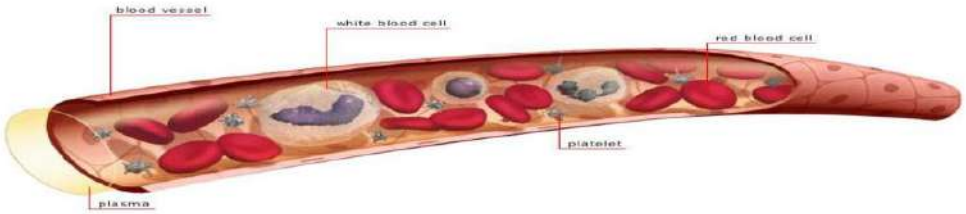
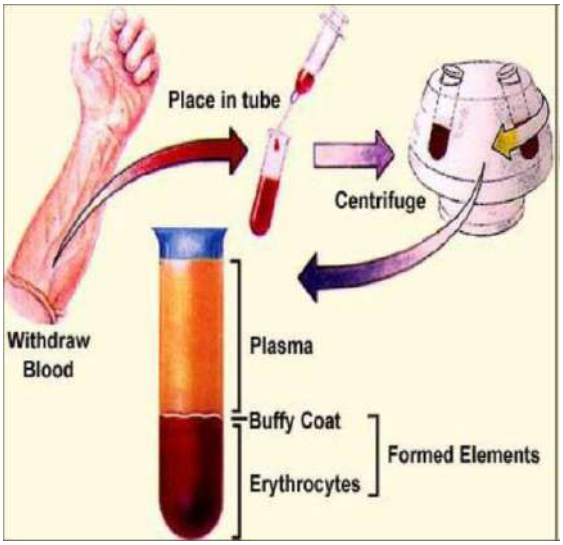
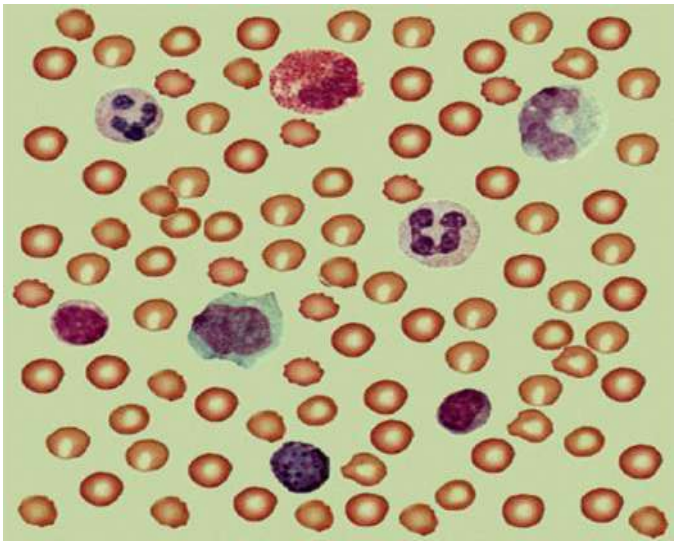
Lecture 1

Blood is a is a fluid connective tissue which is a viscous fluid pumped by the heart through a closed system of blood vessels, it composed of cells (formed elements) and plasma. The cells are the red blood cells, white blood cells, platelets, which are suspended in the fluid portion, the plasma.







Blood film

Functions of the blood include :

1. Transport of O2, nutrients and hormones to the tissues.
2. It carries CO2 to the lungs and other products of metabolism to the kidneys to be excreted.
3. Blood contributes in the regulation of body temperature.
4. Through a constant exchange of molecules with the interstitial fluid, blood helps to maintain the pH and electrolyte concentrations of interstitial fluid within the ranges required for normal cell functions.
5. Blood also serves essential body protective against infections
6. Blood regulation of blood clotting prevent blood loss

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The amount of blood in the body has been measured in different ways. Naturally the volume of blood can be expected to vary with the size of the body. The blood volume of an adult human of average size is about 6-8 % (in man 52-83 mL/kg; woman 50-75 mL/kg).

The normal total circulating blood volume is about 8% of the body weight (5600 ml in a 70 kg man) about 55% of this volume is plasma.

Plasma

Plasma is a part of the extracellular fluid of the body. The normal plasma volume is about 5% of the body weight (3500 ml is a 70 kg man). Plasma consists of an aqueous solution of proteins, electrolytes, and small organic molecules. The major types of protein present in the plasma are albumin (4.5 g/dl), globulins (2.5 g/dl) of α_1, α_2, β_1, β_2 and γ types, and fibrinogen (0.3 g/dl).

Composition of plasma

⊗ Water – 90 %

⊗ Solids – 10 %

⊗ Inorganic chemicals: sodium, calcium, potassium, magnesium, chloride, bicarbonate, phosphate, sulfate – 0.9%

⊗ Organic chemicals: Proteins(serum albumin, serum globulin, fibrinogen) 8%

⊗ Others: – 1.1%

Non-protein nitrogenous substances: urea, uric acid, creatine, creatinine, ammonium salts, amino acids

⊗ Non nitrogenous substances: glucose, fats, cholesterol hormones

Gases: oxygen, carbon dioxide, nitrogen

Functions of Plasma

1. Water:

* Transport medium; carries heat

2. Electrolytes:

* Membrane excitability

* Osmotic distribution of fluid b/t ECF & ICF

* Buffering of pH changes

3. Nutrients, wastes, gases, hormones: just transported

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Proteins

One liter of plasma has 65-85 gram of proteins, concentration of albumins is 45 g/L(4.5 g/dl); globulins 25 g/L (2.5 g/dl) is alpha-1-globulins 1-4 g/L, alpha-2-globulins 4-8 g/L, beta-globulins 6-12 g/L, gamma-globulins – 8-16 g/L. fibrinogen 3 g/L(0.3 .(g/dl)

Plasma which are not contain fibrinogen called serum (it is necessary for understanding the immunology, therapy etc.)

Albumin

Albumin: on 80 % it provides oncotic pressure, contacts with bilirubin, fatty acids, antibiotics, it connects with them and transports them. It produces in liver in average quantity of 17 gram per day.

Globulins

- Globulins produces in lymphatic nodes, in liver, in bone marrow in average quantity of 5 gram per day.
- Alpha-1-globulins connected with carbohydrates (for example 2/3 of all glucose connected with alpha-1-globulins. This is glycoproteins.)
- Alpha-2-globulins connect 90 % of cupper. This is cerruloplasmin. It's may produce in hormones for example, thyroxin, connected by vitamin B12. From this protein produce angiotensin (substances which are take place in increase of blood pressure).
- Beta-globulin carry out 75 % of fats, iron (for example, transferrin).
- Gamma-globulins has protective functions (for example, antibodies).

Fibrinogen

- Fibrinogen is a protein which are produced by liver and take place in hemostasis system. Fibrinogen is dissolved form, which transform in unsolved form – fibrin and provide coagulate hemostasis (plug production) and prevent bleeding.
- Daily production of fibrinogen is 2-4 g/L.

Functions of Plasma Proteins

Plasma Proteins: (albumins, globulins, fibrinogen)

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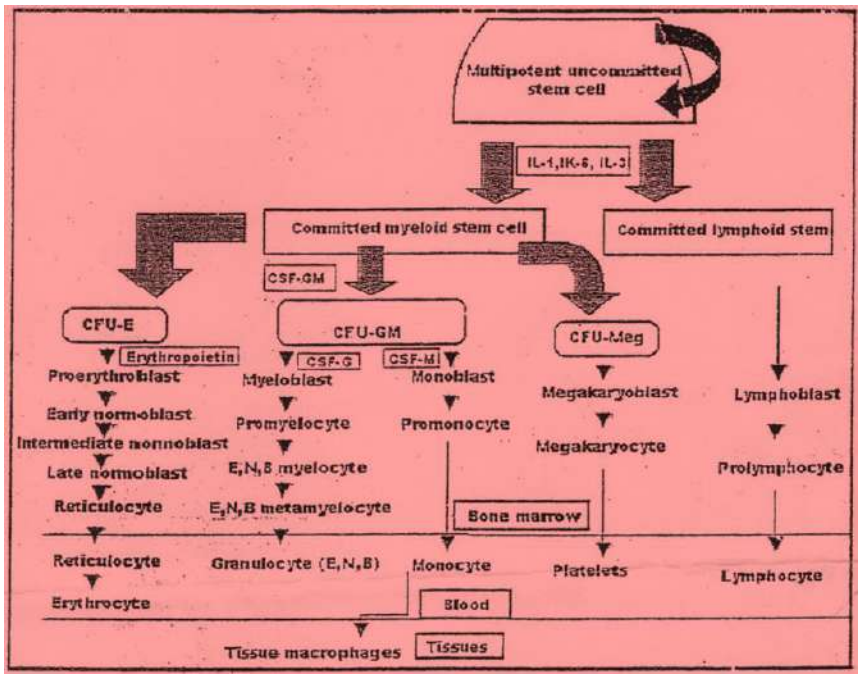
1. Maintaining colloid osmotic balance (albumins)
2. Buffering pH changes
3. Transport of materials through blood (such as water insoluble hormones)
4. Antibodies (e.g. gamma globulins, immunoglobulins)
5. Clotting factors (e.g. fibrinogen)

Hemopoiesis



Formation of blood cells (hemopoiesis) occurs at different anatomical sites during the course of development from embryonic to adult life.

1. In the early few weeks of embryonic life blood cells are produced in the yolk sac.
2. Later on (after the third month of pregnancy) they are formed mainly in the liver, the lymph nodes and the spleen.
3. During the latter part of fetal life and after birth, blood cells are produced by the bone marrow of all bones.
4. By the age of 20 the active red marrow of long bones (except for the upper humerus and femur) has become inactive, yellow and fatty, and produces no more blood cells.
5. Beyond 20 years blood cells are normally formed in the marrow of flat or membranous bones (such as the vertebrae, sternum, ribs and pelvis) and the proximal ends of

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humerus and femur. Even in these bones, the marrow becomes less productive as age increases.

In certain pathological states, when there is increased demand for blood cell production, red marrow reappears in the shafts or the long bones, replacing the fat.

From birth onwards, all blood cells except lymphocytes are normally made only in the bone marrow. Only pathological situations, such as in diseases in which the bone marrow becomes destroyed, does significant hemopoietic activity occur in the liver, spleen and other sites, when it is referred to as extra medullary hemopoiesis.

The bone marrow is one of the largest organs in the body and it is also one of the most active. In the bone marrow, there are multipotent uncommitted stem cells from which all the cells in the circulating blood are derived.

The uncommitted stem cell have two properties: [1] An ability by cell division to give rise to new stem cells (self-renewal) [2] An ability to differentiate into committed stem cells which differentiate into the various differentiated cell types found in marrow and blood. It appears likely that the uncommitted stem develop into the separate pools of committed stem cells for erythrocytes megakaryocytes, lymphocytes, and granulocytes (which include neutrophils, esoinophils, and basophils). Monocytes may arise from the same committed stem cells of the granulocytes.

A committed stem cell that produces erythrocytes is called a colony-forming unit-erythrocyte (CFU-E), likewise colony-forming units-granulocytes-monocytes (CFU-GM) refer to those which form granulocytes and monocytes, and colony-forming units-megakaryocytes (CFU-Meg) to those which form megakaryocytes.

Factors Regulating Hemopoiesis (Hemopoietic Growth Factors): Production of blood cells is regulated by growth factors, which are multiple proteins that control growth, differentiation, and function of cells in one or more of the lines of blood cell production. These factors include:

- **Erythropoietin.**
- **Colony-stimulating factors (CSFs).**
- **Interleukins (ILs 1, 2, 3, 4, 5, 6, 7, 12 and 13).**

In general, their role in hemopoiesis is as follows:

[1] Some ILs act in sequence to convert multipotent uncommitted stem cells to committed stem cells.

[2] The CSFs stimulate the committed stem cells to differentiate to a single line of cells, include granulocyte-monocyte CSF (GM-CSF), granulocyte CSF(G-CSF), and monocyte CSF(M-CSF).

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[3] Proliferation and maturation of cells that enter the blood from the marrow are regulated by multiple growth factors that cause cells in one more of the committed cell lines to proliferate and mature.

These include erythropoietin (related to RBC production), CFSs (related to monocyte and granulocyte production) and ILs (related to basophil and eosinophil differentiation).

Each of the CSFs has a predominant action, but all the CSFs and ILs also have other overlapping actions. These growth factors affect their target cells though binding to specific receptors.

The sites of growth factors production: Erythropoietin is produced mainly by kidney cells, and is a circulating hormone. The other factors are produced by macrophages, activated T-lymphocytes, fibroblasts, and endothelial cells.

Formation of growth factors is controlled factors outside the bone marrow. For instance, in the case of red blood cells, exposure of the body to low oxygen for a long period result in growth induction, differentiation and production of greatly increased numbers of erythrocytes. In the case of some of the white blood cells, infectious diseases cause growth, differentiation, and eventual formation of specific type of white blood cells that are needed to combat the infection.

Red Blood Cells (Erythrocytes)

Red blood cells (RBCs) are non-nucleated, biconcave discs. The red cell membrane is flexible and exhibits a remarkable deformability; the RBC being able to change its shape. The biconcave of the RBC provides a high surface area to volume ratio, allows for maximum surface area (which facilitates gas transport) and greatest deformability.

The average normal RBC count in adult male is 5,200,000 ± 300,000 per microliter of blood, and in adult female is 4,700,000 ± 300,000 per microliter of blood. At birth; the average RBC count is about 5,700,000 per microliter of blood. The number of RBCs varies with age, sex, and altitude. Each RBC has a mean diameter of about 7.8 micrometers and a thickness of 2.5 micrometers at the thickest point and 1 micrometer or less in the center. The surface area of the RBC is about 140 square micrometer. The main constituent of the RBC is hemoglobin.

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Erythropoiesis: It is the process of erythrocyte formation or production. Erythropoiesis occurs at different anatomical sites during the course of development from embryonic to adult life.

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Stages of Erythropoiesis (Stages of differentiation of RBCs): The CFU-E stem cells, under appropriate stimulation, differentiate into large numbers of proerythroblasts. Once the proerythroblast been formed, it divides several more time, eventually forming many mature RBCs as follows:

Proerythroblast ➔ early normoblast ➔ intermediate normoblast ➔ late normoblast ➔ reticulocyte ➔ erythrocyte.

Maturation proceeds with hemoglobin formation in the cytoplasm. After the cytoplasm of late normoblast is filled with hemoglobin and the nucleus is extruded from the cell and the endoplasmic reticulum is reabsorbed, at this stage the cell is called reticulocyte. During the reticulocyte stage, the cell passes to the blood and after 1-2 days in blood it becomes mature erythrocyte. The concentration of reticulocytes among all the red cells of the blood is normally 0.5-1.5% in adults. Reticulocyte count is used as a clinical measurement of erythropoietic activity. The basic substances needed for normal RBC and hemoglobin production are: amino acids (proteins), iron, vitamin B_{12}, folic acid, and vitamin B_6.

Regulation of erythropoiesis: The main factor stimulating RBC production is hypoxia (O_2 deficiency at the tissue level), any condition that causes the quantity of O_2 transported to the tissues to decrease (decreased tissue oxygenation) increases the rate of RBC production, examples on factors, which decrease tissue oxygenation, are:

[1] At very high altitudes O_2 quantity in air is greatly decreased and insufficient O_2 is transported to the tissue.

[2] Diseases of the heart and lungs.

[3] Anaemia.

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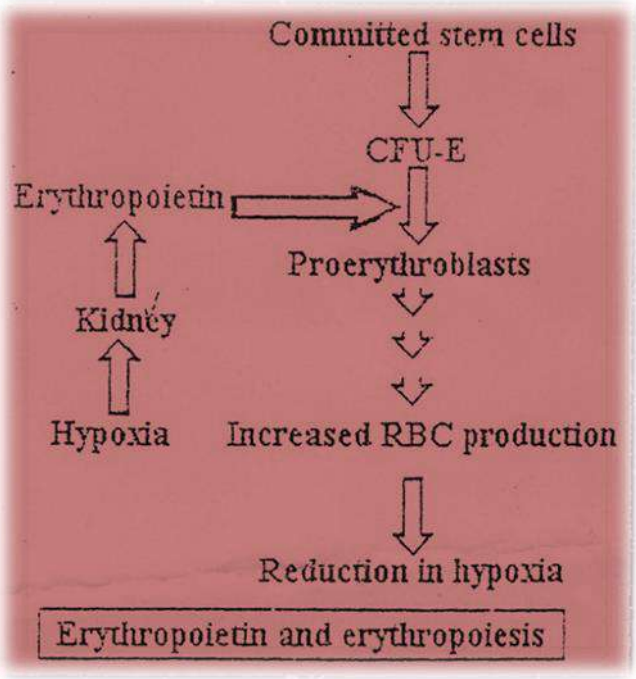

On the other hand when the rate of O_2 transport to the tissues rises above normal, the rate of RBC production is depressed.

Hypoxia does not act directly on bone marrow, but stimulates the secretion of the important regulating hormone (erythropoietin) from the kidney and the erythropoietin stimulates RBC production from the bone marrow until tissue hypoxia is relieved. Erythropoietin stimulates formation of proerythroblasts from erythropoietin-sensitive committed stem cells in bone marrow, and once these proerythroblasts are formed, the erythropoietin causes these cells also to pass more rapidly through the different erythroblast stages than normally, further speeding up the production of new cells. the rapid production of cells continues as long as the person remains in the low oxygen state or until enough red blood cell are produced to carry adequate amount of O_2 to the tissues despite the low oxygen; at this time, the rate of erythropoietin production decreases to a level that will maintain the required number of red cells but not an excess.

In the normal person, about 90% of all erythropoietin is formed in the kidneys, and the remainder is formed in other tissues, mainly the liver. It is not known exactly where in the kidneys the erythropoietin is formed. When both kidneys are removed from person or when the kidneys are destroyed by renal disease, the person invariably becomes very anemic, because the 10% of the normal erythropoietin formed in other

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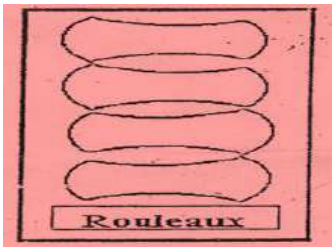
tissues (mainly in the liver) is sufficient to cause only one third to one half as much RBC formation as needed by the body.

Other factors stimulating erythropoietin production include cobalt salts, epinephrine and norepinephrine, and several of the prostaglandins. Androgens (male sex hormones) can also stimulate erythropoietin production, and it is for this reason that RBC count in male is more than in female. ILs, and GM-CSF also play part in erythropoiesis by their role in the development of the relevant erythroid stem cells.

Hematocrit (Hct) or Packed Cell Volume (PCV) : Packed cell volume (PCV) refers to the percentage of the cellular elements (RBCs, WBCs and platelets) in the whole blood. Since the volume of WBCs and platelets is very less, so for all practical purposes the PCV is considered equivalent to the volume of packed red cells or the so-called haematocrit value .When blood, mixed with anticoagulant, is centrifuged for a certain time and at a certain speed, the blood in the tube will separate into 3 layers: bottom layer mainly composed of RBCs, middle very thin layer of white blood cells and platelets, and top layer mainly of plasma.. The PCV is affected by the number of RBCs, the shape of RBCs, and the plasma volume. Clinically, it is used to detect anemia, polycythemia, hemoconcentration, and hemodilution.

Normal ranges in adults: In male 40-54% and in female 36-47% PCV is increased in polycythemia and dehydration and it is decreased in anemia.

Erythrocyte Sedimentation Rate (ESR): When blood, mixed with anticoagulant, is allowed to stand in a special, narrow vertical tube, for a period of time, RBCs settle down (sediment) leaving clear plasma above. The rate at which RBCs sediment is the ESR. It is measured by the distance, which the RBCs have settled down, in millimeters, in a given period of time, which is usually one hour.



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RBCs sediment by rouleaux formation, which means that RBCs aggregate and become arranged one on the top of the other, and by this way, the surface area is reduced, and the weight is increased, leading to increased rapidity of sedimentation. So the factors which increase rouleaux formation increase the ESR, and those factors which decrease rouleaux formation decrease the ESR. Factors affecting the ESR are:

1. The composition of plasma proteins: Increased concentrations of a fibrinogen or globulin increase rouleaux formation and increase ESR. On the other hand, increased concentration of albumin in plasma reduces rouleaux formation and decrease ESR. Also increased concentration of "acute phase proteins" in the plasma increase rouleaux formation and increase ESR. Acute phase proteins are number of plasma proteins, the synthesis of which is increased by different factors released during inflammation or tissue injury, leading to high plasma concentrations of these proteins.

2. Concentration of RBCs: Increased RBC concentration or high Hct increases the viscosity of blood thus increasing the resistance to sedimentation, which leads to decrease in ESR. A marked reduction in RBC concentration or low Hct decreases the viscosity of blood, which accelerates sedimentation, and causes increase in ESR.

3. Shape of RBCs: RBCs with abnormal or irregular shapes such as sickle cells or spherocytes hinder rouleaux formation or interfere with rouleaux formation (they are unable to form rouleaux) leading to decreased ESR.

4. Sex. ESR is greater in the females (5–9 mm) than the males (3–7 mm).

5. Menstruation. ESR is slightly raised during menstruation in the females.

6. Pregnancy. ESR is raised in pregnancy from third month to parturition, and returns to normal after 3–4 weeks of delivery.

ESR is a non-specific test, it doesn't give an indication of the type of the diseases, so it cannot be used for diagnosis, but it is used for prognosis and follow up of patients.

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Lecture 2

HEMOGLOBIN

Hemoglobin (Hb) is the iron containing coloring pigment of RBC. It forms 95% of dry weight of RBC and 30 to 34% of wet weight. The molecular weight of Hb is 68,000. The function of hemoglobin is to carry O2 and CO2 . If Hb is found in plasma as free hemoglobin it leads to the following problems.

1- Increases the viscosity of blood leading to an increase in blood pressure .

2- Increase in the osmotic pressure of blood .

3- Free Hb will be filtered and excreted by the kidneys leading to hemoglobinuria, renal failure and anemia.

It is a globular molecule made up of four subunits, each subunit contains a heme moiety conjugated to a polypeptide. Heme is an iron-containing porphyrin derivative .The polypeptides are referred to collectively as the globin portion of the hemoglobin molecule.

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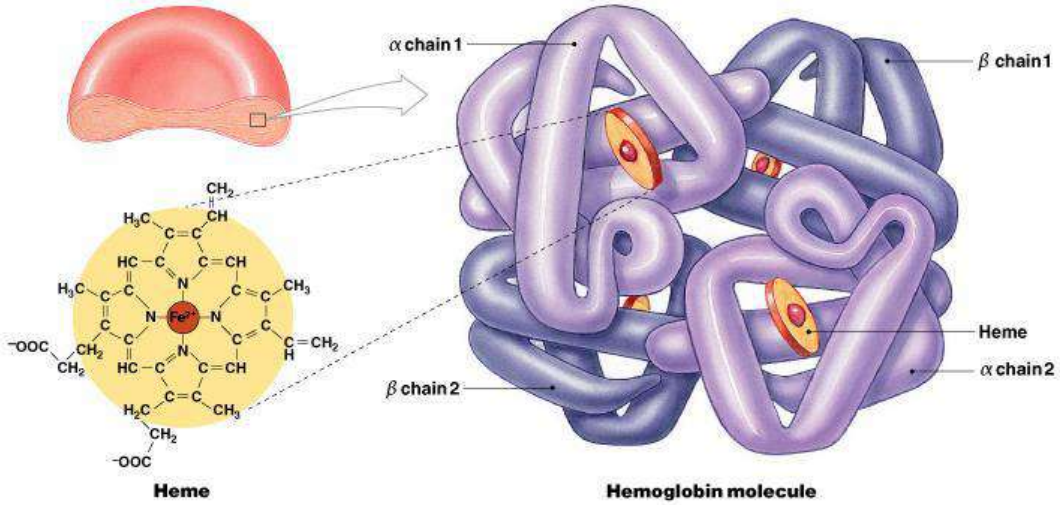

The affinity of Hb for 02 is affected by pH, temperature, and concentration in the RBCs of 2,3- diphosphoglycerate (2,3 DPG), a by-product of glucose metabolism. A fall in pH, a rise in temperature, or an increase in the concentration of 2,3 - DPG decrease affinity of Hb for O2.

types of hemoglobin in Normal Adult

(**HbA**): It is the normal adult Hb. Its molecule consists of four polypeptide chains; ***(alpha (α 2) , beta (β 2))***. the two polypeptides a chains, contains 141 amino acid residues, and β chains, each of which contains 146 amino acid residues. Hb A is the predominant type of Hb in adults (95-97% of total Hb).

HbA2 2.5% of the hemoglobin is ***(α 2, delta (δ 2))*** in which β chains are replaced by δ chains which also contain 146 amino acid residues, but **10** amino acids differ from those in the β chains

Hb1c has a glucose attached to the terminal valine in each chain and it increases in the blood of patients with poorly controlled diabetes mellitus

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Fetal hemoglobin (hemoglobin F) (α 2 , gamma (γ 2)):

Its structure is similar to that of hemoglobin A except that the β chains are replaced by γ chains; The γ chains also contain 146 amino acid residues but have 37 that differ from those in the β chain.

Affinity for oxygen in case of HbF is more than that of HbA, i.e. it can take more oxygen than HbA at low oxygen pressure. It is owing to poor binding of 2,3-DPG by the γ polypeptide chain. Because of this, movement of oxygen from maternal to fetal circulation is facilitated. At PO2 20 mm Hg, HbF is 70% saturated while HbA is only 30%–35% saturated. Resistance to action of alkalies is more in HbF than HbA. This property is used in a photoelectric calorimetric method to estimate HbF in the presence of HbA.

In young embryos there are, in addition, Gower 1 hemoglobin, and Gower 2 hemoglobin.

Reactions of Hemoglobin

1.**Hemoglobin binds O2 to form oxyhemoglobin**, O2 attaching to the Fe2+ in the heme. The affinity of Hb for O2 is affected by pH, temperature, and the concentration in the red cells of 2,3-diphosphoglycerate (2,3-DPG). 2,3-DPG and H+ compete with O2 for binding to deoxygenated hemoglobin, decreasing the affinity of Hb for O2 .

2.**When blood is exposed to oxidizing agents the ferrous iron (Fe2+) is converted to ferric iron (Fe3+), forming methemoglobin**. Methemoglobin is dark-colored, and when it is

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present in large quantities in the circulation, it causes a dusky discoloration of the skin resembling cyanosis.
Some oxidation of hemoglobin to methemoglobin occurs normally, but an enzyme system in the red cells, the dihydronicotinamide adenine dinucleotide (NADH)-methemoglobin reductase system, converts methemoglobin back to hemoglobin. Congenital absence of this system is one cause of genetic methemoglobinemia.
3.**Carbon monoxide reacts with hemoglobin to form carbon monoxyhemoglobin (carboxyhemoglobin).** The affinity of hemoglobin for O2 is much lower than its affinity for carbon monoxide, which consequently displaces O2 on hemoglobin, reducing the oxygen-carrying capacity of blood .

Synthesis of Hemoglobin

The average normal hemoglobin content of blood is 13.5-17.5 g/dL. In male and in female 11.5-15.5 g/dL. At birth, the Hb concentration is high (an average of about 21 g/dl.).

The heme portion of the hemoglobin molecule is synthesized from glycine and succinyl-CoA., and most of this synthesis occurs in the mitochondria. Polypeptides of globin are produced on ribosomes.

Hemoglobinopathies

Thalassaemia (Mediterranean anaemia) is a haemoglobinopathy characterized by following features: Cause. Thalassaemia results due to defect in the synthesis of polypeptide chain α and β of HbA. Types. Depending upon whether α or β chains are not synthesized, α thalassaemia or β thalassaemia may occur,

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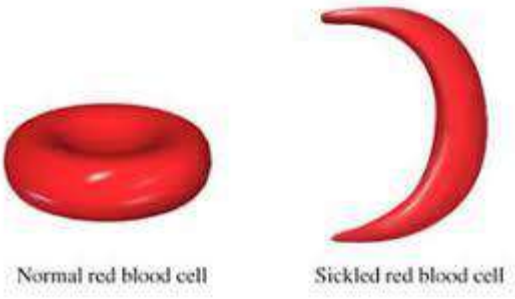
respectively. β thalassaemia is more common and is further of two types: thalassaemia major and thalassaemia minor.

βthalassaemia major	**βthalassaemia minor**
Thalassaemia major is also called as Mediterranean anaemia or Cooley's anaemia and is less common.	Thalassaemia minor is more common.
It is inherited as a homozygous transmission (i.e. abnormal genes are inherited from both the parents) therefore: • There is complete absence of β chain synthesis. • Absence of β chain synthesis results in moderate to severe anaemia • HbF level is markedly increased.	It is inherited as a heterozygous transmission (i.e. abnormal gene is inherited from one parent), therefore: • The synthesis of β chain is not completely absent (partial). • Anaemia is of mild type. • HbF level is either normal or slightly elevated.
The individual suffering from thalassaemia major has short life span, i.e. (dies young 17–18 years).	The individuals suffering from thalassaemia minor comparatively survive longer (up to adult) and transmit abnormal gene to their offsprings

In another type of inherited disorders of Hb, is ***hemoglobin S,*** abnormal types of polypeptides with different amino acid sequences Abnormalities of the Hb chains can alter the physical

characteristics of Hb molecule. in which abnormal Hb ***(sickle-cell Hb or Hb S)*** is produced. .HbS is formed due to substitution of valine for glutamic acid at position 6 in the β chain of HbA. When HbS is reduced (e.g. in low-O2 tension or when pH at tissue level is low), it becomes much less soluble and precipitates into crystals within the RBCs. The crystals elongate producing changes in shape of the cells from biconcave to sickle-shaped cells (sickling). The cells containing HbS are less flexible as compared to the RBCs containing HbA, hence leading to a blockade of microcirculation. Sickle-shaped cells greatly increase blood viscosity, thereby decreasing the blood flow to tissues. Sickle-shaped cells are more fragile and are very liable to undergo haemolysis producing the so-called sickle cell anaemia. The individual with sickle cell trait has resistance to one type of malaria



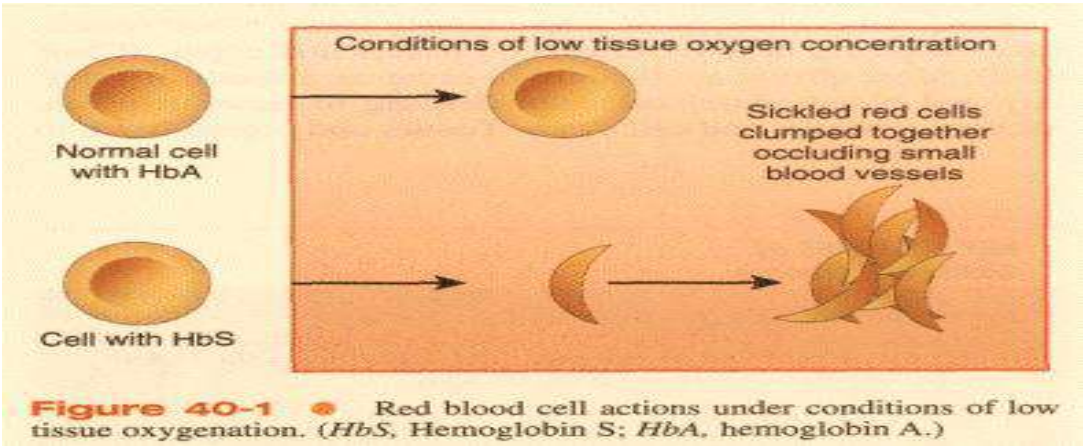


Figure 40-1 Red blood cell actions under conditions of low tissue oxygenation. (*HbS*, Hemoglobin S; *HbA*, hemoglobin A.)

