Introduction to Human Physiology

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Introduction to Human Physiology

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Preface

While teaching physiology to the medical, pharmacology and health science students I was introduced to the basic students, needs in physiology to widen their knowledge in physiology for graduate and to act as a base for further higher education in physiology and health science.

In the recent time the physiological components are widely available by internet search in different forms of books, power point presentation, sessions and animations make most of students lost and face difficulties with these wide materials. So this book is to meet the basic students, needs. An experience was based on a summary work for more than ten years in teaching physiology in Basra University, Pharmacy College and Sultan Qaboos University, College of Science.

The book is come out inform of simplified accessible notes about each topic. Each system begins with anatomical considerations notes before the functional and mechanisms notes .Furthermore each system is supported by common clinical notes and pharmacology notes.

Alhamdulillah to achieve this book which I hope it would be workable and helpful to the students by acting a gate to guide and direct them for further readings and knowledge and not to dispense with the textbooks.

Dr.Azza Sajid Alkinany

Chapter One

Introduction to Physiology 1

General concepts

Physiology is the scientific investigation of functions and processes of living things. Humans have many characteristics of living things such as organization, metabolism, responsiveness, growth, development and reproduction.

Structural and functional organization

Overview

- There are basic chemical characteristics that are responsible for the structure and function of the life:
  - **Cells** are the basic structural and functional units of organisms.
  - **Organelles** are the smallest structures within the cell that perform specific functions.
  - **Tissues** are groups of cells of similar structures, functions and the material surrounded them. The four primary tissue types are: epithelial, connective muscles and nervous tissues.
  - **Organs** are structures composed of two or more tissues that perform specific functions.
  - Organs are arranged into eleven **organ systems** of the human body.
  - Organ systems interact to form a whole functioning organism.
- Although many cells of the body differ from each other in their functions, all of them have certain basic characteristics:
  1- ***Oxygen combines with breakdown products of fats, carbohydrates or proteins to release energy that is required for normal function.***
  2- ***Most cells have the ability to reproduce and whenever the cells are destroyed, the remaining cells generate new cells until the appropriate number is restored.***
  3- ***Cells are bathed in extracellular fluid (ECF), the constituents of which are precisely controlled.***
    - The constancy of **ECF** is necessary for the maintenance of the cells by homeostasis mechanism that monitor, regulate its temperature, osmotic pressure, PH, and composition.

Homeostasis

- Homeostasis is the condition in which the body functions.The body fluids and other factors of internal environment are maintained at levels suitable to support life.
- Homeostasis mechanisms are triggered by the alteration in some physiological properties and act to produce a compensating change to return the system to the normal situation.

- All homeostatic mechanisms consist of **receptors**, **control center** and **effectors.** The receptors are the sensing component that monitors and responds to change in the environment. When the receptor senses a stimulus, it sends information to the control center **(brain).**
- The brain determines an appropriate response to the stimulus. Then it sends signals to the effectors, which can be **muscles**, **organs** or other structures.
- After receiving the signals, a change occurs to correct the deviation by either enhancing it with **positive feedback** or inhibiting it with **negative feedback.**

Positive feedback

- Positive feedback is a mechanism by which an output is enhanced such as protein levels.
- A positive feedback mechanism is rarely used by the body due to risks of the acceleration becoming uncontrollable.
- An example of positive feedback in the body is **blood platelet accumulation,** which in turn causes blood clotting in response to a tear in the lining of the blood vessels.

Negative feedback

- Negative feedback is a mechanism by which the output activity of any organ and system is reduced back to its normal range of functioning.
- An example of this mechanism is **regulating blood pressure**:
  - Blood vessels can resist blood flow against the walls when blood pressure increases.
  - The blood vessels act as the receptors to relay this message to the brain. The brain then sends a message to the heart and blood vessels (the effectors.)
  - The heart rate decreases as the blood vessels diameter increases **(vasodilation**), causing the blood pressure to fall back to its normal range.

Homeostatic imbalance

Overview

- When positive and negative feedback loops are affected in any way, complications may occur, leading to **homeostatic imbalance**.
  Many diseases result from of homeostatic imbalance include **diabetes, dehydration**, **hypoglycemia**, **hyperglycemia, gout** and any disease result from **bloodstream toxins.**
  - ***Diabetes occurs when the control mechanism for insulin becomes imbalance either because deficient insulin or the cells have become resistant to insulin.***
- Aging is a source of homeostatic imbalance as the control mechanisms of the feedback loops lose their efficiency.
- Homeostasis is the property of a system that regulates its internal environment, maintaining stable, relatively constant set of properties e.g.,

temperature or **PH** in which the body's internal environment is kept stable and functional.

Regulation of body functions

1- Nervous system:

This directs the activity of the muscular thereby providing locomotion .It also controls the functions of many internal organs through the automatic nervous system.

- It consists of **afferent nerve fibers**: linking receptors to coordinating system in the brain and spinal cord, and **efferent nerve fibers** that carry information from the coordinating system to the effecter organs.
- There are two major subdivisions of the efferent system: **the somatic nervous system** uses skeletal muscles as effectors for purposive behavior and reflex actions; **the autonomic nervous system** sends its efferent to gland, heart, smooth muscles in hollow organs and blood vessels.

2- Endocrine system:

- This comprises glands which secret hormones into the blood to affect the function of target cells throughout the body.
- Hormonal actions are generally slower and less sharply localized than those of nervous system.
- Hormonal actions are under the control of nervous system through neurohormones produced in the brain (hypothalamus and pituitary gland), that influence other endocrine glands.

The importance of water in the body:

- Water constitutes about 60%of the body weight.It has special properties which are suited to life .About 67%of this fluid in the cells ,the intercellular fluid **(ICF),**and 33%is extracellular fluid **(ECF**).
- The ICF is high in K^+, the positive charge of which balances the negative charge of organic solutes .The ECF is high Na^+ and Cl^- .
- **In a man** about 60%of the body weight is due to water. **In a woman** about 55%of the body weight is water (relatively greater percentage of body weight contributed by fat cells).
- A 70 Kg man has 28Lof intercellular water and 14L of extracellular water.3 L of extracellular water is in the blood plasma. The remaining 11L constitutes the interstitial fluid (lymph) that provides an aquatic habitat surrounding the cells.

Exchange between capillaries and interstitial fluid

- The heart and blood vessels comprises **a circulatory system** that carries water and solutes including hormones and gases through the body.
- In the tissues, capillaries bring the blood within 5-10µm of the most cells, and the solutes like glucose and O_2 must:

1- Cross the capillary walls.
2- Cross the layer of interstitial fluid between the capillary and the cell.
3- Cross the plasma membrane which separates ICF from ECF.

Cell structure and function

Overview

- Cells are the basic structural and functional unit of the body.
- Most cells contain **nucleus** to direct the activities of the cells.
- The nucleus surrounded **cytoplasm.**
- The cytoplasm contain **cytosol** within which sit various types of organelles.
- The cytoplasm is enveloped by cell membrane (plasma membrane).
- **Functions of the cells:**
  1- Cells metabolize and release energy
  2- Cells synthesize molecules.
  3- Cells provide means of communications.
  4- Cells reproduce and provide for inheritance.

The cell membrane

- Cell membrane is a **lipid bilayer** separates the internal cellular environment from ECF.
- The lipid bilayer is composed of phospholipids arranged as **hydrophilic** glycerol backbone and two **hydrophobic** fatty acid tails. Plasma membrane serves as selectively permeable protective barriers
  1- **Fat soluble (hydrophobic) substance,** e.g., steroid hormones can dissolve in the hydrophobic bilayer, therefore can freely cross the membrane.
  2- **Water soluble (hydrophilic) substances,** e.g., Na^+ and glucose cannot dissolve in this bilayer and must pass through pores or use carrier proteins.
- Proteins, carbohydrates and cholesterol are embedded in the lipid bilayer.
- **Membrane proteins** function as signaling, cell-cell recognition (marker molecules), attachment proteins, transport proteins (include channel proteins, carrier proteins and ATP powered pump) and enzymes.
- There are two major classes of membrane proteins**:**
  1- **Integral,** which are permanently bound to lipid bilayer. Most integral proteins are transmembrane proteins which can function as transporters, receptors, structural proteins or mediated cell adhesion, (figure1.1).

  2- **Peripheral** which are temporarily associated with lipid bilayer or with integral protein, Peripheral proteins regulate cell signaling through assembly into multi-protein complexes or activation of their biological activity upon membrane binding.
- The cell membrane is commonly described as **fluid mosaic model, because** proteins can freely move within the phospholipids bilayer. (Figure1.1).
- The **nuclear envelope, endoplasmic reticulum, Golgi apparatus**, **lysosomes**, and the **plasma membrane** comprise the **endomembrane system**

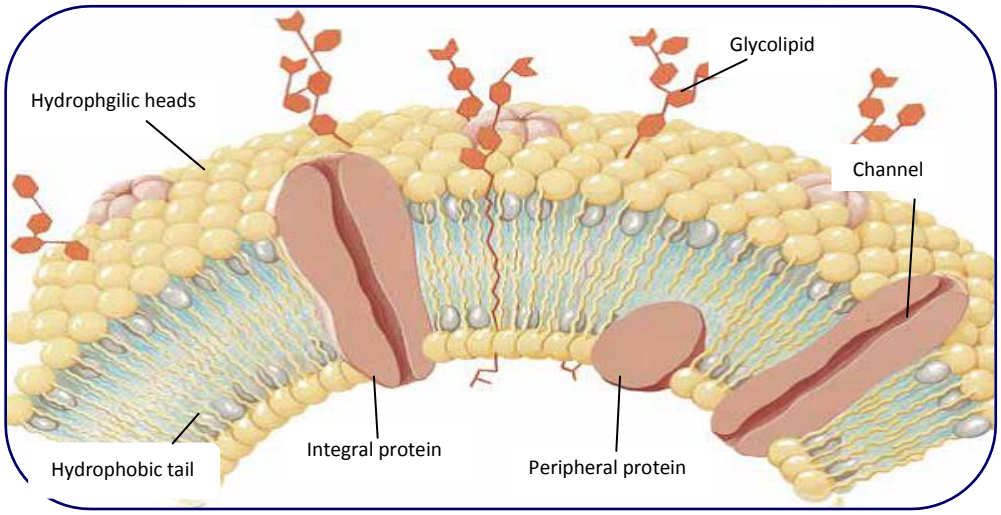


Figure (1.1): Structure of cell membrane.(Scanlon V.C. and Sanders T. Essential of Anatomy and Physiology . Philadelphia, E.A. Davis Company, 2007).

The nucleus

- The nucleus averages about 5 microns in diameter.It is centrally located within the cell and surrounded by two-layer **nuclear envelope,** which separate the cytoplasm from the nucleoplasm (figure1. 2). Each layer of the envelope is a lipid bilayer.
  - The double membranes are fused to form a pore that allows large macromolecules and particles to pass through. The nuclear side of the envelope is lined by the **nuclear lamina**, a network of intermediate filaments that maintain the shape of the nucleus.
- The nucleus contains most of the genes in cell. Within the nucleus, the DNA and associated proteins are organized into fibrous material, **chromatin**. In a normal cell they appear as diffuse mass.
- However when the cell prepares to divide, the chromatin fibers coil up to be seen as separate structures, **chromosomes**.
- A typical human cell has 46 chromosomes, but sex cells (**eggs and sperm**) have only 23 chromosomes. In the nucleus is a region of densely stained fibers and granules adjoining chromatin, the ***nucleolus***.
- In the nucleolus, ribosomal RNA (**rRNA**) is synthesized and assembled with proteins from the cytoplasm to form **ribosomal subunits.**
- The subunits pass from the nuclear pores to the cytoplasm where they combine to form **ribosomes.**
- The nucleus directs protein synthesis by synthesizing messenger RNA (**mRNA**).

- The mRNA travels to the cytoplasm and combines with ribosomes to translate its genetic message into the primary structure of a specific polypeptide chains.

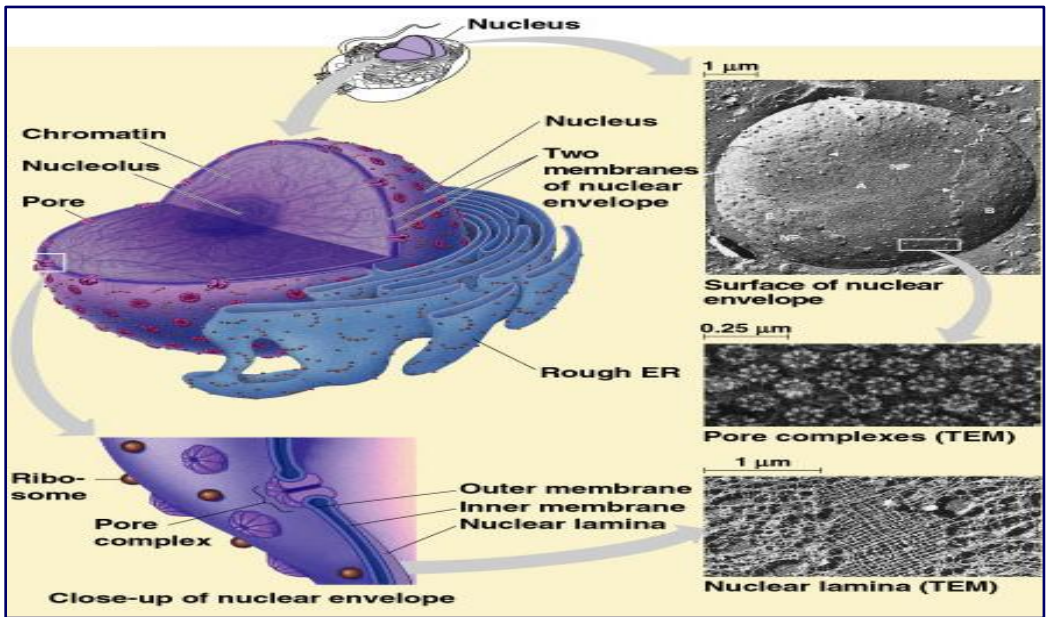


Figure (1.2): Structure of the nucleus.(Reece J.B., Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology.San Francisco, Benjamin Cummings,2014).

Ribosomes

- Ribosomes contain **rRNA** and protein.
- A ribosome is composed of two subunits that combine to carry out protein synthesis.(Figure 1.3).
- Cell types that synthesize large quantities of proteins (**e.g., pancreas**) have large numbers of ribosomes and prominent nuclei.
- Some ribosomes are **free ribosomes** suspended in the cytosol and synthesize proteins that function within the cytosol.
- Other ribosomes are **bound ribosomes** attached to the outside of the endoplasmic reticulum. These synthesize proteins that are either included into membranes or for export from the cell.

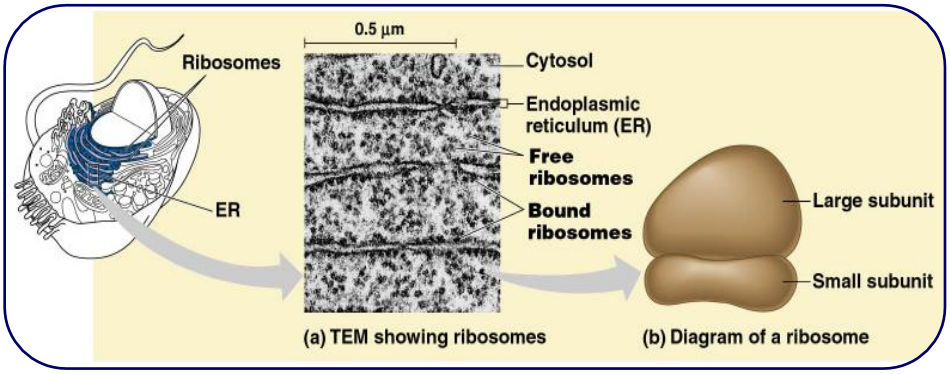


Figure (1.3): The ribosome.(Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology.San Francisco, Benjamin Cummings,2014)

Endoplasmic reticulum

- The endoplasmic reticulum (**ER**) accounts for half the membranes of the cell.
- The ER includes **membranous tubules** and **internal fluid-filled spaces** (the **cisternae).**
- The ER membrane is continuous with the nuclear envelope and the cisternal space of the ER is continuous with the space between the two membranes of the nuclear envelope. Figure (1.4).
- There are two connected regions of ER that differ in structure and function:

1- **Smooth ER** looks smooth because it lacks ribosomes.

- Enzymes of smooth ER synthesize lipids, including oils, phospholipids, and steroids.
- The smooth ER catalyzes a key step in the mobilization of glucose from stored glycogen in the liver.
- An enzyme removes the phosphate group from glucose phosphate, a product of glycogen hydrolysis, permitting glucose to exit the cell.
- Other enzymes in the smooth ER of the liver help detoxify drugs and poisons. These include alcohol and barbiturates.
- Frequent exposure leads to proliferation of smooth ER, increasing tolerance to the target and other drugs.
- Muscle cells are rich in enzymes that pump calcium ions from the cytosol to the cisternae. When nerve impulse stimulates a muscle cell, calcium rushes from the ER into the cytosol, triggering contraction.

2- **Rough ER** looks rough because bound ribosomes are attached to the outside, including the outside of the nuclear envelope.

- Rough ER is abundant in the cells that secrete proteins.
- As a polypeptide is synthesized by the ribosome, it is threaded into the cisternal space through a pore formed in the ER membrane. Many of these polypeptides are **glycoproteins** (polypeptides to which the oligosaccharides are attached).
- These secretory proteins are packaged in **transport vesicles** that carry them to their next stage.
- Rough ER is also a membrane factory. Membrane bound proteins are synthesized directly into the membrane.
- Rough ER enzymes synthesize phospholipids from precursors in the cytosol.

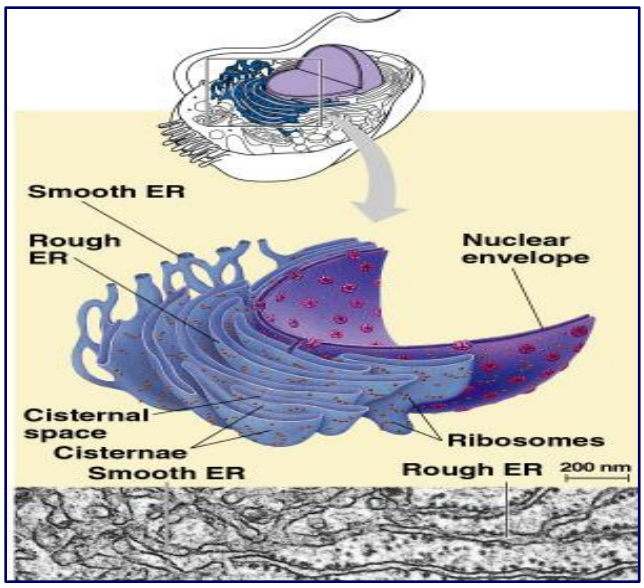


Figure (1.4): Smooth and rough endoplasmic reticulum. (Reece J.B., Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings,2014).

Golgi apparatus

- The Golgi apparatus is a series of closely modified cisternae that functions to modify, package and distribute lipid and proteins produced by the ER.
- The Golgi apparatus consists of flattened **membranous sacs - cisternae.**
  - The membrane of each cisterna separates its internal space from the cytosol
  - One side of the Golgi, the **cis side**, receives material by fusing with vesicles, while the other side, the **trans side,** buds off vesicles that move to other sites. Figure (1.5). During this, products from the ER are modified (modifications of the oligosaccharide portion of glycoproteins).
- The Golgi can synthesize its own macromolecules, including pectin and other noncellulose polysaccharides.
- Finally, the Golgi tags, sorts, and packages materials into transport vesicles**.**

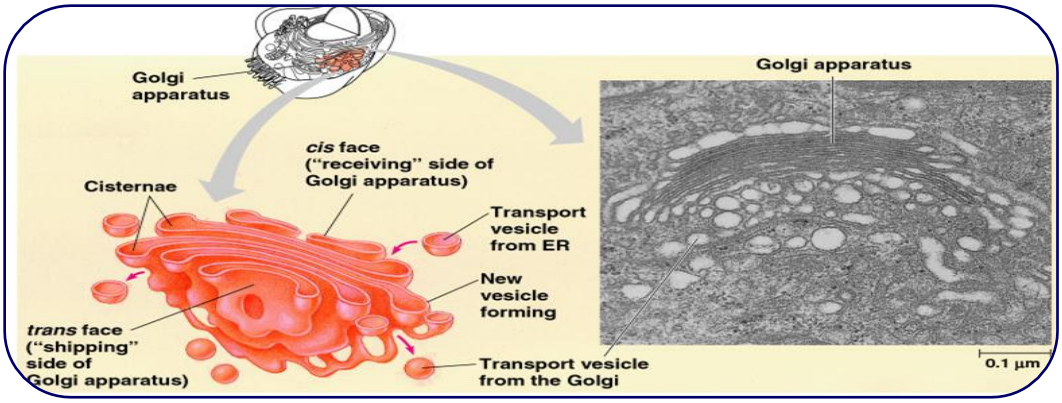


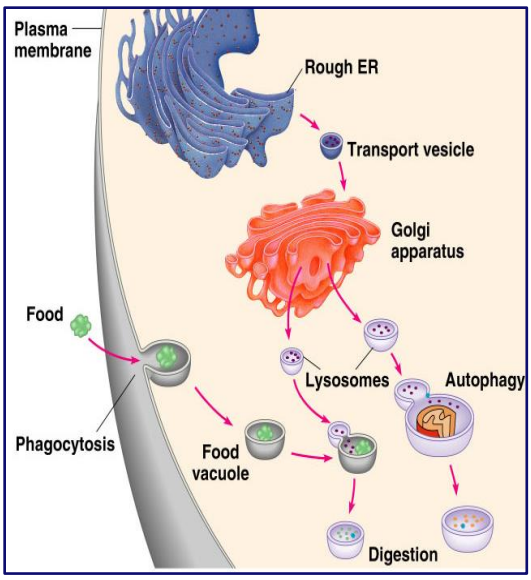
Figure (1.5): Golgi apparatus.(Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

Lysosomes

- The **lysosome** is **a membrane-bounded sac** of hydrolytic enzymes that digests macromolecules.
- Lysosomal enzymes can hydrolyze proteins, fats, polysaccharides, and nucleic acids.These enzymes work best at pH 5.
- While rupturing one or few lysosomes has little impact on a cell, but massive leakage from lysosomes can destroy the cell by **autodigestion.**
- The lysosomes create a space where the cell can digest macromolecules.
- At least some lysosomes bud from the trans face of the Golgi.
- Lysosomes can fuse with food vacuoles formed when a food item is brought into the cell by **phagocytosis**. As the polymers are digested, their monomers pass out to the cytosol to become nutrients of the cell.
- Lysosomes can also fuse with another organelle or part of the cytosol. This process of **autophagy** renews the cell.(Figure1.6).

Clinical note: Several inherited diseases affect lysosomal metabolism.These individuals lack a functioning version of a normal hydrolytic enzyme. Lysosomes are engorged with indigestible substrates. These diseases include **Pompe's disease** in the liver and **Tay-Sachs disease** in the brain.

Clinical note: When mitochondrial dysfunction is inherited through mitochondrial DNA, all offsprings are equally affected, but only female offspring pass on the disorder.However the other type of mitochondrial dysfunction result from defects in specific proteins that are coded by nuclear DNA but function in mitochondria such as **Leber hereditary optic neuropathy (LHON),** which is characterized by loss of vision in the center visual field.



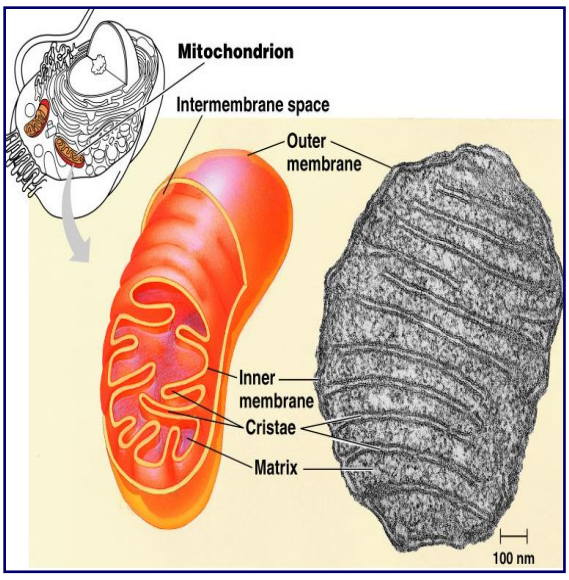


Figure (1.6): Function of the lysosomes. Figure (1.7): Structure of mitochondria (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings,2014).

Mitochondria

- Mitochondrion is the site of cellular respiration, generating ATP from the catabolism of sugars, fats, and other fuels in the presence of oxygen.
- The proteins of the mitochondria come primarily from free ribosomes in the cytosol and a few from their own ribosomes. They have small quantities of DNA that direct the synthesis of the polypeptides produced by these internal ribosomes.
- The number of mitochondria is correlated with aerobic metabolic activity.
- A typical mitochondrion is 1-10 microns long. Figure (1.7).
- Mitochondria are quite dynamic: moving, changing shape, and dividing.
- Mitochondria have a smooth outer membrane and a highly folded inner membrane, the **cristae**. This creates a fluid-filled space between them. The cristae present ample surface area for the enzymes that synthesize ATP.
- The inner membrane encloses the **mitochondrial matrix**, a fluid-filled space with DNA, ribosomes, and enzymes.
- Mitochondria and their DNA are inherited maternally (mitochondria are received only from the egg, not from sperm).

Peroxisomes

- They are membrane bound sacs containing enzymes that transfer hydrogen from various substrates to oxygen. An intermediate product of this process is **hydrogen peroxide (H_2O_2),** a poison, but the peroxisome has another enzyme that converts H_2O_2 to water.
- Some peroxisomes break fatty acids down to smaller molecules that are transported to mitochondria for fuel.
- Others detoxify alcohol and other harmful compounds.

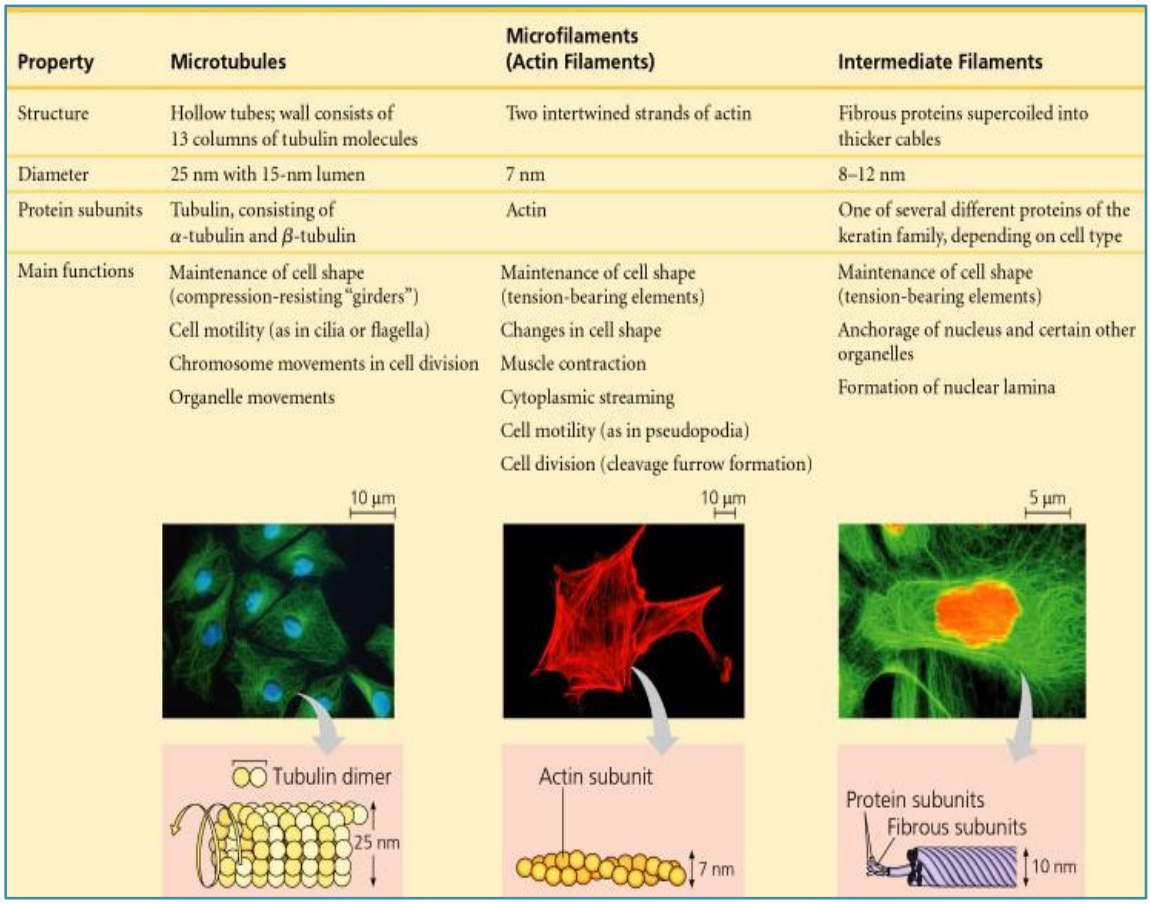
The Cytoskeleton

Overview

- The cytoskeleton is a network of fibers extending throughout the cytoplasm.
- It Provides mechanical support, cell flexibility and cell motility and aids in cell division.
- There are three main types of fibers in the cytoskeleton: **microtubules**, **microfilaments**, and **intermediate filaments** .(Table 1.1)

Table (1.1): The structures and function of the cytoskeleton. (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings,2014).

Property	Microtubules	Microfilaments (Actin Filaments)	Intermediate Filaments
Structure	Hollow tubes; wall consists of 13 columns of tubulin molecules	Two intertwined strands of actin	Fibrous proteins supercoiled into thicker cables
Diameter	25 nm with 15-nm lumen	7 nm	8–12 nm
Protein subunits	Tubulin, consisting of α-tubulin and β-tubulin	Actin	One of several different proteins of the keratin family, depending on cell type
Main functions	Maintenance of cell shape (compression-resisting "girders") Cell motility (as in cilia or flagella) Chromosome movements in cell division Organelle movements	Maintenance of cell shape (tension-bearing elements) Changes in cell shape Muscle contraction Cytoplasmic streaming Cell motility (as in pseudopodia) Cell division (cleavage furrow formation)	Maintenance of cell shape (tension-bearing elements) Anchorage of nucleus and certain other organelles Formation of nuclear lamina



1- Microtubules

- The thickest fibers are hollow rods about 25 microns in diameter. Microtubule fibers are constructed of the globular protein, tubulin.
- They move chromosomes during cell division.
- Another function is as tracks that guide motor proteins carrying organelles to their destination.
- Microtubules are the central structural supports in **cilia** and **flagella.**

2- Microfilaments

- They are the thinnest class of the cytoskeletal fibers, solid rods of the globular protein actin.
- An actin microfilament consists of a twisted double chain of actin subunits.
- Microfilaments are designed to resist tension.
- In muscle cells, thousands of actin filaments are arranged parallel to one another.
- The thicker filaments are composed of a motor protein, myosin, interdigitate with the thinner actin fibers.

3- Intermediate filaments

- They are intermediate in size at 8 - 12 nanometers, specialized for bearing tension.
- Intermediate filaments are built from a diverse class of subunits from a family of proteins called keratins.
- Intermediate filaments are more permanent fixtures of the cytoskeleton than are the other two classes.
- They reinforce cell shape and fix organelle location.

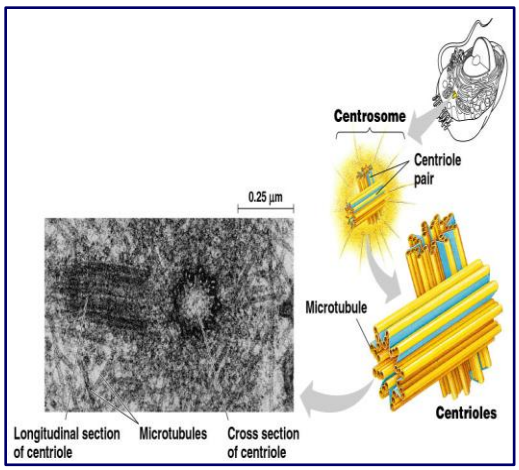
Extra non-membranous-enclosed organelles

1- Microvilli

- They are small fingerlike projections of the plasma membrane.
- Function to increase surface area for absorption of extracellular substance.
- Examples of cells type with microvilli are the brush borders **of the intestinal epithelium** and the **proximal convoluted tubule (PCT)** of the nephron.

2- Centrioles

- They are bundles of microtubules linked by other proteins.
- At least two are present in the centrosome of each cell capable of cellular division. Figure (1.8).
- They are function in the cell division by forming spindle fibers that separate **homologous chromosomes**.



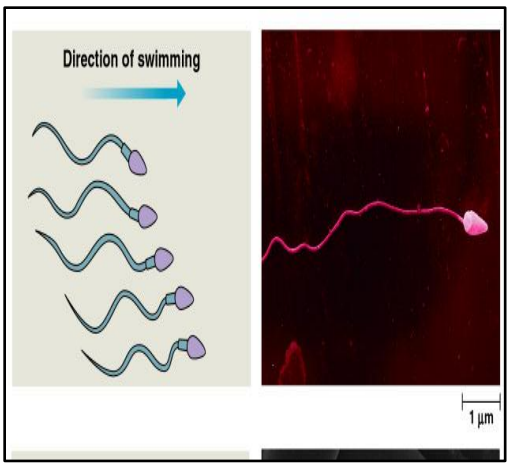


Figure (1.8): Centrioles. Figure (1.9): Movement of flagella

(Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

3- Cilia

- Long fingerlike projections of plasma membrane, differ from microvilli in that they are supported by microtubules.
- They are two types **motile** and **non-motile cilia.**
- Motile cilia function to move fluid and/or secretions along the cell surface, whereas the non-motile cilia play a sensory role.

4- Flagella

- They are Similar in shape to cilia but longer.
- Like cilia they supported by microtubules.
- Function in the movement of cells in the medium.
- The sperm cell is only human cell with flagellum.
- A flagellum has an undulating movement. Figure(1.9)

Transport across membranes

Overview

- **Fat soluble molecules** pass through the plasma membrane by dissolving in the bilayer.
- Small molecules pass through membrane channels .Most channels are positively charged allowing negatively charge ions and neutral molecules to pass.
- **Large polar** substances e.g., **glucose**, **amino acids** transport through the membrane by carrier molecules.
- Large pieces of material enter cells in vesicles.

1- Simple Diffusion

- The process whereby a substance moves down its concentration gradients across a semipermeable membrane.
- This tends to equalize the concentration of substance on both side of the membrane.
- No metabolic energy or carrier protein is required.

a- Diffusion of uncharged substances

- The rate of diffusion **(J)** is dependent on the concentration gradient **(ΔC),** the surface area to diffuse **(A)** and the membrane permeability **(P).**

$$J = PA\,(\Delta C)$$

- Permeability (P) is **directly proportional** to the lipid solubility of the substance and **inversely proportional** to the size of molecules and thickness of the membrane.
- Small hydrophobic molecules have the highest permeability in the lipid bilayer.

b- Diffusion of charged substances

- The net rate of diffusion (J) depends on the **electrical potential differences** across the membrane.
- Positively charge ions **(cations)** tend to diffuse into the cell, whereas negatively charged ions **(anions)** tend to diffuse out of the cells, because at rest the inside of the cell is negatively charged.

c- Diffusion of polar and non polar substances

- Non polar substances e.g**.,** **O_2, CO_2** gases diffuse across the membrane more rapidly than the polar substances do e.g., **water,** due to the relative solubility in the lipid.

d- Diffusion of gases

- Gases have great area to diffuse across the entire surface area of the cell.
- The diffusion rate of a gas **(Vg)** depends on the pressure differences across the membrane **(ΔP),** surface area of the cell **(A)**, the diffusion coefficient **(d)** and thickness of the membrane **(T).**

$$Vg = \frac{\Delta P \times A \times d}{T}$$

Clinical note: Gas exchange in lung normally occurs efficiently across thin lipid – rich pulmonary capillary and alveolar walls. However, in pathologic state such as **pneumonia,** gas exchange becomes less efficient because the accumulation of fluid increases the distance over which O_2 must diffuse.

2- Osmosis

- Osmosis is the movement of water (not dissolved solutes) across a semipermeable membrane.
- A difference in solute concentration across the membrane generates **osmotic pressure** which causes the movement of water from area of low solute concentration **(hypotonic solution)** to that of high solute concentration **(hypertonic solution)**, (figure 1.10).
- **Osmotic pressure** depends on the following :
  1. The concentration of osmotically active particles (osmotic pressure increases with increase solute concentration).
  2. The ability of the particles to cross the membrane, which depends on particles size and charge.
- If the solution on either sides of membrane has equal osmotic pressure, they are said to be **(isotonic solution).**
- If cells placed in an isotonic solution neither swell nor shrink. While in a hypertonic solutionthey the cells shrink. In a hypotonic solution, they swell and may burst (lyse).

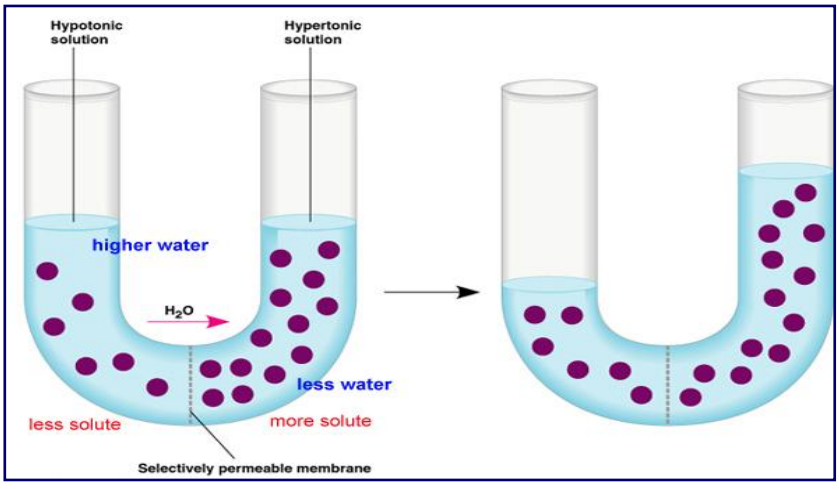


Figure (1.10): Osmosis, the movement of water from thehypotonic solution to the hypertonic solution. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

3- Carrier- mediated transport

- Mediated transport is the movement of a substance across a membrane by means of transport protein.
- The substances transported tend to be large, water soluble molecules.
- Characteristics of carrier mediated transport:
  1. **Stereospecifity of carrier**: Only one isomer of a substance is recognized by the carrier protein.
  2. **Competition for carrier binding sites**. Substances with similar structure can compete for binding to the carrier proteins.
  3. **Saturation of carrier proteins:** when all transport binding sites for a particular substance are occupied, the **transport maximum (T_m)** has been reached; the substance has no longer bind to its carrier and therefore cannot pass through the membrane.
- There are three kinds of mediated transport:

1- Facilitated diffusion :

- Movement of substances down their electrochemical gradient and does not require energy (ATP).
- Stops if the concentration of the substance inside the cell reaches the extracellular concentration or if carrier molecules become saturated.
- The molecules that are transported via facilitated diffusion are not permeable to plasma membrane .Thy include ions and nonpolar molecules that are poorly soluble in water.

2- Active transport :

- **Uphill transport** of a substance against its electrochemical gradient.
- Energy from hydrolysis of **adenosine tri-phosphate (ATP)** is required.
- **Nerve cells** and **muscle cells** have"**sodium pumps**" to move sodium ions **(Na^+)** out of the cells,inspit that Na^+ are more abundant outside the cells. Without the sodium pumps the incoming sodium ions would bring about an unwanted nerve impulse or muscle contraction. Nerve and muscle cells constantly produce ATP to keep their sodium pumps (and similar potassium pumps) working and prevent spontaneous impulses.

Pharmacology note: Proton pump inhibitors such as ***omeprazole*** are used to treat peptic ulcer diseas.These drugs directly inhibit the H+,K+-ATPase (proton) pump of gastric parietal cells .This reduces the acidic content of the stomach and allows for healing of the damaged mucosa.

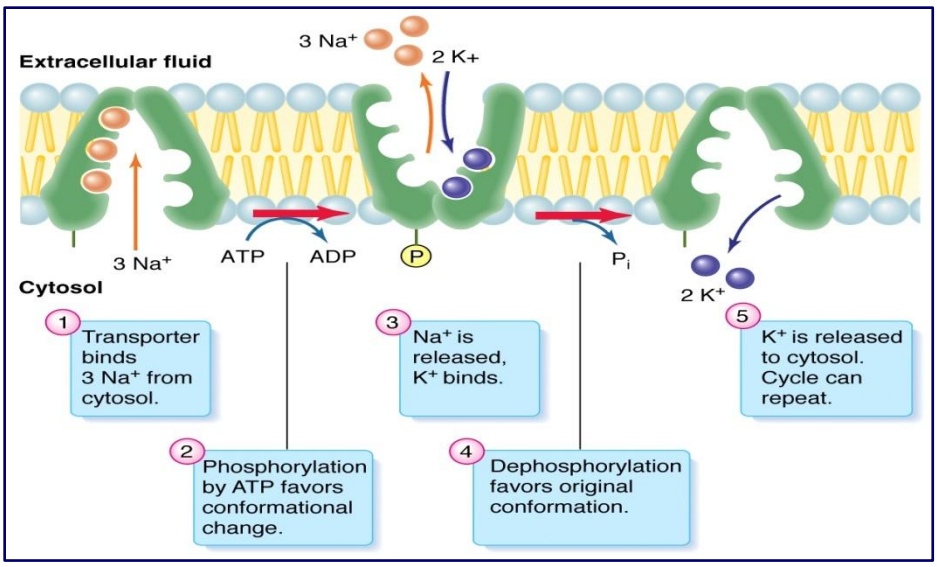


Figure (1.11): Sodium potassium pump in the verve cell. (Randall D., Burggren W. and French K. Eckert Animal Physiology . New York, W.H. Freeman and Company, 2002).

a- Primary active transport:

- The transport of a substance across the plasma membrane directly coupled to ATP hydrolysis.
- Examples include the the Na^+,K^+-ATPase (sodium) pump in the plasma of all cells, the H^+,K^+-ATPase(proton) pump of gastric parietal cells, and the Ca^+-ATPase pump in muscle cells.

b- Secondary active transport:

- The simultaneous movement of two substances across the plasma membrane indirectly coupled to ATP hydrolysis. One substance moves down its concentration gradient, and this drives the uphill transport of other substance against its concentration gradient.
  - **Cotransport (symport):** both substances move in the same direction, e.g., Na^+-glucose cotransport in the epithelial cells of the brush border of the small intestine.
  - **Countertransport (antiport):** the substances move in opposite directions,e.g.,Na^+-Ca^+countertransport of the heart muscle cell moves Ca^+ against its concentration gradient as Na^+ moves down its concentration gradient.

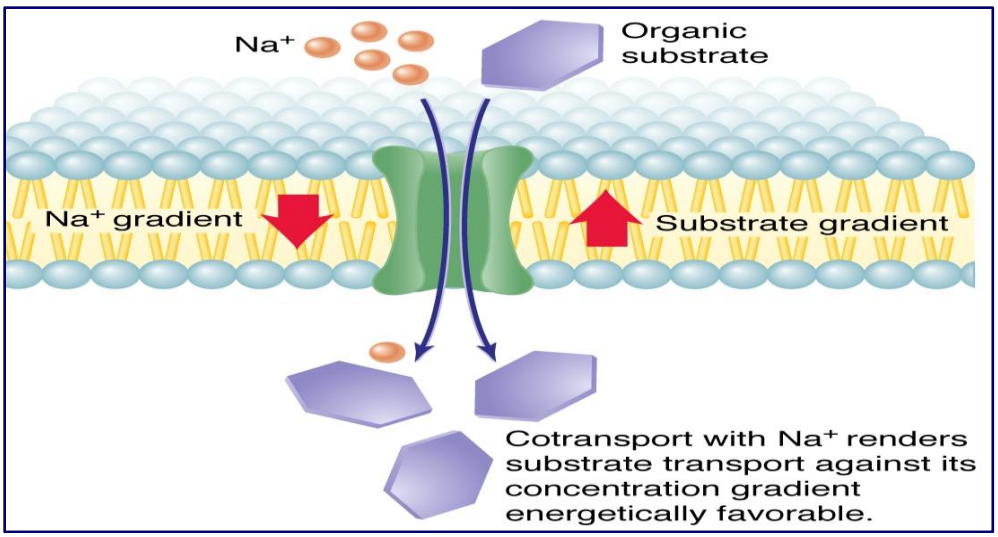


Figure (1.12): Cotransport: Two substances move in the same direction. (Randall D., Burggren W. and French K. Eckert Animal Physiology . New York, W.H. Freeman and Company, 2002).

Pharmacology note: Cardiac glycosides such as **ouabain** and **digitalis inhibit** the Na^+, K+-ATPase (sodium pump in the myocardium) .This increases the amount of sodium inside the cell, triggering the Ca^+-Na^+ countertransport .More calcium is brought into the cell, which increases the contraction of atrial and ventricular myocardium and increases cardiac output.

4- Vesicular transport

- Large molecules, such as **polysaccharides** and **proteins** cross the membrane via vesicles.
- During **exocytosis,** a transport vesicle budded from the Golgi apparatus is moved by the cytoskeleton to the plasma membrane.
- When the two membranes come in contact, the bilayers fuse and spill the contents to the outside.
- During **endocytosis**, a cell brings in macromolecules and particulate matter by forming new vesicles from the plasma membrane.
- **Endocytosis** is a reversal of **exocytosis.**
- A small area of the plasma membrane sinks inward to form a pocket
- As the pocket into the plasma membrane deepens, it pinches in, forming a vesicle containing the material that had been outside the cell
- One type of **endocytosis** is **phagocytosis**, "cellular eating".(Figure1.13,a)
- In phagocytosis, the cell engulfs a particle by extending **pseudopodia** around it and packaging it in a large vacuole.

- The contents of the vacuole are digested when the vacuole fuses with a lysosome.
- In **pinocytosis**, "cellular drinking", a cell creates a vesicle around a droplet of extracellular fluid. This is a non-specific process.(Figure 1.12,b)

Clinical note: In chronic granulomatous disease (CGD), mutations in the proteins of NADH oxidase system result in a reduced ability of phagocytic cells to produce the super oxide radical (O_2^-) and its products the hydroxyl radical (OH^-) and hydrogen peroxide (H_20_2).The enzyme **catalase** breaks down the hydrogen peroxide produced by the phagocytic cell and further decreases the cell's ability to destroy the offending microbe. Microbial killing is severely impaired in these patients and phagocytic cells accumulate forming **granulomas** in area of infection such as skin, lungs, liver, spleen and lymph nodes.

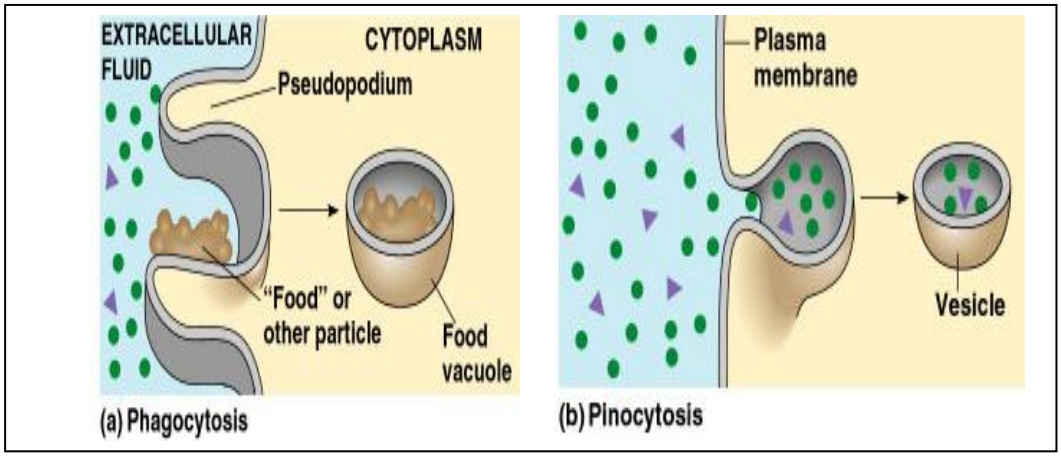


Figure (1.13): a: phagocytosis (cellular eating), b: pinocytosis (cellular drinking). (Marieb E.N .Essential of Human Anatomy and Physiology .San Francisco, Pearson Education, 2012).

- **Receptor-mediated endocytosis** is very specific in what substances are being transported.
  - This process is triggered when extracellular substances bind to special receptors, ligands, on the membrane surface, especially near coated pits.
  - This triggers the formation of a vesicle receptor-mediated endocytosis which enables a cell to acquire bulk quantities of specific materials that may be in low concentrations in the environment.(1.14).
  - Human cells use this process to absorb cholesterol.
  - Cholesterol travels in the blood in **low-density lipoproteins (LDL),** complexes of protein and lipid.

- These lipoproteins bind to LDL receptors and enter the cell by endocytosis.

Clinical note: Familial hypercholesterolemia, an inherited disease, the LDL receptors are defective, leading to an accumulation of LDL and cholesterol in the blood. This contributes to early **atherosclerosis.**

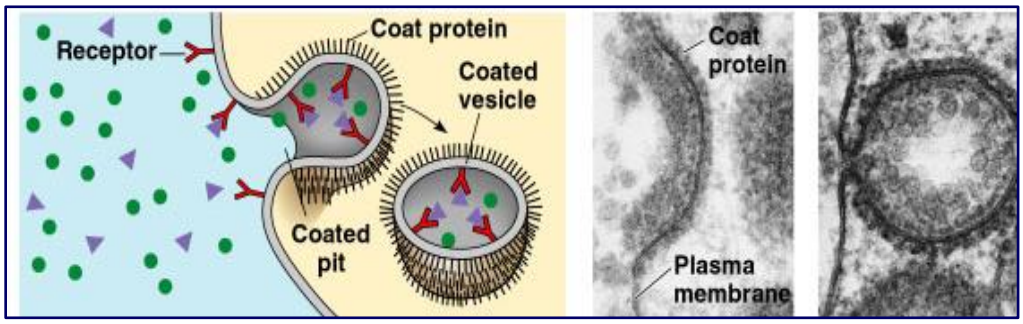


Figure (1.14): Receptor-mediated endocytosis. (Marieb E.N .Essential of Human Anatomy and Physiology .San Francisco, Pearson Education, 2012).

Junctions between cells

1- Tight junctions :(zonula occludens)

- They are attachments between the cells (epithelial cells)
- Intercellular pathway for solutes depending on size, charge and characteristic of the junction.
- They may be **tight** (in renal distal tubule) or **leaky** as in renal proximal tubule.

2- Gap junctions:

- They are the attachments between cells that permit intercellular communication.
- They permit current flow and electrical coupling between myocardial cells.

3- Desmosomes (macula adherence):

- They are cell to cell spot adhesion present on the lateral membrane of cells, resist shearing force in the squamous epithelium.(Figure 1.15).

4- Hemidesmosomes:

- They anchor cells to the extracellular matrix **(ECM).**
- They composed of integrin cell adhesion proteins, which play important roles in cellular attachment and in signal transduction.

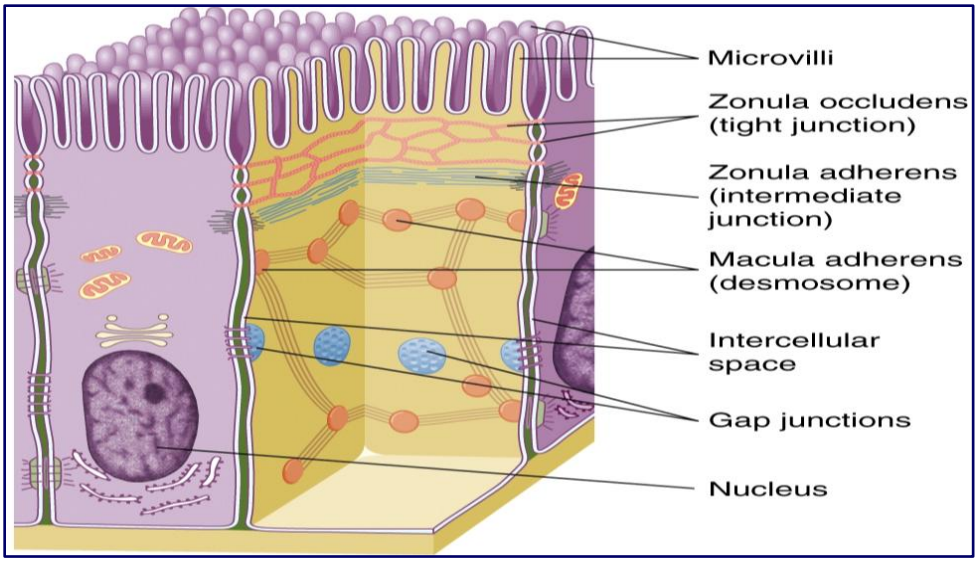


Figure (1.15): A hypothetical cell shows different types of junctions. (Randall D., Burggren W.and French K. Eckert Animal Physiology. New York, W.H. Freeman and Company, 2002).

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Chapter Two

The Cell Cycle and Genes Control of Protein Synthesis

2

Organization of the genetic material within the cell

Overview

- Cell division is a complex process requiring precise replication the genetic material **(DNA).**
- The entire DNA in a cell is called the **cell's genome**.
- The DNA is divided into many **genes**, each of which contains one piece of information necessary for cell function. These structures called **chromosomes**.
- **Chromosomes** consist of long strands of DNA associated with proteins.
- **Chromosome** is composed of **Chromatin** which is made up of DNA and associated proteins. Figure (2.1).
- The chromatin shape changes depending on the **cell cycle stage**. When the cell is not dividing the chromatin is stretched out into long thin strands and is barely visible. After DNA replication and when the cell gets ready to divide, the chromatin condenses to form tightly coiled, highly visible, dark bodies, called chromosomes, which are visible under the microscope.
- In sexually reproducing organisms, these chromosomes are in pairs .One number of each pair is derived from each parent
- Chromosomes numbers are specific to specific type. Most cells are body cells **(somatic cells**).In human somatic cells contain 46 chromosomes, divided into 23 pairs.
- Human gametes (**sperm or eggs**) have 23 chromosomes, half the number in a somatic cell.
- When an egg and sperm combine during reproduction, somatic cell chromosome number will be restored.

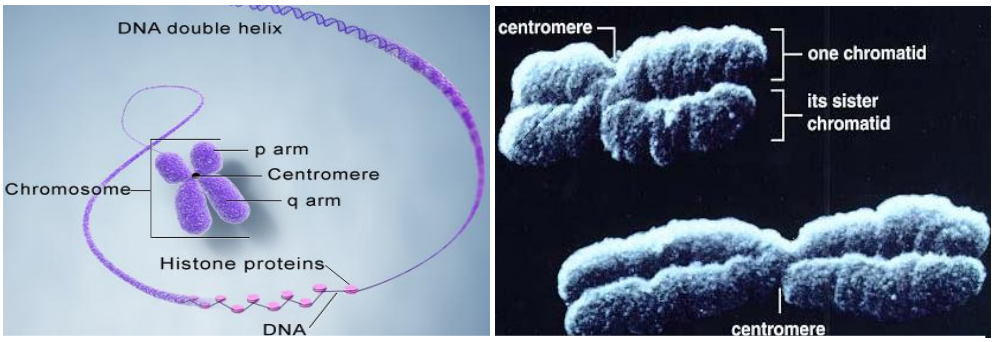

Figure (2.1): Chromosome structure.(Reece J.B., Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

Cell Cycle

Overview

- The cell cycle includes all the events that occur from the cell's formation until it divides to produce two new cells.
- Cell cycle has two stages: **An interphase** and a **cell division** (mitotic phase (M)).Figure (2.2).

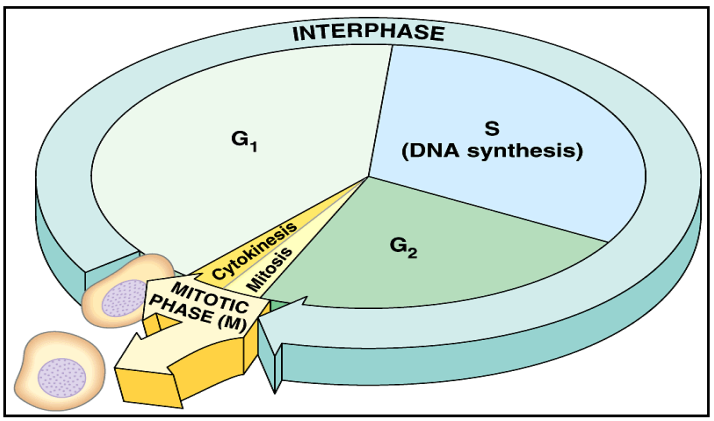

Figure (2.2): Cell cycle. (Marieb E.N .Essential of Human Anatomy and Physiology. San Francisco, Pearson Education, Inc., 2012).

1. Interphase

- Interphase is the phase between cell divisions.
- It represents 90% of the cell cycle.
- During this time ,the cell carries out the metabolic activities necessary for life and perform its specialized functions ,e.g.,secreting digestive enzymes
- It prepares the cell to divide, e.g.an increase in cell size because many cell components double in quantity and replication of cell's DNA.
- The centerioles within the centrosome are also duplicated.
- Consequently when the cell divides, each new cell receives organelles and DNA necessary for continued functioning.
- It has three phases:
  1- **The G_1 phase** (first gap) is for growth.
  2- **The S phase**(synthesis) when the chromosomes are copied (DNA synthesis)
  3- **The G_2 phase** (second gap): the cell completes preparations for division.

DNA replication

- DNA replication is the process by which two new strands of DNA are made using the two existing strands as template.
- During interphase DNA and its associated proteins appear as dispersed chromatin threads within the nucleus.
- When DNA replication begins the two strands of each DNA molecule separate from each other .Each strand work as a template for production of new complementary strand of DNA, which is formed as **complementary nucleotides pair** with the existing nucleotides of each strand of the separated DNA molecule.
- The replication of a DNA molecule begins at special sites, **origins of replication**. There may be hundreds or thousands of origin sites per chromosome .At the origin sites, the DNA strands separate forming a replication "bubble" with **replication forks** at each end.
- The production of new nucleotides strands is catalyzed by **DNA polymerase**, an enzyme that adds new nucleotides at a replication fork.
- The rate of elongation is about 50 per second in human cells.
- The strands are formed differently because the antiparallel orientation of the strands.
- Each DNA strand has a **3' end** with **a free hydroxyl group** attached to **deoxyribose** and a **5' end** with **a free phosphate group** attached to deoxyribose.Figure (2.3).
- The 5' -> 3' direction of one strand runs counter to the 3' -> 5' direction of the other strand.
- DNA polymerases can only add nucleotides to the free 3' end of a growing DNA strand.
- At the replication fork, one parental strand (3'-> 5' into the fork), the **leading strand,** can be used by polymerases as a template for a continuous complimentary strand.
- The other parental strand (5'->3' into the fork), the **lagging strand**, is copied away from the fork in short segments (**Okazaki fragments).** Figure (2.4).
- Okazaki fragments, each about 100-200 nucleotides, are joined by **DNA ligase** to form the **sugar-phosphate backbone** of a single DNA strand.
- As a result of DNA replication, two **identical DNA molecules** are produced. .Each of theseDNA molecules has one strand of nucleotides derived from the original DNA molecule and one newly synthesized strand.

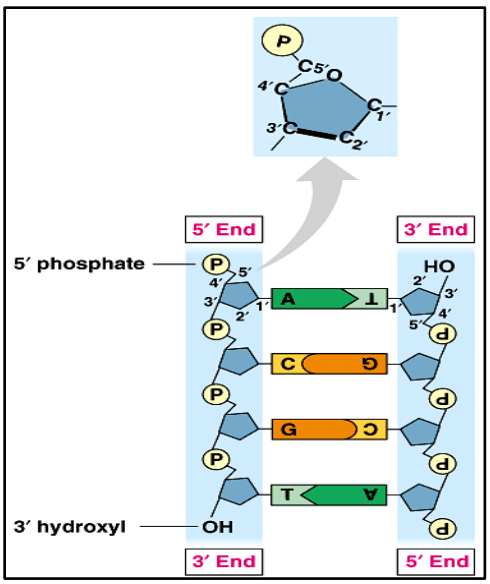

Figure (2.3): Each DNA strand has a 3' end with a free hydroxyl group attached to deoxyribose and a 5' end with a free phosphate group attached to deoxyribose.

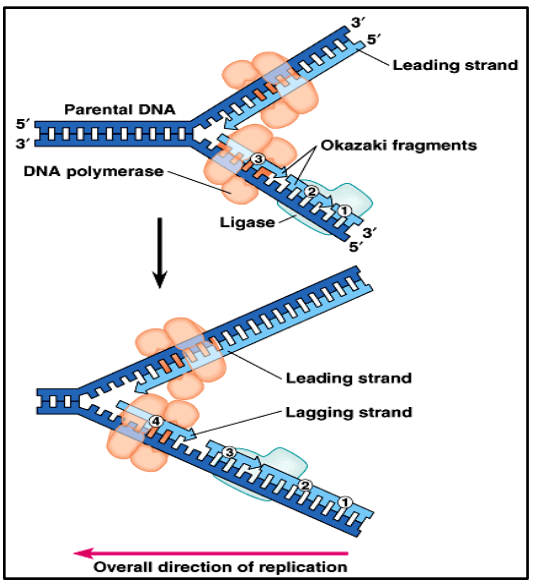

Figure (2.4): Leading strand, lagging strand and Okazaki fragment.

(Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings,2014).

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2. Cell Division

Overview

- A single cell reproduces by cell division, where the cell and its genetic material are copied and passed along to its offspring.
- The cell division is responsible for carrying out three essential functions:
  1- **Reproduction:** In many single cell organisms, simple cell division is the major form of reproduction, in which the cell replicates itself precisely,
  2- **Growth and development**: Sexually producing organism, e.g., a single **fertilized egg** or **zygote** of human exposes to series of divisions to produce trillions of cells.
  3- **Repair and replacement of cells:** The cells continually wear out due to injury and diseases and they must be replaced by other cells.
- Cell division involves two major events: the division of the nucleus, by **mitosis,** to form two nuclei and then division of cytoplasm (**cytokinesis**) to form two new cells.

1-Mitosis

- Mitosis is the division of the nucleus into two nuclei, each of which has the same amount and type of DNA as the original nucleus.
- Mitosis is divided into five phases: **prophase**, **prometaphase, metaphase**, **anaphase**, and **telophase**.(Figure2.5).
- By late interphase, the chromosomes have been duplicated but are loosely packed.
- The centrosomes have been duplicated and begin to organize microtubules into an aster (star).

1. In prophase

- The chromosomes are tightly coiled, with sister chromatids joined together.
- The nucleoli disappear.
- The mitotic spindle begins to form and appears to push the centrosomes away from each other toward opposite ends (poles) of the cell.

2. Prometaphase

- The nuclear envelope fragments and microtubules from the spindle interact with the chromosomes.
- Microtubules from one pole attach to one of two **kinetochores**, special regions of the centromere, while microtubules from the other pole attach to the other kinetochore.

3. Metaphase

- The spindle fibers push the sister chromatids until they are all arranged at the metaphase plate, an imaginary plane equidistant between the poles, defining metaphase**.**

4. Anaphase

- The centromeres divide, separating the sister chromatids.
- Each is now pulled toward the pole to which it is attached by spindle fibers.
- By the end, the two poles have equivalent collections of chromosomes.

5. Telophase

- The cell continues to elongate as free spindle fibers from each centrosome push off each other.
- Two nuclei begin for form, surrounded by the fragments of the parent's nuclear envelope.
- Chromatin becomes less tightly coiled.
- **Cytokinesis**, division of the cytoplasm, begins.

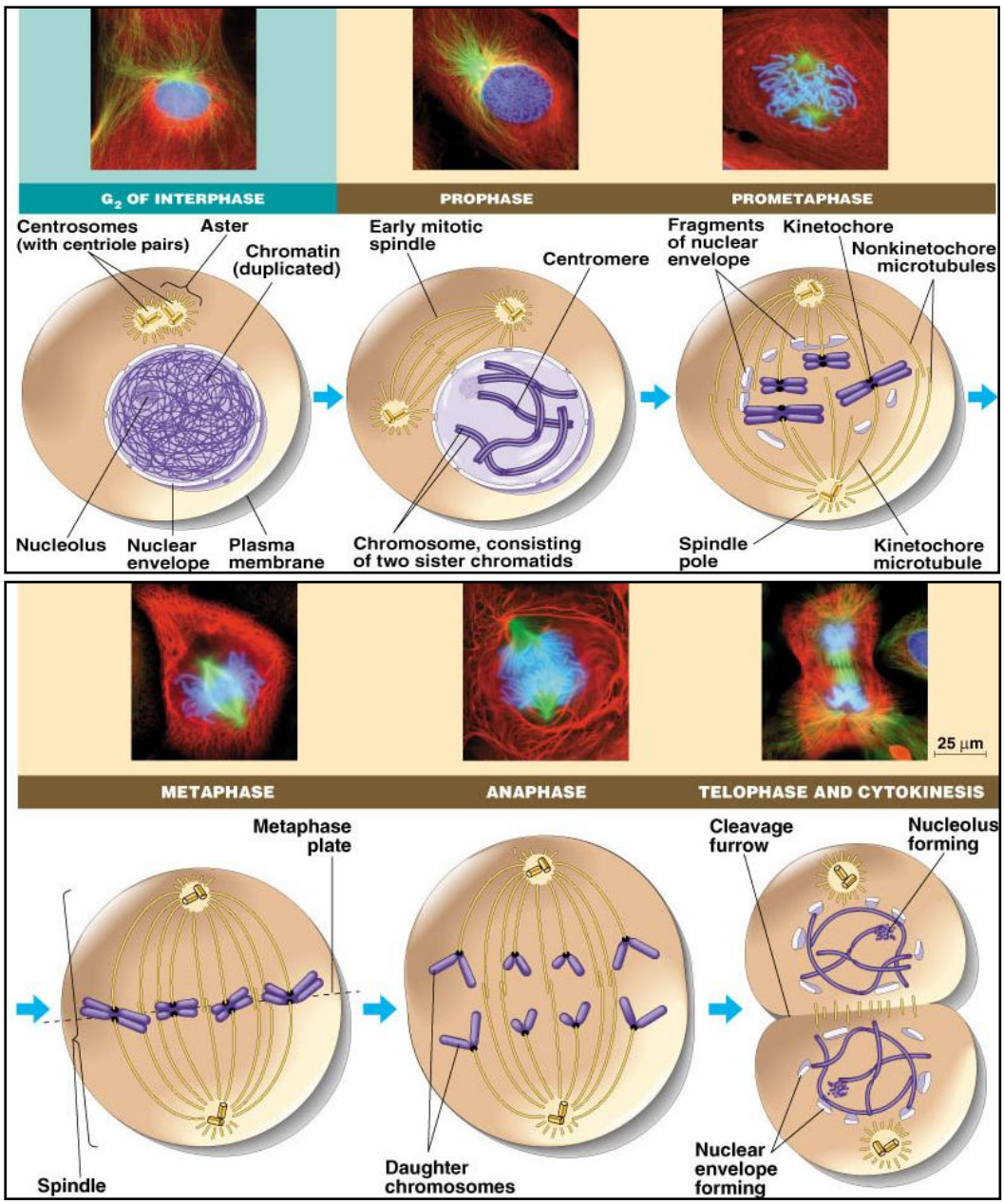
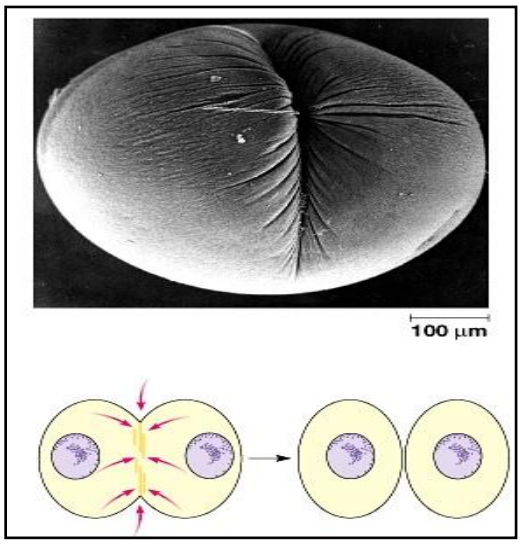


Figure (2.5): Diagramatic and overall view of mitosis phases.(Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings,2014).

2- Cytokinesis

- Cytokinesis is the division of cytoplasm to produce two new cells.
- Cytokinesis begins in anaphase, continues through telophase and end in the following interphase.
- The first sign is the formation of **cleavage furrow**, which form midway between the centrioles.
- A contractile ring composed of actin filaments pulls the plasma membrane inward, dividing the cell into halves. (Figure 2.7).

- Cytokinesis is completed when the membranes of the halves separate at the cleavage furrow to form two separated cells.



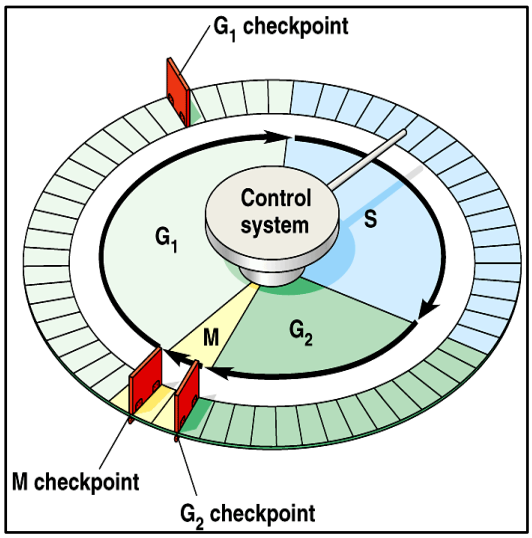


Figure (2.6): Formation of contractile ring. Figure (2.7): Control system.during cytokinesis. (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings,2014).

Regulation of the Cell Cycle

Overview

- The timing and rates of cell division, in different parts the body, are crucial for normal growth, development, and maintenance.
- The frequency of cell division varies with cell type. Some human cells divide frequently throughout life (**skin cells**), others have the ability to divide, but keep it in reserve (**liver cells),** and mature nerve and muscle cells do not divide after maturity.
- The cell cycle events are directed by a **cell cycle control system**. (Figure 2.7).This triggers and coordinates key events in the cell cycle.
- The control cycle has a built-in clock, but it is also regulated by **external adjustments** and **internal controls.**
- A **checkpoint** in the cell cycle is a critical control point where stop or go signals to regulate the cycle.
- Three major checkpoints are found, **the G_1, G_2, and M phases.**
- For many cells, the G_1 checkpoint, the restriction point in mammalian cells, is the most important.
- If the cell receives a go-ahead signal, it usually completes the cell cycle and divides. If it does not receive a go-ahead signal, the cell exits the cycle and

switches to a non-dividing state, the **G_0 phase**. ***Most human cells are in this phase.***

- Liver cells can be "called back" to the cell cycle by external factor (growth factors), but highly specialized nerve and muscle cells never divide.
- Some **control molecules** such as **protein kinases** activate and deactivate other protein . The levels of these kinases are present in constant amounts, but these kinases require a second protein, a **cyclin**,which fluctuate cyclically,to become activated.
- The complex of kinases and cyclin forms **cyclin-dependent kinases** (**Cdks**).
- Cyclin levels rise sharply throughout interphase, then fall abruptly during mitosis. Figure (2.8).

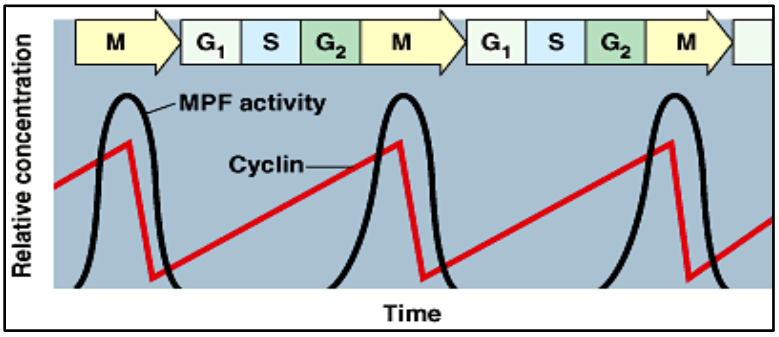


Figure (2.8): Peaks in the activity of Cdk complex, MPF, correspond to peaks in cyclin concentration. (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings,2014.)

- Peaks in the activity of one Cdk complex, **MPF (maturation-promoting factor)**, correspond to peaks in cyclin concentration; trigger the cell's passage past the G_2 checkpoint to the M phase.
- MPF promotes mitosis by phosphorylating a variety of other protein kinases.
- The key G_1 checkpoint is regulated by three Cdk proteins and several cyclins.

External adjustments

- A variety of external chemical and physical factors can influence cell division.
- **growth factors**, proteins released by one group of cells that stimulate other cells to divide,e.g., **platelet-derived growth factors (PDGF),** produced by platelet, in the injuried area resulting in proliferation of fibroblasts to help heal the wound.
- Each cell type probably responds specifically to a certain growth factor or combination of factors.
- The Growth factors appear to be a key in **density-dependent inhibition** of cell division.
- Most animal cells also exhibit **anchorage dependence** for cell division.

Cell cycle controls in cancer cells.

- Cancer cells divide excessively and invade other tissues because they are free of the body's control mechanisms.
- Cancer cells do not stop dividing when growth factors are depleted either because they manufacture their own, , or problem in the cell cycle control system.
- If the cancer cells stop dividing, they do it at random points, not at the normal checkpoints in the cell cycle.
- Cancer cell may divide indefinitely if they have a continual supply of nutrients. In contrast, mammalian cells divide 20 to 50 times under culture conditions before they stop, age, and die.
- The abnormal behavior of cancer cells begins when a single cell in a tissue undergoes a **transformation** that converts it from a normal cell to a cancer cell.
- Normally, the immune system recognizes and destroys transformed cells. However, cells that evade destruction proliferate to form a **tumor**, a mass of abnormal cells.
- If the abnormal cells remain at the originating site, the lump is called a **benign tumor** (most do not cause serious problems and can be removed by surgery),but when cells leave the origin site to impair the functions of an organ or more, this results in a **malignant tumor.**
- In addition to chromosomal and metabolic abnormalities, cancer cells often lose attachment to nearby cells, are carried by the blood and lymph system to other tissues, and start more tumors in a event called **metastasis**. Figure (2.9).
- The causes of cancer are diverse. However, cellular transformation always involves the alteration of genes that influence the cell cycle control system.

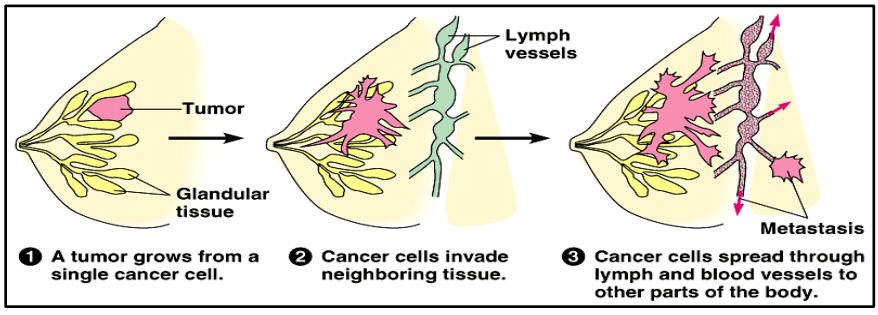


Figure (2.9): Breast malignancy and its metastasis.(Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

Meiosis

- Meiosis is a form of cell division that happens in sexually reproducing organisms by which two nuclear divisions (**meiosis I** and **meiosis II**) occur without the chromosomal replication in between, This leads to produce four haploid gametes (sex cells), each containing one of every pair of **homologous chromosomes** (that is, with the maternal and paternal chromosomes being distributed randomly between the cells).
- **Homologous chromosomes** are pairs of chromosomes, each pair with the same length, centromere position, and staining pattern, and carry genes that control the same inherited characters.
- Each final produced cell has only half as many chromosomes as the parent cell.
- Meiosis reduces chromosomes number by copying the chromosome once, but dividing twice. Figure (2.10).
- The first division, **meiosis I**, separates homologous chromosomes and the second, **meiosis II**, separates **sister chromatids.**
- Mitosis and meiosis have several differences, summarized in table(2.1)

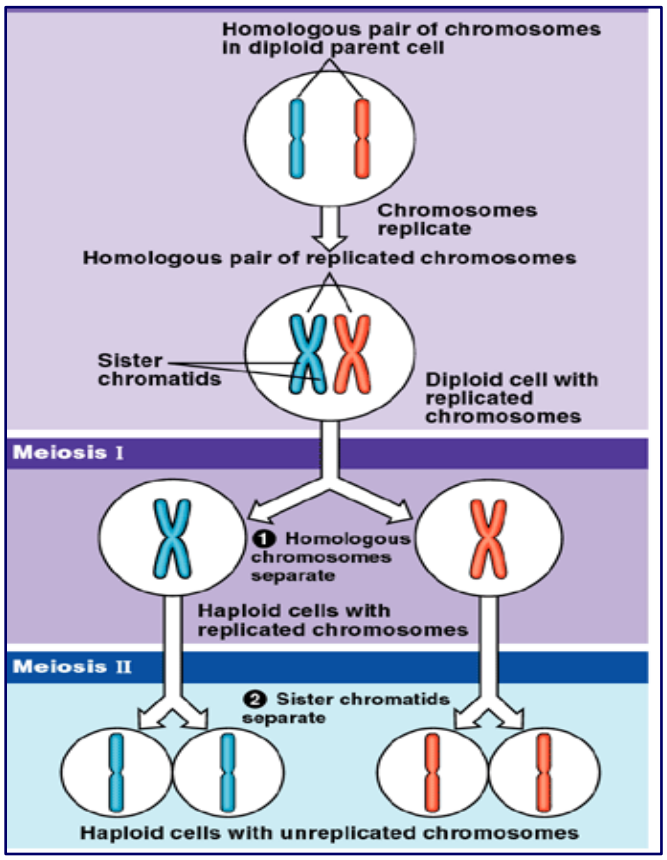


Figure (2.10): The two consecutive cell divisions, meiosis I meiosis II, (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

Table (2.1): The differences in the events that occur during mitosis and meiosis. (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

Event	Mitosis	Meiosis
DNA replication	Occurs during interphase before nuclear division begins	Occurs once, during the interphase before meiosis I begins
Number of divisions	One, including prophase, metaphase, anaphase, and telophase	Two, each including prophase, metaphase, anaphase, and telophase
Synapsis of homologous chromosomes	Does not occur	Synapsis is unique to meiosis: During prophase I, the homologous chromosomes join along their length, forming tetrads (groups of four chromatids); synapsis is associated with crossing over between nonsister chromatids
Number of daughter cells and genetic composition	Two, each diploid ($2n$) and genetically identical to the parent cell	Four, each haploid (n), containing half as many chromosomes as the parent cell; genetically nonidentical to the parent cell and to each other
Role in the animal body	Enables multicellular adult to arise from zygote; produces cells for growth and tissue repair	Produces gametes; reduces chromosome number by half and introduces genetic variability among the gametes

Genes and Proteins synthesis

Overview

- The DNA contains information in the form of specific sequences of nucleotides along the DNA strands.
- The DNA inherited by an organism leads to specific traits by dictating the synthesis of proteins.
- Proteins are the links between genotype and phenotype.
- The study of metabolic defects provided evidence that genes specify proteins.
- **Transcription** and **translation** are the two main processes linking gene to protein

The Transcription and Translation processes

Overview

- Genes provide the instructions for making specific proteins.
- The bridge between DNA and protein synthesis is **RNA**
- The RNA molecule consists of a single strand.
- RNA is chemically similar to DNA, except that it contains ribose as its sugar and substitutes the nitrogenous base uracil for thymine.
- In DNA or RNA, the four nucleotide monomers act like the letters of the alphabet to communicate information.
- The specific sequence of hundreds or thousands of nucleotides in each gene carries the information for the primary structure of a protein, the linear order of the 20 possible **amino acids.**

- **During transcription**, a DNA strand provides a template for the synthesis of a complementary RNA strand. This process is used to synthesize any type of RNA from a DNA template.
- Transcription of a gene produces a **messenger RNA** (**mRNA**) molecule.
- During **translation**, the information contained in the order of nucleotides in mRNA is used to determine the amino acid sequence of a polypeptide..
- Almost all transcription occurs in the nucleus and translation occurs mainly at ribosomes in the cytoplasm. (Figure 2.11).
- **In summary**: genes program protein synthesis via genetic messenger RNA.
- The molecular chain of command in a cell is:[**DNA →RNA → protein].**

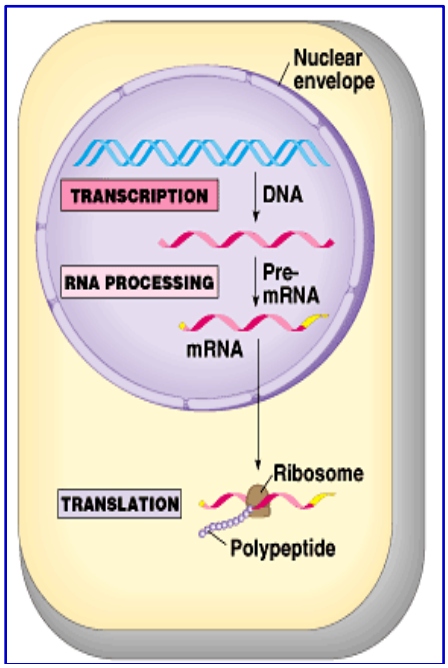


Figure (2.11): RNA processing.

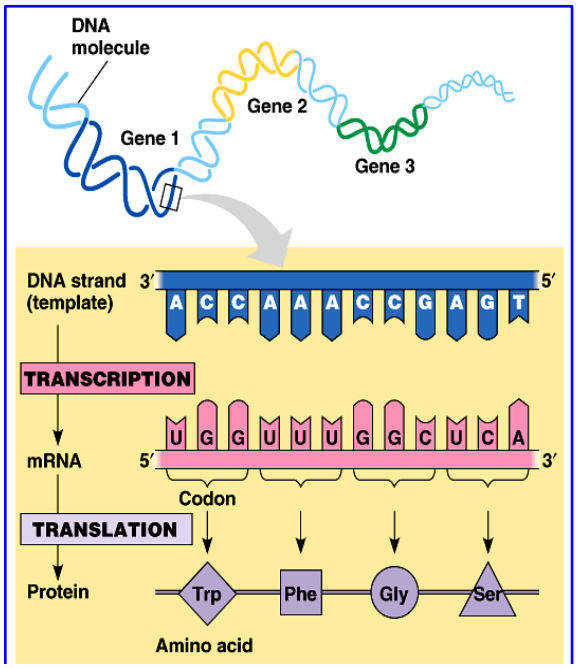


Figure (2.12): Transcription and translation.

(Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

- In the **genetic code**, nucleotide triplets specify amino acids.
- Triplets of **nucleotide bases** are the smallest units of uniform length that can code for all the amino acids.
- In the triplet code, three consecutive bases specify an amino acid, creating 43 (64) possible code words.
- The genetic instructions for a polypeptide chain are written in DNA as a series of three-nucleotide words
- During transcription, one DNA strand, the template strand, provides a template for ordering the sequence of nucleotides in an RNA transcript. Figure(2.12)
- The complementary RNA molecule is synthesized according to base-pairing rules, except that **uracil** is the complementary base to **adenine.**

- **During translation**, blocks of three nucleotides, **codons**, are decoded into a sequence of amino acids. Figure (2.13).
- The **codons** are read in the **5'→3'** direction along the **mRNA.**
- Each **codon** specifies which **one** of the **20 amino** acids will be incorporated at the corresponding position along a polypeptide.
- Because the **base triplets,** the number of nucleotides making up a genetic message must be **three times** the number of amino acids making up the protein product. It would take at least **300 nucleotides** to code for a polypeptide that is **100 amino acids** long. (Figure 2.13).
- 61 of 64 triplets code for amino acids.
- The codon **AUG** codes for the amino acid **methionine** and indicates the start of translation.
- Three codons do not indicate amino acids but signal the termination of translation.

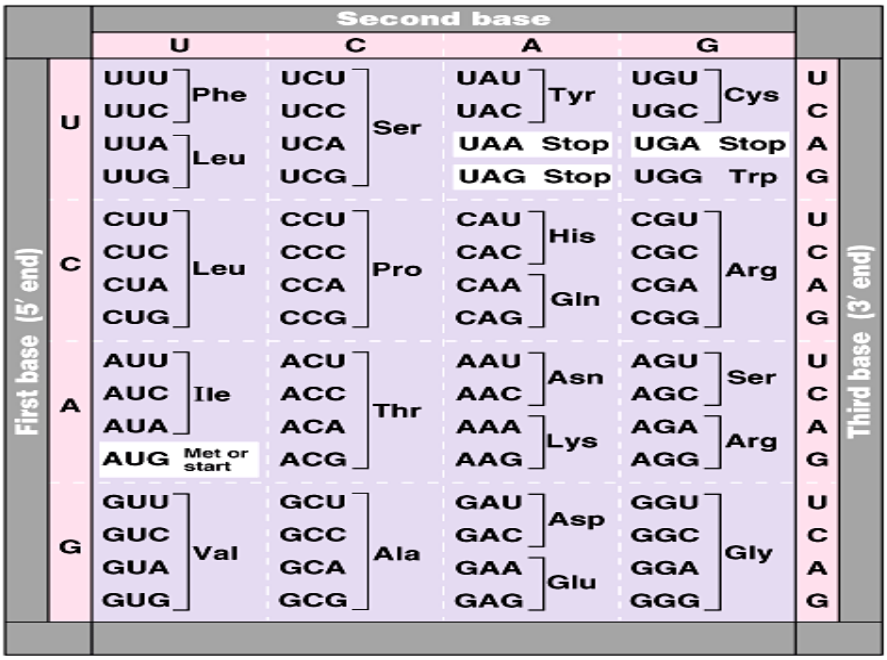


Figure (2.13):64 triplets, 61 for amino acids, AUG codes for aminoacid methionine and to start translation, three codons UAA, UAG, UGA to stop translation. (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

- There are several different codons that would indicate a specific amino acid. However, one codon indicates only one amino acid. But, a specific amino acid may be decoded by several possible codons.
- Both **GAA** and **GAG** specify **glutamate**, but no other amino acid. Codons synonymous for the same amino acid often differ only in the **third codon position.**

- To extract the message from the genetic code requires specifying the correct starting point. This establishes the **reading frame** and subsequent codons are read in groups of three nucleotides.
- The cell's protein-synthesizing machinery reads the message as a series of nonoverlapping three-letter words.
- **In summary,** genetic information is encoded as a sequence of nonoverlapping base triplets, or codons, each of which is translated into a specific amino acid during protein synthesis.

Production of proteins

Translation

- In the process of translation, the cell interprets a series of codons along the mRNA molecule.
- **Transfer RNA (tRNA)** transfers amino acids from the cytoplasm's pool to a ribosome.
- The ribosome adds each amino acid carried by tRNA to the growing end of the polypeptide chain.
- During translation, each type of tRNA links a mRNA **codon** with the appropriate amino acid.(Figure 2.14).
- Each tRNA arriving at the ribosome carries a specific amino acid at one end and a specific nucleotide triplet, an **anticodon**, at the other.
- Codon by codon**,** tRNAs deposit amino acids in the prescribed order and the ribosome joins them into a polypeptide chain.

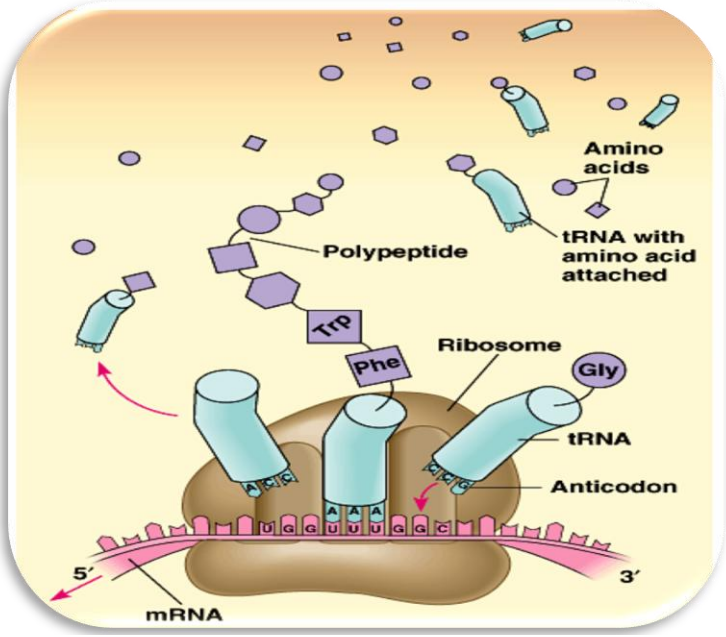


Figure (2.14):Translation of mRNA to produce a protein.(Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

- There are three stages: **initiation, elongation** and **termination.**

  1- Initiation brings together mRNA, a tRNA with the first amino acid, and the two ribosomal subunits.(Figure 2.15).

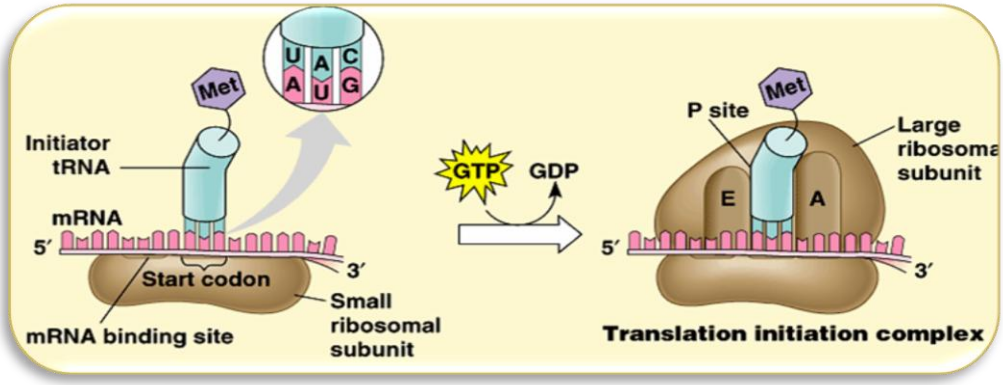


Figure (2.15): The initiation stage. (Reece J.B., Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

2- Elongation consists of a series of ***three steps cycles***, as each amino acid is added to the proceeding one. Figure (2.16)

- **Codon recognition**:an elongation factor assists hydrogen bonding between the **mRNA codon** under the A site with the corresonding **anticodon of tRNA** carrying the appropriate amino acid.
- **Peptide bond formation**:rRNA molecule catalyzes the formation of a peptide bond between the polypeptide in the P site with the new amino acid in the A site.
- **Translocation**,: the ribosome moves the tRNA with the attached polypeptide from the A site to the P site.

- The three steps of elongation continue codon by codon to add amino acids until the polypeptide chain is completed.

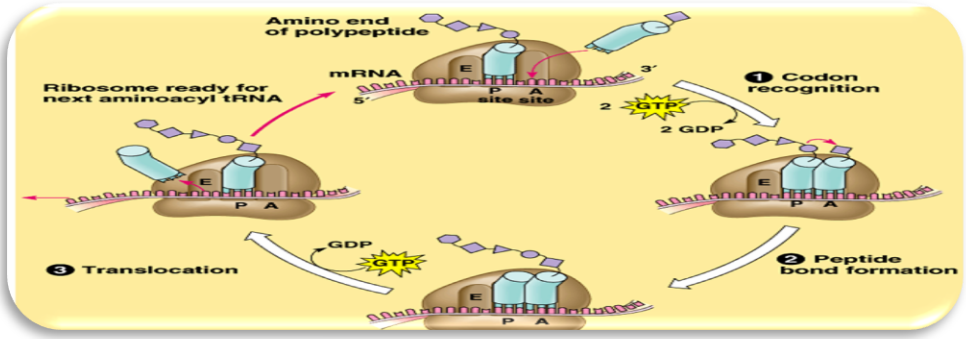


Figure (2.16): steps of elongation. (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

3- Termination occurs when one of the three stop codons reaches the A site. A ***release factor*** binds to the stop codon and hydrolyzes the bond between the polypeptide and its tRNA in the P site. This frees the polypeptide and the translation complex disassembles. Figure (2.17).

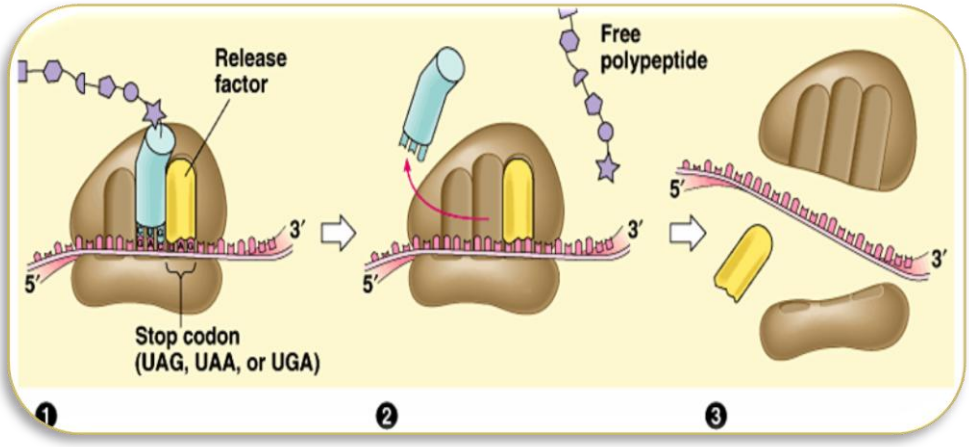


Figure (2.17): Termination stage. (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

- Typically a single mRNA is used to make many copies of a polypeptide simultaneously. Multiple ribosomes, **polyribosomes**, may trail along the same mRNA.
- A ribosome requires less than a minute to translate an average-sized mRNA into a polypeptide.
- During and after synthesis, a polypeptide coils and folds to its three-dimensional shape spontaneously. The primary structure, the order of amino acids, determines the secondary and tertiary structure.
- Proteins may require **posttranslational modifications** before doing their particular job. This may require:
  - Additions like sugars, lipids, or phosphate groups to amino acids.
  - Enzymes may remove some amino acids or cleave whole polypeptide chains.
  - Two or more polypeptides may join to form a protein.

Regulation of Genetic Expression

- Cells become specialized because of **inactivation** of certain parts of the DNA molecule and **activation** of other parts.
- The level of DNA activity and protein production can be controlled internally by regulatory substances secreted by other cells.

Genetic Disorders

- A genetic disorder is a failure of **structure**, **function** or **both** as a result of abnormalities in a person's genetic makeup.
- Genetic disorders involve either a single gene or an entire chromosome, as in the case of **aneuploidy,** (see below).
- A mutation is a change in a gene that usually involves a change in the number or kinds of nucleotide composing the DNA.
- Mutations are known to occur randomly without known cause, but they can be caused by chemicals, radiation and viruses. Agents that cause mutations are called **mutagens.**
- Once a mutation has occurred, however the abnormal trait can be passed from one generation to the next.
- **A point mutation** is a mutation involving a single nucleotide change. For example, **sickle-cell disease** is caused by a mutation of a single base pair in the gene that codes for one of the polypeptides of hemoglobin. Figure (2.18)
- A change in a single nucleotide from T to A in the DNA template leads to an abnormal protein.

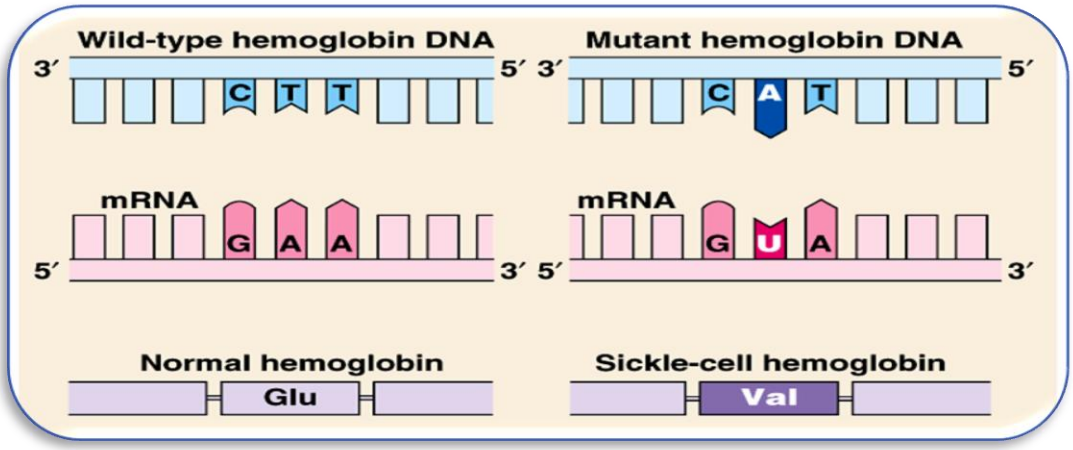


Figure (2.18): A mutation of a single base pair in the gene. (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

- **Structural mutations** are the mutations that change the sequence or number of nucleotides involves changes in chromosome structure.
- **Segregation errors** that may occur during meiosis cause changes in the chromosome number in the gametes. As the chromosomes separate during meiosis, the two members of homologous pair may become stick and not segregate normally .As a result the one of the new daughter cell receives both chromosomes and the other daughter cell receives none .This is called **nondisjunction.** When the gametes are fertilized, the resulting zygote has either 47 chromosomes or 45 chromosomes rather than normal 46, a condition called **aneuploidy**, which are usually lethal. Down syndrome is an example of an aneuploidy that is not always lethal.

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Chapter Three

Nervous System 3

Nervous system

Overview

- The nervous system is unique in that it affects every other system of the body.
- **Functions of nervous system :**
  1. Nervous system detects external and internal stimuli(sensory input)
  2. It Processes and responds to sensory input (integration)
  3. It Controls body movements through skeletal muscles.
  4. It maintains homeostasis by regulation other system.
  5. It is the center for mental activities.

Organization of the nervous system

- The nervous system is anatomically divided into two divisions:

1- The **central nervous system (CNS)** is responsible for analyzing data received from sense organs and making decisions. It consists of the **brain** and the **spinal cord**. Division of nervous system is illustrated in figure (3.1).

