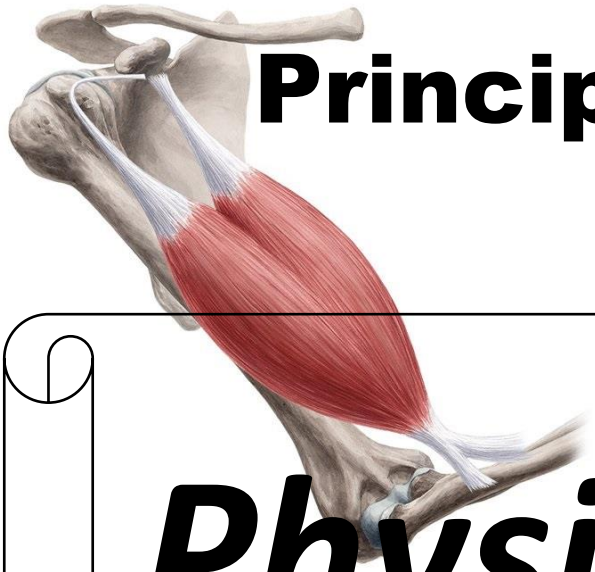
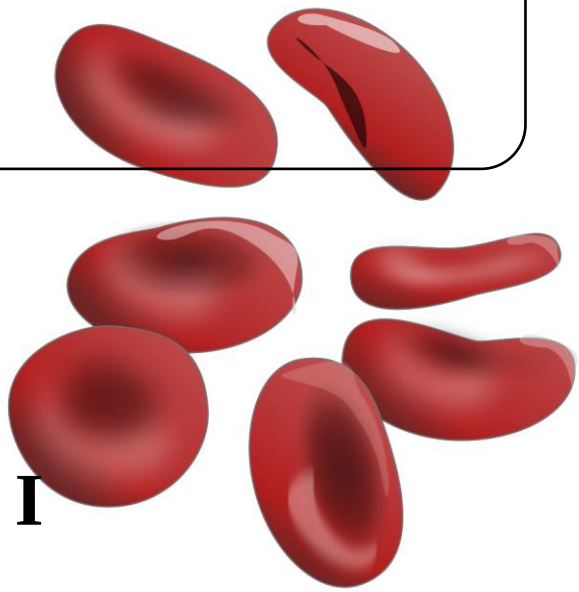


Principles of

Physiology



Physiology I

First Year

Physical Therapy Students

First Semester

Contents

Introduction

Physiology: (physo = nature; logos = study):

Physiology: biological sciences dealing with the normal life phenomena exhibited by all living organisms.

• Human physiology: basic sciences dealing with normal life phenomena of the human body.

• Goal of physiology: is to explain the physical and chemical factors that are responsible for the origin, development and progression of life. Physiology includes many divisions such as:

Cell physiology

Cell physiology is the study of the function of cells (a branch of cytology).

Systemic physiology

Systemic physiology is the study of the function of the body's systems.

Special (organ) physiology

Special (organ) physiology is the study of specific organs of the body.

Pathophysiology:

It is the study of the effects of diseases on organ or system functions (pathos = disease).

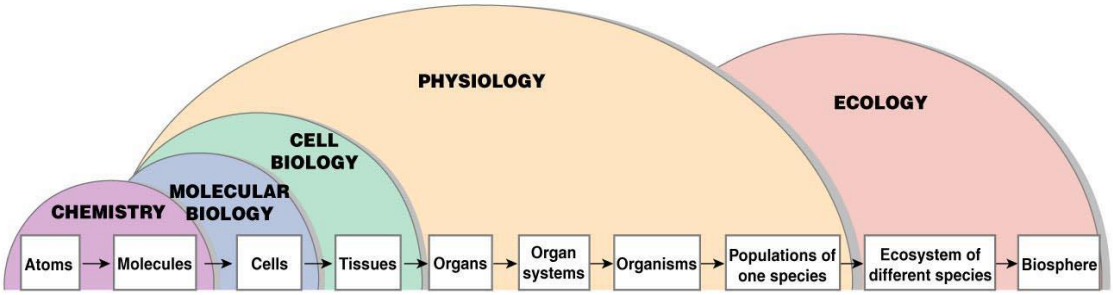


Fig (1) spectrum of physiology related sciences

Physiology is about two questions:

- **Why?** Function explains why it needs to be done
- **How?** Mechanism explains how it does that job

Why do we study Physiology?

- To understand how the human body functions as an integrated whole.
- Recognize changes from the normal condition, i.e that means disease states.
- Knowing normal and diseased conditions are the bases to plan for curing impairments.

Body Fluid Compartments

Body composition

In average young adult male:

- Protein, & related substances represent **18%** of body weight
- Fat represent **15%** of body weight
- Mineral represent **7%** of body weight
- **Water represent 60% of body weight**

Percentage of H_2o in tissues

- Infant: **80%** of body weight
- Male adult: **60%** of body weight
- Female adult: **40-50%** of body weight
- Old age **45%** of body weight

This percentage depends on body fat percentage

Body fluid compartments:

Body fluid is distributed between the intracellular fluid (**ICF**) and extracellular fluid (**ECF**) compartments.

- The ICF compartment consists of fluid contained within all cells in the body. It is approximately **2/3** of the body water.
- The remaining **1/3** of body water is in the ECF compartment, which contains all the fluids outside the cells, including that in the interstitial or tissue spaces and blood vessels.
- There is another small compartment of fluid that is referred to as trans-cellular fluid. It is usually considered to be a specialized type of extracellular fluid This compartment includes fluid in the synovial, peritoneal, pericardial, and intraocular spaces, as well as the cerebrospinal fluid.

Intracellular Fluid Compartment

- The intracellular fluid constitutes about 40 % of the total body weight.
- The fluid of each cell contains its individual mixture of different constituents, but the concentrations of these substances are similar from one cell to another.
- The intracellular fluid of all the different cells together is considered to be one large fluid compartment.

Extracellular Fluid Compartment

- All the fluids outside the cells are collectively called the extracellular fluid. Together these fluids account for about 20 % of the body weight, in a normal adult.
- The two largest compartments of the extracellular fluid are

- *The interstitial fluid*, which is about 3/4 of the extracellular fluid
- *The plasma,* which makes up almost 1/4 of the extracellular fluid.

Plasma exchanges substances continuously with the *interstitial fluid* through the pores of the capillary membranes.

Both ECF and ICF are in a continuous exchanging movement.

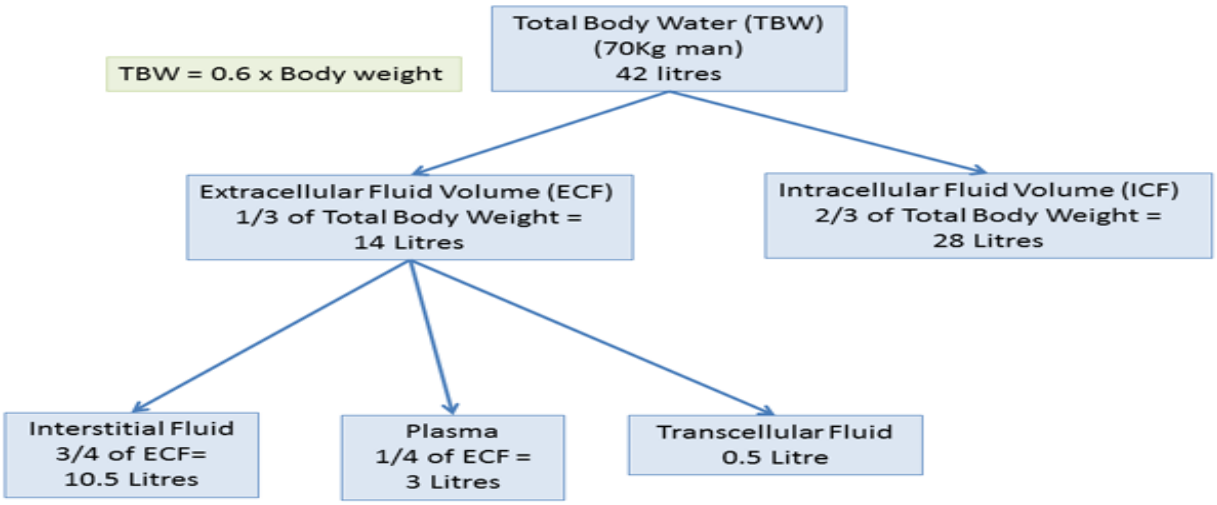


Fig. (2) Body fluid compartments

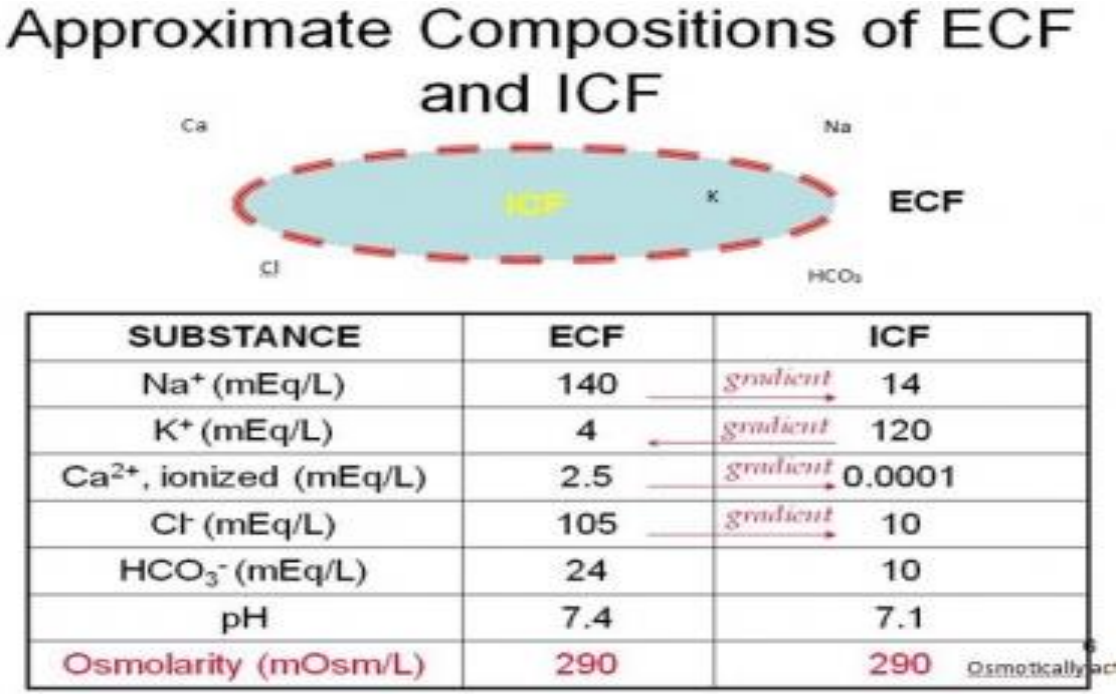
Constituents of Extracellular and Intracellular Fluids

Ionic Composition of ECF

- Plasma and interstitial fluid are separated only by highly permeable capillary membranes, so their ionic composition is similar.
- The most important difference between these two compartments is the higher concentration of ***protein*** in the plasma.
- The plasma proteins have a net negative charge and, therefore, tend to bind cations, such as **Na^+ and K+** ions, thus holding extra amounts of these cations in the plasma along with the plasma proteins.
- Conversely, negatively charged ions (anions) tend to have a slightly higher concentration in the interstitial fluid compared with the plasma, because the negative charges of the plasma proteins repel the negatively charged anions.
- The extracellular fluid contains large amounts of **Na+, Cl-, HCO3** ions, but small quantities of K^+, Mg^+, Ca^{+2}, PO_4^- and organic acids.

Ionic Composition of ICF

- The intracellular fluid contains only small quantities of Na^+ & Cl^- ions and almost no Ca^{+2} ions. Instead, it contains large amounts of **K^+ and PO_4^-** ions and moderate quantities of **Mg^+ & SO_4^-** ions.
- Also, cells contain large amounts of protein, almost four times as much as in the plasma.



SUBSTANCE	ECF		ICF
Na^+ (mEq/L)	140	gradient →	14
K^+ (mEq/L)	4	← gradient	120
Ca^{2+}, ionized (mEq/L)	2.5	gradient →	0.0001
Cl^- (mEq/L)	105	gradient →	10
HCO_3^- (mEq/L)	24		10
pH	7.4		7.1
Osmolarity (mOsm/L)	290		290 Osmotically ac

Table (1) ionic composition of ECF and ICF

Plasma/Interstitial Fluid Exchange

The transfer of water between plasma and interstitial compartments occurs at the capillary level.

Four forces (Starling`s forces) control the movement of water between the capillary and interstitial spaces:

(1) the capillary filtration pressure, which pushes water out of the capillary into the interstitial spaces.

(2) the capillary colloidal osmotic pressure, which pulls water back into the capillary.

(3) the interstitial hydrostatic pressure, which opposes the movement of water out of the capillary.

(4) the tissue colloidal osmotic pressure, which pulls water out of the capillary into the interstitial spaces.

Normally, the combination of these four forces is such that only a small excess of fluid remains in the interstitial compartment. This excess fluid is removed from the interstitium by the lymphatic system and returned to the systemic circulation.

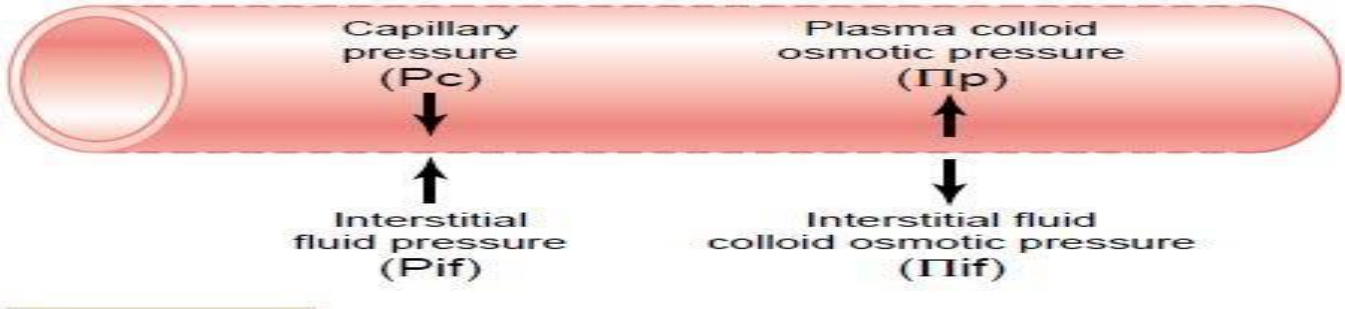


Fig. (3) Forces controlling water movement between capillary and interstitial spaces

Function of major electrolytes:

In terms of body functioning, six electrolytes are most important: **sodium, potassium, chloride, bicarbonate, calcium, and phosphate.** Only functions of Sodium and Potassium will be listed here.

1- Sodium functions:

- Responsible for resting membrane potentials that underlies nerve and muscle function
- Principal cation in ECF sodium salts accounts for 90 - 95% of osmolarity of ECF.

- Most significant solute in determining total body water and distribution of water among the fluid compartments.
- Na+ gradient a source of potential energy for cotransport of other solutes such as glucose, potassium, and calcium.
- Na+- K+ pump generates body heat.
- $NaHCO_3$ has major role in buffering pH in ECF

2- Potassium functions:

- Major intracellular cation
- Extracellular K^+ influences skeletal muscle activities (including cardiac muscles)
- Transmission of nerve impulse
- Acid base balance
- Water & electrolyte balance
- Intracellular potassium concentration is necessary for protein biosynthesis by ribosomes.

Homeostasis

Homeostasis: It is the body's attempt to maintain a constant internal environment. Maintaining a stable internal environment requires constant monitoring and adjustments as conditions change.

Homeostatic functions of the body depend on the functioning of control systems. For each variable of our body there is a control system. **The control system consists of –** 1) the ***receptor*** 2) the ***control center*** 3) the ***effector***.

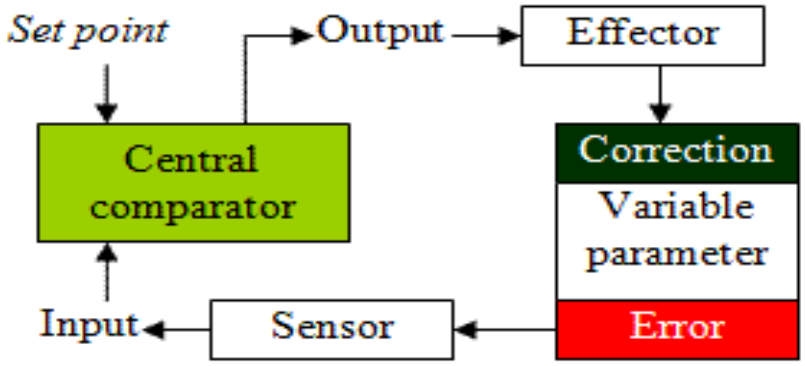


Fig. GP1.2 – Control system in action.

Fig (4) components of control system

- The ***receptor*** receives information that something in the environment is changing.
- The ***control center*** or ***integration center*** receives and processes information from the ***receptor***.
- And lastly, the ***effector*** responds to the commands of the ***control center*** by either opposing or enhancing the stimulus.

For example, in regulating body temperature there are temperature ***receptors*** in the skin, which communicate information to the brain, which is the ***control center***, and the ***effector*** is our blood vessels and sweat glands in our skin.

Negative And Positive Feedback: When a change of variable occurs, there are two main types of feedback to which the system reacts

• ***Negative feedback***:

Definition: a reaction in which the system responds in a way that **reverse** the direction of change, so it allows the maintenance of homeostasis.

Example: when the concentration of carbon dioxide in the human body increases, the lungs are signaled to increase their activity and expel more carbon dioxide.

• ***Positive feedback***:

Definition: a response is to **amplify** the change in the variable.

Positive feedback is less common in naturally occurring systems than negative feedback, but it has its applications.

Examples: a) in nerves, a threshold electric potential triggers the generation of a much larger action potential.

b) Blood clotting in which the platelets activated to produce a circle of increasing number of activated platelets and substances that cause clotting

Harmful Positive Feedback

Although Positive Feedback is needed within homeostasis it also can be harmful at certain times.

Example: high fever can cause a metabolic change that can push the fever higher and higher. In rare occurrences the body temperature reaches 45^0 C and the cellular proteins stop working and the metabolism stops, resulting in death.

Body system and homeostasis

All the body systems are part of the internal environment. On the other hand, the survival of components of the body systems *i.e.* cells, depends on the proper maintenance of the internal environment. Thus, to maintain the homeostasis, body systems also have to take part in the homeostatic mechanisms.

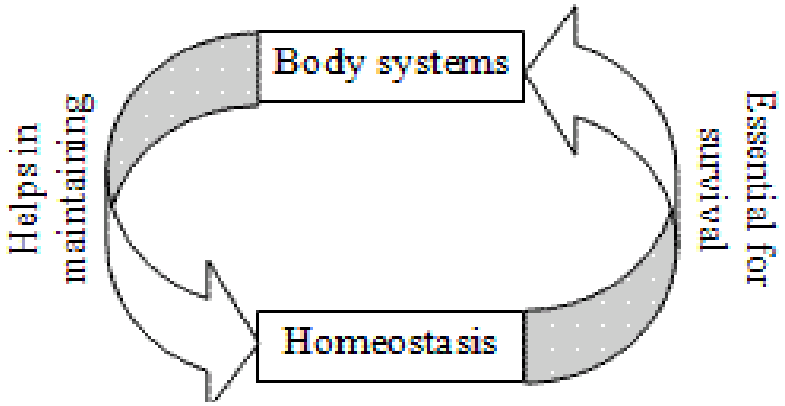


Fig (5) interdependent relation between body systems and homeostatic mechanisms

Each of our body systems, namely, digestive system, circulatory system, respiratory system, excretory system, nervous system, endocrine systems, immune system, musculoskeletal system, integumentary system, contributes to the maintenance of homeostasis by their own way.

The collective target of all the body systems includes:

a. Continuance of adequate concentration of energy sources.
b. Adequate and continuous supply of oxidants.
c. Limit the concentration of waste materials.
d. Keeping of optimum pH for proper functioning.
e. Maintenance of concentration of water, salt and electrolytes.
f. Regulation of volume, pressure and temperature within the sustainable range.

