**1.4 : Blood and circulation: Blood corpuscles, haemopoiesis and formed elements, plasma functions, blood volume, blood volume regulation, human blood groups, haemostasis.**

**BLOOD :-** Blood is the extracellular fluid normally carried by the arteries and veins. It is regarded as connective tissue because it has intercellular material or matrix between its cells. However ,the blood differs from the connective in that its matrix is fluid, does not contain fibers and is not secreted by the cells it contain, and the cells are free.

Blood is considered the “essence of life” because the uncontrolled loss of it can result in death. Blood performs many functions essential to life and often can reveal much about our health.

Blood is a type of connective tissue, consisting of cells and cell fragments surrounded by a liquid matrix. The cells and cell fragments are the formed elements, and the liquid is the plasma. The formed elements make up about 45%, and plasma makes up about 55% of the total blood volume. The total blood volume in the average adult is about 4–5 L in females and 5–6 L in males. Blood makes up about 8% of the total weight of the body. Cells require constant nutrition and waste removal because they are metabolically active.

The cardiovascular system, which consists of the heart, blood vessels, and blood, connects the various tissues of the body. The heart pumps blood through blood vessels, and the blood delivers nutrients and picks up waste products.

*FUNCTIONS OF BLOOD :-*The heart pumps blood through blood vessels, which extendthroughout the body. Blood helps maintain homeostasis in severalways:

1. Transport of gases, nutrients, and waste products. Oxygen enters blood in the lungs and is carried to cells. Carbon dioxide, produced by cells, is carried in the blood to the lungs, from which it is expelled. The blood transports ingested nutrients, ions, and water from the digestive tract to cells, and the blood transports the waste products of cells to the kidneys for elimination.

2. Transport of processed molecules. Many substances are produced in one part of the body and transported in the blood to another part, where they are modified. For example, the precursor to vitamin D is produced in the skin and transported by the blood to the liver and then to the kidneys for processing into active vitamin D. Active vitamin D is transported in the blood to the small intestines, where it promotes the uptake of calcium. Another example is lactic acid produced by skeletal muscles during anaerobic respiration. The blood carries lactic acid to the liver, where it is converted into glucose.

3. Transport of regulatory molecules. The blood carries many of the hormones and enzymes that regulate body processes from one part of the body to another.

4. Regulation of pH and osmosis. Buffers, which help keep the blood’s pH within its normal limits of 7.35–7.45, are in the blood. The osmotic composition of blood is also critical for maintaining normal fluid and ion balance.

5. Maintenance of body temperature. Blood is involved with body temperature regulation because warm blood is transported from the interior to the surface of the body, where heat is released from the blood.

6. Protection against foreign substances. The cells and chemicals of the blood make up an important part of the immune system, protecting against foreign substances, such as microorganisms and toxins.

7. Clot formation. Blood clotting protects against excessive blood loss when blood vessels are damaged. When tissues are damaged, the blood clot that forms is also the first step in tissue repair and the restoration of normal function.

**BLOOD CORPUSCLES :-**

**Red Blood Cells :- life history :-** Under normal conditions, about 2.5 million red blood cells aredestroyed every second. This loss seems staggering, but it representsonly 0.00001% of the total 25 trillion red blood cells containedin the normal adult circulation. Homeostasis is maintainedby replacing the 2.5 million cells lost every second with an equalnumber of new red blood cells. Thus, approximately 1% of thetotal number of red blood cells is replaced each day.

The process by which new red blood cells are produced iscalled “erythropoiesis” andthe time required for the production of a single red blood cellis about 4 days.

Stem cells, from which all blood cells originate,give rise to “proerythroblasts”.

After several mitotic divisions, proerythroblastsbecome early (basophilic) erythroblasts, which stain with a basic dye. The dye stains the cytoplasma purplish color because it binds to the large numbers of ribosomes,which are sites of synthesis for the protein hemoglobin.Early erythroblasts give rise to intermediate (polychromatic)erythroblasts, which stain different colors with basic and acidic dyes.

As hemoglobin is synthesized and accumulates in the cytoplasm,it is stained a reddish color by an acidic dye. Intermediateerythroblasts continue to produce hemoglobin, and then most oftheir ribosomes and other organelles degenerate.

The resultinglate erythroblasts have a reddish color because about one-thirdof the cytoplasm is hemoglobin.The late erythroblasts lose their nuclei by a process of extrusionto become immature red blood cells, which are called “reticulocytes”because a reticulum, or network, canbe observed in the cytoplasm when a special staining techniqueis used. The reticulum is artificially produced by the reactionof the dye with the few remaining ribosomes in the reticulocyte.Reticulocytes are released from the bone marrow into thecirculating blood, which normally consists of mature red bloodcells and 1%–3% reticulocytes. Within 1 to 2 days, reticulocytesbecome mature red blood cells when the ribosomes degenerate.

Cell division requires the B vitamins folate and B 12 , which arenecessary for the synthesis of DNA.

Hemoglobinproduction requires iron. Consequently, adequate amounts offolate, vitamin B 12, and iron are necessary for normal red bloodcell production.Red blood cell production is stimulated by low blood oxygenlevels, typical causes of which are decreased numbers of red bloodcells, decreased or defective hemoglobin, diseases of the lungs, highaltitude, inability of the cardiovascular system to deliver blood totissues, and increased tissue demands for oxygen—for example,during endurance exercises.Low blood oxygen levels stimulate red blood cell productionby increasing the formation of the glycoprotein erythropoietin, which is a hormone produced mostly by thekidneys. Erythropoietin stimulates red bone marrowto produce more red blood cells by increasing the number ofproerythroblasts formed and by decreasing the time required forred blood cells to mature. Thus, when oxygen levels in the blooddecrease, erythropoietin production increases, which increases redblood cell production. The increased number of red blood cellsincreases the blood’s ability to transport oxygen. This mechanismreturns blood oxygen levels to normal and maintains homeostasisby increasing the delivery of oxygen to tissues. Conversely, if bloodoxygen levels increase, less erythropoietin is released, and redblood cell production decreases.

