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للتدريس الجامعي

LECTURE: Physiology

SUBJECT: Lecture 3+4

.ECTURERS: Infinity staff
0795350650
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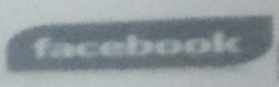

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للتسجيل والإقتراحات

اربد- مقابل البوابة الجنوبية لجامعة اليرموك

م. محمد الحجي : 0795 350 650

Hemoglobin(Hb)

- Each RBC contains 200-300 million molecules of hemoglobin

- Each hemoglobin molecule consists of :
1. 4 protein chains called globin (2 alpha , 2 Beta)
2. The red pigment Heme, which is composed of Fe^{+2} (ferrous iron) and a compound called protoprophyrin (4 iron in center of a ring)

- So, one hemoglobin molecule contain 4 iron atoms so, it can carry 4 Oxygen molecules
  Hb + O_2 ⟷ Oxyhemoglubin (O_2 binds with **heme iron)**
  Hb + CO_2 ⟷ carbaminohemoglubin (CO_2 binds with **globin)**

- Males have usually more hemoglobin content than females due to Testesteron which increase RBCs production so increasing Hb content
- In males every 100ml contain 14-16g hemoglobin, while in females every 100ml contain 12-14g of hemoglobin

- Each gram of Hb carry 1.34ml of O_2
- If hemoglobin content in adult id less than 10g/100ml → Anemia

Heme synthesis:
Acetic acid + glycine → Pyrole
4 Pyrole → protoprophrin
Protopropherin + iron → heme
Heme + Globin → Hemoglubin

Heme in mitochondria
Globin in Ribosome

Types of Hb:
1. Hb A normal adult Hb (2 ά chains each of 141a.a and 2 β chains each of 146 a.a) ----- 96-98%

ii. Hb F normal fetal Hb (2 ά chains and 2 Gamma chains)--- .5-.8 %
iii. Hb A2 (2 ά , 2 delta) --- 1.5-3.5 %

Formation of RBCs:

- This process called Erythropoiesis
- In adults erythropoiesis occurs in Red Bone Marrow, where a Nucleated cells in bone marrow called ***Hematopoietic Stem Cells*** (adult-blood forming-stem cells) divide and differentiate to all types of blood cells
- The entire process requires **4 days.**

- Each minute **200 billion RBCs** is produced in bone marrow to replace equal number of dead cells, and **this requires a continual supply of**

1. vitamin B_{12} which is called antianemic principle → for DNA synthesis
2. Amino acids
3. Folic acid → for RNA synthesis
4. Copper and Cobalt as **catalyst**
5. Iron

Iron is very important in transporting O_2 and absorbed from the deudenum by **active transport**

- **Ferrous (Fe^{+2})** is absorbed **3 times** more than Ferric (Fe^{+3})
- Iron from **animal source** is absorbed more than iron from plant sources
- Iron is required for:

1. Hb synthesis
2. Myoglubin
3. Cytochromes → electron carrier in cellular respiration
4. Enzymes such as Catalase and peroxidase

- Our bodies contains about **4 grams** of iron distributed as follow:
  - **Hb** → 65 – 70%
  - Myoglubin 4%
  - Cytochrome 1%
  - Protein 0.1%
  - **Ferritin in liver** 15-30%

Vitamin B12 (cyanocobalamine)

-water soluble vitamine
-vit B12 can be destroyed by digestive enzyme . intrinsic factor protect it
-prolonged defiecency lead to irreversible neurological damage
- its absorbtion from GI (**terminal ileum**) need intrinsic factor , it is absorbed by pinocytosis .

-intrinsic factor secreted by parietal cells in stomach
-Vit B12 stored mainly in liver in amount (3-5 mg) sufficient to last for couple of year
-increase need in pregnancy , lactation , grouth .

Steps of RBCs production

Hematopoietic Stem cells

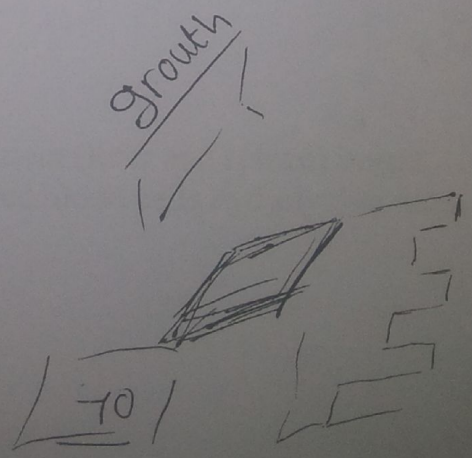
(division)

