fold increase

Microvilli or brush border (Projections arising from cells that make up the villi and contain some enzymes) - 20-fold increase

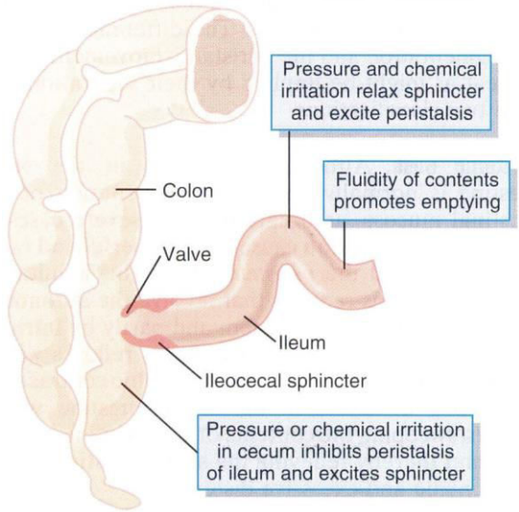
Ileum - Some absorption (bile salts, Vitamin B_{12}, water) occurs here.



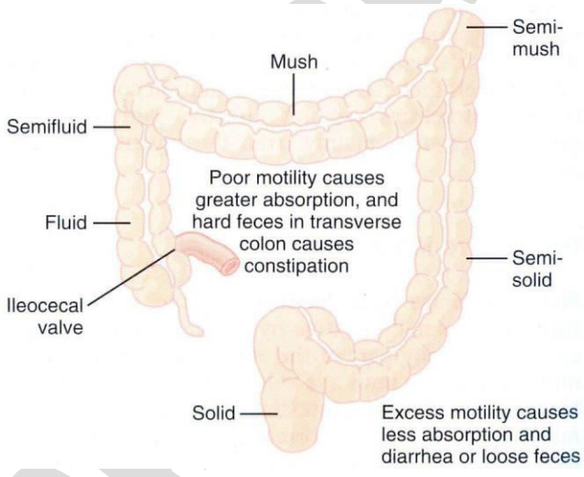
Segmentation movements of the small intestine.



Splanchnic circulation.



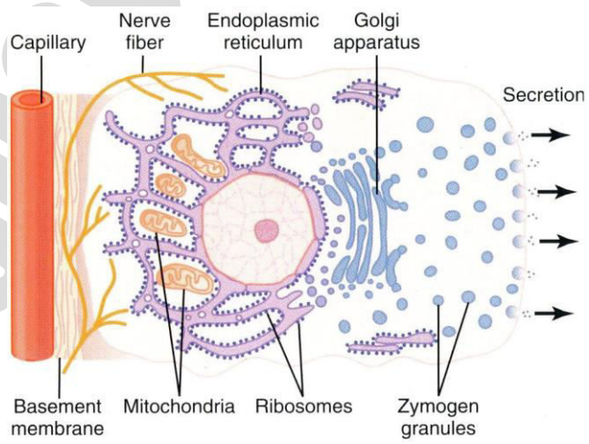
Emptying of the ileocecal valve.



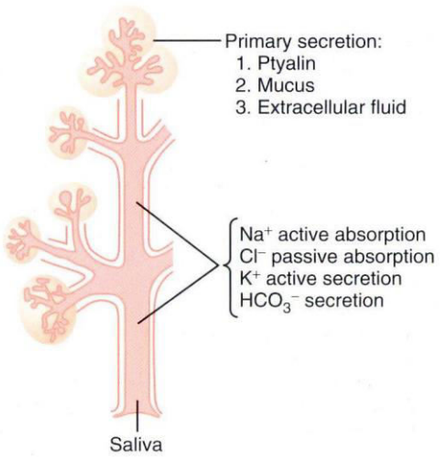
Absorptive and storage functions of the large intestine.

Liver

- Largest internal organ in the body.
- Produces and secretes **bile and bile salts** (derived from cholesterol) which aid in the **emulsification** and absorption of fats by the formation of water-soluble **micelles** that can carry the products of fat digestion to their absorptive site.
- Bile also contains **bilirubin** (derived from the breakdown of heme). Gives bile its yellow color. In the intestine, bilirubin is acted upon by bacteria to produce **urobilinogen** that gives rise to the brown color of feces. When excreted into the urine it contributes to urine's yellowish color.
- Most bile salts are reabsorbed in the small intestine and returned to the liver via the **enterohepatic circulation**.
- Processes nutrients after absorption from the digestive tract via the **hepatic portal system**.
- Stores glycogen and fats; releases glucose and fatty acids into blood.



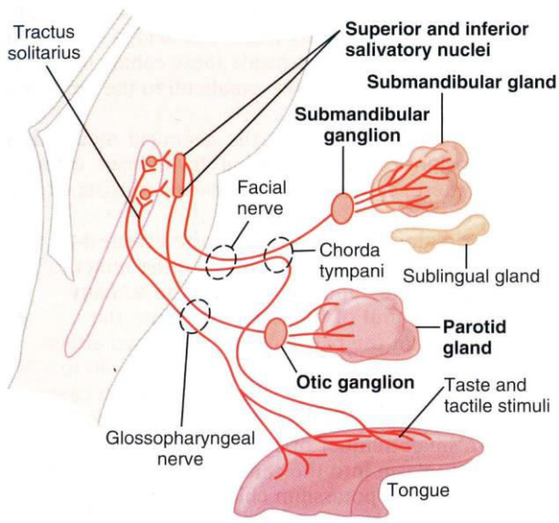
Typical function of a glandular cell for formation and secretion of enzymes and other secretory substances.



Formation and secretion of saliva by a submandibular salivary gland.

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 intestine 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	



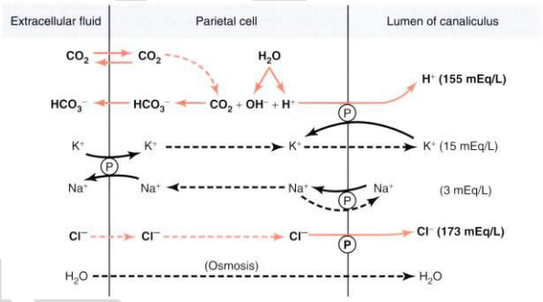
Parasympathetic nervous regulation of salivary secretion.

Gallbladder

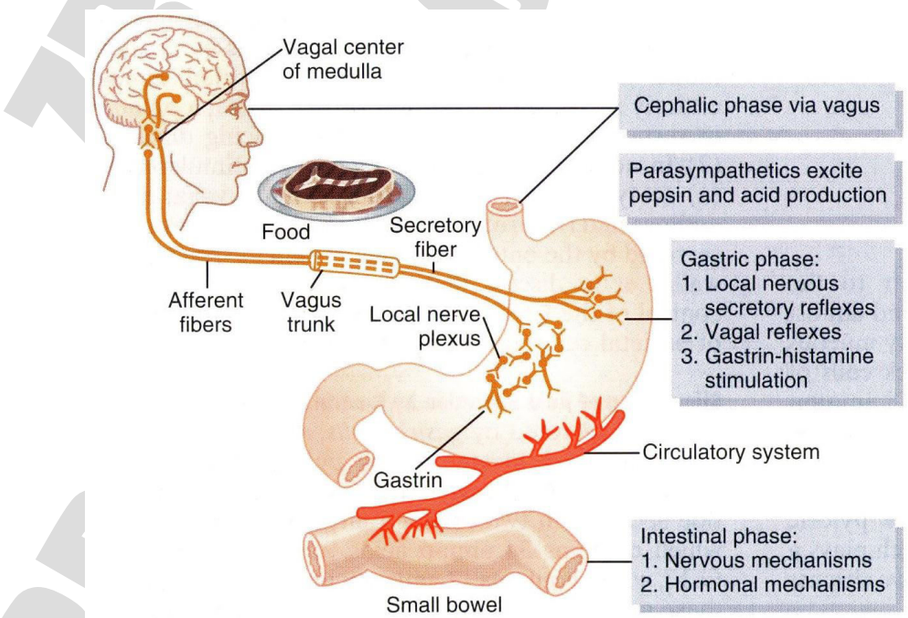
- Located under the liver.
- Stores and concentrates bile.
- Target organ of the hormone CCK.

Pancreas (exocrine portion)

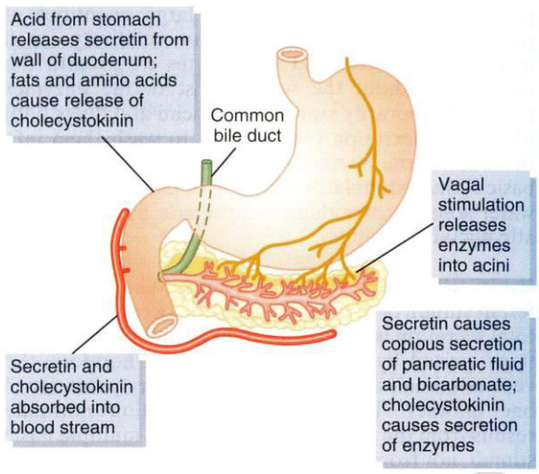
- Secretes enzymes (e.g., **amylase, trypsin, lipase**).
- Many enzymes are produced in inactive form = **zymogens**.
- **Trypsinogen** (inactive form) is activated to trypsin by the brush border enzyme **enterokinase**.
- Secretes bicarbonate which neutralizes stomach acid in the small intestine and facilitates enzyme function.
- Secretion is hormonally regulated by secretin and CCK.



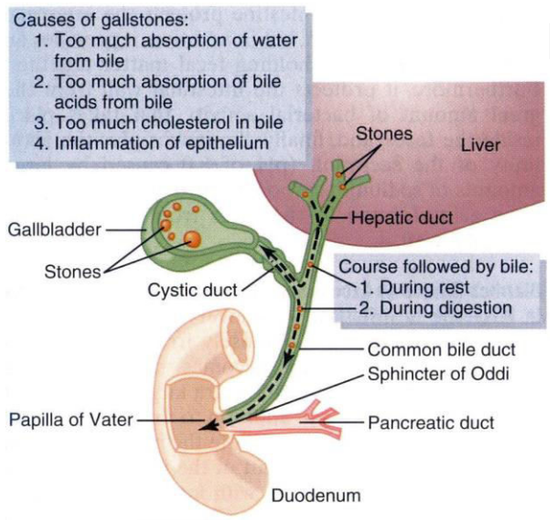
Postulated mechanism for secretion of hydrochloric acid. (The points labeled "P" indicate active pumps, and the dashed lines represent free diffusion and osmosis.)



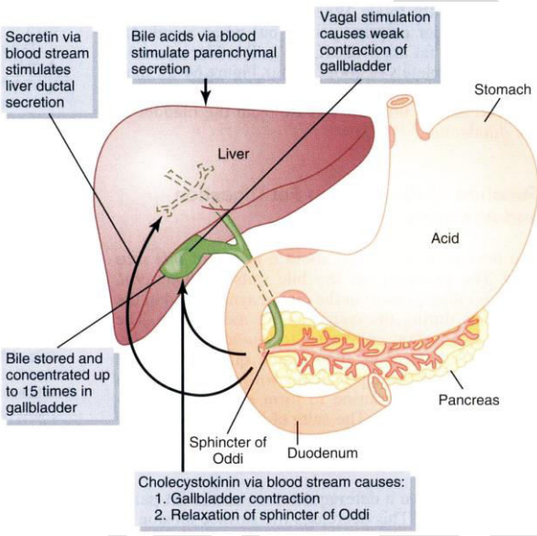
Phases of gastric secretion and their regulation.



Regulation of pancreatic secretion.



Formation of gallstones.



Liver secretion and gallbladder emptying.

Composition of Bile

	Liver Bile	Gallbladder Bile
Water	97.5 g/dl	92 g/dl
Bile salts	1.1 g/dl	6 g/dl
Bilirubin	0.04 g/dl	0.3 g/dl
Cholesterol	0.1 g/dl	0.3 to 0.9 g/dl
Fatty acids	0.12 g/dl	0.3 to 1.2 g/dl
Lecithin	0.04 g/dl	0.3 g/dl
Na^+	145.04 mEq/L	130 mEq/L
K^+	5 mEq/L	12 mEq/L
Ca^{++}	5 mEq/L	23 mEq/L
Cl^-	100 mEq/L	25 mEq/L
HCO_3^-	28 mEq/L	10 mEq/L

Digestion and Absorption CHO, Proteins, and Lipids

Carbohydrates

- Polysaccharides (starch) are digested by amylases (salivary and pancreatic).
- Dietary carbohydrates are presented to the small intestine in the form of disaccharides (lactose, maltose, sucrose).
- Enzymes located in the microvilli break down the disaccharides into monosaccharides.
- **Lactose ⟶ galactose + glucose**
- **Maltose ⟶ glucose + glucose**
- **Sucrose ⟶ fructose + glucose**
- Glucose and galactose are absorbed across the membrane of the microvilli by **secondary active transport (cotransport)**.
- Glucose and galactose leave the epithelial cells by moving down
- Fructose is moved to the blood by facilitated diffusion (passive carrier mediated transport of a substance down its concentration gradient).

Proteins are broken down by pepsin and pancreatic enzymes into free amino acids and small peptides.

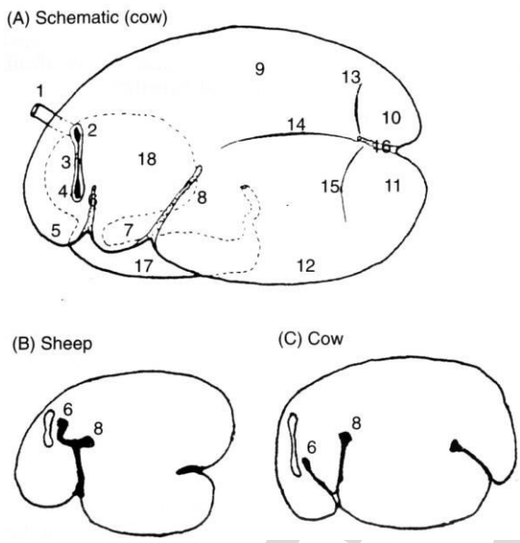
- Amino acids are cotransported into the epithelial cells by secondary active transport.
- Amino acids enter the capillaries within the villi.
- Small peptides are absorbed by a membrane carrier and are further broken down into amino acids by **peptidases**.

Lipids (not water soluble; must be transformed prior to absorption).

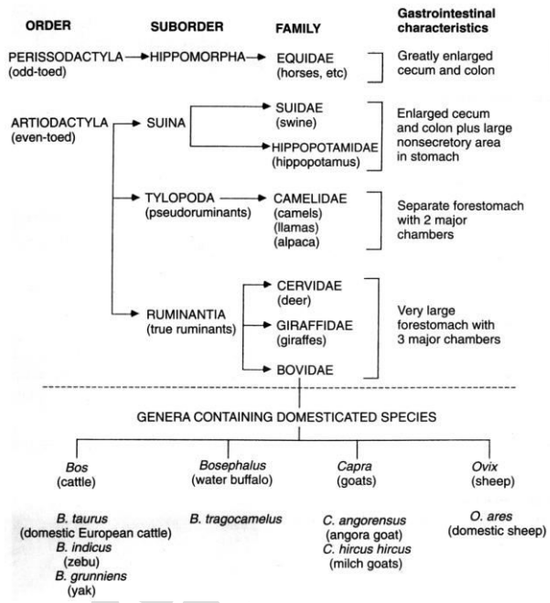
- Dietary fat is emulsified to smaller fat droplets by bile salts.
- Lipase cleaves fat ⟶ monoglycerides and fatty acids (FA).
- Monoglycerides and FA's are carried in micelles, formed from bile components.
- Monoglycerides and FA's leave micelles and diffuse through cell membrane.
- Monoglycerides and FA's are resynthesized into fats.

- Fats aggregate and are coated with protein to form **chylomicrons**.
- Chylomicrons are released from the cell by exocytosis into the **central lacteal** (lymph vessel) of the villi.
- Chylomicrons enter venous blood via thoracic duct.
- Once in the blood the fat component of the chylomicrons is cleaved by the enzyme **lipoprotein lipase** which provides FA's and glycerol to the tissues.

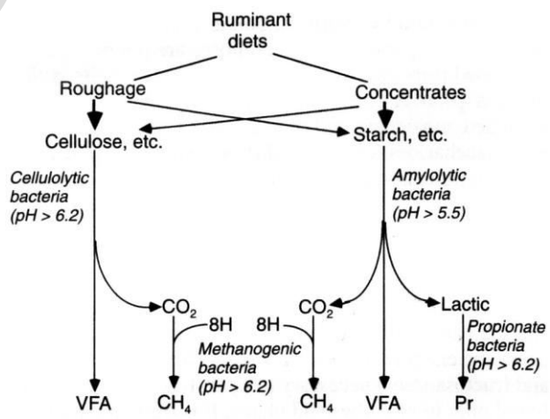
Ruminant Digestion



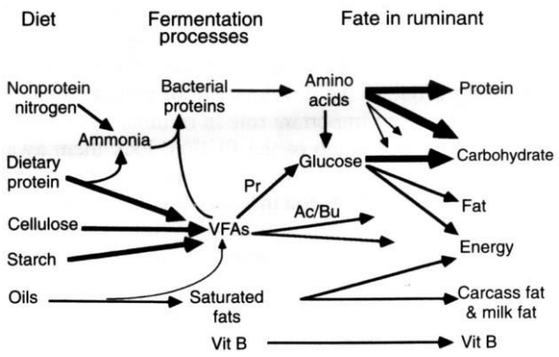
(A) A schematic diagram of a sagittal section through a bovine ruminoreticulum, viewed from the left side, to show the main anatomical features: 1, esophagus; 2, cardiac opening; 3, reticular groove; 4, reticulo-omasal opening; 5, reticulum; 6, ruminoreticular fold; 7, cranial sac of the rumen; 8, cranial pillar; 9,, dorsal sac of the rumen; 10, caudodorsal blind sac; 11, caudoventral blind sac; 12, ventral sac of the rumen; 13,, dorsal coronary pillar; 17, abomasums; 18, omasum. Dotted lines show the outline of the omasum and abomasums, which lie on the right side of the reticulum and rumen. The outlines of a sagittal section through the ruminoreticulum of a sheep (B) and a cow (C) in specimens fixed in situ. The main barrier to flow between the reticulum and the main mass of ruminal contents is the ruminoreticular fold (6) in sheep and the cranial pillar (8) in cattle.