Red blood cells normally stay in the circulation for about 120 days in males and 110 days in females. These cells have no nuclei and therefore cannot produce new proteins or divide. As their existing proteins, enzymes, plasma membrane components, and other structures degenerate, the red blood cells are less able to transport oxygen and their plasma membranes become more fragile.

Eventually, the red blood cells rupture as they squeeze through a tight spot in the circulation. Macrophages located in the spleen, liver, and other lymphatic tissue take up the hemoglobin released from ruptured red blood cells. Within a macrophage, lysosomal enzymes digest the hemoglobin to yield amino acids, iron, and bilirubin. The globin part of hemoglobin is broken down into its component amino acids, most of which are reused in the production of other proteins. Iron atoms released from heme can be carried by the blood to red bone marrow, where they are incorporated into new hemoglobin molecules. The non-iron part of the heme groups are converted to biliverdin and then to bilirubin, which is released into the plasma. Bilirubin binds to albumin and is transported to liver cells. This bilirubin is called free bilirubin because it is not yet conjugated. Free bilirubin is taken up by the liver cells and is conjugated, or joined, to glucuronic acid to form conjugated bilirubin, which is more water-soluble than free bilirubin. The conjugated bilirubin becomes part of the bile, which is the fluid secreted from the liver into the small intestine. In the intestine, bacteria convert bilirubin into the pigments that give feces its characteristic brownish color. Some of these pigments are absorbed from the intestine, modified in the kidneys, and excreted in the urine, thus contributing to the characteristic yellowish color of urine.

Jaundice is a yellowish staining of the skin and sclerae caused by a buildup of bile pigments in the circulation and interstitial spaces. Any process that causes increased destruction of red blood cells can cause jaundice, such as damage by toxins, genetic defects in red blood cell plasma membranes, infections, and immune reactions. Other causes of jaundice include dysfunction or destruction of liver tissue and blockage of the duct system that drains bile from the liver.

**White Blood Cells :-** White blood cells, or leukocytes, form a thin, white layer of cellsbetween plasma and red blood cells when the components ofblood are separated from each other.

White bloodcells lack hemoglobin but have a nucleus.

In stained preparations,white blood cells attract stain, whereas red blood cells remain relativelyunstained.

White blood cells protect the body against invading microorganismsand remove dead cells and debris from the body.

Most white blood cells are motile, exhibiting ameboid movement,which is the ability to move as an ameba does, by puttingout irregular cytoplasmic projections. White blood cells leave the circulation and enter tissues by “diapedesis”\_a process in which they become thin and elongated and slip between or, in some cases, through the cells of blood vessel walls.

The white blood cells can then be attracted to foreign materialsor dead cells within the tissue by chemotaxis. At the site of an infection, white blood cells accumulateand phagocytize bacteria, dirt, and dead cells; then they die.The accumulation of dead white blood cells and bacteria, alongwith fluid and cell debris, is called “pus”.The five types of white blood cells are neutrophils, eosinophils,basophils, lymphocytes, and monocytes.

Neutrophils :-Neutrophils comprise 60%–70% of white blood cells.

* They have small cytoplasmic granules that stain withboth acidic and basic dyes.
* Their nuclei are commonly lobed,with the number of lobes varying from two to five.
* Neutrophilsare often called polymorphonuclearneutrophils, or PMNs, to indicate that their nuclei can occur inmore than one (poly) form (morph).
* Neutrophils usually remainin the circulation for about 10–12 hours and then move into othertissues, where they become motile and seek out and phagocytizebacteria, antigen–antibody complexes (antigens and antibodiesbound together), and other foreign matter.
* Neutrophils alsosecrete a class of enzymes called lysozymes, which arecapable of destroying certain bacteria.
* Neutrophils usually survivefor 1–2 days after leaving the circulation.

Eosinophils :-Eosinophils comprise 2%–4% of white blood cells.

* They contain cytoplasmic granules that stain bright redwith eosin, an acidic stain.
* Eosinophils are motile cells that leavethe circulation to enter the tissues during an inflammatory reaction.
* They are most common in tissues undergoing an allergicresponse, and their numbers are elevated in the blood of peoplewith allergies.
* Eosinophils apparently reduce the inflammatoryresponse by producing enzymes that destroy inflammatory chemicals,such as histamine.
* Eosinophils also release toxic chemicalsthat attack certain worm parasites, such as tapeworms, flukes,pinworms, and hookworms.

Basophils :-Basophils comprise 0.5%–1% of white blood cells.

* They contain large cytoplasmic granules that stain blue or purplewith basic dyes.
* Basophils, like eosinophils and neutrophils, leavethe circulation and migrate through the tissues.
* They increase innumber in both allergic and inflammatory reactions.
* Basophilscontain large amounts of histamine, which theyrelease within tissues to increase inflammation.
* They also releaseheparin, which inhibits blood clotting.

There are 2 kinds of agranulocytes : lymphocytes and monocytes.

Lymphocytes :-Lymphocytes comprise 20%–25% of white blood cells.