2- The **peripheral nervous system (PNS)** is the nerves around the body. It consists of sensory receptors, nerves, ganglia and plexuses. The PNS has two divisions:

- The **sensory system** (**afferent fibers**):transmits action potential from sex organs to the CNS, and usually consists of single neurons that have their cell bodies in ganglia
- The **motor system** (**efferent nerves**): transmit action potential from CNS to glands, muscles. This can be subdivided into:
  - The **somatic system** controls contraction of skeletal muscle.
  - The **autonomic system (ANS)** controls the cardiac muscle, smooth muscle and glands. This further subdivided into:
    1. **Sympathetic division**, which is active during physical activity.
    2. **Parasympathetic division** regulates ***functions at rest*** and ***enteric nervous system,*** which control the digestive system.

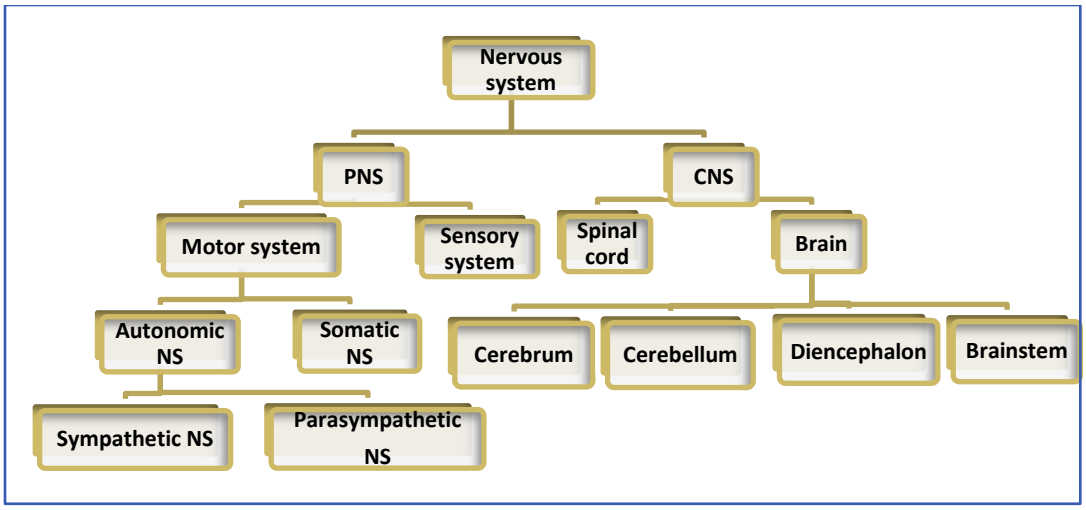


Figure (3. 1): Nervous system divisions.

Cells of the nervous system

- The nervous system is made up of **neurons** (nerve cells) and **neuroglia** to support cells. (Figure3.2).

1-Neurons: This is made up of:

- **The cell body** is the primary site of protein synthesis. It contains the nucleus and cell organelles.
- **Dendrites** are a mass of very short and branched filaments receive impulses from other neurons.
- **The axon** is a very thin tube surrounded by neuroglia and may be >1m long. It transports the impulse around the body. The axon connects to the cell body by an **axon hillock**. This where an impulse (action potential) starts.
- **Synaptic knobs** at the end of the axon pass on the impulse usually use chemical neurotransmitters, to the next neuron.

Type of neurons

1- **Multipolar neurons** have several dendrites and single axon ,e.g., Interneurons and motor neurons
2- **Bipolar neurons** have a single axon and dendrite, they are found as components of sensory organs.
3- **Unipolar neurons** have a single axon .Most sensory neurons are unipolar.

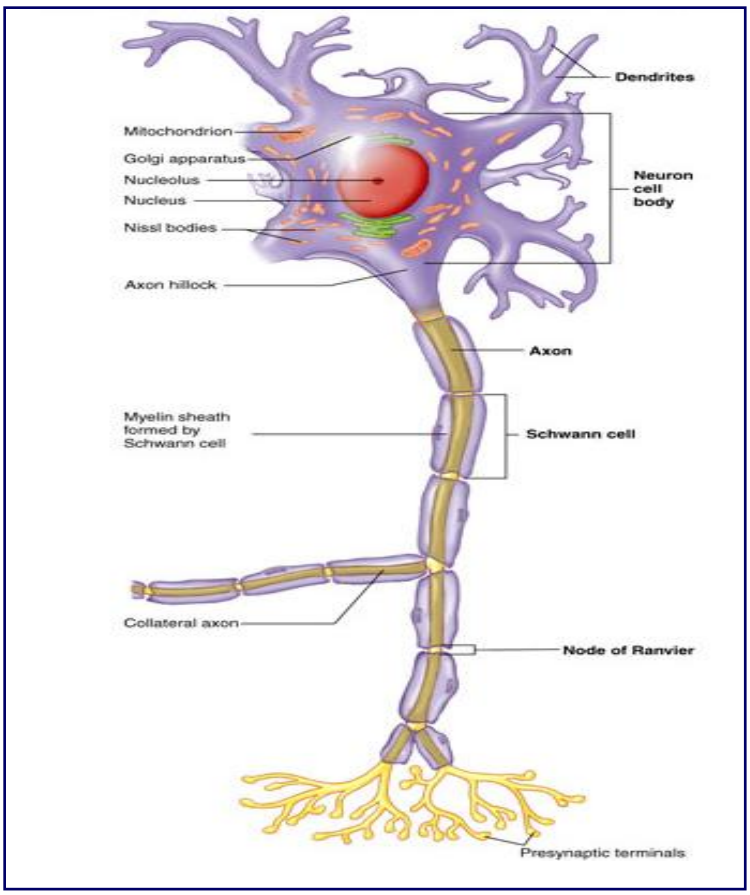


Figure (3.2): Neurons. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

2- Neuroglia.

a- Neuroglia of CNS ,(figure 3.3:a,b,c,d,e)

1. **Astrocytes** provide structural support for neurons and blood vessels. Astrocytes influence the functioning of the blood brain barrier and process substances that pass through it.Astrocytes isolate damaged tissue and limit the spread of inflammation.
2. **Ependymal cells** secrete and circulate using cilia the cerebrospinal fluid surrounding the CNS. The fluid forms a reservoir and transport system for nutrients (water, salts, and sugars) as well as being a shock absorber against physical damage. They line the ventricle of the brain and the central canal of the spinal cord.
3. **Microglia** are amoeboid phagocytic cells that destroy bacteria and dead cells.
4. **An oligodendrocyte** forms myelin sheaths around the axon of several CNS neurons.

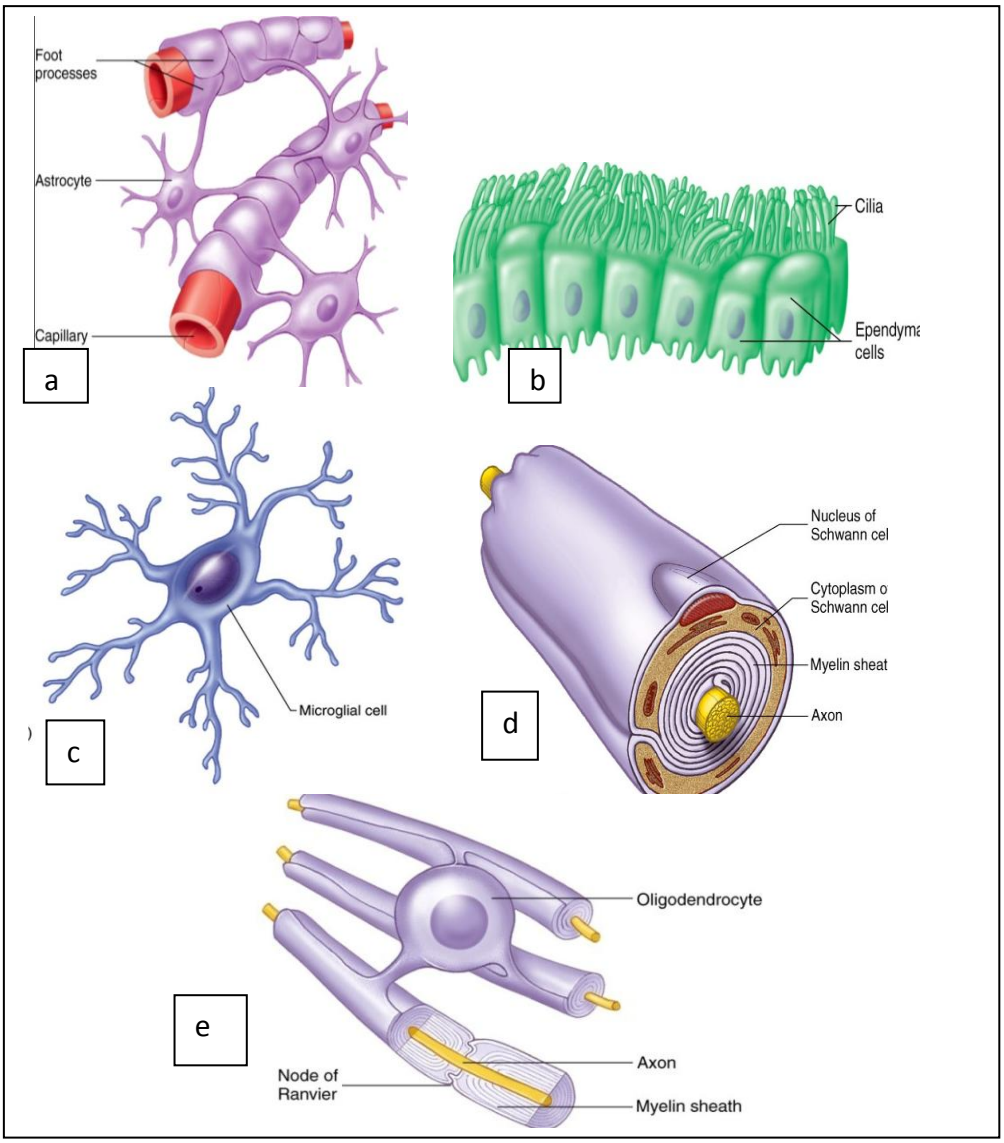


Figure (3.3): Types of Neuroglia, (a): Astrocytes (b): Ependymal cells, (c): Microglia (d): A Schwann cells, (e): An oligodendrocyte. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

b- Neuroglia of PNS

1. **A Schwann cells** form myelin sheath of the axon of the PNS neurons. The cell wraps itself concentrically around the axon to produce a thick myelin sheath. Myelin is a fatty substance forming an insulator, which prevents the impulse from escaping
2. **Satellite cells** support and nourish neuron cell bodies within ganglia.

Myelinated and unmyelinated axon

a. **Myelinated axons** are wrapped by several layers of plasma membrane from Shwann cells or oligodendrocytes .Space between the wrappings are the ***node of Ranvier.*** Figure (3 .4).Myelinated axons conduct action potential rapidly.

b. **Unmyelinated** axons rest in invaginations of Schwann cells or oligodendrocyte. They conduct action potential slowly.

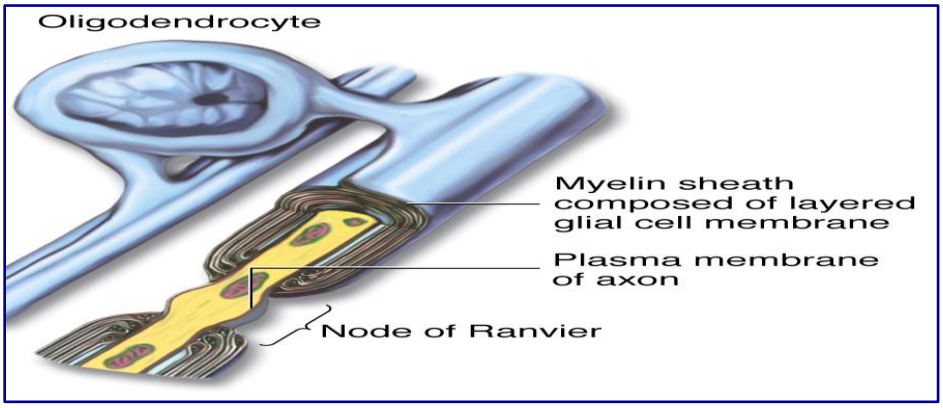


Figure (3.4): Node of Ranvier. (Randall D., Burggren W. and French K. Eckert Animal Physiology . New York, W.H. Freeman and Company, 2002).

Organization of Nervous Tissue

- Nervous tissue can be grouped into **white** and **gray matter**
- Whit matter consists of myelinated axons, it propagates action potential.White matter forms nerve tracts in the CNS and nerves in the PNS.
- Gray matter consists of collections of neurons cell bodies or unmyelinated axons. Gray matter forms cortex and nuclei in the CNS and ganglia in PNS.

Membrane potential, Action Potential and Nerve Transmission

Overview

- Plasma membrane of the neurons is the site of **electrical signaling**, and it plays crucial role in cell to cell interactions that occur during the development.
- Neurons are highly **irritable** or **excitable** (responsive to stimuli).
- When a neuron is adequately stimulated, an electrical impulse is generated and conducted along the axon .This response is called **action potential or nerve impulse.**
- **Action potentials** are important **means** by which cells transfer information from one part of the body to another.
- Electrical properties of the cells result from the **ionic concentration differences** across the plasma membrane.

- There are concentration differences for positively charged ions (**cations**) and negatively charged ions (**anions**) between the intercellular and extracellular fluids. These difference result primary from :
  1. The Na^+ - K^+ pump
  2. The permeability characteristic of the plasma membrane.

Concentration Differences Across The Plasma Membrane

- The Na^+ - K^+ pump moves ions by active transport .K+ move into the cell, and Na^+ move out of it.
- The concentration of K^+ and negatively charged proteins is higher inside, and the concentrations of Na^+ and Cl^- are higher outside the cell.
- Negative charged proteins and other negative charge ions are synthesized inside the cell and cannot diffuse out of it .They repel Cl^- .
- The permeability of the plasma membrane to ions is determined by **leak channels** and **gated ion channels :**
  - **Potassium ions leak channels** are more numerous than **Na^+ leak channels**, thus the plasma membrane is more permeable to K^+ than to Na^+ at rest.
  - **Membrane channels** are large proteins with several subunits of amino acids chains across the membrane. Membrane ions channels may be **leakage channels** (**non gated**), and they are always open, or gated channels. **Gated ion channels** include:
    1- **Ligand gated channels,** open when appropriate chemicals**"neurotransmitters**" bind.
    2- **Voltage gated channels** open and close in response to change in membrane potential.
    3- **Mechanically gated channels** open in response to physical deformation of the receptors.

Resting potential

- A potential difference across the plasma membrane is known as **membrane potential or voltage.**
- In the resting state all body cells(not just neurons) a resting potential of about **-70mv,** so the inside of the cell is **negatively charged** compared with the fluid surrounding the cell. This results from several factors:-

  - The plasma membrane contains **ionic pumps** (using ATP to pump against the concentration gradient), which pump sodium ions out and potassium ions in to the cell. But, **3 Na^+ are pumped out for each 2 K^+ pumped in** (making the outside of the cell more positive).Figure (3.5).

  - Although gradients are set up by the Na/K pump, the ions cannot diffuse back through the plasma membrane. However, the membrane contains specific Na^+ channels and K^+ channels, but the **Na^+ channels are shut**. Thus the Na^+ pumped out cannot diffuse back in. However, the K^+

pumped in, will be able to diffuse back out of the cell (but more slowly than being pumped in), because **some of the K^+ channels are open**. Thus inside the cell is most of the K^+, but outside contains almost all the Na^+ and some of the K^+, giving more positive ions outside than in.

- Inside the cell are **large anions**, too big to escape. The **attraction of their negative charge slows down the escaping K^+ until equilibrium is set up at a potential difference of -70mv.**

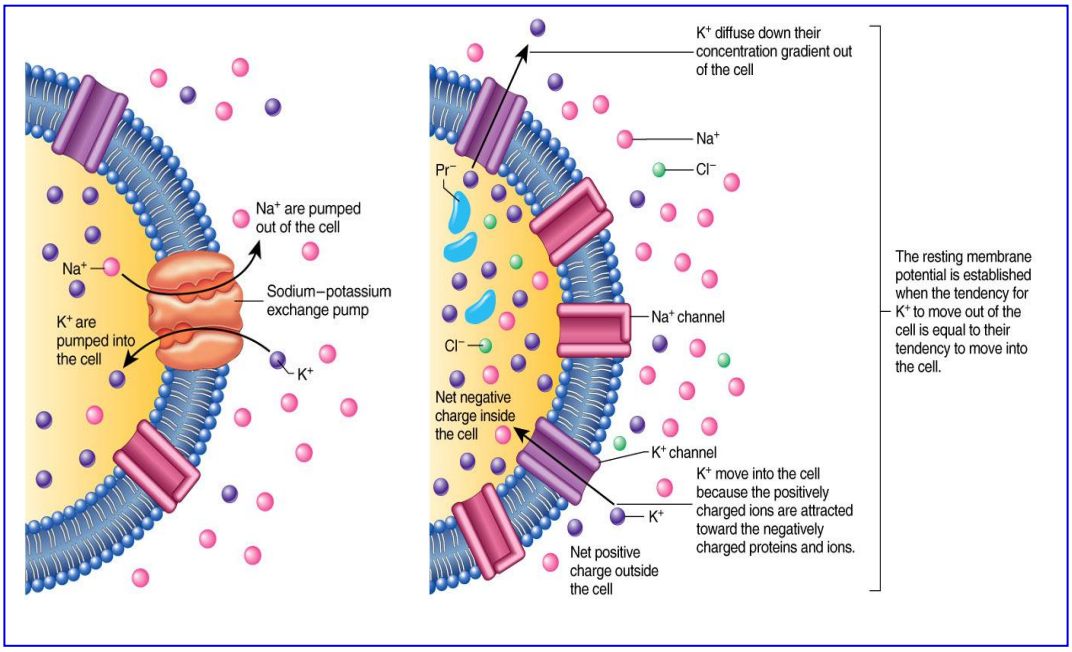


Figure (3.5): Events that involved in the resting membrane potential. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- It is more correct to say that ions diffusion occurs according to the **electrochemical gradients**, recording the effect of both **electrical charge** and **concentration of ions.**
- Membrane potential acts as signals .Neurons use changes in their membrane potential as communication signals for receiving, integrating and sending information.
- A change in membrane potential is produced by :
  - ***Anything that alters ion concentrations on the two sides of plasma membrane.***
  - ***Changes in membrane permeability to any ions.***
- The change in membrane potential produces two types of signals:

1- Graded potentials

- A graded potential is a small change in the resting membrane potential that is confined to a small area of the plasma membrane.
- An increase in membrane permeability to Na^+ can cause **graded depolarization**, and an increase in membrane permeability to K^+ or Cl^- can result in **graded hyperpolarization.**(Figure3.6 : ,a,b).

- ***Depolarization and repolarization: are terms describing membrane potential changes related to resting membrane potential.***
- ***Depolarization*** *: Reduction in membrane potential (inside the membrane becomes less negative than resting potential.)It can result from decrease in K^+ concentration gradient, a decrease in membrane permeability to K^+, an increase in the membrane permeability to Na^+, and an increase in the permeability to Ca^{2+} or decrease in extracellular Ca^{2+} concentration.*
- ***Hyperpolarization*** *occurs when membrane potential increases ,becoming more negative than resting potential (-70 to -75mv).It can result from an increase in the K^+ concentration gradient, an increase in membrane permeability to K^+ ,an increase in membrane permeability to Cl^- ,a decrease in membrane permeability to Na^+ or an increase in extracellular Ca^{2+} concentration.*

- The term graded potential is used because a stronger stimulus produces a greater potential change than a weaker stimulus .
- Graded potentials can summate or added together.
- A graded potential decreases in magnitude as the distance increases from the stimulation.

2- Action potential(AP)

- Action potential is a larger change in the resting membrane potential that spread over the entire surface of the cell.
- Neurons have the ability to suddenly raise the potential difference in the axon to +20mv (**an action potential**), (figure3.7) then reduce back down to -70mv. This is known as an **impulse**. It is mainly controlled by movement of Na^+ and K^+ across the plasma membrane of the axon.
- A rapid change in membrane potential is **action potential** , which varies in response to variety of stimuli.

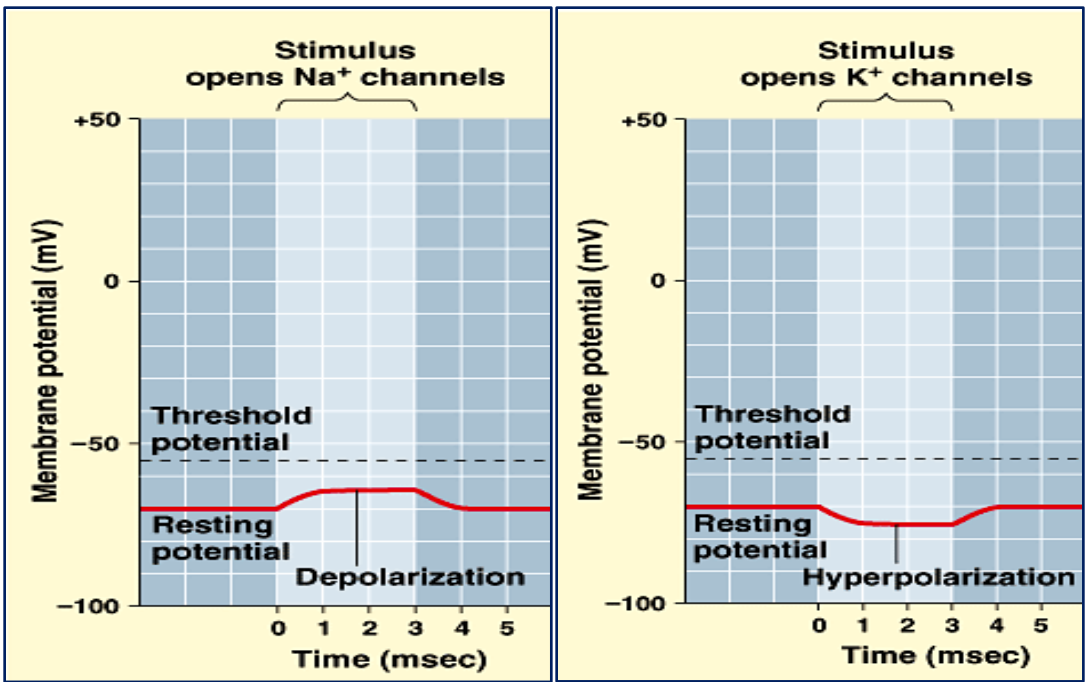


Figure (3. 6): Graded potential, a: Depolarization, b: Hyperpolarization.
(Randall D., Burggren W. and French K. Eckert Animal Physiology . New York, W.H. Freeman and Company, 2002).

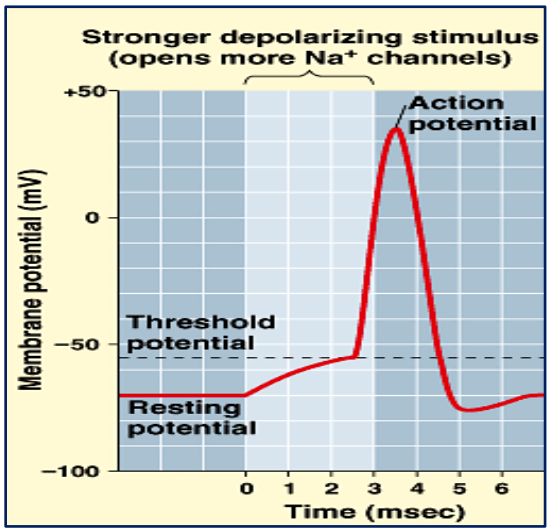


Figure (3.7): Action potential

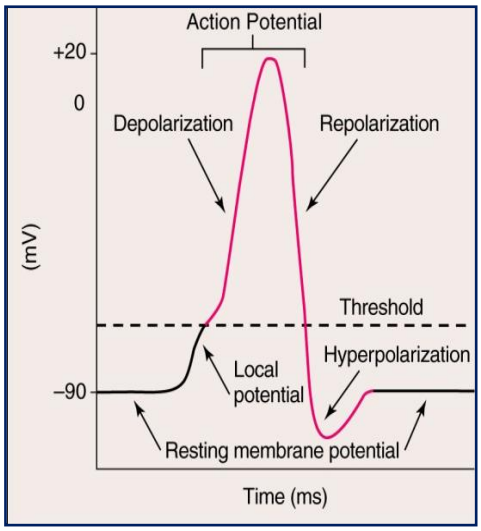


Figure (3.8): Action potential stages
(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Stages of action potential, (Figure3.8):

1- **The resting state.** Closed voltage-gated K^+ channels open slowly in response to depolarization.

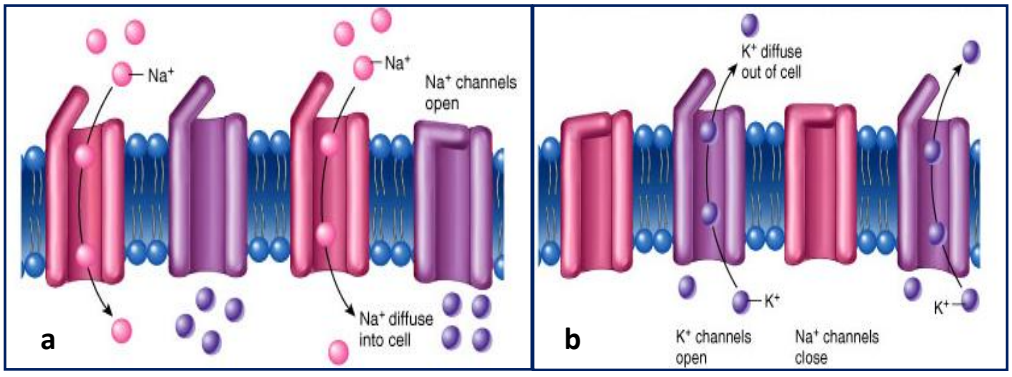
2- **Threshold**. Some sodium ions diffuse along the axon from an action potential to the adjacent resting potential. In addition, the Na^+ are pulled into the resting section by its negative charge. This small number of ions is sufficient to raise the potential from **-70 to -55mv.** At -55mv, the sodium channels open. **(-55mv is a threshold),** if the number of Na^+ is insufficient to raise the potential to -55mv, **no** action potential will result, because the Na^+ gates will not open.

3- **Depolarization**.The open Na^+ channels allow Na^+ to diffuse down its gradient into the axon. The flood of Na^+ makes the inside of the axon rise to +20mv, at which the Na^+ channels shut and the remaining K^+ channels open (a few were already open). This is the action potential.(Figure 3.9:a).

4- **Repolarisation**.With the Na^+ channels shut, no more Na^+ enters the axon, but the Na^+/K^+ pump is still removing Na^+ from the axon (the pump does not stop, but is irrelevant when the channels are wide open). At the same time K^+ is diffusing out through its open channels. Thus both ions are leaving the axon, which becomes progressively more negative. (Figure 3.9: b).

5- **Hyperpolarization or undershoot .**It is a brief period following repolarization. Some K^+ channels still open. K^+ efflux outside the cell .Na^+ channels reset.

- All events involved in action potential are summarized in figure (3.10).



Figure(3.9): a:Depolarization ,b: Repolarization. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

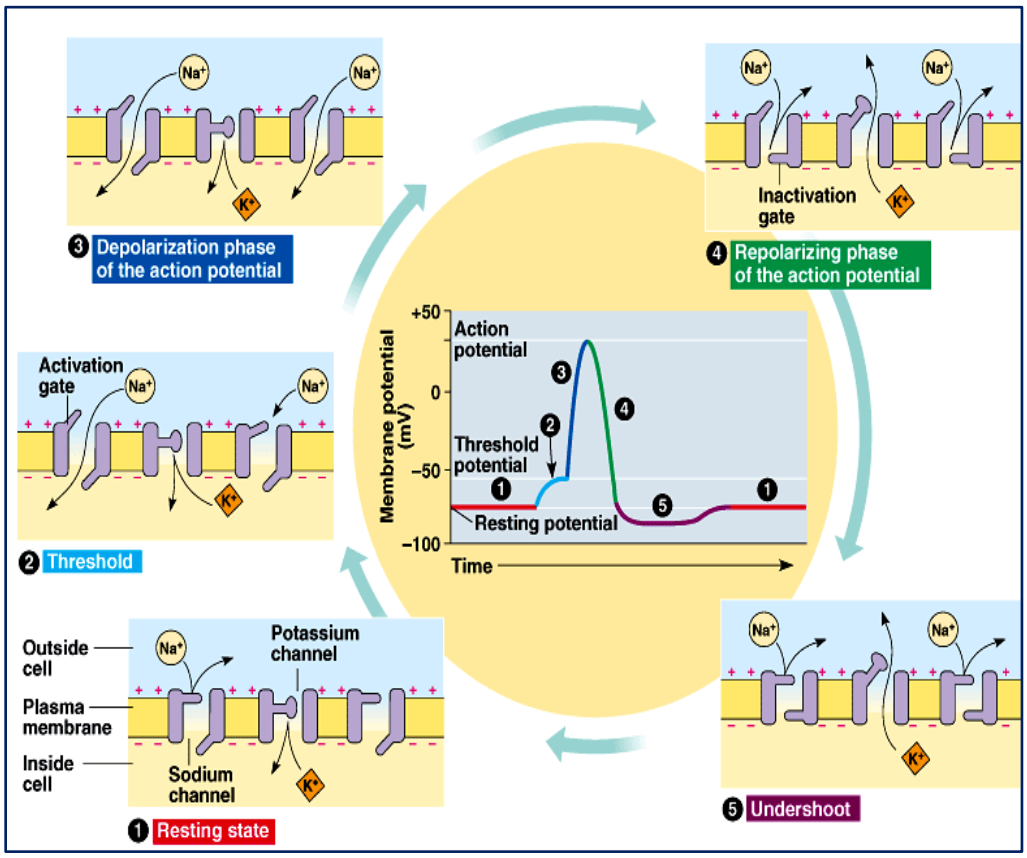


Figure (3.10): Events of action potential.(Randall D. ,Burggren W. and French K. Eckert Animal Physiology . New York, W.H. Freeman and Company, 2002).

Properties of Action Potential

1- All or none phenomenon

- Generation of action potential is determined by the ability of stimulus to cause the cell to reach threshold.
- If the threshold potential is reached, an action potential is generated, if it is not reached, no action potential is generated.
- Regardless of stimulus intensity, the action potential will have the same ***amplitude***.

2-Frequency

- Increased stimulus intensity lead to high frequency of AP generation.That is how can CNS determine whether a particular stimulus intense or weak.
- The strong stimuli cause nerve impulse to be generated more often in a given time interval than do weak stimuli. That is stimulation intensity is coded for by the **number of impulse per second** rather than by increase the strength (amplitude) of the individual AP.

3- Refractory period.

- During refractory period the cells are unable to generate AP .Refractory period is important property of excitable cells to prevent overly rapid generation of action potential, which may cause continual contraction **(tetany).**
- ***Absolute Refractory period:*** AP cannot be generated regardless of stimulation intensity, during the depolarization phase of AP and is due to closure Na^+ channels inactivation gate.
- ***Relative Refractory period:*** Stimulation with much greater intensity than threshold can stimulate another AP. During the repolarization phase K^+ conductance is higher than in resting state, the membrane potential is more negative.

4- Accommodation.

- Cells are held in depolarization phase or depolarized very slowly, inactivation gates on Na+ channels automatically close so no Na+ current. Even if the cell has reached its normal threshold potential, it's impossible for the cell to generate another AP because few Na+ channels open.

Clinical note: In **hyperkalemia,** the extracellular potassium concentration is higher than normal, so there is less of driving force for K^+ to leave the cell and keep the membrane potential at -70mv .Thee cell depolarizes enough to trigger the closure of sodium inactivation gates. This depolarization brings the membrane closer to threshold but no action potential is generated.

Propagation of Action Potential

- Action potential is generated by Na^+ influx through a given area of the membrane. This influx establishes local currents that depolarize the adjacent membrane area in the forward direction, away from origin of the nerve impulse.
- Because the area of originated action potential just generate AP, the Na^+ channels in that area inactivated and no new AP generated, *AP propagates away from its point of origin.*
- If isolated axon is stimulated by electrode, nerve impulse will move away from the point of stimulation in all directions along the membrane .But in the body AP initiated at one end conducted away from that point toward the axons terminals.
- Once AP is initiated, it is self propagating and continues along the axon at a constant velocity like domino effect .This propagation process occurs on unmyelinated axon.
- Propagation process along the myelinated axon is called **Saltatory conduction.**

Transmission of the impulse.

- As an action potential travels along the axon, it raises the potential difference of the resting axon adjacent to it until the threshold has been reached. This is done by diffusion of Na^+ along the axon and results from two factors:-

  1. The section of axon with an action potential has a very high concentration of Na^+ (which have entered the axon through their open channels), while the resting section of axon has a low concentration (due to the Na/K pump and shut channels). This produces a large gradient inside the axon and thus diffusion of Na^+ into the resting section of axon.
  2. The resting section of axon has a negative charge, which attracts the Na^+ from the action section of axon. (Figure3.11).

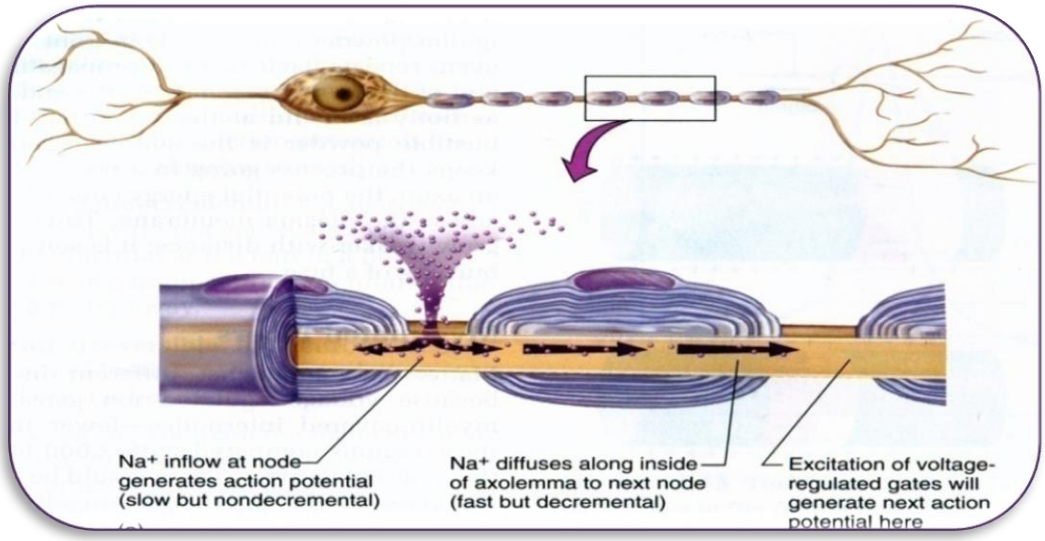


Figure (3.11): Transmission of the impulse (Randall D. ,Burggren W. and French K. Eckert Animal Physiology . New York, W.H. Freeman and Company, 2002)

- Small nerves made up of only a few axons are often **unmyelinated** - although the axon is surrounded by Schwann cells, (Figure3.12: a), these are not wrapped around the axon in many layers of myelin. Such nerves transmit an impulse by **continuous conduction** .This is slow conduction.

Clinical note: Multiple sclerosis is autoimmune disease characterized by inflammation and destruction of the myelin resulting in demyelinated fiber in CNS .It manifested in many different forms:patients have cognitive changes , paresis and optic neuritis.

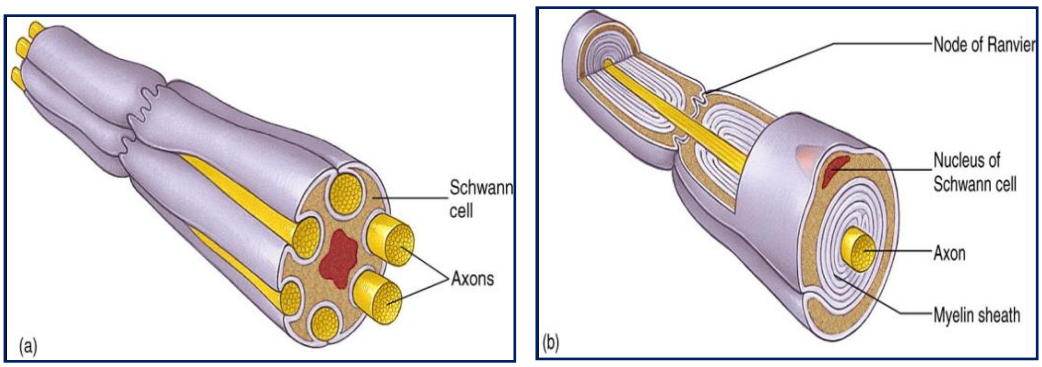


Figure (3.12): a-Small nerve with few unmyelinated axon. b-myelinated axon. (Randall D. ,Burggren W. and French K. Eckert Animal Physiology . New York, W.H. Freeman and Company, 2002).

- Most nerves are made up of hundreds or thousands of axons and are **myelinated**. (Figure3.12:b).The myelin prevents the movement of ions through the plasma membrane. Na^+ and K^+ channels are thus only found in the nodes of Ranvier, between the Schwann cells. The impulse thus jumps from node to node, which is **saltatory conduction**. (Figure 3.13) There are no ionic movements between the nodes. This (compared with continuous conduction) is:-
  - Very fast (up to 120m/sec compared with 15m/sec).
  - Has a very fast recovery (very short refractory period), because only a small number of ions enter the axon and have to be pumped out again.
  - The impulses can have a higher frequency.

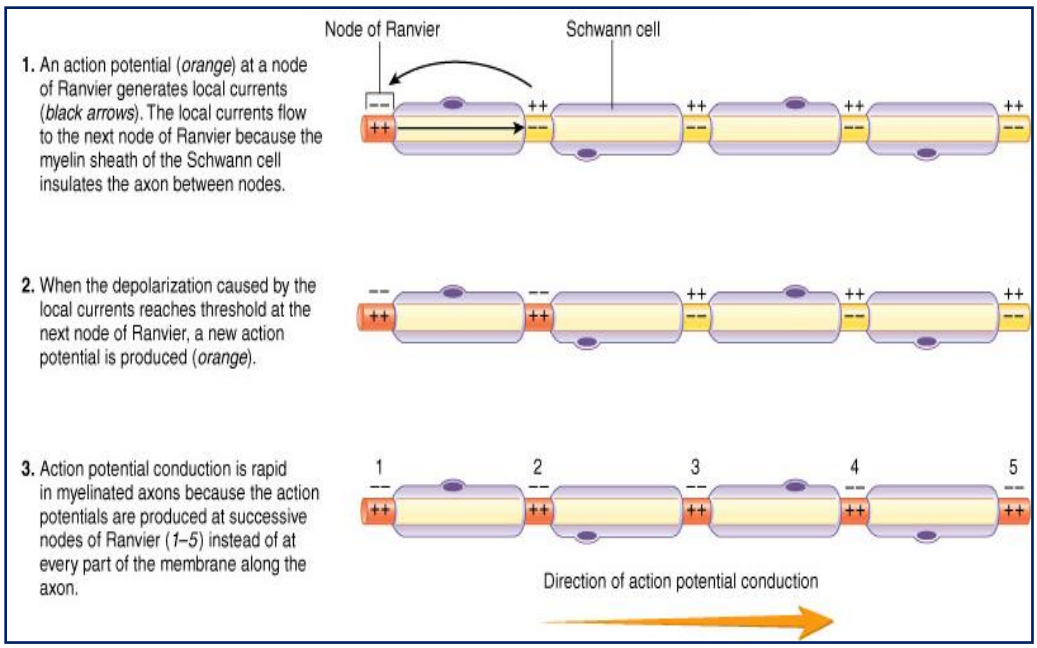


Figure (3.13): Saltatory conduction.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Transmission of AP between the cells:

1- **Electrical transmission:** rare form of action potential transmission, current travels through openings between the cells "**gap junctions"** in cardiac and muscles cells, where there is cytoplasmic continuity between the cells constituents.

2- **Chemical transmission:** primary form by which action potential are transmitted.

The synapse

- Synapse :(clasp or join) ,is a junction that mediate information transfer from one neuron to the next or from a neuron to an effectors cells –its where the action is .
- The impulse reaching the end of the axon and enters the **synaptic knobs** (**presynaptic terminals**). These do not directly connect with the next neuron, but have a narrow gap the (**synaptic cleft**) in between. The **post-synaptic membrane (PSM)** of the next neuron may be either its dendrites or its cell body (synapses connect with both). (Figure 3.14).

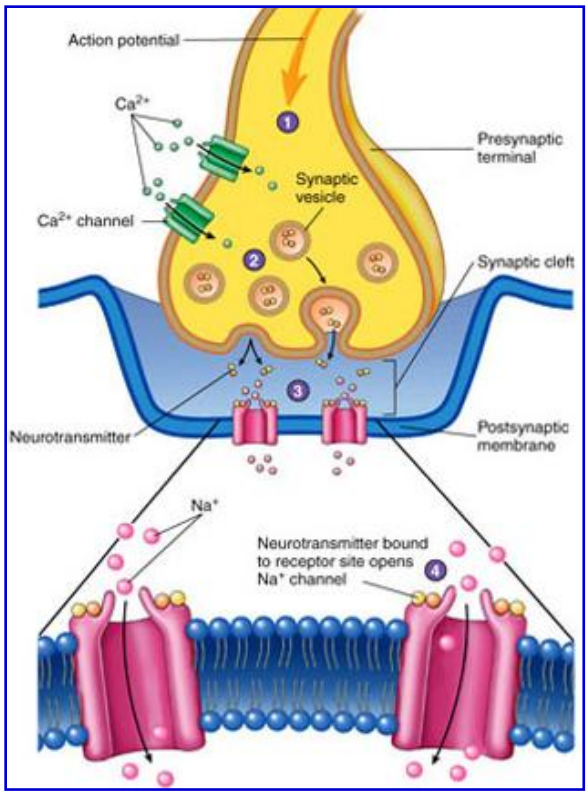
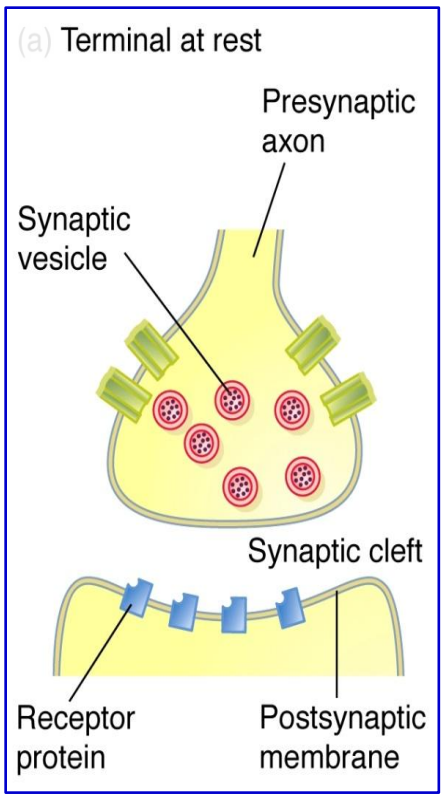


Figure (3.14): Chemical transmission at a synapse.



Figure(3.15): presynaptic terminals at rest.

(Marieb E.N.and Hoehn K.Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

- The impulse diffuses across this gap as a chemical **neurotransmitter,** such as **acetylcholine**. A resting synapse has the neurotransmitter stored inside vesicles in the knob(figure 3.15). The impulse arriving in the synaptic knob results in,(figure3.16):
  - Ca^{2+} channels open to allow Ca^{2+} to diffuse into the **knob.**
  - This causes the vesicles to empty the neurotransmitter into the **synaptic cleft.**
  - The **neurotransmitter** diffuses across to **the post-synaptic** membrane of the next neuron, where it combines with its receptors.
  - Attachment of the neurotransmitter to its receptor opens or closes ionic channels.

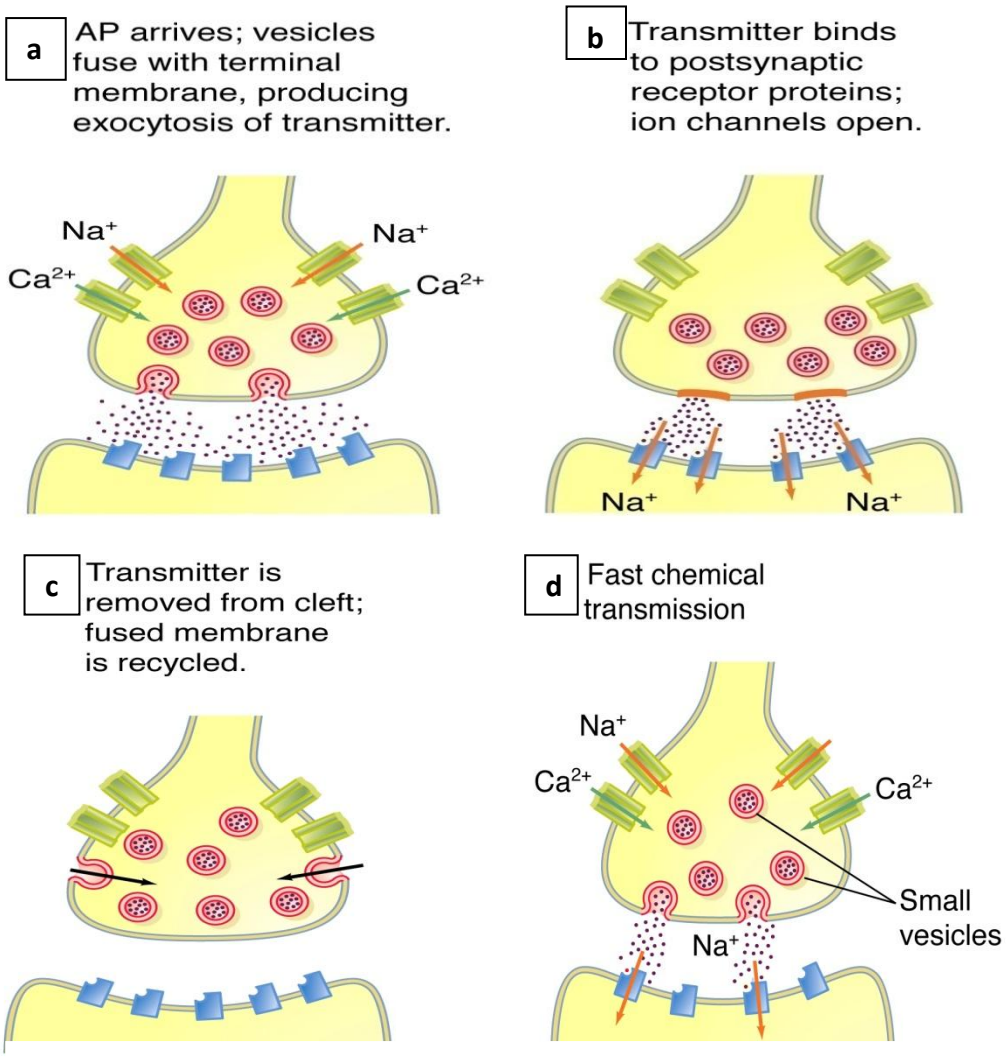


Figure (3.16): The events that occur when impulse arrives the synaptic knob.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- **Postsynaptic potential (EPSP)** or an **inhibitory postsynaptic potential (IPSP)**.EPSPs are a result of localized depolarization caused by increased conductance to Na^+. IPSP are a result of localized hyperpolarization caused by increased conductance to Cl^- or K^+ .
- If summation of IPSP and EPSP at the axon hillock brings the membrane potential to threshold, generation of action potential occurs by opening of voltage- gated sodium channels.

- After use, the neurotransmitter attached to the receptor is **broken down by an enzyme**, e.g. acetylcholine is destroyed by **cholinesterase**, while neurotransmitter still in the cleft is pumped back in to vesicles in the knob. This ends the impulse and so prepares the synapse for the next impulse.

- Each neurotransmitter has its own specific receptor attached to a particular type of channel.
- The same neurotransmitter can produce different effects on different types of cells.

Types of neurotransmitters

1- Acetylcholine: cholineregic transmission

- **Acetylcholine (ACh)** is used by all motor axons, autonomic preganglionic neurons and postganglionic parasympathetic nerves.
- Depending on the postsynaptic, ACh can be either **excitatory** (at the neuromuscular junction by motor neurons) or **inhibitory** (in parasympathetic postganglionic fibers to cardiac muscle).
- Pathophysiology of cholinergic transmission: **myasthenia gravis, Parkinson disease, Alzheimer dementia.**

Clinical note: In the autoimmune disease **myasthenia gravis**, antibodies are made against ACh receptors of the neuromuscular junction in skeletal muscle. These antibodies bind to the ACh receptors on the postsynaptic membrane and block ACh binding resulting in muscles weakness and easy fatigability .Treatment includes administration of **acetylcholinesterase inhibitors** such as **neostigmine** to increase the amount of ACh in the synaptic cleft.

2- Amino acids

- **Glutamate :glutamatergic transmission**
  - **Glutamate** is the primary stimulatory neurotransmitter of the brain.
  - It binds to both stimulatory and modulator receptors.
  - Excess glutamatergic activity is associated with **excitation** and **seizures.**
- **Gamma aminobutyric acid (GABA)**
  - **GABA** is the primary inhibitory neurotransmitter in the brain.
  - It is abundant within the basal ganglia and cerebellum.
  - It is derived from the amino acid glutamate by action of glutamate decarboxylase.
  - Deficient GABA activity may result in **movement abnormalities**, **anxiety disorders**, and **seizure** and **muscles spasm.**

Clinical note:In **Huntington disease** ,there is progressive deterioration of the caudate nucleus and frontal cortex .Clinical symptoms do not appear until the fourth or fifth decade ,by which many patients have already passed on the mutated autosomal dominant gene to their children. Loss of GABA secreting neurons is one factor responsible for the abnormal movement.

Pharmacology note: Because **GABA** is an inhibitory neurotransmitter, GABA agonists such as **benzodiazepines, alcohol and barbiturates** are frequently used as antianxiety agents **(anxiolytics),** suppressing cortical function.

- **Glycine**
  - **Glycine** is the primary inhibitory neurotransmitter of the spinal cord .
  - It increases chloride conductance in the postsynaptic membrane.
  - This results in hyperpolarization of the postsynaptic membrane and inhibition of action potential generation.

Clinical note: Glycine secretion in the spinal cord is inhibited by the tetanus toxin, exposure to which results in excessive stimulation of the lower motor neurons, producing spasmic muscle contraction(i.e., **spastic paralysis**).

3- Monoamines

- These neurotransmitters contain a single amine group in their chemical structure, and include **norepinephrine, serotonin and dopamine**.

Clinical note: The monoamine deficiency theory of depression links depression to a deficiency in at least one of the three monoamine transmitters **norepinephrine, serotonin and dopamine**. Extensive pharmacologic support for this theory has been obtained for over the years, as evidenced by the efficacy of monoamine oxidase inhibitor and tri cyclic antidepressant, which increase levels of monoamine neurotransmitters in the brain .However, these drugs affect levels of other neurotransmitters and have numerous side effects. **Serotonin-specific reuptake inhibitors (SSRIs)** and **non-serotonin-specific reuptake inhibitors (NSRIs)** have been shown to be extremely effective in the treatment of depression with minimal side effects.

- **Norepinephrine: adrenergic transmission**
  - It is derived from amino acid tyrosine.
  - It is synthesized and released by the sympathetic nervous system, adrenal medulla, and locus ceruleus of central nervous system.

- **Serotonin**
  - Serotonin is derived from the amino acid tryptophan
  - Most of the body's serotonin is found in the enteric nervous system of the gut.
  - The serotonin in the brain plays an important role in control of mood.
- **Dopamine: dopaminergic transmission**
  - Dopamine is derived from the amino acid tyrosine.
  - Dopamine is an important neurotransmitter in the brain .It affects sleep, mood, attention, and learning.
  - A lack of dopamine in the brain is associated with **Parkinson's disease.** Excessive dopamine is linked to **schizophrenia.**

Pharmacology note: **Dopamine agonist** such as **bromocriptine** are used clinically to treat **prolactinomas**, the most common type secreting pituitary tumor, they are mainstay of treatment of **Parkinson's disease**.

4- Neuropeptides

- These have **longer duration of action** than the smaller molecular neurotransmitters, partly because they act by altering gene expression, so their effect may continue after they are degraded.
- Neuropeptides may be secreted at the same time as a small –molecule neurotransmitter .This results in an immediate ,rapid response (because of smaller neurotransmitters) and delayed but prolonged response caused by neuropeptide.e.g.,glutamate and neuropeptide **substance P** are **cotransmitted** in the pain pathway ;glutamate causes immediate inhibition of neurotransmission of pain ,whereas **substance P** causes change in the gene expression to produce a lasting effect .
- **Neuropeptide Y, enkephalins, endophrins and nitric oxide** are other examples of neuropeptides.

Spatial and Temporal Summation

- Presynaptic action potentials through neurotransmitters produce graded potentials in postsynaptic neurons .The graded potential can summate to produce an action potential at the trigger zone.
- **Spatial summation** occurs when two or more presynaptic terminals simultaneously stimulate a postsynaptic neuron. (Figure 3.17).
- **Temporal summation** occurs when two or more action potentials arrive in succession at a single presynaptic terminal.

- **Inhibitory and excitatory presynaptic** neurons can converge on a postsynaptic neuron .The activity of the postsynaptic neuron is determined by the integration of the EPSPs and IPSPs in the postsynaptic neuron.

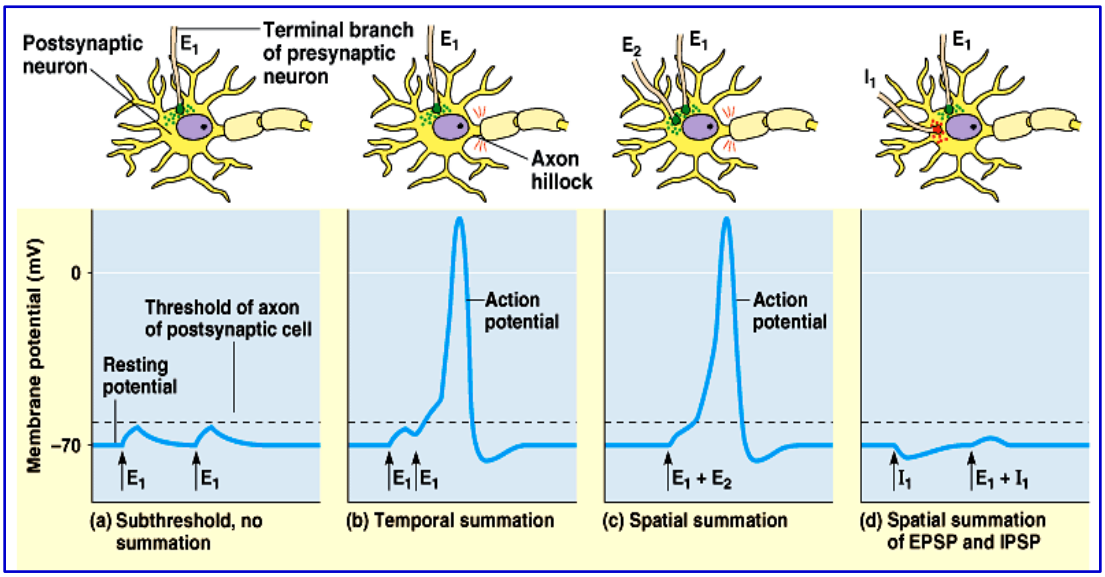


Figure (3.17): Spatial and Temporal Summation. (Marieb E.N .Essential of Human Anatomy and Physiology. San Francisco, Pearson Education,Inc.,2012).

The Spinal cord

Overview

- Spinal cord is extremely important to overall function of the nervous system.
- It is the major communication link between **the brain** and **the PNS**, inferior to the head; it participates in the integration of incoming information and produces responses through reflex mechanism.
- The spinal cord gives rise to 31 pairs of spinal nerves .The spinal cord has **cervical** and **lumbosacral** enlargements where nerves of the limbs enter and leave.
- The spinal cord is shorter than the vertebral column .Nerves from the end of the spinal cord form the **cauda equina .**
- **Meninges of the Spinal Cord:** Three meningeal layers surround the spinal cord: the **dura mater**, arachnoid **mater** and **pia mater.**
- **Cross section of the spinal cord:** The spinal cord consists of **peripheral white matter** and **central gray matter**. (Figure3.18).
- White matter is organized into **funiculi,** which are subdivided into **fasciculi** or **nerve tracts**, which carry action potentials to and from the brain.

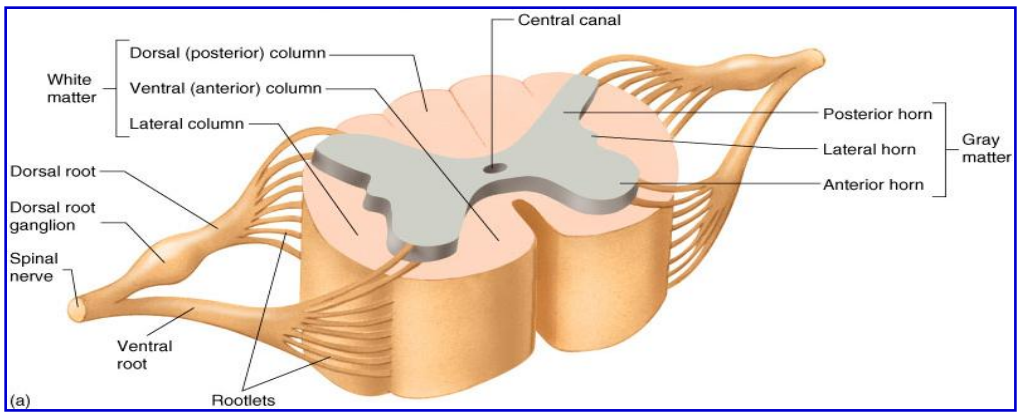


Figure (3.18): Cross section of the spinal cord. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- Gray matter is divided into **horns**. (Figure3.19).
  - **The dorsal horns** contain sensory axons that synapse with interneurons.
  - **The ventral horns** contain the neuron cell bodies of somatic motor neurons
  - **The lateral horns** contain the neuron cell bodies of autonomic neurons.
- The gray and white commissures connect each half of the spinal cord.
- The dorsal root conveys sensory input into the spinal cord and the ventral root conveys the motor output away from the spinal cord.

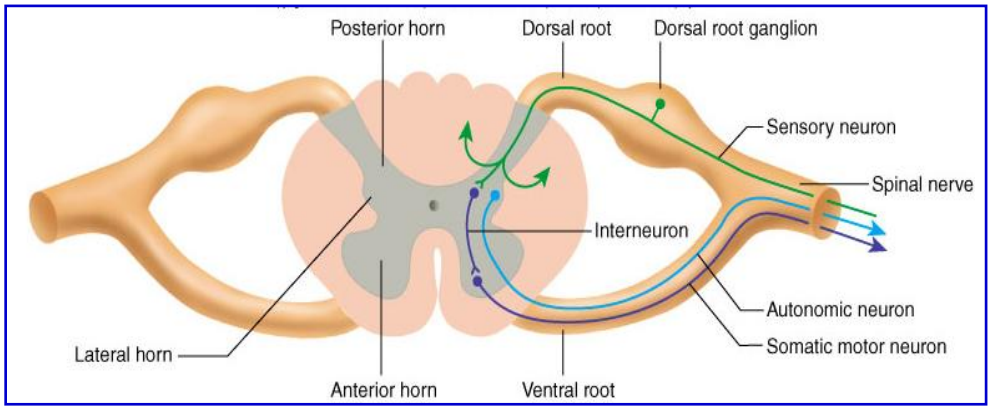


Figure (3.19): Gray matter is divided into horns .(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Reflexes

Overview

- **The reflex arc** has five basic components,(Figure 3.20):
  1- A sensory receptor
  2- A sensory neuron
  3- An interneuron
  4- A motor neuron
  5- An effector organ
- **The reflex arc** is the functional unit of the nervous system.
  - **Sensory receptors** respond to stimuli and produce action potentials in the **sensory neurons.**
  - Sensory neurons propagate action potential to the CNS.
  - **Interneurons** in the CNS synapse with sensory neurons and with **motor neurons.**
  - Motor neurons carry action potentials from CNS to **effector organs**.
  - Effector organs such as **muscles** or **glands** respond to the action potentials.

- Reflexes do not require **conscious thought** and they produce a consistent and predictable result. **(e.g., same response every time the individual touches something hot).**Information will at the same time be sent to the brain, but this involves thousands of neurons and so takes much longer (the individual will already remove the hand before the realizing of touching something hot).
- Reflexes are homeostatic.
- Many reflexes are integrated within the spinal cord and others are integrated within the brain.
- Some reflexes involve **excitatory neurons** and result in a response .Other reflexes involve **inhibitory neurons** and result in the inhibition of a response. Higher brain centers can **suppress** or **exaggerate** reflexes.

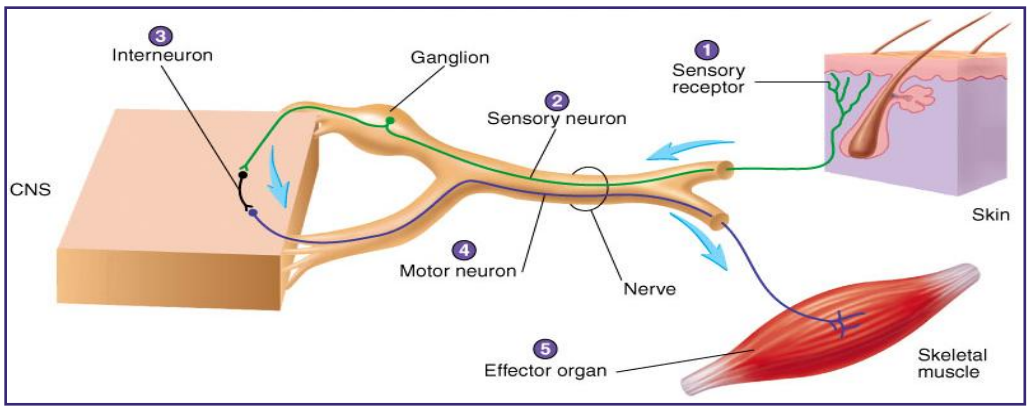


Figure (3.20): Reflex arc components. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- Individual reflexes vary in their complexity:
  - **Monosynaptic reflexes** involve simple neural pathways in which sensory neurons synapse directly with motor neurons.
  - **Polysynaptic reflexes** involve more complex pathways and integrative center with one or more interneurons between the sensory and motor neurons.

Stretch Reflexes:

- A reflex in which muscles contract in response to a stretching force applied to them.
- The sensory receptor of this reflex is the muscle spindle, which consist of 3-10 small specialized skeletal muscle cells.
- The cells are contractile only at their ends and innervated by specific motor neurons called **gamma motor neurons,** originating from the spinal cord and control the sensitivity of the muscle spindle cells.
- Sensory neurons innervate the contractile centers of the muscle spindle cells. Axon of these sensory neurons extends to the spindle cord and synapse directly with motor neurons in the spinal cord called **alpha motor neurons.**
- The stretch reflex is monosynaptic reflex because there is no interneuron between the sensory neuron and the alpha motor neuron.

Knee-Jerk reflex or patellar reflex *is a classic example of the stretch reflex. Clinicians use this reflex to determine whether the higher CNS centers that are normally influence this reflex are functional.*

Golgi Tendon Reflex

- The **Golgi tendon reflex** prevents contracting muscles from applying excessive tension to tendon, so protects muscles and tendon from damage.
- Intense stretch of skeletal muscle results in :
  1- Golgi tendon organs detect tension applied to a tendon.

  2- Sensory neurons conduct action potential to the spinal cord.

  3- Sensory neurons synapse with inhibitory interneurons that synapse with the alpha motor neurons.

  4- Inhibition of the alpha motor neurons causes muscle relaxation, relieving the tension applied to the tendon.

Withdrawal Reflex

- The function of **withdrawal** or **flexor reflex** is to remove a limb or another body part from a painful stimulus.
- The sensory receptors are pain receptors. Stimulation of pain receptors results in:
  1- Pain receptors detect a painful stimulus.
  2- Sensory neurons conduct action potential to the spinal cord
  3- Sensory neurons synapse with the excitatory interneurons that synapse with alpha motor neurons.
  4- Excitation of the alpha motor neurons results in contraction of the flexor muscles and withdrawal the limb from the painful stimulus.

- **Reciprocal innervations:** is associated with the withdrawal reflex and reinforce its efficiency. It causes relaxation of muscles that would oppose the withdrawal movement.

- **Crossed extensor reflex: is** another reflex associated with the withdrawal reflex .In this reflex, during flexion of one limb caused by the withdrawal reflex, the opposite limb is stimulated to extend.

The Brain

Overview

- The brain is that part of the CNS contained within the **cranial cavity.**
- It is the control center for many of the body's functions.
- The brain is divided into 4 main regions,(figure 3.21):
  - **the brainstem** is at the top of the spinal cord; includes medulla, Pons, midbrain and reticular formation.

- **The diencephalon** is the part of the brain located between the brainstem and the cerebrum; includes the thalamus, epithalamus and hypothalamus**.**
- **The cerebrum** makes up most of the brain. Conscious perception, thought and conscious motor activity; can override most other system.
- **Cerebellum** is at the posterior part of the brain. Control of muscle movement and tone; balance; regulates extent of intentional movement and involved in learning motor skills.

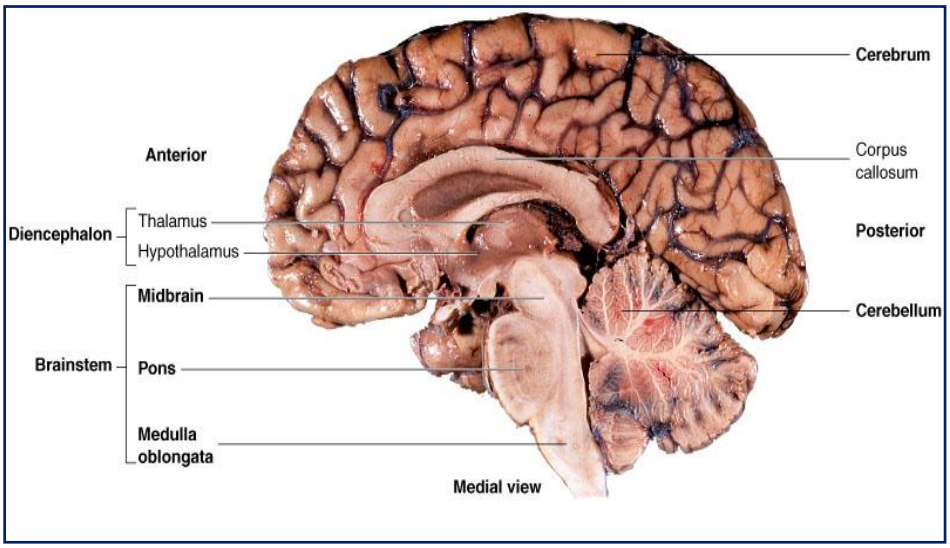


Figure (3.21): A median section of the brain. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- Damage to small brainstem areas often causes death because many reflexes essential for survival are integrated in the brainstem, whereas relatively large areas of the cerebrum or cerebellum may be damaged without life-threatening consequences.

1- Brainstem

- **Medulla Oblongata.**
  - This is the top of the spinal cord (so many neurons pass through it going to the rest of the brain).
  - It contains sensory and motor tracts; cranial nerve nuclei; other related nuclei and part of the reticular formation.
  - It has centers controlling blood circulation, respiration, swallowing, coughing.

- **Medbrain**
  - It located superior to the pons.
  - It contains the **nuclei of cranial nerves III**, **VI(trochlear),**and **V(trigeminal)**
  - It is involved in **visual reflexes**, such as looking towards a loud sound or **bright light**, altering the pupil of the eye, depending on the amount of light, and focusing the lens.
- **Pons**
  - The part of the brainstem just superior to the medulla is the **pons.**
  - It contains ascending and descending tract and several nuclei.
  - The pontine nuclei located in the anterior portion of the pons, relay information from the cerebrum to the cerebellum.
  - Pontine nuclei regulate sleep and respiration. The nuclei of **cranial nerves V-XI** are in the pons.
- **Reticular formation**
  - This is a diffused system consisting of several loosely packed nuclei scattered throughout the length of the brainstem.
  - It receives axon from a large number of sources and especially from nerves that innervate the face.
  - It is involved in "cycle" of activity such as sleep –wake cycle.

2- The diencephalon

- **Thalamus**
  - It is the largest part of the diencephalon, constituting about four – fifth of its weight. (Figure 3.22).
  - It consists of two lobes connected by a small stalk called the **interthalamic adhesion** or **intermediate mass**.
  - The thalamus functions as an **integration center.**
  - Most sensory input synapse in the thalamus .Pain is registered in the thalamus.
  - It influences mood, and action associated with strong emotions such as fear and rage.
  - It has some motor functions.

- **Subthalamus**
  - It is a small area immediately inferior to the thalamus that contains several ascending and descending tracts and the subthalamic nuclei.
  - It is involved in the motor functions.

- **Hypothalamus**
  - The hypothalamus is the most inferior portion of the diencephalon.It contains several small **nuclei** and **tracts.** (Figure3.22) .The most conspicuous nuclei called **mammillary bodies; they** are involved in olfactory reflexes and **emotional response** to odor. They also involved in memory.

- A funnel –shape stalk, the **infundibulum** extends from the floor of the hypothalamus and connects it to the posterior pituitary gland.
- The hypothalamus play an important role in controlling endocrine system because it regulates the **pituitary gland's secretion** of hormones which influence many functions such as metabolism, reproduction ,response to stressful stimuli and urine production.
- Sensory neurons that terminate in the hypothalamus provide input from:
  1- Internal organs
  2- Taste receptors in the tongue
  3- The **limbic system** which is involved in response to smell
  4- Specific cutaneous area ,and the eye
  5- Prefrontal cortex of the cerebrum carrying information relative to mood through the thalamus.
- Hypothalamic nuclei directly control temperature by stimulating sweating and shivering.
- Other hypothalamic nuclei are involved in the control of thirst, hunger and sex drive.
- The hypothalamus is also very important in a number of functions related to mood, motivation, and emotion. This is one reason that strong emotional experience may affect the person's desire or ability to eat and drink.

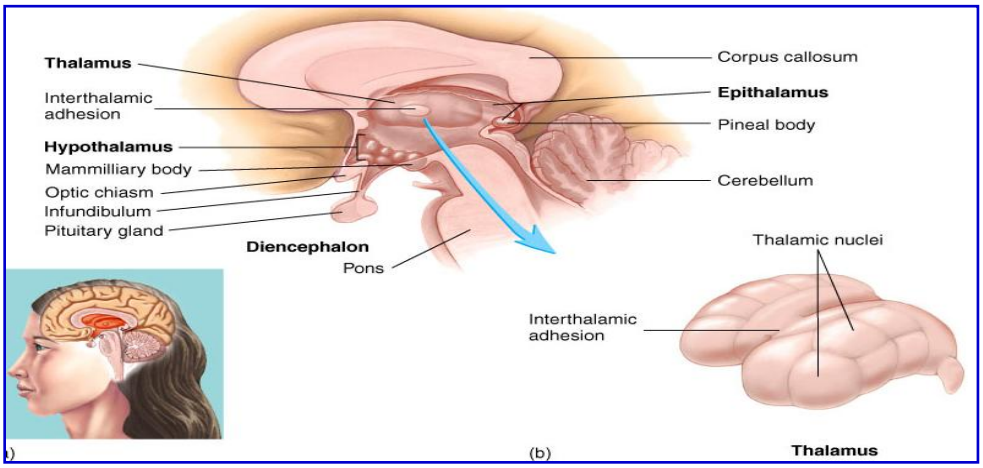


Figure (3.22): General overview of the right half of diencephalon. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

3- Cerebrum

- It is the largest portion of the total brain weight, which is 1200g in females and 1400 g in males.
- The most conspicuous features on the surface are numerous folds called **gyri .**These are to increase surface area of the cortex. The grooves between the **gyri** are called **sulci**.

- **Central sulcus**, which extends the lateral surface of the cerebrum from superior to inferior, is located about midway along length of the brain, (figure3.23).
- Cerebrum is divided into **left** and **right hemispheres** by **longitudinal fissure.** Each hemispheres have lobes:
  1- ***The frontal lobes*** *are involved in smell, voluntary motor function motivation, aggression and mood.*
  2- ***The parietal lobes*** *contain the major sensory areas receiving general sensory input, taste and balance.*
  3- ***The occipital lobes*** *contain the visual centers.*
  4- ***The temporal lobes*** *receive olfactory and auditory input and are involved in memory, abstract thought and judgment.*
- Tracts connect areas of the cortex within the same hemisphere are **association fibers,** between hemispheres are **commissural fibers** and with other parts of the brain and spinal cord are **projection fibers.**
- More complex activities, such as speech and language, and thinking, may involve several different parts of the brain.

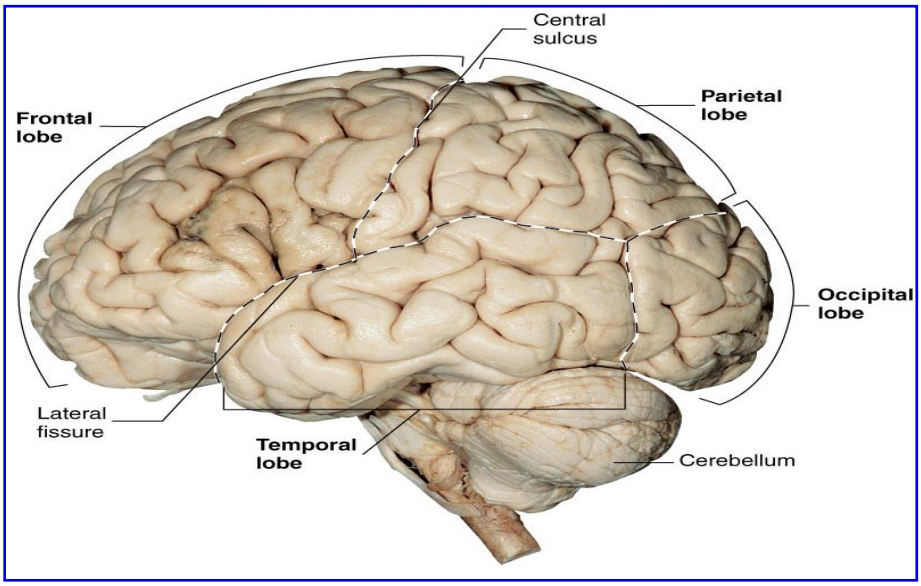


Figure (3.23): Lateral view of the left cerebral hemisphere. (Marieb E.N.and Hoehn K. Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

4- Cerebellum

- The term cerebellum means little brain.
- The cerebellum is attached to the brainstem posterior to the pons.
- It communicates with other regions of the CNS through three large tracts:
  1- **The superior cerebellar peduncles** connect the cerebellum to the midbrain.
  2- **The middle cerebellar peduncles** connect the cerebellum to the pons.
  3- **The inferior cerebellar peduncles** connect the cerebellum to the medulla oblongata.

- The cerebellar cortex contains several cell types: **stellate cells, basket cells, granule cells, Golgi cells and Purkinje cells**.
- The cerebellum consists of three parts,(figure 3.23) :
  1- A small inferior part the **flocculonodular lobe**: control balance and eye movement.
  2- A narrow central **vermis**: vermis with the medial portion of the lateral hemispheres are involved in the control of posture, locomotion and fine motor coordination.
  3- Two large **lateral hemispheres**: The major portions functions in the concert with the frontal lobe of cerebral cortex participate and learn complex movements.

Clinical note: Lateral cerebellar lesion causes a defect known **as decomposition of movement**. The result is a disruption in the timing of the components of a movement, which appear to take place sequentially rather than being coordinated smoothly.

Basal Nuclei

- The basal nuclei are the largest nuclei of the brain and occupy a large part of the cerebrum.
- They are a group of functionally related nuclei located bilaterally in the inferior cerebrum, diencephalon and midbrain.
- They are important in the initiation of **voluntary movements.**
- They include the ***putamen*** and ***caudate*** nucleus, which collectively termed the **striatum**, ***globus pallidus, substantia nigra*** and ***subthalamic nucleus.***
- **Output** of the basal nuclei is to the motor thalamus, which in turn projects to the motor cortex.
- Basal nuclei output is always **inhibitory** in nature.
- The basal nuclei influence movement through one of two pathways, the :
  1- The direct pathways: is activated by binding of dopamine to **D1 receptors** in the striatum. This results in direct inhibition of basal nuclei output to the motor thalamus.
  2- The indirect pathway: inhibited by binding of dopamine to **D2 in the striatum**. The indirect stimulation through the subthalamic of basal ganglia output to the motor thalamus.

Limbic system

- **Limbic system is** parts of the cerebrum and diencephalon which are grouped together.
- Limbic system includes part of the cerebral cortex, basal nuclei, the thalamus, the hypothalamus and the olfactory cortex.

- It plays a role in the basic functions such as: memory, reproduction and nutrients.
- It is also involved in emotional interpretation of sensory input and emotions in general.
- One of the major sources of sensory input into the limbic system is the olfactory neurons.The smell or thought of food stimulates the sense of hunger in the hypothalamus.

Higher functions of the cerebral cortex

- The human brain is capable of many functions besides awareness of sensory input and the control of skeletal muscles.
- Speech, mathematical and artistic ability, sleep, memory, emotions and judgment are functions of brain.

Language

- The major area for **language comprehension** is **Werinke area**, located behind the primary auditory cortex in the posterior part of the superior gyrus of the temporal lobe.
- The major area for **expressing language** is **Broca area** in the prefrontal and premotor facial region of the cortex.
- Language center presents in the **left hemisphere** in 95% of people, even if left handed.
- The **right hemisphere** is dominant with respect to facial expression, intonation, spatial tasks and body language.

Clinical note: Werinke area lesions cause **receptive aphasia** which consists of the inability to comprehend spoken language.
Broca area lesions cause **expressive aphasia** which reflects difficulty piecing together words to produce speech. Patients can understand written and spoken language but unable to express themselves verbally.

Memory

- Memories are caused by changes in the sensitivity of synaptic transmission between neurons as a result of previous neural activity.
- These changes result in memory tracts, (the facilitated pathways developed for the transmission of signals through the neural circuits of the brain, providing for memory).
- ***Memory is divided into three major types:***
  1- **Short –term memories** last for seconds or minutes unless they are converted to long term memories .The basis of short term memory involves synaptic changes.

2- **Intermediate long term memories** last for days to weeks, then forgotten. They result from temporary chemical or structural changes.

3- **Long term memories** can be recalled years later. Formation of long term memories involves structural changes in the nervous system and the formation of stable memory tracts. ***Two types of long-term memory exist:***

- **Declarative or explicit memory** involves the retention of facts such as names, dates and places. This is accessed by part of the temporal lobe called the **hippocampus** and **amygdale** or **ammygdaloid.**
- **Procedural or implicit involves** the development of skills like riding a bicycle or playing piano. Implicit memory is stored in the cerebellum and the premotor area of the cerebrum.

Brain waves

- Waves of electrical activity are large enough to be detected from the outer surface of the head by an **electroencephalogram (EEG).**
- **EEG** records the electrical activity when millions of neurons fire synchronously.
- Both intensity and pattern of electrical activity are determined by the level of excitation of the brain during sleep and wakefulness or in disease states such as **epilepsy**
- There are different types of brain waves,(figure3.24). Characteristics of each of these brain waves are illustrated in table (3, 1).
  1. Alpha wave (8 – 13 Hz).
  2. Beta wave (>13 Hz).
  3. Theta wave (4 – 7.5 Hz).
  4. Delta waves (1 – 3.5 Hz).

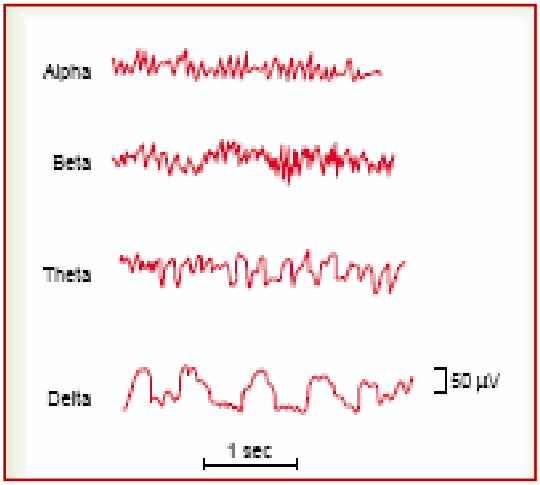


Figure (3, 24): Different brain waves,
(Retrieved from http://www.studyblue.com)

Table (3, 1): Characteristics of the brain waves.

Rhythm	Frequency (Hz)	Amplitude (uV)	Recording	Location
Alpha(α)	8 – 13	50 – 100	Adults, awake rest quiet	Occipital region
Beta(β)	14 – 30	20	Adult, mental activity	Frontal region
Theta(θ)	5 – 7	Above 50	Children, drowsy adult, emotional distress	Occipital region
Delta(δ) **M**	2 – 4	Above 50	Infants , deep sleep, patient with serious organic brain disease	

Sleep

- The sleep –wake cycle is a circadian rhythm .This cycle is driven by the **suprachiasmatic nucleus** of the hypothalamus.
- Sleep is divided into two types: **non-rapid eye movement (NREM**) sleep and **rapid eye movement (REM)** sleep occur in alternating cycle.
- Most dreaming occurs during REM sleep.
- **Aging**, **alcohol,** and **benzodiazepines** decrease the duration of REM sleep.
- Most sleep time is spent in **NREM**.
- NREM sleep can be divided into four stages, on the basis of changes in EEG waves.
  - **Stage 1**: consists of very light sleep and low voltage EEG waves.
  - **Stage 2**: is the primary sleep stage during normal night's sleep.EEG characterized by sleep spindles.
  - **Stage 3**: is a deeper sleep pattern with decrease EEG activity and muscles tone.
  - **Stage 4**: is a deeper sleep with delta waves on EEG recording and further decreasing in muscles tone**.**

Meninges, Ventricles and cerebrospinal fluid

Meninges

- There are three connective tissue membranes. These are: **the dura**, **arachnoid** and **pia mater**.(Figure3.25).
- The meninge surrounds and protects the brain and spinal cord.
- The dura mater is the most superficial and thickest membrane .It is composed of dense irregular connective tissue.
- The **dura mater** attached to the skull and has two layers: the outer layer is called the **periosteal dura** and the inner layer is **meningeal dura.**The meningeal dura is separated from periosteal dura in various regions to form **dural venous sinuses.**
- Meningeal dura is continuous with the dura of spinal cord.
- Arachnoid mater is very thin wispy .The space between this membrane and dura is **subdural space,** which contains a small amount of **serous fluid**.
- The **pia mater** is bound tightly to the surface of the brain. The space between arachnoid and pia mater is the **subarachnoid space**.It contains weblike strands of arachnoid mater and the blood vessels supplying the brain and is filled with **cerebrospinal fluid** (CSF).

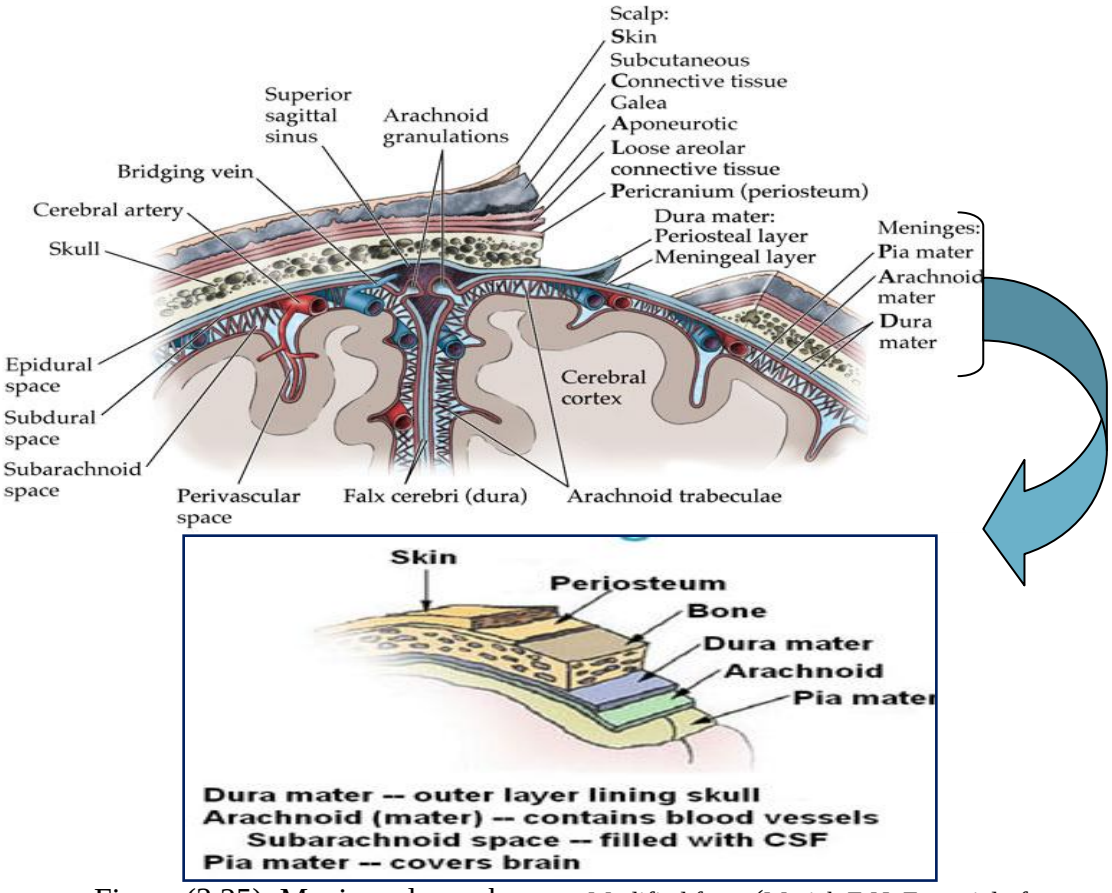


Figure (3.25): Meningeal membranes. Modified from (Marieb E.N .Essential of Human Anatomy and Physiology. San Francisco, Pearson Education,Inc.,2012).

Ventricles

- Ventricles are within each hemisphere of the brain, they secrete and circulate the CSF. (Figure 3.26).
- These ventricles :
  - **The lateral ventricles** is separated from each othe by thin **septa pellucid**
  - **The third ventricle** is located in the diencephalon between the two halves of the thalamus. The lateral ventricles connected to the third ventricle through the ***interventricular foramen.*** (Figure 3.26).
  - **The fourth ventricle** is in the inferior part of the of the potine region. The third ventricle communicates with the fourth ventricle through the ***cerebral aqueduct***.
- The **central canal** of the spinal cord is connected to the **fourth ventricle**.

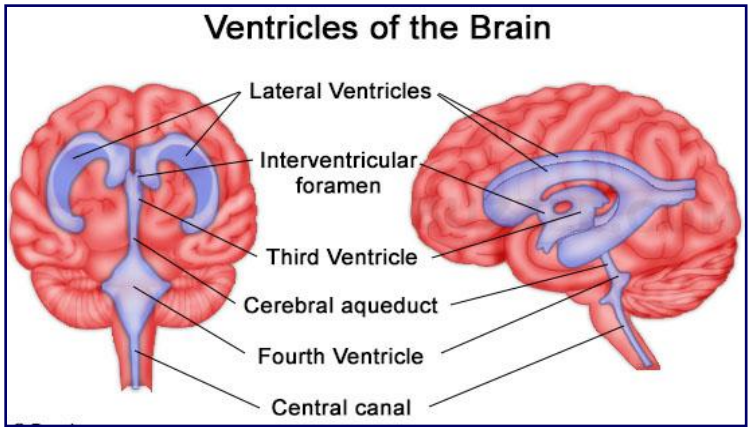


Figure (3.26): Brain ventricles.(Marieb E.N .Essential of Human Anatomy and Physiology. San Francisco, Pearson Education,Inc.,2012).

Cerebrospinal Fluid

- **Cerebrospinal fluid (CSF)** is a fluid similar to the blood serum with most of protein removal.
- It bathes the brain and spinal cord and provides a protective cushion around the CNS.
- CSF allows the brain to float within the cranial cavity, so it does not rest directly on the surface of skull or dura .In addition it protects the brain against the shock of rapid movement of the head.
- It provides some nutrients to CNS tissues.
- About 80-90% of CSF is produced by specialized **ependymal cells** within the lateral ventricles. The remainder produced by similar cells in the third and fourth ventricles. *These specialized cells, their support tissues and the associated blood are collectively called* ***choroid plexuses***.
- CSF is formed through a variety of mechanisms. The majority of the fluid enters the ventricles by following Na^+ concentration gradient.

- **Ependymal cells** of the choroid plexus actively transport Na^+ into ventricles and water passively follows. Large molecules are transported by **pinocytosis.**
- Endothelial cells of the blood vessels in the choroid plexus, which are joined by tight junctions form the **blood brain barrier** or **blood cerebrospinal barrier** .So the substances do not pass between the cells but pass through the cells.
- CSF fills the ventricles, the subarachnoid space of the brain and spinal cord and the central canal of the spinal cord.

Cerebrospinal fluid flow

- The cerebrospinal fluid flows through eight steps:

  1- **Choroid plexus** in the lateral ventricles produces CSF.

  2- CSF flows through interventricular foramina into third ventricle.

  3- Choroid plexus in the third ventricle adds more CSF.

  4- CSF flows down cerebral aqueduct to fourth ventricle.

  5- Choroid plexus in the fourth ventricle adds more CSF.

  6- CSF flows out two lateral apertures and one medial aperture.

  7- CSF fills subarachnoid space and bathes external surfaces of brain and spinal cord.

  8- **At arachnoids villi**, CSF reabsorbed into venous blood of dural venous sinuses and it becomes part of the blood flow that is drained by the internal jugular veins. The flow of CSF is illustrated in figure (3.27).

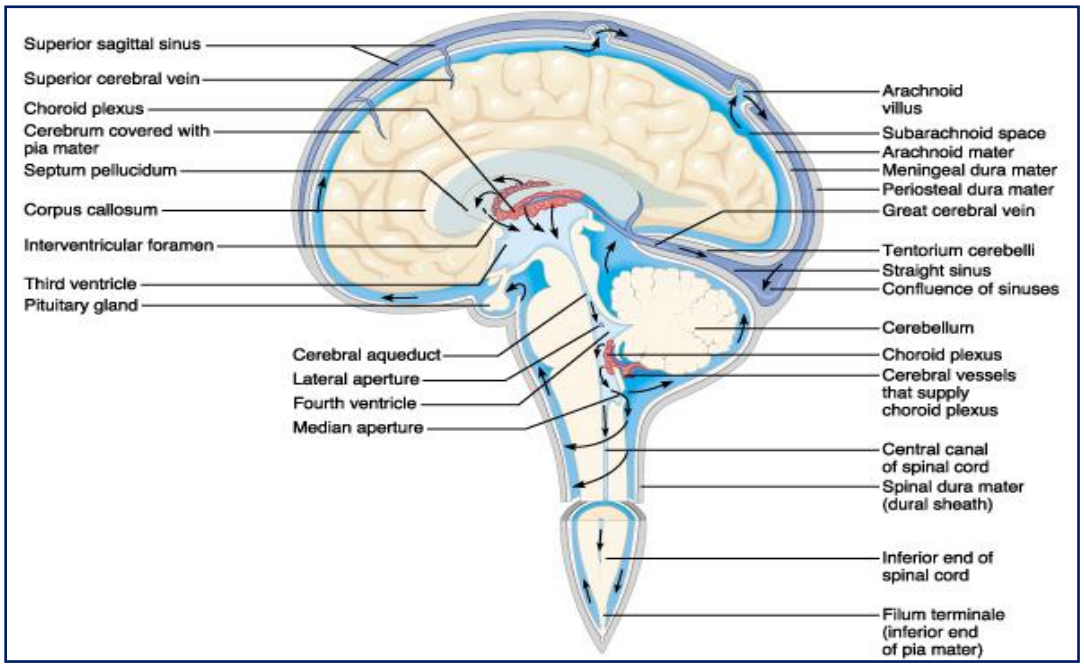


Figure (3.27): Flow of CSF. (Marieb E.N .Essential of Human Anatomy and Physiology. San Francisco, Pearson Education,Inc.,2012).

Blood Supply to the Brain

Overview

- The brain requires a tremendous and constant amount of blood to maintain its normal functions and to meet the demands for glucose and oxygen. This is because:
  - The brain has a very high metabolic rate.
  - Brain cells are not capable of storing high energy molecules for long time.
  - Brain cells depend entirely on glucose as the energy source.
- Even though the brain account for only 2% of the total weight of the body, it receives approximately 15-20% of blood pumped by the heart.
- Interruption of the brain's blood supply for only seconds can cause unconsciousness and interruption of the blood supply for minutes can cause irreversible brain damage.
- Blood reaches the brain through :
  1- **The internal carotid arteries,** which enter the cranial cavity through the **carotid canals**.
  2- **The vertebral arteries** which enter through the **foramen magnum**.
- The vertebral arteries join together to form the **basilar artery** which lies on the ventral surface of the pons.
- The basal artery and internal carotid contribute to the **cerebral arterial circle** (**circle of Willis**).
- Branches from this circle and from the basilar artery supply blood to the brain.

Blood brain barrier

- The arteries within the brain divide into capillaries, which their epithelial cells are surrounded by **processes of astrocytes** .The astrocytes, promote the formation of **tight junctions** between epithelial cells.
- The epithelial cells with their tight junctions form the **blood brain barrier.**
- Blood brain barrier regulates the movements of materials from the blood into the brain. .Most materials cannot pass through the blood brain barrier.
- The materials that enter the brain pass through the epithelial cells.
- **Lipid soluble substances**, e.g., nicotine, ethanol, and heroin can diffuse through the plasma membrane of epithelial cell and enter the brain.
- **Water soluble molecules**, e.g, amino acids and glucose pass the plasma membrane of the epithelial cells by **mediated transport.**

Pharmacology note: The permeability of the blood brain barriers must be considered when developing drugs that affect the CNS. ,e.g,, **Parkinson disease** is caused by a lack of the neurotransmitter dopamine(produced by neurons of the brain). Administering dopamine is not helpful because dopamine cannot pass the blood brain barrier. **Levodopa** a precursor to dopamine,is administered instead because it can cross the blood brain barrier.CNS neurons then convert levodopa to dopamine ,which helps reduce the symptoms of Parkinson disease.

Cranial nerves

Overview

- The **cranial nerves** are composed of twelve pairs of nerves that arise from the nervous tissue of the brain. They are called **cranial nerves** because they either enter or exit the cranium through openings in the skull to reach their targets.
- Like spinal nerves, cranial nerves are bundles of **sensory or motor** fibers, or show **a combination** of these fiber types.
- **Motor components** of the cranial nerves are derived from the cells that located in the brain. These cells send their axons outside the brain, where they will control muscles and glandular tissues.
- **The sensory components** of cranial nerves originate from collections of cells that are located outside the brain (sensory ganglia).
- These 12 pairs of cranial nerves perform sensory, somatic, motor proprioceptive and parasympathetic functions. Here is a brief description for each of these nerves and its function.(Table3, 2)

1- Olfactory (I)

- This type of sensory nerve contributes in the sense of smell.
- It carries the information from nasal epithelium to the olfactory center in brain, in frontal lobe.

2- Optic nerve(I)

- This sensory nerve transforms information about vision to the brain.
- This supplies information to the retina in the form of ganglion cells.

3- Oculomoter nerve(III)

- This is a form of motor nerve that supplies to different centers along midbrain.
- Its functions include superiorly uplifting eyelid, superiorly rotating eyeball, construction of pupil on the exposure to light and operating several eye muscles.

4- Trochlear nerve(IV)

- This motor nerve supplies to the midbrain and performs the function of handling the eye muscles and turning the eye.

5- Trigeminal nerve (v)

- This is a largest cranial nerve.
- It performs many sensory functions related to nose, eyes, tongue and teeth.
- It is divided in three branches that are **ophthalmic**, **maxillary** and **mandibular nerve.**
- This is a type of mixed nerve that performs sensory and motor functions in brain.

6- Abducent nerve (VI)

- This is a motor nerve that supplies to the pons and perform function of turning eye laterally.

7- Facial nerve(VII)

- This motor nerve is responsible for different types of facial expressions, presents over brain stem.
- This also performs some functions of sensory nerve by supplying information about touch on face and senses of tongue in mouth.

8- Vestibulocochlear nerve (VIII)

- This is a motor nerve. It is involved in the sense of hearing and balance.

9- Glossopharyngeal nerve(XI)

- This sensory nerve carries sensory information from pharynx (initial portion of throat) and posterior portion of tongue and palate.
- The information sent is about temperature, pressure. It also covers some portion of taste buds and salivary glands.
- The nerve also carries some motor functions such as helping in swallowing food.

10- Vagus nerve(X)

- This is a type of **mixed nerve** that carries both motor and sensory functions.
- It innervates the muscles of pharynx, palate and larynx .It is involved in the sense of taste.
- The vagus nerve is sensory for the pharynx and larynx and for receptors that monitor blood pressure and gas levels in the blood.
- The vagus nerve provides sensory and parasympathetic innervations to the thoracic and abdominal organs.

11- Spinal accessory nerve(XI)

- This nerve has only a spinal component.It is a motor nerve, supplies the **sternocleidomastoid** and **trapezius muscles.**

12- The hypoglossal nerve(XII)

- It supplies the intrinsic tongue muscles, three of four extrinsic tongue muscles and two throat muscles.

Table (3, 2): Cranial nerves.

Nerves	Type	Function
I Olfactory	sensory	olfaction (smell)
II Optic	Sensory	Vision
III Oculomotor	Motor	eyelid and eyeball muscles
IV Trochlear	Motor	eyeball muscles
V Trigeminal	Mixed	Sensory: facial and mouth sensation Motor: chewing
VI Abducens	Motor	eyeball movement
VII Facial	Mixed	Sensory: taste Motor: facial muscles and salivary glands
VIII Vestibulocochlear	sensory	hearing and balance
IX Glossopharyngeal	Mixed	Sensory: taste Motor: swallowing
X Vagus	Mixed	Sensory for the pharynx and larynx parasympathetic nervous system (PNS)
XI Accessory	Motor	moving head and shoulder
XII Hypoglossal	Motor	tongue muscles

Peripheral Nervous System

Overview

- **The peripheral nervous system (PNS)** consists of all parts of the nervous system, except the brain and spinal cord.
- The PNS connects the CNS to the reminder of the body. Through which the neural signal transmitted to and from the CNS. (Figure 3.28).
- Sensory neurons transmit impulses to the CNS from sensory receptors.
- Motor neurons transmit neural signals from the CNS to the effectors (glands, organs, muscles).
- The PNS is divided into two subsystems:
  1- **The sensory somatic nervous system.**
  2- **The autonomic nervous system.**
- Sensory nervous system comprises 12 pairs of cranial nerves and 31 pairs of spinal cord nerves.
  - Some pairs are exclusively sensory neurons (involved in smell, vision, hearing and balance).
  - Other pairs are made up of motor neurons (included in taste and swallowing).
  - Spinal cord nerves are mixed of sensory and motor neurons .This allows to spinal cord neurons to function as conduit of transmission of the signals of the stimuli and subsequent response.

