كلية المستقبل الجامعة

قسم الصيدلة – المرحلة الثانية

PHYSIOLOGY II

HEMATOLOGY ,L1

Introduction to Blood Physiology

Blood is a vital fluid that circulates throughout the body, delivering oxygen and nutrients to cells while removing waste products. It is composed of plasma, red blood cells, white blood cells, and platelets. Each component plays a critical role in maintaining homeostasis within the body.

Plasma, which makes up about 55% of blood volume, is a yellowish liquid that contains water, proteins, hormones, and electrolytes. **Red blood cells**, or **erythrocytes**, are responsible for carrying oxygen from the lungs to the tissues. **White blood cells**, or **leukocytes**, play a crucial role in the immune system by fighting off infections. **Platelets**, or **thrombocytes**, help with blood clotting to prevent excessive bleeding.

1. RED BLOOD CELLS (ERYTHROCYTES)

- RBCs, also known as *erythrocytes,*
- Function:
  1. Transport O_2 from the lungs to the tissues by means of *hemoglobin (Hb)*.
- Hb must remain inside RBCs to effectively perform its functions in humans. Otherwise, it is filtrated through the glomerular membrane.
  2. Facilitate excretion of CO_2. They contain a large quantity of *carbonic anhydrase,* an enzyme that catalyzes the reversible reaction between CO_2 and H_2O to form carbonic acid (H2CO3).
  3. Buffering blood pH (Hb in the cells is an excellent *acid-base buffer.*
     The RBCs are responsible for most of the acid-base buffering power of whole blood.
- Shape: biconcave disks
- Diameter: ~ 7.8 micrometers
- Thickness: 2.5 micrometers at the thickest point and 1 micrometer or less in the center.
- The volume: 90-95 cubic micrometers.

RBCs squeeze when pass as through capillaries (but do not ruptured)

- Average number:
  - Men: 5,200,000 ± 300,000 per cubic millimeter in man
  - Women: 4,700,000 ±300,000
- Why men have higher number of RBCs than women?
- Living at high altitudes increase the greater numbers of RBCs (why?)

Which is true concerning RBCs
A) They are multinucleated cells
B) Their count approximate 4,000-11,000/ uL
C) Contain hemoglobin with ferric iron
D) Are spherical cells
E) Most powerful buffering system

Which is false concerning RBCs
A) They are non nucleated cells
B) Their count approximate 5 million/ uL
C) Contain hemoglobin with ferrous iron
D) Are biconcave discs
E) The least powerful buffering system

Which is true concerning RBC function
A) They transport oxygen
B) They eliminate CO_2
C) They buffer blood pH
D) A and C are true
E) A, B and C are true

Quantity of Hb in the Cells

- Normal amount of Hb in the cell: 34g/ 100ml of cells (i.e. 34% of the size of RBC is Hb).
  The concentration does not rise above this value because this is the metabolic limit of the cell's Hb-forming mechanism.
- When Hb% decrease (as in anemia), the volume of the RBC also decrease.
- Blood Hb level:
  - Men: 15g/100ml of blood (i.e. 15g/dL) in men
  - Women: 14g/100ml of blood.
  - Hematocrit %: 40-45% *(represents the cell element of blood)*
  - Plasma %: 55% *(represents the fluid element of blood)*
- 1g Hb carry 1.34 ml of O_2 *(when Hb is fully "100%" saturated with O_2)*
- In men: 1.34ml O_2/1g Hb x 15gHb/100ml blood = 20.1 ml O_2 carried by 100ml of blood.
- In Women: _____= __ ml O2 carried by 100ml of blood.

2. PRODUCTION OF RED BLOOD CELLS (Erythropoiesis)

- Area of production:
  - In the early weeks of embryonic life: the *yolk sac*.
  - During the middle trimester of gestation: the *liver* (Major) & *spleen* and *lymph nodes*.
  - During the last month of gestation: the *bone marrow of all bones*.
  - After birth until 5 years: the *bone marrow of all bones*
  - Between 5 - 20 years of age: the *bone marrow of long bones* *(except for the proximal portions of the humerus and tibiae - they become fatty)*
  - After 20 years of age: *bone marrow of* membranous bones (vertebrae, sternum, ribs, and ilium).
  - With advance age: the marrow becomes less productive.

