كلية الطب البشري
Faculty of Medicine

Hematopoietic System-2024

Physiology Lectures (L1-L6)

Presented by:

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Professor of Medical Physiology

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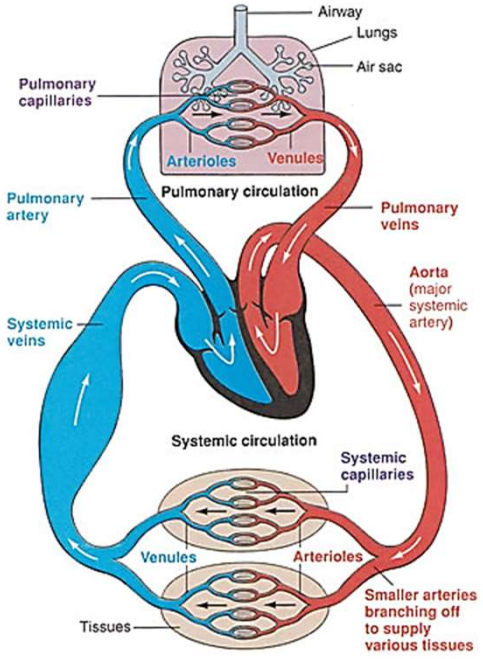

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Functions of blood

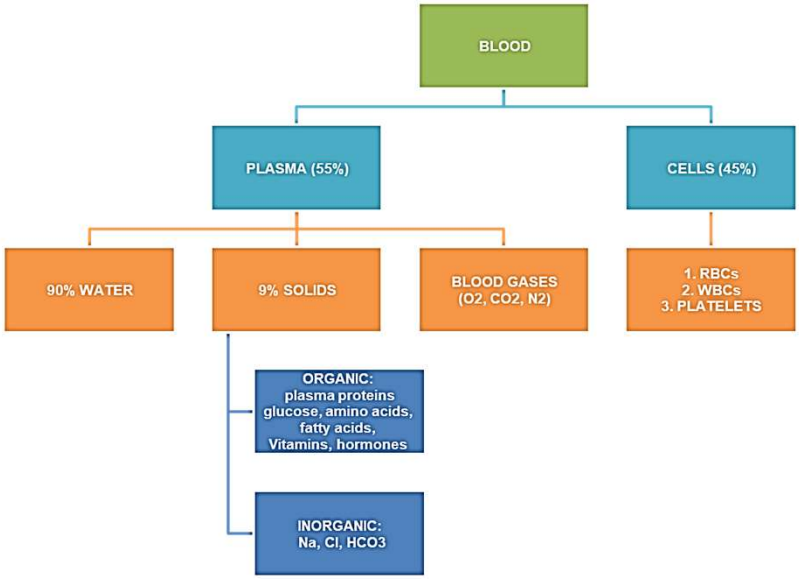
1 – Transport.

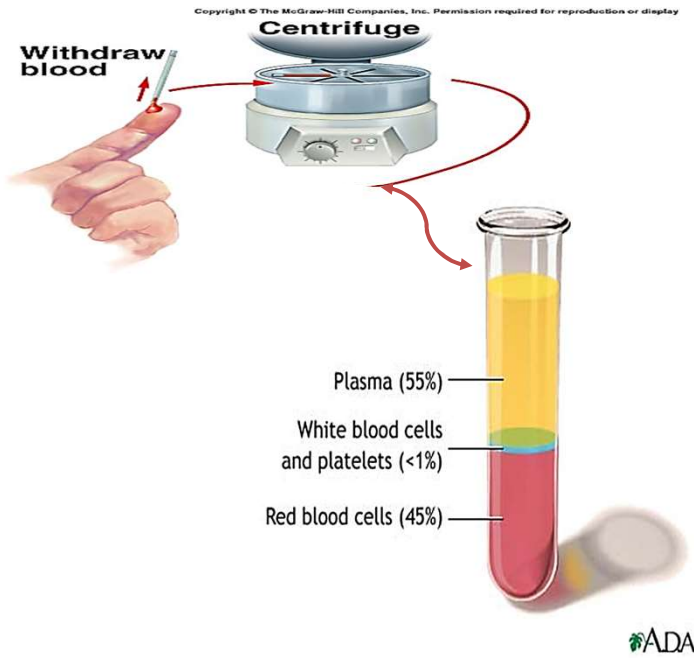
2 – Immune Function

3 – Haemostasis [Stoppage of bleeding]

4 – Homeostasis [Keeping body environment constant].

COMPOSITION OF BLOOD





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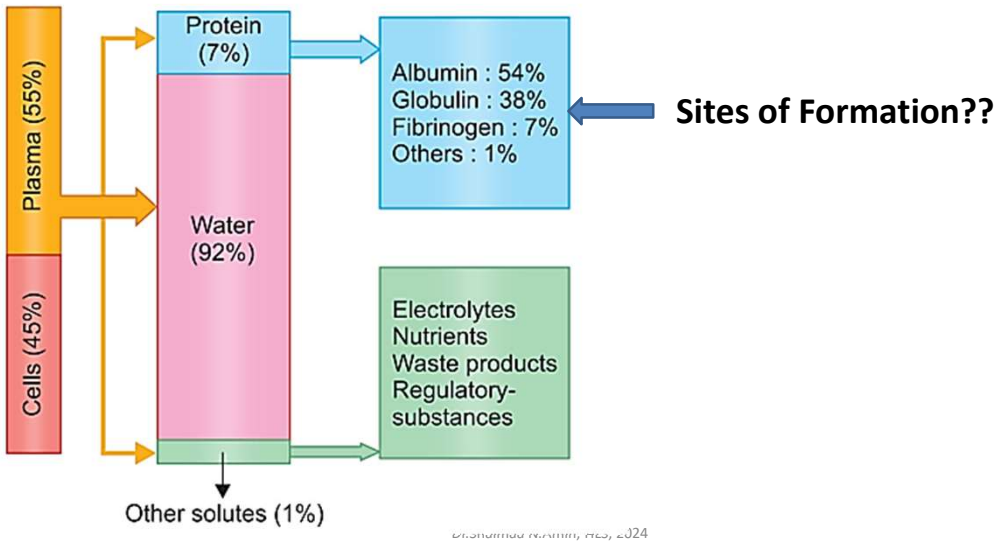
Composition of Plasma



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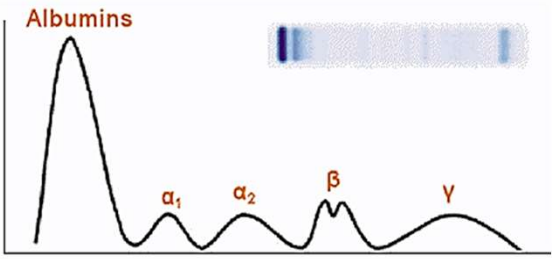
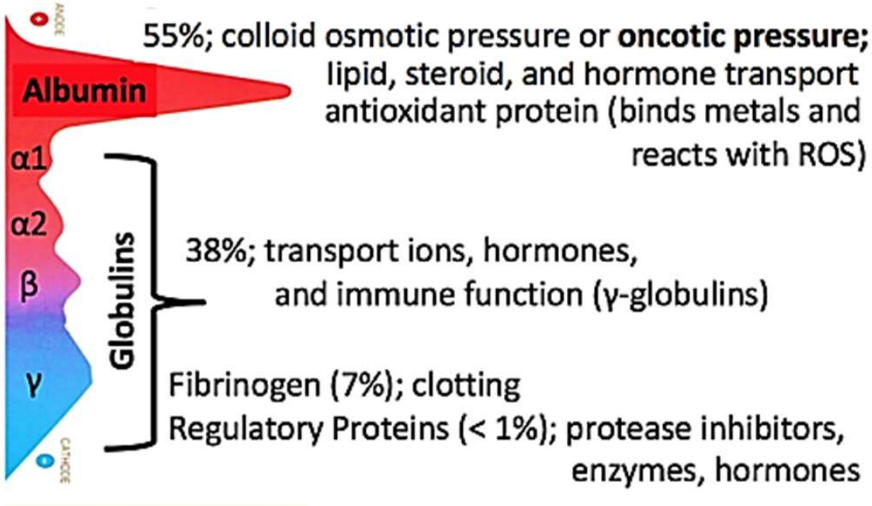
A/G Ratio

- 1.5 to 2.5:1
- Decrease in:
- Liver disease
- Renal disease
- Infections
- Inflammations



Functions of plasma proteins



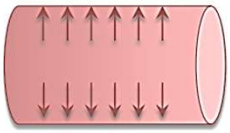
Factors controlling fluid filtration across capillary walls

Movement of fluids across capillary walls depends on the balance of starling forces acting across the capillary walls.

Starling forces
Forces that control the movement of fluid in/out of the capillary

Hydrostatic pressure P

The pressure exerted by blood (water) on the walls of the blood vessel.

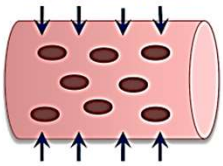


Pushes fluid OUTSIDE

Colloid osmotic(oncotic) pressureπ

(especially albumin)

The osmotic pressure created by the non-diffusible plasma proteins inside the blood vessel.

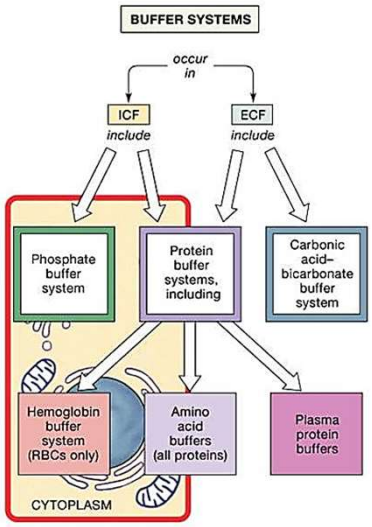


Pulls fluid INSIDE

Edema

Functions of plasma proteins

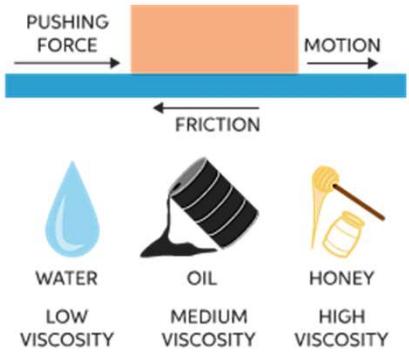
Buffer function



Functions of plasma proteins

Blood viscosity

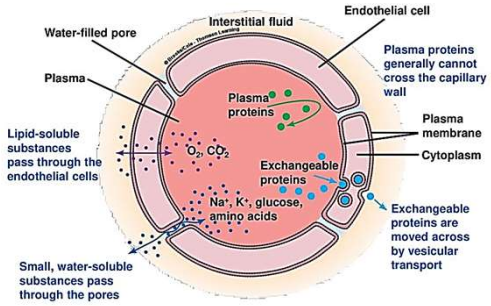
Viscosity is a fluid's resistance to flow or deformation.

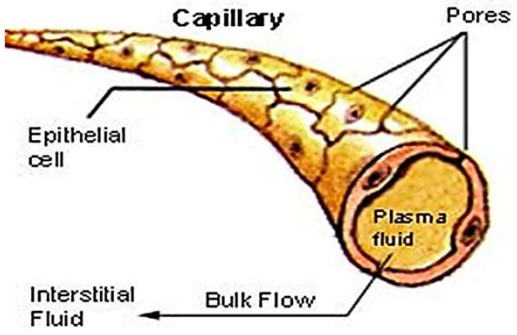


Functions of plasma proteins

Capillary functions

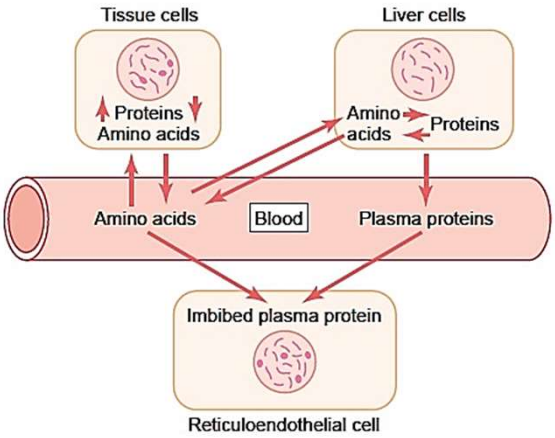
- Plasma proteins ⟶ closes capillary pores ⟶ maintains capillary permeability.





Functions of plasma proteins

Source of amino acids

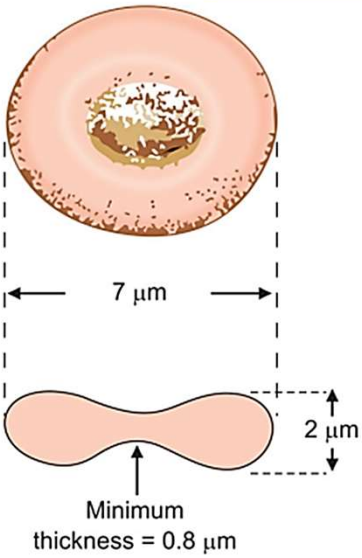


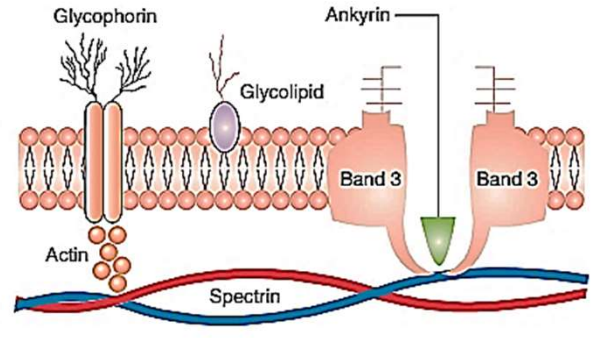
RED BLOOD CORPUSCLES
RBCS
"ERYTHROCYTES"

Erythrocytes (RBCs) count

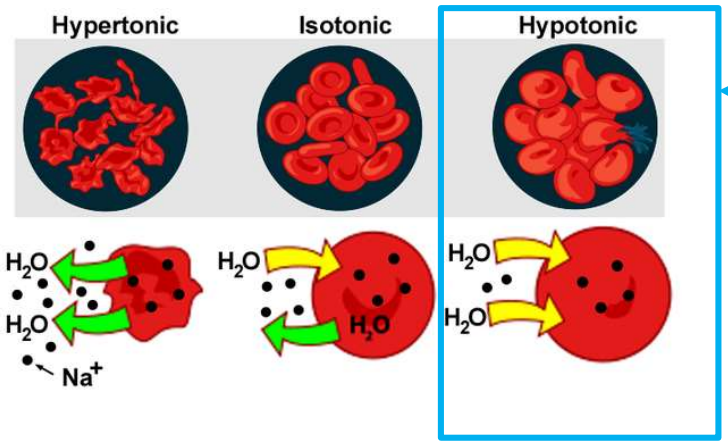
Adult males: 4.5–6 million/mm^3.
Adult females: 4–5.5 millions/mm^3.
Infants: higher RBCs count than adults.
Children: lower RBCs count than adults.
In old age: RBCs count decreases.

RBCS HAVE A BICONCAVE SHAPE

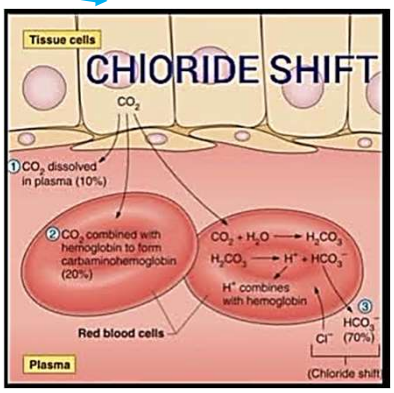


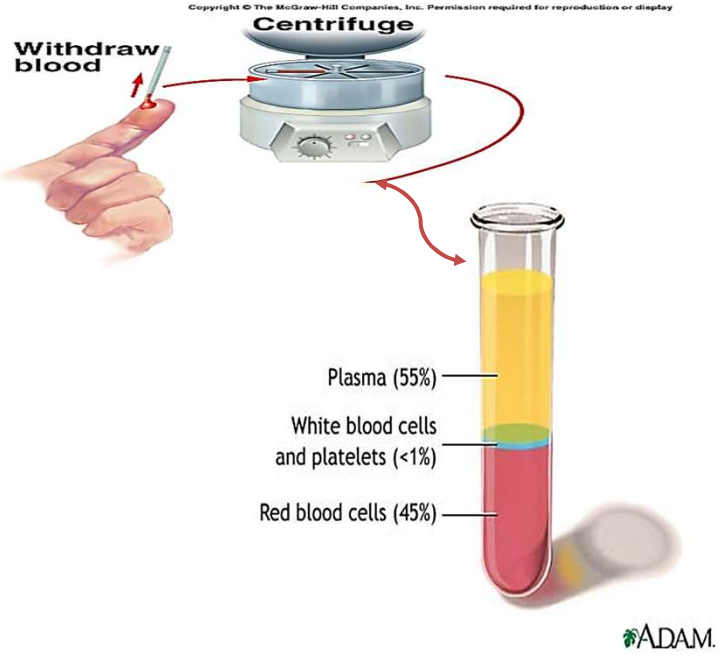


Schematic diagram showing ultra structure of red cell membrane.



Venous Blood





Characteristics of human red cells.