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Destruction of Red Blood Cells and Catabolism of Hemoglobin: RBCs circulate in the blood for an average of 120 days, after that old RBCs are destroyed by macrophages in the mononuclear phagocyte system, in many parts of the body especially in the liver, spleen, and bone marrow. Inside the mononuclear phagocyte system, the Hb is broken into (globin and heme). Globin is catabolized in the liver into amino acids and enters the circulating amino acid pool. The heme is converted into biliverdin. The iron from the heme is converted into transport proteins (transferrin) or to storage proteins (ferritin and hemosiderin)

Biliverdin (green) is converted into bilirubin (yellow), which is enter the liver where it is conjugated with albumin and becomes water-soluble and is secreted by the liver into the bile, which empties into the intestine. In the intestine, and by the action of bacteria, it is converted to urobilinogen (stercobilinogen). Then it is oxidized to stercobilin which is excreted in feces and colors the feces. The normal level of plasma bilirubin is less than 2 mg/dl

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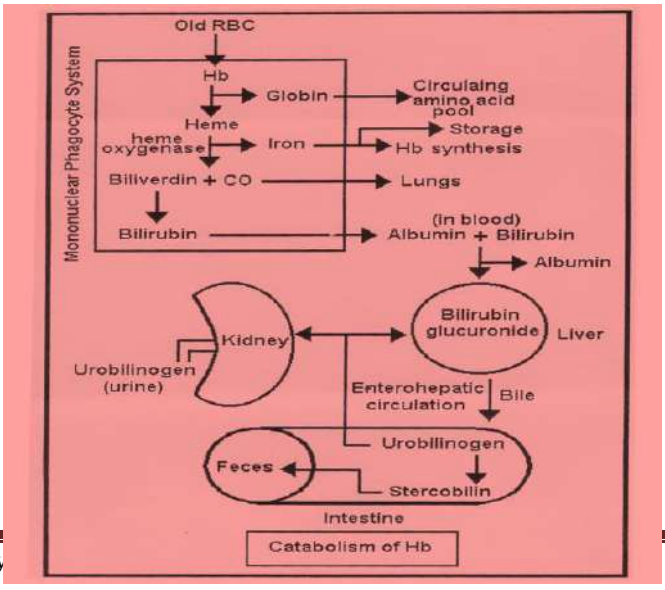

Jaundice: It is the yellowish discoloration of skin and mucous membranes resulting from an increased bilirubin concentration in the body fluids. It is detectable when plasma bilirubin level rises above 2mg/dl. Jaundice can be classified to different types **hemolytic jaundice** ***(as a result of excessive destruction of RBCs)*** **hepatic jaundice** ***(as a result of damage to the liver)***, and **obstructive jaundice** ***(as in cases of obstruction of bile ducts)***.

Disorders of Iron uptake

Iron deficiency causes anemia. Conversely, iron overload causes hemosiderin to accumulate in the tissues, producing hemosiderosis. Large amounts of hemosiderin can damage tissues, causing hemochromatosis. This syndrome is characterized by pigmentation of the skin, pancreatic damage with diabetes ("bronze diabetes"), cirrhosis of the liver, a high incidence of hepatic carcinoma, and gonadal atrophy.

If the abnormality is diagnosed before excessive amounts of iron accumulate in the tissues, life expectancy can be prolonged by repeated withdrawal of blood.

Anemia: It can be defined as reduction in blood Hb level and/or in RBC count below the normal range for the patient's age and sex. Anemia can be classified according to **its cause into:**

1.Inadequate production of normal RBCs by the bone marrow. Examples :

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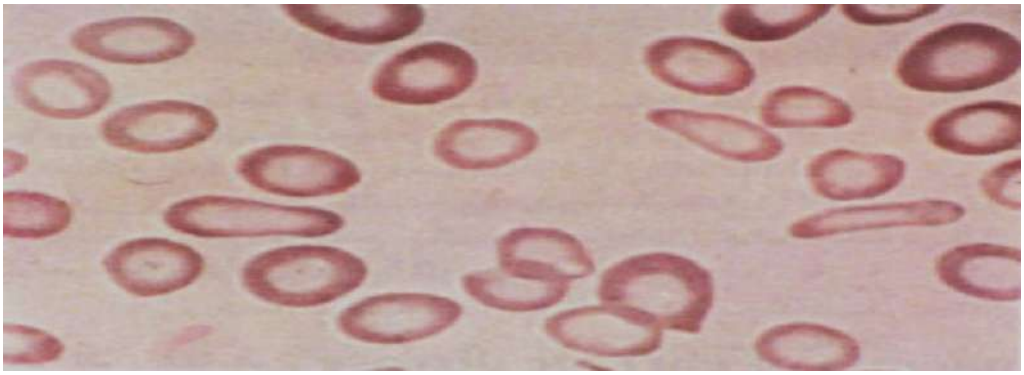
A- Due to deficiency of essential factors (iron, vitamin B 12 and folic acid).

B- Aplastic anemia (bone marrow aplasia).

Iron is imported for Hb formation in RBC. Daily loss of iron in men is about 1 mg, mainly is feces .In women due to menstrual blood loss, the average iron loss reaches to 2 mg/day. The average quantity of iron derived from diet must at least equal that which is lost. In growing children iron requirements are increased. Women also need more iron in diet due to menstruation and pregnancy. If iron is deficient anemia develops in which RBCs are small and contain too little Hb. Iron deficiency anemia is more common in females than in males during the reproductive years.



Iron deficiency anemia

Vitamin B12 is required for DNA synthesis, so it is important for maturation of RBCs. If B 12 is deficient, erythropoiesis is delayed. the erythroblastic cells of bone marrow cannot proliferate rapidly and become larger than normal (called megaloblasts) and produce mainly lager than normal erythrocytes (called macrocytes) which are abnormal in shape and break easily leading to decreased

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number of RBCs in blood and anemia develops which is called megaloblastic anemia or maturation failure anemia. B 12 deficiency can occur due to lack of B 12 **in diet** or more commonly due to lack of **a factor** (**intrinsic factor**) which is secreted by gastric mucosa and is bound to B 12 so that to protect it from digestive enzymes and also assists in absorption of vitamin B 12 in the ileum. In a condition called **pernicious anemia** , there is failure of secretion of intrinsic factor by stomach due to atrophy of gastric mucosa, so **megaloblastic anemia** develops .

Folic acid also essential for DNA synthesis and is concerned with the maturation of RBCs. So its deficiency again leads to slow production of erythroblasts in bone marrow, as a result these grow too large with odd shapes (called megaloblasts) and RBCs formed are mostly large and abnormal in shape and fragile and rapture easily leading to megaloblastic anemia .

Aplastic anemia: Bone marrow may be destroyed and become unable to produce blood cells, such as following excessive x-ray exposure or the use of certain drugs which cause bone marrow aplasia (lack of functioning bone marrow) .

2. Excessive destruction of RBs (hemolysis): Hemolytic anemia results from abnormalities of red cell membrane or Hb, or other causes in which there is excessive destruction of RBCs. Examples are: hereditary spherocytosis (a common membrane defect, in which the RBCs are small and spherical in shape, and fragile), sickle cell anemia, and erythroblastosis fetalis.

3. Blood loss (hemorrhage); **acute** or **chronic**. Acute hemorrhage is loss of large volume of blood over a short period. After rapid hemorrhage the body replaces plasma within 1-3 days, but this leaves a low concentration of RBCs which will return to normal within 3-4 weeks if no more hemorrhage occurs. Chronic hemorrhage is loss of small volume of blood over long period. Therefor , this person needs continuous formation of new RBCs, so he needs more iron than normal, with time if this person doesn't receive extra iron, store of iron is going to be depleted, then the person will suffer from **iron deficiency anemia** .

Polycythemia : It is an increased concentration of erythrocytes in the circulating blood that is above normal for sex and age. Polycythemia could be classified to:

A. Secondary polycythemia that is related to increased erythropoietin production which result for example due to tissue hypoxia in those living at high altitudes.

B. Primary polycythemia(polycythemia vera) is caused by a gene aberration that occur in the hemocytoblastic cell line that produces the blood cell. The blast cells no longer stop producing red cells when too many cells are already present. This causes excess production of red cells without erythropoietin stimulus, and usually there is excess production of white blood cells and platelets as well as. The total blood volume also increases in polycythemia vera.

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Lecture 3

Blood Groups

The ABO blood group consists of blood types A, B, AB and O depending on the presence or absence of two antigens (type A, type B) occur on the surface of the RBC. It is also called (agglutinogens) because they often cause blood cell (agglutination) that cause blood transfusion reactions. Because of the way these agglutinogens are inherited, people may have neither of them on their cells, they may have one, or they may have both at the same time.

Agglutinins react against any AB agglutingen expect those present on a person's own R.B.C the agglutinin that reacts against antigen A is called a agglutinin, or anti -A, it is present in plasma of people with type O or type B blood - that is, anyone who does not possess agglutinogen A. the agglutinin that reacts against antigen B is β agglutinin, or anti-B, and is present in type O and A individuals- those who do not possess agglutinogen B. Each agglutinin molecule has 10 binding sites where it can attach to an A or B agglutinogen. An agglutinin can therefore attach to several RBCs at once bind them together.

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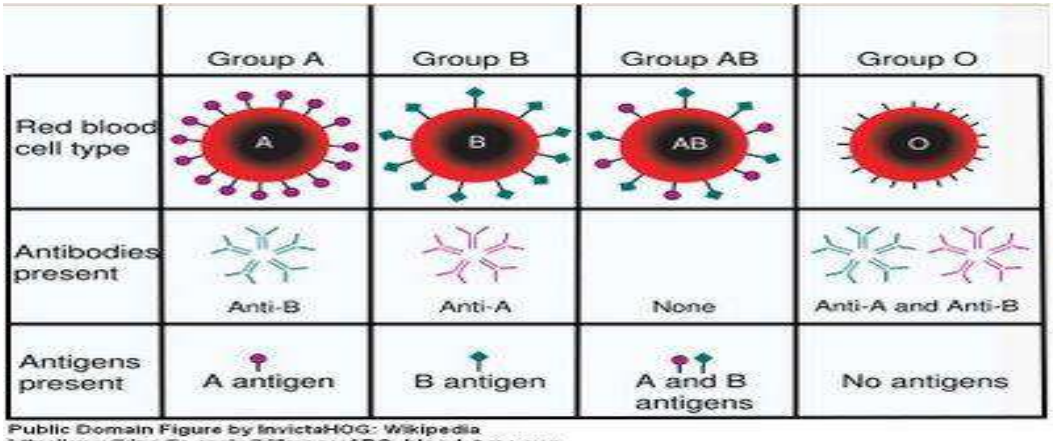

Agglutinins

The agglutinins are gamma globulins, as other antibodies, and they are produced by the same cells that produce antibodies to any other antigens. Most of them are IgM and IgG immunoglobin molecules. But why are these agglutinins produced in people who do not have the respective agglutinogen in their RBCs? However, small amount of group A and B antigens enter the body in the food, in bacteria, and in other ways and these substances initiate the development of the anti A or anti B agglutinins.

Agglutination

Is the process in which RBCs adhere to each other in masses that are bound by these agglutinins.

Blood typing: To determine the ABO blood type of an individual, blood typing is done by mixing an individual's RBCs with each of

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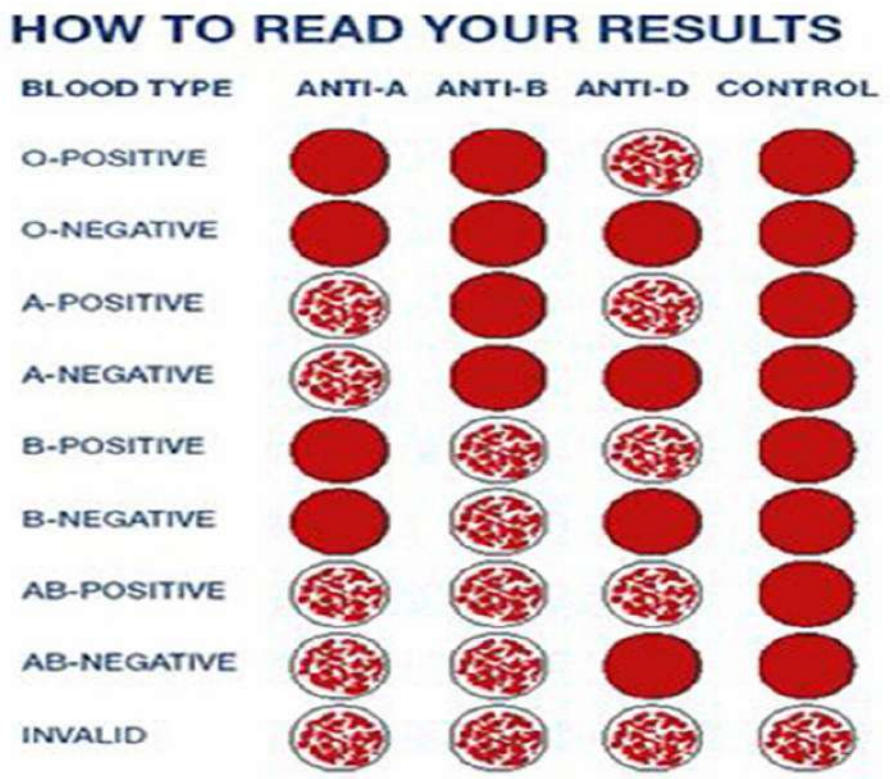
anti-A serum (containing anti-A agglutinins) and anti-B serum I(containing anti-B agglutinins), which are commercially available, on a slide and seeing whether agglutination occurs .

RBC type	Sera	
	Anti-A	Anti-B
O	-	-
A	+	-
B	-	+
AB	+	+

Blood typing showing agglutination of cells of the different blood types with anti-A and anti-B agglutinins
+ and - indicate presence or absence of agglutination, respectively



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The Rh System: The Rh factor named for the rhesus monkey because it was first studied using the blood of this animal, is a system composed of many Ags. Unlike the ABO Ags, the system has not been detected in tissues other than RBCs. There are 6 common types of Rh Ags, these are **C, D, E, c, d, e**. The most common and the most antigenic is the D Ag. Anyone who has agglutinogen D is said to be Rh positive, whereas a person who does not have agglutinogen D is said to be Rh negative, and forms the anti-D agglutinin when injected with D-positive cells. About 85% of all white people are Rh (+) and 15% are Rh (-). In routine blood typing. the Rh typing serum used is anti-D serum .

Unlike the Abs of the ABO system which develop spontaneously, anti-D Abs do not develop without exposure of a D-negative individual to D-positive red cells, This exposure **occurs by:**

1- transfusion of Rh positive blood to Rh negative recipient.
2- Entrance of Rh positive fetal blood into the material circulation of an Rh negative mother .

Transfusion of Rh positive blood to Rh negative recipient:

If Rh positive blood is transfused into Rh negative person for the first time, the anti-Rh agglutinins will develop slowly and the maximum concentration of agglutinins occur about 2-4 months later, so there will be no immediate reaction. But in some persons, the immune response occurs to a much greater extent, and anti-Rh Abs develop in sufficient quantities during the next 2-4 weeks

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and cause agglutination of the transfused Rh positive cells that are still in the blood, these cells are then hemolysis by phagocytosis. So delayed transfusion reaction occurs which is usually mild. But on subsequent transfusion of Rh positive blood into the same person who is sensitized or immunized against the Rh factor, the transfusion reaction is greatly enhanced and can be severe.

Erythroblastosis fetalis: when an Rh negative mother carries an Rh positive fetus (the Rh positive Ag has been inherited from the Rh positive father), and when small amounts of fetal blood enter the maternal circulation at the time of delivery, sensitization of the mother can occur and anti-Rh Abs are formed in the mother after delivery. During the next pregnancy the mother's agglutinins cross the placenta into the fetus to cause RBCs agglutination.

Effect of the mother's antibodies on the fetus

After anti-Rh antibodies have formed in the mother, the diffuse slowly through the placental membrane into the fetus's blood. There they cause agglutination of fetus's blood. The agglutinated RBCs subsequently hemolysis, releasing Hb into blood. The macrophages then convert the Hb into bilirubin, which causes the skin to yellow Jaundice. The antibodies can also attack and damage other cells of the body. The Jaundiced erythroblastotic neonate is usually anemic at birth, and anti Rh agglutinins from mother

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usually circulate in the infant's blood for 1-2 months after birth, destroying more and more RBCs.

The usual treatment is to(1) replace the neonate's blood with Rh^{-ve} blood. About 400 ml of Rh^{-ve} blood is infused over a period of 1.5 or more hours while the neonates own Rh^{+ve} blood is being removed. The Rh^{-ve} cells are replaced with the baby own Rh^{+ve} cells. (2) given Rh immune globin (RhIG) also known as Rhogam, during pregnancy and after delivery to prevent sensitization to the D antigen. It works by binding any fetal red cells with the D antigen before the mother is able to produce an immune response and form anti D IgG.

Transfusion Reactions: In some conditions a patient may need blood transfusion. Transfusion reactions occur when blood is transfused into a recipient with an incompatible blood type i.e. the recipient has agglutinins against **red cells of the donor blood**, so the donor's RBCs are agglutinated. It is very rare that the donor's agglutinins cause agglutination of the recipient's cell, because the plasma of the donor becomes diluted by all the plasma of the recipient, decreasing the titer of the agglutinins to a level too low to cause agglutination. On the other hand, the infused blood (donor blood) does not dilute the agglutinins in the recipient's plasma to a major extent. Therefore the recipient's agglutinins can still agglutinate the donors

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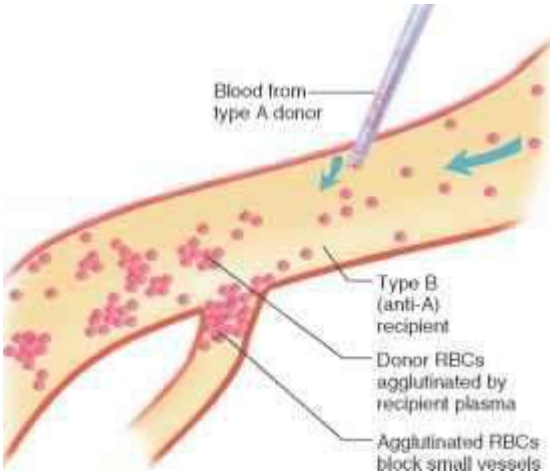

As explained earlier, all transfusion reactions eventually cause either immediate hemolysis resulting from activation of complement system, or later hemolysis resulting from phagocytosis of agglutinated cells. As a result of hemolysis, Hb is released from RBCs into the plasma. The severity of the resulting transfusion reaction may vary from an asymptomatic minor rise in the plasma bilirubin, to severe jaundice and renal tubular damage (caused in some way by the products liberated from hemolysis cells), to renal failure and death .

Before giving a blood transfusion, it is necessary to determine the blood type of the recipient and the blood type of the donor blood, so that the bloods can be appropriately matched. Then cross matching test is done. In cross-matching test the donor's RBCs are mixed with recipient's plasma on a slide and checked for agglutination. If agglutination occurs it means that the donor blood is incompatible with the recipient blood and blood transfusion cannot occur.

Persons with AB group have been called universal recipients because they have no circulating agglutinins and can be taken

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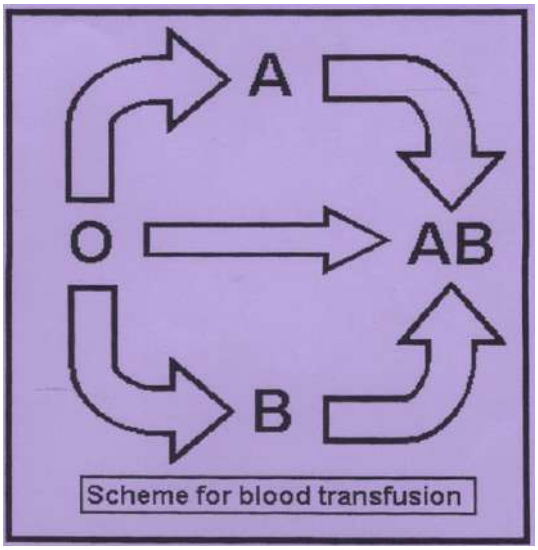
blood of any type without developing transfusion reaction due to ABO incompatibility. Persons with 0 group have been called universal donors, because they lack A and B Ags, and type 0

blood can be given to anyone without producing a transfusion reaction due to ABO incompatibility. However, this does not mean that blood should ever be transfused without being cross matched, since the possibility of reactions of sensitization due to incompatibilities in systems other than ABO system always exists .



A procedure that has recently become common, is to withdraw the patient's own blood in advance of elective surgery and then infuse this blood back (autologous transfusion) if a transfusion is needed during the surgery. With iron treatment, 1000-1500 ml can be withdrawn over a 3-week period. The advantage of this procedure is elimination of the possibility of transfusion reaction, and of transmission of diseases such as AIDS .

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Lecture 4

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White blood Cells (Leukocytes)

Acting together, the white blood cells (WBC) provide the body with powerful defenses against tumors, viral, fungal , bacterial, and parasitic infections. WB are nucleated cells they are classified by several ways. WBC_s are classified according to the presence or absence of specific- staining granules in the cytoplasm into the following.

[A] *Granular leukocytes:*

In which the cytoplasm contains granules, these are classified into polymorphonuclear leukocytes which include:

1- ***Neutrophils:*** Multilobed nucleus, 2-5 lobes depending on the age of the cell. The percentage is 50-70 %

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2- ***Eosinophil***: Multilobed nucleus "usually bilobed" . The percentage is 1-4 %

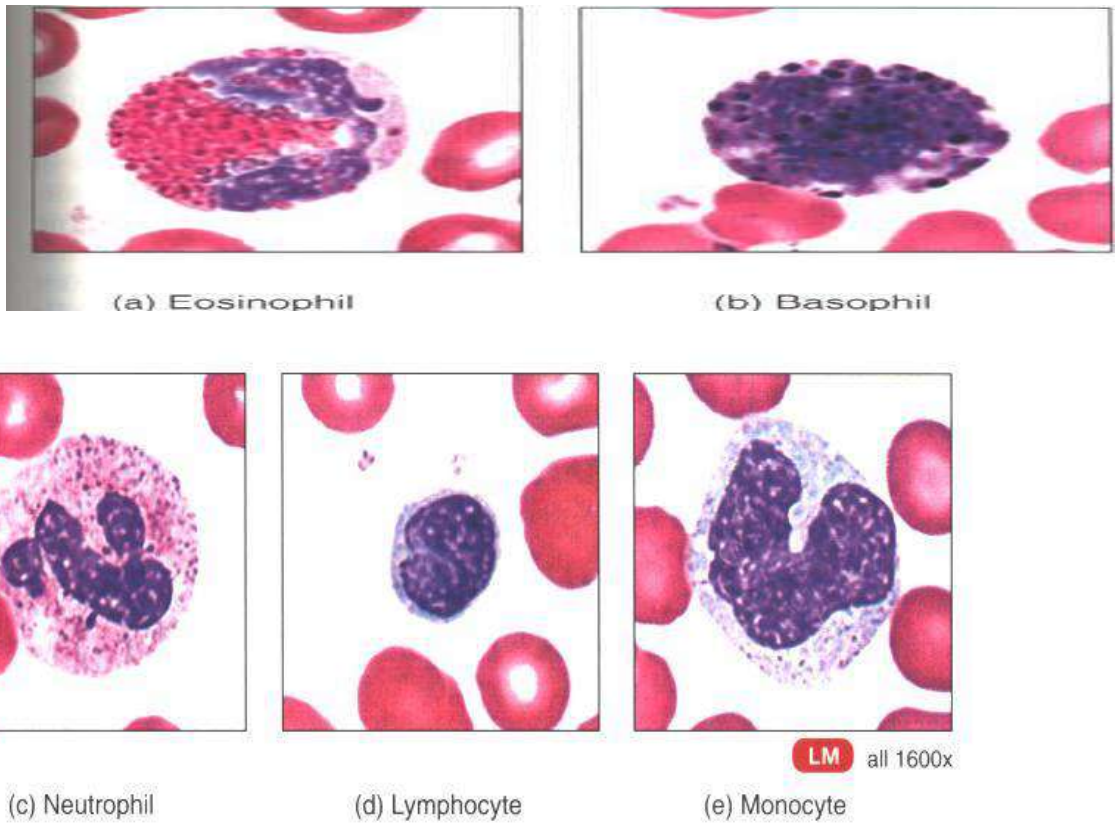
3- ***Basophils***: In this type the nucleus takes the (S) shape. The percentage is 0-1.4 %

[B] *Non granular leukocytes:*

In which there are no granules in the cytoplasm, these are classified into:

1- ***Monocytes***: the nucleus is kidney shaped and they are largest cell in the body. The percentage is 2-8 %

2- ***Lymphocytes:*** they are large lymphocytes and small lymphocytes which depend on the age, the percentage is 20-40 %



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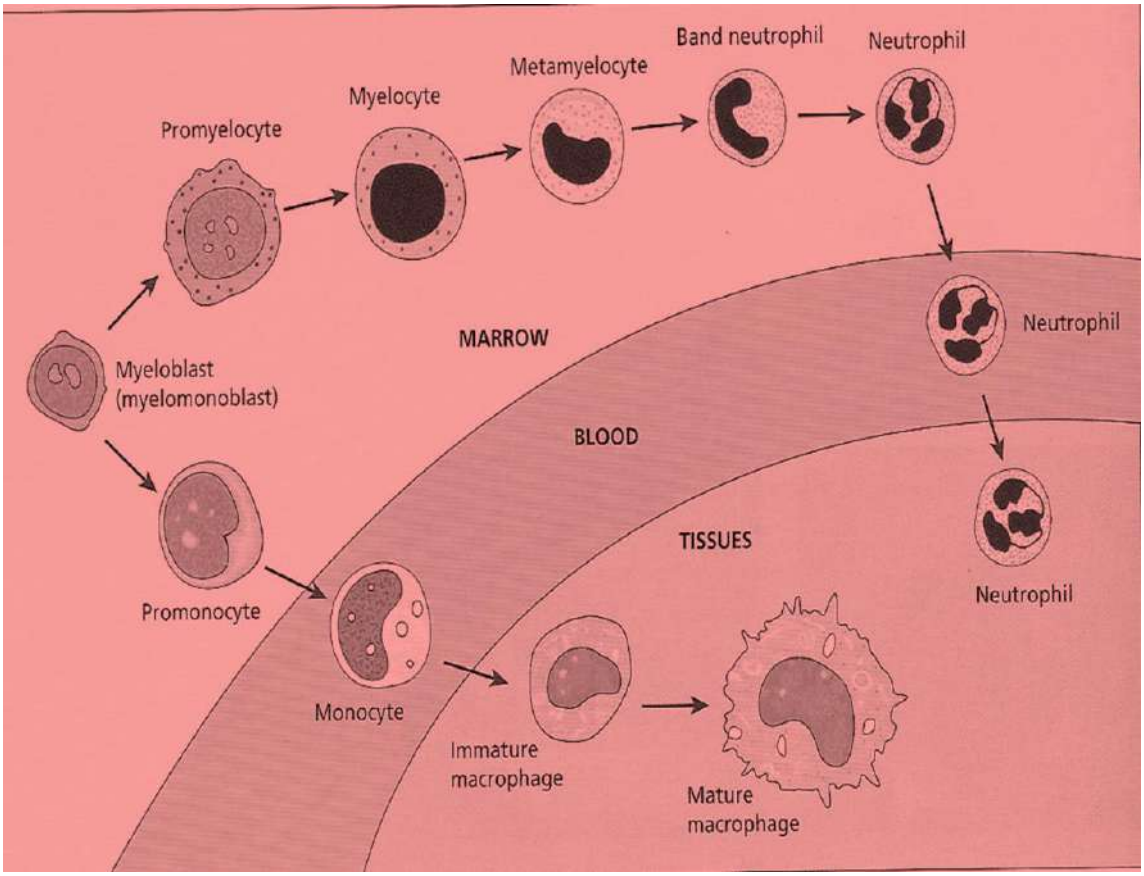
Types of WBC's

Formation of WBCs (leukopoiesis): After birth, the ***granulocytes*** and ***monocytes*** are formed only in the bone marrow. The ***lymphocytes*** are formed in the lymphoid tissue of the bone marrow, thymus, spleen, lymph nodes and others. The WBCs formed in the bone marrow especially the granulocytes, are stored within the marrow until they are needed in the circulatory system. Then when the need arises, different factors cause them to be released. The lymphocytes are mostly stored in the different spaces of lymphoid tissue .



Leukocytosis and leukopenia :

The WBC count is from 4000-11000 cells per cubic millimeter

A- If total WBC count is lower than 4000/microliter of blood, the condition is known as ***leukopenia*** which occurs for example as a result of :

1- Viral infection
2- Typhoid fever
3- Exposure to ionizing radiation or certain drugs which cause bone marrow aplasia .

B- If total WBC count is higher than 11000/microliter of blood, the condition is known as ***leukocytosis*** which could be due to :

1- Pathological causes (for example bacterial infection)
2- Physiological causes (for example in exercise, emotional stress, anxiety, and pregnancy).

Normally at rest, when the blood flow is slow through the tissues, large number of WBCs especially neutrophils adhere or stick to the walls of the capillaries (this process is known as ***margination***) and are isolated from the usual circulation. Hard exercise or stimulation of the circulation by norepinephrine, with rapid blood flow through the capillaries can mobilize the leukocytes and their number increase in the blood leading to physiological leukocytosis .

Life span of WBC:

- Granulocytes: 4-8 hours in blood, 4-5 days in tissues.
- Monocytes: 10-20 hours in blood, months in tissue (tissue macrophages)
- Lymphocytes live for weeks or months.

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The life of granulocytes once released from the bone marrow is normally 4-8 hours circulating in the blood and another 4-5 days in the tissues. But when there is serious tissue infection, this total life span is often shortened to only few hours, because the granulocytes then proceed rapidly to the infected area, perform their functions and eventually are destroyed .

FUNCTIONS OF WBCs

Generally, WBCs play an important role in defense mechanism. These cells protect the body from invading organisms or foreign bodies either by destroying or inactivating them. However, in defense mechanism, each type of WBCs acts in a different way.

❑NEUTROPHILS

Along with monocytes, the neutrophils provide the first line of defense against the invading microorganisms. Neutrophils wander freely all over the body through the tissue.

Mechanism of Action of Neutrophils

Neutrophils are released in large number from the blood. At the same time, new neutrophils are also produced from the progenitor cells. All the neutrophils move by diapedesis towards the site of infection by means of chemotaxis. The chemotaxis occurs due to the attraction by some chemical substances called chemoattractants, which are released from the infected area. After reaching the area, the neutrophils surround the area and get adhered to the infected tissues. The chemoattractants

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increase the adhesive nature of neutrophils so that all the neutrophils become sticky and get attached firmly to the infected area. Each neutrophil can hold about 15 to 20 microorganisms at a time. Now, the neutrophils start destroying the invaders. First, these cells engulf the bacteria and then destroy them by means of phagocytosis (cellular ingestion of the foreign bodies).

Pus and Pus Cells

Pus is the whitish-yellow fluid formed in the infected tissue. During the battle against the bacteria, many WBCs are killed by the toxins released from the bacteria. The dead cells are collected in the center of infected area. The dead cells together with plasma leaked from the blood vessel, liquefied tissue cells and RBCs escaped from damaged blood vessel (capillaries) constitute the pus.

❑EOSINOPHILS

The eosinophils provide defense to the body by acting against the parasitic infections and allergic conditions like asthma. Eosinophils are responsible for detoxification, disintegration and removal of foreign proteins.

▪ Mechanism of Action of Eosinophils

The eosinophils attack the invading organisms by secreting some special type of cytotoxic substances. These substances

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become lethal and destroy the parasites. Some of these substances are:

1. Eosinophil peroxidase
2. Major basic protein (MBP)
3. Eosinophil cationic protein (ECP)
4. Eosinophil derived neurotoxin
5. Interleukin-4 and interleukin-5

❑BASOPHILS

The basophils play an important role in healing processes and acute hypersensitivity reactions (allergy).

Mechanism of Action of Basophils

The basophils execute the functions by releasing some important substances from their granules such as:

1. Heparin which is essential to prevent the intravascular blood clotting

2. Histamine, bradykinin and serotonin which produce the acute hypersensitivity reactions by causing vascular and tissue responses.

3. Proteases and myeloperoxidase that exaggerate the inflammatory responses

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4. Interleukin-4 which accelerates inflammatory responses and kill the invading organisms.

Mast Cell

Mast cell is a large tissue cell resembling the basophil. Usually these cells are found along with the blood vessels and do not enter the blood stream. These cells are predominantly seen in the areas such as skin, mucosa of the lungs and digestive tract, mouth, conjunctiva and nose.

Functions

The mast cells function along with basophils and produce hypersensitivity reactions like allergy and anaphylaxis. These cells act by secreting some substances like histamine, heparin, serotonin, hydrolytic enzymes, arachidonic acid derivatives such as leukotriene C (LTC) and prostaglandin.