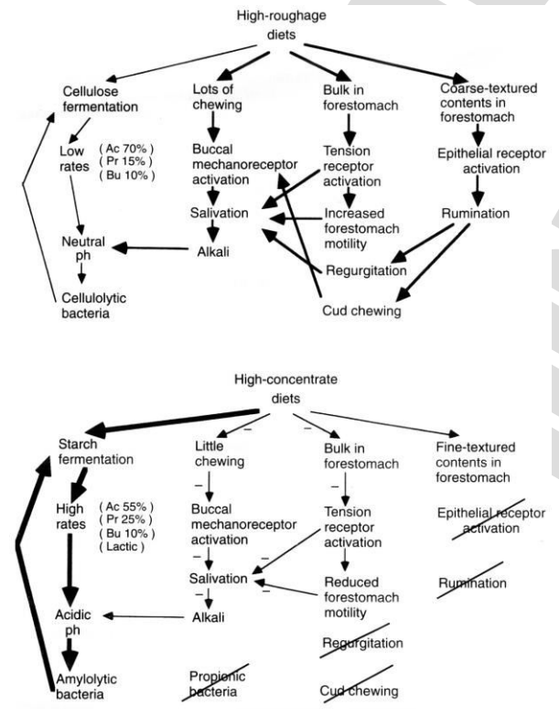
The classification of the large, mainly grass-eating hoofed mammals (ungulates). Microbial fermentation occurs in a greatly enlarged hindgut in the Equidae, in both an enlarged hindgut and a nonsecretory gastric region in a transitional group containing swine, and mainly in a separate large forestomach with two major compartments in pseudoruminants (Tylopoda) and with three major compartments (reticulum,, rumen, and omasum) in true ruminants (Ruminantia). Within the true ruminants, the family Bovidae contains not only the majority of wild species but also the four genera to which the main agriculturally important animals belong.



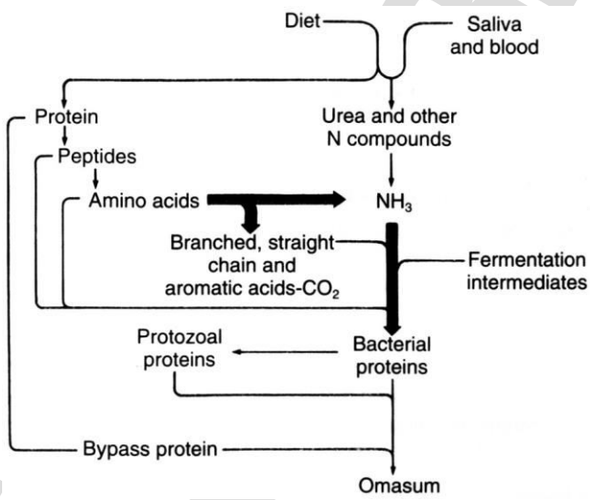
The primary microbes are cellulolytic and amylolytic bacteria. They ferment roughage and concentrates, respectively, to volatile fatty acids (VFAs). Secondary bacteria use some of the other end products. For example, methanogenic bacteria reoxidize reduced coenzymes by using their reducing equivalents (2H) to convert carbon dioxide (and formate) to methane. Propionate bacteria use, and therefore prevent the accumulation of,, lactic acid, but only at relatively high pH values.



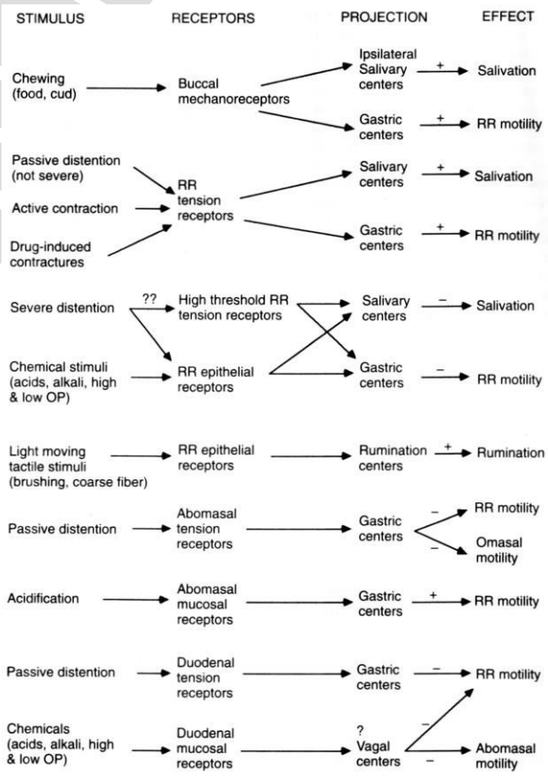
An overview of the fermentation and fate in the ruminant of the main dietary components. The principal volatile fatty acids (VFAs) are acetic (Ac), propionic (Pr), and butyric (Bu) acids. They are mainly present in the dissociated form. Rumen undegradable proteins (not shown here) are not fermented but may be degraded later by the gastrointestinal secretions.



With high-roughage diets, high rates of salivation are evoked by several reflex mechanisms. This gives adequate alkali to buffer the VFAs produced at low rates by the slow cellulolytic fermentation. With high-concentrate diets, much lower rates of saliva and hence of alkali are produced, because the reflex stimuli for salivation are less than with the high-roughage diet. The low alkali availability occurs paradoxically under conditions of high VFA production rates with the added risk of lactic acid accumulation.

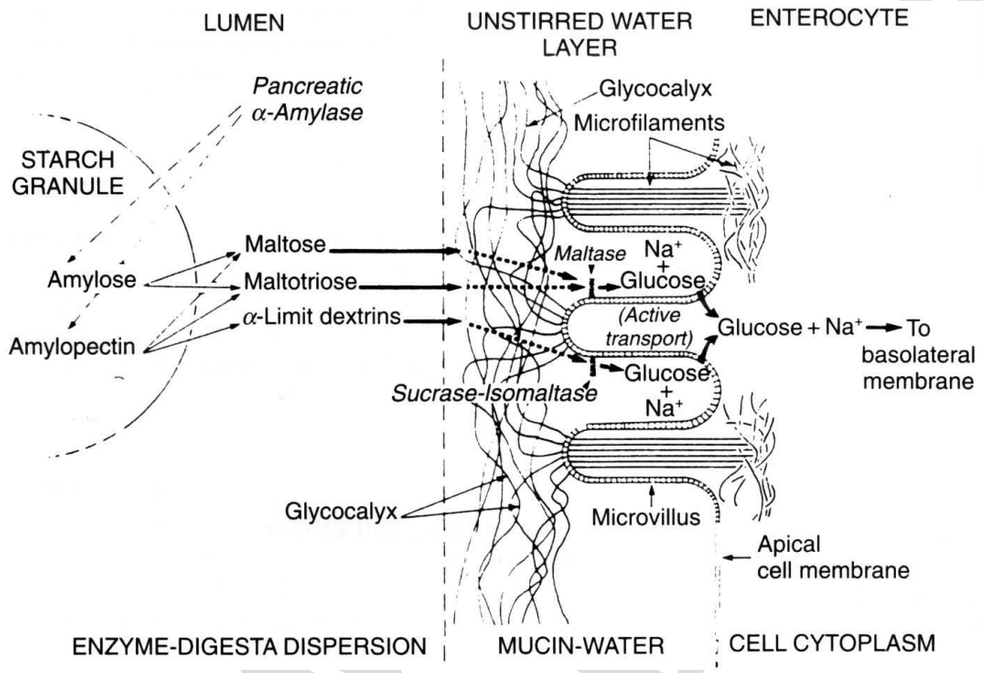


Transformations of nitrogenous substances in the rumen. Ammonia is produced during the microbial metabolism of diverse substrates and is a major source of the nitrogen used for the biosynthesis of microbial cells.



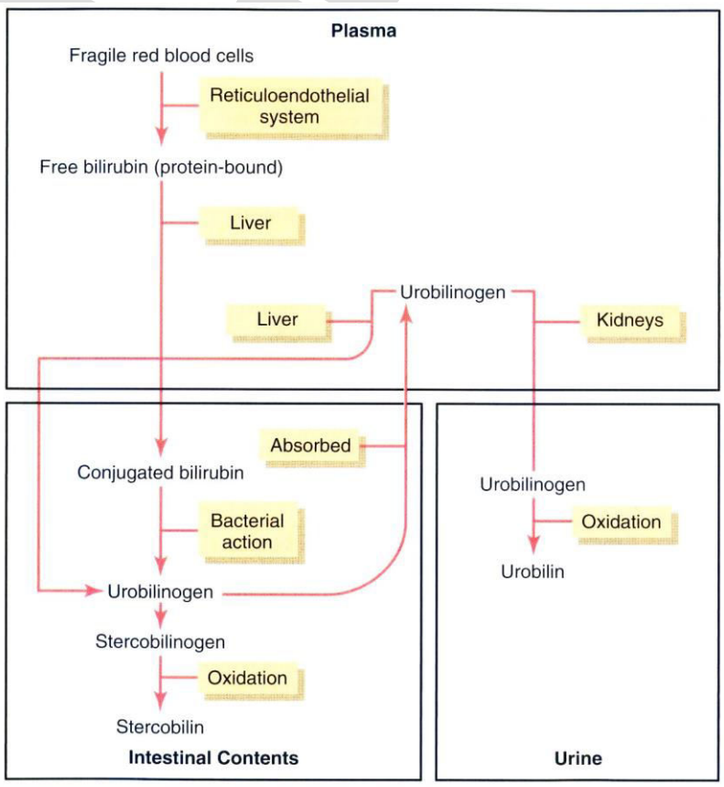
A summary of the alimentary tract sensory receptor mechanisms known to exert reflex effects on salivation and ruminoreticular (RR) motility. OP, osmotic pressure.

Digestion in Fowls

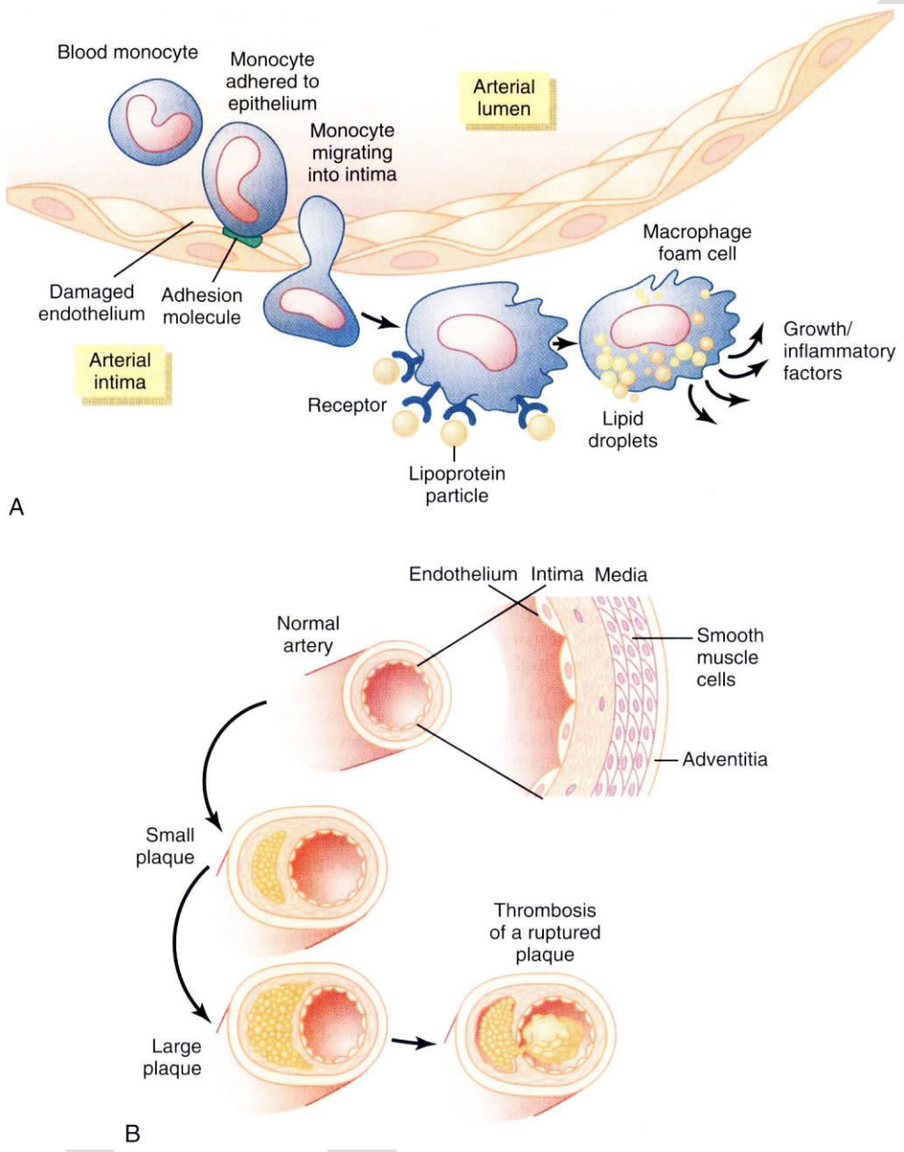


Postulated sequence of events in the digestion of starch by fowl. Starch is normally in granular form, and pancreatic α-amylase progressively hydrolyzes constitutent amylose and amylopectin to maltose, maltotriose, and α-limit dextrins. Enterocytes lining the small intestine project microvilli and a fibrous glycocalyx into the lumen. An aqueous dispersion of mucin from nearby goblet cells is immobilized in these structures to form the "unstirred water layer." Dissolved products from starch digestion must diffuse through this barrier to reach carbohydrases anchored on the surface in order to finalize digestion; however, glucose accrues near active transport sites, and its rate of absorption is improved.

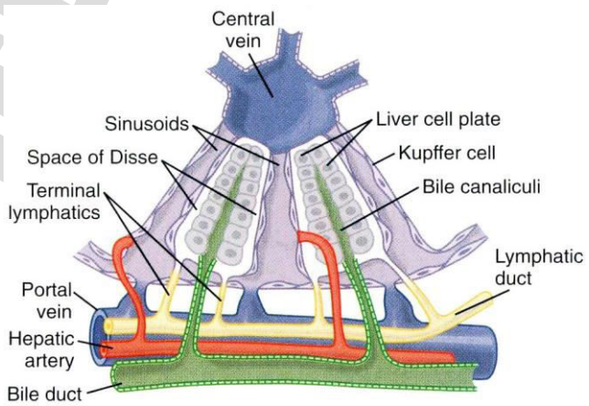
Bilirubin Formation and Excretion



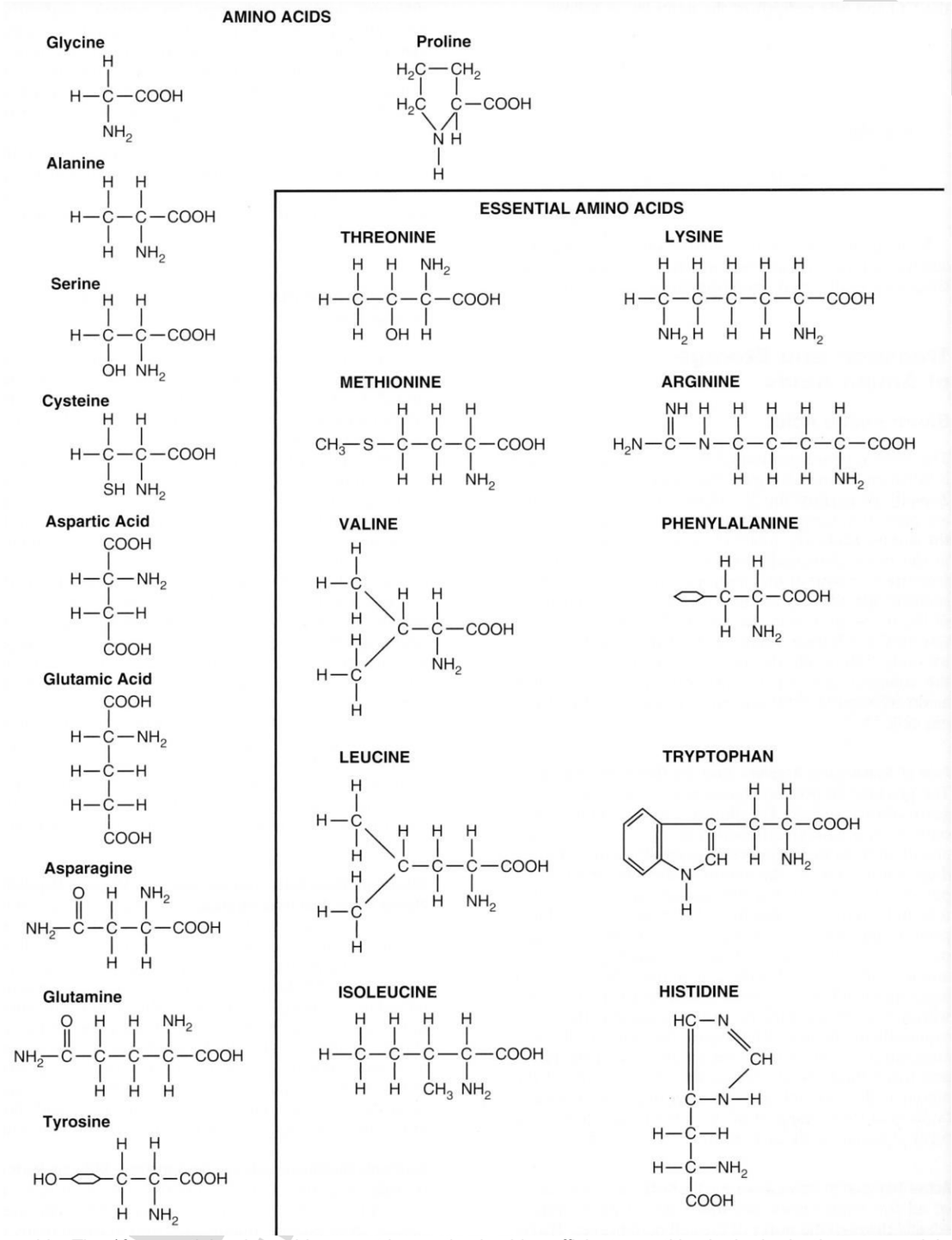
Bilirubin formation and excretion.