Which is true concerning Hb
A) Constitute 43% of RBC size
B) Some Hb circulate freely in plasma
C) Man plasma Hb ~ 15g/dl
D) Each gram Hb carry 1.43ml of O2
E) In woman, each 100ml of blood saturate with 18.7 ml of O2

Which is false concerning Hb
A) Constitute 34% of RBC size
B) Hb must inclosed within RBC
C) Man blood Hb ~ 15g/dl
D) Each gram Hb carry 1.34ml of O2
E) In woman, each 100ml of blood saturate with 20 ml of O2

Which area of RBC production is false
A) In embryonic life: yolk sac
B) Childhood: bone marrow of all bones
C) Adolescence: long bones
D) Adulthood: vertebrate
E) Geriatric: bone marrow of all bones

- Genesis of Blood Cells

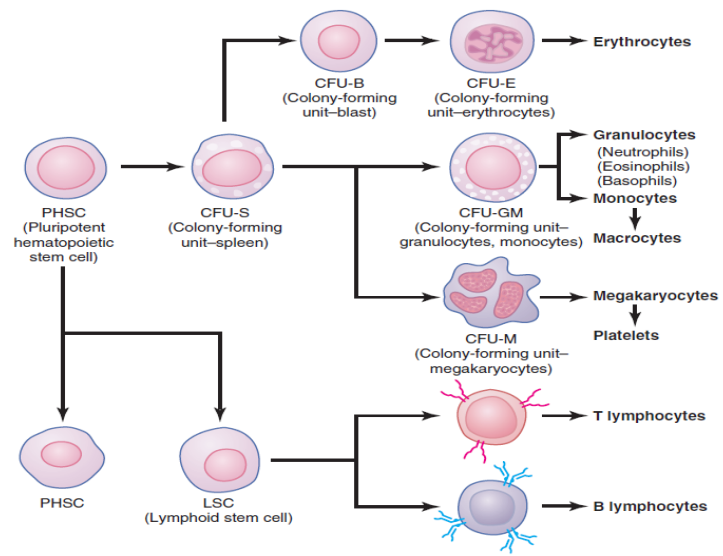
Pluripotential Hematopoietic Stem Cells, Growth Inducers, and Differentiation Inducers

- Undifferentiated bone marrow stem cells called the *Pluripotential hematopoietic stem cell (PHSC).*
- PHSC can differentiate to RBCs, WBCs and platelets.
- PHSC, at intermediate-stage, differentiated to a particular cell line and are called *committed stem cells (CSC).*
- By specific factor, CSC are differentiated into colonies of specific types of blood cells like:
  1. *Colony-forming unit–erythrocyte (CFU-E)* → produces erythrocytes (RBCs).
  2. *Colony-forming unit–granulocytes (CFUGM)* → produce granulocytes (Neutrophils, eosinophils, basophils and monocytes)
  3. *Colony-forming unit-megakaryocyte (CFU-Meg)* → produce megakaryocytes (fragmented to form platelets)
- In the genesis steps there is two set of factors:

1. Growth inducers: growth but not differentiation of the cells (e.g., *interleukin-3*)
2. Differentiation inducers: differentiate committed stem cell to one or more steps toward a final adult blood cell.
3. Source of these factors is outside the bone marrow (e.g., erythropoietin hormone released by kidney in response to hypoxia)

Pluripotential stem cells
A) Differentiate eventually only to erythrocytes
B) Differentiate eventually only to granulocytes
C) Differentiate eventually only to megakaryocytes
D) Differentiate eventually only to lymphocytes
E) Differentiate eventually only to RBCs, WBCs and megakaryocytes

Differentiation of pluripotential stem cells to erythrocytes requires
A) Interleukin-3
B) Erythropoietin
C) Granulocyte-Monocyte colony stimulating factor
D) Granulocyte colony stimulating factor
E) Monocyte colony stimulating factor



Vitamin B12 (Cyanocobalamin) and Folic Acid (Pteroylglutamic Acid) for maturation

