Lectures 4-5

BLOOD PHYSIOLOGY

Blood components

Blood is the only fluid tissue. It is composed of liquid plasma and formed elements. Formed elements include:

1- Erythrocytes, or red blood cells (RBC).
2- Leukocytes, or white blood cells (WBC).
3- Platelets.

Average blood volume is 5–6 L for male and 4–5 L for female. The cells constitute about 45% of blood volume (packed cell volume or hematocrit=0.45). Blood temperature is 38°C. Blood pH is 7.35–7.45.

Formed Elements

Erythrocytes, leukocytes, and platelets make up the formed elements. Only WBCs are complete cells. WBC count may increase to 11,000/mm^3 as normal response to bacterial or viral invasion, leave capillaries via diapedesis and move through tissue spaces. RBCs have no nuclei or organelles, and platelets are just cell fragments. Most blood cells do not divide but are renewed in bone marrow.

Cell Type	Cells/μL	Function
Erythrocytes	4 – 6 million	O_2 and CO_2 transport
Leukocytes: Granulocytes		
Neutrophils	3000 – 7000	Bacterial phagocytosis
Eosinophils	100 – 400	Kill parasitic worms Destroy antigen-antibody complex
Basophils	20 – 50	Mediates inflammation, Heparin
Leukocytes: Agranulocytes		
Lymphocytes (T & B)	1500 – 3000	Cellular or antibody directed immune response
Monocytes	100 – 700	Phagocytosis, Develop into macrophages
Platelets	250,000 – 500,000	Blood clotting, Seal blood vessel tears

The RBC is a biconcave disc. It is anucleated (has no nucleus) and no organelles. The RBC is filled with hemoglobin (Hb). The plasma membrane protein spectrin gives the RBC its flexibility. The biconcave shape provides a huge surface area with minimum volume. The Hb constitutes bout 97% of solid cell contents. ATP is generated anaerobically, so the RBCs do not consume the O_2 they transport. RBC function is transport of respiratory gas. Most O_2 in the blood is bound to Hb. (oxyhemoglobin). Reduced Hb (Deoxyhemoglobin) is Hb without O_2. Carbaminohemoglobin is Hb bound to CO_2.

Functions of Blood

1- Distribution (O_2, CO_2, nutrients, wastes, hormones ...)
2- Regulation (temperature, pH, fluid volume ...)
3- Protection (clotting, prevention of infection: WBC, antibodies, complement)

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Composition of blood plasma

Blood plasma contains over 100 solutes, including proteins, nonprotein nitrogenous substances, organic nutrients, electrolytes and respiratory gases.