* They are the smallest white blood cells, most of whichare slightly larger in diameter than red blood cells.
* The lymphocyticcytoplasm consists of only a thin, sometimes imperceptiblering around the nucleus.
* Although lymphocytes originate in redbone marrow, they migrate through the blood to lymphatic tissues,where they can proliferate and produce more lymphocytes.
* The majority of the body’s total lymphocyte population is in thelymphatic tissues: the lymph nodes, spleen, tonsils, lymphaticnodules, and thymus.
* Although they cannot be identified by standard microscopicexamination, a number of different kinds of lymphocytes playimportant roles in immunity. For example, B cellscan be stimulated by bacteria or toxins to divide and form cellsthat produce proteins called antibodies . Antibodies can attach tobacteria and activate mechanisms that result in the destruction ofthe bacteria. T cells protect against viruses and other intracellularmicroorganisms by attacking and destroying the cells in whichthey are found. In addition, T cells are involved in the destructionof tumor cells and tissue graft rejections.

Monocytes :-Monocytes comprise 3%–8% of white blood cells.

* They are typically the largest of the white blood cells. Monocytesnormally remain in the circulation for about 3 days, leave thecirculation, become transformed into macrophages, and migratethrough various tissues.
* They phagocytize bacteria, dead cells,cell fragments, and other debris within the tissues.
* An increasein the number of monocytes is often associated with chronicinfections.
* Macrophages also stimulate responses from othercells in two ways:

(1) by the release of chemical signals and

(2) byphagocytizing and processing foreign substances, which are presentedto lymphocytes.

 The responses of these other cells help protect against microorganisms and other foreign substances.

Platelets :-Platelets , or thrombocytes, areminute fragments of cells consisting of a small amount of cytoplasmsurrounded by a plasma membrane.

* Platelets are roughlydisk-shaped and average about 3 μm in diameter.
* The surfaceof platelets has glycoproteins and proteins that allow platelets to attach to other molecules, such as collagen in connective tissue.Some of these surface molecules, as well as molecules releasedfrom granules in the platelet cytoplasm, play important roles incontrolling blood loss.
* The platelet cytoplasm also contains actinand myosin, which can cause contraction of the platelet.
* The life expectancy of platelets is about 5–9 days.
* They areproduced within the red marrow and are derived from megakaryocytes, which are extremely large cellswith diameters up to 100 μm. Small fragments of these cells breakoff and enter the circulation as platelets.
* Platelets play an important role in preventing blood loss by

(1) forming platelet plugs, which seal holes in small vessels, and

(2) promoting the formation and contraction of clots, which help seal off larger wounds in the vessels.

**HAEMOPOIESIS and FORMED ELEMENTS :-** About 95% of the volume of the formed elements consists of redblood cells, or erythrocytes. The remaining 5% consistsof white blood cells, or leukocytes, and cell fragmentscalled platelets, or thrombocytes.

Inhealthy adults, white blood cells are the only formed elements possessingnuclei, whereas red blood cells and platelets lack nuclei.White blood cells are named according to their appearancein stained preparations.

Granulocytes are whiteblood cells with large cytoplasmic granules and lobed nuclei. Their granules stain with dyes that make the cellsmore visible when viewed through a light microscope. The threetypes of granulocytes are named according to the staining characteristicsof their granules: neutrophils stain withacidic and basic dyes, eosinophils stain red withacidic dyes, and basophils stain dark purple with basic dyes.

Agranulocytes are white blood cells thatappear to have no granules when viewed in the light microscope.Agranulocytes actually have granules, but they are so small thatthey cannot be seen easily with the light microscope. The two typesof agranulocytes are lymphocytes and monocytes. They have nuclei that are not lobed.

Production of Formed Elements :-

The process of blood cell production, called “hematopoiesisor hemopoiesis”\_occurs in the embryo and fetus in tissues such as theyolk sac, liver, thymus, spleen, lymph nodes, and red bone marrow.

After birth, hematopoiesis is confined primarily to red bonemarrow, with some lymphoid tissue helping in the production oflymphocytes.

In young children, nearly all themarrow is red bone marrow. In adults, however, red marrow isconfined to the ribs, sternum, vertebrae, pelvis, proximal femur,and proximal humerus. Yellow marrow replaces red marrow inother locations in the body.

All the formed elements of the blood are derived from asingle population of stem cells called hemocytoblasts , located inthe red bone marrow.

Hemopoietic stem cells are precursor cellscapable of dividing to produce daughter cells that can differentiateinto various types of blood cells : proerythroblasts, from which red blood cells develop; myeloblasts, from which basophils, eosinophils, andneutrophils develop; lymphoblasts, from whichlymphocytes develop; monoblasts, from whichmonocytes develop; and megakaryoblasts,from which platelets develop.

The development of the cell lines isregulated by growth factors. That is, the type of formed elementderived from the stem cells and how many formed elements areproduced are determined by different growth factors.

Red Blood CellsRed, or erythrocytes, are about 700 times more numerousthan white blood cells and 17 times more numerous thanplatelets in the blood. Males have about 5.4 millionred blood cells per microliter of blood(range: 4.6–6.2 million), whereas females have about 4.8 million/L(range: 4.2–5.4 million). Red blood cells cannot move of their ownaccord; they are passively moved by forces that cause the blood tocirculate.

Structure :-Normal red blood cells are biconcave discs about 7.5 μm indiameter, with edges that are thicker than the center of the cell.

The biconcave shape increases the surface areaof the red blood cell, compared with a flat disc of the same size.The greater surface area makes the movement of gases into andout of the red blood cell more rapid.

In addition, the red bloodcell can bend or fold around its thin center, thereby decreasingits size and enabling it to pass more easily through small bloodvessels.