Factors that alter homeostasis

- **Nutrition:** healthy balanced diet is essential for normal cell function.

- **Toxins:** such like chemical and insecticides as they interfere with cellular function. A commonly seen example of this is drug overdoses ,which affect vital signs causing problems including coma, brain damage and even death.
- **Psychological:** physical health and mental health are inseparable. Thoughts and emotions cause chemical changes to take place either for better or worse.
- **Physical:** Physical maintenance is essential for normal cell function . Adequate rest, sunlight, and exercise are examples of physical mechanisms for influencing homeostasis. Lack of sleep is related to a number of ailments such as irregular cardiac rhythms, fatigue, anxiety and headaches.
- **Genetic:** A variety of diseases result from mutated genes. Genes are sometimes affected by external factors. For example, cancer can be genetically inherited or can be caused due to a mutation from an external source such as radiation.
- **Medical:** medications can maintain homeostasis to face diseases. Example: anti-bodies help to fight infections, or chemotherapy help against cancer cells.

Functions of cell organelles

All living organisms are composed of cells. Eukaryotic cells have a nucleus and membrane bound organelles. The cell is the functional and structural unite of the body.

The cell is composed of:

- Cell membrane surrounding the cell
- Cytoplasm which is the fluid part of the cell in which the other components are embedded.

- Nucleus: that contain the DNA of the cell.
- Cell organelles: that perform different functions such as mitochondria, Golgi apparatus, endoplasmic reticulum lysosmes …. Etc.

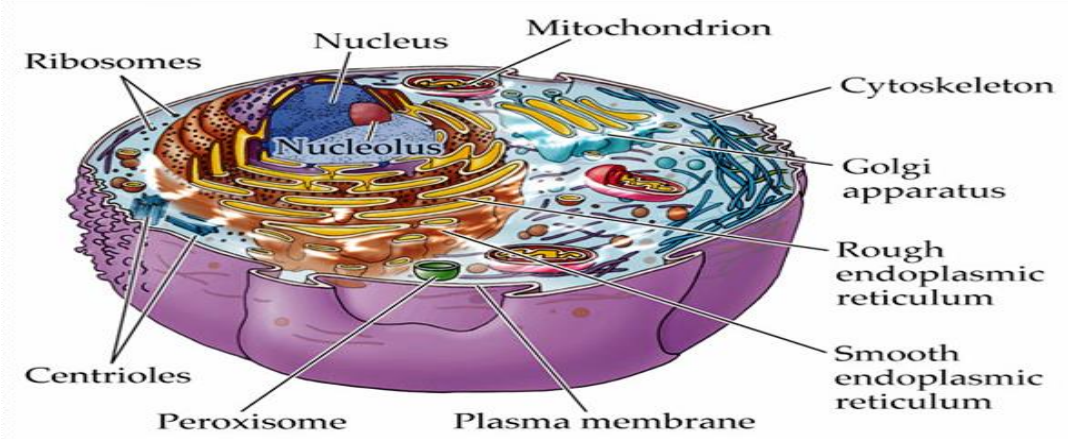


Fig (7)Eukaryotic cell

Cell Parts and Functions:

A) Cell Membrane: serves the following functions:

1. Protection
2. Communication
3. Selectively permeability
4. Respond to environment
5. Recognition
6. It gives form and shape to the cell.

B) The cytoplasm: it is a viscous fluid containing organells. It is composed of interconnected filaments and fibers, fluid (cytosol), organelles and storage substances.

C) Nucleus: contains the genetic material that directs the production of protein and other many cellular processes. It is the central command of the cell. Its main function is to control gene expression and initiate DNA replication.

The nucleus contains the nucleolus where ribosomal RNA is produced Nuclear Envelope has pores that allow material to move in and out.

D) Mitochondria: the powerhouse of the cell. It converts the potential energy of food molecules into ATP by cellular respiration.

E) Endoplasmic reticulum: It helps in movement of substances within the cell. Two types: smooth & rough endoplasmic reticulum

Smooth Endoplasmic Reticulum: performs functions like

- lipid synthesis, carbohydrate metabolism.
- Synthesis of steriods in gland cells
- Regulation of calcium in muscle cells
- Breakdown of toxic substances in liver cells

Rough Endoplasmic Reticulum: covered with ribosomes that give it a rough appearance and performs functions like

- provides surface for ribosomes where synthesis of many secretory proteins takes place.
- It is abundant in protein secreting cells like endocrine glands secreting polypeptide and protein hormones.

F) Golgi apparatus: It stores, modifies and packages proteins into vesicles inside the cell before the vesicles are sent to their destination.

G) Ribosomes: are sites of protein synthesis.

H) Lysosomes: the suicidal bag of the cell for they contain hydrolytic enzymes that can break down large macromolecules and also engulfs another organelle specially the damaged ones.

- Present in abundance in neutrophils & macrophages
- Contain proteolytic enzymes for breakdown of proteins & lipases for fat breakdown
- Can digest proteins, carbohydrate, lipid, DNA & RNA.

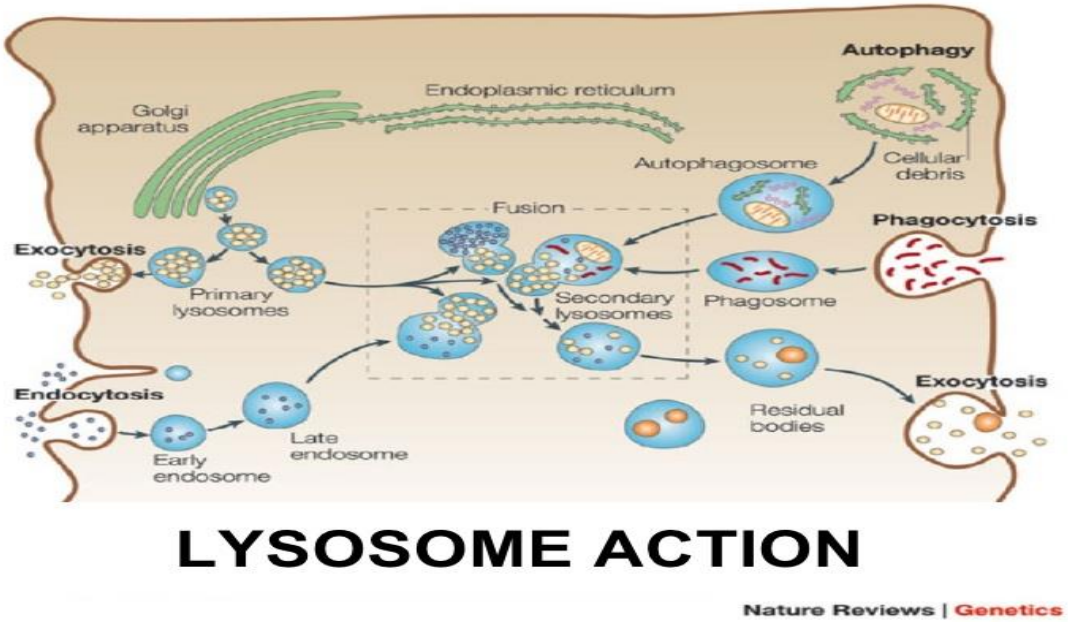


Fig (8) Mechanism of action of lysosomes

H) Peroxisomes are organelles that contain oxidative enzymes, such as D-amino acid oxidase, ureate oxidase, and catalase. They are a major site of oxygen utilization and are numerous in the liver where toxic byproducts accumulate.

J) The cytoskeleton: it is a cytoplasmic system of fibers which is critical to cell motility. It is dynamic three dimensional scaffolding contained within a cell's cytoplasm and is made of protein.

The three major components of the cytoskeleton are microtubules, microfilaments, and intermediate filaments.

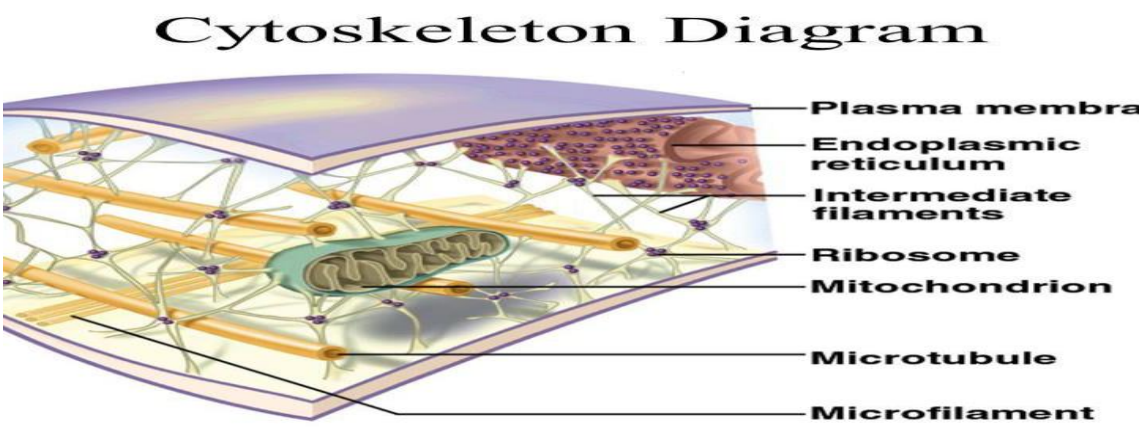


Fig (9) Components of cytoskeleton

I- Microfilaments:

The smallest one of the three components of cytoskeleton They are built from molecules of a globular protein – actin. A microfilament is a twisted double chain of actin subunits (5 nm in diameter).

They make up the major portion of cytoskeleton of all cells and also extend into cell processes, especially where there is movement. Thus, they are found in the microvilli of the brush border of intestinal epitheliun and in cell types where amoeboid movement are prominent.

Function:

1.Changes in cell shape. 2. Muscle contraction.

3.Cytoplasmic streaming. 4.Cell motility.

5. Maintaining cell shape, and anchoring cytoskeletal proteins.

6. Cell division – cleavage furrow formation.

II- Intermediate filaments:

They are fibrous proteins supercoiled into thicker cables (8-10 nm) Intermediate in size between actin filaments and microtubules.

Depending on the cell type, it is presented by one of the several different proteins of the **keratin family.** They are particularly prominent where cells are subjected to mechanical stress, such as in epithelia, along the length of axons, and throughout the cytoplasm of smooth muscle cells.

Function:

1. The main function of Intermediate filament is mechanical support.
2. Maintenance of cell shape (tension-bearing elements)
3. Anchorage of nucleus and certain other organelles
4. Formation of nuclear lamina

III- Microtubules:

They are hollow tubes with wall that consists of 13 columns of tubulin molecules (25 nm in diameter)

The most rigid cytoskeletal filaments , because of their tubelike construction.

Function:

1.Mechanical function: The shape of the cells such as axons and dendrites of neurons, microvilli.

2. Morphogenesis: During cell differentiation, the mechanical function of microtubules is used to determine the shape of the developing cells.

3. cell motility (as in cilia or flagella)

4. chromosome movement in cell division

5. Circulation and transport: Microtubules are involved in the transport of macromolecules, granules and vesicles within the cell.

Plasma membrane and transportation

Plasma Membrane

Functional structure of cell membrane:

It is about 75-100 angstrom thickness. It is semipermeable. Composed of :

1-Lipid bilayer. 2-Proteins. 3-Small amount of carbohydrate.

Function of Lipid Bilayer

1-Phospholipid bilayer

a-important for regulation of passage of substances across the membrane.

b-Together with membrane proteins, phospholipid bilayer account for the selective permeability of the membrane.

2-Cholesterol

a-Increases bilayer strength, flexibility

b-Reduces membrane fluidity

c- Prevent packing of fatty acids that would reduce membrane permeability.

3- Membrane proteins

a-Transmembrane proteins: Along the whole membrane thickness.

-Regulate movement of water soluble substances.

-Channel proteins for passage of ions and small water-soluble molecules.

-Carrier proteins for large molecules and change shape for delivery across membrane.

b-Peripheral proteins: have active site in one side only;

-Receptor proteins: with the active side towards outside

-Membrane bound enzymes: with the active side towards inside

4-Membrane Carbohydrates

Present on the outer surface of the membrane in form of glycolipids & glycoproteinsa-

a- Part of the cell identification b-Important in immune mechanism.

c- Adhesion of adjacent cells together to form tissues.

Transport Across Cell Membrane

According to energy needs, membrane transport can be either:

I- Passive transport

-Substances move from [high]→[low]

-No energy input required

-Includes Simple Diffusion, Facilitated Diffusion & Osmosis.

II- Active transport

-Substances move from low concentration to higher one

-Requires energy input

-Protein carriers (Primary & secondary active transport)

III- Vesicular transport: exocytosis & endocytosis

1- Simple Diffusion

-The passive movement of molecules according to concentration or electric gradient until equilibrium is reached.

-Gases move through plasma membranes by simple diffusion.

-Simple diffusion can occur through:

a- lipid bilayer (O2, Co2, N2 & alchols) depending on lipid solubility.

b- protein channels

Simple diffusion through protein channels: Protein channels are characterized by:

-Selective permeability (according to shape, size, charge, …..etc)

-Presence of gates

Types of channels:

I- According to their selective permeability:

a) +ve charged for negative ions

b) -ve charged for positive ions

c) Un-charged

II- According to presence or absence of gate:

a) Leak channels

b) Gated channels:-

*Voltage gated

*Chemical gated

2- Facilitated Diffusion

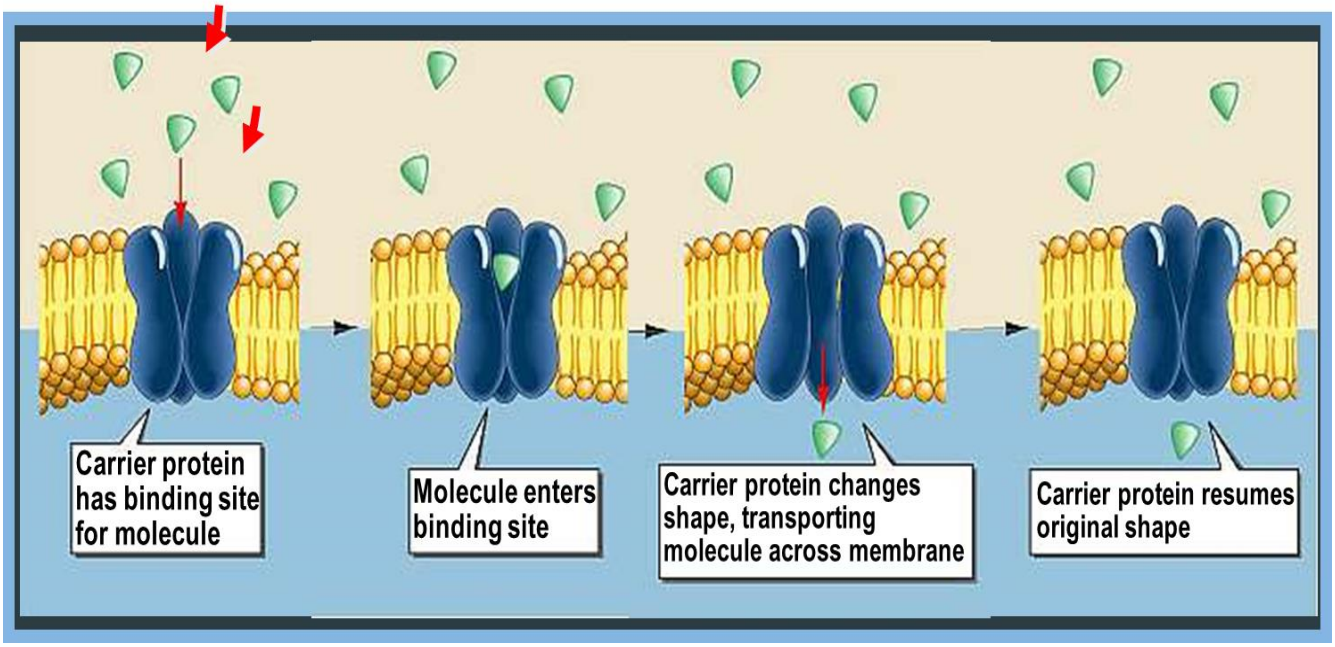
Characters:

a-Down concentration gradient.

b-No energy used.

c-A carrier is needed to assist the diffusion. eg. Transport of AAs & glucose

Mechanism:



Factors Affecting Net Rate of Diffusion

A. membrane permeability: that in turn affected by:

- Thickness of the membrane: that is inversely proportionate with net rate of diffusion.
- Lipid solubility of the substance: that is directly proportionate with net rate of diffusion
- Number of protein channels: that is directly proportionate with net rate of diffusion
- Temperature: that is directly proportionate with net rate of diffusion
- Molecular diameter: that is inversely proportionate with net rate of diffusion

B. Diffusion coefficient: D= P x A

C. Effect of conc. difference

D. Effect of pressure difference

E. Effect of an electrical potential

3- Osmosis

Def.: The diffusion of water across a semi permeable membrane due to concentration differences.

Osmotic pressure: is the force by which water is drawn into the solution through the membrane, depends on number of solute particles

Osmotic pressure is affected mainly by **the number of particles** of the solute.

TONICITY: Is a relative term, comparing the concentration of solutes in two different solutions.

Types of solutions:

1. Isotonic
2. Hypotonic
3. Hypertonic

Colloid osmotic pressure of plasma proteins is 290 mOsm/L

II- Active Transport

Characters:

-It is against concentration gradient

-It needs energy

-It needs carrier

Types:

Active transport by a carrier protein: According to the source of energy:

a-1ry active transport

b-2ry active transport

1- Primary Active Transport

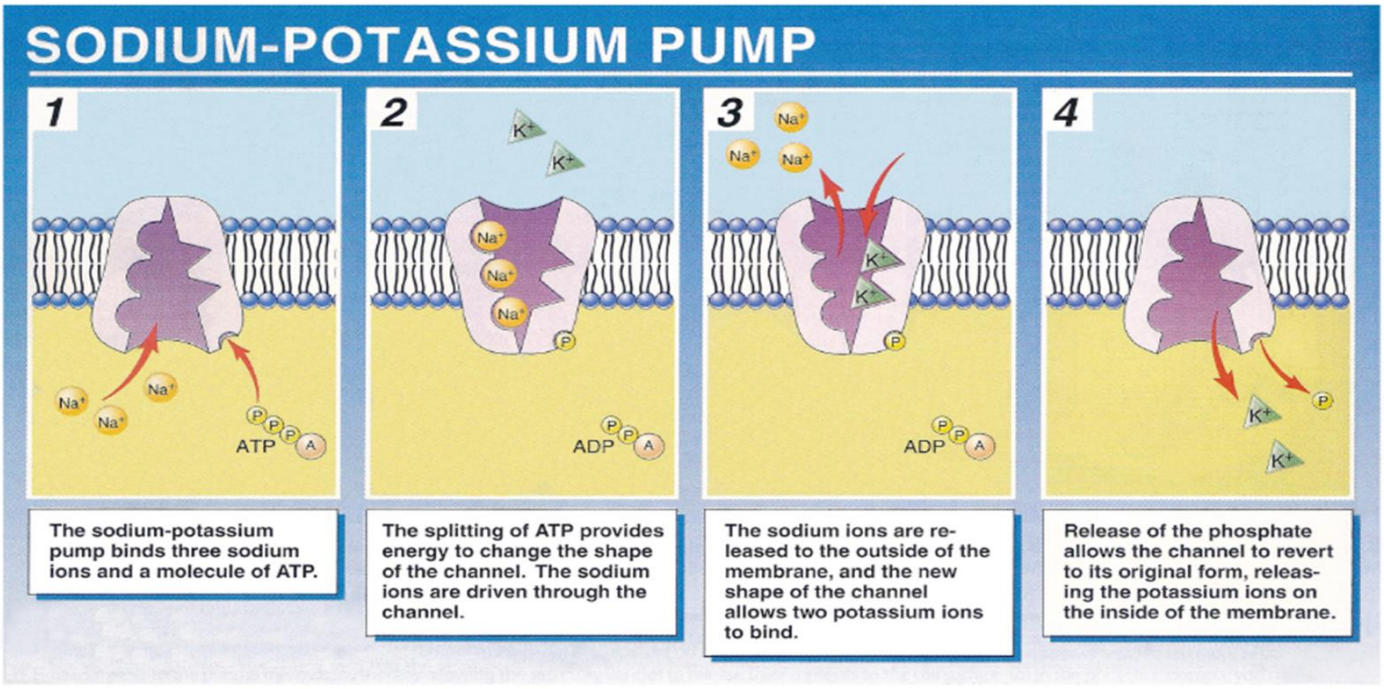
Energy is directly derived from ATP

Examples: -Na^+ - K^+ pump

-H^+ pump

-Ca^{++} pump

Mechanism: (eg. Na^+- K^+ ATPase)



2- Secondary Active Transport

Energy is not directly derived from ATP.