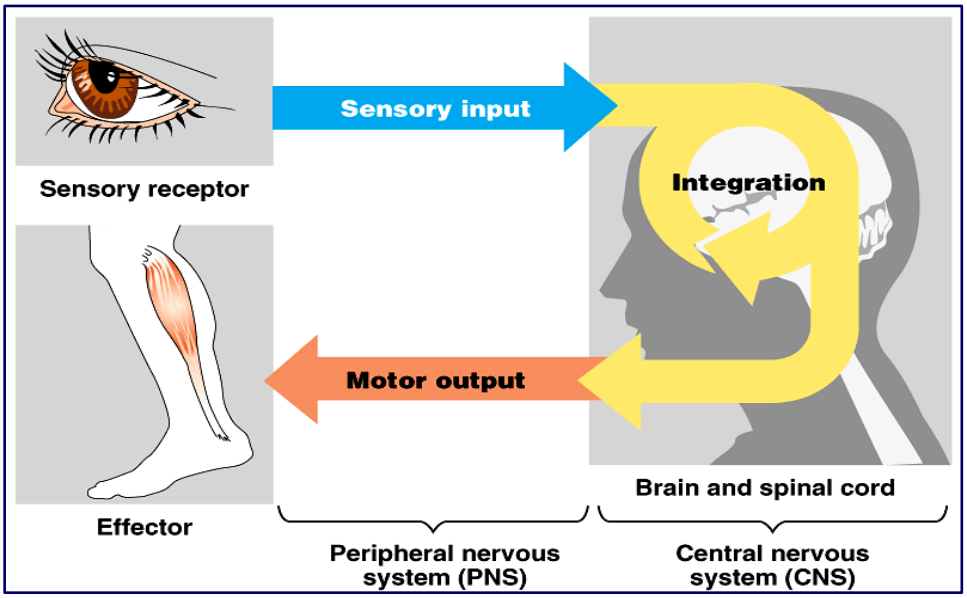


Figure (3.28): Peripheral Nervous System. (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings, 2014).

Sensation

- The sense includes **general sense** and **special sense**.(Figure 3.29).
- The somatic sense includes touch, pressure, temperature, proprioception and pain.
- Sensation or perception is the conscious awareness of stimuli received by sensory receptors.
- Sensation requires a stimulus, a receptor, and conduction of action potential to CNS, translation of action potential and processing of the action potential in CNS.

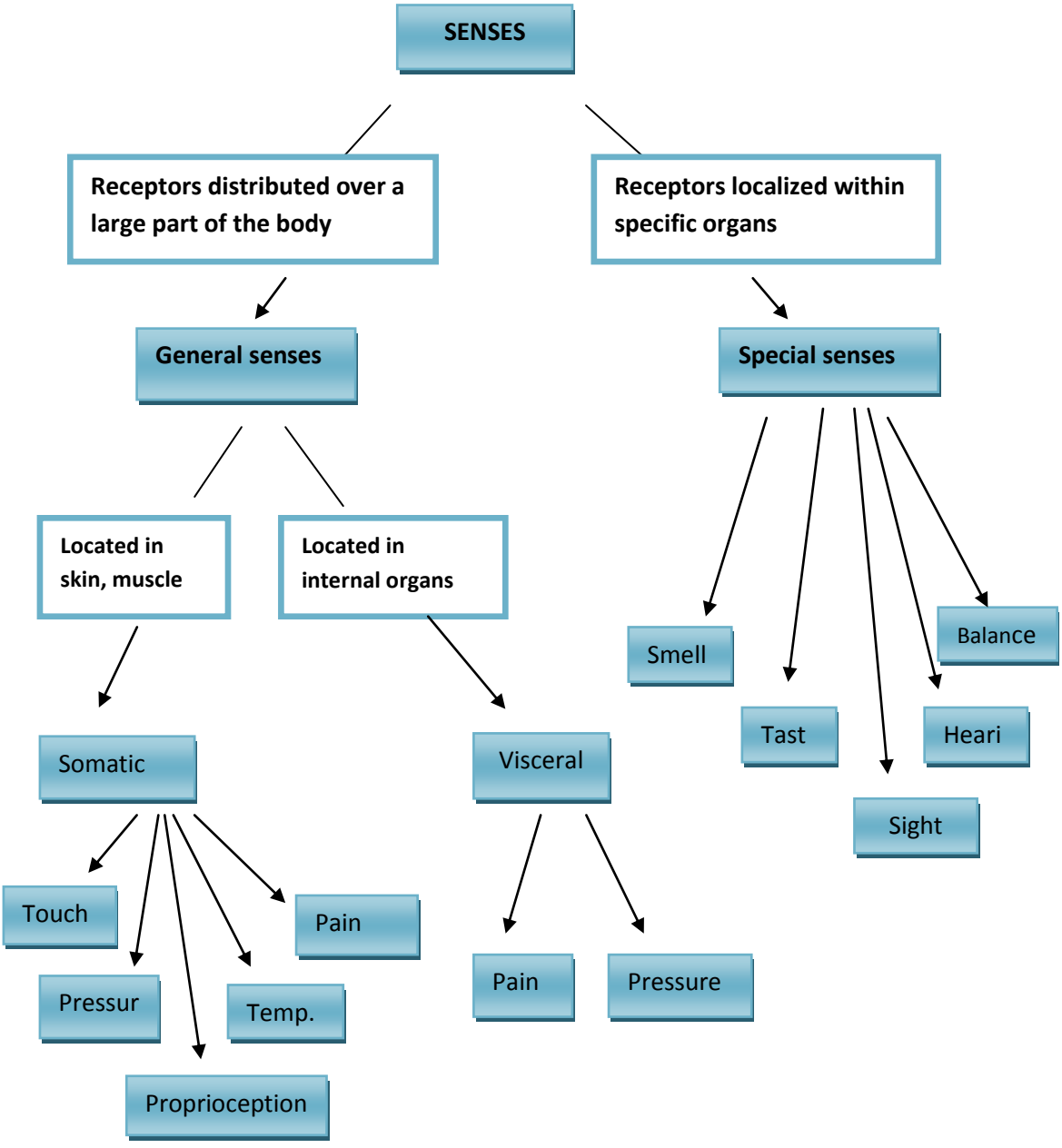


Figure (3.29): Classification of senses.

Sensory receptors

- Sensory receptors are specialized nerves cells that detect environmental stimuli and transducer them through neural signals.
- Receptors include **mechanoreceptors**, **chemoreceptors**, **thermoreceptors, photoreceptors** and **nociceptors.**
- A stimulus produces action potential in a **focal area** of sensory surface (e.g., skin), the **receptive field.**
- The receptive fields allow the body to be **topographically mapped** throughout the whole nervous system from the skin to the brain.
- **Primary receptors** have axons that transmit action potential toward CNS.
- **Secondary receptors** have no axons but release neurotransmitters.
- Some signals need to be transmitted to the CNS rapidly, whereas others can be transmitted more slowly, so different types of sensory fibers have different size and velocities.

Sensory transduction

- A process, in which a stimulus is detected, amplified and conducted to CNS.
- This occurs through changes in membrane potential, this change is called a **receptor potential,** which achieved by opening ion channels allowing current to flow.
- If membrane potential reaches threshold, action potential occurs.
- The signal intensity (e.g., intensity of pain) can be conveyed by recruiting increased membranes of parallel fibers or by increasing the frequency of action potential.

Adaptation

- Adaptation a special characteristic of all sensory receptors.
- Sensory receptors is adapt after period of time to any stimulus. This is either partially or completely.
  - **Slowly adapting (tonic):** receptors continue to transmit impulse to the brain as long as the stimulus is present, such as muscle spindle, pressure receptor slow pain receptors.
  - **Rapidly adapting (phasic):** receptors rapidly adapt to constant stimulus by decreasing their action potential frequently over time, such as light touch receptors, **Meissner corpuscles** and deep pressure **(pacinian corpuscles).**

Sensory pathways

- Sensory pathway is a group of neurons linked synaptically, share common function and course:

1- The receptors potential is created.
2- Receiving of the signal from the receptors by **first order neurons** (cells in the dorsal root ganglia)
3- **Second order neurons** (in the spinal or brainstem) receive signals from the first order neurons and transmitted them to the thalamus.
4- **The third order neurons** are located in the relay nuclei of the thalamus, the ventral posterior nucleus and project to the cerebral cortex.
5- **The fourth order neurons** (in the cortical cortex) confer conscious perception of the stimulus.
6- The orientation of these neurons in the cortex creates a **sensory homunuclu**, which is a map of the body in the brain.(Figure3.30).

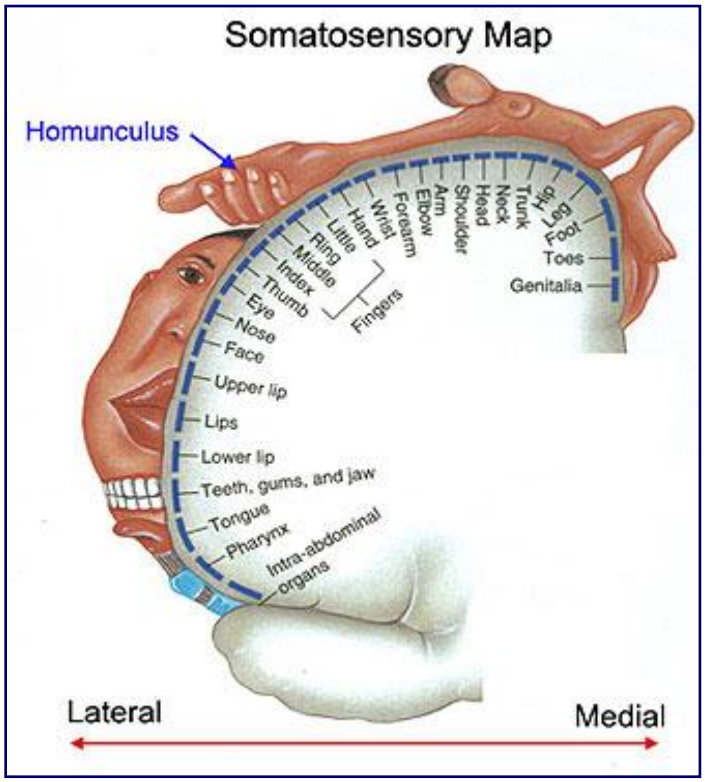


Figure (3.30):The sensory map of the body in the brain.(Barrett K.E.,Barman S.M. Boitano S. and Brooks H.L. Ganong, s Review of Medical Physiology . Singapore, McGraw-Hill Companies,2012).

Pain perception

- Pain is a sensation characterized by a group of unpleasant and complex perceptual and emotional experience that trigger **autonomic**, **psychologic** and **somatic motor** response.
- **Pain components:**
  1- Rapidly conducted action potential by large diameter myelinated axons, resulting in sharp, well localized, pricking or cutting pain.
  2- More slowly propagated action potential carried by smaller myelinated axons causing poorly localized diffuse burning or aching pain.
- **Pain receptors:**
  - Free nerve endings that are located in the skin, muscle and viscera are responsible for detecting and perception of pain **(nociception).**
  - The pain receptors adapt very little and sometime not at all.
  - The pain receptors have very uniform sensitivity, which does not change dramatically from one instant to another.
- Variation in pain result from :
  1- The mechanism by which pain receptors are stimulated.
  2- Differences in the integration of action potential from the pain receptors and complex interactions in the cerebral cortex, cingulated gyrus and thalamus where the emotional components of pain is registered.

Motor tracts

- Motor tracts are **descending pathways** containing axons that carry action potential from cerebrum or cerebellum to the brainstem or spinal cord.
- The descending motor fibers are divided into two groups,(Figure 3.31) :
  1- The direct pathways: maintain muscle tone and control fine skilled movement in the face and distal limbs.
  2- The indirect pathways control conscious and unconscious muscle movements in the trunk and proximal limbs.
- **The corticospinal tracts** control muscles movements below the head.
  - About 75%-85% of the upper motor neurons of the corticospinal tracts cross over in the medulla to form the lateral corticospinal tracts in the spinal cord.
  - The remaining upper motor neurons pass through the medulla to form the anterior corticospinal tracts, which cross over in the spinal cord.
  - The upper motor neurons of both tracts synapse with interneurons that synapse with lower motor neurons in the spinal cord.

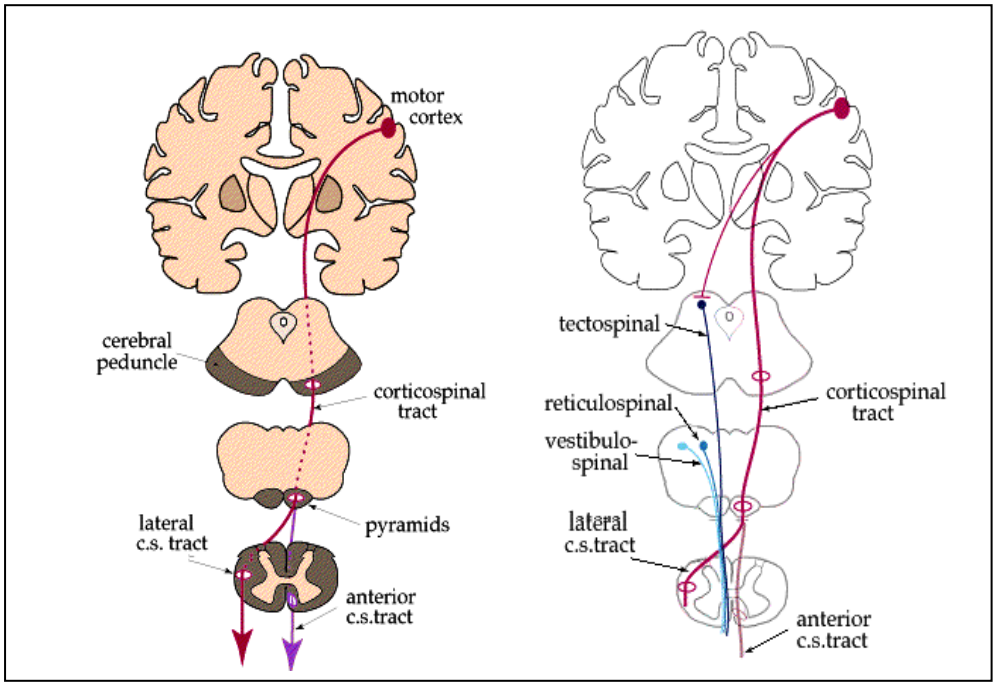


Figure (3,31): Descending motor pathways.Modified from: (Marieb E.N.and Hoehn K.Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

- **The corticobulbar** tracts innervate the head muscles. Upper motor neurons synapse with interneurons in the reticular formation, which inturn synapse with lower motor neurons in the cranial nerve nuclei.
- The indirect pathways include **the rubrospinal, vestibulospinal** and **reticulospinal** tracts and **fibers from the basal nuclei.**

Autonomic nervous system

Overview

- **Autonomic nervous system (ANS)** is the part of nervous system that is responsible for **homeostasis**.It consists of three subsystems :
  1- The sympathetic nervous system.
  2- The parasympathetic nervous system.
  3- The enteric (ENS) nervous system.
- The ANS regulates the activities of smooth muscles, cardiac muscles, endocrine glands and exocrine glands. (Figure 3.32).
- These functions are regulated by **brain centers** in the **hypothalamus** and **brainstem.**
- Some target organs are innervated by both sympathetic and parasympathetic nervous system .Others are controlled by one.
- The ENS controls the activity of gastrointestinal tract.

- The ANS functions involuntarily (reflexively) in an automatic manner without conscious control. The ANS operates through **visceral reflexes.** (e.g., response to cold).

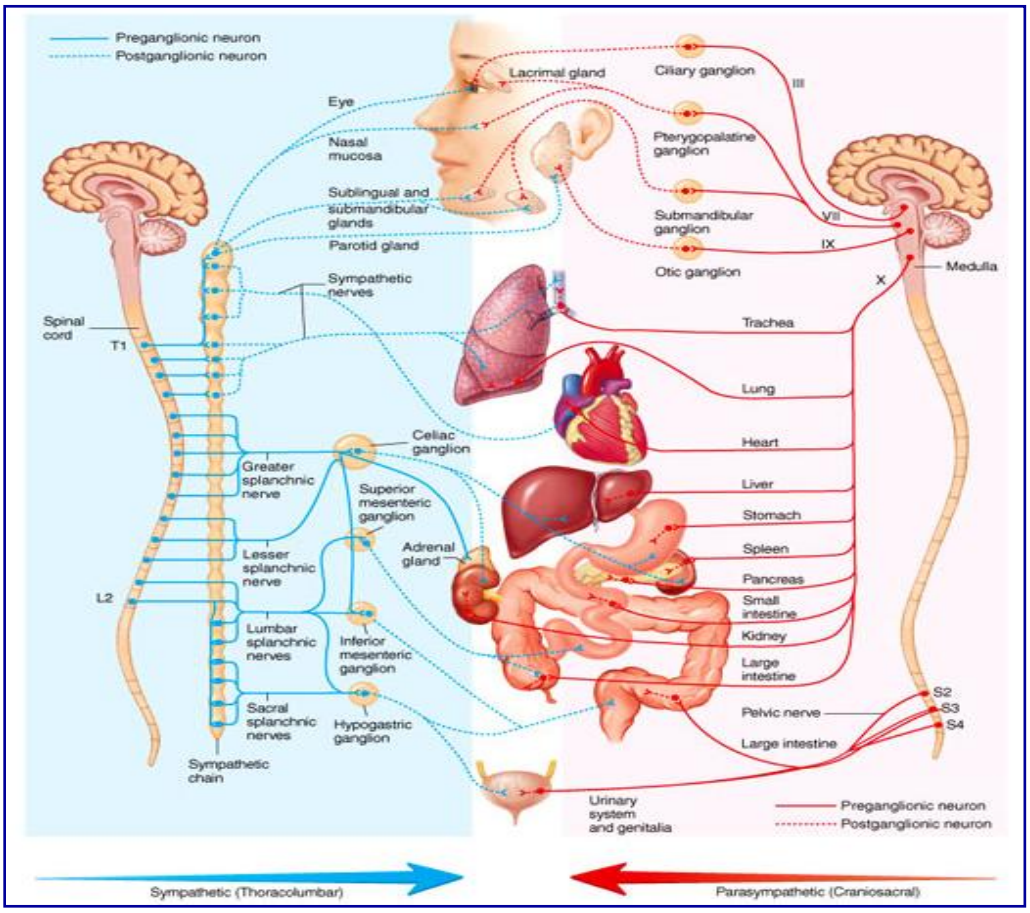


Figure (3.32): Autonomic Nervous system.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- Peripheral motor portion of ANS are made up of two neurons:
  1) Periganglionic neurons 2) Postganglionic neurons.
- The cell bodies of periganglionic neurons are located in the **intermediolateral (IML)** column of the spinal cord and **motor nuclei** of some cranial nerves.
- Periganglionic axons are small diameter myelinated, relatively slowly conducted.
- Autonomic output diffuse by diverging periganglionic axon to average 8-9 postganglionic neurons.
- Postganglionic axons are unmyelinated and terminate on the **visceral effectors.**
- Periganglionic neurons release **acetylcholine (ACh)** at their nerve terminals.

1- Sympathetic nervous system

- The sympathetic nervous system is called **"fight or flight system**" because it is most active in times of stress ,fear or excitement
- The system originates in the spinal cord as **pre-ganglionic neurons**, which connect with **post-ganglionic neurons** going to the organ they act upon.
- This prepares for physical activity by:
  - Increasing ventilation and expanding the respiratory passages.
  - Increasing the cardiac output, blood pressure (so the blood is pumped faster) and blood distribution through vasoconstriction (blood to the muscles at the expense of the gut).
  - Increasing the concentration of blood glucose above normal, by releasing glucose from the liver.
  - Increasing sweating (to cool the body during activity)
  - Inhibiting digestion.

2- The parasympathetic nervous system.

- The parasympathetic nervous system is called the **"rest and digest system"** because it is most active in times of rest and relaxation.
- Parasympathetic pathways are composed **preganglionic** and **postganglionic** neurons.
- The perganglionic nerve fibers originate in the cranial nerve nuclei in the brainstem and in lower spinal cord.
- This system prepares for resting activities by
  - Promoting digestion, defecation and urination.
  - Slowing respiration.
  - Slowing the heart beat.

3- The enteric nervous system

- This system comprises **submucosal and myenteric plexuses**; entirely contained within the gut wall.
- Stimulation of the myenteric plexus increases the **intestinal motility** by stimulation peristalsis and inhibiting contraction of sphincter muscles throughout the intestinal tract.
- The ANS influences functioning of the enteric nervous system :
  - The sympathetic stimulation inhibits peristalsis and increases sphincter tone, thereby inhibiting digestion.
  - The parasympathetic stimulation promotes peristalsis and relaxes the sphincters, thereby enhancing digestion.

Chemical transmission

- Transmission at the synaptic junction between preganglionic and postganglionic neurons, and between postganglionic neurons and autonomic effectors are chemically mediated.
- The principle transmitter agents involved are: **acetylcholine (ACh) and norepinephrine.**
- The autonomic neurons that are **cholinergic(release ACh)**are:
  - All periganglionic neurons
  - All parasympathetic postganglionic neurons
  - Sympathetic postganglionic neurons that innervate sweat glands.
  - Sympathetic postganglionic neurons that end on blood vessels in some skeletal muscles and produce vasodilatation when stimulated.
- The remaining sympathetic postganglionic neurons are **noradrenergic (release norepinephrine).**
- Transmission in autonomic ganglia is mediated by the action of **ACh** on **nicotinic cholinergic receptors** that are blocked by **hexamethonium (Nn receptors**) to distinguish them from the **nicotinic cholinergic receptors (Mm)** located at the neuromuscular junction and blocked by **D-tubocurane.**
- **Noradrenergic neurotransmission :**
  - **Norepineprine** spreads farther and has more prolonged action than ACh
  - **Norepinephrine, epinephrine** and **dopamine** are all found in plasma.
  - The epinephrine and some of dopamine come from the **adrenal medulla,** but most of the norepinephrine diffuses into the blood stream from sympathetic nerve endings.

Autonomic dysfunction

- Drugs, neurodegenerative diseases, trauma, inflammatory processes and neoplasia are factors that can lead to dysfunction of the ANS.
- The types of dysfunction may range from **complete autonomic failure** to **autonomic hyperactivity.**
- Among disorders associated with autonomic failure are orthostatic hypotension, neurogenic syncope, impotence, neurogenic bladder, gastrointestinal dysmotility and Horner's syndrome .
- Autonomic hyperactivity can be basic for neurogenic hypertension, cardiac arrhythmias, neurogenic pulmonary edema, and myocardial injury.

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Chapter Four

Special Senses 4

Special Senses

Overview

- **Special senses** are senses with highly localized receptors to provide specific information about the environment.
- They comprise olfaction, taste, vision, hearing and equilibrium (the vestibular system).

1- Olfaction

- **Olfaction** is the sense of smell.
- Smell is detected by olfactory receptors cells in the mucus-coated olfactory epithelium that lines the **posterodorsal parts** of the nasal cavities.
- Olfactory glands secrete a fluid to bath the cilia of the receptors and acts as a solvent for odorant molecules.
- Olfactory receptors cells are stimulated by binding of odor molecules to their cilia.
- Axon of olfactory receptor cell form the first cranial nerve (CN I).
- Axon of the **mitral cells** of the **olfactory bulb**: form the **olfactory tract** and **lateral olfactory** stria,(figure4.1), which project to **olfactory cortex** and **amygdala** .
- Olfactory receptor cells: only regenerative neurons in adult human.

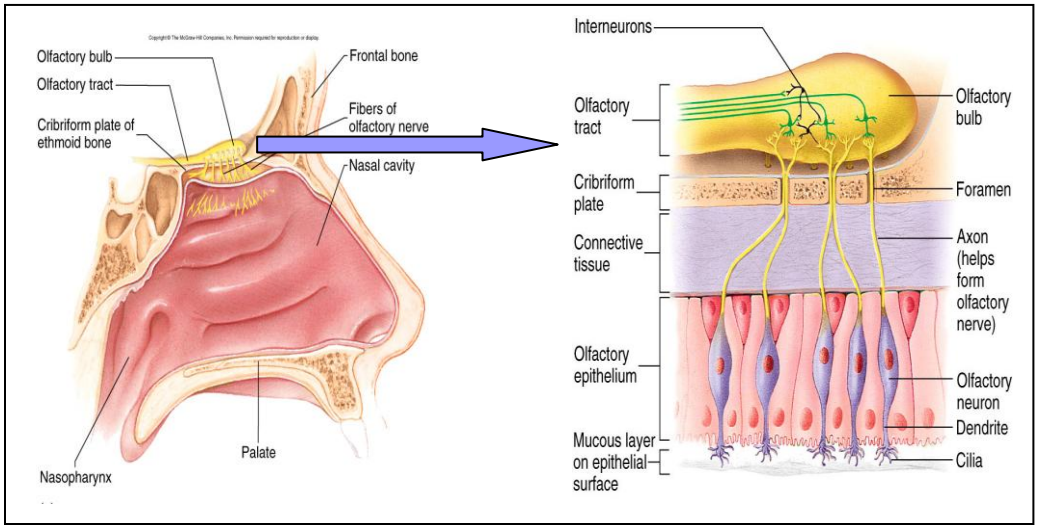
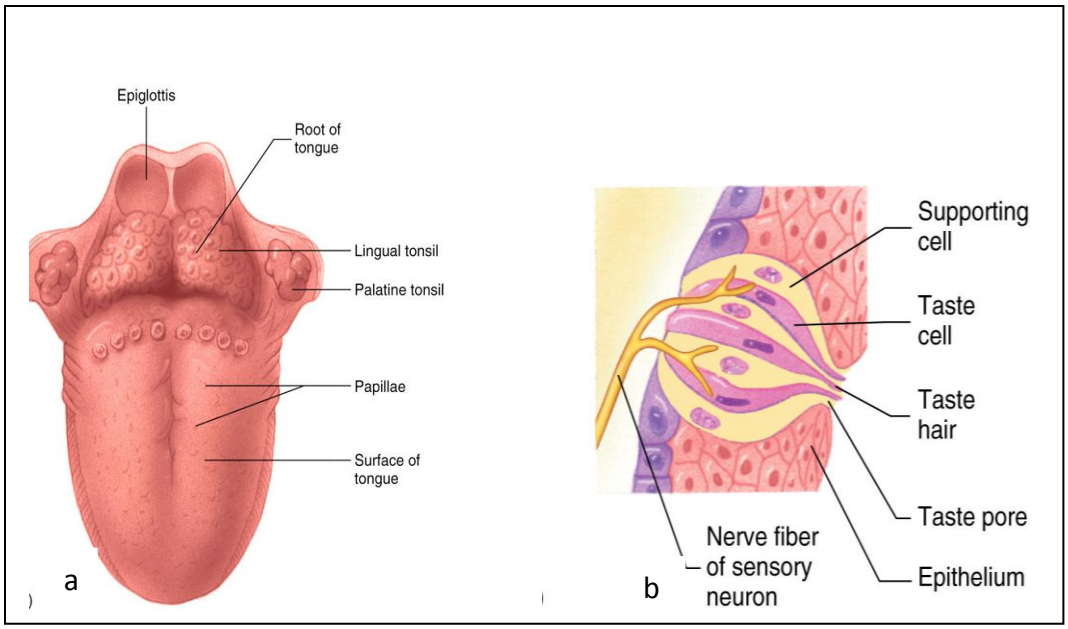


Figure (4.1): Olfactory region, olfactory tract and olfactory bulb. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

- **Olfactory transduction:** Binding of odoriferous molecules to cilia on olfactory cells: results in action potential generation and transduction of signal to olfactory cortex.

2- Taste

- Taste is detected by **taste receptor cells** which are located on specialized **papillae** of the **taste bud**, (figure4.2.b) and are stimulated by taste chemicals.
- Each bud contains about **40 taste cells,** each ending in an exposed hair-like projection, to which chemicals attach.
- The taste cells are a mixture of **5 types: sweet, salt, umami (savory), sour and bitter**, but 1 type will be dominant. Thus the tip of the tongue mainly detects sweet, the front sides detect salt, back sides detect sour and the back of the tongue mainly detects bitter.(Figure 4.2.a).
- **Taste transduction:**
  - The binding of taste chemicals to the taste receptors causes a **depolarization** of the receptors membrane.
  - The depolarization results in action potential that is propagated centrally until the taste sensation is perceived.



Figure(4.2):a ;Surface of the tongue ,b:A taste bud . (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

3- Vision

Structure of the eye

- The eye is a spherical structure filled with liquid **vitreous humor** (**aqueous humor**)in front of the lens, which is enclosed by 3 layers,(figure4.3):

1. **Sclera**
   - Sclera is the outer thick layer.It is white connective tissue that protects the eye from physical damage and helps maintain the spherical shape.
   - There are 6 skeletal muscles, the (**extrinsic eye muscles)** attached to the outside of the sclera, which move the eye ball.
   - At the front of the eye, the white sclera is replaced by a **transparent cornea**, which not only allows the light to enter the eye, but also helps to focus the light on to the **retina**.
2. **Choroid**
   - Choroid is a middle thin vascular layer (provide oxygen to the eye) and black pigment cells (stop internal reflections by absorbing stray light).
   - At the front of the eye, the choroid becomes **ciliary body**, which contains the ciliary muscles that focus the **lens**, by changing its shape.
   - The ciliary body continues interiorly into the **iris**, which controls the amount of light entering the eye.
3. **Retina**
   - Retina is the inner layer which has an outer black layer (like the choroid) and an inner sensory layer, which contains 2 types of receptors: **rods** and **cones**, and 5 types of **association neurons.**

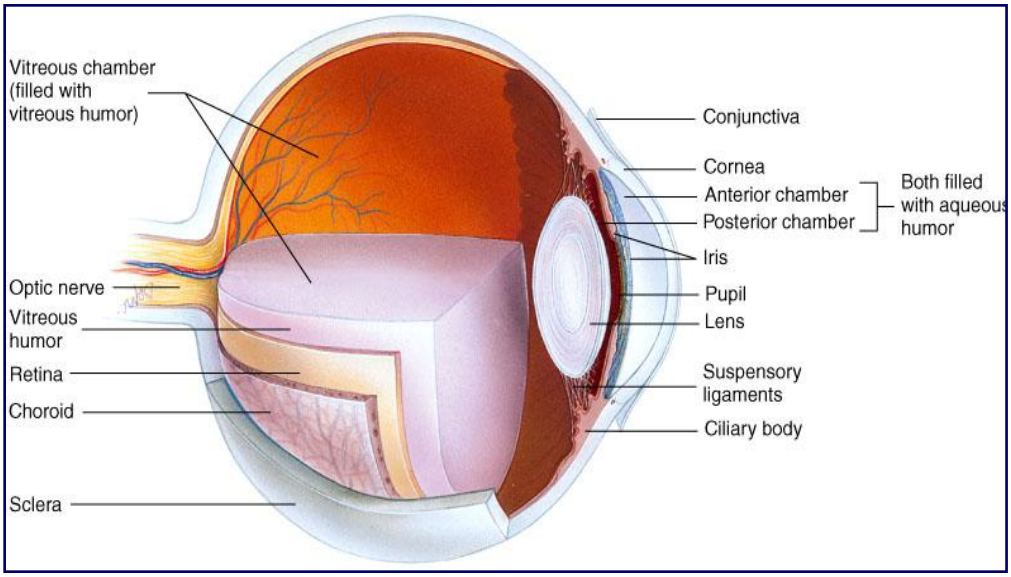


Figure (4.3): The layers of eyeball (sagittal section). (Marieb E.N.and Hoehn K.Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

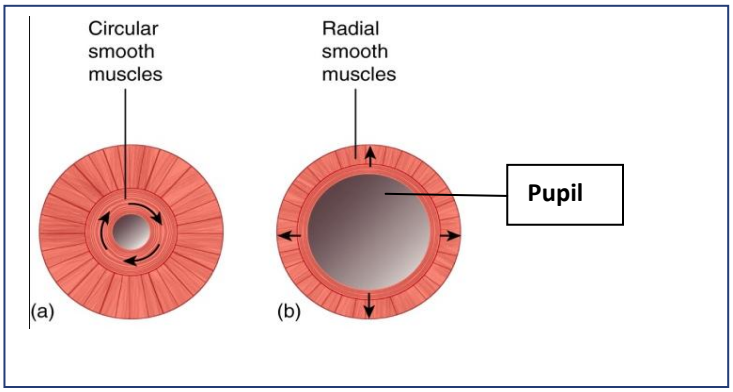
Detection of light

In order to see, the eye must solve the following problems:-

1. Control the amount of light entering the eye.

This is due to the iris, which is made up of 2 concentric areas of smooth muscle.

- **In bright light,** parasympathetic stimulation of the central circular muscle contracts it to reduce the size of the **central pupil** (hole through which the light enters).(Figure 4.4.a).
- **In low light** levels, sympathetic contraction of the outer radial muscle decreases the size of the iris to increase the pupil. (Figure 4.4.b).



Figure(4.4):Controlling the amount of the light entering the eye. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

2. Focus the light on to the retina.

- When looking at an object, the light from that object must be focused on the retina in order to get a sharp picture. Although most focusing is done by the **cornea**, focusing must change for a near object compared with a distant object. This change in focus is done by the **lens**, whose shape can be changed by the ciliary muscle of the **ciliary body**. (Figure 4.5).

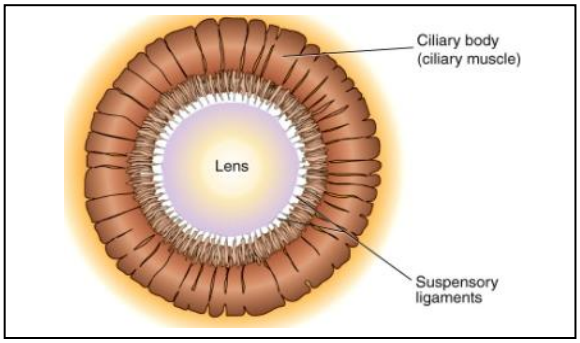


Figure (4.5): The lens and ciliary body. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- **In distant vision,** the muscles are relaxed. Thus suspensory ligaments around the lens stretch it into a flattened shape.
- **For a near object,** the muscles contraction and being circular reduce the central area (like in the iris) to shorten the ligaments. The ligaments are thus relaxed and the lens becomes more rounded as it relaxes. This focusing process is known as **accommodation**. When an object is in focus, it will appear on a small area of the retina known as the **fovea** (in the rest of the retina, the objects are out of focus). (Figure 4.6).

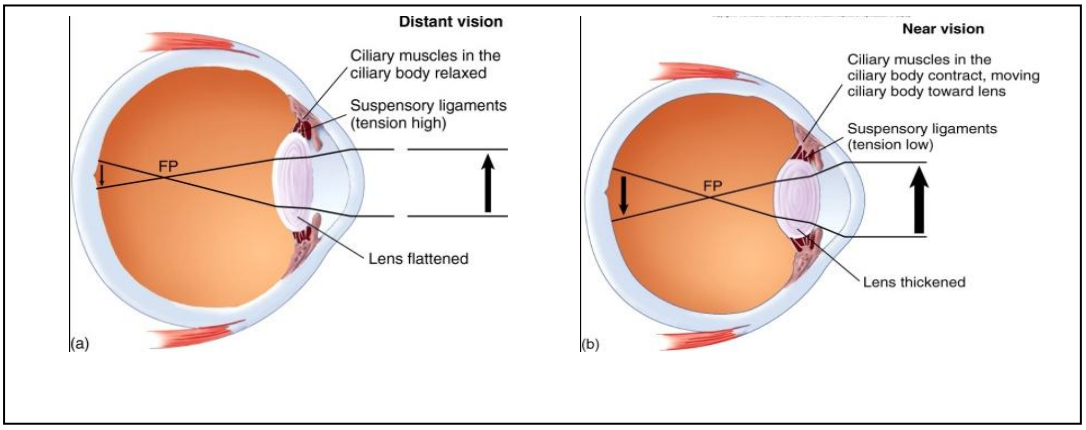


Figure (4.6): Focus and accommodation by the eye,(a): The lens is flattened and the image is focused on the retina,(b): Accommodation for near vision ,the lens is more rounded and the image is focus on the retina.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

3. Detect the light in the retina.

- The receptors detect light using the visual pigment, **rhodopsin**. They are of two types:-

1- **Rods,** (figure 4.8.b) are the most abundant (about 125 m) and are distributed throughout the retina. Because they contain a large amount of rhodopsin, they are very sensitive to light. They work in low light levels such as at night, but are inactive during the day (when all the rods will be highly stimulated, and so cannot produce a picture of light and dark).

2- **Cones** are less abundant (only 6.5 m), (figure 4.8.a) but are **concentrated at the fovea**, where the object you are looking at will be focused. The cones will therefore give a detailed picture of the object you are staring at, but all the peripheral vision will be very blurred (few cones are in the peripheral retina). (Figure 4.7) .Although cones also use a rhodopsin-like pigment; the opsin component of the rhodopsin can be of 3 types, each of which is sensitive to a different color: which are **red, green and blue**. Detection of a color depends on the relative stimulation of the 3 types (thus red will strongly stimulate the red cones, but orange will give less stimulation and yellow give even less). Cones only work in daylight (so, the colors cannot be seen at night, when only the rods are working).

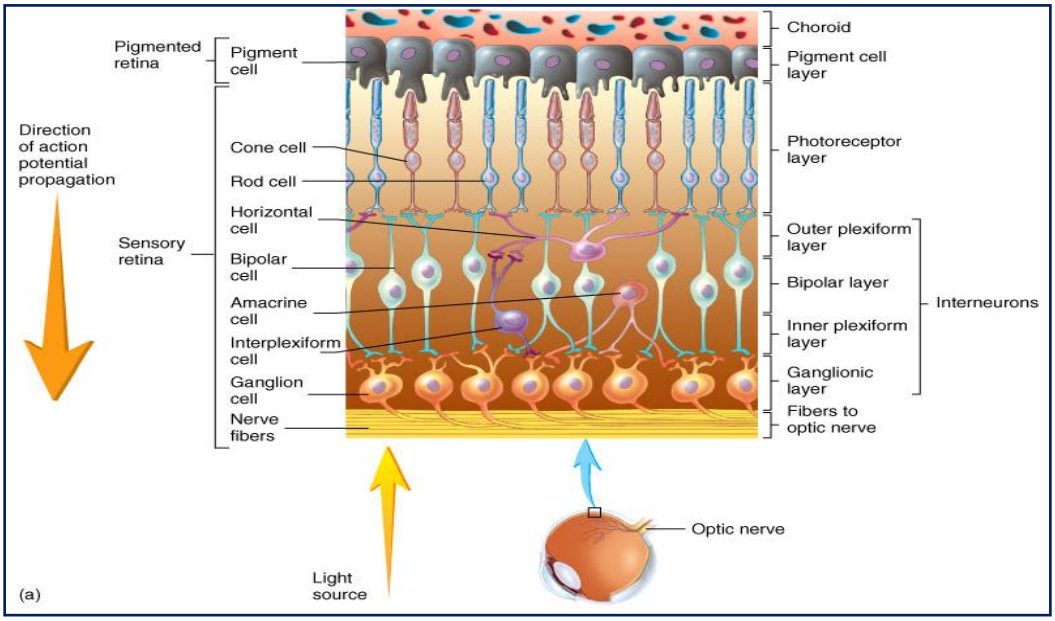


Figure (4.7): Section through the retina with its major layers.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- The rhodopsin is found in the outer part of each receptor, which is made up of parallel discs. (Figure4.8.c). Rhodopsin consists of the pigment **retinal** combined with the protein **opsin**.
- When hit by a photon of light, the **retinal changes shape**, **breaking away from the opsin and releasing energy**, which results in the depolarization of the neuron attached to the receptor**. ATP** is then used to change the retinal back to its original shape and reattach it to the opsin. This **rhodopsin cycle** is illustrated in figure (4.9).

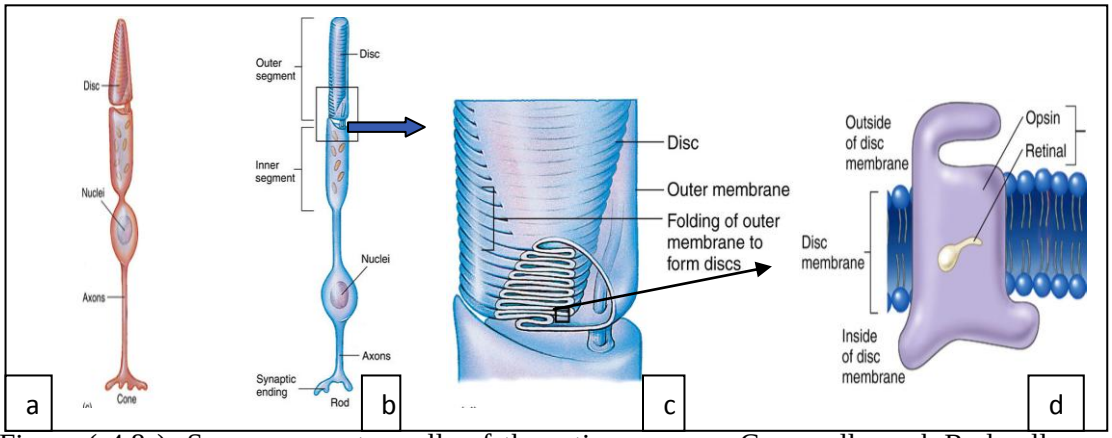


Figure (4.8): Sensory receptor cells of the retina. a: Cone cell, b:Rod cell, c:An enlargement of the discs in the outer segment d: An enlargement of one of the discs.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw – Hill Companies, 2008).

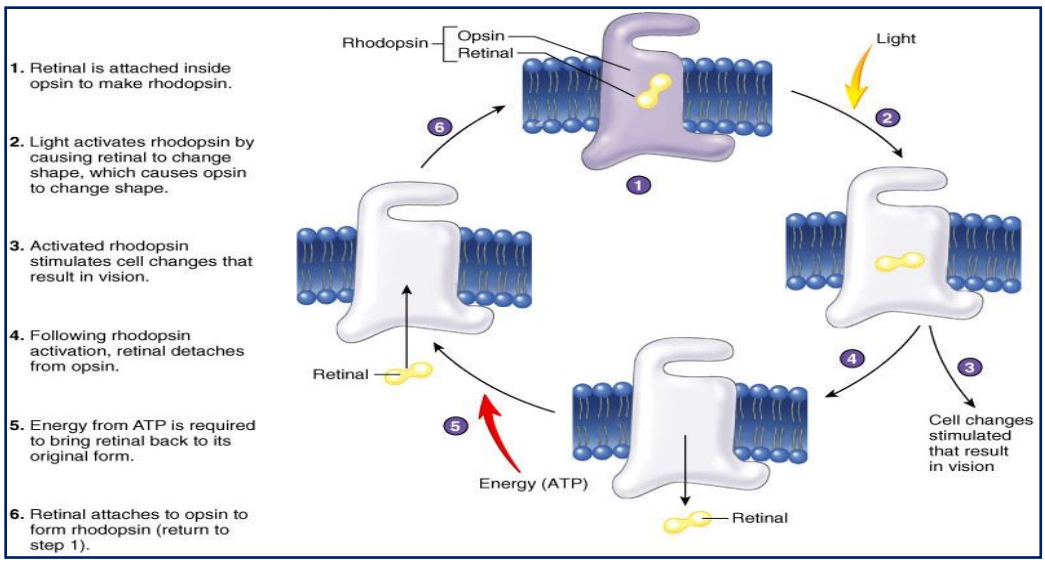


Figure (4.9): The rhodopsin cycle. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- The **five types of interneurons** connected to the rods and cones are responsible for **integration** of the data. By combining the data from the 6,500,000 cones, they make the picture sharper by looking for patterns, such as boundaries between 1 color and another, while at the same time reducing the information down to the 100,000 neurons in the optic nerve. Further integration will then occur in the **thalamus** and in the **occipital lobe of the cerebrum**, where to put final picture together.
- **Note that the light must 1st pass through the interneurons before it is detected by a rod or cone and finally absorbed by the black pigment.**

Clinical note: Myopia is the ability to see close objects clearly but distant objects appear blurry .It is a defect of the eye in which the focusing system, the cornea and lens is optically too powerful or the eye ball is too long .As r result the focal point is too near the lens and the image is focused in front of the retina. Myopia is corrected by a concave lens that counters the refractive power of the eye.

Hyperopia is the ability to see distant objects clearly but close objects appear blurry. It is a disorder in which the cornea and lens system is optically too weak or the eye ball is too short .The image is focused behind the retina .Hyperopia can be corrected by convex lenses that cause light rays to converge as they approach the eye.

Presbyopia is the normal unavoidable degeneration of the accommodation power of the eye that occurs as a consequence of aging .It occurs because the lens becomes sclerotic and less flexible. It can be corrected by using of reading glasses.

Astigmatism is a type of refractive error in which the quality of focus is affected If the cornea or lens is not uniformly curved the light rays do not focus at a single point but fall as a blurred circle. Regular astigmatism can be corrected by glasses that are formed with the opposite curvature gradation.

2. The ear - Hearing.

Structure of the ear

1- The outer ear

- It consists of **pinna** and the **external acoustic meatus** which lined with **hair** and **glands** that secrete wax **(cerumen).**

2- The middle ear

- It is air filled.
- It contains the "**tympanic membrane**" a three layered membrane between the middle ear and the inner, and three small bones **(auditory ossicles)**: ***malleus, incus*** and ***stapes.***
- The stapes inserts into the oval window,
- Sound waves cause the tympanic membrane to vibrate. In turn, the ossicles vibrate, pushing the stapes into the oval window and displacing fluid in the inner ear.
- **Sound is amplified** by the lever action of ossicles and the concentration of sound waves from the large tympanic membrane onto the smaller oval window.

3- The inner ear

- It is fluid –filled
- It consists of a bony labyrinth (**semicircular canals**, **cochlea** and **vestibule**) and a series of ducts called the membranous labyrinth.
- The fluid outside the ducts is **perilymph**. The fluid inside the ducts is **endolymph**. (Figure 4.10).

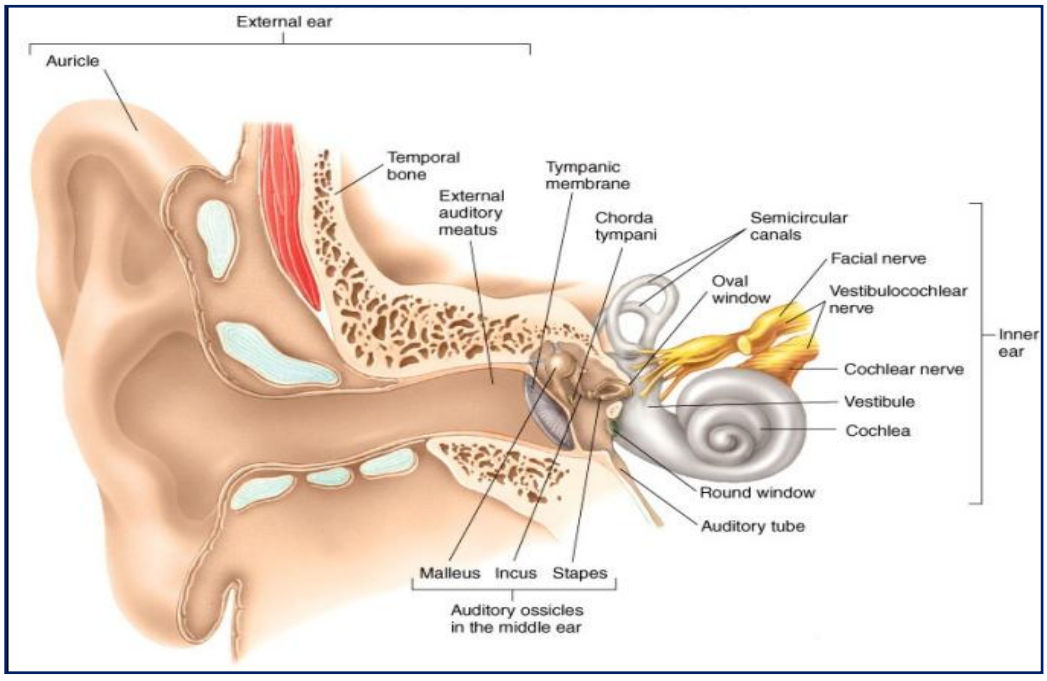


Figure (4.10): Structure of the ear. (Scanlon V.C. and Sanders T. Essential of Anatomy and Physiology . Philadelphia, E.A. Davis Company, 2007).

- The **cochlea** consists of three tubular canals:(Figure4.11)
  - The **scala vestibuli** and **scala tympanic** contain perilymph ,which has a high Na^+
  - The **scala media** contains endolymph ,which has a high K^+ .
- The cochlea is bordered by the "**basilar membrane**" which houses the **organ of Corti** .
- **Organ of Corti** contains **inner and outer hair cells** needed for audition. These cells have cilia embeded in **tectorial membrane**.
- The **spiral ganglion** contains the cell bodies of the auditory nerve(cranial nerveVIII),which synapse on the hair cells.

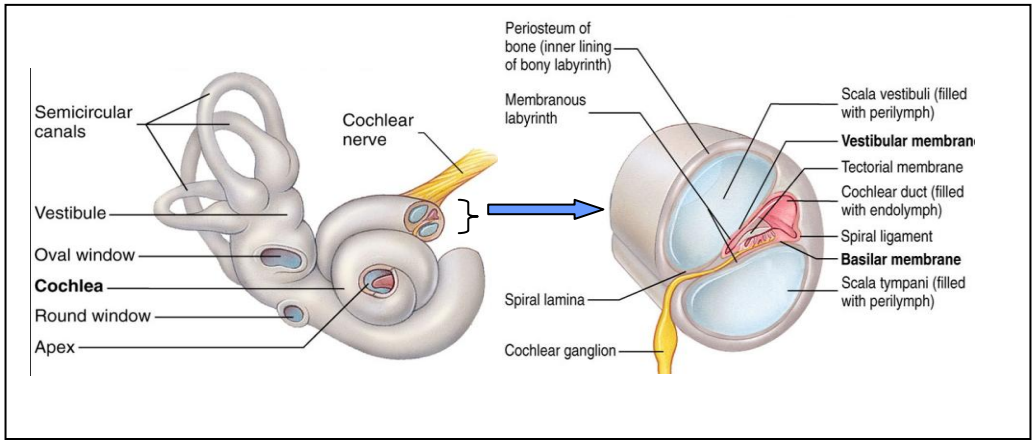


Figure (4.11):Structure of the cochlea. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Auditory transduction

- Sounds waves cause vibration of the organ of Corti.Because the basilar membrane is more elastic than the tectorial membrane ,vibration of the basilar membrane causes the hair cells to bend by a shearing force as they push against the tectorial membrane.

- Bending of the cilia causes changes in the K^+ conductance of the hair cell membrane.Bending in one direction causes depolarization ;bending in the other direction causes hyperpolarization.The oscillating potential that results is the **cochlear microphonic potential.**

- The oscillating potential of the hair cells causes intermittent firing of the cochlear nerves.

Sound encoding

- The frequency that activates a particular hair cell depends on the **location** of the hair cell along the basilar membrane.
  - The **base** of the basilar membrane (near the oval and round window)is narrow and stiff .It responds best to **high frequencies**.

- The **apex** of the basilar membrane (near the helicoterma) is wide and compliant .It responds best to **low frequencies.**

Neural pathways of hearing

- Axons from the **vestibulocochlear nerve** synapse in the **medulla.**
- Axons from the **medulla** project to the **inferior colliculli** to synapse .
- Neurons from the inferior colliculli project to the **thalamus.**
- Thalamic neurons extend to the **auditory cortex.**
- Discrimination of complex features e.g.,recognizing a patterned sequence ,is a property of the **cerebral cortex.**

Clinical not: The term **hearing-impaired** refers to any type or degree of hearing loss. The hearing loss can be **conductive**, **sensorineural,** or a **combination of both**. Conduction deafness involves a mechanical deficiency in the transmission of sound waves from the external ear to the spiral organ. The spiral organ and neural pathways function normally. Sensorineural deafness involves the spiral organ or neural pathways. Sound waves are transmitted normally to the spiral organ, but nervous system's ability to respond to the sound waves is impaired.

3. Body equilibrium.

- Apart from the cochlea, two other sense organs make up the ear:
  - **The vestibule** detects static equilibrium (position of the head).
  - **The semicircular canals** detect kinetic equilibrium (movement of the head).

Static equilibrium

- **The saccule** (at the base of the cochlea) and **the utricle** (at the base of the semicircular canals) both contain **hair cells** in which the microvilli are enclosed in a gelatinous layer containing **otoliths**.
- The hair cells and gelatinous layer are together known as the **macula**. Otoliths are small stones of **protein** and **calcium carbonate,** which press down on the microvilli. (Figure 4.12).
- The hair cells thus form a gravity receptor, in which tilting of the head results in bending of the microvilli: the amount of microvilli bending being proportional to the amount of head tilting.

Kinetic equilibrium

- The semicircular canals are at right angles to each other, so that each is in a different plane: 1) horizontal and 2) vertical. Each canal has at its base a swelling, the **ampulla,** which contains **hair cells** with their microvilli embedded in a mass of jelly, the **cupula** (similar to the macula, but without otoliths).

- The canals are filled with **endolymph**. When the head moves in one plane, e.g. horizontally, the endolymph in the horizontal canal swirls around the circular canal and pushes over the cupula filling the base of the canal. Thus the microvilli inside it are bent. Note that the endolymph appears to move in the opposite direction to the head movement, because the liquid gets left behind as the head starts to move. (Figure 4.13).

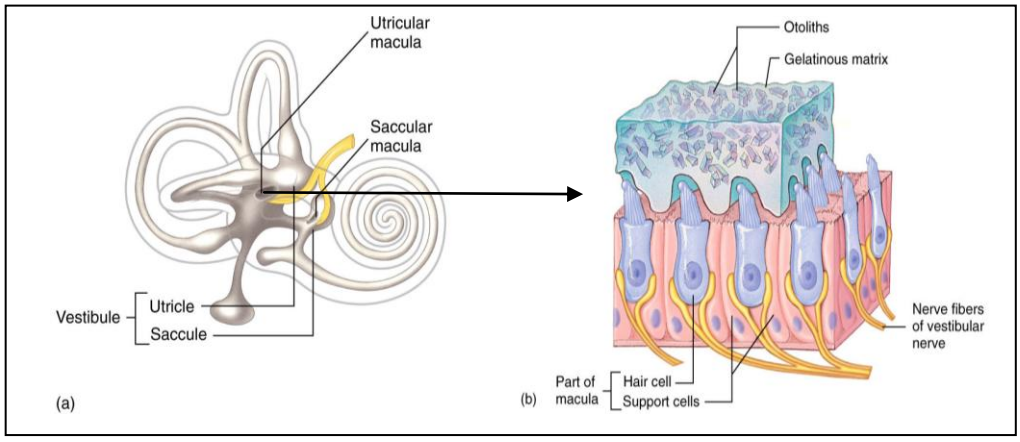


Figure (4.12):Structure of macula. a:utricle and saccule in the vestibule.b: Part of macula ,showing hair cells and otoliths. (Marieb E.N.and Hoehn K.Anatomy and physiology.San Francisco, Pearson Education Inc., 2011).

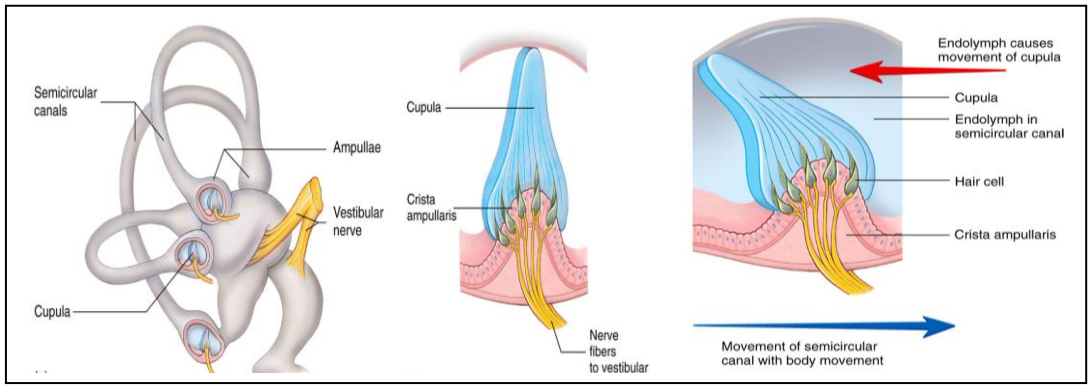


Figure (4.13): Semicircular canals .a: ampullae in the semicircular canal. b: cupula and hair cells. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

The canals measure four factors:

- The **plane** of movement (which of the 3 canals is affected).
- The **direction** of movement (clockwise/ anticlockwise).
- The **velocity** of movement (how far over the cupula is pushed).
- **Acceleration/deceleration** (the rate at which the cupula is pushed over and recovers).

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1. Costanzo L.S. Physiology .4th ed,Philadelphia ,Saunders,2012.
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3. Marieb E.N.and Hoehn K. Anatomy and physiology.4th ed, San Francisco, Pearson Education Inc., 2011.
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Chapter Five

Skeleton and Muscular system 5

Skeletal system

Overview

- The skeleton is made up of: **bone**, **cartilage** and attachment structures (**tendons & ligaments).**

1. Bone. Bone matrix consists of calcium phosphate **(hydroxyapatite)** around a framework of **collagen fibers** (which make the bone flexible and less brittle).

Bone functions:

- **Support** the body by providing a rigid framework.
- **Protection** from damage by enclosing vital parts e.g. the ribs and scapula (shoulder blade) enclose the thorax (heart & lungs); the vertebrae and skull enclose the central nervous system.
- **Movement**. Bones provide a rigid attachment against which muscles contract. Joints between bones control body movements.
- **Mineral storage**. Stores minerals such as calcium ions, so that their blood concentration can be kept constant by releasing from storage as needed. The bone marrow also stores fat.
- **Blood cell formation**. All blood cells (both erythrocytes and leucocytes) are produced by the bone marrow.

2. Cartilage. The matrix of the cartilage is made up of **collagen** which gives strength and flexibility and **proteoglycan: a** polysaccharide storing water (giving smoothness).

Cartilage functions:

- **Model for bone growth.** During growth, cartilage is produced first and gradually replaced by bone.
- **Reduce friction at joints.** At joints, the bone is covered by a layer of cartilage, which provides a smooth plastic-like surface, with a low friction and acts as a shock absorber.
- **Flexible support.** For the nose, ears and trachea.

Bone structure

Bone cells

- **Osteoblasts** produce bone matrix and become **osteocytes.**
  - **Osteoblasts** connect to each other through cell processes and surround themselves with bone matrix to become **osteocytes.**
  - **Osteocytes** are located in **lacunae** and are connected to each other through **canaliculi.**
- **Osteoclasts** are large cells responsible for the resorption of bone.
- **Osteoblasts** originate from **osteochondral progenitor cells.** Osteoclasts originate from stem cells in red bone marrow.
- **Ossification** is the formation of bone by osteoblasts, occurs through the appositional growth.

Compact and Cancellous Bone

1- Compact bone

- Compact bone is dense with few spaces.
- It comprises the outer layer of large bones, but the whole of smaller bones, is made up of **lamellae** (each is a layer of matrix: hydroxyapatite and collagen) arranged concentrically around **Haversian canals** (blood vessels).
- **Osteocytes** (bone cells) lie in between the lamellae and are connected together by **canaliculi** (threads of cytoplasm for food and oxygen transport between cells), which also connect to the Haversian canal
- **Diaphysis of a long bone** is composed of compact bone and it can also contain some cancellous bone.
- **The medullary cavity** fills the center of the large bones. It contains bone marrow, producing the blood cells.
- **The periosteum** is a layer of connective tissue and blood vessels around the outside of all bones and contains osteoblasts.
- **Endosteum** is a single layer of cells that lines the internal surface of all cavities within bones. (Figure 5.1).

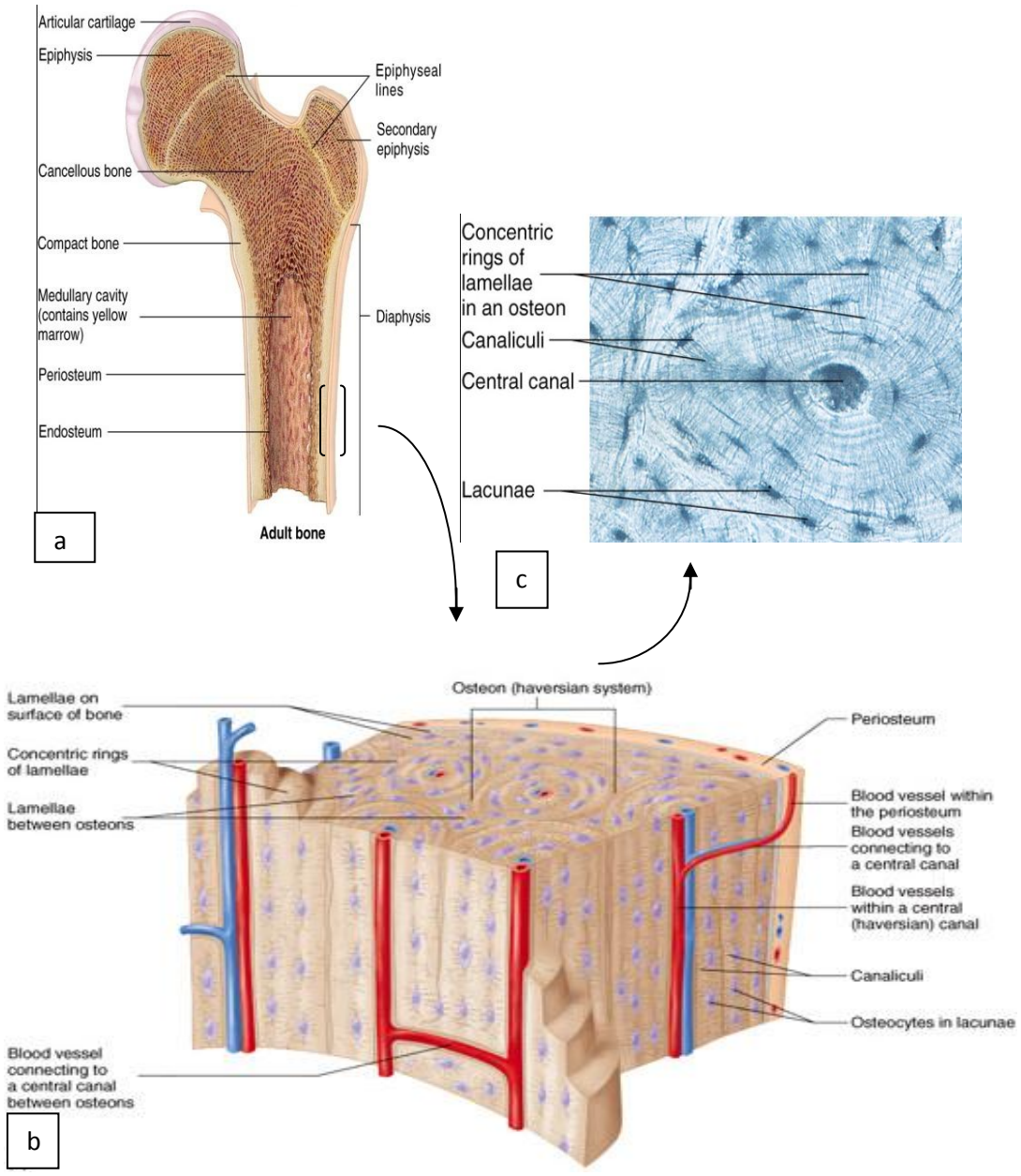


Figure (5.1):Compact bone . a: Long bone .b: Compact bone consists of concentric lamellae(Osteon) surrounding blood vessels within central canals. c:Osteon.Modified from: (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology.New York, McGraw –Hill Companies, 2008).

2- Cancellous bone

- Cancellous bone has many spaces.
- It forms the inner layer of large bones. It forms a network of bone (**trabeculae**) enclosing spaces filled with bone marrow.
- Compared with compact bone, it is still strong but much lighter and so reduces the overall weight of the bone.
- Most **trabeculae** are thin(50-400µm)and consist of several lamellae within osteocytes located in the lacunae between the lamellae.(Figure5.2).

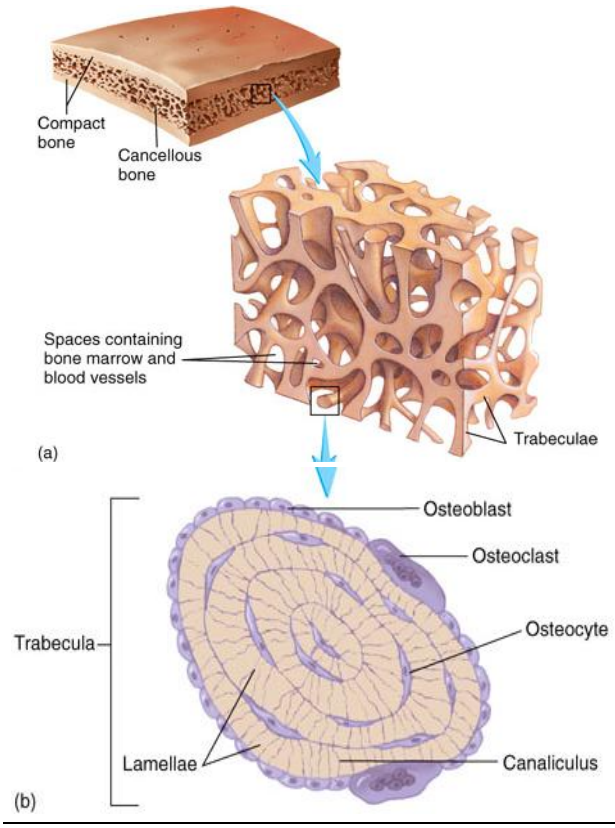


Figure (5.2): Cancellous Bone. a: Trabeculae surround spaces in the bone. b:Transverse section of the trabeculae. .(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

Bone shape

- Individual bones are classified according to their shape as long, short, flat or irregular.
- **Long bones** are longer than they are wide, e.g., most of the upper and lower limbs.
- **Short bones** are about as broad as they are long., e.g., carpal and wrist bones.
- **Flat bones** have thin flattened shape and are usually curved, e.g., ribs, sternum and shoulder blades (scapulae).
- **Irregular bones** have shape that do not fit readily into the other three categories,e.g., vertebrae and facial bones.
- **Flat, short and irregular** bones have an outer covering of compact bone surrounding cancellous bone.

Bone growth

- Most bones develop from a cartilage model.
- The cartilage matrix is calcified and **chondrocytes** die .Osteoblasts form bone on the calcified cartilage, producing cancellous bone.
- Osteoblasts build an outer surface of compact bone beneath the periosteum.
- **Primary ossification centers** form in the diaphysis during fetal development.
- **Secondary ossification centers** form in the epiphyses.
- **Articular cartilage** on the ends of bones and epiphysial plate is cartilage that does not ossify.
- Bones increase in size only by **appositional growth,** the adding of new bone on the surface of older bone or cartilage.
- Trabeculae grow by appositional growth.

Bone remodeling

- Bone remodeling is a process by which the old bone is replaced with new bone. In this process the osteoclasts remove old bone and osteoblasts deposit new bone.
- This process converts the woven bone to lamellar bone.
- It involves in bone growth, bone shape, adjustment of bone to stress, bone repair and calcium regulation in the body.
- The relative thickness of compact bone is maintained by removal bone on the inside by osteoclasts and addition of bone to the outside by osteoblasts.

Factors affecting bone growth

1- Genetic factors determine bone shape and size.

2- Factors that alter the mineralization process or production of organic matrix, such as deficiencies in vitamins D and C can affect bone growth.

3- Growth hormone, thyroid hormone, estrogen and testosterone stimulate bone growth.

4- Estrogen and testosterone cause increased bone growth and closure of the epiphyseal plate.

Clinical note: Giantism is a condition of abnormal increased height that usually results from excessive cartilage and bone formation at the epiphyseal plates of long bones.
Dwarfism: the condition in which a person is abnormally short.
Osteomyelitis is bone inflammation; results from bacterial infection .It can lead to complete destruction of the bone.
Osteomalacia: the softening of bones, results from calcium depletion from bones.
Osteoporosis: results from a reduction in the overall quantity of bone tissues. It occurs when the rate of bone resorption exceeds the rate bone formation. The loss of bone mass makes the bones so porous and weakened that they become deformed and prone to fracture. It increases with age.

Joints

- Bones connected to each other by **joints,** to allow movement. These are:
  1- **Synovial joints** (have a capsule enclosing synovial fluid as a lubricant).
  2- **Fibrous joints** hold two parallel bones together (e.g. lower arm and lower leg).
  3- **Cartilaginous joints** connect the ribs to the sternum.
- Synovial joints have a number of problems to solve:-
  - **Friction.**
    - The ends of the bones are covered by a layer of cartilage. This is smooth and plastic-like, reducing friction, thus preventing one bone damaging the other by rubbing it away.
    - Synovial fluid between the bones acts as a lubricant. The fluid is held in place by being enclosed in the joint capsule, made of connective tissue.
  - **Controlling movement.** The bones are held together by ligaments of collagen fibers. The distribution of these and the shape of the ends of the bones control the **amount of movement** that is possible at the joint.
    - **Hinge joints** only allow movement in one plane e.g. the **fingers** and the **knee.** These are very strong joints, so few muscles are needed.
    - **Ball & socket joints** allow movement in almost any direction e.g. the **shoulder** and **leg/hip joints.** These are more flexible but weaker, so a ring of muscles is needed to control movement.

Clinical note: Damage to the cartilage results in two diseases:-
Osteoarthritis in old people is where the cartilage has been worn away, so the bones (especially the hip and knee joints) rub and damage each other.
Rheumatoid arthritis is an auto-immune disease, in which the leucocytes attack and destroy the cartilage, especially in the fingers and toes, so the joints become deformed and fused together.

Muscular system

Overview

- There are three types of muscle tissues: **Skeletal muscles, cardiac muscles** and **smooth muscles.**
- Skeletal muscle cells and smooth muscle cells are elongated so called muscle fibers.

1- Skeletal muscle

- Skeletal muscle fibers are longest muscle cells, multinucleated and striated.
- Skeletal muscle is voluntary muscle, responsible for overall mobility.
- It contracts rapidly, tires easily and must rest after short period of activity.

2- Smooth muscle

- It is arranged in circular layers around hollow visceral organs such as stomach, urinary bladder and respiratory passages**.**
- It is spindle shape ,not striated
- It contracts involuntary**.**

3- Cardiac muscle

- It occurs only in the heart.
- It is involuntary, without conscious control.
- It can contract without nervous system stimulation, by the heart pacemaker, but neural control allows the heart to speed up for brief period.

Characteristics of muscle tissues

1- **Excitability or irritability** is the ability to receive and respond to a stimulus. The stimulus may be a chemical (neurotransmitters released by nerve cells) or local change in PH.

2- **Contractility** is the ability to shorten when adequately stimulated.

3- **Extensibility** is the ability to be stretched or extended.

4- **Elasticity** is the ability of muscle cell to recoil after being stretched.

Muscles functions

- **Body movement.** Skeletal muscles responsible for all locomotion and manipulation
- **Posture.** Skeletal muscles, by contracting continuously, maintain our body position, e.g. standing or sitting.
- **Respiration.** Skeletal muscles raise and lower the ribs during ventilation of the lungs.
- **Body heat.** The body is homoeothermic, with a constant temperature of 37.5 ^{o}C. This requires production of heat by skeletal muscles, either as a by-product of contraction or by special contractions known as shivering.

- **Communication.** Speaking, writing and facial expressions all depend on skeletal muscles.
- **Heart beat.** Cardiac muscles contract to pump blood around your body.
- **Contraction of internal organs.** Smooth muscles transport materials by peristaltic contractions (a wave of contraction pushes the material along the tube) in the gut, reproductive system, blood vessels, glands, etc. Smooth muscles also mix food in the stomach.

Skeletal muscle structure

- The skeletal muscle is made up of many **fasciculi (bundles),** each of which is made up of many fiber cells.
- The skeletal muscle cells are unusual because:-
  - The **cells lie parallel** to each other, so each cell stretches from one end of the muscle to the other end.
  - **Each cell has many nuclei**. This is because the cells are so huge (maybe 30cm long), that 1 nucleus cannot control the cell. The nuclei are found around the edge of the cell, just under the **sarcolemma** (cell membrane).
  - **Cells contain a network of membrane invaginations (T-Tubules**): to connect sarcolemma and ER ***(sarcoplasmic reticulum in muscle cell***), which is filled with calcium at rest.
  - Each cell has inside it thousands of **myofibrils**, lying parallel to each other. Each myofibril is divided into a long chain of thousands of **sarcomeres**.
  - Each **sarcomere** is separated from the next by a **Z-disk**, which appears as a dark line. Since all the cells have their Z-disk lined up with adjacent cells, dark lines run across the muscle and the cells are said to be "**striated**".(Figure 5.3).

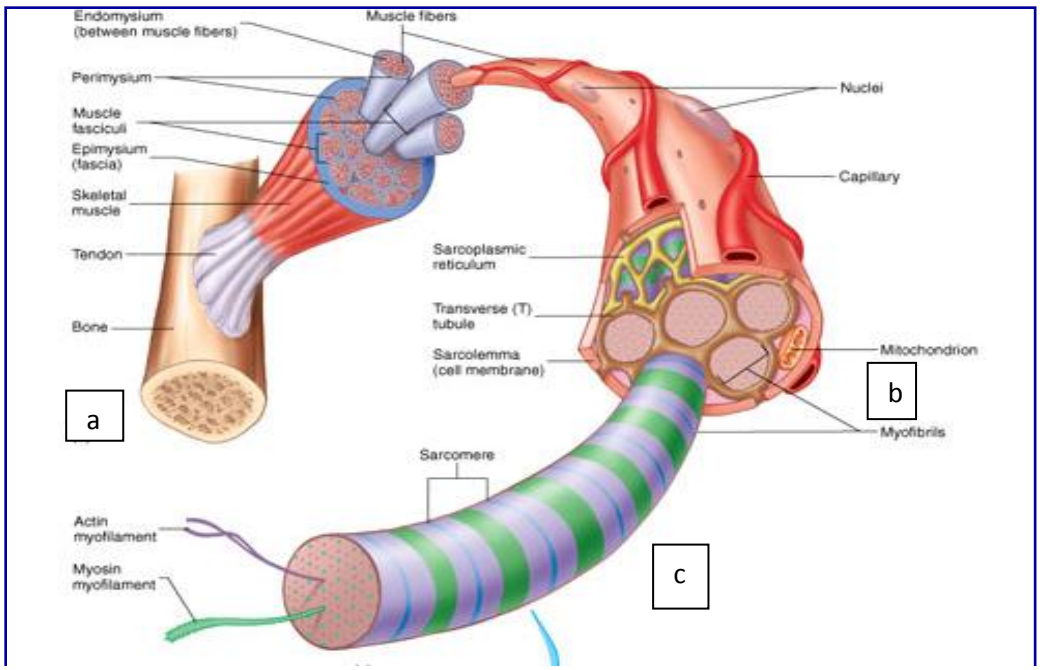


Figure (5.3): Parts of muscle, a:part of muscle attached by tendon to a bone. b:Enelargement of one muscle fiber. c: Myofibril extended out the end of the muscle fiber. : (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

- Each sarcomere contains four types of proteins:-

1- **Actin.** These are spherical molecules attached to each other in a row (Figure5.4.a). Two rows are twisted around each other in a helix to form a **myofilament.** Myofilaments are attached on either side of the Z-disk in parallel rows.

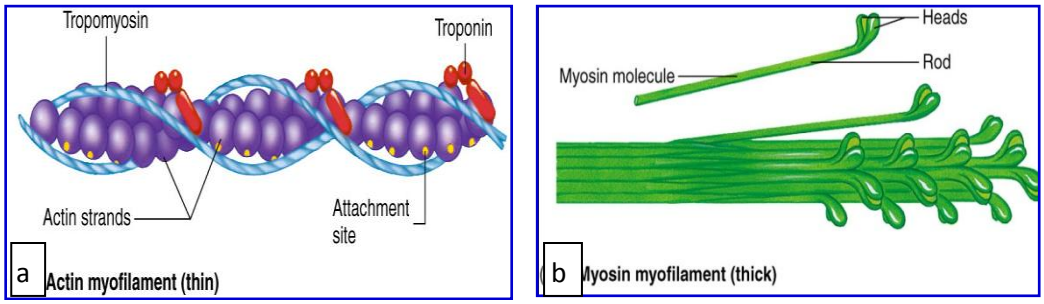


Figure (5.4): Structure of actin and myosin, a: Actin myofilament.b:Myosin myofilament. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

2- **Myosin.** Each molecule is a long rod ending in a head (like a golf club). (Figure5.4.b) .The molecules are arranged in bundles to form a myofilament. These are arranged parallel to each other, lying in between the actin filaments (and so lying in the middle of the sarcomere attached to an **M-line**). (Figure 5.5).The heads of the molecules stick out of the myofilament and attach to the actin, during a muscle contraction.

3- **Troponin.** These are attached to the actin and have Ca^{2+} receptors.
4- **Tropomyosin.** This is attached to the troponin and forms long threads covering the attachment sites on the actin. They prevent myosin attachment, when the muscle is resting. (Figure5.4.a).

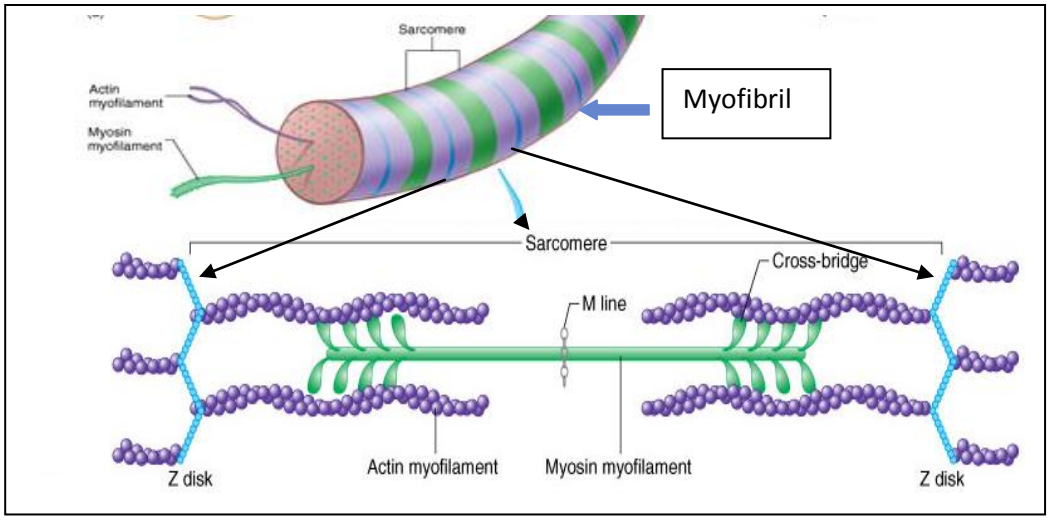


Figure (5.5): Composition of a single sarcomere of a myofibril.Modified from (Marieb E.N .Essential of Human Anatomy and Physiology .San Francisco, Pearson Education,Inc.,2012).

Muscle contraction

Sliding Filament Model

- Muscle contraction is explained by the **sliding filament mechanism,** in which the actin filaments slide over the myosin filaments.
- Since the actin filaments are attached to the Z-discs, the sarcomere becomes shorter as the two Z-discs come towards each other, but there is no change in the length of either the actin or myosin filaments.
- As all the sarcomeres shorten on all the myofibrils, then the whole muscle fiber cell becomes shorter.
- Sliding the actin over the myosin is due to the myosin heads repeatedly attaching to and detaching from the actin. (Figure 5.6).

Motor units

- For a skeletal muscle cell to contract, it must first be stimulated by impulses from a neuron, the **motor neuron** (in the anterior horn of spinal cord).
- Neuron and all muscle fibers are supplied by it is the **motor unit**.
- A single neuron innervates multiple muscle fibers (axon branches to nerve terminals and each nerve terminal supplies one muscle fiber.
- The neuron branches connect with muscle cells by a **neuromuscular junction**.
- When motor neuron transmits action potential all muscle fibers which it innervates, contract.

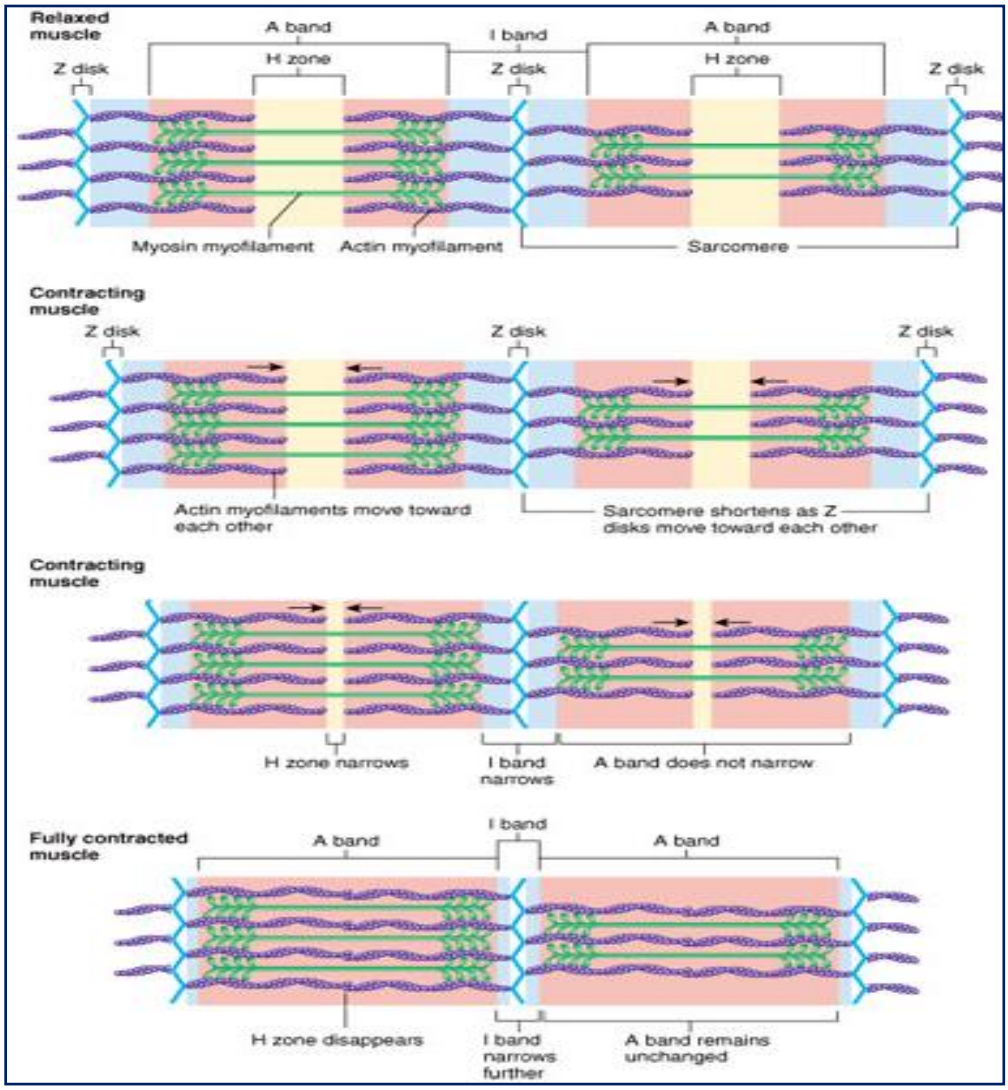


Figure (5.6): Sarcomere shortening.(Marieb E.N .Essential of Human Anatomy and Physiology . San Francisco, Pearson Education,Inc.,2012).

Excitation –contraction coupling and cross –bridge movement

- Because of the huge size of the muscle cells, the impulse is further transported inside the cell by **transverse (T) tubules,** to each sarcomere on each myofibril.
- The arrival of an impulse through the T-tubules causes the **sarcoplasmic reticulum** to release **calcium ions** in to the sarcomeres.
- Calcium ions attach to receptors on the troponin and push it and thus the tropomyosin to one side. This uncovers the actin attachment sites.

  The attachment of the myosin head to the actin requires a constant ATP supply.
- ATP attaches to the myosin head and breaks down in 3 stages:

1- The **ATP** on the myosin head **breaks down** into ADP + PO_4, causing the **myosin head to attach** to the binding site on an actin molecule

2- **A Release of the ADP and PO_4 molecule from the head, releasing the energy .The energy is** used to **bend back the myosin head**. Since this is attached to the actin filament, the bending movement slides the actin filament over the myosin filament.

3- **Attachment of a new ATP** to the **myosin head releases** it from the actin, so that the head can bend forwards in to its resting position (so its lies beside a new actin molecule). (Figure5.7).

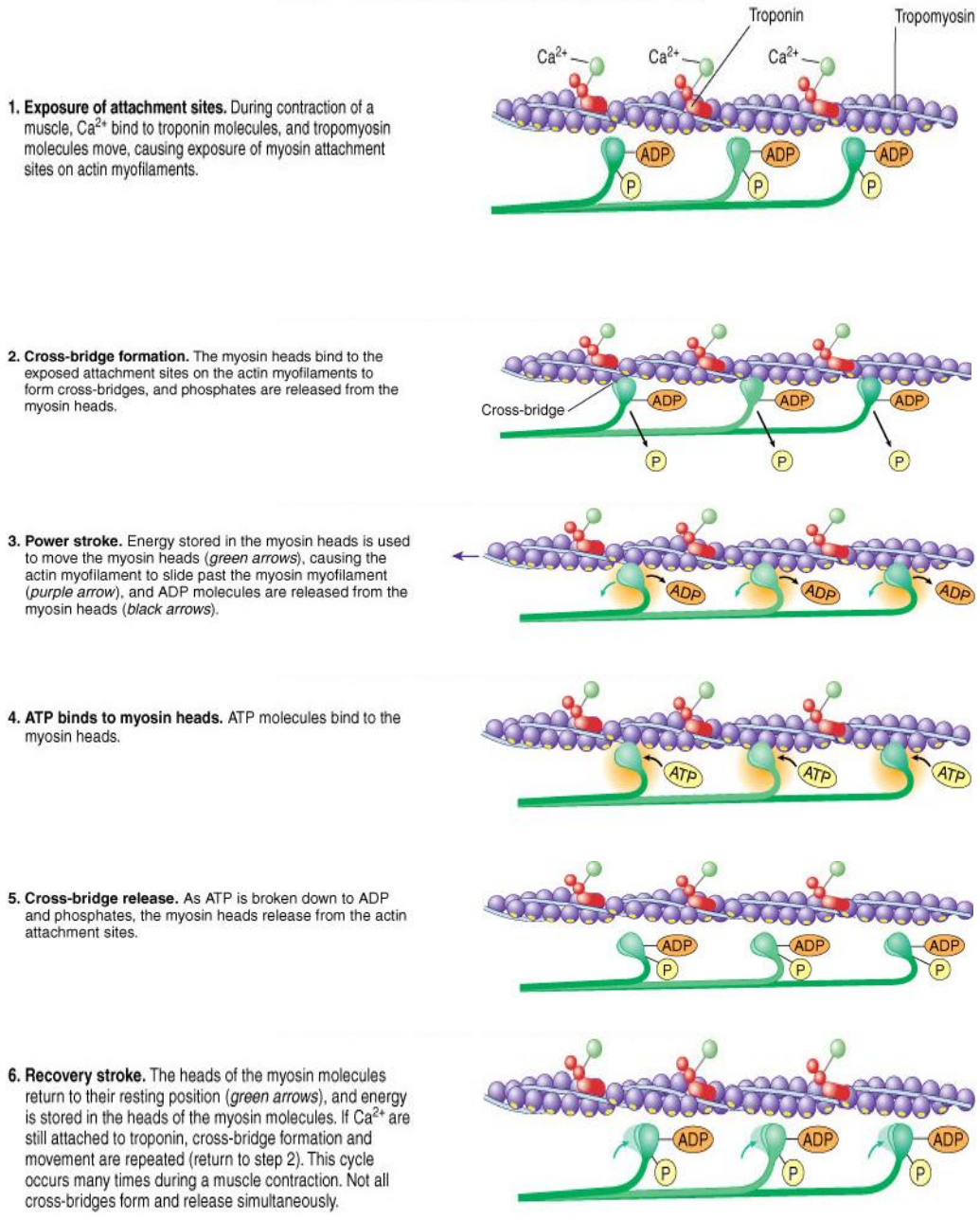


Figure (5.7): Breakdown of ATP and Cross bridge movement. (Marieb E.N.and Hoehn K .Anatomy and Physiology .San Francisco, Pearson Education Inc., 2011).

- As long as there is a constant supply of ATP, the actin will continue to progressively slide over the myosin, causing the sarcomere to shorten.
- The **contraction will end** when there are no more impulses arriving from the neuron. This causes the calcium ions to be pumped back in to the sarcoplasmic reticulum, so that the tropomyosin covers up the binding sites on the actin and pushes the myosin away from the actin.
- When there is no contraction between the actin and myosin, the actin will slide back into its resting *position (due to elastic elements in the muscle that were stretched during the contraction)*, causing the sarcomeres to expand.

The muscle twitch

- When an impulse travels down the neuron, all of its muscle cells will contract and then relax.
- This is investigated by using apparatus that produce a **myogram,** the line it records is called **tracing.**
- Every twitch myogram has **three phases:** (Figure5.8).
  1. **Latent period**: is the first few milliseconds between application of a stimulus to the motor neuron and the beginning of contraction.
  2. **Contraction phase**: is the time which the contraction occurs.
  3. **Relaxation phase**: is the time during which the relaxation occurs initiated by reentry of Ca^{2+} into sarcoplasmic reticulum.

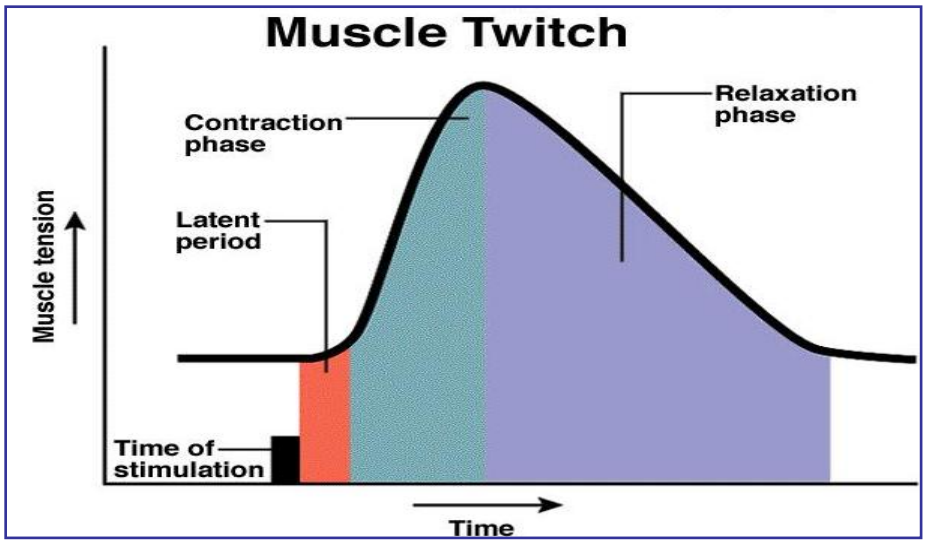


Figure (5.8): The phases of muscle twitch. (Randall D. ,Burggren W. and French K. Eckert Animal Physiology .5th ed. New York, W.H. Freeman and Company, 2002).

Types of contraction

1- **Graded:** the strength of contraction depends primarily on the number of muscle fibers recruited rather than the strength of muscle fibers.

2- **Twitch:** an electrical stimulation of muscle cell above the threshold results in a limited efflux of Ca^{2+} from the sarcoplasmic reticulum into the cytoplasm stimulating a single contraction.

3- **Summation and tetanus:** if muscle is stimulated at a high enough frequency, individual muscle twitches combine (summate) to produce sustained contraction (**tetanus**) (Figure 5.9).

- **Incomplete tetanus:** as the frequency of action potential in skeletal muscle fiber increases, the frequency of contraction also increases, muscle fibers partially relax between the contractions**.**
- **Complete tetanus**: action potentials are produced so rapidly in muscle fibers that no relaxation occurs between them.

4- **Isotonic muscle contraction**

- A constant force is produced while muscle length is changing.
- As the muscle tension increases, the muscle shortens and lifts the load. (e. g, biceps curls in weight lifting).

5- **Isometric muscle contraction:** causes a change in muscle tension but no change in muscle length (e.g., pushing against immovable objects such as a wall).

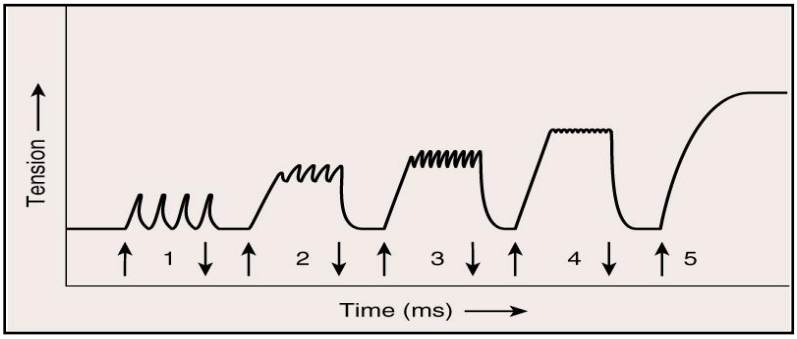


Figure (5.9): Multiple summations.

1-5: *are stimuli of increasing frequency.*

Up arrow*: the start of stimulation .****Down Arrow:*** *the end of stimulation.*

Stimulus frequency ***1*** *produces successive muscle twitches with complete relaxation.*

Stimuli frequencies ***2-4:*** *without complete relaxation.*

Stimulus frequency ***5:*** *causes tetanus –no relaxation between stimuli.*

(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

Regulation of contraction

- Muscle contraction is regulated by the somatic nervous system (under voluntary control).
- The fewer muscle fibers innervated by a given motor neuron the greater precision of control of contraction.
- The strength of skeletal muscle contraction is determined by four factors:
  1- ***Metabolic condition***
  2- ***Amount of load***
  3- ***Recruitment of motor units***
  4- ***Initial length of muscle fibers.***
- The amount of tension that can be generated is determined by the **length – tension relationship** (the extent of actin –myosin myofilament overlap).
  - If the sarcomeres is shortened, the actin –myosin have less room to overlap and develop tension.
  - If the muscle is stretched to a point at which actin and myosin no longer overlap, no cross-bridge can be formed and no tension can develop.

Energy source for muscle contraction

- Energy required for muscle contraction comes from ATP.
- ATP for crossbridge movement and detachment is generated by:

1- **Direct phosphorylation of ADP** by creatine phosphate .This converts ADP back to ATP (by donating a PO_4 + energy). There is only enough creatine phosphate to keep the muscle contracting for a few seconds.

2- **Glycolysis (anaerobic pathway):** ATP is produced by the **breakdown of glucose** .This does not use O_2, but is very inefficient (**2 ATP/ glucose molecule**). To compensate, the cell usually has large stores of **glycogen** that can be broken down into glucose. The cell can only work **anearobically** for 2-3 minutes before it runs out of ATP and the buildup of **lactic acid** inhibits the muscle contraction resulting in **fatigue.**

3- **Aerobic respiration:** This uses O_2 to break down glucose to **36ATP + CO_2 + H_2O.** It is very efficient and there is **no lactic acid**, so it can continue contracting for long periods. But the cell requires:

   a. *Large numbers of* ***mitochondria*** *in the cell to carry out aerobic respiration using Kreb's cycle.*

   b. *A good oxygen supply, so large numbers of* ***capillaries*** *enter the muscle.*

   c. ***Myoglobin*** *inside the* ***muscle cell*** *picks up O_2 from the capillaries and transport around the muscle cell. Myoglobin also stores O_2 when the cell is resting.*

Fatigue: *is the decreased ability to do work .It can develop at three sites:*
1-Psychological fatigue*: is common type involving CNS. The muscles are capable of functioning but the individual perceive that an additional work is not possible.*
2-Muscular fatigue*: results from ATP depletion.*
3-Synaptic fatigue*: results from depletion of ACh in the muscular synapse.*
Rigor motis: *development of rigid muscles several hours after death, that is ATP production stops shortly after death.*

Types of skeletal muscle fibers

1- Fast twitch fibers

- They use glycogen and anaerobic metabolism, fatigue easily but good for explosive high intensity activity of short duration.
- They are whitish in color due to small amount of myoglobin.

2- Slow twitch fibers

- They use aerobic metabolism so do not fatigue easily.
- They are rich in myoglobin, red appearance.
- Common in muscle controlling posture.

Clinical note: Muscle disorders are caused disruption of normal innervations, degeneration and replacement of muscle cells injury, lack of use and diseases.
Atrophy: is a decrease in the size of muscles.
Fibrosis: is replacement of muscle tissues by connective tissues.
Fibrositis : is an inflammation of fibrous connective tissues causing stiffness ,pain and soreness.
Cramps: are painful spastic contractions of muscle that usually result from an irritation within a muscle that causes a reflex contraction.

Smooth muscle

Overview

- Smooth muscle is arranged in a circular layer around hollow organs (**esophagus, respiratory airways**) and blood vessels .Contraction of these muscles reduces the size of the organs.
- The cells are spindle shape .Actin-myosin myofilaments are not arranged into sarcomeres, so the cells are nonstriated in appearance.
- The absence of sarcomeres enable smooth muscle to contract even when the cells are enormously stretched.(smooth muscle contraction is not limited by the length –tension relationship).

- The sarcoplasmic reticulum is loosely arranged within the cells, and there are no T-tubules.
- The cells contain **dense bodies,** structures analogous to the Z disks found in skeletal muscles.