		Male	Female
Hematocrit (Hct) (%)		47	42
Red blood cells (RBC) ($10^6/\mu L$)		5.4	4.8
Hemoglobin (Hb) (g/dL)		16	14
Mean corpuscular volume (MCV) (fL)	$= \frac{Hct \times 10}{RBC\ (10^6/\mu L)}$	87	87
Mean corpuscular hemoglobin (MCH) (pg)	$= \frac{Hb \times 10}{RBC\ (10^6/\mu L)}$	29	29
Mean corpuscular hemoglobin concentration (MCHC) (g/dL)	$= \frac{Hb \times 100}{Hct}$	34	34

RBCs Indices (reflect the functional characteristics of RBCs)

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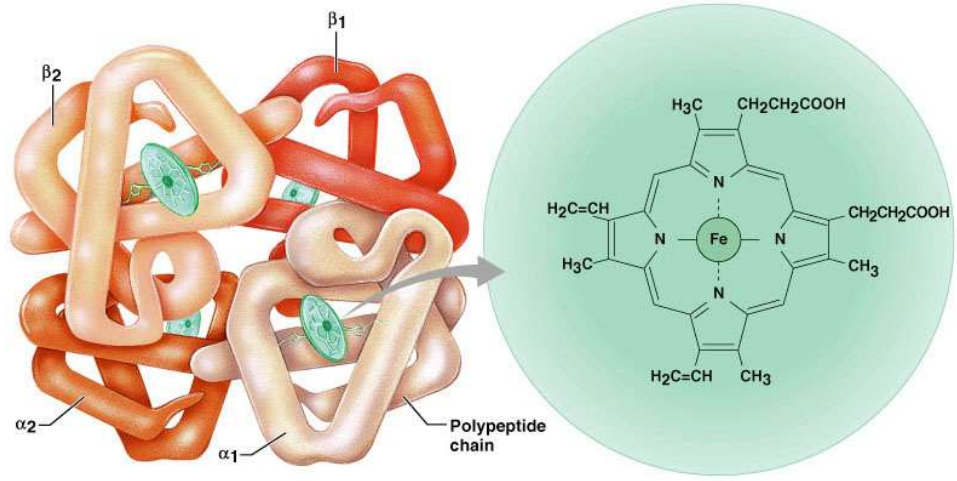
Hemoglobin (Hb)

Structure of Hemoglobin



(a) Hemoglobin (b) Iron-containing heme group

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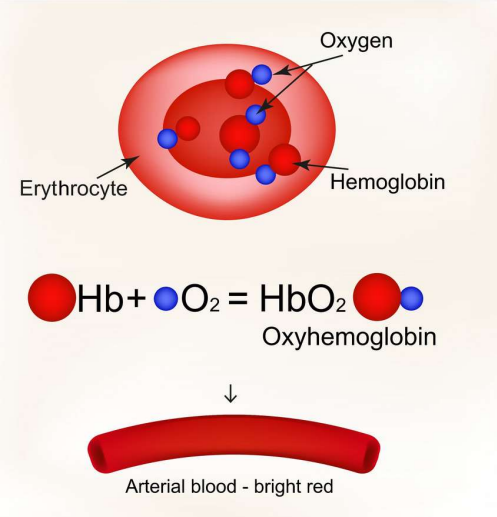
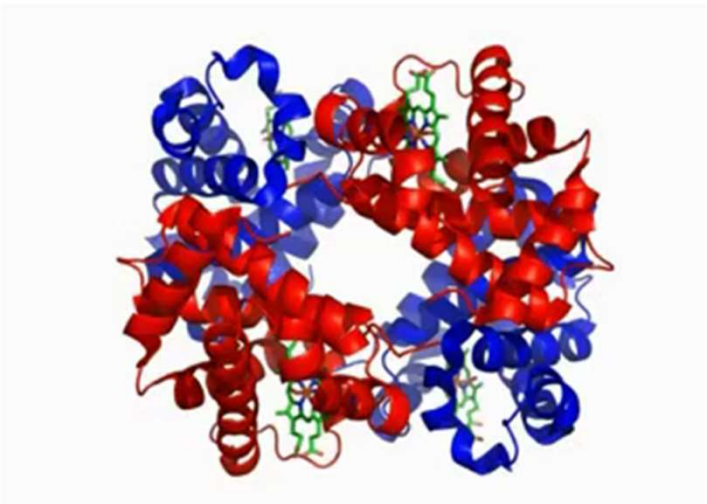
Reactions of Hemoglobin

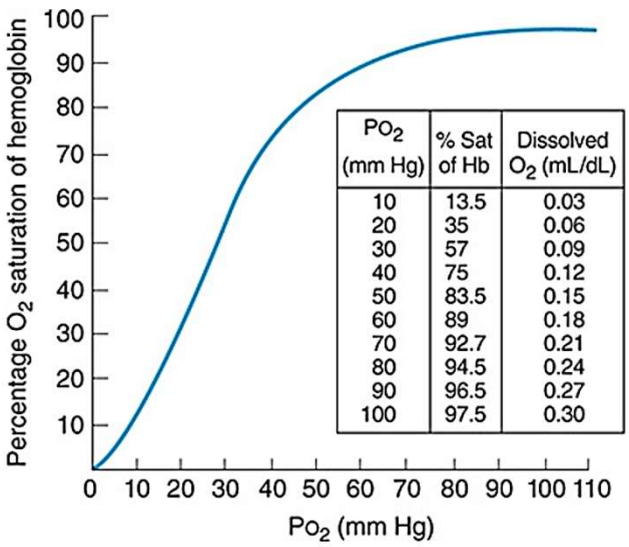
1 - Oxygenation



$$Hb_4 + O_2 \rightleftarrows Hb_4O_2$$
$$Hb_4O_2 + O_2 \rightleftarrows Hb_4O_4$$
$$Hb_4O_4 + O_2 \rightleftarrows Hb_4O_6$$
$$Hb_4O_6 + O_2 \rightleftarrows Hb_4O_8$$



https://www.youtube.com/watch?v=XxElVpgNUF0



PO_2 (mm Hg)	% Sat of Hb	Dissolved O_2 (mL/dL)
10	13.5	0.03
20	35	0.06
30	57	0.09
40	75	0.12
50	83.5	0.15
60	89	0.18
70	92.7	0.21
80	94.5	0.24
90	96.5	0.27
100	97.5	0.30

-**1 Oxygen–hemoglobin dissociation curve.** pH 7.40, temperature

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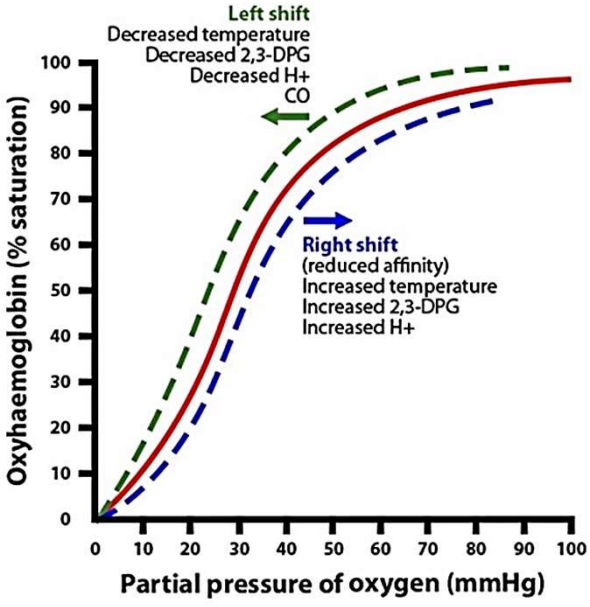

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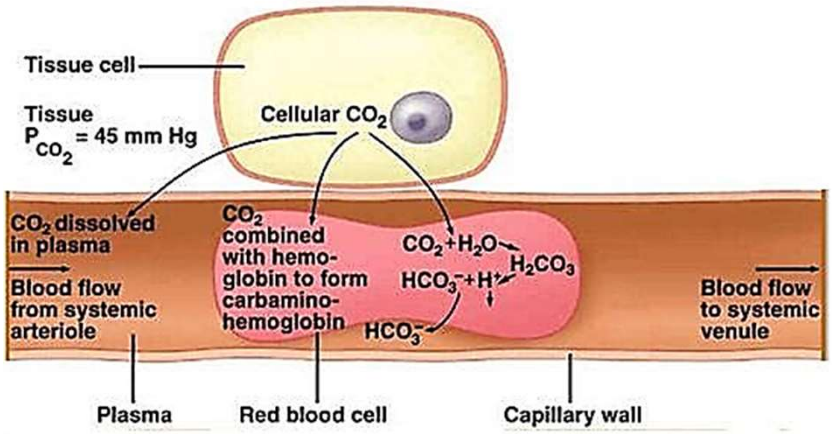
Reactions of Hemoglobin

2 – With CO_2



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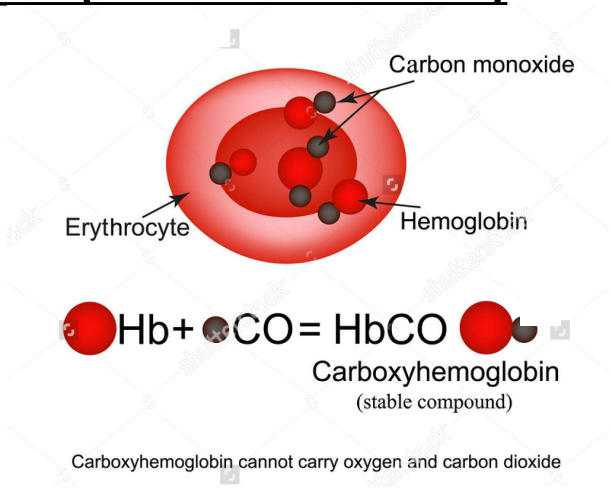
Reactions of Hemoglobin

3 – With CO (Carbon Monoxide)



Carboxyhemoglobin cannot carry oxygen and carbon dioxide

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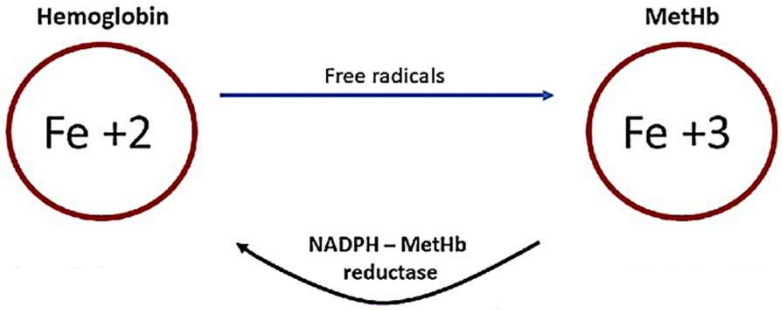
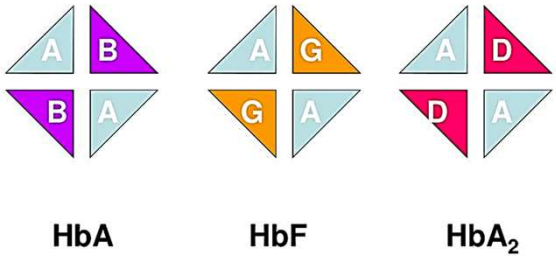
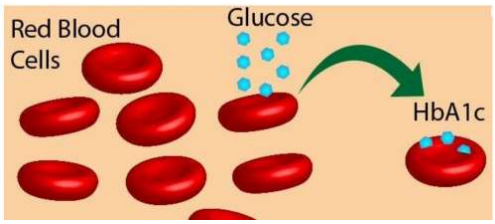
Reactions of Hemoglobin

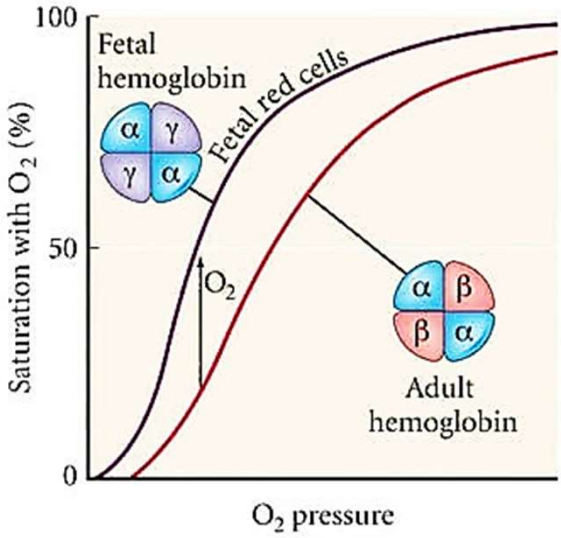
2 – With strong oxidizing agents



Types of Hemoglobin:







Functions of RBCs

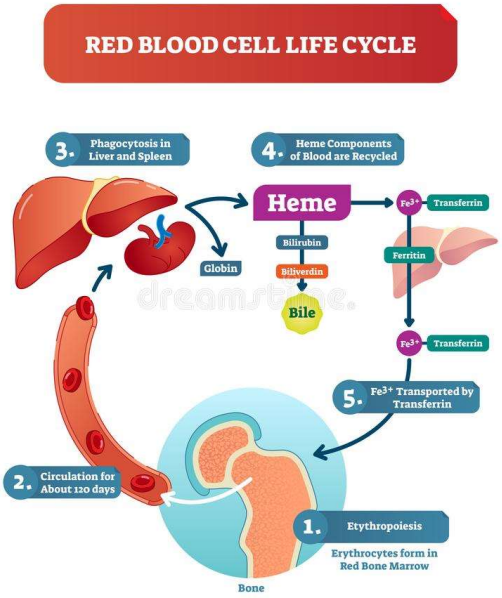
1 – Functions of Hb

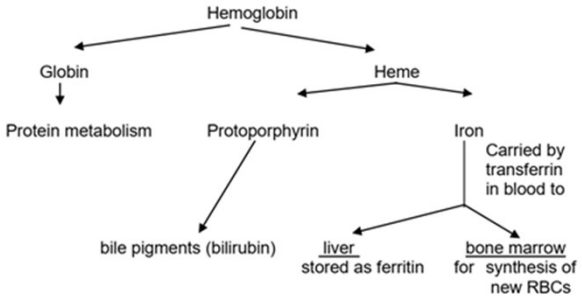
- **O2 transport** from the lungs to tissues.
- **Co2 transport** from the tissues to the lungs.
- **Buffer function**

2 - Functions of RBCs membrane

Keeps Hb inside RBCs.

Hazards of free Hb???

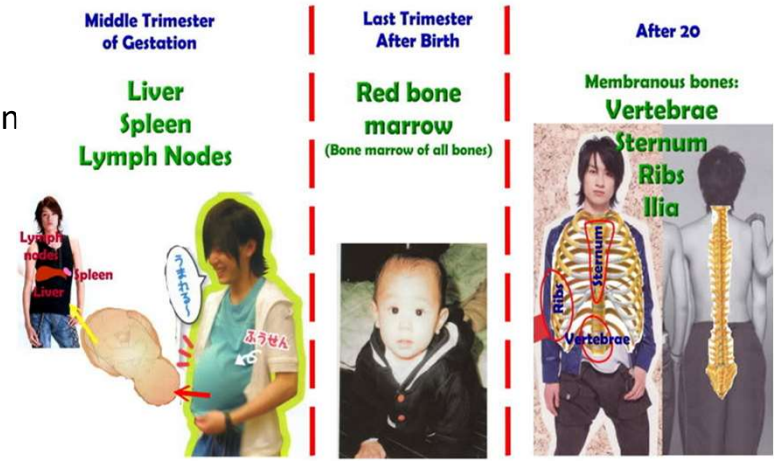




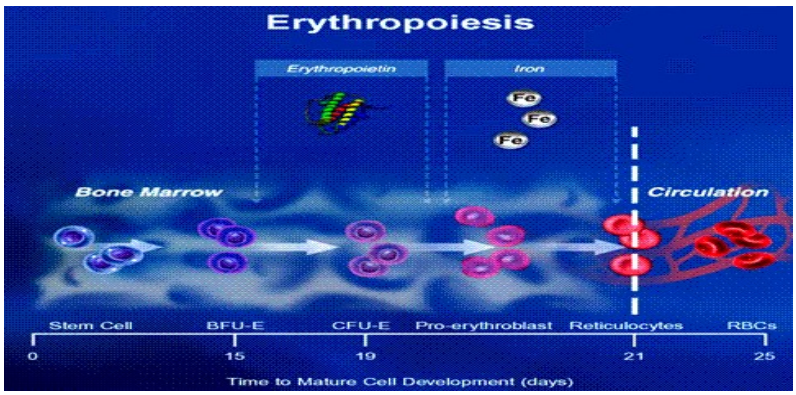
Erythropoiesis

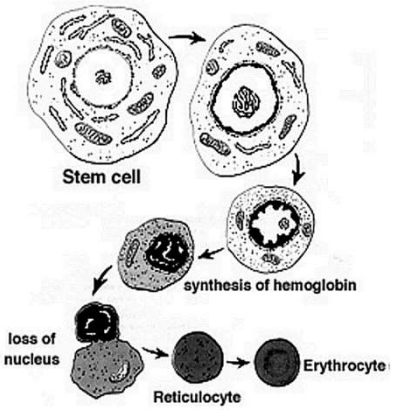
Definition:

It is the process of formation of new erythrocytes.