❑MONOCYTES

Monocytes are the largest cells among the WBCs. Like neutrophils, monocytes also are motile and phagocytic in nature. These cells wander freely through all tissues of the body and provide the first line of defense along with neutrophils.

Monocytes are the precursors of the tissue macrophages. The matured monocytes stay in the blood only for few hours. Afterwards these cells enter the tissues from the blood and become tissue macrophages. Examples of tissue macrophages are

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Kupffer cells in liver, alveolar macrophages in lungs and macrophages in spleen.

The functions of macrophages

are discussed in Monocytes act by secreting certain substances like interleukin-1 (IL-1), colony stimulating factor (M-CSF) and platelet activating factor (PAF).

❑LYMPHOCYTES

The lymphocytes are responsible for development of immunity. Lymphocytes are classified into two categories namely T lymphocytes and B lymphocytes. B-lymphocytes Produce Antibodies, T-lymphocytes directly destroy virus invaded cells and cancer cells.

Neutrophils and monocytes reach the site of infection by the following mechanisms

- **Margination:** when the blood flow is slow through the tissues, large number of WBCs especially neutrophils adhere or stick to the walls or endothelial cells of the capillaries

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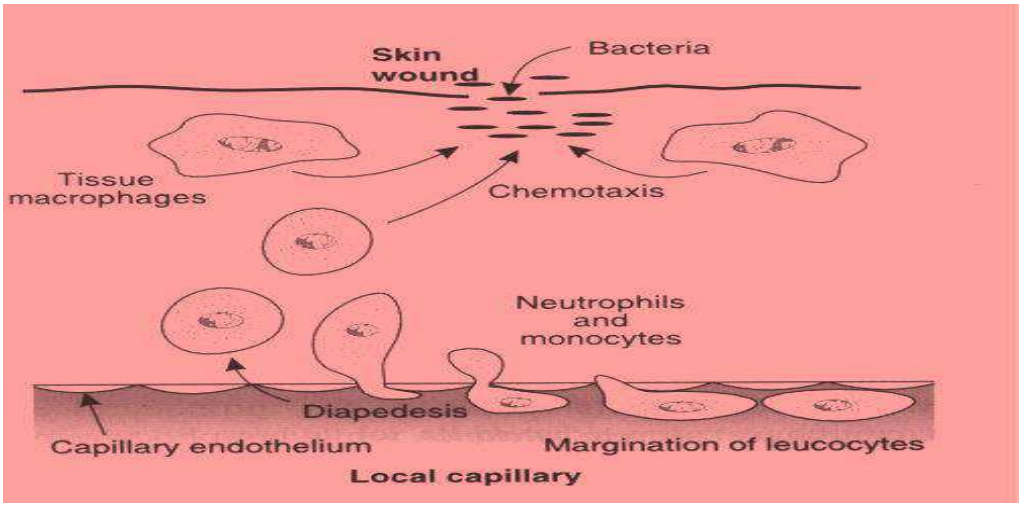
- **Diapedesis:** white blood cells can squeeze through the pores of the blood vessels into the tissue spaces. They move through the tissue spaces by *"amoeboid motion"*

- **Chemotaxis:** Gather in large numbers at spaces of tissue damage and infection by following the chemical track of molecules released by damaged cells or other leukocytes



A particle becomes more susceptible to phagocytosis

1-its surface is rough

2-when it has no protective protein coat which most of the natural structures in the body have and which repels the phagocytes. Damaged or dead tissues and most foreign particles frequently have no protective coats, which make them subject to phagocytosis.

3-Also plasma factors act on foreign particles or infectious agents like bacteria to make them especially susceptible to

phagocytosis (make them "tasty" to the phagocytes).This is called opsonization. In this case antibodies and complement proteins which serve as opsonins coat the bacteria. The coated bacteria then binds to receptors on the phagocyte cell membrane, thus initiating phagocytosis and destruction of the bacteria.

Inflammation: When tissue injury occurs (due to trauma, bacteria, chemicals, heat.. .etc) different substances which cause dramatic secondary changes in the tissues are released by the injured tissues. The complex of tissue changes is called inflammation. It is characterized by:

1. Vasodilatation of local blood vessels with consequent excess local blood flow .
2. Increased permeability of the capillaries
3. Often clotting of the fluid in the interstitial spaces because of excessive amounts of fibrinogen and other proteins leaking from the capillaries.
4. Migration of large numbers of granulocytes and monocytes into the tissue.
5. Swelling of the tissue cells.

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Lecture 5

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Immunity

Immunity is defined as the capacity of the body to resist the pathogenic agents. It is the ability of the body to resist the entry of different types of foreign bodies like bacteria, virus, toxic substances.

Immunity is of two types:

I. Innate immunity

II. Acquired immunity.

▪ INNATE IMMUNITY OR NONSPECIFIC IMMUNITY (Natural)

Innate immunity is the inborn capacity of the body to resists the pathogens. By chance, if the organisms enter the body, innate immunity eliminates them before the development of any disease. This type of immunity represents the first line of defense against any type of pathogens. Therefore, it is also called nonspecific immunity.

- Examples of innate immunity are:

1. Destruction of toxic substances or organisms entering digestive tract through food by enzymes in digestive juices.

2. Destruction of bacteria by salivary lysozyme.

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3. Destruction of bacteria by acidity in urine and vaginal fluid.

ACQUIRED IMMUNITY OR SPECIFIC IMMUNITY

Acquired immunity is the resistance developed in the body against any specific foreign body like bacteria, viruses, toxins, vaccines or transplanted tissues. So, this type of immunity is also known as specific immunity. It is the most powerful immune mechanism

that protects the body from invading organisms or toxic substances. Lymphocytes are responsible for acquired immunity.

Types of Acquired Immunity

Two types of acquired immunity develop in the body (response immunity):

1. Cell mediated immunity or cellular immunity

2. Humoral immunity.

Development and processing of lymphocytes

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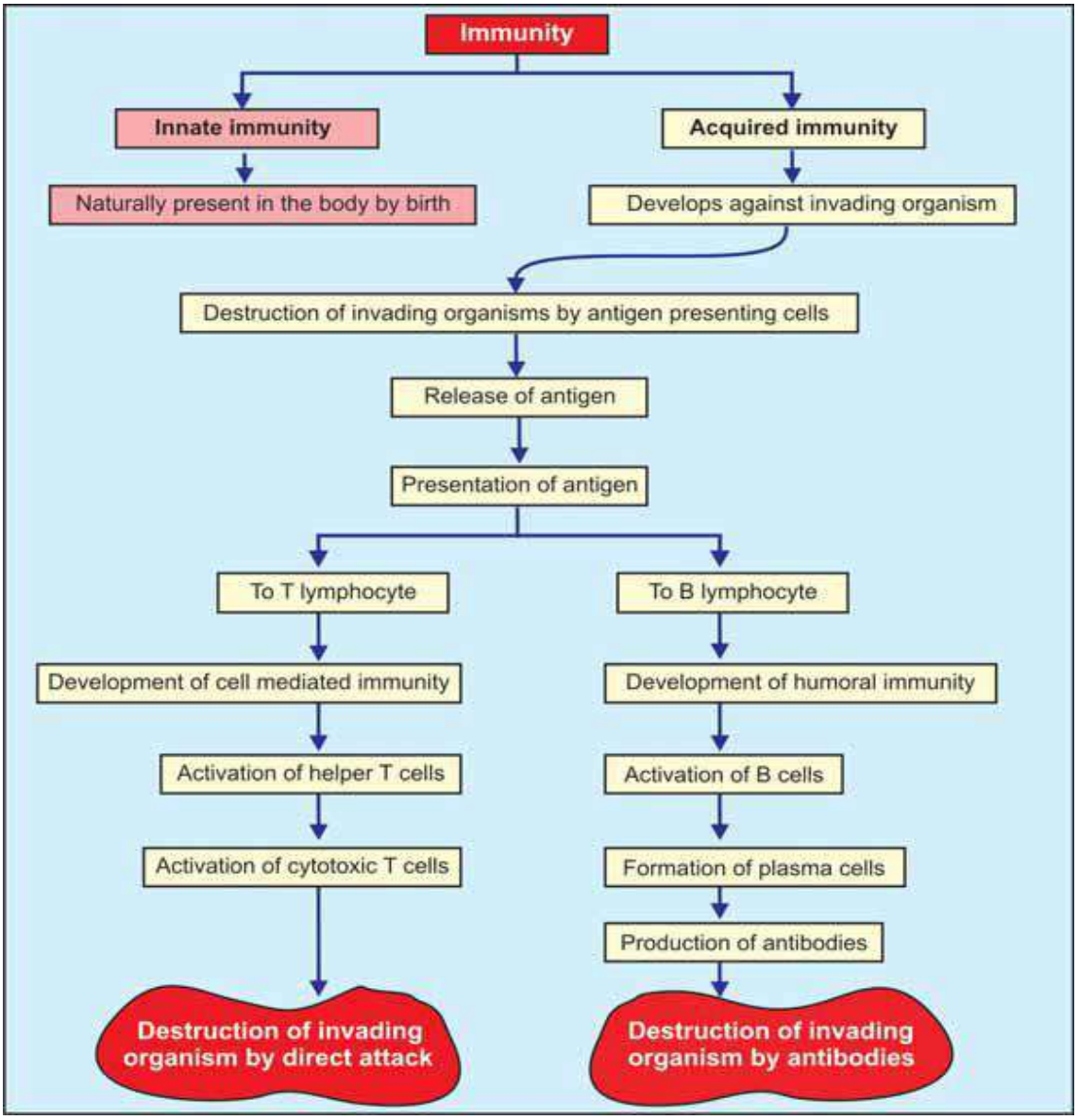

In fetus, lymphocytes develop from bone marrow.

All the lymphocytes are released in the circulation and are differentiated into two categories:

1-T lymphocytes

2-B lymphocytes.

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T LYMPHOCYTES

T lymphocytes are processed in thymus. The processing occurs mostly during the period between just before birth and few months after birth. Thymus secretes thymosin which accelerates the proliferation and activation of lymphocytes in thymus. It also increases the activity of lymphocytes in lymphoid tissues.

Types of T Lymphocytes

During the processing, T lymphocytes are transformed into four types:

1-Helper T cells (CD4) or inducer T cells

2-Cytotoxic T cells (CD8) or killer T cells

3-Suppressor T cells

4-Memory T cells.

Storage of T Lymphocytes

After the transformation, all the types of T lymphocytes leave the thymus and are stored in lymphoid tissues of lymph nodes, spleen, bone marrow and the Gastrointestinal tract.

B LYMPHOCYTES

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B lymphocytes were first discovered in the bursa of Fabricius in birds hence the name B lymphocytes. The bursa of Fabricius is a lymphoid organ situated near the cloaca of birds. The bursa is absent in mammals, and the processing of B lymphocytes takes place in bone marrow and liver.

Types of B Lymphocytes

After processing, the B lymphocytes are transformed

into two types:

1. Plasma cells

2. Memory cells.

Storage of B Lymphocytes

After the transformation, B lymphocytes are stored in the lymphoid tissues of lymph nodes, spleen, bone marrow and the Gastrointestinal tract.

ANTIGENS

DEFINITION AND TYPES

Antigens are the substances, which induce specific immune reactions in the body. The antigens are mostly the conjugated proteins like lipoproteins, glycoproteins and nucleoproteins.

Types of antigens:

1. **Complete antigen or immunogen:**

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- Molecules (proteins or polysaccharides) that are capable of inducing an immune response by themselves are called complete antigen.
- They have high molecular weight (more than 10,000).
- Bacteria, fungi, parasites, viruses are complete antigens.

2. **Incomplete antigen or hapten:**

- They are usually non-proteinous substances
- They are unable to induce immune response by themselves and hence require a carrier molecule to make them immunogenic.
- Serum Protein such as Albumin or Globulin which are non-antigenic components but act as carrier molecules to induce the immune response.
- They have low molecular weight (less than 10,000).
- **Complex haptens** (e.g. capsular polysaccharide of Pneumococci, cardiolipin) are relatively larger molecules and form visible precipitate combining with specific antibodies.
- **Simple haptens** are smaller molecules and don't form visible precipitate with antibodies.
- Polysaccharide "C" of beta-haemolytic Streptococci, glycoproteins etc. are some examples of haptens.

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DEVELOPMENT OF CELL MEDIATED IMMUNITY

The cell mediated immunity is offered by T lymphocytes. It involves several types of cells such as macrophages, T lymphocytes and natural killer cells and hence the name cell mediated immunity. It is also called cellular immunity or T cell immunity. It does not involve antibodies. Cellular immunity is the major defense mechanism against infections by viruses, fungi

and few bacteria. It is also responsible for delayed

allergic reactions and rejection of transplanted tissues.

Cell mediated immunity starts developing when T cells come in contact with the antigens. Usually, the invading microbial or no microbial. organisms carry the antigenic materials. These antigenic materials are released from invading organisms and are presented to the helper T cells by antigen presenting cells.

ANTIGEN PRESENTING CELLS

Antigen presenting cells are the special type of cells in the body which induce the release of antigenic materials from invading organisms and later present these materials to the helper T cells. Major antigen presenting cells are macrophages. Dendritic cells in spleen, lymph nodes and skin also function like antigen presenting cells.

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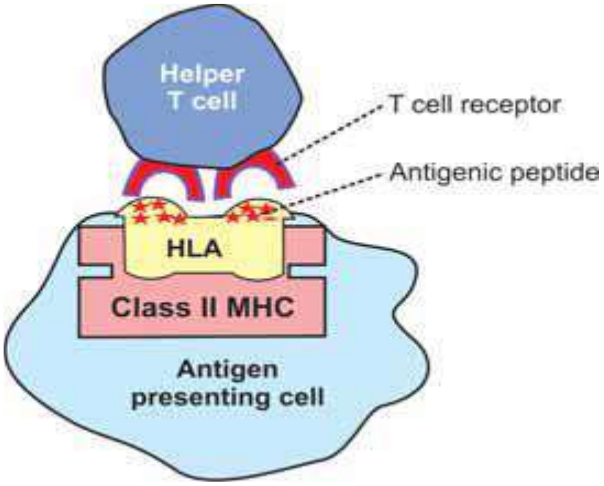
Role of Antigen Presenting Cells

Invading foreign organisms are either engulfed by macrophages through phagocytosis or trapped by dendritic cells. Later, the antigen from these organisms is digested into small peptides. The antigenic peptide products are moved towards the surface of the antigen presenting cells and loaded on a genetic matter of the antigen presenting cells. called human leukocyte antigen (HLA). HLA is present in the molecule of class II major histocompatibility complex (MHC) which is situated on the surface of the antigen presenting cells.

Presentation of Antigen

The antigen presenting cells present their class II MHC molecules together with antigen bound HLA to the helper T cells. This activates the helper T cells through series of events.



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Sequence of Events during Activation of Helper T Cells

1- Helper T cell recognizes the antigen bound to class II MHC molecule which is displayed on the surface of the antigen presenting cell. It recognizes the antigen with the help of its own surface receptor protein called T cell receptor or t cell marker.

2- The recognition of the antigen by the helper T cell initiates a complex interaction between the helper T cell receptor and the antigen. This reaction activates helper T cells.

3- At the same time macrophages (the antigen presenting cells) release interleukin-1 which facilitates the activation and proliferation of helper T cells.

4- The activated helper T cells proliferate and the

proliferated helper T cells enter the circulation for further actions.

5- Simultaneously, the antigen bound to class II MHC molecules activates the B cells also resulting in development of humoral immunity

ROLE OF HELPER T CELLS

The helper T cells which enter the circulation activate all the other T cells and B cells. The helper T cells are of two types:

1-Helper-1 (TH1) cells

2-Helper-2 (TH2) cells.

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Role of TH1 Cells

TH1 cells are concerned with cellular immunity and secrete two substances:

i. Interleukin-2 which activates the other T cells

ii. Gamma interferon which stimulates the phagocytic activity of cytotoxic cells, macrophages and natural killer (NK) cells.

Role of TH2 Cells

TH2 cells are concerned with humoral immunity and secrete interleukin-4 and interleukin-5 which are concerned with:

i. Activation of B cells

ii. Proliferation of plasma cells

iii. Production of antibodies by plasma cell

HLA = Human leukocyte antigen.

ROLE OF CYTOTOXIC T CELLS

The cytotoxic T cells that are activated by helper T cells circulate through blood, lymph and lymphatic tissues and destroy the invading organisms by attacking them directly.

Mechanism of Action of Cytotoxic T Cells

1-The receptors situated on the outer membrane

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of cytotoxic T cells bind the antigens or organisms tightly with cytotoxic T cells.

2-Then, the cytotoxic T cells enlarge and release cytotoxic substances like the lysosomal enzymes which destroy the invading organisms

3-Like this, each cytotoxic T cell can destroy a large number of microorganisms one after another.

Other Actions of Cytotoxic T Cells

1- The cytotoxic T cells also destroy cancer cells, transplanted cells such as those of transplanted heart or kidney or any other cells, which are foreign bodies

2- Cytotoxic T cells destroy even body's own tissues which are affected by the foreign bodies, particularly the viruses. Many viruses are entrapped in the membrane of affected cells. The antigen of the viruses attracts the T cells. And the cytotoxic T cells kill the

affected cells also along with viruses. Because of this cytotoxic T cell is called killer cell.

ROLE OF SUPPRESSOR T CELLS

The suppressor T cells are also called regulatory T cells. These T cells suppress the activities of the killer T cells. Thus, the suppressor T cells play an important role in preventing the killer

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T cells from destroying the body's own tissues along with invaded organisms. The suppressor cells suppress the activities of helper T cells also.

ROLE OF MEMORY T CELLS

Some of the T cells activated by an antigen do not enter the circulation but remain in lymphoid tissue. These T cells are called memory T cells. In later periods, the memory cells migrate to various lymphoid tissues throughout the body. When the body is exposed to the same organism for the second time, the memory cells identify the organism and immediately activate the other T cells. So, the invading organism is destroyed very quickly. The response of the T cells is also more powerful this time.

SPECIFICITY OF T CELLS

Each T cell is designed to be activated only by one type of antigen. It is capable of developing immunity against that antigen only. This property is called the specificity of T cells.

DEVELOPMENT OF HUMORAL IMMUNITY

Humoral immunity is the immunity mediated by antibodies. Antibodies are secreted by B lymphocytes and released into the blood and lymph. Since the B lymphocytes provide immunity through humors, this type of immunity is called humoral immunity or B cell immunity. The antibodies are the gamma globulins produced by B lymphocytes. These antibodies fight against the

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invading organisms. The humoral immunity is the major defense mechanism against the bacterial infection. As in the case of cell mediated immunity, the macrophages and other antigen presenting cells play an important role in the development of humoral immunity also.

ROLE OF ANTIGEN PRESENTING CELLS

The ingestion of foreign organisms and digestion of their antigen by the antigen presenting cells are already explained.

Presentation of Antigen

The antigen presenting cells present their class II MHC molecules together with antigen bound HLA to B cells. This activates the B cells through series of events.

Sequence of Events during Activation of B Cells

1-The B cell recognizes the antigen bound to class II MHC molecule which is displayed on the surface of the antigen presenting cell. It recognizes the antigen with the help of its own surface receptor protein called B cell receptor.

2-The recognition of the antigen by the B cell initiates a complex interaction between the B cell receptor and the antigen. This reaction activates B cells.

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3- At the same time macrophages (the antigen presenting cells) release interleukin-1 which facilitates the activation and proliferation of B cells.

4- The activated B cells proliferate and the proliferated B cells carry out the further actions.

5- Simultaneously the antigen bound to class II MHC molecules activates the helper T cells also resulting in development of cell mediated immunity (already explained).

Transformation of B Cells

The proliferated B cells are transformed into two

types of cells:

1-Plasma cells

2-Memory cells.

ROLE OF PLASMA CELLS

The plasma cells destroy the foreign organisms by producing the antibodies. Antibodies are globulin in nature. The rate of the antibody production is very high, i.e. each plasma cell produces about 2000 molecules of antibodies per second. The antibodies are also called immunoglobulins.The antibodies are released into lymph and then transported into the circulation. The antibodies are produced until the end of lifespan

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of each plasma cell which may be from several days to several weeks.

ROLE OF MEMORY B CELLS

Memory B cells occupy the lymphoid tissues throughout the body. The memory cells are in inactive condition until the body is exposed to the same organism for the second time. During the second exposure, the memory cells are stimulated by the antigen and produce more quantity of antibodies at a faster rate, than in the

first exposure. The antibodies produced during the second exposure to the foreign antigen are also more strong than those produced during first exposure. This phenomenon forms the basic principle of vaccination against the infections.

ROLE OF HELPER T CELLS

Helper T cells are simultaneously activated by antigen. The activated helper T cells secrete two substances called interleukin 2 and B cell growth factor, which promote1:

1-Activation of more number of B lymphocytes

2-Proliferation of plasma cells

3-Production of antibodies.

ANTIBODIES

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An antibody is defined as a protein that is produced by B lymphocytes in response to the presence of an antigen. Antibody is globulin in nature and it is also called immunoglobulin Ig. (The immunoglobulins form 20 percent of the total plasma proteins. The antibodies enter almost all the tissues of the body.

Types of Antibodies

Five types of antibodies are identified:

1-IgA (Ig alpha)

2-IgD (Ig delta)

3-IgE (Ig epsilon)

4-IgG (Ig gamma)

5-IgM (Ig mu)

Among these antibodies, IgG forms 75 percent of the antibodies in the body.

Structure of Antibodies

Antibodies are gamma globulins and are formed by two pairs of chains namely, one pair of heavy or long chains and one pair of light or short chains.

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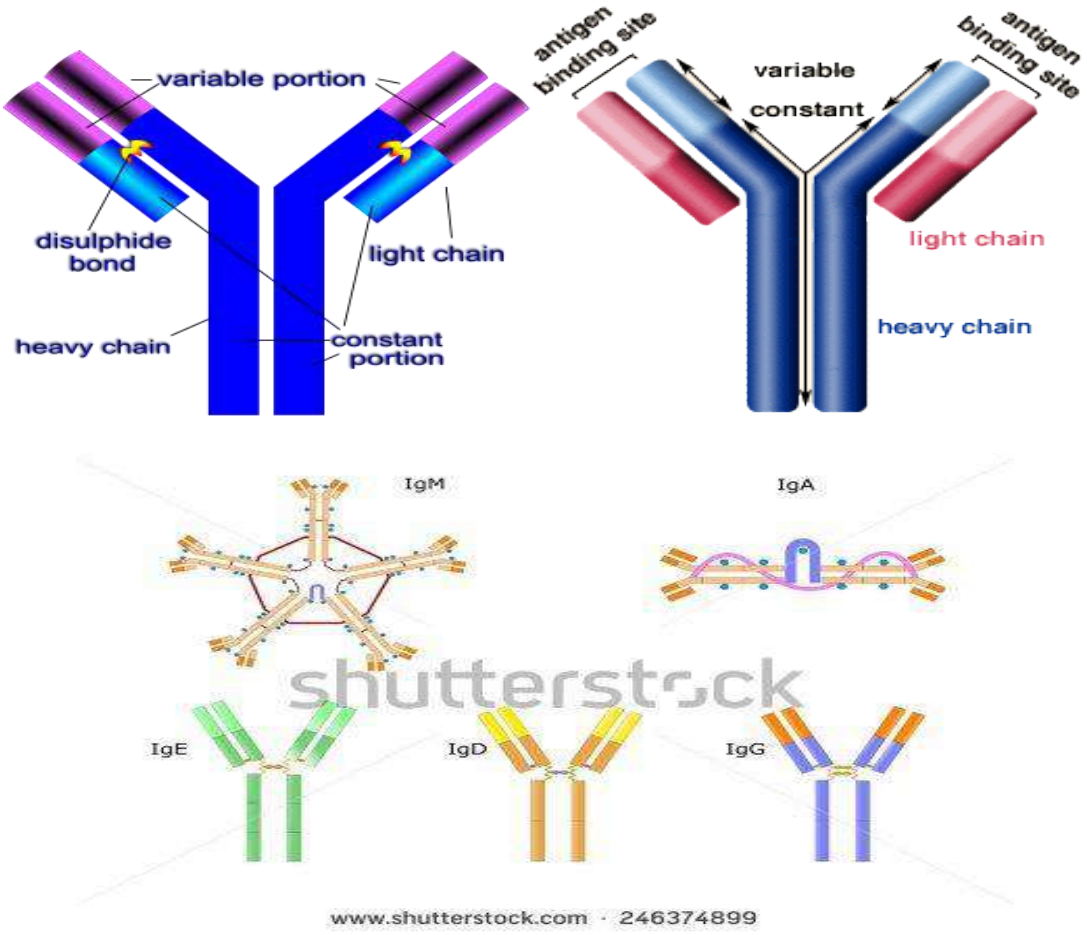

Mechanism of Actions of Antibodies

The antibodies protect the body from the invading organisms in two ways:

1-By direct actions

2-Through complement system.

Direct Actions of Antibodies

Antibodies directly inactivate the invading organism by any one of the following methods:

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i. Agglutination: In this, the foreign bodies like RBCs or bacteria with antigens on their surfaces are held together in a clump by the antibodies.

ii. Precipitation: In this, the soluble antigens toxin are converted into insoluble forms and then precipitated.

iii. Neutralization: During this, the antibodies cover the toxic sites of antigenic products.

iv. Lysis: In this, the antibodies rupture the cell membrane of organisms and then destroy them.

Actions of Antibodies through Complement System

The complement system is the one that enhances or accelerates various activities during the fight against the invading organisms. It contains plasma enzymes, which are identified by numbers from C1 to C9.

Functions of Different Antibodies

1-IgA plays a role in localized defense mechanism in external secretions like tear

2-IgD is involved in recognition of the antigen by B lymphocytes

3-IgE is involved in allergic reactions

4-IgG is responsible for complement fixation

5-IgM is also responsible for complement fixation.

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Specificity of B Lymphocytes

Each B lymphocyte is designed to be activated only by one type of antigen. It is also capable of producing antibodies against that antigen only.

This property of B lymphocyte is called specificity.

NATURAL KILLER CELL

Natural killer (NK) cell is a large granular cell with

indented nucleus. It is considered as the third type of lymphocyte. It is not a phagocytic cell but its granules contain hydrolytic enzymes which causes lysis of cells of invading organisms.

Functions of NK Cell

1-Destroys the viruses

2-Destroys the viral infected or damaged cells, which might form tumors

3-Destroys the malignant cells and prevents development of cancerous tumors

4-Secretes cytokines such as interleukin-2, interferons, colony stimulating factor (GMCSF) and tumor necrosis factor.

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CYTOKINES

Cytokines are the hormone like small proteins acting as intercellular messengers (cell signaling molecules) by binding to specific receptors of target cells. These nonantibody proteins are secreted by WBCs and some other types of cells. Their major function is the activation and regulation of general immune system of the body. Cytokines are distinct from the other cell

signaling molecules such as growth factors and hormones. Cytokines are classified into several types:

1-Interleukins

2-Interferons

3-Tumor necrosis factors

4-Chemokines

5-Defensins

6-Cathelicidins

7-Platelet activating factor.

IMMUNE DEFICIENCY DISEASES

Immune deficiency diseases are group of diseases in which some components of immune system is missing or defective. Normally, the defense mechanism protects the body from invading

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pathogenic organism. When the defense mechanism fails or becomes faulty (defective)

the organisms of even low virulence produce severe disease. The organisms, which take advantage of defective defense mechanism, are called opportunists.

The immune deficiency diseases caused by such opportunists are of two types:

1-Congenital immune deficiency diseases

2-Acquired immune deficiency diseases.

CONGENITAL IMMUNE DEFICIENCY DISEASES

Congenital diseases are inherited and occur due to the defects in B cell, or T cell or both. The common examples are DiGeorge's syndrome (due to absence of thymus) and severe combined immune deficiency (due to lymphopenia or the absence of lymphoid tissue).

ACQUIRED IMMUNE DEFICIENCY DISEASES

Acquired immune deficiency diseases occur due to infection by some organisms. The most common disease of this type is acquired immune deficiency syndrome (AIDS).

Acquired Immune Deficiency Syndrome(AIDS)

It is an infectious disease caused by immune deficiency virus (HIV). AIDS is the most common problem throughout the world

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because of rapid increase in the number of victims. Infection occurs when a lycoprotein from HIV binds to surface receptors of T lymphocytes, monocytes. macrophages and dendritic cells leading to destruction of these cells. It causes slow progressive decrease in immune function resulting in opportunistic infections of several types. The common opportunistic infections, which kill the AIDS patient are pneumonia and skin cancer.

AUTOIMMUNE DISEASES

Autoimmune disease is defined as condition in which the immune system mistakenly attacks body's own cells and tissues. Normally, an antigen induces the immune response in the body. The condition in which the immune system fails to give response to an antigen is called tolerance. This is true with respect to body's own antigens that are called self-antigens or autoantigens. Normally, body has the tolerance against self antigen. However, in some occasions, the tolerance fails or becomes incomplete against self antigen. This state is called autoimmunity and it leads to the activation of T lymphocytes or production of autoantibodies from B lymphocytes. The T lymphocytes (cytotoxic T cells) or autoantibodies attack the body's normal cells whose surface contains the self-antigen or

autoantigen.

Common Autoimmune Diseases

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1-Diabetes mellitus

2-Myasthenia gravis

3-Graves' disease

4- Rheumatoid arthritis

Vaccination: It is the process that has been used to cause immunity against specific diseases. It is done by exposing the body to an Ag (the organism or its toxic products which are made harmless and non-pathogenic, but their Ags are still intact) so that humeral or cellular immune response occurs. If subsequent exposure occurs to the same Ag the response will be more powerful and Abs or activated T cells will react with the Ag and protect the body .

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Lecture 6

PLATELETS (THROMBOCYTES)

Platelets are the smallest of the cellular elements of blood. They are non-nucleated, granulated bodies, 2-4 micrometers in diameter. Their normal concentration in blood ranges from 150,000 to 400,000 per microliter. They are formed in the bone marrow from giant cells, the megakaryocytes, which fragment into platelet which are extruded into the circulation .

The platelet production is regulated by multiple factors including IL-1, IL-3, 1L-6, and GM-CSF that control the production of megakaryocytes .Their life span is 7-10 days, then they are eliminated from the circulation mainly by the tissue Macrophage system .

The membranes of platelets contain receptors for **collagen, vessel wall von Will brand factor** and **fibrinogen**. Their cytoplasm contain **actin, myosin, glycogen, lysosomes**, and **2 types of granules** :

1- Dense granules containing no protein substances such as ADP, ATP, serotonin .
2- Granules containing protein substances such as clotting factors and platelet-derived growth factor which stimulates wound healing. In addition, the platelet membrane contains large amounts of phospholipids that play several activating roles at multiple points in the blood clotting process .

Their most important function is in **hemostasis** and **blood coagulation .**

HEMOSTASIS AND BLOOD COAGULATION: When a small blood vessel is transected or injured, a spontaneous and natural process occurs to arrest bleeding, this process is called "**hemostasis**". It involves a series of events which leads to clot formation and prevention of further blood loss. These include :

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- ✓ **Contraction of the injured vessel (Vascular spasm)**
- ✓ **Formation of platelet plug at the site of injury**
- ✓ **Activation of blood coagulation**
- ✓ **Activation of the fibrinolytic system** which gradually dissolves away the fibrin clot as tissue repair is taking place .

Repair of the vessel wall occurs by the proliferation of smooth muscle cells and fibroblasts, the deposition of new connective tissue matrix, and the in growth of a new luminal lining of endothelial cells.

1- Contraction of the vessel wall (vasoconstriction): This reduces the flow of blood from the vessel rupture. Most of vasoconstriction results probably from direct effect of injury upon vascular smooth muscle cells. Vasoconstrictor substances released from the platelets also contribute to this vasoconstriction.

2- Formation of a platelet plug: when platelets come in contact with the exposed collagen of the damaged blood vessel, they become activated, they begin to swell, put out pseudopodia, become sticky and adhere to collagen and release different substances such as serotonin, and ADP. Their enzymes form thromboxane A2. Serotonin and thromboxane A2 enhance vasoconstriction. ADP and thromboxane A2 activate other nearby platelets and increase their stickiness and this causes circulating platelets to adhere other the platelets already attached to the collagen, so platelets will aggregate (platelets stick to each other) and form platelet plug at the site of the injury.

3- Blood coagulation: The clot begins to develop in 15-20 seconds, if trauma of the vascular wall has been severe, and in 1-2 min if it is minor .