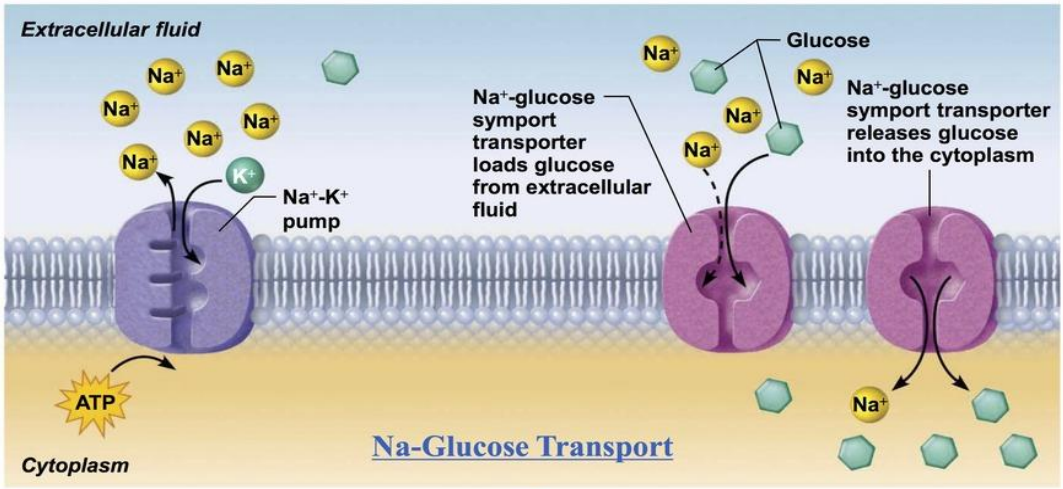
The energy stored in the electrochemical gradient of an ion is used to transport another substance against a concentration or electrochemical gradient.

Examples: -Na- glucose cotransport

-Na-Ca counter-transport

-Na-H counter-transport

Figure 3.10 Secondary active transport is driven by the concentration gradient created by primary active transport. Slide 3



Types of Carriers

1-Uni-porter: Transporter for glucose by facilitated diffusion

2-Symporter: Na-glucose or Na- AA cotransporter

3-Antiporter: Na- H counter transporter

III-vesicular transport

-Large molecules, such as polysaccharides and proteins, cross the membrane in bulk via vesicles.

- There are two types of vesicle transport, ***endocytosis*** and ***exocytosis*** Both processes are **active transport processes**, requiring energy.

-Types:

1-Endocytosis: is the process of capturing a substance or particle from outside the cell by engulfing it with the cell membrane. The membrane folds over the substance and it becomes completely enclosed by the membrane. At this point a membrane-bound sac, or vesicle, pinches off and moves the substance into the cytosol. There are two main kinds of endocytosis:

- **Phagocytosis**, or *cellular eating*, occurs when the dissolved materials enter the cell. The plasma membrane engulfs the solid material, forming a phagocytic vesicle.
- **Pinocytosis**, or *cellular drinking*, occurs when the plasma membrane folds inward to form a channel allowing dissolved substances to enter the cell. When the channel is closed, the liquid is encircled within a pinocytic vesicle.

2- ***Exocytosis*** describes the process of vesicles fusing with the plasma membrane and releasing their contents to the outside of the cell. Exocytosis occurs when a cell produces substances for export, such as a protein, or when the cell is getting rid of a waste product or a toxin. Newly made membrane proteins and membrane lipids are moved on top the plasma membrane by exocytosis.

Physiology Of Blood

PHYSIOLOGY OF BLOOD

Introduction

• Blood is a special form of **connective tissue** in fluid state.

Properties of blood

1. Color: Blood is red in color. Arterial blood is bright red because it contains more oxygen and venous blood is purple red because of more carbon dioxide.

2. Volume: Average volume of blood in a normal adult is **5 L.** In a newborn baby, the volume is **450 ml.** It increases during growth and reaches **5 L** at the time of puberty. In females, it is slightly less and is about **4.5 L**.

3. Reaction and pH: Blood is slightly alkaline and its pH in normal conditions is 7.4 in arterial side and 7.35 in venous blood.

4. Specific gravity:

- Specific gravity of total blood: 1.050 to 1.060
- Specific gravity blood cells: 1.090 to 1.100
- Specific gravity of plasma: 1.020 to 1.025

5. Viscosity: Blood is five times more viscous than water. It is mainly due to red blood cells and plasma proteins.

Composition of blood

Blood consists of

- **liquid plasma** (volume-55-60%)
- **formed elements** (volume-40-45%), that includes:
  - ✓ **Erythrocytes** (red blood cells or RBCs);
  - ✓ **Leukocytes** (white blood cells or WBCs);
  - ✓ **Thrombocytes** (platelets)

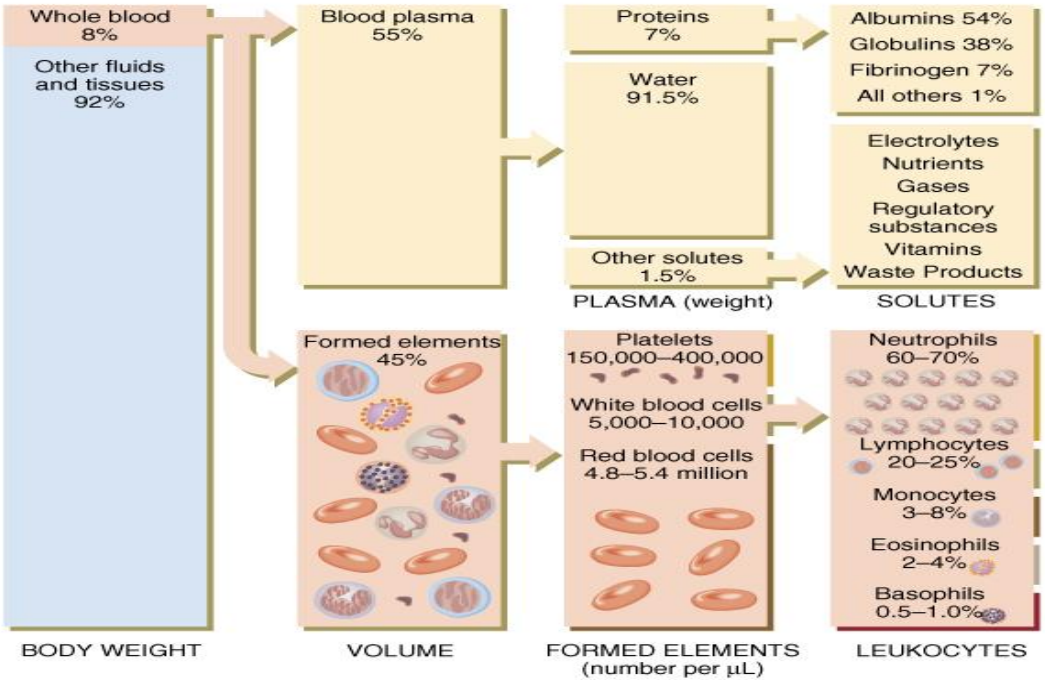


Fig (6) Blood composition

Hematocrit value or packed cell volume (PCV)

- is the percentage of packed RBCs volume to whole blood volume.
- Plasma forms 55% and red blood cells form 45% of the total blood.
- In between the plasma and the red blood cells, there is a thin layer of **white buffy coat.**
- This white buffy coat is formed by the aggregation of WBCs and Platelets.

Blood functions:

1. Nutritive function

- Nutritive substances like glucose, amino acids, lipids and vitamins derived from digested food are absorbed from gastrointestinal tract and carried by blood to different parts of the body for growth and production of energy**.**

2. Respiratory function:

-Transport of respiratory gases (O2 & CO2) is done by the blood.

3. Excretory function:

-Waste products formed in the tissues during various metabolic activities are removed by blood which carried to the excretory organs like kidney, skin, liver, etc. for excretion.

4. Transport of hormones and enzymes:

- Hormones are released from endocrine glands directly into the blood to reach target organs.

5. Regulation of water balance:

-Water content of the blood is freely interchangeable with interstitial fluid. This helps in the regulation of water content of the body.

6. Regulation of acid-base balance:

-Plasma proteins and hemoglobin acts as buffers and help in the regulation of acid-base balance of the body.

7. Regulation of body temperature:

-The high specific heat of blood, it is responsible for maintaining the thermoregulatory mechanism in the body. Blood carries heat from deep structures to sub-cuteneous blood vessels, to get red of excess heat.

8. Defensive function:

-The white blood cells are responsible for this function.

9.Storage function:

-Water and some important substances like proteins, glucose, sodium and potassium are constantly required by the tissues. These substances are taken from blood during the conditions like starvation, dehydration, electrolyte loss, etc.

10. Prevention of blood loss; by blood coagulation.

I-PLASMA

• **Blood plasma** is a pale yellow-colored fluid accounts for 55-60% of blood volume.

• The constituents of plasma are:

1. Water **(91-92%)**

2. Plasma proteins: make up about **7%** of plasma. The main types of plasma proteins are:

Albumin (4 gm/dl). **α, β, γ globulins** (2.7 gm/dl). **fibrinogen** (0.3 gm/dl).

3. **Inorganic salts (electrolytes)** like **Ca, Na, Po4** which are responsible for muscle

contraction, transmission of nerve impulses (action potential).

4. **Nutrients:** glucose, amino acid, fatty acids and glycerol.

5. **Waste products** like urea, creatinine and uric acid they are carried in the blood to the kidney for excretion.

6. **Hormones** and **gases.**

Origin of plasma proteins:

➢ **In embryonic stage**, the plasma proteins are synthesized by the **mesenchyme cells.**

➢ **In adults,** the plasma proteins are synthesized mainly from **reticuloendothelial cells of liver** and also from **spleen, bone marrow**.

➢ **Gamma globulin** is synthesized from **B lymphocytes.**

Functions of plasma proteins:

➢ **Albumins** (about **60%** of total plasma protein).

- They are responsible for maintain normal plasma osmotic pressure. Also act as carrier molecules for free fatty acids, some drugs and steroid hormones.

➢ **Globins** their main functions:

- γ globulins are antibodies (immunoglobulins)
- Transportation of some hormones, (e.g. thyroglobulin carries the hormonethyroxin) and mineral salts (e.g. transferrin carries the mineral iron).

➢ **fibrinogen**: responsible for plasma viscosity.

➢ **Clotting factors and fibrinogen** are responsible for coagulation of blood.

➢ Plasma proteins are responsible for **buffering action** of blood pH.

eg. Lactic acid + Na proteinate = Na lactate +proteinic acid.

➢ Plasma proteins share in **Co2 carriage** by forming carbamino compound with the amino group of p.p.

SERUM

• Serum is the clear **straw-colored** fluid that **oozes** from blood clot after about 45 minutes.

• When the blood is collected in a container, it clots.

• In this process, the **fibrinogen** is converted into **fibrin**

• Volume of the serum is almost the same as that of plasma **(55%).**

• It is different from plasma only by the absence of fibrinogen, i.e. serum contains all the other constituents of plasma except fibrinogen.

• **Serum = Plasma – Fibrinogen**

II- FORMED ELEMENTS

A- Red Blood Cells:

- Red blood cells (RBCs), or erythrocytes, are the most abundant type of blood cell.
- Approximately a quarter of the cells in the human body are red blood cells.
- The cells develop in the bone marrow and circulate for about 100–120 days in the body before their components are recycled by macrophages of the reticulo endothelial system (RES).
- They are red in color due to the presence of hemoglobin which is known as red characteristic pigment.

Normal shape:

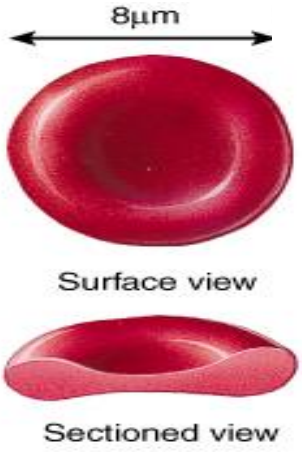


Fig (7): shape of RBCs

- They are a non-nucleated
- They are biconcave disc which is maintained by a network of proteins called spectrin.
- The protein allows the red blood cells to change shape as they are transported through the blood vessel.
- The plasma membrane of a red blood cell is strong and flexible.
- Young red blood cells contain a nucleus, the nucleus is absent in a mature red blood cell and without any organelles such as mitochondria, Golgi apparatus, endoplasmic reticulum. …. etc.

Normal value:

- Number of RBCs: 5- 5.5 million/ mm^3 in men. 4.5- 5 million/ mm^3 in women.

Hb= 14-16 g/dl in adult male . 13-15 g/dl in adult female. At the time of birth, hemoglobin content is very high because of increased number of RBCs

NB. RBCs lack mitochondria and so, the energy is produced from glycolytic process.
• RBC utilizes anaerobic respiration to produce ATP and do not use any of the oxygen they are transporting.

Function of RBCs:

1- They play a vital role in transport of **respiratory gases** (oxygen and carbon dioxide) due to the presence of hemoglobin as a major constituent of RBCs.

2- Buffering Action in Blood: hemoglobin functions as a good buffer and thereby plays a role in the maintenance of acid base balance.

3- In Blood Group Determination: RBCs carry the blood group antigens like A antigen, B antigen and Rh factor. This helps in determination of blood group and enables to prevent reactions due to incompatible blood transfusion.

4- RBCs are important in maintaining **blood viscosity**, that is essential for mentinance of diastolic blood pressure.

Synthesis of RBCs (Erythropoiesis):

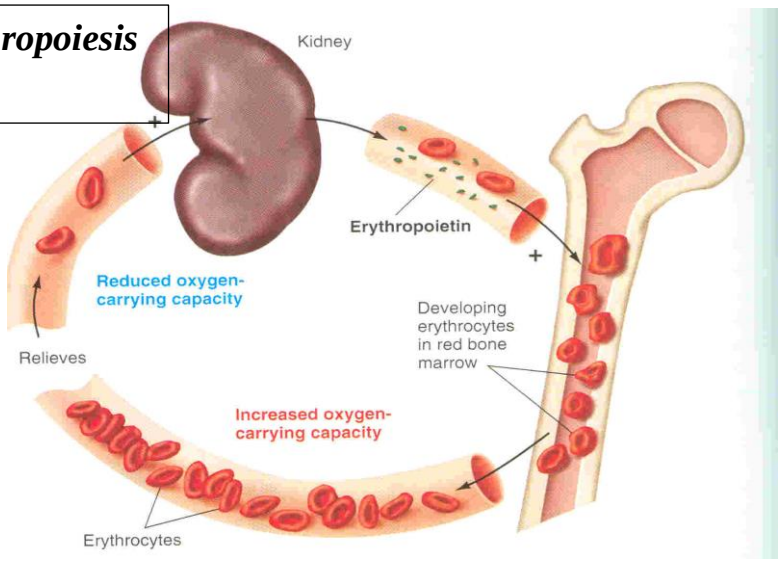
- It is the process of RBC development from **stem cells.**
- It is stimulated by **decreased O2** in circulation, which is detected by the **kidneys,** which then secrete **erythropoietin** hormone**.**
- The process of erythropoiesis lasts about **7 days.**

Factors promoting erythropoiesis:

- **Hypoxia:** is the main stimulating factor. Hypoxia stimulates the kidney & liver to secrete erythropoietin hormone.

- **Erythropoietin hormone**: secreted from the kidney (90%) & liver (10%) and stimulates bone marrow to produce RBCs.
- **The bone marrow**: it is the main site for erythropoiesis.
- **Dietary factors**: especially animal proteins, iron and copper that are essential to form HB.
- **Vitamin B12 and folic acid**: that are important for RBCs maturation.
- **Hormones**: as thyroxin and androgens.
- **The liver**: which stores iron copper vit.B_{12} that are used for **erythropoiesis.**

Fig (8): Hypoxia and erythropoiesis



Site of erythropoiesis

<u>In fetal life:</u> the erythropoiesis occurs in three stages:

1. Mesoblastic stage: during the first two months of intrauterine life, the RBCs are produced from Mesenchyme of yolk sac.

2. Hepatic stage: from third month of intrauterine life, liver is the main organ that produces RBCs. Spleen and lymphoid organs are also involved in erythropoiesis.

3. Myeloid stage: during the last three months of intrauterine life, the RBCs are produced from Red bone marrow and liver.

In newborn babies, children and adults:

in newborn babies, growing children and adults, RBCs are produced only from The red bone marrow.

1. Up to the age of 20 years: RBCs are produced from red bone marrow of all Bones (long bones and all the flat bones).

2. After the age of 20 years: RBCs are produced from membranous bones like Vertebra, sternum, ribs, scapula, iliac bones and skull bones and from the ends Of long bones.

Physiological Factors influencing RBC number

➢ RBC count is very high at birth (8-10 million\mm).

➢ The count is higher in children than in adults.

➢ RBC count is raised at high altitude, in warm temperature, during excitement.

➢ In women RBC count is relatively low during pregnancy.

➢ A fall in RBC count is seen low altitude.

Fate of red blood cells

• When the cells become older (120 days), the cell membrane becomes more fragile.

• Younger RBCs can pass through the capillaries easily.

• Because of the fragile nature, the older cells are destroyed while trying to squeeze through the capillaries.

• The destruction occurs mainly in the capillaries of red pulp of spleen because the diameter of **splenic capillaries is very small**, so, the spleen is called 'graveyard of RBCs'

Function of hemoglobin

• It is carrying the respiratory gases, oxygen and carbon dioxide.

• One molecule of hemoglobin transports four molecules of oxygen.

• There are approximately 250 million hemoglobin molecules in one red blood cell.

• One red blood cell transport 1 billion molecules of oxygen.

• At the capillary end the hemoglobin releases the oxygen molecule into the interstitial fluid, which is then transported into the cells.

• It also acts as a buffer. It is playing an important role in acid base balance.

Types of normal hemoglobin

• Hemoglobin is mainly of two types:

1. **Adult** hemoglobin (HbA) 2. **Fetal** hemoglobin (HbF)

• Replacement of fetal hemoglobin by adult hemoglobin starts immediately after birth.

• It is completed at about 10th to 12th week after birth.

• Both the types of hemoglobin differ from each other structurally and functionally.

• Fetal hemoglobin has a higher affinity for oxygen.

Variations of red blood cells count:

A. Increase in RBC Count

• Increase in the RBC count is known as **polycythemia**.

• It occurs in both physiological and pathological conditions. When it occurs in physiological conditions it is called physiological polycythemia.

i. Physiological polycythemia:

• The increase in number during this condition is marginal and temporary. It occurs in the following conditions:

1. **Age**: At birth, the RBC count is 8 to 10 million/ mm^3 of blood. The count decreases within 10 days after birth due to destruction of RBCs causing physiological jaundice in some newborn babies. In infants and growing children, the cell count is more than the value in adults.

2. **Sex**: Before puberty and after menopause in females the RBC count is similar to that in males. During reproductive period of females, the count is less than that of males (4.5 million/ mm^3).

3. **High altitude**: above 10,000 feet from mean sea level RBC increased more than 7 million/ mm^3. It is due to hypoxia (decreased oxygen supply to tissues) in high altitude.

4. **Muscular exercise**: There is a temporary increase in RBC count after exercise. It is because of mild hypoxia and contraction of spleen.

5. Emotional conditions: RBC count increases during the emotional conditions such as anxiety. It is because of increase in the sympathetic activity.