Red blood cells are derived from specialized cells that losetheir nuclei and nearly all their cellular organelles during maturation.

The main component of the red blood cell is the pigmentedprotein hemoglobin, which occupies about one-thirdof the total cell volume and accounts for its red color.

Otherred blood cell contents include lipids, adenosine triphosphate(ATP), and the enzyme carbonic anhydrase.

Function :-The primary functions of red blood cells are to transport oxygenfrom the lungs to the various tissues of the body and to transportcarbon dioxide from the tissues to the lungs.

Approximately 98.5%of the oxygen in the blood is transported in combination with thehemoglobin in the red blood cells, and the remaining 1.5% is dissolvedin the water part of the plasma.

If red blood cells rupture,the hemoglobin leaks out into the plasma and becomes nonfunctionalbecause the shape of the molecule changes as a result ofdenaturation. Red blood cell rupture followed byhemoglobin release is called “hemolysis”.

Hemolysisoccurs in hemolytic anemia, transfusion reactions, hemolytic disease of thenewborn, and malaria.

Carbon dioxide is transported in the blood in three majorways: Approximately 7% is transported as carbon dioxide dissolvedin the plasma, approximately 23% is transported in combinationwith hemoglobin, and 70% is transported in the formof bicarbonate ions. The bicarbonate ions (HCO 3) are producedwhen carbon dioxide (CO 2 ) and water (H 2 O) combine to formcarbonic acid (H 2 CO 3 ), which dissociates to form hydrogen (H)and bicarbonate ions. The combination of carbon dioxide and water is catalyzed by an enzyme, carbonic anhydrase, which islocated primarily within red blood cells.

*Hemoglobin :-*Hemoglobin consists of four polypeptide chains and four hemegroups. Each polypeptide chain, called a globin, isbound to one heme. Each heme is a red-pigment moleculecontaining one iron atom.

There are three kinds ofhemoglobin: embryonic, fetal, and adult.

The first type of hemoglobinproduced during development is embryonic hemoglobin.By the third month of development, embryonic hemoglobin hasbeen replaced with fetal hemoglobin. At birth, 60%–90% of thehemoglobin is adult hemoglobin. At 2 to 4 years of age, fetal hemoglobinis less than 2% of the hemoglobin and, in adulthood, onlytraces of fetal hemoglobin can be found.

The different kinds of hemoglobin have different affinities for,or abilities to bind with, oxygen.

Embryonic and fetal hemoglobinshave a higher affinity for oxygen than does adult hemoglobin.In the embryo and fetus, hemoglobin picks up oxygen from themother’s blood at the placenta. After birth, hemoglobin picks upoxygen from the air in the baby’s lungs. Even though placentalblood contains less oxygen than air, adequate amounts of oxygenare picked up because of the higher affinity of embryonic and fetalhemoglobins for oxygen.

Although embryonic, fetal, and adult hemoglobins each havefour globins, the types of globins are different.

There are nine types of globins, each with a slightly different amino acid composition.For example, there are two types of alpha globins, each of whichdiffers from the other by one amino acid. Because they are sosimilar, they are usually referred to simply as alpha globins. Thereare also a beta globin, two kinds of gamma globins, a delta globin,and three kinds of embryonic globins.

Most adult hemoglobin hastwo alpha globins (one of each type) and two beta globins.

Fetal hemoglobin has two alpha globins (one of eachtype) and two gamma globins (one of each type).

There are nine globin genes, each of which codes for one ofthe globins. Five of these genes are on chromosome 11 and four areon chromosome 16. The globin genes are active during differentstages of development. The embryonic globin genes are active first,but they become inactive as fetal globin genes become active. In asimilar fashion, the fetal globin genes become inactive as the adultglobin genes become active. Iron is necessary for the normal function of hemoglobinbecause each oxygen molecule that is transported is associated withan iron atom.

The adult human body normally contains about 4gof iron, two-thirds of which is associated with hemoglobin. Smallamounts of iron are regularly lost from the body in waste products,such as urine and feces. Females lose additional iron as a resultof menstrual bleeding and, therefore, require more dietary ironthan do males. Dietary iron is absorbed into the circulation fromthe upper part of the intestinal tract. Stomach acid and vitamin Cin food increase the absorption of iron by converting ferric iron(Fe 3) to ferrous iron (Fe 2), which is more readily absorbed.

When hemoglobin is exposed to oxygen, one oxygen moleculecan become associated with each heme group. This oxygenatedform of hemoglobin is called “oxyhemoglobin”. The oxyhemoglobin in one red blood cell transportsabout 1 billion molecules of oxygen. Each heme molecule binds toone oxygen molecule; there are four heme molecules per hemoglobinand 280 million hemoglobin molecules per red blood cell.

Hemoglobin containing no oxygen is called deoxyhemoglobin .Oxyhemoglobin is bright red, whereas “deoxyhemoglobin” has adarker red color.

Hemoglobin transports carbon dioxide, which does not combinewith the iron atoms but is attached to amino groups of the globin molecule. This hemoglobin form is “carbaminohemoglobin”.

Hemoglobin also transports nitric oxide, which is produced by the endothelial cells lining blood vessels.

In the lungs, at the same time that heme picks up oxygen, in each globin a sulfurcontaining amino acid, cysteine, binds with a nitric oxide molecule to form S –nitrosothiol. When oxygen is released in tissues, so is the nitric oxide, which functions as a chemical signal that induces the smooth muscle of blood vessels to relax. By affecting the amount of nitric oxide in tissues, hemoglobin may play a role in regulating blood pressure because the relaxation of blood vessels results in a decrease in blood pressure.