Types of smooth muscles

1- Single unit(unitary or vesiral) smooth muscle

- Predominant type located in **GIT, bladder, uterus** and **ureters.**
- There are **gap junctions** to transmit nerves impulses causing the contraction of many cells at once.
- They are characterized by the **rhythmic fluctuation** of membrane potential (**slow waves**) that gives rise to **spike potential** which can cause muscle contraction.
- The slow waves are the primary regulator of single –unit smooth muscle, but the activity may be modified through the autonomic nervous system.

2- Multi smooth muscle

- They are located in the **iris, ciliary muscles** of the lens and **vas deferens.**
- They are similar to the skeletal muscle in that each fiber is innervated, therefore functions separately.
- Gap junctions are absent. (Figure5.10.a).
- Regulated by autonomic nervous system.

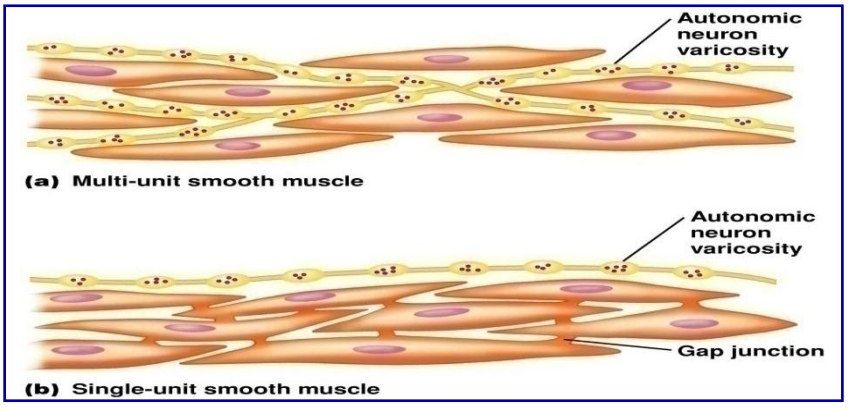


Figure (5.10): Types of smooth muscle.(Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings,2014).

Mechanism of contraction

- Slow waves give rise to spike potentials, which stimulate cell contraction.
- The **initial phase** of contraction is triggered by an increased releasing of cytoplasmic calcium from the sarcoplasmic reticulum.
- **Sustained contraction** is mediated by continued influx of Ca^{2+} into the cytoplasm from interstitium through voltage-gated calcium channels.
- Calcium combines with the **protein calmodulin** to form **(calcium-calmodulin complex)** and activates **myosin light chain kinase (MLCK).**
- **MLCK** phosphorylates the myosin cross bridge.
- Actin and myosin form cross-bridge that contract the muscle cell.
- **Relaxation** occurs when Ca^{2+} has been pumped back into the sarcoplasmic reticulum.

Regulation of contraction

- Smooth muscle is innervated by **autonomic nervous system**.
- **Sympathetic and parasympathetic nerves** are distributed to all organ systems in the body and stimulate smooth muscle activity in many organs at once.
- Parasympathetic stimulation has opposite effects to that of sympathetic stimulation.
- **Hormones** are important in the regulation smooth muscles. Some hormones can increase the Ca^{2+} permeability of the smooth muscle membrane therefore cause contraction without change in resting membrane potential.

Cardiac muscle

Overview

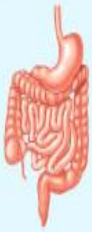
- Cardiac muscle is found in the heart only.
- Cardiac muscle tissue is striated; each muscle contains one nucleus located near the center.
- Adjacent cells join together to form branching fibers by specialized attachment **(intercalated disk),** which have gap junctions allowing the action potential to pass from cell to cell.
- Some cardiac muscle cells are **autorhythmic** .One part of the heart acts as the **pacemaker.**
- Action potentials of cardiac muscle are similar to those of nerve and skeletal muscle, but have much longer duration and refractory period. That is the extracellular Ca^{2+} plays a substantial role in triggering contraction.

Regulation of contraction

- Cardiac cells have an unstable resting membrane potential that allows them to generate their own electrical pacemaker activity.
- Strength and rate of contraction are regulated by autonomic nervous system.
- Sympathetic stimulation has a positive effect through binding of norepinephrin and epinephrine to **adrenergic receptors.**
- Parasympathetic stimulation has negative effect through binding of **ACh** to **muscarinic receptors.**
- The comparison of the three muscle types are summarized in table (5.1).

Pharmacology note: The fact that extracellular calcium plays such an important role in stimulating cardiac muscle contraction is exploited by calcium channel blocking drug such as **diltiazm** and **verapamil.** Calcium channel blocker reduce heart rate and contractility without adversely affecting skeletal muscle functioning and are therefore useful for treating hypertension and a myriad of cardiac condition.

Table (5.1): Comparison among the three muscle types. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Feature	Skeletal Muscle	Cardiac Muscle	Smooth Muscle
			
Location	Attached to bone	Heart	Wall of hollow organs, blood vessels, and glands
Appearance			
Cell shape	Long, cylindrical	Branched	Spindle-shaped
Nucleus	Multiple, peripheral	Usually single, central	Single, central
Special features		Intercalated disks	Cell–cell attachments
Striations	Yes	Yes	No
Autorhythmic	No	Yes	Yes
Control	Voluntary	Involuntary	Involuntary
Function	Move the whole body	Heart contraction to propel blood through the body	Compression of organs, ducts, tubes, etc.

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6. Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology.9th ed. San Francisco, Benjamin Cummings,2014.
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Chapter Six

Cardiovascular system 6

Cardiovascular system

Overview

- Humans have a closed circulatory system, in which blood is confined to vessels and is distinct from the interstitial fluid.
- The heart pumps blood into large vessels that branch into smaller ones leading into the organs.
- Materials are exchanged by diffusion between the blood and the interstitial fluid bathing the cells.

I. Heart

Overview

- The heart consists of 2 pumps lying side by side.
- Each pump has **an atrium**, which collects blood from the veins, and **a ventricle,** which pumps out the blood.
- The **right side** of the heart receives blood from the body and pumps blood through the **pulmonary circulation** which carries the blood to the **lung** and returns it to the **left side** of the heart.
- The **left side** of the heart pumps blood through **systemic circulation** which delivers oxygen (O_2) and nutrients to all remaining tissues of the body .then carries the blood to the **right side** of the heart.
- The heart of 70 Kg healthy person pumps **7200 L** of blood each day, at a **rate 5L/min.**

Systemic and pulmonary circulation

- The **right ventricle** pumps the blood to the **lungs** through the **pulmonary artery**. The blood returns via the **pulmonary vein** into the **left atrium**. This is the ***pulmonary circulation.***
- The **left ventricle** pumps the blood around the body via the **aorta**. Because of the greater distances, this ventricle is larger than the right ventricle; so that it creates a higher pressure (a higher pressure to the lungs would destroy the delicate capillaries). The blood return via the **vena cava** into the **right atrium**. This is the ***systemic circulation.*** (Figure 6.1).

  - The blood thus has a double circulation, so that all the blood going to the tissues is oxygenated (because it earlier went to the lungs) and under high pressure and thus traveling at high velocity.

- There is actually a 3rd circulation: the ***coronary circulation:*** This provides a separate blood supply to the heart muscles.

- The **coronary artery** branches from the **aorta;** the blood from the capillaries is then collected by the **cardiac vein** and returned to the **vena cava.**
- The coronary artery is small for the size of the heart, but gives up **75%** of its oxygen to the cardiac muscle. In contrast, a typical artery in the rest of the body is much larger but gives up **25%** of its O_2 to the body tissues, when the body is at rest (so that a vein contain blood that is still 75% oxygenated), but has the option to increase this when the muscles become active.

▪ The heart muscle is never resting and so has a more constant O_2 demand.

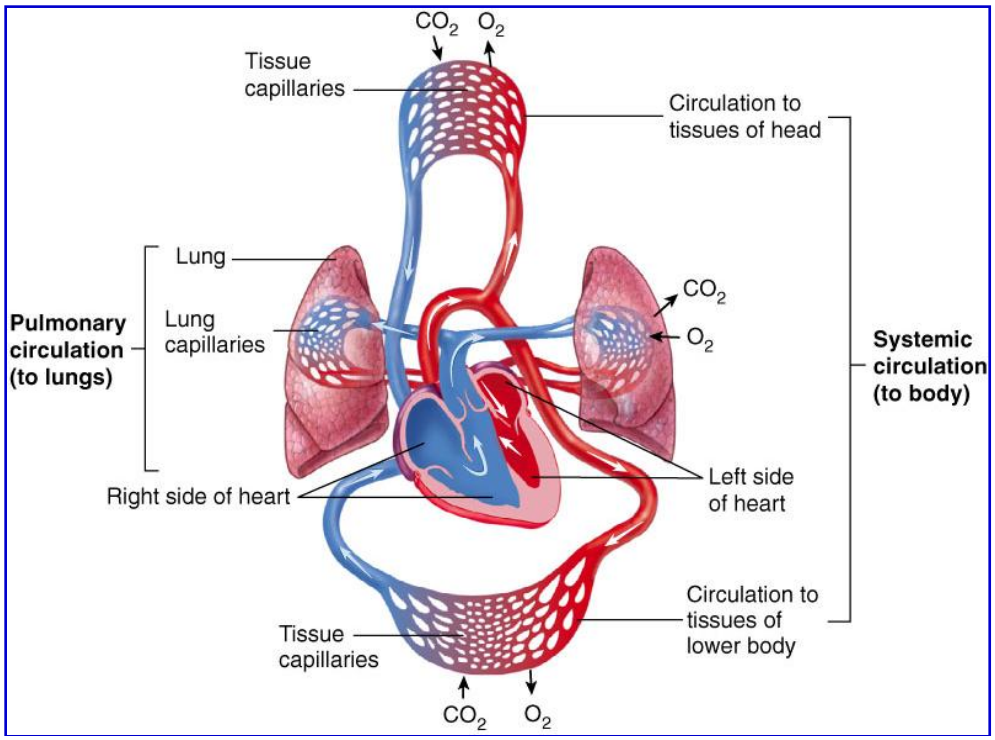


Figure (6.1): Systemic and pulmonary circulation.(Marieb E.N.and Hoehn K.Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

Functions of the Heart

1- Generating blood pressure: This is due to the contraction of the heart.
2- Routing blood: The heart separates the pulmonary and systemic circulation
3- To Ensuring one-way blood flow: Heart valves ensure one-way flow
4- Regulating blood supply: Changes in contraction rate and force match blood delivery to the changing metabolic needs of the tissues.

Heart anatomy

- **Shape:** The adult heart is shaped like a blunt cone. The rounded point of the cone is the apex .The larger flat part is the base.
- **Size:**
  - It is the size of closed fist.
  - It is larger in physically active person than in other healthy adults.
  - The size decreases with age after 65 years, but not in physically active.
- **Location:**
  - The heart lies obliquely in the mediastinum .(Figure 6.2)
  - It is located in the thoracic cavity between the lungs.
  - The base of the heart is directed posteriorly and slightly superiorly.
  - The apex is directed anteriorly and slightly inferiorly.
  - The location is of a clinical importance for positioning the **stethoscope** to hear the heart sounds and positioning the electrodes to record **electrocardiogram (ECG)** from the chest leads.

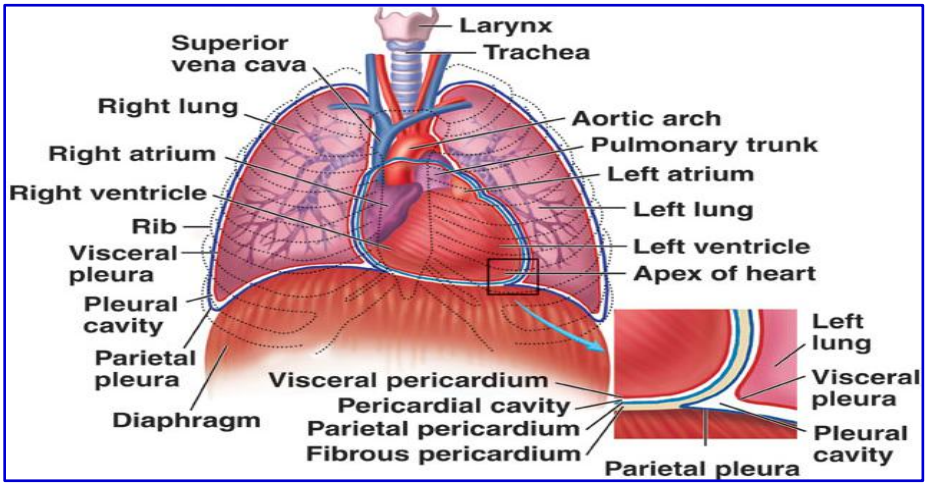


Figure (6.2): Location of the heart. Retrieved from : www.rci.rutgers.edu).

- **More anatomical considerations :**
  - **Pericardium:** is the sac that surrounds the heart and consists of 2 types of pericardium: (Figure 6.3).
    1. **Fiberous pericardium**: helps hold the heart in the place.
    2. **Serous pericardium:** reduces friction as the heart beats.It consists of :
       - Parietal pericardium:lines fibrous pericardium
       - Vesiral pericardium: lines exterior surface of the heart.
       - Pericardial cavity between parietal and vesiral

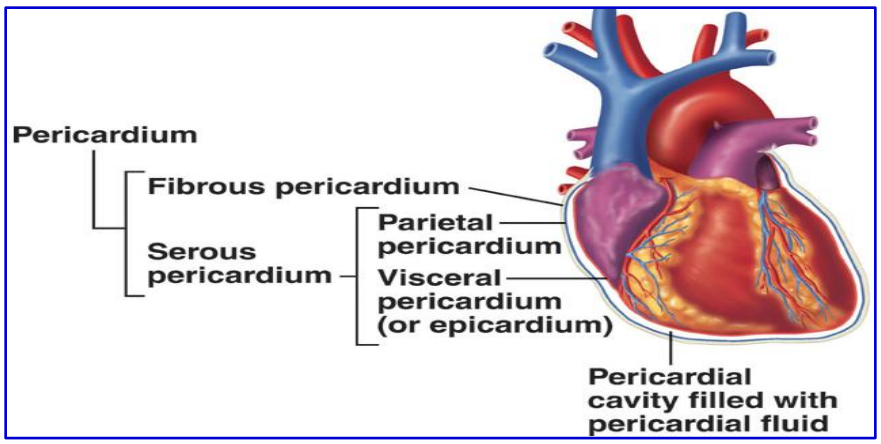


Figure (6.3): Pericardium. (Marieb E.N.and Hoehn K.Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

- **Heart Wall:** The heart wall is composed of 3 layers :(Figure 6.4).

1. **Epicardium:** This serous membrane of smooth outer surface of heart, provides protection against the friction of the rubbing organs
2. **Myocardium**: Middle layer composed of cardiac muscle cell and responsible for heart contraction.
3. **Endocardium**: Smooth inner surface of heart chambers composed of simple squamous epithelium over a layer of connective tissues .It reduces the friction resulting from the blood passing through the heart.

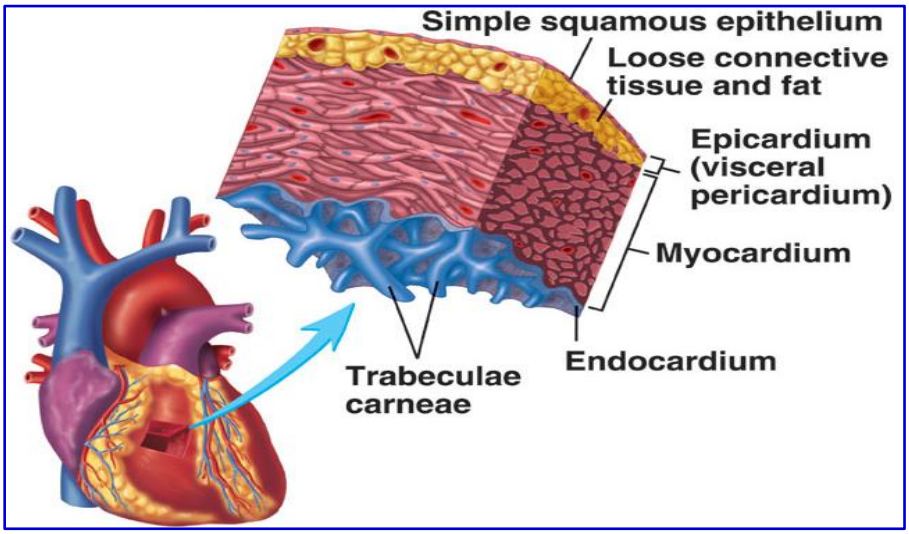


Figure (6.4): Heart wall. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

External Anatomy

- The heart is composed of :
  - **Four chambers** :2 atria and 2 ventricles
  - **Major veins** :Superior vena cava and pulmonary veins
  - **Major arteries** : Aorta and pulmonary trunk.
- Each atrium has a flap the **auricle.**

- The **coronary sulcus** separates the atria from the ventricles.
- The inferior and superior venae cava and the coronary sinus enter the right atrium .The pulmonary veins enter the left atrium.
- The pulmonary trunk exits the right ventricle and the aorta exits left ventricle.(Figure 6.5).
- Coronary arteries branch off aorta to supply the heart.
- Blood returns from the heart tissues to the right atrium through the coronary sinus and cardiac veins.

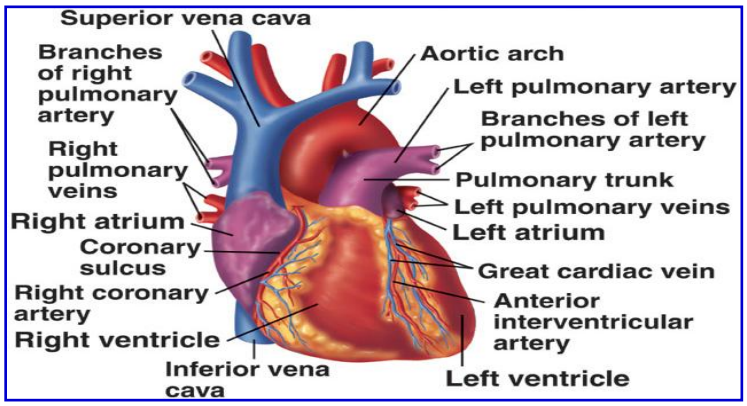


Figure (6.5): Anterior view of the heart. (Marieb E.N .Essential of Human Anatomy and Physiology . San Francisco, Pearson Education,Inc.,2012).

Internal anatomy: Heart chambers and valves

- **Interaterial septum**: separates the atria from each other.
- **Interventricular septum:** separates the ventricles.(Figure 6.6).
- **Tricuspid valve:** separates right atrium and ventricle
- **Bicuspid valve**: separates left atrium and ventricle
- **The chordae tendineae** : attach the papillary muscles
- **Semilunar valve:** separates aorta and pulmonary trunk from the ventricles.

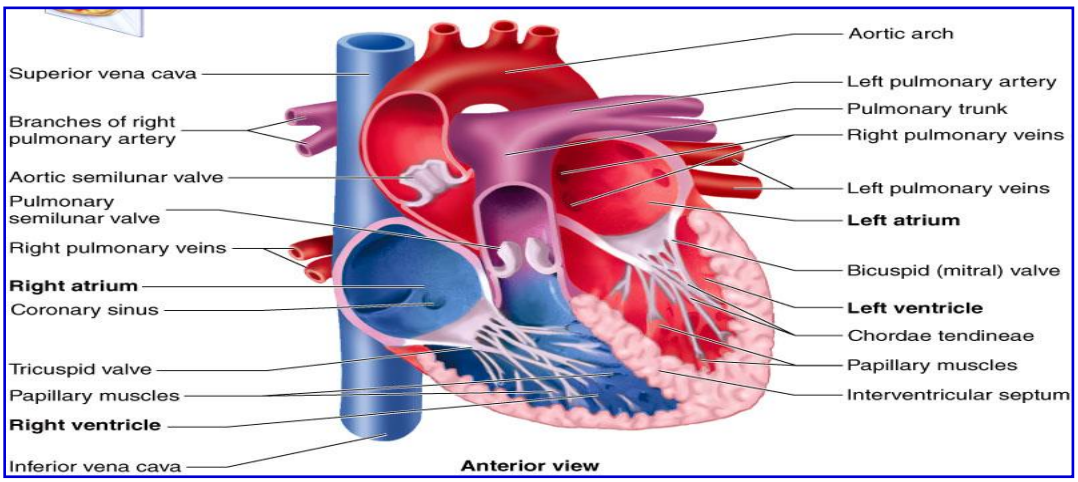


Figure (6.6): Internal anatomy of the heart.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Blood flow through the Heart

- The 2 atria collect the blood from the veins and pump the blood into the ventricles. When the ventricles have filled with blood, they contract together, pushing the blood out through the arteries.
- The 2 ventricles are separated by a septum. The left ventricle has much thicker muscle than the right because it produces a much higher blood pressure around the body (around **120 mm Hg,** compared with **24 mm Hg** from the right ventricle to the lungs).
- The direction of blood flow is controlled by 4 valves **:**

  - **During atrial contraction*:***
    - **The 2 atrial-ventricular (AV**) valves between the atria and ventricles (**tricuspid** for the right ventricle; **bicuspid**: mitral valve for the left ventricle) are both **open,** so blood is pumped into the ventricles.
    - **The pulmonary valve** (at the base of the pulmonary artery) and the **aortic valve** (base of aorta) are **closed,** to prevent arterial blood flowing back into the relaxed ventricles. (Figure 6.7.a).
  - **During the ventricular contraction:**
    - **Tricuspid and bicuspid valves are closed,** due to contraction of papillary muscles attached to the corners of the valve by long tendons (**chordae tendinae**), to prevent the blood being pumped back in to the atria.
    - **The pulmonary and aortic** valves are **open** to allow the ventricular blood to be pumped out in to the arteries. (Figure 6.7 .b).

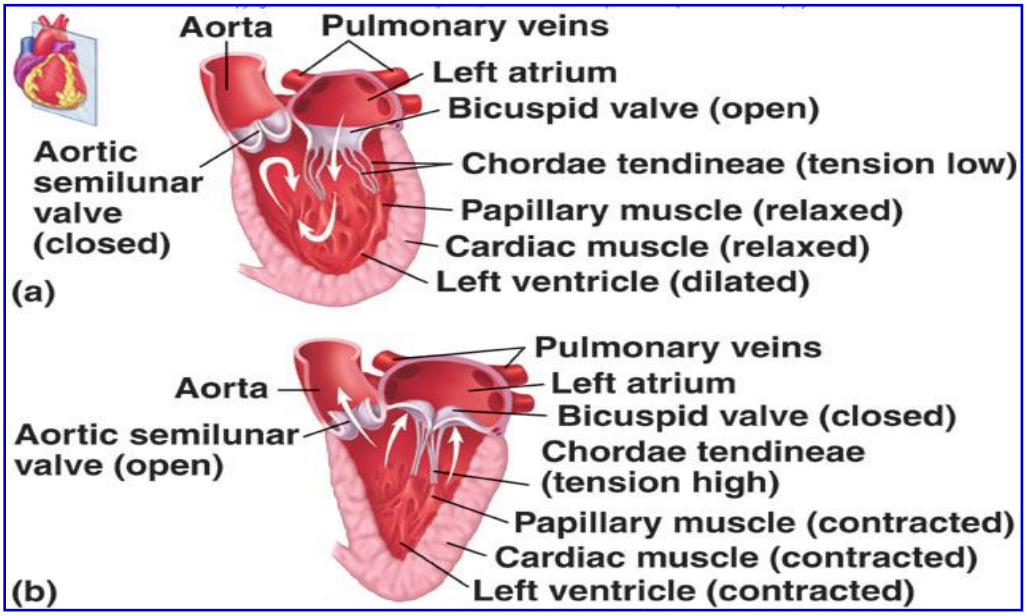


Figure (6.7): Function of the heart valve .a: atrial contraction, b: ventricular contraction. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- There is thus a double contraction of the heart:
  - First a small contraction of the 2 atria.
  - Larger contraction of the 2 ventricles after 0.1 sec later. The left ventricle forces a pressure wave (pulse) through the aorta, which spreads through the other arteries and into the veins. This pressure wave is known as **systole,** while the relaxation of the ventricle gives **diastole** (the resting pressure of the artery).
- Blood from **the body** flows through the **right atrium** into **right ventricle** as the ventricle relaxes, and then to the **lung,** where gas exchange occurs. (***The blood flows from an area of higher pressure in the systemic circulation to area of a lower pressure, the right atrium).***
- **Oxygenated blood** returns from the **lungs** to the **left atrium,** enters **the left ventricle** and is pumped back to the **body. (*Blood flowing through the aorta is distributed to all parts of the body, except to the parts of the lungs which supplied by the pulmonary blood vessels)***. Blood flow through the heart is depicted in figure (6.8).

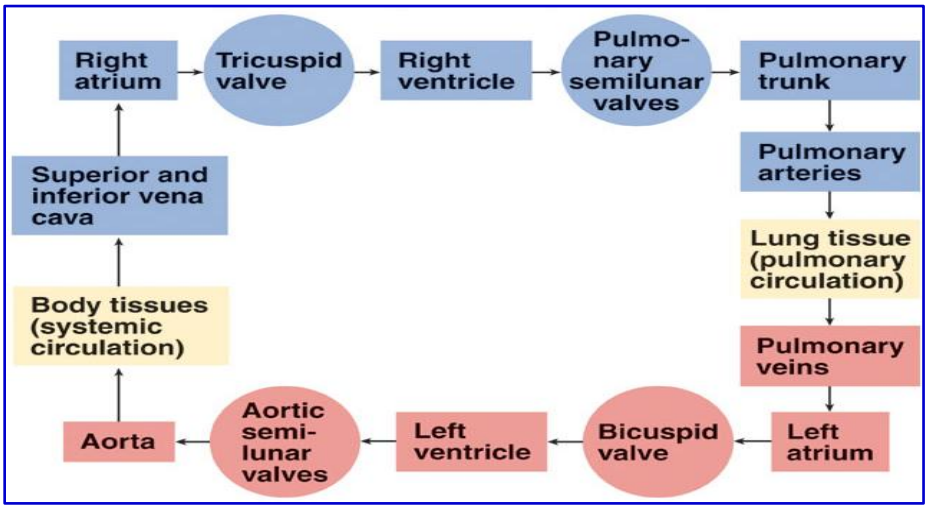


Figure (6.8): Blood flow through the heart. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Pathology note: The aortic valve in some individual is **congenitally bicuspid.** These bicuspid valves are predisposed to early calcification and stenosis, often causing **aortic stenosis** in individuals in their late 40 S or early 50 S. Common cause of the aortic stenosis is the calcification of the normal tricuspid valve (**senile calcific aortic stenosis).**Another cause of aortic stenosis is **rheumatic fever** .Aortic stenosis increases the rate of blood flow through the aortic valve producing turbulent flow and consequently **systolic ejection murmur**.

Pathology note: Mitral Stenosis: the mitral valve becomes stenotic due to abnormal structural changes. The most common is the rheumatic fever. Symptoms of mitral stenosis are dyspnea and exercise intolerance.
In **Mitral regurgitation**, the mitral valve does not form good seal causing blood flow into the left atrium during early systole.

Heart Skeleton ,(Figure 6.9):

- Consists of plate of fibrous connective tissue between atria and ventricles
- Fibrous rings around valves to support them.
- Serves as electrical insulation between atria and ventricles
- Provides site for muscle attachment

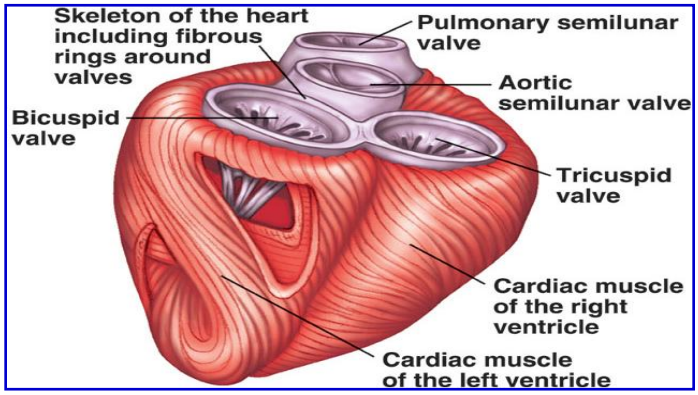


Figure (6.9): Skeleton of the heart. (Marieb E.N .Essential of Human Anatomy and Physiology . San Francisco, Pearson Education,Inc.,2012).

Cardiac muscle,(Figure 6.10):

- Cardiac muscle is similar to skeletal muscle in having **actin** and **myosin** arranged in **sarcomeres** (so the cells are **striated)** forming many myofibrils. Thus contraction takes place in the same way (sliding-filament mechanism)
- **Cardiac muscle differs from skeletal muscle in that:**
  - The cells contract spontaneously, and most cells have no nerves connected to them.
  - It has short cells (only 1 nucleus in the center of each cell), which are branched and connected to other cells by **intercalated discs**.
  - The **intercalated discs** have a large surface area between 1 cell and the next and **many gap-junctions**, allowing the impulse to travel directly from 1 cell to the next.
  - The branching cells results in all the cells being connected together, so that the impulse will travel throughout the whole muscle. Thus cardiac muscle cells function as a unit.
- Cardiac muscle cells have slow onset of contraction and a prolonged contraction time caused by the long time required for calcium to move.

- Cardiac muscle is well supplied with blood vessels that support aerobic respiration.

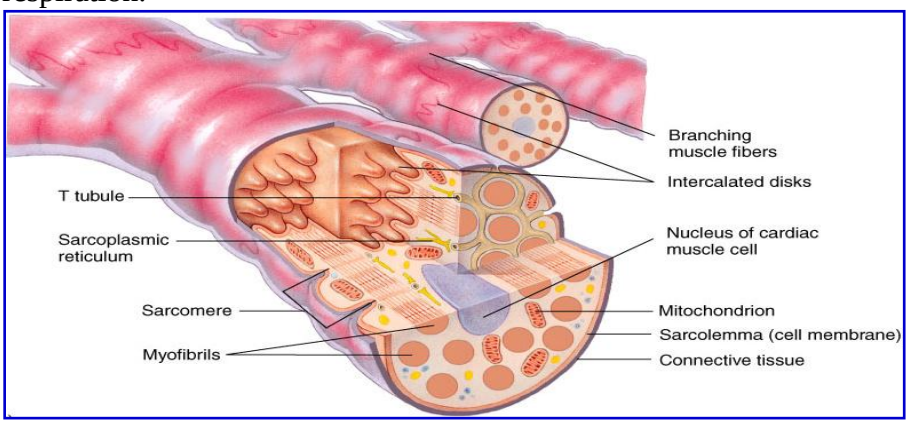


Figure (6.10): Cardiac muscle cells. (Reece J.B. ,Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V. and Jackson R.B. Campbell Biology. San Francisco, Benjamin Cummings,2014).

Conducting system of the heart

- Conducting system of the heart consists of **modified cardiac muscle cells.**
- Modified cardiac muscle cells form : **two nodes** and **conducting bundles**
- Two nodes within the walls of right atrium ,named according to the position in the atrium:
  - **SA node: Sinoatrial node** is medial to the opening of the superior vena cava.
  - **AV node: Atrioventicular node** is medial to the right atrioventicular valve.
- AV gives rise to conducting bundle of the heart **(bundle of His).**
- This bundle passes through a small opening in the fibrous skeleton to reach interventicular septum, where divided to form **right and left bundle branches.**
- Bundle branches extend beneath the endocardium on each side of the interventicular septum to the apices of the right and left ventricles respectively.
- The inferior terminal branches of the bundle branches are called **Purkinje fibers.**
- Purkinje fibers are larger diameter than cardiac muscle fibers. They have fewer myofibrils than most cardiac muscle cells and DO NOT contract as forcefully.
- **Intercalated disk** are well developed between Purkinje fibers and contain **numerous gap junctions**, so: These structural modifications make action potential travels along Purkinje fibers much **more rapidly** than other cardiac muscle tissues.
- AS node generates spontaneous action potential at a greater frequency. This AS node is called the **Pacemaker.**
- The SA node is made up of specialized small diameter cardiac muscle cells that merge with other cardiac muscle cells of the right atrium, thus: The heart contract **spontaneously** and **rhythmically**.

- Once action potentials are produced, they spread from the SA node to the adjacent cardiac muscle fibers.
- The conducting system of the heart which shows how action potential originates and travels through the heart is depicted in figure (6.11).

Electrical properties

Overview

- Cardiac muscles have **resting membrane potential (RMP).**
- RMP depends on low permeability of plasma membrane to Na^{+} ,Ca^{+2} and high permeability to K^{+}
- When cardiac cells are depolarized to threshold level action potentials result**.**
- Action potentials exhibit **depolarization** and then **repolarization.**
- Alterations in membrane channels are responsible for the change in membrane permeability, that produces the action potential.
- Action potential in cardiac muscles last longer than in skeletal muscle .In muscles ,action potentials take less than **2millisecond (ms)** to complete ,but in cardiac muscle take **200-500 ms** to complete.

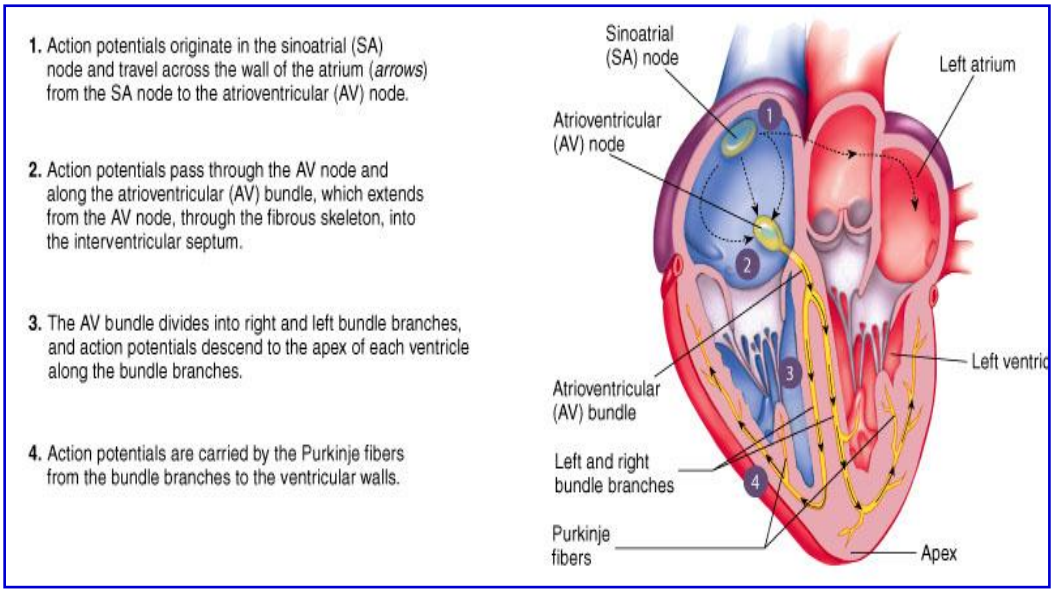


Figure (6.11):The conducting system of the heart. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Action potential in cardiac muscles

- Action potential in cardiac muscle consists of :
  - Voltage gated Na^{+} channels **open** causing Na^{+} to diffuse into the cell. Rapid depolarization occurs until the cells are **polarized** to (+20 mv).
  - Voltage gated K^{+} channels **closed**. Movement of K^{+} is responsible for establishing RMP in cardiac cells. If voltage gated K^{+} channels close, membrane permeability to K^{+} decreases.

- Voltage gated Ca^{2+} channels **begin to open** .This channels open and close slowly as compare to that of Na^{+}.

1- Early repolarization and plateau phase

- Voltage gated Na^{+} channels **close**.
- Voltage gated K^{+} channels **open** causing early polarization.
- Voltage gated Ca^{2+} channels **open** producing **plateau** and **slowing repolarization.** (Figure 6.12.b).

2- Final repolarization phase

- Voltage gated Ca^{2+} channels **close.**
- Many voltage-gated K^{+} channels **open.**

- Action potentials in cardiac muscle are conducted from cell to cell, whereas action potentials in skeletal muscle fibers are conducted along the length of a single muscle fiber, not from fiber to fiber.
- The rate of action potential propagation is slower in the cardiac muscle because cardiac muscle cells are smaller in diameter and shorter than skeletal muscle fibers. The comparison of action potentials in skeletal and cardiac muscle is illustrated in figure (6.12).
- Although the gap junctions of intercalated disk allow the transfer action potential between cardiac muscle cells, they do slow the rate of action potential conduction between the cardiac muscle cells.

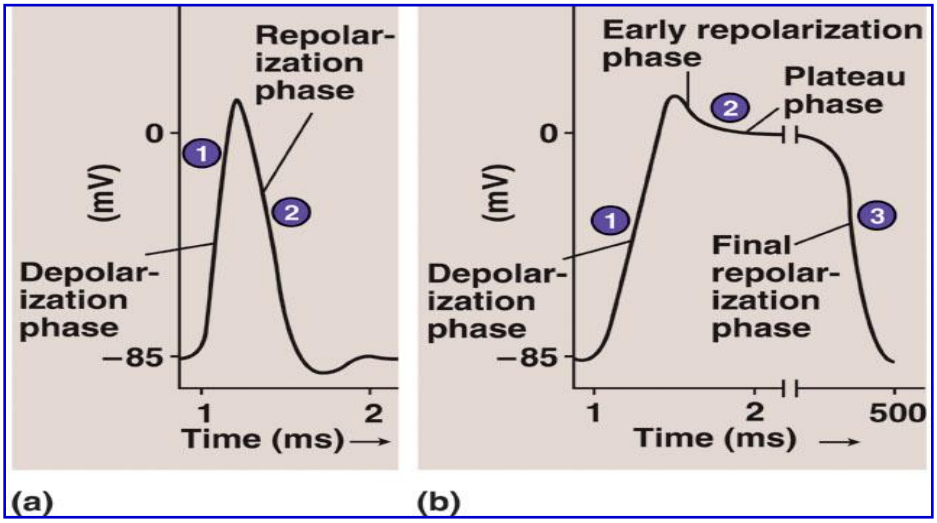


Figure (6.12): Comparison of action potential between skeletal and cardiac muscle. a:Action potential in skeletal muscle. b:Action potential in cardiac muscle . (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Autorhythmicity of cardiac muscle

- The heart is **autorhythmic** because it stimulates itself to contract at regular intervals (rhythmic).
- If the heart is removed from the body and put under normal physiological condition it will continue to beat autorhythmically for long time.
- SA generates action potential spontaneously at regular intervals. Action potentials spread through the conducting system to other cardiac muscle cells causing voltage gated Na^+ channels to open. As a result action potential is produced and cardiac muscle cells contract.
- The production of action potential by SA node is responsible for autorhythmicity of the heart (Figure 6.13).

Figure (6.13):Action potential in SA node.

Permeability changes in pacemaker include:

1-Prepotential phase:

-Voltage gated Na^+ channels open

-Volltage gated K^+ channels close

-Voltage gated Ca^+ channels begin to open

2-Deploarization phase:

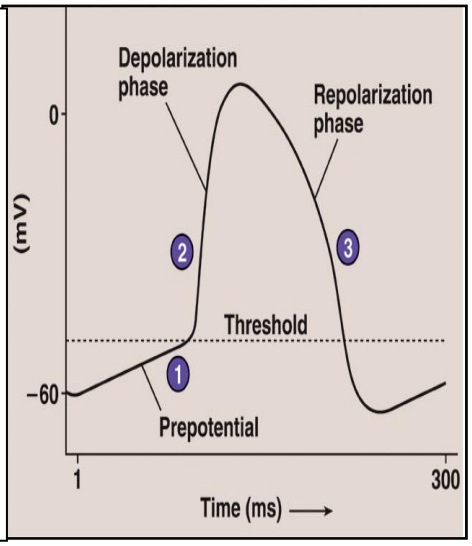
-Voltage gated Ca^{2+} channels open

-Voltage gated K^+ channels close

*3-**Repolarization phase:***

- Voltage gated Ca^{2+} channels close.

-Voltage gated K^+ channels open.



Pharmacology note: Calcium channels blockers e.g., **diltiazem , verapamil** block voltage Ca^{2+} channels preventing the influx extracellular Ca^{2+} during cardiac action potential and causing less Ca^{2+}enter the cardiac cells to activate contractile mechanism .Therefore, these drugs are widely used in treatment of **tachycardia ,arrhythmia** .

The drug **atropine** blocks the **muscarinic receptors** in the heart and increases heart rate .It is therefore useful in treating patients with **acute bradycardia**

Refractory period

- Cardiac muscle cells cannot be excited again immediately after depolarization.
- **Absolute refractory period**: Cardiac muscle cell are completely insensitive to further stimulation
- **Relative refractory period:** Cell exhibits reduced sensitivity to additional stimulation.
- The presence of plateau phase delays repolarization and prolongs the refractory period. The long refractory period ensures that contraction and relaxation are completed before another action potential can be initiated. This prevents occurring of **tetani.**

The Electrocardiogram

- The **electrocardiogram (ECG)** monitors the **electrical activities** in the heart by recording the electrical changes at the surface of the body.
- **Electrodes** are placed on the surface of the body and attached to an appropriate recording device that can detect a small voltage change resulting from action potential in the cardiac muscle.
- Electrodes detect a summation of all the action potentials that are transmitted by the cardiac muscle cells through the heart at a given time.
- ECG is valuable diagnostic tool in identifying a number of abnormal cardiac rhythms e.g., abnormal heart rate, abnormal conduction pathways, hypertrophy or atrophy of portions of heart and the approximate location of damaged cardiac muscle can be detected from analysis of ECG.
- **The normal ECG consists of(Figure6.14) :**
  1- **P wave represents** atrial depolarization.
  2- **QRS complex** composed of 3 individual waves Q,R,S result from ventricular depolarization.
  3- **T wave** represents repolarization of the ventricles. (***Repolarization of atria cannot be seen because it occurs during the QRS complex***.)
     a. ***PQ interval*** is the time between the beginning of P wave and the beginning of the QRS complex .During this time the atria contract and begins to relax. (0.16 second).
     b. ***QT interval*** extends from the beginning of QRS to the end of T wave, represents the time required for ventricles to contract then relax.(0.36 second).

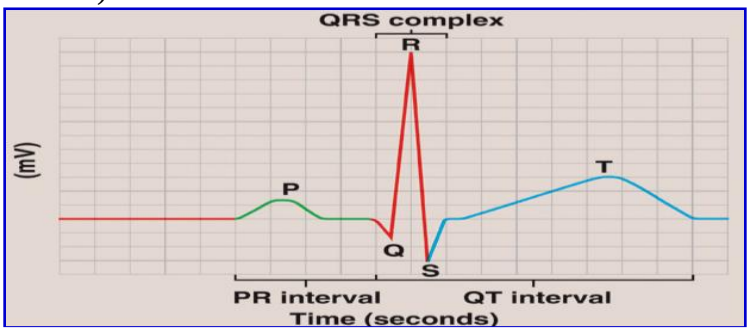


Figure (6.14): The normal Electrocardiogram (Brown T.A. Rapid Review of Physiology. Philadelphia, Mosby, 2012).

Pathology note: Alteration in ECG: (Figure 6.15)
1-Elongation of PQ interval can result from:
-A delay in action potential conduction through the atrial muscle because of damage e.g. caused by ischemia.
-A delay in action potential conduction through the atrial muscle because of dilated atria
-A delay in action potential conduction through AV node and bundle because of ischemia or necrosis of AV node.
2-Unusual long QT interval reflects the abnormal conduction of AP through the ventricles which may result from:
-Myocardial infarction **(MI)**
-Abnormal enlarged left or right ventricles.

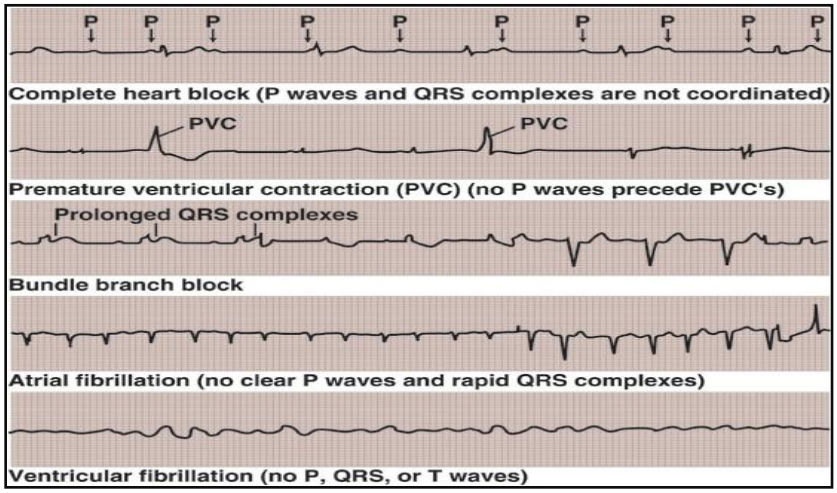


Figure (6.15): Alterations in ECG. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Common cardiac arrhythmias

1- Tachycardia

- It means **fast heart rate(HR).** In adult person, HR is faster than100 beats/min.
- ECG is normal except that HR as determined from the time intervals between QRS complex is 150 beats /min instead of 72beats/min.
- Some causes of tachycardia include increased body temperature, stimulation of sympathetic nerves and simple weakness of the myocardial which increases the HR because this elicits sympathetic reflexes.

2- Bradycardia

- It means **slow HR.** Usually HR is fewer than 60beats/min.

- Stimulation of **vagus verves** causes release of **Ach** in the heart giving a parasympathetic effect.
- The **athlete's heart** is larger and stronger than normal person, which allows the heart to pump a large stroke volume output causing excessive quantities of blood pumped into the arterial tree with each beat initiating feedback circulatory reflexes or other effect to cause **bradycardia**.

Pathology note: In patients with **carotid sinus syndrome**, the baroreceptors in the carotid artery walls are excessively sensitive to even mild pressure .This elicits a strong baroreceptors reflexes and causing intense Ach effect on the heart including extreme Bradycardia.

3- Sinus arrhythmia

- Heart rate varies between 5% during the respiratory cycle and up to 30% during deep respiration.
- Sinus arrhythmia can result from any circulatory condition that alters the strength of sympathetic and parasympathetic nerve signals to the heart sinus node.

4- A premature contraction

- It is shortened intervals between one contraction and the succeeding one.
- Most of premature contractions result from **ectopic foci** in the heart which emits abnormal impulses at odd time during the cardiac rhythm.

Cardiac cycle

- Cardiac cycle is the repeating series of contraction and relaxation that move the blood through the heart (Figure 6.16).
- It is composed of **systole** and **diastol**e.

1- Systole

a. Period of isovolumic contraction

- The atria are relaxed causing blood flow into them from the veins.
- Ventricular contraction leads to ↑ ventricular pressure and AV valves to close.
- Semilunar valves remain closed.

b. Period of ejection

- Ventricular contraction lead to greater increased in ventricular pressure causing push out the blood and opening the semilunar valve.

2- Diastole

a. Period of isovolumic relaxation

- As ventricles begin to relax at the beginning of the ventricular diastole, the blood flow back from the aorta and pulmonary trunk toward the relaxing ventricles causing the semilunar valves to close.

b. Passive ventricular filling

- As ventricular relaxation continues AV valves open causing blood flow from atria into the relaxing ventricles.

c. Active ventricular filling

- Atria contract leading to ↑ arterial pressure and completing ventricular filling while the ventricles are relaxed.

- The events that occur during the cardiac cycle are depicted in figure (6.17).

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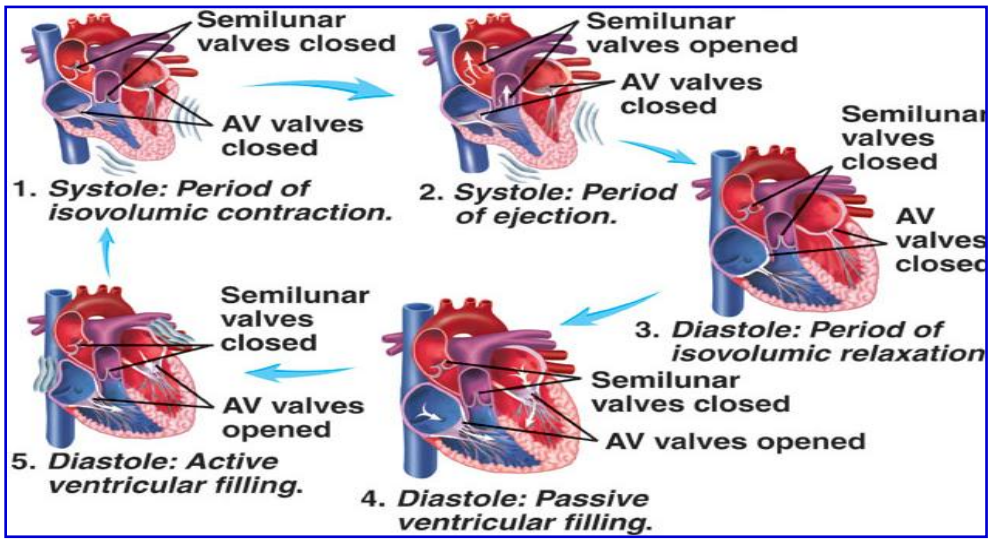

Figure (6.16): Cardiac cycle.(Marieb E.N .Essential of Human Anatomy and Physiology . San Francisco, Pearson Education,Inc.,2012).

Heart sounds

1. **First heart sound or "lubb"**
   Atrioventricular valves and surrounding fluid vibrations as valves close at beginning of ventricular systole
2. **Second heart sound or "dupp"**
   Results from closure of aortic and pulmonary semilunar valves at beginning of ventricular diastole, lasts longer

Pathological note: Blood flow through the cardiovascular system is laminar and silent .In certain circumstances, flow velocity is increased or viscosity is decreased and **turbulent flow** occurs that can produce noise (**murmurs** or **bruits**).

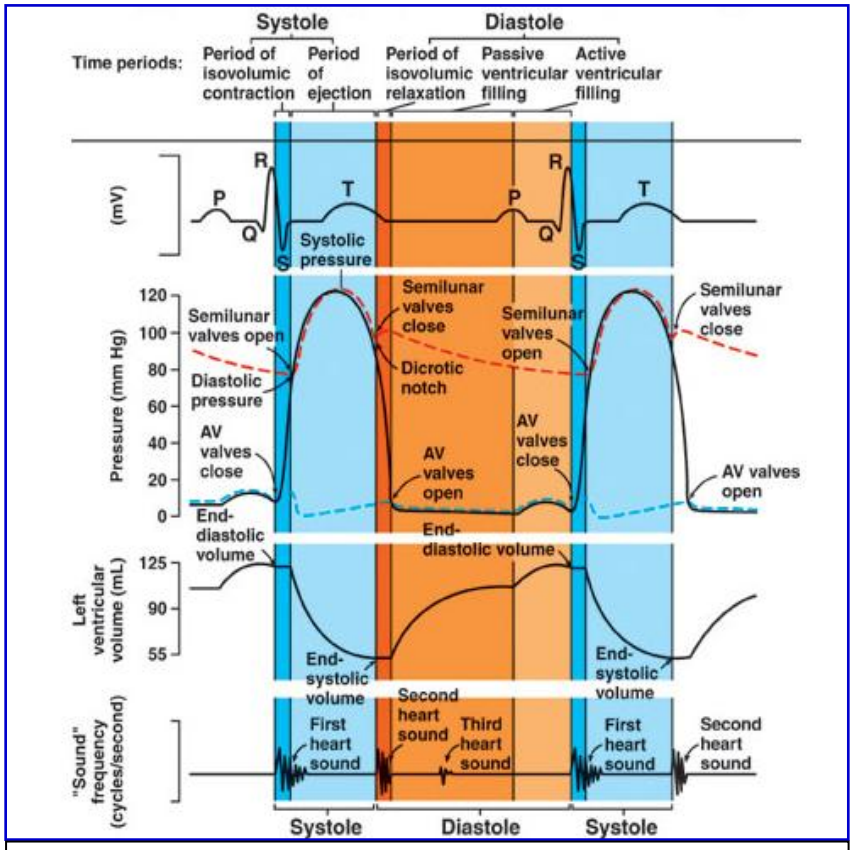

Figure (6.17): Events occurring during the cardiac cycle.
The cardiac cycle is divided into 5 periods (top).From top to bottom: The electrocardiogram; pressure changes for the left atrium (blue line), left ventricle (black line) and aorta (red line); left ventricular volume curve; and heart sounds.

Marieb E.N.and Hoehn K.Anatomy and physiology. San Francisco, Pearson Education Inc., 2011.

Aortic pressure curve

- Blood is ejected into the aorta by contraction of the ventricles, raising the **aortic pressure** and producing **peak systolic pressure** till to **120 mmHg.**
- The elastic recoil of the aorta maintains the aortic pressure and producing **dicrotic notch** or **incisura**, a double pulse can be felt.
- Aortic pressure then gradually falls throughout the rest of ventricular diastole as blood flows through the peripheral vessels .This produces a **diastolic pressure** (**80mmHg).**
- When aortic pressure reaches 80 mmHg the ventricles contract again forcing the blood into the aorta.

Mean Arterial Blood pressure

- Mean arterial pressure **(MAP)** is the average blood pressure in the aorta.
- MAP is proportional to the cardiac output **(CO)** times peripheral resistance **(PR)**.

MAP=CO X PR

  - **Cardiac output (CO)** is the amount of blood pumped by the heart per minute.
  - **Peripheral resistance PR** is the total resistance against which the blood must be pumped.

CO= HR X SV

  - **Heart rate (HR)** is the number of times the heart beats (contracts) per minutes. It is 72 bpm.
  - **Stroke volume (SV)** is the blood volume pumped during each heart beat. It is equal to the end diastolic volume minus end systolic volume.

SV= EDV-ESV

  - **End diastolic volume (EDV)** is the blood volume in the ventricles at the end of diastolic, just before the cardiac contraction. It is increased during exercise because the increased **venous return** ***(amount of blood returning to the heart from the peripheral circulation)***.
  - **End systolic volume (ESV)** is the small quantity of blood remaining in the ventricles at the end of systole. It is decreased during exercise because the heat contracts forcefully.
- ***At rest*** , the value of HR is 72 bpm ,SV is 70 ml/beat ,therefore CO is about 5L/min (CO=72 X 70).
- ***During exercise***, the value of HR is 190 bpm, SV is 115, and therefore CO is about 22L/min.
- The difference between CO when person at rest and maximum CO is called **cardiac reserve** .The greater person's cardiac reserve is the greater person's capacity for doing exercise.
- Lack of exercise and cardiovascular diseases reduce cardiac reserve .Exercise training increases cardiac reserve by increasing CO.

Regulation of MAP

1- Short term:

- **Baroreceptors** are sensory receptors sensitive to stretch.
  - Baroreceptors are located in the **carotid sinuses** and the **aortic arch**.
  - The baroreceptor reflex changes peripheral resistance, heart rate, and stroke volume in response to changes in blood pressure.
- **Chemoreceptors** are sensory receptors sensitive to oxygen, carbon dioxide and PH level in the blood.
- **Epinephrine and norepinephrine** are released from adrenal medulla as a result of sympathetic stimulation .They increase heart rate, stroke volume and vasoconstriction.

2- Long term:

- **Renin –angiotensin –aldosterone mechanism .**Renin is released by the kidney in response to low blood pressure .Renin promotes the production of angiotensin II,which causes vasoconstriction and an increase in aldosterone secretion.
- **Antidiuretic Hormone** is released from the posterior pituitary in response decrease blood pressure resulting vasoconstriction.
- **Aterial natriuretic hormone** is released from the cardiac muscle cells when arterial blood pressure increases resulting in an increase in urinary production, a decrease in blood volume and blood pressure.

Regulation of the Heart

1- Intrinsic regulation

- An increased venous return cause increased **EDV,** which lead to increase the stretch of the ventricular walls, the **preload.**
- The relationship between the preload and SV is the **Starling's law** .An increased preload causes cardiac muscle fiber to contract forcefully and produce greater SV.

2- Extrinsic regulation: Includes neural and hormonal control.

- **Neural regulation:** The cardioregulatory center in the **medulla oblongata** regulates the parasympathetic and sympathetic nervous control of the heart.
  - **Parasympathetic stimulation** is supplied by the **vagus nerve**.
    - Parasympathetic stimulation decreases HR.
    - Postganglionic neurons secrete **Ach** which increases K^+ membrane permeability producing hyperpolarization.
  - **Sympathetic stimulation** is supplied by **cardiac nerves**.
    - Sympathetic stimulation increases the HR and SV.
    - Postganglionic neurons secrete **norepinephrine** which increases membrane permeability to Na^+ and Ca^{2+} producing membrane depolarization.

- **Hormonal regulation:** Epinephrine and norepinephrine are released in the blood from the adrenal medulla causing long lasting effect compared with the neural effect. They increase HR and SV.

Heart homeostasis

- **Effect of blood pressure**
  - Baroreceptors monitor blood pressure: By baroreceptor reflexes, the decrease in pressure (and thus cardiac output) cause increased sympathetic stimulation and decreased parasympathetic stimulation .An increase in pressure has the reverse effect.(Figure 6.18)
- **Effect of pH, carbon dioxide, oxygen.**
  - Chemoreceptors monitor blood CO_2, PH, and O_2 level.
  - Increased CO_2 and PH cause the medullary chemoreceptor reflexes to increase sympathetic stimulation and decrease parasympathetic stimulation of the heart. (Figure 6.19).
  - Carotid body chemoreceptors stimulated by low O_2 level result in a decreased HR and vasoconstriction.
- **Effect of extracellular ion concentration**
  - Increase or decrease in extracellular K^+ decreases heart rate.
- **Effect of body temperature**
  - Heart rate increases when body temperature increases, HR decreases when body temperature decreases.

Clinical note: Heat failure is the result of progressive weakening of the heart muscle and the cardiac output is inadequate to meet the body's metabolic demands.
-**Systolic heat failure**: is pump failure (impaired contractility, increased afterload).
-**Diastolic heart failure:** impaired ventricular filling during diastole, due to stiff ventricle or obstruction ventricular filling (mitral stenosis).

Hypertension results in heart failure due to increase afterload on the heart. Many other factors e.g., advanced age, malnutrition, chronic infection, severe anemia and hyperthyroidism can cause degeneration of heart muscle resulting in heart failure. Hereditary factors can be responsible for increased susceptibility to heart failure.

Angina pectoris is a pain that results from a reduction in blood supply to cardiac muscle. Angina pectoris is characterized by chest discomfort deep to the sternum described as heaviness, pressure or moderately severe pain .Angina pectoris results from narrowed and hardened coronary arterial walls .The reduced blood flow results in reduced oxygen supply to the cardiac muscle cell.

Low oxygen level leads to limited anaerobic metabolism of the cardiac muscle results in reduced PH in the affected area. The decreased PH stimulates pain receptors.

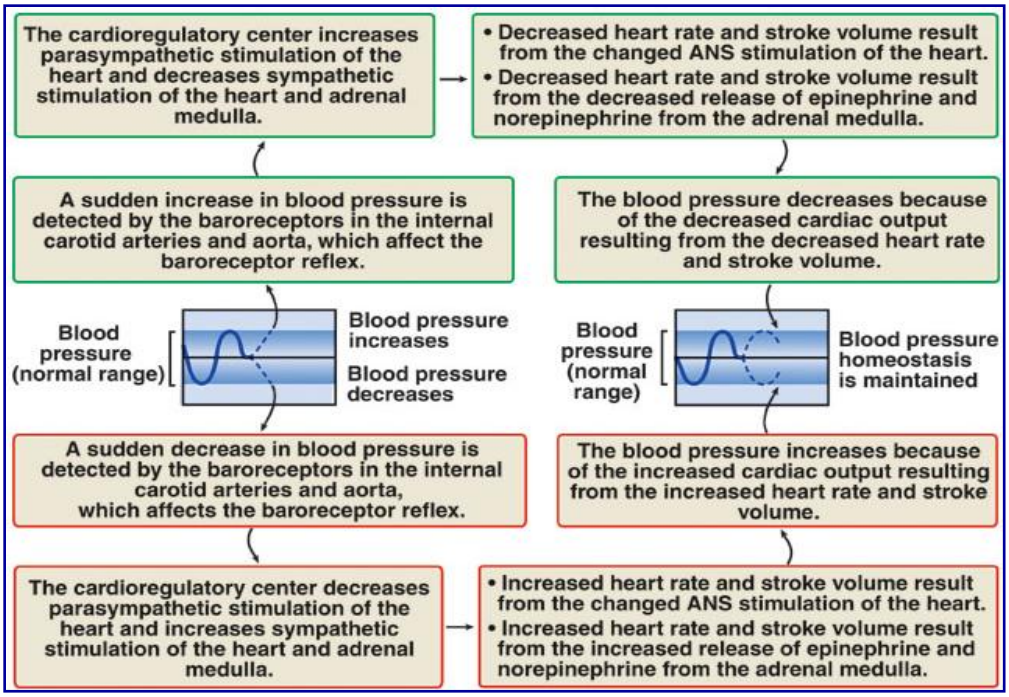

Figure (6.18):The baroreceptors reflexes :Homeostasis in response to changes in blood pressure .(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

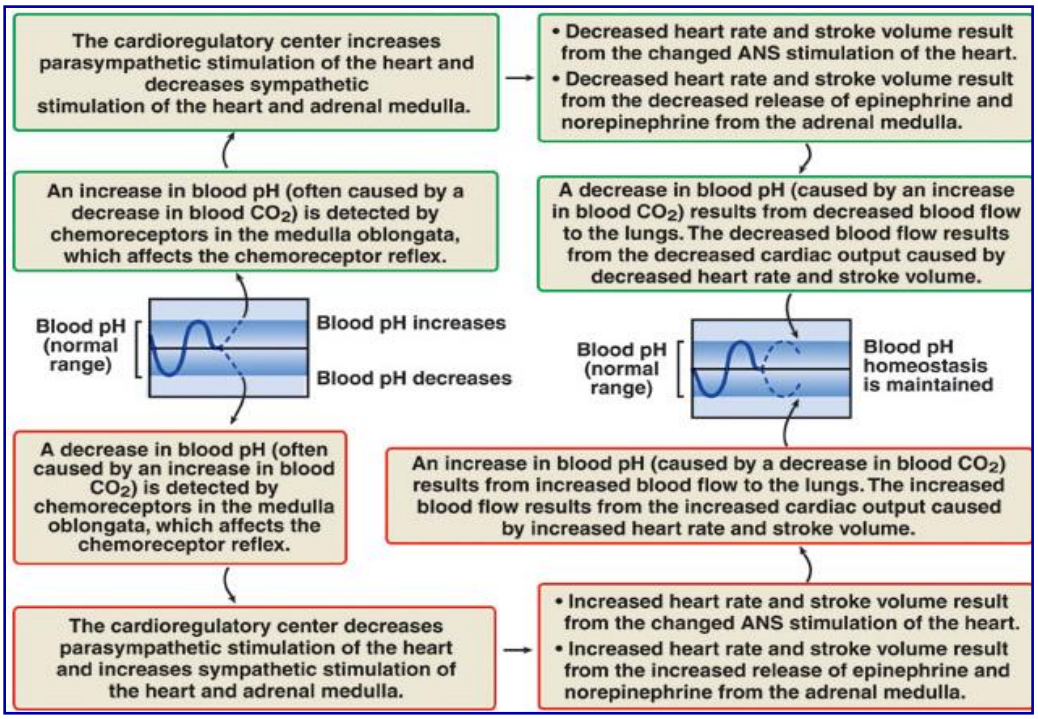

Figure (6.19): Chemoreceptors reflexes: Homeostasis in response to changes in CO_2 and H^+ pressure .(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

II. Blood vessels

1- The arteries

- They are the strongest of the blood vessels.
- They carry the blood under a high pressure away from the heart.
- They have strong vascular walls (figure 6.20) and rapid blood flow.

2- The arterioles

- They are the last branches of the arterial system.
- They have strong vascular walls that can be constricted or dilated in order to alter blood flow to the capillaries in response to changing tissue needs.

3- The capillaries

- The capillaries allow exchange of gases, nutrients and wastes between blood and tissues
- Overall large surface area and low blood flow.
- Two main types:
  1. **Continuous capillaries:** narrow space between cells → permeable to small or lipid soluble molecules
  2. **Fenestrated capillaries:** large pores between cells→ large molecules can pass.

4- The Venules

- They collect the blood from the capillaries.
- Gradually coalesce into large veins.

5- The veins

- They work as conduits to transport blood from the tissue back to the heart.
- They serve as reservoirs for blood.
- They have thin walls, low pressure and rapid blood flow. (Figure 6.20).

Dynamic of blood circulation

The interrelationships among pressure, flow, resistance and the control mechanisms that regulate blood pressure and blood flow through the vessels play critical roles in the in the function of the circulatory system.

Blood flow

- It's the volume of blood flowing through a vessel, an organ or the entire circulation in a given period (ml/min).
- Blood flow through the vessels is **streamlined or laminar.**
- **Turbulent flow** unusual blood flow occurs when the rate of flow exceeds a critical velocity or when the blood passes a constriction, a sharp turn or a rough surface.

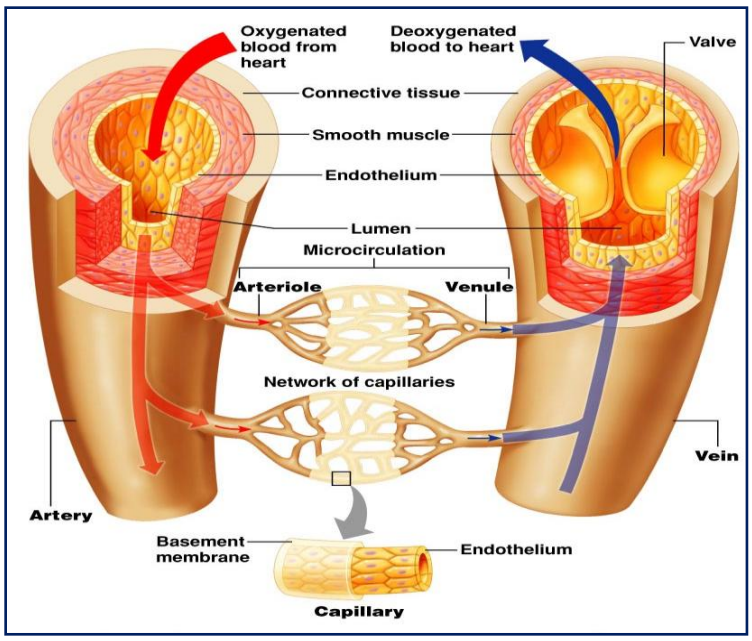

Figure (6.20): Overview of vasculature. (Marieb E.N .Essential of Human Anatomy and Physiology . San Francisco, Pearson Education, Inc.,2012).

Blood pressure

- Blood pressure is the pressure the blood exerts against the inner walls of the blood vessels, and it is the force that keeps blood circulating continuously even between heartbeats.
- Blood pressure is high in the arteries, lower in the capillaries and lowest in the veins. Blood is forced along descending pressure gradients.
- **Measuring of blood pressure:**
  Continuous contraction and relaxation of the heart cause the off and on blood flow ,therefore the blood pressure rises and falls during each beat, thus two arterial blood pressure measurements are made :
  - ***Systolic pressure:*** *is the pressure in the arteries at the peak of ventricular contraction.*
  - ***Diastolic pressure:*** *is the pressure when the ventricles are relaxing.*
- Blood pressures are reported in millimeters of mercury (mmHg), with the systolic pressure written first120 over 80 translated to 120mmHg and a diastolic pressure of 80 mmHg.
- Systolic arterial blood pressure is measured indirectly by the **auscultatory method, which** is used to measure blood pressure in the brachial artery of the arm.
- Because the arterial pressure is the product of the **cardiac output** and **peripheral resistance**, it is affected by any condition that affects either or both of these factors.
- Many factors may influence blood pressure including the activity of the sympathetic nerves, kidneys, drugs and diet.

Clinical note: Hypertension is a sustained elevation of the systemic arterial pressure .It is most commonly due to increased peripheral resistance .It is common and dangerous disease affects 30% of the people over than 50 years of age . mmHg . Hypertension can be caused by many conditions include a decrease in functional kidneys mass, excess aldosterone or angiotensin production and increase resistance to blood flow in the renal arteries .All these conditions cause an increase in total blood volume and cardiac output. Although these conditions may result in hypertension, 90% of the diagnostic cases are called **idiopathic** or **essential hypertension** which means the cause of the condition is unknown.

Hypotension or low blood pressure, the systolic pressure is less than 100mmHg. It may reflect individual variations and is no cause for concern.

Pharmacology note: **Diuretics** (drugs that increase the rate of urine production, **vasodilator drugs** and drugs that cause decrease cardiac output normally used to treat essential hypertension.

Angiotensin –converting enzyme (ACE) inhibitors are effective in lowering blood pressure in many people who suffer from hypertension. ACE inhibitors are class of drugs that inhibit angiotensin –converting enzyme which converts angiotensin I to angiotensin II.

Pharmacology note: Daily taking an **aspirin** reduces the chance of heart attack**.**Aspirin inhibits the synthesis of prostaglandins in the platelets and prevents clot formation.

Resistance

- It is the sum of all the factors that inhibit blood flow.
- There are three important sources of resistance :

1- Viscosity :

- It is a measurement of the resistance of a liquid to flow.
- As the viscosity increases, the pressure required for the liquid to flow increases.
- The viscosity is influenced by the hematocrit (it increases when the hematocrit increases).

2- Total blood vessels length

The longer vessels are the greater resistance.

3- Blood vessel diameter

- Changes in blood vessel diameter alter peripheral resistance .Blood in direct contact with blood vessel walls flows relatively slowly because the friction between the blood and the lining of the vessel, while the fluid in center flows more freely.

- **Laplace's law** states that the force acting on the wall of blood vessel is proportional to the diameter of the vessel times blood pressure.

$$F = D \times P$$

{F: force, D: diameter, P: pressure.}

The effect of blood pressure and vessel resistance on blood flow

- **Poiseuille's equation** describes the relationship between pressure ,vessel radius ,viscosity and vessel length on blood flow. A small variation in vessel radius translated into large change in blood flow.

$$\text{Blood flow } (\Delta Q) = \frac{\pi \Delta P r^4}{8 \eta l}$$

{ΔP: *The pressure difference between two ends of the of the vessel*
η: viscosity, l: blood vessel length, r^4: *The fourth power of vessel radius}* .

Vascular compliance

- It is the tendency of blood vessels volume to increase as blood pressure increases.
- The compliance depends on the stretch ability of the blood vessel walls.
- Compliance is expressed by the following formula :

$$\text{Compliance} = \frac{\text{Increase in volume (ml)}}{\text{Increase in pressure (mmHg)}}$$

- The venous system has a larger compliance, and acts as a blood reservoir. Most of volume is in the veins (64%).
- Smaller blood volumes are in the arteries (15%) and capillaries (15%).

Pathological note: Arteriosclerosis is the hardening of the arteries .It consists of degenerative changes in the arteries making them less elastic and increase resistance to blood flow .It becomes more sever with advancing age. Advanced arteriosclerosis reduces blood circulation and increases the heart work.
Atherosclerosis is a common type of arteriosclerosis caused by deposition of cholesterol on the wall of the arteries to form a plaque. It affects medium and large arteries including coronary arteries.

Capillary blood pressure

- Capillary blood pressure is low .It is about **35 mmHg** by the time the blood reaches the capillaries, and falls to **15 mmHg** at the end of the capillary bed.
- The low capillary blood pressure is important because :
  - The capillaries are fragile and the high pressure would rupture them.
  - Most capillaries are permeable thus even the low pressure force solute containing fluid out of the blood stream into the interstitial space.

Capillary exchange and interstitial fluid volume regulation.

- **Capillary exchange** is the movement of substances into and out of capillaries.
- It is the process by which the cells receive everything they need to survive and eliminate metabolic products.
- Small molecules and lipid soluble molecules move by **diffusion** through the cell membrane. (Figure 6.21).
- Larger molecules, charged molecules must pass through membrane channels, by **exocytosis** or in between 2 cells.
- Water movement is controlled by the **capillary hydrostatic** and **osmotic pressures.**

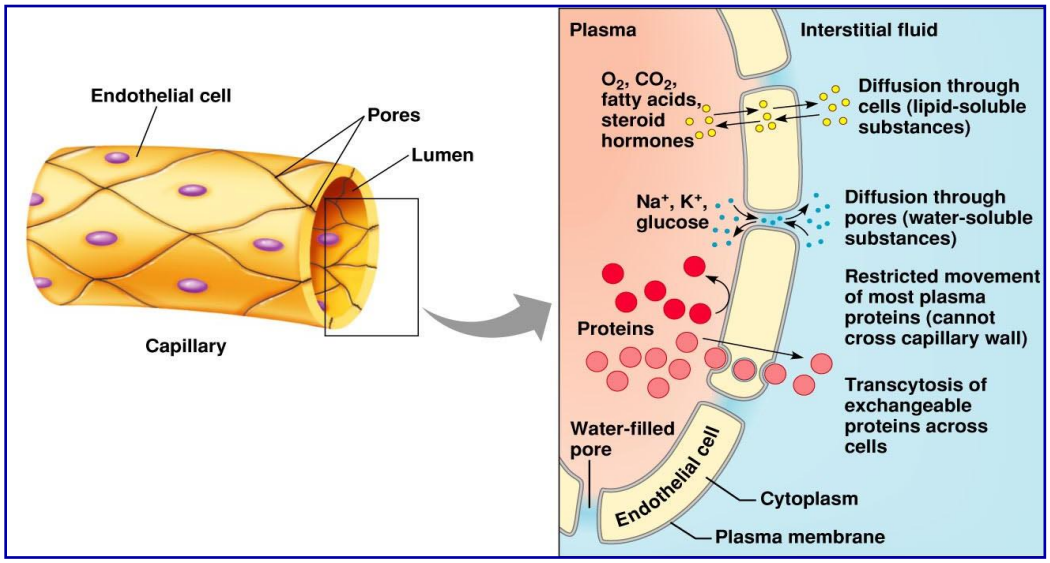

Figure (6.21): Material exchange across the capillary membrane. Retrieved from (www.studyblue.com).

- **Arterial side of the capillary:**
  - High capillary hydrostatic pressure (**BHP**), lower capillary osmotic pressure (**BOP,** due to proteins and other molecules in the blood) → **Net filtration pressure** pushes fluid from the blood toward the tissue (but the proteins remain in the capillary).(Figure 6.22).

- **Venous side of the capillary:**

- Lower hydrostatic pressure (due to resistance) and higher capillary osmotic pressure → Net filtration pressure moves fluid back toward the capillary. (Figure 6.22).

- Interstitial fluid hydrostatic (**IFHP**) and osmotic pressures (**IFOP**) remain identical.
- Fluid moves toward the tissues at the arteriole side and reenters the capillary at the venous side.
- For every **1 liter** of fluid entering the tissues, only **0.85 L** reenter the capillary. The remaining **0.15 L** is reabsorbed as lymph by lymphatic capillaries and eventually returned back to blood circulation
- Alterations in the forces affecting fluid movement across the capillary membrane are responsible for **edema.**

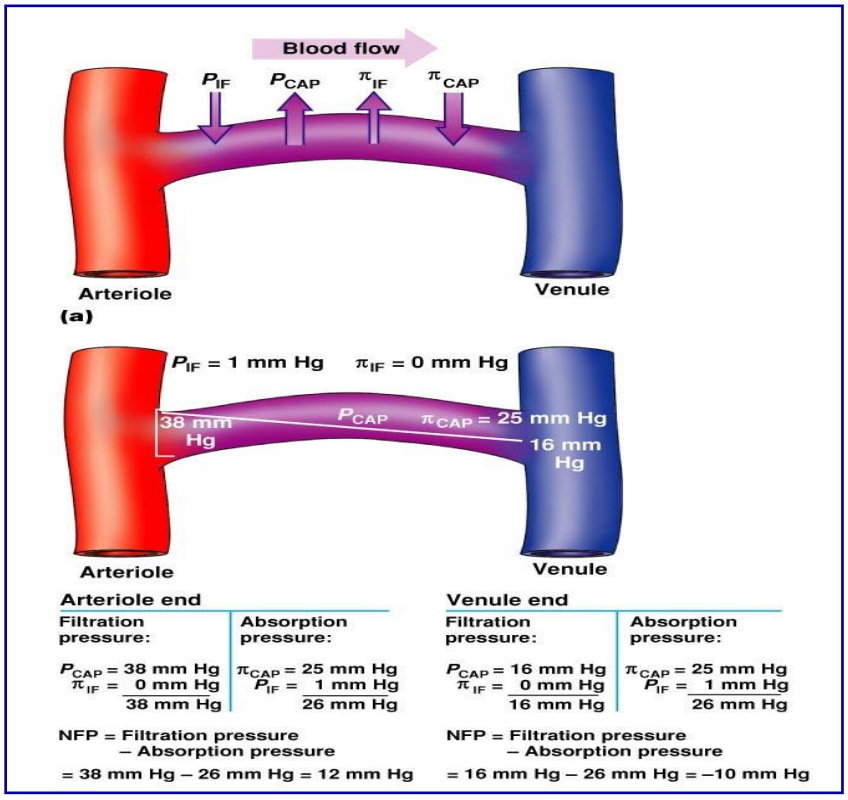

Figure (6.22): Fluid exchange at the arterial and venous ends according to the total pressure differences. (Marieb E.N.and Hoehn K.Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

Clinical note: Edema is the result of increased permeability of the capillary walls allowing the plasma proteins to move from capillaries into the interstitial fluid. This causes an increase in the **colloid osmotic pressure** of the interstitial fluid leading to a net increase in the amount of fluid moving from capillary into the interstitial space.

Local control of blood flow by the tissue

- Blood flow through the tissue is proportional to the metabolic needs of the tissue.
- Control of blood flow by **metarterioles** (no sphincters) and **precapillary sphincters**(on the arteriole and beginning of capillaries) can be regulated by **vasodilators substances** and lack of nutrients.
- Because of autoregulation which is the same mechanism to that of vasomotion (periodic contraction and relaxation of the capillary sphincters resulting in cyclic blood flow through the capillary.

Circulatory insufficiency or shock

- Shock is a state of inadequate tissue perfusion which often occurs in **hypotensive state.**
- This inadequate tissue perfusion invokes compensatory responses from sympathetic nervous system through diversely located barareceptors and chemoreceptors.
- **Signs and symptoms** include cold and clammy skin, rapid and weak pulse, confusion and reduced urinary output.

Types of shock

1- Circulatory shock

- The heart fails as a pump, it is unable to maintain a cardiac output sufficient to meet the body's metabolic demands in the presence of an adequate **intravascular** volume**.**
- The most common cause is **sever left ventricular dysfunction** .Other causes include **valvular diseases.**

2- Distributive shock

- Vasodilatation decreases the peripheral resistance thereby lowering blood pressure to an inadequate level.
- There are several causes of the distributive shock :
  - **Neurogenic shock**: sympathetic tone to the vasculature is removed (severing the spinal cord in the cervical region).
  - **Septic shock**: cytokines released in response to the toxins cause vasodilatation.
  - **Anaphylactic shock**: histamine and prostaglandins are released in response to allergens cause vasodilatation and increased permeability resulting in fluid loss into the interstitium.

3- Hypovolemic shock

- An effective circulatory volume due to not enough fluid within the vascular compartment.
- It occurs mainly as a result of hemorrhage.
- It may occur in conditions such as dehydration.

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Chapter seven

Blood 7

Blood

Overview

- Blood is a type of connective tissue consisting of cells and cell fragments surrounded by a liquid matrix.
- It is only the fluid tissue in the body.
- Blood performs many essential functions to life and uncontrolled loss of it can result in death.

Functions of blood

- Transport function
  - Transport of gases, nutrients and waste products.
  - Transport of processed molecules (transport of the precursor to vitamin D from skin to the liver, then to the kidney for processing into active form.
  - Transport of hormones and enzymes.
- Regulation of PH and osmosis.
- Maintenance of body temperature.
- Protection against foreign substances by the cells and chemical of the blood, which make up important part of the immune system.
- Clot formation .Blood clotting protects against excessive blood loss when blood vessels are damaged.

Blood components

1- Plasma

- Plasma is the fluid portion of the blood .It is a pale yellow fluid that contains of about **91%** water and **9%** other substances (proteins, ions, organic and inorganic molecules.)
- Normal plasma volume is **5%** of the body weight.
- It is colloid liquid containing proteins :
  - **Albumin:**
    - It is about 58% of the plasma proteins .It maintains osmotic pressure that pulls the water into the blood.
    - It transports substances in the blood: thyroid hormones, and fatty acids.
  - **Fibrinogen:** It is about 40% of plasma proteins .It is responsible for the formation of blood clots.
  - **Globulins**
    - It is about 38% of plasma proteins. They are divided into **α, β** and **γ globulins** .They transport substances in the blood.
    - Globulins provide protection against microorganisms, as part of immunity.

- **Serum:** is the plasma without the clotting factors.
- All plasma proteins are produced by the liver or blood cells.
- Plasma volume remains relatively constant because water intake through the gastrointestinal tract matches water loss through the kidney, lung and skin.

Clinical note: Hypoproteinemia: when the plasma proteins levels are low. Plasma proteins decrease in prolonged starvation, malabsorption syndrome. They are also low in liver diseases due to depression of hepatic proteins synthesis and low in nephrosis due to losing of large amounts of albumin in the urine. Plasma protein depletion causes a decrease in the plasma oncotic pressure and edema tends to develop.

2- Formed elements

Red blood cells

Overview

- Red blood cells (**RBCs**) or **erythrocytes** constitute **95%** of the formed elements.
- Normal erythrocytes are biconcave discs with a diameter is 7.5micrometers at the thickest point and 1 micrometers at the center. (Figure 7.1).
- They are flexible; their shape can change as the cells squeeze through the capillaries due to the stretchability of their membrane.
- The average number of the erythrocytes is **5.2 millions/mm^3** in man and **4.7millions/mm^3** in woman.
- They have no nucleus and their life span is about 120 days.

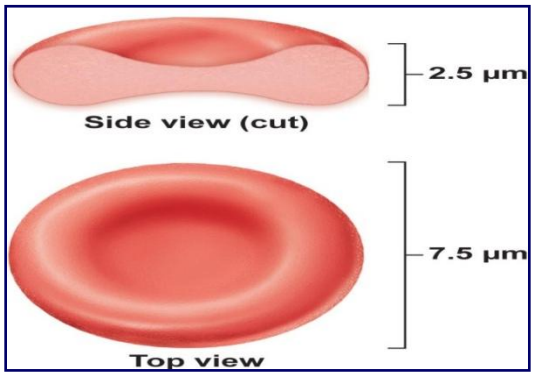
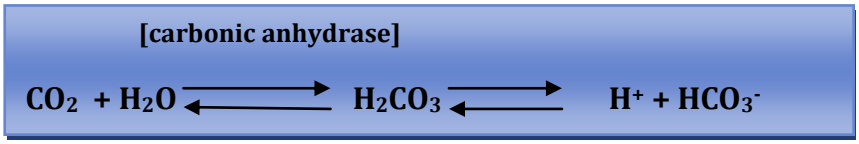


Figure (7.1): Shape and dimension of red blood cell.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

Function of red blood cells

- The major function of red blood cells is to contain hemoglobin (Hb), which carries the oxygen from the lungs to the tissues.
- The contain a large quantity of **carbonic anhydrase** :an enzyme that catalyzes the reversible reaction between carbon dioxide (**CO_2)**and water to form **H_2CO_3 .**This to increase the efficiency of **CO_2** transport ,in form of bicarbonate from the tissue to the lungs ,where it converted to **CO_2** and expelled into the atmosphere.



- Hemoglobin in the red blood cells is an acid –base buffer, so the red blood cells are responsible for the acid base buffering power of whole blood.

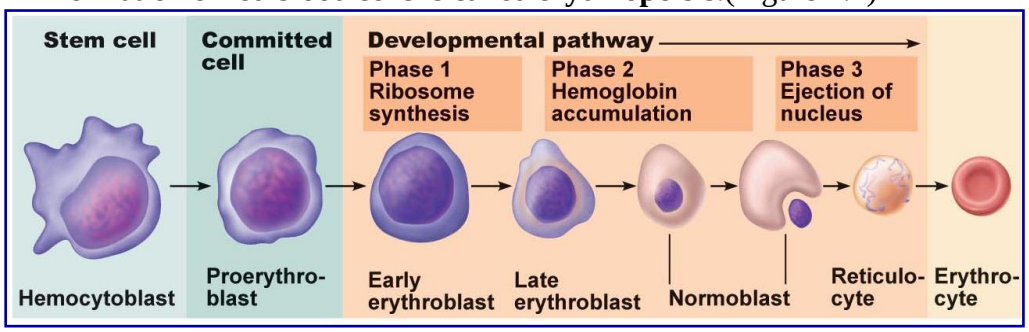
Formation of blood cells

Overview

- The process of blood cells production is called **hematopoiesis.**
- In the **embryo and fetus,** hematopoiesis occurs in tissues such as the yolk sac, liver, thymus, spleen, lymph nodes and bone marrow.
- **At birth**, hematopoiesis is confined to red bone marrow with some lymphoid tissues helping to produce lymphocytes.
- **In young children,** they are produced in the marrow of all bones.
- **In adults, they** are produced in the bone marrow of the ribs, sternum, vertebrates, pelvis and proximal femur and hummers.

Stages of the hematopoiesis

- All the formed elements of blood cells are produced derived from a single population of stem cells called **hemocytoblasts** in the red bone marrow.
- **Hemopoitic stem cells** are precursor cells capable of dividing to produce daughter cells that can differentiate into various types of cells:**proerythroblast**
- Proerythroblasts give rise to **late erythroblasts**, which lose their nuclei and released to the blood as **reticulocytes**. Reticulocytes form red blood cells. Formation of red blood cells is called **erythropoisis**.(Figure 7.2)



Figure(7.2): Erythropoiesis.(Marieb E.N.and Hoehn K.Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

- **Myoblasts** originated from hemopoietic stem cells form basophils, eosinophils and neutophils.
- **Lymphoblasts** give rise to lymphocytes, monoblasts form the monocytes and **megakaryocytes** form the platelets. (Figure 7.3).
- The development of cell lines is regulated by different **growth factors**.

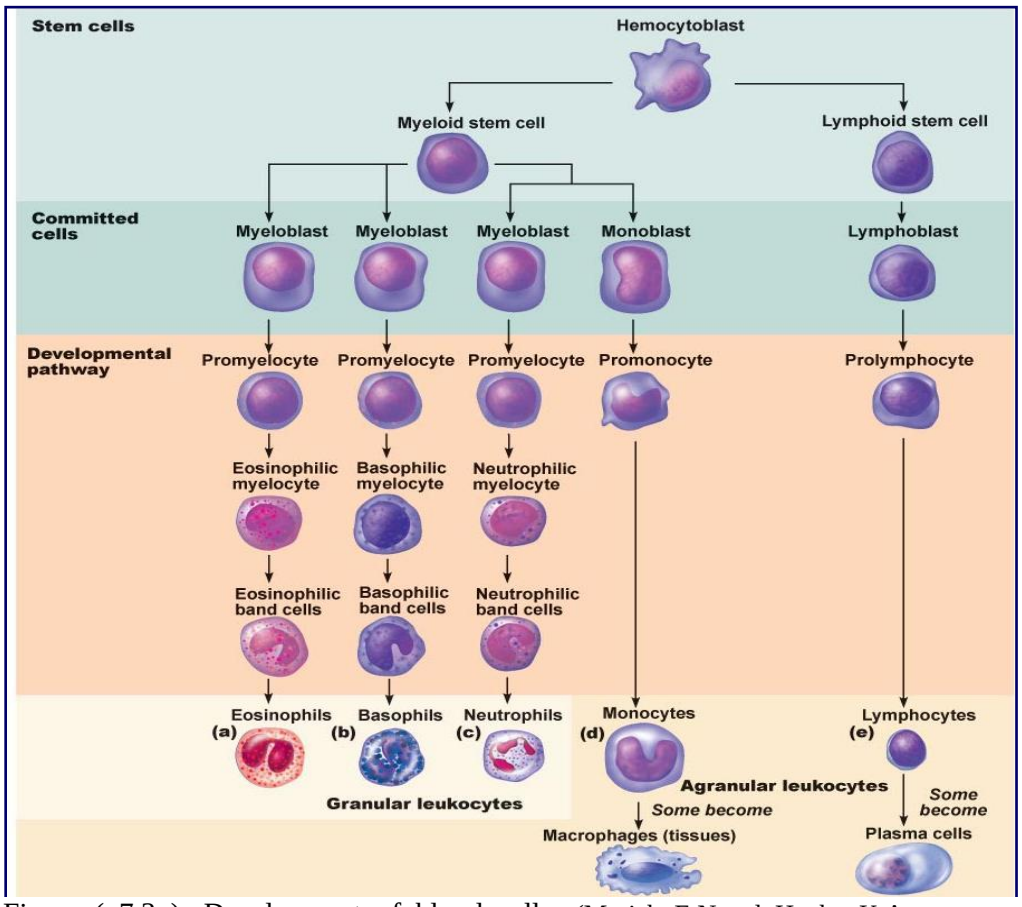


Figure (7.3): Development of blood cells. (Marieb E.N.and Hoehn K.Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

Regulation of red blood cells production

- **Tissue oxygenation**: The condition that causes the quantity of O_2 transported to the tissues to decrease increases the rate of red blood cells production. Many factors can decrease tissues oxygenation(figure7.4) :
  - **Anemia:** extreme anemia induces the bone marrow to produce large quantity of red blood cells.
  - **High altitude**: at a high altitude the quantity of O_2 in the air is greatly decreased causing insufficient O_2 transported to the tissues (**hypoxia**), the red blood cells production is greatly increased.

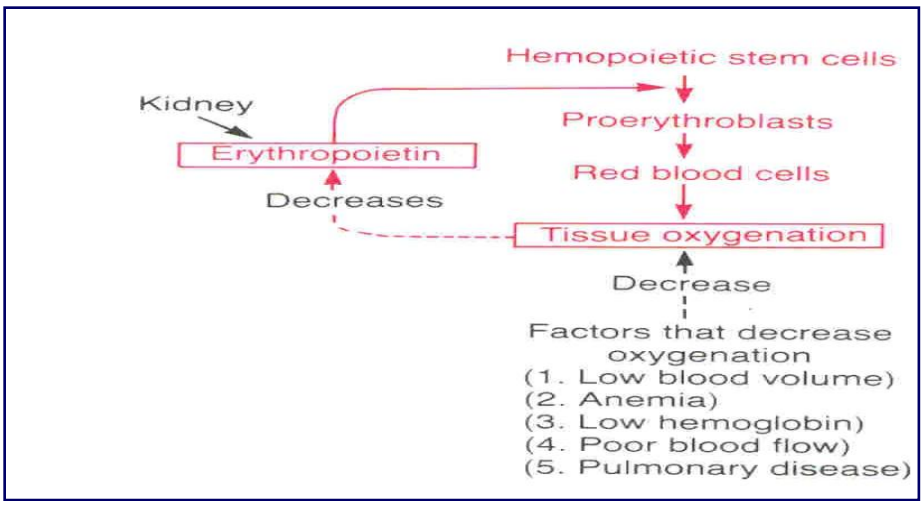


Figure (7.4): Factors affecting on the tissue oxygenation and RBC formation. Guyton A.C. and Hall J.E., Textbook of Medical Physiology. Philadelphia, Saunders, 2015).

- Various diseases of circulation that cause decreased blood flow can also increase the rate of red blood cells production e.g., prolonged heart failure and lungs diseases ,because the cause tissue hypoxia .

- **Erythropoietin** : is a circulating hormone stimulates red blood cells production in low oxygenation state .It is formed in the kidney in about **90%** and the reminder in the liver .
- **In the absence of erythropoietin,** hypoxia has no effect on stimulation of red blood cells production .But when erythropoietin is functional, hypoxia causes a marked increase in erythropoietin production and then enhances red blood cells production until the hypoxia is relieved.
- When both kidneys are destroyed by renal disease, the person becomes invariably anemic because the normal erythropoietin formed in the liver is sufficient to cause **1/3-1/2** of red blood cells formation needed by the body.
- An adequate amount of **folic acid**, **vitamin B12** and **iron** are necessary for normal red blood cells production.

Fate of red blood cells

- Red blood cells stay in the circulation for about 120 days .As their components degenerate, the cells become less able to transport O_2 and their plasma membranes become more fragile and rupture as they squeeze through a tight spot in the circulation and Hb is released.
- The released Hb is taken up by the **macrophages** which are located in the spleen, liver, and other lymphatic tissues.
- Lysosomal enzymes of the macrophages digest the Hb to yield **amino acids**, **iron** and **bilirubin**.
- Amino acids are reused in the production of other proteins, iron atoms are carried by the blood to the bone marrow, while the non iron part of the heme

group is converted to **biliverdin** and then to bilirubin, which is released to plasma.

- Bilirubin binds to albumin and is transported to liver cells, which is converted to **conjugated bilirubin**, the part of the bile (fluid secreted from the liver into the small intestine).

Hemoglobin

- **Hemoglobin (Hb)** is the oxygen carrying pigment in the red blood cells.
- Hb consists of four polypeptides chains:**2 α globin chains** & **2 β globin chains** .Each polypeptide chain is bound to one heme .Each heme contains one **iron atom.** (Figure 7.5).
- Iron atom is necessary for normal function of Hb; each O_2 that is transported is associated with an iron atom.
- Dietary iron is absorbed into the circulation from the upper part of the intestinal tract. **Stomach acids** and **vitamin C** in the food increase absorption of iron by converting **ferric iron (Fe^{3+})** to **ferrous iron (Fe^{2+})** which is more absorbed.
- There are three kinds of Hb with different affinity for binding with O_2 :
  1- **Embryonic Hb:** is the first type of Hb provided during the development.
  2- **Fetal Hb:** This replaces the embryonic Hb at the third month of development.
  3- **Adult Hb:** At birth 60-90% of the Hb is adult Hb .At 2-4 years of age; fetal Hb is less than 2% .At adulthood only trace of fetal Hb may be found.

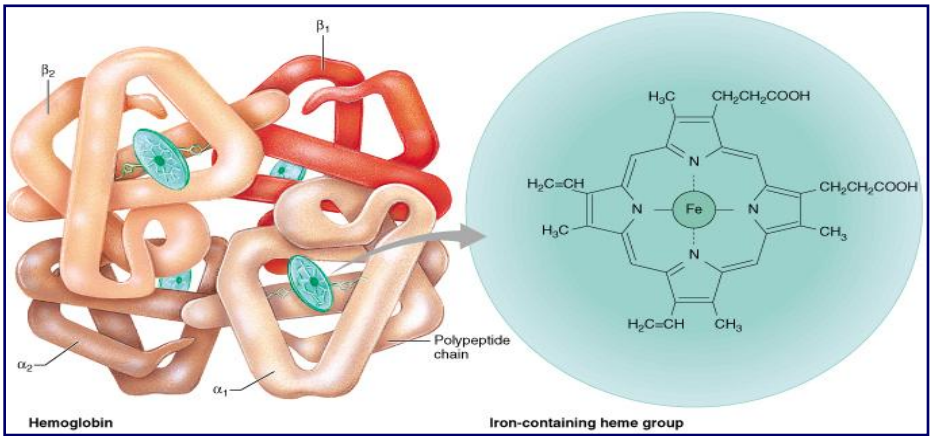


Figure (7.5): Hemoglobin structure. (Marieb E.N. Human Anatomy and Physiology. San Francisco Benjamin Cummings; Addison Wesley Longman.2001)

Hemoglobin functions

- **Transport O_2:** When Hb exposed to O_2, one oxygen molecule associates with each heme to form **oxyhemoglobin.** Hb containing no O_2 is called **deoxyhemglobin .**
- **Transport CO_2: Hb** transport CO_2 by attachement to amino groups of globin molecule .This form of Hb is called **carbaminohemoglobin.**

- Hb transports **nitric oxide** produced by the endothelial cells lining the blood vessels.

Clinical note: Jaundice is a yellowish staining of the skin caused by a buildup of a bile pigment in the circulation and intestinal space due to increased destruction of red blood cells.

White blood cells

Overview

- White blood cells **(WBCs)** or **leukocytes** are about **4.000-11.000/mm^3.**
- They are complete cells contain nuclei and usual organelles.
- White blood cells protect the body against microorganisms and remove dead cells and debris.
- White blood cells have some special characteristics :
  - They are motile exhibiting (amoeboid movement)by forming cytoplasmic projections.
  - The leave the circulation and enter the tissues by slipping between the cells of blood vessels wall. This process is called **diapedesis .**
  - They attract to the foreign materials by **chemotaxis** ,at the site of infection. They accumulate and engulf bacteria and dead cells (**phagocytosis**), then die.
  - Accumulation of dead WBCs, bacteria along with fluid and cells debris is called **pus.**
- **Leukocytosis**: is when total WBCs count above 11.000cells/mm^3 .This indicates for bacterial or viral infection in the body.
- **Leukopenia:**is abnormal low WBCs count ,caused by drugs such as corticoids and anticancer agents.

Clinical note: Leukemia is abnormal huge production of one or more of WBSc types because of cancerous bone marrow .The new formed WBCs are immature and lack their protective function and the patients become very susceptible to infection. The excess production of WBCs in bone marrow interfere RBCs and platelets formation resulting in anemia and bleeding.

White blood cells classification

- White blood cells are classified into two major groups **(granulocytes and agranulocytes)** depending on the presence of visible granules in the cytoplasm.(Figure7.6) .

i. **Granulocytes**

1- Neutrophils

- They comprise 60-70% of WBCs.
- They have small cytoplasmic granules that stain with both acidic and basic dyes.

- Their nuclei are multilobed (2-5lobes) so they are called polymorphonuclear neutrophils **(PMNs).**
- PMNs have very strong **phagocytic activity.** They stay for10-12hours in the circulation before leaving to the tissues to do their phagocytic function, to engulf bacteria, fungi and antigen –antibodies complex which are destroyed during the **respiratory burst** (a phase of elevated O_2 consumption that occurs in the neutrophils monocytes and macrophages shortly after phagocytosing materials).
- They secret an enzyme called **lysozyme** which destroys certain bacteria.

2- Eosinophils

- Eosinophils comprise 2-4% of WBCs.
- They contain cytoplasmic granules that stain **red** with acidic stain (**eosin**), with **blue red nucleus** that resembles an old fashioned telephone.
- They have weak phagocytic activity .Their number increases during parasitic infection.
- They are most common in tissues undergoing **an allergic** response and their numbers are elevated in blood of people with allergies.