6. Increased environmental temperature: Increase in atmospheric temperature increases RBC count.

7. After meals: There is a slight increase in the RBC count after taking meals. It is due to need for more oxygen for metabolic activities.

ii- Pathological Polycythemia

• Pathological polycythemia is the abnormal increase in the RBC count. Red cell count increases above 7 million/ mm^3 of the blood, it is of two subdevisions: **primary polycythemia** and **secondary polycythemia.**

a- Primary Polycythemia (Polycythemia Vera)

• It is a disease characterized by persistent increase in RBCs count above 14 million/ mm^3 of blood.

• This is always associated with increased white blood cell count above 24,000/ mm^3 of blood. It is occurring in myeloproliferative disorders like malignancy of red bone marrow.

b- Secondary Polycythemia

• This is secondary to some of the pathological conditions (diseases) such as:

➢ Respiratory disorders like emphysema.

➢ Congenital heart disease.

➢ Chronic carbon monoxide poisoning.

➢ Poisoning by chemicals like phosphorus and arsenic.

➢ Repeated mild hemorrhages.

Cause: All these conditions lead to hypoxia which stimulates the release of erythropoietin. Erythropoietin stimulates the bone marrow resulting in increased RBCs count.

B. Decrease in RBC Count

Decreased RBCs count can be physiological or pathological

i. Physiological decreased RBCs:

In the following physiological conditions:

1. High barometric pressures: At high barometric pressures as in deep sea, when the oxygen tension of blood is higher, the RBCs count decreases.

2. During sleep: RBCs count decreases slightly during sleep and immediately after getting up from sleep. Generally, all the activities of the body are decreased during sleep including production of RBCs.

3. Pregnancy: In pregnancy, the RBCs count decreases, due to increase in ECF volume. Increase in ECF volume, increases the plasma volume resulting in hemo-dilution. Therefore, there is a relative reduction in the RBC count.

ii. Pathological decreased RBCs: (Anemia)

• Anemia is the blood disorder, characterized by the reduction in:

1. Red blood cell (RBC) count
2. Hemoglobin content
3. Packed cell volume (PVC).

- **Causes**:

1. Decreased production of RBC
2. Increased destruction of RBC
3. Excess loss of blood from the body.

• All these incidents are caused either by inherited disorders or environmental influences such as nutritional problem, infection and exposure to drugs or toxins.

Etiological classification

• On the basis of etiology, anemia is divided into five types:

1. Hemorrhagic anemia
2. Hemolytic anemia
3. Nutrition deficiency anemia
4. Aplastic anemia
5. Anemia of chronic diseases

1. Hemorrhagic Anemia

• Hemorrhage refers to excessive loss of blood. It occurs both in acute and chronic hemorrhagic conditions.

2. Hemolytic Anemia

• Hemolysis means destruction of RBCs. It is classified into two types:

A. Extrinsic hemolytic anemia: caused by destruction of RBCs by external factors.

B. Intrinsic hemolytic anemia: caused by destruction of RBCs, and productions of unhealthy RBCs, which are short, lived and are destroyed soon.

3. Nutrition Deficiency Anemia

• It occurs due to deficiency of a nutritive substance necessary for erythropoiesis. The substances which are necessary for erythropoiesis are iron, proteins and vitamins like C, B12 and folic acid.

4. Aplastic Anemia

• Aplastic anemia is due to the disorder of red bone marrow. Bone marrow disorder occurs in the following conditions:

➢ Repeated exposure to X ray or gamma ray radiation.

➢ Presence of bacterial toxins, benzene, radium, etc.

➢ Tuberculosis.

➢ Viral infections like hepatitis and HIV infections.

5. Anemia of Chronic Diseases

• It is characterized by short lifespan of RBCs, caused by disturbance in iron metabolism or resistance to erythropoietin action.

Blood Groups

• The membrane of human red cells contains antigens which are oligopolysaccarides and called agglutinogens.

They are of 2 types:

A agglutinogen & **B** agglutinogen

• Plasma contains antibodies specific for these agglutinogens that are called agglutinins. They are of 2 types: anti-A agglutinin (α) and anti-B agglutinin (β)

Classification of blood groups:

- ***Blood group A: (39%)***

A agglutinogen on cell membrane and β agglutinin in plasma.

- ***Blood group B: (10-15%)***

B agglutinogen on cell membrane and α agglutinin in plasma.

- ***Blood group AB: (5%)***

Both agglutinogens on cell membrane and No agglutinin in plasma.

- ***Blood group O: (40%)***

No agglutinogen on cell membrane and Both α & β agglutinins in plasma.

The Rh grouping system

- Rh antigen (Rh factor) is about 40 kinds and Rh factors related to clinic are D, E, C, c, e and the most important is D antigen.
- Membrane of RBC has D antigen meaning Rh Positive, otherwise, Rh negative.
- Most of people (85%) are Rh Positive and 15% persons are Rh negative.
- Rh blood group antibody is of type IgG, that is small and can pass through the placenta.
- Neither Rh +ve, nor Rh –ve persons naturally has antibodies for Rh in their sera.

Significance of Rh:

In blood transfusion :

Rh -ve person cannot receive blood from Rh+ve person, whereas Rh+veperson can receive blood from Rh -ve person without any problems.

- If a Rh -ve person receive blood from Rh +ve person for the first time, due to this exposure, there will be formation antibodies(anti-RhD)
- So, if a second transfusion is done again with Rh+ve blood, then, the antibodies which are already present causes clumping.
- Medico-legal:
- ABO & Rh grouping is important in disputed parenthood.

Erythroblastosis fetalis :

If a Rh -ve mother carry a Rh +ve fetus, due to placental barrier the blood doesn't mix. However during delivery some Rh +ve from fetus reaches mother. So, the mother will start producing antibodies against Rh. During consecutive pregnancies, this may cause destruction of RBCs in the fetus causing haemolytic anaemia (erythroblastosis fetalis).

So after each pregnancy, the mother will receive anti-RhD (prophylaxis)to prevent this incompatibility.

B- White Blood Cells (WBC) or LEUCKOCYTES

• White blood cells (WBCs) or leukocytes are the colorless and nucleated formed elements of blood (leuko is derived from Greek word leukos = white).

• In comparison to RBCs, the WBCs are larger in size and lesser in number.

• Functionally, these cells are important like RBCs because of their role in defense mechanism of body. They are able to move out of blood vessel walls into the tissues.

• They are protecting the body from invading organisms by acting like soldiers.

• White blood cells are able to produce a continuous supply of energy, unlike the red blood cells.

• They are able to synthesize proteins, so their life span can be from a few days to years.

• Number: There are approximately 5000–10,000 WBCs / mm^3 blood.

• The number may increase in infections to approximately 25,000 / mm^3 blood.

• An increase in white blood cells is called leukocytosis, and an abnormally low level of white blood cell is called leukopenia.

• There are two main types of white blood cells, classified according to the presence of cytoplasmic granules as follow:

i- Granulocytes (contain granules in the cytoplasm). They are classified depending on the staining property of granules into three types:

➢ Neutrophils ➢ Eosinophils ➢ Basophils

ii- A granulocytes (without granules in the cytoplasm as in granulocyte):

➢ Monocytes ➢ Lymphocytes.

a-*Neutrophils*

• Neutrophils are the most abundant WBCs (65%) and play an important role in the immune system.

• They form approximately 60–65% of granulocytes and are phagocytes.

• Nucleus is multilobed. The number of lobes in the nucleus depends upon the age of cell. In younger cells, the nucleus is not lobed. And in older neutrophils, the nucleus has 2 to 5 lobes.

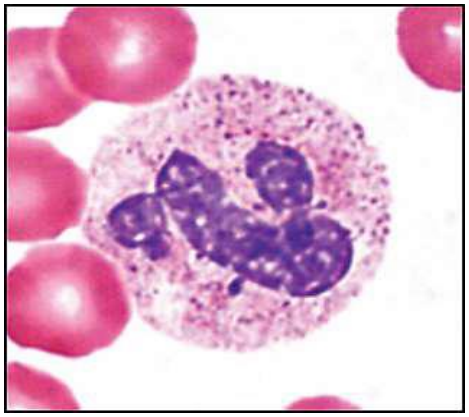


Fig (9): neutrophils

Function: (Phagocytize bacteria)

• The neutrophils ***along with the monocytes*** constitute the first line of defense against the micro-organisms and other injurious agents that enter the body.

• Neutrophils are the first immune cells to arrive at a site of infection, through a process known as ***chemotaxis.***

• They are capable of moving out of blood vessel walls by a process called ***diapedesis*** and are actively phagocytic.

• They contain lysozymes; therefore, their main function is to protect the body from any foreign material and capable of ingesting microorganisms.

• Febrile response: The neutrophils contain a fever producing substance called endogenous pyrogen, which is an important mediator of febrile response to the bacterial pyrogens.

Life span:

• A non-active neutrophil lasts approximately 12 h, while an active neutrophil may last 1–2 days.

• A deficiency of neutrophils is called ***neutropenia***.

• The number of neutrophils increases in pregnancy, infection, leukemia, metabolic disorders such as acute gout, inflammation, myocardial infarction.

b-Eosinophils

• Eosinophils form approximately 2–4% of WBCs and have B-shaped nuclei. They are 10–12 μm in diameter.

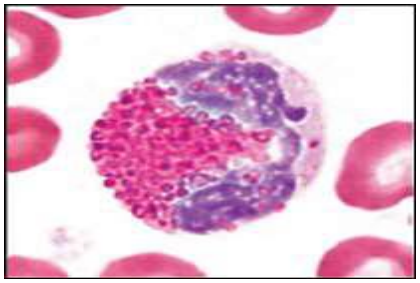


Fig (10): Eosinophils

Function:

• They are phagocytes. Like neutrophils, they migrate from blood vessels and contain lysosome enzymes and peroxidase in their granules, which are toxic to ***parasites***, resulting in the destruction of the organism.

Number: increase in allergy (e.g. hay fever and asthma) and parasitic infection (e.g. tapeworm infection).

c-Basophils

basophils are the least abundant, accounting for approximately 1% of WBCs, they contain elongated lobed nuclei and are 8–10 μm in diameter.

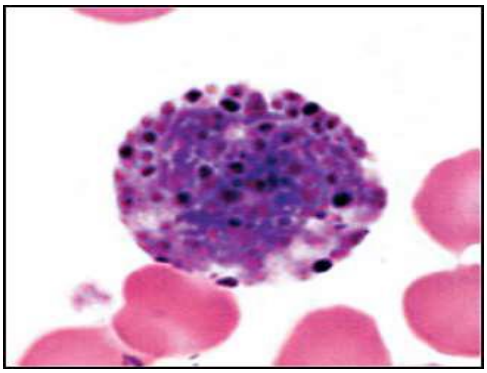


Fig (11): Basophils

Function:

• In inflamed tissue they secrete granules containing heparin, histamine and other proteins that promote inflammation.

• Basophils play an important role in providing immunity against parasites and also in the allergic response.

They are similar in function to the mast cells that are present in the perivascular connective tissue.

ii- A granulocytes:

a-Monocytes

• Monocytes account for 5% of WBCs and are circulating leucocytes.

• Monocytes develop in the bone marrow and spread through the body in 1–3 days.

• The nucleus of the monocyte is kidney- or horseshoe shaped and their diameter 12-20 μm.

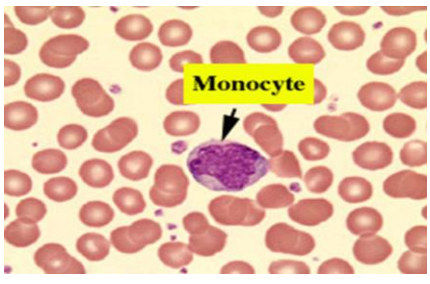


Fig (12): Monocyte

Function:

Some of the monocytes migrate into the tissue, where they develop into macrophages and engulf pathogens or foreign proteins.

- Macrophages play a vital role in immunity and inflammation.
- Phagocytosis of bacteria and necrotic tissue.Can ingest >100 bacteria.

- Can kill tumor cells.
- Secrete substances to help tissue repair after inflammation.
- Examples of tissue macrophages: Kopffer cells of liver, microglia in brain and alveolar macrophages in lungs.

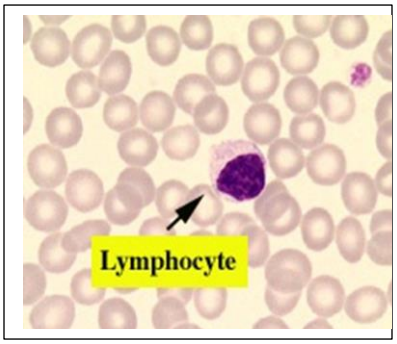


Fig (13): Lymphocyte

Lymphocytes

• Lymphocytes account for 25% of the leucocytes, and most are found in the lymphatic tissue such as the lymph nodes and the spleen.

• They get their name from the lymph the fluid that transports them. They can leave and re-enter the circulatory system.

• Two types of lymphocytes are identified, and they are T- and B-lymphocytes.

- T-lymphocytes originate from the thymus gland.
- B-lymphocytes originate in the bone marrow.

• **Life span** ranges from a few hours to years.

Function:

➢ T-lymphocytes are concerned with cellular immunity.

➢ B-lymphocytes are concerned with humoral immunity. Produce antibodies that attach to antigen.

Variations of white blood cells count:

A. Increase in WBC Count

i. Leukemia

• The leukemia is the condition, which is characterized by abnormal and uncontrolled increase in WBC count more than 1,000,000/mm^3.

• Begins in the bone marrow and results in high numbers of abnormal WBCs.

• These WBCs are not fully developed and are called blasts or leukemia

cells.

• Leukemia is cancer of the body's blood-forming tissues, including the bone marrow and the lymphatic system.

ii- Leucocytosis:

- Increased number of leucocytes in blood.
- It may be :

Physiological: as in case of emotion, stress, food intake and exercises.
Pathological: inflammation and cancer

B. Decrease in WBC Count

- Abnormally low concentration of leucocytes in blood.

Only pathological : as in case of severe viral infection auto-immune disease, chemotherapy and radiation injury.

Reticulo-endothelial sysem:

A heterogeneous population of tissue fixed phagocytic cells.

Function:

- Defensive function: trapping foreign particles entering lymphatics and phagocytose them.
- Repair function: after inflammation RE cells phagocytose necrotic issues
- Removal of senile RBCs.

Platelets:

• Platelets are small oval bodies consisting of some cytoplasm surrounded by a plasma membrane.

• They are produced in the bone marrow from megakaryocytes.

• They are approximately 2–4 μm in diameter.

• Normally, platelets are of several shapes, spherical, rod shaped, oval or disk shaped.

• The life span is approximately 5–9 days.

• The surface of platelets contains proteins and glycoproteins that allow them to adhere to other proteins such as collagen in the connective tissues.

• Platelets play a vital role in blood loss by the formation of platelet plugs, which seal the holes in the blood vessels and release chemicals that aid blood clotting.

• Normal range: 150,000-300,000/ mm3.

• Increased platelet production is the function of thrombopoietin hormone that is secreted by the liver.

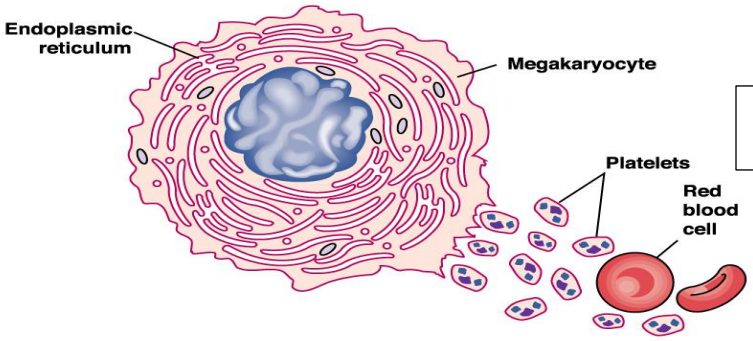


Fig (14): Megakaryocyte

Function of platelets:

- Hemostasis : is the most important function. It is produced by formation of platelet plug.
- Blood coagulation: platelets are essential for interensic pathway of coagulation (release of pl f III).
- Clot retraction: by action of actomyocin like protein
- Storage of certain substances eg. Serotonin (against conc gradient).
- Phagocytosis of carbon, immune complexes and viruses.

Hemostasis

Def.: it is the process of stopping bleeding to minimize blood loss from a damaged vessel, while maintaining blood in a fluid state with in the vascular system.

Stages of hemostasis: three stages:

i. Vascular spasm. ii. platelet plug formation. iii. formation of blood clot.

i. Vascular Spasm:

- local myogenic spasm initiated by direct damage to the vascular wall (lasts for 20-30 min).

- local vasoconstrictors from traumatized tissues and platelets (thrompoxane A2 & serotonin).

- The more severely a vessel is traumatized, the greater the degree of vascular spasm. The spasm can last for many minutes. **Why?**
- To give time for the processes of platelet plugging and blood coagulation to take place.

ii. **Formation of platelet plug:**

- **Platelet Adhesion**: when get in contact with damaged endothelium.
- **Platelet Activation**: so become sticky with irregular shape and release substances that attract nearby platelets.
- **Platelet Aggregation**: and formation of a plug that closed the hole of the damaged vessel.

iii. **Formation of blood clot:**

- If the hole of injured vessel is large , blood clot is necessary to stop bleeding.
- Blood clot begins to develop in 1-2 min after injury.
- Coltting factors: are plasma proteins that exist in the blood in an inactive state (pro-enzymes), but can be called into action when tissues or blood vessels are damaged.
- The activation of clotting factors occurs in a sequential manner.
- **Three stages for clot formation:**
    - **Stage 1:** formation of prothrombin activator.
    - **Stage 2:** conversion of prothrombin into thrombin by prothrombin activator.

- **Stage3:** conversion of fibrinogen into fibrin.

I. Formation of prothrombin activator

Two ways are involved :

- **Intrinsic pathway**: which is triggered by elements that lie within the blood itself (intrinsic to the blood) when blood comes in contact with damaged vessel wall (or glass of test tube) stimulates the activation of a cascade of clotting factors so blood clots within the vessel.