Proerythroblasts

(division and maturation)

Basophilic Erythroblast

(division and maturation)



Polychromatic Erythroblast **(start hemoglobin production)**

↓ (loss of nuclei)

Reticulocyte (no nucleus)

↓ (go to circulating blood, and lose the reticulum)

Mature Erythrocytes

Factors affecting RBCs production

Any condition leads to Hypoxia (low O_2 reaching the tissues) cause an increase in RBCs production such as:

1. High altitude
2. Low O_2 in the atmosphere
3. Pulmonary diseases
4. Cardiovascular diseases
5. Low Hb (anemia)

- If O_2 reaching the blood is Low (hypoxia) → kidneys release a hormone called **Erythropoietin** → stimulate RBCs production in bone marrow (Erythropoeisis) → ↑ RBCs → ↑ O_2 delivery to tissue.
- Liver also produce erythropoietin in low amounts and inactive form of this hormone called Erythropeitinogen

Destruction of RBCs

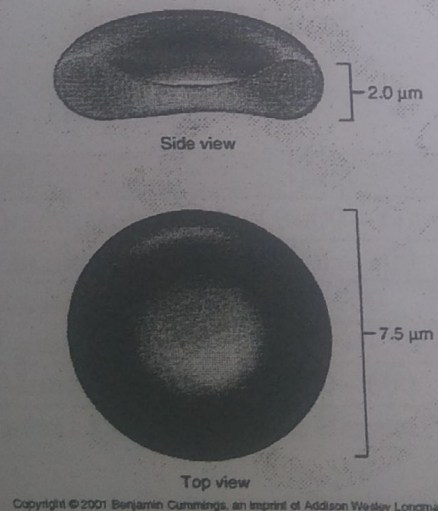
- Life span of RBCs 105-120 days
- Macrophage cells in Reticulo-endothelial system (liver and spleen) ingest (phagocytose) aged, abnormal, fragmented red blood cells hydrolyzing them.

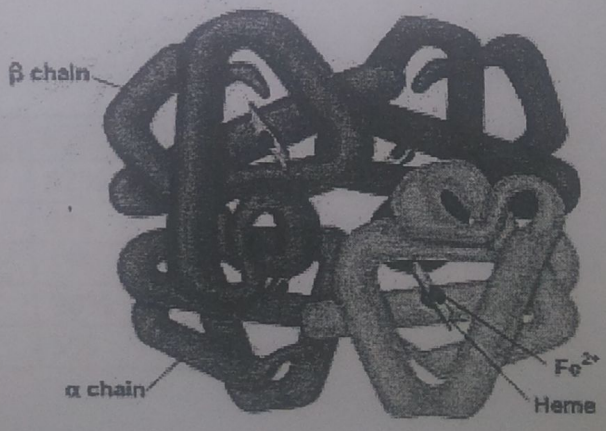
Breakdown of Hemoglubin produce:

1. from Globin part → amino acids used for energy or synthesis of new proteins
2. from Heme part → Iron, which stored as ferritin returned to bone marrow for synthesis of New Hb

→ Yellow pigment called Bilirubin and Green pigment Biliverdin which transported to liver to be excreted with bile to GIT

- Jaundice: any blockage of the excretory pathway will result in accumulation of billirubin in the blood, and the patient turns yellow .





II. White blood Cells (Leukocytes)

- only formed element that are complete , All have Nuclei and in general larger than RBCs

- There are **two types** of WBCs:

a. **Granulocytes** (polymorphonuclear) :
   i. Neutrophils
   ii. Eosinophils
   iii. Basophils

b. **Agranulocytes** (mononuclear)
   i. Lymphocytes (T-lymphocytes and B-lymphcytes)
   ii. Monocytes

White Blood Cells Number:

- **4000-10000** WBC/mm3, this number change in certain abnormal condition as in appendicitis → % of neutrophils increases
- Counting the % of different WBCs in a normal healthy person called **Differential Count.**

WBC	Normal Range	Percentage %
Neutrophils	3000 – 6000	62%
Eosinophils	150 – 300	2%
Basophils	0 – 100	1%
Lymphcytes	1500 – 3500	30%
Monocytes	300 - 600	5%

1. Netrophils
2. Eosinphils
3. Basophils

never Let monkey eat Banana

- **A decrease** in the number of WBCs called **Leukopenia**
- **An increase** in the number of WBCs called **Leukocytosis** (lymphocytosis , granulocytosis , neutrophilia)

Formation of white blood cells:

- **Granulocyte** (Neutrophils, Eosinophils, Basophils) and **Monocytes** are **phagocytic** cells and originate from **Red Bone Marrow** (Myeloid tissue -- myloblast).