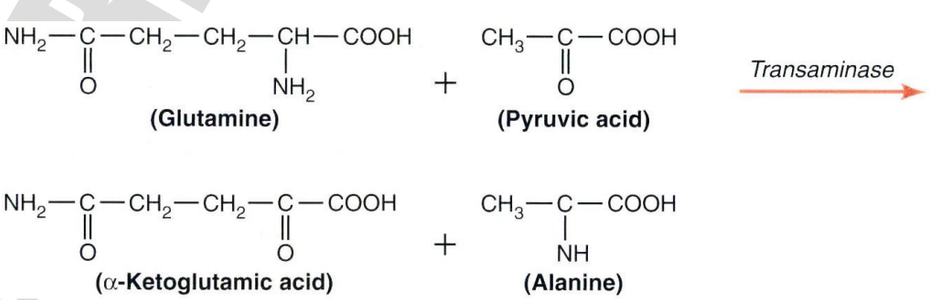
Development of atherosclerotic plaque. A, Attachment of a monocyte to an adhesion molecule on a damaged endothelial cell of an artery. The monocyte then migrates through the endothelium into the intimal layer of the arterial wall and is transformed into a macrophage. The macrophage then ingests and oxidizes lipoprotein molecules, becoming a macrophage foam cell. The foam cells release substances that cause inflammation and growth of the intimal layer. B, Additional accumulation of macrophages and growth of the intima cause the plaque to grow larger and accumulate lipids. Eventually, the plaque could occlude the vessel or rupture, causing the blood in the artery to coagulate and form a thrombus.



Basic structure of a liver lobule, showing the liver cellular plates, the blood vessels, the bile-collecting system, and the lymph flow system composed of the spaces of Disse and the interlobular lymphatics.



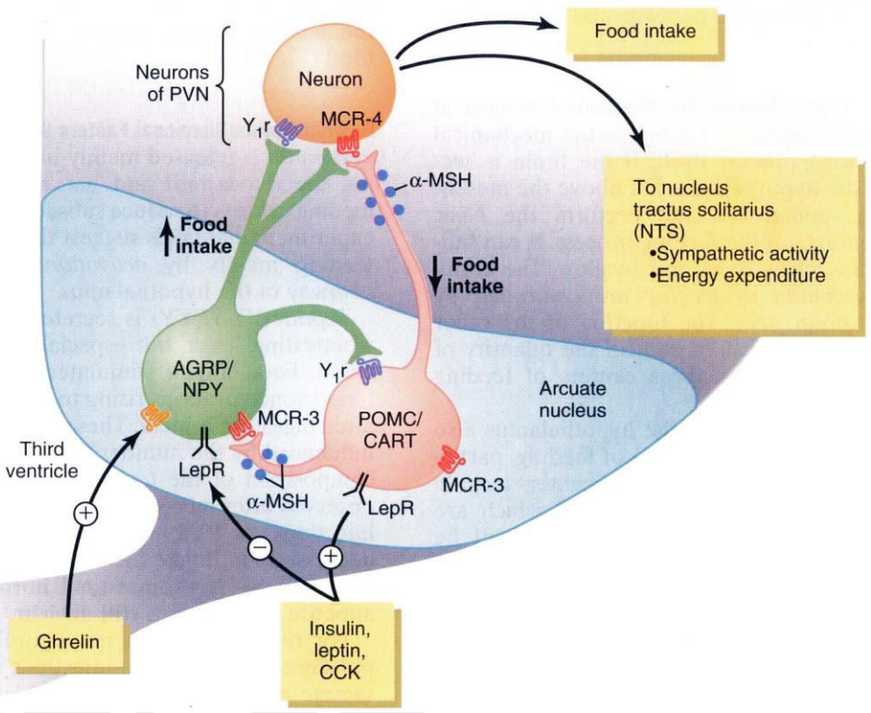
Amino acids. The 10 *essential* amino acids cannot be synthesized in sufficient quantities in the body; these essential amino acids must be obtained, already formed, from food.



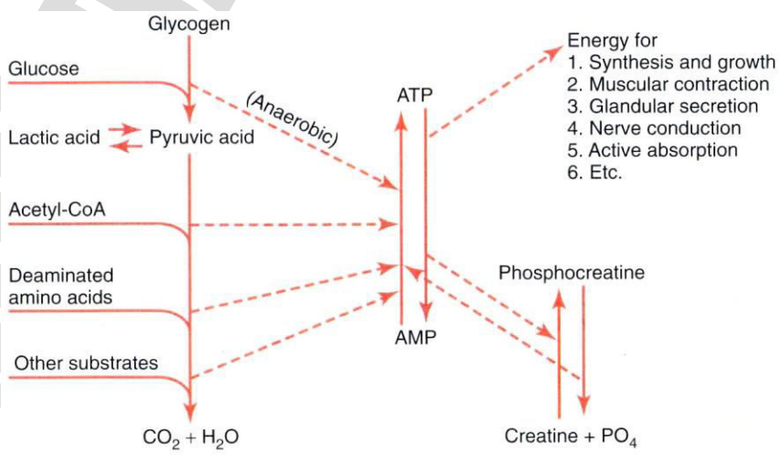
Synthesis of alanine from pyruvic acid by transamination.

Neurotransmitters and Hormones That Influence Feeding and Satiety Centers in the Hypothalamus

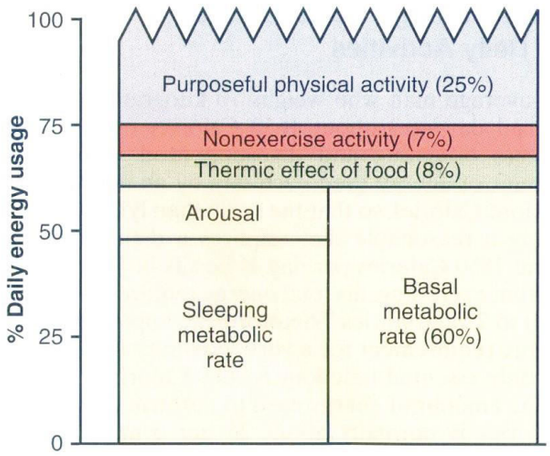
Decrease Feeding (Anorexigenic)	Increase Feeding (Orexigenic)
α-Melanocyte-stimulating hormone (α-MSH)	Neuropeptide Y (NPY)
Leptin	Agouti-related protein (AGRP)
Serotonin	Melanin-concentrating hormone (MCH)
Norepinephrine	Orexins A and B
Corticotropin-releasing hormone	Endorphins
Insulin	Galanin (GAL)
Cholecystokinin (CCK)	Amino acids (glutamate and γ-aminobutyric acid)
Glucagon-like peptide (GLP)	Cortisol
Cocaine- and amphetamine-regulated transcript (CART)	Ghrelin
Peptide YY (PYY)	



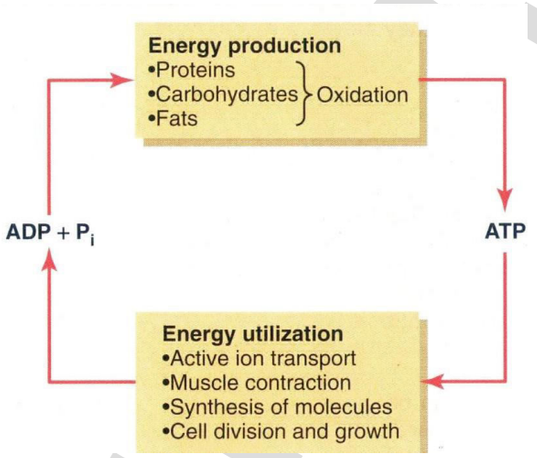
Control of energy balance by two types of neurons of the acute nuclei: (1) pro-opiomelanocortin (POMC) neurons that release α-melanocyte-stimulating hormone (α-MSH) and cocaine- and amphetamine-regulated transcript (CART), decreasing food intake and increasing energy expenditure; And (2) neurons that produce agouti-related protein (AGRP) and neuropeptide Y (NPY), increasing food intake and reducing energy expenditure. A-MSH released by POMC neurons stimulates melanocortin receptors (MCR-3 and MCR-4) in the paraventricular nuclei (PVN), which then activate neuronal pathways that project to the nucleus tractus solitarius (NTS) and increase sympathetic activity and energy expenditure. AGRP acts as an antagonist of MCR-4). Insulin, leptin, and cholecystokinin (CCK) are hormones that inhibit AGRP-NPY neurons and stimulate adjacent POMC-CART neurons, thereby reducing food intake. Ghrelin, a hormone secreted from the stomach, activates AGRP-NPY neurons and stimulates food intake. LepR, leptin receptor; Y_1R, neuropeptide Y1 receptor.



Overall schema of energy transfer from foods to the adenylic acid system and then to the functional elements of the cells.



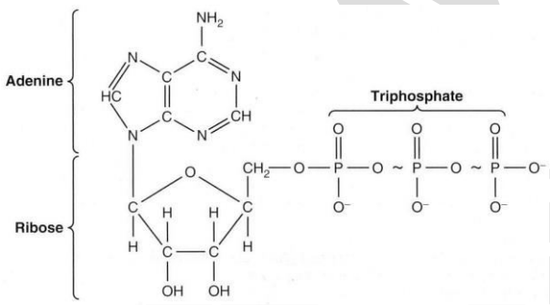
Components of energy expenditure.



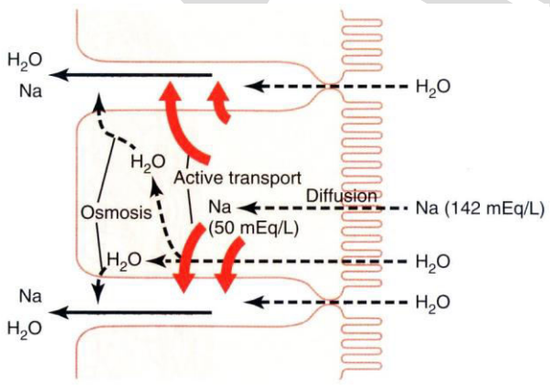
Adenosine triphosphate (ATP) as the central link between energy-producing and energy-utilizing systems of the body. ADP, adenosine diphosphate; P_i, inorganic phosphate.

XV. METABOLISM

ATP and Energy Production

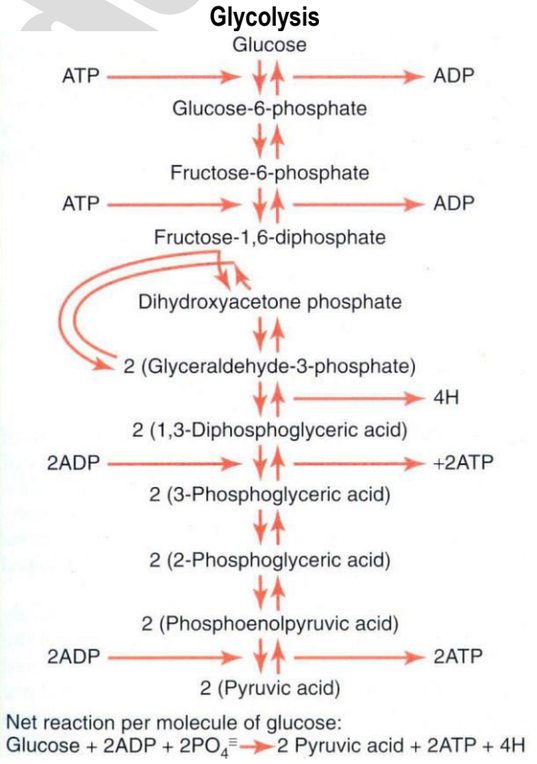


Chemical structure of adenosine triphosphate (ATP).



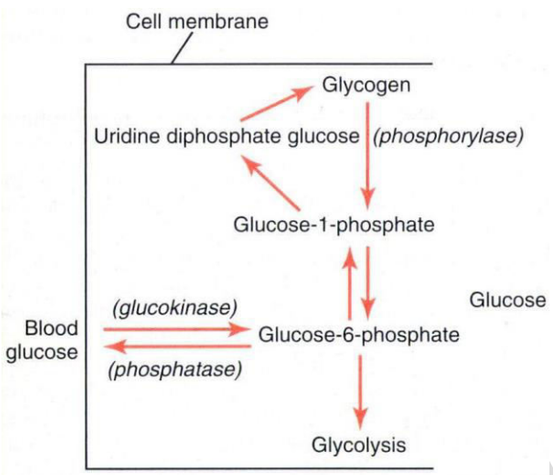
Absorption of sodium through the intestinal epithelium. Note also osmotic absorption of water – that is, water "follows" sodium through the epithelial membrane.

Glycolysis

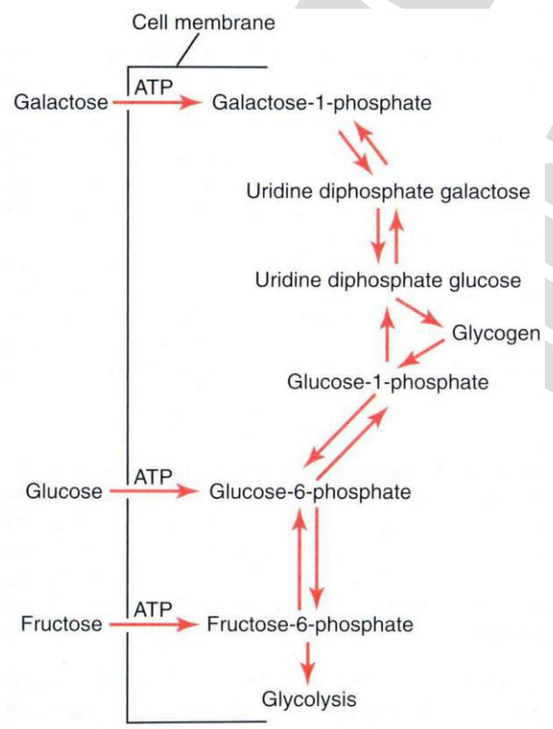


Sequence of chemical reactions responsible for glycolysis.