In adult males	:	4.5–6 (average 5.2) millions per cu mm of blood
In adult females	:	4–5.5 (average 4.7) millions per cu mm of blood
In newborns	:	6–8 millions per cu mm of blood
In children	:	3–5 millions per cu mm of blood


Erythropoiesis
Erythropoietin
Iron
Fe
Fe
Fe
Bone Marrow
Circulation
Stem Cell
BFU-E
CFU-E
Pro-erythroblast
Reticulocytes
RBCs
0
15
19
21
25
Time to Mature Cell Development (days)


Stem cell
synthesis of hemoglobin
loss of nucleus
Reticulocyte
Erythrocyte

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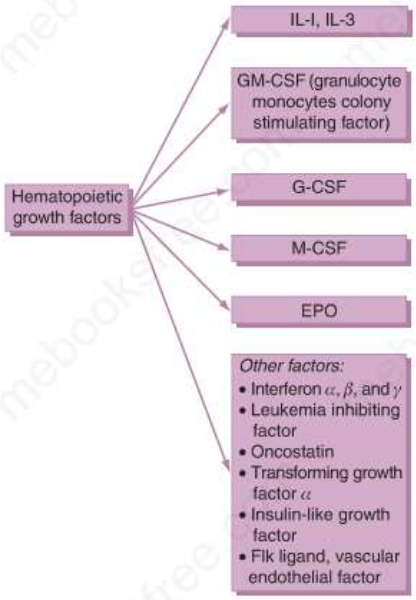
Hematopoietic growth factors
IL-I, IL-3
GM-CSF (granulocyte monocytes colony stimulating factor)
G-CSF
M-CSF
EPO
Other factors:
• Interferon α, β, and γ
• Leukemia inhibiting factor
• Oncostatin
• Transforming growth factor α
• Insulin-like growth factor
• Flk ligand, vascular endothelial factor

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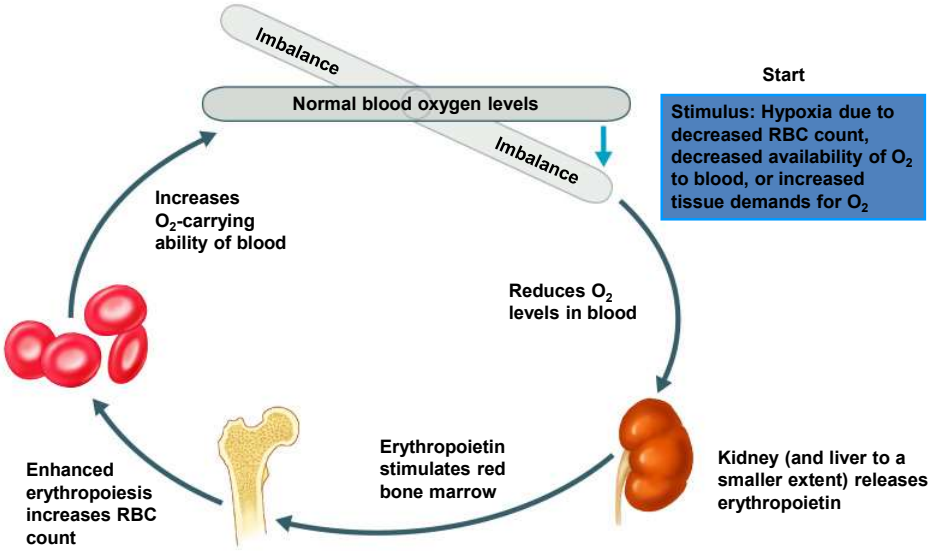
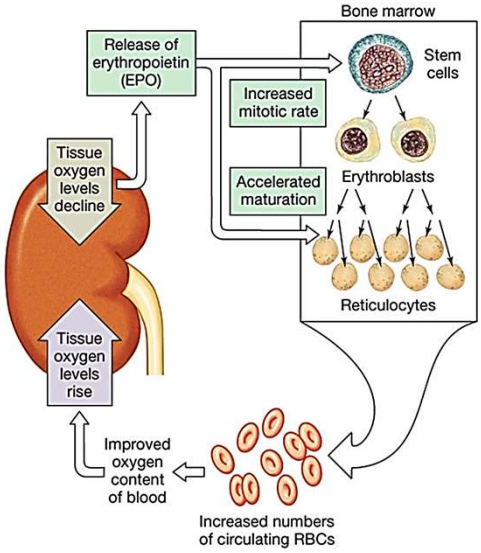
Erythropoietin Mechanism



Factors Affecting Erythropoiesis:

1-Oxygen Supply to the Tissues:



Factors Affecting Erythropoiesis:

(2)Diet:

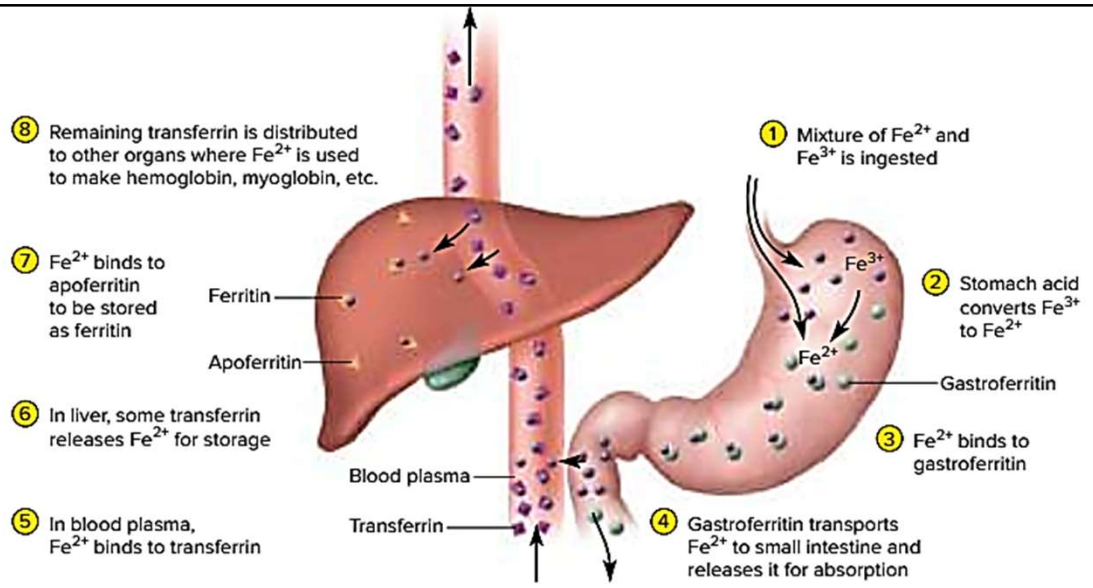
A) Iron

B) Vitamin B 12

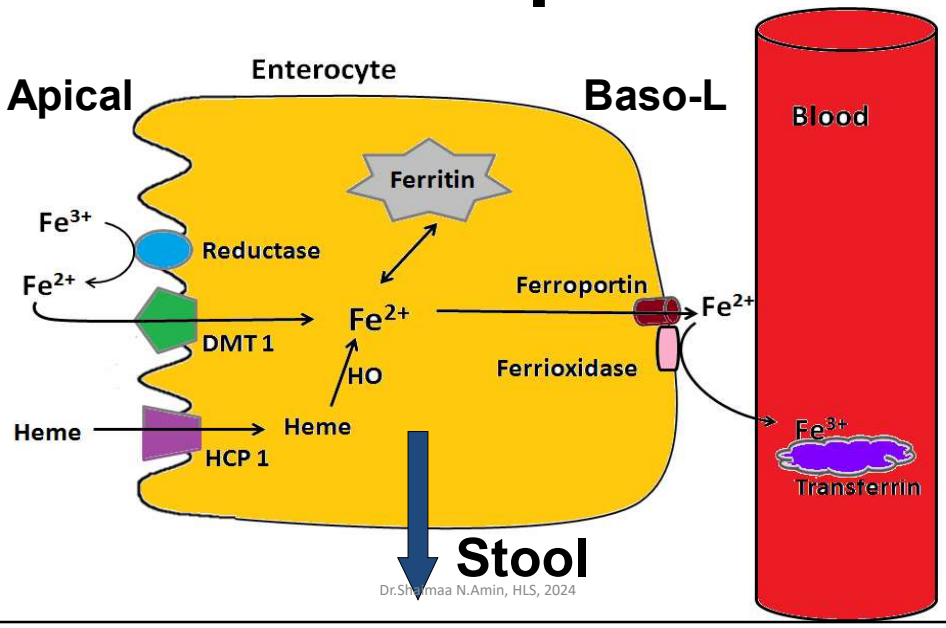
C) Folic acid

D) Vitamin C

E) Copper and Cobalt



Iron absorption



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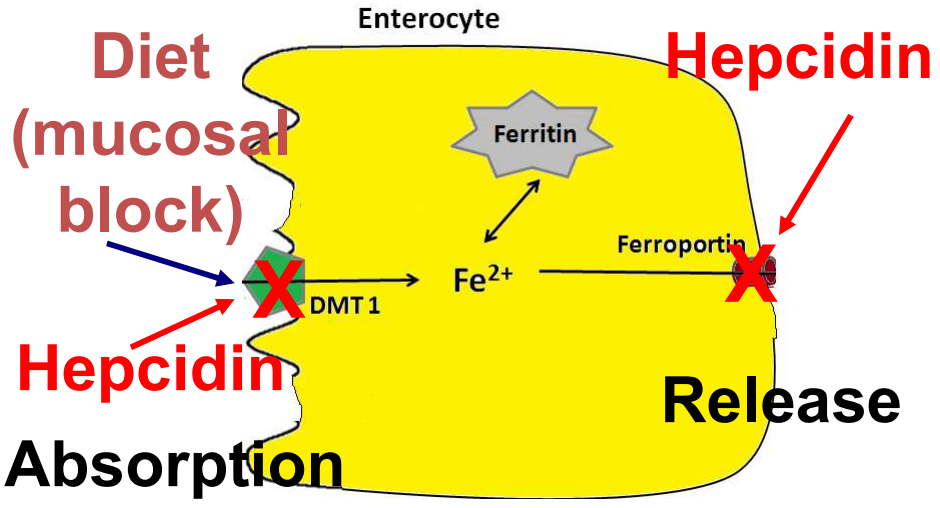
Regulation of iron absorption



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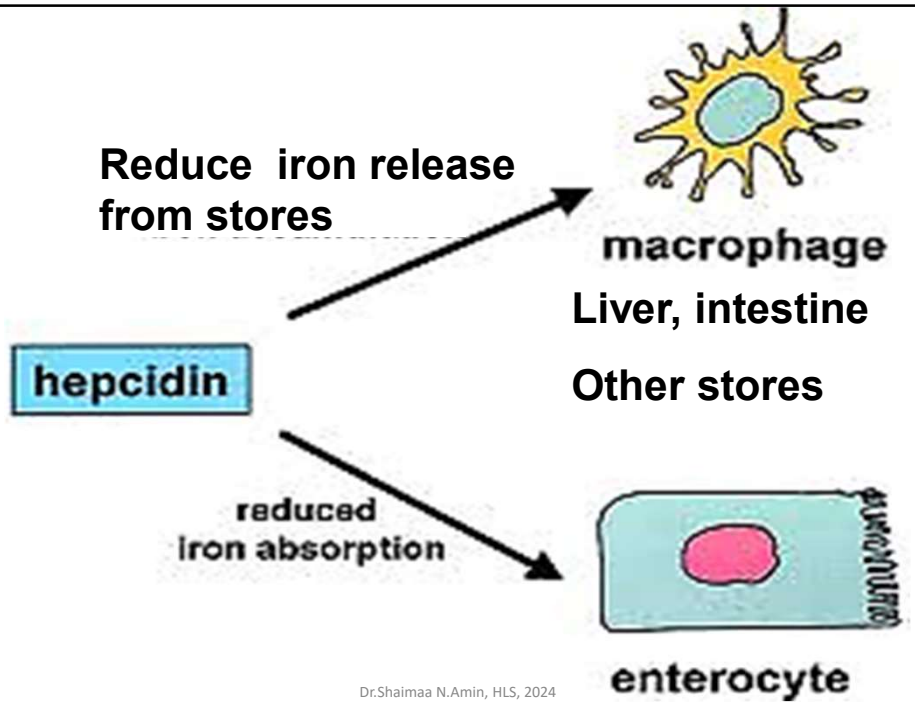
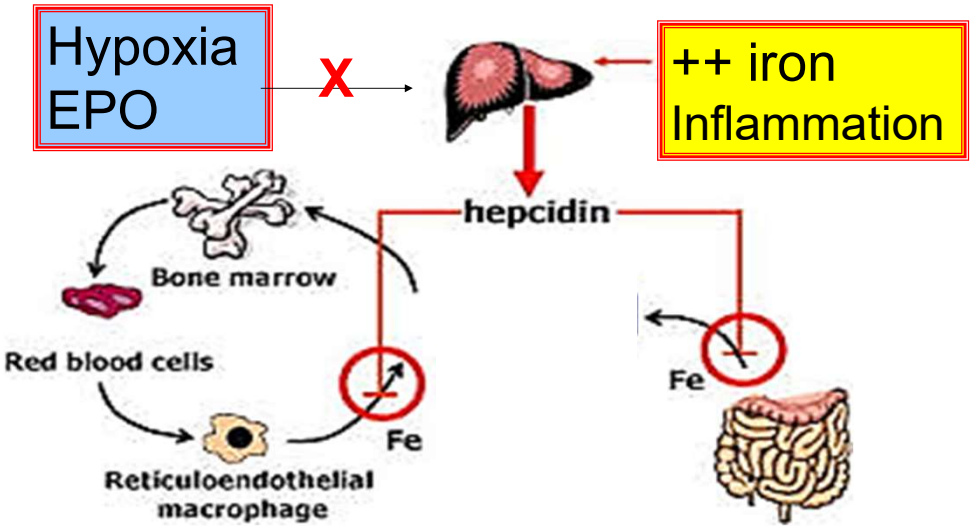
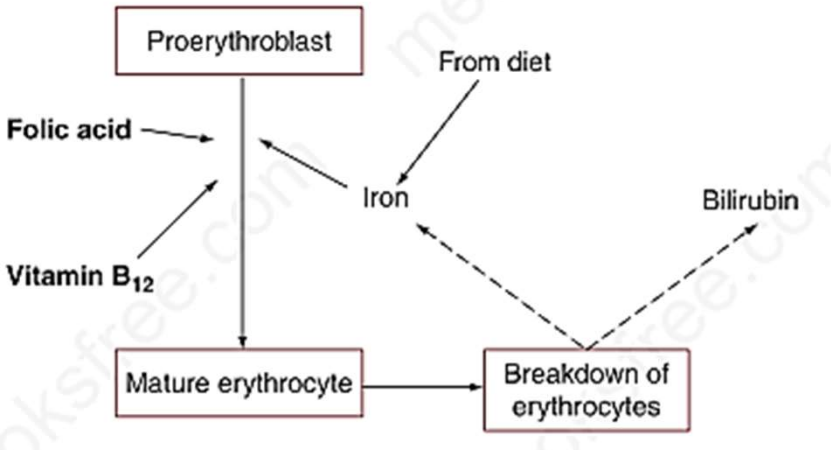


Factors affecting hepcidin secretion



CAUSES OF IRON DEFICIENCY

Cause	Disease or Condition
Increased demand	Infancy and childhood Pregnancy
Inadequate intake	Dietary deficiency
Impaired absorption	Sprue Diarrhea Gastrectomy
Increased loss	Gastrointestinal bleeding Heavy menstrual bleeding Aspirin intake



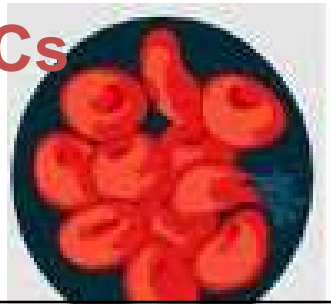
Vitamin B12 & folic acid

- **Synthesis of DNA** (thymidine P3)
- **Deficiency:**

-- RBCs division & maturation

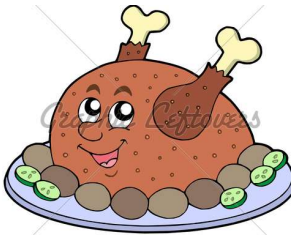
→ large fragile RBCs

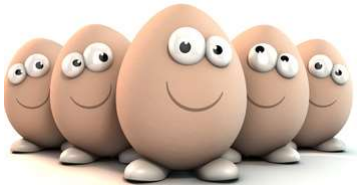
→ anemia



Vit. B12 (Cyanocobalamine, Maturation F, Extrinsic F)

- *Sources?*
- *Daily requirements*?
- Storage?
- Deficiency?