3- Basophils

- Basophils comprise 0.5-1% of WBCs.
- They contain large histamine containing granules that stain **blue** with basic dyes .
- Their numbers increase in both **allergic and inflammatory reactions**.
- They release histamine that makes the blood vessels leaky and attract other WBCs to the inflammatory sites.

ii. Agranulocytes

1- Lymphocytes

- Lymphocytes comprise 20-25% 0f WBCs.
- They are the smallest WBCs, have large dark purple nucleus that occupies most of the cell volume. (Figure 7.7).
- Lymphocytes tend to take up residence in the **lymphatic tissues** where the play an important role in the **immune response**.

2- Monocytes

- Monocytes comprise 3-8% of WBCs.
- They are the largest cells of the WBCs with kidney shape nucleus.
- They remain in the circulation for 3 days then leave the circulation and become transported into macrophages and migrate through different tissues.
- They have a capability to phagocytize large quantities of bacteria, viruses, necrotic tissues or other foreign particles.
- An increase in the number of monocytes is associated with **chronic infection.**

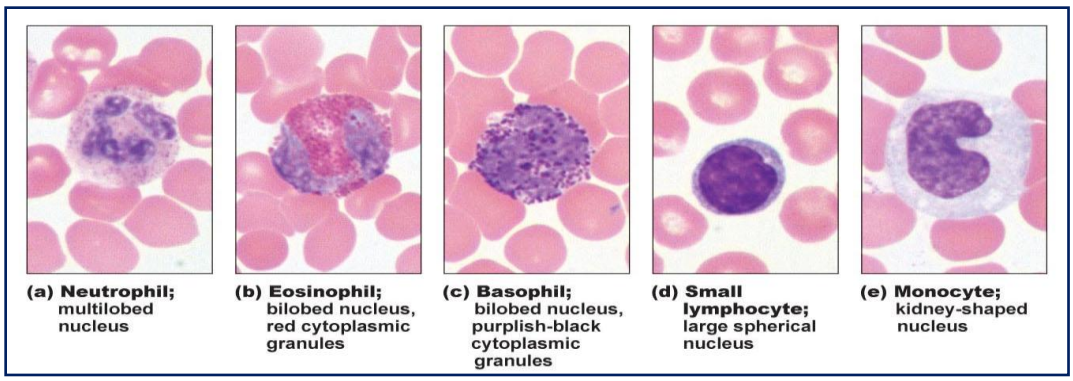


Figure (7.7): Different types of leukocytes. (Marieb E.N .Essential of Human Anatomy and Physiology . San Francisco, Pearson Education,Inc.,2012).

Platelets

- Platelets or thrombocytes are fragments of bizarre multinucleated cells called **megakaryocytes**, produced in bone marrow.
- The normal platelets count is about 300.000cells/mm^3.
- Life expectancy of platelets is 5-9days.
- Platelets play an important role in controlling blood loss by:
  - Forming platelets plugs to seal holes in small blood vessels.
  - They promote the formation of clots to seal off larger wounds in the vessels.

Hemostasis

- A number of events occur to prevent excessive blood loss when a blood vessel is damaged.
- There are three major events that cause the hemostasis :

1- Vascular spasm

- Immediate and temporary vasoconstriction of a damaged vessel, decreasing blood loss (Figure 7.8). Vasoconstriction causes the vessel to go into spasm. This is result from the following:
  1. *Nerve reflexes*
  2. *Local myogenic spasm*
  3. *Releasing of serotonin by anchored platelets.*

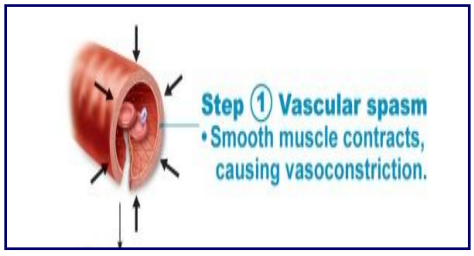


Figure (7.8):Vascular spasm.

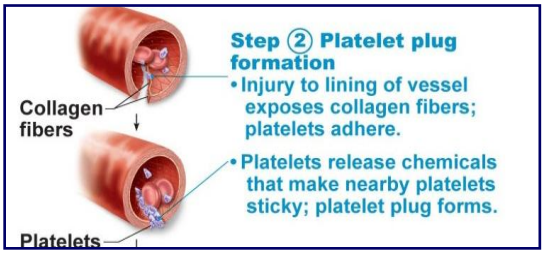


Figure (7.9): Platelets plug formation.

(Marieb E.N .Essential of Human Anatomy and Physiology . San Francisco, Pearson Education,Inc.,2012).

2- Platelets plug formation

- A platelet plug is an accumulation of platelets forming a mass that can seal up small breaks in blood vessel.(Figure 7.9).
- An injury to the lining vessels exposes collagen fibers causing platelets to adhere to the damaged site forming a small mass (a platelets plug).
- **Mechanism of platelets plug formation :**
  - When platelets come in contact with damaged vascular surface such as collagen fibers in the vascular wall or damaged endothelial cells, they change their characteristics; begin to swell forming numerous pseudopodes, their contractile proteins contract causing the release of granules that contain **multiple active factors.** They become sticky and stick to collagen fibers.
  - They secret ADP and their enzymes form **thromboxane A2** into the blood acting on additional platelets and causing them to adhere to the original present platelets.

3- Coagulation

- Coagulation or blood clotting results in formation of clot which is a network of threadlike protein fibers called **fibrin** that traps blood cells and fluid. .(Figure 7.10).
- A blood clot formation depends on number of proteins called **coagulation factors** in the plasma which normally found in an inactive state but after injury these they are activated to produce a clot.
- Activation of clotting factors is a complex process involving many chemical reactions some of which require **calcium ion, phospholipids** and **clotting factor V.**

Figure (7.10): Coagulation. (Marieb E.N .Essential of Human Anatomy and Physiology. San Francisco, Pearson Education, Inc., 2012).

- Blood clots within 3-6minutes and the mechanism of clotting takes place in three steps:

1. *A complex cascade of chemical reactions occur in blood involving more than dozen coagulation factors leading to form* ***prothrombin activator.***
2. *Conversion of* ***prothrimbin*** *to* ***thrombin*** *by the act of prothrombin activator.*

3. *Conversion of **soluble fibrinogen** into **insoluble fibrin** by the action of thrombin.*
   - The first stage of coagulation occurs through **extrinsic** or **intrinsic** pathway (figure 7.11) to produce **factor X.**
   - The extrinsic pathway begins with the release of **thromboplastin** from the damaged tissues.
   - The intrinsic pathway begins with the activation of **factor XII.**
   - Prothrombin activator is formed at the end of this stage.
   - Prothrombin activator goes through the second stage to activate formation of **thrombinIIa,** which stimulates formation of fibrin at the end of third stage. (Figure 7.12).

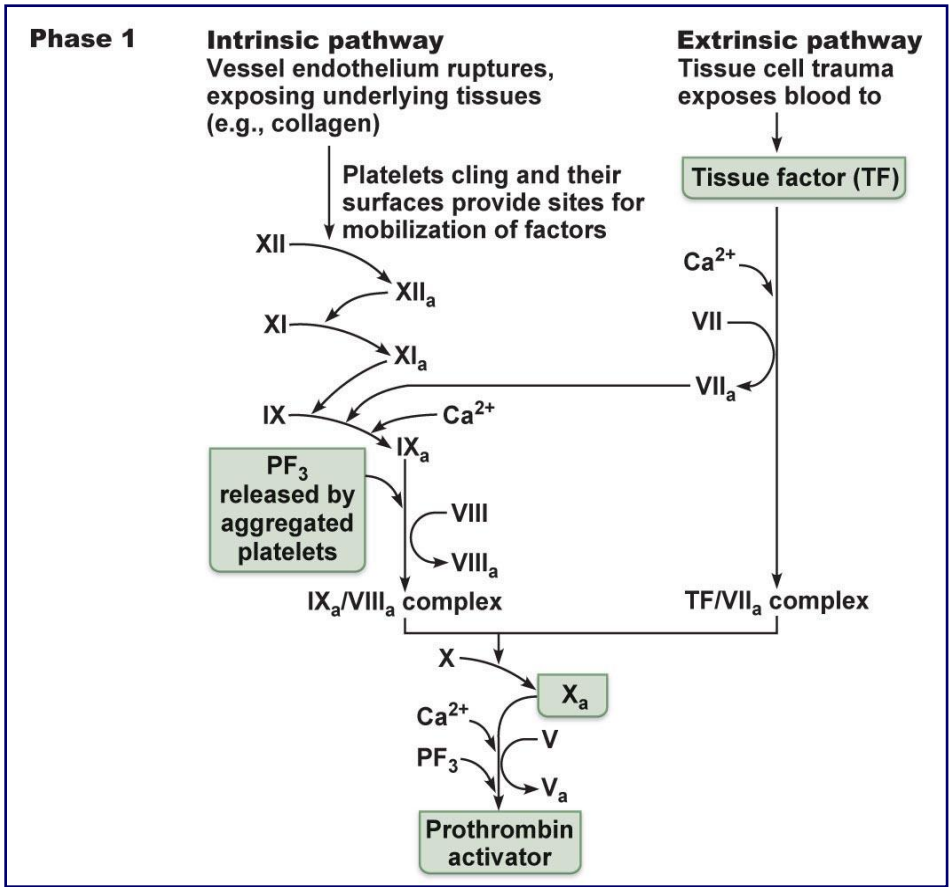


Figure (7.11): A sequence of chemical reactions of clot formation through the extrinsic and intrinsic pathway.(Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2010).

- **Calcium ions** are required for promotion of all the blood clotting (except the first two), therefore in the absence of calcium ions blood clotting does not occur.
- Many of factors involved in clot formation require **vitamin K** for their production .About half comes from the diet and half comes from bacteria within large intestine.

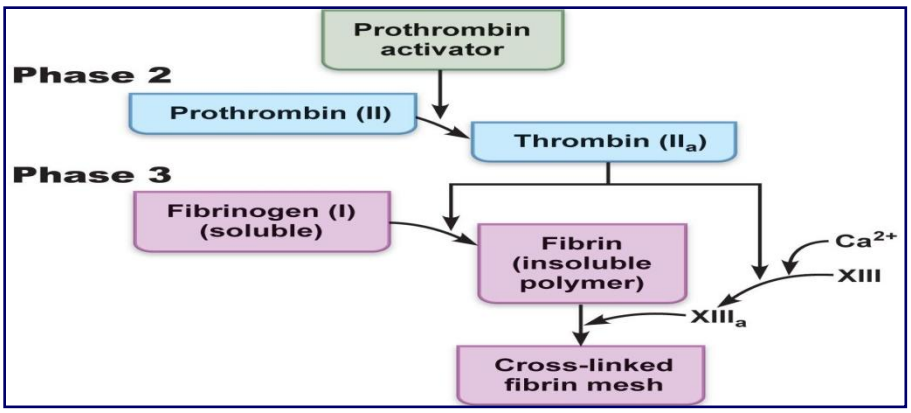


Figure (7.12): Stage2, 3 of the coagulation.(Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2010).

Disorders of hemostasis

1- Unwanted clot

- Unwanted clot sometimes formed in intact blood vessels (in the legs).
- A clot that develops and persists in an unbroken blood vessel is called **thrombus.** If the thrombus is large enough it may prevent the blood from flowing to the ells beyond the blockage.
- If a thrombus breaks away from the vessel wall and float freely in the blood it becomes **embolus,** which causes problem when it lodge in a too narrow vessels to pass through, e.g., **cerebral embolus** which may cause a stroke.
- Unwanted clot may be caused by anything that roughens the endothelium of blood vessels e.g., severe burns, accumulation of fatty materials).
- A number of anticoagulants e.g., **aspirin, heparin and dicumarol** are used for thrombus –prone patients.

2- Thrombocytopenia

- Thrombocytopenia is a condition in which the number of platelets is greatly reduced resulting in chronic bleeding through small vessels and capillaries.
- It has several causes including*: **increased platelets destruction, infection, and decrease in production caused by pernicious anemia, drugs therapy, radiation therapy or leukemia.***

3- Hemophilia

- Hemophilia is a term applied to several different hereditary bleeding disorders that result from a lack of any of the factors needed for clotting. Even minor tissue trauma may result in prolonged bleeding and can be life threatening.

Blood grouping

- Blood groups are classified on the basis of presence a protein on the surface of RBCs (antigen) called **agglutinogens** the**,** best known of these are A and B.
- There are four major blood types on the basis of agglutinogens present in their red cells .These are **A,B,AB** and **O.**

- Antibodies are recognizers present in the plasma that attach to RBCs bearing agglutinogens differ from those on the patients (blood recipients) .Those antibodies called **agglutinins.**
- Antibodies can bind to RBCs antigens resulting in **agglutination** or **hemolysis.**

Transfusion

- Transfusion is transfer of blood or blood components from one individual to another.
- The interaction between the agglutinogens and agglutinins cause **a transfusion reaction,** which include clotting in blood vessels, kidney damage and death.
- **An infusion**: is the introduction of a fluid other than blood such as saline or glucose solution into the blood.

1- ABO Blood groups

1- **Individual with type A blood**: have aggulinogen A on their red cells and antibodies against aggulinogens B called anti-B-agglutinin. [If their plasma is mixed with type B cells ,the agglutinins and B-cell agglutinogens react causing type B cells to be clumped (agglutinated) and hemolyzed].
2- **Individual with type B blood** have anti -A agglutinins. (Figure 7.13).
3- **Individual with type O –blood** have both anti -A and anti -B agglutinins. This is **an universal donor** because there are no regular anti-O agglutinins so this type can be given to anyone of the other type ,but this does not mean that the blood should ever be transfused without being cross matched except in the extreme emergencies.
4- **Individual with type -AB blood**.This is **un universal recipient** because there are no circulating agglutinins and can be given blood from any type without developing transfusion.

2- Rh group

- The Rh group is so named because it was first studied in the rhesus monkeys.
- **Rh-positive (Rh^+):** blood individual has certain Rh-antigens (D-antigens), whereas **Rh –negative**: blood has no D antigen.
- If an Rh- person receives mismatched blood (Rh^+) after transfusion the immune system becomes sensitized and produces anti-Rh^+ antibodies against foreign blood type .Hemolysis does not occur with the first transfusion because it takes time for the body to react and make antibodies But ,the second time of transfusion ,a typical transfusion occurs.
- **Hemolytic disease of the newborn (erythroblastosis fatalis)** occurs when Rh^- mother carries a Rh^+ fetus .A first pregnancy ,the baby is healthy .But the mother will form anti-Rh^+ antibodies ,the mother's antibodies will pass cross the placenta and destroy the baby's RBCs.

- It has been possible to prevent hemolytic disease of the newborn by administering a therapeutic injection of Rh antibodies into the Rh^- maternal circulation within 72 hours after delivery of an Rh^+ infant.

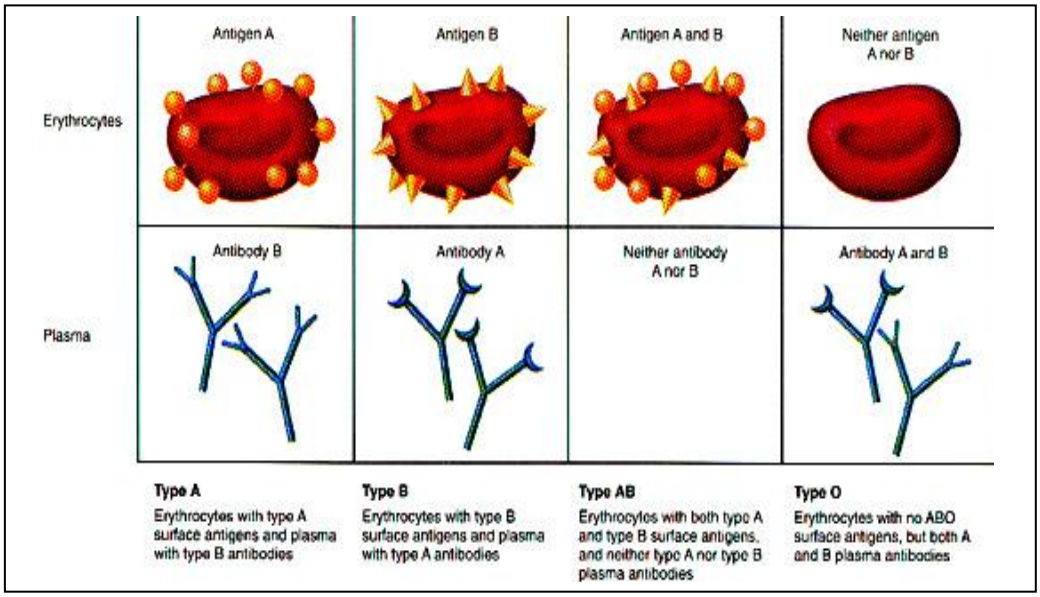


Figure (7.13): ABO Blood groups.(Randall D. ,Burggren W. and French K. Eckert Animal Physiology . New York, W.H. Freeman and Company, 2002).

Disorders of the blood

Anemia

- Anemia means deficient of hemoglobin in blood, which can be caused by either too few blood cells, or too little hemoglobin in the cells.
- **Types of anemia :**

1- ***Blood loss anemia.*** After rapid hemorrhag the RBCs concentration can return to normal level within 3 – 6weeks.

2- ***Iron deficient anemia:*** In chronic blood loss, a person cannot absorb enough Fe from intestine to form hemoglobin as rapidly as it is loss. The RBCs are then produced are much smaller than normal in sizes and have too little hemoglobin inside, this giving rise to **microcytic hypochromic anemia.**

3- ***Aplastic anemia:*** Bone marrow aplasia means lack of functioning bone marrow.This occurs when person exposed to gamma radiation from explosion of atomic bomb, that can sustain complete destruction of bone marrow followed in few weeks by lethal anemia. Also excessive X-rays treatment a certain industrial chemical and even drugs can cause some effect (benzene, and arsenic compound).

4- ***Megaloblastic anemia:*** It is slow production of erythroblast in the bone marrow, due to lack of vitamin B12, folic acid and intrinsic factor from stomach mucosa. As result red cells grow to large in size with ***odd shape (peculiar shape)*** *called* **megaloblast,** also resulted if patient have **intestinal**

sprue, in which folic acid and B12 and other vitamins B compounds are poorly absorbed, often developed **Megaloblastic anemia (pernicious anemia).** In these cases erythroblast cannot proliferated rapidly enough to form normal number of RBCs. These cells have fragile membrane and are easily ruptured, leaving person in dire need of an adequate number of cells.

5- ***Hemolytic anemia:*** different abnormalities of RBCs, many of which are hereditary acquired, make cells more fragile, so that they are ruptured easily as they pass through capillaries especially in spleen. The number of red cells is normal and some time is greater than normal produced in some hemolytic disease. The life span is shorter, that the cells destroyed faster than they produced leading to serious anemia , some of these are:

- ***Sickle cell anemia:*** *is present in western Africa and American black. The cells have abnormal type of Hb (Hbs), containing* ***faulty β-chain*** *in Hb molecule, that,* ***glutamic*** *at the position 6 in beta chain is substituted by* ***valine*** *amino acid. When this Hb is exposed to low concentration of oxygen, it precipitates into long crystals inside RBCs. These crystals elongate the cell, so that the cells appear in* ***sickle shape,*** *rather than biconcave disc(figure7.14) . The crystals damage the cell membrane, so that the cells become highly fragile causing to serous anemia. If person who has sickle disease and exposed to low oxygen tension for long time may lead to death, because of hemolysis of RBCs.*

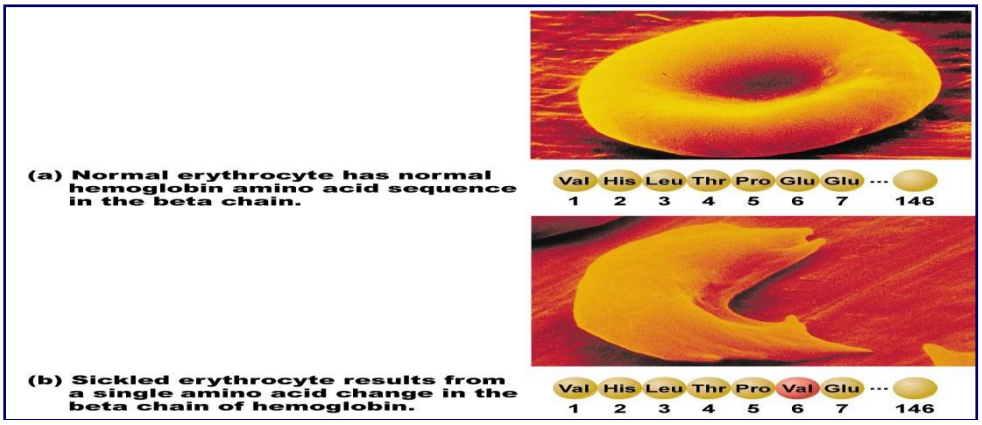


Figure (7.14): Sickle cell anemia. (Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2010).

- ***Erythroblastosis fetalis*** *:(See hemolytic diseases of newborn).*
- ***Thalassemia:*** *in which both of alpha and beta chain of Hb are changed. The red cells become more fragile, it is either beta thalassemia or alpha thalassemia.*
- ***Spherocytic anemia:*** *the red cells are spherical in shape rather than biconcave disc; and hemolyzed more rapidly than the normal cells in hypotonic sodium chloride solution, leading to a reduction in the number of RBCs. This disease is congenital hemolytic. The spherocyte*

cells also removed by spleen. The reason for spherocytosis is due abnormalities of protein network that maintain the shape and flexibility of red cell membrane.

- ***Enzyme glucose 6-phosphate dehydrogenase deficiency.*** *This enzyme catalyzes the initial step in oxidation of glucose via the* ***hexose phosphate pathway****. In this pathway generates ADPH, which needed in some way for the maintenance of red cell fragility.*

Effect of anemia on function of circulatory system

- The viscosity of blood mostly depended on blood concentration of RBCs.
- In anemia the viscosity may decrease to less than 1.5 normal value. This decreases the resistance, leading to greater blood flow to the tissues and return to the heart.
- Increased cardiac output and pumping workload on the heart.

Polycythemia

- It means an increase in the number of the RBCs, there are 2 types of polycythemia:

1- Secondary polycythemia: In case of tissues hypoxia, when O_2 level decreases in the air, such as high altitude, or failure of oxygen delivery to the tissues such in cardiac failure; the blood forming organ automatically produced large amount of blood cells. Red cells count increases up the 7 million/ mm^3.

2- Primary polycythemia (polycythemia vera or Erythremia).This is a pathological condition in which red cells account increases to 7.000.000 – 8.000.000 Cells / $mm^3$and hematocrit may be 60-70%.

- **Polycythemia Vera** is caused by a genetic aberration in hemocytoblast cells that produced the blood cells. The blast cells no longer stop producing red cells in addition to increase of white blood cells and platelets.

Effect of polycythemia on circulatory system.

- Increased viscosity leading to sluggish blood flow through the peripheral blood vessels.
- Increased blood viscosity causes a decrease in venous blood return to the heart.
- Blood volume is greatly increased in polycythemia.
- The arterial pressure mostly normal in most people with polycythemia, but 1/3 of them arterial pressure is elevated.
- Persons with polycythemia, their skin has ruddy complexion with a bluish tint, because of hypoxic occurs in blood capillaries of skin at venous plexus, which might be related to sluggish movement.

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Chapter eight

Lymphatic system and Immunity 8

I. Lymphatic system

Overview

- Lymphatic system consists of lymph, lymphatic vessels, lymphatic tissues, lymphatic nodes and nodules and lymphatic organs.
- **Functions:**
  1- It maintains fluid balance in tissues.
  2- It absorbs fats from the small intestine
  3- Defense functions.
    - *The innate defenses hinder pathogen entry, prevent the spread of diseases causing microorganisms, and strengthen the immune response.*
    - *The adaptive defenses protect against disease by destroying foreign cells and inactivating toxins with antibodies.*

Lymphatic vessels

- **Lymphatic capillaries** carry lymph away from tissues.
- Lymphatic capillaries join to form **lymphatic vessels.**
  - Lymphatic vessels have valves to control one way flow of lymph.
  - Contraction of lymphatic vessels smooth muscle, skeletal muscle action and thoracic pressure changes move the lymph.
- **Lymphatic nodes** are along the lymphatic vessels. After passing through lymphatic nodes ,lymphatic vessels form **lymphatic trunks** and **lymphatic ducts.**
- Lymphatic trunks and ducts empty into the blood at thoracic veins (junctions of the internal jugular and subclavian veins).
- Thoracic duct is the largest lymphatic vessel.
- The jugular, subcalavian and bronchomediastinal trunks may unite to form the **right lymphatic duct.**

Lymphatic tissues and organs

- Lymphatic tissues are reticular connective tissue that contains **lymphocytes** and other cells.
- Lymphatic tissues can be surrounded by capsule (e.g., **lymph nodes, spleen**) or they are non capsulated (e.g., **lymphatic nodules, tonsil**).
- Although all lymphoid organs have roles in protecting the body, only **lymph nodes** filter lymph.
- **Lymphatic nodules** are small aggregates of lymphatic tissues (e.g., **Peyer's patches** in the small intestine)

- **Tonsils:** are large groups of lymphatic nodules in the oral cavity and nasopharynx. Their job is to trap and remove any bacteria and foreign pathogens entering the throat. They are three groups:
  1. ***Palatine tonsils*** *are on the each sides of the junction between the oral cavity and the pharynx.*
  2. ***Pharyngeal tonsils*** *are near the junction between the nasal cavity and pharynx.*
  3. ***Lingual tonsils*** *are on the posterior surface of the tongue.*
- Sometimes the palatine or pharyngeal tonsils become chronically infected and must be removed, while lingual becomes infected less often than the others and is difficult to remove.

- **Lymphatic nodes:** lymphatic tissues in the nodes are organized into **cortex and medulla**. Sinuses extend through the lymphatic tissue. (Figure 8.1).
  - They protect the body by removing bacteria and other a foreign materials from lymphatic stream and by producing lymphocytes, that function in the immune response.
  - They filter the lymph which is transported toward the heart through thousands of nodes that cluster along the lymphatic vessels.
  - **Macrophages** are present within the lymph nodes ,which engulf and destroy bacteria ,virus and foreign substances in the lymph .

- **The spleen:** is soft blood rich organ that filters the blood.
  - It is located in the left side of the abdominal cavity beneath the diaphragm**.**
  - It filters and cleanses the blood of bacteria, virus and other debris**.**
  - It destroys worn out RBSc and returns some of their broke down products to the liver**.**
  - It stores of platelets and acts as reservoir**.**

- **Thymus:**
  - Lymphoid mass found in the throat overlying the heart.
  - It produces hormone **(thymosin)** which function in programming of certain lymphocytes, so they can carry out their protective functions.

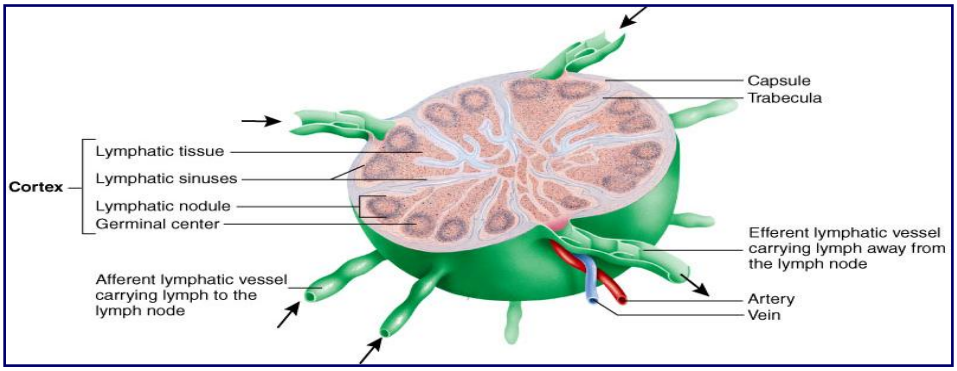


Figure (8.1): Structure of a lymph node. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Lymphatic circulation

Overview

- Normally fluid efflux exceeds influx across the capillary walls, but the extra fluid enters the lymphatic channels and drain through them back to the blood. This prevents the interstitial fluid from rising.
- The normal 24hours lymph flow is 2-4L.
- Lymphatic vessels can be divided into two types :

1. Initial lymphatic vessels

- They lack valves and have no smooth muscles in their walls.
- They are found in organ like intestine, skeletal muscles.
- Lymph (tissue fluid) enters the initial lymphatic vessels through a loose junction between the endothelial cells in their walls.
- The lymph in these channels moves by muscles contraction of the organs and by contraction s of the arterioles and venules which is often associated with them.

2. The collecting lymphatic vessels

- The initial lymphatic vessels drain into collection lymphatic vessels which have valves, smooth muscles in their walls and peristaltic, propelling the lymph along these channels.(Figure 8.2).
- The flow of lymph in the collecting vessels is further added by skeletal muscles contraction, the negative intrathoracic pressure during inspiration and the suction effect of blood flow of the veins in which the lymphatic terminate.

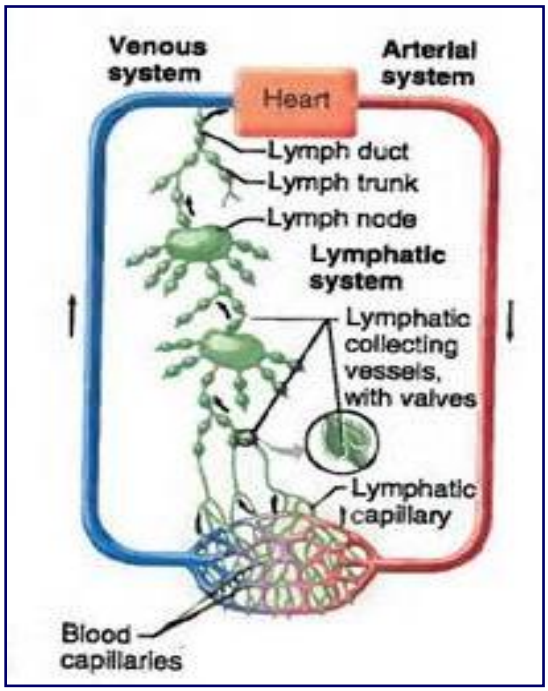


Figure (8.2): Lymphatic vessels. (Marieb E.N .Essential of Human Anatomy and Physiology. San Francisco, Pearson Education,Inc.,2012).

II.Body defense and immune mechanism

- **Immunity** is the ability of the body to resist almost all types of organisms and toxin that tend to damage the tissues and organs.
- Immunity may be***: Innate immunity*** or ***acquired (adaptive) immunity.***

1- Innate immunity

Overview

- Innate immunity is **non- specific defense** .It responds immediately to protect the body from all foreign substances.
- The first line of defense against the diseases- causing microorganisms is the **skin** and **mucus membrane** lining the digestive, respiratory, urinary and reproductive tracts.
- **The acidity** of the stomach secretion, urine and female reproductive canal have a protective effect by inhibiting bacterial growth.
- **Phagocytosis process:** the cellular ingestion of the offending agents.
- Presence of **certain chemical compounds** in the blood that destroy the foreign microorganisms and toxins ,these are:
  1- ***Lysozyme***
  2- ***Complement complex***
  3- ***Natural killer lymphocytes for infected cells, tumor cells and foreign cells.***

Internal defenses: cells and chemicals

- It is **a second line of defense**, includes **natural killer cells**, **phagocytes, inflammatory response** and a variety of **chemical substances** that kill pathogens and help repair.

1- Natural killer cells

- A unique group of lymphocytes that can lyse and kill cancer cells, viruses infected body cells.
- Natural killer cells (**NK**) are not phagocytic but they attack the target cells and release lytic chemicals.
- Natural killer cells release powerful inflammatory chemicals.

2- Inflammatory response

- Inflammatory response is non -specific response that is triggered wherever body tissues are injured by: physical trauma, heat, infection by bacteria and viruses**.**
- The most common indicators of acute inflammation are pain, redness, heat and swelling**.**

The events of the inflammatory process

- The injured cells release inflammatory chemicals (histamine and kinins)that cause :
  1- Dilatation of blood vessels in the inflamed area and become more leaky

- Dilatation of the blood vessels increases blood flow to the area accounting for the redness and heat. Increased permeability of the capillaries allows plasma to leak from the blood into the tissues space causing the swelling.

2- They activate pain receptors.

3- They attract phagocytes and WBCs to the area.

- Migration of large number of **granulocytes** into the tissue
- **Monocytes** follow the **neutrophils** into the inflamed area, which become **macrophages** and exhibit great capability to ingest bacteria.
- **Clotting proteins** leaked from the blood into the inflamed area are activated and begin to wall off the damaged area within fibrin to prevent spread of pathogens to the neighboring tissues.
- The adaptive response mediated by lymphocytes (the third line of defense) is activated when the damaged area contains the invading pathogens.

Pathological note: In sever infected area creamy yellow **pus** may form in the wound .Pus is a mixture of dead neutrophils, breakdown cells and living and dead pathogens. If the inflammatory mechanism fails to clear the infected area, a sac of pus may become walled off forming an abscess.

3- Phagocytes

- Phagocytes **(macrophages, neutrophils)** engulf foreign particles by process called **phagocytosis**.
- Phagocytosis is a selective process by which the phagocytes ingest only the foreign particles by forming a cytoplasmic extension around these particles, forming a phagocytic vesicle or **phagosome** inside the cytoplasm.
- The vesicle is then fuses with the **proteolytic enzymes** of the **lysosome,** which digest the contents of the vesicle.
- Monocytes turn to macrophages when entering the tissues .They become activated and much more powerful than neutrophils .These macrophages can engulf **100 bacteria** and also have the ability to engulf malaria parasite, even whole blood cell, while the neutrophils phagocytize **5-10 bacteria** before they die.
- Neutrophils and macrophages have **oxidizing agents** which are powerful bactericidal agents include: superoxide **(O_2^-),** hydrogen peroxide **(H_2O_2)** and hydroxyl ion **(OH).**

Life span of the phagocytes

- The life span of the neutrophils is **4-8 hours** in the blood and **3-5days** in the tissue. The life span may shorten to few hours in serious infection.
- Monocytes have transit time 12 hours in the blood .they are transformed into macrophages in the tissue, and stay there for months or even years unless they are destroyed by phagocytic action.

4- Basophils, Mast cells and Eosinophils

- **Basophils** are motile white blood cells derived from red bone marrow .They can leave the blood and enter infected tissues.
- **Mast cells** are non-motile cells in connective tissues .They located in the skin, lung, gastrointestinal tract and urogenital tract.
- Basophil and mast cells can be activated through innate immunity (e.g., complement) or through adaptive immunity.
- They release chemicals e.g., **histamine** and **leukotrienes** which produce an inflammatory response and activate other mechanisms such as smooth muscle contraction in the lungs.
- **Eosiophils** are produced in bone marrow, enter the blood and leave to the tissues within few minutes. They release enzymes which break down the chemicals produced by basophils and mast cells. They secrete effective enzymes to kill some parasites. Their number greatly **increases** in **parasitic infection** and **allergic reactions.**

5- Antimicrobial proteins

- Antimicrobial proteins enhance the innate defense either by attacking microorganisms directly or by hindering to produce.
- The most important of these are :the **complement system** and **interferon**

1- Complement system

- **Complement system** is a group of at least **20 plasma proteins** that circulate in the blood in an inactive state. These proteins are named **C1-C9** and factors **B, D and P (properdin).**
- It is nonspecific defense mechanism enhance the effectiveness of both innate and adaptive defense.
- When complement becomes attached to foreign cells such as bacteria, fungi, it is activated and becomes the major factor in the fight against the foreign cells. This is the **complement fixation.**
- Complement fixation leads to form **membrane attack complex (MAC)** that causes lesions in the foreign cell's surface.
- The lesions make the water to move inside the cell causing it to burst.
- Activated complement amplifies the inflammatory response by :
  1. Releasing of vasodilators and chemotaxis chemicals which attract neutrophils and macrophages into the region.
  2. **Opsonization :** the complement causes the cell membrane of the foreign cells to become sticky so they are easy to phagocytize.
- Complement can be activated by either the **alternative** or **classical pathway.**

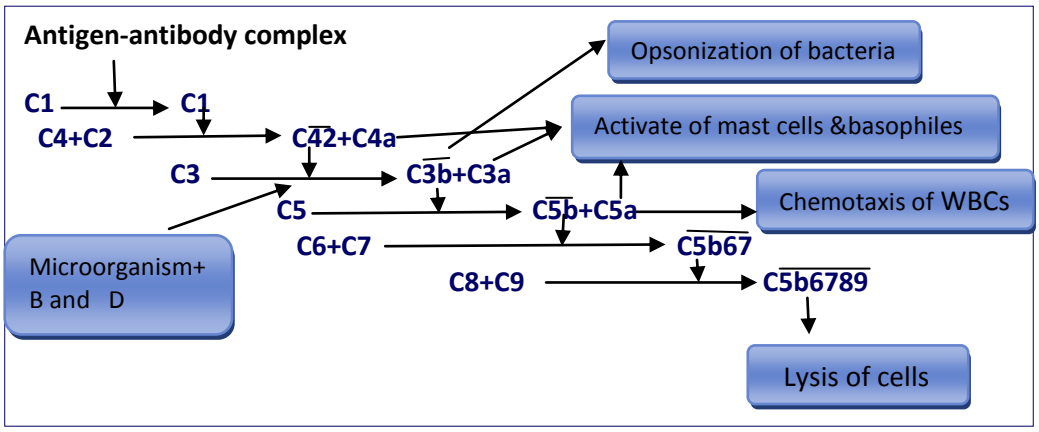


Figure (8.3): Cascade of reactions during activation of the classic pathway of complement. (Guyton A.C. and Hall J.E., Textbook of Medical Physiology . Philadelphia, Saunders, 2015).

1- **Alternative pathway:** is part of innate immunity initiated when complement proteins **C3** becomes activate. Activated C3 can combine with some foreign substances and activate the complement cascade.
2- **Classical pathway:** is part of the adaptive immunity, (figure 8.3).

2- Interferon

- **Interferon** is a small protein that protects the body against viral infection and some forms of cancer.
- Interferon molecules diffuse to nearby cells to bind to their membrane receptors. This binding stimulates the synthesis of protein that interferes with the ability of the viruses to multiply within these still healthy cells.

Pharmacology note: Interferon may play a role in controlling some cancers that are induced by viruses. Interferons activate macrophages and natural killer cells which attack tumor cells. Interferons are produced through genetic engineering in sufficient quantities for clinical uses .They are effective in treating certain viral infections and cancers e.g., **hepatitis c** ,viral disorder that can cause **cirrhosis** and liver cancer and treat of genital warts caused by herpes virus.

Fever

- Fever or high body temperature is a systemic response to invading microorganism.
- Body temperature is regulated by a part of hypothalamus.
- Temperature is set at **37C° (98.6 F°)** but it can be reset upward in response to **pyrogens** (a chemical secreted by WBCs and macrophages when exposed to foreign cells or substances).
- High fever is dangerous because an excess heat scrambles enzymes and other body proteins.

- Mild and moderate temperature fever seems to benefit the body by increasing the metabolic rate of the tissue cells, specially speeding up repair process.

2- Adaptive immunity

Overview

- Adaptive immunity is a specific defense system and functional system that recognizes foreign substances (antigen) and acts to destroy.
- It protects the body from a wide variety of pathogens and abnormal body cells.
- When it fails, some of devastating diseases such as cancer, rheumatoid arthritis, and AID may result.
- There are three important aspects of the adaptive immunity :
  1- **It is antigen specific:** It recognizes and acts against particular pathogens or foreign substances.
  2- **It is a systemic:** the immunity is not restricted to initial infection site.
  3- **It has memory:** It recognizes even stronger attacks on previously encountered pathogens.
- Adaptive immunity may be :

1- Humerol immunity:

- It is due to circulating antibodies **(Ab)** in the body's fluid.
- It is major defense against bacterial infections.

2- Cellular immunity:

- This is mediated by lymphocytes products of high molecular weight called**: Lymphokins**
- It is responsible for delayed allergic reaction and rejection of transplants of foreign tissues.
- It constitutes a major defense against infections by viruses, fungi and few bacteria like: **tubercle bacilli.**

Antigens

- Antigens **(Ag)** are large complex molecules recognized by the body as a foreign.
- Variety of substances can act as antigens including: all foreign proteins, nucleic acids, many large carbohydrates and some lipids. Proteins are the strongest antigens.
- Pollen grains, bacteria, fungi and viruses particles are antigenic because their surfaces bear such foreign molecules.
- **Complete antigens** provoke an immune response and bind with the products of that response (antibodies and sensitized lymphocytes).
- **Incomplete antigens or hatpins** are small molecules that are unable to cause immune response by themselves, but do when they bind to body proteins forming complexes which are recognized as a foreign.

Cells of adaptive immune system

1- Lymphocytes

- Lymphocytes arise from **hematoblast** of red bone marrow.
- They exist in two major types :
  1. ***T-cells*** *arise from lymphocytes that migrate to the* ***thymus****, where they undergo a maturation process of 2-3 days. They are responsible for cellular immunity.*
  2. ***B-cells*** *develop immune-competence in* ***bone marrow*** *and provide humeral immunity.*
- T-cells and B-cells migrate to the lymph nodes, spleen and loose connective tissues, where their encounter with antigens.
- T-cells and B-cells are morphologically indistinguishable and can be identified with special technique.

2- Antigen presenting cells

- Antigens presenting cells (**APCs**) present the antigens to the cells that will deal with these antigens.
- The major types of cells acting as APC are: **dendritic cells** in connective tissues and epidermis, **macrophages** and **B-lymphocytes.**

Macrophages

- Macrophages arise from the monocytes produced in the bone marrow.
- They are widely distributed throughout the lymphoid organs and connective tissues, where they act as phagocytic in the innate defense system.
- Macrophages and other APCs phagocytize pathogens and present part of the antigens on their surface for recognition by T-cells.

Humeral (antibody-mediated) immune response

- Clonal selection of B-cells occurs when antigens bind to their receptors causing them to proliferate.
- The resulting family of identical cells descended from the same ancestor cell is called **a clone.**
- The clone formation is the **primary humeral response** to antigen.
- Most clone members become **plasma cells,** which secrete antibodies.
- Other clone members that do not become plasma cells; become **memory cells,** which are capable of responding to the same antigens at later meeting with them. They are responsible for the immunological memory.
- This later immune response is the **secondary humeral response.**
- B-cells proliferation is clarified in details in figure (8.4).

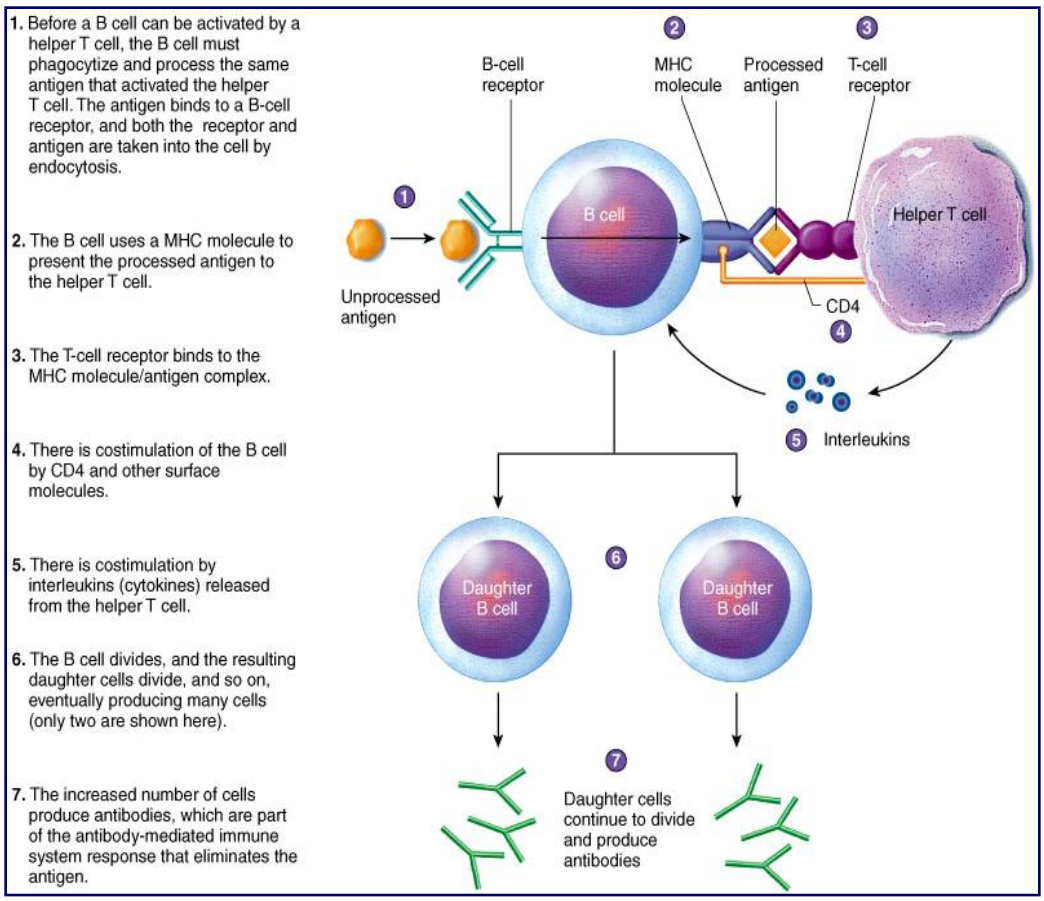


Figure (8.4): Proliferation of B-cells. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

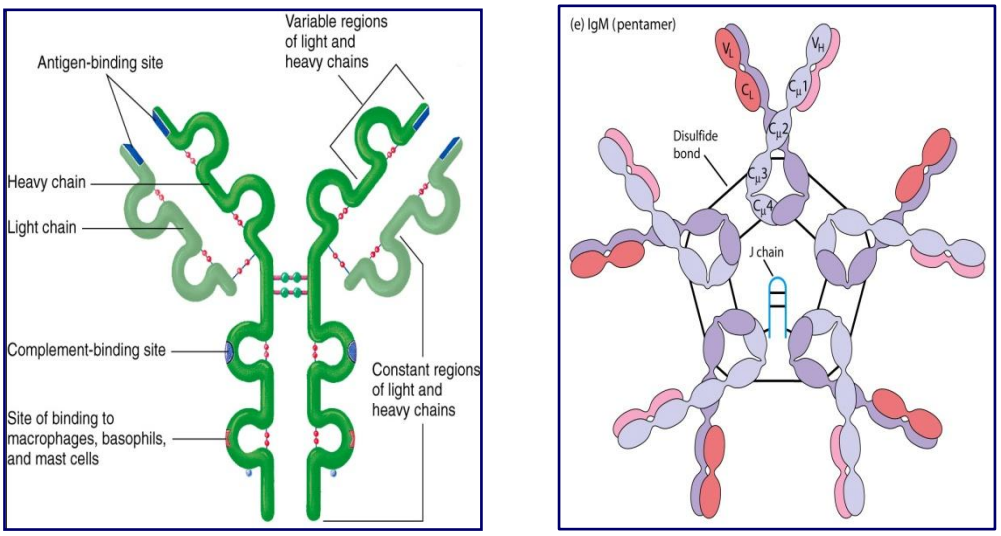
Active and passive humeral immunity

- **Active humeral immunity** is when B cells encounter antigens and produce antibodies against them.
  - **Naturally acquired**: during bacterial and viral infection the person may develop the signs and symptoms of the disease.
  - **Artificially acquired:** by receiving **vaccines** which contain dead or attenuated pathogens .The vaccine provides immunological memory.

- **Passive immunity:** It is when the person receives antibodies from an outside source without having manufactured them. Some examples are:
  - The fetus receives antibodies from the mother, because it does not have a working immune system. Antibodies (being small proteins) can cross in to the fetus.
  - After birth, while the baby's immune system is continuing to be set up, the baby continues to receive the mother's antibodies in her milk.

Antibodies

- Antibodies are **gamma globulins** (immunoglobulin (**Ig**). They are made up of 4 polypeptides (2 long "heavy" chains and 2 short "light" chains) arranged in a **"Y' shape.** (Figure 8.5.a).
- The two arms have **"variable regions",** because there are the **2 receptors** into which a correctly shaped antigen can fit. The rest are **"constant regions"** which have binding sites for the receptors that activate complement proteins and leucocytes, such as phagocytes and basophiles.



(a) **(b)**

Figure (8.5): a: Structure of an antibody, b: Structure of IgM.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- There are **5 types** of antibodies:

1- IgM is the first antibody in the blood produced to fight an infection. Unlike others, it has a star shape from 5 "Y" molecules joined together, giving 10 receptors (figure 8.5.b).Thus it can attack many parasites simultaneously - useful when there is a high pathogen concentration. It does not directly kill pathogens, but:

- It activates complement proteins e.g. **perforin** to kill bacteria.
- It attracts phagocytes and stimulates them to attack the pathogen.
- It clumps (joins) together many pathogens, so they are unable to attack the cells.
- It blocks the pathogen receptors that it uses to enter the cells.

2- IgG replaces IgM during the latter part of an infection (when the concentration of parasites is reduced), because it has a more stable long-lasting molecule. It acts in the same way as IgM.

3- IgA is found in tears and saliva. It prevents parasites from attaching to and entering mucous membranes.

4- IgE stimulates mast cells and basophiles to secrete histamine, starting inflammation.

5- IgD is involved in activating B-lymphocytes.

Primary and secondary responses

1-Primary response

- Primary response is a slow response of the body immunity to a particular pathogen at the first time exposure to this pathogen.
- The immune system is unprepared and activation of B-lymphocytes takes time and clonal selection takes even longer. The pathogen thus has up to 2 weeks, in which to multiply and during this period, the body will be ill or even die. Once antibody production starts up by plasma cells, there will be such a large population of pathogens that they will be very difficult to control.

2-Secondary response

- Secondary response is when the body is next infected by the pathogen (maybe years later), the immune system is prepared.
- The memory cells detecting the pathogen arrival will rapidly divide to form normal plasma cells and start antibody production within a few hours.
- The pathogen is thus eliminated before it has time to establish itself and before the body shows any symptoms of the disease.
- Many diseases, e.g. **yellow fever, measles** and **polio**, the person can only get once in the life, because he will have immunity against future infection.

Cellular (cell mediated) immune response

- **Immunocompetent T cells** are activated to form a clone by binding with a recognized antigen.
- T cells are not able to bind with free antigen, but the antigen must be presented by macrophages and APCs.
- Clonal selection occurs and clone members differentiate into **effector T cells** or **memory cells.**
- There are several different classes of T-cells:
  1- **Cytotoxic(killer)Tcells** are specialized in killing virus infected cell, cancer cell or foreign graft cells .They do their function by binding tightly to the foreign cells and release toxic chemicals called **perforins** which kill the cells.
  2- **Helper T cells** interact with the B cells bound to the antigens. They liberate chemicals (**cytokines**) that enhance the killing activity of the macrophages.
  3- **Regulatory (suppressor)** Tcells release chemicals that suppress the activity of both T and B cells to terminate the immune response after an antigen has been destroyed in order to control immune system activity.

Disorders of immunity

- The most important disorders of the immune system are:
  1-Autoimmune diseases
  2-Allergies
  3-Immunodefeciencies

1- Autoimmune diseases

- Autoimmune diseases occur when the body's self tolerance breaks down and antibodies or T cells attacks the body's own tissues.
- Most forms of autoimmune diseases result from the appearance of hidden self antigens or changes in structure of self antigens and antibodies formed against foreign antigens that resemble self antigens.
- The most autoimmune diseases include:
  1- **Rheumatoid arthritis** which is chronic inflammatory disorder and systematically destroy the joints.
  2- **Multiple sclerosis (MS)** which destroy the white matter (myeline sheaths of the brain and spinal cord).
  3- **Myasthenia gravis** which impairs communications between nerves and skeletal muscles.
  4- **Graves' disease** in which the thyroid gland produces excessive amount of thyroxin.
  5- **Type I diabetes mellitus** which destroys pancreatic beta cells resulting in deficient production of insulin.
  6- **Systemic lupus erythematosus (SLE)** a systemic disease that occurs mainly in young women affect kidneys, heart, lungs and skin.
  7- **Glomerulonephritis**: is a sever impairment of the kidney function.

2- Allergy or hypersensitivity

- The immune system overreacts to even harmless antigens causing tissues destruction.
- In hyperreactivity reactions, the antigen is called **allergen**. The process that eliminates the allergen also produce undesirable side effect such as very strong inflammatory reaction.
- Hypersensitivity reactions are categorized as :
  1- I**mmediate reaction** such as **hay fever** and **anaphylaxis** due to IgE. The symptoms occur within few minutes of exposure to the allergens.
  2- **Delayed reaction** is mediated by T cells .The symptoms take several hours and days to develop such as **contact dermatitis**, **poison ivy cosmetics and drugs.** This type reflects the activity of T cells, macrophages and cytokines.

Pharmacology note: Penicillin is a hapten of a clinical importance. It does not evoke the immune system response. It can breakdown and bind to serum proteins to form a combined molecule that can produce an allergic reaction which commonly produces a rash and fever.

3-Immunodeficiency

- Immunodeficiency is a failure of part of the immune system to function properly.
- Immunodeficiency disorders include many diseases.
- It may be **acquired** due to inadequate proteins in the diets which inhibit proteins synthesis thereby decreasing antibodies. Stress may also depress immune system.
  - **AID** is **a**cquired **i**mmunodeficiency **d**isease by viruses that attack and destroy the T-helper cells.
- Congenital immunodeficiency can involve inadequate B cells formation, inadequate T cells or both as in severe combined immunodeficiency disease (**SCID**).

Transplantation

- Genes that code for the production of **MHC molecules** are called **major histocompatibility complex** genes.
- Histocompatibility is the tissues' ability to get along when tissues are transplanted from one individual to another.
- There are four types of grafts:
  1. **Autografts** are tissue grafts transplanted from one site to another in the same person.
  2. **Isografts** are tissue grafts donated by genetically identical persons (identical twin).
  3. **Allografts** are tissue grafts taken from a person other than an identical twin.
  4. **Xenografts** are tissue grafts harvested from a different animal species.
- Tissue matching tests are done to ensure the best match possible.
- Organ transplantation is followed by immunosuppressive therapy.
- The rejection of the transplanted organ is a real problem. The rejection may be:
  - **Acute rejection** of a graft occurs several weeks after transplantation. It results from a delayed hypersensitivity reaction and cell lysis.
  - **Chronic rejection** may occur at a late time .Immune complexes form in the arteries supplying the graft, blood supply fails and the graft is rejected.

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Chapter nine

Respiratory system 9

Respiratory system

Overview

- **Respiratory system** is the system responsible for equipment of air to the body tissues.
- **Respiration** is a complex process by which living organisms exchange O_2 and CO_2 between the organism and the environment.
- Respiration is important in obtaining energy by oxidation of food substances. The obtained energy is stored in form of high energy phosphate compounds like ATP.
- Respiration includes many processes:
  1- **External respiration:** exchange of air between the external environment and pulmonary alveoli.
  2- **Exchange of gases** between the alveolar air and the blood flowing along the pulmonary capillaries.
  3- **Transport of gases** by the blood.
  4- **Exchange of gases** between the tissue cells and blood in the tissue capillaries.
  5- **Internal respiration:** consumption of O_2 by the cells and production of CO_2.

Functions of respiratory system:

- In addition to the main function of the respiratory system which is **the gas exchange** between the organism and the environment, the respiratory can perform other **non respiratory functions** include the following:
  1- **Protective function:** respiratory system provides a protection against some microorganisms by preventing them from entering the body or by removing them from the respiratory surface. These are done by:
     - Ciliary activity moves the superficial liquid lining layer continuously toward the pharynx.
     - Neutrophils, lymphocytes and alveolar macrophages are present in the alveoli defense against bacteria and viruses.
     - Lungs synthesize immunoglobulin IgA for its own defense.
  2- **Acid –Base balance:** respiratory system can alter blood PH by changing blood CO_2 level so as to keep the blood PH at a level 7.4.This is done through the **chemoreceptors** and **respiratory center integrations.**

3- **Olfaction: the** sensation of smell occurs when air born molecules are drawn into the nasal cavity.

4- **Metabolic functions of the lungs:** these functions include:

- Regulation of blood pressure: endothelial cells of the pulmonary capillary secrete an enzyme called **angiotensin converting enzyme (ACE),** which converts angiotensin I to active angiotensin II**,** a potent vasoconstrictor.
- Lungs synthesize hormones like **serotonin, histamine, prostaglandin E2, F2 and G2** and release them to the circulation under various circumstances such as histamine, bradykinin and prostaglandins are released during asthma attack .Heparin histamine, serotonin and prostaglandinsE2and F2 are released during anaphylactic shock.
- **Bradykinin** , norepinephrine ,serotonin and prostaglandins are degraded and removed by the lungs.

Structural considerations

Respiratory system is composed of the followings:

1- Respiratory airways.
2- Two lungs
3- Chest walls which consist of muscles of respiration such as the diaphragm, external inter costal muscles, internal intercostal muscles and abdominal muscles and the rib cage.
4- Part CNS concerned with the control of respiratory muscles.

Respiratory airways

1- Upper respiratory airways

- Upper respiratory airways have several physiological functions in addition to air conduction, such as swallowing, conditioning of air (warming and humidification) before its passage to the trachea and defense mechanism.
- Upper respiratory airways include many parts: the **external nose**, **nasal cavity and pharynx.**
  - **Nose:** Mucous membrane of the nose is lined by ciliated columnar epithelium containing scattered goblet cells.
  - **Pharynx** is lined by ciliated columnar epithelium with goblet cells. Oropharynx is lined by stratified squamous epithelium.

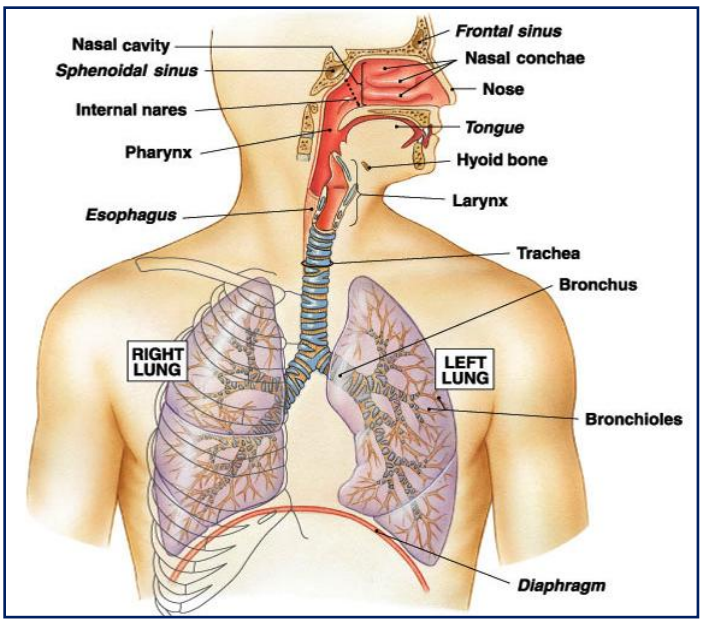


Figure (9.1): Structure of respiratory system. Retrieved from: www.thinglink.com

2- Lower reparatory airways

- The lower respiratory tract consists of larynx, trachea, bronchi and bronchioles, alveolar ducts and alveoli in the lungs. (Figure9.1).
- **Larynx:** upper part of the larynx and vocal cords are lined by stratified squamous epithelium. Lower part is lined by ciliated columnar epithelium.
- **Trachea** is a tube extends from the larynx to the bifurcation in the mediastinum.
  - It is lined with **'C' shaped rings of cartilage**, which prevent the collapse of the tube when the air pressure is reduced during inspiration (otherwise breathing would be impossible).
  - The dorsal surface of the trachea has no cartilage, but instead has **smooth muscles**, which contract to reduce the size of the trachea, (e.g. during coughing or an asthma attack).Smooth muscles relax during swallowing (food passing down the esophagus)and also to expand the trachea during exercise (so air breathed in faster).(Figure 9.2).

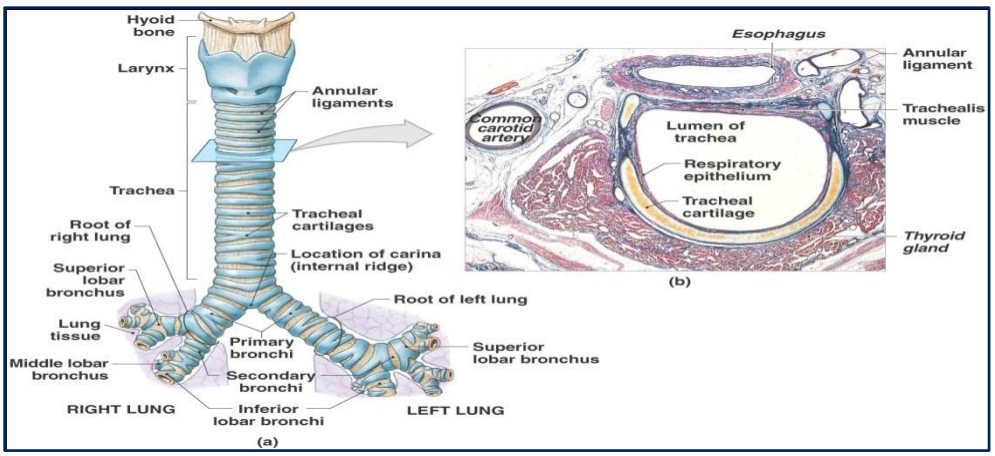


Figure (9.2): Structure of trachea. a: longitudinal section, b: cross section.(Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2010).

Tracheobronchial Tree

- Trachea the **first generation respiratory passageway** is divided into right and left main bronchi, which are the **second generation respiratory passageway.**
- Bronchus in turn is divided into small branches: the **bronchioles** inside the lung.(Figure 9.3).
- **Bronchioles** are further divided into very small bronchioles: the **respiratory bronchioles**.
- There are 20- 25 generations before reaching finally to the **alveolar duct** and **alveoli.**
- The inner surface of the trachea (bronchi and bronchioles) is lined with mucus secreting goblet cells (the mucus traps foreign particles, e.g. dust and parasites) and ciliated cells carrying the mucus to the nose
- **Conducting zone** extend from the trachea to terminal bronchioles which are ciliated for removal of debris. It is anatomically incapable of gas exchange but they work as a passageway for air movement. It constitutes the anatomical dead space.
- **Respiratory zone** extends from the respiratory bronchioles to the alveoli. It is a site for gas exchange. (Figure 9.4).

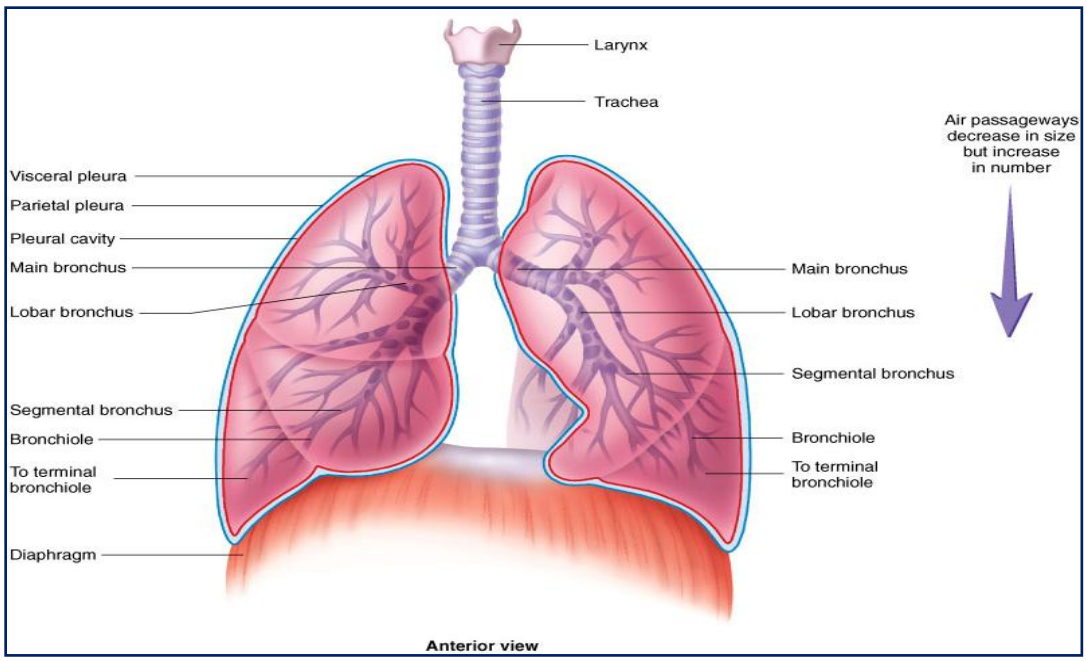


Figure (9.3): Tracheobronchial Tree.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

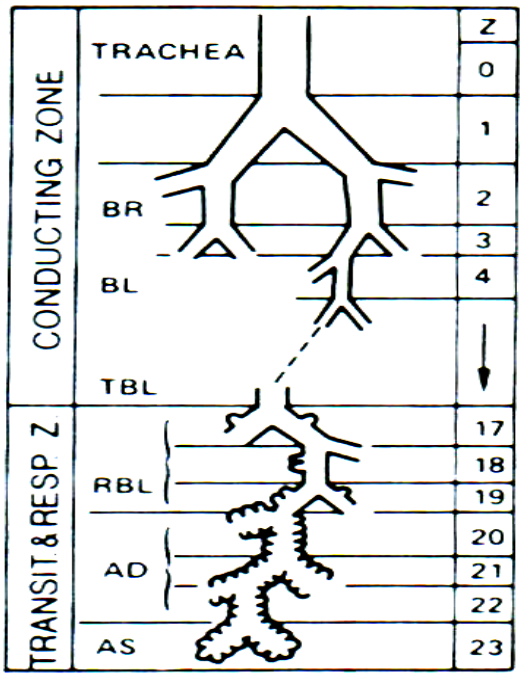


Figure (9.4): Conducting zone and respiratory zone.(LevitzkyM.G.PulmonaryPhysiology.Singapore, McGraw-Hill,Inc.,1995).

The lungs

- Lungs are principle organs of the respiratory system. Each lung is conical shape resting on the diaphragm.
- The right lung is larger than the left lung. The right lung has three lobes while the left lung has two lobes .Each lobe is supplied by a lobar bronchus. The lobes are divided into **bronchopulmonary segments** which are supplied by the segmental bronchi (Figure 9.5).
  - Nine bronchopulmonary segments are present in the left lung.
  - Ten bronchopulmonary segments are present in the right lung.
- The lung is surrounded by a double layered serous membrane called **pleura:**
  - **Parietal pleura** is the outer layer of the pleura
  - **Visceral pleura** are the inner layer, directly connected to the lung.
  - **Pleural cavity** – slit-like potential space filled with 2 ml mucoid **pleural fluid,** which is secreted by parietal pleura.
- **Function of the pleural fluid:**
  1- It keeps the two pleura layers together.
  2- It acts as a lubricant to help the sliding movement between the two layers.
  3- It is essential for the proper expansion and contraction of the lungs.

Pathology note: Pleural effusion: an accumulation of significant quantity of fluid in the pleural cavity .It results from blockage of lymphatics ,increased pulmonary capillary pressure which leads to excessive transudation of fluid into the pleural cavity as in cardiac failure, reduced plasma colloid osmotic pressure in the hyperproteinemia ,and infection or inflammation of the pleura lead to damage the capillary membrane.

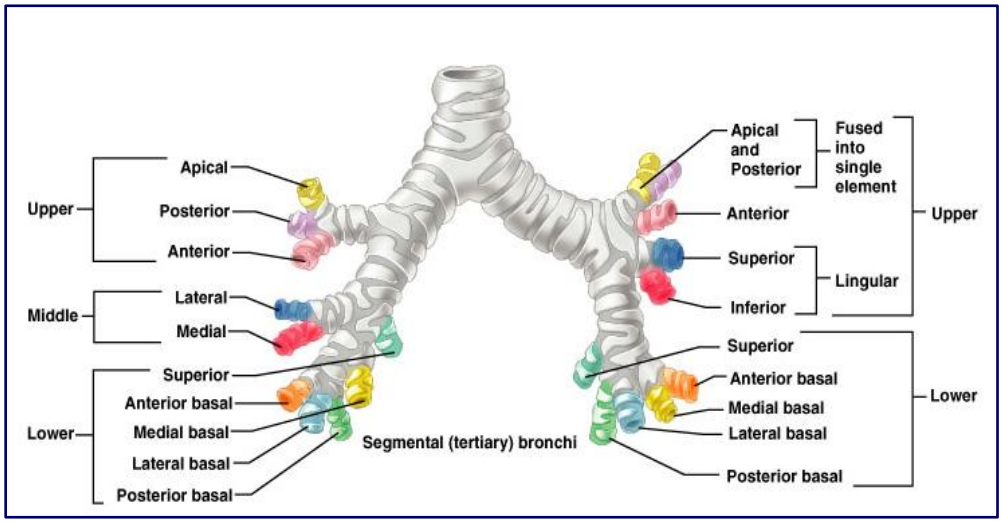


Figure (9.5): Bronchopulmonary segments. Retrieved from www.slideshare.net

Pulmonary ventilation

Overview

- Pulmonary ventilation means inflow and outflow of air between the atmosphere and the lung alveoli.
- Air moves from the region of a high pressure to one of a lower pressure.
- A pressure difference is established by the mechanics of pulmonary ventilation: **inspiration** and **expiration.**
- The muscles cause the lungs to expand and contract.
- Lungs can be expanded and contracted in two ways:
  - **Downward and upward movement of the diaphragm** to lengthen or shorten the chest cavity.
  - **Elevation and depression of the ribs** to increase and decrease the anterior-posterior diameter of the chest cavity.
- Normal quiet breathing is accomplished by the movement of the diaphragm.

Inspiration

- Inspiration is an active process.
- The dome shaped **diaphragm** flattens as it contracts. This increases the height of the thoracic cavity.(Figure 9.6).
- The **external intercostal muscles** contract to raise the ribs .This increases the circumference of the thoracic cavity
- During deep or forced inspiration, additional muscles are recruited**: scalene, sternocleidomastoid and pectoralis minor.**
- Intrapleural pressure becomes more negative (-2.5 − -6)mmHg ,due to increase thoracic volume ,as compare to the atmospheric pressure, therefore air flows into the lung.

Expiration

- Quiet expiration in healthy people is a passive process(no muscle contraction)
- Inspiratory muscles relax
- Relaxing diaphragm moves superiorly (up). (Figure9.6).
- Elastic fibers in lung recoil
- Volumes of thorax and lungs decrease simultaneously, increasing the pressure to slightly positive so the air flows out of the lungs.
- Expiration during the exercise or lung diseases becomes active process requiring use of accessory muscles like internal intercostal muscles and abdominal muscles.

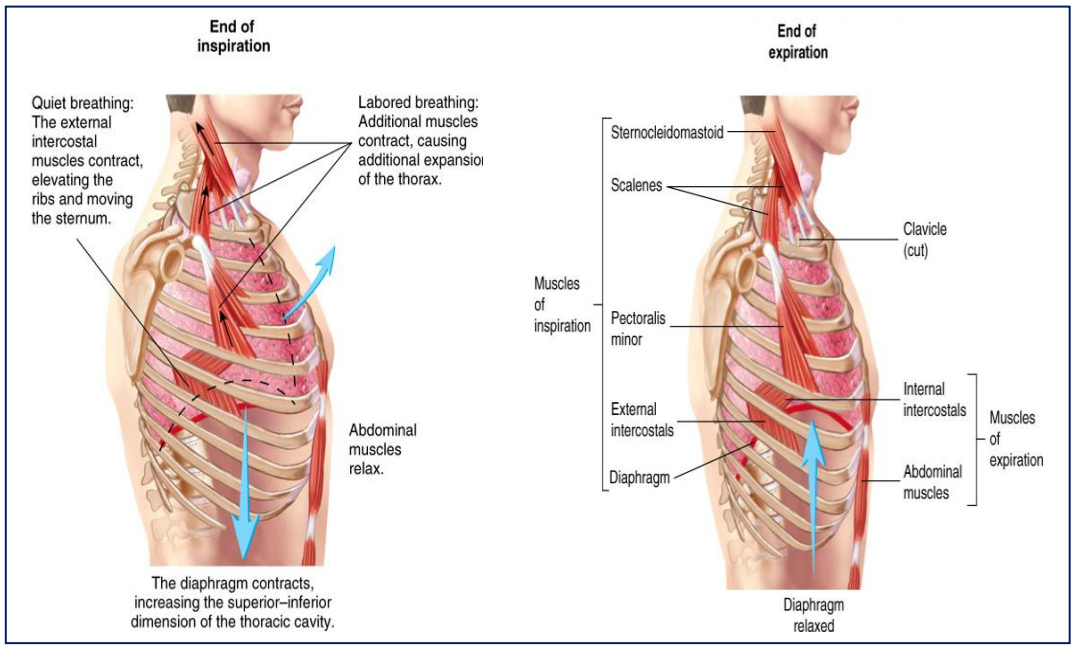


Figure (9.6): Respiratory muscles action during inspiration and expiration. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

Basic concepts of air movement and pressure

Pulmonary pressure

- The lungs have tendency to collapse due to their elastic structures, therefore they collapse like a balloon to expel the air through the trachea when there is no force to keep it inflated.
- The lung floats in the thoracic cavity surrounded by pleural fluid that lubricates movement of the lung in the thoracic cavity.

- **Pleural pressure** is the pressure of the fluid in the thin space between the lung and the chest wall .This is slightly negative, and becomes more negative at the beginning of the inspiration, reaching to about **-6 cm of H_2O** or even **-7.5cm of H_2O** by increasing the force that expands the lung.
  - **During inspiration:** pleural pressure decreases because thoracic volume increases according to the **Boyle's law**. (Table 9.1).
  - **During expiration:** pleural pressure increases because thoracic volume decreases. (Figure 9.7).

- **Atmospheric pressure** is the pressure exerted by the weight of the air in the atmosphere (760 mmHg at sea level)

- **Alveolar pressure:** is the pressure of the air inside the alveoli.
  - If the glottis is open, no air moves into or out of the lungs .The pressure in all parts of the respiratory tree and all the ways to the alveoli is equal to the atmospheric pressure (0 cm of H_2O).
  - **During inspiration** the alveolar pressure falls to (-1cm of H_2O) as compare to the atmospheric pressure. (Figure 9.7).
  - **During expiration,** alveolar pressure slightly increases to +1cm of H_2O to force 0.5 litter of inspired air out of the lung during 2-3 seconds of expiration.

- **Transpulmonary pressure** is the differences between the alveolar pressure and pleural pressure.
  - Pressure differences between the alveoli and the pressure on the outer surface of the lung measures the elastic force of the lung that tends to collapse the lung, which is known as **recoil pressure.**

- Pulmonary pressures and volumes changes during respiratory cycle (inspiration and expiration) are illustrated in figure (9.8).

Table(9.1):Gas laws

Description	Importance
Boyle's law: The pressure of a gas is inversely proportional to its volume at a given volume.	When alveolar volume increases, pleural pressure decreases below atmospheric pressures causing airflow into the lungs ,and vice versa when alveolar volume decreases
Dalton's law: The partial pressure of a gas in a mixture of gases is the percentage of the gas in the mixture times the total pressure of the mixture of gas.	The greater the difference in partial pressure between 2 points, the greater the rate of gas movement.
Henry's law: The concentration of a gas dissolved in a liquid is equal to the partial pressure of the gas over the liquid times the solubility coefficient of the gas.	A small amount of the gases in air dissolves in the fluid lining the alveoli (CO_2 is 24times more soluble than O_2, therefore CO_2exits through the respiratory membrane more readily than O_2 enters).

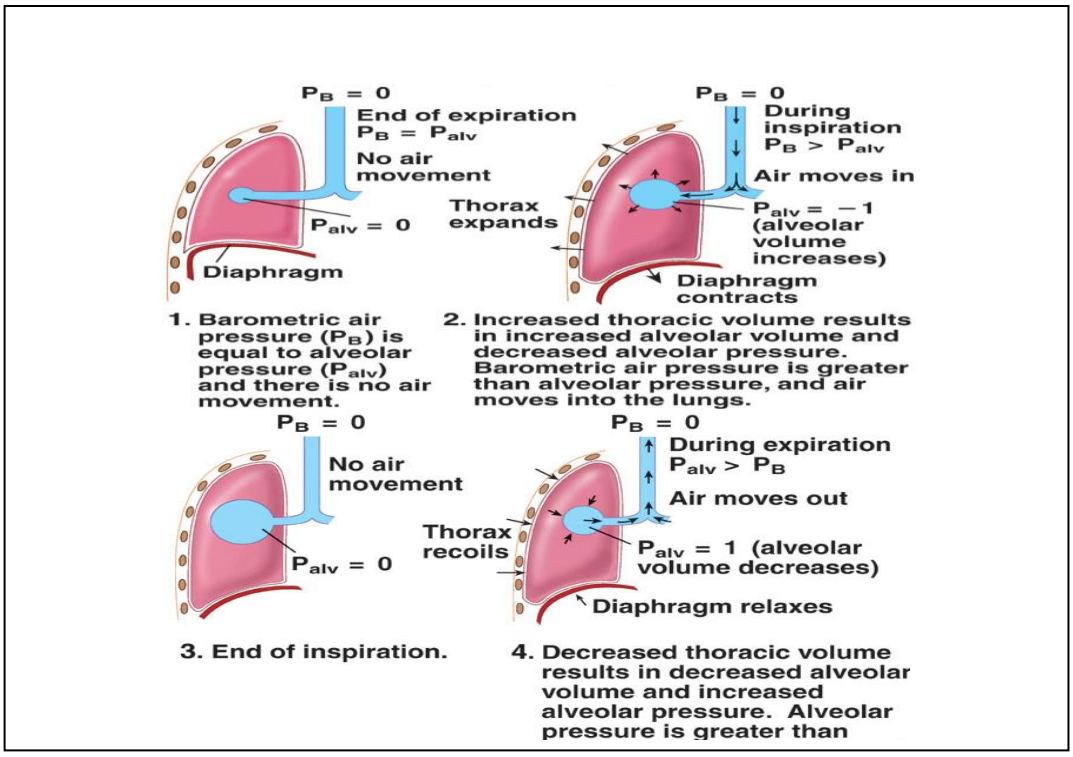
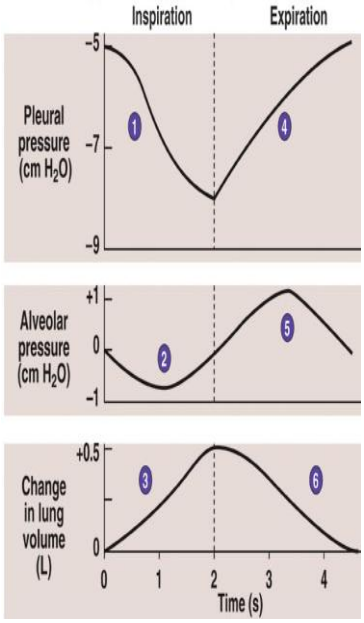


Figure (9.7): Alveolar pressure during inspiration and expiration. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

1-Pleural pressure ↓because thoracic volume ↑

2- As inspiration begins alveolar pressure ↓below the atmospheric pressure because the decreased pleural pressure causes alveolar volume to ↑

3-Air flows into the lungs because the alveolar pressure is lower than atmospheric pressure.



4- Pleural pressure ↑because thoracic volume ↓.

5-As expiration begins alveolar pressure ↑below the atmospheric pressure because the increased pleural pressure causes alveolar volume to ↓

6-Air flows out of the lungs because the alveolar pressure is greater than atmospheric pressure.

Figure (9.8): Pressures and volumes changes during the respiratory cycle. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

Work of breathing

- Work of breathing is pressure volume work performed in moving air into and out of the lungs. Most of this work is performed during inspiration.
- Work of breathing must overcome three sources of resistance encountered during inspiration :

1- **Airway resistance** is generated between air molecules and the walls of conducting airways.

- Most of the total airway resistance comes from the large conducting airways, because they are arranged in series and airflow resistances are **additive.**

$$R_{total} = R1 + R2 + R3 + \text{-----} R_n$$

- Small airways provide little resistance because they arranged in parallel and airflow resistance in parallel are added **reciprocally.**

$$1/R = 1/R1 + 1/R2 + 1/R3 + \text{-----} 1/R_n$$

Pathophysiology note: Airway diameter can be reduced(and increased airway resistance)by number of cases e.g., airway diameters are reduced by smooth muscle contraction and excess inflammatory secretions **in obstructive airway diseases** such as **asthma** and **chronic bronchitis** .As a result work caused by airway resistance increases

Pharmacology note :Many classes of drugs affect large airway diameter by affecting bronchial smooth muscles tone .For example **β_2 –adrenergic agonists** such as **albuterol** which stimulates bronchodilation .Other classes of drugs prevent bronchoconstriction or inhibit inflammation e.g., **steroids anticholinergics ,leukotriene receptors antagonists and lipoxygenase inhibitors** .

2- **Compliance work**: is the work performed to overcome elastic recoil of the lungs. It accounts for the largest proportion of the total work of breathing.

Pathology note: In **emphysema** compliance work is reduced because the destruction of lung tissues and loss of elastic tissues of the lung, but in pulmonary fibrosis, compliance work is increased because the fibrotic tissues require more work to expand.

3- **Tissues resistance**: is generated as the pleural surfaces slide over each other during respiratory cycle .It accounts for a small portion (5%) of the total work of breathing.

Pulmonary compliance

- Pulmonary compliance is a measure of lung dispensability.
- It is defined as the extent to which the lung will expand for each unit increase in transpulmonary pressure. Compliant lungs are easy to distend.

$$C = \frac{\Delta V}{\Delta P}$$

- Total lung compliance of both lungs and thorax is **200ml/cm.H_2O**, every time transpulmonary pressure increases 1 cm.H_2O lung volume will expand 200 ml.
- The diagram which shows the relation between lung volume change and change in transpulmonary pressure refers to **compliance diagram**. (Figure 9.9).
- Compliance diagram shows two curves for expiration and inspiration.

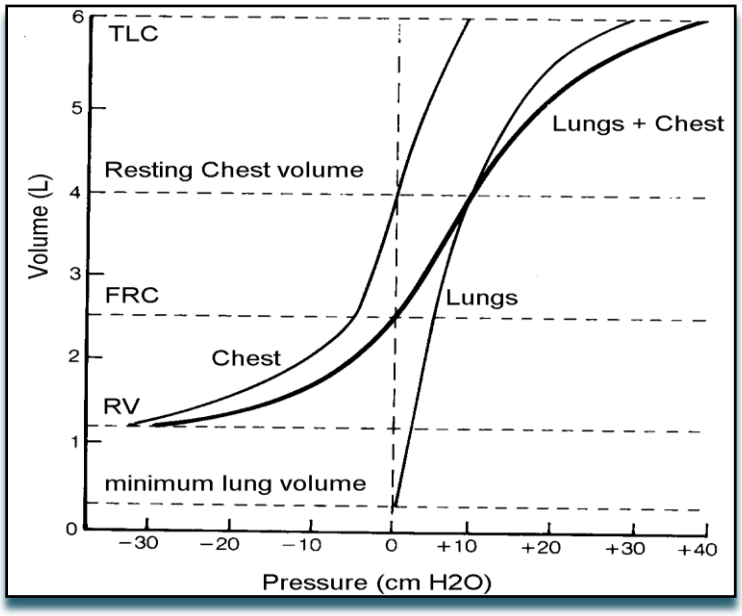


Figure (9. 9): Total lung compliance, TLC: total lung capacity, FRC: functional residual capacity, RV: residual volume.(Brown T.A. Rapid Review of Physiology. Philadelphia, Mosby, 2012).

- **Compliance is determined by:**
  - **Elastic force** which is caused by **elastic tissues** of the lungs (elastin and collagen fibers).It represents **one third** of the total lung elasticity.
  - Elastic force caused by **surface tension** of the fluid that lines the inside wall of the alveoli (caused by air fluid interface).It represents **two thirds** of the total lung elasticity.

Pulmonary surfactant

- Surfactant is a surface tension lowering agent present in the alveolus between the alveolar fluid and air.
- It is a complex mixture of phospholipids (**dipalmitoyl phosphocholine**), proteins and Ca^{2+}.
- It is secreted by **type II alveolar epithelial cells** which are 10% of the surface area of the alveoli.
- **Role of surfactant :**
  - Surfactant reduces surface tension. The surface tension of normal fluid lining the alveoli without surfactant is **50 dynes/cm,** while that for fluid lining the alveoli with normal surfactant is about **5-30dynes/cm**.
  - It reduces compliance resistance of the lungs.
  - It maintains alveolar stability .It prevents over distention or collapse **(atelectasis)** of the alveoli. When there is increase in the diameter of the alveoli, during inspiration, the number of surfactant molecules per unit area decreases and the surface tension increases.
- Surfactant production is decreased by the effect of smoking, histamine and hypoxia while its production increases by hormonal effect (insulin, thyroid hormone and glucocorticoid hormone).

Clinical note: Absence of surfactant from the fluid lining the alveoli especially in some newborn babies known as **respiratory distress syndrome** of newborn babies **(hyaline membrane disease),** which is fetal if it is not treated .That is why the premature babies may be at risk if they are born before the 6-7 months of gestation.

Alveolar ventilation

- Volume of air moves in and out of the lungs with each normal breath .This represents the **tidal volume (V_T).**The typical V_T is about **500ml.**
- There are 12-15 breathes per minute ,therefore the total air volume leaving the lung per minute **(minute ventilation)** ,which is measured as in the following equation :

Minute ventilation= respiratory rate X V_T
= 12 breathes /min X 500 ml
= 6000ml/min

- **Not** all the air that passes the lips reaches the alveolar gas compartment ,where the gas exchange occurs, but about **150 ml** remains behind in the **anatomical dead space** .So the **alveolar ventilation** (air volume entering g the respiratory zone) is calculated as in the following equation :

Alveolar ventilation (AV) =12 breathes /min X(500 ml – 150 ml)
= 4.2 Lit/minute

- Alveolar ventilation represents the fresh inspired air for gas exchange.

Lung volume and capacities

Overview

- The way to study the pulmonary ventilation is known **spirometry,** which is done by recording the volume of air moved into and out of the lungs. The device which is used to study the lung volumes is the **spirometer, while** the record is the **spirogram.**
- Lung volumes and capacities are divided into two types
  1. **Static lung volumes and capacities**
  2. **Dynamic lung volumes and capacities.**
- There are normal physiological differences in lung volumes and capacities, e .g; they are less in women than those in men in about 20-25%.They are greater in large and athletic people than in small asthenic people.

Clinical note: Lung volumes tend to decease in **restrictive lung diseases** (e.g., **pulmonary fibrosis**) because of limitations of pulmonary expansion and they tend to increase in **obstructive lung diseases** (e.g., **emphysema**) as a result of increased compliance.

Static lung volumes and capacities (figure 9.10)

- Static lung volumes are not changed with time. They include the following :
  1- **The tidal volume (TV):** The volume of air inspired or expired with each normal breath (500ml).
  2- **The Inspiratory Reserve Volume (IRV):** The extra air volume that can be inspired forcefully after inspiration of normal tidal volume.(3000 ml).
  3- **The Expiratory Reserve Volume (ERV):** The extra amount of air that can be expired forcefully after the end of normal tidal expiration.(1100ml).
  4- **The Residual Volume (RV):** Air volume remaining in the lungs after the most forceful expiration. (1200ml).

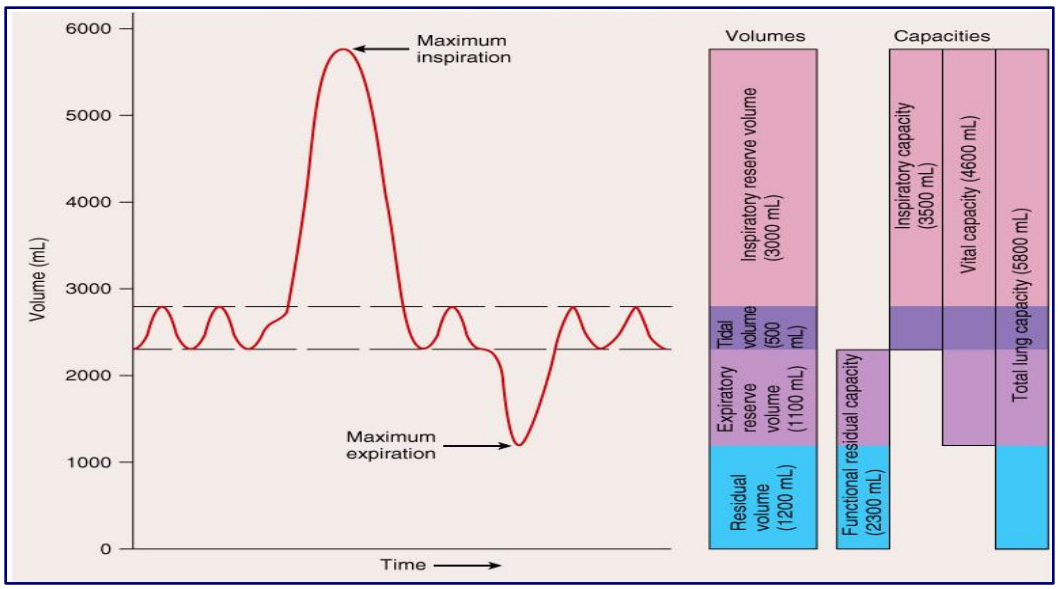


Figure (9.10): Static lungs volumes and capacities. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

- Two or more of these volumes together are called: **pulmonary capacities.**

1- The Inspiratory Capacity(IC): amount of air that can be breathed beginning at the normal expiratory level and distending the lung to the maximum amount (3500ml).

IC=TV+IRV

2- The functional Residual Capacity (FRC): amount of air remaining in the lungs at the end of normal expiration. (2300ml).

FRC=RV+ERV

3- Vital Capacity (VC): maximum amount of air that can be expelled from the lung after first filling the lungs to their maximum extent then expiring to the maximum extent. (4600ml).

VC=TV+IRV+ERV

4- The Total Lung Capacity (TLC): The maximum volume which lungs can be expanded with the greatest possible inspiratory effort.(5800 ml).

TLC=TV+IRV+ERV+RV
TLC=VC+RV

Clinical note: There are two major categories of respiratory diseases, which can alter the dynamic lung volumes:

Chronic Obstructive Pulmonary Diseases (COPD): the diseases that interfere with airflow. They are characterized by increased airway resistance to air flow caused by excessive secretion or increased contraction of bronchial smooth muscle.

Asthma: is a disease characterized by increased constriction of the bronchi and bronchioles in response to various stimuli causing air narrowing and decrease ventilation efficiency. The symptoms include rapid shallow breathing wheezing, cough and shortness of breath.

Chronic bronchitis: is the inflammation of the bronchioles causing swelling of the walls of the bronchioles and bronchi and reducing air passage through them.

Emphysema results in damage to the alveoli, so that the walls become less elastic (taking longer to inflate and deflate).

Chronic Restrictive Pulmonary Disease (CRPD): is a chronic disorder that causes a decrease in lung's ability to expand. It is characterized by reduced lung volume. The most common restrictive lung diseases are **interstitial lung fibrosis** including sarcoidosis granulomatous disorder and extrapulmonary restrictive lung diseases including **scoiliosis.**

Dynamic lung volumes

- Dynamic lung volumes quantify the time rate of gas flow along the airways.
- They are of a clinical importance in the assessment of airways resistance, specifically during expiration, therefore they are of interest in patients with **COPD** like :**asthma** ,**emphysema** ,**chronic bronchitis .**These are:

1- **Forced Vital Capacity (FVC):** The maximum air volume which can be expired forcefully after maximum inspiration.(Figure 9.11).

2- **Forced Expiratory Volume at the first second of expiration (FEV_1):** Maximum air volume which can be expired forcefully at the first second of expiration after maximal inspiration.

3- **FEV1%:** Is the ratio of air expired forcefully at the first second related as a percentage of total amounts of air expired during FVC.

FEV1%=FEV1/FVC X 100

4- **Peak Expiratory Flow (PEF):** is the maximal flow rate which is achieved during force expiration. (Figure 9.11).

5- **Maximum Voluntary Ventilation (MVV):** is the maximal air volume which can be expired by breathing deeply and rapidly with maximal voluntary effort for a short time.

6- **Forced Expiratory Time (FET):** is the time required to expire all air in the lung by using the force.

7- **Estimated Lung Age**: is the age when the person pulmonary function is normal.

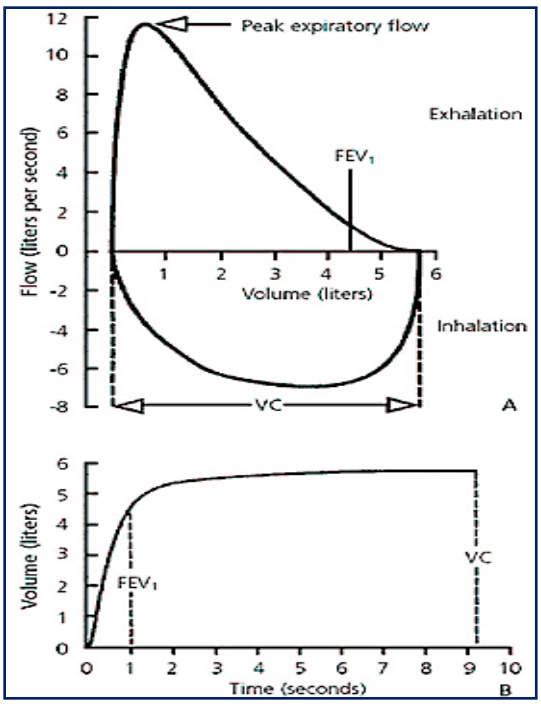


Figure (9.11):a: Expiratory flow curve showingPEF ,b:expiratory volume to showing FEV1and FVC.(Levitzky M.G. Pulmonary Physiology . Singapore,McGraw-Hill,Inc.,1995)

Pathology note: FEV1 and **FVC** are reduced in lung diseases and the degree of reduction depends on the nature of the diseases. In **obstructive diseases** the expiratory volumes are reduced because of airway narrowing, therefore FEV1 is reduced more than is FVC and FEV1% is reduced. In **restrictive diseases,** inspiration is limited by noncompliance of the lung leading to limited expiratory volumes. FVC is reduced more than is FEV1 resulting normal FEV1% or even increased, because the elastic recoil of the lung is preserved.

Gas exchange

Overview

- Gas exchange across the respiratory membrane occurs by **diffusion.**
- Respiratory gases diffuse from area of high partial pressure to area of low pressure.
- **Partial pressure**: is the pressure of each gas alone, which is used to express the concentration of the gas.
  - Partial pressure of O_2 and CO_2 are designed as **PO_2** and **PCO_2** respectively
  - Partial pressure of a gas is calculated by multiplying its **fractional concentration by the total pressure**, for example the percentage of O_2

is 21% of the total pressure 760 mmHg (atmospheric pressure), therefore thePO_2 is **160 mmHg**

- Atmospheric air ,alveolar air and expired air have different concentrations of gases because:
  1- Air is humidified before it reaches the alveoli.
  2- A constant diffusion of O_2 from the alveoli into the blood, while CO_2 is constantly diffusing from the pulmonary blood to the alveoli.
  3- The alveolar air is only partially replaced by atmospheric air.

Diffusion of gases through the respiratory membrane

- There are about 300 millions alveoli in the two lungs.
- The alveolar walls are thin ,within them is a solid network of interconnecting capillaries, and blood flows in the alveolar walls as a **sheet**
- Gas exchange occurs through the membrane of all the terminal portions of the lungs (***not only the alveoli***).These membranes are known the **respiratory membrane or** the **pulmonary membrane**.

Respiratory membrane

- The respiratory membrane is composed of the following layers(figure9.12):
  1- A layer of fluid lining the alveoli that contains surfactant.
  2- The alveolar epithelium
  3- An epithelial basement membrane.
  4- A thin interstitial space between the alveolar epithelium and the capillary membrane.
  5- A capillary basement membrane that, in many places, fuses with epithelial basement membrane.
  6- The capillary endothelial membrane.
- The membrane is very thin, about 0.6 µm as average, and total surface area is70 m^2 in normal adult .The total amount of blood in the lung capillaries is 60-140 ml, therefore the gas exchange is very rapid.
- The diameter of pulmonary capillaries is 5 µm, so the RBCs must squeeze through them (RBC touches the membrane) and O_2, CO_2 dot need to pass through the plasma.

- **Factors affecting the rate of diffusion through the respiratory membrane**
  1- The thickness of the membrane.
  2- The surface area of the membrane.
  3- The diffusion coefficient of the gas in the substance of the membrane.
  4- The pressure differences between the two sides of the membrane.

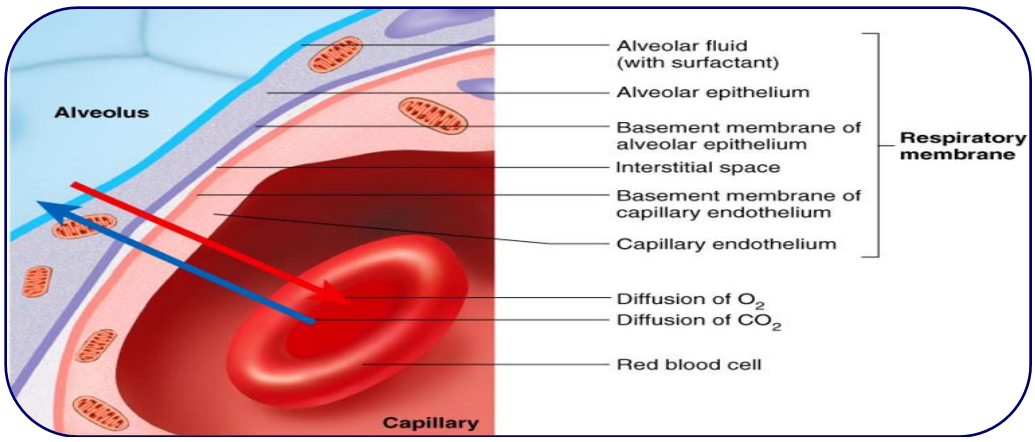


Figure (9.12): The respiratory membrane. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

Diffusing capacity of the respiratory membrane

- Diffusing capacity is the volume of gas that is able to diffuse across the respiratory membrane in 1 minute with pressure gradient across the membrane of 1 mmHg.
- Exchange of O_2 is normally so efficient that is **perfusion limited** (***the amount of O_2 that enters the arterial circulation is limited only by the amount of blood flow to the lung***).
- The diffusing capacity of the lung for CO_2 is 20 times greater than that for O_2.At rest the diffusing capacity for O_2 is 21ml/min/mmHg, while its 440ml /min/mmHg for CO_2.
- All factors that affect diffusion through the respiratory membrane can affect the diffusing capacity.
- The diffusing capacity for O_2 increases during exercise.