**PLASMA and functions :-** Plasma is the liquid part of blood. It is a pale yellow fluidthat consists of about 91% water and 9% other substances, such asproteins, ions, nutrients, gases, and waste products.Plasma is a colloid, which is a liquid containing suspendedsubstances that do not settle out of solution. Most of thesuspended substances are plasma proteins. Based on molecularsize and charge, the plasma proteins can be classified as albumin,globulins, and fibrinogen. Almost all of the plasma proteins areproduced by the liver or blood cells, a notable exception being proteinhormones. Albumin makes up 58% of the plasmaproteins and is important in the regulation of water movementbetween tissues and blood. Because albumin does not easily pass from the blood into tissues, it plays an important role in maintaining blood colloid osmotic pressure. Other molecules, such as fatty acids, bilirubin, and thyroid hormones, are transported in the blood attached to albumin. Globulins account for 38% of the plasma proteins. Many substances in the blood are transported by globulins and, as part of immunity, globulins provide protection against microorganisms. Fibrinogen constitutes 4% of the plasma proteins and is responsible for the formation of blood clots. Serum is plasma without the clotting factors. The water, proteins, and other substances in the blood, such as ions, nutrients, waste products, gases, and regulatory substances, are maintained within narrow limits. Normally, water intake through the digestive tract closely matches water loss through the kidneys, lungs, digestive tract, and skin. Therefore, plasma volume remains relatively constant. Suspended or dissolved substances in the blood come from the liver, kidneys, intestines, endocrine glands, and immune tissues, such as the lymph nodes and spleen. Oxygen enters blood in the lungs and leaves the blood as it flows through tissues. Carbon dioxide enters blood from the tissues and leaves the blood as it flows through the lungs.

**THE BLOOD VOLUME :-** The volume of blood remains constant. In adult human beings, the total volume of blood is 5 litres.

The average volume of blood is calculated on weight basis i.e. approximately 70ml of blood for each kilogram body weight. The fluid volume of blood is not affected even when large volume of water is taken. The excess amount of water is got rid of by enhanced urine output.

Similarly during haemorrhage, considerable amount of blood is lost which is soon restored to normal value. After haemorrhage, the fluids from tissues move into the blood vessels to restore the blood volume. At the same time the urine output is lowered considerably to make good the losses. Apart from restoring the fluid volume of blood, the loss of erythrocytes is also compensated by their increased rate of production in the spleen and the bone marrow.

Several methods are used for determining the total blood volume in the body. The most reliable and efficient method is the “radio isotope method”. In this method, albumin is combined with I3. Albumin does not diffuse through capillaries, and I3 can be determined easily. If the plasma volume and percentage of blood corpuscles are known, the total amount of blood can be calculated as follows:

BLOOD VOLUME= PLASMA VOLUME X 100

 100 - HAEMATOCRIT

Generally, blood volume remains constant since the normal blood pressure has to be maintained at all time. However, under certain conditions the volume may vary within narrow limits.

**BLOOD VOLUME REGULATION:-** REGULATION OF RED BLOOD CELL PRODUCTION :-ROLE OF ERYTHROPOIETIN :-

The total mass of RBCs in the circulatory system is regulated within narrow limits, so that :

1. an that an adequate number of red cells is always available to provide sufficient transport of oxygen from lungs to tissues, yet

2. The cells do not become so numerous that they impede blood flow.

Tissue oxygenation is the most essential regulator of red blood cell production. Any condition that causes the quantity of oxygen transported to the tissue to decrease ordinarily increases the rate of RBC production. Thus when a person becomes extremely anemic as a result of hemorrhage or any other condition, the bone marrow begins to produce large quantities of RBC. Also destruction of major portions of the bone marrow by any means, especially by X-ray therapy, causes hyperplasia of the remaining bone marrow, thereby attempting to supply the demand for red blood cells in the body.

At very high altitudes, where the quantity of oxygen in the air is greatly decreased, insufficient oxygen is transported to the tissues, and the red cell production is greatly increased. In this case, it is not the concentration of RBCs in the blood that controls red cell production but the amount of oxygen transported to the tissues in relation to tissue demand for oxygen.

Various diseases of the circulation that cause decreased blood flow through the peripheral vessels, and particularly those that cause failure of oxygen absorption by the blood as it passes through the lungs, can also increase the rate of red cell production. This is especially apparent in prolonged cardiac failure and many lung diseases, because the tissue hypoxia resulting from these conditions increases red cell production, with the resultant increase in hematocrit and usually total blood volume as well.

Erythropoietin stimulates red cell production, and its formation increases in response to hypoxia. The principal stimulus for RBC production in low oxygen states is a circulating hormone called erythropoietin, a glycoprotein with a molecular wt. of about 34000 Da. In the absence of erythropoietin, hypoxia has little or no effect in stimulating RBC production. But when the erythropoietin system is functional, hypoxia causes a marked increase in erythropoietin production, and the erythropoietin in turn enhances red blood cell production until the hypoxia is relieved.

*Role of the kidneys in the formation of Erythropoietin :-* In the normal person, about 90% of all erythropoietin is formed in the kidneys,the remainder is formed mainly in the liver. It is not known exactly where in the kidneys the erythropoietin is formed. One likely possibility is that the renal tubular epithelial cells secrete the erythropoietin, because anaemic blood is unable to deliver enough oxygen from the peritubular capillaries to the highly oxygen consuming tubular cells, thus stimulating erythropoietin production.

