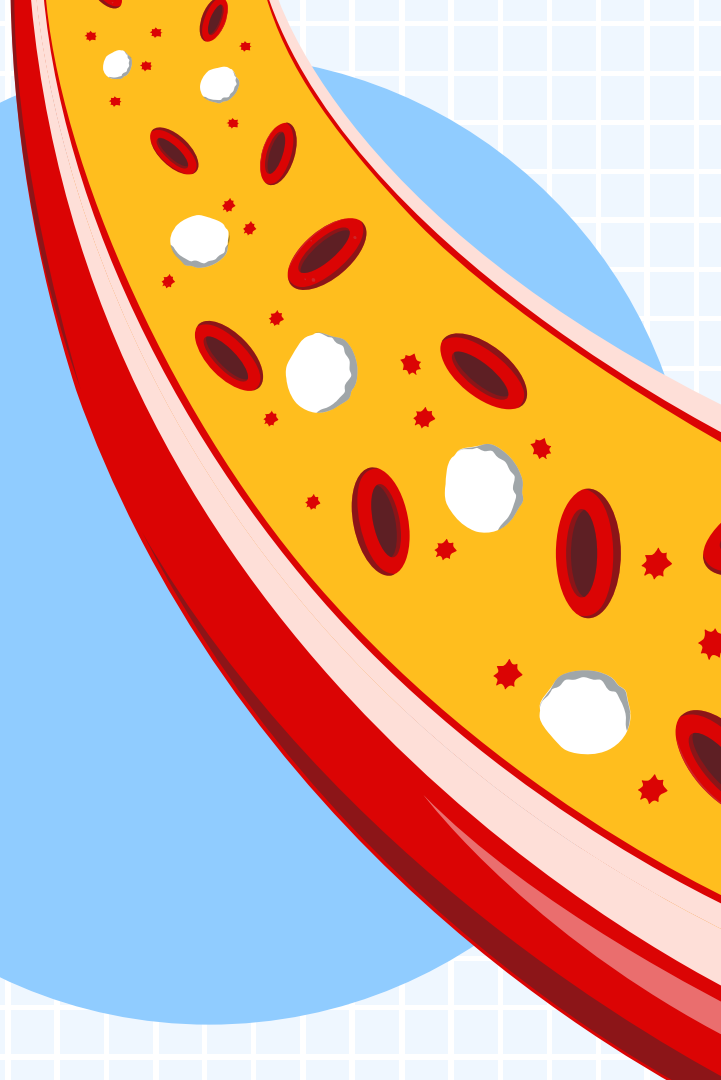
MODULE

HLS (HEMO & LYMPH)

Physiology Lectures
Lecture No. (4+5)
Slides By: Malek Hassan
Notes By:



Hayat Batch-Scientific Team

Blood Groups

Blood Groups are genetically determined antigens present on the membranes of red cells. These antigens can be detected by reactions with the corresponding antibodies in plasma.

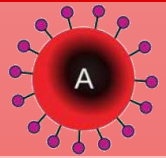
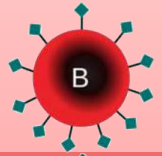
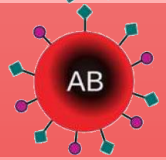
ABO System :

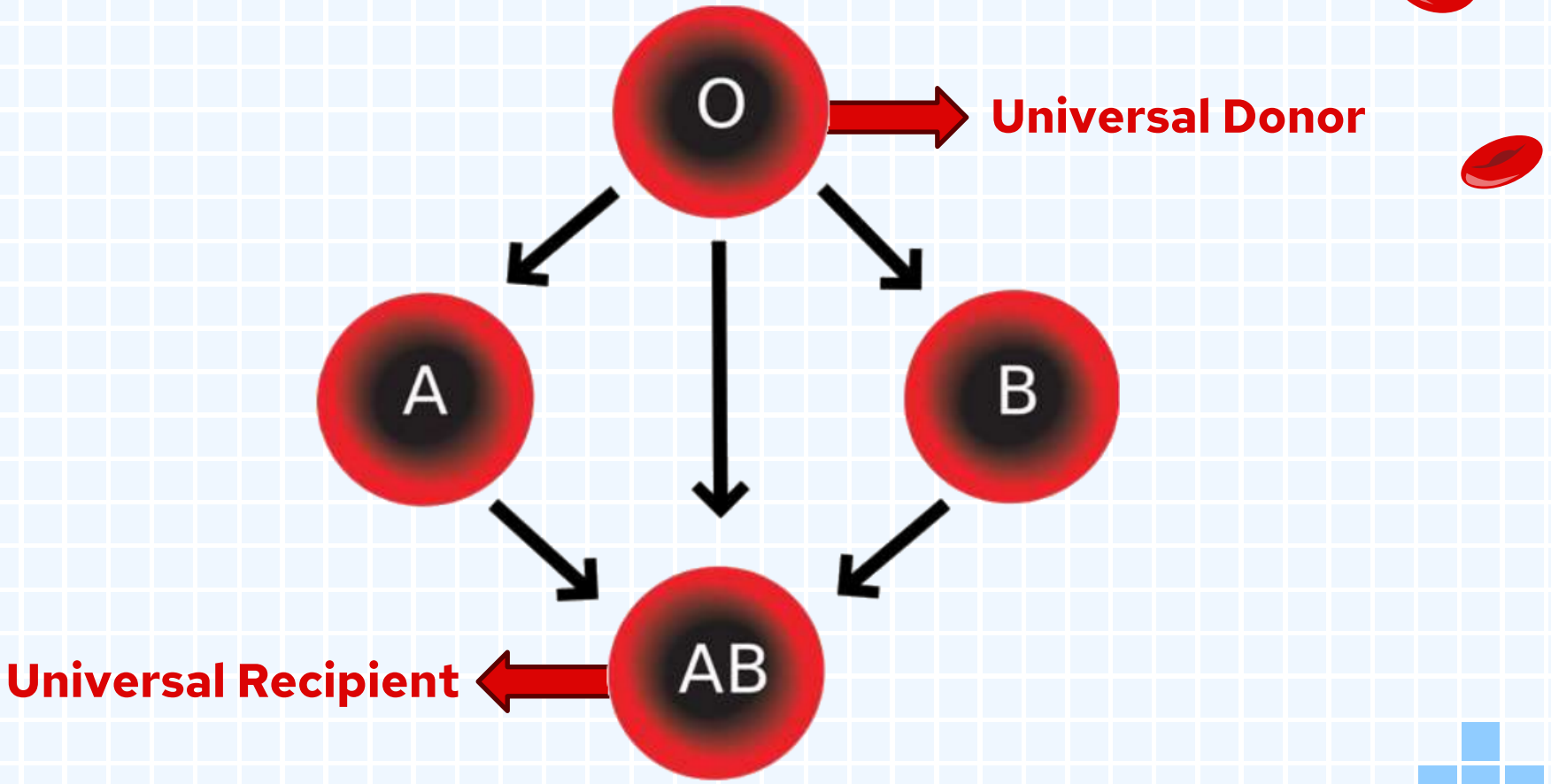
- The cell membrane of RBCs has either A or B antigens.
- A antigens are present on RBCs of 40% of the population, and B antigens are present on RBCs of 10% of the population. In comparison, both are present on RBCs of 5% and absent in RBCs of 45% of the population. Thus, there are four groups of people according to the presence or absence of antigens A and B on RBC membranes

Antibodies against red cell agglutinogens are called agglutinins. Antigens very similar to A and B are common in intestinal bacteria and possibly in foods to which newborn individuals are exposed. Therefore, infants rapidly develop antibodies against the antigens not present in their own cells. Thus, type A individuals develop anti-B antibodies, type B individuals develop anti-A antibodies, type O individuals develop both, and type AB individuals develop neither

Blood Groups

The Reaction between Antigens on RBCs and the corresponding antibodies in plasma results in the agglutination of RBCs, so the Antigens are called Agglutinogens, and the Antibodies are Agglutinins.

Genotype	Blood group (Phenotype)	Agglutinogen	Agglutinin
AA.AO		 A-Antigen	 Anti-B
BB.BO		 B-Antigen	 Anti-A
AB		 AB-Antigen	---
OO		--	 Anti-A, Anti-B


O
Universal Donor
A
B
AB
Universal Recipient

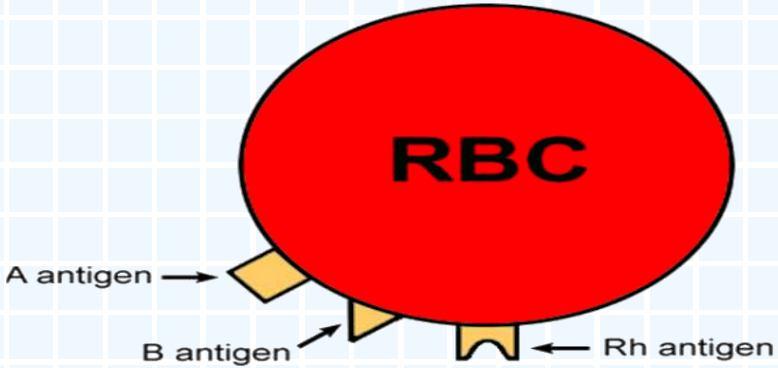
Blood Groups

Rh Blood Type : D factor

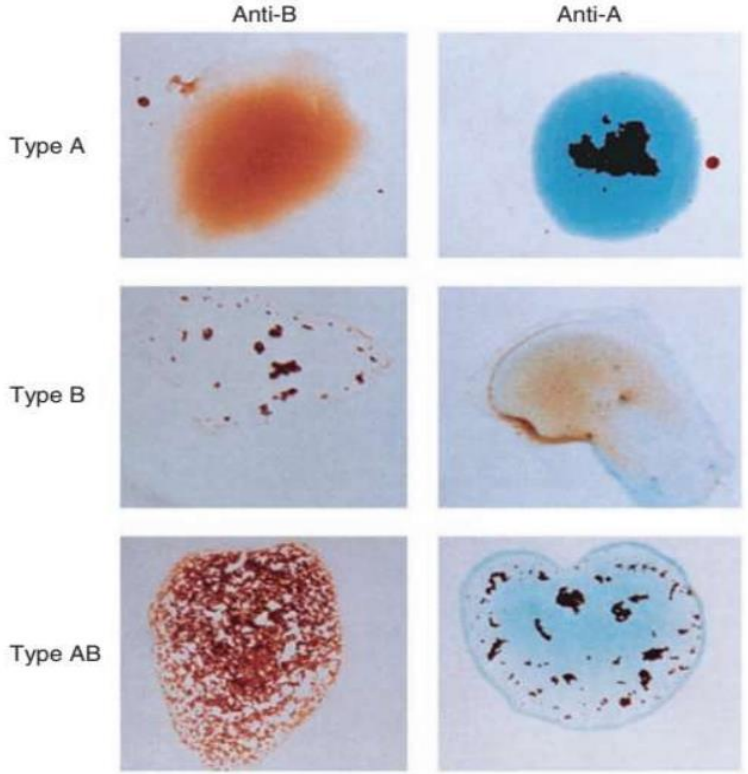
- This is an Antigen on the RBC membrane of 85% of the population who are said to be Rh-positive. It was first discovered in the Rhesus Monkey.
-
- Rh Antibodies are formed in the plasma of a Rh-negative person if he is transfused with Rh-Positive blood, and the person, in this case, is sensitized to the Rh factor. So, if that person receives Rh-positive blood again, agglutination and hemolysis of the RBCs results.

- Rh-Positive person never forms Anti-D antibodies whether he receives Rh-Positive or Rh-Negative blood.

  - 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"



Blood Groups



Red cell agglutination in incompatible plasma.

Blood Groups

Importance of Rh factors :

Erythroblastosis Fetalis : (Hemolytic Disease of the newly born)

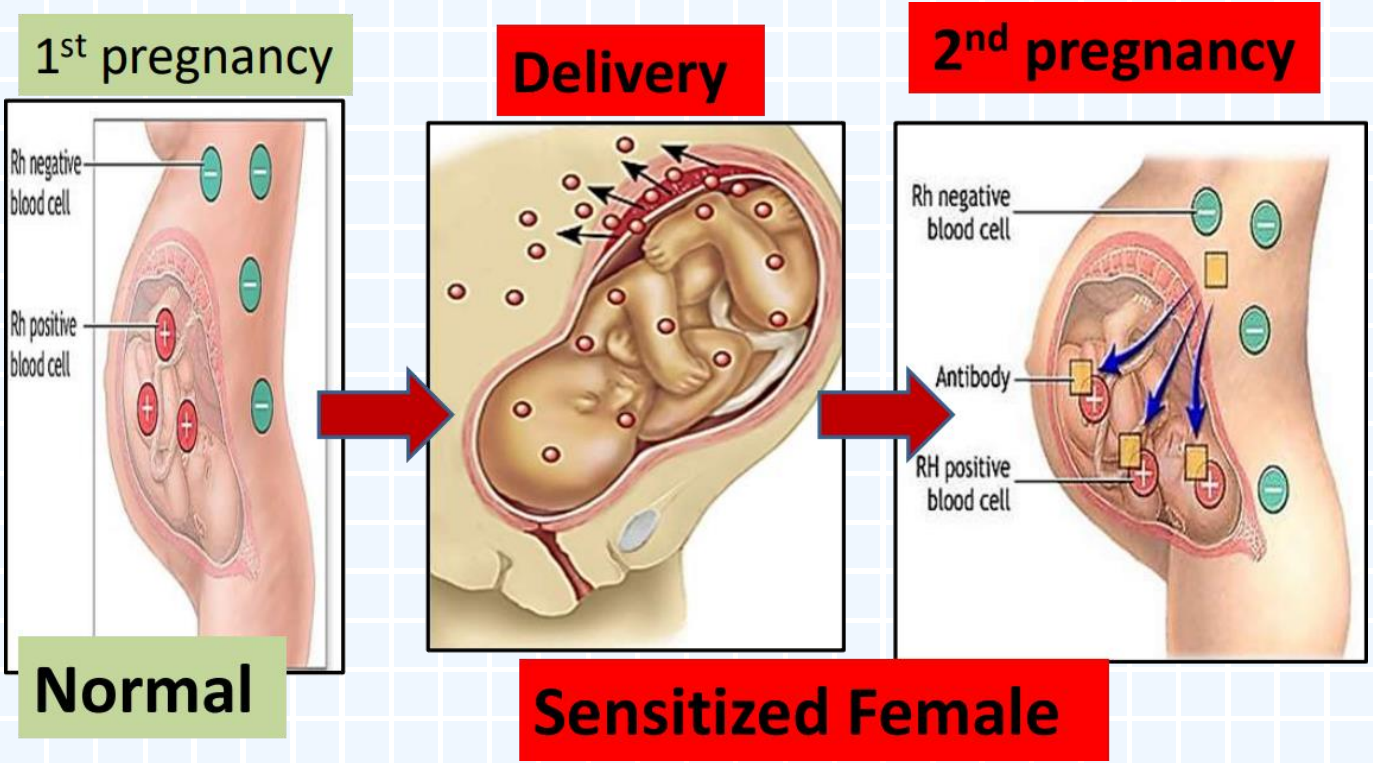
When a Rh-Positive Male marries a Rh-Negative Female, the fetus will be Rh-Positive. During delivery, many Rh-positive fetal red cells enter the mother's circulation, and anti-D agglutinins of the immunoglobulin G type are formed in the mother's blood, which is now sensitized to the D antigen. When the Rh-Negative sensitized mother becomes pregnant again with a Rh-Positive fetus, the antibodies (IgG) in her blood cross the placenta to the fetus leading to agglutination and hemolysis of fetal RBCs. Usually, the first baby escapes the damage, but the next babies are affected. The affected baby is severely anemic and jaundiced at birth due to excessive bilirubin formation. The Blood-Brain Barrier of the fetus is not well developed; bilirubin reaches the brain causing damage, a condition called kernicterus. In more severe conditions, the baby is born dead.