Glycogenesis and Glycogenolysis

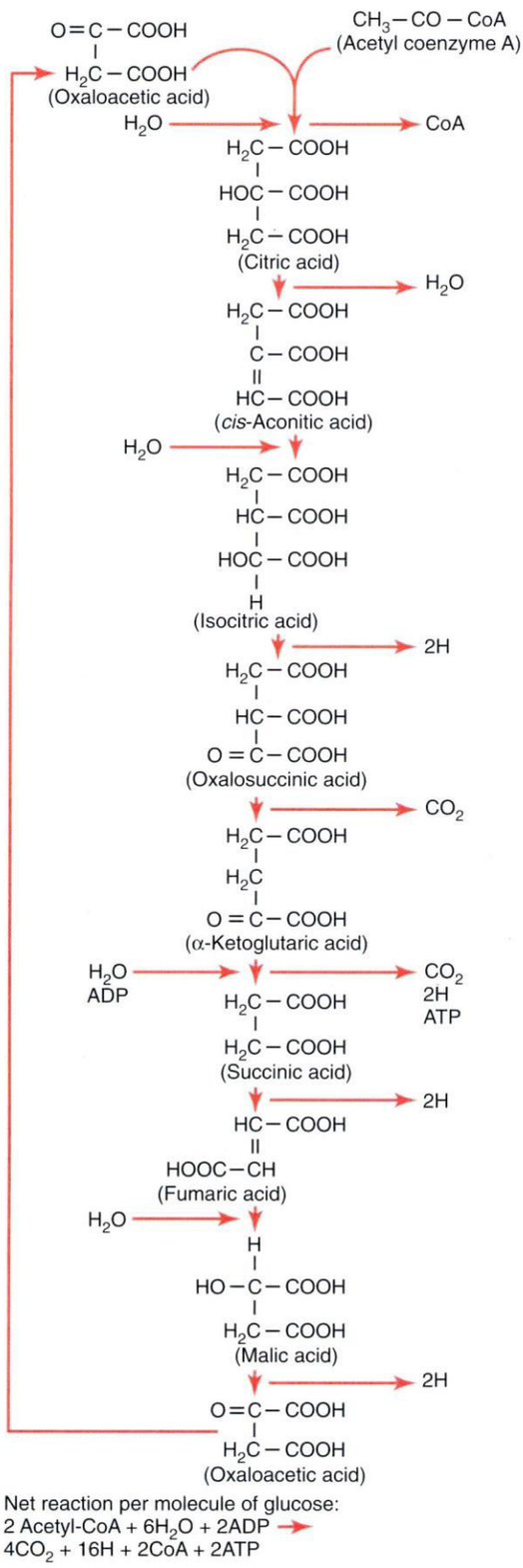


Chemical reactions of glycogenesis and glycogenolysis, showing also interconversions between blood glucose and liver glycogen. (The phosphatase required for the release of glucose from the cell is present in liver cells, but not in most other cells.)



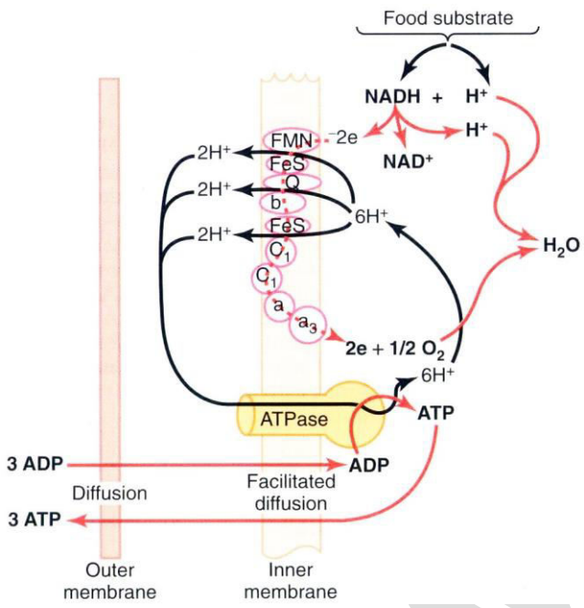
Interconversions of the three major monosaccharides – glucose, fructose, and galactose – in liver cells.

Kreb Cycle



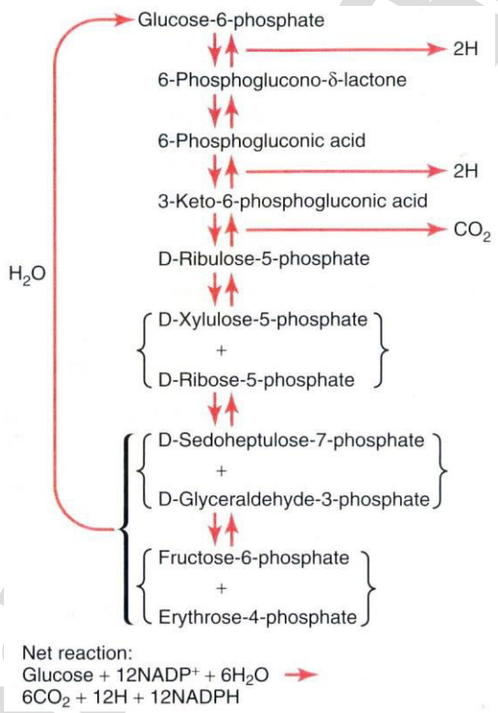
Net reaction per molecule of glucose:
$2\ \text{Acetyl-CoA} + 6H_2O + 2ADP \rightarrow 4CO_2 + 16H + 2CoA + 2ATP$

Chemical reactions of the citric acid cycle, showing the release of carbon dioxide and a number of hydrogen atoms during the cycle.



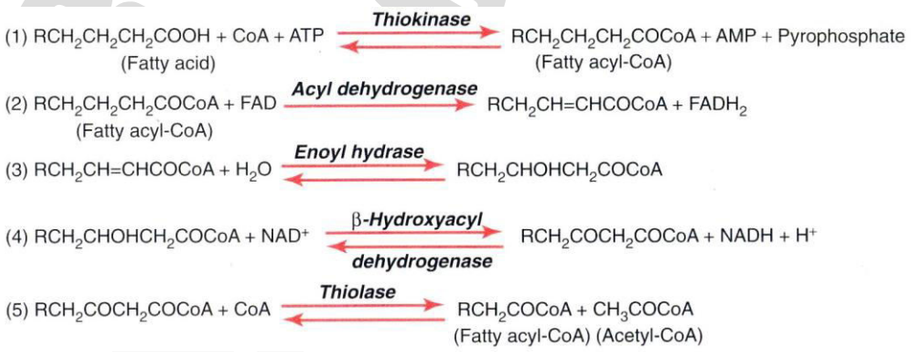
Mitochondrial chemiosmotic mechanism of oxidative phosphorylation for forming large quantities of ATP. This figure shows the relationship of the oxidative and phosphorylation steps at the outer and inner membranes of the mitochondrion.

Pentose Phosphate Pathway

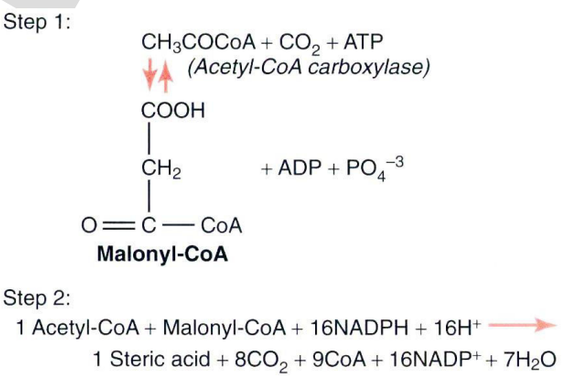


Pentose phosphate pathway for glucose metabolism.

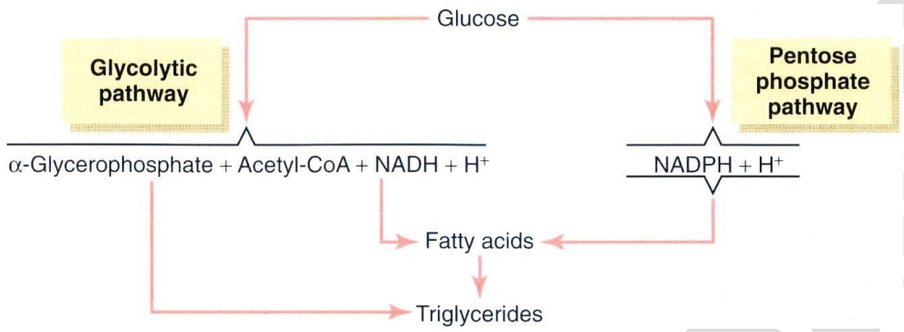
Beta-Oxidation and Synthesis of Fats



Beta-oxidation of fatty acids to yield acetyl coenzyme A.



Synthesis of fatty acids.



Overall schema for synthesis of triglycerides from glucose.

XVI. ENDOCRINOLOGY

Hormones - substances that are secreted by endocrine glands causing chemical adjustments throughout the body.

Chemical messenger- any substance produced by a cell of endogenous or exogenous origin that plays a physiological role in the control of the activity of another cell.

Routes of Delivery

Hormone delivery is by several routes:

1. Endocrine – released by endocrine cells into the blood
2. Neurocrine - neuron contacts its target cells by axonal extensions causing released hormone into a synaptic cleft between the two cells
3. Neuroendocrine - hormone released by a nerve in the blood
4. Paracrine - hormone diffuses to its adjacent target cells through the immediate extracellular space
5. Lumonal - hormone is released into the lumen of the gut
6. Pheromonal route - hormone is released into the environment
7. Autocrine - once released, hormone may feed back on the cell of origin

Classification of Hormones

Protein Hormones

- building blocks are amino acids
- production is dependent on the proper substrate, presence of an energy supply and necessary biological stimulation
- after production by a particular gland, the peptide hormones are usually stored within the gland until needed; they are then secreted into the efferent capillaries
- circulate in the blood in free form

- Steroid Hormones
  - building block is acetate leading to cholesterol with delicate alterations determining which steroid is finally released
  - cholesterol synthesis is mainly in the liver but appreciable amounts ore formed in the intestine
  - steroid hormones are not stored but are released as produced
  - circulate in the blood bound to specific carrier proteins

Tyrosine derivatives - account for about 5 % of mammalian hormones

Two types -

a. catecholamines secreted by the adrenal medulla (adreno-medullary hormones share similar mechanism of action of polypeptide hormones)
b. iodothyronines more closely resemble steroid hormones

Eicosanoid Hormones

- derived from polyunsaturated fatty acids with 20 carbon atom
- major precursor is arachidonate and are produced exclusively within the plasma membrane of cells.

Mechanism of Hormone Secretion

1. General principles

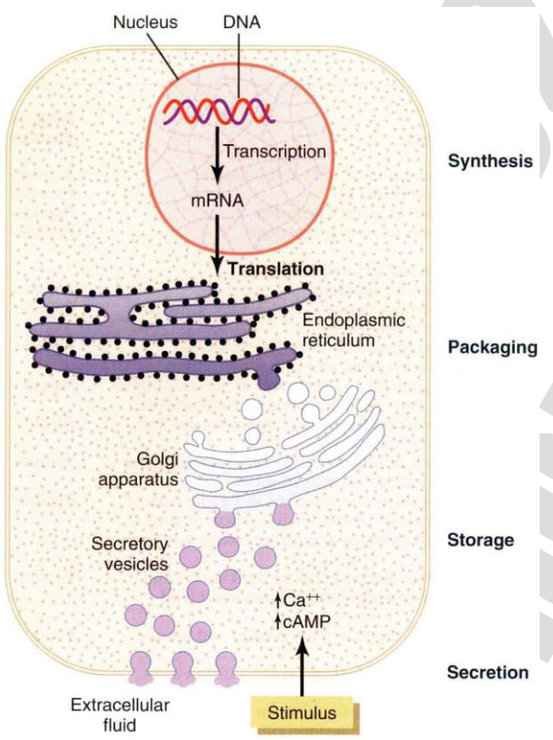
target cell - specific cells that respond to the presence of particular hormones due to the presence of specific receptor sites

receptors - molecular components of cells that provide the specificity for hormone-cell interaction.

- they provide the means by which hormones initially react with the cells
- receptors recognize differences in hormone structure and thus provide receptor specificity

- hormone receptors possess a recognition function that must then be converted to an action function
- receptor number is in a continuous state of change, usually with the change in state of cellular development or differentiation
- hormones may regulate the number of their own or other receptors

2. Peptide Hormone Action
   - peptide hormones are large and don't pass through the plasma membrane
   - they exert their action initially on the surface of the target cell



Synthesis and secretion of peptide hormones. The stimulus for hormone secretion often involves changes in intracellular calcium or changes in cyclic adenosine monophosphate (cAMP) in the cell.

3. Steroid and Thyroid Hormone Action
- Steroid and thyroid hormones ore small molecules (about MW 3(X)) that diffuse freely into most cells of the body
- it is most likely that these hormones enter all cells but only manifest their action in those which possess receptors
- their primary effect is on gene expression rather than on enzyme activities or transport processes
- primary site of action is in the cell nucleus rather than on the plasma membrane
- full impact is achieved in hours rather than minutes because their biological effects depend on the synthesis of new proteins

Some Hormones That Use the Adenylyl Cyclase–cAMP Second Messenger System

Adrenocorticotropic hormone (ACTH)
Angiotensin II (epithelial cells)
Calcitonin
Catecholamines (β receptors)
Corticotropin-releasing hormone (CRH)
Follicle-stimulating hormone (FSH)
Glucagon
Human chorionic gonadotropin (HCG)
Luteinizing hormone (LH)
Parathyroid hormone (PTH)
Secretin
Somatostatin
Thyroid-stimulating hormone (TSH)
Vasopressin (V_2 receptor, epithelial cells)

Hypothalamic Hormones

hypothalamic nuclei - clusters of neurons symmetrically located around the third ventricle whose axons extend into the median eminence and into the neurohypophysis

- Many of the hypothalamic hormones (TRH, CRH, somatostatin) are found in other portions of the nervous system and in different peripheral tissues.
- They are released in a pulsatile manner

1. Releasing Hormones

a. Thyrotropin Releasing Hormone (TRH)
   - the ability of TRH to stimulate TSH release appears to be restricted to homeotherms
   - the presence of TRH in the brain does not necessarily restrict its role to TSH secretion and thyroid function it also stimulates release of PRL in humans, cattle, sheep and rats

b, Somatocrinin (Growth Hormone Releasing Hormone, GHRH or GRH)
   - there is a high degree of sequence similarity in the first 29 residues of somatocrinin from different species

c. Gonadotropin Releasing Hormone (GnRH)
   - all GnRH structures in vertebrates are decapeptides

d. Corticotropin Releasing Hormone (CRH)

e. Prolactin Releasing Factor (PRF)
   - TRH is a potent stimulus to PRL secretion but it is unclear whether TRH is the physiological PRF

2. Release-Inhibiting Hormones

a. Somatostatin (Somatotropin Release Inhibiting Hormone, SRIH)
   - episodic secretion of STH by pituitary is the net result of a delicate interplay
     - between STH releasing factor and STH release inhibiting hormone
     - inhibits secretion of GH, TSH, ACTH, gastrin, cholecystokinin (CCK), glucagon, insulin, rennin
     - inhibits secretion of gastric juice, emptying of stomach and platelet aggregation
     - diminishes the production and transmission of nerve impulses.

b. Prolactin Release' Inhibiting Factor (PIP)
   - evidence is overwhelming that PIP is dopamine

c. MSH Release Inhibiting Factor (PIF)
   - evidence suggest that dopamine is the physiological MIF

Pituitary Hormones

- Adenohypophysis- an upgrowth of glandular tissue from the pharynx
  - dependent upon humoral connection with the hypothalamus
  - secretory granules are unique to endocrine cells synthesizing polypeptide and catecholamine hormones and provide a mechanism for intracellular storage of substantial amounts of preformed hormone
  - when signal for hormone is given, secretory granules are directed to the periphery of the endocrine cell and granule core is extruded out by exocytosis
  - granule core is fragmented and rapidly transported into circulation
  - excess hormone is degraded by fusion of hormone containing granules with Lysosomes
  - Non-granulated, presumably non -secretory cells are also present in the pars distal is, pars intermedia and neurohypophysis.