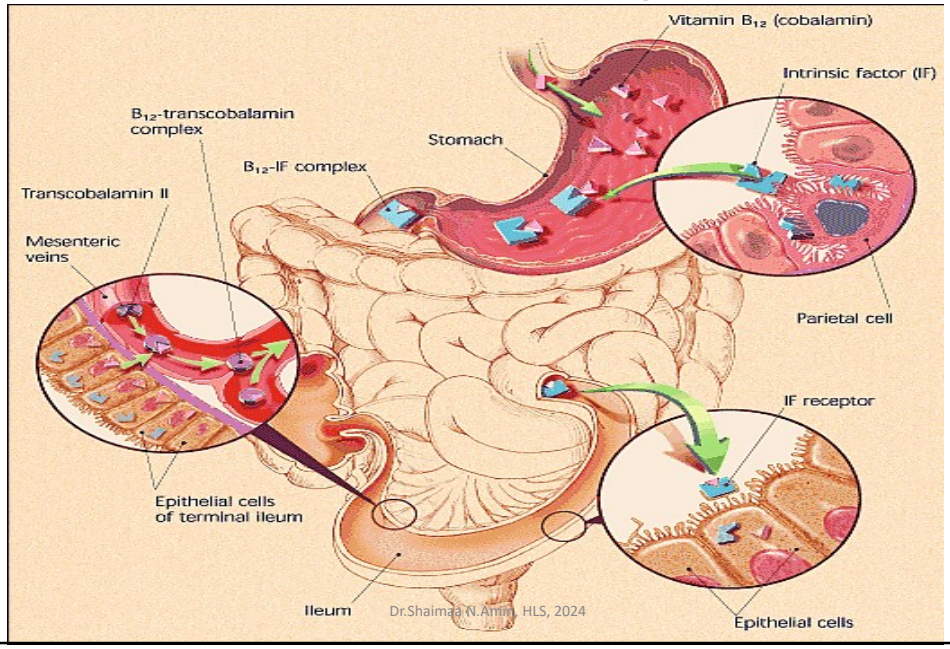




Failure of absorption

(not diet) except in vegetarians.

Vit.B12 Absorption



- ***Sources?***
- ***Deficiency?***
  - -- Diet
  - -- Absorption
  - Drugs

Folic acid

Factors Affecting Erythropoiesis:

(3) Hormones

(4) Healthy Liver and Bone Marrow:

-

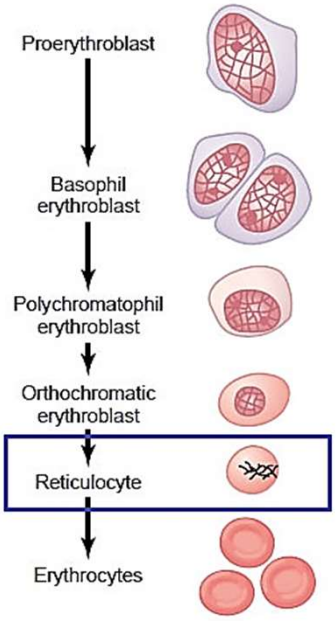
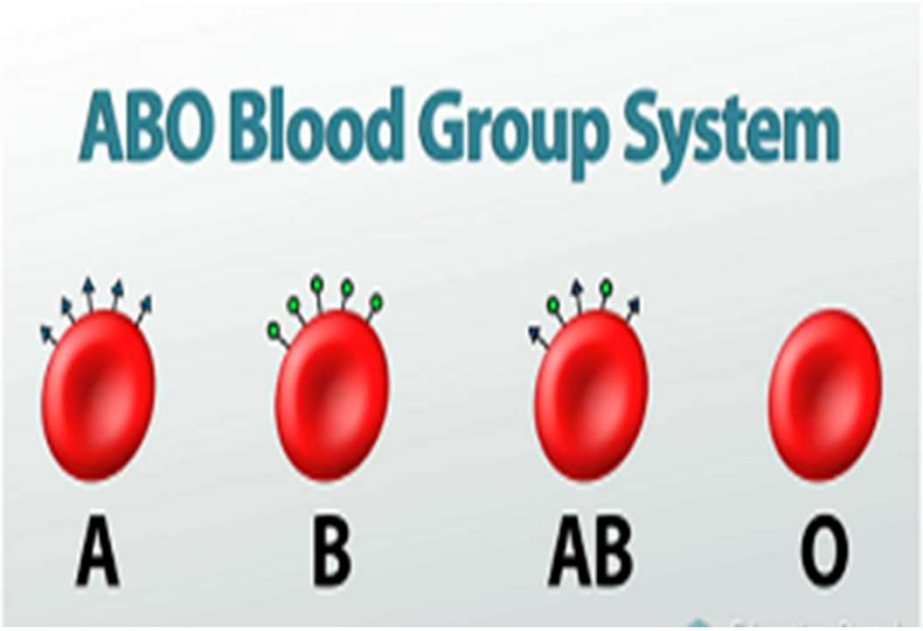


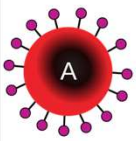
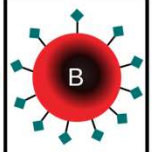
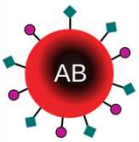
Table 1 Age-specific blood cell indexes

Age	Hemoglobin g/dL (g/L)	Hematocrit (%)	MCV, μm³ (fL)	MCHC, g/dL (g/L)	Reticulocytes
• 26–30 weeks' gestation*	13.4 (134)	41.5 (0.42)	118.2 (118.2)	37.9 (379)	–
• 28 weeks' gestation	14.5 (145)	45 (0.45)	120 (120)	31.0 (310)	(5 to 10)
• 32 weeks' gestation	15.0 (150)	47 (0.47)	118 (118)	32.0 (320)	(3 to 10)
• Term† (cord)	16.5 (165)	51 (0.51)	108 (108)	33.0 (330)	(3 to 7)
• 1–3 days	18.5 (185)	56 (0.56)	108 (108)	33.0 (330)	(1.8–4.6)
• 2 weeks	16.6 (166)	53 (0.53)	105 (105)	31.4 (314)	
• 1 month	13.9 (139)	44 (0.44)	101 (101)	31.8 (318)	(0.1–1.7)
• 2 months	11.2 (112)	35 (0.35)	95 (95)	31.8 (318)	
• 6 months	12.6 (126)	36 (0.36)	76 (76)	35.0 (350)	(0.7–2.3)
• 6 months–2 years	12.0 (120)	36 (0.36)	78 (78)	33.0 (330)	
• 2–6 years	12.5 (125)	37 (0.37)	81 (81)	34.0 (340)	(0.5–1.0)
• 6–12 years	13.5 (135)	40 (0.40)	86 (86)	34.0 (340)	(0.5–1.0)
• 12–18 years					
– Male	14.5 (145)	43 (0.43)	88 (88)	34.0 (340)	(0.5–1.0)
– Female	14.0 (140)	41 (0.41)	90 (90)	34.0 (340)	(0.5–1.0)
• Adult					
– Male	15.5 (155)	47 (0.47)	90 (90)	34.0 (340)	(0.8–2.5)
– Female	14.0 (140)	41 (0.41)	90 (90)	34.0 (340)	(0.8–4.1)

Abbreviations:
MCV: Mean corpuscular volume; MCHC: Mean corpuscular hemoglobin concentration.
* Values are from fetal samplings.
† Less than one month, capillary hemoglobin exceeds venous: 1 hour—3.6 gm difference; 5 days—2.2 gm difference; 3 weeks—1.1 gm difference. Adapted with permission from Siberry GK, Lannone R, Eds. The Harriet Lane handbook: a manual for pediatric house officers, 15th edn. St Louis: Mosby, 2000.

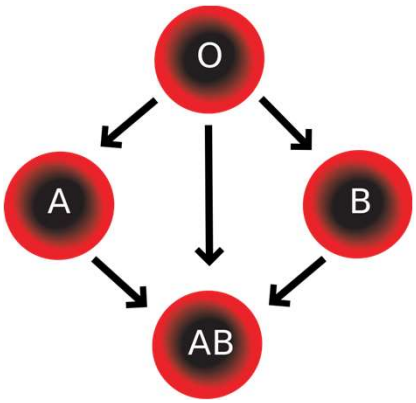


Blood Typing

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in plasma	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens in red blood cell	 A antigen	 B antigen	 A and B antigens	None

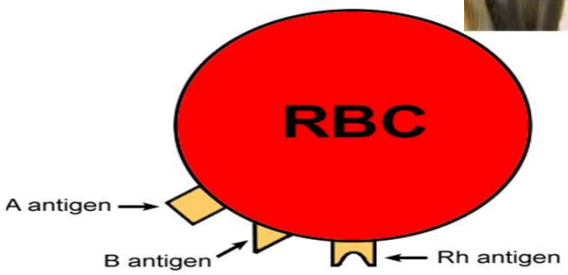
Blood Transfusion

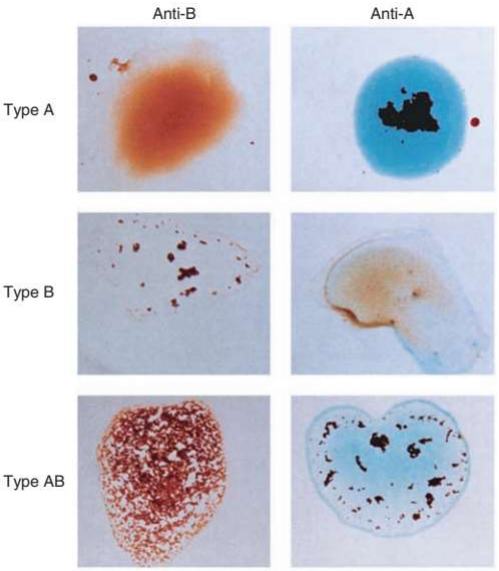
- O: universal donor
- AB: universal recipient



Rh Factor

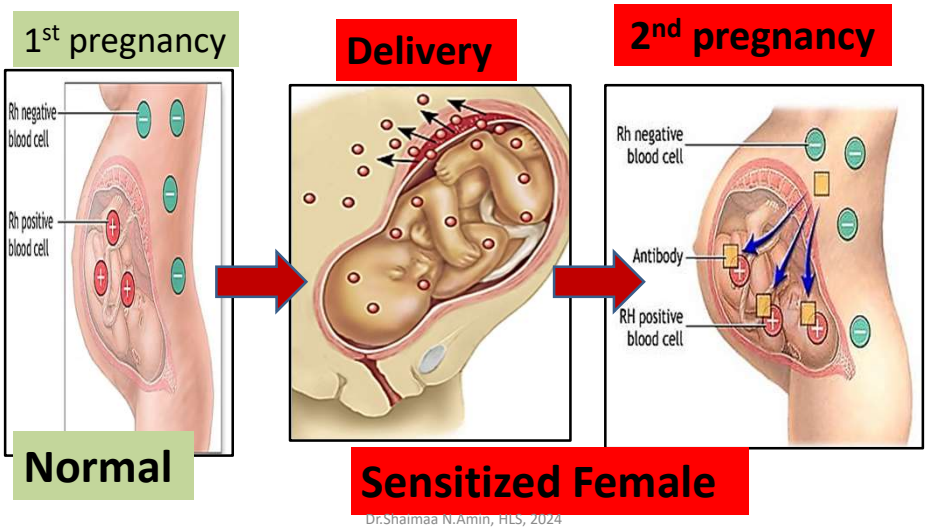
- A third antigen determines the Rh factor
  - It is called D
- A person with the D antigen is "positive"
- A person without the D antigen is "negative"





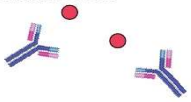
Red cell agglutination in incompatible plasma.

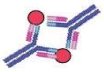
Erythroblastosis Fetalis



Treatment

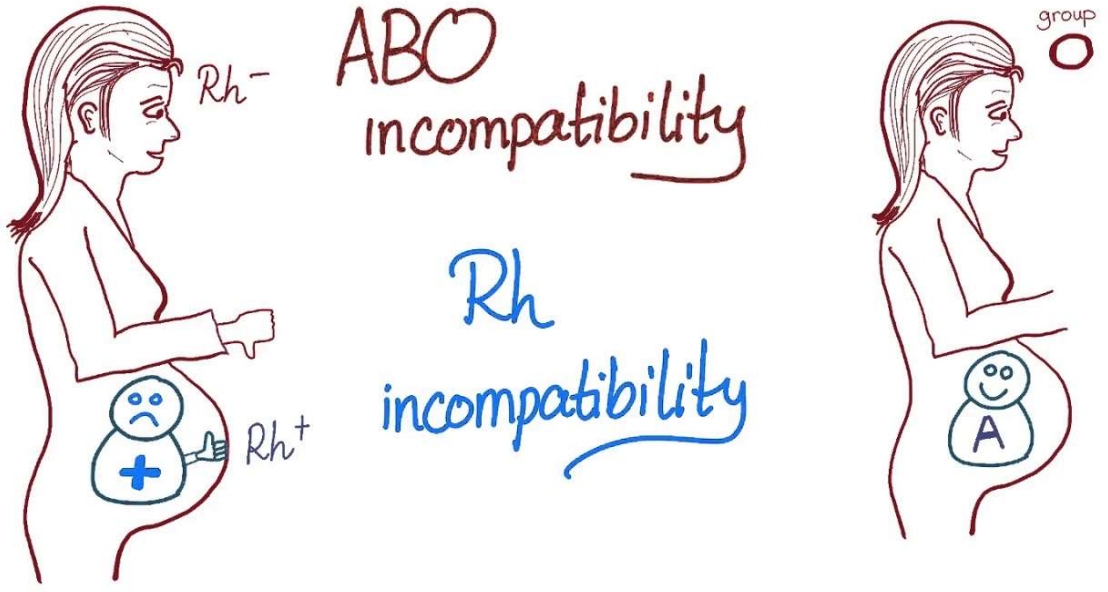
Administration of Rhogam (antibodies to Rh + cells) to mother just after delivery of the first child





Rhogam neutralises Rh+ cells thus preventing the production of anti-RH+ antibodies

Can 1st baby get erythroblastosis fetalis



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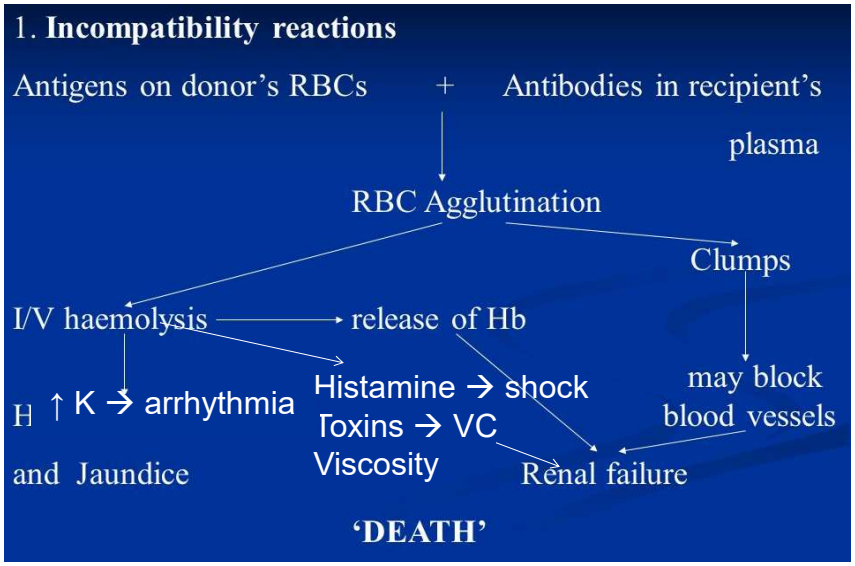
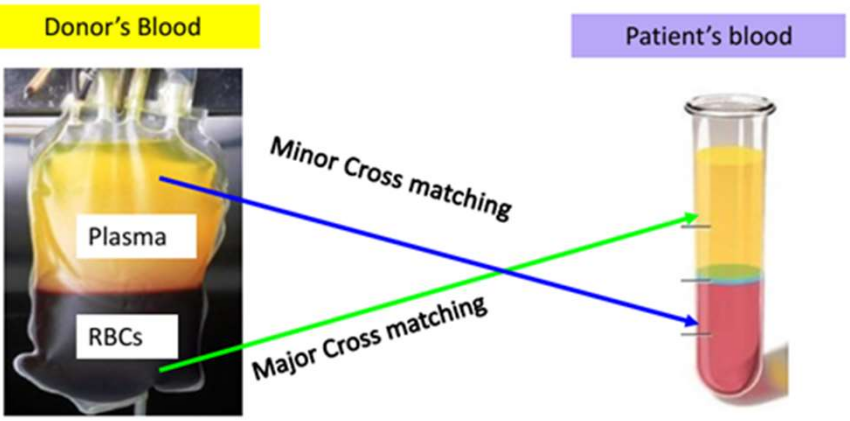
Importance of blood group determination



60

Importance of blood group determination



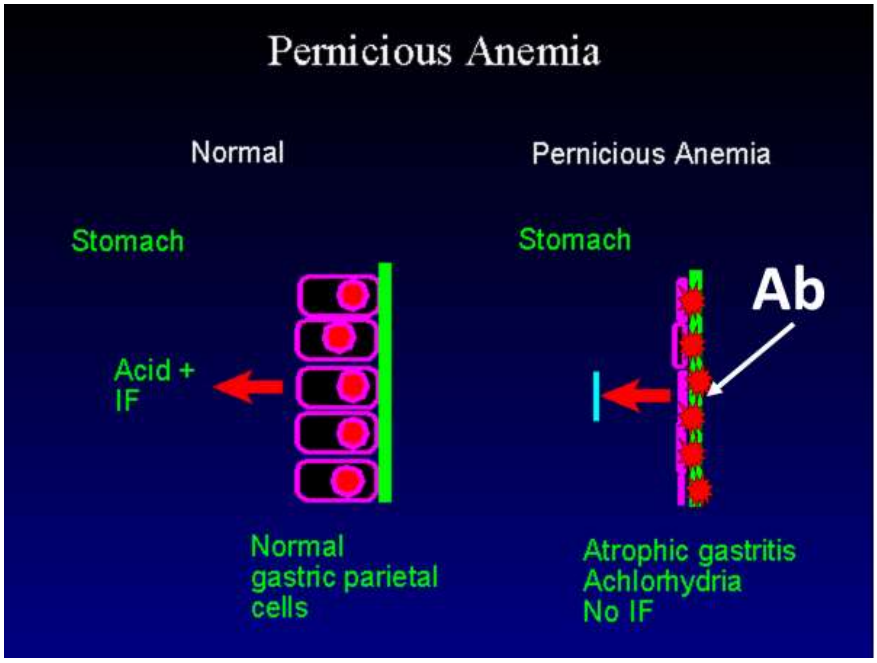
Patient's Plasma + Donor's RBCs = Major Cross-Match

Donor's Plasma + Patient's RBCs = Minor Cross-Match

Anaemia???