- The first baby may be affected if a previous transfusion already sensitizes the Rh-Negative mother with Rh-Positive blood.

Blood Groups

Importance of Rh factors :

Erythroblastosis Fetalis : (Hemolytic Disease of the newly born)

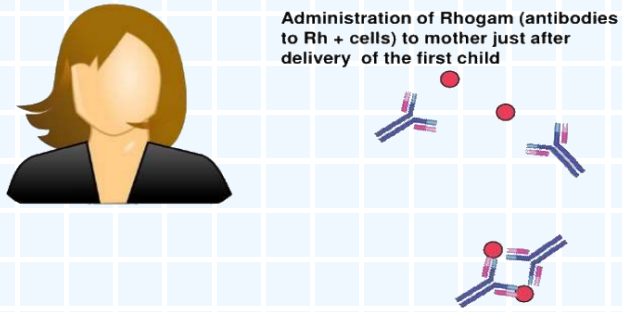


Blood Groups

Prevention :

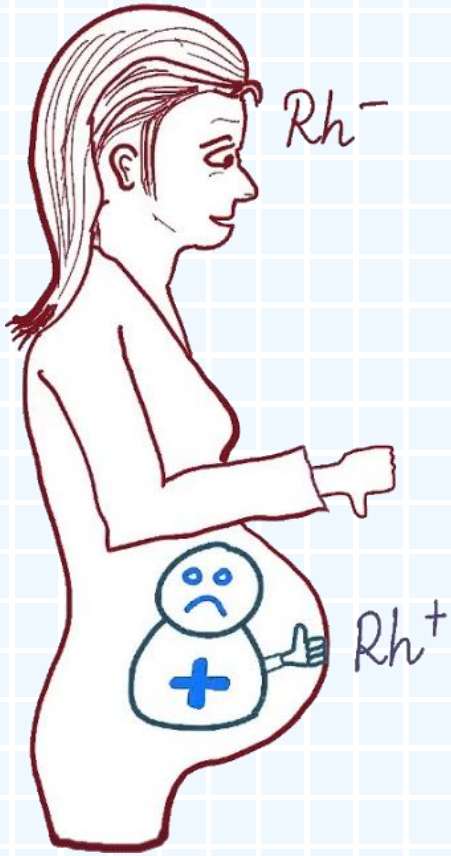
1. **Rh-Negative** Female should never receive **Rh-Positive** blood
2. When a **Rh-Negative** Female delivers **Rh-Positive** baby, anti-D antibodies are given to her immediately after delivery to neutralize the D-Antigen of the **Rh-Positive** fetal red cells that entered her blood, thus preventing sensitization of the mother. If a **Rh-Negative** person is transferred with **Rh-Positive** blood, he will produce Agglutinins against the Rh factor (D-Antigen). If, after some time, this person is transfused again with **Rh-Positive** blood, Agglutination Occurs.

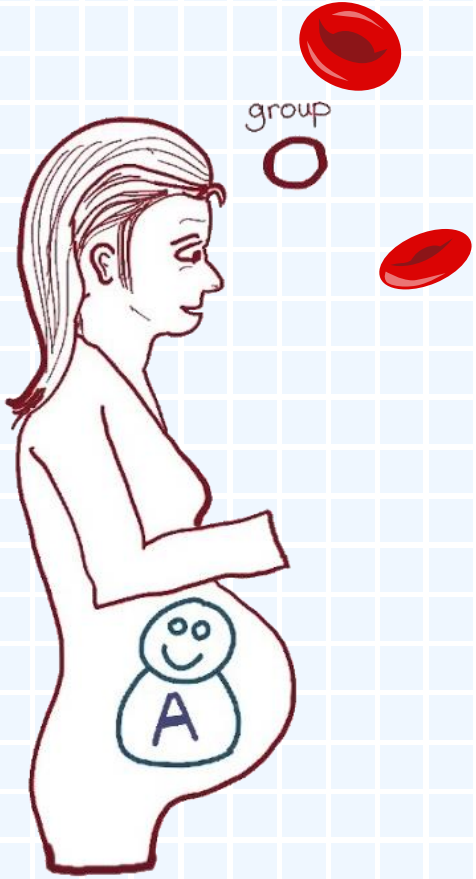
Treatment



ABO incompatibility

Rh incompatibility

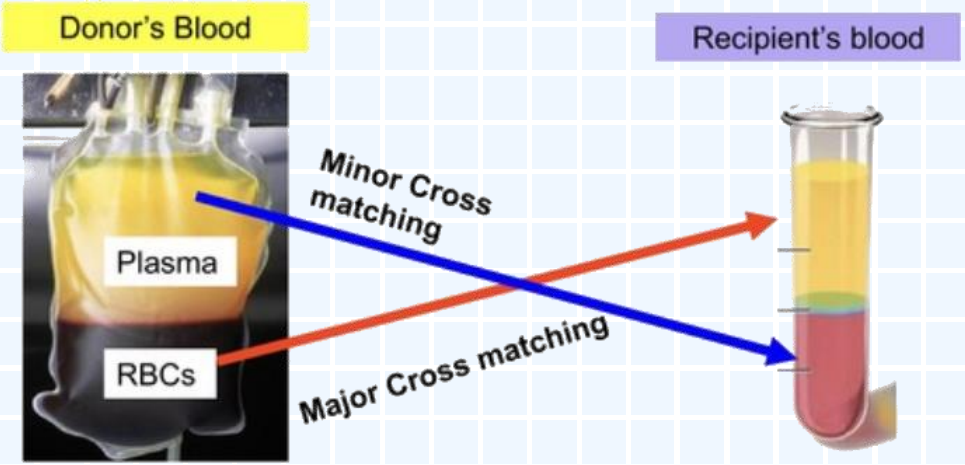




Blood Groups

Importance of blood group determination :

Blood Transfusion. Normally donor's red cells agglutinate with the corresponding antibodies of the recipient's plasma. The reverse rarely occurs due to the dilution of the donors' agglutinins in the large volume of the recipient's blood. It is important to do a cross-matching test by adding the donor's blood to the recipient's serum before blood transfusion.

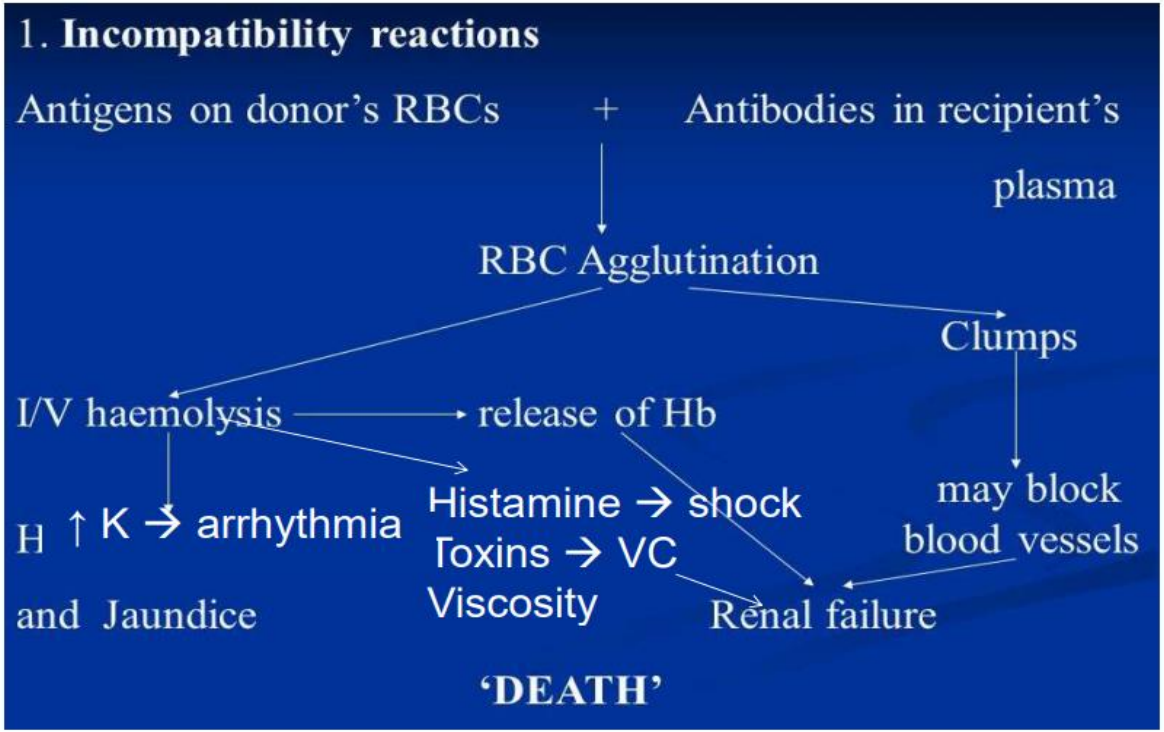


Donor RBCs + Recipient Plasma = Major Cross-Match

Donor Plasma + Recipient RBCs = Minor Cross-Match

Blood Groups

Importance of blood group determination :



Blood Groups

When incompatible blood is transfused

The mismatched transfusion reaction occurs immediately. The reaction is primarily due to the agglutination of the donor's red cells followed by their hemolysis. This is called **Acute Hemolytic Transfusion Reaction.** Usually, it occurs due to ABO incompatibility. The severity of the reaction depends on the degree of hemolysis.

The complications of mismatched transfusion are:

1. **Shivering and fever** (febrile reactions) usually occur
2. **Hemoglobinemia and Hemoglobinuria**
3. **Hemolytic Jaundice**
4. **Acute Renal Failure.** Renal failure occurs due to blocking the renal tubules and damaging the tubules and the release of toxic substances from the lysed red cell causes renal vasoconstriction
5. **Hyperkalemia** (due to the release of potassium ions from red cells). This may cause cardiac arrest in diastole.

Balance must be maintained between the rate of cell production and that of red cell loss from the circulation; imbalance results in either decreased red cell mass (anemia) or increased red cell mass (polycythemia).

Anemia

Definition: It is a **decrease in the Oxygen-Carrying capacity of the blood**, which may be due to: **Decreased number of RBCs** or **decreased hemoglobin content of the blood**.

Classification and Causes of Anemia :

Using the erythrocyte parameters **Mean Corpuscular Volume** (**MCV**) and **Mean Corpuscular Hemoglobin** (**MCH**). **Anemias can be classified according to cell volume (MCV): Microcytic**, **Normocytic** or **Macrocytic**.

According to the ratio of Hb Concentration /Erythrocyte count (MCH): Hypochromic, **Normochromic** or **Hyperchromic**.

1. **Microcytic Hypochromic Anemia** (Iron Deficiency Anemia)
2. **Macrocytic Anemia** (Megaloblastic Anemia)
3. **Normocytic Normochromic Anemia**

Anemia

Classification and Causes of Anemia :

1. **Microcytic Hypochromic Anemia (Iron Deficiency Anemia) :**

In this type of anemia, the size of RBCs is smaller than normal (Microcytic), and their hemoglobin content is less than normal (Hypochromic). It is caused by iron deficiency.

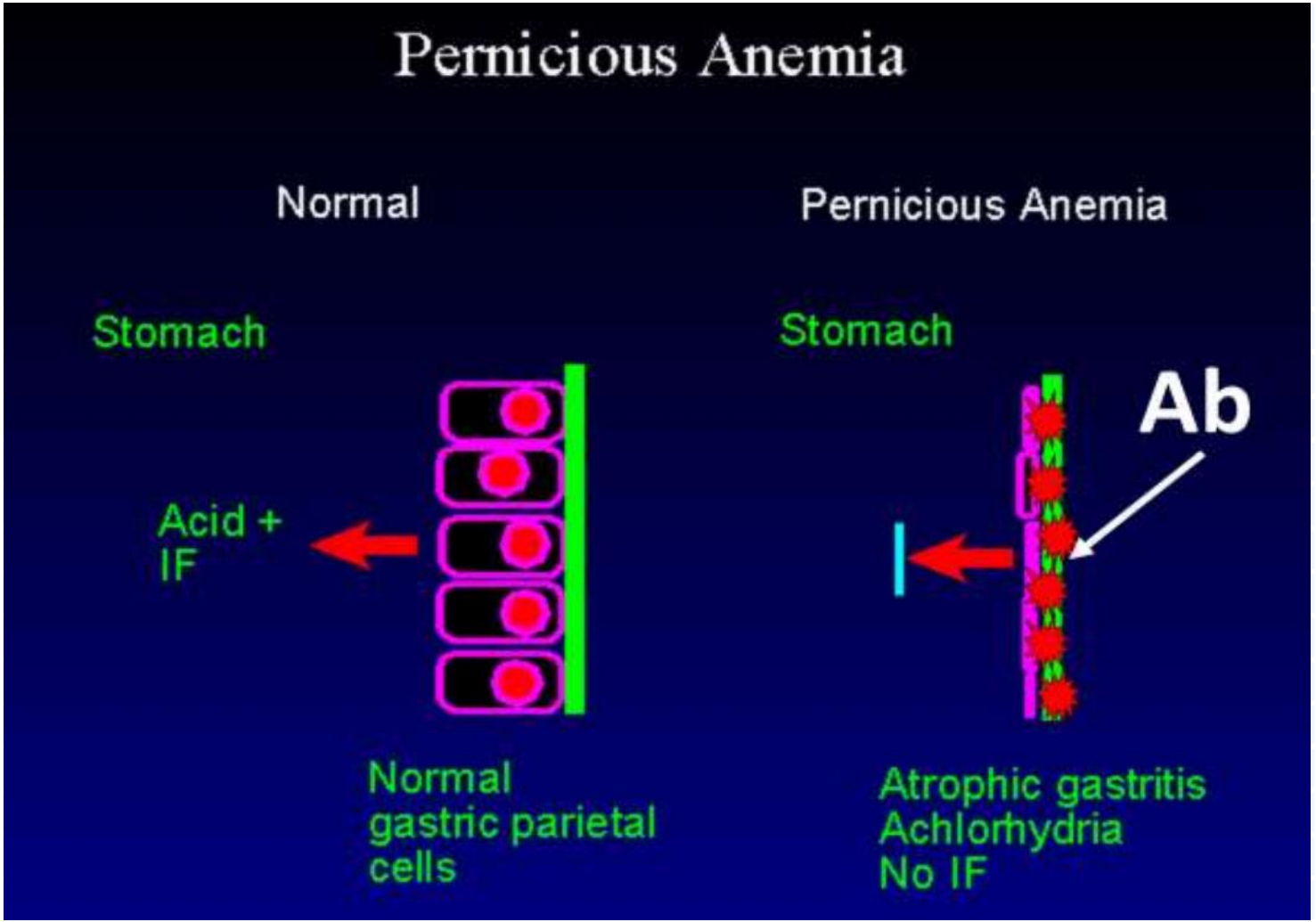
1. **Macrocytic Anemia (Megaloblastic Anemia) :**

In this type of anemia, the size of RBCs is larger than normal. It is caused by Vitamin B12 or folic acid deficiency.

1. **Normocytic Normochromic Anemia :**

In this type of anemia, the size of RBCs and their Hb content are normal, but their number is decreased.

Pernicious Anemia



Anemia

Causes of Normocytic Normochromic Anemia :

- **Acute Blood Loss (Hemorrhagic Anemia):** In sudden and rapid hemorrhage, the body replaces plasma within 1-3 days, but bone marrow cannot replace RBCs that quickly. Therefore, RBCs become diluted in plasma. RBCs count returns to normal within 3-4 weeks.
- **Bone Marrow Depression (Aplastic Anemia):** Depression of the bone marrow will decrease all blood elements (RBCs, WBCs, and platelets). It may be due to exposure to X-rays and atomic irradiation, malignancy or viral infection and drugs.
- **Excessive Breakdown of RBCs (Hemolytic Anemia):** may be due to intrinsic or extrinsic factors.
  - Intrinsic factors: as in sickle cell anemia and G6PD deficiency.
  - Extrinsic factors: as in:
    a. Infections, e.g., streptococci and malaria
    b. Chemical poisons, e.g., benzene derivatives
    c. Incompatible blood transfusion
    d. Snake venom.