- The two vitamins, *vitamin B12* and *folic acid are essential for* thymidine triphosphate (in DNA) synthesis.
- Lack of either vitamin B12 or folic acid causes *maturation failure* in the process of erythropoiesis manifested as:
- Failure of nuclear maturation and cell division *(Abnormal and diminished DNA)*
- Erythroblasts fail to proliferate rapidly yielding larger RBCs called *macrocytes* that:
  - ✓ *Has a flimsy (weak) and irregular membrane*
  - ✓ *Large size*
  - ✓ *Oval instead of the being biconcave disk.*
  - ✓ *Function normally but fragile (their age 40-60 days)*

Vitamin B12

- Source of vitamin B12: food
- Absorption site: ileum (carrier mediated absorption require intrinsic factor that combine with vitamin B12)
  Intrinsic factor is a glycoprotein secreted by parietal gastric cells
- Once absorbed, vitamin B12 stored in large quantities in liver and released slowly when needed.
- 1-3µg of vitamin B12 is needed each day for normal RBCs production.
- Liver storage amount represents 1000times the needed daily amount.
- Atrophic gastric mucosa → deficiency of intrinsic factor
- 3-4 years of defective B12 absorption are usually required to cause maturation failure anemia.
- Lack of vitamin B12 in blood → ***pernicious anemia***.

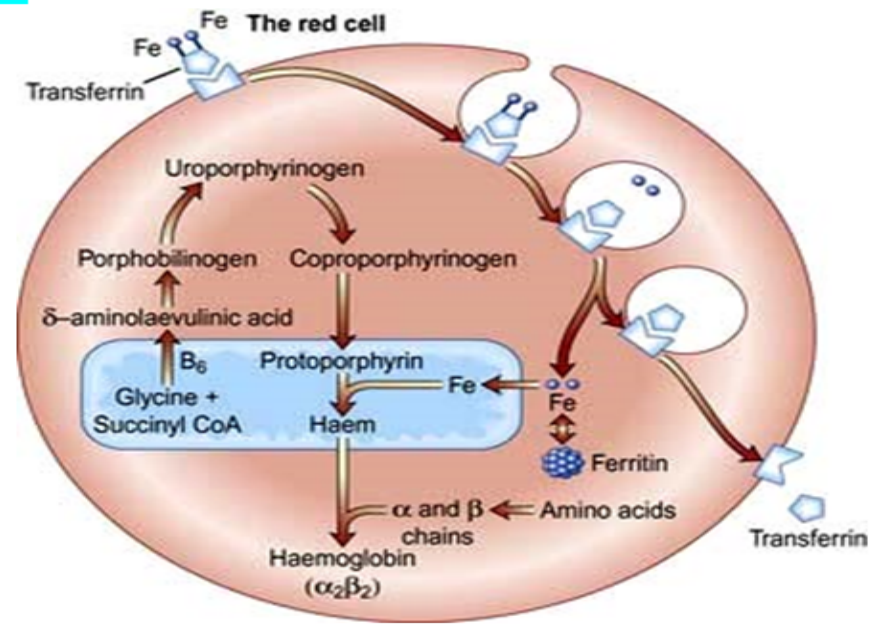
Folic acid

- Source of folic acid: green vegetables, some fruits, and meats (especially liver)
- It is easily destroyed during cooking.
- People with GI absorption abnormalities (*sprue*), have serious difficulty absorbing both folic acid and vitamin B12.
- Maturation failure usually occurs by deficiency of intestinal absorption of both folic acid and vitamin B12.

Hemoglobin Formation

- Synthesis begins in the proerythroblasts and continues into the reticulocyte (until become mature).
- Succinyl-CoA (formed in the Krebs cycle) + glycine → pyrrole molecule
- 4 pyrroles combine together → protoporphyrin IX
- protoporphyrin IX + 1 iron atom → *heme* molecule.
- heme molecule + *globin* (long polypeptide chain synthesized by ribosomes, alpha, beta, gamma or delta chains) → Hb chain
- 4 Hb chains → 1 molecule of Hb
- *hemoglobin A* (*2α, 2β*): The most common form of Hb in the adult human.
- 1 molecule of Hb = 4 Hb chains = 4 irons = carry of 4 molecules (8 atoms) of O_2
- The types of Hb chains determine the binding affinity of Hb for O_2.
- Replacement of *glutamic acid by valine* in each of the *2β* chains → *sickle cell anemia*.