Types of anemia

	Microcytic hypochr.	Normocytic normochr.	Macrocytic (megaloblastic)
BI	Small	Normal	Large
??			



Hemolysis

Intrinsic disorders

Hereditary spherocytosis

-- G-6-PD enzyme

Sickle cell anemia

Extrinsic disorders

Erythroblastosis fetalis

Infections

Snake venom

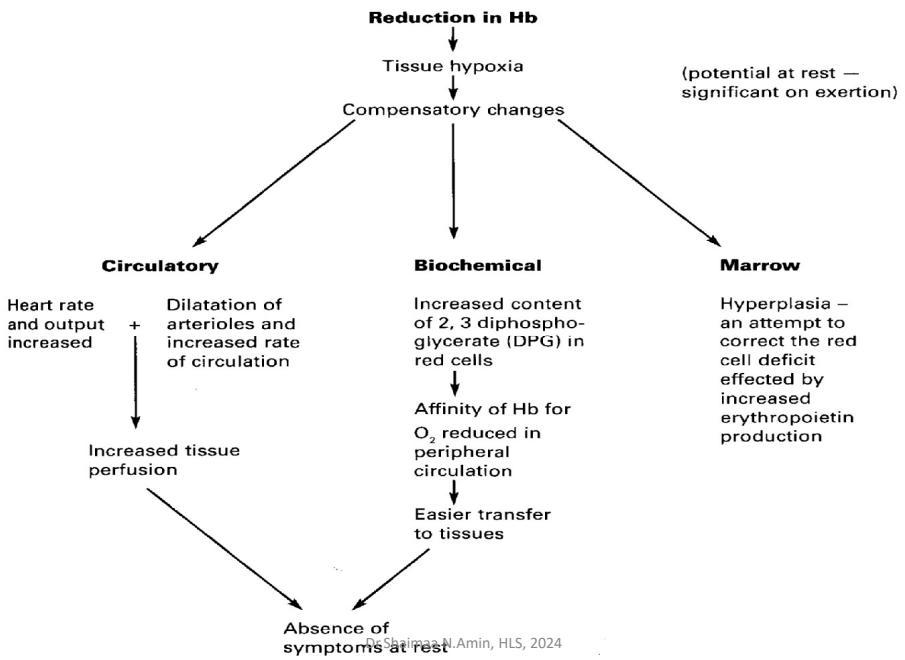
Poisons

C/P

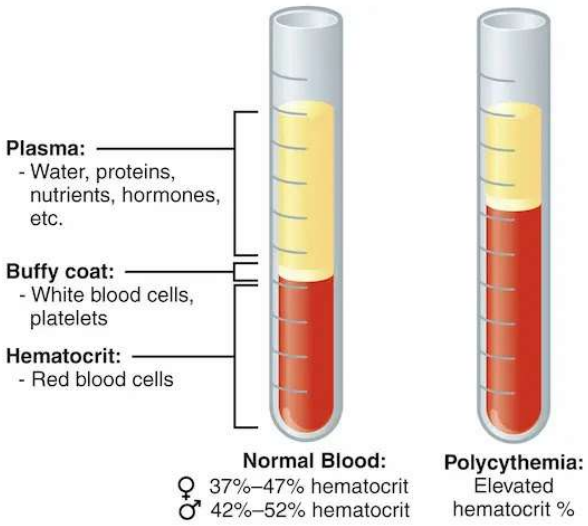
Jaundice

++ reticulocyte count

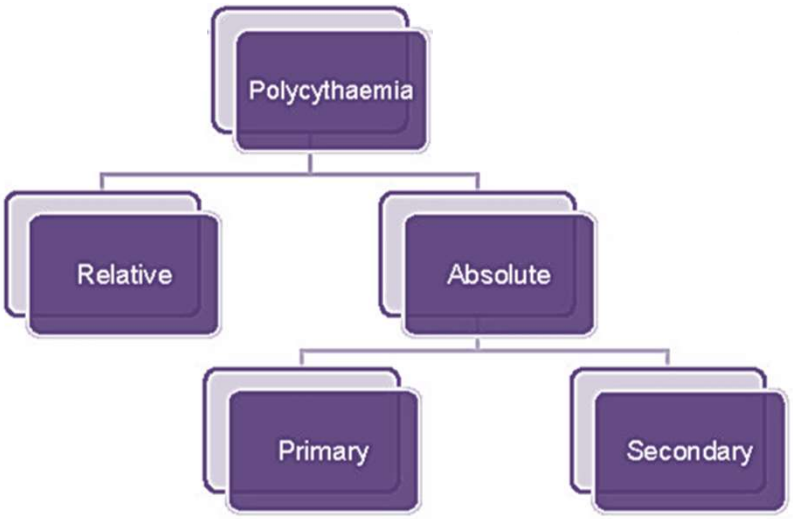
Effect of anaemia



Polycythemia



Polycythemia



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Hemostasis and Blood Coagulation

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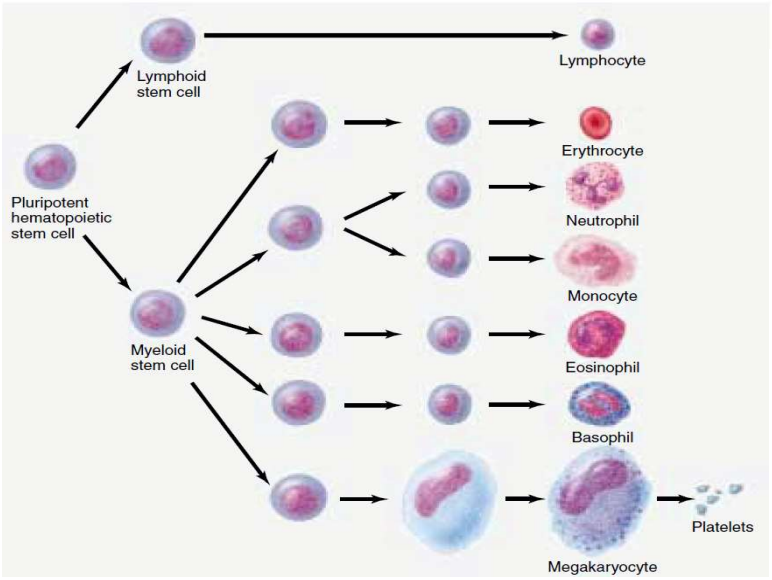
Platelets



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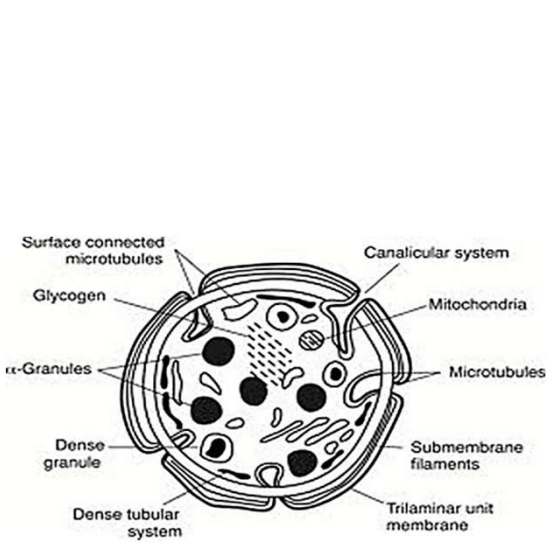

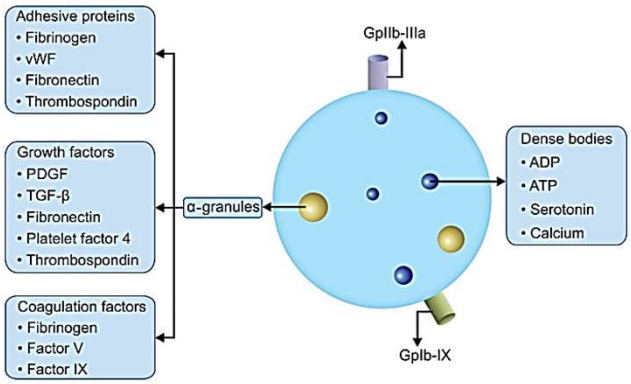

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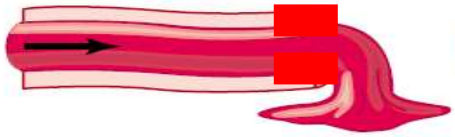
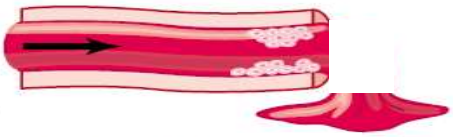
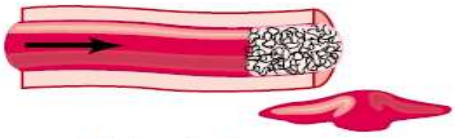
Hemostasis



1 VC

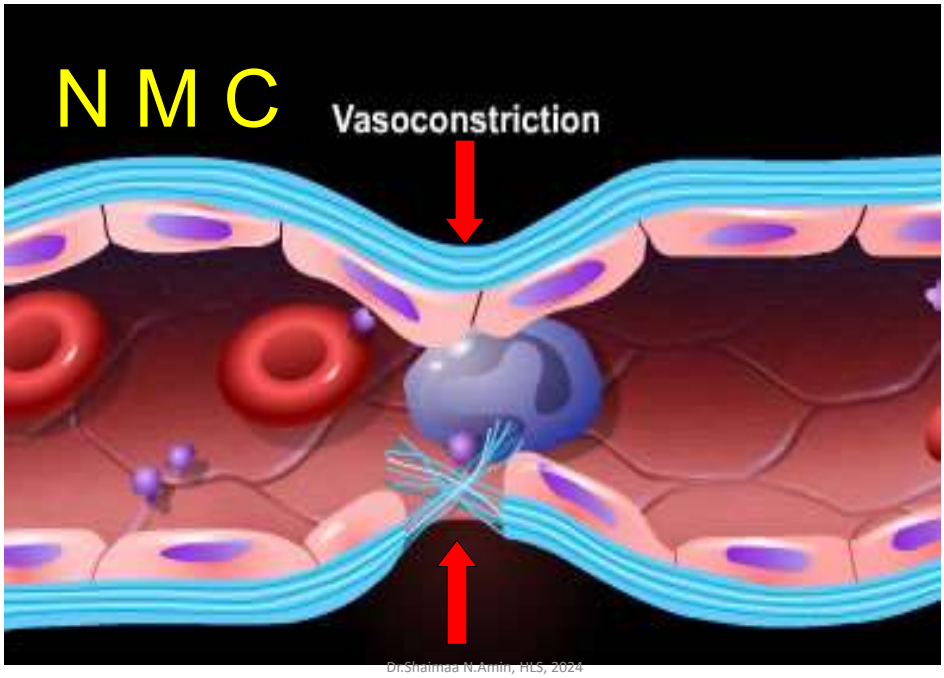


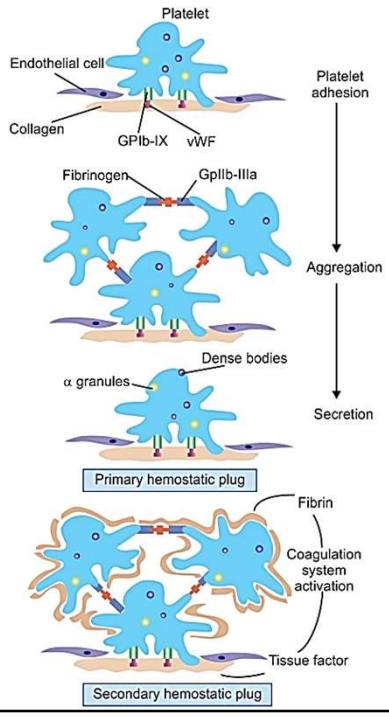
2. Platelets plug



3. Fibrin clot forms

4. Dissolve clot





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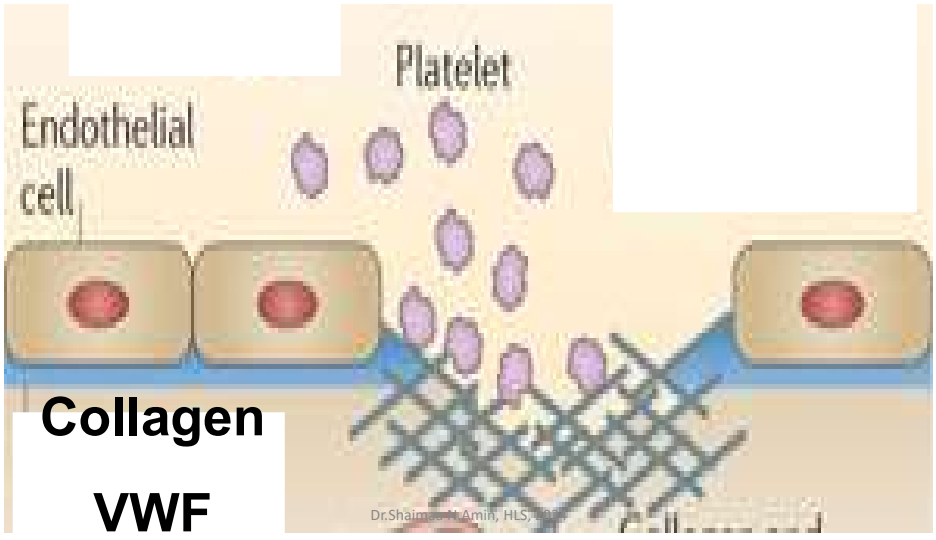
Why platelets adhere only to injured endoth.?



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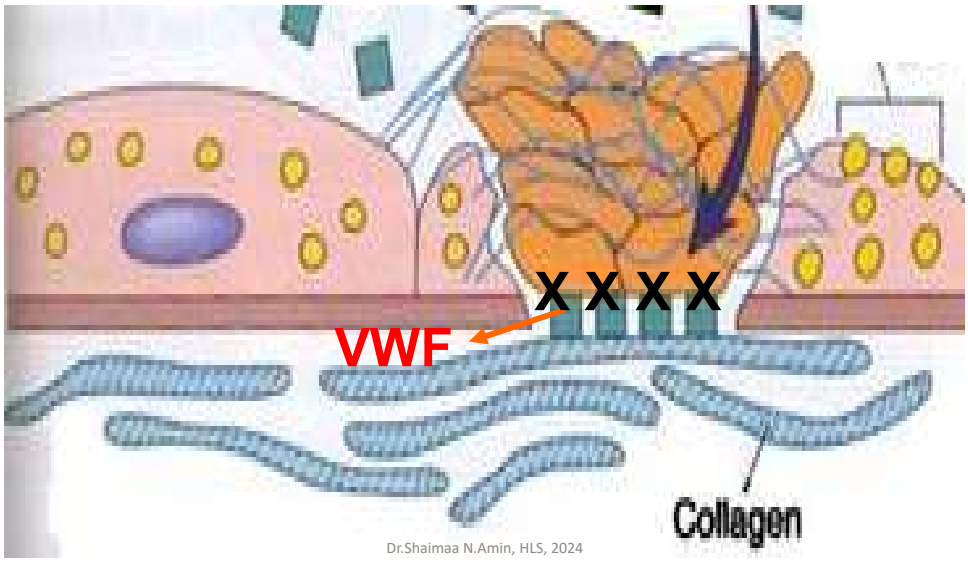
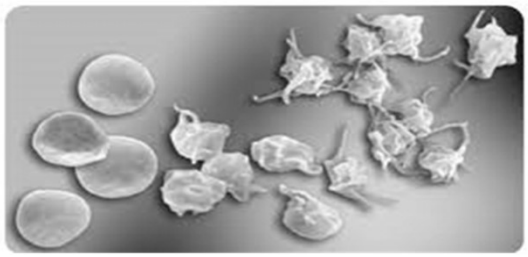
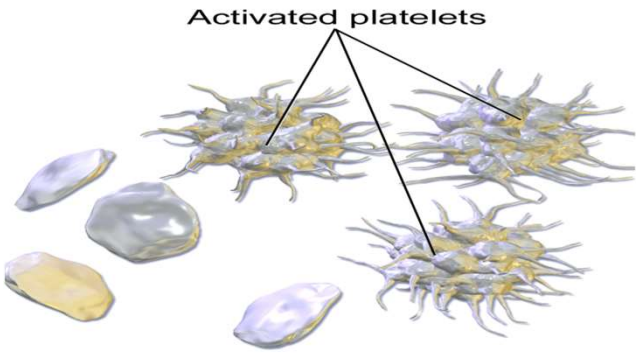
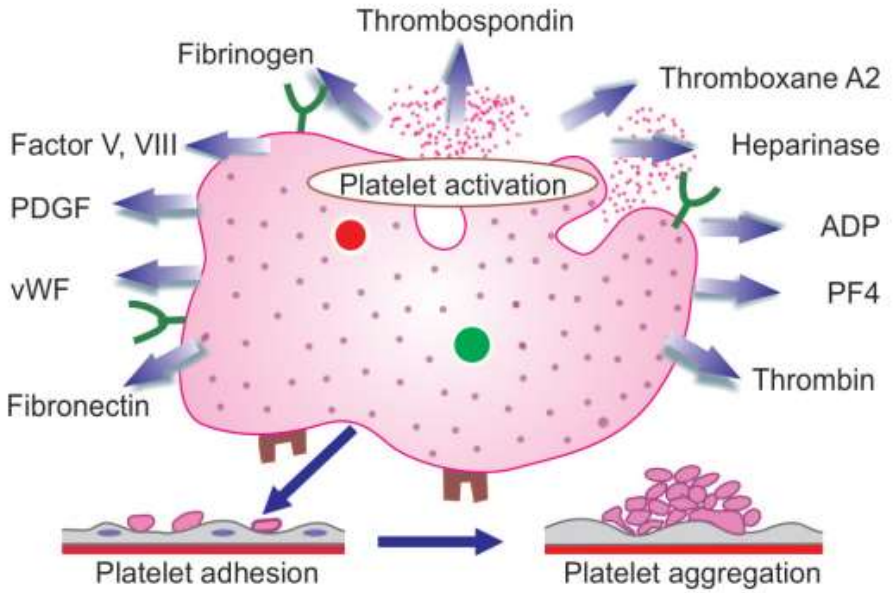
Platelets Plug: Adhesion