Hemolysis

Intrinsic Disorders

- Hereditary Spherocytosis
- G-6-PD Enzyme
- Sickle Cell Anemia

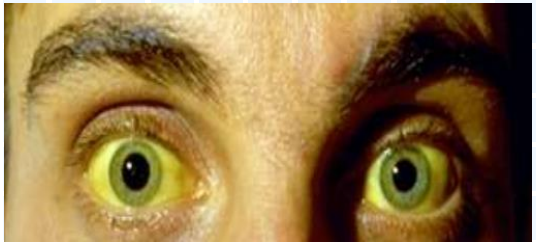
Extrinsic Disorders

- Erythroblastosis Fetalis
- Infections
- Snake Venom
- Poisons

C/P

Jaundice

++ Reticulocyte count



Anemia

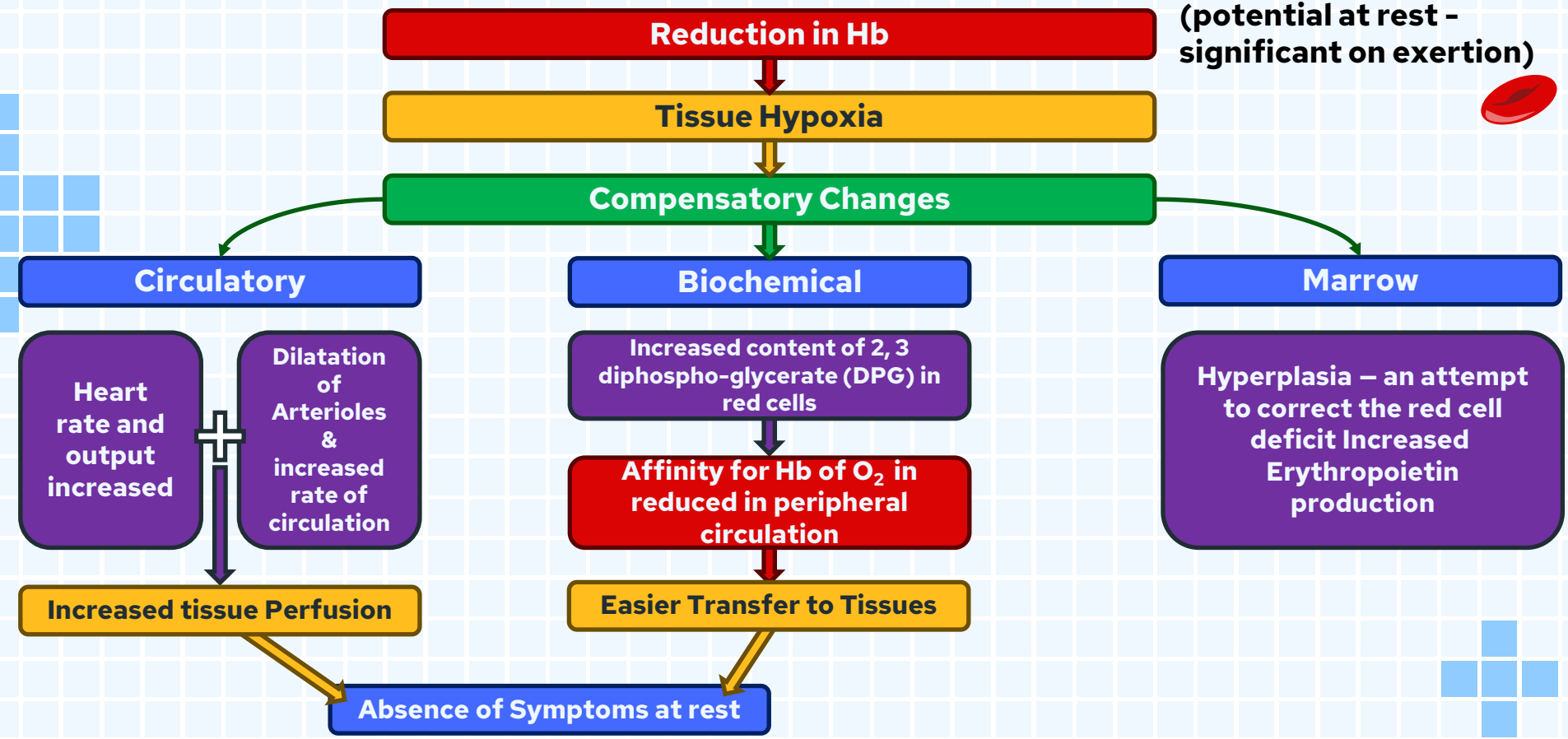
Conditions Associated with an (increase) in Reticulocytes :

- **Hemolytic Anemias:** Immune hemolytic anemia, RBC membrane defects, Sickle cell diseases.
- **Following Hemorrhage**
- **Following treatment of Anemias**

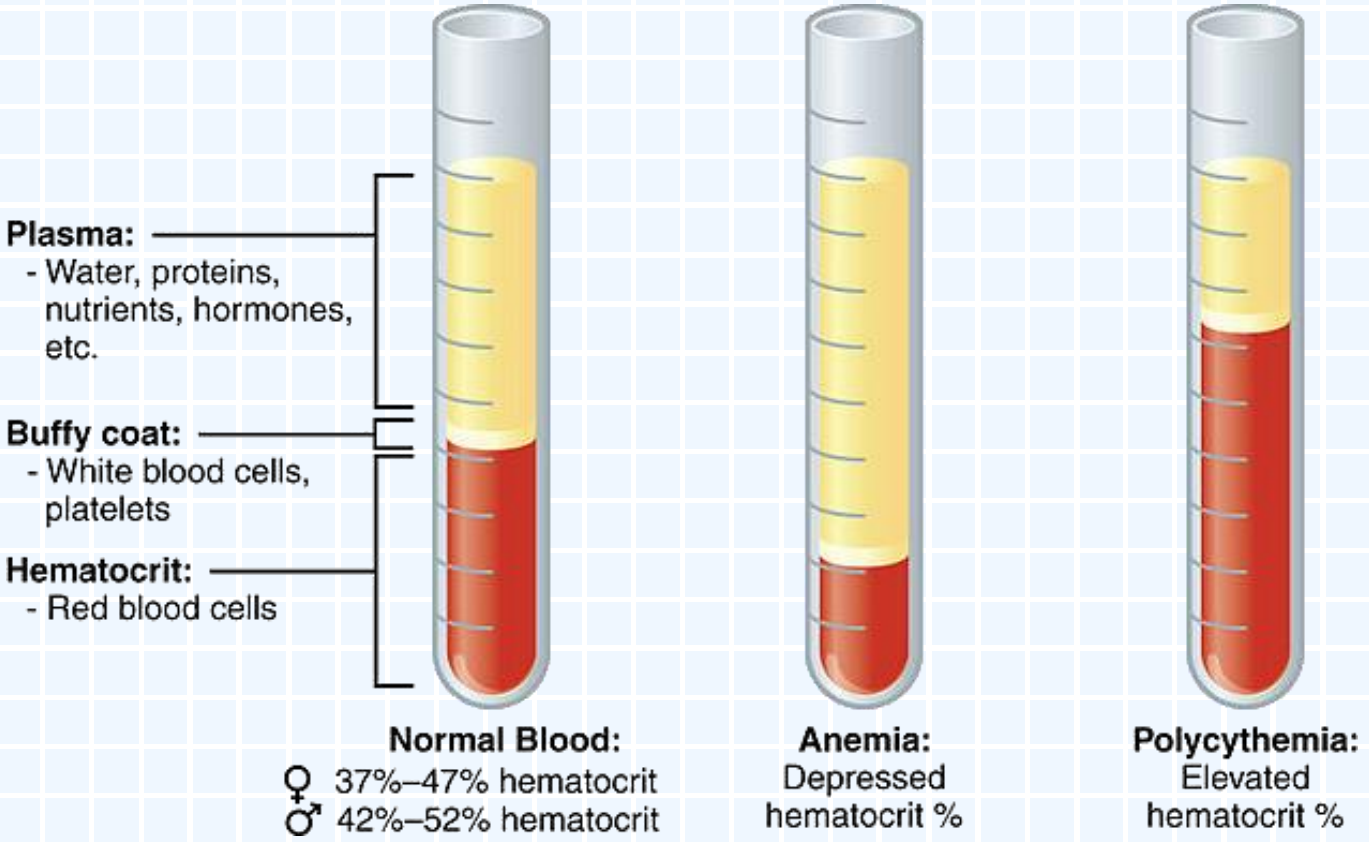
Conditions Associated with a (decrease) in Reticulocytes :

- Iron deficiency Anemia
- Aplastic Anemia

Effect of Anemia



Polycythemia



Polycythemia

It represents an increase in the number of red cells.

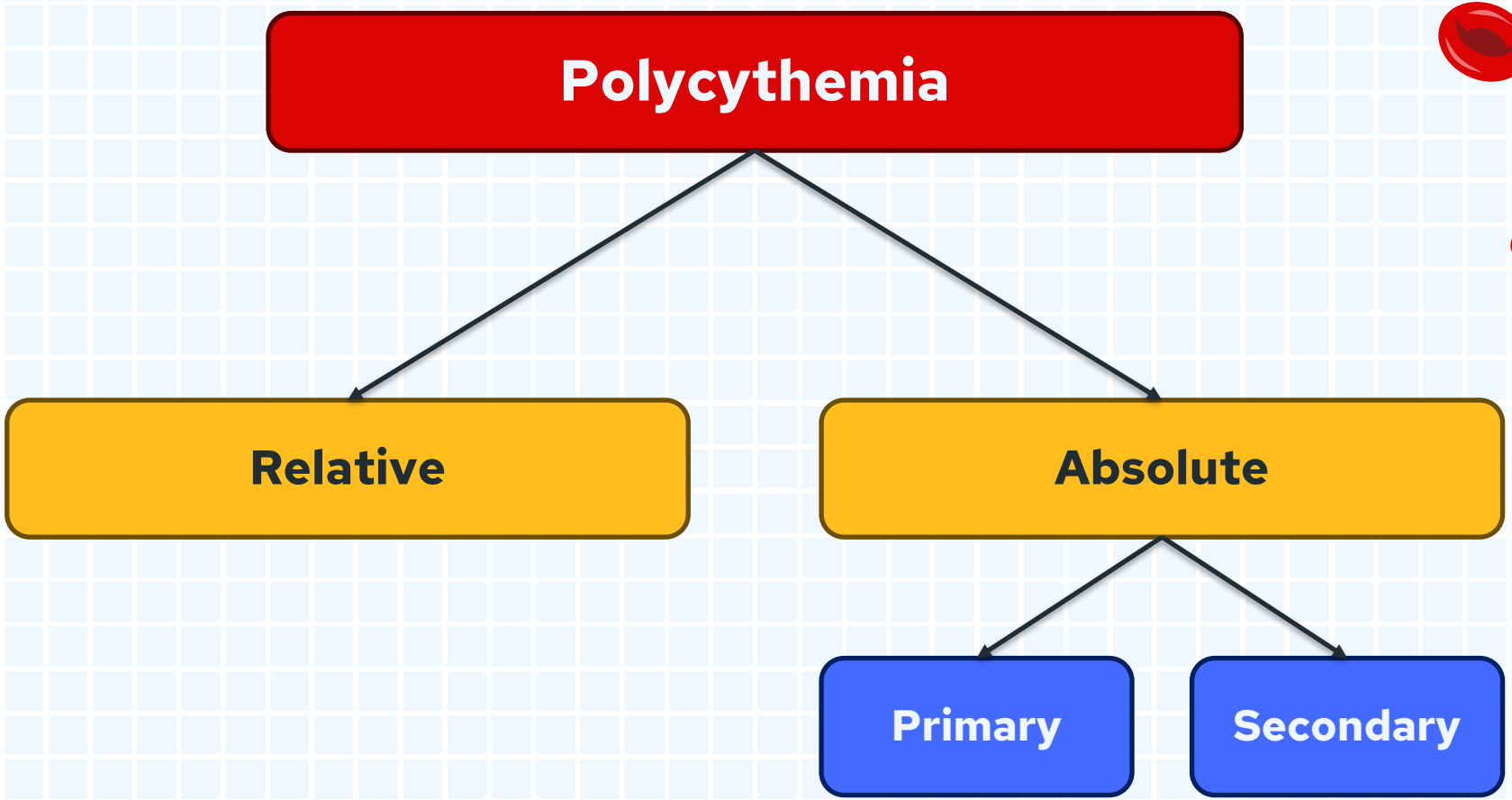
It exists in two main forms :

A-Absolute Polycythemia:

1. The primary form, also called polycythemia vera, is a clonal neoplastic disorder of hematopoietic stem cells.
2. The secondary forms are conditions of increased red cell production that usually occur due to increased erythropoietin secretion. In the primary form, the cause of the disease is the abnormality of hemopoietic stem cells characterized by uncontrolled proliferation of cells of erythroid, granulocytic, and megakaryocytic series, increasing all forms of formed elements of blood. In secondary forms, the cause of the disease is excess erythropoietin secretion that increases red cell production (mostly without an increase in granulocytes and platelets).

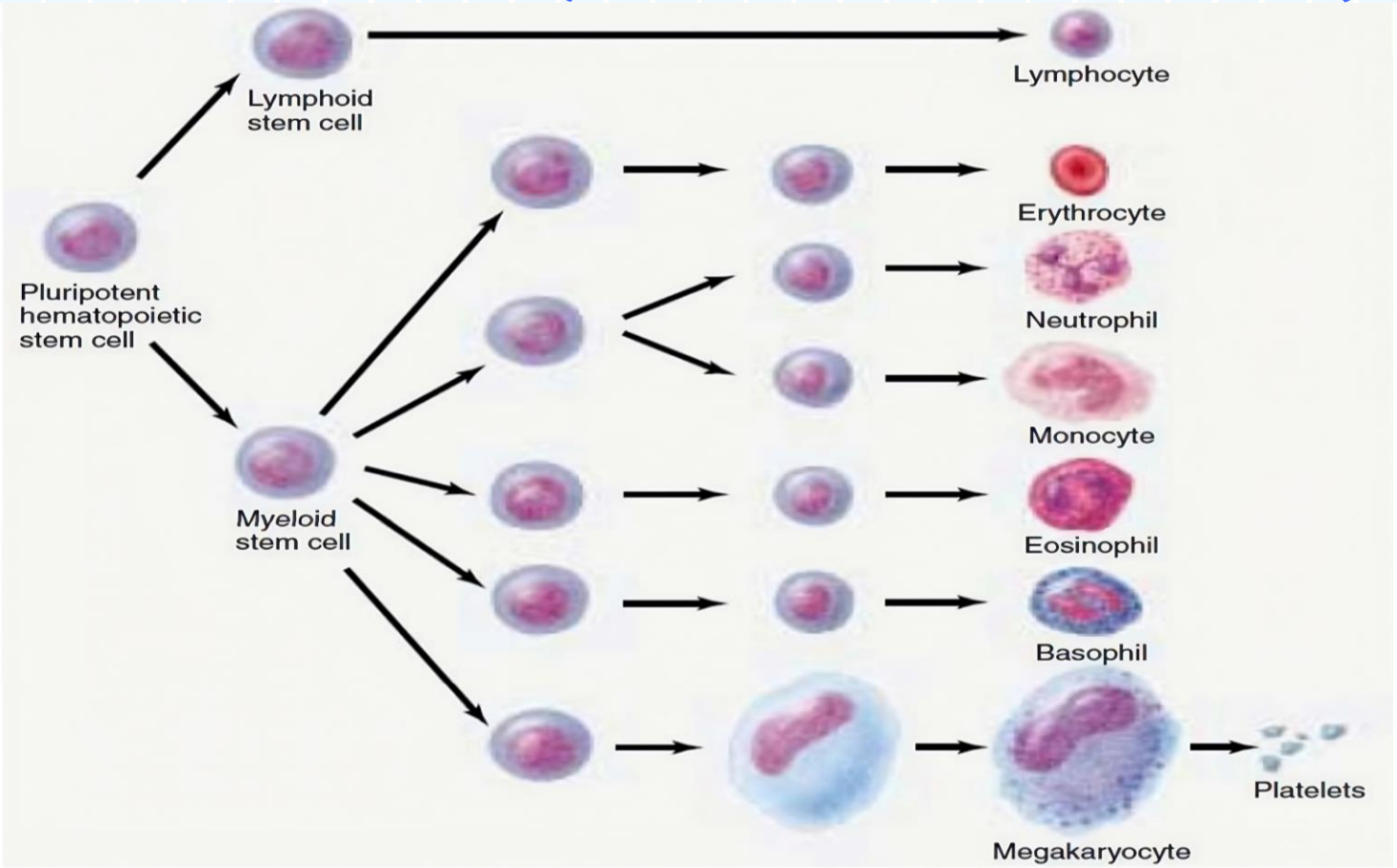
B-Relative Polycythemia:

The relative or apparent polycythemia is not true polycythemia but a spurious increase in red cells due to dehydration.