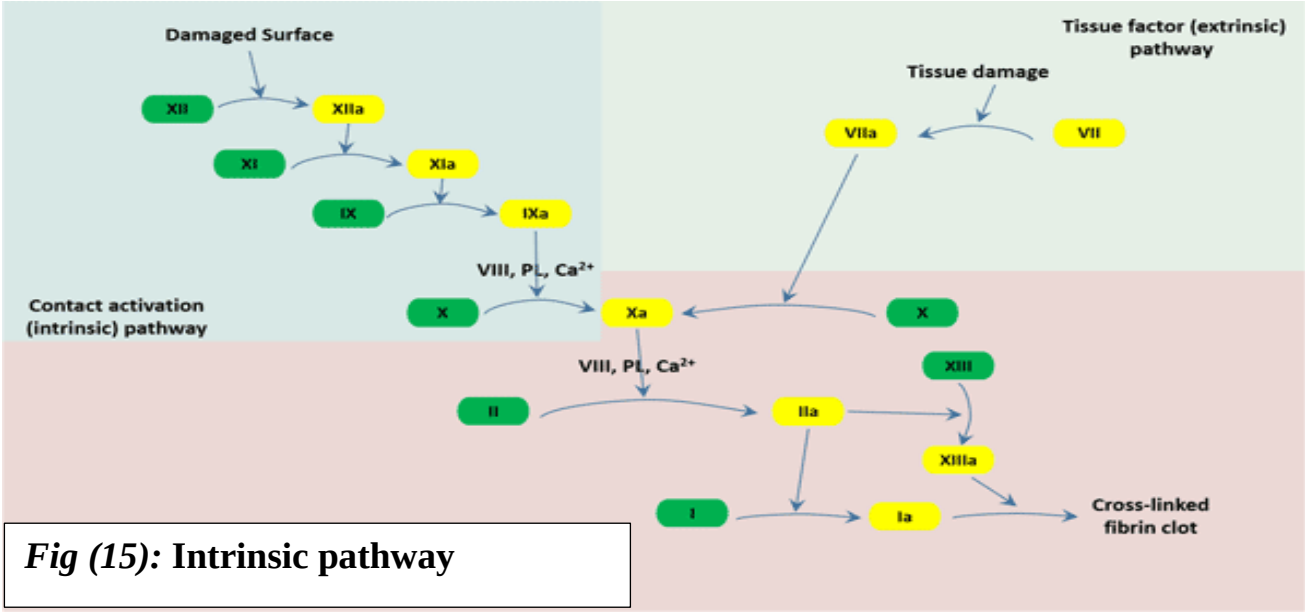
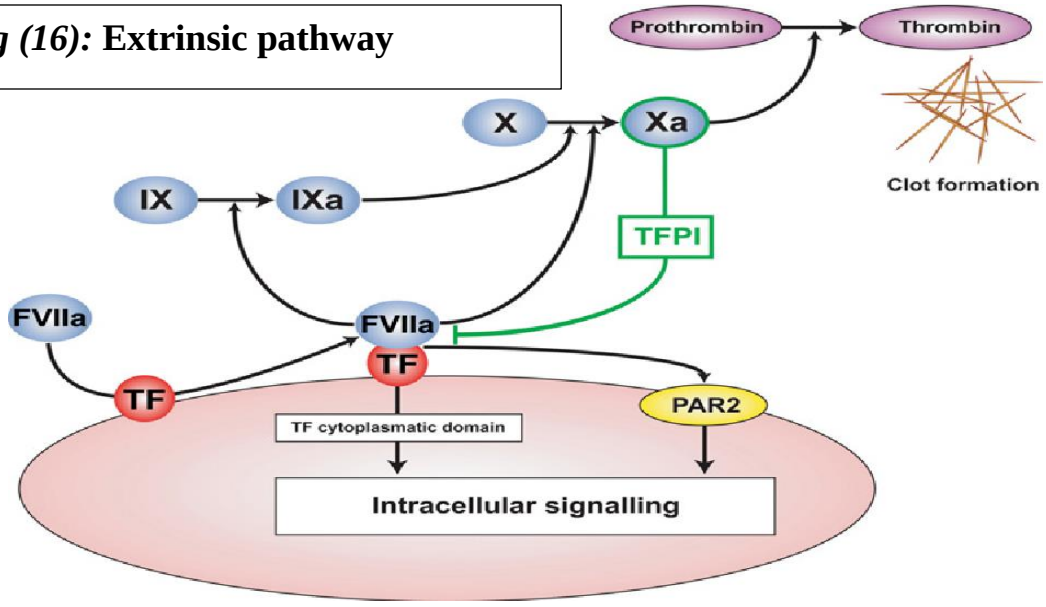


Fig (15): **Intrinsic pathway**

- **Extrinsic Pathway**: The extrinsic pathway is triggered by tissue damage outside of the blood vessel. This pathway acts to clot blood that has escaped from the vessel into the tissues.

Fig (16): **Extrinsic pathway**



- **The result of both extrinsic or intrinsic pathways is activation of factor X (Xa).**
- **Xa complexes with Va and platelet factor 3 in presence of Ca+2 ions to form prothrombin activator.**

<u>Factors preventing blood coagulation in blood vessels:</u>

1) **Endothelial surface factors.**
    - **Smoothness** of vascular endothelium.
    - A layer of **glycocalyx** adsorbed to the endothelium that repels clotting factors and platelets.
    - The endothelial bounded protein **thrombomodulin** that : binds with thrombin.
    - Together with thrombin form a complex that a activates plasma protein **C** (which in turn aaa inactivate Va & VIIIa)
2) **Antithrombin action of fibrin and antithrombin III.**
    - Fibrin catch 85-90% of the formed thrombin, preventing spread of the clot.

- The α globulin (antithrombin III) can bind with heparin forming antithrombin heparin co-factor.
- This factor inactivate both Ixa & Xa

3) Presence of heparin.

- Heparin is a powerful anticoagulant released from liver and basophiles, but normally its level in blood is low.
- It acts both in vivo and in vitro.
- Can be injected IV and the action appears after few minutes & lasts for hours.
- Mechanism of action:
    - a- activates antithrombin III.
    - b- inhibits prothrombin conversion to thrombin.
    - c- inhibits fibrinogen conversion to fibrin.

Anticoagulants:

Two main drugs are used to antagonize excessive coagulation, heparin and dicumarol.

A- Heparin: as discussed above.

B- Dicumarol:

- It is a powerful anticoagulant that is a natural chemical substance of combined plant and fungal origin. It acts in vivo only.
- Can be taken orally and the action appears after few hours& lasts for many days.
- Mechanism of action:

    a- antagonize vitamin K.

    b- inhibits prothrombin formation.

    c- inhibits formation of factors VII, IX & X.

Lymphatic System

The lymphatic system is part of the circulatory system and it transports a clear fluid called lymph.

• The lymphatic system consists of:

➢ Lymph ➢ Lymph vessels ➢ Lymph nodes

➢ Lymphatic organs such as spleen and the thymus.

Lymph:

• Lymph is a clear fluid found inside the lymphatic capillaries and has a similar composition to plasma.

• Lymph is the ultra-filtrate of the blood, which occurs at the capillary ends of the blood vessels.

• The body contains approximately 1–2 L of lymph. Lymph transports plasma proteins, bacteria, fat from the small intestine and damaged tissues to the lymph nodes for destruction.

• The lymph contains lymphocytes and macrophages, which play an important role in the immune system.

Functions of the lymphatic system

1. The lymphatic system aids the immune system in destroying pathogens and filtering waste.
2. The lymphatic system removes excess fluid, waste, debris, dead blood cells, pathogens, cancer cells and toxins.
3. The lymphatic system also works with the circulatory system to deliver nutrients, oxygen and hormones from the blood to the cells that make up the tissues of the body.
4. Important protein molecules are formed by cells in the tissues. These molecules are too large to enter the capillaries of the circulatory system, these protein molecules are transported by the lymph to the bloodstream.

Physiology of nerves

The Nerve

Functional structure of the nerve cell:

1. Cell body or soma

Has a single nucleus with prominent nucleolus & housed the organelles.

2. Dendrites (little trees)

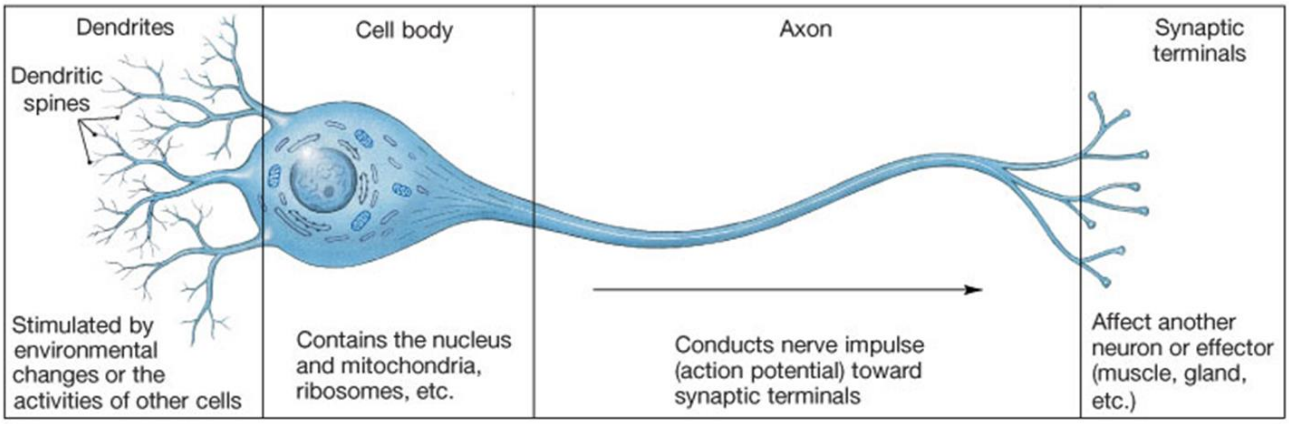
the receiving or input portion of the neuron

3. Nerve fiber= axon

-Long, thin cylindrical process of cell.

-Conduct impulses away from cell body-propagates nerve impulses to another neuron or effector organ.

Axon ends with swollen tips called synaptic knobs contain vesicles filled with neurotransmitters.



-Synapse between nerve cells.

Myelination

-It's a protective insulator covering of the axon.

-Formed by schwann cells .

-Double layer membrane of a single schwann cell wraps itself several times around axon.

-Schwann cell nucleus lies in the outermost layer.

Function of nerve cell Surroundings

The plasma membrane: for generation of the nerve impulse.

Neurilemma: is essential for nerve regeneration after its cut.

Myelin sheath: acts as insulator except at its ends (nodes of Ranvier) where exchange of ions take place.

Membrane Potential

-All animal cells generate a small voltage across their membranes.

-This is because there is a large amount of small organic molecules in the cytoplasm.

-To balance this, animal cell pump Na^+ out of the cells.

-This regulates osmosis but it leaves a large number of organic molecules .

-These are overall negatively changed ions in the cytoplasm.

-Thus the cell has a potential difference (voltage) across its membrane.

-*The intracellular fluid consists of*:

Mostly K^+

Organic anions (phosphate, sulfate & protein ions)

Small amounts of Na^+ & Cl^-

-*The extracellular fluid consists of:*

Mostly Na^+ & Cl^-

Small amounts of K^+

Resting Membrane Potential

Def: it is the potential difference between the inside & outside of the nerve during rest. In large nerves it is -90 mv

Causes of resting membrane potential (RMP):

1- Leakage of Na^+ & K^+

2- Active transport of Na^+ & K^+ across the membrane

3-Organic anions inside the membrane that cannot leak to outside.

1- Leakage of Na^+ & K^+

-The two important ions in a nerve cell (neurone or neuron) are K^+ and Na^+

-According to concentration of gradient Na^+ leak to interior, while K^+ leak to outside

-Na^+ ions move more slowly across the membrane than K^+ ions

-This is because although the Na^+ ion is smaller than the K^+ ion Na^+ has a larger coating of water molecules giving it a bigger diameter.

2- Active transport of Na^+ & K^+ across the membrane

Na-K pump is present in all cells.

It pumps 3 Na outside for each 2 K pumped to inside.

3-Organic anions inside the membrane that cannot leak to outside.

Action Potential

Def: a rapid transient change in the membrane potential when excited.

***Site*:** cells of excitable tissues (nerve & muscle tissues).

***Stages of action potential*:**

1- Depolarization stage: (-90 mv → -55 mv or threshold of stimulation → zero mv or isopotential → overshooting to -35 mv).

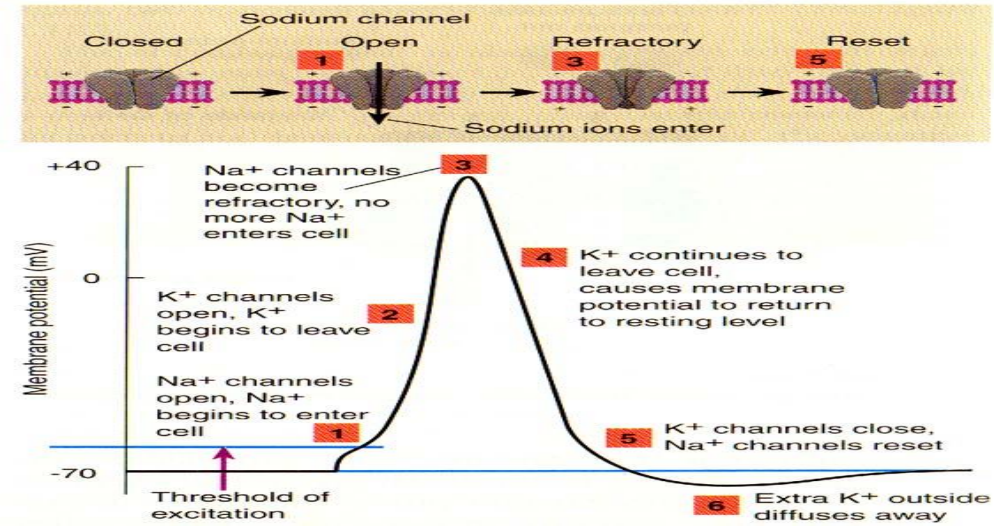
2- Repolarization stage: (spike potential 70%, negative after potential -70 mv & positive after potential -94mv).

3- Re-establishing of RMP: (diffusion of Na^+ & K^+, followed by $Na^+ – K^+$ pump).

Depolarization: losing of the normal resting polarized state of the membrane.

When the voltage gated Na^+ channels open, they cause a depolarization of the neighboring membrane.

This causes the Na^+ and K^+ channels in that piece of membrane to be activated



-The voltage gated channels in the neighboring membrane then open, causing that membrane to depolarize.

-That depolarizes the next piece of membrane, etc.

-It takes a while for the Na+ channels to return to their voltage-sensitive state. Until then, they won't respond to a second depolarization. (ARP)

Repolarization: return of the inner side to its negativity.

Three stages:

1)Spike potential: 70% of action potential.

2)-ve after potential: the inner side is less –ve than resting state.

3)+ve after potential: the inner side is more –ve than resting (hyperpolarized)

Re-establishing of RMP: return of membrane potential to its resting status

two stages:

1)Back diffusion of Na & K ions

2)Active pump by Na-K pump.

Excitability

Def: the ability of the tissue to respond to a stimulus to generate action potential.

It is a property of all living tissues, but vary from one to another.

The most excitable tissues are: nervous and muscular tissues.

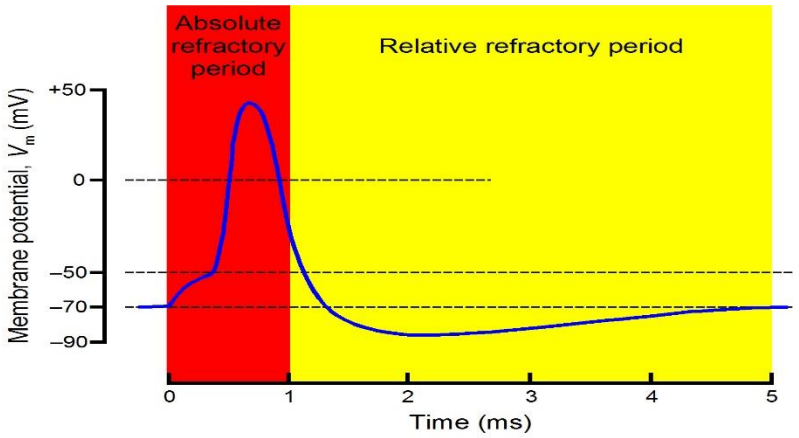
Excitability varies in the same tissue under different conditions:

-***Absolute refractory period:*** This is the time during which another stimulus given to the neuron (no matter how strong) will not lead to a second action potential.

Mechanism: opening of the Na^+ channels, spontaneously and rapidly leads to their inactivation. At the peak of the action potential, all Na^+ channels become inactivated. When Na^+ channels are inactivated, they cannot be immediately opened again Recovery from inactivation is a time- and voltage-dependent process, and full recovery usually takes about 3-4 ms. Therefore, it takes about 3-4 ms for all Na^+ channels to come out of inactivation in order to be ready for activation (opening) again. This takes from the initiation of the action potential to immediately after the peak. Thus, because Na^+ channels are inactivated during this time, additional depolarizing stimuli do not lead to new action potentials. The absolute refractory period takes about 1-2 ms.

-Relative refractory period **:** The period during which a stronger than normal stimulus is needed in order to elicit an action potential

Mechanism: After the absolute refractory period, Na^+ channels begin to recover from inactivation and if strong enough stimuli are given to the neuron, it may respond again by generating action potentials. However, during this time, the stimuli given must be ***stronger*** than was originally needed when the neuron was at rest. This situation will continue until all Na^+ channels have come out of inactivation.



Absolute and relative refractory periods

The stimulus: an agent or change in the environment used to excite a cell by depolarizing its membrane.

Types of stimuli according to the Nature of the Stimulus:

1)Mechanical

2)Thermal

3)Chemical

4)Osmotic

5)Electromagnitic

6)Electrical: experimentally it is preferable.

Propagation of the Action Potential

-*Def.*: Spreading of local current to adjacent area of membrane which then depolarized to threshold and generate AP.

-Nerve is excited at any point at its length, then the impulse is propagated to the end of this nerve.

-When impulse reaches the end of the nerve it causes release of chemical transmitters from the synaptic knob, that stimulate the next neuron dendrites or the effectors organ to generate AP.

-The impulse normally passes only in one direction (towards the nerve terminal).

-***Mechanism of conduction*:**

1- Contiguous conduction: Occurs in unmyelinated nerves & in muscles

Events:

-When AP is elicited at any point of an excitable membrane ------> this part becomes locally depolarized.

-The AP flow from the depolarized area to the neighboring resting part & stimulating it.

-This newly depolarized area causes propagation of AP to the neighboring area also & so on till the nerve ending.

2- Saltatory conduction: Occurs in thick myelinated nerves.

-Events:

Ions cannot flow only through the nods of Ranvier.

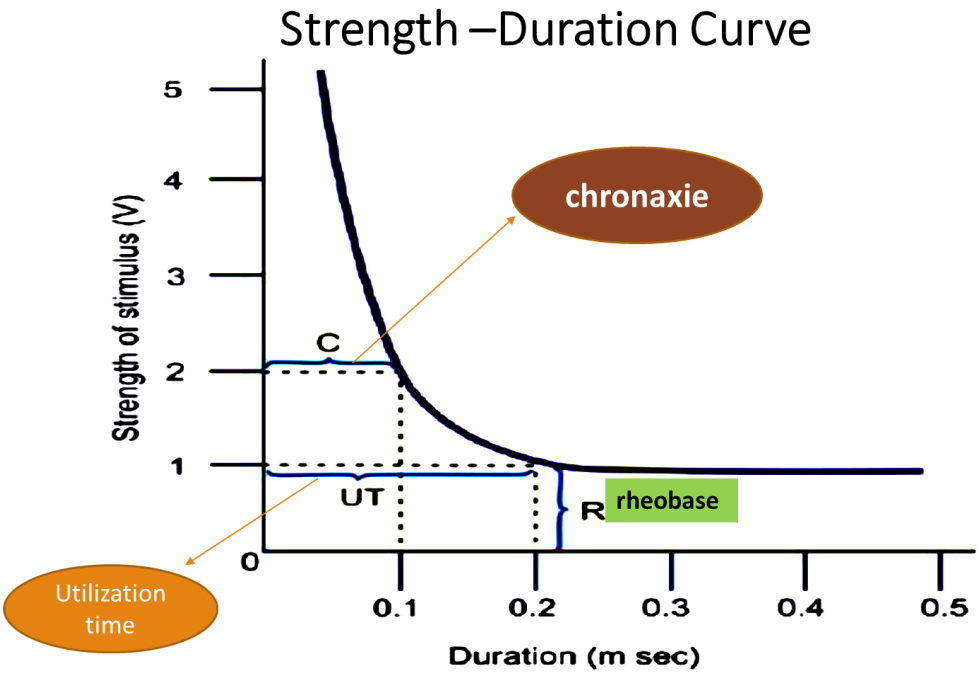
The AP is conducted from node to node.

Function of saltatory conduction:

a)Increases the velocity of nerve conduction, as the depolarization is limited to the nodes & Na leakage is minimal.

b)Saves energy required by sodium pump to return sodium outside.

Strength –Duration Curve



Definition*:* It is relationship between the strength of a given stimulus and the time needed by this stimulus to produce a response.

Interpretation of the Curve:

A- The stronger the stimulus, the shorter is the time needed for excitation.

B- Rheobase (R) (threshold) is the minimum stimulus strength required for stimulation, below which no excitation occur whatever the duration.

C- Utilization time (UT) is the time needed by the rheobase to stimulate.

D- Chronaxie (C): It is a minimal duration required for stimulation by a current of double the rheobase.

Significance of Chronaxie:

-The shorter the chronaxie the greater the excitability.

-Chronaxie is constant for each excitable tissue types.

-Chronaxie is indicator of tissue excitability

Nerve fibers are highly excitable (helping its rapid response). (Nerve (0.1 ms)> skeletal muscle (0.2 ms) > cardiac muscle (1.0 ms) > smooth muscle (5.0 ms)

Physiology of Muscles

Physiology Of Skeletal Muscles

Skeletal muscles are found throughout the body and functions to contract in response to voluntary stimulus. Skeletal muscle serves many purposes including maintaining body posture

Functions of skeletal muscle

- Moving the body and objects
- Beginning the swallow reflex
- Changing thoracic volume to inhale or exhale.
- Communication (Verbal and Facial)
- Production of body heat (Thermogenesis)
- Unlike smooth muscle and cardiac muscle, skeletal muscle receives neural input that allows conscious control of the muscles.