At times, hypoxia in other parts of the body, but not in the kidneys, stimulates kidney erythropoietin secretions, which suggest that there might be some non-renal sensor that sends an additional signal to the kidneys to produce this hormone. In particular, both norepinephrine and epinephrine and several of the prostaglandins stimulate erythropoietin production. When both kidneys are removed from a 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 tissues (mainly in the liver) is sufficient to cause only one third to one half the red cell formation needed by the body.

*Effect of erythropoietin in erythrogenesis :-* When an animal or a person is placed in an atmosphere of low oxygen, erythropoietin begins to be formed within minutes to hours, and it reaches maximum production within 24 hours. Yet almost no new RBC appear in the circulating blood until about 5days later. From this fact, as well as other studies, it has been determined that the important effect of erythropoietin is to stimulate the production of proerythroblast from hematopoietic stem cells in the bone marrow. In addition, once the proerythroblast are formed, the erythropoietin causes these cells pass more rapidly through the different erythroblastic stages than they normally do, further speeding up the production of new red blood cells. The rapid production of cells continues as long as the person remains in a low oxygen state or until enough RBCs have been produced to carry adequate amounts of oxygen to the tissues despite the low oxygen,at this time the rate of erythropoietin production decreases to a level that will maintain the required no. of red cells but not an excess.

In the absence of erythropoietin, few RBCs are formed by the bone marrow. At the other extreme , when large quantities of erythropoietin are formed, and if there is a plenty of iron and other required nutrients available, the rates of RBC production can rise to perhaps 10 or more times normal. Therefore, the erythropoietin mechanism for controlling RBC production is a powerful one.

**BLOOD GROUPING**:-

If large quantities of blood are lost during surgery or in an accident, the patient can go into shock and die unless a transfusion or an infusion is performed. A transfusion is “the transfer of blood or blood components from one individual to another”.

When large quantities of blood are lost, red blood cells must be replaced to restore the blood’s oxygen-carrying capacity. An infusion is “the introduction of a fluid other than blood, such as a saline or glucose solution, into the blood”.

In many cases, the return of blood volume to normal levels is all that is necessary to prevent shock. Eventually, the body produces red blood cells to replace those that were lost. Early attempts to transfuse blood from one person to another were often unsuccessful because they resulted in transfusion reactions, which included clotting within blood vessels, kidney damage, and death. It is now known that transfusion reactions are caused by interactions between antigens and antibodies.

In brief, the surfaces of red blood cells have molecules called antigens and, in the plasma, molecules called antibodies are present. Antibodies are very specific, meaning that each antibody can combine only with a certain antigen. When the antibodies in the plasma bind to the antigens on the surfaces of the red blood cells, they form molecular bridges that connect the red blood cells. As a result, agglutination, or clumping, of the cells occurs. The combination of the antibodies with the antigens can also initiate reactions that cause hemolysis. Because the antigen–antibody combinations can cause agglutination, the antigens are often called agglutinogens, and the antibodies are called agglutinins.

The antigens on the surface of red blood cells have been categorized into blood groups, and more than 35 blood groups, most of which are rare, have been identified. For transfusions, the ABO and Rh blood groups are among the most important. Other well known groups include the Lewis, Duffy, MNSs, Kidd, Kell, and Lutheran groups.

*ABO Blood Group :-*

 In the ABO blood group, type A blood has type A antigens, type B blood has type B antigens, type AB blood has both A and B antigens, and type O blood has neither A nor B antigens on the surface of red blood cells.

The genes for the ABO blood group are on chromosome 9.

The ABO blood group is an example of co-dominance in that the A and B antigens can be expressed at the same time.

Plasma from type A blood contains anti-B antibodies, which act against type B antigens, whereas plasma from type B blood contains anti-A antibodies, which act against type A antigens. Type AB blood has neither type of antibody, and type O blood has both anti-A and anti-B antibodies.

The ABO blood types are not found in equal numbers. In Caucasians in the United States, the distribution is type O, 47%; type A, 41%; type B, 9%; and type AB, 3%. Among African- Americans, the distribution is type O, 46%; type A, 27%; type B, 20%; and type AB, 7%.

Antibodies normally do not develop against an antigen unless the body is exposed to that antigen. One possible explanation for the production of anti-A and/or anti-B antibodies is that type A or B antigens on bacteria or food in the digestive tract stimulate the formation of antibodies against antigens that are different from one’s own antigens. In support of this explanation is the observation that anti-A and anti-B antibodies are not found in the blood until about 2 months after birth. For example, an infant with type A blood produces anti-B antibodies against the B antigens on bacteria or food. An infant with A antigens does not produce antibodies against the A antigen on bacteria or food because mechanisms exist in the body to prevent the production of antibodies that react with the body’s own antigens.

A blood donor gives blood, and a recipient receives blood. Usually, a recipient can receive blood from a donor if they have the same blood type. For example, a person with type A blood can receive blood from a person with type A blood. No ABO transfusion reaction would occur because the recipient has no anti-A antibodies against the type A antigen. On the other hand, if type A blood were donated to a person with type B blood, a transfusion reaction would occur because the person with type B blood has anti-A antibodies against the type A antigen, and agglutination would result.

Historically, people with type O blood have been called “universal donors” because they usually can give blood to the other ABO blood types without causing an ABO transfusion reaction. Their red blood cells have no ABO surface antigens and, therefore, do not react with a recipient’s anti-A or anti-B antibodies. For example, if type O blood is given to a person with type A blood, the type O red blood cells do not react with the anti-B antibodies in the recipient’s blood. In a similar fashion, if type O blood is given to a person with type B blood, no reaction occurs to the recipient’s anti-A antibodies.