Polycythemia
Relative
Absolute
Primary
Secondary

Hemostasis and Blood Coagulation

PLATELETS (THROMBOCYTES)



PLATELETS (THROMBOCYTES)

- Platelets are small, non-nucleated, granulated bodies.
- The normal platelet count is 300,000/mm^3. Decreased platelet number is called **Thrombocytopenia.**
- The diameter of platelets is about 2-4 µm.

Formation of Platelets :

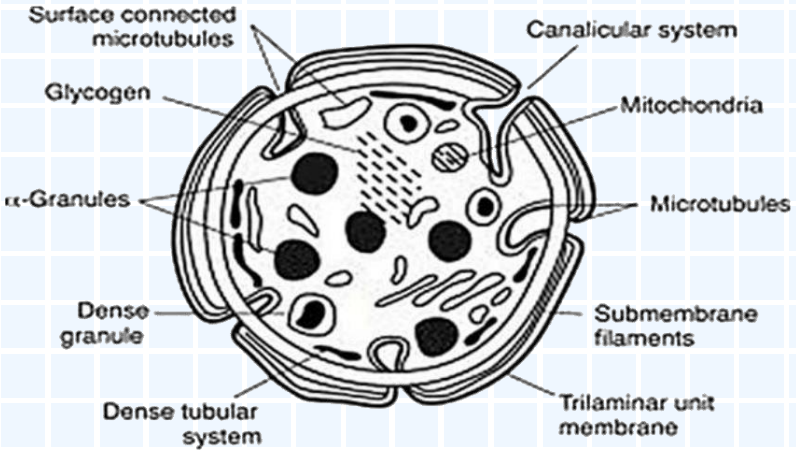
Platelets are formed in the bone marrow from megakaryocytes.

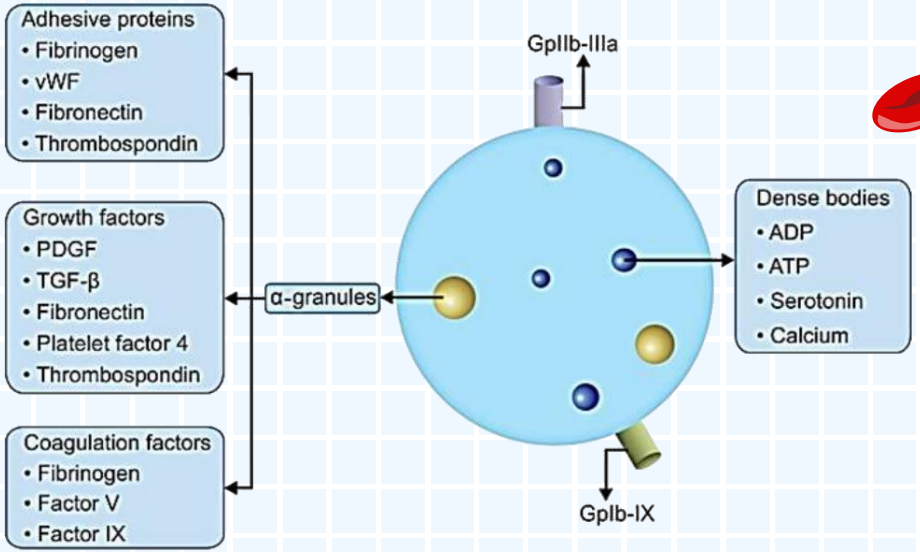
Structure of Platelets :

A. Platelet Membrane:

- It contains receptors for Collagen, von Willebrand factor, and fibrinogen.
- It has a glycoprotein coat containing phospholipids, which form:
  - Platelet Factor 3 (PF3) (helps blood clotting)
  - Platelet-Activating Factor (PAF) (activates phospholipase C).
- The membrane invaginates to form an open canalicular system, i.e., a large surface area for the uptake of extracellular calcium and release of intracellular materials.

PLATELETS (THROMBOCYTES)





PLATELETS (THROMBOCYTES)

Structure of Platelets :

B. Platelet Cytoplasm:

The cytoplasm contains many active substances:

1. **Beneath the membrane:**
   a. **A Skeleton of Microtubules**, which maintain the shape of platelets.
   b. **Contractile Proteins : Actin, Myosin and Thrombosthenin**, which allow platelets to contract and change their shape.

2. **Intracellular organelles:**
   Remnants of Golgi apparatus and Endoplasmic Reticulum Mitochondria for the synthesis of ATP and ADP, Lysosome **containing Hydrolytic Enzymes.**

3. **Glycogen granules:**
   For **Energy production.**

PLATELETS (THROMBOCYTES)

Structure of Platelets :

B. Platelet Cytoplasm:

The cytoplasm contains many active substances:

4. **Enzymes for the synthesis of prostaglandins from phospholipids of platelet membrane.**

   Prostaglandins are local factors that mediate vascular and local tissue reactions.

5. **Two types of granules:**

   a. Dense granules: they contain non-protein substances (ADP, serotonin, calcium)

   b. Alpha granules: they contain proteins (Some clotting factors, platelet-derived growth factor (PDGF) that helps growth of endothelium i.e., wound healing)

PLATELETS (THROMBOCYTES)

HEMOSTASIS

It means Stoppage of Bleeding from an injured Blood Vessel.

The Hemostatic process consists of the following:

A. **Vasoconstriction of injured blood vessel**
B. **Temporary Platelets Plug formation by platelet reactions.**
C. **Fibrin Blood Clot Formation to stabilize the temporary platelet plug.**
D. **Limitation reaction to Dissolve Clot after wound healing.**

PLATELETS (THROMBOCYTES)

HEMOSTASIS

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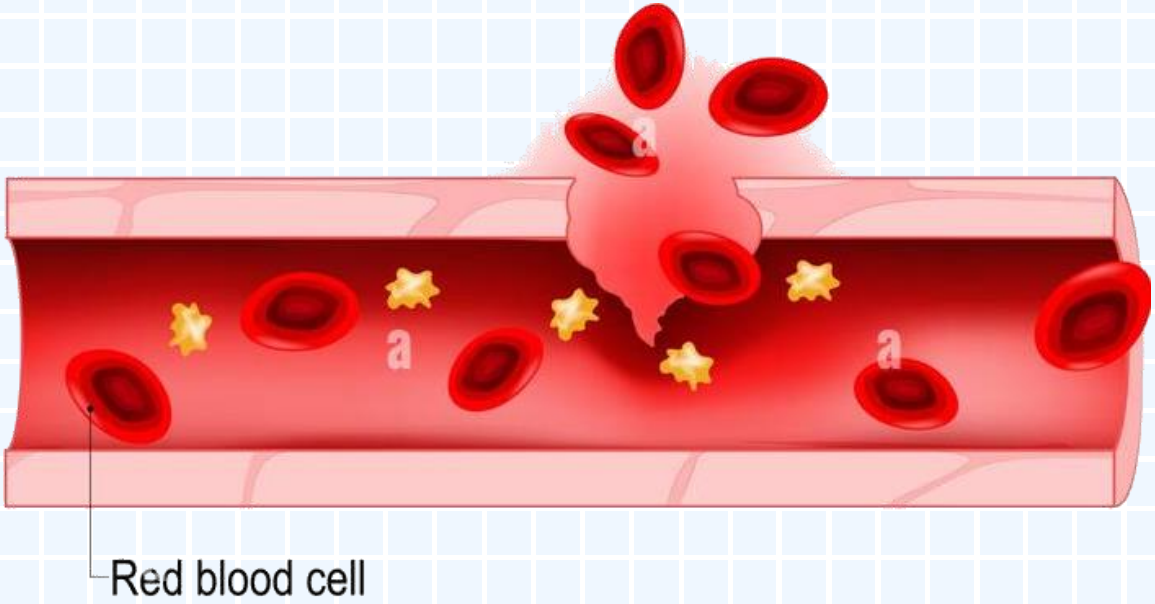

PLATELETS (THROMBOCYTES)

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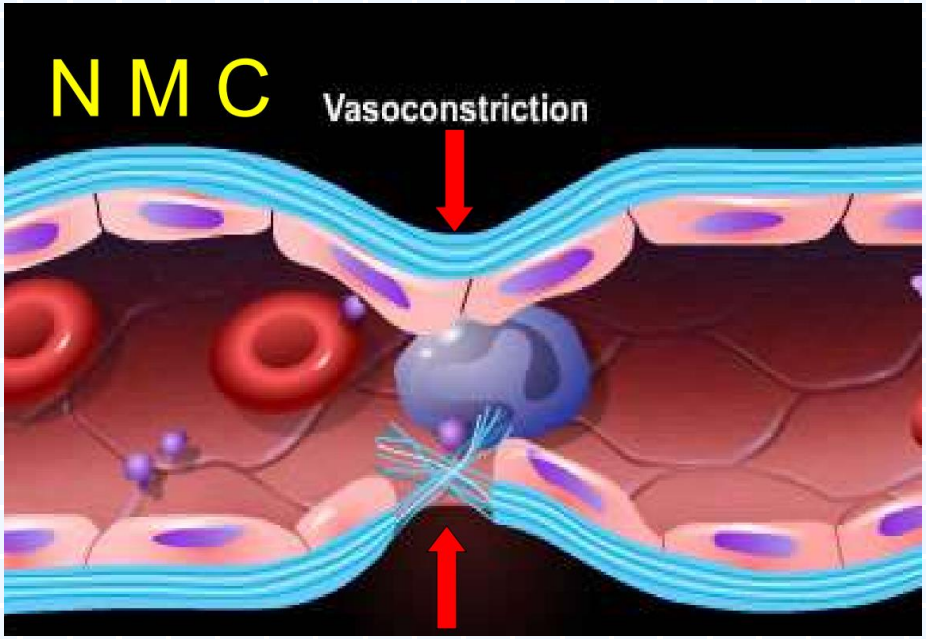


PLATELETS (THROMBOCYTES)

I. Local Vasoconstriction:

Injury to the blood vessel is immediately followed by its constriction. **This reduces the blood flow from the vessel and allows platelets to adhere at the site.** The vasoconstriction may be so strong that it completely obliterates the lumen of the injured vessel.

Vasoconstriction is due to the following:

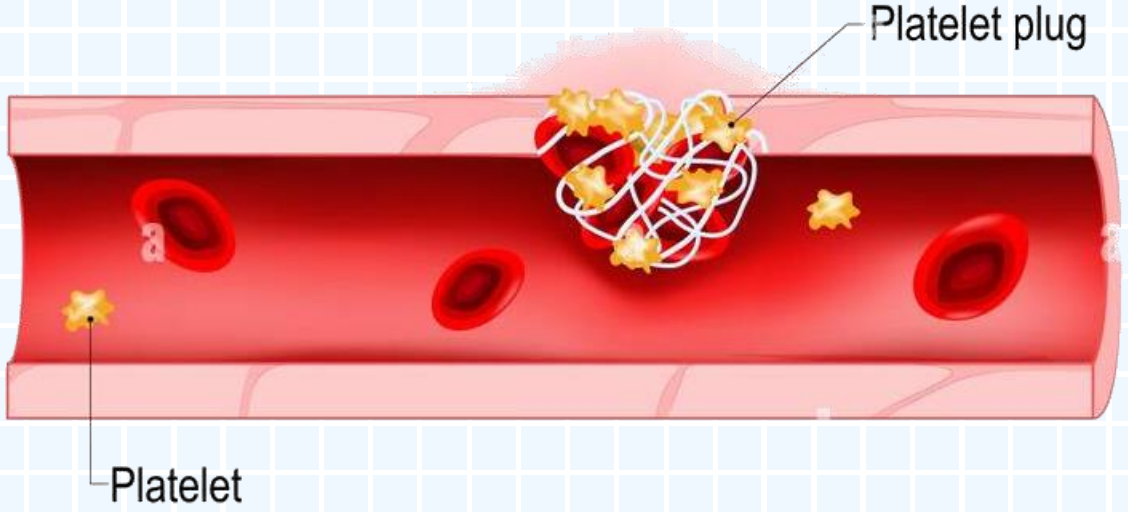
1. **Nervous Reflexes:** initiated by pain sensation from the traumatized vessel.
2. **Local Myogenic Contraction:** due to direct damage of the blood vessels. The degree of myogenic contraction is proportional to the amount of damage, i.e., a longitudinal cut in a vessel causes less spasm than a transverse cut.
3. **Chemical Substances:** Serotonin and Thromboxane A2 liberated from platelets cause vasoconstriction

PLATELETS (THROMBOCYTES)

HEMOSTASIS

The Hemostatic process consists of the following:

B. Temporary Platelets Plug formation by platelet reactions.



PLATELETS (THROMBOCYTES)

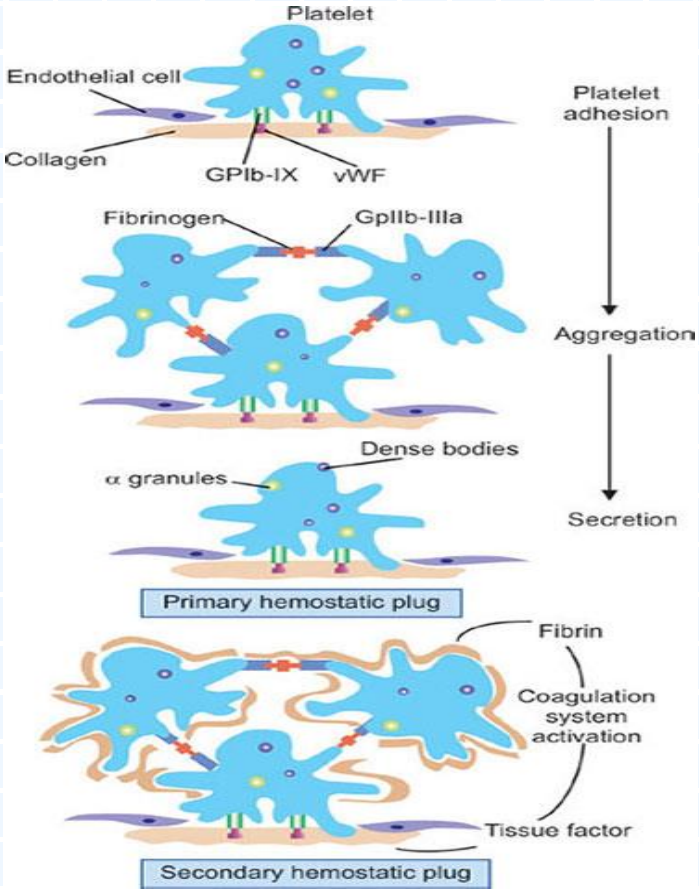
II. Formation of Temporary Platelet Plug: (Platelets reactions)

When a blood vessel is injured, platelets form a mechanical plug to seal the injury site. The platelet plug can stop blood loss if the injury is small.