Platelets Plug: Activation







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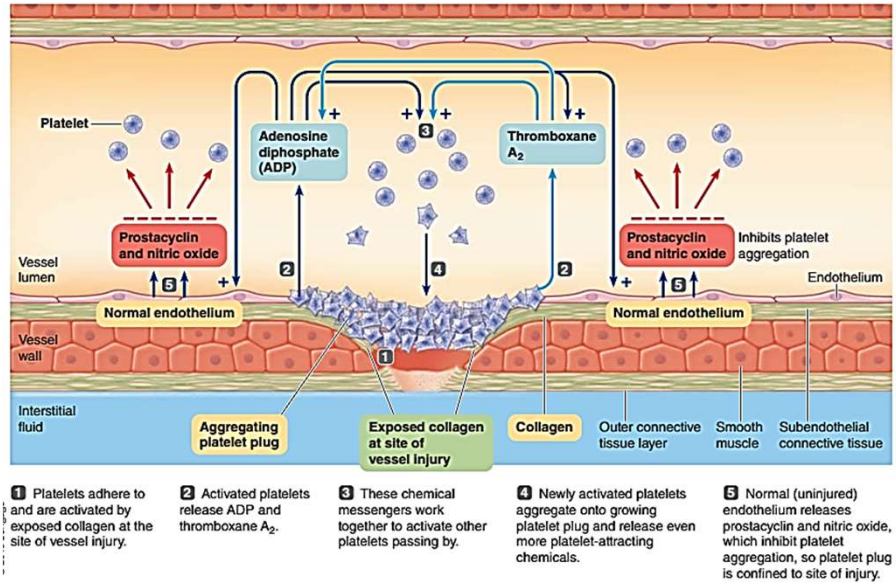

› FIGURE 10-11 **Formation of a platelet plug.** Platelets aggregate at a vessel defect through a positive-feedback mechanism involving the release of adenosine diphosphate (ADP) and thromboxane A_2 from platelets, which stick to exposed collagen at the site of the injury. Platelets are prevented from aggregating at the adjacent normal vessel lining by the release of prostacyclin and nitric oxide from the undamaged endothelial cells.

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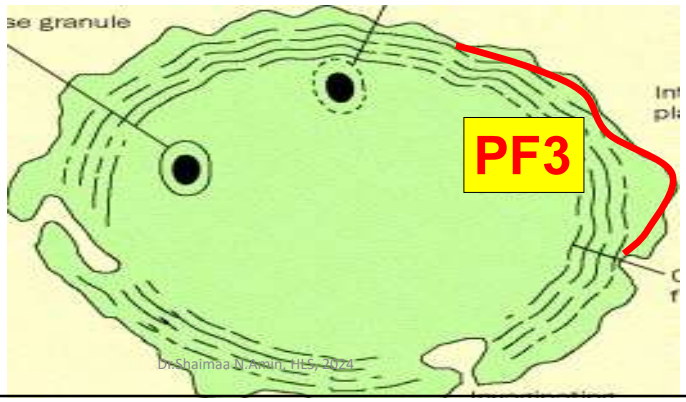
Platelets plug: Proclotting

- **PF3** provids an ideal surface for concentration & activation of clotting factors.



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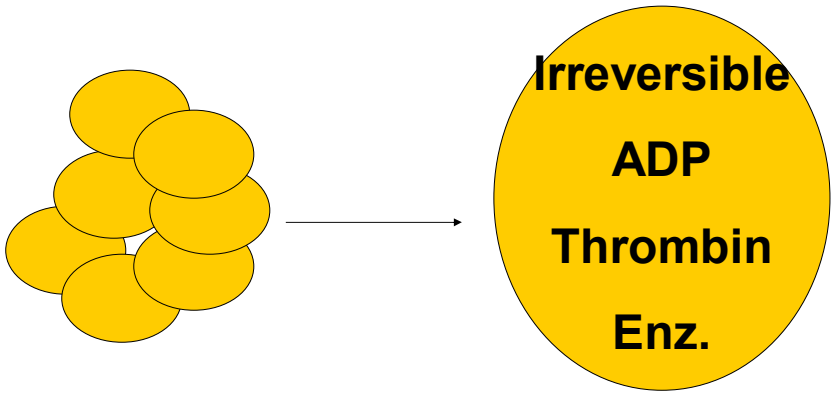
Platelets plug: Fusion



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Vascular Injury

↓

Platelet adhesion

↓

activation & release

↓

ThxA2, ADP

↓

Platelet aggregation

↓

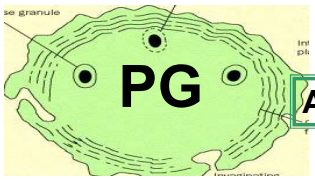
Platelet fusion

81

Membrane phospholipids

↓ PLase

Arachidonic acid



Aspirin -- COX

PG

Thx A2

VC

++ Platelet release

++ aggregation

--cAMP

PC

VD

↓ Platelet release

↓ aggregation

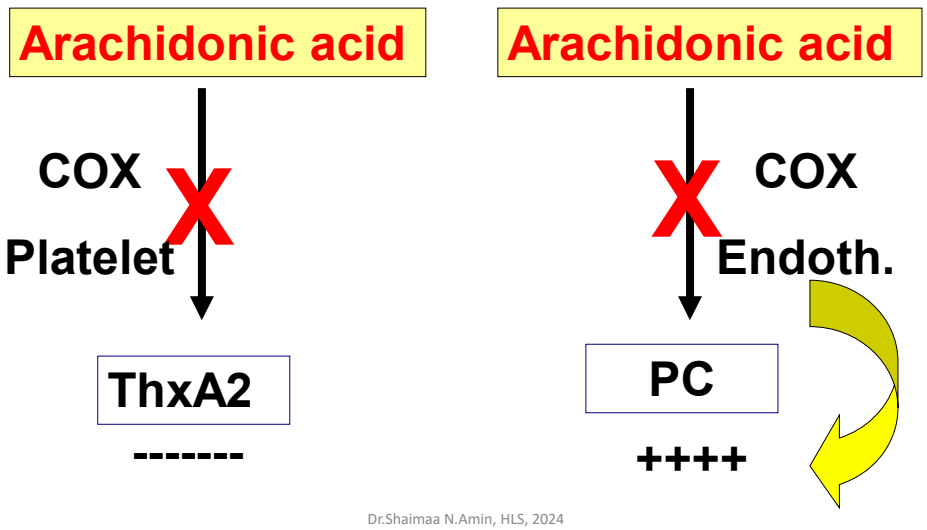
++ cAMP

82

Note

- Aspirin inhibits COX → --- TxA2 & PC
- Endothelium produce new COX
- Platelets cannot manufacture new COX
- Administration of small amounts of aspirin for prolonged periods → -- clot → preventing MI.

Aspirin

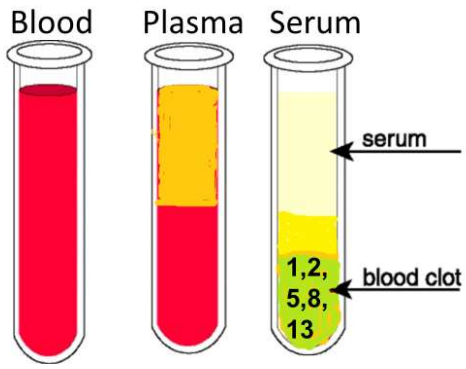


Blood Clotting

- Plasma proteins (B- globulins)
- **Inactive** serine protease enz.
- Activation → cascade effect.
- 3 groups.

Fibrinogen group

- **I , V, VIII & XIII. (1, 5+8 = 13)**
- **Activated by thrombin.**
- **Not present in serum.**



Prothrombin group

- **II, VII, IX & X. (1972)**
- **Need vit. K for synthesis**
- **Prothrombin is not present in serum.**

Contact Group

- **XI and XII.**
- **Present in serum**

Mechanism of clotting

1- Prothrombin —X→ **thrombin**

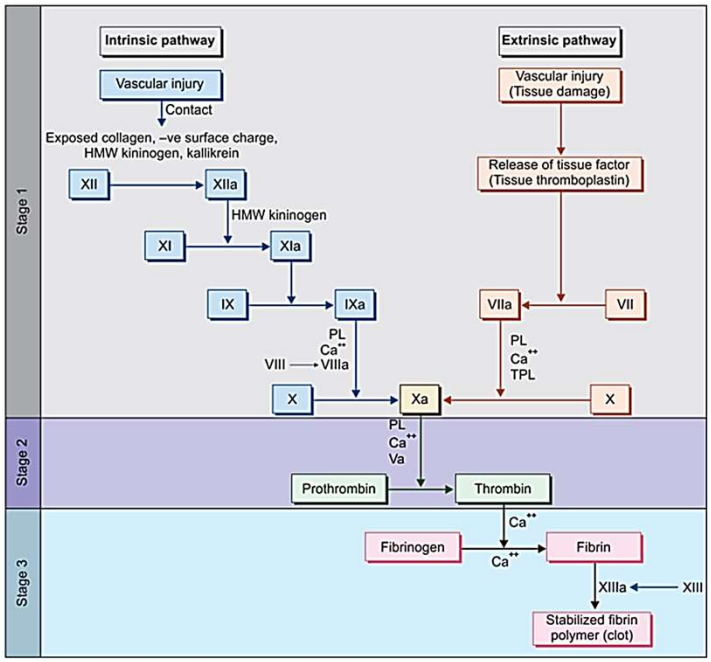
2- Fibrinogen —**thrombin**→ **fibrin m.**→

Fibrin **polymerize**→ **loose** mesh

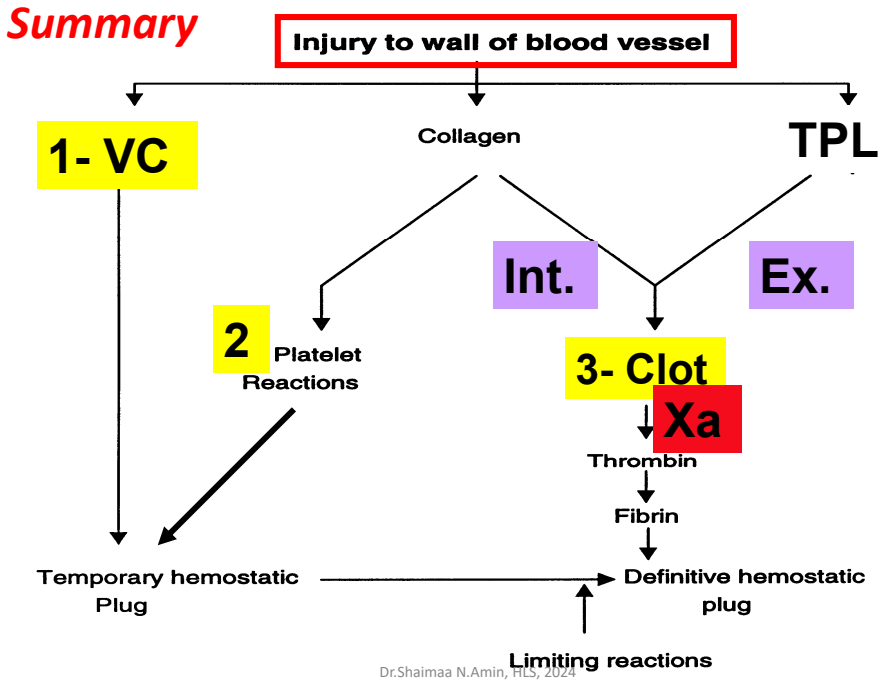
↓ **XIII**

3- Tight stabilize fibrin clot

4. Factor X is activated by either **intrinsic or extrinsic pathways.**


Intrinsic pathway
Vascular injury
Contact
Exposed collagen, –ve surface charge, HMW kininogen, kallikrein
XII
XIIa
HMW kininogen
XI
XIa
IX
IXa
PL
Ca++
VIII
VIIIa
X
Xa
Extrinsic pathway
Vascular injury (Tissue damage)
Release of tissue factor (Tissue thromboplastin)
VIIa
VII
PL
Ca++
TPL
X
PL
Ca++
Va
Prothrombin
Thrombin
Ca++
Fibrinogen
Ca++
Fibrin
XIIIa
XIII
Stabilized fibrin polymer (clot)
Stage 1
Stage 2
Stage 3

89


Summary
Injury to wall of blood vessel
1- VC
Collagen
TPL
Int.
Ex.
2
Platelet Reactions
3- Clot
Xa
Thrombin
Fibrin
Temporary hemostatic Plug
Definitive hemostatic plug
Limiting reactions

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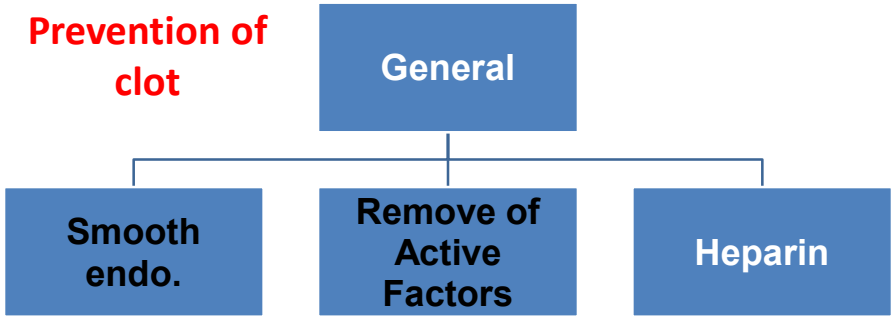
Anticlotting Mechanisms (Limitation reactions)



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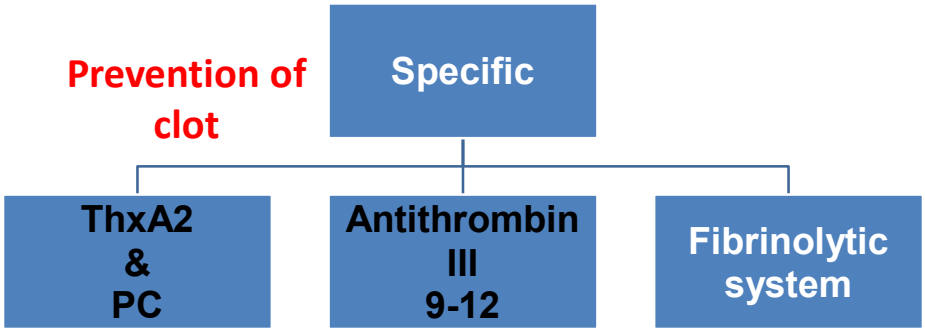
Anticlotting Mechanisms (Limitation reactions)



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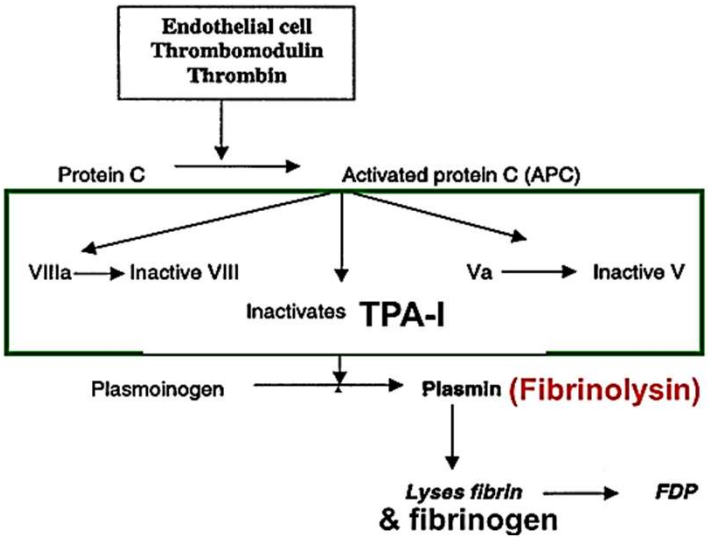
Fibrinolytic system