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Mechanism of Blood Coagulation

The clotting takes place in three steps:

1- in response to rupture of the vessel or damage to the blood, the complex of activated substances collectively called prothrombin activator.

2-the prothrombin activator catalyzes the conversion of prothrombin into thrombin.

3- the thrombin acts an enzyme to convert fibrinogen into fibrin fibers, that enmesh platelets, blood cells and plasma to form the clot.

Conversion of prothrombin to thrombin

Prothrombin is a plasma protein, an alpha 2 globulin, having a molecular weight of 68.700. it is present in normal plasma in a concentration 15 mg/dl. It is unstable protein that can easily fragmented into thrombin which has a molecular weight 33.700 in presences of prothrombin activator and calcium ions.

Prothrombin is formed by the liver, vitamin K is required by the liver for normal formation of prothrombin.

Conversion of fibrinogen to fibrin

Fibrinogen is a high molecular weight protein (340.000) that occurs in the plasma in quantities of 100-700 mg/dl. It is formed in the liver.

Thrombin is a protein enzyme with proteolytic capabilities, it act on fibrinogen to remove four low-molecular weight peptides from each molecule of fibrinogen, forming a molecule fibrin monomer that has the automatic capability of polymerizing with other fibrin molecule forming long fibrin fibers that form the reticulum of clot. There are two reaction

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pathways to coagulation, one of them, extrinsic mechanism, is initiated by clotting factors released by the damaged blood vessel and perivascular tissues. The reaction pathway it use only clotting factors found in the blood itself called intrinsic mechanism.

The extrinsic mechanism is the damage of blood vessel release lipoprotein mixture called thromboplastin (factor III) in the presences of Ca, thromboplastin activates factor VII, which then activates factor X. the **extrinsic and intrinsic pathways differ only in how they arrive at active factor X.**

The intrinsic mechanism, when platelets degranulate, they release factor XII(Hageman factor) and then this leads to activated factors XI. IX and VIII, in that order, each serving as an enzyme that catalyzes the next step and finally to factor X. this pathway also requires ca ions and platelet thromboplastic factor (PF3).

Once factor X is activated the remaining events are identical in the intrinsic and extrinsic mechanism . F X combines with F III and V in the presence of Ca and PF3 to produce an enzyme, prothrombin (f II) converting it to enzyme thrombin. Thrombin then converts fibrinogen to fibrin. Fibrin forms a loose mesh at first, but factor VIII causes the formation of covalent cross-links that convert this to fibrin polymer- a dense aggregation of fibers that forms the structural basis of the clot.

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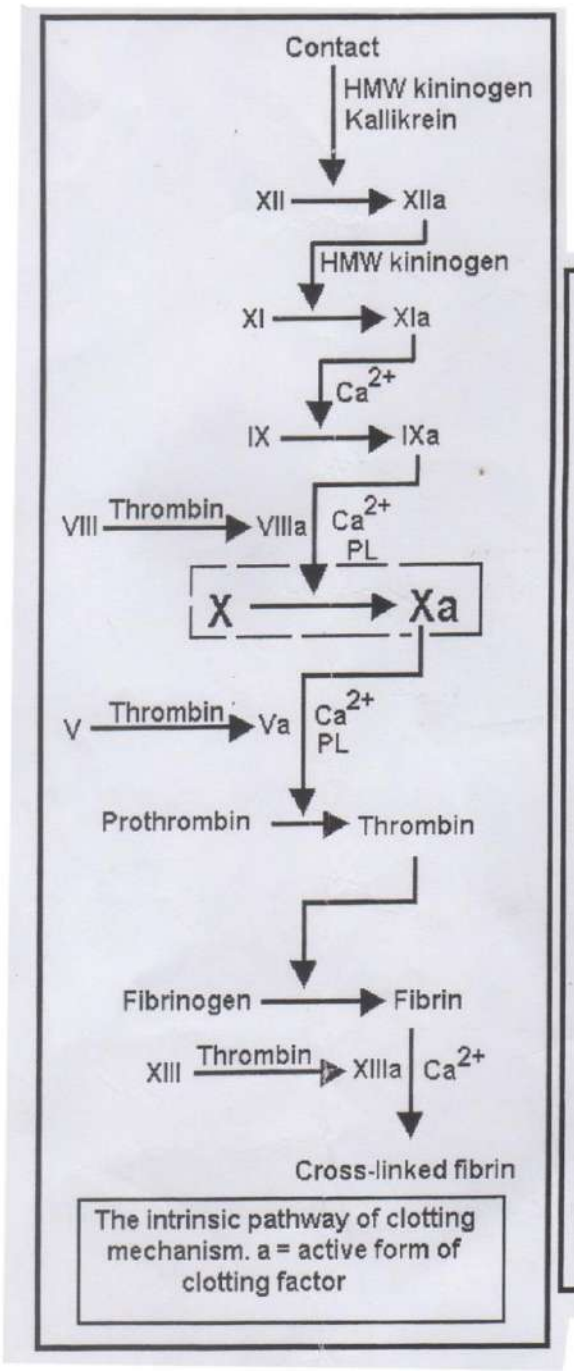

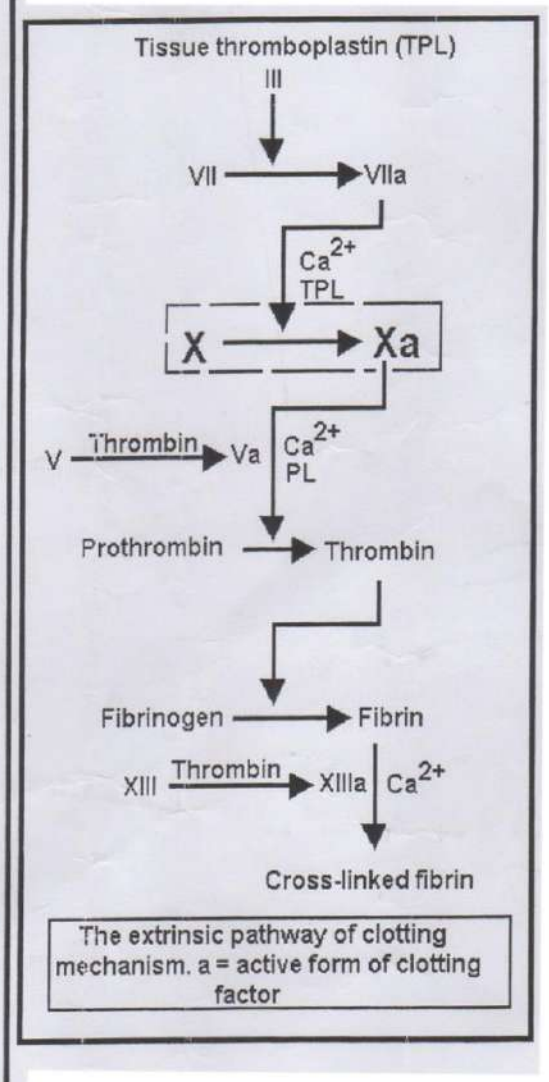

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Factors	Names
I	Fibrinogen
II	Prothrombin
III	Tissue thromboplastin
IV	Calcium
V	Proaccelerin
VII	Proconvertin
VIII	Antihaemophilic factor
IX	Christmas factor
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin-stabilizing factor
HMW-K	High momecular weight kininogen (Fitzgerald factor)
Pre-K	Prekallikrein (Fletcher factor)
Ka	Kallikrein
PL	Platelet phospholipid

System for naming blood-clotting factors

Prevention of clotting in the normal vascular system (Intravascular)

1- Endothelial surface factor

A- the smoothness of endothelium, which prevents contact activation of the intrinsic clotting system

B- layer of glycocalyx, a mucopolysaccharides adsorbed to the inner surface of the endothelium, which repels the clotting factor and platelets.

C-A protein bound with endothelial membrane, thrombin which bind thrombomodulin, this dulin-thrombin not only slows the clotting process, but also activates a plasma protein, protein C that acts as an anticoagulant by inactivating factors V and VIII

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2- Antithrombin factor: the most important anticoagulant in the blood itself that remove thrombin from blood, the most powerful

1- the fibrin fibers that themselves are formed during the process of clotting

2- an alpha-globulin called antithrombin III or antithrombin- heparin co factor , about 85-90% of thrombin formed adsorbed to the fibrin fibers as they develop. The thrombin that does not adsorb to fibrin fibers, soon combine with antithrombin III, which block the effect of the thrombin on the fibrinogen and inactivate it within 12-20 minutes.

3- Heparin: is a conjugated polysaccharide, formed by the basophilic mast cells located in the pericapillary connective tissue throughout the body. It prevents blood coagulation by combining with antithrombin –heparin co factor which makes this factor combine with thrombin. The antithrombin heparin complex removes several other activated coagulation factors in addition to thrombin from circulating blood, the others include factors XII, XI, IX and X.

Prevention of blood coagulation outside the body

1- **Heparin:** it prevents the blood coagulation when added to the sample of blood outside the body as well as in the body.

2- **Calcium-deionizing agent** used for preventing coagulation is sodium, ammonium, or potassium citrate. The citrate ion combines with Ca in the blood to cause an unionized Ca compound, and lack of Ca prevents coagulation.

3- **Coumarin derivatives:** these are used internally to prolong the coagulation time from the normal range of about 2-3 minutes to 10 minutes.

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Vitamin K is essential for the formation of prothrombin by the liver, these substances when given they interfere with action of Vit. K and this cause a decrease in the formation of prothrombin by the liver and this causes prolongation of coagulation time, and this prevents the occur of blood clots.

4- Activation of the fibrinolytic system(Fibrinolysis): Clot dissolved by activity of plasmin, an enzyme which hydrolyzes fibrin.

Blood disease

1- decreased prothrombin, factor VII,IX and X caused by vitamin K. Hepatitis, cirrhosis, acute yellow atrophy and the presence of a stone in the common bile duct and this effect on the absorption of vit. K all these factors cause a severe tendency to bleed. These liver diseases often cause decreased production of prothrombin and the other factor both because of poor vitamin K absorption and because of the diseased liver cells.

2- Hemophilia: it is a genetic disease which affects the male only, the female is not affected by the disease, because at least one of her two X chromosomes will have the appropriate gene. If one of her X chromosomes is deficient, she will be a hemophilia carrier.

There are three types of Hemophilia:

1- Classical hemophilia (hemophilia A): this is caused by the deficiency of factor VIII.

2- Hemophilia B: this caused by deficiency of factor IX.

3- Hemophilia C: this caused by the deficiency of factor XI.

The treatment by giving the patient deficient factor.

3- Thrombocytopenia: this means the presence of a very low quantity of platelets in the circulating system, this caused by drugs, chemicals and

1-Textbook of Human Physiology for Dental Students(2013) Second Edition Indu Khurana
2-Review of Medical Physiology, 2005 Twenty-Second Edition William F. Ganong, MD

sometimes due to unknown reason, in this case it is called idiopathic thrombocytopenia.

The treatment by giving the patient blood containing fresh blood platelets. Ordinary, bleeding does not occur until the number of platelets in the blood below 50000 ul rather than normal 150000-300000 levels as low as 10000 ul are frequently lethal

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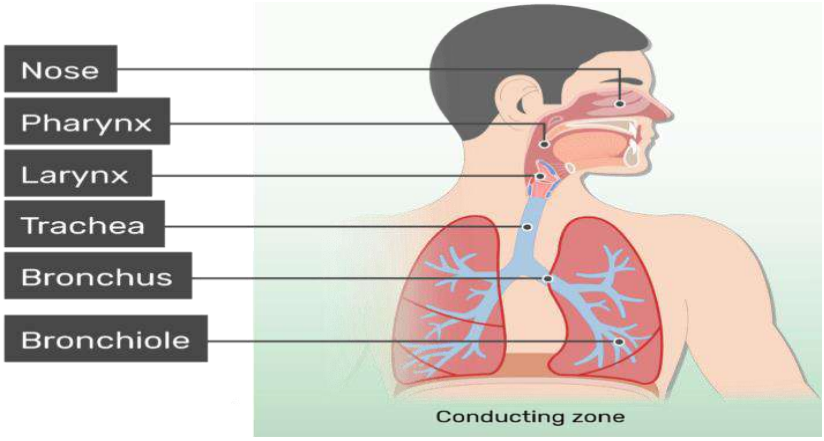
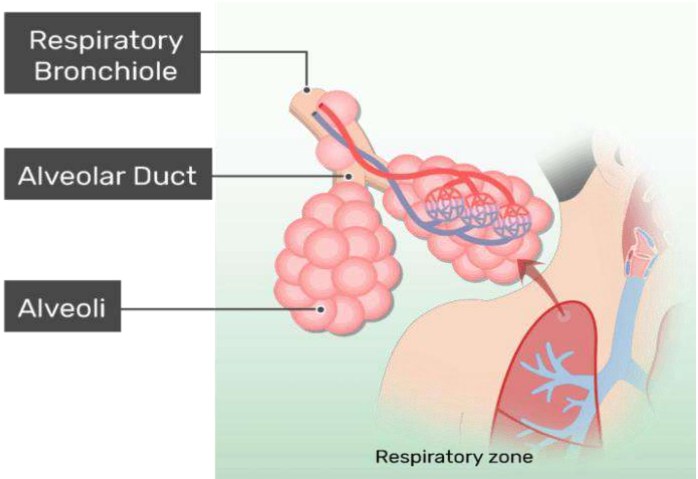
Lecture 7,8,9

Respiratory system

The goals of respiration are to provide oxygen to the tissues and to remove carbon dioxide. Functionally, the respiratory system is separated into a conducting zone and respiratory zone. The conducting zone consists of the nose, pharynx, larynx, trachea, bronchi, and bronchioles. These structures form a continuous passageway for air to move in and out of the lungs.

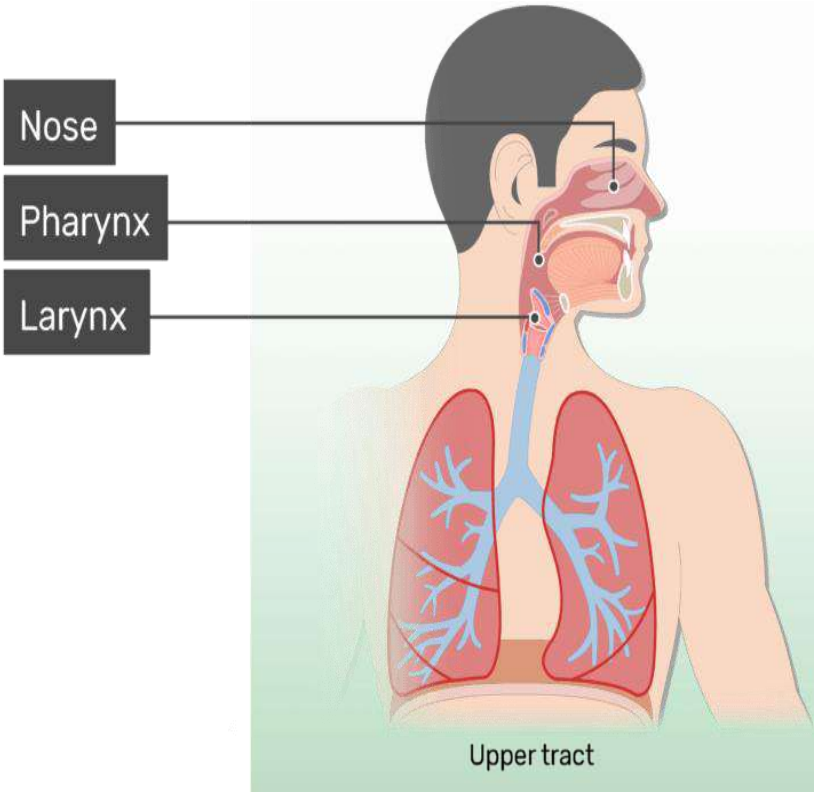


The respiratory zone is found deep inside the lungs and is made up of the respiratory bronchioles, alveolar ducts, and alveoli. These thin-walled structures allow inhaled oxygen (O2) to diffuse into the lung capillaries in exchange for carbon dioxide (CO2).

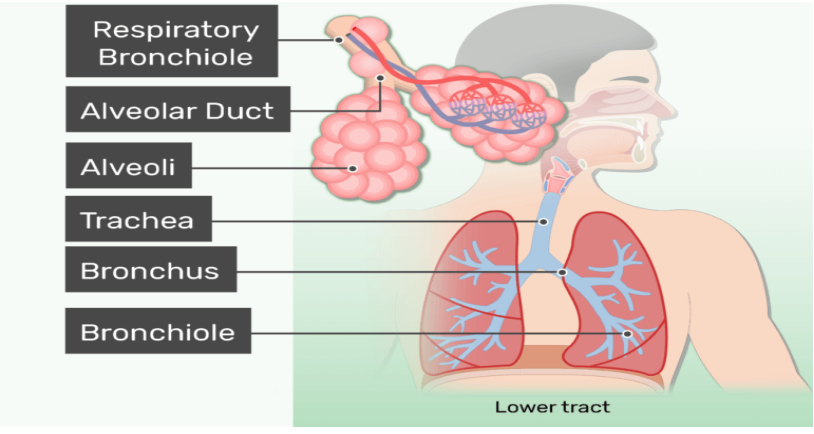


Anatomically, the same structures are often divided into the **Upper Respiratory Tract** and the **Lower Respiratory Tract**. The upper

respiratory tract structures are found in the head and neck and consist of the **nose**, **pharynx**, and **larynx**.



The lower respiratory tract structures are located in the thorax or chest and include the **trachea**, **bronchi**, and **lungs (= bronchioles, alveolar ducts, and alveoli).**



The term respiration includes three separate but related functions

- pulmonary ventilation(breathing), which means the inflow and outflow of air between the atmosphere and the lung alveoli.

- diffusion of oxygen and carbon dioxide between the alveoli and the blood.
- transport of oxygen and carbon dioxide in the blood and body fluids to and from the body's tissue cells.

Respiratory System Functions

1- Gas exchange: Oxygen enters blood and carbon dioxide leaves.

2- Regulation of blood pH : Altered by changing blood carbon dioxide levels

3- Voice production movement of air past vocal folds makes sound and speech.

4- Olfaction smell occurs when airborne molecules drawn into nasal cavity.

5- Protection against microorganisms by preventing entry and removing them.

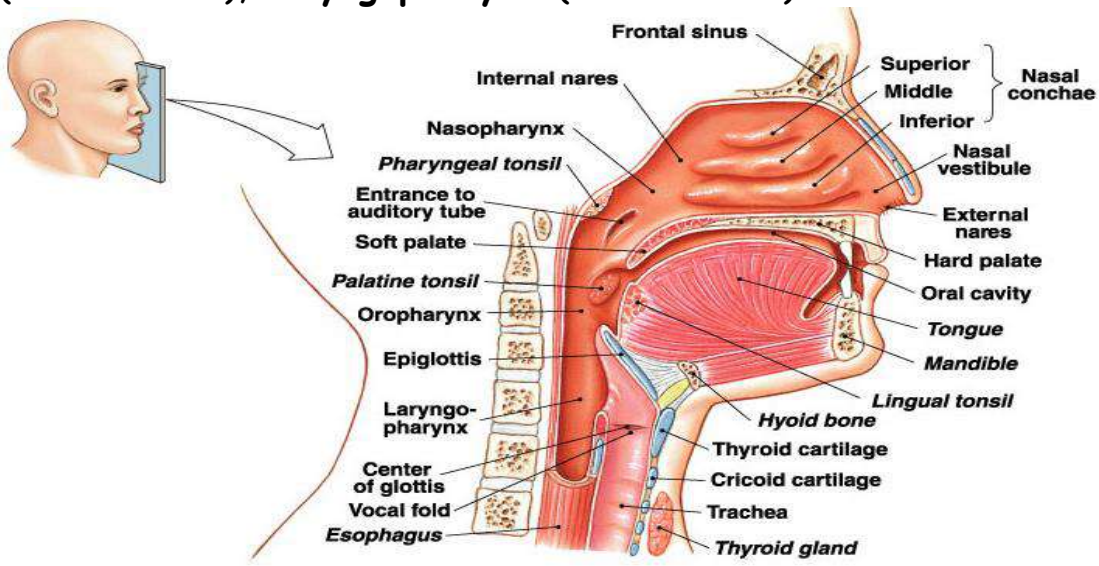
The Upper Respiratory System

The upper respiratory tract consists of the nose and the pharynx. Its primary function is to receive the air from the external environment and filter, warm, and humidify it before it reaches the delicate lungs where gas exchange will occur. Air enters through the nostrils of the nose and is partially filtered by the nose hairs, then flows into the nasal cavity. The nasal cavity is lined with epithelial tissue, containing blood vessels, which help warm the air; and secrete mucous, which further filters the air. The endothelial lining of the nasal cavity also contains tiny hair like projections, called **cilia**. The **cilia serve to transport dust and other foreign particles, trapped in mucous, to the back of the nasal cavity and to the pharynx**. There the mucus is either coughed out, or swallowed and digested by powerful stomach acids. After passing through the nasal cavity, the air flows down the pharynx to the larynx.

Pharynx

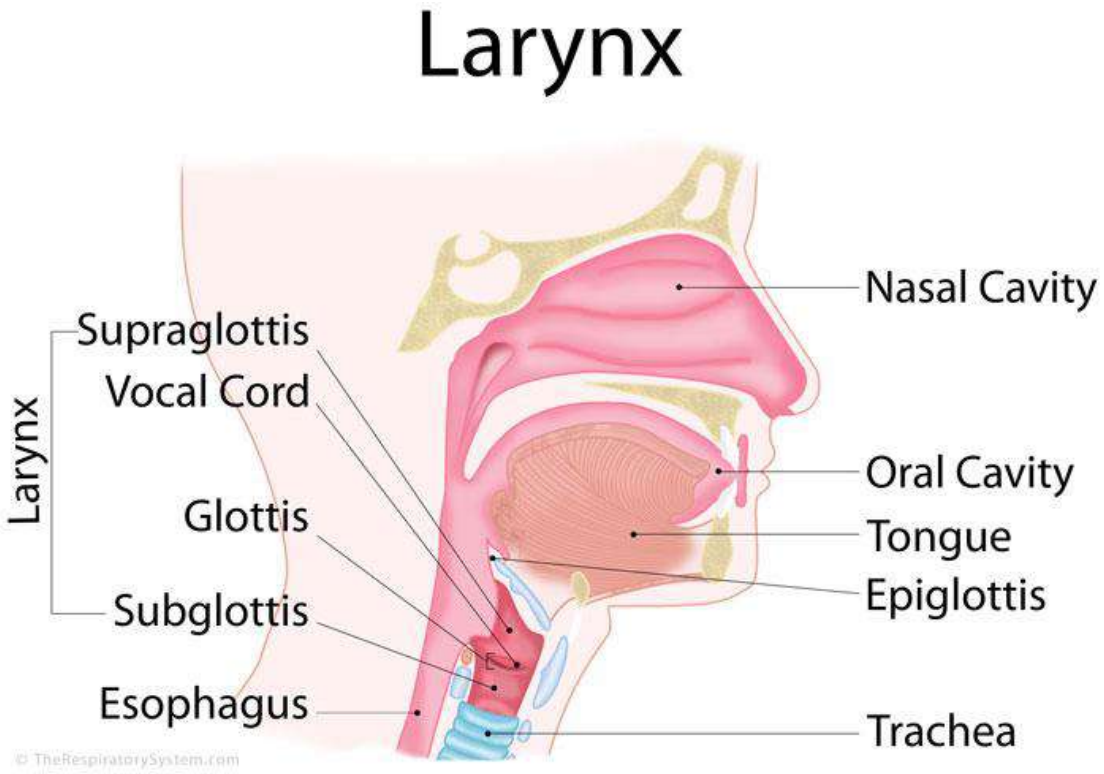
The pharynx is part of both the digestive and respiratory systems. For the digestive system, its muscular walls function in the process of swallowing,

and it serves as a pathway for the movement of food from the mouth to the esophagus. As part of the respiratory system, it allows for the movement of air from the nose and mouth to the larynx in the process of breathing. Pharynx is three parts; **Nasopharynx** (air only), **Oropharynx** (food and air), **Laryngopharynx** (food and air).



Larynx

The larynx is a tough, flexible segment of the respiratory tract connecting the pharynx to the trachea in the neck. It plays a vital role in the respiratory tract by allowing air to pass through it while keeping food and drink from blocking the airway. The larynx is also the body's "voice box" as it contains the vocal folds that produce the sounds of speech and singing.



trachea

The trachea is a wide, hollow tube that connects the larynx (or voice box) to the bronchi of the lungs.

Functions of the trachea

1. Air conduction

The primary function of the trachea is to provide air passage to lungs for respiration, i.e. to inhale air rich in oxygen and exhale carbon dioxide.

2. Protection

The lining of the trachea has a sticky mucous lining that traps foreign substances. These trapped substances are expelled upwards and can either be excreted from the body as phlegm or swallowed in the esophagus. If a foreign object accidentally gets into the trachea, the cilia cells get irritated and induce coughing to expel the object.

3. Thermoregulation

When the air is cold, the trachea helps to humidify and warm the air entering the lungs.

When the air is hot, heat is carried away in exhaled air through evaporation of water.

Bronchi

The trachea divides into two bronchi(tubes). One leads to the left lung, the other to the right lung. Inside the lungs each of the bronchi divides into smaller bronchi called broncheoli.

The bronchiole

The bronchi branches off into smaller tubes called bronchiole which end in the pulmonary alveolus.

Pulmonary alveoli

Tiny sacs(air sacs) delineated by a single-layer membrane with blood capillaries at the other end.

The lungs

A pair of organs found in all vertebrates. The structure of the lungs includes the bronchial tree- air tubes branching off from the bronchi into smaller and smaller air tubes, each one ending in a pulmonary alveolus.

The act of breathing

The act of breathing has two stages inhalation- the intake of air into the lungs through expansion of chest volume. Exhalation- the expulsion of air from the lungs through contraction of chest volume.

Inhalation and exhalation involves muscles:

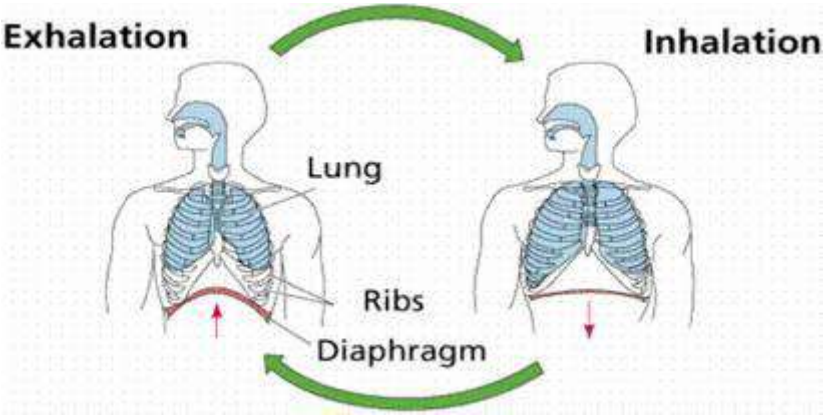
1- rib muscles: the muscle between the ribs in the chest.

2- diaphragm muscle: muscle movement- the diaphragm and rib muscle are constantly contracting and relaxing (about 16 times per minute), thus causing the chest cavity to increase and decrease.

During inhalation-the muscles contract, contraction of the diaphragm muscle- causes the diaphragm to flatten, thus enlarging the chest cavity.

Contraction of the rib muscles-causes the ribs to rise, thus increasing the chest volume. The chest cavity expands, thus reducing air pressure and causing air to be passively drawn into the lungs. Air passes from the high pressure outside the lungs to the low pressure inside the lungs.

During exhalation-the muscles relax and diaphragm curves return to the former position, the ribs descend and chest volume decreases. The chest cavity contracts thus the air in the lungs expelled through the upper respiratory tract.



External respiration

External respiration is the exchange of gases between the air filling the alveoli and the blood in the capillaries surrounding the walls of the alveoli. Air entering the lungs from the atmosphere has a higher partial pressure of oxygen and a lower partial pressure of carbon dioxide than does the blood in the capillaries. The net result of external respiration is the movement of oxygen from the air into the blood and the movement of carbon dioxide from the blood into the air.

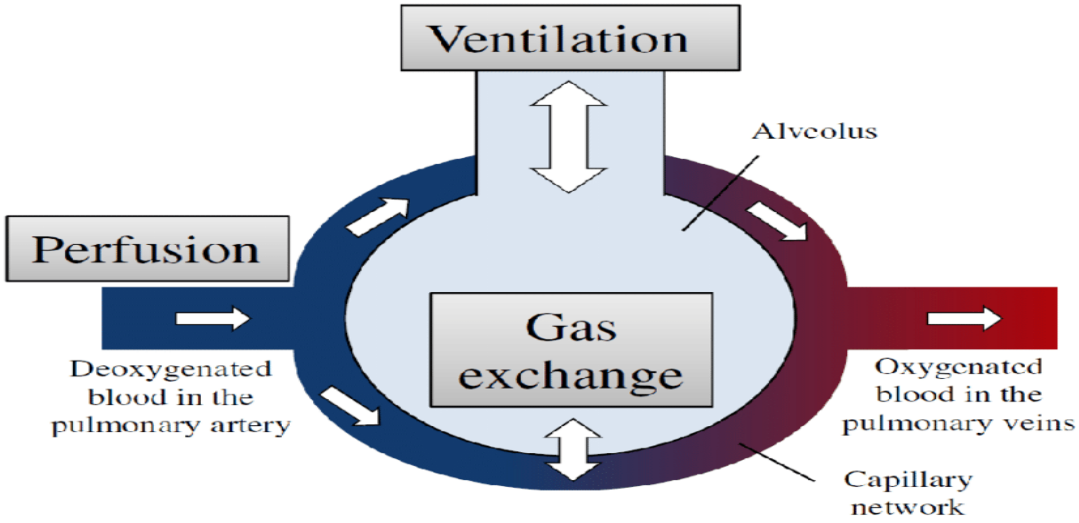
Internal respiration

Internal respiration is the exchange of gases between the blood in capillaries and the tissues of the body. Capillary blood has a higher partial pressure of oxygen and lower partial pressure of carbon dioxide than the tissues through which it passes. The net result of internal respiration is

the diffusion of oxygen into the tissues and the diffusion of carbon dioxide into blood.

Gas exchange

Is a biological process through which different gases are transferred in opposite directions across a specialized respiratory surface. In respiration oxygen is required to enter cells whilst waste carbon dioxide must be removed. The exchange of gases essentially occurs as a result of diffusion down a concentration gradient- gas molecules moving from an area of high concentration to low concentration.



Both oxygen and carbon dioxide are transported around the body in the blood through arteries, veins and capillaries. They bind to hemoglobin in red blood cells, although this is more effective with oxygen. Carbon dioxide also dissolves in the plasma or combines with water to form bicarbonate ions, this reaction is catalyzed by the carbonic anhydrase enzyme in red blood cells.

Only 1.5 percent of oxygen in the blood is dissolved directly. Most oxygen. 98.5 percent , is bound to a protein called hemoglobin and carried to the tissues. Each hemoglobin molecule bind to four oxygen molecules.

Some environmental factors and diseases can affect oxygen carrying capacity; the same is true for carbon dioxide levels, blood pH, and body temperature.

Factors that affect oxygen binding

The increase in carbon dioxide and subsequent decrese in pH reduce the affinity of hemoglobin for oxygen. Increasing temperature will weaken and denature the bond between oxygen and hemoglobin which in turn decreases the concentration of the oxyhemoglobin. Diseases, such as sickle cell anemi and thalassemia, decrease the blood's ability to deliver oxygen to tissues.

Forces controlling lung volumes

Pleural pressure, airways resistance, and surface tension

Pulmonary Volumes and Capacities

Most pulmonary volumes and capacities can be measured with a

spirometer. The total lung capacity, functional residual capacity, and residual volume cannot be measured with a spirometer.

·Tidal volume (VT) is the volume of air (about 500 mL) inspired

and expired with each normal breath.

·Inspiratory reserve volume (IRV) Maximum amount of additional air (about 3000 ml) that can be inspired from the end of a normal inspiration

·Expiratory reserve volume (ERV) The maximum volume of additional air (about 1100 mL) that can be expired from the end of a normal expiration

·Residual volume (RV) The volume of air (about 1200 mL) remaining in the lung after a maximal expiration.

Pulmonary Capacities Are Combinations of Two or More

Pulmonary Volumes.

·Inspiratory capacity (IC) Maximum volume of air (about 3500mL) that can be inspired from end expiratory position.