The Platelet reactions in Hemostasis include:

1. **Platelet Adhesion:**
2. **Platelet Activation:**
3. **Release Reaction:**
4. **Platelet Aggregation:**
5. **Platelet Procoagulant Activity:**
6. **Platelet Fusion:**

PLATELETS (THROMBOCYTES)



PLATELETS (THROMBOCYTES)

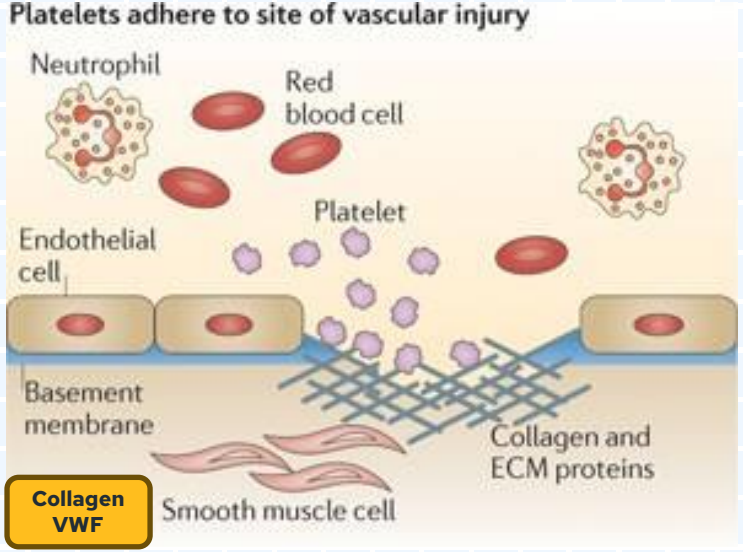
II. Formation of Temporary Platelet Plug: (Platelets reactions)

The Platelet Reactions in Hemostasis include:

1. **Platelet Plug : Adhesion :**

   Normally, Platelets Do Not adhere to healthy blood vessels. However, When a blood vessel is cut, Subendothelial Collagen and Von Willebrand factor are exposed, and platelets adhere to them by their membrane receptors.

Why Platelets adhere only to injured Endothelial?

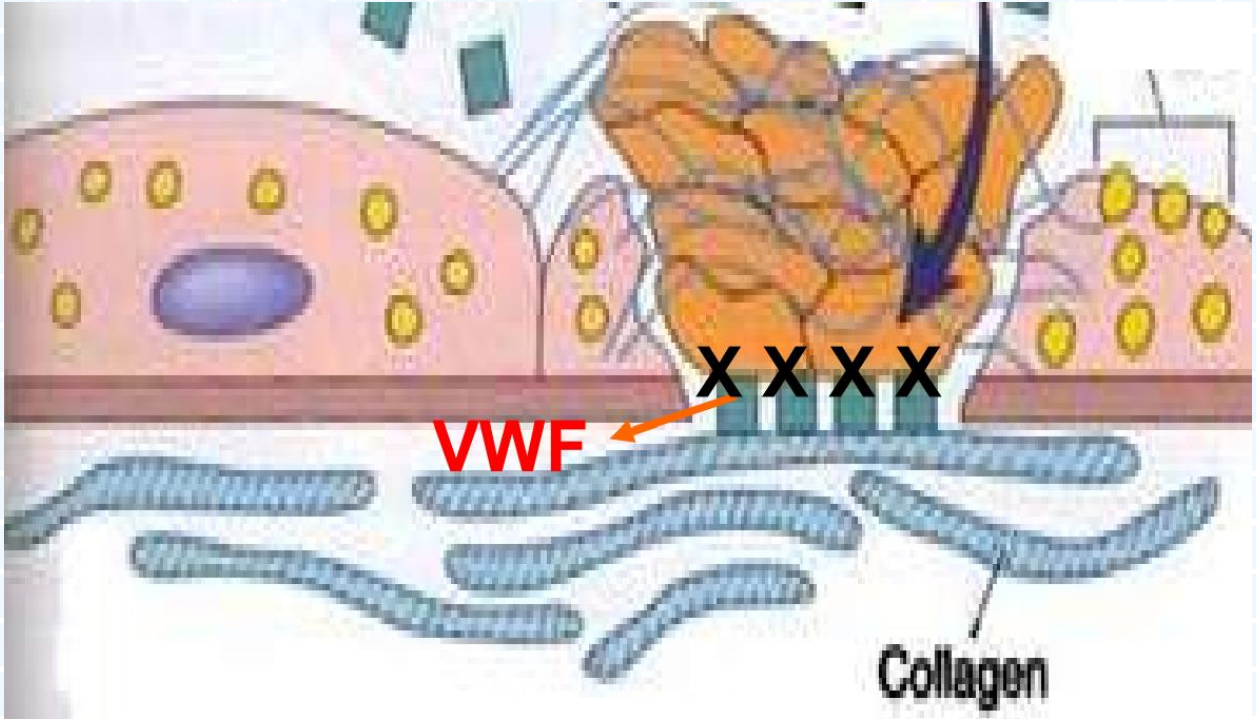


PLATELETS (THROMBOCYTES)

II. Formation of Temporary Platelet Plug: (Platelets reactions)

The Platelet Reactions in Hemostasis include:

1. **Platelet Plug : Adhesion :**



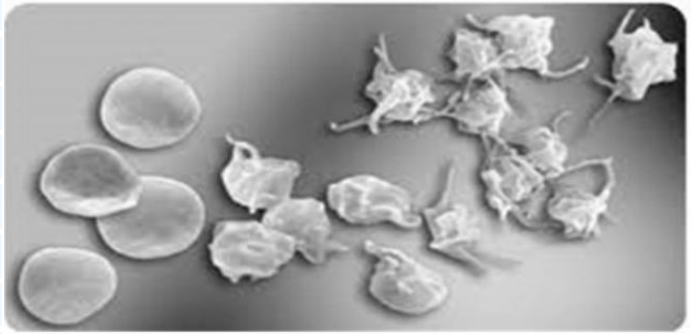
PLATELETS (THROMBOCYTES)

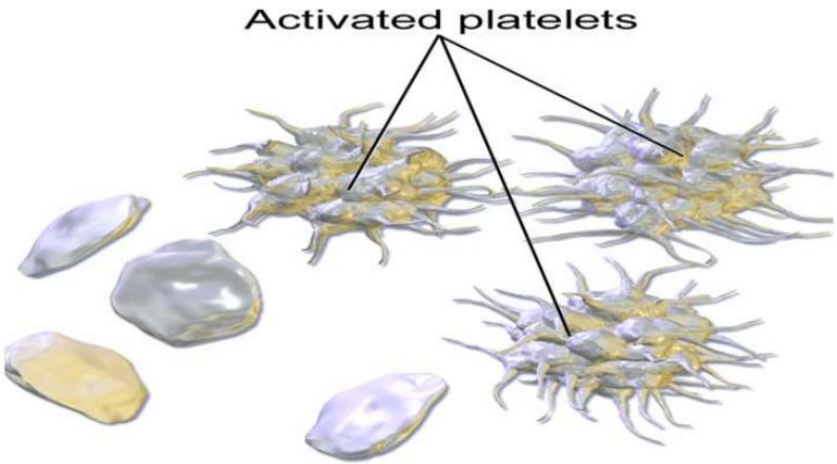
II. Formation of Temporary Platelet Plug: (Platelets reactions)

The Platelet reactions in Hemostasis include:

2. Platelet Plug : Activation :

The adhesion of platelets to Collagen and VWF activates the platelets: they swell, change their shape, put out pseudopodia, stick to other platelets, and their contractile proteins contract forcefully, causing the release of the platelet granules.





PLATELETS (THROMBOCYTES)

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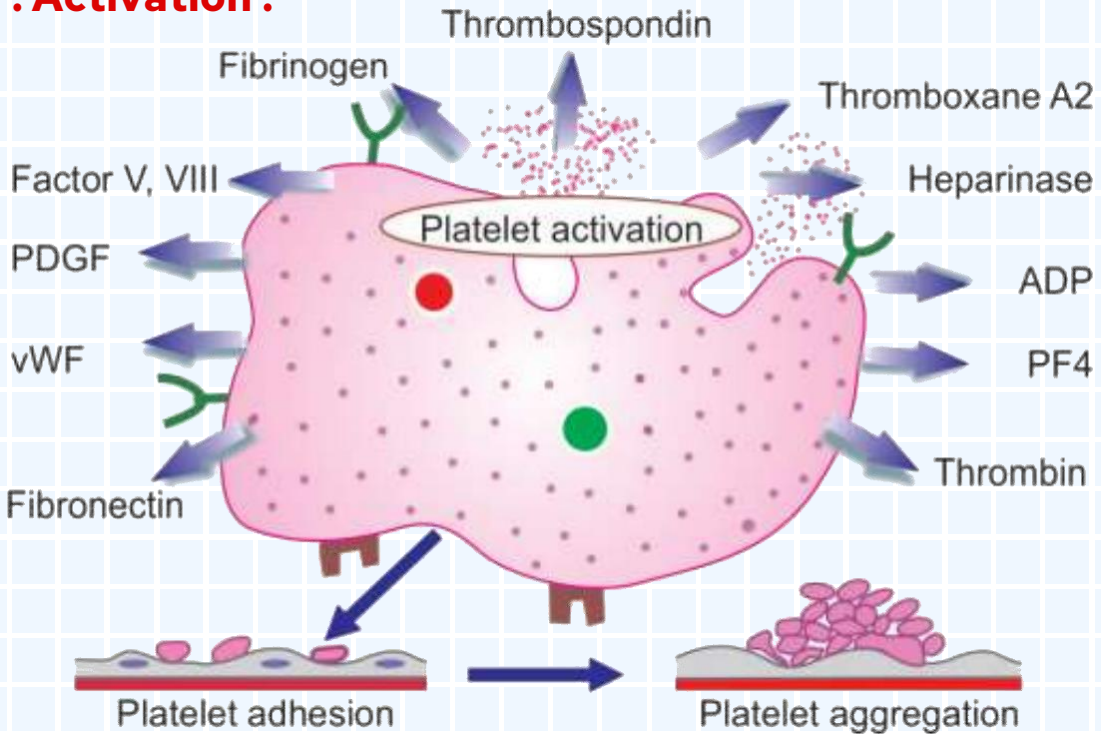
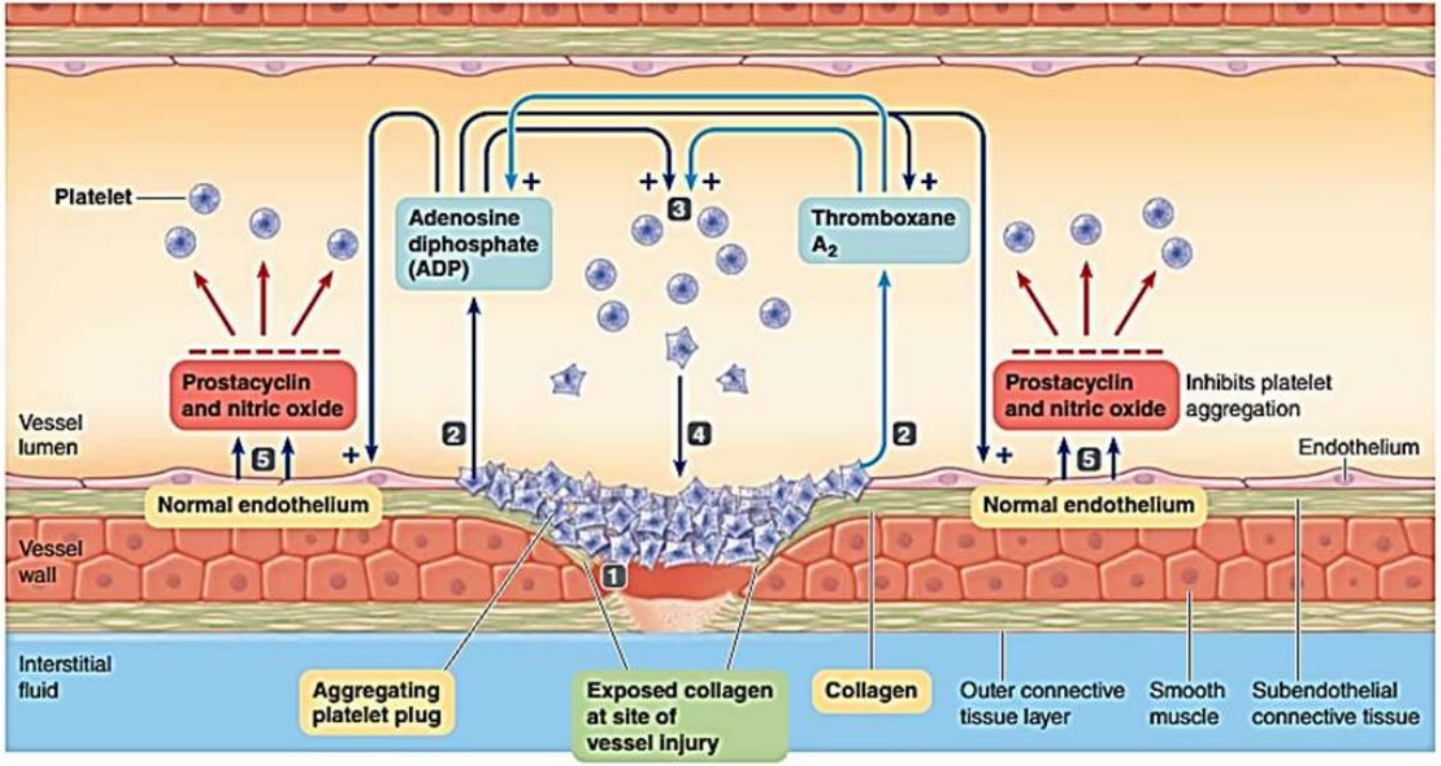
The Platelet reactions in Hemostasis include:

2. Platelet Plug : Activation :





1 Platelets adhere to and are activated by exposed collagen at the site of vessel injury.

2 Activated platelets release ADP and thromboxane A_2.

3 These chemical messengers work together to activate other platelets passing by.

4 Newly activated platelets aggregate onto growing platelet plug and release even more platelet-attracting chemicals.

5 Normal (uninjured) endothelium releases prostacyclin and nitric oxide, which inhibit platelet aggregation, so platelet plug is confined to site of injury.

› **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.

PLATELETS (THROMBOCYTES)

II. Formation of Temporary Platelet Plug: (Platelets reactions)

The Platelet Reactions in Hemostasis include:

3. Release Reaction :

When the contents of Dense and α granules are released, they go into action:

- **Platelet-derived growth factor (PDGF) stimulates the growth of the endothelial lining of blood vessels, helping their repair.**
- **Platelet-activating factor (PAF) is produced from membrane phospholipids of platelets. It activates a chain of reactions that ultimately lead to the formation of arachidonic acid from membrane phospholipids. Arachidonic acid is then converted by cyclooxygenase to prostaglandin. In platelets, the enzyme thromboxane A2 synthase converts prostaglandin to thromboxane A2, which causes vasoconstriction, and helps the release reaction and platelet aggregation.**

Simultaneously, in the walls of healthy blood vessels, the Enzyme Prostacyclin Synthase acts on prostaglandins, resulting in prostacyclin formation.
Prostacyclin is a powerful Vasodilator that inhibits platelet aggregation and release reaction. As its actions are opposite to those of Thromboxane A2, prostacyclin keeps the platelet plug localized to the injury site.