The term universal donor is misleading, however. The transfusion of type O blood, in some cases, produces a transfusion reaction for two reasons. First, other blood groups can cause a transfusion reaction. Second, antibodies in the donor’s blood can react with antigens in the blood of the recipient. For example, type O blood has anti-A and anti-B antibodies. If type O blood is transfused into a person with type A blood, the anti-A antibodies (in the type O blood) react against the A antigens (in the type A blood). Usually, such reactions are not serious because the antibodies in the donor’s blood are diluted in the larger volume of the recipient’s blood, and few reactions take place.

Blood banks separate donated blood into several products, such as packed red blood cells; plasma; platelets; and cryoprecipitate, which contains von Willebrand factor, clotting factors, and fibrinogen. This process allows the donated blood to be used by multiple recipients, each of whom may need only one of the blood components. Type O packed red blood cells are unlikely to cause an ABO transfusion reaction when given to a person with a different blood type because it has very little plasma with anti-A and anti-B antibodies.

*Rh Blood Group:-* The Rh blood group is so-named because it was first studied in rhesus monkeys.

People are Rh-positive if they have a certain Rh antigen (the D antigen) on the surface of their red blood cells, and people are Rh-negative if they do not have this Rh antigen.

The gene for the D antigen is on chromosome 1.

About 85% of Caucasians in the United States and 88% of African-Americans are Rh-positive. The ABO blood type and the Rh blood type usually are designated together. For example, a person designated as A positive is type A in the ABO blood group and Rh-positive.

The rarest combination in the United States is AB negative, which occurs in less than 1% of all Americans.

Antibodies against the Rh antigen do not develop unless an Rh-negative person is exposed to Rh-positive blood. This can occur through a transfusion or if blood crosses the placenta to a mother from her fetus. When an Rh-negative person is exposed to Rh-positive blood, the person can become sensitized to the Rh antigens and produce anti-Rh antibodies.

Rh incompatibility can pose a major problem in some pregnancies when the mother is Rh-negative and the fetus is Rh-positive. If fetal blood leaks through the placenta and mixes with the mother’s blood, the mother becomes sensitized to the Rh antigen. The mother produces anti-Rh antibodies that cross the placenta and cause agglutination and hemolysis of fetal red blood cells. This disorder is called “hemolytic disease” of the newborn (HDN), or erythroblastosis fetalis, and it may be fatal to the fetus. In the mother’s first pregnancy, there is often no problem. The leakage of fetal blood is usually the result of a tear in the placenta that takes place either late in the pregnancy or during delivery. Thus, there is not enough time for the mother to produce enough anti-Rh antibodies to harm the fetus. If sensitization occurs, however, it can cause problems in a subsequent pregnancy in two ways. First, once a woman is sensitized and produces anti-Rh antibodies, she may continue to produce the antibodies through her life. Thus, in a subsequent pregnancy, anti- Rh antibodies may already be present. Second, and especially dangerous in a subsequent pregnancy with an Rh-positive fetus, if any leakage of fetal blood into the mother’s blood occurs, she rapidly produces large amounts of anti-Rh antibodies, and HDN develops. Prevention of HDN is often possible if the Rh-negative mother is given an injection of a specific type of antibody preparation, called Rho (D) immune globulin (RhoGAM). The injection can be given during the pregnancy, before delivery, or immediately after each delivery, miscarriage, or abortion. The injection contains antibodies against Rh antigens. The injected antibodies bind to the Rh antigens of any fetal red blood cells that may have entered the mother’s blood. This treatment inactivates the fetal Rh antigens and prevents sensitization of the mother. However, if sensitization of the mother has already occurred, the treatment is ineffective.

If HDN develops, treatment consists of slowly removing the blood of the fetus or newborn and replacing it with Rh- negative blood. The newborn’s skin is also exposed to full-spectrum white light because it helps breakdown bilirubin in the blood as the blood flows through the skin. The bilirubin is derived from the hemoglobin released from ruptured red blood cells. High levels of bilirubin are toxic to the nervous system and can cause destruction of brain tissue.

**HEMOSTASIS :-** Hemostasis\_the stoppage of bleeding,is very important to the maintenance of homeostasis. If notstopped, excessive bleeding (from a cut or torn blood vessel) canresult in a positive-feedback cycle\_consisting of ever-decreasingblood volume and blood pressure, which disrupts homeostasisand results in death. Fortunately, when a blood vessel is damaged,a number of events occur that help prevent excessive blood loss.Vascular spasm, platelet plug formation, and coagulation can causehemostasis.

*1.Vascular Spasm* **:-** Vascular spasm is “the immediate but temporary constriction of ablood vessel resulting from contraction of smooth muscle withinthe wall of the vessel”. This constriction can close small vesselscompletely and stop the flow of blood through them.

Damageto blood vessels can activate nervous system reflexes that causevascular spasms.

Chemicals also produce vascular spasms. Forexample, during the formation of a platelet plug, platelets releasethromboxanes, which are derived from certainprostaglandins, and endothelial cells release the peptide endothelin.

*2. Platelet Plug Formation :-*A platelet plug is “an accumulation of platelets that can seal upsmall breaks in blood vessels”.

Platelet plug formation is very importantin maintaining the integrity of the circulatory system becausesmall tears occur in the smaller vessels and capillaries many timeseach day, and platelet plug formation quickly closes them. Peoplewho lack the normal number of platelets tend to develop numeroussmall hemorrhages in their skin and internal organs.

The formation of a platelet plug can be described as a series ofsteps, but in actuality many of the steps take place simultaneously.