  When this type of Hb is exposed to low oxygen, it forms elongated crystals inside the RBCs that are sometimes 15 micrometers in length. These crystals make it almost impossible for the cells to pass through many small capillaries, and the spiked ends of the crystals are likely to rupture the cell membranes, leading to sickle cell anemia.



- Hb combines loosely and reversibly with O_2.
- O_2 *does not* combine with the 2 + bonds of the iron in the Hb.
- O_2 binds loosely and reversibly with one of the coordination bonds of the iron atom.
- O_2 does not become ionic oxygen but is carried as molecular oxygen to the tissues
- O_2 is released into the tissue fluids still in the form of molecular oxygen rather than ionic oxygen.

Which is false concerning Hb synthesis
A) Synthesized in the mitochondria
B) Synthesized primary from amino acids
C) Iron is incorporated into protoporphyrin X in blast stage
D) Each Hb molecule maximally carry 8 molecules of O_2
E) Each Hb molecule contain 4 globin chains

Which is true concerning Hb synthesis
A) Synthesized in mitochondria from acetyl CoA and glutamate
B) Protoporphyrin X compose of 2pyrrole rings
C) Each hem molecule contain 2 irons
D) Each Hb molecule associate with 4 molecules of O2
E) HbS contain normal 2alpha-2beta chains

3. IRON METABOLISM

- Importance: Formation *hemoglobin*, *myoglobin*, *cytochromes*, *cytochrome oxidase*, *peroxidase*, and *catalase*.
- Total quantity in the body: 4-5g
  - ✓ *65% of which in Hb*
  - ✓ *4% in myoglobin*
  - ✓ *1% in heme oxidases*
  - ✓ *0.1% bound transferrin*
  - ✓ *15-30% stored in form of ferritin in reticuloendothelial system and liver cells).*

Iron is an essential metal that is found in the followings *EXCEPT*
A) Catalases
B) Oxidases
C) Respiratory chain complexes
D) Myoglobin and hemoglobin
E) NAD+

Transport and Storage of Iron

- In plasma, iron bound a beta globulin called apotransferrin to form *transferrin*.
  [Transferrin is the transported "plasma" form of iron in plasma]
- From transferrin, iron can be released to any tissue cell at any point in the body.
- Excess iron in the blood is deposited *especially* in the liver hepatocytes and less in the reticuloendothelial cells of the bone marrow.
- In the cell cytoplasm: iron bound with a protein called *apoferritin* to form *ferritin*.
  Ferritin represents the stored form of iron.
- When ferritin is saturated, smaller quantities of iron is in insoluble form called Hemosiderin.
- Hemosiderin: can be observed microscopically as large particles.
- Ferritin particles: can only be observed by an electron microscope.
- Transferrin molecule binds strongly with receptors in the cell membranes of erythroblasts in the bone marrow and ingested into the erythroblasts by endocytosis *(See figure above)*
- Inside bone marrow cells, transferrin delivers the iron directly to the mitochondria for heme synthesis.
- Low serum transferrin → *hypochromic anemia* (i.e., RBCs that contain much less Hb than normal).
- After 120 days, RBCs are destroyed and their Hb released and ingested by monocyte-macrophage cells (iron is liberated and is stored mainly in the ferritin to be used as needed for the formation of new Hb).

Which is false about iron hemostasis
A) absorption is enhanced in anemic conditions
B) In blood, iron is bounded to beta globulin
C) In enterocytes, iron is bound to apoferritin
D) Hemosiderin is an insoluble form of cellular iron
E) Macrophage release iron from old RBCs

Daily Loss of Iron

- In man: ~ 0.6 mg/day, mainly into the feces + lost when bleeding occurs.
- In woman: ~ 1.3 mg/day, mainly into the feces + menstrual loss of blood.