- neurohypophysis - a downgrowth of nervous tissue from the brain
  - hormones released by neurohypophysis are synthesized by the cells of the hypothalamus and migrate along nerve fibers to the posterior pituitary where they are stored in the nerve endings until released
  - composed of secretory cells coiled pituicytes and nerve fibers which arise from cells in the hypothalamus

1. Adenohypophyseal Hormones

a. Somatotropin and Prolactin

1. Somatotropin (Growth Hormone, GH, 5TH)
   - synthesized by acidophils (somatotrophs) of pars distalis
   - release is stimulated by GHRH, inhibited by GHRII-l (somatostatin)
   - circulates in the plasma complexes to one or more binding proteins
   - complete protein molecule is not necessary for STH activity
   - essential for post-natal growth and for normal carbohydrate, lipid, nitrogen and mineral metabolism
   - effects promote growth of skeleton and organs as kidneys, livers, intestines, pancreas, and adrenal glands
   - absence of STH leads to dwarfism in the younq while overproduction leads to gigantism, in the adult, excess STH leads to acromegaly
   - human STH made by recombinant DNA techniques is now available for therapeutic use but is expensive and has some adverse side effects

2. Prolactin (PRL)
   - there is evidence for the existence of a prolactin releasing factor from the hypothalamus
   - secretion is inhibited by prolactin release inhibiting factor
   - the mammotropic action of PRL requires the participation of severalhormones including estrogens, cortocosteroids, insulin, thyroxine, progesterone and STH

b. Glycoprotein Hormones

1. Thyrotropin (TSH)
   - synthesized by bosophilic thyrotrophs of the pars distalis
   - release is stimulated by TRH from hypothalamus
   - stimulates growth and activity of thyroid gland
   - in the amphibian, is responsible for inducing metamorphosis
   - in the mammal, clays an important role in thermogenesis

2. Gonadotropins (gonadotrophic hormones) FSH & LH
   - released in response to gonadotropin releasing hormone (GnRH) from the hypothalamus
   - FSH stimulates development and ripening of ovarian follicle
   - LH promotes final maturation of ovarian follicle and ovulation promotes formation of the corpus luteum
   - as levels of estrogen, secreted by developing ovarian follicle, increases in the blood, FSH secretion is reduced as

levels of progesterone, which is secreted by the corpus lutetium increases
- in the male, FSH stimulates spermatozoa production
- LH (called interstitial cell stimulating hormone, ICSH) stimulates secretion of testosterone

c. Pro-opiomelanocortin (POMG) peptide family

1. Corticotrophin (ACTH)
- synthesized within basophils of pars distalis but corticotroph cells are often chromophobic
- is a single chain polypeptide of 39 amino acids
- regulates growth and function of adrenal cortex
- ACTH has melanotropic activity because the first 13 amino acids are similar to those comprising alpha MSH, excessive ACTH leads to hyperpigmentation

2. Neurohypophyseal Hormones
- ADH is synthesized in the supraoptic nucleus, oxytocin in the paraventricular nucleus, both are part of the hypothalamus
- they are secreted separately into the blood stream together with their appropriate neurophysins
- they circulate unbound to proteins and have very short plasma half-lives
- primarily metabolized in the liver

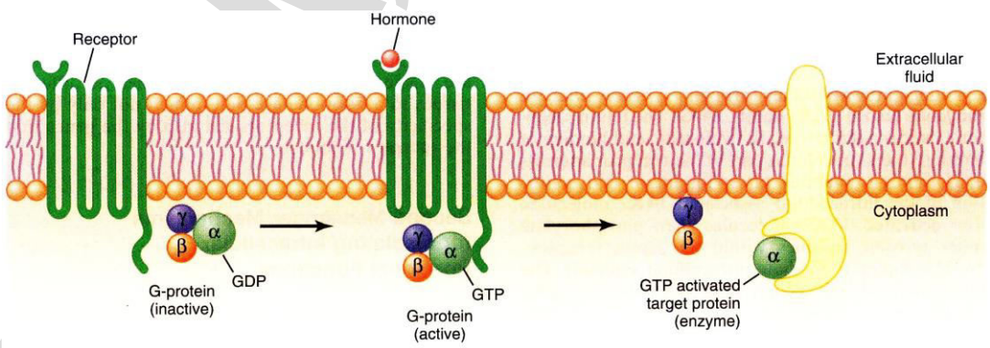
a. Oxytocin
- Plays a role in stimulating milk release from the mammary gland and stimulating uterine contraction at term

b. Antidiuretic Hormone (ADH, vasopressin)
- primary physiologic stimulus for its release is increased osmolality of plasma
- target cells of ADH in mammals are those of the distal convoluted tubules and collecting structures of the kidney which are relatively impermeable to water

3. Pars Intermedia Hormone
- re!atively avascular but an extravascular, multibranched transport system penetrates the parenchyma of pars intermedia.

a. Melanocyte Stimulating Hormone (αMSH, α-melanotropin)

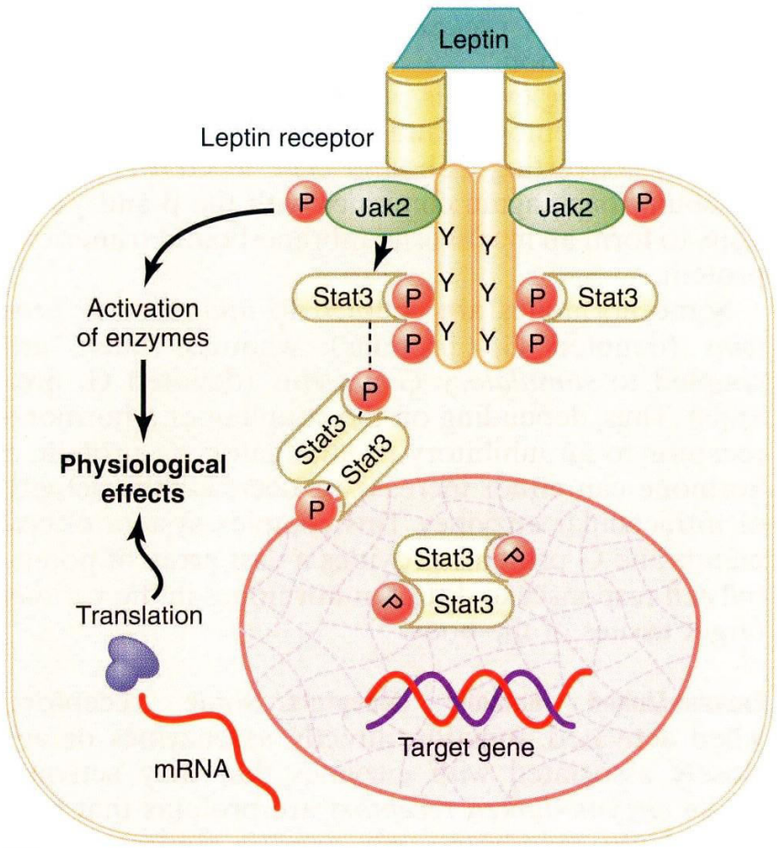
-secretion is inhibited by MSH release inhibiting factor (MIF)
-melanotropins enhance melanin production within melanocytes resulting in darkening of the skin
-melanin produced within the melanocytes is released into surrounding cells of the skin
-seasonal alterations in pigment cell melanogenic activity are an important aspect of an animal's ability to conform to yearly change in environmental conditions
-dermal chromatophore unit a functional unit containing the three chromatophore types present in poikilotherms (xanthopores, iridophores, and melanophores)



Mechanism of activation of a G protein-coupled receptor. When the hormone activates the receptor, the inactive α, ß, and γ G protein complex associates with the receptor and is activated, with an exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP). This causes the α subunit (to which the GTP is bound) to dissociate from the ß and γ subunits of the G protein and to interact with membrane-bound target proteins (enzymes) that initiate intracellular signals.

Comparison of Endocrine and Nervous System Characteristics

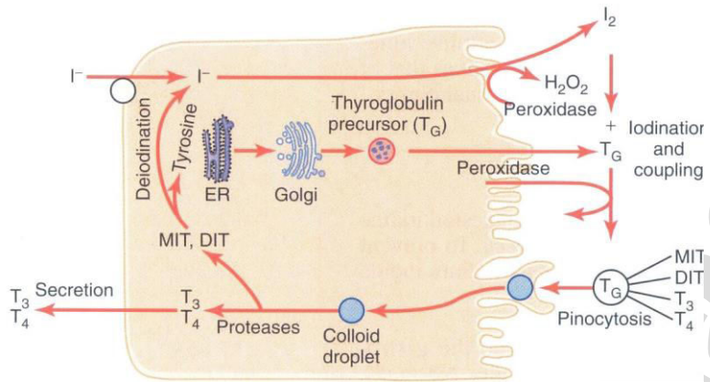
Characteristic	Endocrine System	Nervous System
General function	Regulation of body functions to maintain homeostasis	Regulation of body functions to maintain homeostasis
Reaction to stimuli	Slow	Fast
Duration of effects	Long	Short
Target tissues	Virtually all body cells and tissues	Muscle and glandular tissues
Chemical messenger	Hormone	Neurotransmitter
Messenger producing cells	Endocrine gland cells or modified neurons	Neurons
Distance from chemical message production to target	Long (via bloodstream)	Short (across synaptic space)



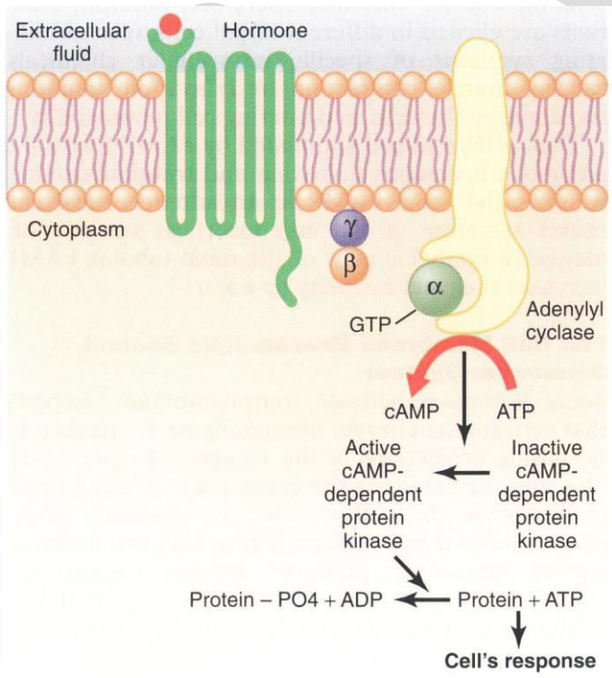
An enzyme-linked receptor – the leptin receptor. The receptor exists as a homodimer (two identical parts), and leptin binds to the extracellular part of the receptor, causing phosphorylation and activation of the intracellular associated janus kinase 2 (JAK2). This causes phosphorylation of signal transducer and activator of transcription (STAT) proteins, which then activates the transcription of target genes and the synthesis of proteins. JAK2 phosphorylation also activates several other enzyme systems that moderate some of the more rapid effects of leptin.

Endocrine Glands, Hormones, and Their Functions and Structure

Gland/Tissue	Hormones	Major Functions	Chemical Structure
Hypothalamus	Thyrotropin-releasing hormone (TRH)	Stimulates secretion of TSH and prolactin	Peptide
	Corticotropin-releasing hormone (CRH)	Causes release of ACTH	Peptide
	Growth hormone–releasing hormone (GHRH)	Causes release of growth hormone	Peptide
	Growth hormone inhibitory hormone (GHIH) (somatostatin)	Inhibits release of growth hormone	Peptide
	Gonadotropin-releasing hormone (GnRH)	Causes release of LH and FSH	
	Dopamine or prolactin-inhibiting factor (PIF)	Inhibits release of prolactin	Amine
Anterior pituitary	Growth hormone	Stimulates protein synthesis and overall growth of most cells and tissues	Peptide
	Thyroid-stimulating hormone (TSH)	Stimulates synthesis and secretion of thyroid hormones (thyroxine and triiodothyronine)	Peptide
	Adrenocorticotropic hormone (ACTH)	Stimulates synthesis and secretion of adrenocortical hormones (cortisol, androgens, and aldosterone)	Peptide
	Prolactin	Promotes development of the female breasts and secretion of milk	Peptide
	Follicle-stimulating hormone (FSH)	Causes growth of follicles in the ovaries and sperm maturation in Sertoli cells of testes	Peptide
	Luteinizing hormone (LH)	Stimulates testosterone synthesis in Leydig cells of testes; stimulates ovulation, formation of corpus luteum, and estrogen and progesterone synthesis in ovaries	Peptide
Posterior pituitary	Antidiuretic hormone (ADH) (also called vasopressin)	Increases water reabsorption by the kidneys and causes vasoconstriction and increased blood pressure	Peptide
	Oxytocin	Stimulates milk ejection from breasts and uterine contractions	Peptide
Thyroid	Thyroxine (T_4) and triiodothyronine (T_3)	Increases the rates of chemical reactions in most cells, thus increasing body metabolic rate	Amine
	Calcitonin	Promotes deposition of calcium in the bones and decreases extracellular fluid calcium ion concentration	Peptide
Adrenal cortex	Cortisol	Has multiple metabolic functions for controlling metabolism of proteins, carbohydrates, and fats; also has anti-inflammatory effects	Steroid
	Aldosterone	Increases renal sodium reabsorption, potassium secretion, and hydrogen ion secretion	Steroid
Adrenal medulla	Norepinephrine, epinephrine	Same effects as sympathetic stimulation	Amine
Pancreas	Insulin (β cells)	Promotes glucose entry in many cells, and in this way controls carbohydrate metabolism	Peptide
	Glucagon (α cells)	Increases synthesis and release of glucose from the liver into the body fluids	Peptide
Parathyroid	Parathyroid hormone (PTH)	Controls serum calcium ion concentration by increasing calcium absorption by the gut and kidneys and releasing calcium from bones	Peptide
Testes	Testosterone	Promotes development of male reproductive system and male secondary sexual characteristics	Steroid
Ovaries	Estrogens	Promotes growth and development of female reproductive system, female breasts, and female secondary sexual characteristics	Steroid
	Progesterone	Stimulates secretion of "uterine milk" by the uterine endometrial glands and promotes development of secretory apparatus of breasts	Steroid
Placenta	Human chorionic gonadotropin (HCG)	Promotes growth of corpus luteum and secretion of estrogens and progesterone by corpus luteum	Peptide
	Human somatomammotropin	Probably helps promote development of some fetal tissues as well as the mother's breasts	Peptide
	Estrogens	See actions of estrogens from ovaries	Steroid
	Progesterone	See actions of progesterone from ovaries	Steroid
Kidney	Renin	Catalyzes conversion of angiotensinogen to angiotensin I (acts as an enzyme)	Peptide
	1,25-Dihydroxycholecalciferol	Increases intestinal absorption of calcium and bone mineralization	Steroid
	Erythropoietin	Increases erythrocyte production	Peptide
Heart	Atrial natriuretic peptide (ANP)	Increases sodium excretion by kidneys, reduces blood pressure	Peptide
Stomach	Gastrin	Stimulates HCl secretion by parietal cells	Peptide
Small intestine	Secretin	Stimulates pancreatic acinar cells to release bicarbonate and water	Peptide
	Cholecystokinin (CCK)	Stimulates gallbladder contraction and release of pancreatic enzymes	Peptide
Adipocytes	Leptin	Inhibits appetite, stimulates thermogenesis	Peptide



Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. MIT, monoiodotyrosine; DIT, diiodotyrosine; T_3, triiodothyronine; T_4, thyroxine; T_G, thyroglobulin.



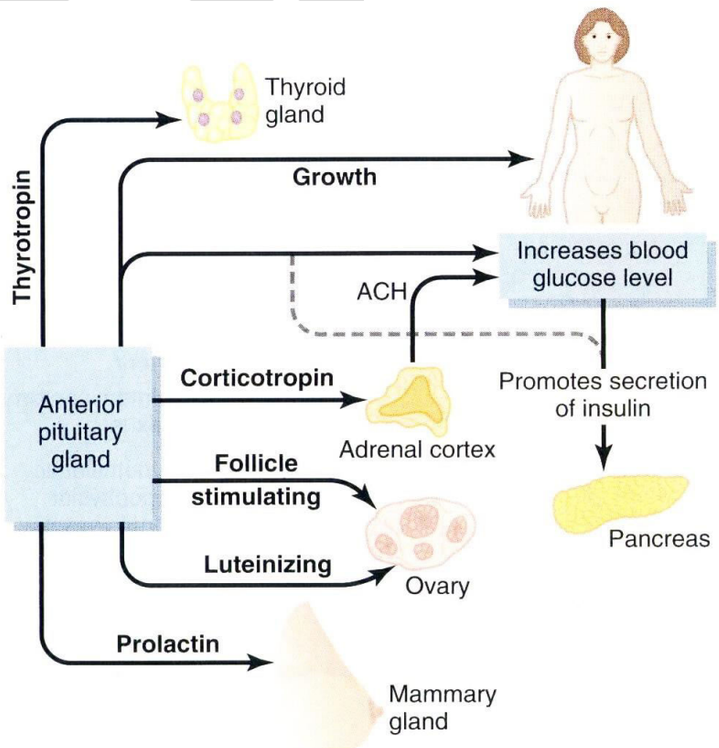
Cyclic adenosine monophosphate (cAMP) mechanism by which many hormones exert their control of cell function. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

Cells and Hormones of the Anterior Pituitary Gland and Their Physiological Functions

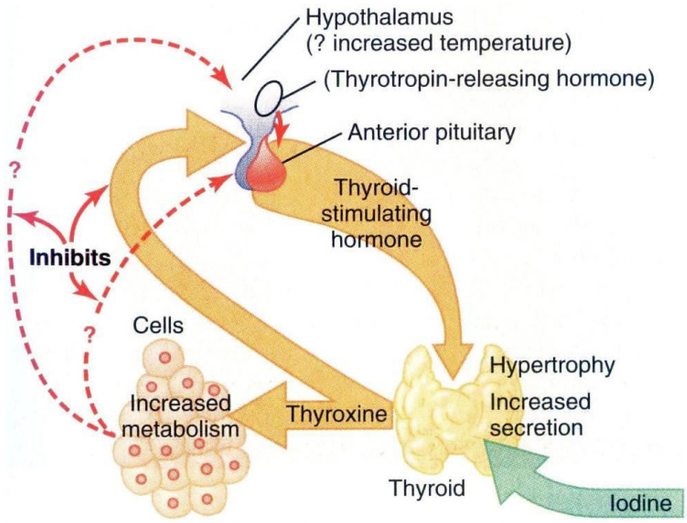
Cell	Hormone	Chemistry	Physiological Actions
Somatotropes	Growth hormone (GH; somatotropin)	Single chain of 191 amino acids	Stimulates body growth; stimulates secretion of IGF-1; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotropic hormone (ACTH; corticotropin)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (TSH; thyrotropin)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
	Luteinizing hormone (LH)	Glycoprotein of two subunits, α (89 amino acids) and β (115 amino acids)	Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes, Mammotropes	Prolactin (PRL)	Single chain of 198 amino acids	Stimulates milk secretion and production
IGF, insulin-like growth factor			