1. Platelet adhesion occurs when platelets bind to collagen exposed by blood vessel damage. Most platelet adhesion is mediated through von Willebrand factor (vWF), which is a protein produced and secreted by blood vessel endothelial cells. Von Willebrand factor forms a bridge between collagen and platelets by binding to platelet surface receptors and collagen. In addition, other platelet surface receptors can bind directly to collagen.

2. After platelets adhere to collagen, they become activated. In the platelet release reaction, adenosine diphosphate (ADP), thromboxanes, and other chemicals are extruded from the platelets by exocytosis. The ADP and thromboxane bind to their respective receptors on the surfaces of other platelets, resulting in their activation. These activated platelets release additional chemicals, thereby producing a cascade of chemical release by the platelets. Thus, more and more platelets become activated.

3. As platelets become activated, they change shape and express fibrinogen receptors that can bind to fibrinogen, a plasma protein. In platelet aggregation, fibrinogen forms a bridge between the fibrinogen receptors of different platelets, resulting in the formation of a platelet plug.

4. Activated platelets express phospholipids (platelet factor III) and coagulation factor V, which are important in clot formation. Plavix (clopidogrel bisulfate) reduces the activation of platelets by blocking the ADP receptors on the surface of platelets. It is used to prevent clotting and, with other anticlotting drugs, to treat heart attacks.

*3. Coagulation :-*Vascular spasms and platelet plugs alone are not sufficient toclose large tears or cuts. When a blood vessel is severely damaged,coagulation, or blood clotting , results in theformation of a clot.

A blood clot is “a network of threadlike proteinfibers, called fibrin , that traps blood cells, platelets, and fluid”**.**

The formation of a blood clot depends on a number of proteins,called coagulation factors, found within plasma.Normally, the coagulation factors are in an inactive state and donot cause clotting. After injury, the clotting factors are activatedto produce a clot. This activation is a complex process involving many chemical reactions, some of which require calcium ionsand molecules on the surface of activated platelets, such asphospholipids and coagulation factor V.The activation of clotting proteins begins with the extrinsicand intrinsic pathways. These pathways convergeto form the common pathway, which results in the formation of afibrin clot.

* Extrinsic Pathway :-The extrinsic pathway is so-named because it begins withchemicals that are outside of, or extrinsic to, the blood. Damaged tissues release a mixture of lipoproteinsand phospholipids called thromboplastin,also known as tissue factor (TF), or factor III. Thromboplastin,in the presence of Ca 2, forms a complex with factor VII, whichactivates factor X, which is the beginning of the commonpathway.
* Intrinsic Pathway :-The intrinsic pathway is so-named because it begins with chemicalsthat are inside, or intrinsic to, the blood.Damage to blood vessels can expose collagen in the connective tissuebeneath the epithelium lining the blood vessel. When plasmafactor XII comes into contact with collagen, factor XII is activatedand it stimulates factor XI, which in turn activates factor IX.Activated factor IX joins with factor VIII, platelet phospholipids,and Ca 2 to activate factor X, which is the beginning of the commonpathway.Although once considered distinct pathways, it is now knownthat the extrinsic pathway can activate the clotting proteins in the intrinsic pathway. The thromboplastin/factor VII complex fromthe extrinsic pathway can stimulate the formation of activated factorsIX in the intrinsic pathway.
* Common Pathway :-On the surface of platelets, activated factor X, factor V, plateletphospholipids, and Ca 2 complex to form prothrombinase.Prothrombinase converts the soluble plasma protein prothrombininto the enzyme thrombin. Thrombin converts the soluble plasmaprotein fibrinogen into the insoluble protein fibrin. Fibrin formsthe fibrous network of the clot. Thrombin stimulates factor XIIIactivation, which is necessary to stabilize the clot.Thrombin can activate many of the clotting proteins, suchas factor XI and prothrombinase. Thus, thrombin is part of apositive-feedback system in which thrombin production stimulatesthe production of additional thrombin. Thrombin also hasa positive-feedback effect on coagulation by stimulating plateletactivation.

*Control of Clot Formation :-*Without control, coagulation would spread from the point ofinitiation to the entire circulatory system. Furthermore, vessels ina healthy person contain rough areas that can stimulate clot formation,and small amounts of prothrombin are constantly beingconverted into thrombin.

To prevent unwanted clotting, the bloodcontains several anticoagulants, which preventcoagulation factors from initiating clot formation. Only whencoagulation factor concentrations exceed a given threshold in alocal area does coagulation occur.

At the site of injury, so manycoagulation factors are activated that the anticoagulants are unableto prevent clot formation. Away from the injury site, however, theactivated coagulation factors are diluted in the blood, anticoagulantsneutralize them, and clotting is prevented.

Examples of anticoagulants in the blood are antithrombin,heparin, and prostacyclin. Antithrombin\_a plasma protein producedby the liver, slowly inactivates thrombin. Heparin\_producedby basophils and endothelial cells, increases the effectiveness ofantithrombin because heparin and antithrombin together rapidlyinactivate thrombin. Prostacyclin\_is a prostaglandinderivative produced by endothelial cells. It counteractsthe effects of thrombin by causing vasodilation and inhibiting therelease of coagulation factors from platelets.

Anticoagulants are also important when blood is outside thebody. They prevent the clotting of blood used in transfusions andlaboratory blood tests. Examples include heparin, ethylene-diamine-tetraacetic acid (EDTA),and sodium citrate. EDTA and sodium citrate prevent clot formationby binding to Ca 2, thus making the ions inaccessible forclotting reactions.