Absorption of Iron from the Intestinal Tract

- Area of absorption: all parts of the small intestine.
- Mechanism of absorption:

  (1) Apotransferrin
  - ✓ Apotransferrin (in the bile) binds with free iron and also with certain iron compounds, such as Hb and myoglobin from meat.
  - ✓ The resulted transferrin binds with receptors in the membranes of the intestinal epithelial cells.
  - ✓ Transferrin-carrier complex is absorbed by pinocytosis into epithelial cells.

  (2) Divalent metal transporter-1 (DMT1)
  - ✓ Ferrous (but not ferric) ions bound to DMT1 and the complex absorbed into epithelial cells
- Later on epithelial transferrin is released into the blood capillaries as plasma transferrin.
- The rate of iron absorption is slow (few milligrams/day) even if larger amounts present at the site of absorption

Regulation of Total Body Iron by Controlling Rate of Absorption

- When apoferritin become saturated with iron → the rate of additional iron absorption decrease.
- When apoferritin become depleted → GI rate of absorption accelerate 5 times or more than normal.
- Thus, total body iron is regulated mainly by altering the rate of absorption.

Which is true about iron hemostasis
A) Stomach is the major site of iron absorption
B) Absorption require carrier mediated transport
C) Iron is absorbed in ferric form
D) Absorbed iron is bound intracellularly to apotransferrin
E) Absorbed iron is transported in free form in blood

Which is false about iron hemostasis
A) Small intestine is the major site of iron absorption
B) Absorption is by simple diffusion
C) Iron is absorbed in ferrous form
D) Absorbed iron is bound intracellularly to apoferritin
E) Absorbed iron is transported as apotransferrin in blood

4. THE LIFE SPAN OF RED BLOOD CELLS IS ABOUT 120 DAYS

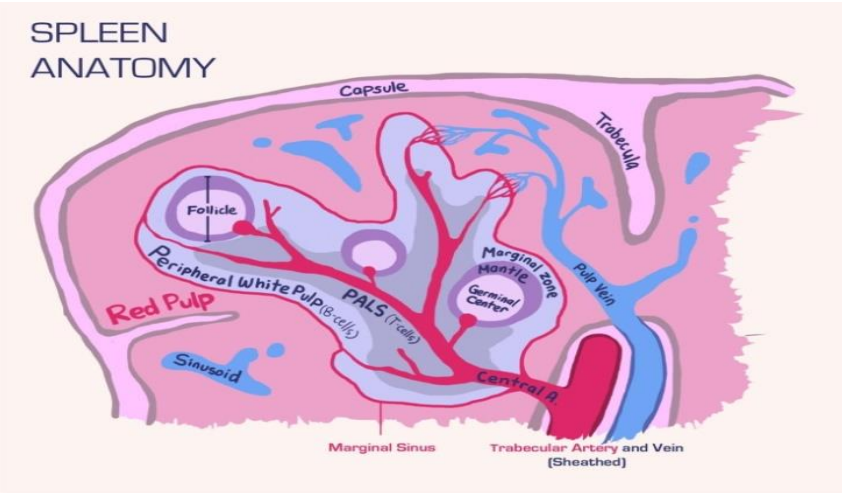
- Normally RBC life: 120days after which they destroyed in spleen.
- RBCs do not have a nucleus, mitochondria, or endoplasmic reticulum.
- RBCs have cytoplasmic enzymes that function for:
  - ✓ Anaerobic glucose metabolism (glycolysis)
  - ✓ Maintain pliability "flexibility" of the cell membrane
  - ✓ Maintain membrane transport of ions
  - ✓ Keep the iron of the Hb in the ferrous (Fe^{+2}) form rather than ferric (Fe^{+3}) form
  - ✓ Prevent oxidation of the proteins in the RBCs
- After 120 days, the metabolic systems of old RBCs become progressively less active and the cells become more and more fragile.
- Fragile RBCs rupture when pass through the red pulp of the spleen.
- Most RBCs must pass (squeeze) through narrow spaces of the spleen red pulp (space diameter = 3µm, RBC diameter = 8µm).
- When the spleen is removed, the number of old abnormal RBCs circulating in the blood increases considerably.