- Most of **Lymphocytes** and originate from hematopoietic stem cells in **Lymphatic tissue** (lymphoblastic cell) such as lymph nods, tonsils, spleen and thymus and protect body through immune system.

  - Red bone marrow is Myeloid tissue, while Yellow marrow contains Fat and not active in blood production.

life span of WBC

- Granulocyte : in blood stay 4-8 hours , in Tissue 5 days (in serious infection survive for few hours only)
- monocyte : in blood for 10-20 hours , in tissue become macrophage and live for months
- Lymhpocyte : circulate btw blood and lymphatic tissue , survive for weeks and months .

Action of phagocytic cell

1. **Margination**
2. **Diapedesis**: WBC cross capillary wall . leakucyte slip out of capillaries through small pores between endothelial cell (all leukocyte can do)
   Margination : factors realeased from inflamed tissue , WBC stick to capillary wall , facilitate diapedesis in inflammation .
3. **ameboid motion**
4. **Chemotaxis**: chemical substances produced by leukocyte or tissue → attract WBC toward chemicals
   (bacterial or viral toxin , degenerative product of damaged tissue , complement complex , reaction product of p.clotting)

5. **Phagocytosis** : . ingestion of invading agent (Bacteria , virus , foreign body , d.tissue)
it can be selective , or by antibody (opsonization)

Mostly done By **neutriphills** , **Macrophages.**

Neutrophills : can ingest 3-20 bacteria , non-dividing , short live , dominant in Blood .

Macrophage : can ingest 100 bacteria , long lived , dominant in tissue (alveolar macrophage in lung , kupffer cell in liver , brain microglial cells) , More powerful phagocytic cell .

both contain proteolytic enzyme to digest foreign body , but microphages contain lipase that destroyed lipid (TB)

III. Platelets (Thrombocytes)

- 2 – 4 µm in diameter, irregular spindle or Oval shape
- No Nucleus with a life span of one week (short)
- Adults have average 250'000/ mm^3 (150'000 - 400'000 are normal values), newborn infants have less number of platelets
- No difference between males and females in number of plateletsto
- Produced from a mother stem cells called ***Megakarycytes*** in red bone marrow , production regulated by thrombopiotein
- Function in hemostasis and blood clotting
- 75% of platlet in the circulation , 25% in the spleen ??

Hemostasis

Stop bleeding and prevent loss of body fluid, rapid repair of any break in the vascular endothelium

Occurs in **4 steps**:

a. vascular spasm (vasoconstriction)

b. platelet aggregation : formation of temporary *platelet plug* form *sticky platelets*
c. clot formation : blood coagulation
d. clot Retraction

Platelet Aggregation

- platelet normally don't clot normal vessels.
- trauma cause damage to the endothelium → expose the sub endothelial collagen
- damaged endothelium release VWF (vonwillbrand factor) cause platelet adhesion to collagen
- platlet sticking cause platelet degranulation (realease ADP , Sertonin , Thrombaxone A2) stimulate more platlets to aggregate forming **platlet Plug**

Platlet Adhesion → Platelet Degranulation → platelet aggregation → platelet Plug

- Platelet Plug is Fragile , Easily disoged from the vessels wall .