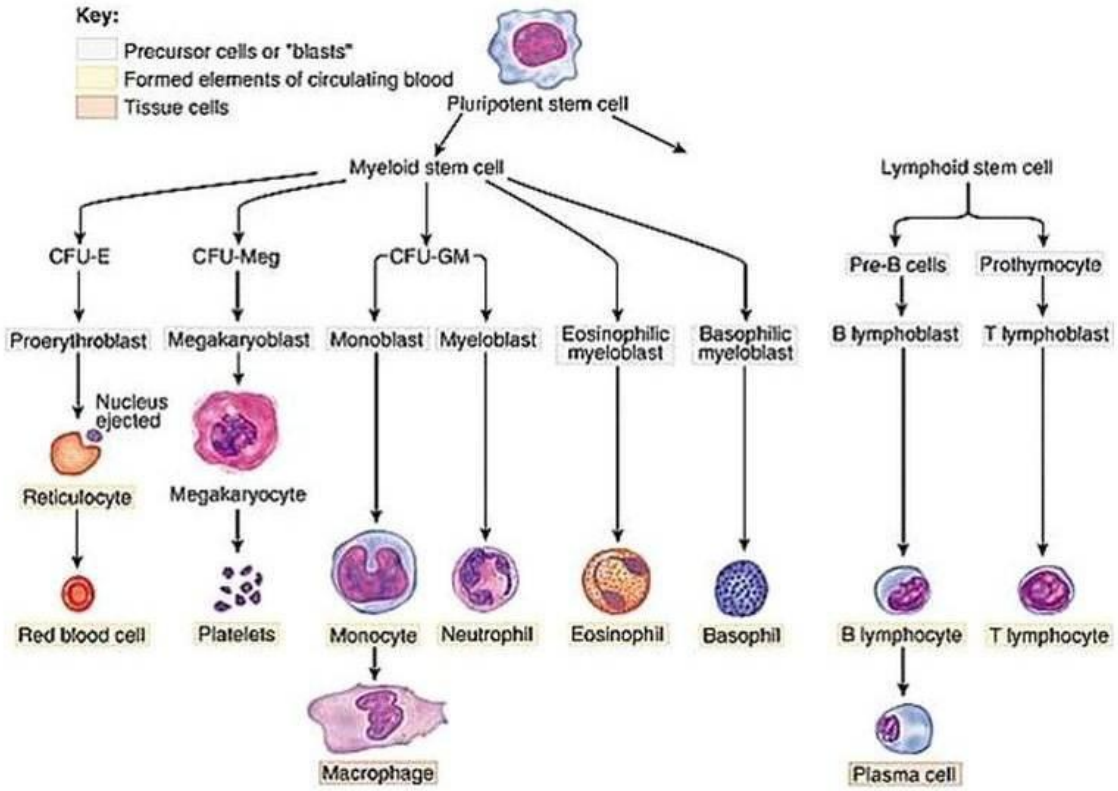
Determination	Traditional Units	SI Units
Bilirubin (S)	Conjugated: up to 0.4 mg/dL Total: up to 1.0 mg/dL	Up to 7 µmol/L Up to 17 µmol/L
Calcium (S)	8.5-10.5 mg/dL; 4.3-5.3 meq/L	2.1-2.6 mmol/L
Chloride (S)	100-108 meq/L	100-108 mmol/L
Cholesterol (S)	< 200 mg/dL	< 5.17 mmol/L
Cholesteryl esters (S)	60-70% of total cholesterol	
Copper (total) (S)	70-155 µg/dL	11.0-24.4 µmol/L
Cortisol (P) (fasting)	5-25 µg/dL	0.14-0.69 µmol/L
Creatinine (P)	0.6-1.5 mg/dL	53-133 µmol/L
Glucose, fasting (P)	70-110 mg/dL	3.9-6.1 mmol/L
Iron (S)	50-150 µg/dL	9.0-26.9 µmol/L
Lactic acid (B)	0.5-2.2 meq/L	0.5-2.2 mmol/L
Lipids, total (S)	450-1000 mg/dL	4.5-10 g/dL
Magnesium (S)	1.4-2.0 meq/L	0.7-1.0 mmol/L
Osmolality (S)	280-296 mosm/kg H_2O	280-296 mmol/kg H_2O
PCO_2 (arterial) (B)	35-45 mm Hg	4.7-6.0 kPa
pH (B)	7.35-7.45	
Phosphatase, alkaline (S)	13-39 units/L (adults)	0.22-0.65 µmol·s^{-}1/L
Phospholipids (S)	9-16 mg/dL	2.9-5.2 mmol/L
Phosphorus,inorganic (S)	2.6-4.5 mg/dL (infants 1st year: up to 6.0 mg/dL)	0.84-1.45 mmol/L
PO_2 (arterial) (B)	75-100 mm Hg	10.0-13.3 kPa
Potassium (S)	3.5-5.0 meq/L	3.5-5.0 mmol/L
Total protein (S)	6.0-8.0 g/dL	60-80 g/L
Albumin (S)	3.1-4.3 g/dL	31-43 g/L
Globulin (S)	2.6-4.1 g/dL	26-41 g/L
Pyruvic acid (P)	0-0.11 meq/L	0-110 µmol/L
Sodium (S)	135-145 meq/L	135-145 mmol/L
Urea nitrogen (S)	8-25 mg/dL	2.9-8.9 mmol/L
Uric acid (S) Women	2.3-6.6 mg/dL	137-393 µmol/L
Uric acid (S) Men	3.6-8.5 mg/dL	214-506 µmol/L

Production of Blood Cells

The process of blood cell formation is referred to as hematopoiesis (or hemopoiesis). It occurs in the red bone marrow of the axial skeleton and girdles, epiphyses of the humerus and femur.