Major Endocrine Glands

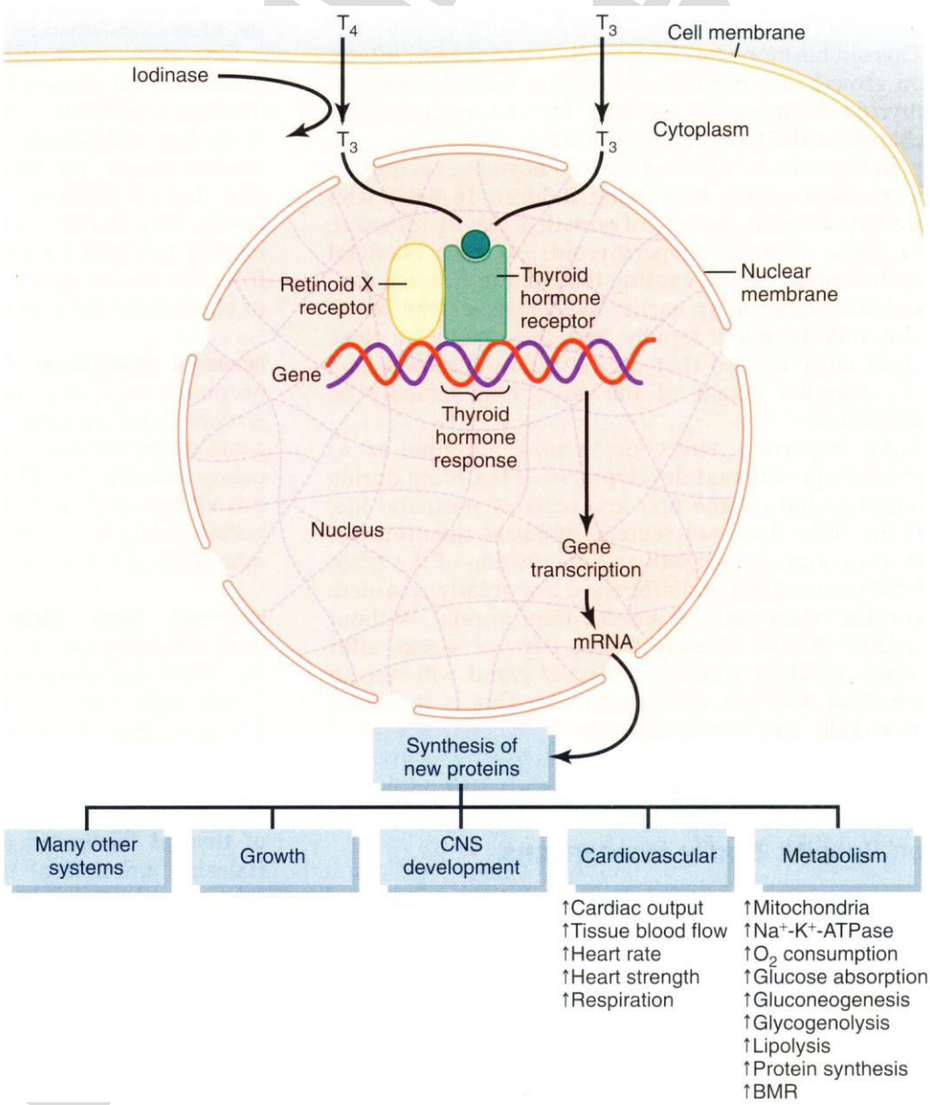
Gland	Hormone	Target	Action
Anterior pituitary	Growth hormone	All body cells	Growth, metabolic regulation
	Prolactin	Female—mammary gland	Lactation
		Male—no known effect	None
	Thyroid-stimulating hormone	Thyroid gland	Thyroid hormone production
	Adrenocorticotropic hormone	Adrenal cortex	Adrenal cortical hormone production
	Follicle-stimulating hormone	Female—ovary (follicles)	Oogenesis
		Male—testis (seminiferous tubules)	Spermatogenesis
	Luteinizing hormone	Female—ovary (follicle/corpus luteum)	Ovulation and corpus luteum production
		Male—testis (interstitial cells)	Testosterone production
	Melanocyte-stimulating hormone	Unknown	Unknown
Posterior pituitary	Antidiuretic hormone	Kidney	Water conservation
	Oxytocin	Female—uterus	Contraction at parturition
		Mammary gland	Milk letdown
		Male—no known effect	No known effect
Thyroid	Thyroid hormone	All body cells	Growth, metabolic regulation
	Calcitonin	Bones	Prevents hypercalcemia
Parathyroid	Parathyroid hormone	Kidneys, intestines, bones	Prevents hypocalcemia
Adrenal cortex	Glucocorticoid hormones	Whole body	Increased blood glucose, blood pressure maintenance
	Mineralocorticoid hormones	Kidneys	Sodium and water retention, potassium elimination
	Sex hormones	Whole body	Minimal effects
Adrenal medulla	Epinephrine and norepinephrine	Whole body	Part of "fight or flight" response
Pancreas (islets)	Insulin	All body cells	Movement of glucose into cells and its use for energy
	Glucagon	Whole body	Increased blood glucose
Testis	Androgens	Whole body	Anabolic effect, development of male secondary sex characteristics
Ovary	Estrogens	Whole body	Preparation for breeding and pregnancy
	Progestins	Uterus	Preparation for and maintenance of pregnancy



Metabolic functions on the anterior pituitary hormones. ACH, adrenal corticosteroid hormones.



Regulation of thyroid secretion.



Thyroid hormone activation of target cells. T_4 and T_3 readily diffuse through the cell membrane. Much of the T_4 is deiodonated to form T_3, which interacts with the thyroid hormone receptor, bound as a heterodimer with a retinoid X receptor, of the thyroid hormone response element of the gene. This causes either increases or decreases in transcription of genes that lead to formation of proteins, thus producing the thyroid hormone response of the cell. The actions of thyroid hormone on cells of several different systems are shown. mRNA, messenger ribonucleic acid.

Gastrointestinal Hormones

- synthesized within a system of clear cells scattered within GI tract mucosa from stomach to colon (referred to as diffuse or dispersed endocrine system)
- clear cells - enterochromaffin-like (ECL) cells, in which one surface of ECL reaches the lumen providing a receptive surface for metabolic recognition
- ECL cells are classified as derived from certain cell types designated as D (somatostatin), G (gastrin), S (secretin)

A. Gastrin Family

1. Gastrin
   - Present in the gastric juice making it available in the luminal surface and basal surface
   - Peptide fragments, amino acids and to a lesser extent, free FA's is primary physiological stimulus for its secretion

Functions:

- Stimulate secretion of HCL and pepsinogen
- Regulates growth of mucosal cells of the stomach
- Causes stimulation of lower esophageal sphincter pressure and relaxation of pyloric sphincter

2. Cholecystokinin (CCK)
   - Stimulates pancreatic enzyme secretion and gallbladder contraction
   - Inhibits gastric emptying, stimulate secretin mediated pancreatic bicarbonate secretion

B. Secretin Family

1. Secretin
   - Secretion is stimulated by the presence of acidic chyme in the duodenal mucosa
   - stimulate pancreatic bicarbonate secretion

2. Gastric Inhibitory Peptide (GIP) Physiological functions:
   - inhibit gastric acid secretion and gastric emptying
   - has a synergistic action with insulin since GIP potentiates
   - stimulates intestinal juice secretion such as glucagon and Vasoactive intestinal peptide

3. Vasoactive Intestinal Peptide (VIP)
   - distributed throughout entire length of mammalian and avianintestinal tract (esophagus to colon) and pancreas
   - causes yasodilation and has hypotensive effects causing smooth muscles relaxation
   - antagonized the effects of constrictor agents in the small intestine

Thyroid and Parathyroid Hormones

A. Thyroid Hormone

1. Triiodothyronine (T3) and thyroxine (T4)

Extracellular synthesis of hormones occurs within the follicular lumen, and complexed with iodide by covalent bonds

follicular cells trap iodide at the base of the cell and transported by secondary active transport

iodide is then converted by a peroxidase to oxidized iodide at the luminal surface

oxidized iodide is incorporated into tyrosyl groups of thyroglobulin as monoiodotyrosine and diiodotyrosine residues

In the thyroglobulin iodinoted tyrosines undergo oxidation that results in formation of T4 and smaller amounts of T3

Colloid is engulfed by follicular cell pseudopods and transported into the cells as colloid droplets

Thyroglobulin is degraded and hormones are released into the cytoplasm and extracellular space by diffusion

Thyroglobulin, T3 and T4 are secreted into circulation

iodinated tyrosines are deiodinated and recycled for use within the cell

require specific binding proteins in the plasma and in the cell cytosol to gain access to nuclear receptors that is synthesized in liver

binds to specific thyroid hormone receptor genes called thyroid hormone receptor β and thyroid hormone receptor α.

circulating T4 and T3 penetrates cell membrane by an energy-dependent process

the actions of the thyroid hormones on the plasma membrane and mitochondria are rapidly initiated events that control increased heart rates, oxygen consumption and ATP production

Its effects is primarily on:

- In growth and development - required both for the production of STH and for its systemic actions. Required for the normal development of the brain and together with prolactin play an Important role in the development mammary gland
- Thermogenesis - stimulate mitochondrial oxygen consumption and production of ATP

3. Permissive actions -required for the actions of other hormones
   - Diet - the production of T3 is increased during short-term overfeeding
   - thyroid hormones inhibit TSH secretion at pituitary and hypothalamic levels

- thyroid secretion is stimulated by lowered ambient temperature

2. Calcitonin

- secretion is stimulated by perfusion of hypercalcemic blood to the thyroid, estrogens and androgens, gastrin, cholecystoninin, secretin, glucagons, pentagastrin and cAMP (which is the second messenger controlling CT secretion)
- promotes bone mineral metabolism, vitamin D regulator and serves as satiety hormone

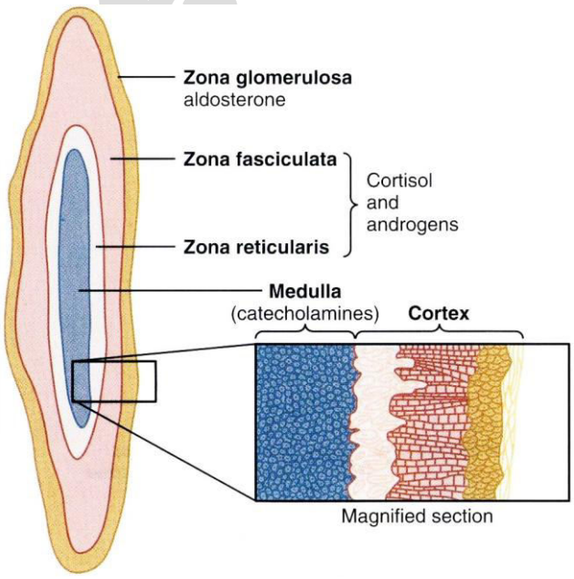
B. Parathyroid hormone / parathormone (PTH)

- secreted by parathyroid gland that is embedded on the surface of the thyroid gland
- degraded and metabolize primarily in the kidney
- its release is controlled by circulating levels of Ca~
- vitamin D is inhibitory to PTH secretion
- Its effect is primarily exerted on bone metabolism
- In the kidneys it causes increase renal tubular reabsorption of calcium and renal excretion of $P0_4^3$, enhances ionization of plasma calcium and Mg^4 reabsorption and inhibits exchange of H for Na ions by the tubules
  - It enhances intestinal uptake of calcium which is mediated indirectly through its effect on vitamin D metabolism

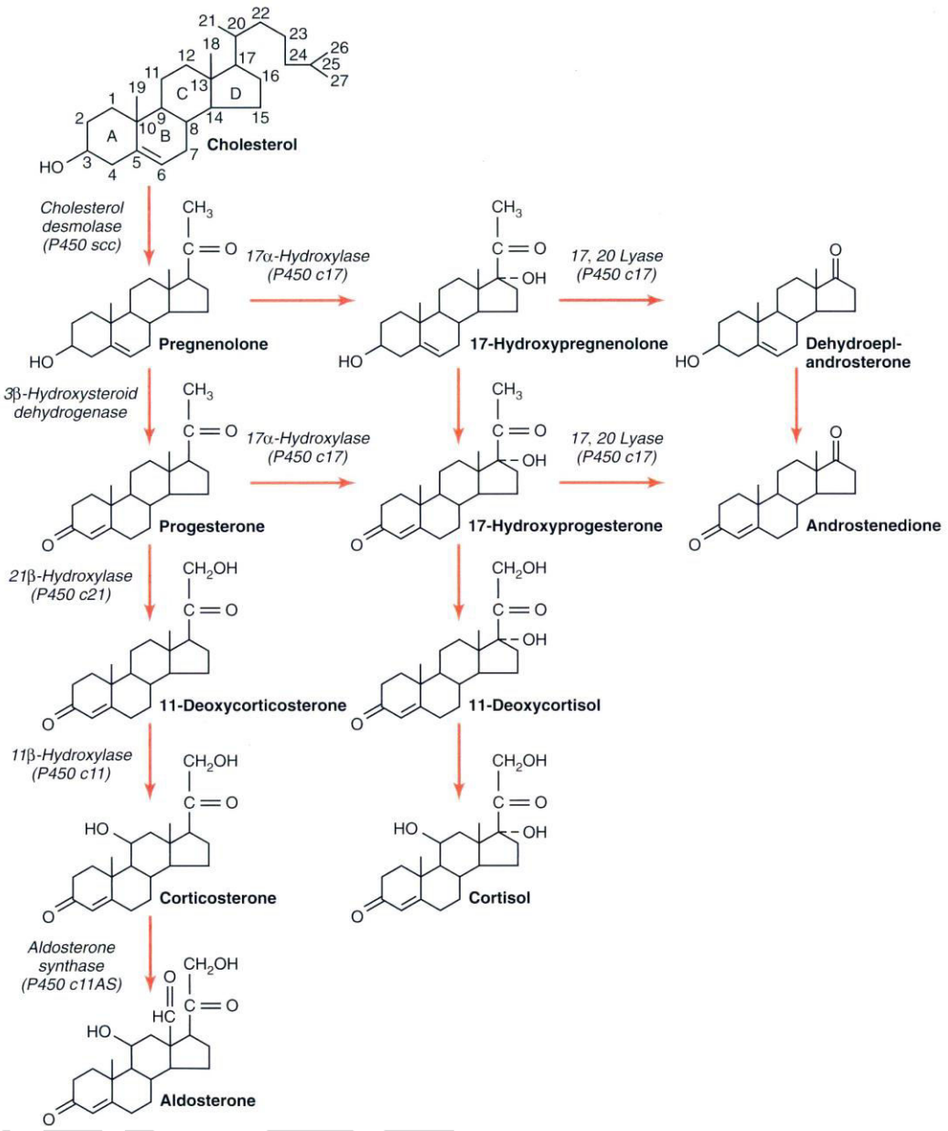
C. Calcium Homeostasis

1. Calcium
   - plasma Ca^{++} concentration is maintained within very narrow limits to ensure normal processes operate
   - most of the calcium in the body is in the skeletal system

- Vitamin D
- A 2 fat-soluble substances called *cholecalciferol* (vitamin D3) and eigocalciferol (vitamin D2)
- these metabolites mediate their actions on a number of target tissues and in its absence causes bones to fail mineralization
- Calcitonin inhibits the actions of the two hormones on osteoclasts but not on osteoblasts
- Parathormone and vitamin D activate similar cellular processes
- It increases Ca^{++} absorption from the intestine and causes translocation of PO_4^{-3} across the gut epithelium
- It causes demineralization to provide calcium and possible PO_4^3, thus maintaining the critical plasma levels of these ions
- 1,25-dihydroxycholecalciferol stimulates tubular reabsorption of Ca^{++} in the kidney and interacts with target-tissue nuclear receptors to activate transcriptional and translational processes



Secretion of adrenocortical hormone by different zones of the adrenal cortex and secretion of catecholamines by the adrenal medulla.



Pathways for synthesis of steroid hormones by the adrenal cortex. The enzymes are shown in italics.

Adrenal Steroid Hormones in Adults; Synthetic Steroids and Their Relative Glucocorticoid and Mineralocorticoid Activities

Steroids	Average Plasma Concentration (free and bound, µg/100 ml)	Average Amount Secreted (mg/24 hr)	Glucocorticoid Activity	Mineralocorticoid Activity
Adrenal Steroids				
Cortisol	12	15	1	1
Corticosterone	0.4	3	0.3	15.0
Aldosterone	0.006	0.15	0.3	3000
Deoxycorticosterone	0.006	0.2	0.2	100
Dehydroepiandrosterone	175	20	—	—
Synthetic Steroids				
Cortisone	—	—	1.0	1.0
Prednisolone	—	—	4	0.8
Methylprednisone	—	—	5	—
Dexamethasone	—	—	30	—
9α-fluorocortisol	—	—	10	125

Glucocorticoid and mineralocorticoid activities of the steroids are relative to cortisol, with cortisol being 1.0.