Human body contains over 400 skeletal muscles about 40-50% of total body weight

Functional structure of skeletal muscles:

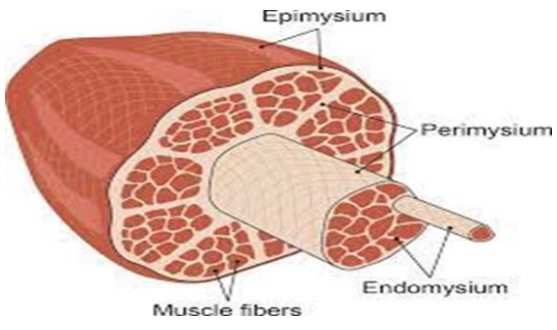
Skeletal muscle is composed of many cells, referred to as muscle fibers ranging from 10 to 80 mm in diameter. Most fibers extend all the length of the muscle. These fibers are multinucleate cells with nuclei found at the periphery of the cell.

I- Connective tissue coverings of the skeletal muscles:

The sarcolemma is surrounded by a connective tissue covering called the **endomysium**. Capillaries to supply the fibers and nerve tissue to that individual fiber are present in the **endomysium**.

Many muscle fibers are grouped into **fascicles**, which are encased by a connective tissue covering known as the **perimysium**.

The fascicles further group to form a muscle, which is encased by the **epimysium**.



II- Skeletal muscle organelles:

Each muscle fiber (cell) is composed of:

The sarcolemma: corresponding to the cell membrane. The sarcolemma encloses each muscle fiber. The sarcolemma is composed of a lipid bilayer and a thin outer coat of polysaccharides which contacts the basement membrane.

The sarcolemma invaginates within the muscle fiber to form deep T-tubules (transverse tubules). These T-tubules are a major location for ion exchange.

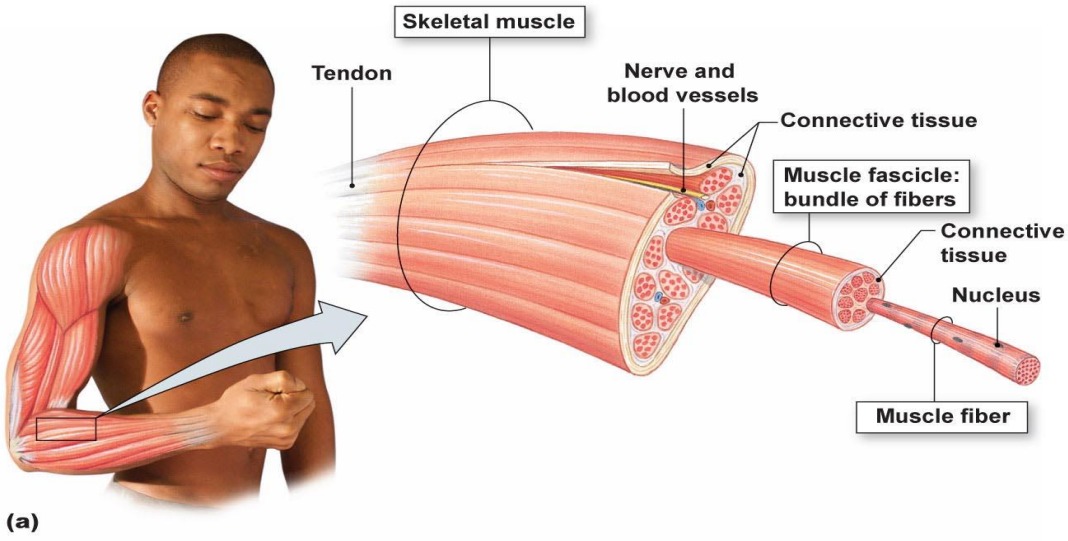
The main function of sarcolemma is propagation of action potential to initiate contraction

The sarcoplasm: (cytoplasm) which is composed of usual intracellular constituents, like:

- **Many nuclei**
- **Many mitochondria**
- **Sarcotubules or T-tubules** allow the action potential to pass rapidly from the sarcolemma to the interior of the cell, so that deep lying myofibrils may be activated.
- **The sarcoplasmic reticulum:** The cisternae (two ends of the tubule) are the site of Ca^{++} storage and release for excitation- contraction coupling. The membrane of cisternae contains Ca^{++}- ATPase (Ca^{++} pump), which transport Ca^{++} from the intracellular fluid into the interior.
- **Bundles of myofibrils** Each muscle fiber is composed of several hundred to several thousand myofibrils. Myofibrils are composed of actin (thin filaments) and myosin (thick filaments) along with support proteins
    - The thick and thin filaments are arranged longitudinally in ***sarcomeres***.
    - Repeated units of thick and thin filaments cause the ***cross-striated*** appearance of the skeletal muscle

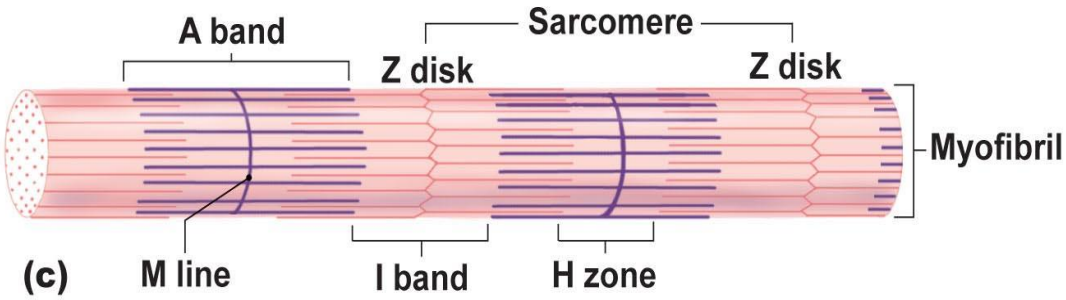
- **Sarcomere** is the basic ***contractile unit (functional unite)*** of muscle fiber. Each sarcomere is composed of two main types of protein filaments:

- **Contractile filaments:—**actin and myosin—which are the active structures responsible for muscular contraction.
- **Non-contractile filaments:-**titin and actinin- for stabilization of contractile ones.
- **Titin** is a large abundant protein., that functions for:
  - stabilization of the thick filament, center it between the thin filaments,
  - prevent overstretching of the sarcomere, and to recoil the sarcomere like a spring after it is stretched
- **α-Actinin** is a small non contractile protein, that functions for:
  - attachment of actin filaments to the Z-lines.
  - cross-linking the thin filaments in adjacent sarcomeres, to coordinates contractions between sarcomeres in the horizontal axis.



Microscopic Structure of skeletal muscles

As mentioned above arrangement of actin and myosin gives skeletal muscle its microscopic striated appearance and creates functional units called sarcomeres. The sarcomeres are arranged longitudinally and include the M line, Z disk, H band, A band, and I band when viewed under electron microscopy as shown below:

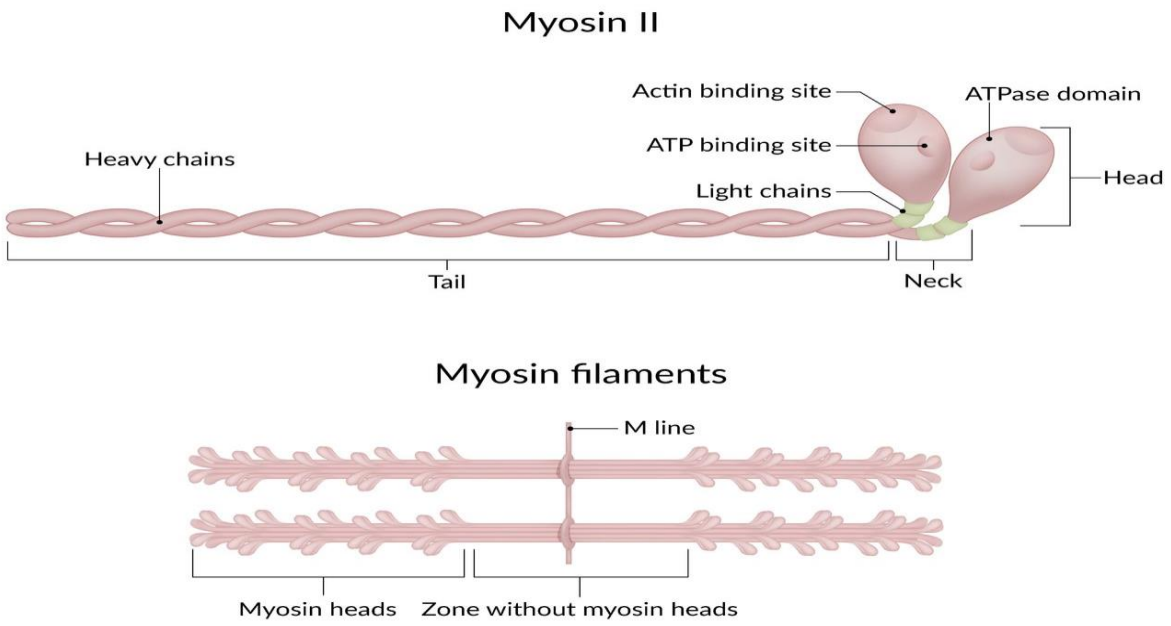


- **The Z line,** or Z disk: is the terminal boundary of the sarcomere where alpha-actinin acts as an anchor for the actin filaments.
- **The M line** is the central-most line of the sarcomere where myosin filaments are anchored together through binding sites within the myosin filament.
- **The H band** contains the M line and is the central region of the sarcomere that contains only myosin filaments.
- **The A band (dark band)** is a larger portion of the sarcomere that contains the entirety of the myosin fibers and includes regions of actin and myosin overlap.
- **The I band (light band)** covers the terminal regions of two adjacent sarcomeres and contains only actin filaments.
- ***Both the H band and I band shorten with muscle contraction, while the A band is a constant length.***

Molecular characteristics of contractile filaments:

A- Thin filaments are double helical structures known as actin, and are composed of monomeric units of F-actin, Tropomyosine and troponin

- **F-actin**: exhibits polarity and creates a positive and negative end within the sarcomere, with the positive end situated toward the terminal end of the sarcomere. F- actin contains the active sites with which the cross-bridges of the myosin filaments interact to cause muscle contraction.
- **Tropomyosine:** is a helical protein that runs along the actin double helix within its groove. In resting state, the tropomyosins lie on top of the active sites of the actin strands.
- **Troponin:** This is a complex of three loosely bound protein sub-unites, each of which plays a specific role in the control of muscular contraction.
    - ***Troponin I*** inhibits the interaction between myosin and F-actin during rest and this function is lost at activity.
    - ***Troponin C*** is the calcium acceptor protein that initiates contraction.
    - ***Troponin T*** binds the other two troponin sub-units to tropomyosin.
- **B- Thick filament:** (Myosin) is the most abundant muscle protein, accounting for more than 40% of the myofibrillar proteins in skeletal muscles. Myosin filaments are composed of 4 light chains and 2 heavy chains. The light chains are the location of the power stroke while each heavy chain, is further subdivided into two regions:
    - the ***myosin head*** that binds actin and contains an ATPase portion
    - the ***tail*** portion that dimerizes and assembles into bipolar thick filaments.



Types of muscle fibers:

There are three types of muscle fibers.

Type I fibers (slow oxidative fibers): are slow-twitching fibers that obtain ATP primarily from oxidative phosphorylation. The myosin heads cleave ATP more slowly than the other two types of fibers and are best suited for endurance types of contraction.

Type IIa fibers (fast oxidative fibers): are a faster twitching fiber used for intermediate endurance contractions.

Both types I and IIa fibers are considered red fibers and contain high numbers of mitochondria, as well as the protein myoglobin, which confers the red coloration to the fibers.

Type IIb fibers (fast glycolytic fibers) are the fastest twitching fibers that produce the greatest force for the shortest amount of time. They considered white fibers

with low levels of myoglobin and a high concentration of glycolytic enzymes and glycogen stores since they produce ATP primarily from glycolysis.

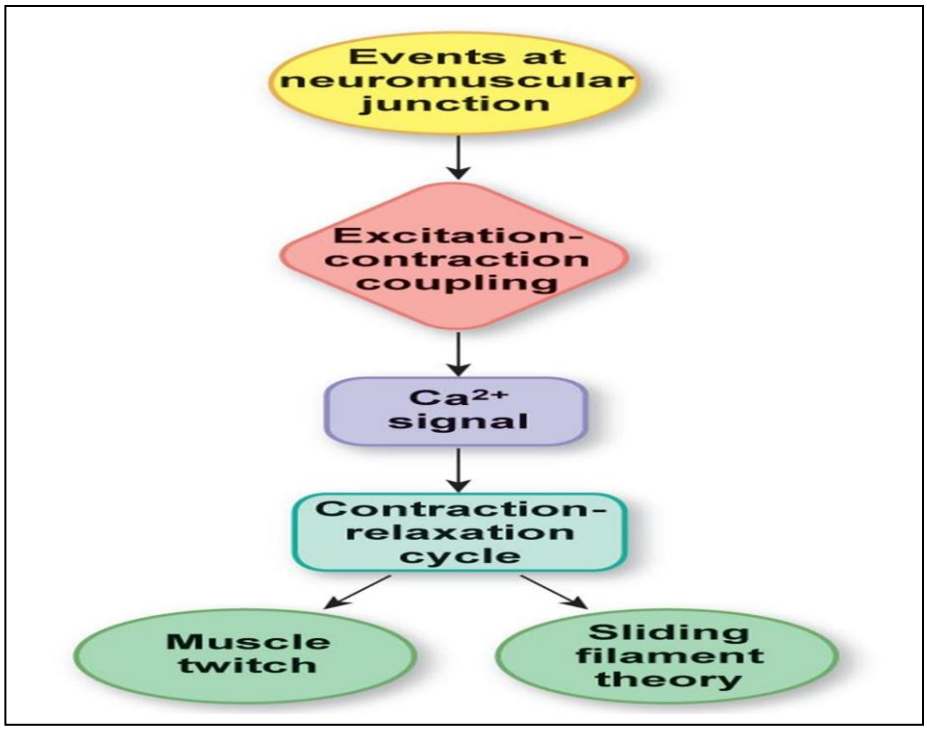
Type IIb fibers are also the largest diameter fibers because they have the highest density of actin and myosin proteins.

The muscle mechanics

Excitation-contraction coupling is the mechanism by which neural action potentials is converted to cross-bridge cycling, i.e., contraction.

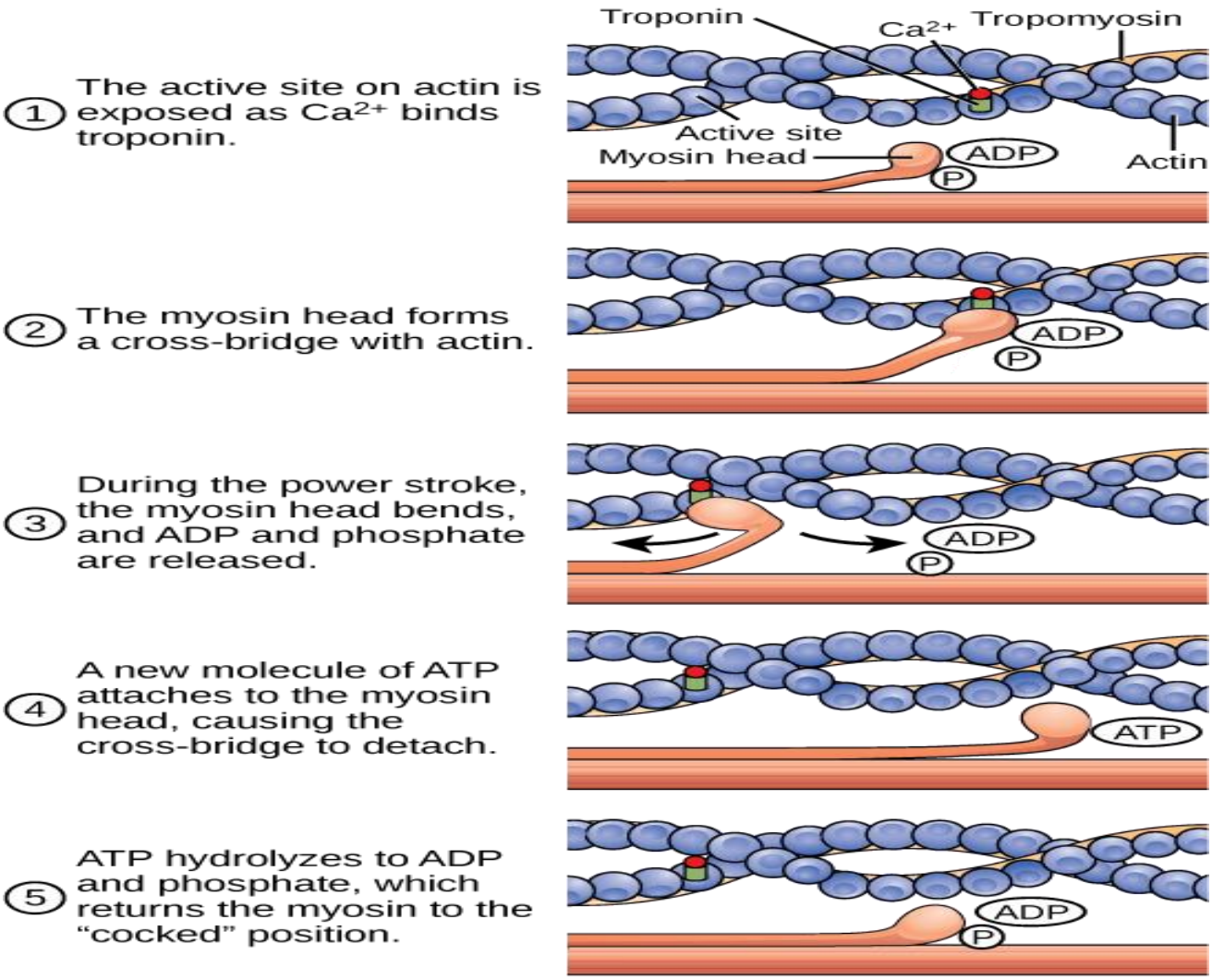
- Action potentials of the motor neuron cause release of acetylcholine (ACh) from the neuron terminus at the neuromuscular junction, or motor end plate.
- The ACh causes depolarization at the neuromuscular junction and transmits the action potential to the muscle fiber.
- In this process, action potentials travel along the cell membrane and into the T tubules to carry the signal to the interior of the muscle fiber.
- Depolarization causes a conformational modification in the dihydropyridine receptors of the T tubules.
- This conformational change opens ryanodine receptors on the terminal cisternae of the sarcoplasmic reticulum to release Ca^{+2} from storage in the sarcoplasmic reticulum into the intracellular fluid (ICF), increasing the concentration of ICF Ca by **ten** folds.
- The increased ICF concentration of Ca^{+2} causes a conformational change of the troponin complex by binding troponin C on the actin filament.

- Each troponin C can bind a maximum of 4 Ca^{+2} ions, and binding is cooperative in nature (similar to hemoglobin binding of oxygen), which allows a small change in Ca^{+2} to saturate the troponin C binding sites.
- The conformational change of troponin C uncovers the myosin binding sites on actin by pulling tropomyosin out of the way, which begins the cross-bridge cycling that causes skeletal muscle contraction.
- After excitation and subsequent depolarization of the T tubules **ceases (as acetyl choline is rapidly hydrolyzed by acetylcholinesterase enzyme)**, Ca^{+2} is released from troponin C and sequestered by the sarcoplasmic reticulum in the terminal cisternae through a Ca-ATPase in the membrane of the sarcoplasmic reticulum.
- Sequestration of Ca allows tropomyosin to cover the myosin binding sites on actin, which causes relaxation of the muscle.



Mechanism of muscle contraction:

Cross-bridge cycling is the mechanism by which skeletal muscle contracts. At the beginning of this cycle, myosin is bound tightly to actin in a step termed **rigor**.