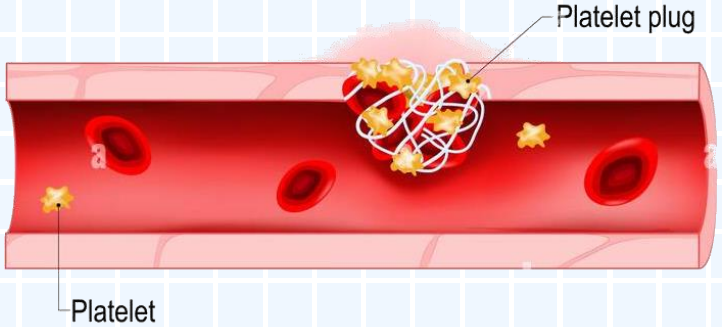
PLATELETS (THROMBOCYTES)

II. Formation of Temporary Platelet Plug: (Platelets reactions)

The Platelet Reactions in Hemostasis include:

4. Platelet Aggregation :

Released ADP and Thromboxane A2 cause platelet aggregation at the injury site. Platelet aggregation activates more and more platelets, leading to more release reactions and liberating more ADP and Thromboxane A2. This self-propagating process forms a platelet plug that closes the blood vessel.



PLATELETS (THROMBOCYTES)

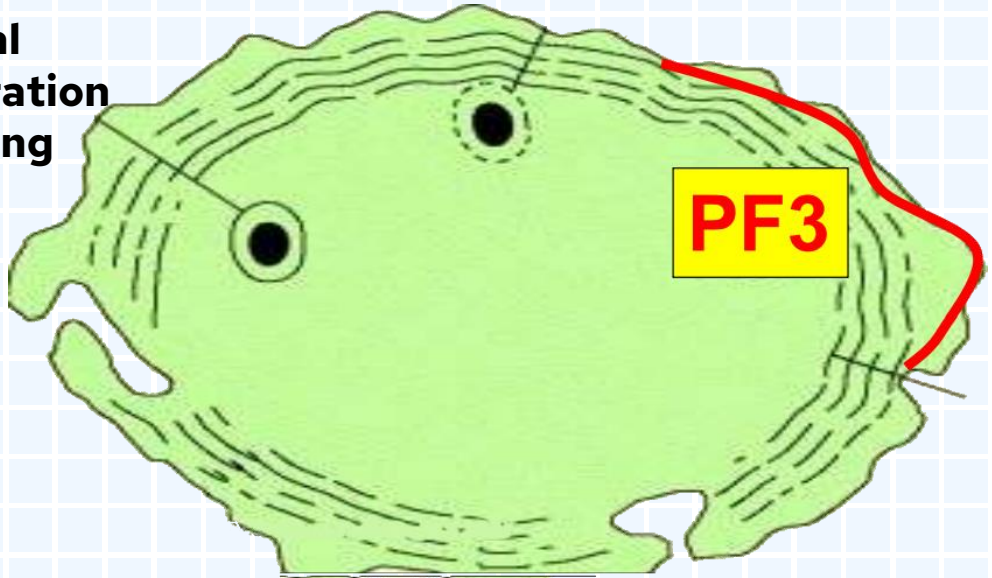
II. Formation of Temporary Platelet Plug: (Platelets reactions)

The Platelet Reactions in Hemostasis include:

5. Platelet Procoagulant activity (Proclotting) :

Platelet release and aggregation result in the exposure of **Platelet Factor 3** (PF3) on the platelet membrane. PF3 helps to start blood coagulation by activating some clotting factors.

PF3 provides an ideal surface for concentration & activation of clotting factor.



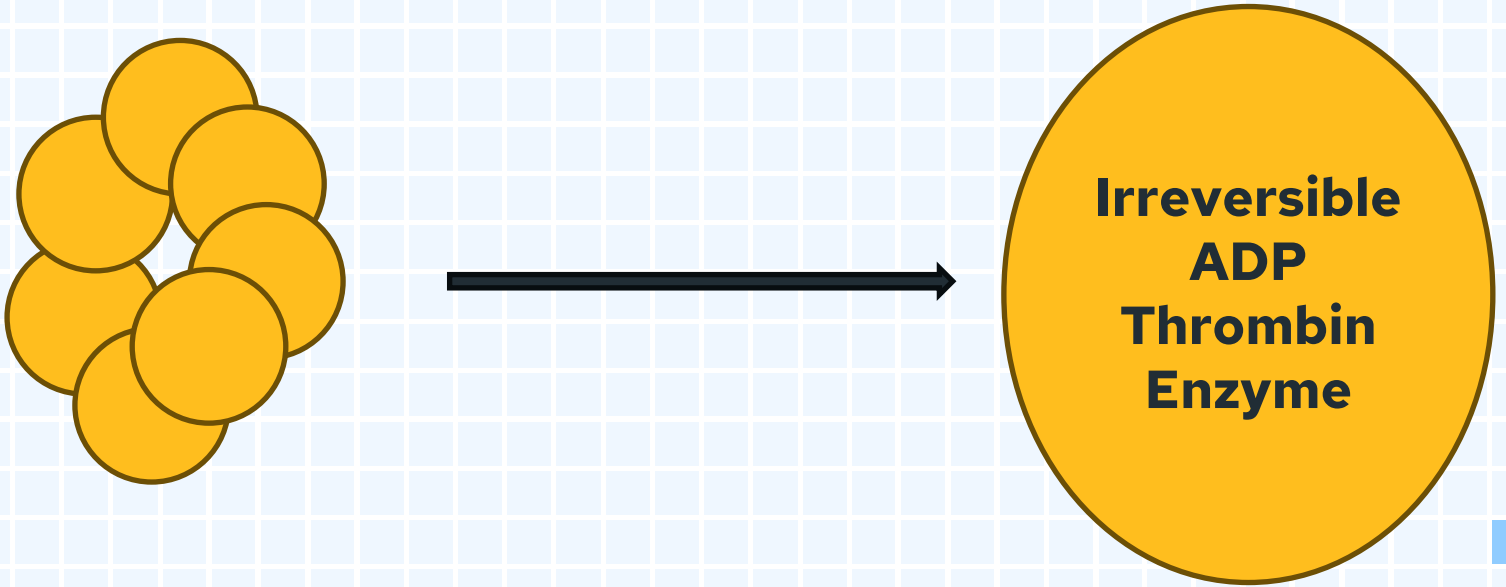
PLATELETS (THROMBOCYTES)

II. Formation of Temporary Platelet Plug: (Platelets reactions)

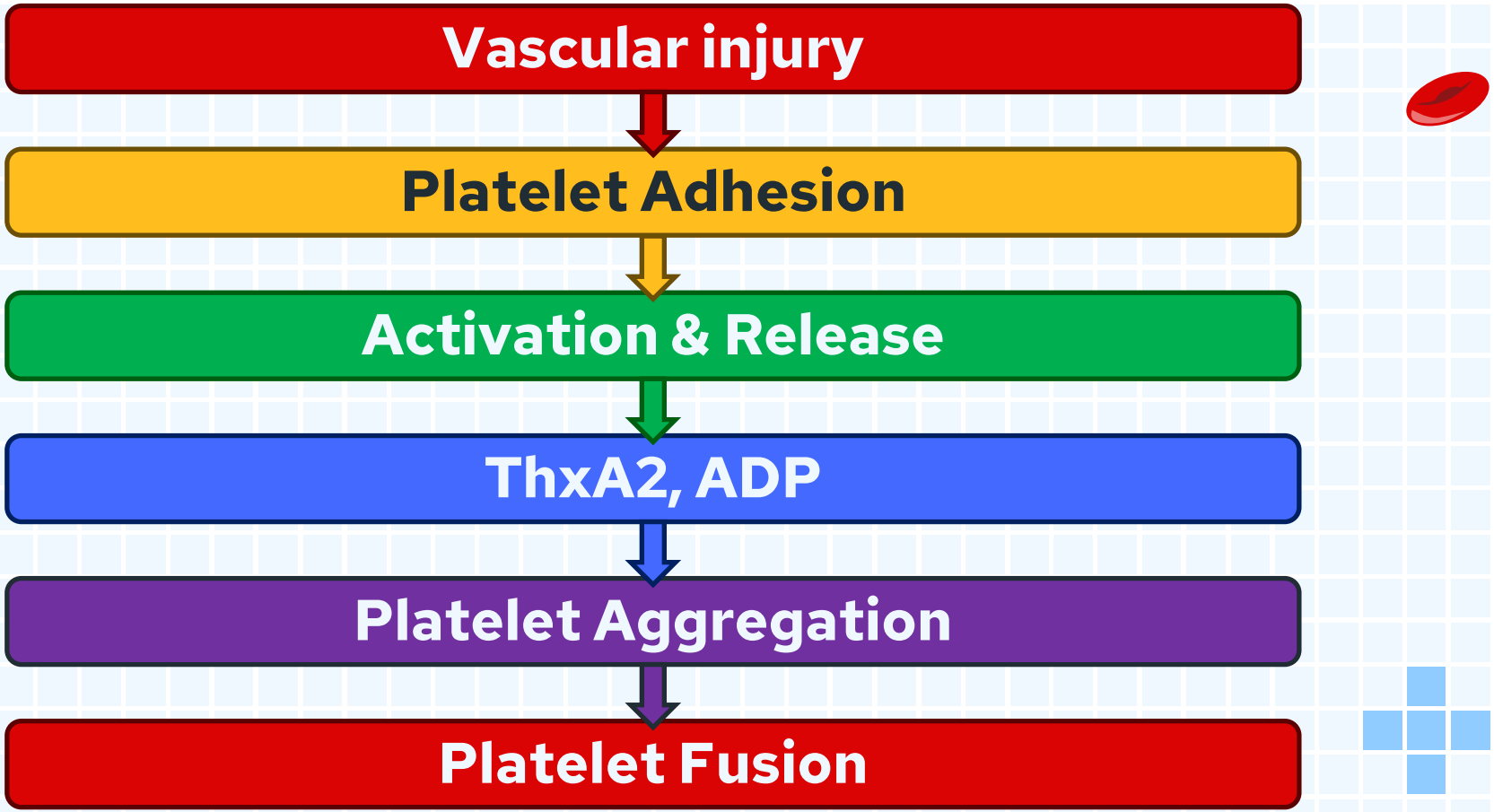
The Platelet Reactions in Hemostasis include:

6. Platelet Plug : Fusion :

Aggregated platelets undergo irreversible fusion. This is produced by the high concentration of ADP and platelet enzymes.



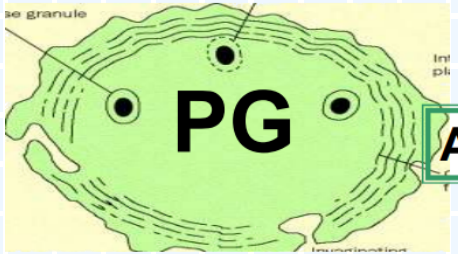
PLATELETS (THROMBOCYTES)



PLATELETS (THROMBOCYTES)

Membrane phospholipids

PLase



Arachidonic acid

Aspirin --

COX

PG

Thx A2

VC

++ Platelet release

++ aggregation

--cAMP

PC

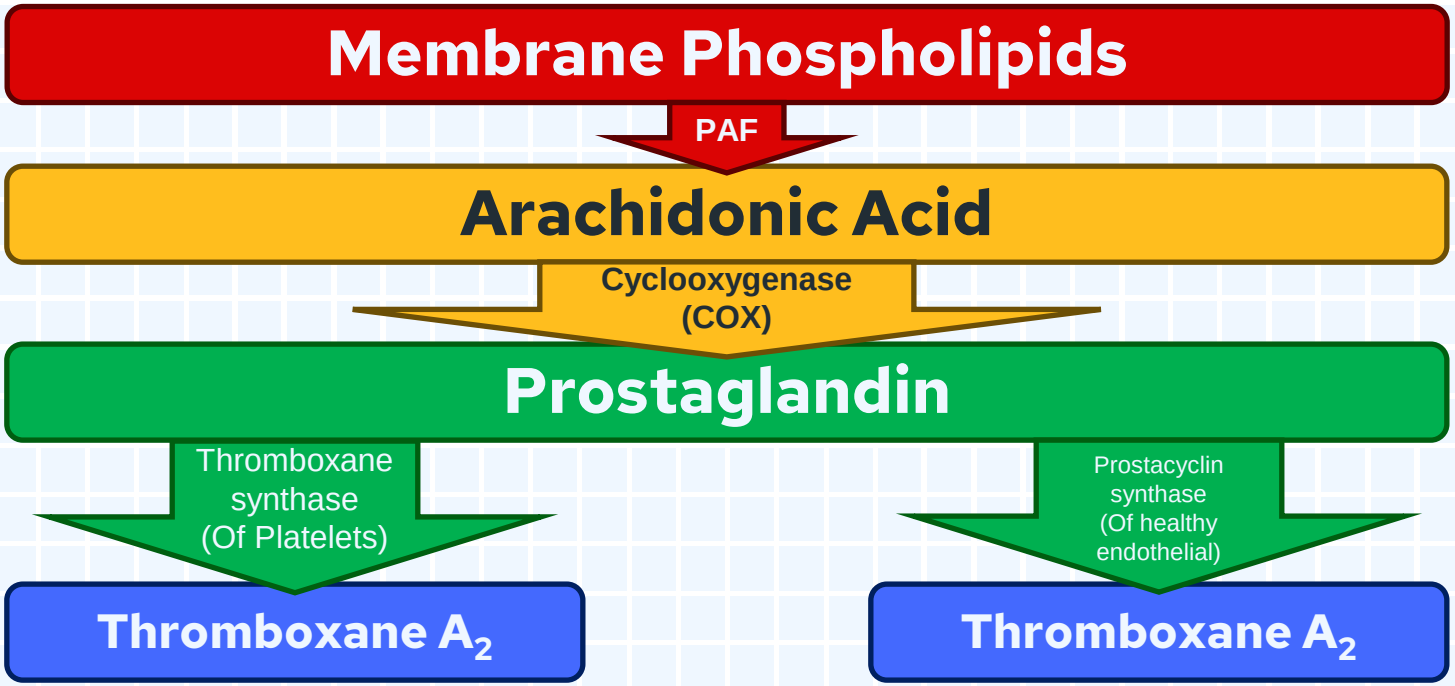
VD

↓ Platelet release

↓ aggregation

++ cAMP

PLATELETS (THROMBOCYTES)