Hemocytoblast gives rise to all formed elements. Hemocytoblast differentiates into myeloid stem cell or lymphoid stem cell. When myeloid stem cell differentiates into proerythroblast, the latter produces reticulocyte. Reticulocyte throws out its nucleus to become RBC.

Formation of WBC is called leucopoiesis. All leukocytes originate from hemocytoblast. Myeloid stem cell becomes myeloblast or monoblast. Lymphoid stem cell becomes lymphoblast. Myeloblast develops into eosinophil, neutrophil, or basophil. Monoblast develops into monocyte. Lymphoblast develops into lymphocytes (B or T).



Formation of RBC (erythropoiesis) is triggered by hypoxia (less PO_2) which leads to release of erythropoietin (EPO) from the kidneys. It depends on adequate supplies of iron, amino acids, and B vitamins, lipids, carbohydrates, iron and folic acid. The body stores iron in Hb (65%), liver, spleen, and bone marrow. Intracellular iron is stored in protein-iron complexes such as ferritin and hemosiderin. Circulating iron is loosely bound to the transport protein transferrin.

The life span of an erythrocyte is 100–120 days. Old erythrocytes become rigid and fragile, and their hemoglobin begins to degenerate. Dying erythrocytes are engulfed by macrophages. Heme and globin are separated and the iron is salvaged for reuse. Heme is degraded to a yellow pigment called bilirubin. The liver secretes bilirubin into the intestines as bile. The intestines metabolize it into urobilinogen. This

degraded pigment leaves the body in feces, in a pigment called stercobilin. Globin is metabolized into amino acids and is released into the circulation.

Clinical considerations: Anemia

Anemia means blood has abnormally low oxygen-carrying capacity. It is a symptom rather than a disease itself. Anemia is characterized by fatigue, paleness, shortness of breath, and chills.

Types of anemia:

1- Insufficient Erythrocytes

-Hemorrhagic anemia – result of acute or chronic loss of blood
-Hemolytic anemia – prematurely ruptured erythrocytes
-Aplastic anemia – destruction or inhibition of red bone marrow

2- Decreased Hemoglobin Content

A- Iron-deficiency anemia results from:

-A secondary result of hemorrhagic anemia
-Inadequate intake of iron-containing foods
-Impaired iron absorption

B- Pernicious anemia results from deficiency of vitamin B_{12} which is caused by lack of intrinsic factor needed for absorption of B_{12}

3- Abnormal Hemoglobin

-Thalassemias – absent or faulty globin chain in hemoglobin. The erythrocytes are thin, delicate, and deficient in hemoglobin.

-Sickle-cell anemia – a defective gene coding for an abnormal hemoglobin called hemoglobin S (HbS). HbS has a single amino acid substitution in the beta chain. This defect causes RBCs to become sickle-shaped in low oxygen situations.

Clinical considerations: Polycythemia

Polycythemia is excess RBCs that increase blood viscosity. Three main polycythemias are: polycythemia vera, secondary polycythemia, and blood doping

Clinical considerations: Leukemias

Leukemias are cancerous conditions involving white blood cells. Myelocytic leukemia involves myeloblasts. Lymphocytic leukemia involves lymphocytes. Acute leukemia primarily affects children. Chronic leukemia is more prevalent in older people. Cancerous leukocytes occupy bone marrow and immature white blood cells are found in the bloodstream. The numerous white blood cells produced are not functional. Death is caused by internal hemorrhage and overwhelming infections.

Hemostasis

Hemostasis (blood clotting) is a series of reactions designed for stoppage of bleeding. During hemostasis, three phases occur in rapid sequence:

1-Vascular spasm: It is an immediate vasoconstriction in response to injury.