Perfusion -limited and diffusion-limited gas exchange

- Perfusion -limited gas exchange: diffusion can be increased only if blood flow increases, e.g., O_2 uptake under normal condition.
- Diffusion- limited exchange: diffusion continues as long as pressure differences exist across the respiratory membrane, e.g., O_2 diffusion during heavy exercise at high altitude.

Pulmonary blood flow

- The pressures in the pulmonary circulation are low compared with those of systemic circulation.
- In the **upright position** ,perfusion in the apices of the lung is different from that of the bases because the effects of gravity, therefore there are **three zones** of pulmonary blood flow:

1- Zone 1(top of the lung)

- It has **no** blood flow because alveolar pressure is greater than artery pressure.
- It can occur when pulmonary artery pressure is decreased (hemorrhage) and when alveolar pressure is increased.

2- **Zone 2(middle of the lung)**
   - It has an intermittent blood flow that occurs during systole (the artery pressure is greater than the alveolar pressure) while during diastole (the artery pressure is less than the alveolar pressure).
3- **Zone 3(base of the lung)**
   - It has a continuous blood flow because pulmonary capillary pressure remains greater than alveolar pressure during the cardiac cycle.

- In the **lying position,** blood flow in normal person blood flow is **continuous** because all areas of the lung at the same level to the heart.

Alveolar ventilation and pulmonary circulation perfusion

- In normal conditions there is match between the alveolar ventilation and alveolar blood flow .This maintained the effective gas exchange between the air and the blood. This concept is called **ventilation –perfusion ratio (AV/Q)**
- Increased alveolar ventilation or increased pulmonary circulation leads to increase gas exchange.
- The balance between the alveolar ventilation(AV) and blood flow(Q) can be disrupted in 2 ways:
  1- Alveolar ventilation exceeds the body's ability to pick up oxygen .This occurs because of inadequate cardiac output due to heart attack.
  2- Alveolar ventilation may be not great enough to provide O_2, e.g. bronchial **asthma.**
- **Shunted blood:** The blood which is not completely oxygenated.
- There are two types of shunts: **anatomic** and **physiologic shunt.**
- **Anatomic shunt**: occurs when the blood would normally go to the lung is diverted elsewhere, such as **fetal blood flow.**
- **Physiologic shunt**: when the blood supplying the lung is not involved in gas exchange such as **bronchial arterial circulation** and in pathologic state, the **pneumonia** and **pulmonary edema.**

Oxygen and carbon dioxide transport in the blood

Overview

- Oxygen diffuses through the respiratory membrane into the blood.
- In the blood O_2 combines reversibly with hemoglobin (98.5%) and smaller amount dissolves in the plasma (1.5%).
- Oxygen is transported by Hb from pulmonary capillary to the tissues capillaries where some O_2 is released.
- The released O_2 diffuses from the blood to the tissue cells to be used in **aerobic respiration.**
- Carbon dioxide is produced during aerobic metabolism and diffuses from the cells into the tissue capillaries.
- In the blood CO_2 is transported in three ways:
  1- Dissolved in plasma.
  2- In combination with Hb.
  3- In form of bicarbonate.

Partial pressure gradient of oxygen and carbon dioxide

1- Oxygen partial pressure gradient

- Oxygen moves from the alveoli, where PO_2 is 104mmHg into the blood where PO_2 is 40 mmHg.
- In the blood the PO_2 decreases to 95mmHg due to the mixing with deoxygenated blood.
- Oxygen moves from the tissue capillaries (PO_2=95mmHg) into the tissue where PO_2 is 40 mmHg.(Figure 9.13).

2- Carbon dioxide partial pressure

- Carbon dioxide of the tissue (PCO_2 is 45 mmHg) moves into the tissue capillaries (PCO_2 is 40 mmHg). (Figure 9.13).
- Carbon dioxide moves from the capillaries (PCO_2 is 45mmHg) to the alveoli (PCO_2 is 40mmHg).

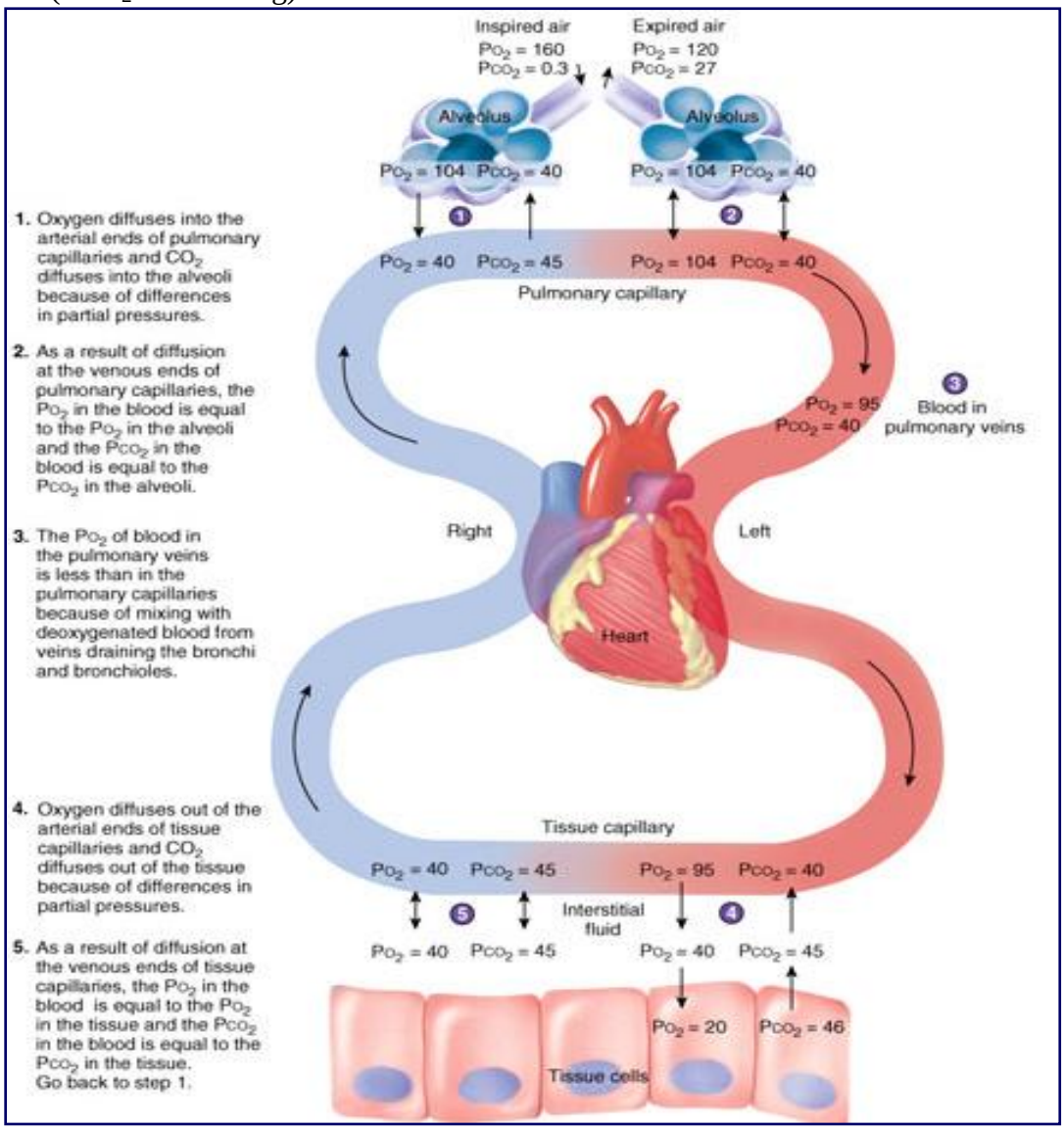
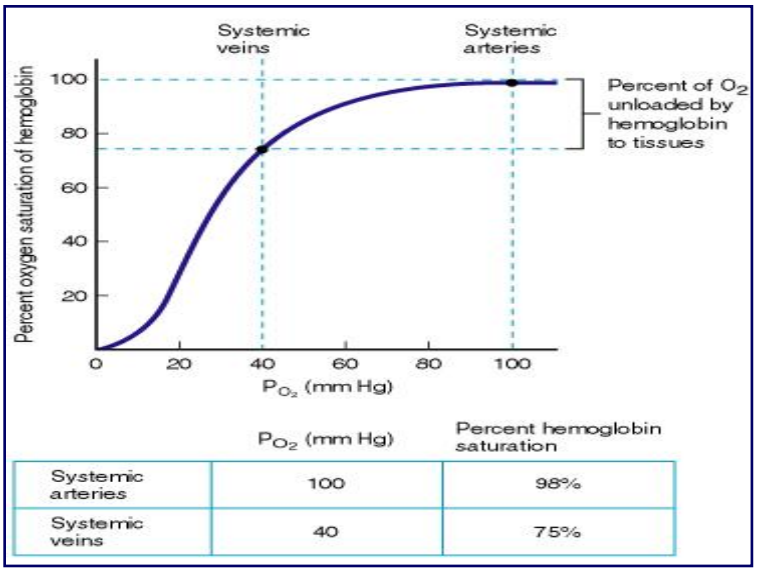


Figure (9.13): Gas exchange according partial pressure gradient of O_2 and CO_2. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

Oxygen-Hemoglobin dissociation curve

- **Oxygen-Hb dissociation curve** is to describe the saturation percentage of Hb in the blood at different blood level PO_2 values.
- Hemoglobin is 100% saturated with O_2 if four O_2 molecules are bound to each Hb molecule. Hb is 50% saturated with O_2 if two O_2 molecules are bound to each Hb molecule.
- Hemoglobin is 98% saturated when PO_2 in blood leaving pulmonary capillaries is 104mmHg.Decrease in PO_2 in pulmonary capillaries have small effect on Hb saturation .Even if PO_2 decreases to 60mmHg, the Hb is still 90% saturated. Hb is very effective in picking up the O_2 in the lungs.
- Hemoglobin saturation is 75% when the PO_2 of blood leaving the tissue capillaries is 40 mmHg, because 23% of O_2 picked up in the lung is released and diffuse into the tissues.(Figure9.14).In the tissues , a small change in PO_2 results in large change in Hb saturation



	P_{O_2} (mm Hg)	Percent hemoglobin saturation
Systemic arteries	100	98%
Systemic veins	40	75%

Figure (9.14): Oxygen-Hb dissociation curve. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

The Bohr effect

- The effect of of PH on the oxygen-Hb dissociation curve is called the **Bohr effect.**
- Based on the fact that when O_2 binds to Hb, certain amino acids in the Hb molecule release H^+ ions [$Hb + O_2 \leftrightarrow HbO_2 + H^+$]
- An increase in H^+ (a decrease in pH) pushes the reaction to the left, causing O_2 to dissociate from Hb
- Hb affinity for O_2 is decreased when H^+ ions bind to Hb, therefore O_2 is released from Hb
- H^+ concentration increases in active tissues, which facilitates O_2 unloading from Hb so that it may be utilized by the active tissues

- **In the tissues,** factors such as a decreased PH (Bohr effect) ,increased PCO_2 and increased temperature cause the O_2-Hb dissociation curve shifts to the right (***an increased release of O_2***),(Figure9.15.a).
- **In the lungs** ,an increased PH, a decreased PCO_2 and decreased temperature cause the O2-Hb dissociation curve shifts to the left***(an increase in Hb ability to pick up O_2)***,(Figure 9.15.b).
- The substance **2, 3-biphosphoglycerate** binds to Hb and reducing its affinity for O_2.
- Fetal Hb has a greater affinity for O_2 than does maternal Hb.

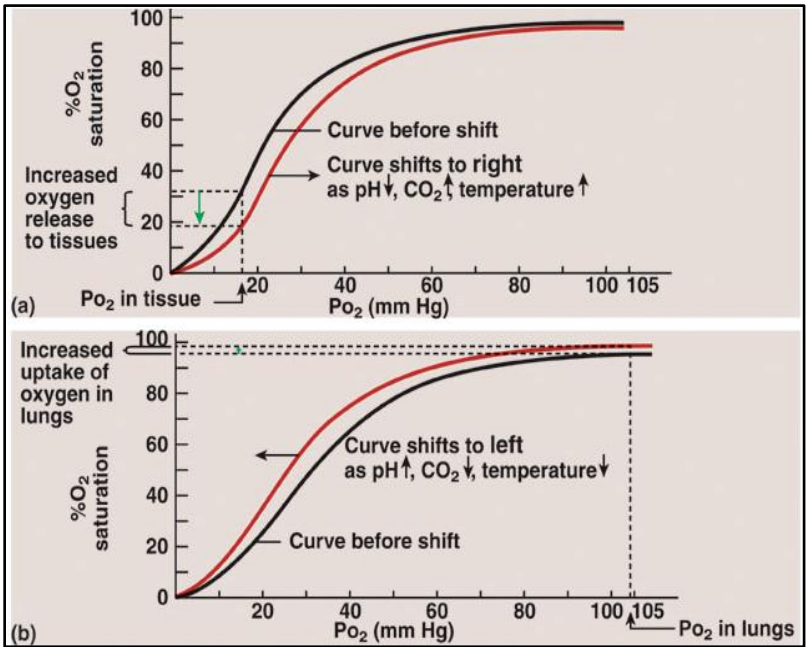


Figure (9.15): Factors affecting O_2-Hb dissociation curve to (a): shift to right in the tissues and (b): shift to left in the lungs. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

Transport of Carbon dioxide

- Carbon dioxide is byproduct of cellular respiration .It diffuses across the cell and capillary membranes into the blood and enters the RBCs.

1- In the RBCs, CO_2 is combine with water to form H_2CO_3,in the presence of **carbonic anhydrase** .**70%** of CO_2 is transported as HCO_3^-

- The H_2CO_3 dissociates to form bicarbonate HCO_3- and H^+.
- Chloride shift : Cl^- enters the RBCs in exchange for HCO_3^- ,which travels freely in blood to the lung.
- In the pulmonary capillary HCO_3^- enters RBCs in exchange for Cl^- and converted to CO_2 to expire. (Figure 9.16).

2- Approximately **20%** of CO_2 is transported in the blood as **carbaminohemoglobin,** by binging to amino groups of Hb. This causes a right –shifting of O_2-Hb dissociation curve.

3- Approximately **10%** of CO_2 is transported as dissolved CO_2.

Halden effect :

- **Halden effect** illustrates the role of O_2-Hb reaction in CO_2 transport .
- Deoxygenated Hb binds more CO_2 than oxyhemoglobin and form carbaminohemoglobin .Whenever the Hb is oxygenated it diplaces CO_2 from its combination.
- Halden effect occurs because (deoxygenated Hb has more affinity for CO_2 and so there is an increased pickup of CO_2 from the tissues,while oxyhemoglobin has less affinity for CO_2)and ,so CO_2 is released from the blood to the alveoli.
- The importance of Halden effect is to doublicat the CO_2 amount released from the blood into the lungs and to doublicate the CO_2 pick up from the tissues.

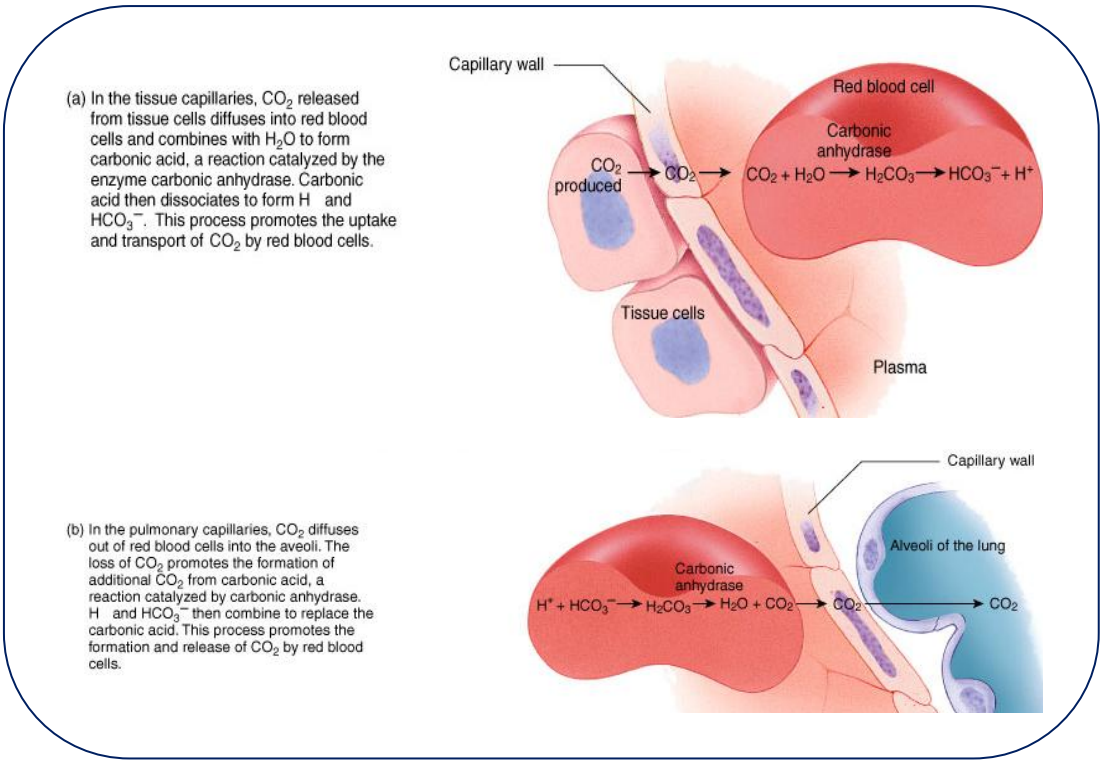


Figure (9.16): Carbone dioxide exchange, a: in the tissues, b: in the lung. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

Regulation of respiration

- The basic rhythm of respiration is controlled by two groups of neurons located in the in the **medulla oblongata :**

1- Two dorsal respiratory groups:

- They are located bilaterally in the dorsal part of the medulla oblongata.
- They control the basic rhythm of respiration which is accomplished by neurons that spontaneously generate action potential which stimulate respiratory muscles.

2- Two ventral respiratory groups :

- They are located bilaterally in the ventral part of the medulla oblongata.
- They stimulate the expiratory muscles which are important in the forced expiration.

- **Pneumotaxis center :**
  - Groups of neurons located in the **pone.**
  - It inhibits inspiration, limiting the size of TV.
- Controlling of respiratory muscles is voluntary and made by the neural communications between **higher brain center** and **brain stem** as in holding of breath, emotional upset and irritant that alter normal breathing pattern.

Chemoreceptors

1- Peripheral receptors

- They are located in the **carotid artery** and **aortic bodies.**
- They detect the chemical concentration of blood and cerebrospinal fluid (changing level of CO_2, O_2 and PH).
  - They are sensitive to low arterial O_2 concentration.
  - Low arterial PH ($\uparrow H^+$) occurs when CO_2 level increases.
  - Decreased O_2 causes increase in ventilation **(hyperventilation**).

2- Central chemoreceptors

- They are located on the **ventral surface** of the **medulla**.
- They keep the PCO_2 within normal by having indirect response to the amount of CO_2 dissolved in cerebrospinal fluid.
- High PCO_2 (**hypercapnia)** and ↓PH stimulate **hyperventilation.**

Chemoreceptors reflexes

- Chemoreceptors maintain normal level of arterial CO_2 through chemoreceptors reflexes.
- Increased CO_2 lead to increase H^+ (↓PH) resulting in stimulation of chemoreceptors.
- Decreased PH is caused by exercise, breath holding and other metabolic causes.
- **Herring-Breuer reflex**: the reflex that limits the degree of inspiration and prevents over inflation of the lung.

Hypoxia

- **Hypoxia** refers to insufficient O_2 supply to the tissues, while **hypoxemia** refers to insufficient O_2 in the blood which may be caused by high altitude, anemia, CO poisoning pulmonary edema and fibrosis.
- **As a response to hypoxemia :**chemoreceptors increase their firing ,control breathing centers regulate the respiratory rate (tachypnea)and heart rate (tachycardia) and cause large TV .All these events result in increased oxygenation at the pulmonary membrane and increase delivery of O_2 to the tissues.

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Chapter 10

Urinary system 10

Urinary system

Overview

- The urinary system consists of **two kidneys** , a single midline **urinary bladder, two ureters** which carry the urine from the kidney to the urinary bladder and **a single urethra** which carries the urine from the bladder to the outside of the body(figure 10.1).
- The kidneys make up the main purification system of the body. They control the composition of the blood by removing the waste products and conserving the useful substances.
- The kidneys are the major excretory organ among other excretory organs of the body: skin, liver, lungs and intestine.

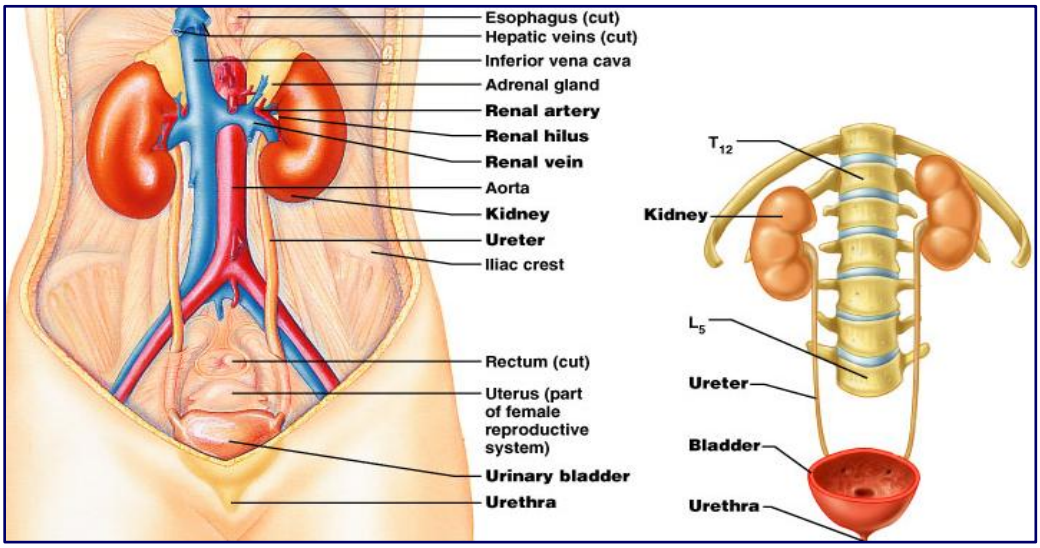


Figure (10.1): Structure of the urinary system. (Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2006).

Functions of the kidneys

1. Excretory functions

- Kidneys filter blood producing large volume of large molecules (proteins , RBCs)are retained in the blood ,small molecules and ions enter the filtrate.
- Most of filtrate volume is reabsorbed back into the blood.
- Metabolic waste, toxic materials and excess ions remain in a small volume of filtrate.
- Additional waste products are secreted into the filtrate resulting urine formation.

2. Regulatory function

- Regulation of blood volume and pressure by controlling the extracellular fluid volume (ECF) in the body by producing either a large volume of diluted urine or small a small volume of concentrated urine.
- Regulation of concentration of solutes in the blood by regulation of concentration of major ions (Na^+,Cl^-,HCO_3^-,HPO_4^{2-}).
- Regulation of PH of ECF by secreting variable amounts of H^+ .
- Regulation the synthesis of RBCs by secreting of erythropoietin hormone.
- Vitamin D synthesis therefore regulates Ca^{2+} blood level.

Structural considerations

- The kidneys are paired of bean shaped organs that lie behind peritoneal lining of the abdominal cavity.
- Each kidney is surrounded by a thin capsule to resist stretch and limit the swelling.
- The renal artery, renal vein, renal lymphatic and ureter enter and leave the kidney through a helium on the midline concave surface of the kidney.

Internal structure of the kidneys

- There are two distinguished layers inside the longitudinal section of the kidney .The outer layer the **cortex** and the inner layer the **medulla**.
- The medulla is made up of series of cone shape **pyramids** which project to the **minor calyces**. (Figure 10.2).
- Minor calyces open into **major calyces** which open into **renal pelvis**.
- The renal pelvis leads to the ureter which drains into the bladder.

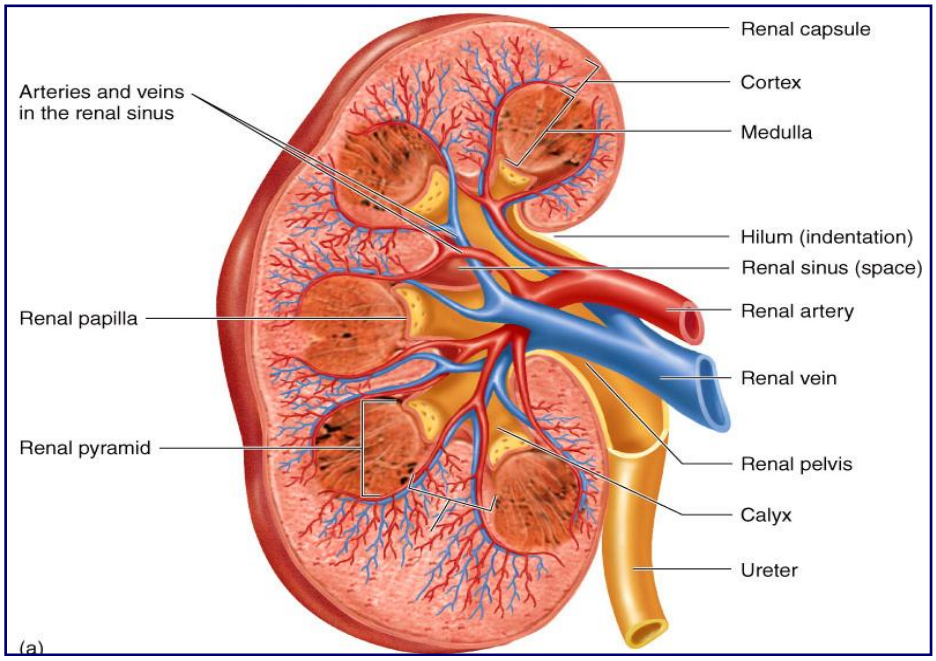


Figure (10.2): Longitudinal section of the kidney.(Marieb E.N .Essential of Human Anatomy and Physiology . San Francisco, Pearson Education,Inc.,2012).

Structure of the nephron

Overview

- The functional unit of the kidney is the **nephron** (where the blood is filtrated)
- Nepheron is blind end tubules running from the **Bowman's capsule** into the renal pelvis.(Figure 10.3).
- There are about one million nephrons in each kidney.
- The nephron begins at the **glomerulus** ***(comprises a tuft of glomerular capillaries with the Bowman's capsule)***. (Figure 10.5 .a**)**.
- The capillaries are derived from the **afferent arterioles** and drain into the **efferent arterioles.**
- Many branches of capillaries of capillaries form cluster that invaginates into the Bowman's capsule (Figure 10.5.a**)**.
- The glomerulus and the Bowman's capsule form the **renal corpuscle.**
- The materials leave the blood in the glomerulus and enter the Bowman's capsule through the **filtration membrane**.
- Fluid from Bowman's capsule flows into the coiled segment **(proximal convoluted tubule)**, then into **loop of Henle**, down into the medulla.

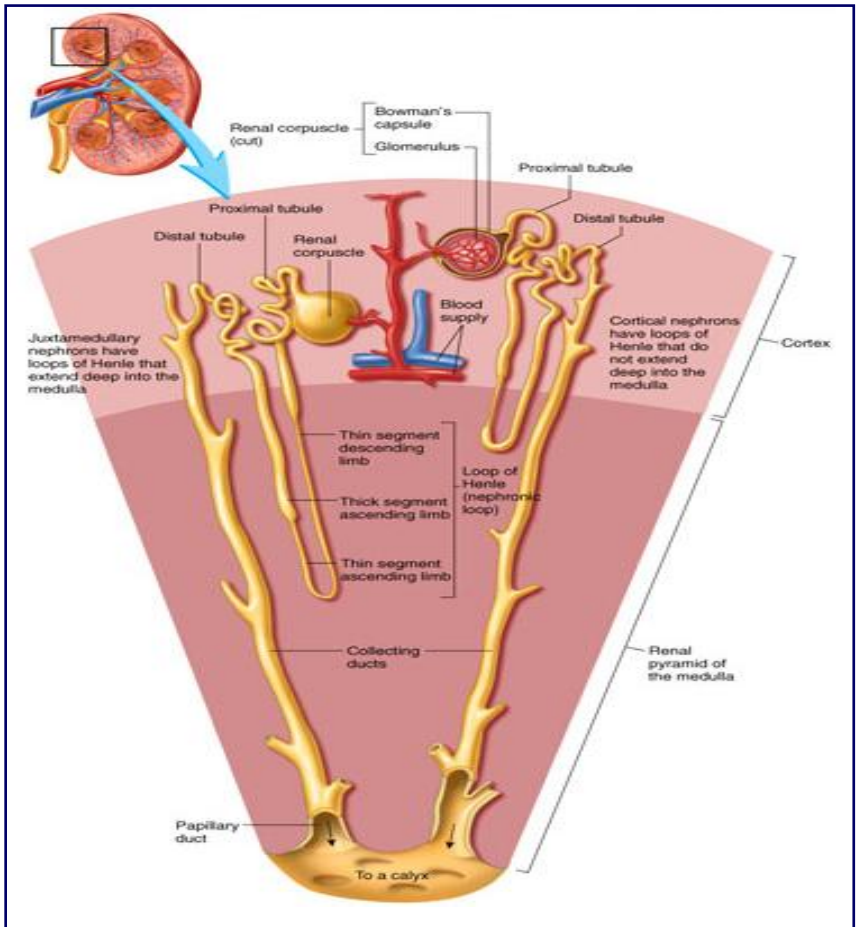


Figure (10.3): The nephron. . (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- **There are two types of nephrons:**

1- Cortical nephrons :

- The glomeruli are in the two thirds of the cortex.
- Short loop of Henle, that dips into the outer medulla.

2- Juxtamedullary nephrons

- Glomeruli are in the inner cortex.
- Long loop of Henle extends deeply into the medulla

- **Proximal convoluted tubule** is about 14 mm long ,60 µm in diameter .It is composed of simple cuboidal epithelial cells ,made up the wall.
- **Loops of Henle** are continuous of proximal convoluted tubule .Each loop has two limbs: **descending and ascending. (**Figure 10.3).
  - The ascending limb of loop of Henle leads into a second coil section: **the distal convoluted tubule.**
- **Distal convoluted tubule** begins at a special structure: the **juxtaglomerular apparatus.** Figure 10.5.b).
- **Collecting duct:** The cells of collecting duct have some microvilli and numerous mitochondria. The absorb Na^+, K^+ and Cl^- actively.

Juxtaglomerular apparatus (Figure 10.5. b)

- The tubule passes between the afferent arteriole that supplies blood to the glomerulus and the efferent arteriole that drains it. This short section of the tubular cells is known as **macula densa**
- Juxtaglomeruler apparatus secretes enzyme **rennin ,** and play an important role in the regulation of filtrate formation and blood pressure.
- The distal tubules of several nephrons join to form a **collecting duct** that passes through the medulla to the papilla.
- The overall structure of the nephron is summarized in a diagram (figure10.4).

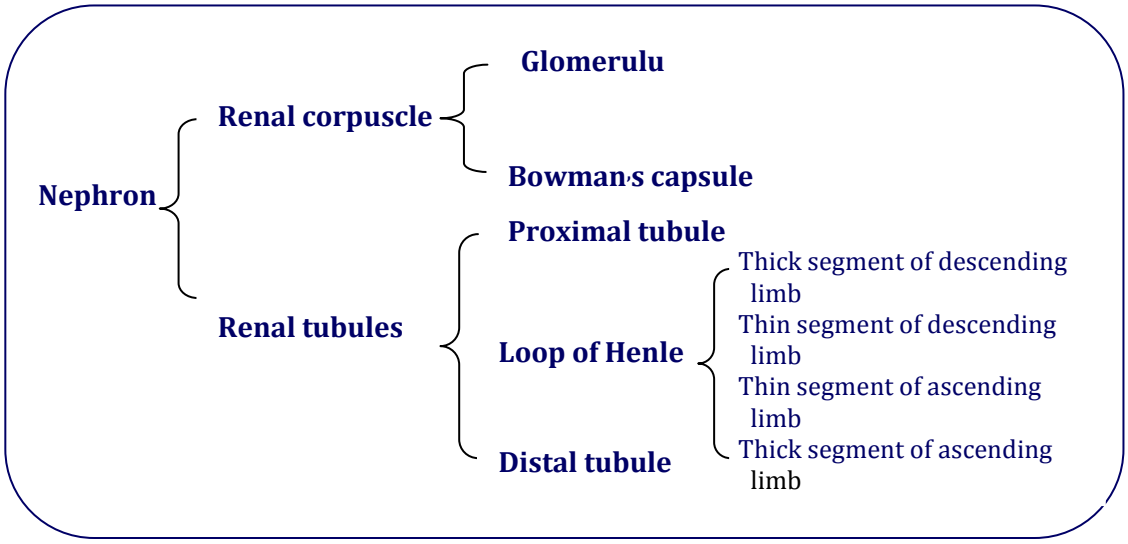


Figure (10.4): Overall structure of nephron.

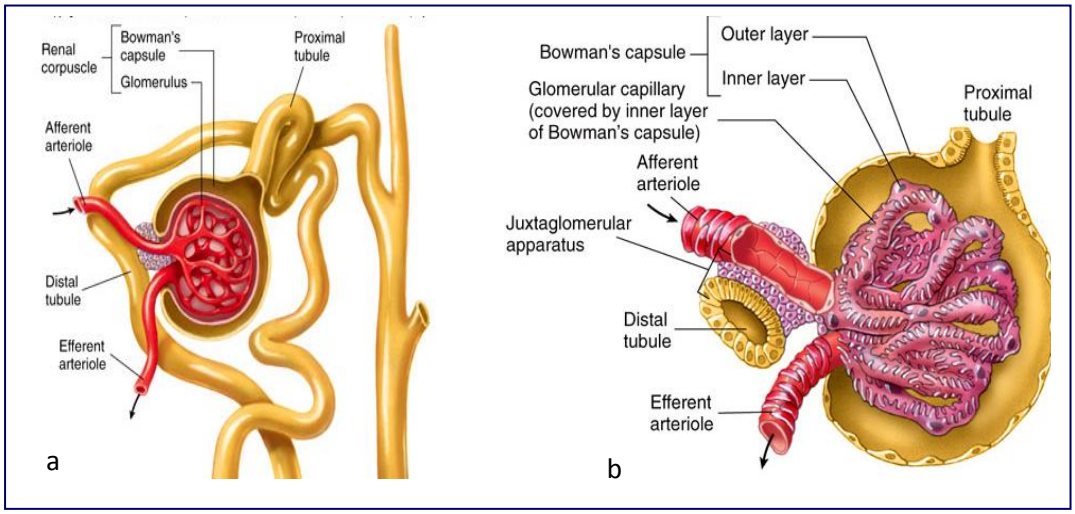
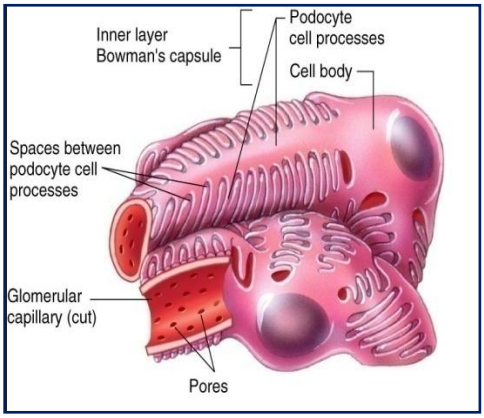


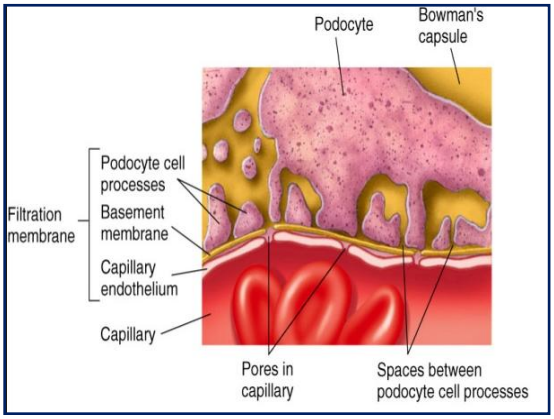
Figure (10.5):**a:** The renal corpuscle consists of Bowman's capsule and glomerulus, **b:**Bowman's capsule covers the glomerular capillaries. Juxtaglomerular apparatus consists of cells from the wall of the afferent arteriole and the distal convoluted tubule. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Structure of the glomerulus

- Glomerulus is composed of **fenestrated capillaries** (Figure 10.6).
- The filtrated fluid passes from the capillaries into the Bowman's capsule through the **filtration membrane**.
- The filtration membrane consists of(figure 10.7) :
  1. ***Fenestrated glomerular capillary endothelium.***
  2. ***Basement membrane.***
  3. ***Podocytes processes***



Figure(10.6):Fenesterated capillaries of the glomerulus.



Figure(10.7):Filtration membrane.

(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008).

Renal blood flow

Overview

- The **renal artery** enters the kidneys at the **hilum** (figure10.2).
- The renal artery branches to form **interlobar arteries,** which radiate out towards the cortex**.**(Figure 10.8.a).
- Interlobar arteries diverge near the base of the pyramid to form **arcuate.**
- **Interlobular arteries** project from the arcuate.
- Interlobular arteries give rise to the **afferent arterioles** that supply the glomerular **capillaries.**(Figure10.8.b).
- **Efferent arterioles** arise from the glomerular capillaries to carry the blood away from the glomeruli.
- When the efferent arteriole exists the glomerulus, it gives rise to plexus of capillaries, **peritubular capillaries** around the proximal and distal tubules.
- **Vasa recta** is a specialized part of the peritubular capillaries course into the medulla along the loop of Henele of the juxtamedullary nephrons, then back toward the cortex.
- Veins form from peritubular capillaries are: **interlobular veins** to **arcuate vein** to **interlobar vein** to **renal vein .**

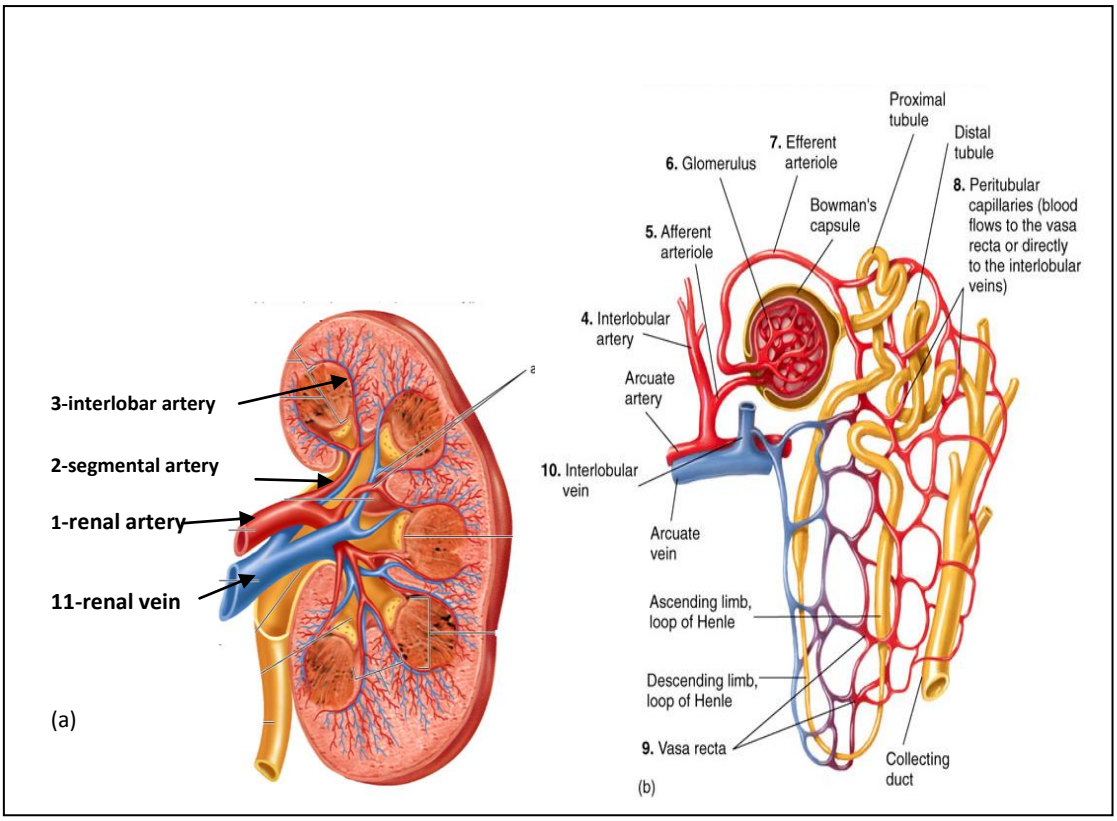


Figure (10.8):a: Blood flow to the kidney ,b:blood flow to the nephron. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Renal nerve supply

- The kidney has rich **sympathetic noradrenergic** innervations which supply renal artery and its branches, juxtaglomerular apparatus and renal tubules.

Urine formation

- Three major processes are essential for urine formation: ***Filtration , tubular reabsorption and tubular secretion***

1- Filtration

- F**iltration** is the movement of water and small solutes from blood flowing through the glomerulus across the filtration membrane as a result of pressure differences into the Bowman's capsule forming the **filtrate**.
- Most substances in the plasma (except for proteins) are freely filtrated, so their concentrations in the glomerular filtrate in the Bowman's capsule are the same in the plasma.

Glomerular blood flow

- The part of the total cardiac output that passes through the kidney is called **renal fraction.**
- The normal cardiac output is **5600ml/min**, while the renal fraction is **1200 ml/min** which represents **21%** and varies from **12-30%.**

Glomerular filtrate

- **Glomerular filtrate** is the fluid filtrated through the glomerular membrane into Bowman's capsule.
- **Filtration membrane** is composed of three layers (mentioned previously) each of these layer is several hundred times as permeable as the capillary membrane ,which accounts for the volume of the glomerular filtrate formed each minute ,but still of high degree of selectivity for the size of passing molecules.

The permeability of the G. membrane to substances of different molecular weights =

$$\frac{\text{Concentration of dissolved substance on the filtrate side of the membrane}}{\text{Its concentration on the plasma side}}$$

- The reasons for the high selectivity of the glomerular membrane are :
  1. **Size of the pores** in the glomerular membrane is large enough to pass molecules with diameter 8 nanometers.
  2. **Electrical charges** of the molecules .The pores are lined by glycosylated proteins which have strong negative electrical charges.
- Glomerular filtrate has the same components of the plasma except it has no significant amount of proteins.

The glomerular filtration rate (GFR)

- The glomerular filtration rate (**GFR**) is the quantity of glomerular filtrate formed each minute in all nephrons of both kidneys. It is **125ml/min** in normal person.
- Glomerular filtrate formed each day is **180 Lit/day;** over 99% of the glomerular filtrate is reabsorbed in the tubules, while remaining is passing into the urine.
- Normal plasma flow through the kidney is **650 ml /min** and GFR of both kidneys is **125ml/min,** so the average filtration fraction is 19%.

Factors that affect the GFR

GFR= Filtration pressure x Kf

- The factors that determine the **filtration pressure** (glomerular pressure, plasma colloid osmotic pressure and Bowman's capsule pressure) will determine the GFR.
- The conditions that affect these pressures and therefore affect the GFR are:
  1- **Renal blood flow**: an increase in the rate of blood flow through the nephrons increases the GFR by increasing the glomerular pressure which enhances the filtration process.
  2- **Afferent arteriolar constriction** decreases the rate of blood flow into the glomerulus and also decreases the glomerular pressure causing a decrease in the filtration rate.
  3- **Efferent arteriolar constriction** causes an increase in the resistance to outflow from the glomeruli .This increases the glomerular pressure and increase in efferent resistance causes slight increase in the GFR.
  4- **Sympathetic stimulation of the kidneys** causes the afferent arterioles to constrict, thereby decreasing the GFR.
     - With **strong sympathetic stimulation**, glomerular blood flow and glomerular pressure are reduced so that glomerular filtration decreases to only a few percent of normal and the urinary output can fall to zero for as long as 5 to 10 minutes**.**
  5- **Arterial pressure**
     - When the arterial pressure rises, afferent arteriolar constriction occurs automatically .This prevents a significant rise in glomerular pressure despite the rise in the arterial pressure. Therefore, the GFR increases only few percent even when the mean arterial pressure rises to 150 mmHg. This phenomenon is called **autoregulation.**
     - An increase in arterial pressure can greatly increase the urinary output even though it affects GFR slightly.

Pathological note: **glomerular nephritis** results from inflammation of the filtration membrane within the renal corpuscle. The inflammation leads to increased membrane permeability and accumulation of WBCs in the area ,resulting in high concentration of plasma proteins that enter the filtrate along with WBSc. Glomerular nephritis may be **acute** when occurs within 1-3 weeks after bacterial infection ,or **chronic** which is long term and progressive .The filtration membrane becomes thick and replaced by connective tissues .

Reabsorption and secretion in the tubules

Overview

- The filtrate entering the nephrons flows through the following tubules:
  1- The proximal tubule
  2- The loop of Henele
  3- The distal tubule
  4- The collecting tubule
  5- The collecting duct.
- Substances are selectively reabsorbed or secreted by the tubular epithelium.
- Reabsorption plays greater role than does secretion in the formation of urine, but secretion is important in the determining the amounts of K^+ and H^+.
- The resulting fluid entering the pelvis is urine
- The tubules separate the substances that are to be conserved in the body from those be eliminated in the urine.
- Water in the glomerular filtrate is reabsorbed in about **99%** as it passes through the tubules.
- **Glucose** and **amino acids** are entirely reabsorbed.

Renal transport mechanism

Overview

- Substances are reabsorbed or secreted by:
  1- Trancellular transport: Transport across tubular epithelial cells from the tubular lumen into tubular epithelial cells across the luminal membrane, (figure 10.9) and from inside the epithelial cell into the interstitium and peritubular capillaries across the **basolateral membrane.**
    - It involves **active transport** and **passive transport**.
    - Active transport is responsible for transport of Na^+
    - **Secondary Active Transport** utilizing Na^+ gradient (Sodium Symport).It is used for transporting glucose, amino acids, ions, metabolites.

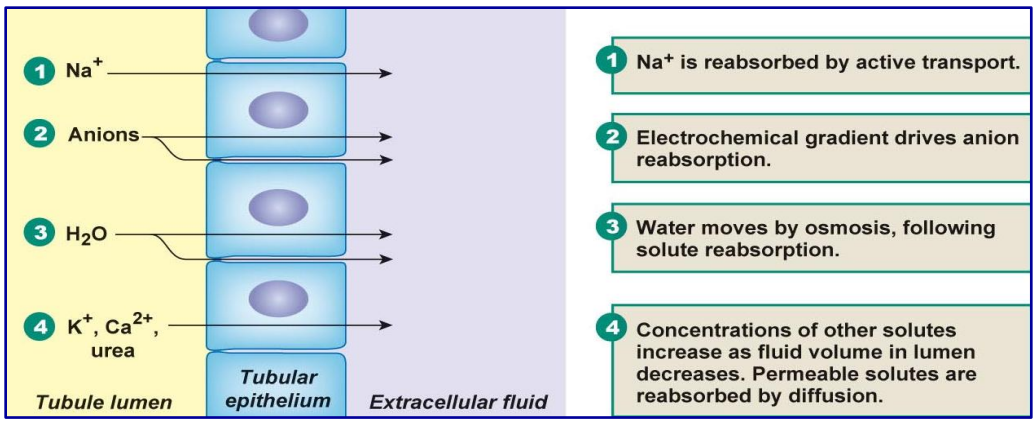


Figure (10.9): Trancelluar transport. Retrieved from: www.studyblue.com

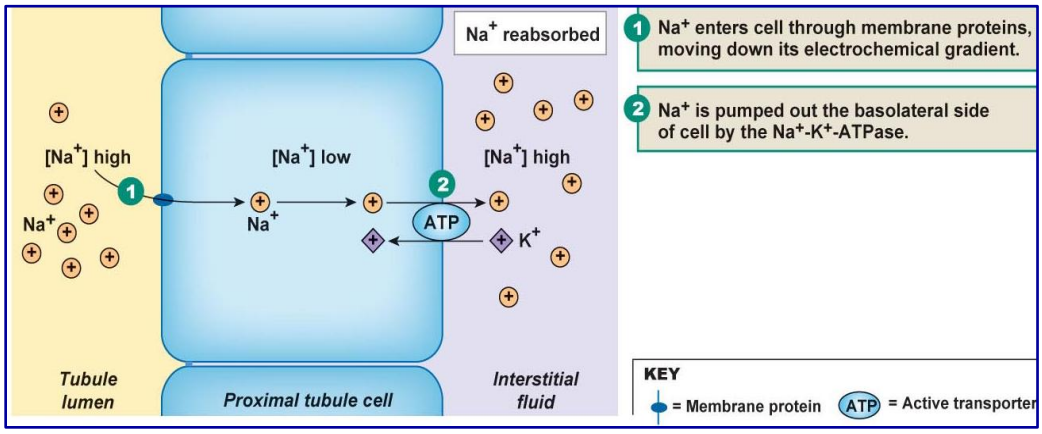


Figure (10.10):Na^+ is pumped into the interstitial fluid ,K^+ is pumped into the tubular cell. Retrieved from : www.studyblue.com

2- **Paracellular transport** done via tight junction and lateral intercellular space

- It is important for electrolytes K^+, Ca^{+2} and varies in the permeability in different tubules.
- It allows to leak amount of solute and fluid in the **proximal tubule,** while in **collecting tubule** is more limited.

Tubular transport maximum

- **Transport maximum(T_m)** is a limit for the amount of transported substances per unit time.
- It exists for substances that are actively reabsorbed, because the carriers responsible for transport become saturated.
- When the carriers are saturated, excess of substances is excreted.
- The renal threshold for a substance is the plasma concentration at which this substance first occurs in the urine.

Renal clearance

- **Clearance** is the plasma volume from which a substance has been completely cleared per the kidney per unit of time.
- A substance which is freely filtered across the glomerulus and neither reabsorbed nor secreted into the tubule **(e.g., insulin)** its rate of clearance is equivalent to GFR. The concept of clearance is to estimate GFR.
- A substance has a clearance greater than that of insulin; it must have been secreted into the tubular fluid.
- A substance has lower clearance than that of insulin; it must have been reabsorbed from the tubular fluid.
- Clearance can be calculated by the following equation :

Clearance =Amount excreted in urine in 1 minute/ Plasma concentration

1-The proximal tubule

- About 2/3 of the glomerular filtrate is reabsorbed from the proximal tubule.
- About 60-70% of Na^+, water and urea is reabsorbed.
- Complete reabsorption of Cl^- ,HCO_3^- ,HPO_3^-K,glucose,aminoacids and proteins
- H^+, ammonia and organic acids are secreted into the tubule.

1- Sodium reabsorption

- Sodium reabsorption in the proximal tubule is important because it conserves total body Na^+ and the reabsorption of Cl^- , H_2O, glucose and amino acids depends upon it.
- Sodium is pumped out of cells into the interstitial fluid by Na^+/K^+ ATPase pump on the basolateral membrane of the proximal tubule cells. This makes the intercellular concentration of Na^+ lower relative to the lumen ,so the Na^+ diffuse passively from the lumen into the cells down electrochemical gradient and are actively pumped out of the cells in exchange with K^+ at the basolateral membrane. (Figure 10.10)
- Three Na^+ leave for 2 K^+ enter the cell.
- Potassium ions entering the cell ,leave the via K^+ channels on the basolateral membrane therefore intercellular concentration of K^+ in the body is not changed by Na^+/K^+ pump.

2- Chloride

- Sodium reabsorption is accompanied by water reabsorption ,leading to increase Cl^- concentration in the tubular lumen along the length of the proximal tubule.Therefore Cl^- move passively into the cell and then into the interstitial fluid.
- The increased negativity of the intestinal fluid causes some Na^+ to move passively into the intestinal fluid from the lumen.

3- Water reabsorption

- Transport of Na^+ and Cl^- into the lateral intercellular space causes **osmotic flow** of water from the lumen into the same space.
- Water and solutes transport from the lateral intercellular space into the peritubular capillaries by **osmotic** and **hydrostatic pressure gradients.**
- Some water and solutes may leak back into the tubular lumen.
- The volume of reabsprbed water depends partly on the **filtration fraction** :
  - If the filtration fraction increases then more water will be filtrated at the glomerulus leaving high protein concentration in the glomerular capillaries and raising the oncotic pressure in the peritubular capillaries causing an increase in reabsorption from the lateral space.
  - If the filtration fraction decreases, the opposite happens.

4- Glucose reabsorption

- All glucose in the filtrate is reabsorbed in the proximal tubule at a normal level of plasma glucose.
- Glucose is cotransported with Na^+ at the luminal membrane .When Na^+ moves down its electrochemical gradient, glucose diffuses from the cell into interstitial fluid and then to the peritubular capillaries.
- The normal plasma concentration of glucose is **(0.6-1 mg/ml).**
- The transport maximum for glucose is about 375mg/ml in man350 mg/ml for woman).The renal threshold for glucose (the plasma concentration at which glucose first appears in urine is 375mg/ml divided by GFR (125ml/min), which is **0.3 mg/ml** for man).
- When plasma glucose is high, in diabetes mellitus, glucose appears in urea **(glycosuria).**

5- Bicarbonate reabsorption

- Hydrogen ions enter the lumen in exchange with Na^+ or they are secreted by **H^+ ATpase .**
- Hydrogen ions combine with HCO_3^- filtrated at the glomerulus to form H_2CO_3.
- H_2CO_3 dissociate to H_2O and CO_2, raising the luminal PCO_2.This reaction is catalyzed by **carbonic anhydrase.**
- Carbone dioxide diffuse into the cells, by reverse reaction H^+ and HCO_3^- are formed. H^+ replaces those that enter the lumen.$HCO3^-$ diffuse across the basolateral cell membrane with Na^+ into the interstitial space, then absorbed into peritubular capillaries.

6- Amino acids

- Amino acids are freely filtered at the glomerulus ,so they occur in the filtrate at the same concentration in plasma**(3 mmol/lit).**
- They are reabsorbed by cotransport with Na^+ at the luminal membrane.

7- Phosphate

- Phosphate is a breakdown product of protein metabolism .Its concentration in plasma is **1 mmol/Lit.**
- It is freely filtered at the glomerulus and cotransport with Na^+ at luminal border of the proximal tubule.
- An increase in phosphate concentration in plasma causes an increase in phosphate excretion.
- Its reabsorption is regulated by **hormone PTH** and increased by **calcitriol.**

8- Potassium

- Potassium is filtered freely at the glomerulus and present in the filtrate at the concentration equal to that in the plasma **(4-5 mmol/Lit).**
- It is reabsorbed passively into the cells of proximal tubule through the paracellular pathway and active transport at the luminal border (figure10.11).

9- Calcium

- Plasma Ca^{2+} level is **2.5 mmol/Lit**. About 40-50% of calcium is bound to protein and cannot be filtrated by the glomerulus.
- The ionized form Ca^{2+} is freely filtered by glomerulus.
- Calcium is reabsorbed from the proximal tubule in parallel with Na^+ and water, so Ca^{2+} enters the cells passively down its electrochemical gradients and leaves the cells by Ca^{2+}/Na^+ countertransport or by Ca^{2+} ATPase mechanism.

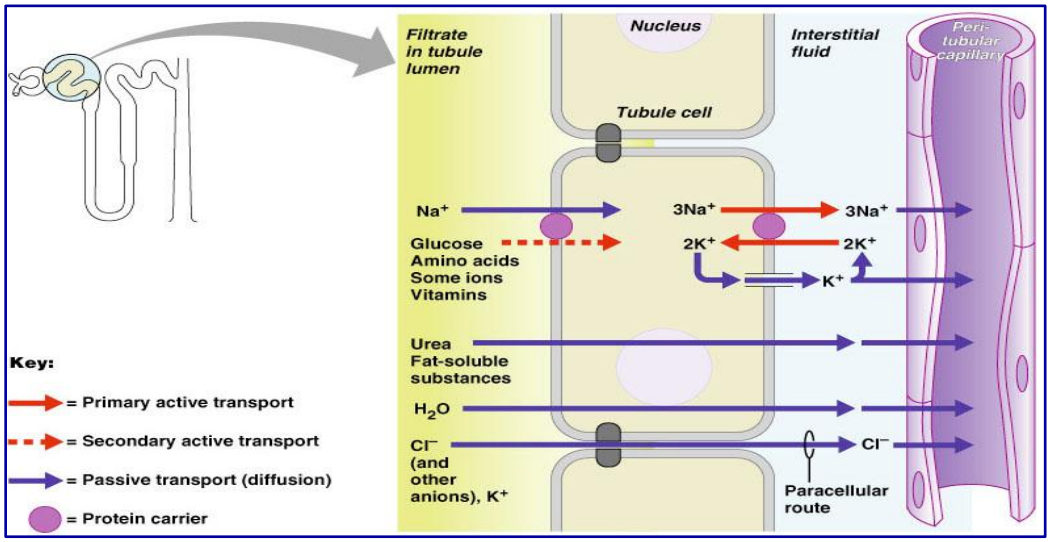


Figure (10.11): Reabsorption of different ions and substances by proximal cells (Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2006).

10- Urea

- Urea is the product of protein metabolism .Its concentration in plasma is **2.5-7 mmol/Lit.**
- It is freely filtered .About 50% of it is reabsorbed by the end of proximal tubule.And ions reabsorption increases urea concentration in the lumen of tubule; therefore it diffuses out of tubule down its concentration gradient.

11- Organic cations and anions

- Proximal tubule secrets organic cations and anions ,some of which are the end products of metabolism that circulate in plasma ,e.g., bile salt ,oxalate, urate, prostaglandins and creatinine.
- The proximal tubule secrets **exogenous organic compounds** e.g.,(polycyclic aromatic hydrocarbon)(**PAH),** which is used to determine renal plasma flow and **drugs** such as penicillin, aspirin, morphine and quinine.
- Most of them are bound to plasma protein and cannot be filtered so eliminated by secretion into the lumen.

2- Loop of Henle, distal tubule and collecting duct

Overview

- The part of the nephron after the proximal tubule can be divided into: **the thin descending and ascending limbs of loop of Henle**, the **thick ascending limb**, **the early and late part of distal lobule** and **the collecting duct**.(Figure10.3).
- These tubules have different functional have different functional characteristics but they have a common role (**concentrating the urine**).
- The descending limb has a high permeability to water and low solute permeability (water moves across the descending limb into the interstitium until osmotic equilibrium).
- The thin and thick ascending limbs have low permeability to water. The thick ascending limb reabsorbs Na^+ from the tubular fluid. It plays a major role in the diluting the tubular fluid.
- The distal tubule and collecting duct reabsorb Na^+ :
  - In the presence of **ADH** , the late part of distal tubule and collecting duct become very permeable to water. This allows water to move out until reaching to the osmotic equilibrium.
- Urea plays an important role in concentrating process.
  - The highest urea permeability is found in the inner medullary part of the collecting duct.
  - The thick ascending limb, distal tubule and cortical parts of collecting duct have no permeability to urea but the thin limb of ascending and descending of the loop of Henle are permeable to urea.
  - Urea moves passively down its concentration gradients.
- The distal tubule and the collecting duct are important in the secreting K^+, H^+ and in reabsorption of Cl^- and HCO_3^- .

Loop of Henle

- The descending loop has a high permeability to water and low permeability to solutes.
  - As the filtrate descends, the higher osmotic pressure causes the water to suck out, but small quantities of NaCl can diffuse in.

- By the **bottom** of the loop the osmotic pressure of filtrate increases to **1200 mOsm.**15% of the water is reabsorbed in the descending loop of Henle, so the volume of filtrate is now only 20% of the original.
- In the **thin segment** of the ascending loop, the walls are not permeable to water, so as it moves up through progressively lower salt concentrations, some **salt will diffuse out**, to reduce its osmotic pressure**.** (Figure10.12.a)
- In the **thick segment** of the ascending loop, there are Na^+ pumps (like in the proximal tubule). **Na^+ is pumped out**, while **Cl^- follows passively**; **K^+ also moves out by cotransport**. This progressively dilutes the filtrate ***(water will not be removed because the walls throughout the ascending loop are not permeable).*** By the **top** of the loop (as the tubule re-enters the cortex), the filtrate will **be hypotonic (100 mOsm**). (Figure10.12.b).

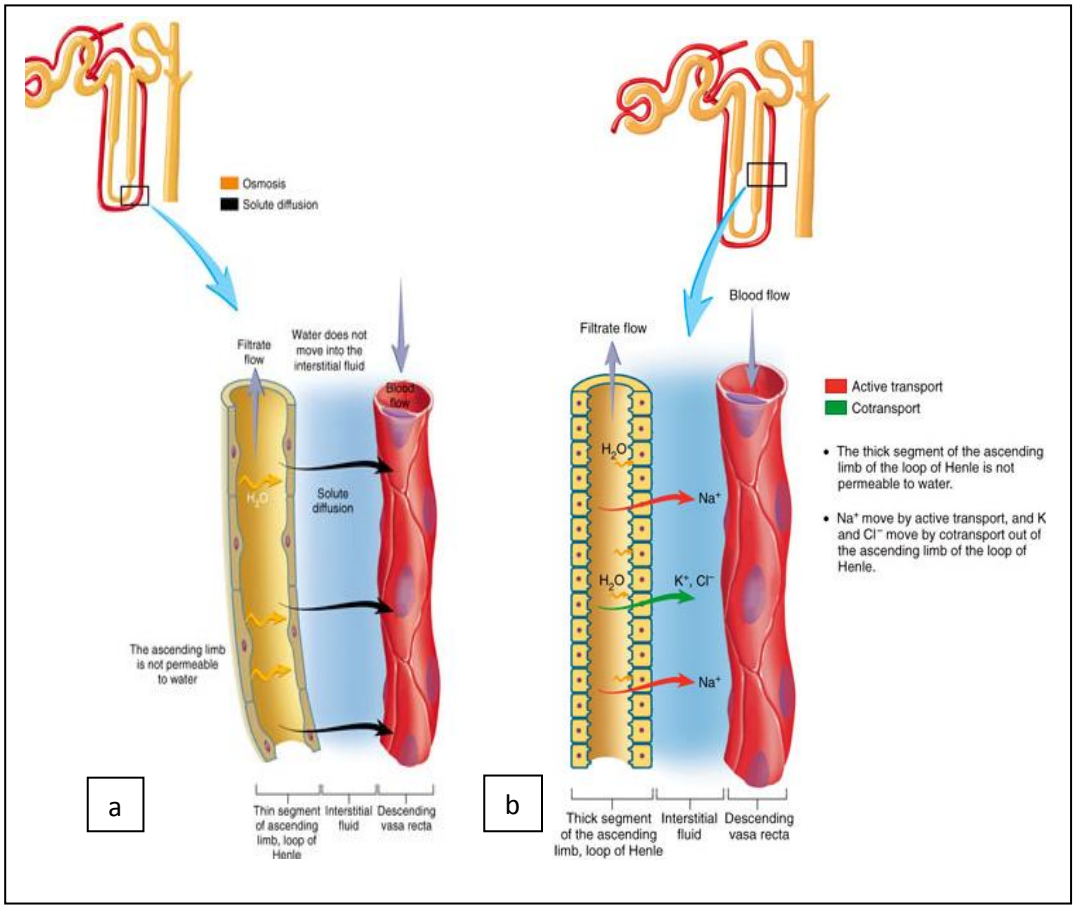


Figure (10.12): Reabsorption in the loop of Henle,**a:** reabsorption in the thin segment of the ascending limb ,**b**:reabsorption in the thick segment of the ascending limb. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- The descending loop thus loses water (and thus reduces its volume); the ascending loop loses salt (no further change in volume).

Distal tubule

- Osmotic pressure of the filtrate is less than the surrounding plasma .Some water diffuse out and some salt diffuse in to return osmotic pressure to **300 mOsm.**
- **Aldosterone** acts in this section by activating Na^+/K^+ pump (Na^+ moves out, K^+ moves in unlike loop of Henle).

Collecting duct

- There are two types of cells :
  1- **The principle cells** reabsorb Na^+ and secret K^+ in the presence of ADH, also reabsorb water.
  2- **The intercalated cells** secret H^+ and reabsorb HCO_3^-.
- As the collecting duct passes through the deepest layer of the medulla (which have very high concentration of NaCl) the maximum reabsorption of water occurs (by osmosis), raising the osmotic pressure of the filtrate to over **1200mOsm**. (Figure10.13).
- In the presence of ADH, water passes through the cells from the lumen to the interstitial fluid down the osmotic gradient.

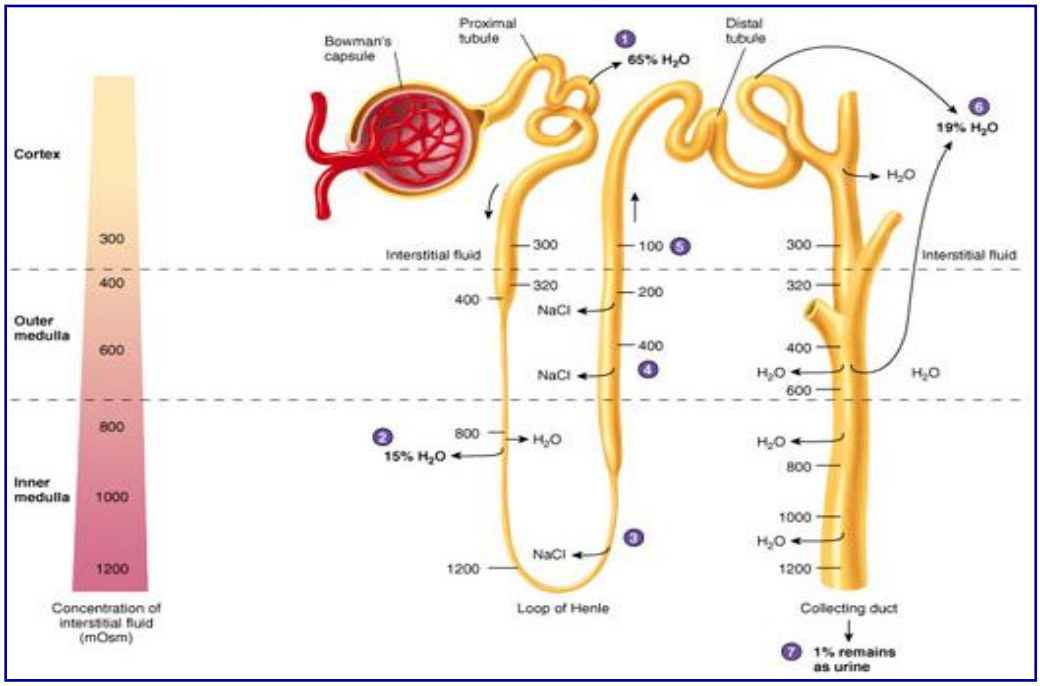


Figure (10.13): Urine concentration mechanism along the nephron parts.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

The countercurrent mechanism

- The kidney's ability to establish an osmotic gradient rest primarily in the loop of Henle, which folds back on itself to form **countercurrent system** .
- The salt removed from the ascending limb and used to concentrate the fluid within the descending limb by creating **hyper osmolar interstitium.**

- **Active transport of NaCl** from the ascending limb of loop of Henle and **urea trapping** within medullary interstitium are other factors that countercurrent system depends on.

Urea trapping

- Urea contributes to the medullary concentrating gradients. It is freely filtrated in the glomerulus and partially reabsorbed in the proximal tubule.
- The cortical and medullary portions of the collecting tubule are **impermeable** to urea, whereas the inner medullary collecting tubules are **variably permeable** to urea.
- In the presence of **ADH** ,urea concentration in the collecting tubules becomes high due to removing of water through open channels.ADH increases the permeability of inner medullary collecting tubule to urea allowing more urea to diffuse into the medullary interstitium causing more hypertonic medulla which enable further concentration of the urine.

Vasa recta

- Vasa recat is a capillary network that supplies the nephron.
- It has a hairpin configuration that prevents these vessels from dissipating the concentration gradient.
- The vessels are efficient in exchange O_2 and CO_2 with the cells in then deeper medulla.
- Large change in blood flow in the vasa recta can reduce or increase the medullary interstitial osmolality beyond its normal value.

Potassium excretion

- Most potassium is intercellular **(140mmol/Lit),** while extracellular plasma concentration is kept low **(4 mmol/Lit)** to maintain the resting potential of the body cells.
- The distribution of Na^+ and K^+ between the intercellular and extracellular compartments is maintained by Na^+/ K^+ ATPase pump which moves Na^+ out and K^+ into the cells.
- The kidney plays a major role in the regulating K^+ excretion in about 90%. About 5-10% is lost in the faeces and sweat.
- Acute renal failure results in **hyper kalmia** due to decrease ability of the kidney to excrete K^+ due to decrease ability of the kidney to excrete K^+.
- Proximal tubule reabsorbs 80% of K^+.
- Distal tubule and collecting tubule secret K^+, and aldosterone increases the activity of Na^+/ K^+ pump ,increasing the intercellular concentration of K^+ and pumping Na^+ out of the cells .
- Potassium is also regulated by flow rate of tubular fluid and changes in acid-base balance.

Pharmacology note: Several drugs can affect K^+ distribution, e.g., **digitalis** which is used in the treatment of **congestive heart failure** and overdose impairs the Na^+/K^+ ATPase and may cause sever **hyperkalemia** (due to inability of K^+ to be moved intercellularly. **Insulin and albuterol (a β2-receptor agonist**),used to treat sever hyperkalemia .They can shift K^+ to intercellular location.

Renal regulation

1. **The sympathetic nonadrenergic fibers** supply the afferent ,efferent arterioles and tubules

- **A strong increase** in the renal sympathetic causes vasoconcentraction to the arterioles by the baroreceptors reflex and renal blood flow decreases. Although the GFR is autoregulated but it may fall.
- **An increase** in the renal sympathetic activity results in direct increase reabsorption of Na^+ by the proximal tubule.
- **An increase** in sympathetic activity stimulates **rennin** secretion and **angiotensin II** production.
- **A reduced renal sympathetic stimulation** results in an opposite effect.

2. **Renin-angiotensin system**

- Renin is an enzyme that is synthesized, stored and secreted in a specialized region (**the juxtaglomerular apparatus**).(Figure10. 5. b).
- Renin is stimulated by 3 factors:
  1- Increased renal sympathetic activity
  2- Reduced renal perfusion pressure.
  3- Decreased NaCl delivery to the **macula densa** (***distinct cells of the distal tubule that are close to the afferent, efferent arterioles and Bowman's capsule***) .These cells respond to change in the composition of the tubular fluid.
- Renin cleaves the **angiotensin I** from **angiotensinogen** .Angiotensin I is then converted to **angiotensin II** by **angiotensin converting enzyme** (**ACE**) in the vascular endothelium.
- Angiotensin II has the following effects:
  1- I t causes vasoconcentraction
    - **In the systemic circulation,** it increases arterial blood pressure.
    - **In the kidneys,** it constricts the efferent arterioles raising the pressure in glomerular capillaries and help in GFR.
  2- It stimulates Na^+ reabsorption by the proximal tubule the Cl^- and water.
  3- It stimulates the **aldosterone** secretion by the **adrenal cortex**.
  4- It stimulates **ADH** secretion from the **posterior pituitary gland.**
  5- It stimulates thirst by an action on the brain.
- Angiotensin II has a negative feedback effect on rennin secretion.

3. Prostaglandins

- Prostaglandins are **localized hormone** .Their synthesis is increased by renal sympathetic activity, when angiotensin II levels are high and when rennin release is stimulated.
- Renal prostaglandins are vasodilator help to prevent excessive reduction in renal blood flow.

4. Aldosterone

- Aldosterone is a hormone synthesized and secreted by the **adrenal cortex.**
- It is stimulated to release when the concentration of angiotensin II and plasma K^+ increase.
- It acts within the kidney to stimulate Na^+ absorption and K^+ secretion by the distal tubule and collecting duct.

5. Atrial Natriuretic Peptide

- **Atrial natriuretic peptide (ANP)** is a polypeptide hormone synthesized and released by the **myocardial cells** of the atrium.
- **ANP** tends to oppose the rennin-angiotensin system action:
  1- Vasodilatation within the kidney.
  2- Inhibition of aldosterone secretion.
  3- Inhibition of ADH.

6. Antidiuretic Hormone(ADH)

- ADH is released from the **posterior pituitary** gland.
- Its secretion is stimulated by an increase in plasma osmolality and decrease in the arterial blood pressure.
- ADH has the following effects:
  1- Vasoconstriction of arterioles of the systemic circulation (including the kidney) by acting on **vasopressin V1 receptors**.
  2- It increases water reabsorption by the kidney (↑water permeability of the collecting duct).
  3- It increases the urea permeability of the medullary portion of the collecting duct.

7. Parathyroid Hormone(PTH)

- **Parathyroid hormone (PTH)** is secreted by the **parathyroid gland.**
- It secretion is stimulated by decrease in the concentration of plasma Ca^{2+} .
- PTH stimulates the production of **calcitriol** which increases $Ca^{2+,}$ phosphate absorption from the gastrointestinal tract and stimulates bone reabsorption.
- In the kidney, PTH stimulates Ca^{2+} reabsorption by the thick ascending limb of loop of Henele and distal tubule, raising the Ca^{2+} plasma level.

Urine collection and Micturition

Passage of urine from kidney to bladder

Overview

- Urine moves from the **collecting ducts** of the renal tubules to the **renal pelvis** by **hydrostatic pressure.**
- Urine moves from the **pelvis** into the **ureter** by the **smooth muscles contraction.**
- The **peristaltic wave** which propagates along the ureters length propels urine into the bladder to store the urine.

Micturition

- The flow of urine to the urinary bladder is relatively continuous.
- The urinary bladder acts as a reservoir for urine until it can be eliminated at appropriate time.
- The bladder can distend to accommodate the large volume of fluid .The maximum volume it can contain is **1L,** and discomfort begins when urine volume exceeds **500ml.**
- The capacity of the urinary bladder to distend is due to the following factors:
  1- The walls of the bladder contain large folds, which unfold to enlarge the lumine of the urinary bladder.
  2- The lining of urinary bladder is stretchable transitional epithelium.
  3- Smooth muscle wall of the urinary bladder stretch to accommodate the fluid volume.
- The bladder expands as the urine flows into it , but the internal pressure does not increase(because its structure) until the bladder volume becomes large.

Micturition reflex

- Micturition reflex is activated when the bladder wall is stretched resulting in elimination of urine from the urinary bladder **(micturition).**
- Integration of the micturition reflex occurs in the **sacral region** of the spinal cord and modified in the pons of cerebrum.(Figure 10.14).
- When urine fills the bladder stimulates **stretch receptors** which produce action potential.
- Action potential is carried by sensory neurons to **spinal cord** through the **pelvic nerves.**
- Action potential is carried to the bladder through parasympathetic fibers
  - **Parasympathetic stimulation** causes contraction of smooth muscles of the bladder and decrease somatic motor action potentials causing the **external urinary sphincter** to relax.
- Urine flows from the bladder to the **urethra** by increase the pressure.
- The micturition reflex produces a series of contractions of the urinary bladder.

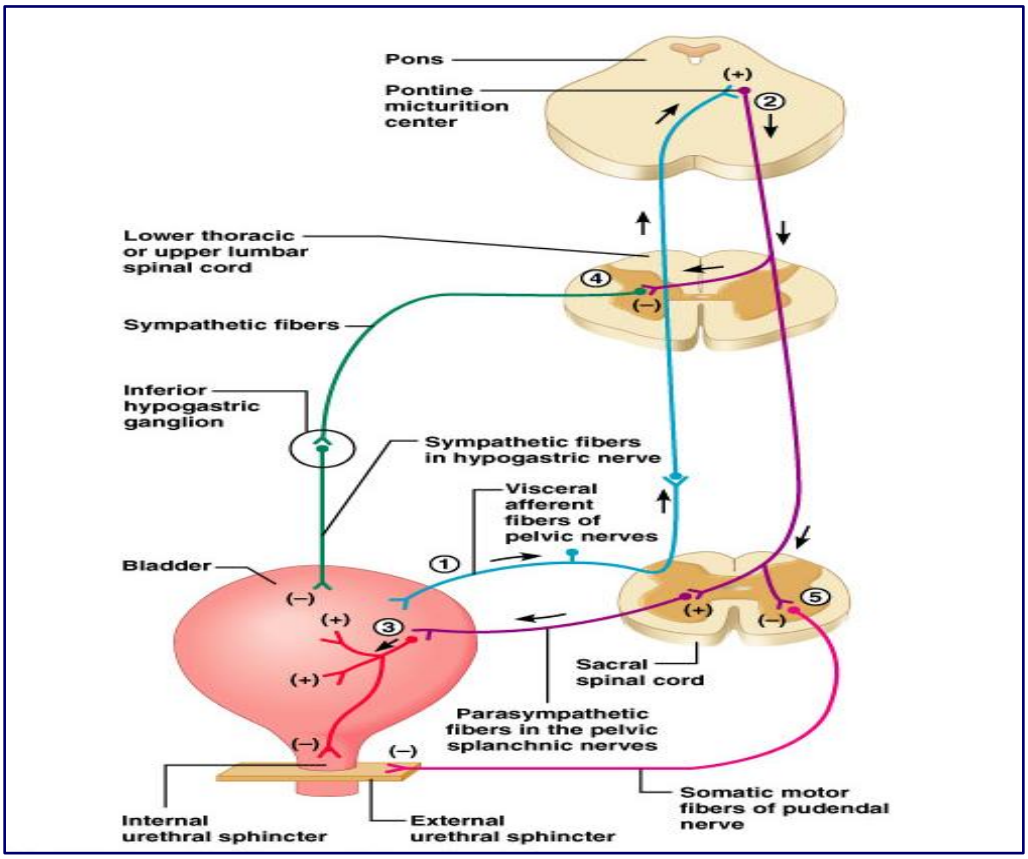


Figure (10.14): Control of micturition. (Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2006).

Regulation of micturition

- **Ascending pathways** carry an increased action potential up the spinal cord to the pons and cerebrum when the bladder becomes stretched .This increases the conscious urge to urinate.
- **Descending pathways** carry the action potential to the sacral region of the spinal cord to **inhibit** micturition reflex to prevent automatic urination when bladder is full.

Pathology note: Renal failure results from any condition that interferes with kidneys function. **Acute renal failure** is an extensive kidney damage lead to accumulate urea in the blood and **acidosis.** It results from acute glomerular nephritis, damage of tubules and some poisons. In complete renal failure death occurs in 1-2 weeks. **Chronic renal failure** is when many nephrons are permanently damaged and the remaining functional nephrons cannot compensate. It results from chronic glomerular nephritis, trauma to the kidney, congenital abnormalities or tumor and kidney stones. Chronic renal failure causes the GFR to decrease and the kidneys lose their ability to excrete the metabolic waste products and accumulation the solute in the body fluids resulting in water retention and **edema.**

Anatomical considerations of the ureters, urinary bladder

- **Ureters** are tubes extend from the kidney to the urinary bladder .They extend inferiolrly and medially from the renal pelvis at the renal hilum of each kidney to reach the urinary bladder.
- **Urinary bladder** is a hallow muscular container that lies in the pelvic cavity, posterior to the symphysis pubis.
- The ureters enter on its posterolateral surface.
- **The urethra** transports urine to the outside of the body .It exists the bladder inferiorly.
- The triangular area of bladder's wall between the two ureters posteriorly is called **trigone** which is histologically distinct from other region.(Figure10.15.b).
- The walls of ureters and the bladder are lined with:
  - Transitional epithelial mucosa.
  - Smooth muscle muscularis (stimulated to contract by parasympathetic fiber)
  - Fibrous connective tissue adventitia.
- The outlet of the bladder into the urethra is graduated by two sphincters:
  1. **Internal sphincter** involuntary sphincter of smooth muscle.
  2. **External sphincter** is skeletal muscle surrounds the urethra as it extends through the pelvic floor. It acts as a valve that controls the flow of urine through the urethra.

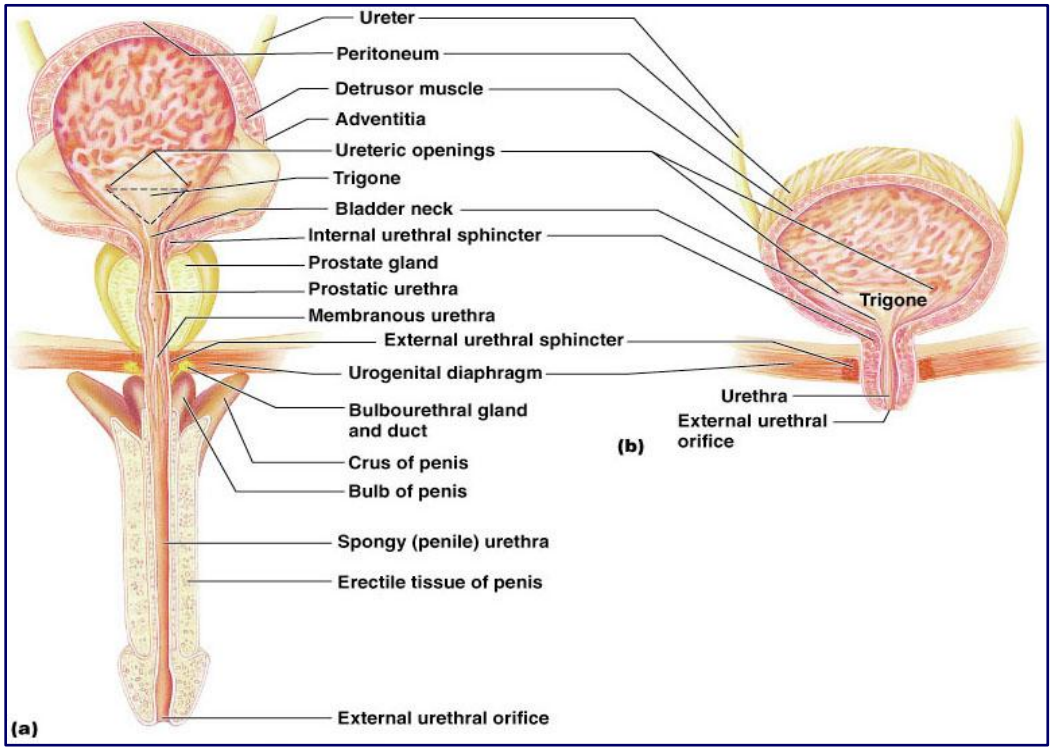


Figure (10.15): Basic structures of urinary bladder and urethra. (Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2006).

- **In male**, the urethra has three regions (Figure 10.15.a):
  1. **Prostatic urethra**: runs within the prostate gland
  2. **Membranous urethra** : runs through the urogenital diaphragm
  3. **Spongy urethra**: passes through the penis and opens via the external urethral orifice.
- **In female,** it is shorter than in male and opens into the vestibule anterior to the vaginal opening.

Diuretics

- Diuretics are agents that increase the rate of urine formation.
- **Diuresis** is an increase in urine volume with loss of water and solutes.
- **Mechanism of action:**
  - Diuretics are ions transport inhibitors that decrease the reabsorption of Na^+ at different site of nephron.
  - Sodium and other ions (Cl^-) enter in greater amounts than normal along with water to maintain osmotic equilibrium.
- Diuretics are used to treat different disorders such as hypertension, several types of edema and liver cirrhosis.
- The use of diuretics may cause complications such as electrolytes imbalance and dehydration.
- There are different classes of diuretics act at different sites of nephron (table10.1), because each class interacts with luminal sodium transport.

Table (10.1):Different classes of diuretics. (Brown T.A. Rapid Review of Physiology. Philadelphia, Mosby, 2012).

Class of diuretics	Site of action	Mechanism	Clinical uses
Carbonic anhydrase inhibitors	Proximal convoluted tubule	↑bicarbonate excretion	High altitude sickness ,glaucoma
Thiazide diuretics (HCTZ metolazone)	Distal convoluted tubule	↓activity of Na+,Cl- cotransporter	Hypertension, diabetes insipidus
K^+ sparing diuretics	Collecting tubule	↓NO.of open Na+ channels in the tubular cells	Liver cirrhosis
Loop diuretics (furosemide)	Loop of Henle	↓Na^+-K^+-$2Cl^-$ in the thick ascending loop of Henle	Pulmonary edema associated with congestive heart failure
Osmotic diuretics(mannitol)		Osmotic diuresis	Cerebral edema

Body fluid regulation

Overview

- Water balance is regulated by mechanisms that prevent the large change in plasma osmolality.
- Plasma osmolality (concentration of body fluid) is measured in terms of the amount of dissolved substances per unit mass of water (it is given in unit mol/kg).
- Plasma osmolality is determined by plasma Na^+ concentration.
- Na^+ balance is regulated by mechanism that prevents large change in extracellular fluid volume (**ECV**).
- Change in Na^+ balance leads to changes in the **ECV** not in osmolality.
- Plasma osmolality is regulated by changes in water intake and excretion, whereas Na^+ balance is regulated by changes in Na^+ excretion.

Regulation of body fluid osmolality

- Water is lost from the body by :
  - Breathing
  - Sweating
  - In faeces
  - Via the kidney, the most important to keep plasma osmolality constant.
- Water is provided for the body by drinking and by water content in the food.
  - The fluid ingested by drinking is regulated by sensation of thirst.
  - Osmoreceptors play a major role in the regulation of water by kidneys and thirst.
  - ADH regulates water excretion and osmolality.
  - Osmoreceptors respond to change in plasma osmolality by shrinking or swelling, resulting in change in ADH output from the posterior pituitary gland.
- An excessive loss of water from the body leads to increase plasma osmolatity and the osmoreceptors stimulate secretion of ADH(which conserves water) and cause sensation of thirst.

Regulation of extracellular fluid volume

- An increase in ECF volume results in an increase in ANH secretion and decreases in aldosterone, ADH and sympathetic stimulation of afferent arterioles.

Regulation of intracellular fluid composition

- Large molecules e.g., proteins are synthesized within the cells and influence the concentration of solutes inside the cells.
- Electrolytes' concentrations are determined by transport mechanism and electrical charges.
- Water movement across the plasma membrane is controlled by osmosis, which is affected by the changes of concentration of solutes in the extracellular and intracellular fluids.

Regulation of acid –base balance

- The maintenance of H^+ concentration within narrow range is essential for normal metabolic reactions, because H^+ affect the activity of many enzymes and chemical reactions within the body.
- The mechanisms that regulate the H^+ concentration are: **buffer systems, respiratory system and the kidneys**

Acids and bases

- **Acids** are substances that release H^+ into a solution, while base binds to H^+ and removes them from the solution.
- Acids and bases are either strong or weak .**Strong acids** dissociate completely to form ions in the solution. **Weak acids** dissociate partially. Equilibrium is established between that acid and the forms ions.
- Weak acids are common in living system because they play an important role in the preventing significant changes in the body fluid PH.
- Buffer systems resist changes in the PH of solution .Buffer within the body fluids regulate PH by binding to excess H^+ or by releasing H^+ when H^+ concentration decreases.
- There are several buffer systems function together to resist PH changes of body fluids :

1- Carbonic acid /Bicarbonate buffer system

- Carbonic acid H_2CO_3 is weak acid dissolved in water :
  $\mathbf{H_2CO_3 \rightleftharpoons HCO_3^- + H^+}$
  The carbonic acid /bicarbonate buffer system depends on the equilibrium that is established between H_2CO_3 and (H^+, HCO_3^-).
- Adding of H^+ to the solution leads to a large portion of H^+ binds to HCO_3^- to form H_2CO_3 .On the other hand if H^+ are removed from a solution containing H_2CO_3, more H_2CO_3 dissolves to form HCO_3^- and H^+. Thus the large PH change is resisted.

2- Protein molecules buffer system

- They provide three fourths of the buffer capacity.
- Hemoglobin is one of the most important intracellular proteins.
- The capacity of these proteins is due to the functional groups of amino acids e.g., carboxyl and amino groups ,which act as weak acids and base:
  - AS the H^+ concentration increases, more H^+ ions bind to the functional groups. When H^+ decreases, more H^+ ions are released from the functional group.

3- Phosphate buffer system

- Phosphate containing molecules e.g., DNA, RNA, ATP and HPO_4^{-2} in solution act as buffers.
- Phosphate ions act as weak acids can bind to H^+ to form H_2PO_4 when H^+ increase and release H^+ when these ions decrease.

Respiratory regulation of acid- base balance

- Carbon dioxide reacts with H_2O to form H_2CO_3.This reaction is catalyzed by **carbonic anhydrase** in the RBCs.
- Many H_2CO_3 dissocite to form H^+ and HCO_3^-.
- Increased CO_2 leads to decrease PH and decreased CO_2 leads to increase PH.
- Deceased PH in the body fluid stimulates respiratory center to increase the rate and the depth of ventilation **(hyperventilation)** in order to eliminate the excess CO_2 from the body and reducing H^+ resulting from dissociation of H_2CO_3.
- Increased PH in the body fluid causes **hypoventilation** to increase the level of CO_2 and H^+.

Clinical note: Respiratory Acidosis: when PH value of the body fluid is less than 7.35, while **respiratory alkalosis** when PH of body fluid is more than 7.45. Both respiratory acidosis and alkalosis are due to **respiratory abnormalities.**

Metabolic acidosis or metabolic alkalosis is caused by cases other than respiratory abnormalities. **Metabolic acidosis** characterized by abnormal **low HCO_3^-** in systemic arterial blood .Loss of HCO_3^- results from severe diarrhea or renal dysfunction.

Metabolic alkalosis is characterized by abnormal **high HCO_3^-** in systemic arterial blood. It is caused by non-respiratory loss of acid, vomiting of acidic stomach contents, gastric suctioning, excessive intake of alkaline drugs (antacids), use of certain diuretics and severe dehydration.

Renal regulation of acid- base balance

- Renal tubules regulate acid base balance by increasing or decreasing the H^+ into the filtrate and HCO_3^- reabsorption.
- **Carbonic anhyrase** in the nephron cells catalyzes the formation of H_2CO_3 from CO_2 and H_2O.
- Secretion of H^+ into the filtrate by **antiport mechanism** in exchange for Na^+ causing to decrease PH of the filtrate.
- Bicarbonate ions move into the interstitial fluid and then diffuse into the capillaries.
- In the capillaries HCO_3^- combine with H^+ causing to decrease the H^+ concentration and increase blood PH.

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6. Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . 8th ed. New York, McGraw –Hill Companies, 2008.

Chapter eleven

Digestive system 11

Digestive system

Overview

- The digestive system also called **gastrointestinal system** consists of an **alimentary canal** and **accessory organs** (salivary glands, tongue, teeth, liver, gallbladder and pancreas).
- The system is responsible for mechanical and chemical breakdown of food to smaller molecules to be absorbed into the circulation and used by the body cells.

Functions of digestive system

1- **Ingestion** is taking the food into the stomach.

2- **Mastication**: food is chewed by the teeth to break the large food particles into smaller with larger surface area for the enzymes to work.

3- **Propulsion** is the movement of food from one part to other of the digestive tract, by peristaltic waves. Peristalsis is done by muscles contractions.

4- **Mixing** is mixing the food particles with digestive secretion to break them into smaller pieces.

5- **Secretion** is to lubricate, liquefy and digest the food.
   - Mucus is secreted along the entire tract to protect the epithelial cells of the tract from the damaging effect of acid stomach and digestive enzymes.
   - Water secretion is to liquefy the food and make it easier to digest.
   - Liver secretions break the large fat droplets into smaller droplets to facilitate the digestion and absorption of fat.
   - Enzymes secreted by the oral cavity, stomach intestine and pancreas break the large particles of food into smaller particles to be absorbed by the intestinal walls.

6- **Digestion**
   - **Mechanical digestion**: is breakdown the large food particles into smaller ones.
   - **Chemical Digestion:** is the breakdown of covalent chemical bonds in organic molecules by digestive enzymes.

7- **Absorption** is the passage of food from the digestive tract into the circulation. This requires diffusion, facilitated diffusion, active transport and endocytosis.

8- **Defecation** is elimination of waste products of digestion from the body in form of semi solid (feces).

Regions of digestive system. (Figure 11.1).

- **Mouth** has salivary glands, teeth and tongue.
- **Pharynx** with tubular mucus glands.
- **Esophagus** with tubular mucus glands.
- **Stomach** which contains glands and mucous cells.
- **Small intestine** consists of duodenum, jejunum and ileum with accessory organs (liver, gallbladder and pancreas).
- **Large intestine** includes the, colon, rectum and anal canal with mucous glands.
- **Anus**

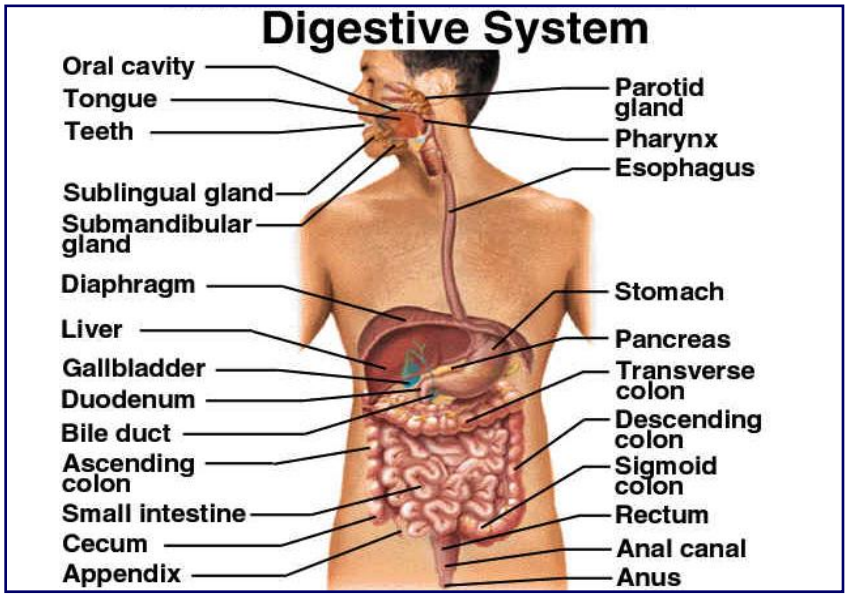


Figure (11.1): Digestive system regions. (Marieb E.N .Essential of Human Anatomy and Physiology . San Francisco, Pearson Education,Inc.,2012).

Oral cavity

- Oral cavity is called **buccal cavity.** It involves in the ingestion process.
- The digestive function is associated with its accessory organs e.g., teeth, salivary glands and tongue.
- It has a propulsive process to push the food through the pharynx and esophagus into the stomach.

Structural considerations

Teeth

- Teeth are special structures in the mouth that break down food physically by chewing and grinding (**mastication**).
- There are 32 teeth on 2 jaws in adults, in which each jaw consists from the front of: **2 pairs of incisors**, **1 pair of canines**, **2 pairs of premolars** and **3 pairs of molar** teeth.
- Incisors are designed to cut the food, while premolars and molars having a flattened surface are used to grind the food.

Tongue

- Tongue is a muscular organ that contains receptors called taste bud.
- The taste buds help in taste sweet, salt, sour and bitter sensations.
- The tongue is involved in speech, mastication and moving the food around the mouth and swallows it.
- It has intrinsic and extrinsic skeletal muscle fibers. The intrinsic one is to change the shape of the tongue while the extrinsic is to move the tongue.
- The interior two thirds is covered with different papillae :
  1- **Filiform papillae** give the rough surface to licking semisolid food and provide friction to manipulate it.
  2- **Fungi form papillae**, **vallvate papillae** and **foliate papillae** which house taste buds. (Figure 11.2).

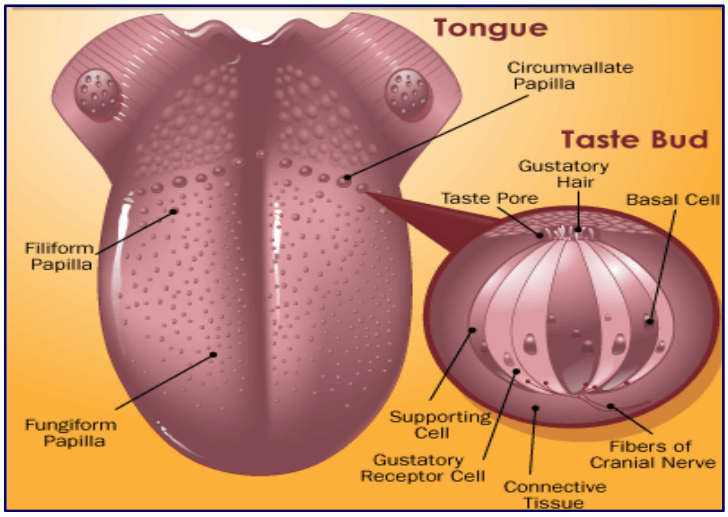


Figure (11.2): Different types of papillae on the tongue surface. Retrieved from :www.authorstream.com

The palate

- The palate forms the roof of the mouth .It has 2 distinct parts :
  1- **Hard palate** is bony structure separate the mouth from the nasal cavity.
  2- **Soft palate** is a mobile fold formed of skeletal muscle that rises reflexively to close the nasopharynx during swallowing.
     - The muscular structure that projects downward from the free edge of the soft palate is the **uvula** which prevents food from entering the nasopharynx during swallowing.

Salivary glands

- There are three pairs of glands that secret **saliva.**
  1- **Parotid gland** lies anterior to the ear.
  2- **Sublingual gland** lies beneath the tongue.
  3- **Submandibular gland** lies underneath the chin.
- **Saliva has several functions:**
  1- It cleans the mouth.

2- It dissolves food chemicals to be tasted.
3- It moistens food to compact it in a **bolus.**
4- It contains enzymes for chemical breakdown of starchy food.

- Saliva has high watery content (97-99%).It is hypotonic and PH is 6.7-7.
- Its solute includes:
  - **Electrolytes** Na^+, K^+, Cl^- and HCO_3^-
  - **Organic components** such as:

1- LgA antibodies to give a protection against bacteria
2- Lysozymes
3- Salivary amylase digests the starch (polysaccharides to disaccharides).
4- Mucoprotein is to lubricate the oral cavity and hydrate foodstuff.

- Food is chewed and mixed with saliva to form a **bolus** (lump of food) which is easier to swallow and pass the pharynx.
- **Pharynx** is the tube that carries the food to the esophagus.
- When bolus is swallowed, muscle action causes epiglottis to close over larynx.