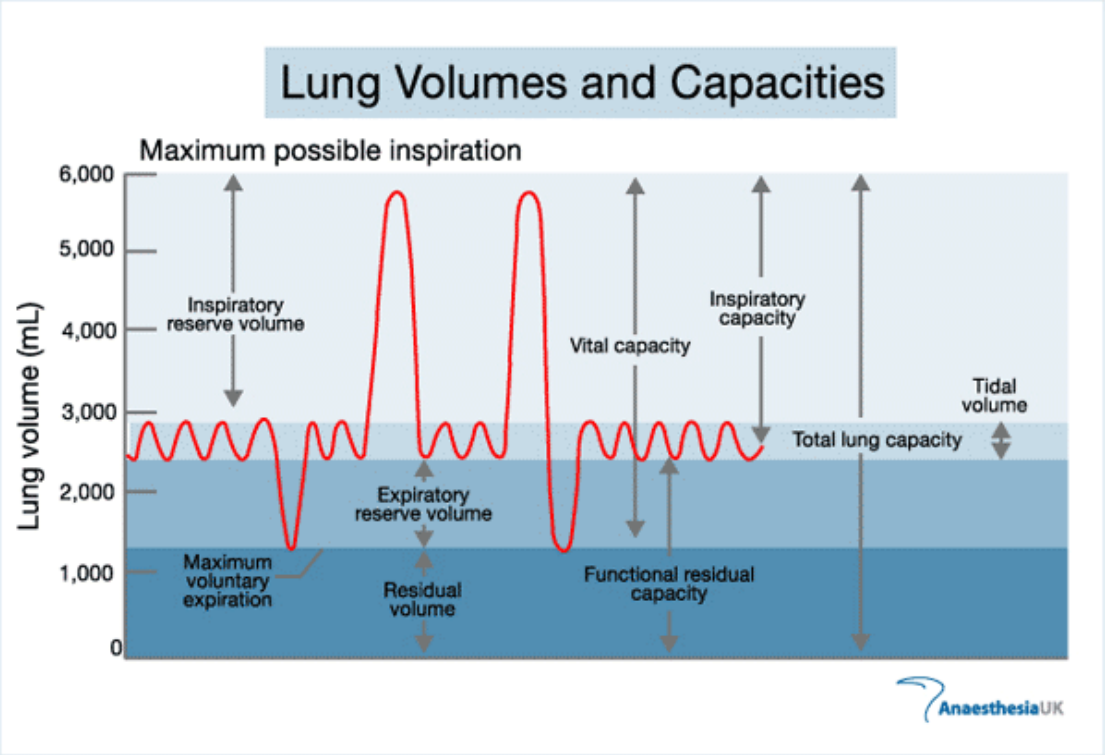
Called a capacity because it is the sum of tidal volume and inspiratory reserve volume.

•**Functional residual capacity (FRC)** The volume of air (about 2300 mL). remaining in the lung at the end of a normal expiration. Called a capacity because it equal residual volume plus expiratory reserve volume.

•**Vital capacity (VC)** The maximum volume of air (about 4600 mL)that can be forcefully expelled from the lungs following a maximal inspiration. Called a capacity because it is the sum of inspiratory reserve volume, tidal volume and expiratory reserve volume.

•**Total lung capacity (TLC)** The volume of air (about 5800 mL) contained in the lungs at the end of a maximal inspiration. Called a capacity because it is the sum of the 4 basic lung volumes.

TLC= RV+IRV+TV+ERV



Minute Respiratory Volume and Alveolar Ventilation

The Minute Respiratory Volume is the total amount of new air that is moved into the respiratory passages each minute. It is equal to the tidal volume multiplied by the respiratory rate. The normal tidal volume is about 500 mL, and the normal respiratory rate is about 12 breaths per minute; therefore the minute respiratory volume normally averages about 6 L/min.

Alveolar Ventilation **is the rate at which new air reaches the gas exchange areas of the lungs.** During inspiration, some of the air **never reaches** the gas exchange areas but, instead, fills respiratory passages; this air(150 ml) is called **dead space air.** Because alveolar ventilation is the total volume of new air that enters the alveoli, it is equal to the respiratory rate multiplied by the amount of new air that enters the alveoli with each breath.

Lung disease

Lung disease is any problem in the lungs that prevents the lungs from working properly. There are three main types of lung disease:

Airway diseases (Obstructive Disease) Make it more difficult to get air out of the lungs. These diseases affect the tubes (airways) that carry oxygen and other gases into and out of the lungs. They usually cause a narrowing or blockage of the airways. Airway diseases include asthma, chronic obstructive pulmonary disease (COPD) and Chronic bronchitis.

Lung tissue diseases (restrictive disease) Makes it more difficult to get air in to the lungs. These diseases affect the structure of the lung tissue. Scarring or inflammation of the tissue makes the lungs unable to expand fully (restrictive lung disease). This makes it hard for the lungs to take in oxygen and release carbon dioxide. An example of Lung tissue diseases include Fibrosis, Sarcoidosis, Muscular diseases , Chest wall deformities

Lung circulation diseases these diseases affect the blood vessels in the lungs. They are caused by clotting, scarring, or inflammation of the blood vessels. They affect the ability of the lungs to take up oxygen and release carbon dioxide. These diseases may also affect heart function. An example of a lung circulation disease is pulmonary hypertension.

Patterns of breathing

Normal rhythmic breathing is called **eupnea** (12-15 BPM). **Apnea** means no breathing while **dyspnea** is a conscious shortness of breathing (as in asthma). **Hypopnea** is a decrease (and **hyperpnea** is an increase) in the rate

or depth of breathing regardless whether the subject is conscious or unconscious. **Tachypnea** is a rapid shallow breathing. The normal pattern of breathing is the ramp signal which is characterized by gradually increasing cycles which last for 2 seconds and represent inspiration followed by sudden cut off which lasts for 3 seconds and represents expiration.

Lecture 10,11

Body Fluid

Body is formed by solids and fluids. The fluid part is more than 2/3 of the whole body. The maintenance of a relatively constant volume and a stable composition of the body fluids are essential for homeostasis. The relative constancy of the body fluids is remarkable because there is continuous exchange of fluid and solutes with the external environment, as well as within the different body compartments.

Water forms most of the fluid part of the body, plays a large part in normal body functions. Drinking enough water is essential for physiological processes such as circulation, metabolism, temperature regulation, and waste removal. Water is the main constituent of cells, tissues and organs; and is vital for life. It is the medium in which all transport systems function, allowing exchanges between cells, interstitial fluid and capillaries. Water maintains the vascular volume and allows blood circulation, which is essential for the function of all organs and tissues.

Daily intake of water

Water is added to the body by two major sources:

- It is ingested in the form of liquids or water in food, which together normally adds about 2200 ml/day to the body fluids.
- It is synthesized in the body by oxidation of carbohydrates, adding about 300 ml/day. However, intake of water is highly variable among different people and even within the same person on different days, depending on climate, habits, and level of physical activity.

Daily loss of body water

- Insensible Water Loss: Some water losses cannot be specifically regulated. For example, humans experience a continuous loss of water by evaporation from the respiratory tract and diffusion through the skin, which together account for about 900 ml/day of water loss under normal conditions. It occurs continually in all living humans.
- Insensible water loss through the skin occurs independently of sweating and is present even in people who are born without sweat glands; the average water loss by diffusion through the skin is about 300 -400 ml/day. This loss is minimized by the cornified layer of the skin, which provides a barrier against excessive loss by diffusion.
- Fluid Loss in Sweat: The amount of water lost by sweating is highly variable, depending on physical activity and environmental temperature. The volume of sweat normally is about (100 ml/day), but in very hot weather or during heavy exercise fluid loss in sweat occasionally increases to 1-2 L/hour. This fluid loss

would rapidly deplete the body fluids if intake were not also increased by activating the thirst mechanism.

- Water Loss in Feces: Only a small amount of water (100 ml/day) normally is lost in the feces. This loss can increase to several liters a day in people with severe diarrhea. For this reason, severe diarrhea can be life threatening if not corrected in a few days.
- Water Loss by the Kidneys: The remaining water loss from the body occurs in the urine excreted by the kidneys. Multiple mechanisms control the rate of urine excretion. In fact, the most important means by which the body maintains a balance between water intake and output, as well as a balance between intake and output of most electrolytes in the body, is by controlling the rates at which the kidneys excrete these substances. For example, urine volume can be as low as 0.5 L/day in a dehydrated person or as high as 20 L/day in a person who has been drinking remarkable amounts of water.

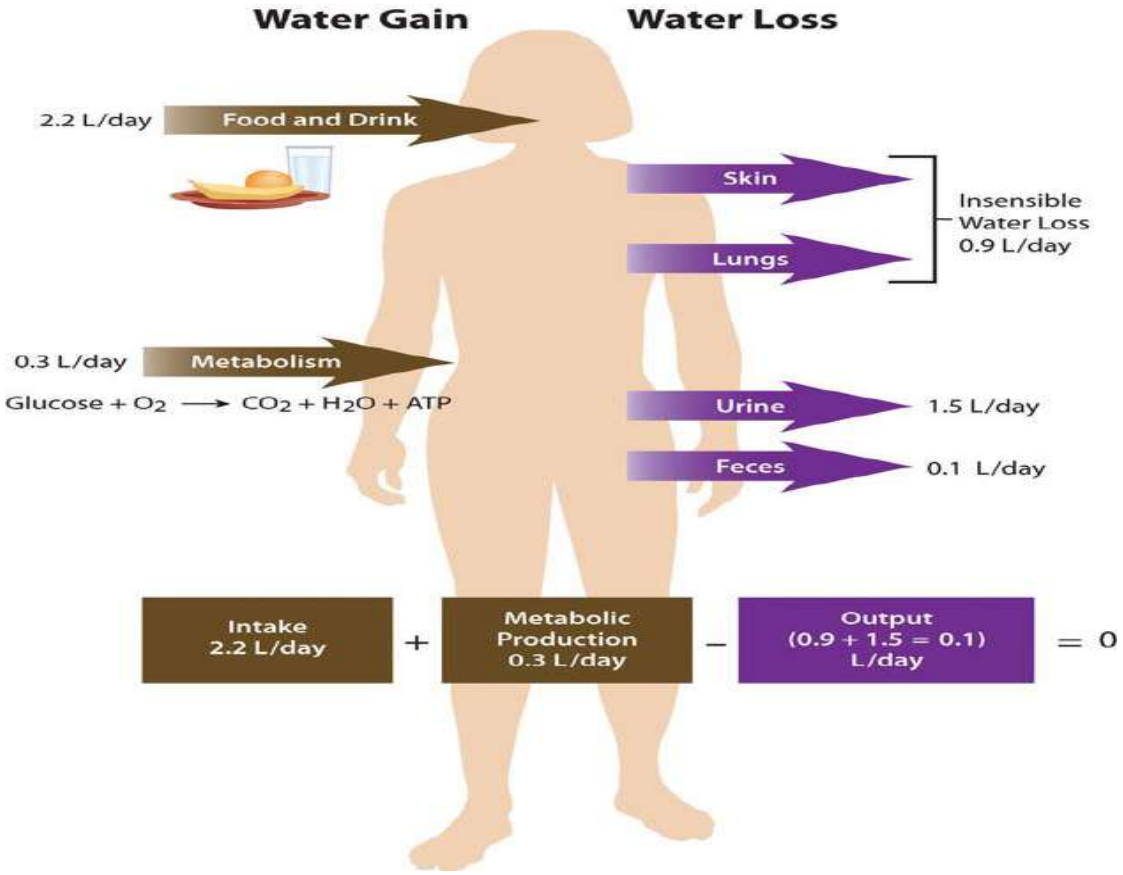


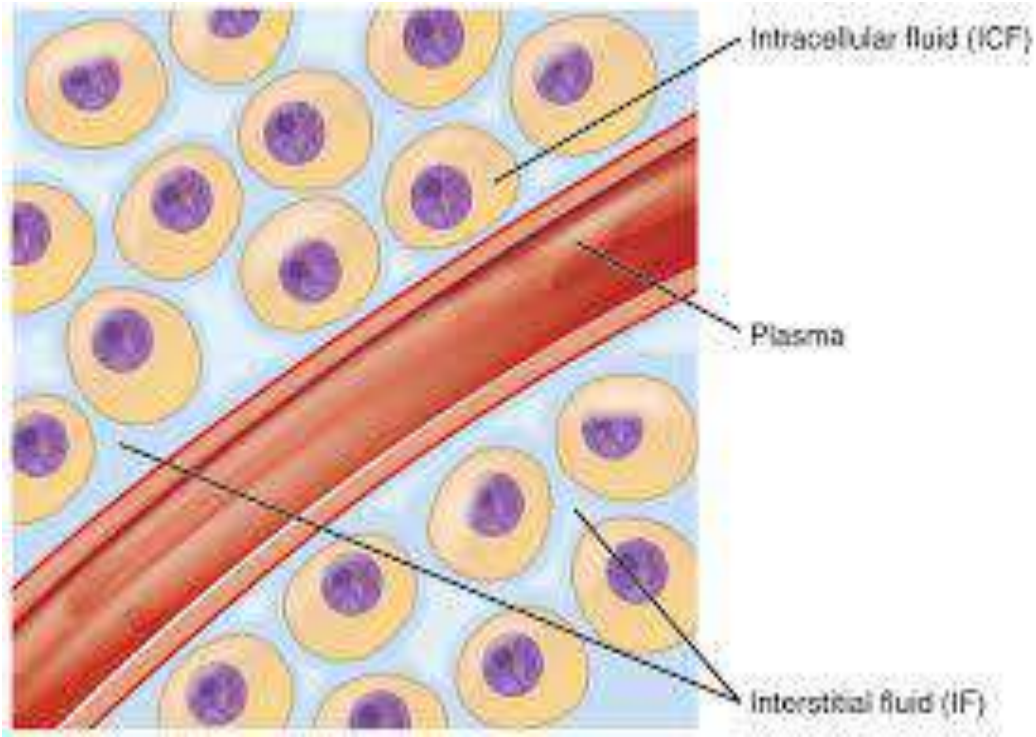
Figure: Daily Fluid Loss and Gain

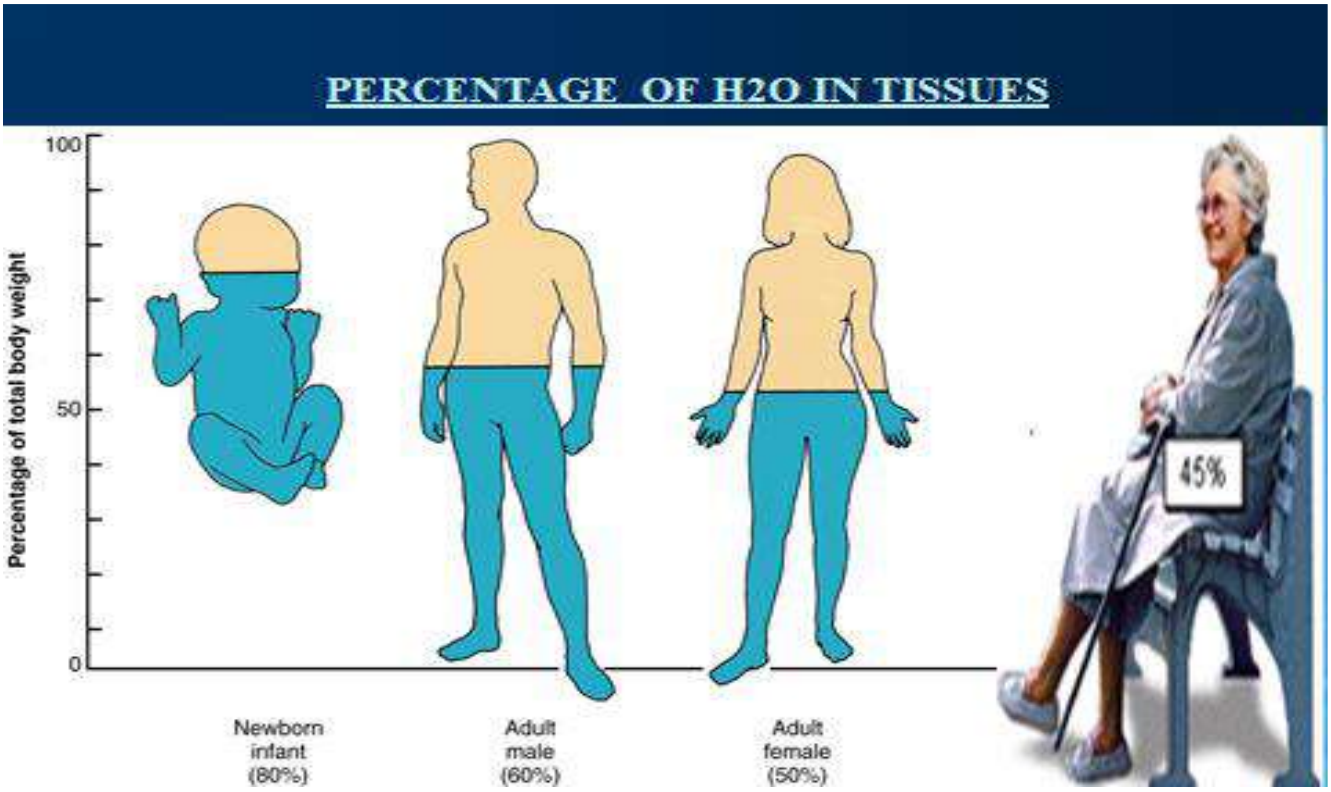
Body Fluid Compartments

The total body fluid is distributed mainly between two compartments: the ***extracellular fluid*** and the ***intracellular fluid***. The extracellular fluid is divided into the ***interstitial fluid*** and **the blood *plasma***.

There is another small compartment of fluid that is referred to as ***transcellular fluid;*** this compartment includes fluid in the synovial, peritoneal, pericardial, and intraocular spaces, as well as the cerebrospinal fluid; it is usually considered to be a specialized type of extracellular fluid. All the transcellular fluids together constitute about 1 to 2 liters.

In the average 70-kilogram adult human, ***the total body water is about 60 per cent of the body weight***, or *about 42 liters*. This percentage can change, depending on age, gender, and degree of obesity. As a person grows older, the percentage of total body weight that is fluid gradually decreases. This is due in part to the fact that aging is usually associated with an increased percentage of the body weight being fat, which decreases the percentage of water in the body. Because women normally have more body fat than men, they contain slightly less water than men in proportion to their body weight.





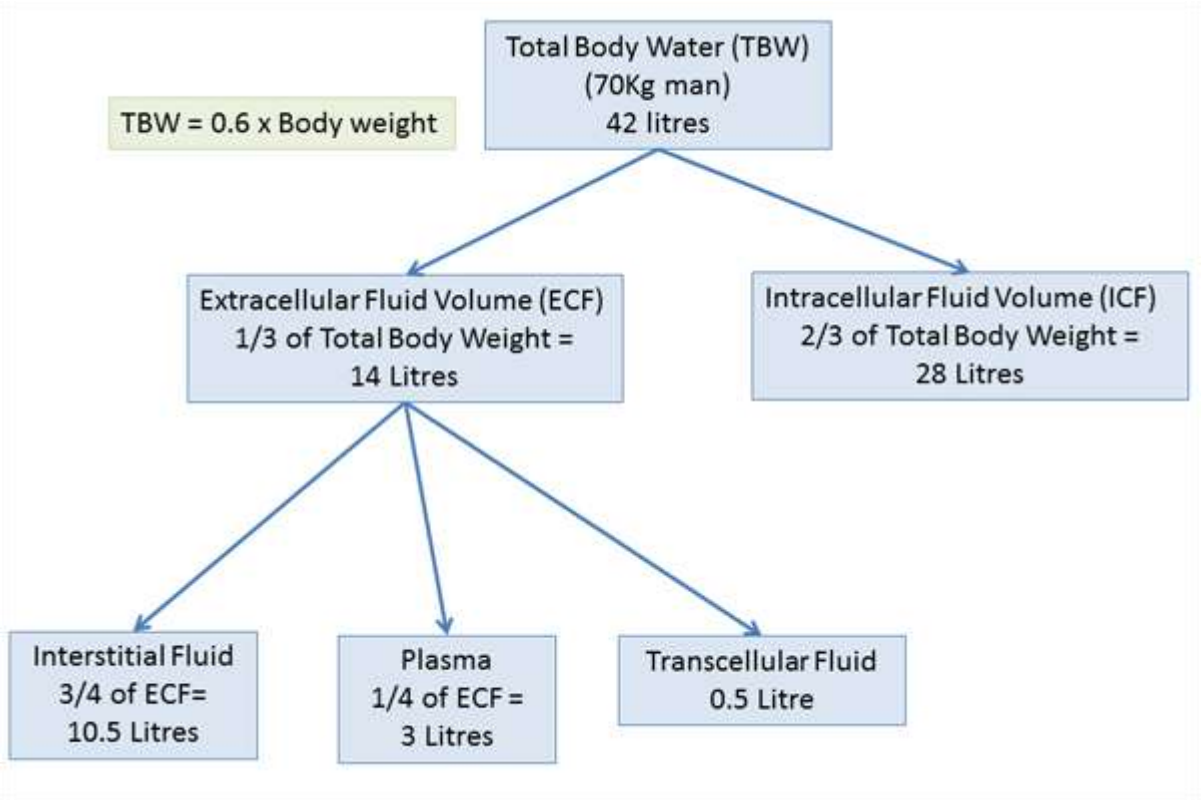
Intracellular Fluid Compartment

About ***28 of the 42 liters*** of fluid in the body are inside the 75 trillion cells and are collectively called the *intracellular fluid*. Thus, the intracellular fluid constitutes about ***40 per cent of the total body weight*** in an "average" person. 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.

Extracellular Fluid Compartment

All the fluids outside the cells are collectively called the *extracellular fluid*. Together these fluids account for about ***20 per cent of the body weight, or about 14 liters*** in a normal 70-kilogram adult. The two largest compartments of the extracellular fluid are the ***interstitial fluid***, which makes up more than ***three fourths*** of the extracellular fluid, and the ***plasma***, which makes up almost ***one fourth*** of the extracellular fluid, or about **3 liters**. The plasma is the noncellular part of the blood; it exchanges substances continuously with the interstitial fluid through the pores of the capillary membranes. These pores are highly permeable to almost all solutes in the extracellular fluid except the proteins. Therefore, the extracellular fluids are constantly mixing, so that the

plasma and interstitial fluids *have about the same composition* ***except for proteins***, *which have a* ***higher concentration in the plasma***.



Important Constituents of Extracellular Fluid

Because the plasma and interstitial fluid are separated only by highly permeable capillary membranes, their ionic composition is similar. The most important difference between these two compartments is the ***higher concentration of protein in the plasma***. The extracellular fluid, including the plasma and the interstitial fluid, contains ***large amounts of sodium and chloride ions, reasonably large amounts of bicarbonate ions, but only small quantities of potassium, calcium, magnesium, phosphate, and organic acid ions***. This allows the cells to remain continually bathed in a fluid that contains the proper concentration of electrolytes and nutrients for optimal cell function.

Important Constituents of the Intracellular Fluid

The intracellular fluid is separated from the extracellular fluid by a cell membrane that is highly permeable to water but not to most of the electrolytes in the body. The intracellular fluid contains ***large amounts of potassium and phosphate ions plus moderate quantities of magnesium and sulfate ions***, all of which have low concentrations in the extracellular fluid. Also, cells contain ***large amounts of protein***,

almost four times as much as in the plasma. In contrast to the extracellular fluid, ***it contains*** only ***small quantities*** of sodium and chloride ions and almost calcium ions.

Ion	Plasma, mmoles/L	Interstitial fluid, mmoles/L	Skeletal muscle cell, mmoles/L
Cations			
Na^+	142.0	145.1	10.0
K^+	4.3	4.4	140.0
Ca^{2+}(ionized)	2.5	2.4	1.0
Mg^{2+}(ionized)	1.1	1.1	17
Others	4.0		
Total	154	153	168
Anions			
Cl^-	114.0	117.4	4.0
HCO_3^-	24.0	27.1	7.0
HPO_4^{2-}, $H_2PO_4^-$	1.0	1.2	40.0
Proteins	1.5	0.1	3.0
Other	10.0	6.2	84.0
Total	154	153	138

Two major factors contribute to the movement of fluid from one compartment to another:

1- hydrostatic pressure

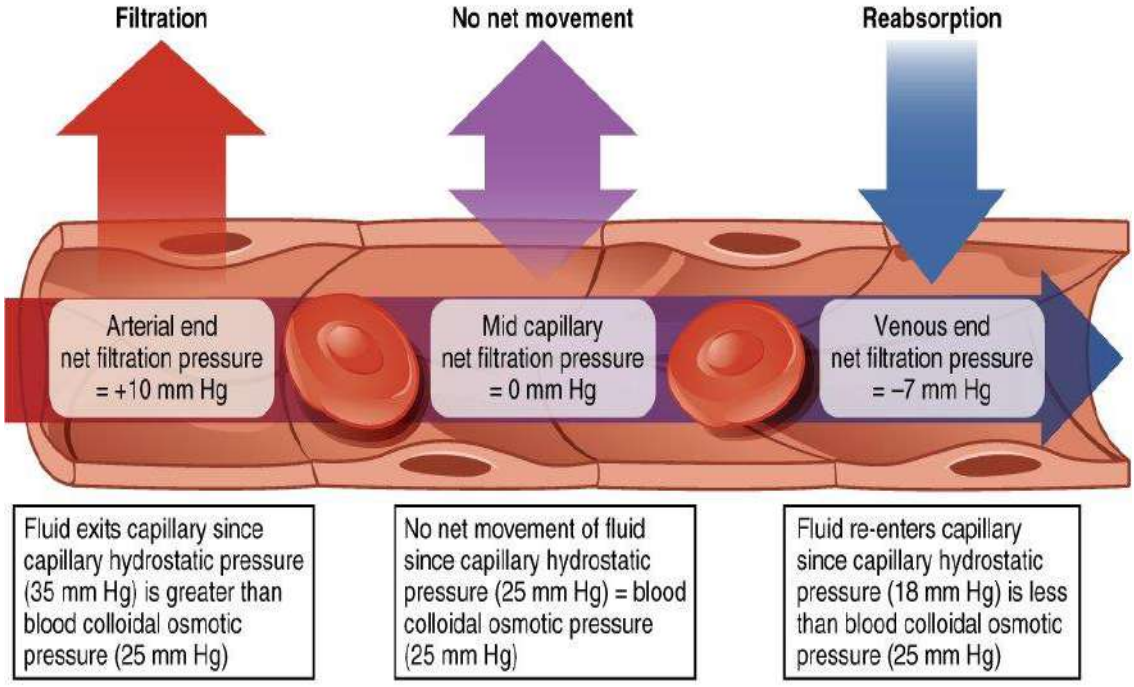
2- osmotic pressure

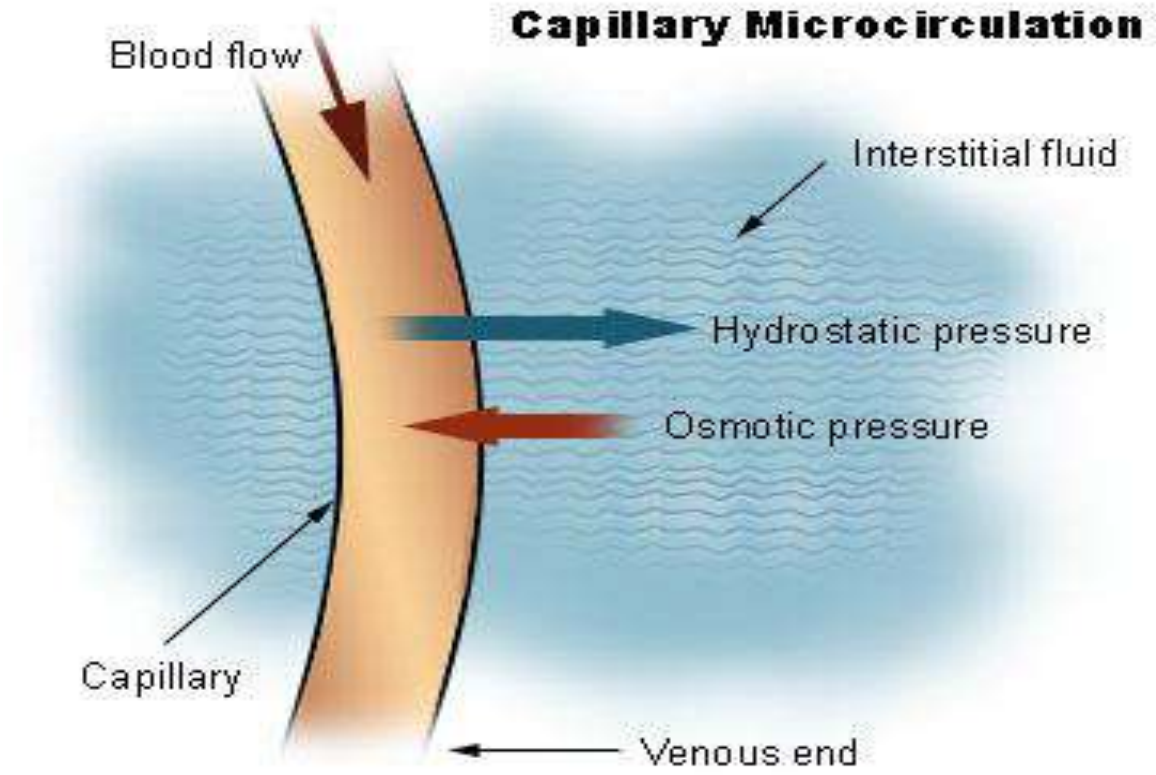
Hydrostatic pressure refers to the pressure that any fluid in a confined space exerts. If fluid is in a container, there will be some pressure on the wall of that container, we can see that the pressure pushing against its wall is greater at the bottom, than it will be at the top. This is partly related to the force of gravity.

The capillaries are the equivalent of a column shaped container, turned on its side. The pressure that blood exerts in the capillaries is known as blood pressure. The force of hydrostatic pressure means that as blood moves along the capillary, fluid moves out through its pores and into the interstitial space. This movement means that the pressure exerted by the blood will become lower, as the blood moves along the capillary, from the arterial to the venous end.

Osmotic pressure Osmotic pressure is the minimum pressure which needs to be applied to a solution to prevent the inward flow of its pure solvent across a semipermeable membrane. For example, in blood vessels, fluids leave the plasma at the arteriolar ends of capillaries and enter the interstitial spaces because of the net outward force of hydrostatic pressure (blood pressure). Fluid returns to the plasma from the interstitial spaces at the venular ends of capillaries because of the net inward force of colloid osmotic pressure due to the plasma proteins. Likewise, tissue fluid and lymph, fluid leaves the interstitial spaces and enters the lymph capillaries due to the hydrostatic pressure of the interstitial fluid. Hydrostatic pressure in the cells and surrounding interstitial fluid is ordinarily equal and remains stable. Therefore, any net fluid movement is likely to be the result of changes in osmotic pressure.

Due to the pressure of the blood in the capillaries, blood hydrostatic pressure is greater than interstitial fluid hydrostatic pressure, promoting a net flow of fluid from the blood vessels into the interstitium. However, because large plasma proteins, especially albumin, cannot easily cross through the capillary walls, their effect on the osmotic pressure of the capillary interiors will to some extent balance the tendency for fluid to leak from the capillaries. In conditions where plasma proteins are reduced (e.g. from being lost in the urine or from malnutrition), or blood pressure is significantly increased, a change in net filtration pressure and an increase in fluid movement across the capillary result in excess fluid build-up in the tissues (edema).





Thirst Mechanism: Why Do We Drink?

Thirst is an osmoregulatory mechanism to increase water input. The thirst mechanism is activated in response to changes in water volume in the blood, but is even more sensitive to changes in blood osmolality. Blood osmolality is primarily driven by the concentration of sodium cations. The urge to drink results from a complex interplay of hormones and neuronal responses that coordinate to increase water input and contribute toward fluid balance and composition in the body. The "thirst center" is contained within the hypothalamus, a portion of the brain that lies just above the brain stem. In older people the thirst mechanism is not as responsive and as we age there is a higher risk for dehydration. Thirst happens in the following sequence of physiological events:

1. Receptor proteins in the kidney, heart, and hypothalamus detect decreased fluid volume or increased sodium concentration in the blood.
2. Hormonal and neural messages are relayed to the brain's thirst center in the hypothalamus.
3. The hypothalamus sends neural signals to higher sensory areas in the cortex of the brain, stimulating the conscious thought to drink.
4. Fluids are consumed.
5. Receptors in the mouth and stomach detect mechanical movements involved with fluid ingestion.
6. Neural signals are sent to the brain and the thirst mechanism is shut off.