2-Platelet Plug Formation: The platelets stick to exposed collagen fibers, form a platelet plug and attract more platelets.

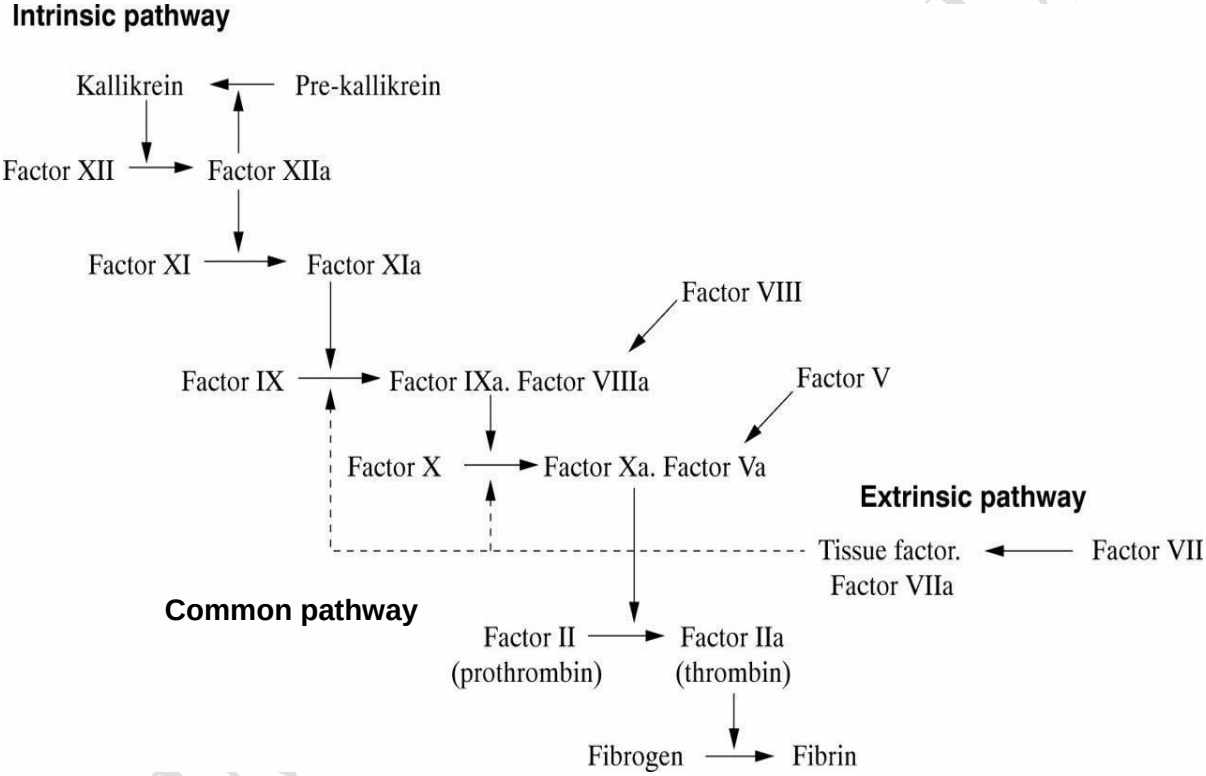
3-Coagulation: It is a set of reactions in which blood is transformed from a liquid to a gel. Coagulation follows intrinsic and extrinsic pathways. The final three steps of this series of reactions are:

-Prothrombin activator is formed

-Prothrombin is converted into thrombin

-Thrombin catalyzes the joining of fibrinogen into a fibrin mesh

Fibrin, strengthens and stabilizes the clot.



Clinical considerations: Thromboembolytic disorders

Thrombus is a clot that develops and persists in an unbroken blood vessel. Thrombi can block circulation, resulting in tissue death. Coronary thrombosis is thrombus in blood vessel of the heart. Embolus is a thrombus freely floating in the blood stream. Pulmonary emboli can impair the ability of the body to obtain oxygen. Cerebral emboli can cause strokes

Pharmacological considerations: Prevention of Undesirable Clots

Substances used to prevent undesirable clots include aspirin (antiprostaglandin), heparin, warfarin and flavonoids (substances found in tea, red wine, and grape juice).