Anticoagulants

In vitro :

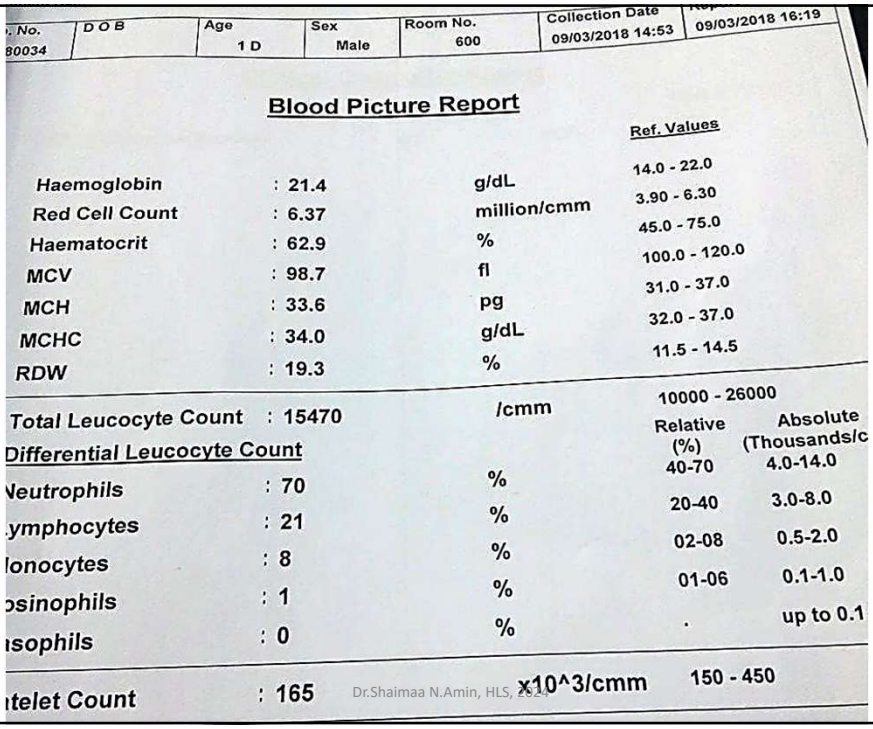
- **Na citrate:** deionize Ca
- **Na oxalate:** precipitate Ca
- **Silicon tube**
- **Heparin**

In vivo

	Heparin	Dicumarol
Origin	Mast cells & basophils.	Plant
Action	Facilitates action of Antithrombin III	Competitive inhibition with Vit.K R
Site of action	In vivo & vitro	Only in vivo.
Onset/ duration	Rapid & short	Slow & long
Administration	IV / SC	Orally
Antidote	Protamine sulphate 1% Blood transfusion	Vit. K

Hemostatic Function Tests

- CBC
- Bleeding & clotting time
- PT
- INR
- aPTT
- PC



No.	DOB	Age	Sex	Room No.	Collection Date	Rep.
80034		1 D	Male	600	09/03/2018 14:53	09/03/2018 16:19

Blood Picture Report

			Ref. Values	
Haemoglobin	: 21.4	g/dL	14.0 - 22.0	
Red Cell Count	: 6.37	million/cmm	3.90 - 6.30	
Haematocrit	: 62.9	%	45.0 - 75.0	
MCV	: 98.7	fl	100.0 - 120.0	
MCH	: 33.6	pg	31.0 - 37.0	
MCHC	: 34.0	g/dL	32.0 - 37.0	
RDW	: 19.3	%	11.5 - 14.5	
Total Leucocyte Count	: 15470	/cmm	10000 - 26000	
Differential Leucocyte Count			Relative (%)	Absolute (Thousands/c
Neutrophils	: 70	%	40-70	4.0-14.0
Lymphocytes	: 21	%	20-40	3.0-8.0
Monocytes	: 8	%	02-08	0.5-2.0
Eosinophils	: 1	%	01-06	0.1-1.0
Basophils	: 0	%	.	up to 0.1
Platelet Count	: 165	x10^3/cmm	150 - 450	

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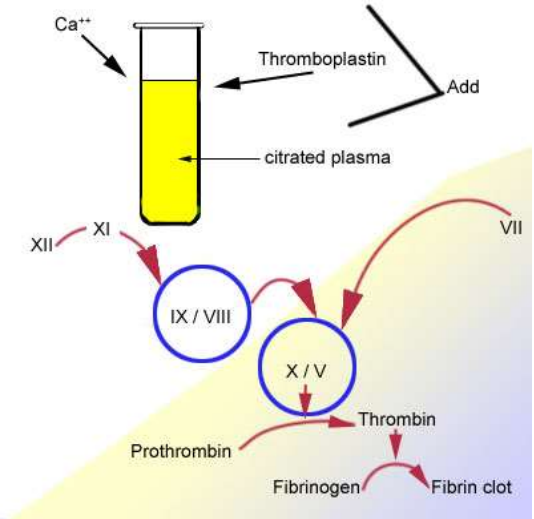
The Extrinsic Pathway and the PT



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International normalised ratio

The INR was devised to standardize the results.

$$INR = \left\{ \frac{PT\ (pat)}{Pt\ (n)} \right\}^{ISI}$$

PT (pat)= Patient's prothrombin time
PT (n) = Normal reference range
ISI = International sensitivity index
(the optimal ISI is 1.3 to 1.5)

labpedia.net

- Activated Partial Thromboplastin Time test (aPTT)

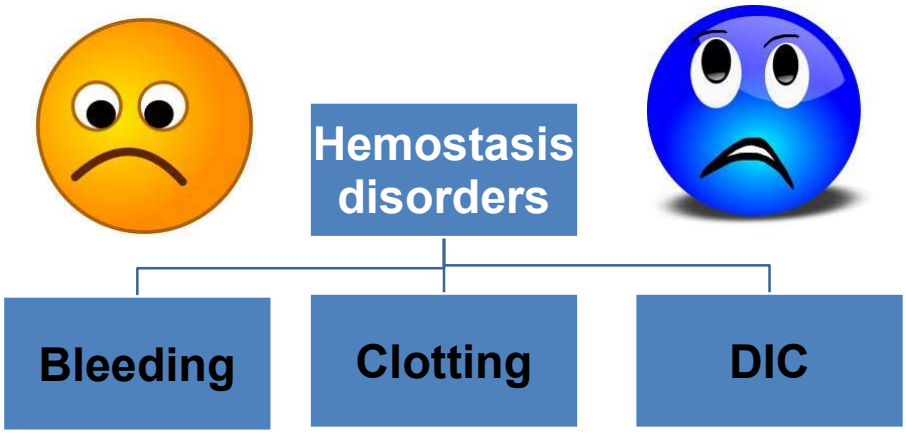
-Prothrombin concentration(PC)

No.	D O B	Age	Sex	Room No.	Collection Date	Report Date
034		1 D	Male	600	09/03/2018 14:53	09/03/2018 1

Coagulation Report

				Normal Values
Prothrombin Time (PT)	:	17.7	sec	10.1 - 15.9
Prothrombin Activity	:	55.0	%	
INR	:	1.62		Less Than 1.
Partial Thromboplastin Time (PTT)	:	45	sec	31 - 54

101



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Excessive bleeding

- **Thrombocytopenic purpura** (++ bleeding time)
- **Vitamin K deficiency** (++ clotting time)
- **Hemophilia** (++ clotting time)

Purpura

Causes of --- vit. K

- Inadequate intake
- Inadequate absorption,
- Inadequate utilization
- Vitamin K antagonist, such as warfarin

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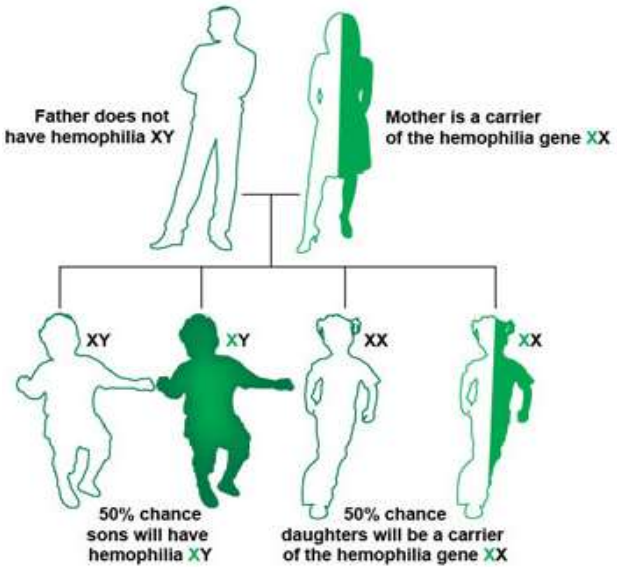
Hemophilia

A (8)

B (9)

C (11)



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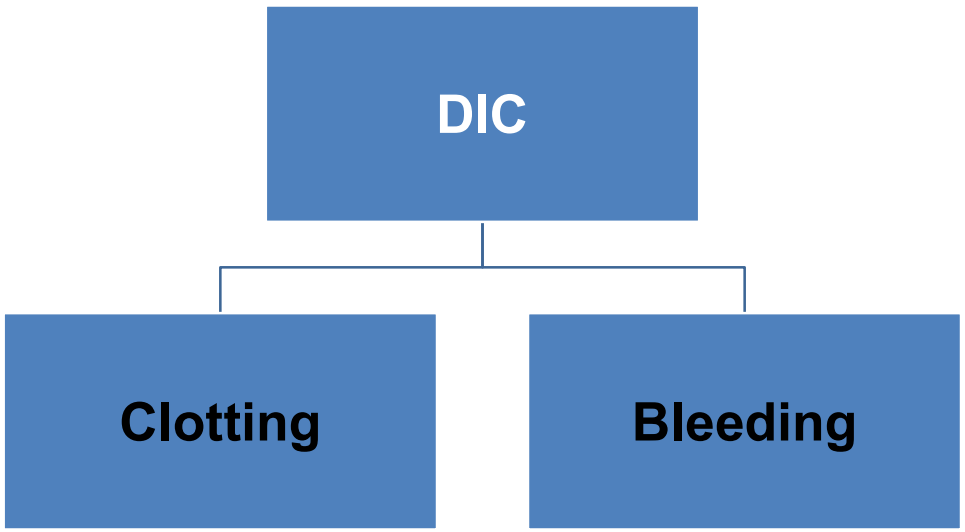
HEMOPHILIA

++ Clotting
Thromboembolic Conditions

Slow blood flow:

- long bed rest
- varicose veins
- atherosclerosis

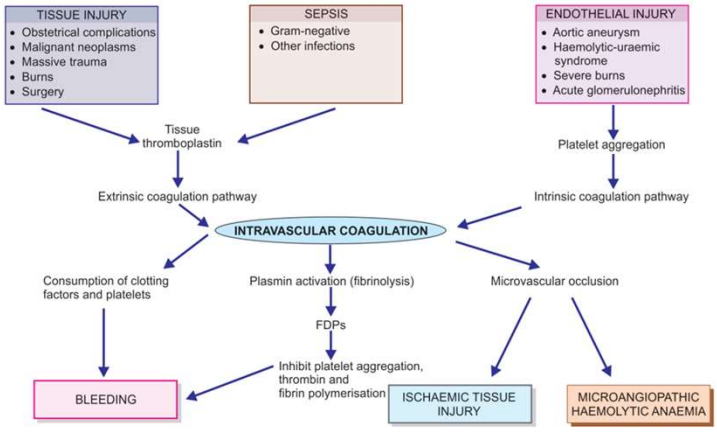


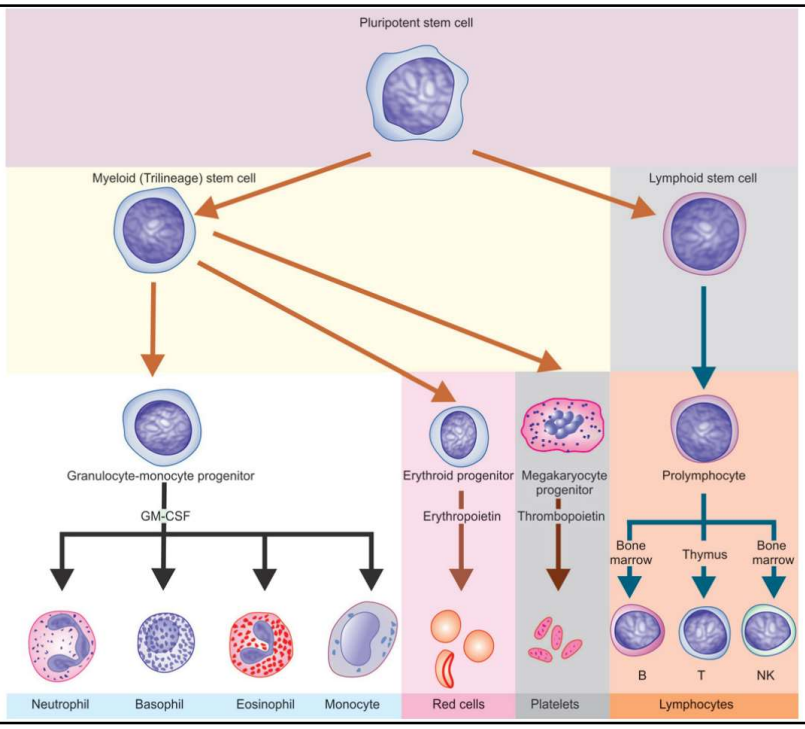
Disseminated Intravascular Coagulation (DIC)

Definition and Etiology

DIC is a clinicopathological syndrome in which there is **widespread intravascular coagulation** that occurs due to procoagulants that are introduced into or produced by blood circulation.

1. The procoagulant activity overcomes the natural anti-coagulant mechanisms. This is also called ***consumption coagulopathy*** or ***defibrination syndrome.***
2. This is a hemorrhagic disorder in which diffused intravascular coagulation results in defects of hemostasis.
3. In this disease, **coagulation factors and platelets are overutilized**. This results in bleeding.
4. The most common procoagulant stimulus is the ***tissue factor (tissue thromboplastin) exposure to the blood***, that activates extrinsic pathway of coagulation





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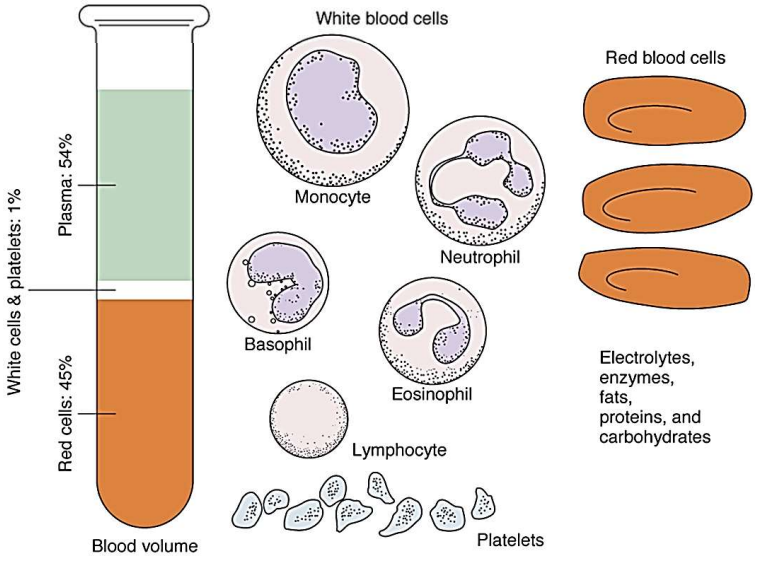
White Blood Cells