1. Vasoconstriction
2. ↑ Platelet release
3. ↑ Platelet aggregation

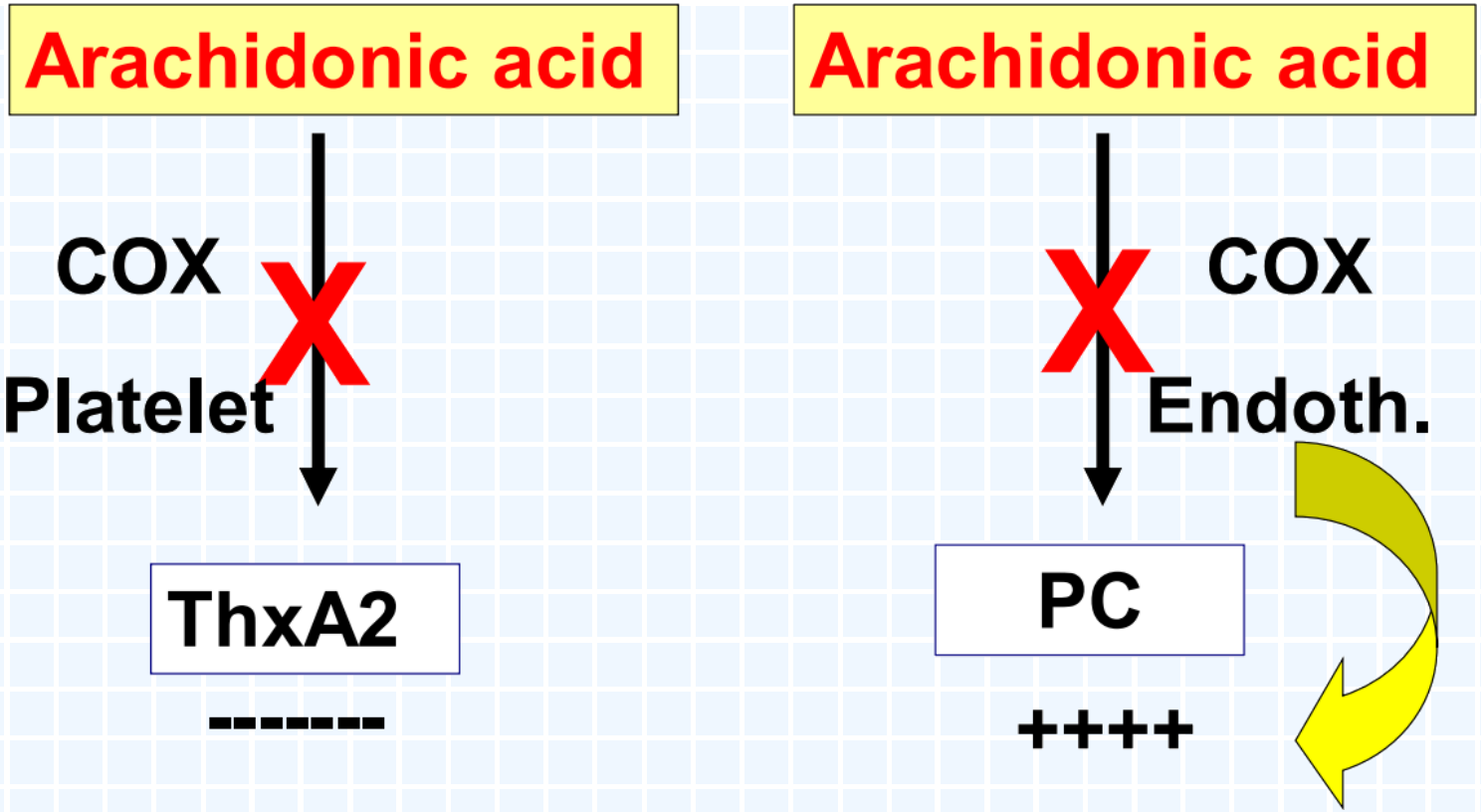
1. Vasodilatation
2. ↓ Platelet release
3. ↓ Platelet aggregation

Aspirin

Note:

- **Aspirin inhibits Cyclooxygenase (COX) ⟶ Decreases the synthesis of both Thromboxane A_2 and Prostacyclin. The**
- **Endothelial cells can start to produce new Cyclooxygenase (COX) within a few hours, while.**
- **Platelets cannot produce new Cyclooxygenase (COX).**
- **Therefore, The daily intake of Small amounts of Aspirin reduces clot formation and prevents Myocardial Infarctions.**

Aspirin


Arachidonic acid
COX
Platelet
ThxA2

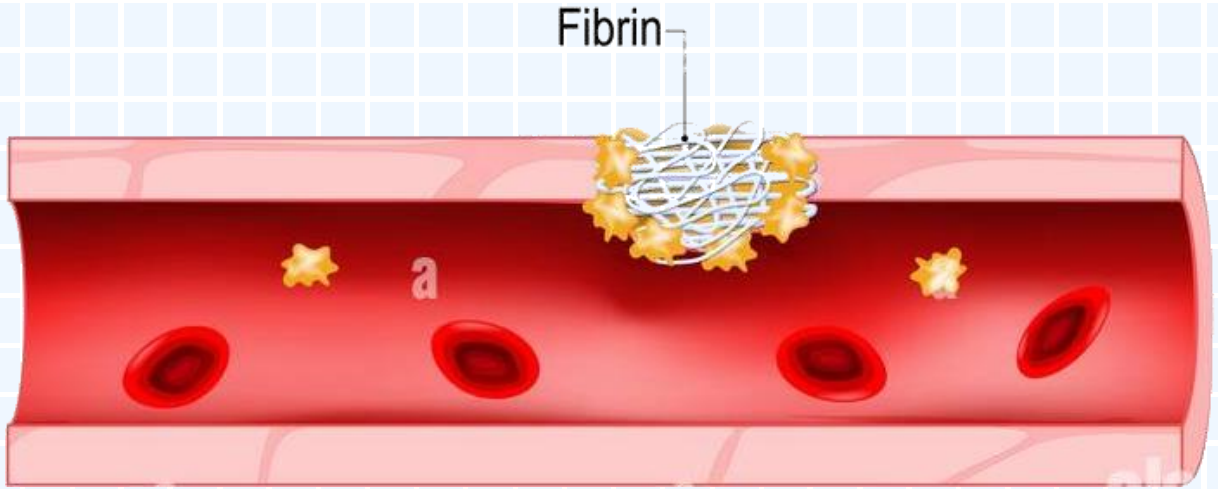
Arachidonic acid
COX
Endoth.
PC
++++

PLATELETS (THROMBOCYTES)

HEMOSTASIS

The Hemostatic process consists of the following:

C. Fibrin Blood Clot Formation to stabilize the temporary platelet plug.



PLATELETS (THROMBOCYTES)

HEMOSTASIS

The Hemostatic process consists of the following:

C. **Fibrin Blood Clot Formation** to stabilize the temporary platelet plug.

The Clotting factors are Plasma Proteins, mostly (β- globulins). They are Proteolytic Enzymes (Serine Protease), which are present in blood in an inactive form. When activated, they activate other inactive enzymes in cascade reactions, which end in clot formation.

PLATELETS (THROMBOCYTES)

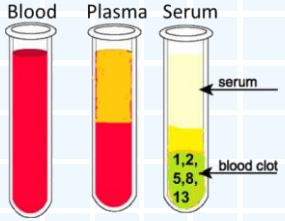
HEMOSTASIS

The Hemostatic process consists of the following:

C. Fibrin Blood Clot Formation to stabilize the temporary platelet plug.

Clotting Factors were given numbers to simplify the description of the clotting mechanisms. They are given an "a" when they are activated.

1. **Fibrinogen Group :**
   - **I , V, VIII & XIII (13 = 8+5 ,1) .**
   - **Activated by Thrombin.**
   - **Not present in Serum.**



2. **Prothrombin Group :**
   - **II, VII, IX & X (1972) .**
   - **Need Vitamin K for synthesis**
   - **Prothrombin is Not present in serum.**
3. **Contact Group :**
   - **XI and XII.**
   - **Present in serum**

PLATELETS (THROMBOCYTES)

HEMOSTASIS

The Hemostatic process consists of the following:

C. **Fibrin Blood Clot Formation** to stabilize the temporary platelet plug.

The Clotting Mechanism :

The loose platelet plug changes to a definitive blood clot by conversion of soluble fibrinogen to insoluble fibrin.

Fibrinogen forms loose fibrin which becomes a dense fibrin clot by forming cross-linkages. **This reaction is Catalyzed by factor XIII and Ca^{2+}**

Activated by Either Intrinsic or Extrinsic pathways.

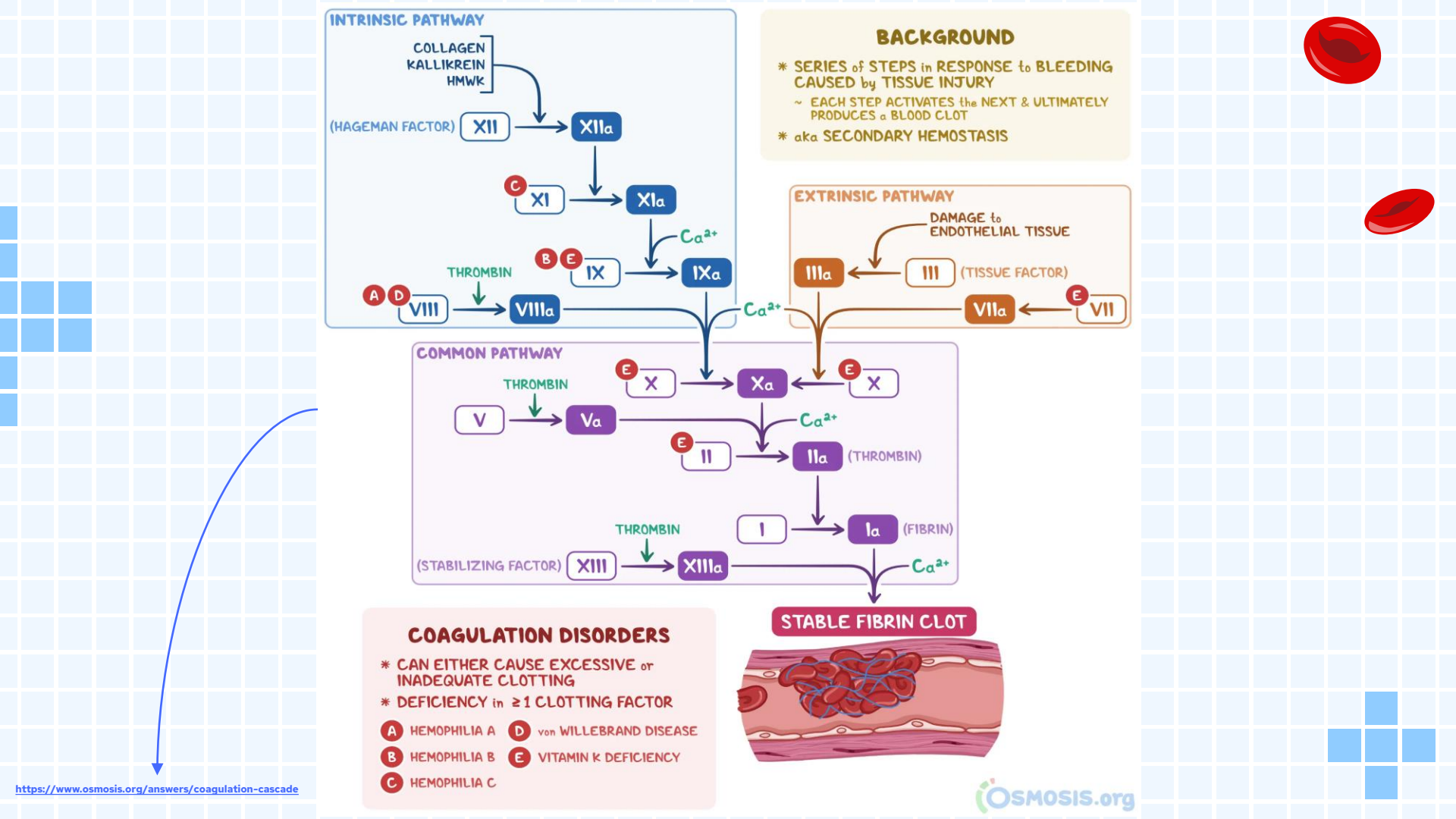
Prothrombin —(Xa)→ **Thrombin**

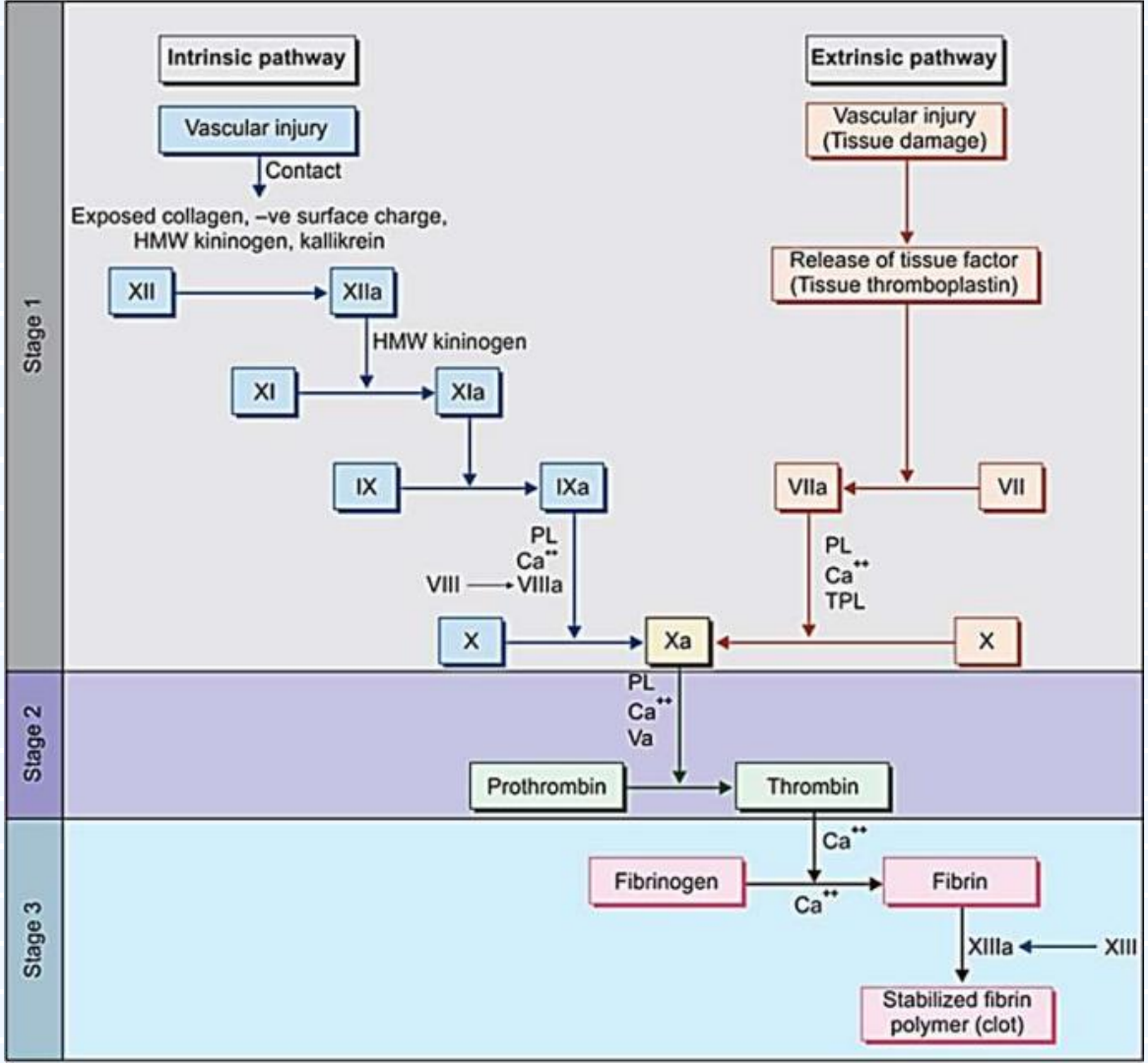
The Conversion of Fibrinogen to Fibrin is Catalyzed by Thrombin, which is formed from Prothrombin in the presence of Active factor X.