NB. As long as there is adequate Ca to maintain an uncovered actin binding site, the myosin head will form a cross-bridge with actin. This cycle repeats as long as Ca is bound to troponin C. In the absence of ATP - such as in death- this is a semi-permanent state called ***rigor mortis***.

NB2: During contraction, the actin on each side of a sarcomere **slide** inward toward the myosin center pulling the Z line closer together, so the sarcomere shortens. During contraction **no shortening** of actin and myosin, **only sliding** on each other.

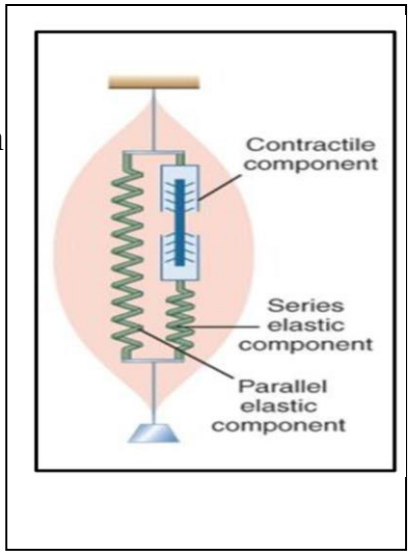
Types of muscle contraction

To distinguish between different types of skeletal muscle contraction, we will discuss the components of skeletal muscles at first.

Components of skeletal muscles:

1- **Active component:** which is represented by the contractile elements of the myofibril (actin and myosin). Its function is to shorten the muscle.
2- **Passive components:** which are subdivided into:

- **Series elastic (SE) elements:** such as **tendons**, that are in line (series) with the contractile component. Act as spring to store elastic energy.
- **Parallel elastic (PE) element**: that is provided by the muscle membranes, supplies resistance when a muscle is passively stretched. It is parallel to both CE and SE. presented by muscle membranes. It maintains the resting length of the CE and supports SE during resting tension. Also help to resist passive stretch.



<u>Types of muscle contraction:</u>

Muscle contractions can be described based on two variables: force and length.

Force itself can be differentiated as either tension or load. Muscle tension is the force exerted by the muscle on an object whereas a load is the force exerted by an object on the muscle.

1- Isometric contraction: When muscle tension changes without any corresponding changes in muscle length. Isometric contraction is said to be due to the stretching of SE. as only some sarcomeres are shortened, pulling others and the tendon.Isometric contractions are frequently used to maintain posture.

Isometric contractions are sometimes described as yielding or overcoming.

- A **yielding contraction** occurs when a muscle contraction is opposed by resistance. For example, when holding a heavy weight steady, neither raising nor lowering it.

- An **overcoming contraction** occurs when a muscle contraction is opposed by an immovable object, such as the contraction generated in the muscles when pushing against a wall.

2- Isotonic contraction: contractions maintain constant tension in the muscle as the muscle changes length. Isotonic muscle contractions can be either concentric or eccentric.

- **A concentric contraction** is a type of muscle contraction in which the muscles shorten while generating force, overcoming resistance. For example, when lifting a heavy weight, a concentric contraction of the biceps would cause the arm to bend at the elbow, lifting the weight towards the shoulder.

- An **eccentric contraction** results in the elongation of a muscle while the muscle is still generating force; in effect, resistance is greater than force generated. Eccentric contractions can be both voluntary and involuntary. For example, a voluntary eccentric contraction would be the controlled lowering of the heavy weight raised during the above concentric contraction. An involuntary eccentric contraction may occur when a weight is too great for a muscle to bear and so it is slowly lowered while under tension.

In natural movements that underlie locomotor activity, muscle contractions are multifaceted as they are able to produce changes in length and tension in a time-varying manner. Therefore, neither length nor tension is likely to remain constant when the muscle is active during locomotor activity.

During muscle contraction, many changes occur (excitability, metabolic, thermal, ----). We will discuss some of these changes below.

1-Excitability changes during muscle contraction:

Excitability is the ability to respond to a stimulus, which may be delivered from a motor neuron or a hormone.

Phases of excitability:

The absolute refractory period (ARP): This is the time during which another stimulus given to the muscle will not lead to a second response, whatever the stimulus intensity.

The relative refractory period (RRP): is the interval of time during which a second action potential can be initiated, but initiation will require a greater stimulus than before. Refractory periods are caused by the inactivation gate of the Na^+ channel.

Factors decreasing the excitability:

- A high extracellular fluid Ca^{++} ion concentration (competitive inhibition of Na channels)
- Local anesthetics (blockade of Na channels)
- Neuromuscular blockers (no passage of impulse from nerve to muscle)

2-Metabolic changes during muscle contraction:

- When a muscle fiber contracts, its intrinsic supply of ATP is only sufficient to maintain the contraction for a few seconds.
- Thereafter, energy comes from the transfer of the phosphate group from creatine phosphate to the ADP molecule. This provides enough energy for another 15 seconds of contraction.
- After that, energy must come from the breakdown of carbohydrates and lipids—first from within the muscle fiber and then from elsewhere in the body.
- The main intrinsic source of metabolic energy in a muscle fiber comes from the breakdown of **glycogen** into glucose.
- In the absence of oxygen (anaerobic glycolysis), a molecule of glucose is broken down into **lactic acid**, with the generation of two ATP molecules during the process.
- In the presence of O2 and through the activities of mitochondria, a molecule of glucose gets broken down into CO2 and H2O, with the generation of 36 molecules of ATP instead of the two that result from anaerobic glycolysis.

3- Thermal changes during muscle contraction:

a- Resting heat: The muscle produces heat during rest. It is due to the resting basal metabolic processes.

b- Activity heat: The heat produced when the muscle contracts. It occurs in two phases:

- **Initial heat** represents the waste heat of the anaerobic reaction
- **Recovery heat**

Initial heat is sub-divided into:

1. **Activation heat:** due to conduction of the AP and the changes produced by it to start the contraction.
2. **Shortening heat:** occurs during mechanical contraction.
3. **Work heat:** occurs when the muscle lifts a load.
4. **Maintenance heat:** occurs when the muscle contracts tetanically to maintain the contracted state.

Recovery heat:

- Nearly of the **same magnitude** as the initial heat.
- It is released during a much **longer time**.
- It is the waste heat of the oxidative processes that **re-synthesis glycogen**.

Mechanical efficiency of the muscle

Definition: the percentage of energy input that is converted into work instead of heat.

The energy output appears as:

- Work done
- As energy stores

- The rest is dissipated as heat.

The efficiency of skeletal muscle is about of 20-30 % of the total energy.

Factors affecting Mechanical efficiency:

1- Type of contraction: The mechanical efficiency is **20-30 %** in isotonic contraction, **zero %** in isometric contraction.

2- Type of fuel: Carbohydrate is the main source of energy supply. Fat is a medium source of energy. Proteins are poor source for muscular fuel.

3- Optimum rate of contraction: At the ideal rate of movements per minute, the best mechanical efficiency was obtained.

4- Optimum length of muscle fibers: There is an optimum length of muscle fibers to get the best mechanical efficiency. Sarcomeres produce maximal tension when thick and thin filaments overlap between about 80 percent to 120 percent, approximately 1.6 to 2.6 micrometers.

5- Training: The mechanical efficiency is **increased** in athletic than in non-trained persons due to:

· Optimum use of muscle fibers.

· Optimum rate of movement.

· Carbohydrates used as fuel.

· Vascularization.

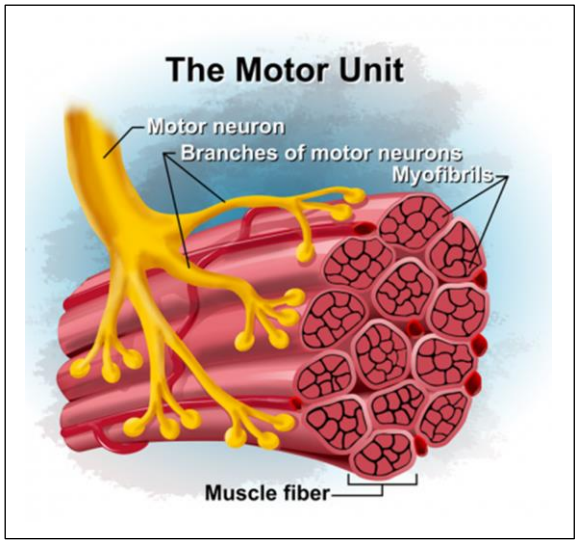
6- Cooling: **moderate** cooling increases the viscosity of the muscle and so decreases the mechanical efficiency.

7- Fatigue: Accumulation of lactic acid during fatigue depresses the mechanical efficiency.

Motor Unite

Motor unit is made up of a motor neuron and the skeletal muscle fibers innervated by that motor neuron's axonal terminals.

Groups of motor units often work together to coordinate the contractions of a single muscle.



All of the motor units within a muscle are considered as a **motor pool.**

- All muscle fibers in a motor unit are of the same fiber type (red or white).
- When a motor unit is activated, all of its fibers contract.
- The force of a muscle contraction is controlled by the number of activated motor units.
- the muscles that act on the largest body masses have motor units that contain more muscle fibers, whereas smaller muscles contain fewer muscle fibers in each motor unit.
- Muscles which possess more motor units are able to control force output more finely.
- Muscles that function over a prolonged period, such as lower back muscles, will asynchronously recruit fibers so that fatigue is not easily occur.

Muscle Adaptation to Exercise

The properties of skeletal muscles are affected by:

- The regularity with which a muscle is used.
- The duration and intensity of its activity,

Muscle adapts to exercise training to become a more effective energy provider this is achieved by:

- Improving the capacity for oxygen extraction from the blood supply
- Altering cellular control of energy metabolism

Effect of exercise:

- Increased size of muscle fibers
- Increased capacity for ATP production.
- NB: during adult life the change in muscle size is due to change in size of fibers, not the number.

Aerobic exercise:

- Exercise of low intensity and long duration
- Ex. running and swimming
- **Adaptation of the muscle is in form of:**
  - produces increases in the number of mitochondria.
  - Increase in the number of capillaries around these fibers.
  - Slight **decrease** in fiber diameter, and thus small decrease in the maximal strength of muscles
  - Respiratory and circulatory systems change to improve the delivery of oxygen & fuel to the muscle.
- **Significance of adaptation:**

- Increase in the capacity for endurance activity

- Minimize fatigue.

Strength training exercise:

- Exercise of short-duration & high-intensity
- Ex. weight lifting
- **Adaptation of the muscle is in form of:**
  - **Hypertrophy** of white muscle fibers due to the increased synthesis of actin and myosin filaments,
  - Increase **glycolytic activity** by increasing the synthesis of glycolytic enzymes .

- Such muscles, although **very powerful**, have little capacity for **endurance, and fatigue rapidly**

- **Significance of adaptation:**

- Increase in the strength of the muscle
- Bulging muscles of a conditioned weight lifter.

Effect of aging on skeletal muscle

With age, muscles undergo progressive loss of muscle mass and strength.The age-related loss of muscle function is known as **Sarcopenia.**

Causes of sarcopenia:

- Decreases in total fiber number, especially fast-twitch fibers
- Reduced muscle power
- Loss in motor neurons.
- Endocrine changes: increased insulin resistance, increased parathormone level, decrease GH, decrease sex hormones and decrease vit D.

Smooth muscle physiology

The main function of smooth muscle is contraction. Smooth muscle consists of two types: single-unit and multi-unit.

Smooth-muscle fibers differ from skeletal muscle fibers in that:

- spindle-shaped cells
- lack striations
- have a single nucleus

- capable of cell division.
- The thin filaments do not have troponin, but the smooth muscle contains calmodulin, a calcium binding protein.

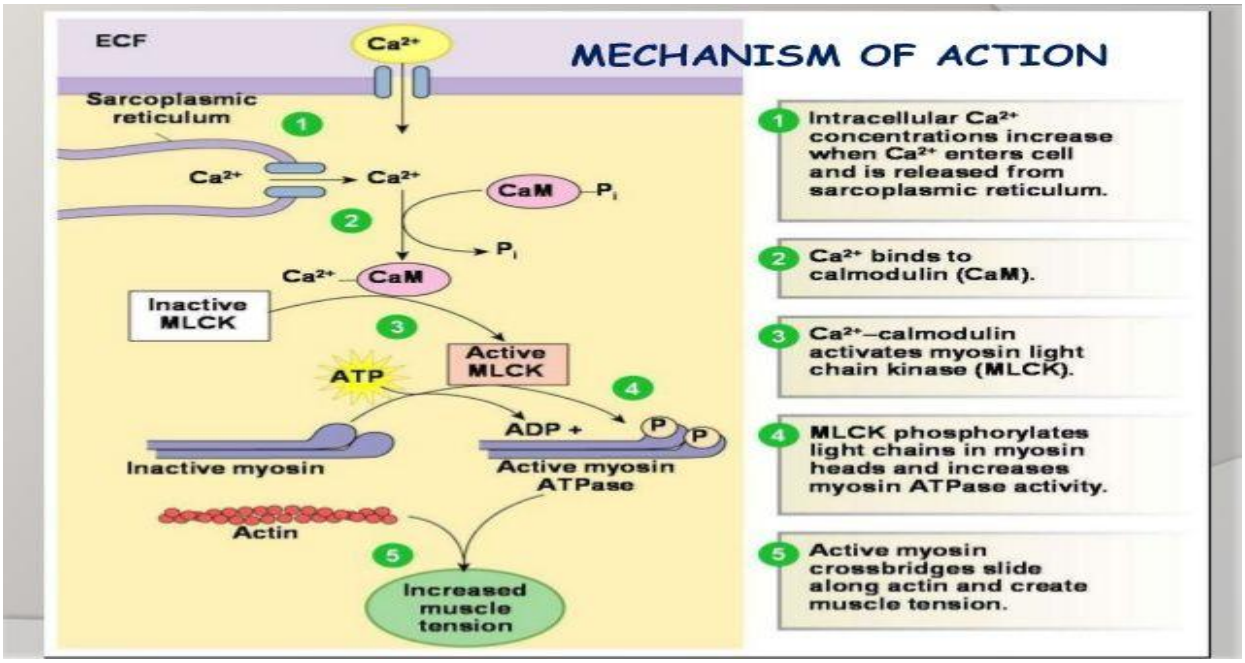
Smooth-muscle fibers are similar to skeletal muscle fibers in that:

- they contain actin and myosin filaments
- contract by a sliding-filament mechanism.

The general functions of smooth muscle are:

- Gastrointestinal tract - propulsion of the food bolus
- Cardiovascular - regulation of bl.ood flow and pressure via vascular resistance
- Renal - regulation of urine flow
- Genital - contractions during pregnancy, propulsion of sperm
- Respiratory tract - regulation of bronchiole diameter
- Integument - raises hair with erector pili muscle
- Sensory - dilation and constriction of the pupil as well as changing lens shape

Mechanism Of Smooth Muscles Contraction:



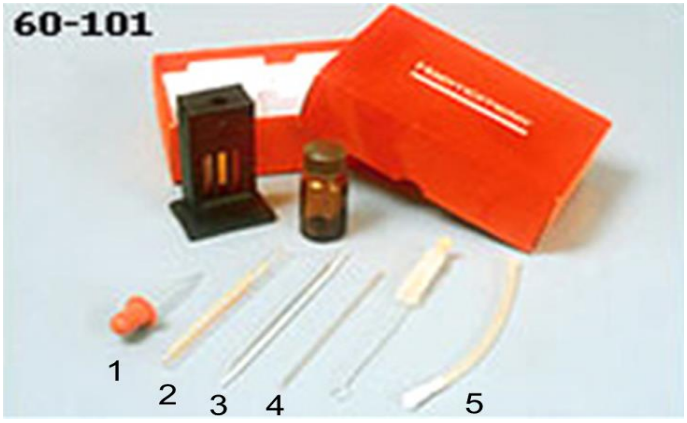
1. Depolarization of membrane or hormone/neurotransmitter activation
2. L-type voltage-gated calcium channels open
3. Calcium-induced calcium release from the SR
4. Increased intracellular calcium
5. Calmodulin binds calcium
6. Myosin light chain kinase activation
7. Phosphorylation of myosin light chain
8. Increase myosin ATPase activity
9. Myosin-P binds actin
10. Cross-bridge cycling leads to muscle tone

The contraction ends when the phosphate group is removed from myosin head by phosphorylase enzyme And When IC calcium level decreases

Practical Part

Hemoglobin determination

Sahli's hemoglobinometer



1. Dropper pipette
2. Sahli Tube
3. Sahli's pipette
4. Glass rod
5. Mouthpiece

Housing containing comparator block

For estimation of Hb in blood, we need:

Graduated Sahli tube with two scales:

Hg in gms/100ml

Precentage of Hg in 100 ml

Sahli pipette.

Glass rod.

Dropper pipette.

N 10 HCl.

Distilled water.

Principles of test

Hg + HCL→ acid hematin (higher conc. of Hg→ the more intense the hematin color)

1. HCL until 10%mark (5 drops of 0.1 HCL).
2. Suck blood until 20 micro ml (0.02 ml) in Sahli pipette.
   acid hematin (brownish in color) will be formed.

3. Add water drop by drop.
4. Wait 10 minutes
5. Read scale by gram/ 100 ml blood.

Precautions :

1. No blood stick tip of pipette: false high reading
2. No large amount of HCL: lighter final color
3. No squeeze the finger (tissue fluid): false low reading
4. At least 10 minutes for complete conversation of Hb to acid haematin
5. Full arm length, good light &graduations not in front

In normal:

Male 16±2 g / 100 ml blood. Female 14 ±2 g / 100 ml blood.

Increase Hb

1-Polycythemia. 4-Dehydration.

2-Hypoxia. 5-High altitude.

3-Cong heart disease.

Decrease Hb -Anemia

Haematocrite value

Definition

Percentage ratio of packed cell volume to total blood.

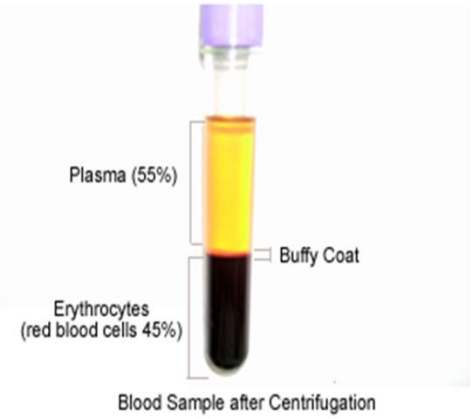
Hematocrite centrifuge

- Heparinized capillary tube.
- Hematocrite centrifuge.
- Hematocrite reading scale.

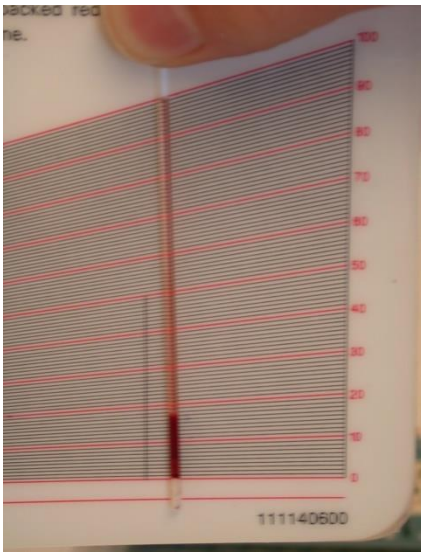
– Hold tube in a horizontal position and allow the blood to enter until the tube is one-half to three fourths full.

– Centerifuge for 15 min.

- The specific gravity of RBCs is 1090.
- The specific gravity of Plasma is 1030.
- The specific gravity of WBCs is intermediate (Buffy coat).
- So on centrifugation the RBCs which are heavier than plasma sink to the bottom of the tube and the plasma stays above the RBCs.



Blood Sample after Centrifugation



-In normal:

Male 46% (43-49). Female 41% (36-45).

Changes

I-Physiological

*Small vessels< large vessels. The distribution of blood cells in the vascular system is not homogeneous, red cell concentration in the small vessel compartment being significantly lower than in the large vessel compartment

*Arteries< veins. CO_2 shift Cl^- so RBCs withdrawal water &become larger in volume

II-Pathological

-Increase (dehydration & polycythaemia). -Decrease (overhydration & anaemia).