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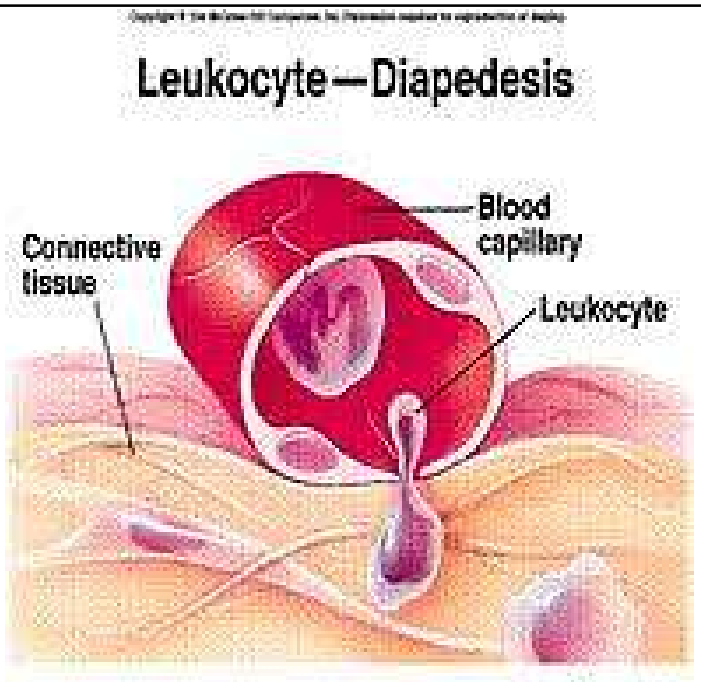
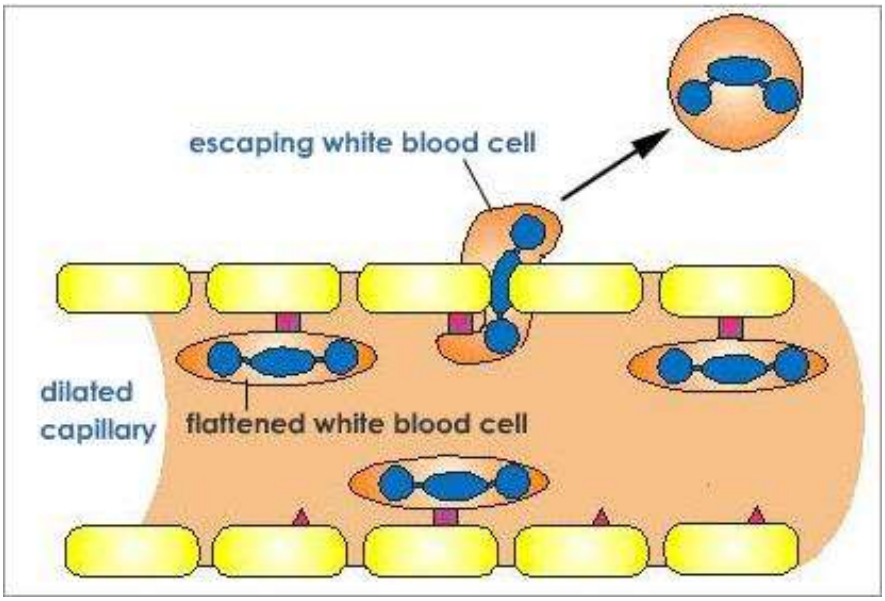
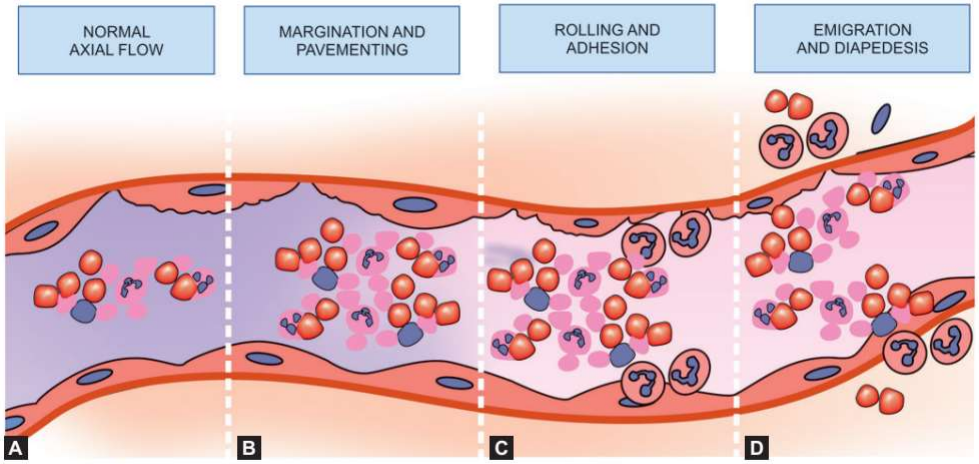

Leukocyte—Diapedesis
Blood capillary
Connective tissue
Leukocyte

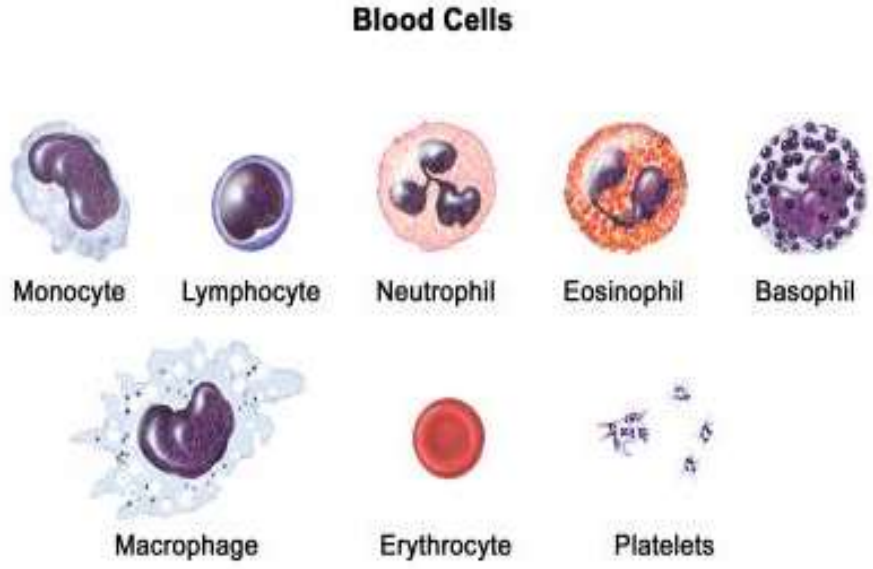

escaping white blood cell
dilated capillary
flattened white blood cell

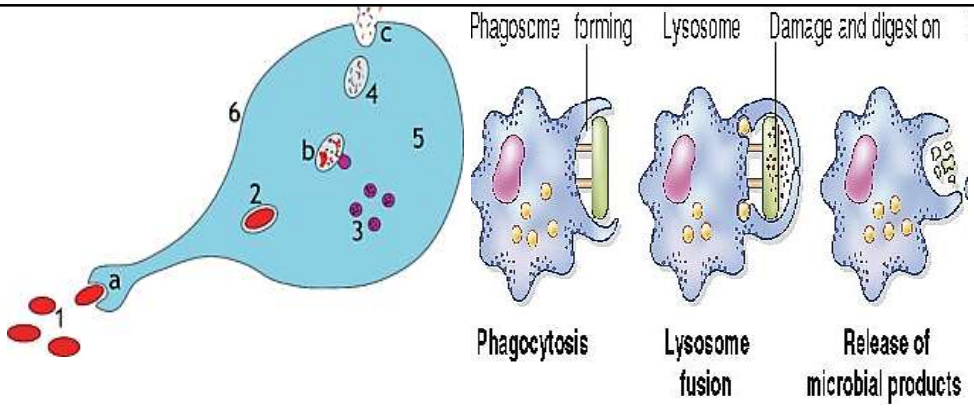


Figs. 17.10A to D: Details of diapedesis of neutrophils. It occurs in three phases: margination and pavementing, rolling and adhesion, and emigration and diapedesis.

Differential white blood cells:

- **A granular Leukocytes**
- **Granular Leukocytes**



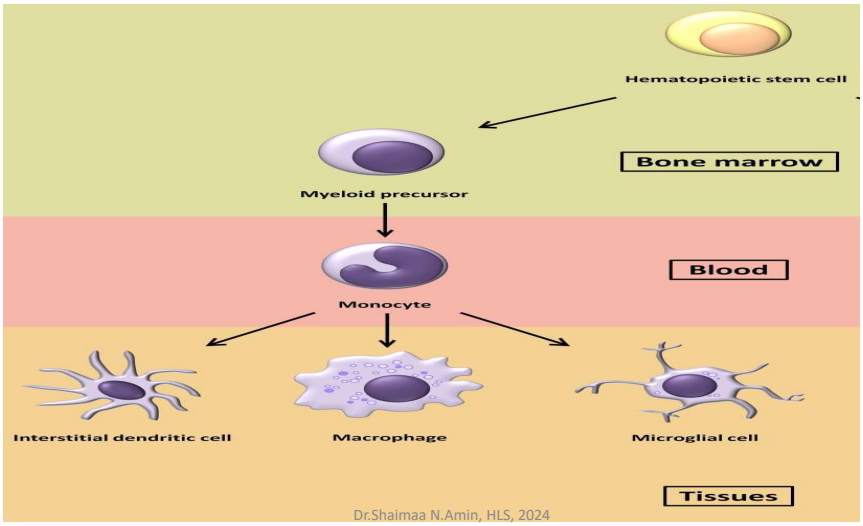


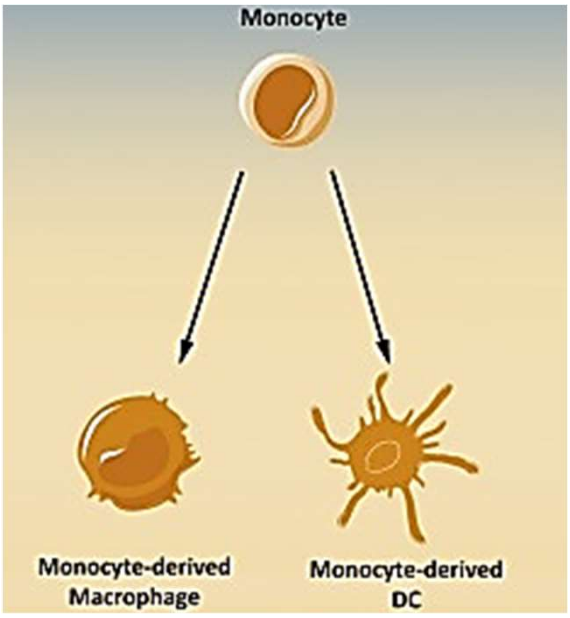
a. Ingestion through phagocytosis, a food vacuole is formed.
b. The fusion of lysosomes with the food vacuole; the pathogen is broken down by enzymes
c. Waste material is expelled or assimilated

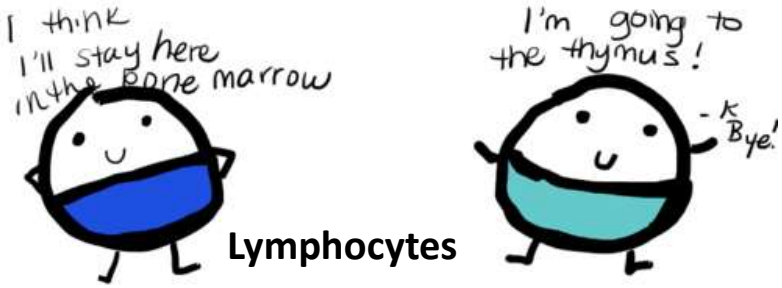
Parts:

1. Pathogens
2. food vacuole
3. Lysosomes
4. Waste material
5. Cytoplasm
6. Cell membrane

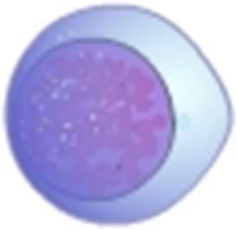
Monocytes-macrophage system







Lymphocytes



Immunity

-Immunity refers to all physiological mechanisms that enable an organism to recognize and defend against infectious agents.

-These body defences can be grouped in two categories:

-Non-specific immunity
-Specific immunity

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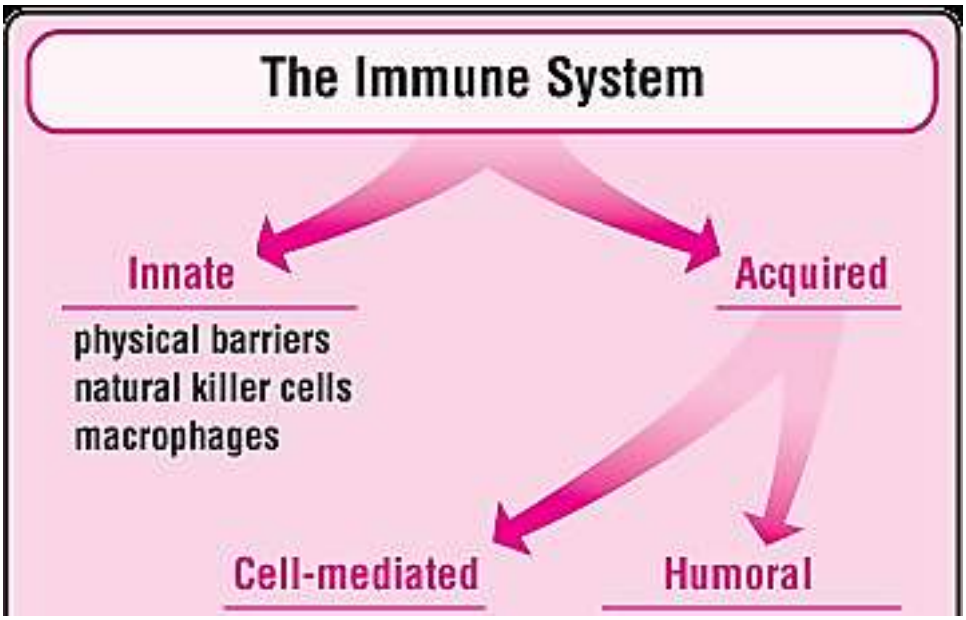

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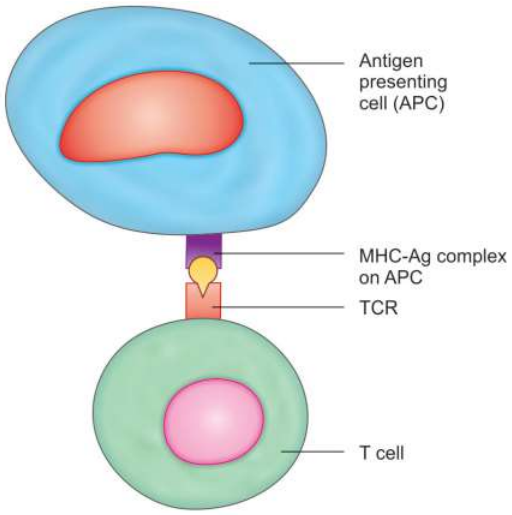
The cellular Immunity:

-This type of immunity is mediated by T-Lymphocytes.
-T-Lymphocytes defend body against:
Viruses, Fungi , T.B. ,Cancer cells and Foreign transplanted tissues.



MHC Antigens

Major histocompatibility complex or MHC antigens are self-antigens that help in identifying and rejecting the foreign antigens:

1. They are also called ***HLA antigens*** (human leucocyte associated antigens), as they were first identified on the membrane of leucocytes. However, afterward they were found to be present on the surface of all the body cells except in red cells (remember, red cells contain blood group antigens).
2. Like blood group antigens they are chemically glycoproteins. They are made up of α **and** β **subunits**.

Mechanism of Action of MHC Antigens

The proteins in the cells are continuously broken down to their peptide fragments. MHC I molecules pick up the peptide fragments containing 8–10 amino acids, whereas MHC II molecules pick up peptides containing 13–17 amino acids:

1. When a peptide fragment of a self protein is picked up by the MHC antigen and expressed on the surface of the APC along with MHC proteins, T cells ignore it.
2. However, when the peptide fragment is of a foreign protein, T cells recognize it and get activated that induce cell- mediated immunological responses.

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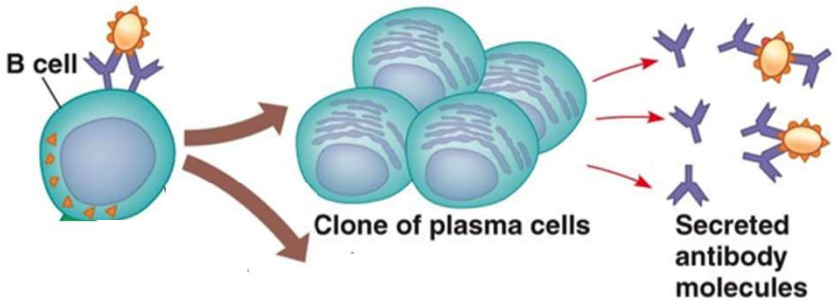
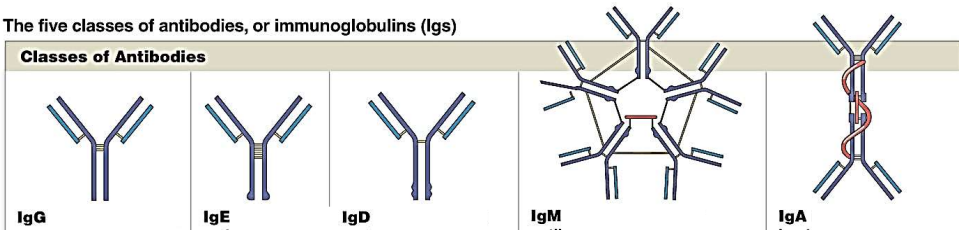
Humoral Immunity:





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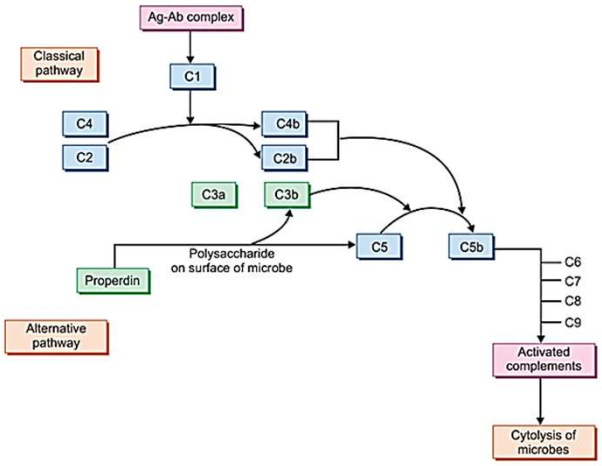

The complement system