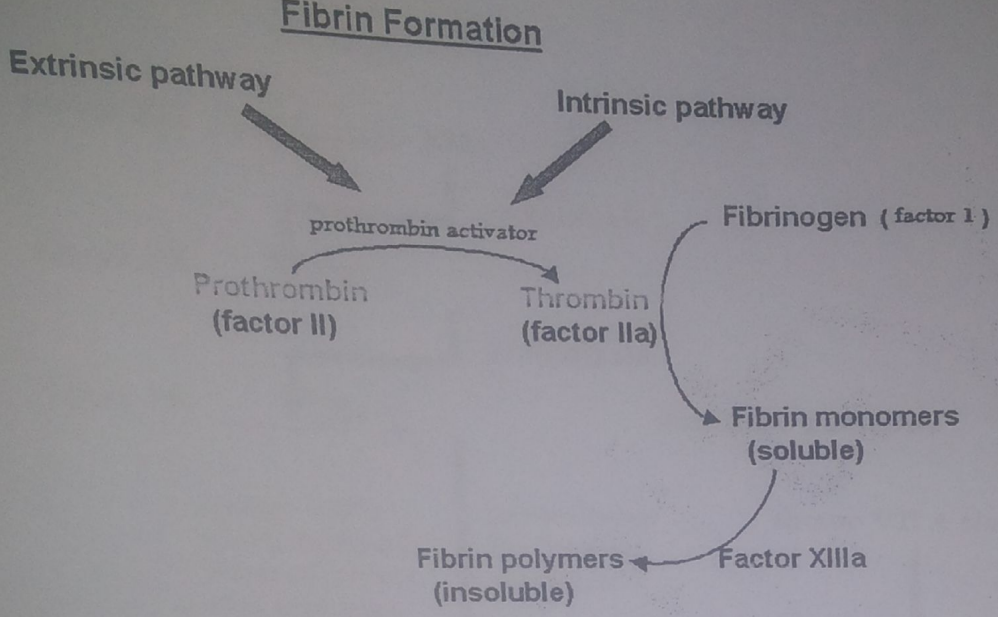
Blood Clotting

Formation a net of fibers that trap RBCs and platelets to seal injury and stop bleeding.

General Mechanisim of Blood Clotting → when vessels injured , activated substance called **Prothrombin Activator** → convert prothrombin to Thrombin → the thrombin convert Fibrinogen to fibrin fibers

exercise :-

Intrinsic & Tissue خارجي
في الدم



Prothrombin : called factor II , synthesized in the liver coninously , need vitamin K , MW = 68000

Fibrinogen : synthesized in the liver , fibrin form the Meshwork of the Clot , Strengthen by Factor XIII (Fibrin stabilizing factors)

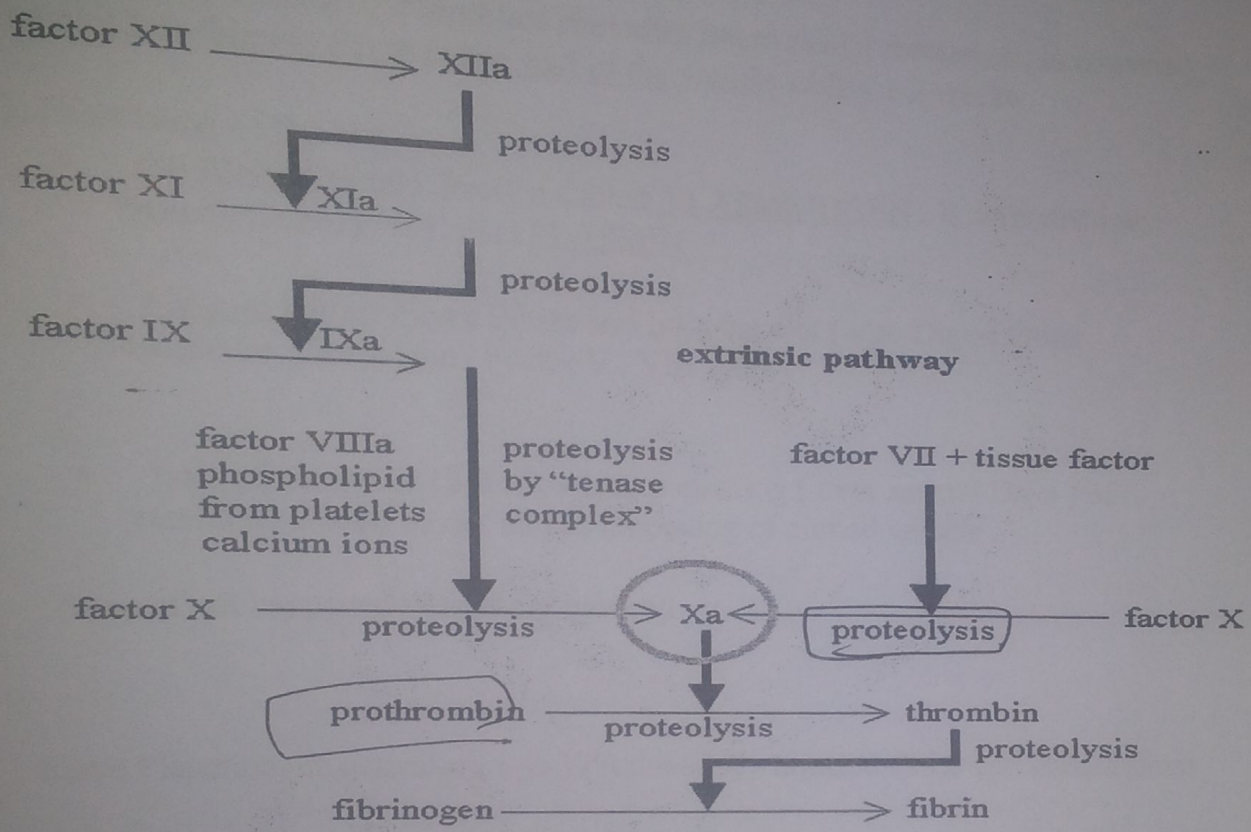
Question : what Is the prothrombin Activator ? Its factor Xa , with the help of factor Va , in the presence of Ca+2 and phospholipid

Question : How Prothrombin Activator Formed ?