Regulation of salivation

- Salivary secretion is under control of parasympathetic and sympathetic nervous system.
  1- **Parasympathetic stimulation** increases watery output and enzyme-rich saliva.
  2- **Sympathetic division** causes release of mucin rich saliva.
    - Strong stimulation inhibits saliva release (dry mouth).
    - Fear and fatigue reduce nerve activity and secretion.

Esophagus

- Esophagus is the muscular tube that extends from the pharynx to the stomach.
- It is about 2.5 cm long, lies in the mediastinum, posterior to the trachea.
- It transports food from the pharynx to the stomach.
- The movement of the materials is regulated by the **upper esophageal sphincter** (at the upper end) and **lower esophageal sphincter** (at the lower end).
- The esophagus consists of an adventitia, muscular layer, submucosal layer (with mucous glands) and stratified squamous epithelium.

Steps of swallowing

1- **Buccal phase**: Tongue pushes the bolus against soft palate backing the mouth and triggering swallowing reflex.
2- **Pharyngeal phase**: Relaxing the upper esophageal sphincter, epiglottis closes to prevent swallowed material from entering the airways.
3- **Esophageal phase:** Food moves downward into the esophagus by peristaltic movement and by gravity help (figure 11.3).

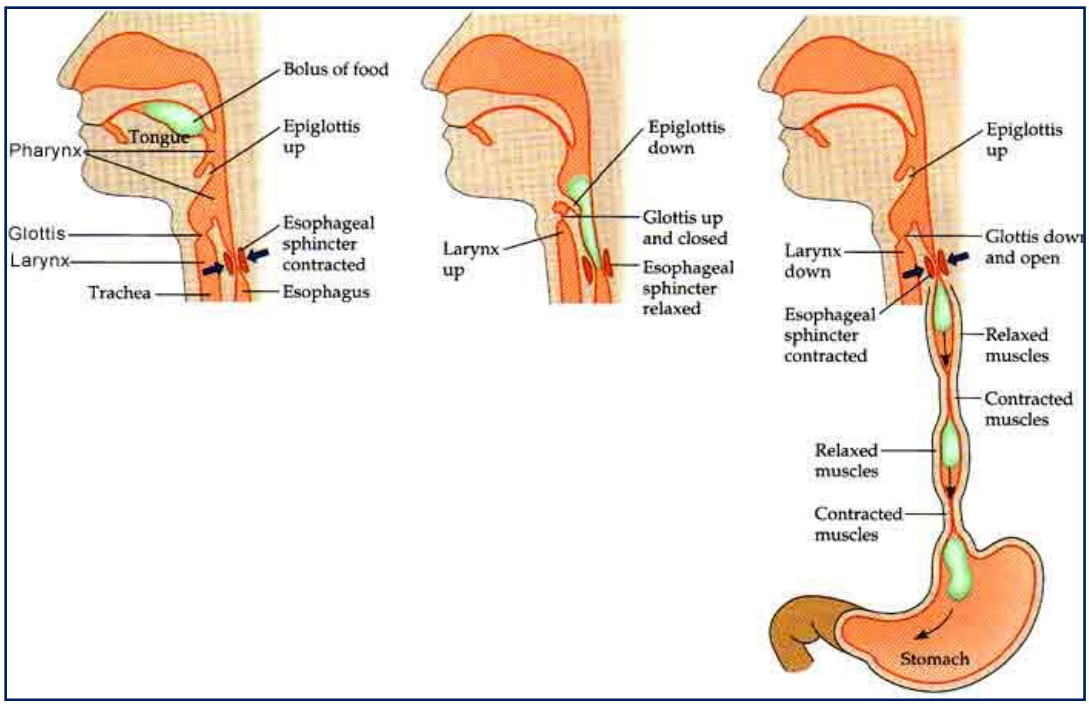


Figure (11.3): Steps of swallowing .Modified from : (Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2010).

Stomach

Anatomical and histological considerations

- Stomach is the enlarged part of the digestive tract that receives the food from the esophagus.
- It lies in the left superior part of the abdomen.
- The opening between the esophagus and the stomach is **esophageal or cardiac opening** which surrounded by **cardiac sphincter**.
- The part to the left of the cardiac part is the **fundus** (figure 11.4.a).
- The largest part of the stomach is the **body** which turns to the right to form a **greater curvature** and lesser curvature to the left.
- The narrow part of the body is the **pyloric part**. The wide part of the pyloric part is the **pyloric antrum** while the narrow part is the **pyloric canal** which opens into the small intestine through the **pyloric orifice**, which surrounded by **pyloric sphincter**.
- The wall of the stomach consists of the following:
  1- An external serosa.
  2- A muscle layer (longitudinal, circular and oblique) (Figure11.4.b)
  3- Simple columnar epithelium (surface mucous cells),which function as:
    - Protection the stomach walls from being damaged by acidic secretion and digestive enzymes.
    - Producing an alkaline mucous to neutralize the acidity and as a barrier to the digestive enzymes.
- The mucous membrane that lining the stomach contains **rugae** which disappear when the stomach fills with food.

- The epithelium forms numerous **gastric pits**, which are opening to the **gastric glands.**
- Gastric glands contain:
  1- **Mucous neck cells** produce mucus.
  2- **Parietal cells** produce hydrochloric acid and intrinsic factor.
  3- **Chief cells** produce pepsinogen.
  4- **Endocrine cells** produce regulatory hormones.

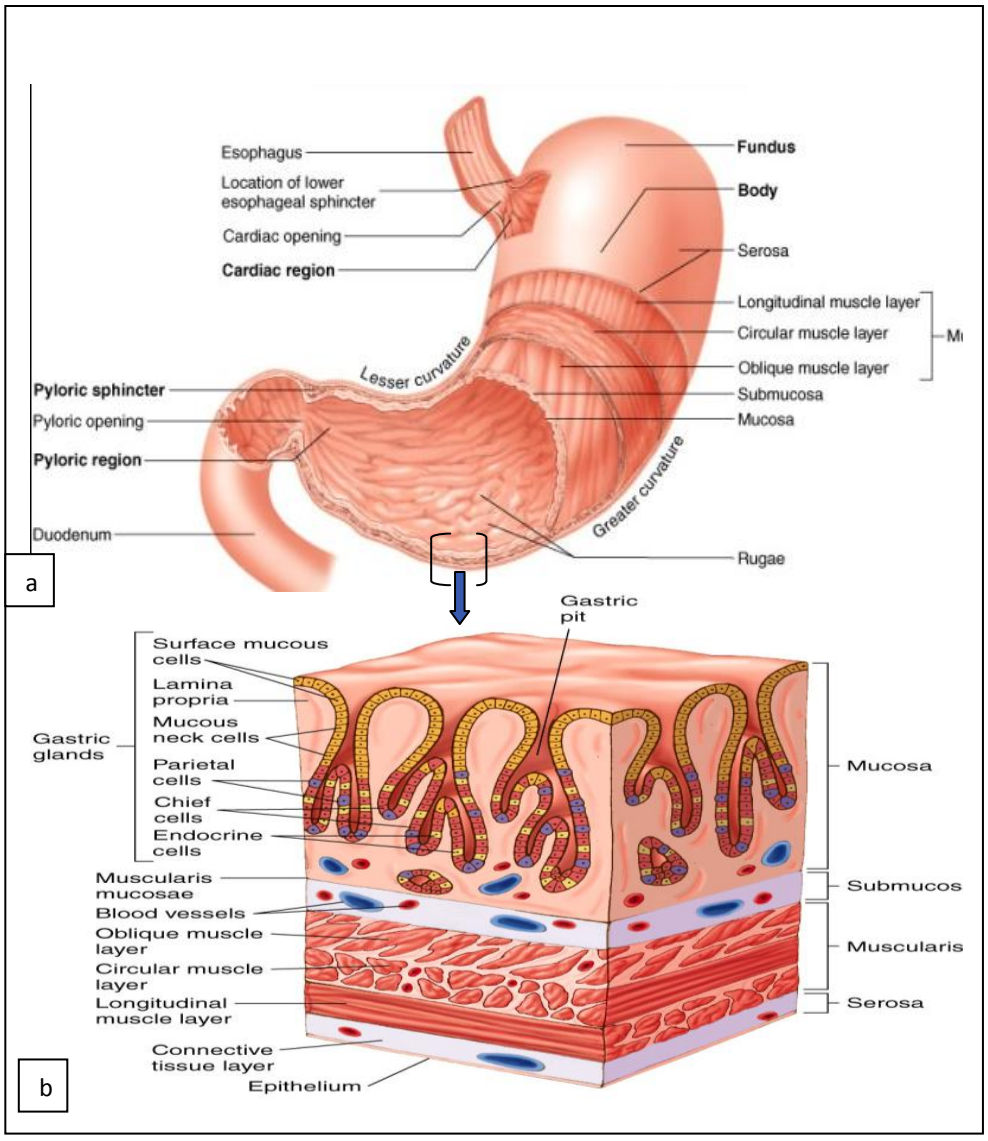


Figure (11.4): **a**-anatomy of the stomach, **b**-Stomach wall.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Function of the stomach

- **Store food:** Food is temporarily stored in the stomach, and then released gradually into the duodenum, because presence of rugae makes it able to expand.
- **Mixing the food with enzyme:** Food is mixed with stomach secretion to form the **chyme** (semi liquid material).
- **Secretion**: Such as mucus, HCl, gastrin, histamine, intrinsic factor and pepsinogen.
  - **Intrinsic factor:** is a glycoprotein that binds to vitamin B12 to make it ready to be absorbed by the ileum.B12 is required in production of RBCs.
  - **Hydrochloric acid**: results in low PH (1-3), which kills microorganisms and activates pepsin.
    - Hydrogen formed from O_2 and H_2O enters the parietal cells.
    - Carbonic anhydrase inside the cells catalyzes reaction between the CO_2 and H_2O to form H_2CO_3, which dissociate to form H^+ and HCO_3^-
    - H^+ transported actively by proton pump (H^+- K^+ pump) into the lumen of the stomach.
    - Chloride ions diffuse with H^+ from the cells (to reduce the energy required to transport H^+ against the concentration gradient).
    - HCO_3^- is exchanged for Cl^- down the concentration gradient and Cl^- enters the cells.(Figure 11.5).

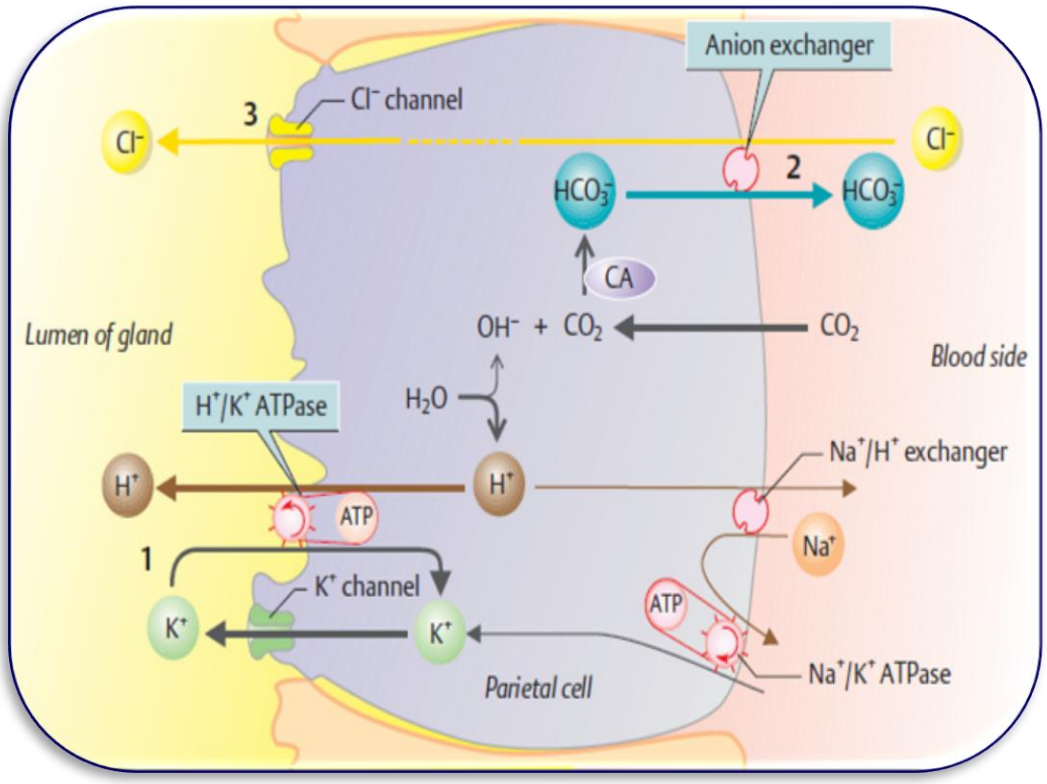


Figure (11.5): Production of HCl by the parietal cell. Retrieved from: tube.medchrome.com

- **Pepsinogen** is secreted by the chief cells and split by HCl into smaller active molecules **(pepsin).** Pepsin starts protein digestion by cleavage of some covalent bonds in the protein to break them into polypeptides chains.
- **Endocrine cells** secret gastrin and histamine.

Regulation of secretion function

Regulation of stomach secretion is divided into ***three phases:***

1- Cephalic phase, (figure 11.6)

- The tastes, smell, thinking of foods activate the hunger center in the **medulla oblongata.**
- Action potentials are sent from medulla oblongata along the parasympathetic neurons within vagus nerves to the stomach to activate enteric plexus neuron.
- Postganglionic neurons stimulate parietal cells, chief cell and endocrine cells.
- Gastrin is carried through the circulation to the stomach again to stimulate secretion of HCl and pepsinogen.

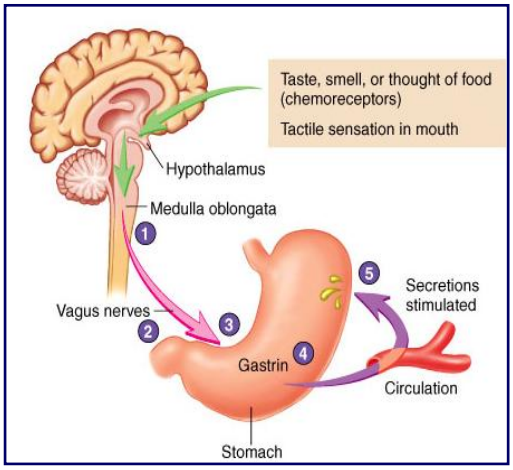


Figure (11.6): Cephalic phase

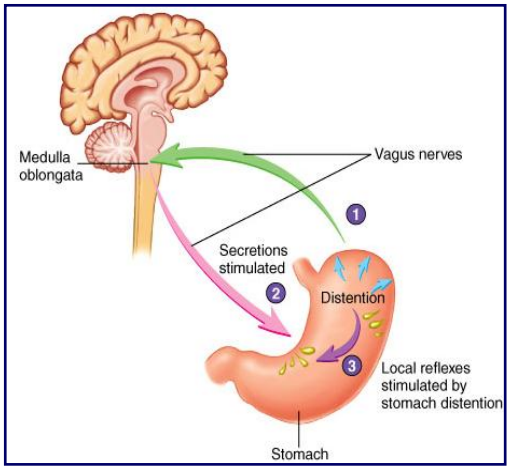


Figure (11.7): Gastric phase

(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

2- Gastric phase

- Distention of the stomach walls stimulates the stretch receptors and parasympathetic reflex. Action potentials are carried by vagus nerve to the medulla oblongata.
- Medulla oblongata increases action potential to stimulate parietal cells, chief cells and endocrine cells.
- Activation the local reflexes to increase stomach secretion.
- Gastrin travels through the circulation backing to the stomach to stimulate additional secretion. (Figure11.7).

3- Intestinal phase

- Small quantities of chyme are released into the duodenum, at intervals, through the pyloric sphincter valve.
- Acidic chyme in the duodenum (**PH<2**)or lipid content inhibits gastric secretion by several mechanisms:
  - Stimulation the chemoreceptors by increased H^+ concentration or lipid. Chemoreceptors generate action potentials which travel to the medulla oblongata where they inhibit parasympathetic stimulation to decrease gastric secretion.
  - H^+ or lipids activate local reflexes to inhibit gastric secretion.
  - **Secretin** secretion inhibits gastric secretion by inactivation parietal cell and chief cells. **Cholecystokinin (CCK)** inhibits gastric secretion. (Figure 11.8).

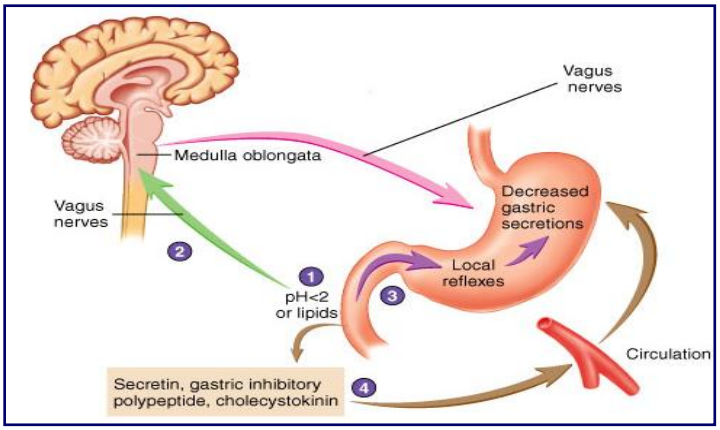


Figure (11.8): Intestinal phase. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

Pharmacology note: **Gastric acid secretion Inhibitors**: there are **H_2 receptors** (histamine receptors on the parietal cells different from **H_1 receptors** involved in allergic reactions). Drugs that affect allergic reaction do not affect stomach acid secretion. **Cimetidine** (Tagamet) and **ranitidine** (zantac) are histamine receptors antagonists that prevent the binding of histamine to the receptors on parietal cells.These drugs are effective inhibitors of gastric acids secretion .**Cimetidine** is used to treat increased gastric acid secretion resulting from **gastritis** and **gastric ulcer.**

Gastric motility

1- Gastric filling

- Relaxation of the proximal segment of the stomach (fundus and the proximal portion of the body) to receive the food bolus.
- Swallowing a bolus of food triggers a vasovagal reflexes which causes the lower esophageal sphincter to open and proximal segment to dilate (receptive relaxation).

2- Mixing of stomach contents is accomplished by**:**

- ***Mixing wave*** to break the food into smaller pieces and mix it with the gastric secretion. Wave contraction occurs every 20 seconds proceeding from the body of the stomach toward the pyloric sphincter. It is 80% of the contraction.
- ***Peristaltic waves*** are more powerful than mixing wave and less frequently. They force the chyme toward the pyloric sphincter. It is 20% of the contraction.
- Gastric contraction is increased by parasympathetic stimulation and hormones (**gasterin** and **motlin**).While sympathetic stimulation and hormones **secretin** and **gastric inhibitory peptides (GIP)** decrease the contraction.

3- Emptying of stomach

- Stomach is empty within 3-4 hours after the meal.
- The pyloric sphincter remains partially closed. The peristaltic contractions are able to push a small amount of chyme through the pyloric opening and duodenum by **pyloric pump.**
- Emptying of stomach is regulated by hormones and nervous mechanisms:
  1- **Hormones:** Fats in the duodenum stimulate the releasing of **GIP** which decreases peristaltic contraction and slowing the passage of the chyme into the duodenum.**CCK** is the major inhibitory hormone of the gastric motility.
  2- **Nervous mechanism:** The receptors in the duodenal mucosa are sensitive to the **distention** and **acidity**; therefore the impulses along sensory and motor fibers in the vagal nerves cause reflex inhibition to the peristaltic contraction.

Pharmacology note: **Metoclopramide** is a D2 receptor antagonist and 5-HT3 antagonist which is prokinetic agent used in treatment of nausea and vomiting in patients who have delayed gastric emptying **(gastroparesis).**

Clinical note: Patients with long uncontrolled diabetes mellitus may develop sever dysfunction of gastric motility **(gastroparesis)** which occurs as a result of damage to the autonomic nerves that supply the stomach.This makes the patients suffer from nausea and vomiting.In this case, **Metoclopramide** can relief the symptoms.

Small intestine

Anatomical and histological considerations

- **Small intestine** is a convoluted tube extends from the **pyloric sphincter** to the **ileocecal valve** where it joins the large intestine.
- It is where the greatest amount of digestion and absorption occur.
- It consists of three parts: **Duodenum** is about 25 cm long ,**jejunum** (2 m long)and **ileum**(3.5 m).(Figure 11.9).

- There are two major **accessory glands** associated with duodenum: **liver** and **pancreas.**

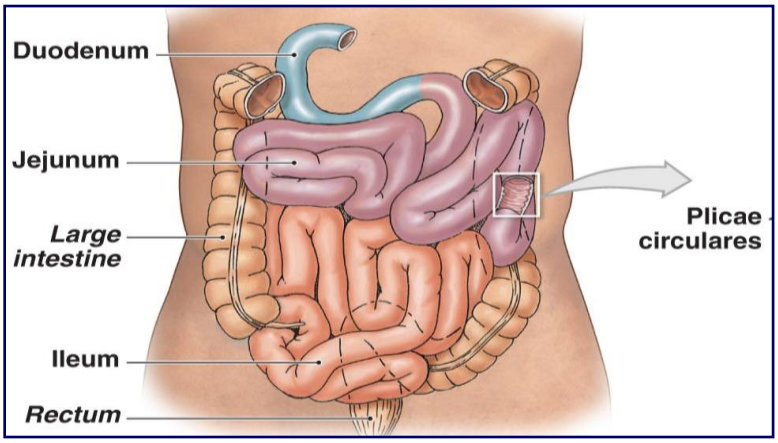


Figure (11.9): Parts of small intestine. (Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2010).

Duodenum

- Duodenum is the first part of the small intestine, curves around the pancreas.
- The bile duct (***that deliver the bile from the liver)*** and pancreatic duct (***that carries the pancreatic juice***) unit in the **hepatopancreatic ampulla**.
- The hepatopancreatic ampulla opens in to the duodenum via the major **duodenal papillae**.(Figure 11.11).
- The entry of bile and pancreatic juice is controlled by the **hepatopancreatic sphincter**.
- The mucosa and submucosa in the surface of the duodenum form structural modifications to increase the efficiency of digestion and absorption(figure11.10):
  1- **Circular folds (plicae):** permanent folds of the mucosa and submucosa, about 1cm long .These structures force the chyme to spiral through the lumen and slow the movement to allow more time for absorption.
  2- **Villi:** finger like projections of mucosa, about 0.5-1.5 mm in length. Each villus is covered by simple columnar epithelium and contains blood capillary network and lymphatic capillary called **lacteal. (**Figure11.10).
  3- **Microvilli:** cytoplasmic extensions from the cells that make up the villi surface. These are for further increase the surface area. These microvilli on the entire epithelial surface form the **brush border.**
- There are four types of cells in the mucosa of the duodenum:
  1- **Absorptive cells**: produce digestive enzymes.
  2- **Goblet cells:** produce protective mucus.
  3- **Granular cells:** protect the intestinal epithelium from bacteria.
  4- **Endocrine cells:** produce regulatory hormones.
- The epithelial cells are produced within the invaginations of the mucosa, called **(crypst of Lieberkuhn)** at the base of the villi.
- The tubular mucous glands in the submucosa are called **Brunner gland.**

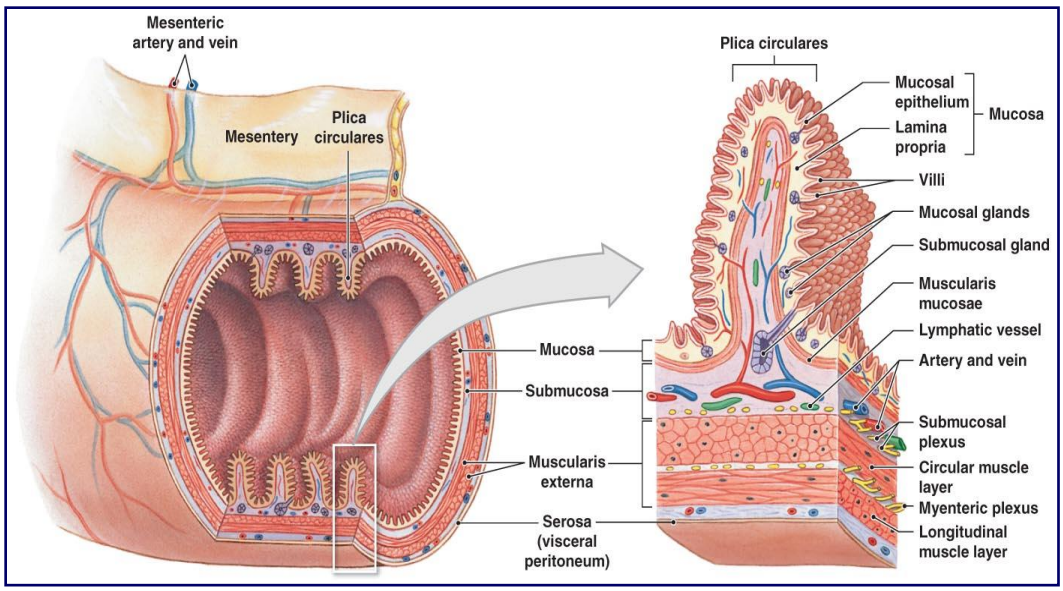


Figure (11.10): Histological modifications in the small intestine. (Marieb E.N.and Hoehn K.Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

Jejunum and ileum

- Jejunum and ileum show decreasing in the diameter, wall thickness, number of folds and villi.
- They hang in the central and lower part of the abdominal cavity suspended from the posterior abdominal wall(**mesentery**)
- These two parts are the major site for absorption.
- There are numerous lymphatic nodules called **Peyer's patches** which have immune function against microorganisms entering the mucosa.

Small intestine secretions

- The secretion produced by the mucosa of the small intestine contains: **mucus**, **electrolytes (**HCO_3^- neutralize the PH) and **water**.
- The intestinal secretions lubricate and protect the walls of small intestine from the digestive enzymes and acidic chyme. They also keep the intestinal contents in a liquid form.
- Secretions from the intestinal mucosa, liver and pancreas enter the small intestine to do their digestive functions. ***Most digestive enzymes are produced by the pancreas.***
- Intestinal mucosa release secretin and CCK to hepatic and pancreatic secretion.
- Enzymes of the intestinal mucosa are surface bond enzymes attached to microvilli. These enzymes are:
  1- ***Disaccharidase:*** breaks down the **disaccharides** to produce **monosaccharides.**
  2- ***Peptidase:*** hydrolyzes the **peptide bonds** between the amino acids in polypeptide chains.

- Break down products of digestion are absorbed through the microvilli and enter the circulation.
- Vagus nerves, secretin and chemicals or tactile sensation of the duodenal mucosa stimulate the duodenal glands and goblet cells.
- The chyme takes 3-4hours to move from the pyloric region to the ileocecal junction.

Intestinal motility

- There are two kinds of movement of the intestine:
  1- **Segmental contraction**: is accomplished by smooth muscle in the walls of the small intestine. It is propagated for short distance .It mixes the intestinal contents.
  2- **Peristaltic contraction:** propel the contents along the digestive tract. They are continuations of peristaltic contraction in the stomach.

Clinical note: Duodenal glands secretion is inhibited by the sympathetic stimulation, resulting in reducing the protective mucous layer on the duodenal wall.Therefore the person who is highly stressed and has an elevated sympathetic activity may illustrate more susceptibility to **duodenal ulcer.**

Regulation of the intestinal motility

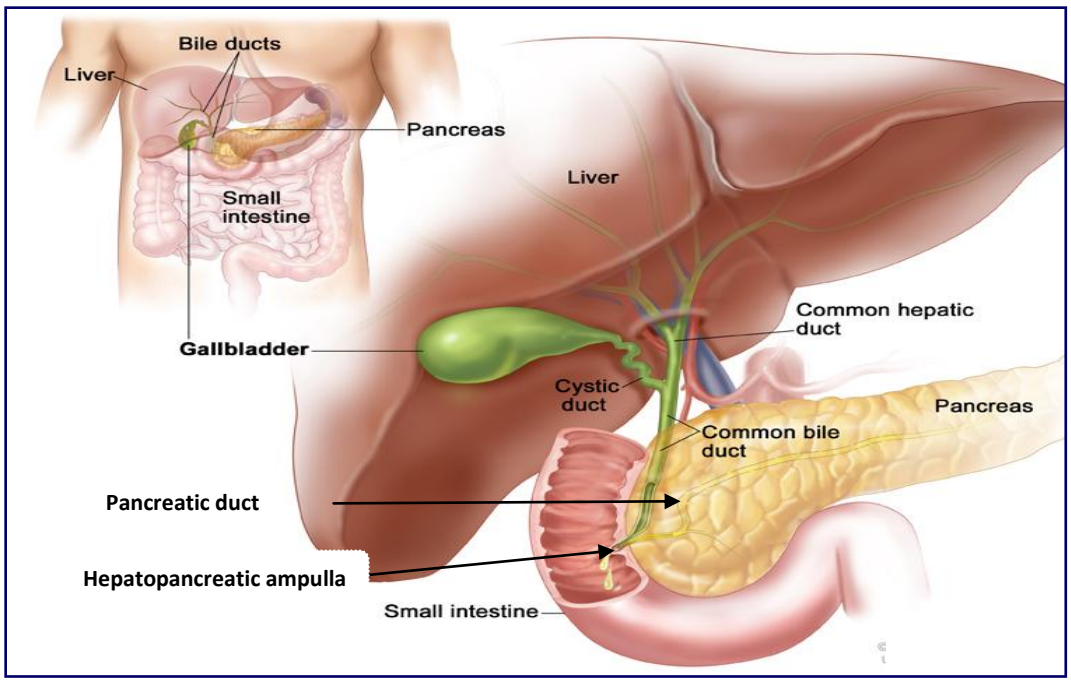
- Local mechanical and chemical stimuli are important in the regulating the intestinal movement.
- Smooth muscle contraction due to distention of intestinal walls, acidic solution and presence of amino acids or peptides stimulate intestinal contraction.
- Local reflex and parasympathetic stimulate contraction.

Pharmacology note: The antibiotic **erythromycin** is sometime used as a laxative in constipated adults because its common side effects (nausea, diarrhea).It produces these effects by stimulating the motilin receptors

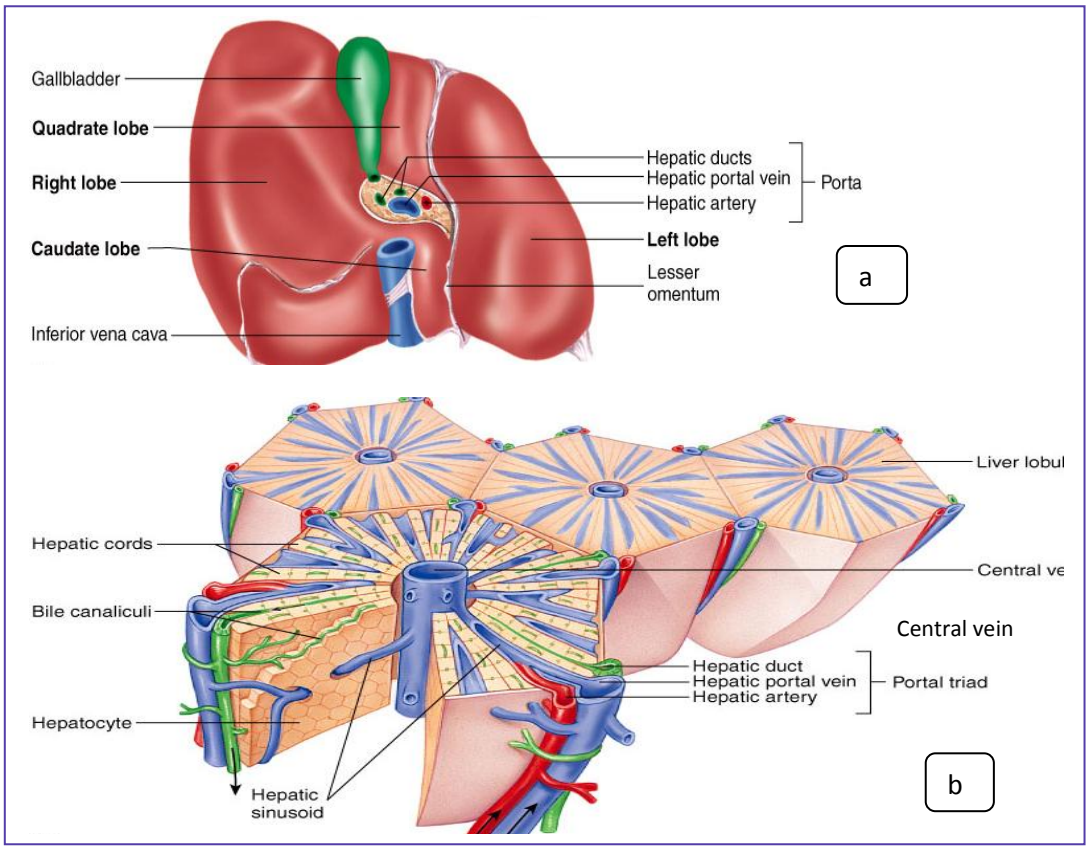
Liver

Anatomical and histological considerations

- Liver is the largest organ in the body, about 1.36 Kg weight.
- It is located in the right upper quadrant of the abdomen.
- It consists of **two major lobes**: left and right and **two minor lobes**: caudate and quadrate. (Figure 11.12 , a).
- **A porta** is the site where the vessels, ducts and nerves enter and exit the liver.
- The bile is transported out of the liver by the **hepatic duct**.
- The right and left hepatic ducts unit to form **common hepatic duct.**



Figure(11.11):Anatomical structures of the liver and ducts system . (Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2010).



Figure(11.12):a:Lobes of the liver,b:Liver histology. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- Common hepatic duct joins the **cystic duct** (from gallbladder) to form **common bile duct** which joins the **pancreatic duct** at the **hepatopancreatic ampulla.**
- Hepatopancreartic ampulla empties into the duodenum at the major **duodenal papillae.** (Figure 11.11).
- The liver is made up of millions lobules,each with a centarl vein and portal triad at the corner (composed of hepatic duct,hepatic porta; vein and hepatic artery).(Figure 11.12 . b).
- **Hepatic cords** radiate out from the central vein.
- Hepatic cord is composed of **hepatocytes**.The spaces between the hepatic cords are the **hepatic sinusoids** which empty into the central vein.

Functions of the liver

1- Bile production :Liver produces and secrets the **bile** which play a role in digestion by:

- Neutrilze and dilute the acidic chyme.
- Bile salts emulsify the fats.
- Bile contains bile pigment**(bilurubin)**from hemoglobin destruction.
- Bile contains cholesterol,fat and fat soluble hormones.
- Control of bile secretion and release is summerized in figure(11.13).

2- Storage

- Storage of excess glucose in the blood in form of glycogen.Hepatocytes control blood sugar by preventing hyperglycemia when the blood passes from the intestine to the liver through the hepatic vein,and secret glucose again to the circulation when needed.
- Storage of fats ,vitamins(A,B12,D,E and K),copper and ions.

3- Interconversion of the nutrients

- The liver converts some nutrients into other form (**fructose** into **glucose).**
- Ingested fats are combined with **choline** and **phosphorus** in the liver to form **phospholipids.**

4- Detoxification

- Some ingested food produce harmful by-products when metabolized. The liver detoxify these by-products by altering their structures to less toxic,or eliminated easily e.g.,**ammonia** (by-product of amino acids metabolism)into **urea** which is less toxic and secreted into the circulation then eliminated by the kidney.

5- Phagocytic activity

- Phagocytic cells of the liver **(kupffer cells)** have the ability to phagocyteize dying RBCs,WBCs and some bacteria entering the circulation.

6- Synthesis of blood components

- Liver produces many blood proteins such as: albumins, fibrinogen, globulins, heparin and clotting factors.

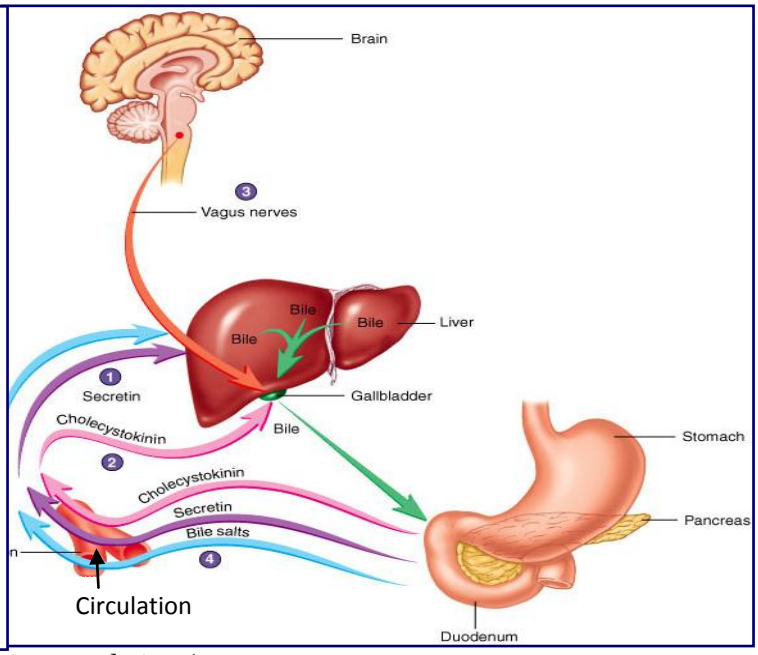
Clinical note: Hepatitis is the inflammation of the liver that results from alcohol consumption or infection (viral infection).**Hepatitis A** is called infectious hepatitis, **hepatitis B** is called serum hepatitis ,is more chronic infection and **hepatitis C**.It is caused by one or more virus types which is spread by the blood transfusion and sexual intercourse. If it is not treated ,liver cells die leading to loss of liver function and liver failure.

1-Duodenum secrets secretin which is carried to the liver to stimulate HCO_3^- into the bile.

2-CCK produced by the duodenum is carried to the gallbladder to contract and release bile into the duodenum.

3- Vagus nerve stimulation to contract and release bile into the duodenum.

4-Bile salt stimulate bile secretion



Figure(11.13): Bile secretion regulation.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Gallbladder

- Gallbladder is a small sac on the inferior surface of the liver.It stores the **bile**.
- **Bile** is secreted by the liver and flows to the gallbladder to store in about40-70ml.
- Water and electrolytes are absorbed while salt and pigment become concentrated.
- After a meal ,the gallbladder contracts in response to CCK and vagal stimulation and secrets the bile into the small intestine.

Clinical note: Gallstone results from excess cholesterol in the bile due to high cholesterol diet or high concentration of cholesterol in the gallbladder. Gallstones may pass out of gallbladder and enter the cystic duct, blocking the release of bile.In some cases they move down and block the pancreatic duct resulting in pancreatitis. They must be removed surgically.

Pancreas

Anatomical considerations

- The pancreas is composed of both **endocrine** and **exocrine** tissues.
- It consists of **a head** in the curvature of the duodenum ,**body** and **tail** which extends to the spleen.(Figure 11.14. a).
- **Endocrine part** consists of **ilets of Langerhans .**The ilets cells produce:
  1- **Insuline** which regulates blood glucose level.
  2- **Glucagon** which is important in contrilling glucose and amino acids levelin the blood.
  3- **Somatostatin hormone** which regulates insulin and glucagon.
- **Exocrine tissues** composed of lobules that contain **acini. (**Figure11.14.b).
- The acini connect to a duct system that leads to pancreatic duct.

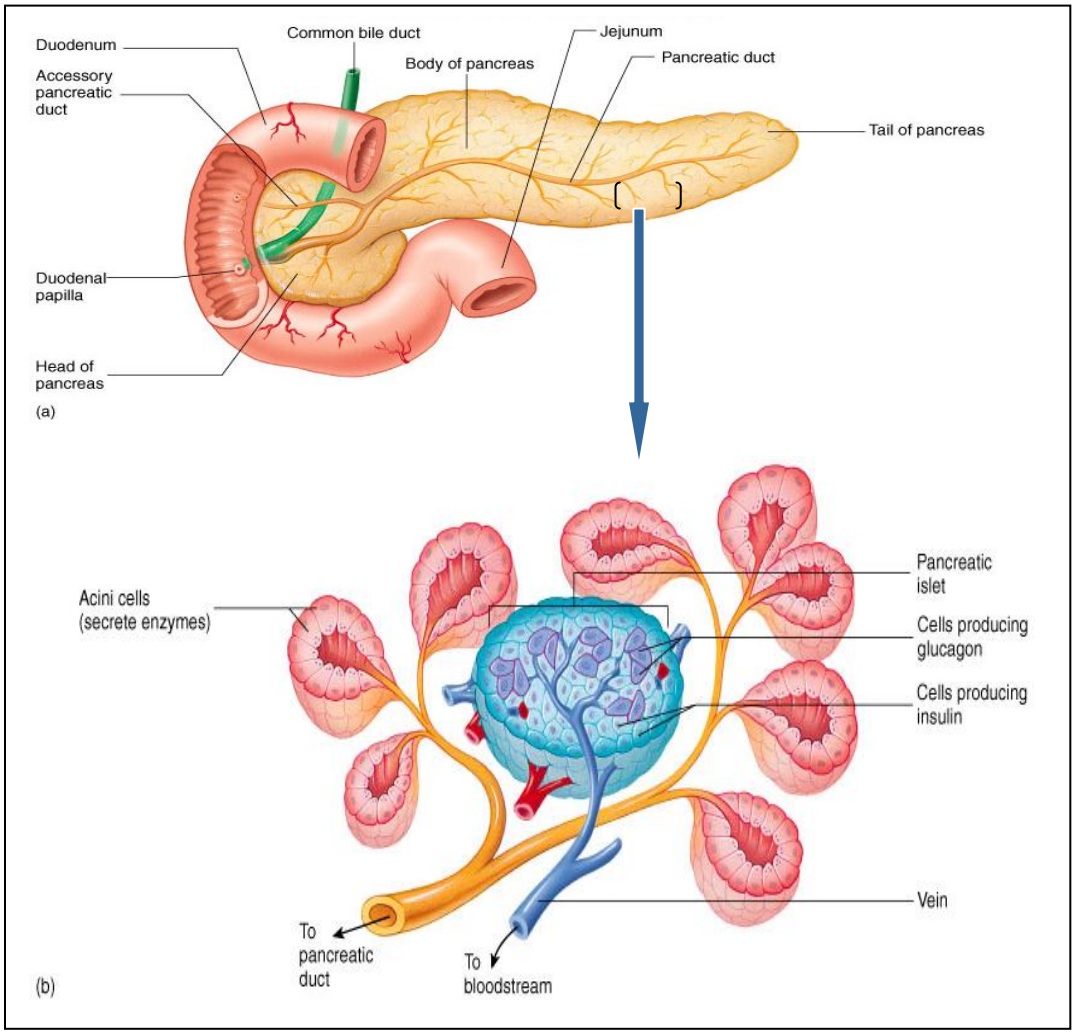


Figure (11. 14): a: Structure of the pancreas, b: histology of the pancreas. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Pancreatic secretion

- The exocrine secretions are called **pancreatic juice**, which delivered to the duodenum through the pancreatic duct.
- The pancreatic juice is composed of :
  - **An aqueous component**. This contains Na^+, K^+ and HCO_3^- that neutralizes the acidic chyme entering the small intestine and activates pancreatic enzyme.
  - **Enzymatic components:**

  1- **Proteolytic enzymes:** digest **tyrosine**, **chymotrypsin** and **carboxypeptides**. They are secreted in inactive form to prevent digestion of the tissues that producing them.
    - **Enterokinase** is an intestinal enzyme produced in active form to activate the **trypsinogen** to **trypsin** which activates more **trypsinogen** and **chymotrypsinogen.**

  2- **Pancreatic amylase:** digests **polysaccharides**.

  3- **Pancreatic lipases** break down lipids into monoglycerides, free fatty acids and cholesterol.

  4- **Deoxyribonucleases and ribonucleases** break down DNA and RNA.

Regulation of pancreatic secretion.

- The pancreatic secretion is regulated by **hormonal** and **neural mechanisms.**
- An acidic chyme in the duodenum stimulates the release of **secretin**.
- Secretin stimulates the watery secretion of the pancreas which contains HCO_3^- to increase PH of the chyme in the duodenum.
- **Cholecystokinin** released from the duodenum stimulates bile release from the gallbladder and secretion of enzymatic components of the pancreas.
- Parasympathetic stimulation through vagus nerves stimulates the pancreatic juice secretion, while sympathetic stimulation inhibits the secretion.

Clinical note:Pancreatitis is the inflammation of the pancreas that involves the release of pancreatic enzymes within the pancreas which digest pancreatic tissues.It may result from alcoholism,certain drugs viral infection and cancer.Its symptoms range from mild abdominal pain to systemic shock.

Large intestine

Anatomical considerations

- Large intestine is the portion of the digestive tract that extends from ileocecal junction to the anus.
- It consists of **cecum, colon**, **rectum** and **anal canal.** (Figure11.15).
- The chyme in the colon is converted to feces where it stored until eliminated by defecation

Cecum

- Cecum is the first portion of the large intestine where the large intestine meets the small intestine at ileocecal junction.
- It is attached to a small blind tube, about 9 cm long called **vermiform appendix**, which its walls contain lymphatic nodules.

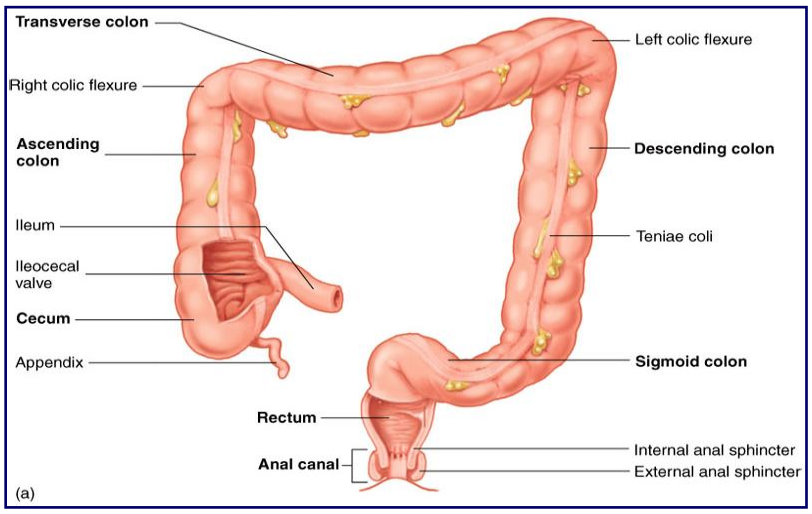


Figure (11. 15): Large intestine. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Colon

- Colon is the second portion of the large intestine.
- It consists of ascending colon, transverse colon, descending colon and sigmoid colon which ends at the rectum.
- The longitudinal muscle layer is incomplete and form three bands **called teniae coli** that cause pouches called **haustra** when it contracts.
- The mucosa of the large intestine is simple columnar epithelium with tubular glands called **crypts.**

Rectum

- The rectum is a muscular expandable tube begins at end of the sigmoid colon and ends at the anal canal.
- Movement of fecal material into rectum triggers defecation urge.

Anal canal

- Anal canal is the last portion of the digestive tract that ends at the anus.
- It is surrounded by the **internal sphincter** (composed of smooth muscles) at the superior end and **external sphincter** (composed of skeletal muscles) at the end of the anal canal.

Large intestine motility

- **Segmental movement** is to mix the contents of the colon.
- **Mass movement** is to a strong contraction responsible for propel the colon contents toward the anus.

- Local reflexes (gastro and duodenocolic reflexes) integrate mass reflexes, which are mediated by :
  1- Parasympathetic stimulation.
  2- Hormones (CCK, gastrin).
  3- Thoughts or smell of food; movement of the chyme into the duodenum stimulate large intestine movement.

Defecation

- Defecation is the elimination of feces by reflexes activity.
- It requires relaxation of the internal and external sphincters.
- Movement of the feces from the colon into the rectum stimulates the **defecation reflexes.**
- Feces is formed by water and salt reabsorption, secretion of mucus and action of the microorganisms.
- About 1500 ml of the chyme enters the cecum each day and 90% is reabsorbed.

Defecation reflexes

- The feces in the rectum stimulate local reflexes.
- Action potential is produced and propagated to the defecation center in the spinal cord.
- Action potential stimulates colon and rectum contraction and relaxation of internal anal sphincter.
- Action potential is propagated to the brain through the ascending nerve.
- The descending nerves from the brain regulate the defecation reflex center.
- Action potential from the brain controls the external anal sphincter.
- The voluntary action regulates the movement through the external sphincter.

Secretion of the large intestine

- **Mucus** is the major secretion of the large intestine. It lubricates the walls of the colon and causes the fecal material to hold together.
- Tactile and parasympathetic stimulations increase the mucous secretion.
- The epithelial cells secrete HCO_3^- to neutralize the decreased PH by the bacterial actions.
- Sodium ions are absorbed by active transport and water move by osmosis. The feces consists of water, solid undigested food, microorganisms and sloughed off epithelial cells.
- Microorganisms constitute 30% of the dry feces. They are responsible for vitamin K production and gas production.

Digestion and absorption

- **Digestion** is the break down the organic materials into their main components parts.
- **Absorption and transport** are means by which the molecules are moved out of the digestive tract and distributed throughout the body.
- Transport is done by two routs:

1- **Water soluble materials, water and ions** are transported to the liver through the **hepatic portal vein**.
2- **Lipid soluble products** are transported to the circulatory system through the **lymphatic system**.

- There are three types of food: **carbohydrates**, **proteins** and **lipids** which are digested and absorbed in the small intestine.

Carbohydrates

- **Carbohydrates** are first exposed to digestion in **the mouth** by the effect of **salivary amylase** to produce **maltose**, **maltotrios** and **dextrin.**
- In **the duodenum:**
  - More **amylase** is secreted from the pancreas.
  - **Maltase, sucrase** and **α-dextrinase** hydrolyze the oligosaccharides to glucose.
  - **Lactase** degrades lactose to galactose and glucose.
  - **Sucrase** degrades sucrose to fructose and glucose.
- **Monosaccharides** (glucose and galactose) are taken into the intestinal epithelial cells by **symport** depending on Na^+ - K^+ pump.(Figure11.16).
- Monosacchrides move out the epithelial cells by **facilitated diffusion** to the intestinal villi capillaries, and then they are carried to the liver by the **hepatic portal vein.**
- In the liver, non-glucose sugar is converted to glucose.
- Glucose enters the cells by **facilitated diffusion** which is regulated by insulin.

Clinical note: Lactose intolerance results from the absence of lactase and thus inability to hydrolyze lactose (in milk and dairy products) to glucose and galactose to absorb .Therefore non absorbed lactose and water remain in the lumen of digestive tract resulting in **osmotic diarrhea**.

Pharmacology note: Carbohydrates digestion can be impaired in diabetic patients by α-glucosidase inhibitors **(acarbose).**These drugs inhibit the intestinal enzymes sucrose,maltase and amylase leading to impairing carbohydrates digestion and glucose absorption.This facilitates glucose control in diabetic patients,but the carbohydrates remain in the gut causing adverse effects (nausea and diarrhea).

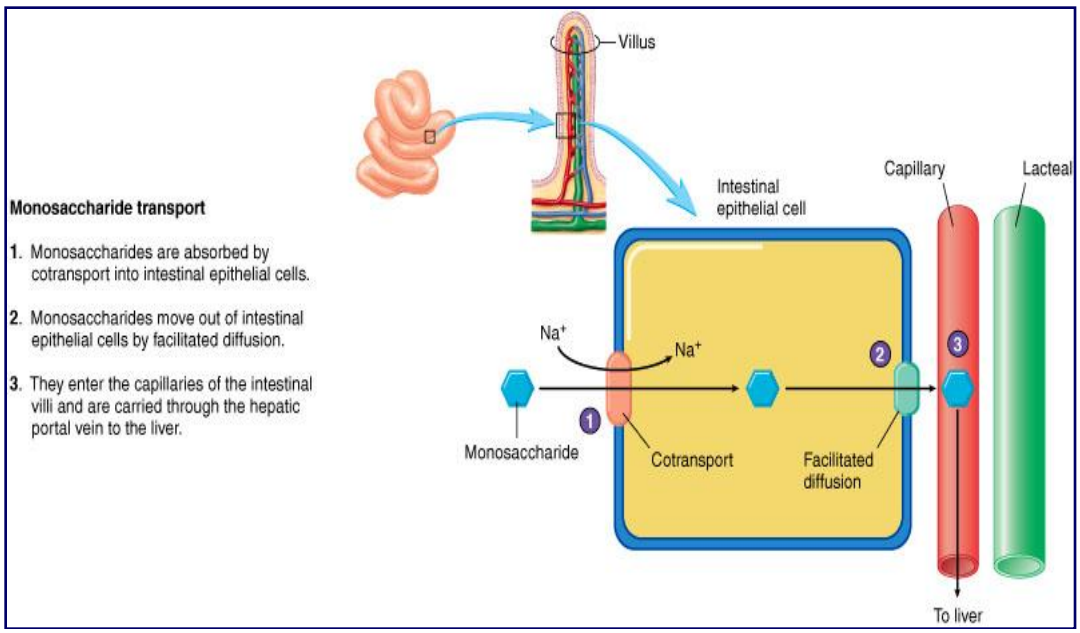


Figure (11.16): Monosaccharides transport.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Proteins

- Proteins are made of long chains of **amino acids.**
- Proteins are broken down into shorter chains of **polypeptides chains** by protein digesting enzyme (**pepsin**) which is secreted in inactive form and activated by **HCl.**
- **In the small intestine** polypeptides chains expose to digestion **by proteolytic enzymes** of pancreas and intestinal mucosa:
  1- **Endopeptidases act** at anterior peptides bonds, e.g.**, trypsin**, **chymotrypsin** and **elastase.**
  2- **Exopeptidases** act at the carboxyl and amino ends of the polypeptide chains, such as **carboxypeptidase.**
- Digestive products of the proteins can be absorbed as **amino acids**, **dipeptides** and **tripeptides.**
  1- **Transport of free amino acids:**
    - Amino acids absorbed by Na^+ dependent amino **cotransport** that occurs in the luminal membrane.
    - Amino acids are transported then from cells to the blood by **facilitated diffusion.** (Figure11.17).
  2- **Transport of dipeptides and tripeptides**
    - They are absorbed by H^+ dependent cotransport that occurs in the luminal membrane.
    - They are hydrolyzed by peptidase to amino acids in the intestinal cells.
    - Amino acids are carried to the liver through the hepatic portal vein where to be modified and distributed throughout the body.

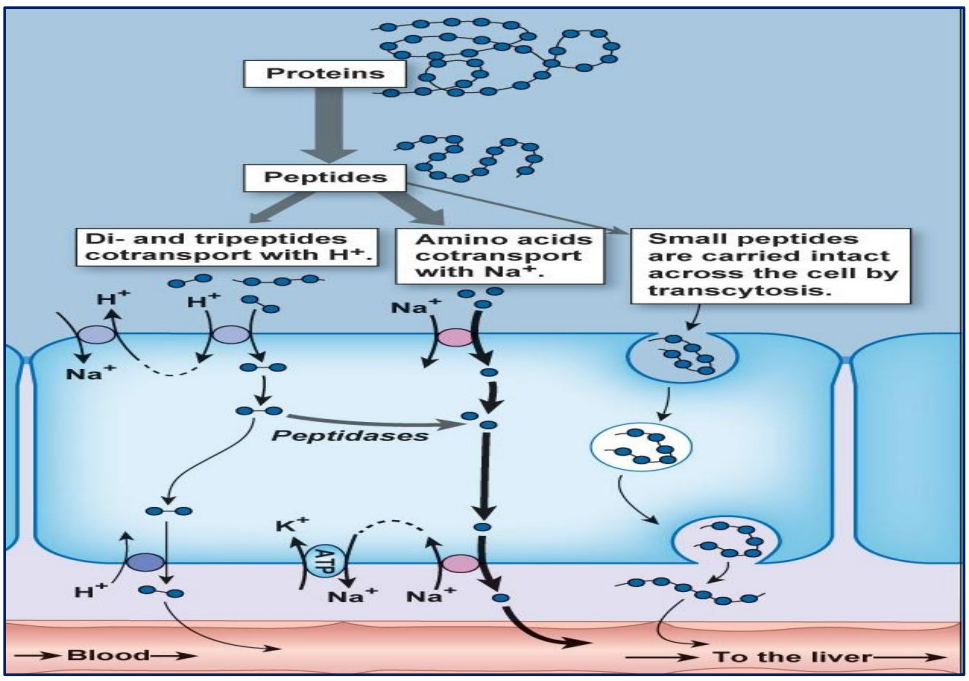


Figure (11.17): Transport of protein.(Marieb E.N. and Hoehn K. Human Anatomy and Physiology.San Francisco, Pearson Education Inc., 2010.Retrieved from :www.studyblue.com).

Lipids

- **Lipids** are insoluble in water. They include: **triglycerides**, **phospholipids, cholesterol, steroids** and **fat soluble vitamins.**
- **Digestion of the lipids :**
  1- **In the stomach**
    - The first step of lipids digestion is **emulsification .**Emulsification is break down the large lump of fat into much smaller droplets to increase the surface area for attack by lipase.
    - **Lingual lipase** digests the **triglycerides** into **monoglycerides** and **free fatty acids.**
  2- **In the small intestine**
    - **Emulsification of lipids by** bile acids for further increase in the surface area for digestion.
    - **Pancreatic lipase** hydrolyzes lipids into **fatty acids, monoglycerides**, **cholesterol** and **lysolecithin.**
    - **Formation of micelles:** Fatty acids and monoglycerides are enclosed by bile salt to form **micelles.** Fatty acids and monoglycerides at the center of the micelles and the hydrophilic ends are directed outward.
- **Lipids absorption**
  1- **Micelles** make the products of the lipid digestion in contact with the epithelial cells of the small intestine. **Fatty acids**, **monoglycerides** and **cholesterol** pass by **simple diffusion** through the plasma membrane into the cells.

2- In the intestinal cells, lipids digestion products are converted into **triglycerides**, **cholesterol ester** and **phospholipids**.Proteins coat the triglycerides to form **chylomicrons.**

3- **Chylomicrons** are transported out of the intestinal cells by **exocytosis.**They enter the lacteals of the intestinal villi and carried through the lymphatic system to the general circulation. (Figure11.18).

Lipids transport

- Lipids are transported through the blood in combination with proteins.
- Lipids combined with proteins are called **lipoproteoins.**Lipoproteins are two types**:**
  1- **Low density lipoprotein (LDL)**: its components are (99 % lipids and 1% proteins).It is considered to be bad, because when excess it deposits cholesterol on the arterial walls.
  2- **High density lipoprotein (HDL)**: its components are (55% lipids and 45% proteins).It is good because it transports cholesterol from the tissues via blood to the liver to be removed from the body in the bile.

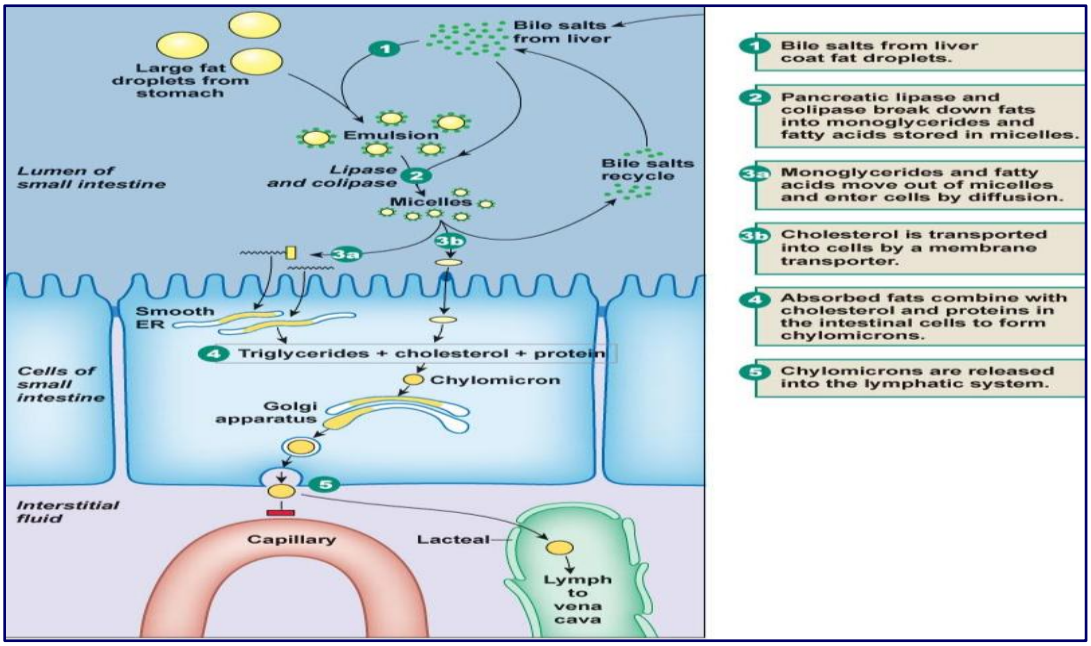


Figure (11.18): Digestion and absorption of lipids. (Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2010.Retrieved from :www.studyblue.com).

Absorption of water

- Water is transported through the intestinal membrane by osmosis **(Isosmotic absorption**):
  - When chyme is diluted, water is absorbed into the blood of the villi, through the intestinal mucosa.
  - Water is transported from the plasma to the chyme when hyperosmotic solution is discharged from the stomach into the duodenum.

- About 9 L of water enter the digestive tract each day,92% is reabsorbed in the small intestine ,6-7% is reabsprbed in the large intestine and 1% is secreted in the feces, (figure 11.19).

Absorption of electrolytes

1- Apsorption of NaCl

- Na^+ is actively absorbed in the jejunum and ileum.
- Na^+ moves **into** the intestinal cells down its electrochemical gradient across the luminal membrane by :
  1. Passive diffusion
  2. Na^+ -glucose and Na+ - amino acid cotransport.
  3. Na^+ - Cl cotransport
  4. Na^+ - H^+ exchange.
- Na^+ pump **out of** cell against its electrochemical gradient by the Na^+ - K^+ pump in the basolateral membrane.

- **Absorption of Cl^-** accompanies the absorption of Na^+ by:
  1. Passive diffusion
  2. Na^+ - Cl- cotransport.
  3. Cl^- -HCO_3^- exchange.

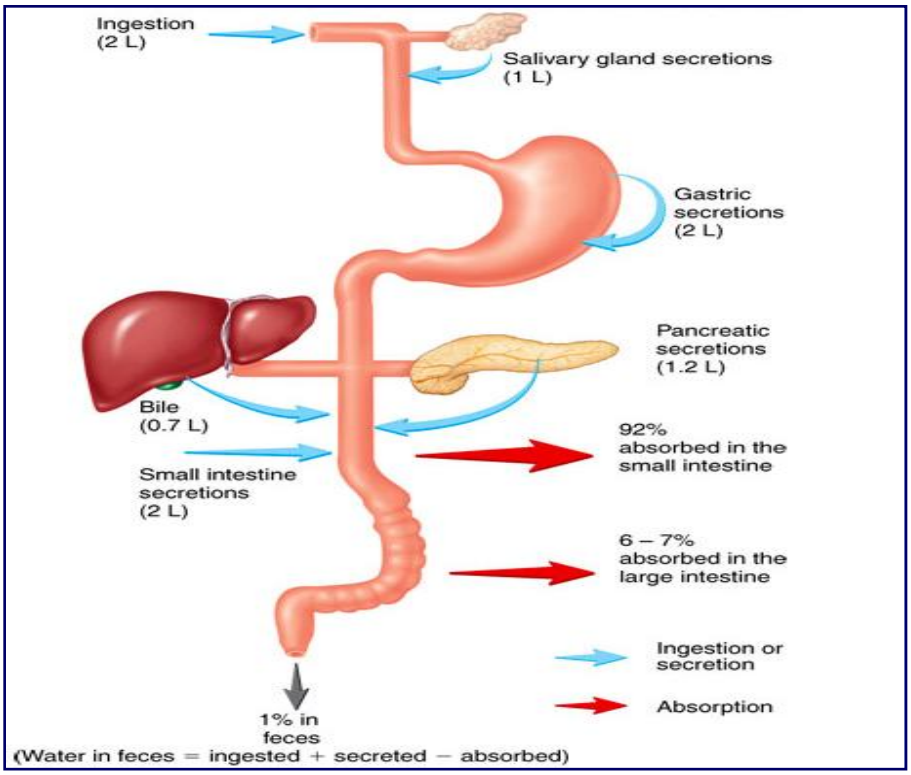


Figure (11.19): Water volume along the digestive tract.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

2- Absorption of K+

- Dietary K^+ is absorbed passively in the small intestine via paracellular route.
- K^+ is actively secreted in the colon and is regulated by **aldosterone.**
- K^+ secretion by the colon is elevated in **diarrhea**.An excessive loss of K^+ causes **hypokalemia**.

3- Absorption of Ca^{2+}

- Calcium is absorbed actively by the blood of the duodenum**.**
- Its absorption is controlled by **parathyroid hormone** and active form of vitamin D **(1, 25-dihydroxycholecalciferol)** produced in kidney.

Clinical note: Renal failure or **vitamin D deficiency** results in a decrease in Ca^{2+} absorption causing **rickets** in children and **osteomalacia** in adults.

Absorption of vitamins

- Fat soluble vitamins **(A, D, E and K)** are absorbed along with other fats.
- Water soluble vitamins are absorbed by Na^+ dependent **cotransport** mechanism.
- Vitamin **B12** requires **intrinsic factor** for absorption.

Clinical note: Gastroectomy results in loss of gastric parietal cells which produce intrinsic factor, therefore administration of vitamin B12 is important to avoid **pernicious anemia**.

Absorption of iron

- Iron is essential for oxidative metabolism and DNA synthesis.
- Iron is contained in the RBCs .It is present as **heme iron** (iron bond to hemoglobin and myoglobin) and **non heme iron (Fe^{3+})** which reduced to **Fe^{2+}** prior to absorption.
- Iron absorption occurs mainly in the duodenum and upper jejunum.
  - In the intestinal cells heme iron is degraded and free Fe^{2+} is released.
  - Free Fe^{2+} binds to (**apoferritin**) and transported to the blood.
  - Free Fe^{2+} circulates in the blood bound to **transferrin** which transported from small intestine to the liver, then to the bone marrow for hemoglobin synthesis.
- Iron deficiency is the most common cause of anemia.

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Chapter Twelve

Endocrine system 12

Endocrine system

Overview

- Endocrine system is a coordination and communication system, regulates the activities of all other body structures by releasing of chemical substances: **hormones.**
- **Hormones** are secreted from endocrine glands and carried to all part of the body by the circulatory system.
- The cells that are able to recognize the hormones and respond to them are **target cells.**
- The target cells must have **specific receptors** for specific hormone.
- Some hormones travel **free** as soluble compounds .Whereas others travel mainly **bound**, associated with specific binding proteins.
- The effectiveness of specific hormone depends on :
  1. Concentration of free hormone.
  2. Concentration of hormone receptors.
  3. Effectiveness of the transduction mechanism.
- All endocrine diseases are due to a quantitative or qualitative in hormone synthesis or altered tissue sensitivity to the hormone.

Function of endocrine system

1- Metabolism and tissues maturation.
2- Ions regulation ,it helps regulate blood PH
3- Water balance by controlling the solutes in the blood.
4- Immune system regulation, control production of immune cells.
5- Heart rate and blood pressure regulation.
6- Control blood glucose and other nutrients.
7- Control the reproductive functions.
8- Uterine contraction during delivery and milk release in the lacting female.

Mechanism of hormones action

- All hormones must interact with a cellular receptor, which then transduces a signal and generate a cellular response.

- **The receptors may be :**
  - **Intracellular receptors.** These are usually found in the nucleus, but may be in the cytoplasm. (Figure 12.1) The hormone thus must first pass through the plasma membrane, and so must be fat soluble. On combining with the receptor, it triggers the production of mRNA, which directs ribosomes in the cell to secrete proteins. Production of proteins may take several hours, so this type of hormone known as steroids, is slow acting. (Figure 12.2).

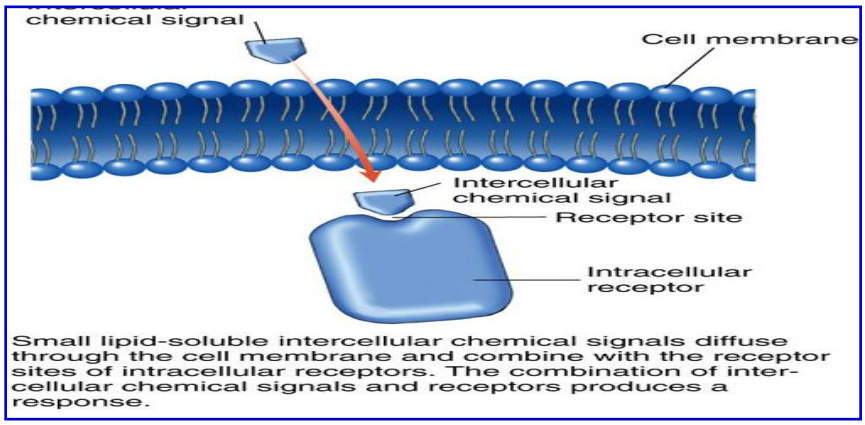


Figure (12.1): Intracellular receptors. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

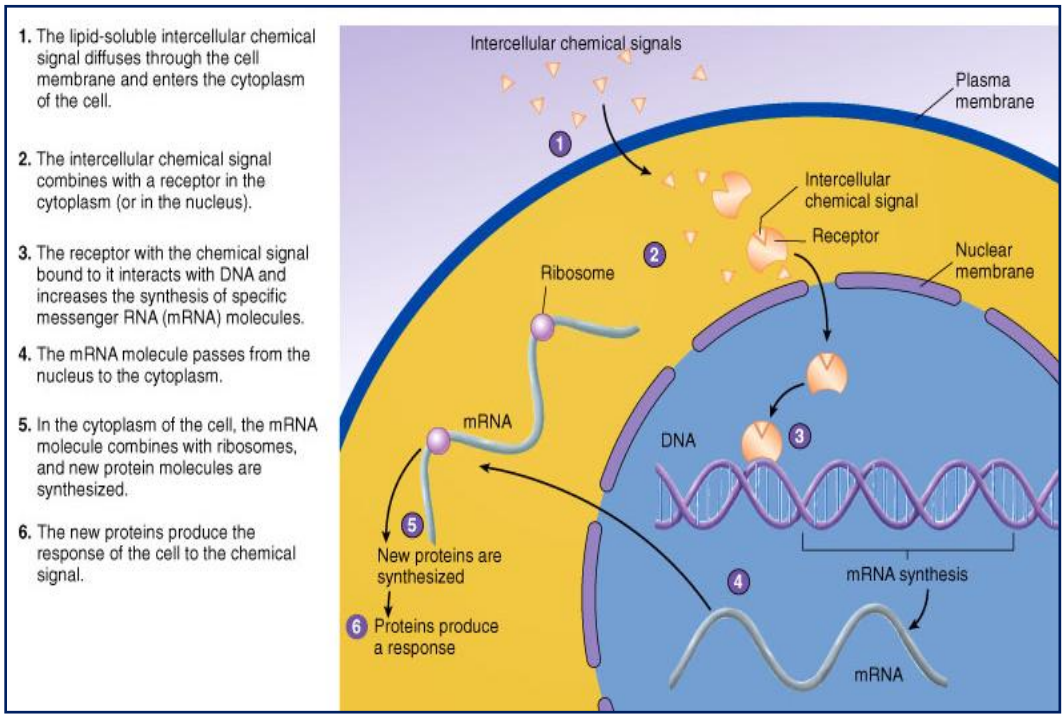


Figure (12.2): Intracellular receptors work. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

- **On the plasma membrane.** Hormones that are water soluble cannot cross the plasma membrane, but attach to receptors on the outside of the membrane. This triggers a response inside the cell. The response may be:
  - **Opening ion channels** to allow ions move in or out of the cell (**neurotransmitter**).
  - **Activate a G-protein (which then usually activates an enzyme).** The receptor has a **G protein** attached to it, which is activated when the hormone attaches to the receptor. The G protein produces an **intracellular activator,** such as cyclic adenosine monophosphate (**cAMP**), cyclic guanosine monophosphate (**cGMP**), inositol triphosphate (**IP3**) and diacylglycerol (**DAG**). These may activate an enzyme.(Figure 12.3.a).
  - **Directly activate an enzyme attached to the receptor**. (Figure12.3.b).

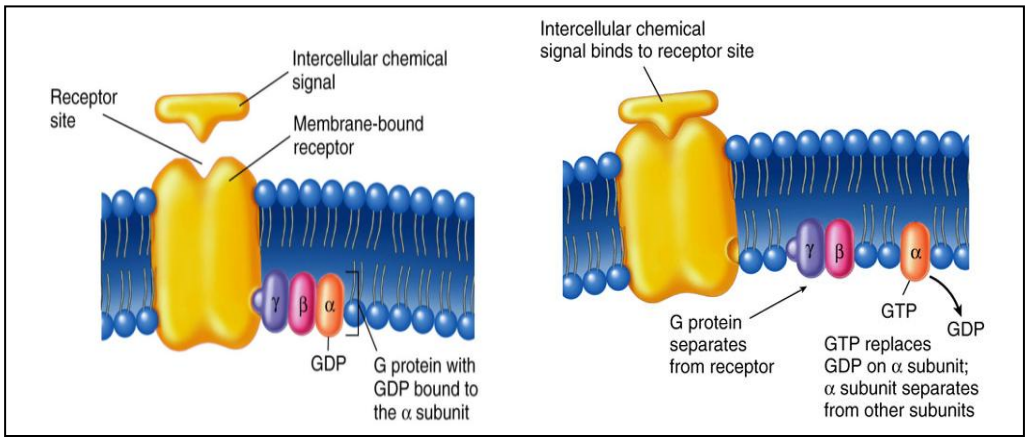


Figure (12.3.a): Membrane –bound receptors that activate G protein.

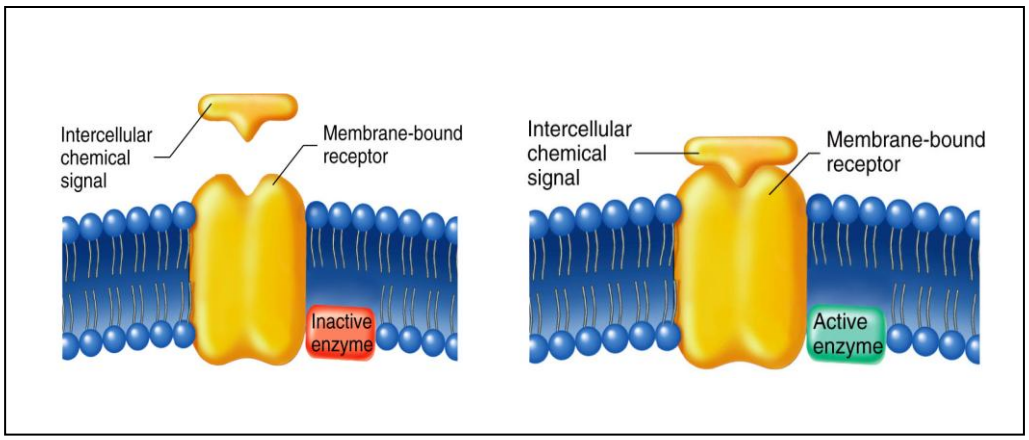


Figure (12.3.b): Membrane bound receptors directly activate an enzyme.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Types of hormones

1- Protein, peptide, amino acid

- They are hydrophilic, stored in a vesicle and released on demand.
- They bind to membrane bound receptors on the target cells.
- Ex: **growth hormone(GH)**

2- Thyroid hormones

- They are unique that they derived from amino acid tyrosine.
- They diffuse into the cell, bind to a receptor and alter gene expression.
- Ex**: thyroid hormones(T3,T4)**

3- Steroid hormones

- They are lipid soluble compounds derived from **cholesterol** that are able to enter all cells of the body and diffuse through lipid rich membrane.
- They cannot be stored, but produced continually, synthesis and secretion increase on demand.
- Ex: **sex steroid (like testosterone, progesterone, and estrogen); adrenal steroid (cortisol, aldosterone).**

Regulation of hormone secretion

1- Negative feedback.

- The most common applied for hormone regulation.
- It is self limiting.
- A hormone has biological actions that directly or indirectly inhibit further secretion of the hormone.
- Ex: **insulin** is secreted by **pancreatic β cells** in response to an increase in blood glucose, in turn causes increase intake of glucose into the cells, causing decreased blood glucose. Decreased blood glucose concentration decreases insulin secretion.

2- Positive feedback

- This is rare, an explosive and self reinforcing.
- A hormone has biological actions, directly or indirectly cause more secretion of the hormone.
- Ex: the surge of **luteinizing hormone (LH),**that occurs just before ovulation is a result of positive feedback of **estrogen** on the **anterior pituitary** .LH then acts on the ovaries and cause more secretion of estrogen.

Pituitary gland and Hypothalamus

Overview

- The **pituitary gland** or **hypophysis** secrets nine major hormones that regulate numerous body functions and secretory activity of several other endocrine glands.
- The hypothalamus of the brain and the pituitary gland are major sites where the nervous and endocrine systems interact.
- The **posterior pituitary** is an extension of the hypothalamus.
- **Hormones, sensory information** that enters the CNS and **emotions** in turn influence the activity of the hypothalamus.

Structure of the pituitary gland

- The pituitary gland is 1cm in diameter and 0.5-1.0 gm weight.
- It rests in the **sella turcica** of the **sphenoid bone.**
- It is located inferior to the hypothalamus and connected to it by a stalk of tissue called **infundibulum.**
- The pituitary gland is divided functionally into two parts:(Figure 12.5).

1- The posterior pituitary gland

- The posterior pituitary is called **neurohypophysis** because it's continuous with the brain.
- Secretions of the posterior pituitary are **neurohormones** because the posterior pituitary is an extension of the nervous system.

2- The anterior pituitary gland

- The anterior pituitary is subdivided into three areas with indistinct boundaries.
  1- **The pars tuberalis**
  2- **The pars distalis:** enlarged distal portion of the anterior pituitary.
  3- **The pars intermedia**: is adjacent to the posterior pituitary.
- Hormones secreted by the anterior pituitary are **not neurohormones**, because the anterior pituitary is not derived from neural tissue.

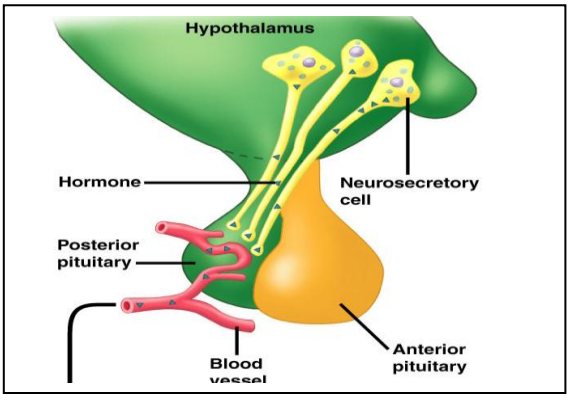


Figure (12.5): The 2 functional parts of the Pituitary gland ,anterior part and posterior which is an extensionof the hypothalamus. Retrieved from: www.slideshare.net

Relationship of the pituitary to the brain

- The **hypothalamohypophysial portal system** connects the hypothalamus and the anterior pituitary. (Figure 12.6).
- **Hypothalamus neurons** produce and secret neurohormones.
- These neurohormones leave the blood and act on the cells of anterior pituitary.
- Neurohormones are:
  1- **Releasing hormones:** increase the secretion of anterior pituitary.
  2- **Inhibitory hormones**: decrease the secretion of the anterior pituitary.
- In response to the releasing hormones, the anterior pituitary secrets hormones that enter the secondary capillaries and carried by general circulation to their target tissues.
- **Hypothalamohypophysial system** provides means by which the hypothalamus using neurohormones as chemical signals to regulate the secretory activity of the anterior pituitary.

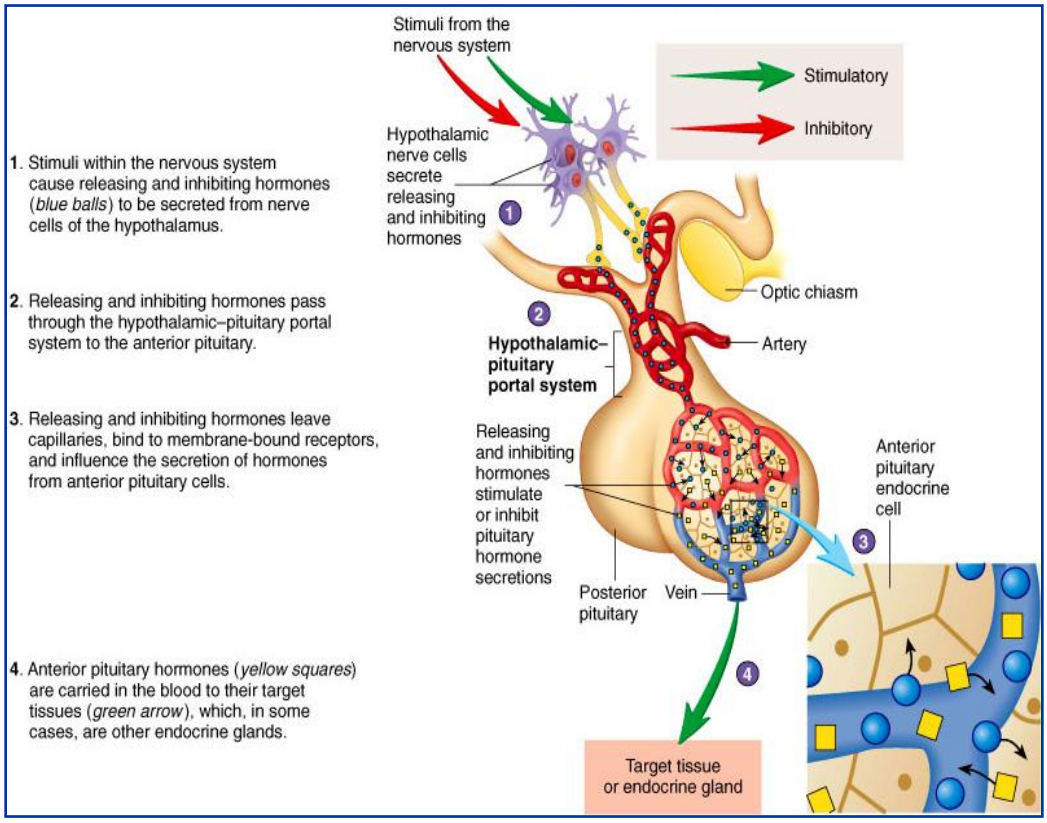


Figure (12.6): Relationship between the hypothalamus and anterior pituitary. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

- **Several releasing and inhibiting hormones are produced in the hypothalamus:**

1. **TRH**(*Thyrotropin Releasing Hormone).*This hormone will affect the anterior pituitary which will then affect thyroid gland activity
2. **PRH**(*Prolactin Releasing Hormone*) and **PIH**(*Prolactin Release-Inhibiting Hormone).*These two hormones will affect the secretion of prolactin from the anterior pituitary
3. **CRH** (*Corticotropin Releasing Hormone).*This hormone affects **ACTH** release from the anterior pituitary
4. **GnRH**(*Gonadotropin Releasing Hormone).*This hormone will affect the anterior pituitary which will then affect the gonadal release of sex hormones
5. **GHRH**(*Growth Hormone Releasing Hormone*)
6. **GHIH (**Growth *Hormone Inhibitory Hormone)* or **SS** (*Somatostatin)* Both **6, 7 affect** secretion of growth hormone by the anterior pituitary.

- Relationships among the hypothalamus, anterior pituitary and the other endocrine glands or (target tissues) are illustrated in figure (12.7).

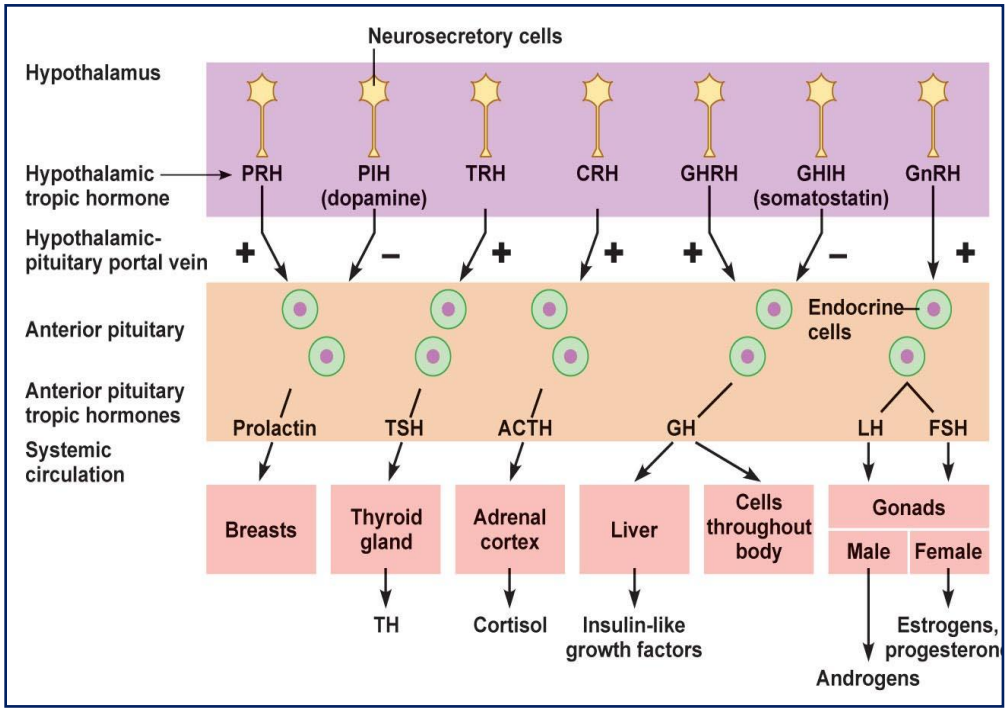


Figure (12.7): Relationship among the hypothalamus, anterior pituitary and the other endocrine glands or (target tissues). (Marieb E.N.and Hoehn K. Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

Anterior pituitary Hormones

Overview

- They are protein ,glycoprotein or polypeptides,
- Each hormone is secreted by a separate cell type.
- Theses hormones are:

1- Growth Hormone(GH)

- **Growth hormone (GH)** or (**somatotropin)** stimulates growth in most tissues, play a role in the regulation of growth and determining how tall a person becomes.
- It regulates metabolism
- It stimulates the uptake of amino acids and conversion into protein; stimulates the breakdown of fat and synthesis of glucose.
- GH stimulates the production of **somatomedins,** which both promote bone and cartilage growth.
- GH is regulated by **GHRH** and **GHIH.**
- GH secretion increases in response to an increase in blood amino acids; low blood glucose or stress.
- High blood glucose level inhibits secretion of GH .
- Rhythm of GH secretion occurs, daily peak level correlated with deep sleep.

Pathological conditions

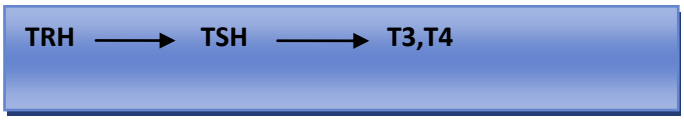
- Several pathological conditions are associated with abnormal secretion of GH.
- The cause for hypersecretion or hyposecretion of GH is the result of tumors in the hypothalamus; pituitary; synthesis of structurally abnormal GH and the lack functional receptors in target tissues.

Clinical note: Chronic hyposecretion of GH in infants and children leads to **dwarfism (pituitary dwarfism).**It results in a short stature due to delayed bone growth .On the other hand hypersecretion of GH leads to **gigantism (acromegaly)**

2- Thyroid Stimulating Hormone (TSH)

- It is called **thyrotropin** also; glycoprotein in nature consisting of **α, β** subunits which bind to membrane bound receptors of the thyroid gland.
- This hormone stimulates thyroid gland to synthesize and secrete of thyroid hormones (**T3, T4**).
- **TSH** increases the activity of **phospholipase** which activates the mechanism that opens Ca^{+2} channels and increases Ca^{+2} concentrations in the cells of thyroid gland.

- **TSH** is controlled by TRH from the hypothalamus.



3- Adrenocorticotropic Hormone(ACTH)

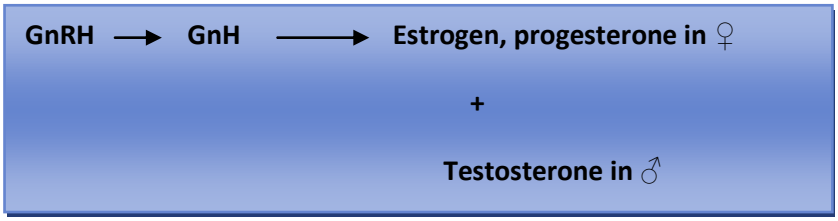
- **ACTH** is a peptide hormone.
- It stimulates synthesis of **cortisol** and **androgen** from the **adrenal cortex.**
- It is controlled by **CRH** from the hypothalamus ***(androgen do not feedback inhibit ACTH)***

4- Melanocyte Stimulating Hormone(MSH)

- It binds to membrane bound receptors on the skin **melanocytes.**
- It stimulates **melanin** secretion and deposition in the skin.

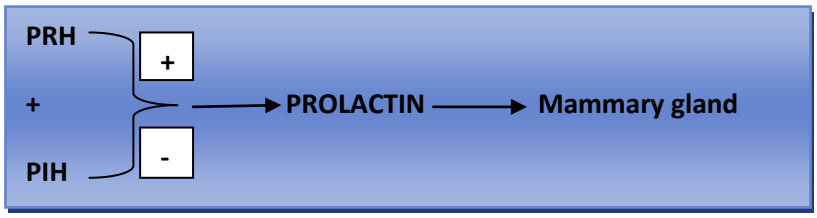
5- Gonadotropin Hormone(GnH)

- It is a glycoprotein hormone.
- The two major important hormones are **Luteinizing Hormone (LH)** and **Follicle Stimulating Hormone(FSH),**which are secreted from anterior pituitary to the blood and stimulate the production of gametes :**sperms in the testes** and **oocytes in the ovaries.**
- LH and FSH control the production of reproductive hormones **(estrogen and progesterone in the ovaries** and **testosterone in the testes).**
- Releasing LH and FSH is under the influence of hypothalamic releasing hormone (**GnRH**).



6- Prolactin

- It s a protein hormone.
- It plays an important role in milk production in the mammary gland of lacting females.
- Prolactin is controlled by Prolactin Releasing Hormone (**PRH**) and Prolactin Inhibitory Hormone (**PIH**) from the hypothalamus.



Relationship among the hypothalamus, posterior pituitary and target tissue

- Posterior pituitary gland does not produce its own hormones, but stores and releases hormones that it receives from the hypothalamus.
- The axons of the hypothalamic neurons extend from the hypothalamus through the infundibulum into the posterior pituitary forming tract called: **hypothalamohypophysial tract.**(Figure12.8)
- Neurohormones produced in the hypothalamic neuron pass down the axon in tiny vesicles and stored in secretory vesicles in the enlarged end of the axon.
- Action potential in the bodies of hypothalamic neurons propagated along the axon to the axon terminals in the posterior pituitary.
- Action potential causes the release of neurohormones to the circulatory system.

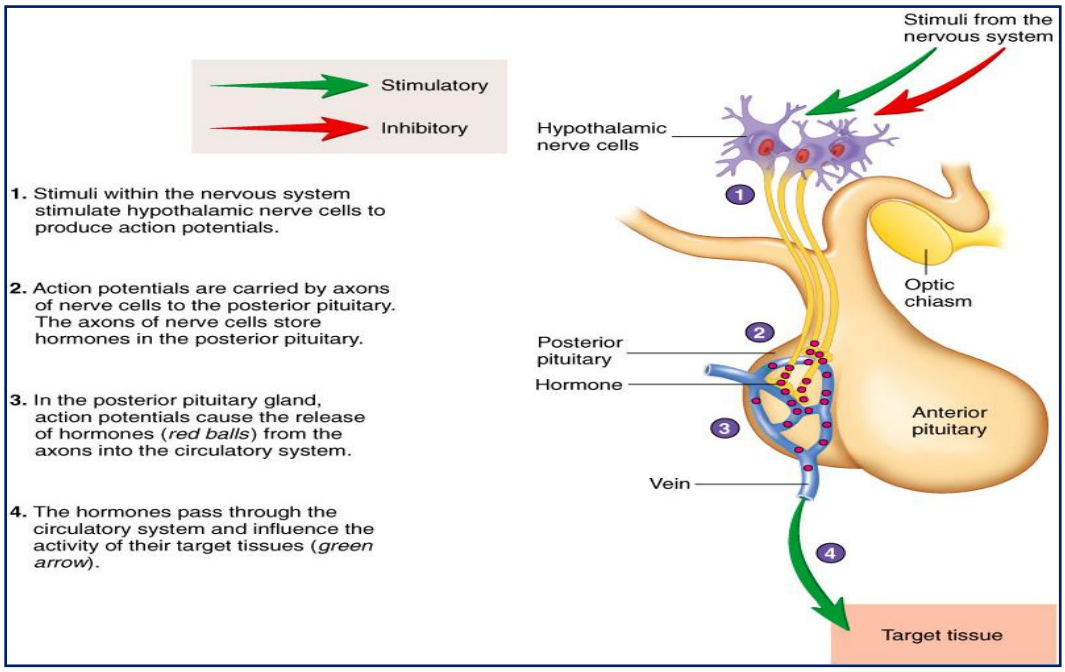


Figure (12.8): Relationship among the hypothalamus, posterior pituitary and target tissues. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology. New York, McGraw –Hill Companies, 2008)

Posterior pituitary Hormones

- Posterior pituitary stores and secrets **two polypeptides hormones**: **ADH *(Anti diuretic Hormone)*** *and* ***oxytocin.***

1- ADH *(Anti diuretic Hormone)*

- It is named antidiuretic hormone because it prevents the output of large amount of urine (**dieresis**).
- It is called **vasopressin** because it constricts blood vessels and raises blood pressure when large amount are released.
- It is synthesized in the hypothalamus and released by posterior pituitary in response to action potential from the axon terminal, to the blood and carried to the primary target tissue (**kidney tubules**).
- ADH promotes the water retention in the kidney tubules and reduces urine volume.
- The secretion rate for ADH changes in response to alterations in blood **osmolality** and blood volume .**Increased osmolality** (increased concentration of solutes in the solution) results in:
  - **Indirect stimulation** of ADH by: increased frequency of action potential in **osmoreceptors** (specialized neurons synapse with ADH neurosecretory cells in the hypothalamus resulting in an increased action potential in the axon of ADH neurosecretory cells leading to increase ADH secretion.
  - **Direct stimulation** of ADH neurosecretory cells.
- **Decreased osmolality results in less secreted ADH.**

2- Oxytocin

- **Oxytocin** is synthesized by neurocells in the hypothalamus, and then transported through the axon to the posterior pituitary, where it stored in the axon terminals.
- Oxytocin stimulates smooth muscles contraction of the uterus so help in the explosion of the fetus from the uterus during delivery.
- It causes expel the uterine epithelium and small amount of blood during menses.
- It is responsible for milk ejection in the lacting females.

Classification of Endocrine diseases

- A hormone deficiency or excess can occur as a result of defect anywhere along the **hypothalamic –pituitary –target tissue axis.**
- It is important to determine the location of defect to make an accurate diagnosis.

- ***Primary endocrine diseases:*** *Ex: the defect is in the thyroid gland itself, makes it unable to produce thyroid hormones effectively .This disease is known as primary hypothyroidism.*
- ***Secondary endocrine disease:*** *The defect is in the* ***pituitary*** *such as decrease secretion of* ***TSH*** *from the pituitary can cause* ***secondary hypothyroidism.***
- ***Tertiary endocrine disease:*** *Ex: decrease hypothalamic TRH secretion, (rare) causes tertiary hypothyroidism.*

Thyroid Gland

Overview

- Thyroid gland is composed of two lobes connected by a narrow band of thyroid tissue (**isthmus**).(Figure12.9)
- The lobes are lateral to the upper portion of the trachea, inferior to the larynx.
- Thyroid gland is one of the largest endocrine gland with a weight of 20 gm.
- It is highly vascularized and appears more red than the surrounding tissues.
- It contains numerous small **sphere follicles**, (figure12.10) .The center of each thyroid follicle is filled with proteins called **thyroglobulin**, which is synthesized and secreted by the cells of the thyroid follicles.
- Large amount of thyroid hormones are stored in the follicles as part of the thyroglobulin.
- Between the follicles there is a network of loose connective tissue which contains capillaries.
- There are scattered **parafollicles** among the follicles these parafollicles secrete **calcitonin.**
- **Calcitonin** regulates calcium level in the body fluid .It Reduce Ca^{2+} level in the body fluid when Ca^{2+}level become elevated.

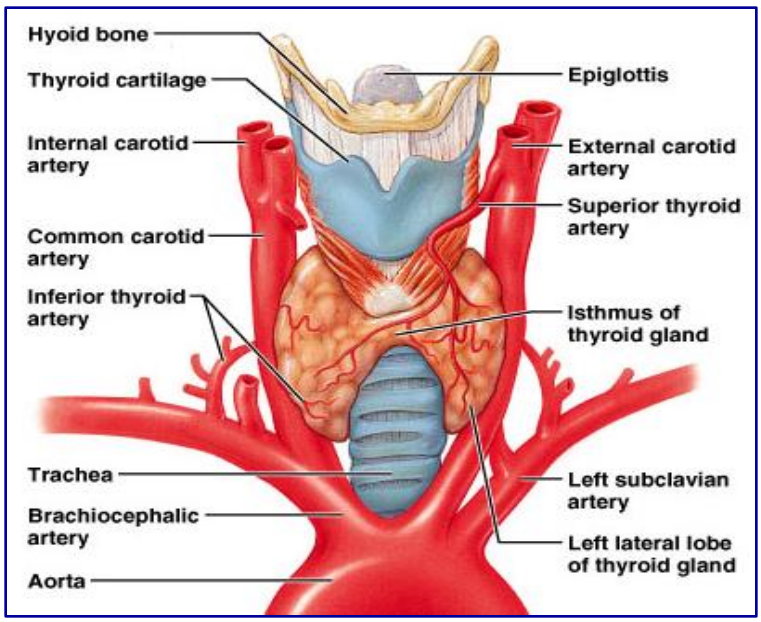


Figure (12. 9): The two lobes of thyroid gland connected by isthmus.(Marieb E.N Essential of Human Anatomy and Physiology.San Francisco, Pearson Education,Inc.,2012).