Blood indices

I-Mean corpuscular volume :The average size of a red blood cell.

$$MCV = \frac{\text{hematocrit}(\%) \times 10}{\text{RBC count}(\text{millions} / \text{mm}^3 \text{ blood})}$$

-Normal 80-100 fl (femtoliter) -Abnormal microcytic &macrocytic

II-Mean corpuscular Hemoglobin: The average amount of hemoglobin (Hb) per red blood cell.

$$MCH = \frac{\text{hemoglobin concentration in one liter}}{\text{RBCs count}}$$

-Normal 27-31 pg/cell (picograms) -Abnormal hypochromic &hyperchromic

III-Mean corpuscular hemoglobin concentration: The average concentration of hemoglobin per red blood cell. Normal 34 ±2%

$$MCHC = \frac{\text{hemoglobin}(g / 100ml) \times 100}{\text{hematocrit}(\%)}$$

-Diminished ("hypochromic") in microcytic anemias.

-Normal ("normochromic") in macrocytic anemias(due to larger cell size, though the hemoglobin amount or MCH is high, the concentration remains normal).

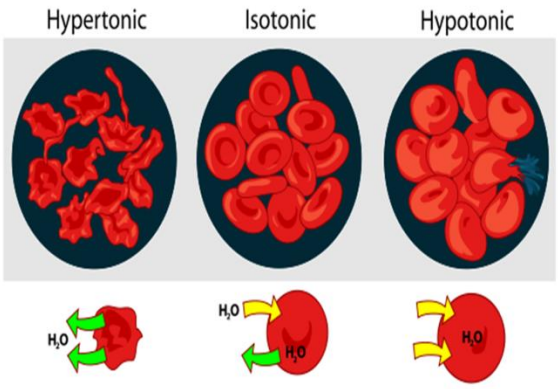
-Elevated ("hyperchromic") in hereditary spherocytosis, sickle cell disease.

Osmotic fragility test

Normal RBCs have biconcave surface in plasma.

If put in hypotonic solution →spherical→hemolysis.

Hereditary spherocytosis RBCs are spherocytic in plasma (isotonic solution =0.9).



– 8 test tubes.

– Distilled H_2O.

– NaCl in distilled H_2O of the following Concentration (0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55).

- Place 5 ml of NaCl solutions in test tubes in serial order.
- Place 5 ml distilled H_2O in the 8th tube.
- 1ml of fresh blood of each tube.
- Invert gently each tube to mix the blood & saline (don't shake the tubes).
- Wait for 30 minutes.

Note :the depth of color of supernatant fluid

Volume of RBCs at the bottom of the tube.

- ❖ supernatant fluid is clear & RBCs at the bottom of the tube means no hemolysis.
- ❖ RBCs at the bottom of the tube & supernatant fluid is colored red means incomplete hemolysis.
- ❖ No RBCs at the bottom of the tube & supernatant fluid is equality colored. Means complete hemolysis.

Normal RBCs

Beginning of hemolysis →0.50

Partial hemolysis →0.45

Complete hemolysis →0.35

Hereditary spherocytosis

Partial hemolysis > 0.45 (0.70)

Complete hemolysis > 0.35 (0.5)

Sickle cell anaemia &Iron deficiency anemia

Partial hemolysis < 0.45

Complete hemolysis < 0.35

Haemolysis occurs abnormally

I-Early

- Hereditary spherocytosis
- Autoimmune spherocytosis
- Poisoning
- Sever burn
- Macrocytic anaemias
- Old red cells
- Glucose 6 phosphate dehydrogenase deficiency

II-Delayed

- Sickle cell anemia.
- Thalassemia
- Iron deficiency anemia

Erythrocyte sedimentation rate test (ESR)

Definition

The distance sediments by RBCs in a vertical blood column at the end of one or two hours.

-Blood sample remain fluid by anticoagulant (Na citrate bind to the calcium the cascade of coagulation cannot begin) so erythrocytes gradually settle to the bottom of container

-Three stages of sedimentation process

- ❖ Aggregation of erythrocytes into rouleax
- ❖ A period of rapid fall
- ❖ A phase of packing of rouleax at bottom of the tube

-Mechanism

↑ fibrinogen & globulin→ ↓ negative charge (↓repel) → aggregation and stick of RBCs → rouleax → more rapid sedimentation.

So formation of rouleax depend on plasma proteins.

N.B: ↓ albumin → ↑ESR

1. 2 ml of blood + 0.5 ml Na citrate.
2. Graduated vertical tube (0 -200 m ml) from top to bottom (Westergren's tube).
3. The height of the column of clear plasma at the top of the red column in Westergren's tube is noted at end of 1 hour & again at end of 2 hours.

	1st hour	2nd hour
❖ Male	5	10 m ml
❖ Female	8	16 m ml

Clinical significance

Not specific

- The effect of treatment & progress of disease (improving, not effect or complication).
- The severity of disease.
- The activity of disease (T.B or rheumatic fever show periods of activity & periods of rest).

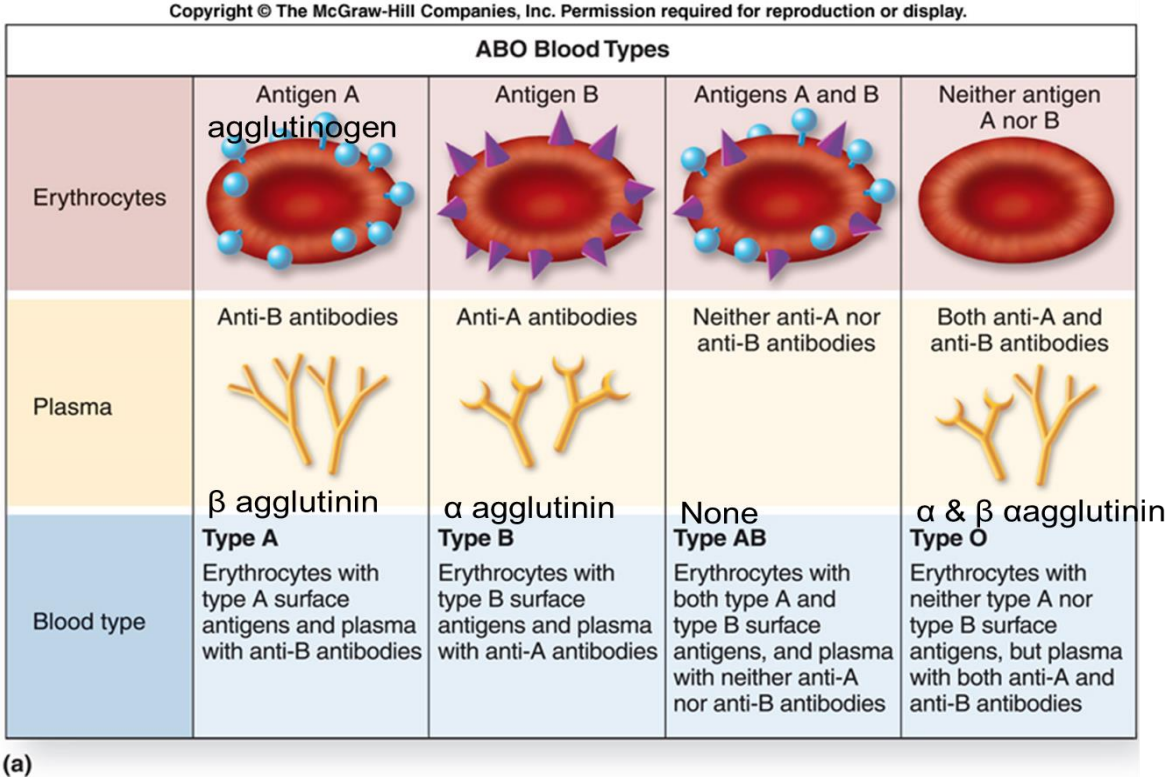
- Diagnosis of pelvic swelling in female (in malignant ↑ while in benign is normal).

Blood grouping

Human RBCs have 30 antigens on its membrane.

Agglutinogens (antigens) +agglutinins (antibodies) → agglutination.

In actual practice most agglutination in transfusion are caused by two antigen-antibody system (ABO & Rh system).



(a)

The strength of agglutination reaction is not the same for every person. In some cases, it may be necessary to observe the cells under the microscope.

-Rh incompatibility is dangerous in marriage

-(Erythroblastosis foetalis = sever jaundice & anaemia).

1st baby can be saved.

-85%of people are Rh positive &15%of people are Rh negative.

-In egypt 92% of people are Rh positive.

Bleeding time

-Filter paper.

-Wipe the blood drop every 15 second until no more blood stains appear on the filter paper.

-Record the time from pricking the finger until bleeding stops=bleeding time.

-Bleeding time = number of blood drops x 15 second.

-Normal (2-6 min). -Prolonged (clinical by purpura)

- **Platelets :**

Thrombocytopenia (defect in number =quantities)

1ry(unknown cause)

2ry (aplasia of BM)

1. Exposure to X ray
2. Radioactive substances
3. Neoplastic deposits
4. Drug sensitivity

Thrombasthenia (defect in function =qualitative)

→1ry,2ry(sever uremia &exposure to drugs as aspirin).

- **Vascular disorders.**

Coagulation time

- Non-heparinized capillary tubes.
- At 30 second break off 0.5 cm of capillary tube and seen a fibrin thread between the two pieces tubing.
- Normal (5-8 min).
- Prolonged in hemophilia (A=VIII,B=IX &C=XI), vit k deficiency, liver disease(factors II, VII, IX and X), obstructive jaundice& uses anticoagulant.

The Simple Muscle Twitch

A brief muscle contraction followed by relaxation=mechanical response. It is produced by a single adequate stimulus directly or indirectly through its nerve. Its duration 0.1 sec in frog but 0.08 sec in human.

Adequate stimulus in

Strength: at least threshold stimulus.

Duration: adequate time.

Sudden application.

Types of stimuli

1. Electrical
2. Chemical
3. Mechanical
4. Thermal
5. Electromagnetic

Electrical stimulus is preferred:

Similar to natural stimuli

Easily controlled (its intensity & duration)

Not cause nerve damage

Can repeated

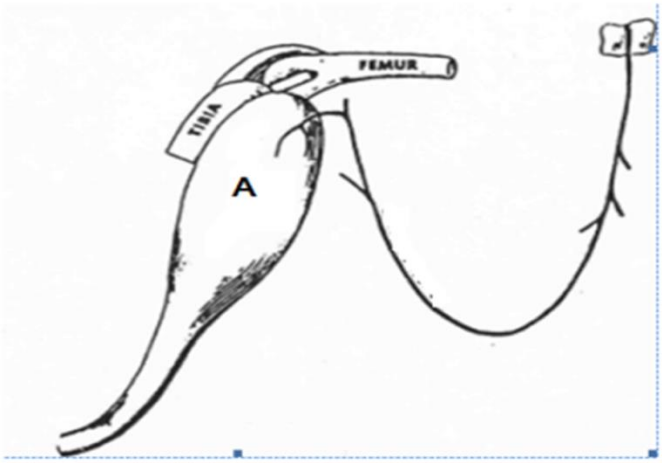
Types of electrical currents:

Galvanic current (battery)

Constant, low intensity and long duration.

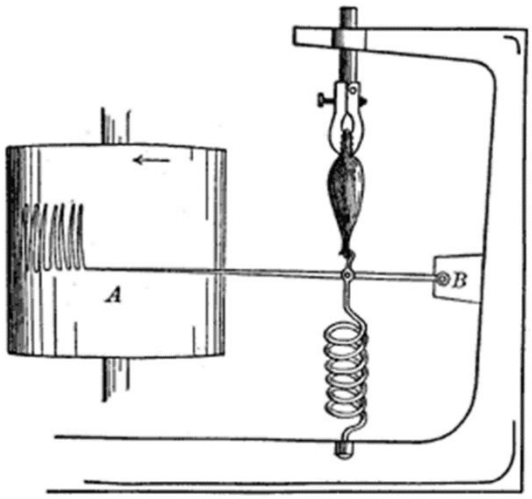
Faradic current

Alternating current, high intensity and short duration.



Nerve muscle preparation

1. Tendon of Gastrocnemius muscle
2. Gastrocnemius muscle
3. Knee joint
4. Sciatic nerve with its roots from 3 or 4 segments of spinal cord.



Apparatus: Kymograph

Latent period:

The time between the application of stimulus and start of contraction=0.01 sec.

1. Conduction of the nerve impulse along the nerve fiber.
2. Development of the end plate potential.

3. Conduction of impulse along the surface of the muscle.
4. Development of mechanical response.
5. Conduction of the response to the recording drum.

Contraction period:

During this period ,the muscle shortens to maximum and performs work=0.04 sec.

Relaxation period:

During this period ,the muscle restores its resting (original) length =0.05 sec.

The effect of 2 successive stimuli

Latent period (ARP) → no response.

Contraction phase (RRP) → new contraction summated to preceding (stronger and prolonged).

The early relaxation phase (supernormal phase) → 2 peaks with higher second peak.

The end of relaxation phase → 2 separate twitches but the second slightly higher in amplitude (heat liberated leads to warming muscle and ↑ availability of Ca).

The effect of repeated stimulation (Genesis of tetanus)

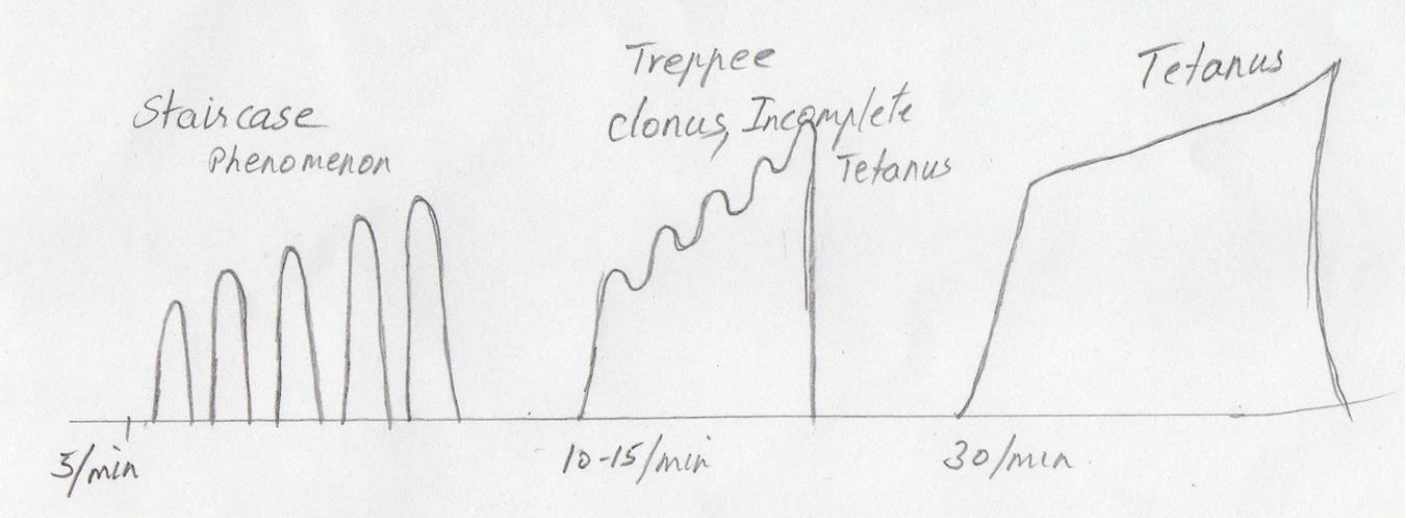
If the frequency slow (stimuli fall after relaxation phases → separate twitches = treppe or staircase phenomenon).

If ↑ the frequency (stimuli fall during relaxation phase → incomplete tetanus = clonus), number of stimuli can be calculated by contractions of mechanical response.

N.B Clonus: succession of contractions with incomplete relaxation.

If ↑ ↑ the frequency (stimuli fall during contraction phase →complete tetanus), number of stimuli can be calculated by action potentials of electrical response.

N.B Tetanus: succession of contractions without relaxation = continous contraction.



The effect of temperature on simple muscle twitch

***Warming* (warm ringer at 30°c for 30 sec)**

- Increase the strength of contraction.
- Decrease latent period.
- Shortening all phases of simple muscle twitch.
- ❖ Increase permeability of Na.
- ❖ Increase metabolism.
- ❖ Decrease of viscosity of protein to facilitate moving of cross bridges.

Over warming >45°c → denatured protein & sustained contraction (heat rigor).

***Cooling* (cool ringer at 5°c for 1 min)**

- Decrease the strength of contraction
- Increase latent period.
- Prolonged all phases of simple muscle twitch.
- ❖ Decrease permeability of Na.
- ❖ Decrease metabolism.

- ❖ Increase of viscosity of protein to inhibit moving of cross bridges.

Over cooling ***<5°c*** →destruction of protein& prevent muscle contraction

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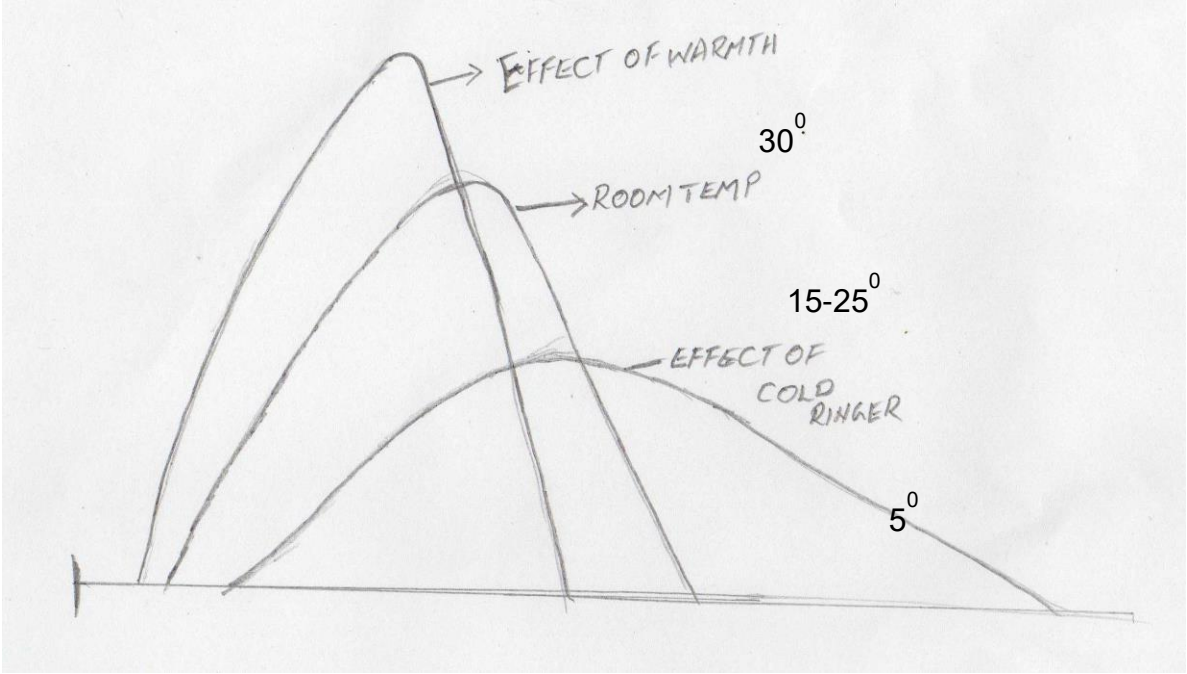

The effect of fatigue on simple muscle twitch

- ⏵ Fatigue

A temporary decrease in work capacity caused by work itself and disappears after rest.

-Decrease the strength of contraction.

-Prolong all phases of simple muscle twitch specially relaxation phase.

Site of fatigue:

Motor end plate and muscle

N.B nerve itself not fatigue

Causes of fatigue:

1. Exhaustion of the chemical transmitter (Ach).
2. Reduction of the sources of energy (ATP,CP & glycogen).

3. Accumulation of lactic acid.

The effect of temperature on clonus

Warming: clonus → separate contractions (shortening duration of contractions).

Cooling: clonus → complete tetanus (prolongation duration of contractions).

The effect of fatigue on clonus

Clonus → complete tetanus (prolongation duration of contractions).