Adrenal Gland Hormones

Adrenal Glands

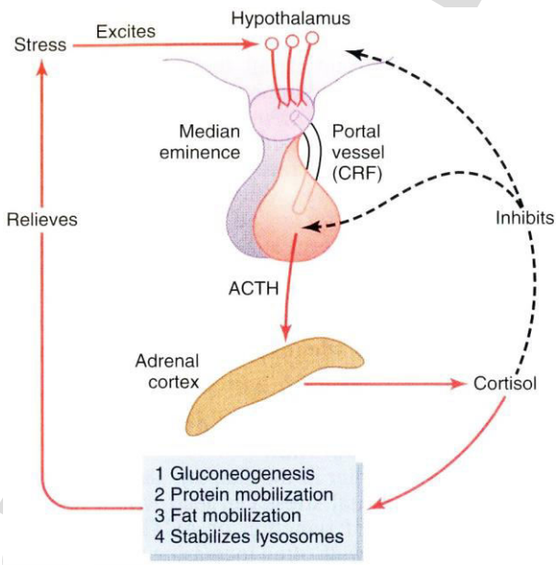
- composed of steroidogenic and chromaffin tissue that forms a cortical mass surrounding an inner medullary component of chromaffin tissue in many mammals
- all domestic animals have paired glands except for birds which have clusters of intermixed cortical and medullary tissue near the kidneys

A. Adrenal Cortex
- steroidogenic cells are filled with lipid droplets called *liposomes* that contains cholesterol
- mitochondria is abundant and smooth endoplasmic reticulum are well developed for hormone production
- associated with mineralocorticoids production specifically zona glomerulosa
- cholesterol a precursor in hormone production that is derived from plasma with a small portion synthesized in from acetyl CoA
- mammalian steroids are formed from cholesterol through a series of reactions occurring either in the mitochondria or ER
- cholesterol converted to pregnenolone within the mitochondria that is then release

Three types of hormone according to their effects

1. Glucocorticoids
- cortisol are synthesized in zona fasciculada while corticosterone are synthesized in zone fasciculata and reticularis
- hormone is not stored but released into plasma once made and are sparingly water-soluble
- cortisol circulates in plasma in two forms, protein bound and unbound or free form
- Protein bound can either bind to transcortin (corticosteroid-binding globulin) and plasma albumin
- It modified in the liver making the lipophilic steroid molecule soluble in water and can be excreted in the kidneys
- It affects carbohydrate, lipid and protein metabolism; in the liver action is anabolic while catabolism occurs in skeletal muscle and adipose tissue
- excessive secretion of glucocorticoids is antagonistic to the actions of insulin predisposing animals to diabetes mellitus.
- It can suppress the immune response and inflammatory response
- Required for the functioning of the sympathoadrenal system and for the maintenance of normal water and electrolyte balance
- necessary for the maintenance of normal blood pressure and cardiac output

2. Mineralocorticoids
- Aldosterone are synthesized in the zona glomerulosa
- has no specific plasma transport protein and forms a very weak association with albumin
- rapidly cleared from plasma by the liver where it forms tetrahydoaldosterone 3-glucuronide that is excreted tithe urine
- Stimulate active Na transport in the distal convoluted tubules and collecting tubules of the kidney causing Na retention
- It promotes secretion of K^+, H^+, and NH_4 by the kidney and affect ion transport in other epithelial tissues including sweat glands, intestinal mucosa, and salivary glands
- Aldosterone stimulates Na transport in urinary bladder without affecting permeability to water



- Mechanism for regulation of glucocorticoid secretion. ACTH, adrenocorticotropic hormone; CRF, corticotrophin-releasing factor.

3. Sex hormones
- zona fasciculata and reticularts produce significant amounts of the androgen precursor that is converted in extra-adrenal tissue.
- Androgen is used as a substrate for conversion to estrogens

- Adrenal Medulla
- an extension of the sympathetic nervous system that is considered a specialized ganglion without axonal extensions
- hormones that are produced are not necessary to life but required for adaptation to acute and chronic stress
- Epinephrine is the major product that constitute about 80% of the cathecolamines in the medulla
- Norepinephrine is mostly made in organs innervated by sympathetic nerves while the rest is made in other nerve endings reaching target sites via circulation
- Dopamine is a neurotransmitter within the CNS
- tyrosine is transported into the cell where it is converted to dahydrophenylalanine (DOPA) by the enzyme tyrosine hydroxylase
- DOPA is decarboxylated to dopamine
- Dopamine is converted to norepinephrine within the chromaffin granule
- Produced norepninephrine is converted to epinephrine by PNMT outside the granule
- adrenal medulla contains the chromaffin granules that are capable of synthesis, uptake, storage and secretion of catecholamines

- all the contents of the storage granules are released during vesicular exocytosis through neural stimulation of the medulla requiring calcium
- neuronal re-uptake is an important mechanism for conserving these hormones
- Norepinephrine or epinephrine of neural or humoral origin interact with adrenergic receptors of the plasma membrane of target cells
- depending on the nature of the adrenergic receptors, signal transduction and second-messenger production follows like:

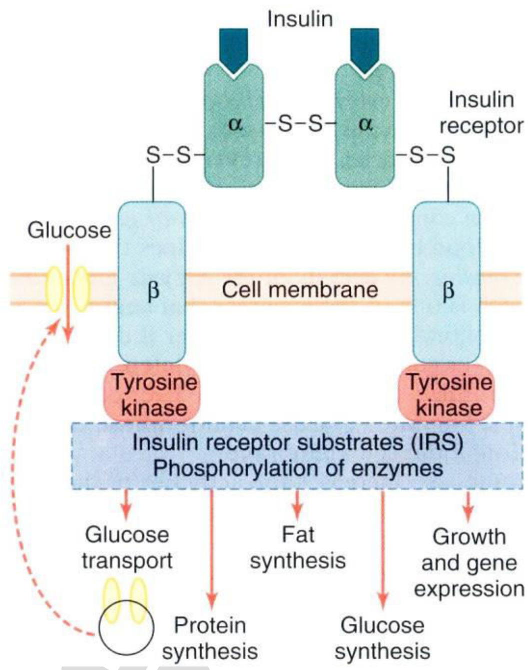
α_1 adrenergic receptors – stimulates breakdown of phosphoinositides

α_2 adrenergic receptors – inhibits adenylate cyclase

β_1 and β_2 adrenergic receptors – stimulates adenylate cyclase

Effects:

1. Metabolism
   - Epinephrine stimulates hepatic glycogenolysis and glucose release
   - skeletal muscle may provide an even greater total source of glycogen
   - Catecholamines inhibits insulin secretion and stimulates secretion of glucagons
   - It also stimulates lipolysis in adipose tissue
   - Epinephrine decreases the release of ammo acids from skeletal muscle
1. Cardiovascular
   - Epinephrine increases both the force and rate of the heartbeat by stimulating β-adrenergic receptors in the cardiac muscle
   - It enhances blood platelet adhesiveness and reduces clotting tine by its action α_1 adrenergic receptors found on platelet
   - Catecholamines may induced decreased blood flow to the kidneys and reduces glucose clearance from circulation that may result to prolonged hyperglycemia
3. Respiratory system
   - Catecholamines causes relaxation of bronchial smooth muscle
4. Sympathoadrenal activity and stress
   - sympathoadrenal system can be activated by hypoglycemia, hypoxia, hemorrhage, circulatory collapse, and during extensive stress, that result in stimulation of the heart, constriction of splanchnic, cutaneous and renal vessel and preservation skeletal muscle blood flow



Schematic of the insulin receptor. Insulin binds to the α-subunit of its receptor, which causes autophosphorylation of the ß-subunit receptor, which in turn induces tyrosine kinase activity. The receptor tyrosine kinase activity begins a cascade of cell phosphorylation that increases or decreases the activity of enzymes, including insulin receptor substrates, that mediate the effects of glucose on glucose, fat, and protein metabolism. For example, glucose transporters are moved to the cell membrane to facilitates glucose entry into the cell.

Factors and Conditions That Increase or Decrease Insulin Secretion

Increase Insulin Secretion	Decrease Insulin Secretion
• Increased blood glucose	• Decreased blood glucose
• Increased blood free fatty acids	• Fasting
• Increased blood amino acids	• Somatostatin
• Gastrointestinal hormones (gastrin, cholecystokinin, secretin, gastric inhibitory peptide)	• α-Adrenergic activity
• Glucagon, growth hormone, cortisol	• Leptin
• Parasympathetic stimulation; acetylcholine	
• β-Adrenergic stimulation	
• Insulin resistance; obesity	
• Sulfonylurea drugs (glyburide, tolbutamide)	

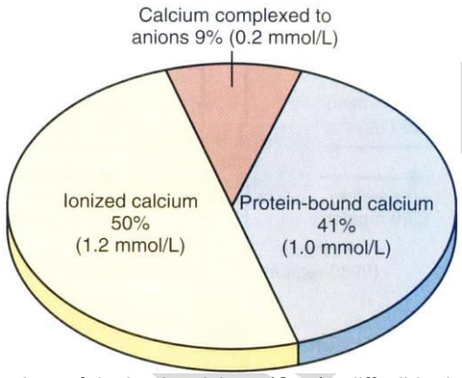
Pancreatic Hormone

1. Insulin
   - ribosome on the rough ER synthesized proinsulin
   - proteolysis of proinsulin occurs in the Golgi apparatus and pack into secretary granules
   - granules continue to mature as they traverse the cytoplasm toward the plasma membrane
   - stimulation causes granules to fuse with plasma membrane, releasing their contents into the extracellular fluid by exocytosis.
   - Neurotransmitter acetylcholine stimulates insulin release when increase in plasma glucose is detected
   - Insulin release is also stimulated by glucagon but inhibited by somatostatin.
   - Growth hormone has a direct beta-inducing properties causing increase basal insulin levels before an increase in blood glucose
   - epinephrine and norepinephrine inhibit insulin secretion even stimulated by presence of glucose

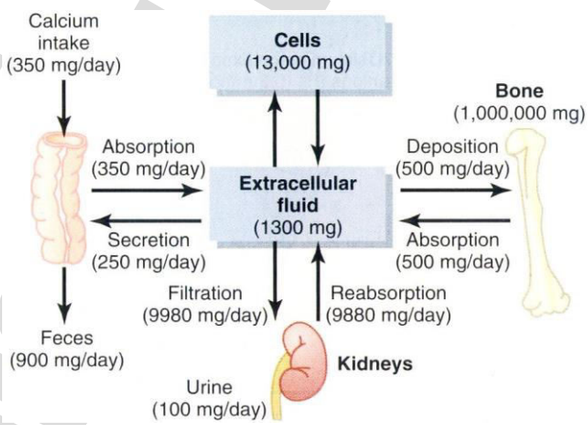
   MOA
   - Hepatocytes are permeable to glucose
   - Increase glucose transport in adipose tissue and muscle cells
   - Stimulate the enzyme glucokinase that favors rapid phosphorylation
   - Cell permeability to many amino acids are increased in presence of insulin
   - Primary effect is to decrease blood glucose level
   - Inhibit lypolysis in liver and adipose tissue by inhibiting lipase activity and increases fat storage
   - Stimulates protein synthesis

2. Glucagon
   - Antagonizes effect of insulin and circulates in plasma in free form
   - inactivated primarily in the liver
   - activate other sources of energy by stimulating glycogenolysis and lipolysis
   - the primary target organ of glucagons is the liver promoting glycogenolysis

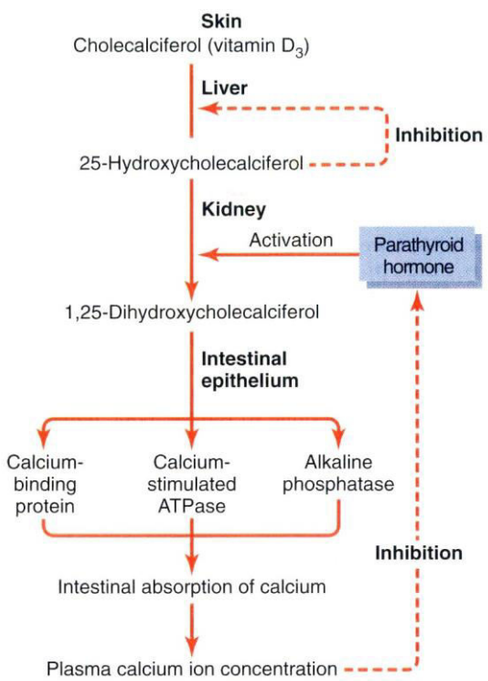
3. Somatostatin
   - synthesized delta cells as a large prohormone
   - inhibits release of other islet cell hormones
   - prolongs gastric emptying, decrease gastrin secretion, inhibits secretin, CCK and vasoactive inhibiting peptide secretion



Distribution of ionized calcium (Ca^{++}), diffusible but un-ionized calcium complexed to anions, and nondiffusible protein-bound calcium in blood plasma.



Overview of calcium exchange between different tissue compartments in a person ingesting 1000 mg of calcium per day. Note that most of the ingested calcium is normally eliminated in the feces, although the kidneys have the capacity to secrete large amounts by reducing tubular reabsorption of calcium.



Activation of vitamin D_3 to form 1,25-dihodroxycholecalciferol and the role of vitamin D in controlling the plasma calcium concentration.

XVII. REPRODUCTIVE PHYSIOLOGY

Physiology of Male Reproductive Organs

Chromosomal sex: XY = Male (mammals)
Male Sexual Development sex-determining region of Y chromosome (SRY) and **testis determining factor** (**tdf**) directs differentiation of the gonads into testes.

Wolffian ducts, under the influence of testosterone (T), give rise to the internal male reproductive organs (e.g., epididymis, vas deferens, seminal vesicles).

Other embryonic structures give rise to other reproductive organs (penis, scrotum, prostate) and are mediated by **dihydrotestosterone (DHT)**, which results from the conversion of testosterone in the target cell by the enzyme **5-alpha reductase**.

Male brain differentiation requires conversion, within the brain, of T $\longrightarrow$ E_2 by the enzyme **aromatase** (reaction = **aromatization**).

Alpha-fetoprotein helps protect against masculinization of the female brain.

1. Testis - From Latin meaning "witness."

Seminiferous Tubules (ST)

• House germ cells and Sertoli cells.
• Site of **spermatogenesis**

Sertoli Cells

Support and nourish developing sperm
Phagocytose damaged germ cells
Provide **blood-testis barrier**
Secrete **mullerian inhibition factor (MIF)**
Secrete **inhibin** and **activin**
Secrete **androgen-binding protein (ABP)**

Cells of Leydig = **interstitial cells**

- Produce and secrete **androgens** (male sex hormones) which is referred to as **steroidogenesis**
- Found between seminiferous tubules

Functions of Androgens: To affect the development, growth, and maintenance of primary and secondary sex characteristics.

2. **Epididymis** - Location of sperm maturation for motility and fertility, concentration, and storage between ejaculations.

3. **Vas Deferens** - Stores and transports sperm.

4. **Seminal Vesicles** - Produce seminal fluid; secrete fructose to supply energy to sperm.

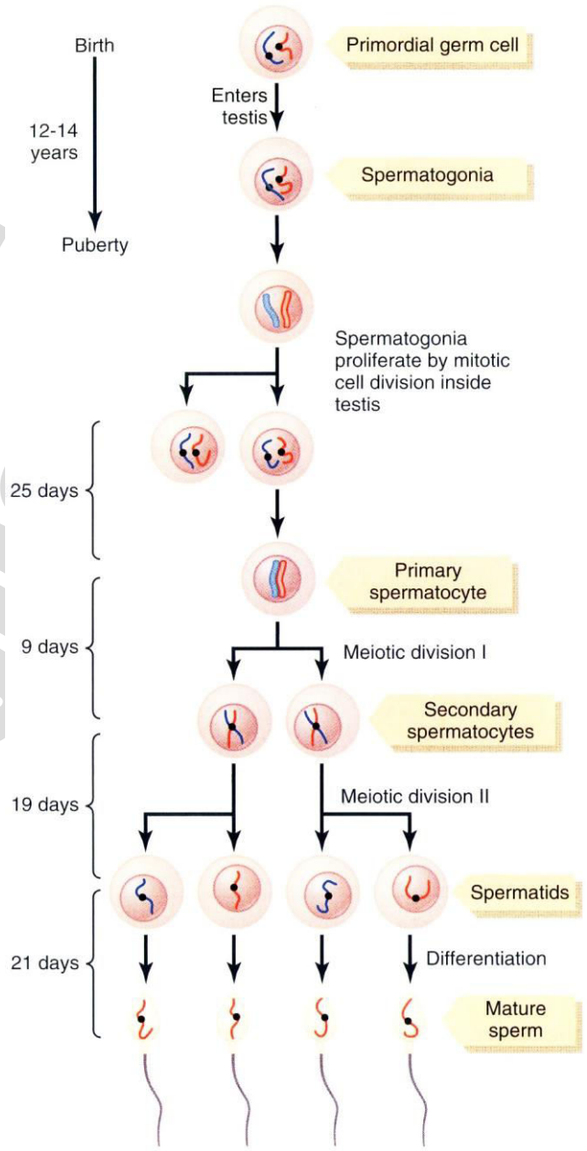
5. **Prostate** - Contributes alkaline secretions to seminal fluid which neutralize acidic vaginal secretions.

6. **Bulbourethral glands** - Secrete mucus-like substance for lubrication of urethra = **pre-ejaculatory fluid**.

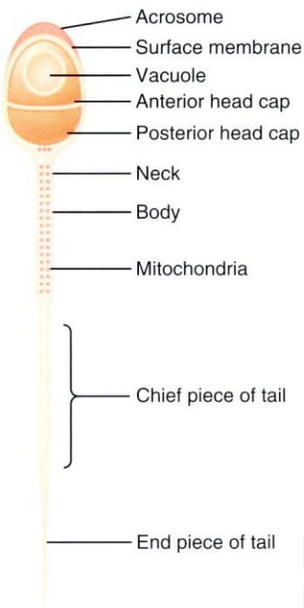
7. **Penis** - Copulation and urination

8. **Scrotum** - Houses testes and provides lower temperature for sperm maturation.