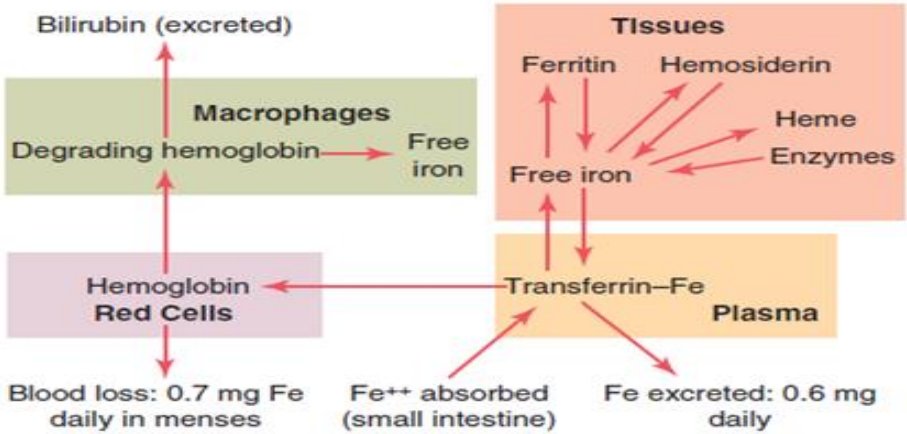
RBCs are ruptured in the following conditions except
A) Sickling crisis
B) Eating fava bean in G6PD deficient individuals
C) Gestation of Rh- mother with Rh- fetus
D) Aging after 120 days
E) Subjected to hemolytic bacterial toxins

After 120 days, RBCs are destructed in spleen because
A) The spleen contain macrophages
B) The sinusoids of red bulb are extremely narrow
C) Aged RBCs have pliable membrane
D) RBCs do not have DNA, RNA and ribosomes
E) None is related

Destruction of Hemoglobin by Macrophages

- Ruptured RBC releases their Hb.
- Hb phagocytized immediately by macrophages
- Macrophage distribute in many tissues (liver "Kupffer cells", spleen and bone marrow)
- In next few hours to days, the macrophages release iron from the Hb
- Iron passes back into the blood and bind with apotransferrin to form transferrin.
- Transferrin deliver iron to bone marrow (for the production of new RBCs) or to the liver and other tissues (for storage in the form of ferritin).
- The porphyrin portion of the Hb molecule is converted by the macrophages, through a series of stages, into the bile pigment bilirubin
- Bilirubin is released into the blood and later removed from the body by secretion through the liver into the bile.





When RBCs are destructed by any cause
A) Macrophages engulf broken RBCs
B) Macrophage digest hem
C) Macrophage convert pyrroles into bilirubin
D) Macrophages digest globin chains
E) All are related

Which is false about the fate of RBC contents
A) Iron circulates as transferrin
B) Iron delivered to the liver for storage
C) Hem converted eventually to bilirubin
D) Globin chains replenish amino acid pool
E) Non is false

5. ANEMIAS

Which is false microscopic appearance of RBCs in the following conditions
A) Iron deficiency: microcytic, hypochromic RBCS
B) Vitamin B12 deficiency: macrocytic, hypochromic RBCs
C) Erythroblastosis fetalis: basophilic RBCs
D) Bone marrow aplasia: normochromic, normocytic RBCs
E) RBCs hemolysis: microcytic, hypochromic RBCs

- **Definition**: Anemia means deficiency of Hb in the blood
- **Cause**: too few RBCs or too little Hb in the RBCs.
- **Types**:

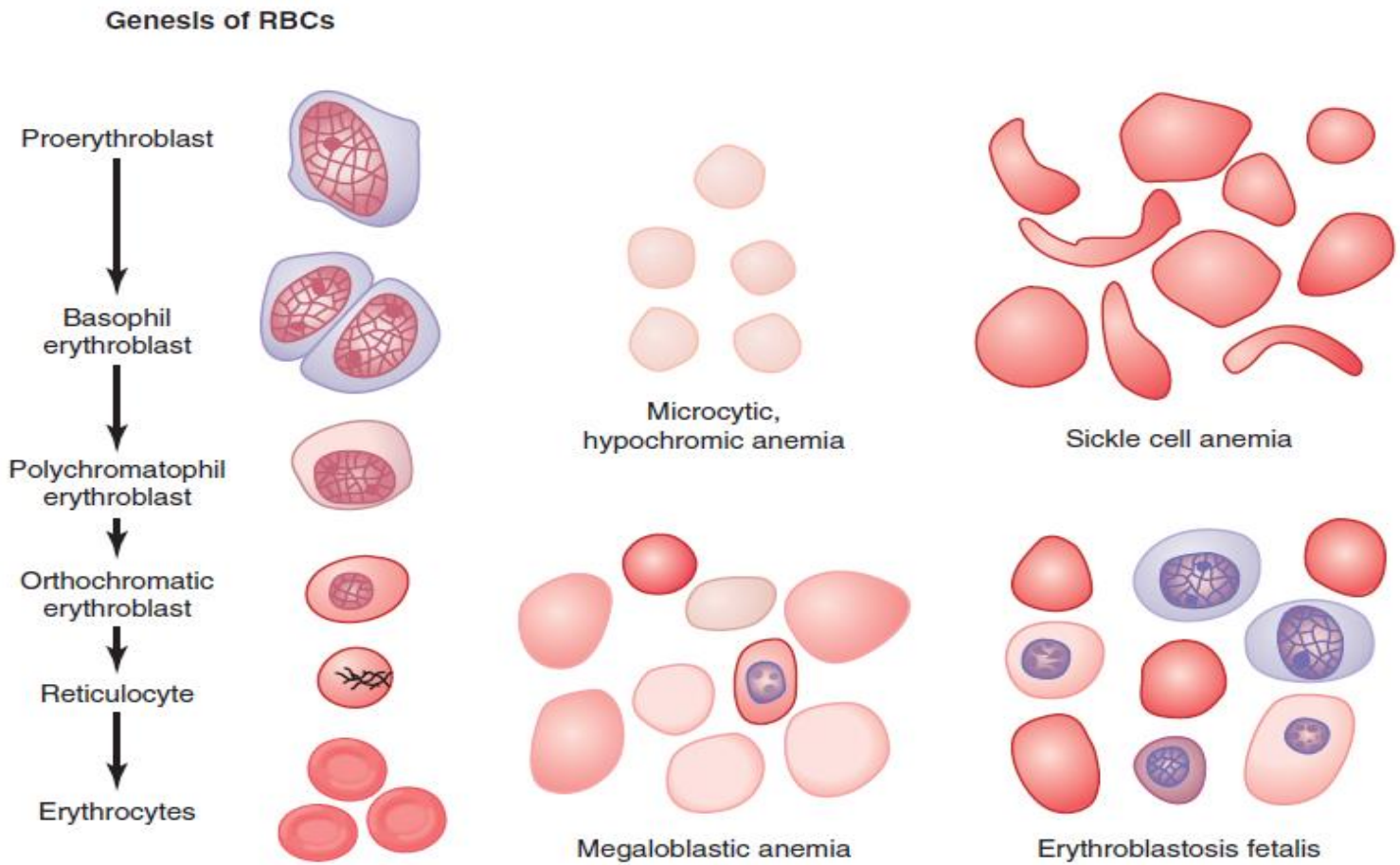
1. **Blood loss anemia** (also called *microcytic, hypochromic anemia*)
   - **Cause**: hemorrhage (bleeding)
   - **Prognosis**:
     - ✓ ***Acute blood loss***: after stop of bleeding RBC count return normal in 3-6 weeks
     - ✓ ***Chronic blood loss***: low ability to absorb iron to form Hb as rapidly as it is lost leading to small size RBC (*microcytic*) *low Hb content* (*hypochromic*)
2. **Aplastic anemia**
   - **Cause**: Bone marrow dysfunction (bone marrow aplasia – failure of differentiation) due to:
     - ✓ *Ionizing radiation; Chemotherapeutic drugs; Benzene; Insecticides; Autoimmune diseases like systemic lupus erythematosus; Unknown reason (idiopathic aplastic anemia)*
   - **Prognosis**: death unless treated with blood transfusions or by bone marrow transplantation
3. **Megaloblastic anemia** (also called *pernicious anemia*)
   - **Cause**: Deficiency of vitamin B12, folic acid, and intrinsic factor → slow reproduction of erythroblasts due to intestinal sprue, gastric atrophy or gastrectomy
   - **Prognosis**: RBCs grow too large and fragile and rupture easily, and are called *megaloblasts*
4. **Hemolytic anemia**
   - **Cause**: premature destruction of RBCs due to **hereditary** causes (G6PD deficiency, favism)