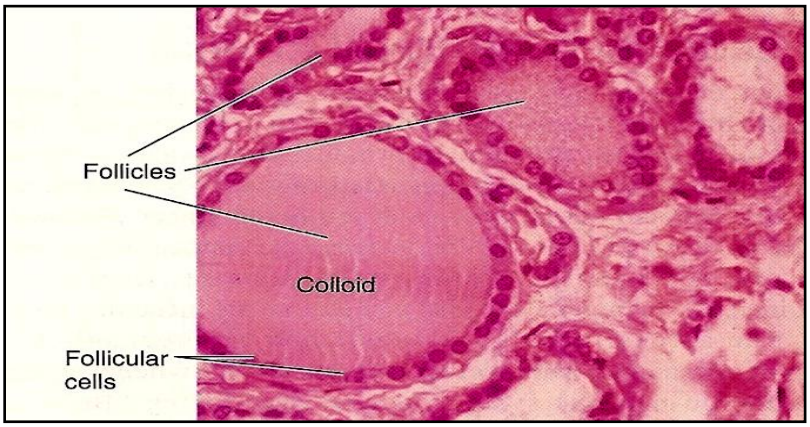


Figure (12.10): Follicles of the thyroid gland. (Marieb E.N .Essential of Human Anatomy and Physiology . San Francisco, Pearson Education,Inc.,2012).

Thyroid Hormones

- The major secretory products of the thyroid gland are:
  1- **Triiodothyronine (T3),** which constitutes 3-10% of the thyroid hormones.
  2- **Tetraiodothyronine or thyroxin (T4)** constitutes 90-97% of the thyroid hormones.
- **T3**and**T4** are of a clinical importance, secreted from the thyroid follicles.
- **Calcitonin**: is other hormone secreted by the **parafollicular cells** of thyroid gland.

Synthesis of T3, T4

- **TSH** from anterior pituitary stimulates thyroid hormones (**T3,T4**) synthesis and secretion.
- **T3**and**T4** then stored in the follicles and released to the circulation by the effect of TSH.
- Because **iodine** is a component of T3and T4, an adequate amount of iodine in diet is required for thyroid hormones.
- The steps for synthesis of thyroid hormones include:(Figure 12.11)

1- **Iodide (I^-)** are taken up by thyroid follicle cells by active transport.

2- **Thyroglobulins** which contain numerous **tyrosine** amino acid molecules are synthesized within the cells of the follicles.

3- I^- is oxidized to **iodine I** by **peroxidase** .

4- ***Either*** one iodine atom is bound to each tyrosine molecules of the thyroglobulin to form **monoiodotyrosine (MIT),**
Or two of iodine atoms bound to tyrosine to form **diiodotyrosine .** This event occurs close to the time the thyroglobulin molecules are secreted by **exocytosis** into the lumen of the follicle.

I + TYROSINE ⟶ MIT

Or: 2I + TYROSINE ⟶ DIT

5- In the lumen **two diiodotyrosine molecules** combine to form **T4,**or **one monoiodotyrosine** and **one doiodotyrosine** combine to form **T3**.Large amounts of T3andT4 are stored within the thyroid follicles as part of thyroglobulin .

6- Thyroglobulin is taken into the follicle cells by **endocytosis.**

7- Thyroglobulin breaks down to **amino acids** and **T3andT4** by **proteolytic enzymes.**T3,T4 diffuse out of the follicle cells and enter the circulation. The remaining amino acids are used again to synthesize more thyroglobulin.

Pharmacology note: Formation of **DIT** and **MIT** is called **organification,** which is inhibited by **thionamides propylthiouracil (PIU)** and **methimazole**, which are used to treat **hyperthyroidism.**

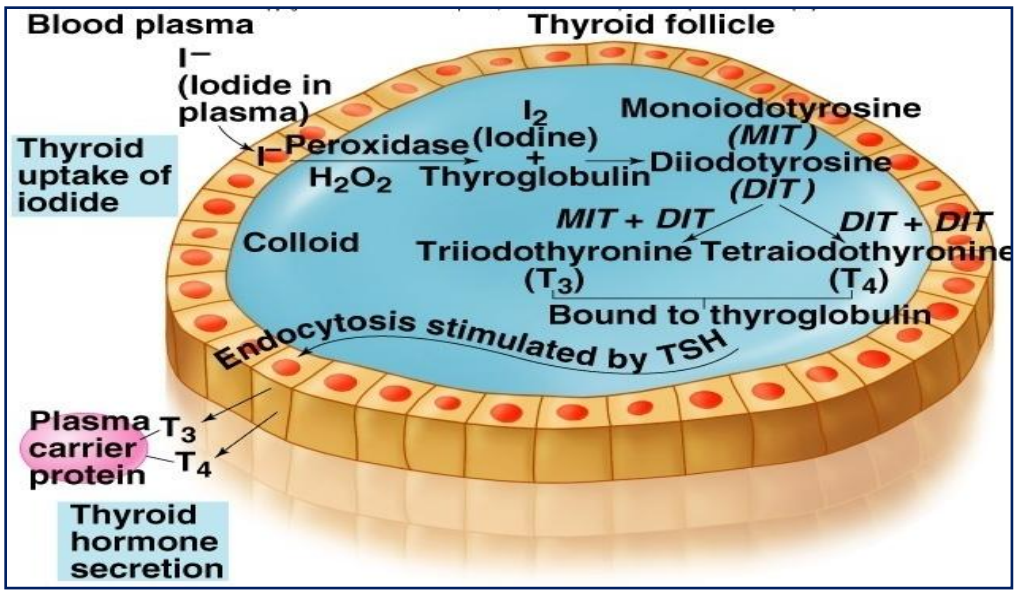


Figure (12.11): The steps for synthesis of thyroid hormones. Retrieved from: www.ruisimeao.com

Transport of T3, T4

- 70-75% of circulating T3andT4 are bound to **thyroxin binding globulin (TBG**), which is synthesized by the liver.
- 20-30% of T3,T4 are bound to other plasma proteins **(Albumin).**
- 30-40% of T4 is converted to T3 in the body tissues.
- T3 is the major hormone that interacts with the target cells and is several times more potent than T4.
- Much of circulating T4 eliminated by conversion to **tetraiodothyroacetic acid**.

Pharmacology note: **Amiodarone** is an iodine –rich drug (40%by weight) that is commonly used for rate control of tachyarrhythmias such as **atrial fibrillation.** On the other hand amiodarone causes thyroid dysfunction, both hyperthyroidism (common) and hypothyroidism (rare), necessitating frequent monitoring of thyroid function.

Physiological effects of T3, T4

- T3andT4 affect every tissues in the body but not in identical response:
  1- They regulate the metabolism at a normal metabolic rate:

- ↑ Thyroid hormones lead to ↑ the basal metabolic rate.
- ↑ Thyroid hormones level lead to ↑ the rate of metabolism of protein, fat and glucose.
- ↑ Metabolic rate produces heat, causing **heat intolerance**.

2- Blood level of cholesterol decline.

3- ↑Activity of $Na^+ - K^+$ pump which leads to ↑ body temperature.

4- They can alter the number and activity of mitochondria to produce more ATP.

5- They potentiate **catecholamine actions**.

- Thyroid hormones up regulate expression and stimulate activity of **β-adrenergic receptors** in the tissues such as heart and skeletal muscles causing enhanced sensitivity to circulating catecholamine.
- They act directly on the heart, stimulate contractility and increase the heart rate, result in high output **congestive heart failure.**
- In muscles, they contribute to **muscle tremors**

Pharmacology note: By preventing catecholamine from binding to their receptors, β-adrenergic antagonists (β-blocker) such as **propranolol** can ameliorate many of the symptoms of hyperthyroidism associated with sympathetic activity **(tachycardia, tremors).**

Regulation of thyroid hormones (T3, T4)

1. **TRH** released from the hypothalamus pass through the hypothalamohypophysial portal system to the anterior pituitary.
2. Anterior pituitary secrete **TSH** which pass through the general circulation to the thyroid gland.
3. **TSH** causes increased release of **T3**and**T4** from thyroid gland into general circulation.
4. **T3**and **T4** act on target tissues to produce a response.
5. T3 and T4 have an inhibitory effect on the secretion of TRH from the hypothalamus and TSH from the anterior pituitary. (Figure 12.12).

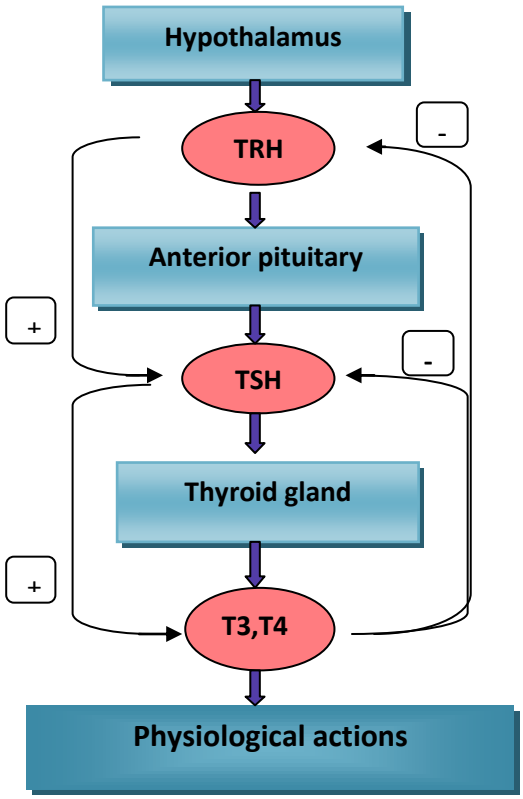


Figure (12.12): Thyroid hormones regulation.

Pathological conditions

1- Hyperthyroidism

- It refers to a pathological **increase** in thyroid hormones synthesis.
- Manifestations of hyperthyroidism include:
  1- Weight loss with increased appetite.
  2- Heat intolerance.
  3- Diarrhea
  4- Often atrial fibrillation.
- T3andT4 concentrations are elevated in hyperthyroidism .TRH and TSH vary in concentration depending on the cause of hyperthyroidism.

Clinical note: **Thyrotoxicosis:** symptoms associated with pathological elevated level of thyroid hormones irrespective of etiology (gland destruction or increases synthesis).
Graves's disease: The most common cause of hyperthyroidism, immunoglobulin G **(IgG**) antibodies mimics TSH and stimulates TSH receptors on thyroid gland.
Thyroditis: is caused by viral infection and autoimmune destruction as in **Hashimoto.**

2- Hypothyroidism

- It refers to decrease synthesis of thyroid hormones.
- Manifestation of hypothyroidism :
  1- Weight gain ,constipation
  2- Cold intolerance.
  3- Bradycardia and atrial fibrillation
  4- Dulled mentation.
  5- Congenital hypothyroidism may cause mental retardation **(cretinism)**.
- T3, T4 are decreased, TRH, TSH concentration vary with the cause of hypothyroidism.

3- Euthyroid sick syndrome

- Low to normal T3, T4 in ill patients with no appearance signs of thyroid dysfunction.

Clinical note: Abnormal enlargement of thyroid gland may result from conditions that cause hypothyroidism as well as conditions that cause hyperthyroidism. **Iodine deficiency goiter** when dietary iodine intake is very low and there is too little iodine to synthesis T3,T4 as a result blood level of T3,T4 decrease and the person may exhibit symptom of hypothyroidism.

Calcitonin Hormone

- **Calcitonin** is secreted by the **parafollicular cells** of the thyroid gland.
- Increased level of Ca^{2+} in the blood leads to an increase secretion of calcitonin.
- The primary target tissue for calcitonin is the **bone**.
- Calcitonin causes decrease in **osteoclast** and lengthens the life span of **osteoblast** result in decrease in blood Ca^{2+} level and phosphate.
- Ca^{2+} level is regulated primarily by another hormone **(parathyroid hormone)** that is why complete **thyroidectomy** does not result in high blood Ca^{2+}.

Parathyroid Gland

Overview

- Parathyroid glands are embedded in the posterior part of each lobe of the thyroid gland.(Figure 12.13).
- Parathyroid glands are made up of two cell types :
  1- **The chief cells** :secret **parathyroid hormone(PTH)**
  2- **Oxyphils** with unknown function.

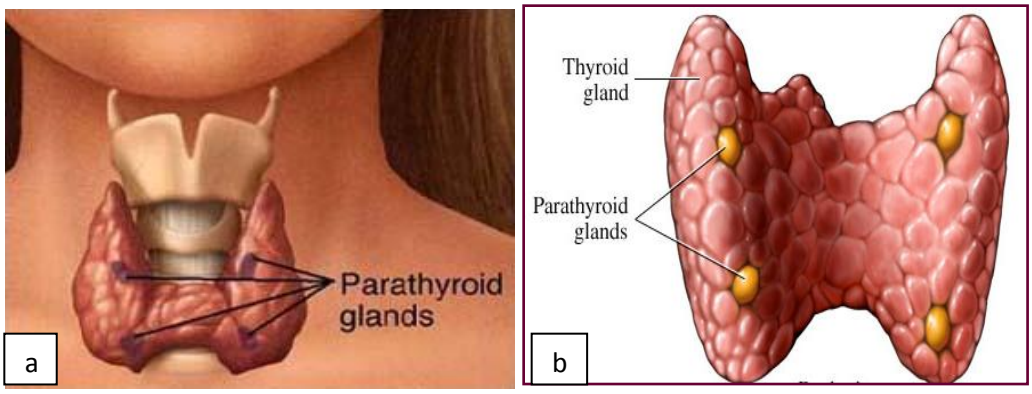


Figure (12.13): a: Position of the parathyroid glands in the thyroid gland.
b: Back view of the thyroid gland. Retrieved from: www.ent-surgery.com.am

Parathyroid hormone (PTH)

- PTH is a polypeptide hormone.
- It regulates the Ca^{2+} level in the body fluid (normal Ca^{2+} level is **8-10mg/dl**). (Figure 12.14).
- **Bone, intestine** and **kidney** are the major target tissues.
  - ***In the bone,*** PTH stimulates **osteoclast activity**, leading to bone resorption and release of Ca^{2+} and phosphate, resulting in an increase blood Ca^{2+} level.
  - ***In the kidney*** :
    1- PTH induces Ca^{2+} reabsorption, so less Ca^{2+} level leaves the body in the urine.
    2- PTH increases the enzymatic formation of active vitamin D.
  - ***In the intestine***: Active vitamin D causes increase in the rate of Ca^{2+} and phosphate absorption resulting in elevated blood Ca^{2+} level.

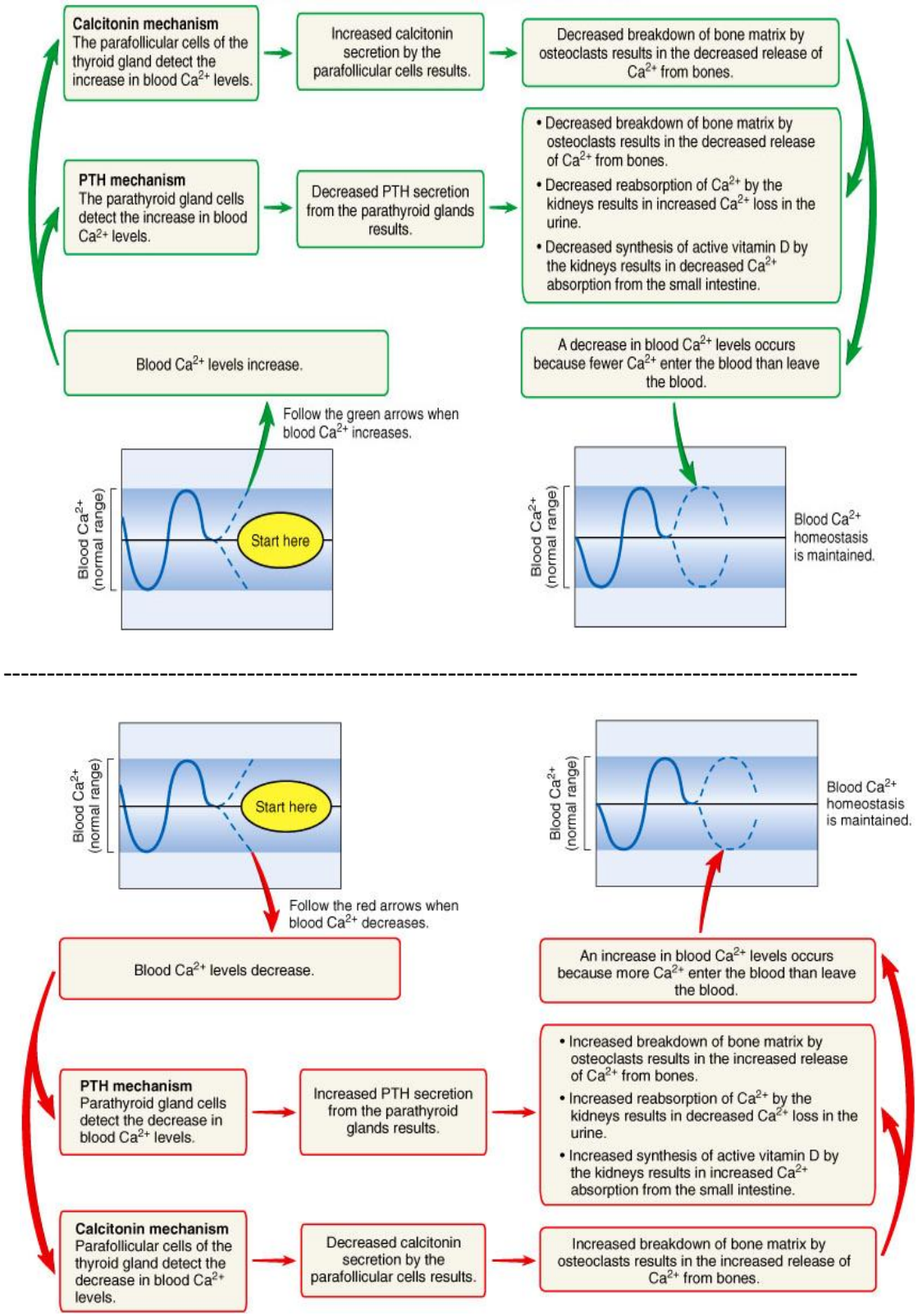


Figure (12.14): Regulation of blood Ca^{2+} level by PTH.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Pathological conditions of PTH

1- Hyperparathyroidism

- ***Primary Hyperparathyroidism*(↑PTH,↑Ca^{2+})**
  - It caused by **adenoma** and **hyperplasia**
- ***Secondary Hyperparathyroidism*(↑PTH,↓Ca^{2+})**
  - It occurs during chronic stimulation of PTH due to decrease serum Ca^{2+}
  - Ex: renal failure, vitamin D deficiency, or malabsorption syndromes.

2- Hypoparathyroidism

- Decreased PTH occurs mainly by accidental removal of parathyroid during thyroid surgery and (or) parathyroid surgery.

Adrenal Gland

Overview

- There are two adrenal glands (Figure 12.15). These glands have a similarity in anatomical structure, function, secreted hormones.
- The two glands are located above the two kidneys, i.e. one gland above each kidney; exactly at the position of 12th thoracic vertebra.
- Adrenal glands are also termed **suprarenal glands** (due to the position). The term **(adrenal**) comes from the fact that these glands secrete the hormone (**adrenaline**) in cases of stress.
- Adrenal gland consists of two distinct layers; **Cortex** and **Medulla**.
- These two layers differ in their anatomical structure and in their functions.

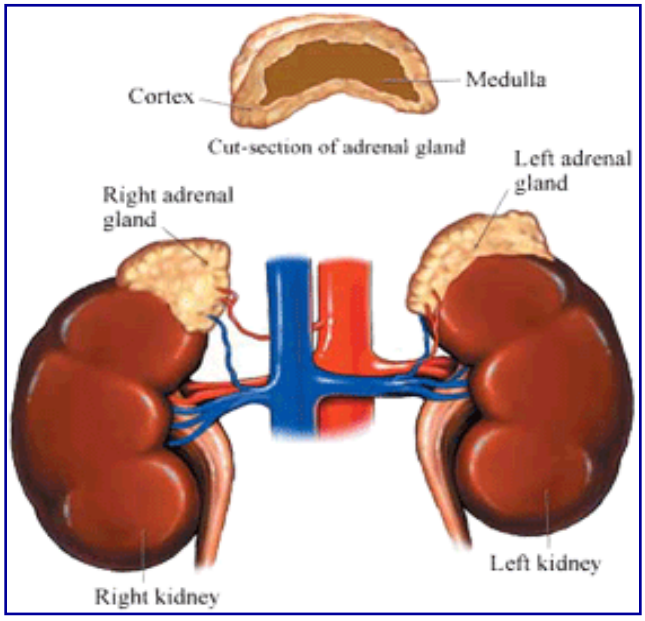


Figure (12.15): Adrenal glands. Retrieved from www.adrenalfatique.co.nz

1- Adrenal medulla

- Adrenal medulla arises from **neural crest cells** and functions as part of CNS.
- It is composed of closely packed cells, devoted to synthesis of **catecholamines**, which include adrenaline **(epinephrine)** and noradrenaline **(norepinephrine).** Both hormones are secreted in stressful situations.

Physiological effects of catecholamines

- Catecholamines cause general physiological changes that prepare the body for physical activities. (Figure 12.16).
- In case of (***fight or flight***) , catecholamines cause :
  - Elevation of blood pressure .
  - Increasing blood sugar.
  - Increasing heart rate.
  - Increased metabolic rate.
  - Affects peripheral nervous system.

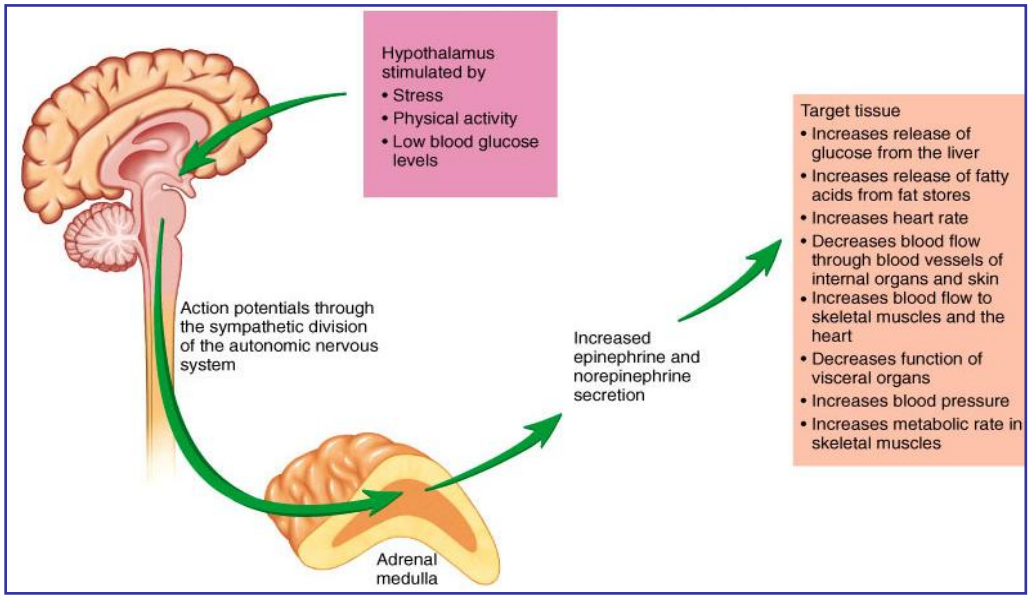


Figure (12.16): Actions of adrenal medulla hormones. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Pathological conditions

- **Pheochromocytoma:** Is a tumor In the adrenal medulla (very rare) that causes hypersecretion of catecholamines which leads to:
  1. Hypertension.
  2. Very high blood sugar.
  3. High rate of heartbeat.

2- Adrenal cortex

- It is derived from mesoderm
- Adrenal cortex is devoted to the synthesis of ***CORTICOSTEROID HORMONES*** due to the presence of large amounts of fats specially ***cholesterol*** which is the precursor of these hormones.
- Adrenal cortex exhibits three functional zones:
  1. **Zona glomerulosa**
  1. **Zona fasciculata**
  2. **Zona reticularis**

1. Zona glomerulosa

- The outer most layer of the cortex.
- It is the main site for production of (**Mineralcorticoids**)
- The main mineralcorticoid in human is **aldosterone** while there are some endogenous hormones which have a mineralcorticoid function (***progesterone & deoxycorticosterone***).
- Aldosterone hormone is a derivative of cholesterol.
- Its normal level is about **(4-9 Mg /100 ml blood).** About **2-18 Mg** of aldosterone is wasted with urine daily.
- Aldosterone acts on kidneys to provide active reabsorption of sodium and passive absorption of water. (increases the blood pressure)
- It causes secretion of both potassium ions and protons from the collecting ducts and distal tubules.
- Aldosterone synthesis is regulated by :(Figure12.17).
  - ***Angiotensin II.***
  - ***Adrenocrticotropic hormone (ACTH).***
  - ***Blood level of Na^+ and K^+.***

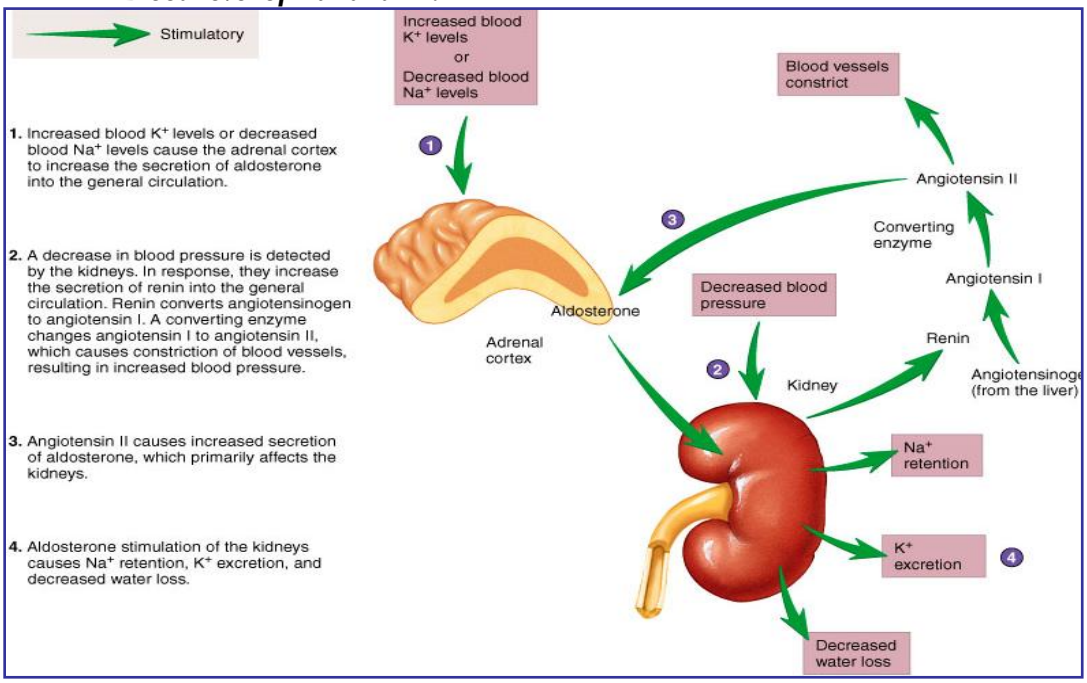


Figure (12.17): Aldosterone regulation. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Pathological conditions of aldosterone

1- **Natural increase:** is due to deficiency of sodium and plenty of potassium in the diet and heavy sweat.
2- **Natural decrease:** is due to deficiency of potassium in the diet and having large amounts of water and drinks.
3- **Conn disease**

- It occurs due to increased activity of zona glomerulosa.
- It leads to increased secretion of aldosterone which results in a high blood pressure, low blood potassium and high blood sodium levels.

2- Zona fasciculate

- The central region of the adrenal cortex.
- It is the main site for production of (**Glucocorticoids**)
- The primary glucocorticoid in human is (**cortisol**).
- Cortisol (**a stress hormone)** secretion is stimulated by hypoglycemia or stressful conditions, anxiety, and when the sympathetic nervous system is activated.
- Cortisol has a diurnal pattern of secretion based on daily pattern of **ACTH.**
- Its primary function is to increase blood sugar and stores of sugar in the liver as glycogen.
- Zona fasciculata can produce (**7-7.5 mg/day**) of cortisol hormone.
- Biosynthesis of cortisol is done by conversion of **cholesterol** to **pregnenolone**.

Physiological effects of cortisol

1. Cortisol has anti – insulin effect. It contributes to "hyperglycemia" by stimulation of hepatic gluconeogenesis and inhibition of peripheral utilization of glucose.
2. It increases gastric acid secretion.
3. It cooperates with adrenaline to create memories of short – term events.
4. It has an anti – inflammatory action as inhibits secretion of histamine from basophils and mast cells and it can cause immune suppression
5. It elevates blood pressure by increasing the expression of adrenergic receptors in various tissues.
6. Cortisol may weaken the bones by inhibiting **osteoblasts** and stimulating bone degrading cells (**osteoclast**).

Regulation of cortisol secretion

- **CRH** is released by the hypothalamus as response to stress and decreased blood glucose. (Figure 12.18).
- CRH affects the anterior pituitary to release **ACTH**.
- ACTH stimulates the secretion of **cortisol** by the adrenal cortex.
- Cortisol acts on the target tissues to cause its effects.
- Cortisol has **negative feedback** effect to inhibit CRH releasing from the hypothalamus and decrease ACTH secretion from anterior pituitary.

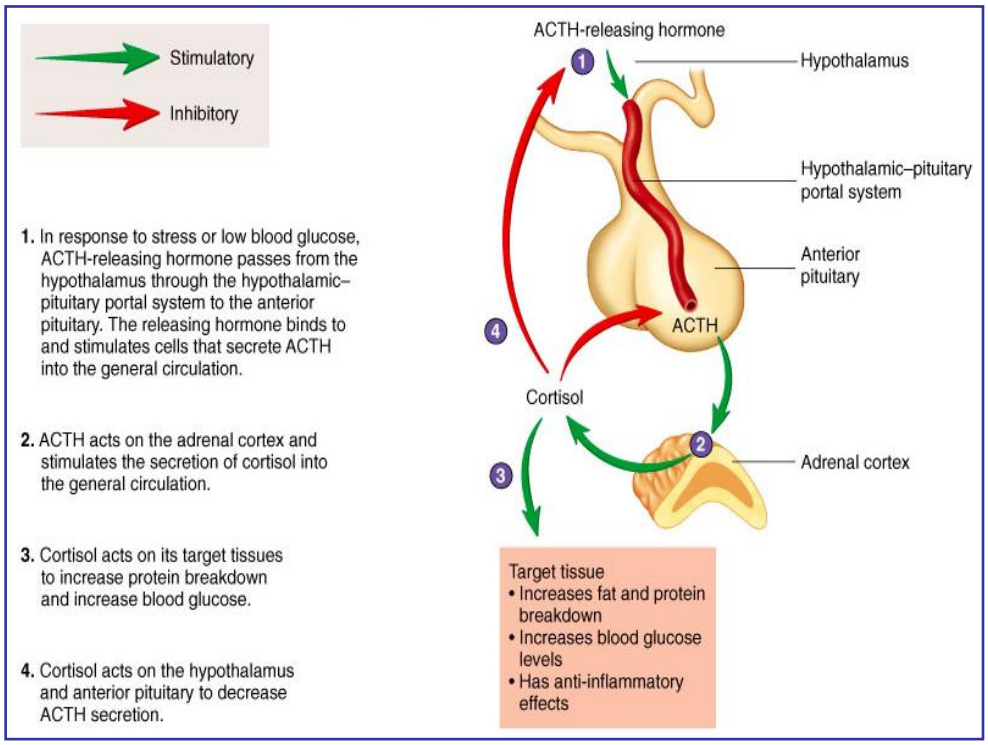


Figure (12.18): Regulation of cortisol secretion. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Pathological conditions of cortisol

1-Hypercortisolism (*Cushing syndrome)*

- The condition results from increased amount of cortisol hormone in the blood.
- It may be caused by:
  - Tumors in cortisol secreting cells.
  - Tumors in ACTH secreting cells.
  - **Iatrogenic** (Taking glucocorticoids drugs).
- Symptoms of Cushing syndrome include :
  - Rapid weight gain.
  - Increased growth of body and facial hair
  - Very high blood sugar which may lead to **diabetes mellitus.**
  - High blood pressure
  - Loss of minerals which leads to **osteoporosis**

2-Hypocortisolism (*Addison disease*)

- Addisone disease is due to an inadequate secretion of cortisol.
- The causes of Addison disease are:
  - **Iatrogenic** is the most common cause, occurs because of abrupt cessation of chronically administrated cortisol.
  - Primary adrenal insufficiency causing increase level of **ACTH.**

- Secondary adrenal insufficiency or chronic use of steroid, the ACTH is low.

- Symptoms of Addison include:
  - Low blood sugar.
  - Low blood pressure.
  - High potassium levels in the blood.
  - Full body weakness and loss of energy.

3-Zona reticularis

- It is the interior layer of the adrenal cortex.
- It is responsible for production of (**Androgens**) and (**Estrogen**)
- The main adrenal androgen is ***Testosterone,*** while the main adrenal estrogen is ***Estradiol***

1- Testosteron

- Testosterone is secreted in both males and females , but in males in a larger amount so , its effects appear clearly on males and therefore , it is the "muscularity hormone"
- In males, it is secreted mainly from **Leyding cells** in the testes, and a small amount from **adrenal reticularis**.
- In females, it is secreted from **Thecal cells in** the ovaries, placenta and a small amount from adrenal reticularis.
- Its activity is mediated by **LH** and **FSH.**

Physiological effects of testosterone

1- Regulation the production of sperms (**spermatogenesis**)
2- Development and maintenance of male reproductive organs and secondary sex characteristics.
3- Stimulating protein synthesis (**anabolic effect**)

2-Estradiol

- Estradiol is the predominant sex hormone in females.
- It is produced primarily by ***granulosa cells*** in ovaries, in addition to small amount from adrenal reticularis.
- During pregnancy, its amount increases due to secretion from placenta also.
- It is present in males but in lower amounts than females.
- Its activity is mediated by **LH** and **FSH.**

Physiological effects of estradiol

- Growth of female reproductive organs.
- Maintaining of oocytes in ovaries.
- During pregnancy, it promotes uterine blood flow and stimulates breast growth.
- Regulation of menstrual cycle.
- It affects liver to synthesize lipoproteins, binding proteins and proteins of blood clotting.

Pancreas

Overview

- Pancreas is an exocrine and endocrine organ.
- Its function as **exocrine** is the secretion of digestive enzymes and bicarbonates, into the duodenum ,while its function as **endocrine** is to synthesize and release hormones by the cells of the **Islet of Langerhans** into the circulation
- It is located horizontally behind the stomach, upper left abdominal quadrant.
- Humans have roughly **one million islets.** (Figure12.19)
- The **islets of Langerhans** are clusters of **4 types endocrine cells** these are:
  1. **β cells**-secrete ***insulin*** and amylin;
  2. **α cells**- secrete ***glucagon;***
  3. **δ cells**-secrete ***somatostatin***
  4. **γ cells**-secrete a ***polypeptide*** of unknown function.
- Nerves from both divisions of autonomic nervous system innervate the pancreatic islets.
- There is well developed capillary network surround each islet.
- Pancreatic hormones play an important role in regulating the concentrations of nutrients in the circulating especially glucose and amino acids.
- Insulin and glucagon maintain blood sugar at level of **100mg/100ml** of blood.

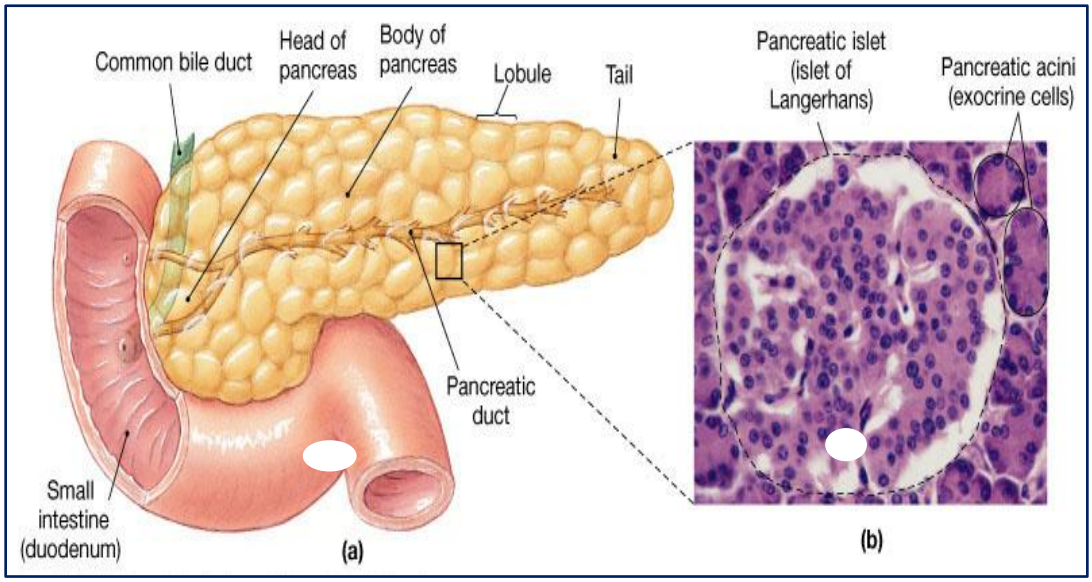


Figure (12.19): The pancreas. (Marieb E.N. and Hoehn K. Human Anatomy and Physiology . San Francisco, Pearson Education Inc., 2010).

1-Insulin

- Insulin is a rather small protein, with a molecular weight of about 6000 Daltons. It composed of 2 chains held together by disulfide bonds.
- It is continuously produced but production increases when there is a high blood glucose ,it thus to decrease blood glucose by :
  1- Encouraging all cells to take up more glucose out of the blood.
    - Insulin molecules binds to **membrane bound receptors** on the target cells (the **GLUT-4** is the major transporter used for uptake of glucose which is made available in the plasma membrane through the action of insulin).Then the receptors cause specific protein in the membrane to become phospherylated, part of the cells response to insulin is to increase number of transport proteins in the membrane of cells for glucose and amino acids .
    - Finally insulin and its receptors are taken by **endocytosis.**
    - Insulin molecules are released from receptors and broken down within the cell. The receptors can again become associated with plasma membrane.

  2- Stimulate the **liver** to convert glucose to glycogen.
  3- Stimulate the **adipose tissues** to convert glucose to fat.
  4- Acts on **satiety center** of the hypothalamus so that no longer feel hungry to stop eating more sugar.

Physiological effects of insulin

1- Action of insulin on the liver

- ↑ Glucose uptake when glucose level is high
- ↑ Glucose use to:
    - ↑ **glycogenesis** and ↓**glycogenolysis**
    - ↑ **glycolysis , ↓gluconeogenesis**
- ↑ Fatty acid synthesis and very **low density lipoprotein** formation, ↓ **ketogenesis**
- ↓ Urea cycle activity.

2- Action of insulin on the adipose tissues

- ↑ Glucose uptake by ↑**GLUT-4** availability.
- ↑ Glucose use to:
    - ↑ Glycolysis.
    - ↑ production **of α-glycerol phosphate**
- ↑ Esterification of fats.
- ↓ Lypolysis

3- Action of insulin on the muscle

- ↑ Glucose uptake by ↑ GLUT-4 availability.
- ↑ Glucose use to:
    - ↑ Glycogenesis and ↓ glycogenolysis
    - ↑ Glycolysis.
- ↑ amino acid uptake
- ↑ Protein synthesis, ↓ proteolysis.

Regulation of insulin secretion (Figure12.20.a,b)

1- The factors that increase insulin secretion are:

- ↑ Blood glucose
- ↑ Amino acids
- ↑Fatty acids
- Glucagon
- Ach

2- The factor that decrease insulin secretion are:

- ↓ Blood glucose
- Somatostatin
- Epinephrine and norepinephrine

Pathophysiology of insulin

- **In the absence of insulin the following events occur:**
  - **1-** Movement of glucose and amino acids into the cells decline.
  - **2-** Satiety center cannot detect the presence of glucose in the extracellular fluid result in intense sensation of hunger inspite of high blood glucose **(polyphagia)**
  - **3-** These events lead to increase blood glucose level.
  - **4-** Increase urine volume (**Polyuria)**: [↑ concentrations of glucose enter kidney tubules result in water osmosis and increase amount of water in the urine].
  - **5-** Increase sensation of thirst **(polydipsia**).
  - **6-** The patients present initially in **diabetic ketoacidosis (DKA)** (the acidity of some **ketone bodies (aceton)** which formed during the **lipolysis** in adipose tissue which metabolize the fatty acids to **ketone bodies).**

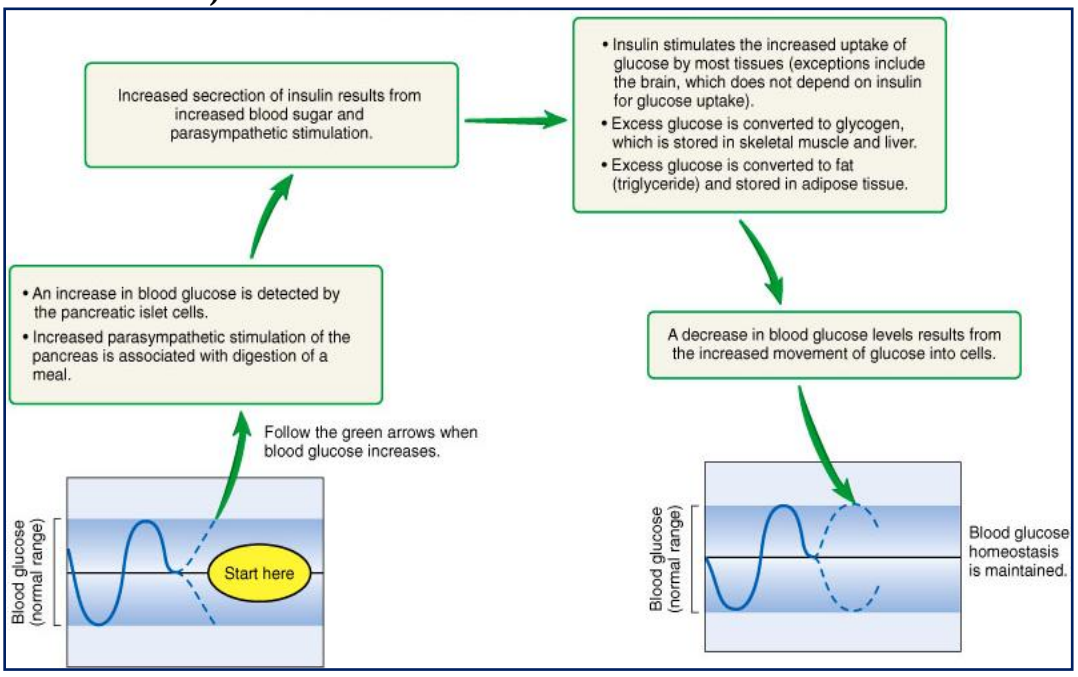


Figure (12.20. a): Blood glucose homeostasis .Events occurring in case of increased blood glucose. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

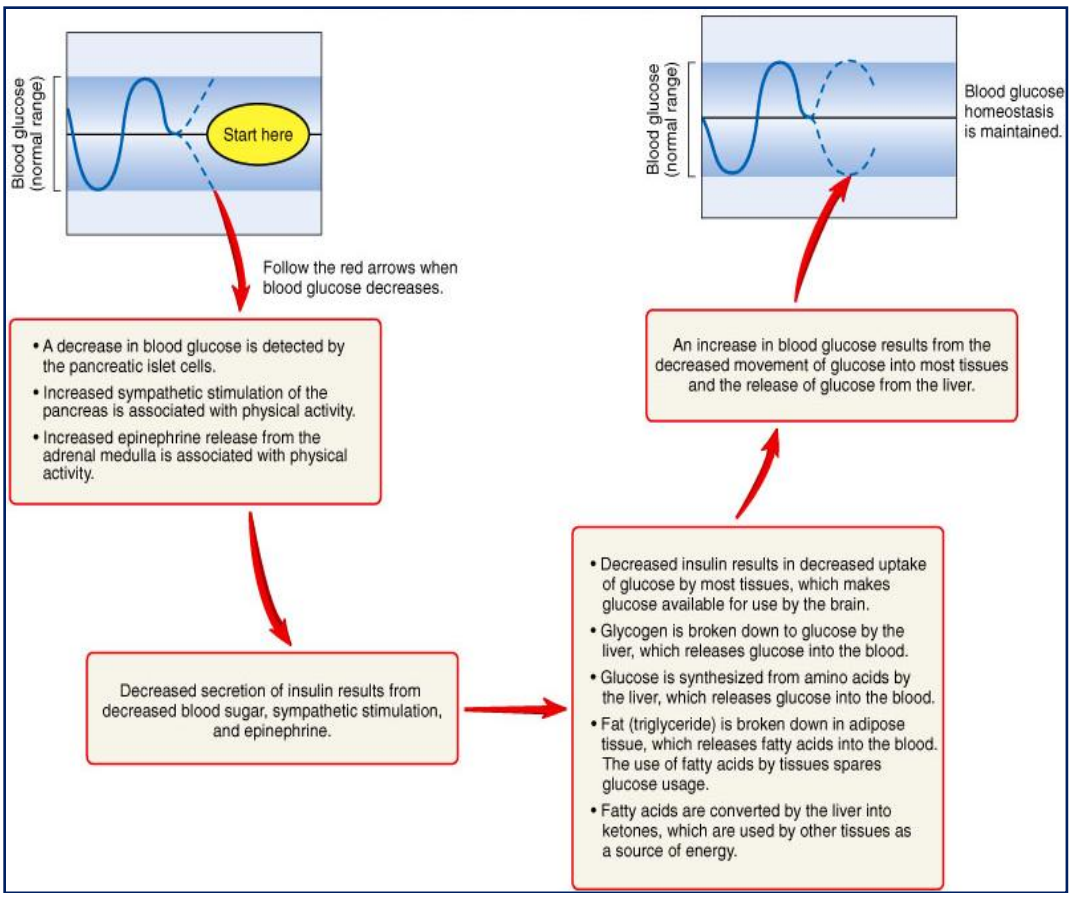


Figure (12.20. b): Blood glucose homeostasis .Events occurring in case of decreased blood glucose.

Clinical note: **Diabetes mellitus** is due to insulin problems. There are 2 types: **Type 1: insulin dependent**. This is a genetically controlled (inherited). Auto-immune disease in which the pancreas has insufficient β cells (due to destruction by antibodies) and so produces insufficient insulin. This means that:

- Blood glucose is excessively high and exceeds the kidney threshold resulting in excretion of glucose in the urine.
- Insulin is required for cells to take up glucose, so cell death occurs and the satiety center of the hypothalamus cannot record the blood glucose. The person thus keeps eating sugar, further boosting blood glucose and thus excretion. As cells switch to fat and protein metabolism as an alternative to glucose, the body wastes away. **Treatment** requires insulin injections throughout life.

Type 2 : Non-insulin dependent. Lack of **insulin receptors** on target cells means that although insulin is normal, cells cannot take up glucose and die. This form of diabetes is associated with extreme overweight (and thus prolonged over-consumption of glucose and so prolonged excessive insulin production damaging receptors). In developed countries, it is one of the fastest expanding diseases. It is easily controlled by dieting.

Pharmacology note: One way to reduce plasma glucose is to stimulate the β cells to secrete more insulin. The **sulfonylurea drugs** (**e.g. tolbutamide, glyburide)** stimulate insulin secretion by closing membrane spanning K^+ channels on β cells resulting in depolarization followed by K^+ influx that triggers insulin secretion. This drug is useful in type 2 diabetes. However these drugs cause a significant risk for hypoglycemia.

2-Glucagon

- Glucagon is the primary hormone of the fasting state
- It is a primary regulator of plasma glucose homeostasis.
- Glucagon function is to increase plasma glucose levels, thereby opposing the action of insulin.

Regulation of glucagon

- The primary stimulus for glucagon secretion is amino acids
- Glucagon secretion is also stimulated by low blood glucose levels and inhibited by high levels.

Physiologic effect of glucagon

- In the fasting state glucagon promotes **hepatic glycogenolysis** and **gluconeogenesis.**
- Glucagon stimulates β-oxidation of the fat by the liver which liberates energy that can be used to support **hepatic gluconeogenesis.**
- Glucagon has a minimal metabolic action on the adipose tissues and muscle. These actions include **stimulation of lipolysis** in adipose tissue and **inhibition of glucose utilization** by the peripheral tissues.

3- Somatostatin (SS)

- **SS** is secreted by a broad range of tissues, including pancreas, gastrointestinal tract (GIT) and regions of the central nervous system outside the hypothalamus.
- A majority of the circulating SS appears to come from the pancreas and GI tract.
- It inhibits the secretion of GH.

Physiologic Effects of SS

- SS acts by both **endocrine and paracrine** pathways to affect its target cells.
- It affects the anterior pituitary to decrease GH.
- SS appears to act primarily in a paracrine manner to inhibit the secretion of both insulin and glucagon.

- It also has the effect in suppressing **pancreatic exocrine secretions**, by inhibiting CCK -stimulated enzyme secretion and Secretin stimulated bicarbonate secretion.
- It has an inhibitory effect on the secretion of some GIT hormones such as **gastrin, CCK** and **VIP**
- SS is often referred to as having neuromodulatory activity within the central nervous system, and appears to have a variety of complex effects on neural transmission.

Hormones of the pineal body

- The **pineal gland** (pineal body) in the epithalamus of the brain secretes hormones that act on the hypothalamus or gonads to inhibit the reproductive functions.
- **The secretory products are:**
  1- **Melatonin**: can decrease GnRH secretion from the hypothalamus and may inhibit reproductive functions through this mechanism. It may also help regulate sleep cycle.
  2- **Arginine vasotocin:** works with melatonin to regulate the reproductive functions.

The thymus

- The thymus is located in the neck, posterior to the heart in the thorax.
- It secretes hormone called thymosin.
- Both the thymus and thymocin play a role in the immune system development and maturation.

Hormones of the gastrointestinal tract

- Several hormones are released from GIT .They regulate the digestive function by influencing the activity of stomach, intestine, liver and pancreas (they are discussed in chapter 11).

Hormones of the reproductive system

- Reproductive hormones are secreted by ovaries, testes, placenta and pituitary gland.

1. The main endocrine glands of the male reproductive system are the **testes.**
   - The main hormone secreted by testes is the **testosterone**.
   - The function of the testes depends on the secretion of **FSH** and **LH** from the anterior pituitary.

2. The main endocrine glands of the female reproductive system are the **ovaries**
   - Functions of the ovaries depend on the secretion of **FSH** and **LH.**
   - The main hormones secreted by the ovaries are:

- **Estrogen :**is a steroid hormone work on most cells to control:
  1- Uterine and mammary glands development and function.
  2- Secondary sex characteristics and maturation of genitalia.
  3- Sexual behavior and menstrual cycle.

- **Progesterone :**is a steroid hormone responsible for:
  1- Uterine and mammary glands development and function.
  2- Secondary sex characteristics and maturation of genitalia.

- **Inhibin:** a hormone secreted by the ovaries to inhibit secretion of FSH.
- **Relaxin**: a hormone secreted by the ovaries to increase the flexibility of the connective tissues of the symphysis pubis and help in dilation of cervix of the uterus to facilitate the delivery.

3. **The placenta:** During the first one third of pregnancy placenta secretes **LH-like substance**, which is necessary to maintain the pregnancy.

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Chapter thirteen

Reproductive system 13

Reproductive system

Overview

- The reproductive system controls the development of the structural and functional differences between male and female.
- Differences between males and females depend on a single chromosome (**Y chromosome**) and single pair of endocrine structures (**the gonads**): testes in the male and ovaries in the females.
- The gonads have a dual function :the production of germ cells (gametogenesis) and secretion of sex hormones .The testes secrete large amounts of **androgen** principally **testosterone** but they also secrete small amounts of **estrogen** .The ovaries secret large amount of estrogens and small amounts of androgen.
- It has profound effects on the behavior.
- Reproduction is an essential characteristic of the living organism. The functional male and female reproductive systems are necessary for individual to reproduce.
- The male reproductive system produces **sperm cells** and can transfer them to the female.
- The female reproductive system produces **oocytes** and can receive sperm cells.
- One sperm cell may unit with an oocyte.
- Both male and female reproductive systems have number of similarities. Many reproductive organs of males and females are derived from the same embryologic structures.
- Some hormones are same in both sexes.

The male reproductive system

Structural considerations

1- Testes:

- There is a pair of testes enclosed in a scrotal sac.
- The testes are divided by septa into compartments that contain the seminifrous tubules ,where the sperm cells are produced(**spermatogenesis**)
- The seminifrous tubules become straight to form (**tubulus recti**) which lead to (**rete testis**),(figure 13.1.a).
- The rete testis opens into the **efferent ductules** of the **epididymis** which is a coiled tubule system located in the testis that is site of sperm cells maturation.
- **Spermatozoa** pass through the tail of the epididymis into the **vas deferens.**

- The end of the ductus defernse **(ampullae**) and the **seminal vesicle** join to form **ejaculatory duct**.
- The ejaculatory ducts pass through the **prostate** and empty into the **urethra** within the prostate.
- The urethra exits from the pelvis and passes through the penis to the outside of the body.
- ***Sertoli cells:*** cells are present in the testis to provide food to the developing sperm.
- ***Interstitial cells* or *Leydig cells*:** clusters of endocrine cells are located between the seminiferous tubules secrete the hormone **testosterone**. (Figure 13.1.b).

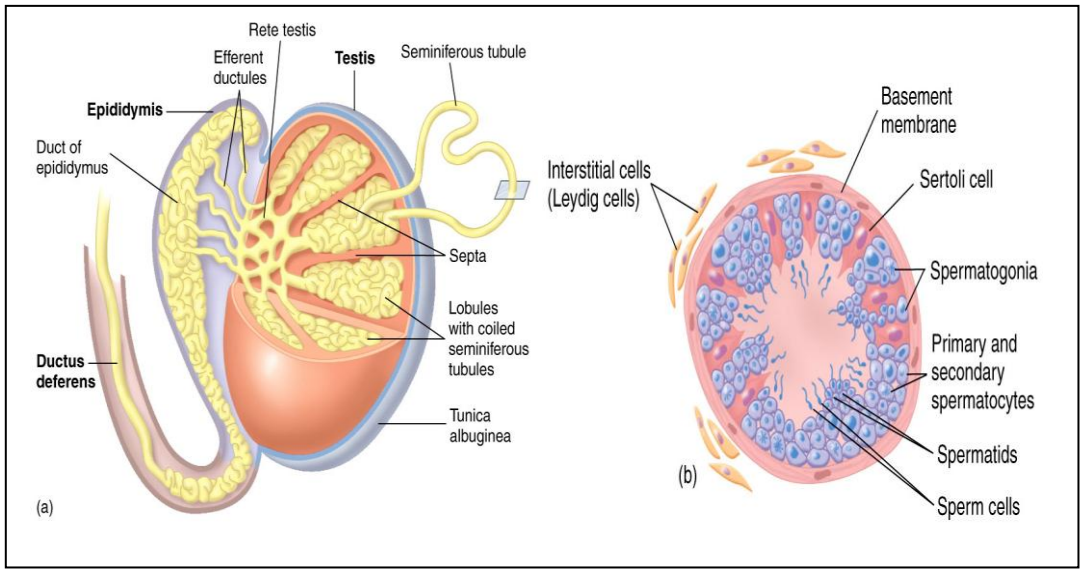

Figure (13.1):a:Gross anatomy of the testis shows internal structures ,b:Cross section of a seminiferous tubule. Spermatogonia are near the periphery and mature sperm cells are near the lumen of the seminiferous tubule. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

2- Scrotum

- The scrotum contains the testes and is divided into two internal compartments by incomplete connective tissue septum.
- **The outer layer** of the scrotum includes the skin, a layer of superficial fascia consisting of loose connective tissue and a layer of smooth muscle called: **the dartos.**
- The **dartos** and **cremaster muscles**(extension of abdominal muscles into scrotum)have a role in temperature regulation of the testes:
  - ***When the scrotum is exposed to cool temperature :***
    - The dartos muscle contracts so the skin of the scrotum becomes firm and wrinkled and reducing its overall size.
    - The cremaster muscles contract to help pull the testes near the body to keep them warm.
  - ***When the scrotum is exposed to warm temperature (exercise ,fever):***

- The dartos and cremaster muscles relax and the skin of scrotum becomes loose and thin allowing the testes to descend away from the body to keep the testes cool.

- The regulation of temperature of the testes is important in the spermatogenesis.

Sperm cells development

- Before puberty, the testes remain simple and unchanged from the time of their initial development.
- The interstitial cells are not prominent at this period, lumen of the seminiferous tubule are not functional.
- At 12-14 years of age, the interstitial cells increase in number, a lumen develops in each seminiferous tubule and sperm cells production begins.
- Sperm cells development (**spermatogenesis**) occurs in the seminiferous tubules (*the process by which germ cells divide and differentiate to form sperm cells*).
- Interstitial cells and sertoli cells produce a number of hormones such as **androgen**, estrogen and **inhibin.**
- Tight junction between the sertoli cells form **blood testis barrier** .It isolates the sperm cells from immune system .As the sperms develop, they form surface antigens that could stimulate an immune response resulting in their destruction.

Spermatogenesis steps

- The **spermatogonia** divide by mitosis on the outer layer of the seminiferous tubule.One daughter cell remains a spermatogonium (to divide again by mitosis).Other daughter cell becomes a **primary spermatocyte**. (Figure13.2).
- The primary spermatocytes divide by the first meiosis to form **secondary spermatocytes.**
- The secondary spermatocytes divide by secondary meiosis to form **2 spermatids .**Each spermatid contains one of each of the homologous chromosome pair.(Each sperm contains 22 of autosom and either x or y chromosome).
- Spermatids differentiate to form the sperm cells. Each spermatid undergoes the last phase of spermatogenesis to form a mature sperm (**spermatozoa**).
- At the end of the spermatogenesis sperm cells gather around the lumen of the seminiferous tubule (head directed toward the surrounding sertoli cells and the tail directed to the center of the lumen).
- Finally the sperm cells released into the lumen of the seminiferous tubule.

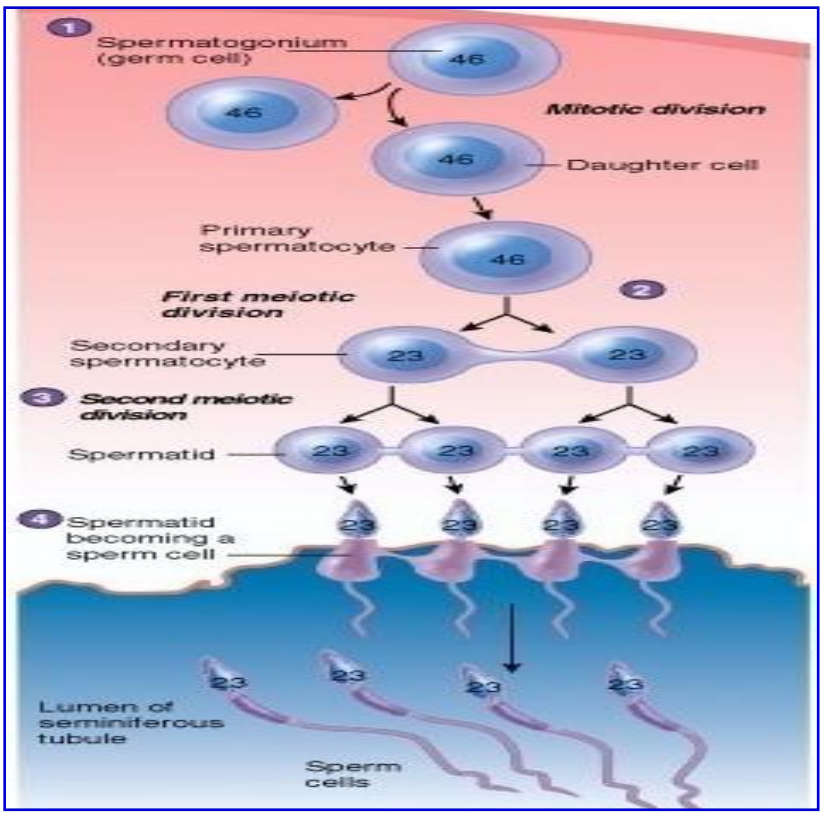

Figure (13.2): Spermatogenesis. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

- **The mature sperms have:**
  1. **The head: contains** chromosome, at leading end has a cap **(acrosome**) which contains enzymes necessary to penetrate the female sex cell.
  2. **Mid piece**: has large number of mitochondria to produce ATP necessary for microtubule movement.
  3. **Tail or flagellum:** the movement of microtubule past one another within the tail causing the tail to move. (Figure 13.3).

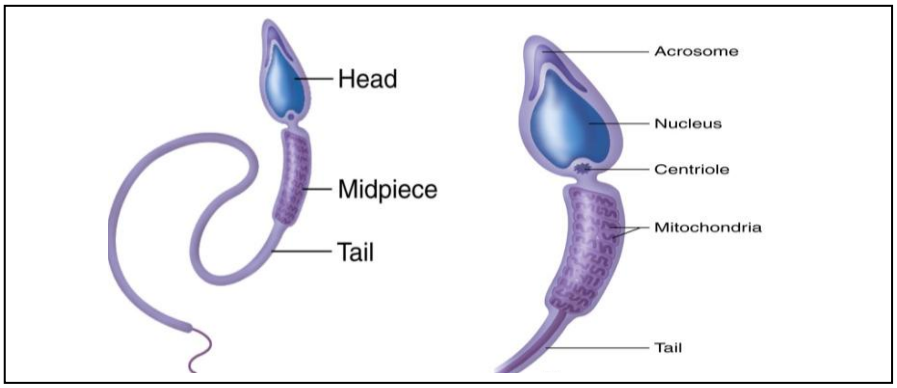

Figure (13.3): Structure of a mature sperm cell. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

3- Epididymis

- A long tube (6 cm) located along the superior and posterior margin of the testis.
- Each epididymis consists of a head, a body and a tail.
- Sperm cells that leave the testis are immature .They complete their maturation as the pass through the epididymis.
- Mature sperms are stored in the tail of the epididymis.

4- Ductus deferens or vas deferense

- Ductus deferens a fibromuscular tube that emerges from tail of the epididymis.(Figure13.1).
- It ascends along the posterior of the testis medial to the epididymis and becomes associated with the blood vessels and nerves that supply the testis.
- The end of the ductus deferens enlarges to form **ampullae.**
- The sperms are stored in the proximal portion of the ductus, near the epididymis.

5- Spermatic cord: consists of:

1. Proximal ductus deferens
2. Testicular artery and venous plexus
3. Lymphatic vessels and nerves
4. Cremaster muscles and connective tissue.

6- Ejaculatory duct

- Each ductus deferens at the ampullae joins the short duct from the **adjacent seminal vesicle,** to form the **ejaculatory duct.**
- Each ejaculatory duct (2-5 cm) passes through the **prostate gland** and ends by opening in the **urethra** . (Figure 13.4).

7-Urethra

- The male urethra is about (20 cm long), extends from the urinary bladder to the distal end of the penis.
- It is a passageway for both urine and male reproductive fluid.
- It is divided into 3 regions:
  1. **prostatic urethra**
  2. **Membranous urethra**
  3. **Spongy urethra (penile urethra).**

8-Penis

- It is located anterior to the scrotum and functions to transfer sperms to the female reproductive system.
- It consists of 3 columns of erectile tissues that are wrapped in connective tissue and covered with skin:
  - The 2 dorsal columns are the **corpora cavernosa**

- The single midline ventral column surrounds the urethra is the **corpus spongium**.

- It is 3 parts: **The root attaches** it to the pubic arch, **the body** and **the glans**.
- The **prepuce** covers the glans.

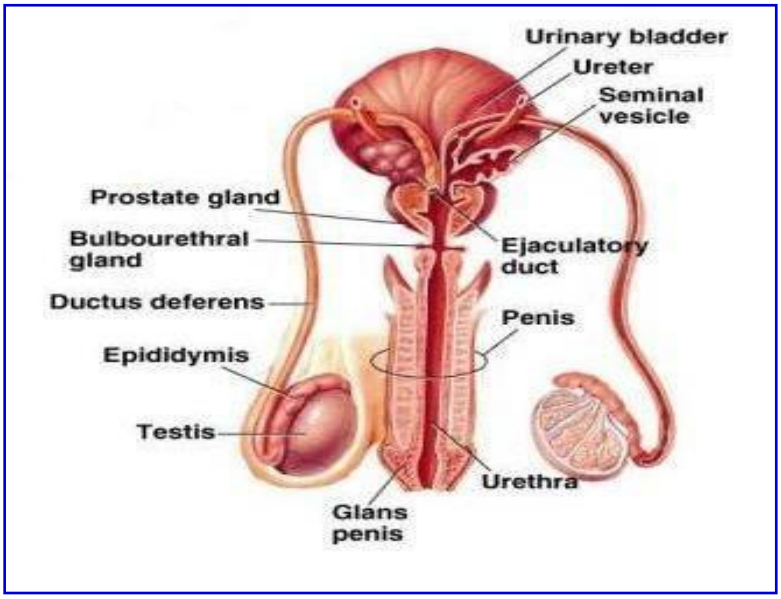

Figure (13.4): Male reproductive structures. www.slideshare.net

Accessory glands

1- Seminal vesicles

- The seminal vesicles are sac shape gland located next to the ampullae of the ductus deferens.
- Each gland is 5 cm long and tapers into short excretory duct that joins the ampullae to form the **ejaculatory duct.**
- The seminal vesicles have a capsule containing fibrous connective tissue and smooth muscle.

2- Prostate gland

- The prostate gland consists of glandular and muscular tissues
- It is about the size (4cmx2cm) and shape of a walnut.
- It is located dorsal to the **symphysis pubis** at the base of the urinary bladder.
- The muscular parts are covered by a layer of columnar epithelial cells which form secular dilation into which the columnar cells secrete **prostatic fluid.**
- Prostatic fluid is carried by prostatic duct into prostatic urethra.

3- Bulbourethral glands

- The bulbourethral glands are pair of small gland located near the membranous part of the urethra.
- Each gland is a compound mucous gland that emptied into spongy urethra.

Semen

- **Semen** is a mixture of gland secretions and sperm cells :
  - 60% of seminal vesicle production: contains fructose and fibrinogen.
  - 30%of the prostate fluid: make the seminal fluid more neutral.
  - 5% of the bulbourethral secretion: The bulbourethral gland and urethral mucosa glands produce mucus which neutralizes the acidic PH of the urethra.
  - 5% of the testicular secretion: contains sperm cells.

Regulation of male reproductive function

- Regulation of male reproductive system depends on both **hormonal** and **neural mechanism** :
  - **Hormones** are responsible for development of the reproductive structures, maintenance the functional capacity and development of secondary sexual characteristics.
  - **Neural mechanisms** are involved on sexual behavior and control of sexual act.

Regulation of sex hormones secretion:

- The pituitary gland produces 2 hormones acting on the testes:
  1. **Follicle stimulating hormone (FSH)** stimulates sperm development by increasing activity of **Sertoli cells** (to produce food for the sperms).
  2. **Luteinising hormone (LH)** controls secretion of **testosterone** by the **interstitial cells.**
- **Testosterone** controls the male **secondary sexual characters**, such as increasing facial hair, changes in the skeleton, distribution of fat, etc. It also stimulates sperm development**.**

Puberty:

- **Puberty** is the age at which the individuals become capable of sexual reproduction, which normally begins when a boy is 12-14 years old.
- ***Before puberty***, small amount of testosterone inhibit **GnRH** release from the hypothalamus.
- ***At puberty*** the hypothalamus becomes much less sensitive to the inhibitory effect of androgens.
  - ↑Secretion of GnRH lead to ↑LH and FSH release.
  - ↑LH level causes the interstitial cells to secrete ↑amount of testosterone.
  - Testosterone still has negative feedback effect on GnRH secretion, but not complete suppressing .

Male sexual act

- **Testosterone** is required to initiate and maintain male sex behavior.
- The male sex act is a complex series of reflexes that results in the **erection, emission** and **ejaculation.**
- Stimulation of the sexual act can be tactile or psychological.

- Action potentials are conducted by sensory neurons from the genitals through the **pudendal nerve** to the **sacral region** of the spinal cord, where the reflexes that result in the male sexual act are integrated.
- Action potentials travel from the spinal cord to the **cerebrum** to produce conscious sexual sensation.
- **Parasympathetic stimulation** is responsible for :
  - **Erection:** is due to vasodilatation of blood vessels that supply the erectile tissues.
  - The glands of the urethra and the bulbourethral produce mucosa.
- **Sympathetic stimulation** causes erection, emission and ejaculation.
  - **Emession:** is the discharge of secretion of seminal vesicle, prostate gland, bulbourethral and sperm cell from epididymis into the urethra to form semen.
  - **Ejaculation: is** the forceful expulsion of semen from urethra by contraction of urethra in the floor of the pelvis and the muscles at the base of the penis.

Clinical note: erectile dysfunction or **impotence** is the inability to achieve or maintain the erection, may be due psychic causes or due to nerve damage and exposure to surgery such as prostate surgery.

Pharmacology note: Erection can be achieved in some people by oral medication such as: **sildenafil (Viagra),tadafil(Cialis)** or **verdenafil (Livitra). Sildenafil** block the activity of the enzyme that converts cGMP to GMP. Consequently it allows cGMP to accumulate in smooth muscle cells in the artery of erectile tissues and cause them to relax.

Clinical note: Benign prostatic hypertrophy (BPH): Nonmalignant enlargement of the prostate gland; common in older men.
Epididymitis: Inflammation of an epididymis; usually starts as an urinary tract infection.
Prostate cancer: Most common form of cancer in men over 40; risks of developing it increase with age.
Prostatitis: Inflammation of the prostate gland; may be acute or chronic.
Testicular cancer: Malignant growth in one or both testicles; more common in males 15–30 years; more aggressive malignancy

The Famle reproductive system

Structural considerations

- Female reproductive system consists of the ovaries, uterus, uterine tube, vagina, accessory glands, external gentilia (Figure 13. 5) and breast.
- Internal reproductive organs are within the pelvis between the urinary bladder and the rectum.
- A group of ligaments holds the internal organs in the place.
- The board ligament is an extension of the peritoneum that spread out on both side of uterus and to which the ovaries and uterine tubes are attached.

1- Ovaries

- The ovaries serve a dual purpose: produce female gametes (**ova**) and produce sex hormones (**estrogen and progesterone**).
- The two ovaries are small organs about 2-3.5 cm long, 1-1.5cm wide.
- The ovaries are hold by a group of ligaments: (Figure 13.5).
  1- ***Mesovarium*** *(mesentery of the ovary) attaches the ovaries to the posterior surface of the board ligament.*
  2- ***Suspensory ligament:*** *extends from the mesovarium to the body wall.*
  3- ***Ovarian ligamen****: attaches the ovaries to the superior margin of uterus.*
- The vesiral peritoneum is made up of simple cuboidal epithelium called **germinal epithelium.**
- There is a capsule of dense connective tissue **(tunical albuginea**) below the germinal epithelium.
- The denser outer part of the ovary is called the **cortex,** while the looser inner part is called the **medulla**.
- The connective tissue of the ovary is called **stroma**, through which **ovarian follicles** (numerous small vesicles) are distributed.
- Each ovarian follicle contains (**an oocyte).**

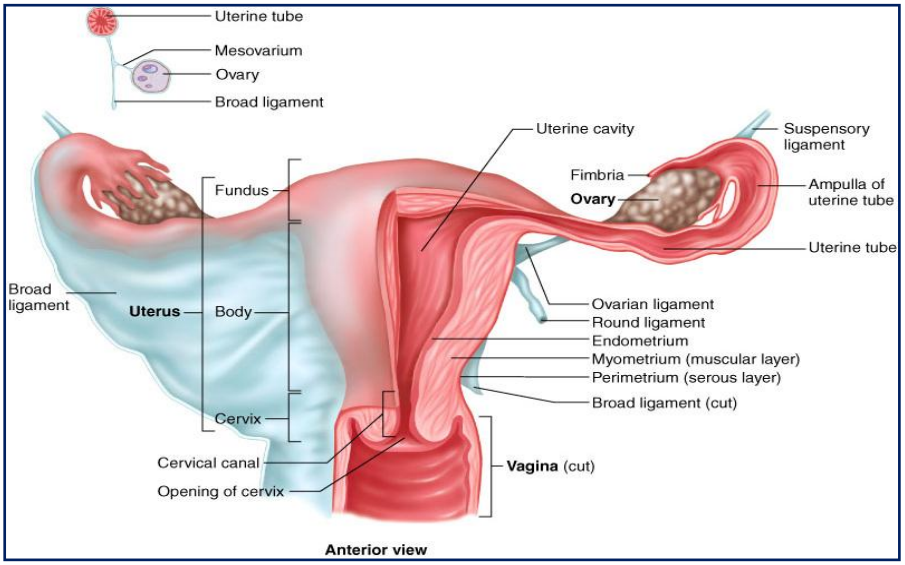

Figure (13.5): Structures of female reproductive system. (Marieb E.N.and Hoehn K. Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

Oocyte development and fertilization

- Formation of female sex cells begin in the fetus .By the 4th month of development, the ovaries contain 5 million (**oogonia**).
- The **oocytes** develop from oogonia. (Figure13.6).
- **Primary oocytes** begin at the first meiosis and stop at the prophase I and remain in this state until there are about 2 million of primary oocytes at birth.
- From birth to puberty the number decreases to 800-400 thousands.
- Only 400 primary oocytes complete development and give rise to **secondary oocytes** and the **polar body** released from the ovaries.
  - **Ovulation:** release of secondary oocytes from the ovary, the polar body either degenerates or divides to form 2 polar bodies.
  - The secondary oocyte begins the second meiosis and stop in metaphaseII.
- **After ovulation**: the secondary oocytes may be fertilized by a sperm cell.
  - **Fertilization:** begins when a sperm cell binds to the plasma membrane and penetrates into the cytoplasm of the secondary oocyte.
- Secondary oocyte completes the **second meiosis** to form 2 cells, each with 23 chromosomes.
  - One of these cells is small and degenerates .The other large one.
  - 23 chromosomes from sperm cell join with 23 chromosomes from the female cell to form the **zygote.**
- The zygote has 23pair of chromosomes .All cells of human body contain **23pairs** of chromosomes except for the male and female sex cells (23 chromosomes).
- The zygote divides by mitosis to form 2 cells which divide to form 4 cells and so on.
- The mass cells formed after 7 days after ovulation may implant to the wall of the uterus.
- The implanted mass of cells continues to develop to form a new individual after 9 months of pregnancy.

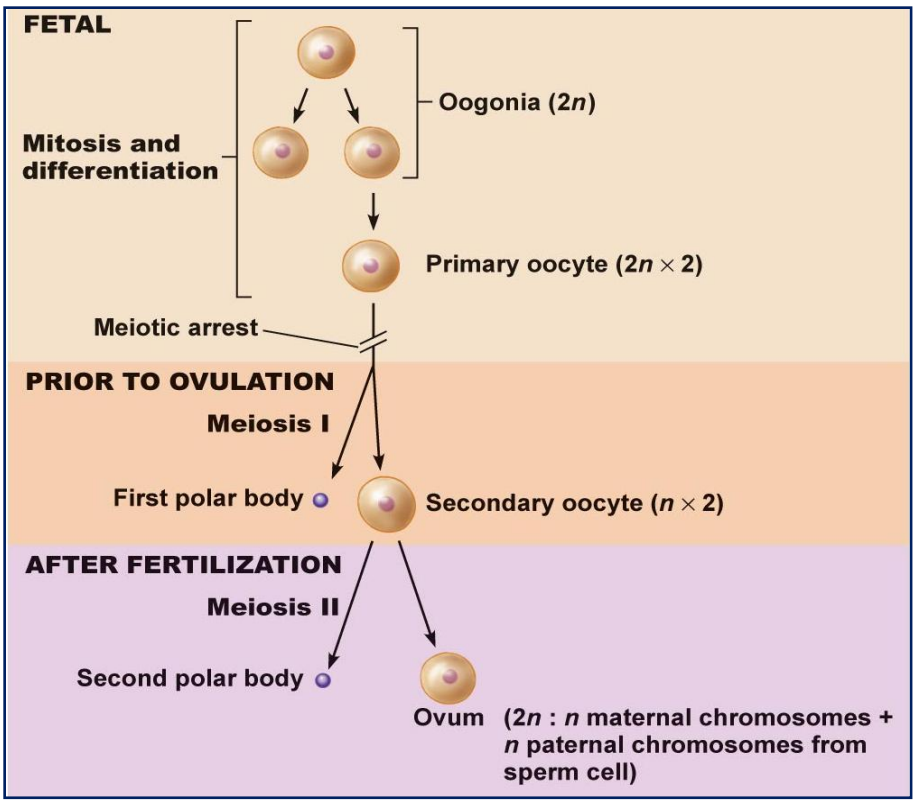

Figure (13.6): Oocyte development and fertilization. (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology .New York, McGraw –Hill Companies, 2008).

Follicle development

- A **primordial follicle** is a primary oocyte surrounded by a single layer of flat cells (**granulomas cells**).
- A primordial follicle becomes a **primary follicle** as the granulosa cells become enlarged.
- Primary follicle enlarges .Granulosa cells form more than one layer of cells .A **zona pellucid** forms around the primary oocyte.
- The primary follicles become **secondary follicles** when fluid filled vesicles develop among the granulose cells and well **developed theca** becomes apparent.
- Formation of **mature follicle** when the fluid filled vesicles form a single antrum.
- **Ovulation** occurs when the follicle swells and ruptures and the **secondary oocyte** is released from the ovary.
- The mature follicle becomes the **corpus luteum.**If pregnancy occurs, the corpus luteum persists .If no pregnancy occurs, it becomes the **corpus albicans.** (Figure 13.7).

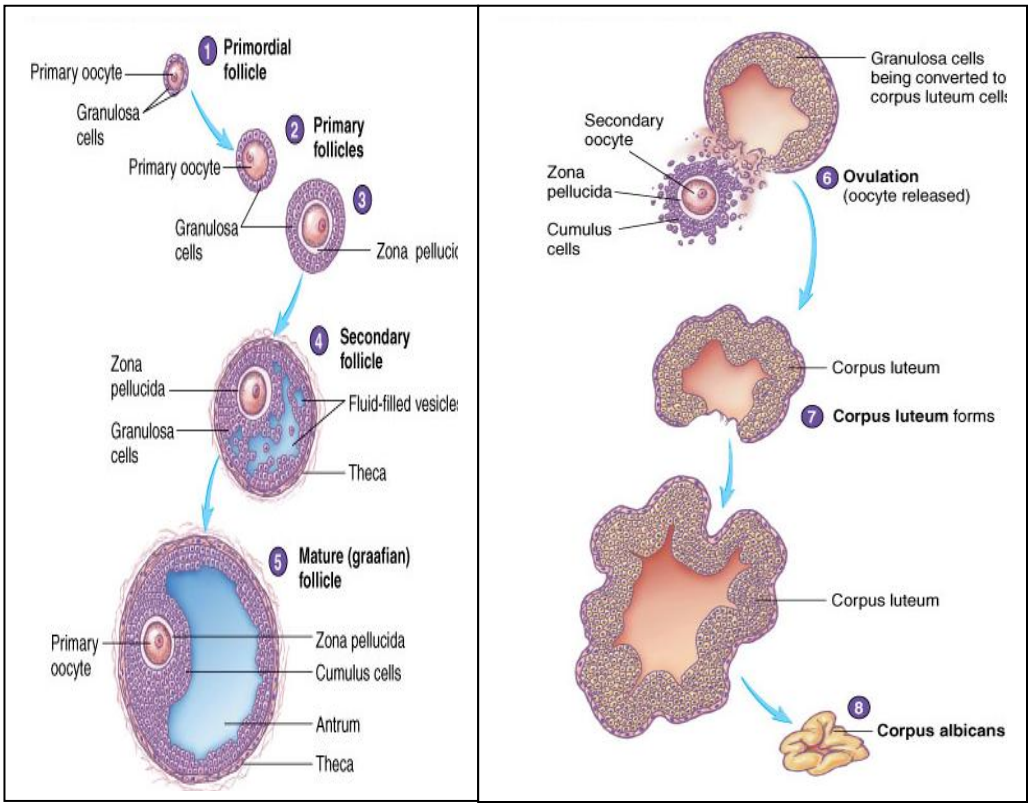

Figure (13.7): Maturation of follicle and oocyte.(Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

2- Uterine tube

- There are two uterine tubes (**fallopian**); each one is on each side of the uterus associated with an ovary.
- Each tube is located along the superior margin of the broad ligament.
- The uterine tube opens directly into the peritoneal cavity to receive oocyte from the ovary.
- It expands to form **infundibulum** and the long thin process is called **fimbriae** surrounds the opening of the infundubulum**.** The inner surface of the fimbriae consists of a ciliated mucus membrane.
- The part of the uterine tube that is nearest the infundibulum is called the **ampulla**.
- The uterine tube consists of an outer serosa, middle muscular layer and an inner mucosa with simple ciliated columnar epithelium.
- The mucosa provides nutrients for the oocyte or (if fertilization occurs) for development of embryonic mass.

Movement of oocyte

- **Cilia** move the oocyte over the fimbriae surface into the infundibulum.
- **Peristaltic movement** and cilia move the oocyte within the uterine tube.
- Fertilization occurs in the ampullae, where the zygote remains for several days.

3- Uterus

- Uterus is a pear shape muscular organ in the upper female reproductive tract.
- The **fundus** is the upper portion of the uterus , where the pregnancy occurs.
- The **cervix** is the lower portion of the uterus that connects with the vagina and serves as a sphincter to keep the uterus closed during pregnancy until the time to deliver a baby.
- The wall of the uterus consists of **perimeterum** (myometrium: smooth muscle layer) and the **endometerium**: the inner lining of vascular and glandular material.
  - The endometerium thicknes during the menstrual cycle to allow implantation of the fertilized egg.
  - If fertilization does not occur, the endometerium sloughs off and expelled as menses flow.

4- Vagina

- It a muscular ridged sheath connecting the external genitals to the uterus.
- The vagina is folded into longitudinal folds.The hymen covers the vestibular opening of the vagina. (The vestibule is the space into which the vagina and urethra open).

5- Memory glands

- The memory glands are the organs of milk production, located within the breast which is supported by Cooper's ligaments.
- The memory glands are modified sweat glands.
- The general structure of the breast is similar in both males and females before puberty.
- The female breast begins to enlarge during the puberty under the influence of **estrogen** and **progesterone.**
- The memory gland consists of **glandular lobes** and **adipose tissue**.
- The lobes consist of lobules that are divided into alveoli.
- The lobes connect to the nipple, which is surrounded by **areola** through the **lactiferous ducts**. (Figure13.8).

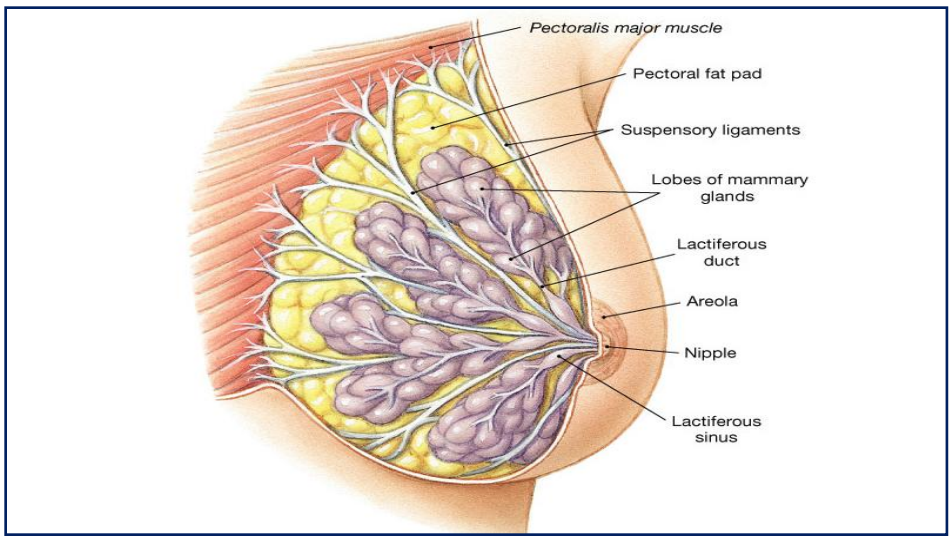

Figure (13.8): Structure of the breast . (Marieb E.N.and Hoehn K. Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

Puberty

- Puberty begins with the first menstrual bleeding (menarche), between the ages 11-16 years.
- The reproductive organs begin to enlarge.
- Fat is deposited in the breast and around the hips.
- The ducts of the breast develop, pubic and axillary hair grows.
- **GnRH** , **LH** and **FSH** are secreted in greater quantities.

Menstrual cycle

- The term **menstrual cycle** refers to the cyclic changes that occurs in sexually mature non pregnant females and culminate in menses. It is due to changes in the uterus and cyclic changes in hormone secretion in the ovary and uterus .It is about 28 days. (Figure 13.9).
- **Menses** is a period of mild hemorrhage, which occurs once each month, during which the uterine epithelium is sloughed and expelled from the uterus.
- The first day of menses is day 1 of the menstrual cycle .Menses lasts 4-5days.
- Ovulation occurs in the 14 of the 28 days menstrual cycle.
- The time between ovulation and the next menses is typically 14.
- The time between the ending of the menses and the ovulation is called: ***follicular phase*** *due to rapid development of ovarian follicle, or* ***Proliferative phase*** *because of rapid proliferation of the uterine mucosa.*

- The period after ovulation and before the next menses is called: ***luteal phase*** *because of existence of corpus luteum, or* ***Secretory phase*** *because of secretion of uterine glands*.

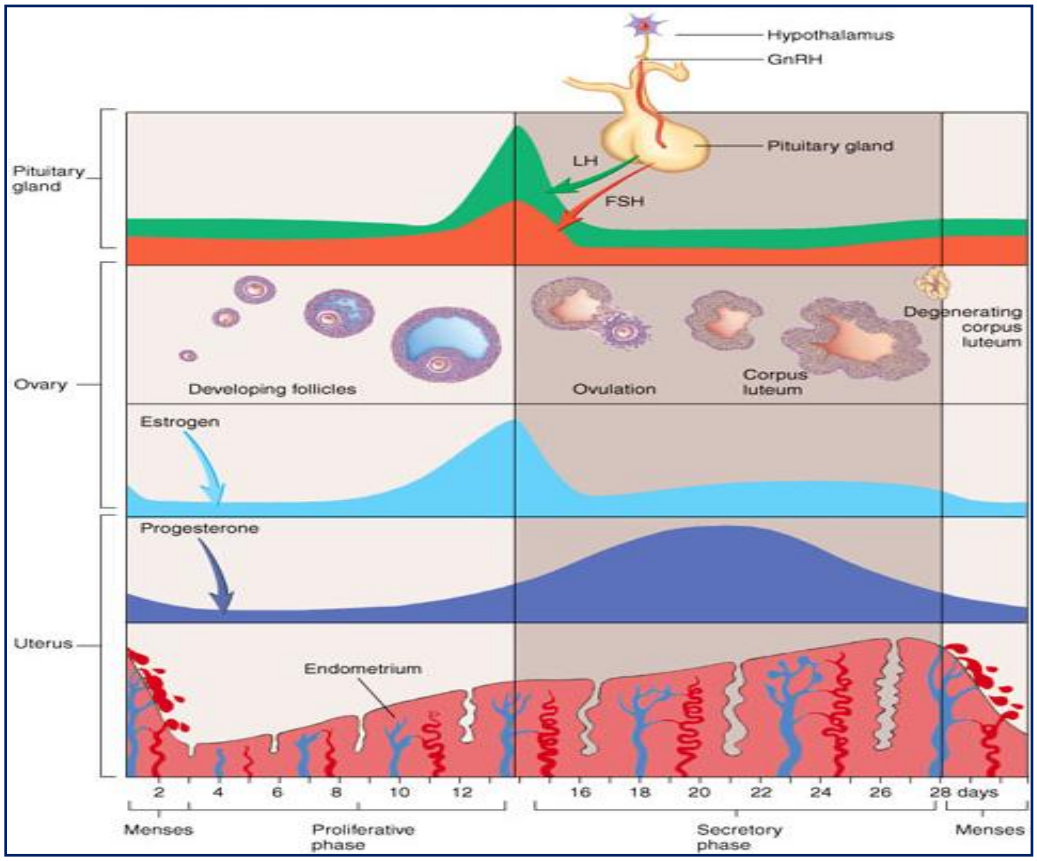

Figure (13.9): Menstrual cycle.(Marieb E.N.and Hoehn K. Anatomy and physiology. San Francisco, Pearson Education Inc., 2011).

Clinical note: **Dysmenorrhea** a condition with severe menstrual cramps is the result of strong myometrial contractions that occur before and during menstruation. The cramp can result from excessive prostaglandin secretion as part of inflammatory process.
Amenorrhea: absence of menstrual cycle .If it is due to abnormal pituitary function and the female will not begin to menstruate at puberty .This is called **primary amenorrhea.** If a female has had normal menstrual cycles and later stops menstruation, this is called secondary amenorrhea .Anorexia is one cause of this condition.

Pharmacology note: **Nonsteroidal anti-inflammatory drugs (NSAIDs)** such as aspirin or ibuprofen are effective in treatment of some painful menstruation because they inhibit prostaglandin biosynthesis.

Ovarian cycle

- Refer to events occurring in a rhythymicity in the ovaries of sexually mature nonpregnent women during the menstrual cycle.
- The **hypothalamus** and **anterior pituitary** release hormones that control these events.
- **FSH** from the anterior pituitary is responsible for the initiating and development of primary follicles.
- Although several follicles begin to mature during each cycle, normally one is ovulated .The remaining follicles degenerate.
- Early in the menstrual cycle, the release of **GnRH** from the hypothalamus increases the release of **FSH, LH** by anterior pituitary.
- **FSH and LH** stimulates follicular growth and maturation .**FSH** exerts the main effect on the **granulose cells. LH** exerts its main effect on the **theca interna** and later on the granulosa cells.
- **LH** stimulates the theca interna to produce **androgens** which diffuse from the theca interna to granulosa cells.
- **FSH** stimulates the granulosa cells to convert **androgen** to **estrogen.**
- In addition **FSH** increases **LH receptors** in the granulosa cells and the estrogen produced by the granulosa cells increases LH receptors in the theca interna cells .(**theca interna and granulosa cells cooperate to produce estrogen**). Estrogen increases receptors for LH in both theca interna and granulosa cells.
- After LH receptors in the granulosa cell increase ,LH stimulate granulosa cells to produce **progesterone** which diffuse from granulosa cells to the theca interna cells where it is converted to **androgen .**
- Thus the production of androgen by theca interna cells increases and conversion of androgen to estrogen by granulosa is responsible for gradual increase in the estrogen secretion by these cells throughout the follicular phase.
- FSH level decrease during the follicular phase because follicle cells produce **inhibin**.
- As estrogen level increases during the follicular phase have negative feedback on the FSH, LH.

- The gradual increase in the estrogen in the late follicular phase begins to have positive feedback on FSH, LH .This leads to great stimulation for LH and FSH secretion.
- As a result of positive LH, FSH increase rapidly in large amount just before ovulation. This is called **FSH surge** and **LH surge**.LH surge initiates ovulation and converts ovulated follicles to **corpus luteum.**
- FSH makes the follicle more sensitive to the LH by synthesis of LH receptors .Shortly after ovulation the follicles production of estrogen decreases and corpus luteum cells begin to release **progesterone**.
- Increased progesterone has negative feedback on the **GnRH** and as a result LH and FSH decrease.
- **If fertilization** of the oocyte occurs, the outer layer of the developing embryo begins to secret **human chorionic gonadotropin (HCG)** which keep the corpus luteum from degeneration as a result blood level of estrogen and progesterone **does not decrease** and the menses does not occur .**In case of fertilization does not occur,** HCG is not produced and the cells of corpus luteum begin to atrophy after 25 days of cycle. Blood level of estrogen and progesterone **decrease** rapidly which result in **menses.**

Uterine cycle:

1-Menstrual phase:

- **Menses:** the functional layer of the endometrium sloughs off as the spiral arteries remain in a constricted state in response to decrease level of progesterone and estrogen.
- Functional layer tissue and some blood make up the menstrual fluid .The basal layer of endothelium remains.

2-Proliferative phase:

- The basal portion of the endometrium is called basal layer.
- The epithelial cells of the basal layer proliferate in response to estrogen as a result; the epithelial cells and loose connective tissue on which they rest form the spiral shape uterine gland.

3-Secondary phase:

- The endothelial layer reaches the greater thickness and the spiral artery remains dilated due to the presence of progesterone. (Figure 13.20).

Clinical note: **Endometriosis** is a condition in which endometrial tissue is found in abnormal location, reduces fertility .Generally it results from some endomertrial cells passing from the uterus through the uterine tubes into pelvic cavity.

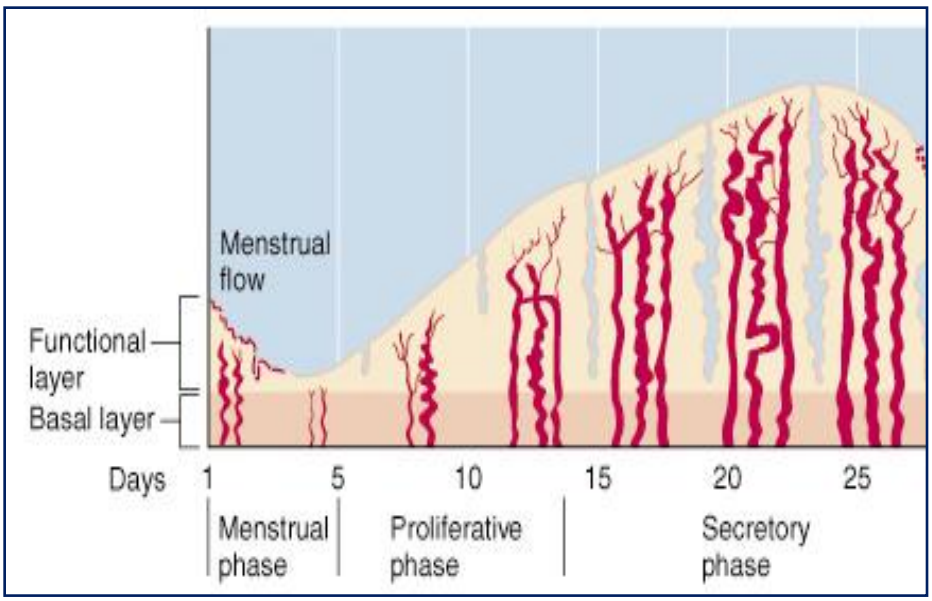

Figure (13.20): Phases of menstrual cycle.(Marieb E.N .Essential of Human Anatomy and Physiology . San Francisco, Pearson Education,Inc.,2012).

Female fertility and pregnancy

- In case of fertilization to occur,intercourse must take place 5 days before and 1 day after ovulation if
- Sperm cells transport to the ampullae depend on the ability of the sperm s to swim and on contraction of the uterus and uterine tubes.
- The oocyte can be fertilized for up to 24 hours after ovulation.
- One sperm enters the secondary oocyte and fertilization occurs.
- For the next several days ,a sequence of cell divisions occurs while the developing embryo passes through the uterine tube to the uterus.(Figure 13.21).
- By 7-8 days after ovulation the endometrium of the uterus has been prepared for implantation.
- **Estrogen** and **progesterone** cause the endometrium to reach to maximum thickness and secretory activity and embryo begins to implant.
- The outer layer of the developing embryo is the **trophoblast**(forms placenta)
- The trophoblast secretes **HCG** which is transported in the blood to the ovary and causes the corpus luteum to remain functional.
- Estrogen and progesterone secreted by the corpus luteum are essential for the maintenance of pregnancy.
- After the first 3 months of pregnancy the placenta has become an endocrine that secretes sufficient quantities of estrogen and progesterone.

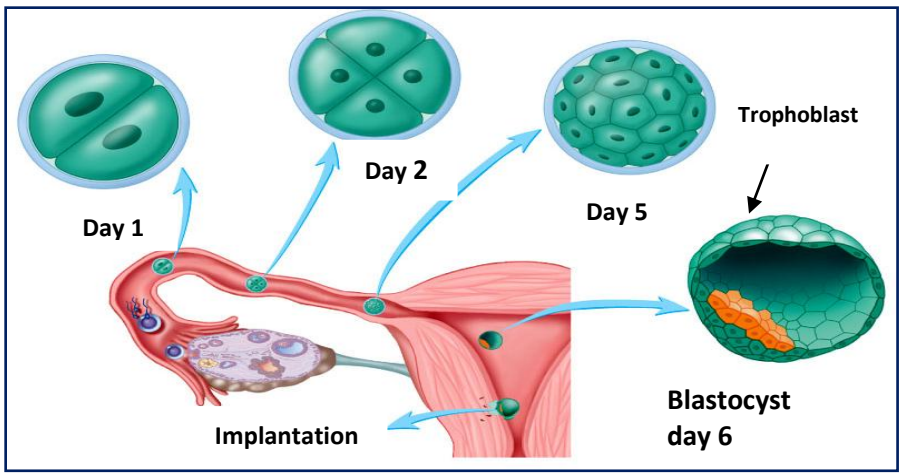

Figure (13.21): Blastocyst (Seeley R.R., Stephens T.D. and Tate P. Anatomy and Physiology . New York, McGraw –Hill Companies, 2008).

Menopause

- The cessation of menstrual cycle is called **menopause**.
- The menstrual cycle of a woman 40-45years old becomes less regular and evaluation does not occur.
- Menopause is associated with changes in the ovaries, the number of follicles remaining is small and the remaining follicles become less sensitive to stimulation by LH and FSH.
- Morphological changes occur in the females in response to reduced amount of estrogen and progesterone.
- A variety of symptoms occur in some women during this period: hot flashes, irritability, fatigue, anxiety and emotional disturbance.

Pharmacology note: Symptoms that occur during the climacteric may be treated by administration small amount of estrogen in combination with progesterone, then gradually decreasing this treatment .On the other hand some potential side effects of hormonal therapy are concern such as increase risk for breast, ovarian and uterine cancer. Some data indicate that risk for heart attacks, strokes and blood clots is also increased.

Clinical note: Ovarian cyst: fluid filled sacs that grow on or in the ovaries. Most ovarian cysts are noncancerous and not harmful but may sometimes become cancerous in women over 40 years.
Pelvic inflammatory disease (PID): Inflammation of female reproductive organs most often due to sexually transmitted diseases.
Fibroids: Benign tumors in the uterine wall affect 25% of the women between 35-55 years.

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