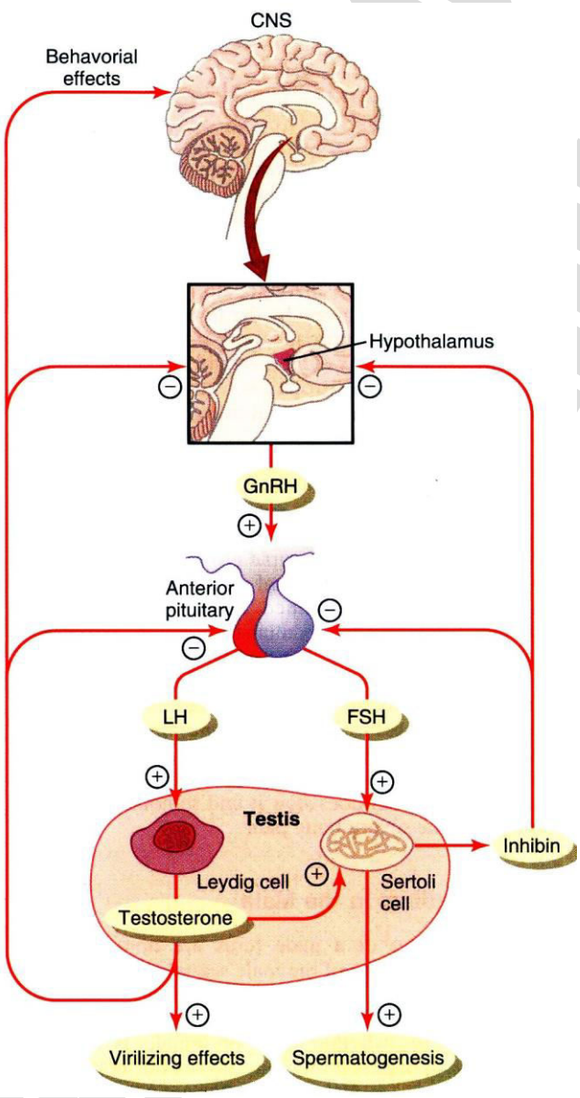
Spermatogenesis



Cell divisions during spermatogenesis. During embryonic development the primordial germ cells migrate to the testis where they become spermatogonia. At puberty (usually 12 to 14 years after birth in humans), the spermatogonia proliferate rapidly by mitosis. Some begin meiosis to become primary spermatocytes and continue through meiotic division I to become secondary spermatocytes. After completion of meiotic division II, the secondary spermatocytes produce spermatids, which differentiate to form spermatozoa.



Structure of the human spermatozoon.



Feedback regulation of the hypothalamic-pituitary-testicular axis in males. Stimulatory effects are shown by ⊕and negative feedbacks inhibitory effects are shown by (-).

GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

Primary and Secondary Sex Characteristics

Primary Sex Characteristics = male sex and accessory organs

Secondary Sex Characteristics:

1. Distribution and pattern of body hair

2. Growth of larynx and thickening of vocal cords which causes a lower voice.

3. Behavior - Aggression, territoriality, libido (sex drive)

4. Musculoskeletal development

Some Androgen Target Organs: (However, some effects typically attributed to androgens may actually be due to estrogen.)

1. Bone - Anabolic actions of androgens trigger both the "growth spurt" and then the closure of epiphyseal plate to limit growth.
2. Skeletal and cardiac muscle - Larger in males
3. Red blood cells (RBC) - Stimulate hemoglobin synthesis and erythropoiesis (RBC production) - Greater number in males
4. Central nervous system
   - **Sexually dimorphic nucleus** of hypothalamus - Larger in males

Erection center in spinal cord – Larger

Endocrinology of the Male Reproductive System

Castration causes an increase in LH and FSH which demonstrates that the testes exert negative feedback control on the reproductive axis.

GnRH is released in a **pulsatile** manner. Therefore, LH and FSH are also released in this manner.

LH receptors found on Leydig cells.

FSH receptors found on Sertoli cells.

- Both T and FSH appear necessary for spermatogenesis although there is significant debate on the relative roles of each.

Inhibin - Testicular protein that selectively inhibits FSH at the anterior pituitary gland.

Activin - Testicular protein that selectively stimulates FSH at the anterior pituitary gland.

Prolactin - May up regulate number of LH receptors on Leydig cells.

Hyperprolactinemia (increased levels of PRL in blood), however, can cause testicular dysfunction (e.g., decreased testosterone, impotence).

Melatonin - Inhibits GnRH, gonadotropins, and testosterone secretion.

Endocrinology of the Male Reproductive System

Adenohypophyseal Hormone
- secreted in the anterior pituitary gland by stimulation gonadotropes by of Gonadotropin Releasing Hormone (GnRH)
- inhibited by *inhibin* produced by the granulose cells

a. Follicle stimulating hormone (FSH) -
- Causes growth and development of the follicles and secretion of estrogen

b. Luteinizing hormone (LH)
- In females, it causes maturation of the follicles
- Controls the production of precursor molecule for estrogen synthesis
- Preovulatory surge and basal levels is needed for the formation and initial maintenance of corpus luteum, respectively

Control of LH and FSH secretion
A. tonic episodic system
- Control the continuous basal secretion of gonadotropins and stimulates the growth of the follicles

B. surge system
- controls the brief massive secretion of LH that causes ovulation

Functions of Ovary

- Site for oogenesis or production of the ovum
- Secretes the female sex hormones estrogen and progesterone

a. Folliculogenesis
- Is the development of ovarian follicles stimulated by FSH and LH
- Promotes formation of ovarian structure especially granulose cells which secretes estrogen

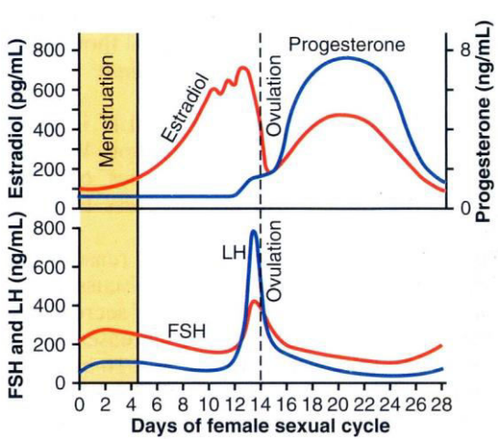
b. Steroidogenesis

1. Progesterone
- Produced and secreted by the placenta during pregnancy, corpus luteum and minimal secretion occurs in adrenal cortex
- It stimulates growth of the endometrium and development of mammary gland as preparation for pregnancy
- Inhibits uterine contraction during pregnancy
- Regulates the secretion of FSH and LH
- Maintains pregnancy

2. Estrogen
- produces negative feedback to the hypothalamus to inhibit secretion GnRH
- secretion is stimulated FSH and LH
- promotes development of female organs
- increase bone growth and sodium reabsorption in the kidney, promote protein anabolism, initiates sexual receptivity and regulate sexual behavior
- during fetal development, it promotes the development of female body and organ and inhibit development of male genital organs

Estrous cycle

- sexual behavior pattern that observe in female mammals except primates during puberty that is characterized by regular brief period of sexual receptivity
- has two phases the *Follicular phase* and *Luteal phase*
- Follicular phase includes:
  - Proestrus that is characterized by follicular growth mediated by FSH, LH and estrogen
  - Estrus which is the period of sexual receptivity and characterized by ovulation in most species except cow, and formation of corpus luteum begin. This period is controlled by estrogen and LH
- Luteal phase includes:
  - Metestrus, wherein development of corpus luteum occurs and begins secreting progesterone
  - Diestrus where maximal development of corpus luteum occur
  - Anestrus, prolong period of sexual rest that is characterized by minimal follicular development



Approximate plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle.

Ovulation

- An increase in production of estrogen by the follicles as a result of LH surge
- Three different type of ovulation

a. *Spontaneous ovulation* wherein mature follicles spontaneously ovulate and automatically formed functional CL that exists for a definite period of time. Observed in cow, sow, doe and primates (seasonal breeders) and also in mare, ewe and bitch (non-seasonal breeders)

b. *Spontaneous ovulation with functional CL becomes when mating occurs* which is observed in rats and mouse. In here, cervical stimulation is needed for CL to became functional

c. *Induced ovulation* is observed in rabbit, cat, mink ferret and camels wherein maturation and ovulation of follicles occur after copulation

Mechanism of Luteolysis

- Mediated by $PGF_{2\alpha}$ which is synthesized and released in pulsatile manner 14 days after ovulation causing luteolysis
- $PGF_{2\alpha}$ reduces blood supply to CL by constriction arterial system and binds to specific receptors on cell membrane of lutein cells that can interfere with steroidogenesis
- Causes contraction of uterus and induction of labor

Placentation

- Development amnion and allantois that provides nutrients to fetus from dam and removes waste products from fetus to darn
- Presence of fetus in the female reproductive tract maintain functional corpus luteum thus ensuring the production of progesterone and development of endometrium

Hormones that Regulate Pregnancy and Parturition

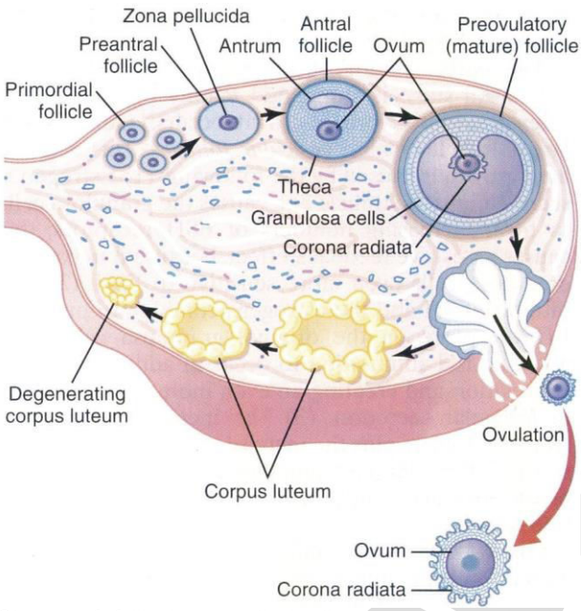
a. Progesterone – secreted by corpus luteum and placenta that function primarily to maintain pregnancy by preventing uterine contraction
b. Relaxin – produced by the placenta and maintain uterine relaxation during pregnancy
c. Prolactin – produced by the anterior pituitary glands for milk synthesis, initiation and maintenance of lactation
d. Placental lactogen – also produced by the placenta that increases protein synthesis and lipolysis while decreasing gluconeogenesis

Hormone Regulation during parturition

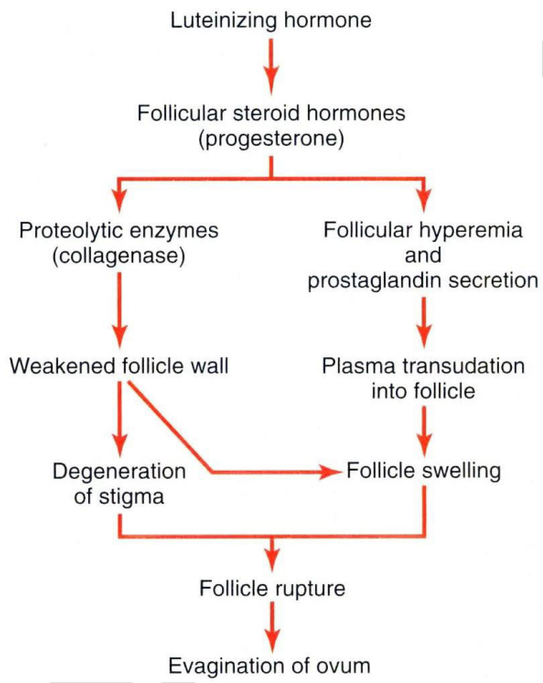
- Fetal adrenal gland secretes corticosteroids that initiates change of secretion from progesterone to estrogen
- Decrease in progesterone level are observed before parturition thus reducing the inhibitory effect on uterine contraction
- Estrogen secretion is increased causing myometrial contraction
- Endometrium secretes $PGF_{2\alpha}$ before parturition increasing uterine contractility and sensitivity to oxytocin. Also causes relaxation of the cervix
- Presence of fetus in the birth canal causes release of oxytocin from the posterior pituitary gland aiding fetal expulsion
- Trophoblastic cells produce relaxin causing relaxation of the cervix and softening of tissue surrounding the cervical canal including sacrosciatic and sacroiliac ligament.

Development of mammary gland, initiation and maintenance of lactation

- Estrogen and progesterone secreted by the placenta gestation period contributes to the development of the mammary gland
- Hormonal interaction by growth hormone, parathormone prolactin, cortisol and insulin causes secretion of colostrurn and responsible for milk synthesis throughout lactation.
- Suckling reflex causes stimulation of hypothalamus causing increase secretion of oxytocin. Oxytocin stimulates myoepithelial contraction in mammary gland causing release of milk.
- Suckling reflex also maintains production of milk by inhibition of dopamine that causes increase in secretion and release of Prolactin, which is responsible of milk production



Stages of follicular growth in the ovary, also showing formation of the corpus luteum.



Postulated mechanism of ovulation.

Zootechnics of Reproduction

FACTORS RELATED TO FEMALE REPRODUCTION

ANIMAL	ONSET OF PUBERTY (MO)	AGE FIRST SERVICE (AVERAGE)	LENGTH OF ESTROUS CYCLE (D)	LENGTH OF ESTRUS	GESTATION PERIOD (D)
Mare	18 (10–24)	2–3 yr	21 (19–21)	5 d (4.5–7.5 d)	336 (323–341)
Cow	4–24	14–22 mo	21 (18–24)	18 h (12–28 h)	282 (274–291)
Ewe	4–12 (first fall)	12–18 mo	16½ (14–20)	24–48 h	150 (140–160)
Sow	3–7	8–10 mo	21 (18–24)	2 d (1–5 d)	114 (110–116)
Bitch	6–24	12–18 mo	6–12 mo	9 d (5–19 d)	63 (60–65)

	TIME OF OVULATION	OPTIMUM TIME FOR SERVICE	ADVISABLE TIME TO BREED AFTER PARTURITION
Mare	1–2 d before end of estrus	3–4 d before end of estrus; or 2nd or 3rd d of estrus	About 25–35 d or second estrus; about 9 d or first estrus only if normal in every way
Cow	10–15 h after end of estrus	Just before middle of estrus to end of estrus	60–90 d
Ewe	12–24 h before end of estrus	18–24 h after onset of estrus	Usually the next fall
Sow	30–36 h after onset of estrus	12–30 h after onset of estrus	First estrus 3–9 d after weaning pigs
Bitch	1–2 d after onset of true estrus	2–3 d after onset of estrus; or 10 to 14 d after onset of proestrus bleeding	Usually first estrus or 2–3 mo after weaning pups

STAGES OF LABOR AND RELATED EVENTS IN FARM ANIMALS

STAGE OF LABOR	MECHANICAL FORCES	PERIOD	RELATED EVENTS
I. Dilation of cervix	Regular uterine contractions	Beginning of uterine contractions until cervix is fully dilated and continuous with vagina	Maternal restlessness, elevated pulse and respiratory rates Changes in fetal position and posture
II. Expulsion of fetus[a]	Strong uterine and abdominal contractions	From complete cervical dilation to end of delivery of fetus	Maternal recumbency and straining Rupture of allantochorion and escape of fluid from vulva Appearance of amnion (water bag) at vulva Rupture of amnion and delivery of fetus
III. Expulsion of fetal membranes	Uterine contractions decrease in amplitude	After delivery of fetus to expulsion of fetal membranes	Maternal straining ceases Loosening of chorionic villi from maternal crypts Inversion of chorioallantois Straining and expulsion of fetal membranes

[a]In polytocous species (sow) and twin-bearing species (sheep and goat), this stage cannot be separated from the next stage (III).

Avian Reproductive Physiology

A. Anatomy of Female Reproductive System

1. Ovary
   - Left ovary and oviduct are the only functional
   - right ovary is rudimentary
   - function is similar with mammalian ovary

2. Oviduct
   a. Infundibulum - site of fertilization, serves as sperm reservoir after copulation and contribute to formation of chalazae
   b. Magnum- secretes albumin
   c. Isthmus – secretes shell membrane and produces fluid for albumen
   d. Uterus or shell gland - secretes more fluid for albu men and calcium carbonate for formation of shell
   e. Vagina - transport egg from uterus going to out of the cloaca

B. Sexual maturation
   - Estrogen causes increased in size and weight of ovary and increasing the size and development of oviduct
   - It affects color and shape of feathers and promotes protein anabolism

C. Oogenesis
   - Liver serves as the major source of yolk proteins and phospholipids for growing follicle
   - FSH stimulates the growth and maturation of follicles by increasing uptake of yolk proteins by ovarian follicle
   - Estrogen secretion is similar with mammals
   - Estrogen stimulates the production of yolk precursor in the liver

D. Ovulation
   - One ovum is ovulated at a time
   - LH is regulated by progesterone secreted by ovary

E. Oviposition
   - controlled by *arginine vasotocin* or vasotocin produced by hypothalamus that stimulates uterine contraction

D. Molting
   - process of losing of feathers that occurs once a year for 1-1.5 months when exposed to natural lighting causing inability of animals to lay egg for the given period
   - causes inhibition of ovulation and oviposition, and regression the reproductive tract
   - decrease levels of LH and progesterone in the blood