The Kidneys Detect Blood Volume

The kidneys are two bean-shaped organs, each about the size of a fist and located on either side of the spine just below the rib cage. The kidneys filter about 190 liters of blood and produce (on average) 1.5 liters of urine per day. Urine is mostly water, but it also contains electrolytes and waste products, such as urea. The amount of water filtered from the blood and excreted as urine is dependent on the amount of water in, and the electrolyte composition of, blood.

Kidneys have protein sensors that detect blood volume from the pressure, or stretch, in the blood vessels of the kidneys. When blood volume is low, kidney

cells detect decreased pressure and secrete the enzyme, renin. Renin travels in the blood and cleaves another protein into the active hormone, angiotensin. Angiotensin targets three different organs (the adrenal glands, the hypothalamus, and the muscle tissue surrounding the arteries) to rapidly restore blood volume and, consequently, pressure.

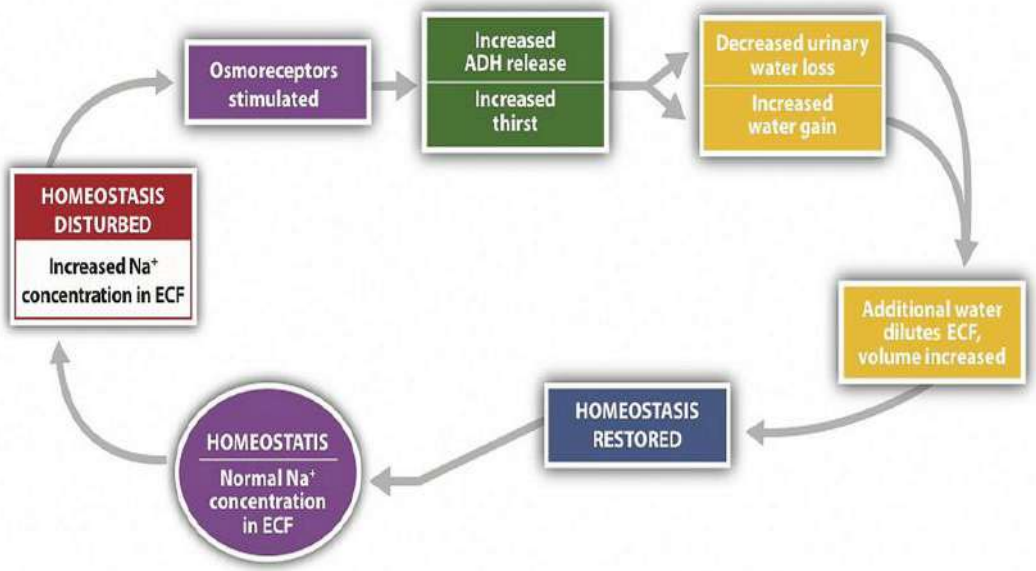
First, angiotensin travels to the outer perimeter of the adrenal glands and stimulates release of the hormone aldosterone. Aldosterone travels back to the kidneys and stimulates the sodium-potassium pump. As a result of the pump's work, the blood reabsorbs the sodium from the liquid that has already been filtered by the kidneys.

Water follows sodium into the blood by osmosis, resulting in less water in the urine and restored fluid balance and composition of blood.

Next, angiotensin travels to the hypothalamus where it stimulates the thirst mechanism and the release of antidiuretic hormone. Antidiuretic hormone travels back to the kidneys where it increases water reabsorption.

Lastly, angiotensin targets smooth muscle tissue surrounding arteries, causing them to contract (narrow) the blood vessels, which assists in elevating blood pressure.

The Hypothalamus Detects Blood Osmolality



Sodium and fluid balance are intertwined.

Osmoreceptors (specialized protein receptors) in the hypothalamus detect sodium concentration in the blood. In response to a high sodium level, the hypothalamus activates the thirst mechanism and concurrently stimulates the release of antidiuretic hormone. Thus, it is not only kidneys that stimulate antidiuretic- hormone release, but also the hypothalamus. This dual control of antidiuretic hormone release allows for the body to respond to both decreased blood volume and increased blood osmolality.

The Adrenal Glands Detect Blood Osmolality

Cells in the adrenal glands sense when sodium levels are low, and when potassium levels are high, in the blood. In response to either stimulus, they release aldosterone. Therefore, aldosterone is released in response to angiotensin stimulation and is also controlled by blood electrolyte concentrations. In either case, aldosterone communicates the same message, which is to increase sodium reabsorption and consequently water reabsorption. In exchange, potassium is excreted.

The mechanisms involved in regulating water input and output are intertwined with those controlling electrolyte balance. In a healthy individual, this multilevel coordinated control of fluid and electrolyte levels in the body ensures homeostasis. However, in a

person with heart failure, the crosstalk between organs can have dire consequences. Heart failure results in a decrease in blood output from the heart, which lowers blood pressure. In response to the lower blood pressure the kidneys release renin, leading to the release of antidiuretic hormone. Antidiuretic hormone acts on the kidneys and increases water reabsorption, thereby increasing blood volume and pressure. This makes the heart work harder and exacerbates the heart condition. To block this response, people with heart failure are treated with drugs that block the kidneys' compensatory response. Diuretics are drugs that act either by inhibiting the actions of antidiuretic hormone or by promoting sodium excretion in the urine. This increases water output and blood pressure is reduced. Diuretics, along with other drugs, are useful in treating heart failure and in decreasing blood pressure in people with hypertension.

Body Fluid-Related Diseases and Disorders

1- Acidosis

Acidosis describes increased acidity in the blood and other tissues; acidosis is the process leading to the state of academia, usually measured as arterial pH below 7.35. there are two types of acidosis

A- Metabolic acidosis may occur as a result of increased metabolic acids, either from increased production of metabolic acids, or decreased excretion of acids by the kidneys. The lungs compensate for metabolic acidosis by increasing the exhalation of CO2.

B- Respiratory acidosis occurs from an increased concentration of carbon dioxide in the blood, usually due to hypoventilation resulting from pulmonary problems. In respiratory acidosis, carbon dioxide concentration rises, but bicarbonate is normal or increased.

2- Alkalosis

- Alkalosis is the increased alkalinity of blood and other tissues, generally occurring when the blood pH is above 7.45. Alkalosis may be respiratory or metabolic.
- Respiratory alkalosis may be caused by hyperventilation, which causes a loss of carbon dioxide.
- Metabolic alkalosis may be caused by prolonged vomiting, which reduces the amount of hydrochloric acid in the stomach, diuretics, dehydration, endocrine disorders, or consumption of alkali.

3- Edema

Edema is an abnormal accumulation of fluid beneath the skin or in one or more cavities of the body that produces swelling. During edema, there is either increased secretion of fluid into the interstitium or impaired removal of this fluid from the interstitium, resulting in fluid accumulation. Edema may also occur as a result of cardiac failure due to the rise in hydrostatic pressure. A fall in osmotic pressure occurs in nephrotic syndrome and liver failure, and may cause edema.

4- Dehydration

decrease in water content of the body is known as dehydration. dehydration is of three types:

1. Mild dehydration when fluid loss is about 5% of total body fluids.

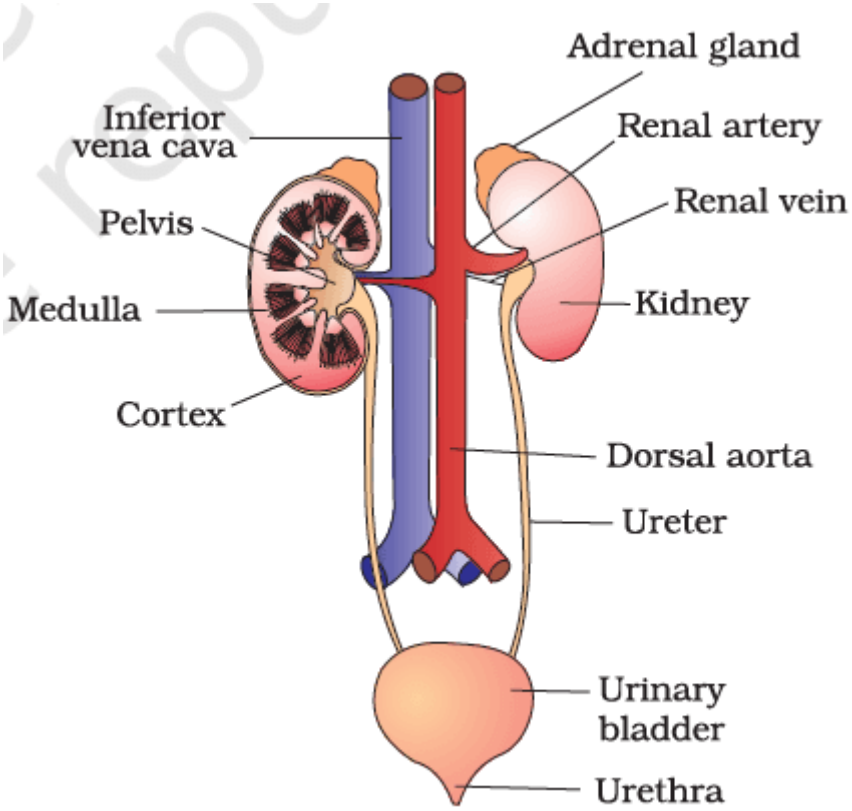
2. Moderate dehydration when fluid loss is about 10%.

3. Severe dehydration when fluid loss is about 15%.

Lectures 12,13,14

The urinary system

urinary system consists of the kidneys, ureters, urinary bladder and the urethra. One of the major functions of the Urinary system is the process of excretion.



Excretion is the process by which the unwanted substances and metabolic wastes are eliminated from the body. Although different organs such as gastro intestinal (GI) tract, liver, skin and lungs are involved in removal of wastes from the body, their excretory capacity is limited. But, the renal system or urinary system has maximum capacity of excretory function.

The kidney

The two kidneys lie on the posterior wall of the abdomen, outside the peritoneal cavity. Each kidney of the adult human weighs about 150 grams

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and is about the size of a clenched fist. The medial side of each kidney contains an indented region called the hilum through which pass the renal artery and vein, lymphatic, nerve supply, and ureter, which carries the final urine from the kidney to the bladder ،where it is stored until emptied. The kidney is surrounded by a tough, fibrous capsule that protects its delicate inner structures.

Kidneys perform several vital functions besides formation of urine. By excreting urine, kidneys play the principal role in homeostasis. Thus, the functions of kidneys are:

1. Role of homeostasis The primary function of kidneys is homeostasis. It is accomplished by the formation of urine. During the formation of urine, kidneys regulate various activities in the body, which are concerned with homeostasis such as:

i. Excretion of Waste Products.

Kidneys excrete the unwanted waste products which are formed during metabolic activities:

a. Urea – end product of amino acid metabolism.

b. Uric acid – end product of nucleic acid metabolism.

c. Creatinine – end product of metabolism in muscles.

d. Bilirubin – end product of hemoglobin degradation.

e. Products of metabolism of other substances

f. Harmful foreign chemical substances like toxins, drugs, heavy metals, pesticides, etc.

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ii. Maintenance of Water Balance

Kidneys maintain the water balance in the body by conserving water when it is decreased and excreting water when it is excess in the body.

iii. Maintenance of Electrolyte Balance Maintenance of electrolyte balance, especially sodium is in relation to water balance. Kidneys retain sodium if the osmolarity of body water decreases and eliminate sodium when osmolarity increases.

iv. Maintenance of Acid–Base Balance

The kidneys contribute to acid-base regulation, along with the lungs and body fluid buffers, by excreting acids and by regulating the body fluid buffer stores. The kidneys are the only means of eliminating from the body certain types of acids, such as sulfuric acid and phosphoric acid, generated by the metabolism of proteins.

2. Hemopoietic function

Kidneys stimulate the production of erythrocytes by secreting erythropoietin, which stimulates the production of red blood cells by hematopoietic stem cells in the bone marrow. Erythropoietin is the important stimulating factor for erythropoiesis. Kidney also secretes another factor called thrombopoietin, which stimulates the production of thrombocytes.

3. Endocrine function

Kidneys secrete many hormonal substances in addition to erythropoietin and thrombopoietin. The hormones secreted by kidneys are:

i. Erythropoietin

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ii. Thrombopoietin

iii. Renin

iv. 1, 25-dihydroxycholecalciferol (calcitriol)

v. Prostaglandins.

4. Regulation of blood pressure

Kidneys play an important role in long-term regulation of arterial blood pressure by excreting variable amounts of sodium and water. The kidneys also contribute to short term arterial pressure regulation by secreting hormones and vasoactive factors.

5. Regulation of blood calcium level

Kidneys play a role in the regulation of blood calcium level by producing the active form of vitamin D,1,25-dihydroxyvitamin D3 (calcitriol), by hydroxylating this vitamin. Calcitriol is essential for normal calcium deposition in bone and for calcium reabsorption by the gastrointestinal tract.

6. Glucose Synthesis (gluconeogenesis)

The kidneys synthesize glucose from amino acids and other precursors during prolonged fasting, a process referred to as gluconeogenesis. The kidneys' capacity to add glucose to the blood during prolonged periods of fasting rivals that of the liver.

The components of kidney are arranged in three layers:

1. Outer cortex

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Cortex is dark and granular in appearance. It contains renal corpuscles and convoluted tubules. At intervals, cortical tissue penetrates medulla in the form of columns, which are called renal columns or columns of Bertini.

2. Inner medulla

Medulla contains tubular and vascular structures arranged in parallel radial lines. It is divided into 8 to 18 medullary or Malpighian pyramids.

3. Renal sinus.

Renal sinus consists of the following structures:

i. Renal pelvis: Upper expanded part of ureter.

ii. Subdivisions of pelvis –major calyces and minor calyces.

iii. Branches of nerves, arteries and veins.

iv. Loose connective tissues and fat.

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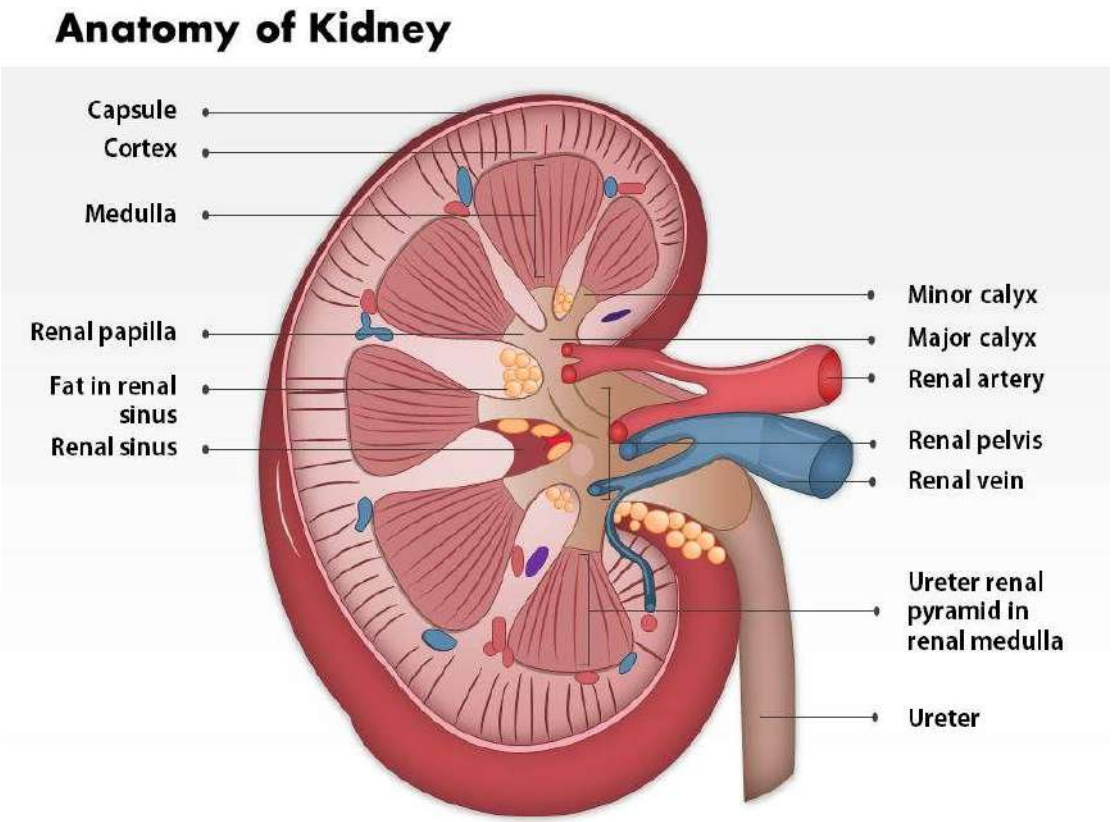

The kidney consists of :

[A] Nephron

[B] blood vessels

[C] Nerves

[A] nephron it is the basic structural and functional unit of the kidney and capable of forming urine by itself. There are about 1-1.3 million nephrons in each kidney in human.

The kidney cannot regenerate new nephrons. Therefore, with renal injury, disease, or normal aging, the number of nephrons gradually decreases. After age 40 years, the number of functioning nephrons usually decreases about 10 percent every 10 years. Each nephron is formed by two parts:

1. A blind end called renal corpuscle or Malpighian corpuscle

2. A tubular portion called renal tubule.

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Renal corpuscle

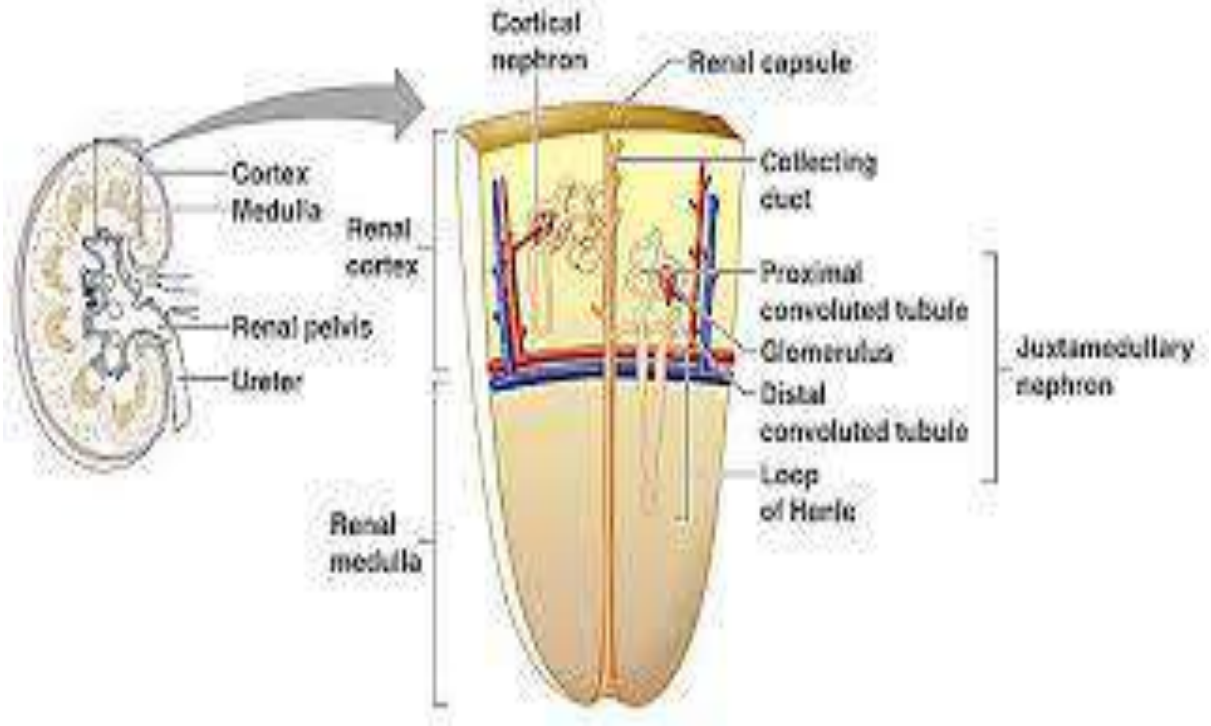
The renal corpuscle is also known as Malpighian corpuscle. It is a spheroidal and slightly flattened structure with a diameter of about 200 µ. The function of the renal corpuscle is the filtration of blood which forms the first phase of urine formation. Renal corpuscle is situated in the cortex of the kidney either near the periphery or near the medulla. Based on the situation of renal corpuscle, the nephrons are classified into two types:

1. Cortical nephrons or superficial nephrons

Cortical nephrons are the nephrons, which have their corpuscles in the outer cortex of the kidney near the periphery. These are short and comprise about 80-85% of the total nephrons .

2. Juxtamedullary Nephrons

Juxtamedullary nephrons are the nephrons which have their corpuscles in the inner cortex near medulla or corticomedullary junction. These have long loops of Henle and extend into the medulla. These are about 20%



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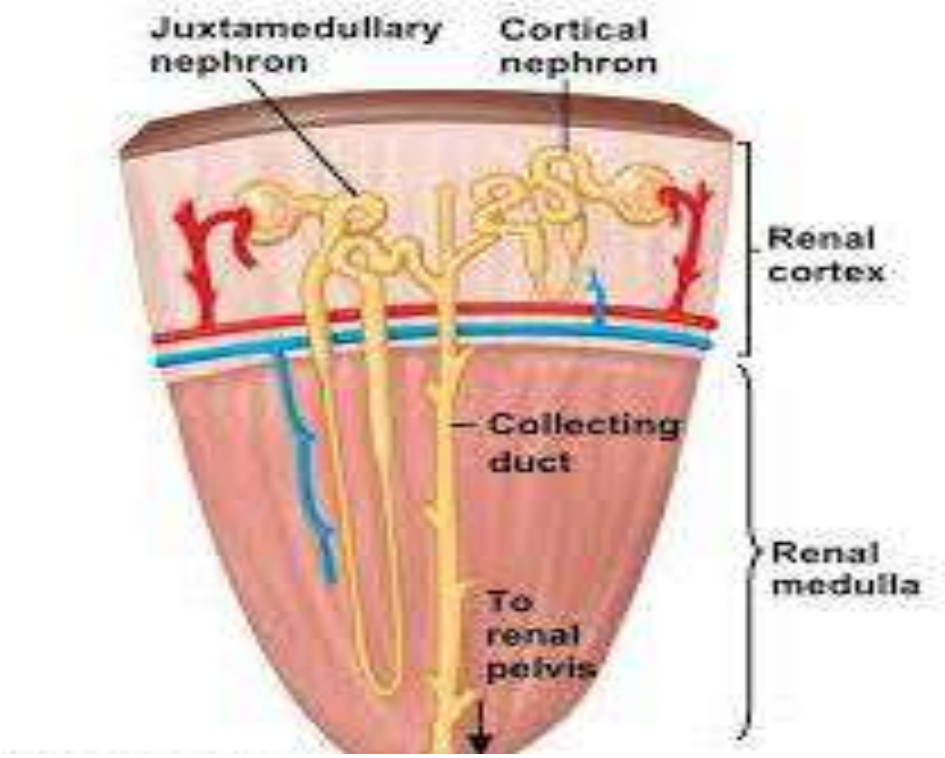

Features of two types of nephron

Features	Cortical nephron	Juxtamedullary nephrons
Situation of renal corpuscle	Outer cortex near the periphery	Inner cortex near medulla
Loop of Henle	Short Hairpin bend penetrates only up to outer zone of medulla	Long Hairpin bend penetrates up to the inner zone of medulla
Function	Formation of urine	Mainly the concentration of urine and formation of urine

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Structure of renal corpuscle and tubular portion of nephron.

The **renal corpuscle** is formed by two portions:

1. Glomerulus. is a cluster of branching capillaries enclosed by Bowman's capsule.

2. Bowman's capsule. It is encloses the glomerulus. The structure of Bowman's capsule is like a funnel with filter paper.

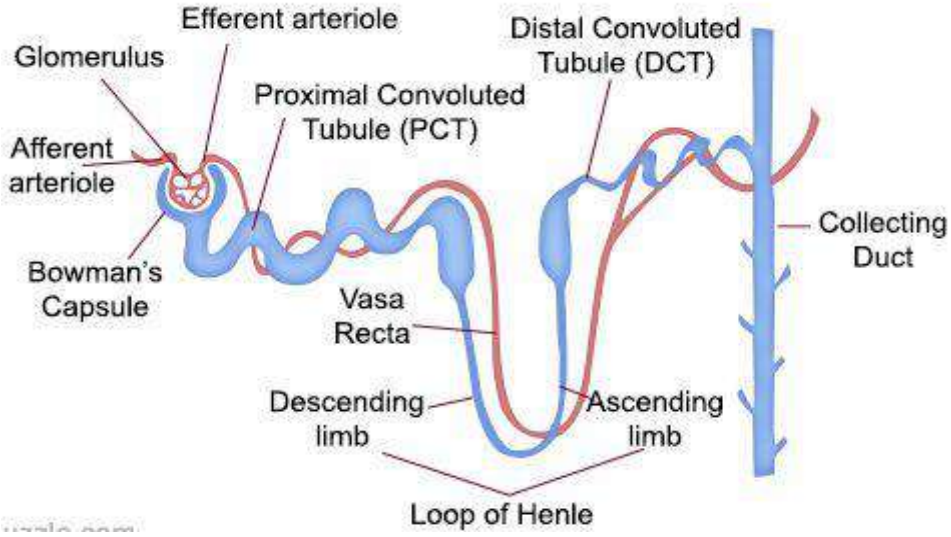
Tubular portion of nephron

The tubular portion of nephron is the continuation of Bowman's capsule. It is made up of three parts:

1. The proximal convoluted tubule.

2. Loop of Henle.

3. The distal convoluted tubule



1. Proximal convoluted tubule

Reabsorption in the proximal tubule is of the filtered Na and H_2O,almost all the filtered glucose, amino acids, organic acids, and small amount of protein which is present, as well as much of the K, Ca, po_4 and urea are reabsorbed in the proximal tubule.

2. Loop of Henle

Loop of Henle consists of:

i. Descending limb : Descending limb of loop of Henle is made up of thick descending segment and thin descending segment. The thick descending segment is the direct continuation of the proximal convoluted tubule. It descends down into medulla. The thick descending segment is continued as thin descending segment.

ii. Hairpin bend : The thin descending segment is continued as hairpin bend of the loop. The hairpin bend is continued as the ascending segment of loop of Henle.

iii. Ascending limb: Ascending Limb Ascending limb of Henle's loop has two parts, thin ascending segment and thick ascending segment. Thin ascending segment is the continuation of hairpin bend. The thin ascending segment is continued as thick ascending segment. Thick ascending segment ascends to the cortex and continues as distal convoluted tubule.

3.The distal convoluted tubule (Collecting duct)

. Its permeability to water is under the control of ADH similar to the cortical collecting duct.

. It is permeable to urea (unlike the cortical collecting duct).

. It is capable of secreting H ions against concentration gradient.

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B-Blood vessels of kidneys are highly specialized to facilitate the functions of the nephrons in the formation of urine. Renal arteries supply the blood to the kidneys.

In the adults, during resting conditions both the kidneys receive 1,300 mL of blood per minute or about 26% of the cardiac output. Kidneys are the second organs to receive maximum blood flow, the first organ being the liver which receives 1,500 mL per minute.

RENAL BLOOD VESSELS

Renal artery arises directly from abdominal aorta and enters the kidney through the hilum. While passing through renal sinus, the renal artery divides into many segmental arteries, which subdivide into interlobar arteries .Each interlobar artery passes in between the medullary pyramids. At the base of the pyramid, it turns and runs parallel to the base of pyramid forming arcuate artery. Each arcuate artery gives rise to interlobular arteries. The interlobular arteries run through the renal cortex perpendicular to arcuate artery. From each interlobular artery, several afferent arterioles arise.

The afferent arteriole enters the Bowman's capsule and forms glomerular capillary tuft. The **afferent arteriole** divides into 4 or 5 large capillaries. Each large capillary divides into small capillaries, which form the loops. And, the capillary loops unite to form the **efferent arteriole**, which leaves the Bowman's capsule. The efferent arterioles form a second capillary network called **peritubular capillaries** which surround the tubular portions of the nephrons.