Clinical considerations: Bleeding Disorders

Thrombocytopenia: Platelet counts less than 50,000/mm^3 due to suppression or destruction of bone marrow (e.g., malignancy and radiation). Patients show petechiae with spontaneous, widespread hemorrhage. Inability to synthesize procoagulants by the liver results in severe bleeding disorders. The causes might be vitamin K deficiency, hepatitis or cirrhosis.

Hemophilias: Hereditary bleeding disorders caused by lack of clotting factors. Hemophilia A is the most common type (83% of all cases) due to a deficiency of factor VIII. Hemophilia B results from a deficiency of factor IX. Hemophilia C is mild type, caused by a deficiency of factor XI. Symptoms include prolonged bleeding and painful and disabled joints.

Human blood groups

External surfaces of RBC membranes have 30 varieties of naturally occurring glycoprotein antigens. They promote agglutination and, so, called agglutinogens. Presence (or absence) of these antigens is used to classify blood groups. The ABO blood groups refer to the presence (or absence) of antigens A and/or B.

Specific antibodies for theses antigens are present in (or absent from) the blood plasma. They are anti-A and anti-B antibodies. A subject with blood group A has antigen A on RBC membrane and antibody B in his plasma. Conversely, a subject with blood group B has antigen B on RBC membrane and antibody A in his plasma.

The subject who donates his blood is called the donor while that who receives blood is called the recipient. When a subject with blood group B donates his blood to a subject with blood group A, the antibodies B in the recipient's plasma attack the antigens B on the received blood RBCs resulting in serious hemolytic reactions.

Other probabilities are shown in the table below. Accordingly, the blood group O is the universal donor (the generous blood which gives all because it has no antigens to be attacked by the recipient's antibodies) while the blood group AB is the universal recipient (it receives from all because it has no antibodies to attack any antigen on the donated blood RBCs).

ABO Blood groups			
Blood group	RBC Antigen	Plasma Antibody	Blood that can be received
AB	A and B	None	A, B, AB and O
B	B	Anti-A	B and O
A	A	Anti-B	A and O
O	None	Anti-A and Anti-B	O

Presence of the Rh antigens on RBCs is indicated as Rh^+. Subject with Rh^+ blood has antigen Rh on RBC membrane (so, he has no Rh antibodies in his plasma). However, even the subject with Rh^- blood has no Rh antibodies in his plasma (the Rh antibodies are not spontaneously formed in the plasma of Rh^- individuals), but if it happens that an Rh^- individual receives Rh^+ blood (accidently or during operation), Rh antibodies will then be formed in his plasma and, hence, when that "sensitized" subject receives an Rh^+ blood at a second occasion, a typical transfusion reaction will occur.

Clinical considerations: Hemolytic disease of newborn

Rh^- mother becomes sensitized when Rh^+ blood (from her first Rh^+ baby or an Rh^+ transfusion) causes her body to synthesize Rh^+ antibodies. Rh^+ antibodies of mother cross the placenta and attack and destroy the RBCs of the second Rh^+ baby.

Pharmaceutical considerations: Hemolytic disease of newborn

Drugs like RhoGAM can prevent the Rh^- mother from becoming sensitized by the first Rh^+ baby's antigens and, hence, prevents the formation of Rh^+ antibodies in the mother's plasma. Treatment of hemolytic disease of the newborn involves pre-birth transfusions and exchange transfusions after birth.

Transfusion Reactions

Transfusion reactions occur when mismatched blood is infused. Donor's cells are attacked by the recipient's plasma agglutinins causing diminished oxygen-carrying capacity, clumped cells that impede blood flow, ruptured RBCs that release free hemoglobin into the bloodstream, circulating hemoglobin precipitates in the kidneys and causes renal failure