   Hereditary spherocytosis → small, spherical (rather than biconcave), fragile RBCs that destructed in the spleen.

A) *Sickle cell anemia:* Hb S (*abnormal β chain*) of sickle RBCs when exposed to low O_2 conc., precipitated into long crystals that elongate the cell and give it the appearance of a sickle rather than a biconcave disk → damages the cell membrane, so the cells become highly fragile, leading to serious anemia.

- Sickle cell disease "sickling crisis": low tissue O_2 tension ⊢→ sickling and ruptured RBCs → further decrease in O_2 tension → more sickling and RBC destruction.
- Once the process starts, it progresses rapidly, eventuating in a serious decrease in RBCs within a few hours and, in some cases, death.

B) *Erythroblastosis fetalis:* Rh^+ RBCs in the fetus are attacked by antibodies from an Rh^- mother → fragile and rapid ruptured RBCs (the child born with anemia). The extremely rapid formation of new RBCs to make up for the destroyed cells in erythroblastosis fetalis causes a large number of early *blast* forms of RBCs to be released from the bone marrow into the blood.


Genesis of RBCs
Proerythroblast
Basophil erythroblast
Polychromatophil erythroblast
Orthochromatic erythroblast
Reticulocyte
Erythrocytes
Microcytic, hypochromic anemia
Sickle cell anemia
Megaloblastic anemia
Erythroblastosis fetalis

6. POLYCYTHEMIA (increased RBCs count)

Secondary Polycythemia # *physiological polycythemia*

- In high altitudes areas or in mountains O2 tension is reduced → atmospheric hypoxia (too little O_2 in the breathed air). Living in these areas → tissue hypoxia
- In Heart failure patient: failure of fast Hb oxygenation and O2 delivery to the tissues → tissue hypoxia.
- In response to hypoxia, the blood-forming organs automatically produce large quantities of extra RBCs.
- This condition is called *secondary polycythemia*.
- The RBC count commonly rises to 6-7 million/mm^3 (30% above normal)
- A common type of secondary polycythemia, called *physiological polycythemia*, occurs in natives who live at altitudes of 14,000 to 17,000 feet, where the atmospheric O2 is very low. This blood count allows these people to perform reasonably high levels of continuous work even.

Polycythemia Vera (Erythremia) # *pathological polycythemia*

- The RBC count may be 7-8 million/mm3
- Hematocrit may be 60-70% (instead of the normal 40-45%)
- Blood viscosity sometimes increases (to 10 times that of water).
- WBCs and platelets increase as well.
- Total blood volume (sometimes twice the normal)
- Many blood capillaries become plugged by the viscous blood
- The entire vascular system becomes intensely engorged.
- Cause: genetic aberration in the hemocytoblastic cells that produce the blood cells. The blast cells no longer stop producing RBCs (cancer like)

Which is false about polycythemia

A) Dehydration causes secondary polycythemia
B) Primary polycythemia is a bone marrow response to hypoxia
C) Polycythemia vera is a hemocytoblast cancer
D) Blood count of RBCs, WBCs and platelets is above the normal range
E) Blood turned highly viscous


Thank you.


AL-MUSTAQBAL UNIVERSITY COLLEGE
كلية المستقبل الجامعة
قسم الصيدلة
أسست عام ٢٠١٧


AL-MUSTAQBAL UNIVERSITY COLLEGE
وقل رب زدني علما
كلية المستقبل الجامعة
اسست عام ٢٠١٠