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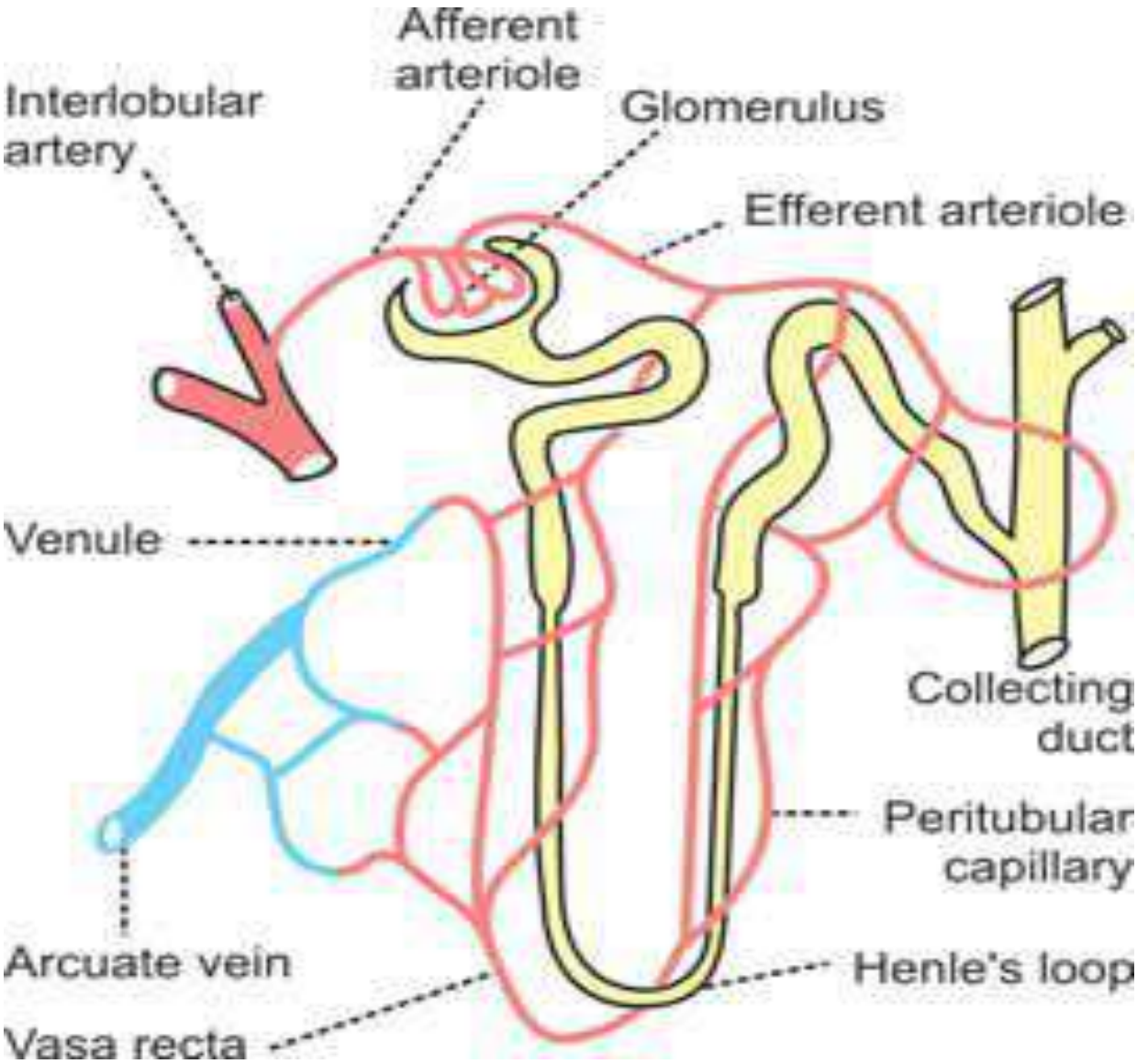

Thus, the renal circulation forms a portal system by the presence of two sets of capillaries, glomerular capillaries and peritubular capillaries. The peritubular capillaries are found around the tubular portion of cortical nephrons only. The tubular portion of juxtamedullary nephrons are supplied by some specialized capillaries called vasa recta. Vasa recta arise directly from the efferent arteriole of the juxtamedullary nephrons and run parallel to the renal tubule into the medulla and ascend up towards the cortex . The peritubular capillaries and vasa recta drain into the venous system. Venous system starts with peritubular venules and continues as interlobular veins,

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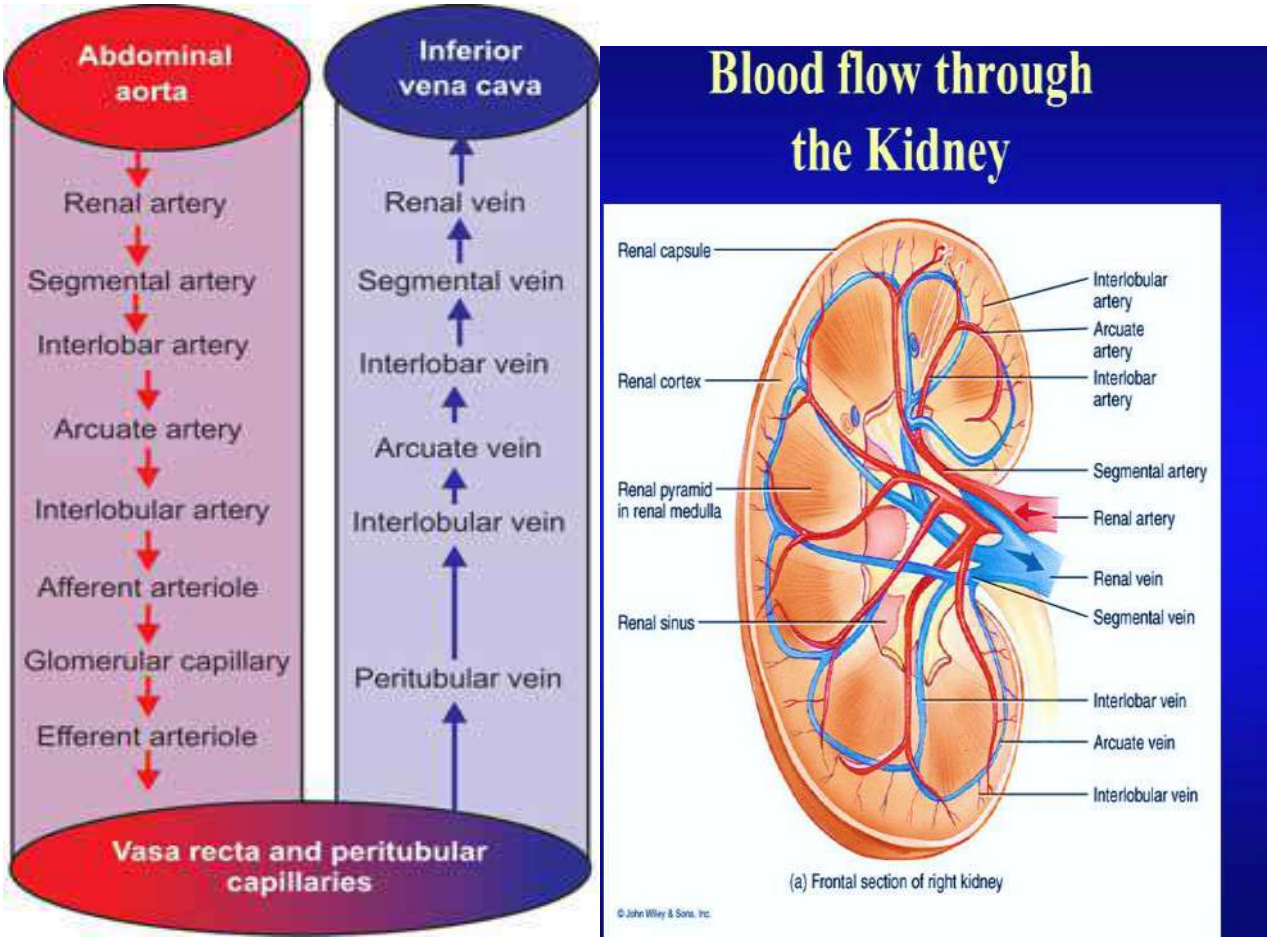
arcuate veins, interlobar veins, segmental veins and finally the renal vein .Renal vein leaves the kidney through the hilum and joins inferior vena cava.



(C) Nerve supply: the kidney has a rich adrenergic sympathetic nerve supply distributed to the:

a- vascular smooth muscle to cause vasoconstriction.

b- juxtaglomerular cells to cause renin secretion.

c- tubular cells to stimulate Na and H_2O reabsorption.

Urine formation

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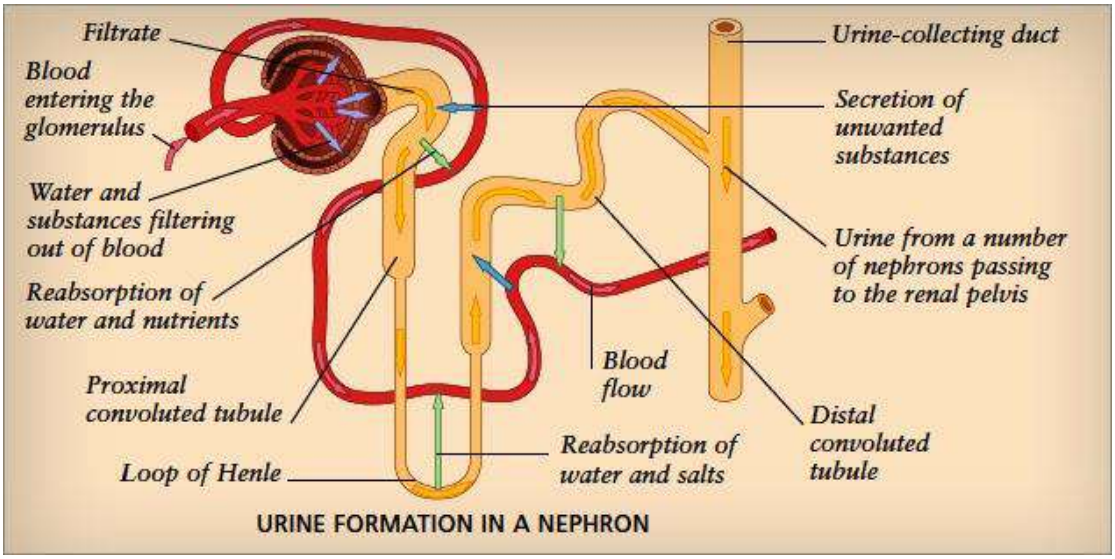
Urine formation is a blood cleansing function. Normally, about 26% of cardiac output enters the kidneys to get rid of unwanted substances. Kidneys excrete the unwanted substances in urine. Normally, about 1 to 1.5 L of urine is formed every day.



URINE FORMATION IN A NEPHRON

The mechanism of urine formation includes the following processes:

1. Glomerulus filtration. 2. Tubular reabsorption. 3. Tubular secretion. Then water conservation and finally Excretion.

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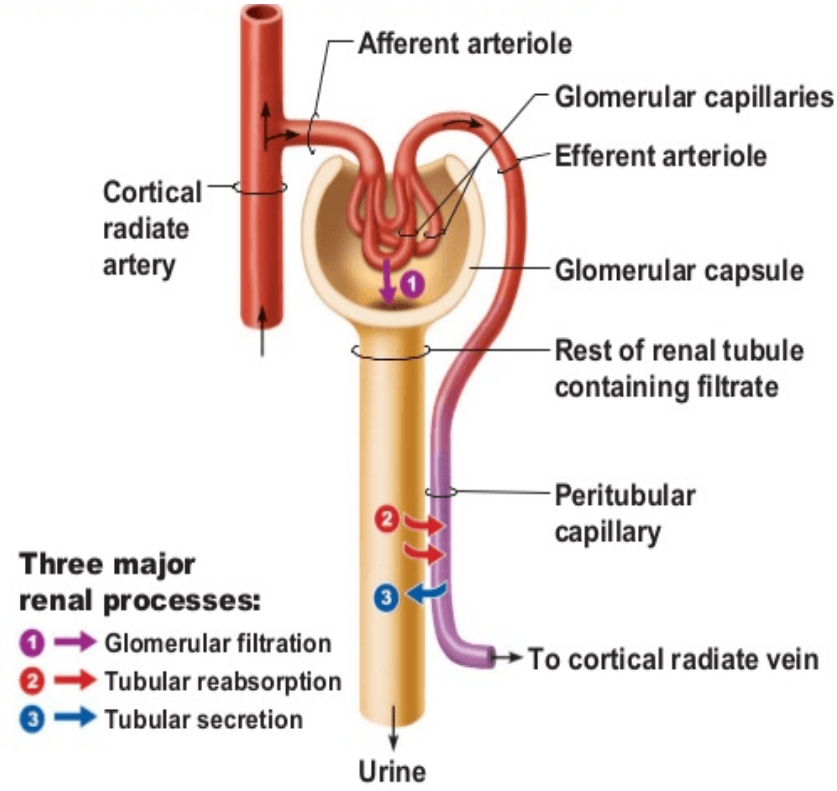

Glomerular Filtration

Glomerular filtration rate (GFR): It is the fluid that filtrate through the glomerulus into Bowman`s capsule each minute in all nephrons of both kidneys which is about 125 ml/min or 180 L/day .

The selectivity of the glomerular membrane depends on:

[1] Size of the molecules

[2] The electrical charges of the molecules:

Pressure determining filtration The pressures, which determine the glomerular filtration rate (GFR), are:

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1. Glomerular capillary pressure. It is the pressure exerted by the blood in glomerular capillaries. It is about 60 mm Hg and, varies between 45 and 70 mm Hg. Glomerular capillary pressure is the highest capillary pressure in the body.

2. Colloidal osmotic pressure in the glomeruli. It is exerted by plasma proteins in the glomeruli. The plasma proteins are not filtered through the glomerular capillaries and remain in the glomerular capillaries. These proteins develop the colloidal osmotic pressure which is about 25 mm Hg. It opposes glomerular filtration.

3. Hydrostatic pressure in the Bowman's capsule. It is the pressure exerted by the filtrate in Bowman's capsule. It is also called capsular pressure. It is about 15 mm Hg. It also opposes glomerular filtration.

Net Filtration Pressure

Net filtration pressure is the net fluid pressure across glomerulus. it determines the filtration rate of the kidney, the filtration membrane limits the medium-sized, large sized proteins and cells to pass through it , therefore these components remain in capillaries even after the filtration process. this results in creating a higher osmotic pressure in the glomerular capillaries (60 mm Hg) and nearly zero osmotic pressure in the Bowman's capsule. the hydrostatic pressure (15 mm Hg) in the Bowman's capsule allows the water to flow through the membrane. thus the net filtration pressure is the result of the influence of both hydrostatic as well as colloid osmotic pressure. It is otherwise known as effective filtration pressure or essential filtration pressure. The net filtration pressure = 60 – (25 + 15) = 20 mm Hg. =Glomerular capillary pressure – {Colloidal osmotic pressure + Hydrostatic pressure in Bowman's capsule}

*** Normal net filtration pressure is about 20 mm Hg, and, it varies between 15 and 20 mm Hg.

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Tubular Reabsorption

It is the process by which water and other substances are transported from renal tubules back to the blood. Large quantity of water (more than 99%), electrolytes and other substances are reabsorbed by the tubular epithelial cells.

The reabsorbed substances move into the interstitial fluid of renal medulla, then move into the blood in peritubular capillaries. Tubular reabsorbtion mainly occurs in the proximal tubule and the Loop of Henele.

Selective reabsorption

Tubular reabsorption is known as selective reabsorption because the tubular cells reabsorb only the substances necessary for the body. Essential substances such as glucose, amino acids and vitamins are completely reabsorbed from renal tubule. Whereas the unwanted substances like metabolic waste products are excreted through urine.

Mechanism of reabsorption

The basic transport mechanisms involved in tubular reabsorption are of two types:

1. Active reabsorption.

2. Passive reabsorption.

1. Active Reabsorption

Active reabsorption is the movement of molecules against the electrochemical gradient. It needs liberation of energy which is derived from ATP. By using Na+, K+ ATP pumps. The substances reabsorbed actively from the renal tubule are sodium, calcium, potassium, phosphates, sulfates, bicarbonates, glucose, amino acids, ascorbic acid, uric acid and ketone bodies.

2. Passive Reabsorption

Passive reabsorption is the movement of molecules along the electrochemical gradient. This process does not need energy. The substances reabsorbed by passively are chloride, urea and water. By using:

- ☒ Na^+ symporters (glucose, amino acid, etc.).
- ☒ Na^+ antiporters (H^+).
- ☒ Ion channels.
- ☒ Osmosis.

Regulation of tubular reabsorption Tubular reabsorption is regulated by three factors:

1. Glomerulo tubular balance. It is the balance between the filtration and reabsorption of solutes and water in kidney. This process helps in the constant reabsorption of solute particularly sodium and water from renal tubule.

Mechanism of Glomerulotubular Balance

Glomerulotubular balance occurs because of osmotic pressure in the peritubular capillaries. When GFR increases, more amount of plasma proteins accumulate in the glomerulus. Consequently, the osmotic pressure increases in the blood, by the time it reaches efferent arteriole and peritubular capillaries. The elevated osmotic pressure in the peritubular capillaries increases reabsorption of sodium and water from the tubule into the capillary blood.

2. Hormonal factors.

The hormones which regulate GFR are: Aldosterone, Angiotensin II, Antidiuretic hormone, Parathormone and Calcitonin.

3. Nervous factors.

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Activation of sympathetic nervous system increases the tubular reabsorption (particularly of sodium) from renal tubules. It also increases the tubular reabsorption indirectly by stimulating secretion of renin from juxtaglomerular cell. Renin causes formation of angiotensin II which increases the sodium reabsorption.

Tubular secretion

is the process by which the substances are transported from blood into renal tubules. It is also called tubular excretion.

Substances secreted in different segments of renal tubules

1. Potassium is secreted actively by sodium-potassium pump in proximal and distal convoluted tubules and collecting ducts.

2. Ammonia is secreted in the proximal convoluted tubule. 3. Hydrogen ions are secreted in the proximal and distal convoluted tubules. Maximum hydrogen ion secretion occurs in proximal tubule.

*** Thus, urine is formed in the nephron by the processes of glomerular filtration, selective reabsorption and tubular secretion.

Renal Function Tests

Properties of urine

- ☒ Volume: 1000 to 1500 mL/day.
- ☒ Reaction: Slightly acidic with pH of 4.5 to 6.
- ☒ Specific gravity: 1.010 to 1.025.
- ☒ Color: Normally, urine is straw colored.
- ☒ Odor: Fresh urine has light aromatic odor. If stored for some time, the odor becomes stronger due to bacterial decomposition.

Renal function tests: are the groups of tests that are performed to assess the functions of kidney.

The renal function tests are of three types:

1) Examination of urine alone.

2) Examination of blood alone.

3) Examination of blood and urine.

Routine Examination of Urine

During the routine examination of urine, the following are determined:

i. Specific gravity: Normally it is 1.010 to 1.025. But, in some conditions like chronic nephritis, it is decreased.

ii. Presence of normal constituents of urine in abnormal quantity:

Normally, substances like water, salt, amino acids and creatinine are excreted in urine either in greater or lesser amount. But, if abnormally large amount is excreted, it suggests some abnormal functional status of kidney.

- If 4 to 5 liters of water is excreted consistently per day, it is suggestive of diabetes insipidus.
- Abnormally low amount of water excretion indicates nephritis.
- Abnormal amount of salts or nutritive substances like amino acids appear in urine during congenital tubular defects.
- Abnormal albumin excretion occurs in defective filtration.
- Abnormal amount of glucose is excreted in diabetes mellitus.

iii. Microscopic examination: This reveals the presence of red blood cells, pus cells, epithelial cells and crystals which suggests the renal pathology.

Examination of blood

The level of plasma proteins, urea, uric acid and creatinine are determined in blood. The blood level of these substances is altered in renal failure.

Examination of blood and urine

Plasma Clearance

Plasma clearance is defined as the amount of plasma that is cleared off a substance in a given unit of time. It is also known as renal clearance

The determination of clearance value for certain substances helps in assessing the following renal functions:

1. Glomerular filtration rate
2. Renal plasma flow
3. Renal blood flow.

To determine the plasma clearance of a particular substance, measurement of the following factors is required:

1. Volume of urine excreted.
2. Concentration of the substance in urine.
3. The concentration of the substance in blood.

The formula to calculate clearance value is:

$C = UV/P$

C = Clearance

U = Concentration of the substance in urine.

V = Volume of urine flow.

P = Concentration of the substance in plasma.

Micturition

Micturition is a process by which urine is voided from the urinary bladder. It is a reflex process. However, in grown up children and adults, it can be controlled voluntarily to some extent.

Relation between renal disease and oral health Chronic kidney disease (CKD), the gradual and usually permanent reduction of the glomerular filtration rate (GFR) of the kidneys, leads to increases in serum creatinine and blood urea nitrogen (BUN) levels, resulting in uraemia or azotaemia. Uraemia develops and adversely affects every system of the body .Oral

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manifestations of chronic renal disease is common during the progression of uraemia.

Oral manifestations in uraemia:

- Enlarged (asymptomatic) salivary glands
- Decreased salivary flow
- Dry mouth
- Odor of urea on breath
- Metallic taste
- Increased calculus formation
- Low caries rate
- Enamel hypoplasia
- Dark brown stains on crowns
- Bleeding from gingiva
- Prolonged bleeding
- Candidal infections
- Tooth erosion (secondary to regurgitation associated with dialysis)

Radiographic manifestations

- Demineralization of bone
- Loss of bony trabeculation
- Ground-glass appearance
- Loss of lamina dura
- Giant cell lesions, "brown tumors"
- Socket sclerosis
- Pulpal narrowing and calcification
- Tooth mobility
- Arterial and oral calcifications.

Dental problems with renal disease

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- Uraemic patients have more dental problems than healthy controls in oral mucosa, teeth, salivary glands and jaw bones, problems that seem to develop before dialysis.
- Xerostomia, uraemic stomatitis
- periodontal disease and maxillary and mandibular radiographic alterations can be observed in patients with chronic renal failure. Periodontal diseases are highly prevalent among patients with chronic renal failure, specifically gingivitis, excessive plaque formation and poor oral hygiene in uraemic patients; however, there are previous reports that periodontal diseases and other dental problems, such as loss of teeth, periapical lesions and mucosal lesions, are contradictory findings.
- Other studies have confirmed that periodontal health is poor in haemodialysis patients and that it correlates with markers of malnutrition and inflammation.

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Lectures

15,16,17,18,19

Cardiovascular system

Components of cardiovascular system

Heart (Cardia): muscular organ function as a pump, creates pressure needed to push blood through vessels.

Vascular system: permits blood flow from the heart to tissue cells and back to heart (Arteries, Arterioles, Capillaries, Venules, veins).

The heart

The heart is a muscular organ enclosed in a fibrous sac (the pericardium). The pericardial sac contains watery fluid that acts as a lubricant as the heart moves within the sac. The wall of the heart is composed of

- cardiac muscle cells, termed the myocardium.
- The inner surface of the wall is lined by a thin layer of endothelial cell; termed the endocardium.
- The outer layer of the heart wall; termed the epicardium is it is also known as visceral pericardium as it forms the inner layer of the pericardium.
- PERICARDIUM (serous pericardium)

Pericardium is the outer covering of the heart. It is made up of two layers

- Outer parietal pericardium which forms a strong protective sac around the heart
- Inner visceral pericardium or epicardium that covers myocardium.

these two layers are separated by a space called pericardial cavity which contains a thin film of fluid.

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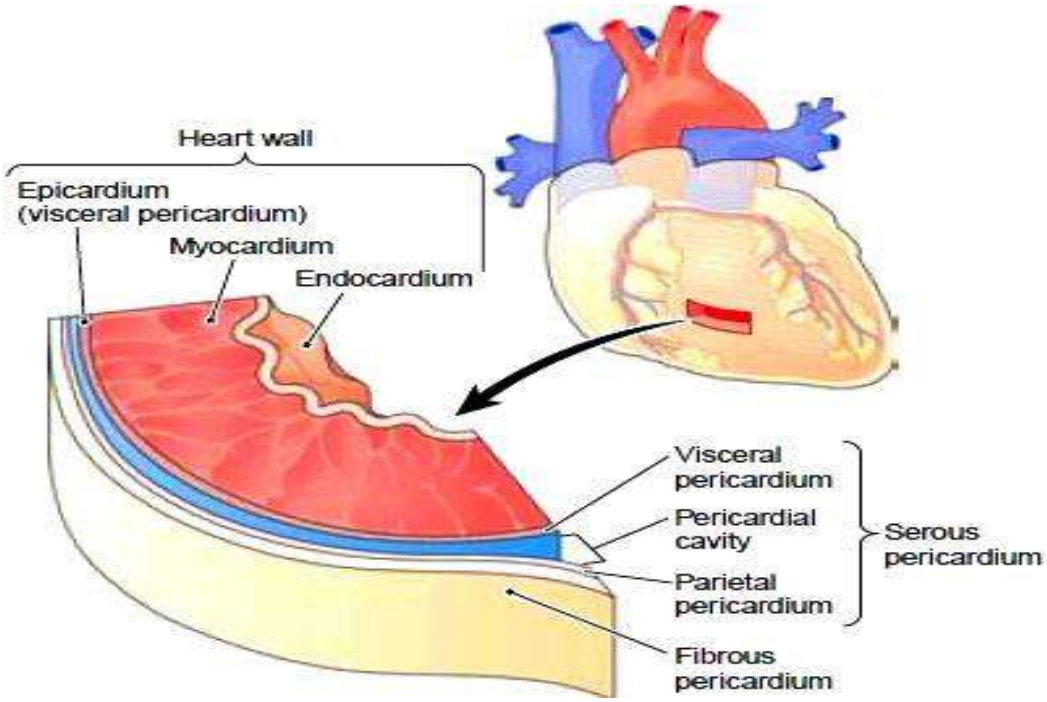
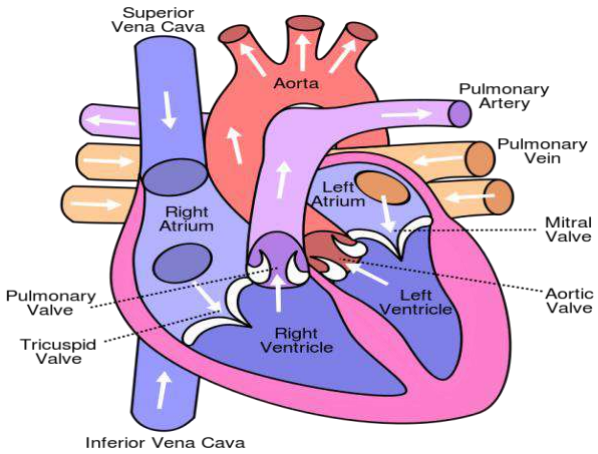


The heart is actually two separate pumps; a **right heart** which pumps blood through the **pulmonary artery** into the **lung**, and a **left heart** which pumps blood through the **aorta** into the **peripheral organ**. Each of these two pumps is consist of two chambers, an **atrium** and a **ventricle**, separated by **atrioventricular valve** (left, mitral valve and right, tricuspid valve). The right atrium and ventricle (some time called the right pump) are separated from the left atrium and ventricle (left pump) by a muscular wall or septum . This septum normally prevents mixture of the blood from the two sides of the heart. Blood exists from the right ventricle through the pulmonary valve to the pulmonary trunk, and from the left ventricle through the aortic valve into the aorta .



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The heart valves:

Four types of valves regulate blood flow through the heart.

☒ The atria ventricular valves(AV valves) {between atria and ventricles}

a- Mitral valve (bicuspid valve) {located between left atrium and left ventricle}

b- Tricuspid valve {located between right atrium and right ventricle}

☒ the semilunar valves {between the arteries and the ventricles}

c- Aortic valve {between the left ventricle and the aorta}

d- pulmonary valve {between the right ventricle and the pulmonary trunk{

The function of the heart valves

The function of AV valves is to prevent backflow (prevent regurgitation, leakage) of blood into the atria during ventricular contraction.

The aortic and pulmonary valves approximated to prevent regurgitation of blood from aorta and pulmonary arteries into the ventricles.

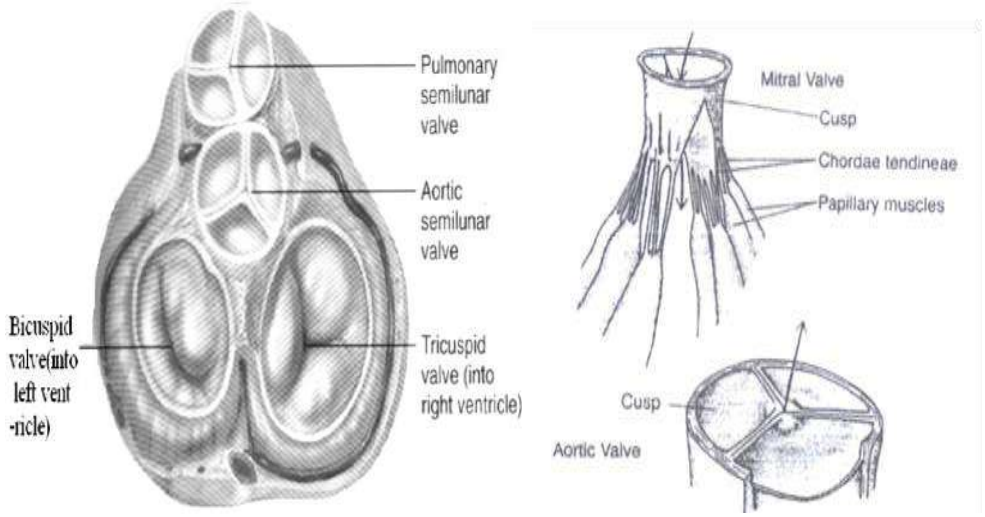

Figure: Mitral (two cusps) and Aortic (three cusps) valves.

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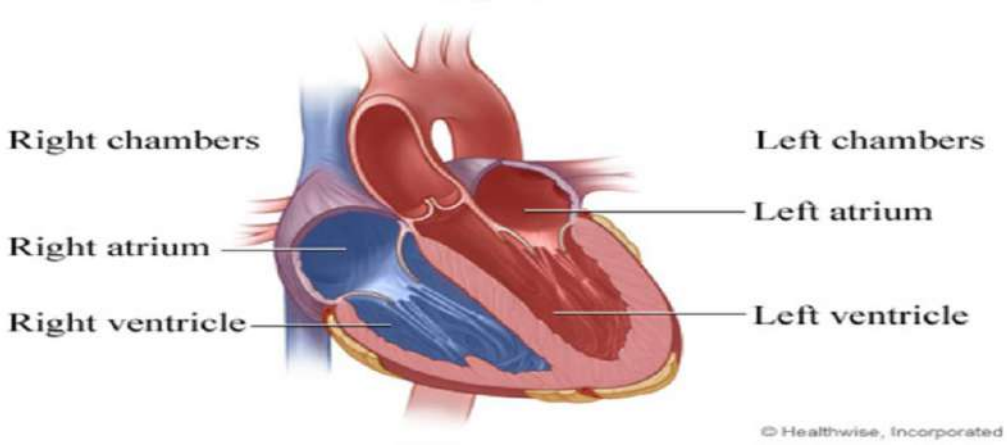
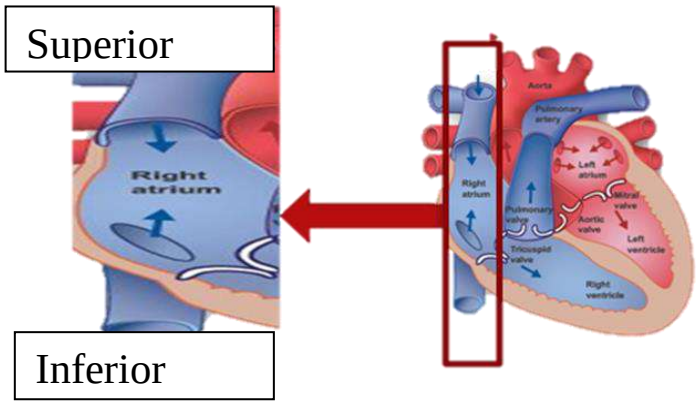
Heart Chambers.

The heart has four chambers, atria and two ventricles. The atria are smaller with thin walls, while the ventricles are large and much stronger



Atrium

There are two atrium on either side of the heart. On the right side is the atrium that contains blood which is poor in oxygen. The left atrium contains blood which has been oxygenated and is ready to be sent to the body. The right atrium receives de-oxygenated blood from the superior vena cava and inferior vena cava. The left atrium receives oxygenated blood from the left and right pulmonary veins. Atria facilitate circulation primarily by allowing uninterrupted venous flow to the heart, preventing the inertia of interrupted venous flow that would otherwise occur at each ventricular systole.



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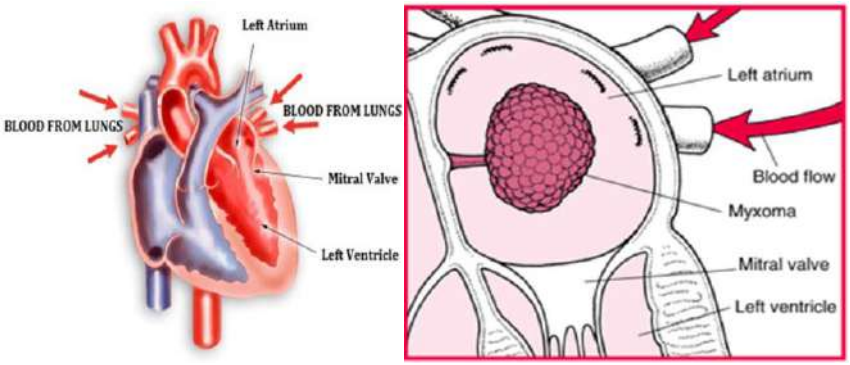
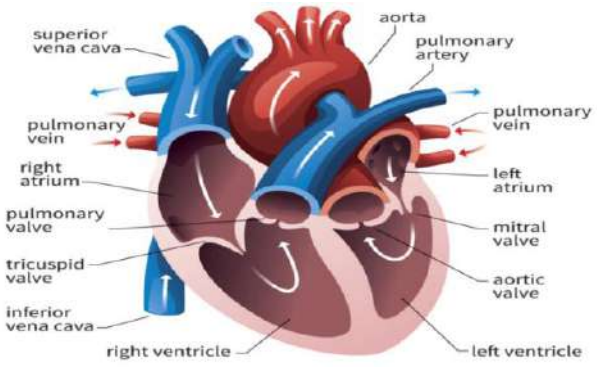


Ventricles

The ventricle is a heart chamber which collects blood from an atrium and pumps it out of the heart. There are two ventricles: the right ventricle pumps blood into the pulmonary circulation for the lungs, and the left ventricle pumps blood into the aorta for systemic circulation to the rest of the body. Ventricles have thicker walls than the atria, and thus can create the higher blood pressure. Comparing the left and right ventricle, the left ventricle has thicker walls because it needs to pump blood to the whole body. This leads to the common misconception that the heart lies on the left side of the body.



The cardiac conduction system

The cardiac conduction system is a group of specialized cardiac muscle cells in the walls of the heart that send signals to the heart muscle causing it to contract. The main components of the cardiac conduction

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system are the SA node, AV node, bundle of His, bundle branches, and Purkinje fibers. The SA node (anatomical pacemaker) starts the sequence by causing the atrial muscles to contract. From there, the signal travels to the AV node, through the bundle of His, down the bundle branches, and through the Purkinje fibers, causing the ventricles to contract. This signal creates an electrical current that can be seen on a graph called an Electrocardiogram (EKG or ECG). Doctors use an EKG to monitor the cardiac conduction system's electrical activity in the heart.

This system consists of

1- Sinus node "SA" node: also called sinoatrial node, located in the right atrium. It is concerned with the generation of rhythmical impulse; it is the pacemaker of the heart that initiates each heartbeat. This automatic nature of the heart beat is referred to as automaticity.

2- Internodal pathways conduct the impulse generated in SA node to the AV node.

3- The AV node (atrioventricular node), located near the right AV valve at the lower end of the interatrial septum, in the posterior septal wall of the right atrium. At which impulse from the atria is delayed before passing into the ventricles.

4- The AV bundle (bundle of His) conducts the impulse from the atria into ventricles.