1. Intrinsic Pathway : triggered when Blood exposed to rough surface (collagen) , Slow need 1-6 minutes
2. Extrinsic Pathway : Triggered by Tissue factor (phospholipid from damaged tissue , tissue damage , fast start in 15 Second.

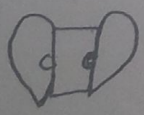
Both Pathways End in Formation of **Prothrombin Activator .**

Heparin



Clot Retraction

- it is Platelet Induced process , Occure within 30-60 minutes , it is Stabilzes the clot Further.
- the platelet entrapped in the clot contract , pull the Surrounding Fibrin Strands , sequeezing liquids → compact the Clot , draw the edge of the vessels together .

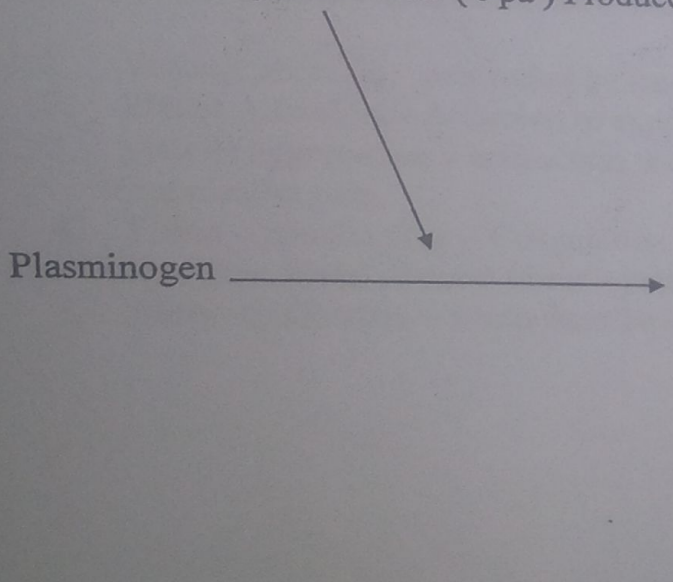


Fate of Blood Clot

1.invasion of the clot by Fibroblast start after hours of clot formation , in convert the clot into fibrous tissue in the wall of the vessels within 1-2 weeks .

2. Dissolving of the clot :
   - the Blood Contain Protien Called PLASMINOGEN , If avtivated into Proteolytic enzyme Called PLASMIN
   - Plasmin Digest Fibrin Fibers and lysis the clot (also Digest Other coagulant , fibrinogen , Factor V , VIII , XII)
   - lysis of the Blood Clot allows slow clearing (over several Days) of externous clotted blood allows reopening of clotted vessels .
   - if not happened vessels get blocked

tissue Plasminogen activator (t-pa) Produced by injuried tissue and endothelium



This is the Basis of Using t-Pa \ or streptokinase for treating clot In Miocardial Infarction.

IMPORTANT notes In Blood Clotting :

1. All factors or Procoagulant present in bood In **INACTIVE** form .
2. INJURY to tissue , blood vessels wall , cells , Platlets , is essential for initiation of blood clotting
3. Ca+2 is required for all steps of intrinsic and extrinsic pathway except For converting Factor XII → XIIa
4. clotting promotes mor clot formation (Positive feedback)
5. most Of the clotting Factor produced in the Liver (Except Factor VIII (8) , And VWF)
6. formation of clotting factor X , IX , VII , II ,and anticoagulant (Protien C , Protien S) , are Vitamin K dependent .

Summary Of sequence of Events after Vessels Injury

1. Vasoconstriction – controlled by smooth muscle , enhance by chemicals .
2. Platlet Adhesion - Adhesion to exposed subendothelial collagen
3. platelet aggregation – interaction and adhesion of platelet on to another to form platelet plug
4. Fibrin – platelet plug – Coagulation factor interact on the platelet surface to produce fibrin , formin fibrin – patelet plug
5. fibrin stabilization – fibrin must be stabilized by factor XIII