5- The left and right bundles of purkinje fibers, which conduct the cardiac impulse to all parts of the ventricles. The purkinje fibers distribute the electrical excitation to the myocytes of the ventricles.

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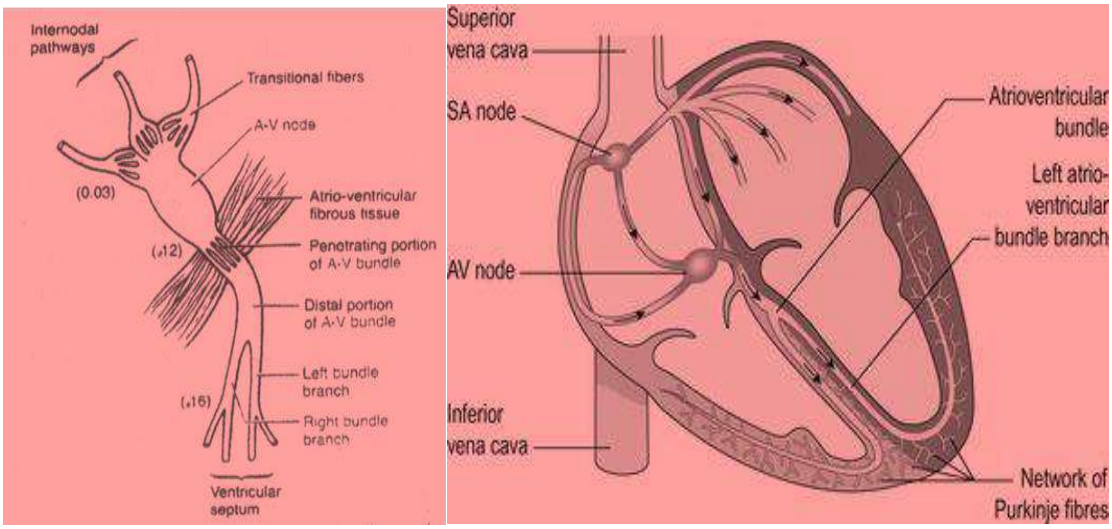
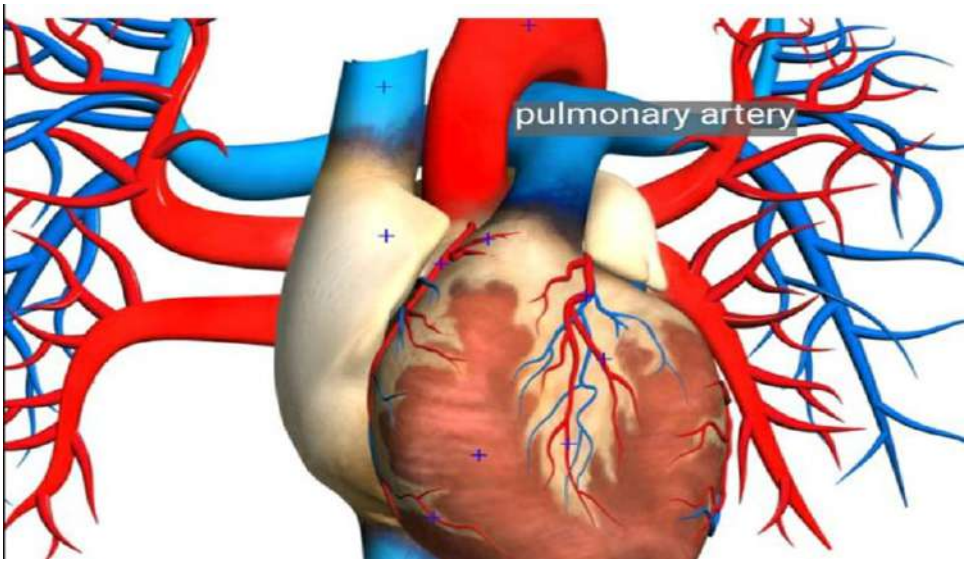


Blood vessels

Arteries

Arteries are muscular blood vessels that carry blood away from the heart, oxygenated and deoxygenated blood. The pulmonary arteries will carry deoxygenated blood to the lungs and the systemic arteries will carry oxygenated blood to the rest of the body. Arteries have a thick wall that consists of three layers. The inside layer is called the endothelium, the middle layer is mostly smooth muscle and the outside layer is connective tissue. The artery walls are thick to that when blood enters under pressure the walls can expand.



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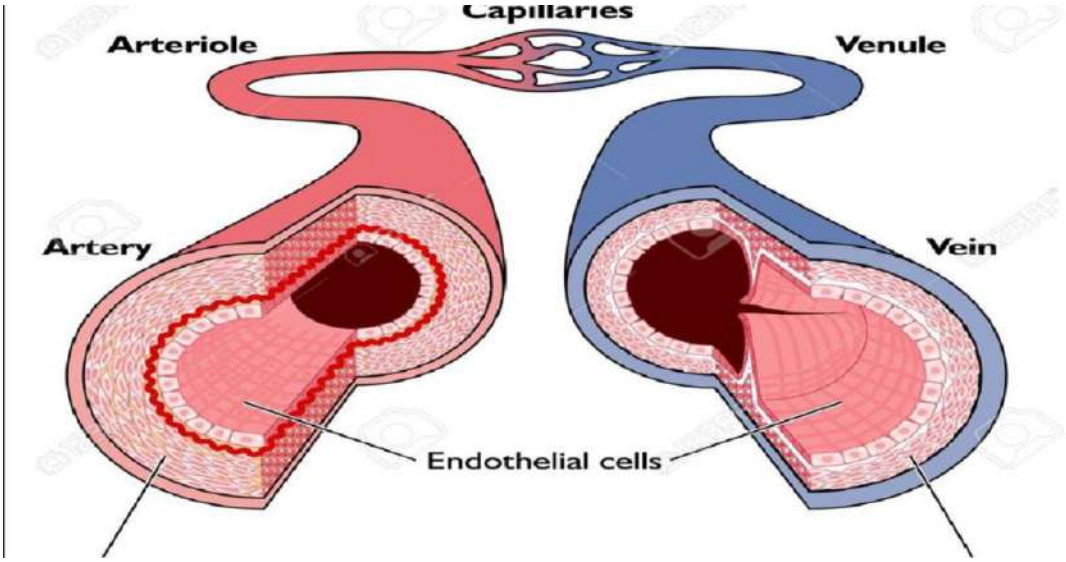

Arterioles

An arteriole is a small artery that extends and leads to capillaries arterioles have thick smooth muscular walls. These smooth muscles are able to contract (causing vessel constriction) and relax (causing vessel dilation).

Capillaries

Capillaries are the smallest of a body's vessels; they connect arteries and veins, and most closely interact with tissues. They are very prevalent in the body; total surface area is about 6,300 square meters. Because of this, no cell is very far from a capillary, no more than 50 micrometers away. The walls of capillaries are composed of a single layer of cells, the endothelium, which is the inner lining of all the vessels. This layer is so thin that molecules such as oxygen, water and lipids can pass through them by diffusion and enter the tissues. Waste products such as carbon dioxide and urea can diffuse back into the blood to be carried away for removal from the body.

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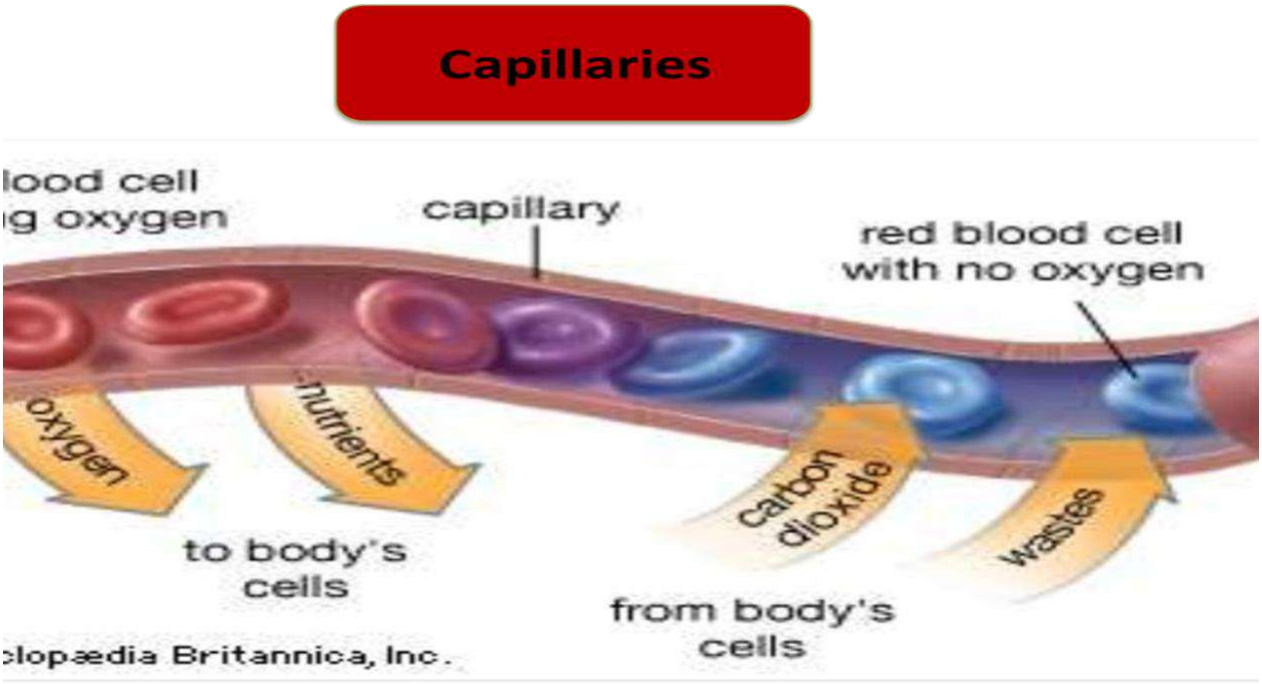

Veins

Veins carry blood to the heart .the pulmonary veins will carry oxygenated blood to the heart while the systemic veins will carry deoxygenated to the heart. Most of the blood volume is found in the venous system; about 70% at any given time. The veins outer walls have the same three layers as the arteries, differing only because there is a lack of smooth muscle in the inner layer and less connective tissue on the outer layer. Veins have low blood pressure compared to arteries and need the help of skeletal muscles to bring blood back to the heart. Most veins have one- way valves called venous valves to prevent backflow caused by gravity. They also have a thick collagen outer layer, which helps maintain blood pressure and stop blood pooling. If a person is standing still for long periods or is bedridden, blood can accumulate in veins and can cause varicose veins . The hollow internal cavity in which the blood flows is called the lumen. A muscular layer allows veins to contract, which puts more blood into circulation. Veins are used medically as points of access to the blood stream, permitting the withdrawal of blood specimens for testing purposes, and enabling the infusion of fluid, electrolytes, nutrition and medications(intravenous delivery).

Venules

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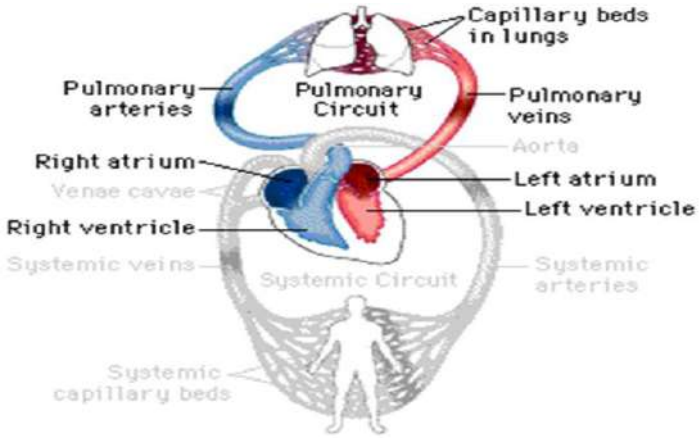
A venule is a small vein that allows deoxygenated blood to return from the capillary beds to the larger blood veins, except in the pulmonary circuit were the blood is oxygenated. Venules have three layers; they have the same makeup as arteries with less smooth muscle, making them thinner.

The circulatory system

The circulatory system is extremely important in sustaining life. It's proper functioning is responsible for the delivery of oxygen and nutrients to all cells, as well as the removal of carbon dioxide, wast products ,maintenance of optimum pH, and the mobility of the elements, proteins and cells, of the immune system. In developed countries, the two leading causes of death, myocardial infarction and stroke.

The pulmonary circuit

In the pulmonary circuit, blood is pumped to the lungs from the right ventricle of the heart. It is carried to the lungs via pulmonary arteries. At lungs, oxygen in the alveolae diffuses to the capillaries surrounding the alveolae and carbon dioxide inside the blood diffuses to the alveolae. As a result, blood is oxygenated which is then carried to the heart's left half – to the left atrium via pulmonary veins. Oxygen rich blood is prepared for the whole organs and tissues of the body. This is important because mitochondria inside the cells should use oxygen to produce energy from the organic compounds.



The systemic circuit

The systemic circuit supplies oxygenated blood to the organ system. Oxygenated blood from the lungs is returned to the left atrium, then the ventricle contracts and pumps

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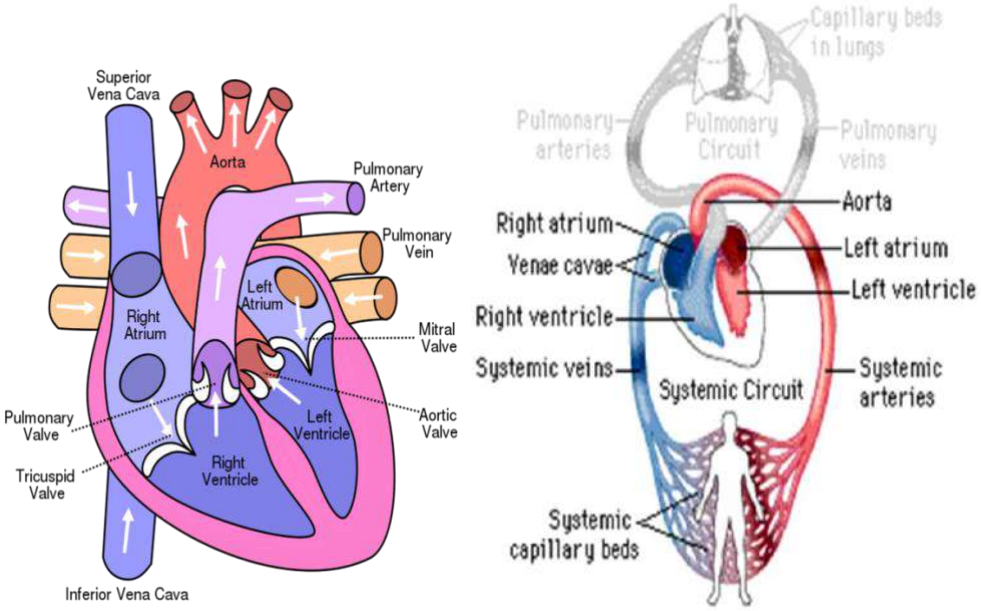
blood into the aorta. Systemic arteries split from the aorta and direct blood into the capillaries. Cells consume the oxygen and nutrients and add carbon dioxide, wastes, enzymes and hormones. The veins drain the deoxygenated blood from the capillaries and return the blood to the right atrium.



Portal circulation:

Veins from the digestive organs and spleen send their blood through **the hepatic portal vein** to the liver. This circulatory pathway allows the liver to modify the blood returning to the heart such as by removing excess glucose or toxins such as bacteria or alcohol specifically, blood from the capillaries of the spleen, stomach, pancreas, gallbladder and intestines flows into **superior mesenteric vein** and **the splenic vein**. These veins converge to form the portal vein. Blood from the left and right gastric veins empties into the hepatic portal vein.

The portal vein channels the blood into the liver, the blood is the distributed to innumerable microscopic sinusoid, which are the capillaries of the liver the blood flows out of the sinusoids into hepatic vein. From there the blood flows into the inferior vena cava where it is returned to the heart.

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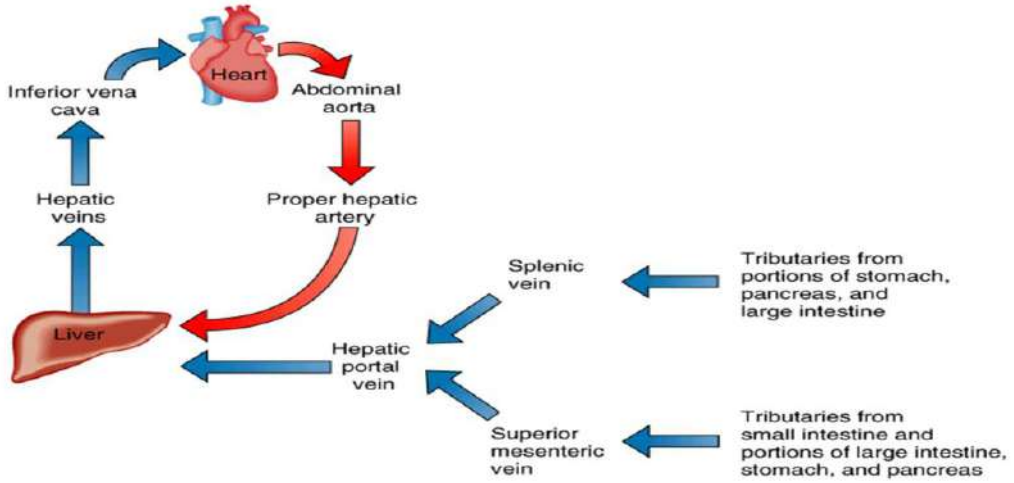

Heart sounds

When the stethoscope is placed on the chest wall over the heart ,two sounds are normally heard during each cardiac cycle (1st and 2nd heart sounds). Heart sounds associated with closure of the valves with their associated vibration of the flaps of the valves and the surrounding blood under the influence of the sudden pressure changes that develop across the valve. That is, heart sound does not produced by the opening of the valve because this opening is a slow developing process that

1- the first heart sound (s_1): is caused by closure of the A V valves when ventricles contract at systole. The vibration is soft, low-*pitched lub.

2-The second heart sound (s_2): is caused by closure of the aortic and pulmonary valves when the ventricles relax at the beginning of diastole. The vibration is laud, high-pitched dup. It is rapid sound because these valves close rapidly and continue for only a short period i.e., rapid, short and of higher pitch dup.

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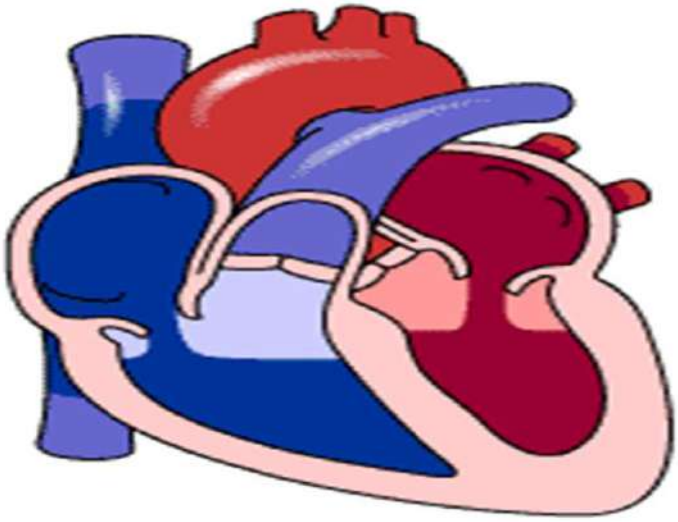

3- The third heart sound (s_3): is caused by rapid filling of the ventricles, by blood that flow with a rumbling motion into the almost filled ventricles; at the middle one third (1/3) of diastole i.e., it is caused by the vibration of the ventricular filling that follows the opening of A V valves. It is a low-pitched sound and can be heard after the S_2 . it is heard in normal heart; in children and in adult during exercise. It is also heard in anemia , and AV valve regurgitation.

4- the fourth heart sound(S_4): it is an atrial sound when the atria contract(at late diastole). It is a vibration sound (similar to that of S_3) associated with the flow of blood into the ventricle. It is not heard in normal hearts but occurs during ventricular overload as in severe anemia thyrotoxicosis (hyperthyroidism) or in reduced ventricular compliance and in hypertension. If present, it is heard before S_1 .

Heart murmurs

They are abnormal sound , can be produced by blood flowing rapidly in the usual direction but through an abnormally narrowed valve **(stenosis),** by blood flowing backward through a damaged, leaky valve(**regurgitation valve)** or by blood flowing between the two atria or two ventricles through a small hole: **ASD**(atrial septal defect) **VSD**(ventricular septal defect).

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The heart rate

The heart rate refers to the ventricular rate of beating per min. It can be determined by counting the arterial radial pulse, the heart sounds (using the stethoscope) or the number of cycles in an ECG record/minute. Normally, it averages 72 beats/min (range 60-100 beats/min) in young adult males during rest. Heart rate higher than 100 beats/min is called tachycardia and a rate lower than 60 beats/min is called bradycardia.

Regulation of the heart rate:

The heart rate is regulated (SA node discharge) by the following factors:

1- Nervous regulation

The heart receives both sympathetic and parasympathetic (vagal) nerves. Activity in the sympathetic nerves increases the heart rate, while activity in the parasympathetic nerves decreases the heart rate.

2- Chemical regulation

A- Effect of changes in blood gases.

- ✓ Hypoxia.
- ✓ Hypercapnia, acidosis.

B- Effects of hormones, drugs and chemicals:

- ✓ Adrenaline
- ✓ Thyroxin
- ✓ Atropine

3- SA node activity

Cardiac output

Cardiac output is the amount of blood pumped by each ventricle per minute, expressed in liters/minute. Normally, it is about 5 liters per minute.

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The cardiac output (CO) is determined through multiplying the heart rate (HR) by the stroke volume (SV).

CO = HR X SV

Heart rate = the number of heart beats/minute (average; 72 beat/minute).

Stroke volume = the volume of blood ejected by each ventricle with each beat.

If the HR = 72 beats/min., and the SV is of 70 ml;

Cardiac output = 72 X 70 = 5.04 liters.

As the cardiovascular system is closed system, cardiac output of the left ventricle equals to the cardiac output of the right ventricle i.e., the two sides of the heart have the some output per minute. It is also the valume of blood flowing through either the systemic or pulmonary circulation per minute. In other words, cardiac output is quantity of blood pumped into the aorta each minute by the heart. This is also the quantity of blood that flows through the circulation.

Cardiac output = arterial blood flow = pulmonary blood flow.

Cardiac output varies widely with the level of activity of the body.

Therefore, the level of body metabolism, exercise, age and size of the body influence the cardiac output. For young, healthy men, this resting cardiac output averages about 5.6 liter/min., for young women, this value is 10 – 20% less, but it is not constant. It might be increased even up to 30 liters/min., depending on the activity of the body. Therefore, cardiac output is a variable parameter usually it is not less than 5 liter/min., at rest to supply the body with oxygen and to maintain normal BMR (basal metabolic rate). The highest cardiac output recorded is 48 liters/min., in the Roadrunners (Hyper dynamic circulation which mean the some blood volume; 5 liters circulating at a higher speed). Blood volume is about 5 – 6 liters. So the heart pumps the whole blood in one minute.

Control of cardiac output:

The cardiac output is controlled by the following factors.

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1- Venous return (preload).

2- Heart rate (HR)

3- Myocardial contractility.

Arterial blood pressure

Arterial blood pressure is the pressure exerted by the blood on the arterial walls (BP). It normally fluctuates during the cardiac cycle between a maximum called the systolic blood pressure (SBP) and a minimum called the diastolic blood pressure (DBP).

The systolic BP normally averages 120 mmHg in young adult males (range 90-140 mmHg), and is produced by **ejection of blood into the aorta during left ventricular systole** (> 140 represent systolic hypertension). The diastolic BP normally averages 80 mmHg(range 60-90 mmHg), and is produced as a result of **the elastic recoil of the aorta during ventricular diastole**(>90 mmHg represents diastolic hypertension).

The arterial blood pressure (ABP) is often reported as the systolic over the diastolic pressure (e.g 120/80). BP value less than normal lower limit called hypotension(e.g. SBP<90 mmHg).

Pulse pressure: the difference between both the systolic and diastolic BP and it normally averages 40 mmHg.

Pulse pressure= systolic BP- diastolic BP= 120-80= 40 mmHg

The mean arterial blood pressure:

Mean BP = diastolic BP+1/3 pulse pressure= 80+13=93 mmHg.

Function of the arterial blood pressure:

1-It maintains tissue perfusion(ex. Blood flow) throughout different tissues.

2- It produces the capillary hydrostatic pressure, which is the main force concerned with tissue fluid formation(interstitial fluid).

Measurement of the arterial blood pressure:

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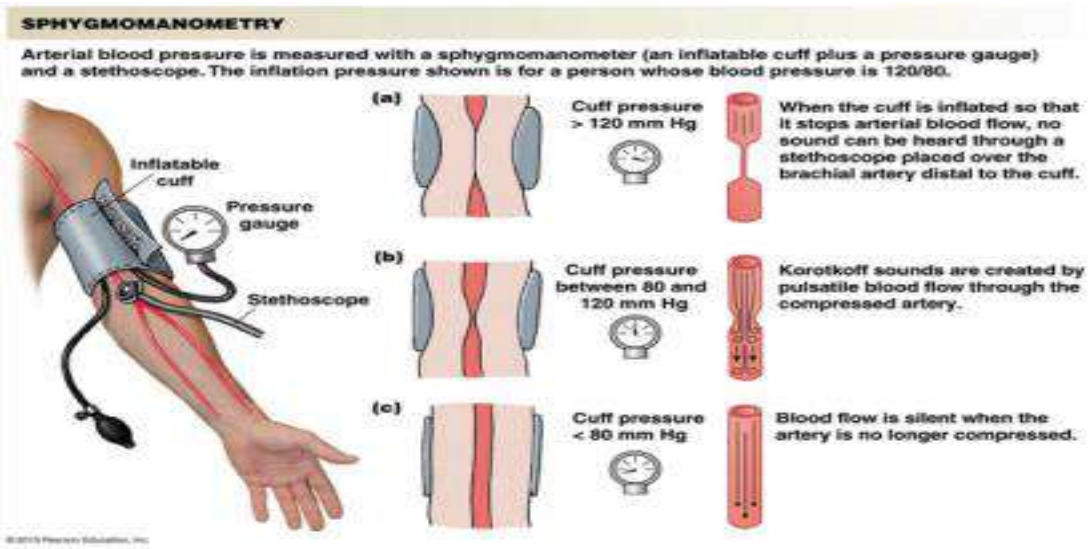
This is performed by the sphygmomanometer apparatus, which consists of an inflatable rubber cuff connected to a mercury manometer. The cuff can be air inflated by a small hand pump(bulb), and deflated by opening the attached air-control valve. This apparatus can measure the arterial BP by two methods

1- **Palpatory method**: this is an inaccurate method that measures the systolic pressure only.

2- **Auscultatory** method: this is an accurate method that measures both the systolic and diastolic blood pressures.



Physiological factors that affect the arterial blood pressure:

1- Age . the arterial BP is very low at birth (about 70-80/40-50 mmHg) then it rises progressively till about 120/80 mmHg at the age of 20 years. It rise continues gradually after that age, but its rate increases markedly after the age 40 years due to the normal gradual loss of arterial elasticity, so that it becomes normally about 150/90 mmHg after the age of 60 years.

2- Sex: the arterial BP is generally slightly higher in adult males than in females. However, it becomes slightly higher in females after the menopause.

3- Body region: the arterial BP is normally higher in the lower limbs than in the upper limbs.

4- Body built: the arterial BP is usually high in obese persons.

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5- Race: the arterial BP is often high in western countries(probably due to genetic factors, stress, environmental or dietary factors may contribute).

6-Meals: the arterial BP increases slightly after meals(especially the systolic) due to vasodilation (VD) in the splanchnic area, which increases both the venous return (VR) and cardiac output(CO).

7-Exercise: the arterial BP markedly increases during exercise, especially the systolic (the diastolic pressure is often not changed or even decreases).

8- Emotions: the arterial BP increases considerably in most emotions especially the systolic(due to increased sympathetic stimulation).

9- Intercourse: the systolic BP often increases during intercourse.

10-Sleep: the arterial BP is often slightly decreased during quiet sleep(due to decrease of the sympathetic activity) but it may increase during nightmares.

11-Environmental temperature: in hot environments, the systolic pressure may increase slightly due to tachycardia, but the diastolic pressure often fells due to cutaneous VD. On the other hand, exposure to cold increases both the systolic and diastolic pressures due to cutaneous vasoconstriction(VC).

12- Gravity: on standing, the force of gravity increases the mean arterial pressure and the venous pressure below a reference point in the heart(in the right atrium) and decreases them above that point by about 0.77 mmHg.

Cardiovascular Disease

1- Hypertension or high blood pressure is a medical condition where in the blood pressure is chronically elevated. Hypertension is defined as systolic pressure over 140 and diastolic over 90 mmHg.

2- Atherosclerosis is a disease affecting the arterial blood vessel. It is commonly referred to as a hardening or furring of the arteries. It is caused by the formation of multiple plaques within the arteries.

Risk factors:

high blood pressure, diabetes , smoking , family history healthy

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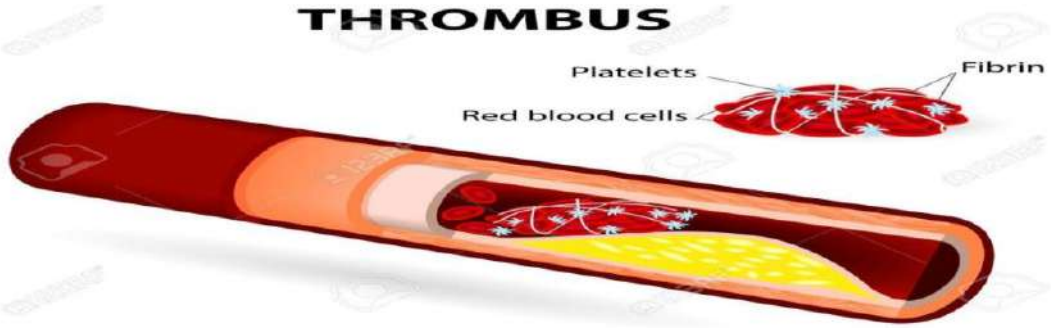
treated by :aspirin

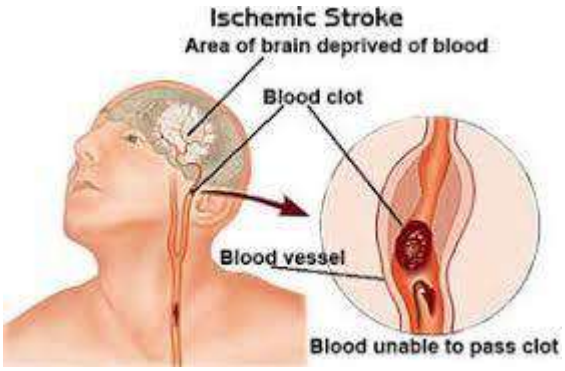
3- Thrombus or blood clot, is the final product of the blood coagulation step in hemostasis. It is achieved via the aggregation of platelets that form a platelet plug.



4- Embolism occurs when an object migrates from one part of the body through circulation and causes a blockage(occlusion) of a blood vessel in another part of the body.

5- stroke also known as cerebrovascular accident(CVA), is an acute neurological injury whereby the blood supply to a part of the brain is interrupted. Strokes can be classified into two major categories: ischemic and hemorrhagic. About 80% of strokes are due to ischemia.

ischemia is a restriction in blood supply to tissues, causing a shortage of oxygen that is needed for cellular metabolism (to keep tissue alive).



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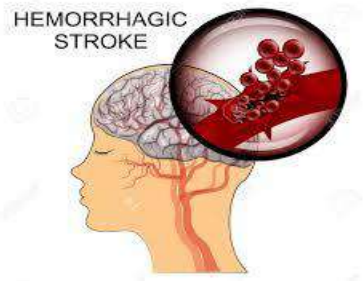
Hemorrhagic: Pertaining to bleeding or the abnormal flow of blood. Affect the 15 million of the world's population.



Reasons:

a-deficiency o2.

b- lack of blood.

C- smoking

6- Angina pectoris is chest pain due to ischemia (a lack of blood and hence oxygen supply) of the heart muscle, generally due to obstruction or spasm of the coronary arteries(the heart's blood vessels).

Reasons:

1-coronary Atherosclerosis.
2- coronary artery stenosis.
3- Anemia

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