Fibrinogen → **Fibrin Monomer + 2 pairs of polypeptide chains**

Fibrin Monomers Polymerize → **Loose Mesh of Fibrin**

Loose Mesh of Fibrin —(Cross Linkage; XIII + Ca^{2+})→ **Thrombin**


INTRINSIC PATHWAY
COLLAGEN
KALLIKREIN
HMWK
(HAGEMAN FACTOR) XII
XIIa
C XI
XIa
Ca2+
B E IX
IXa
THROMBIN
A D VIII
VIIIa
Ca2+
EXTRINSIC PATHWAY
DAMAGE to ENDOTHELIAL TISSUE
IIIa
III (TISSUE FACTOR)
E VII
VIIa
COMMON PATHWAY
THROMBIN
E X
Xa
E X
V
Va
Ca2+
E II
IIa (THROMBIN)
I
Ia (FIBRIN)
THROMBIN
(STABILIZING FACTOR) XIII
XIIIa
Ca2+
BACKGROUND
* SERIES of STEPS in RESPONSE to BLEEDING CAUSED by TISSUE INJURY
~ EACH STEP ACTIVATES the NEXT & ULTIMATELY PRODUCES a BLOOD CLOT
* aka SECONDARY HEMOSTASIS
COAGULATION DISORDERS
* CAN EITHER CAUSE EXCESSIVE or INADEQUATE CLOTTING
* DEFICIENCY in ≥1 CLOTTING FACTOR
A HEMOPHILIA A
B HEMOPHILIA B
C HEMOPHILIA C
D von WILLEBRAND DISEASE
E VITAMIN K DEFICIENCY
STABLE FIBRIN CLOT
https://www.osmosis.org/answers/coagulation-cascade
OSMOSIS.org


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
Stage 1
PL
Ca++
Va
Prothrombin
Thrombin
Stage 2
Ca++
Fibrinogen
Ca++
Fibrin
XIIIa
XIII
Stabilized fibrin
polymer (clot)
Stage 3

PLATELETS (THROMBOCYTES)

HEMOSTASIS

The Hemostatic process consists of the following:

C. Fibrin Blood Clot Formation to stabilize the temporary platelet plug.

Factor X is Activated by Either Intrinsic or Extrinsic pathways.

A. Intrinsic Pathway :

This System is called Intrinsic, as the Phospholipids involved in the reactions arise from platelets (PF3), i.e., it is present in plasma.

Initiation of the pathway may occur either:

i. **In Vivo: by contact of blood with Subendothelial Collagen of the damaged vessel.**

ii. **In Vitro: by contact of blood with:**

- **Electronegative charged wet surfaces, e.g., a glass of a test tube.**
- **Collagen Fibers**

1. **Any of the previously mentioned factors activates factor XII.**
2. **XIIa activates factor XI, which in turn activates IX.**
3. **IXa forms a complex with VIIIa and activates factor X in the presence of phospholipids (PL) and Ca^{2+}**

PLATELETS (THROMBOCYTES)

Factor X is Activated by Either Intrinsic or Extrinsic pathways.

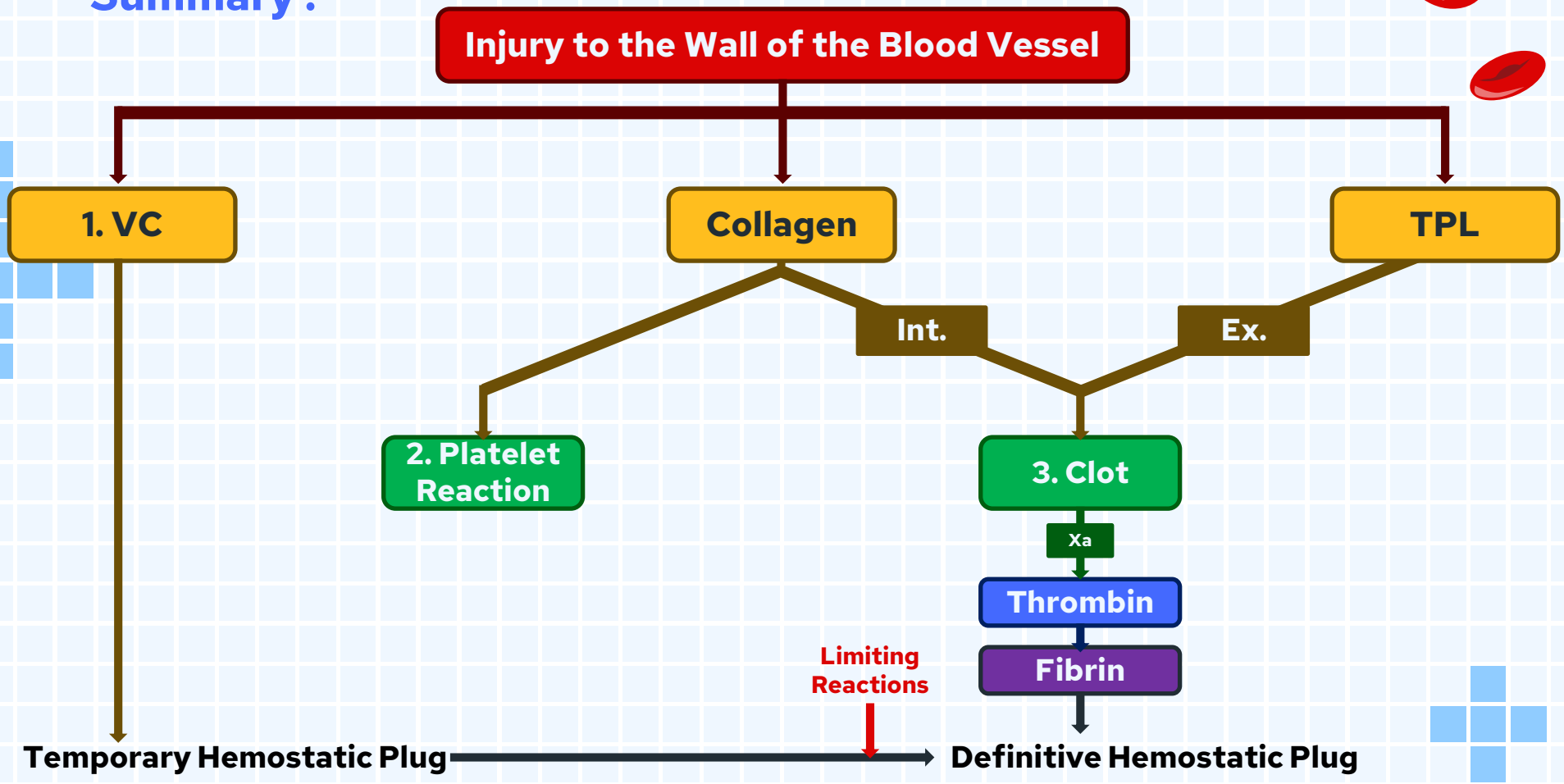
B. Extrinsic Pathway :

- This system is called Extrinsic as it requires the presence of phospholipids from outside blood vessels.
- It is initiated Only in Vivo by factor III : Tissue Thromboplastin (TPL) released from damaged tissues.
- TPL activates factor VII, which directly activates factor X in the presence of Ca^{2+}, TPL and PL, and indirectly through the activation of factor IX.

Common Part in Both Pathways :

- Xa (activated by intrinsic and extrinsic pathways) catalyzes the conversion of Prothrombin to Thrombin in the presence of factor V, PL, and Ca^{2+} .
- Finally, Thrombin transforms Soluble Fibrinogen into Insoluble Fibrin.
- Thrombin in the presence of Ca^{2+} also activates factor XIII, which stabilizes the Fibrin Clot. Platelets, Blood Cells and Plasma become entangled in the clot.
- Contraction of the Platelets in the Fibrin Mesh causes clot retraction and squeezes serum out.
- The Serum is devoid of Fibrinogen, Prothrombin and factors V, VIII and XIII which become consumed during clotting.

Summary :


Injury to the Wall of the Blood Vessel
1. VC
Collagen
TPL
Int.
Ex.
2. Platelet Reaction
3. Clot
Xa
Thrombin
Fibrin
Limiting Reactions
Temporary Hemostatic Plug
Definitive Hemostatic Plug

PLATELETS (THROMBOCYTES)

Important Notes :

- Von Willebrand factor (vWF) is a glycoprotein crucial to Primary Hemostasis through Platelet and Subendothelial Collagen Adhesion and the Intrinsic Coagulation Cascade, through factor VIII stabilization. It resides in the Plasma, Subendothelial Matrix & Storage Granules within Endothelial cells & Platelets.

- During Primary Hemostasis, vascular injury exposes vWF bound to Subendothelial Collagen. Then, Glycoprotein 1b (GP1b) receptors on the surface of nearby platelets adhere to the exposed vWF, triggering Platelet Activation and a Cascade of Events which includes the release of platelet storage granule content such as vWF from alpha granules and the recruitment of more platelets to form a plug at the site of damaged Endothelium.

- Plasma vWF supports the Intrinsic Coagulation Cascade by stabilizing factor VIII, thereby increasing its circulating half-life. During the Intrinsic Coagulation Pathway, Thrombin cleaves the factor VIII binding site with vWF, allowing the release (activation) of factor VIIIa to continue the clotting process. By serving as a carrier for factor VIII, vWF influences the Common Coagulation Pathway and the generation of Thrombin and Fibrin.

PLATELETS (THROMBOCYTES)

Important Notes :

- The Extrinsic Pathway is Very Rapid (15 sec.), while the Intrinsic Pathway is Slow (1-6 min.).
- Injury of a Blood Vessel will trigger both the Intrinsic System (by Collagen) and the Extrinsic System (by TPL).
- In the test tube, clotting occurs Only by the Intrinsic system (glass or addition of collagen).
- In Intravenous Thrombosis, blood clotting occurs via the Intrinsic System, which is initiated by The Exposure of Clotting Factors to Collagen.

Thrombin functions :

- Activates Fibrinogen to Fibrin.
- Activates the other factors of the Fibrinogen group (V, VIII, and XIII)
- Accelerates the actions of factors IX, X, and XI
- Accelerates the formation of more Thrombin from Prothrombin (Positive Feedback).
- Accelerates Platelet Aggregation and Fusion.

Therefore, as soon as a small amount of Thrombin is formed, the clotting reactions are markedly enhanced by Thrombin, and the clot continues to grow until this process is Stopped by Limiting Reactions.

PLATELETS (THROMBOCYTES)

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PLATELETS (THROMBOCYTES)

HEMOSTASIS

The Hemostatic process consists of the following:

D. **Limitation Reaction to Dissolve Clot** after wound healing.

PLATELETS (THROMBOCYTES)

HEMOSTASIS

The Hemostatic process consists of the following:

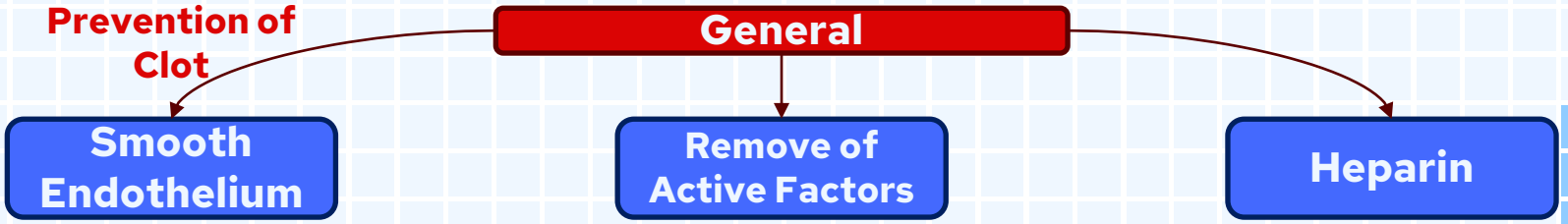
D. Limitation Reaction to Dissolve Clot after wound healing.

Anticlotting Mechanisms = Limiting Reactions

The Tendency of blood to clot is balanced in Vivo by limiting reactions that prevent blood clotting in healthy Blood vessels and break down any clots already formed.

A. General Limiting Reactions:

1. **Smooth Vascular Endothelium prevents activation of platelets & factor XII.**
2. **Rapid Blood flow Removes Activated Clotting Factors and inactivates them in the liver. So, slow blood flow favors Intravascular Thrombosis.**
3. **Heparin is a natural Anticoagulant present in the blood.**



HEMOSTASIS

The Hemostatic process consists of the following:

D. **Limitation Reaction to Dissolve Clot** after wound healing.

B. Specific limiting reactions:

1. **Thromboxane A2 and Prostacyclin:** The formation of **Thromboxane A2** at the site of Blood vessel injury allows clot formation, while the synthesis of **Prostacyclin** by healthy Endothelium prevents the spread of the blood clot to neighboring healthy areas and obstruction of the lumen of blood vessels.
2. **Antithrombin III:**
   This Circulating Inhibitor of Blood Coagulation binds to active factors **II**, **IX**, **X**, **XI**, and **XII**, blocking their activity. This binding is facilitated by Heparin.
3. **The Fibrinolytic System:**

- **Thrombomodulin** is produced by most Endothelial cells. This protein binds Thrombin to form the Thrombomodulin-Thrombin complex, which activates protein C.
- **Activated protein C** (APC) causes:
  - Inactivation of factors Va and VIIIa, and
  - Inactivation of the inhibitor of tissue Plasminogen activator (tPA)=(TPA-I), increases the formation of plasmin.
- **Plasmin** (fibrinolysin) lyses **Fibrin** and **Fibrinogen**, forming **Fibrinogen Degradation Products** (FDP), inhibiting **Thrombin**.

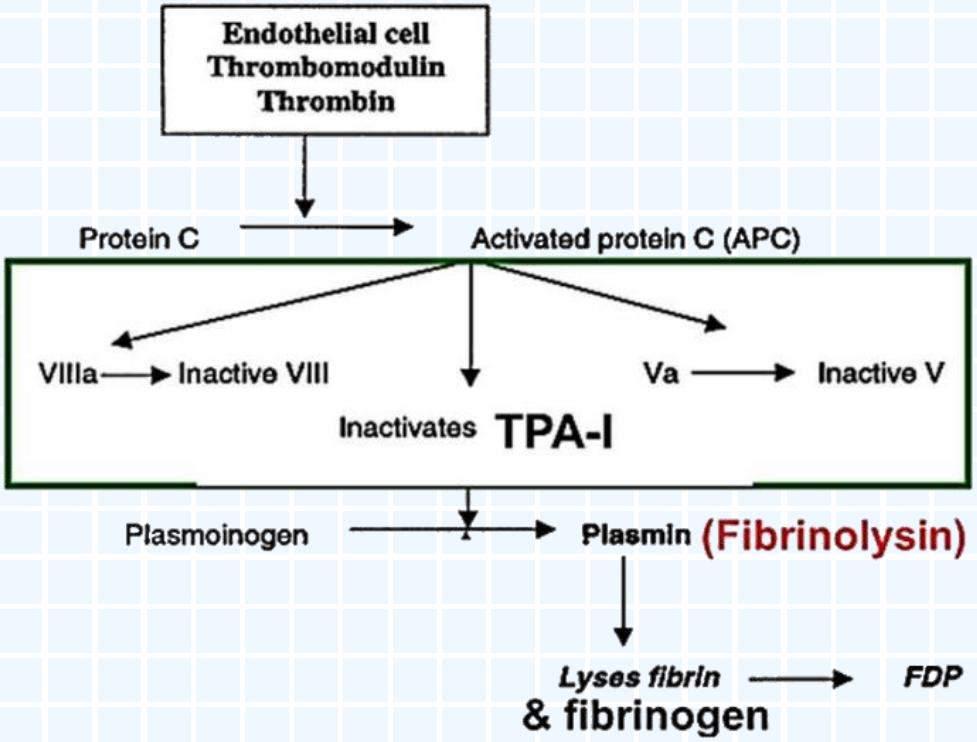
HEMOSTASIS

The Hemostatic process consists of the following:

D. **Limitation Reaction to Dissolve Clot** after wound healing.

B. Specific limiting reactions:

3. The Fibrinolytic System:



HEMOSTASIS

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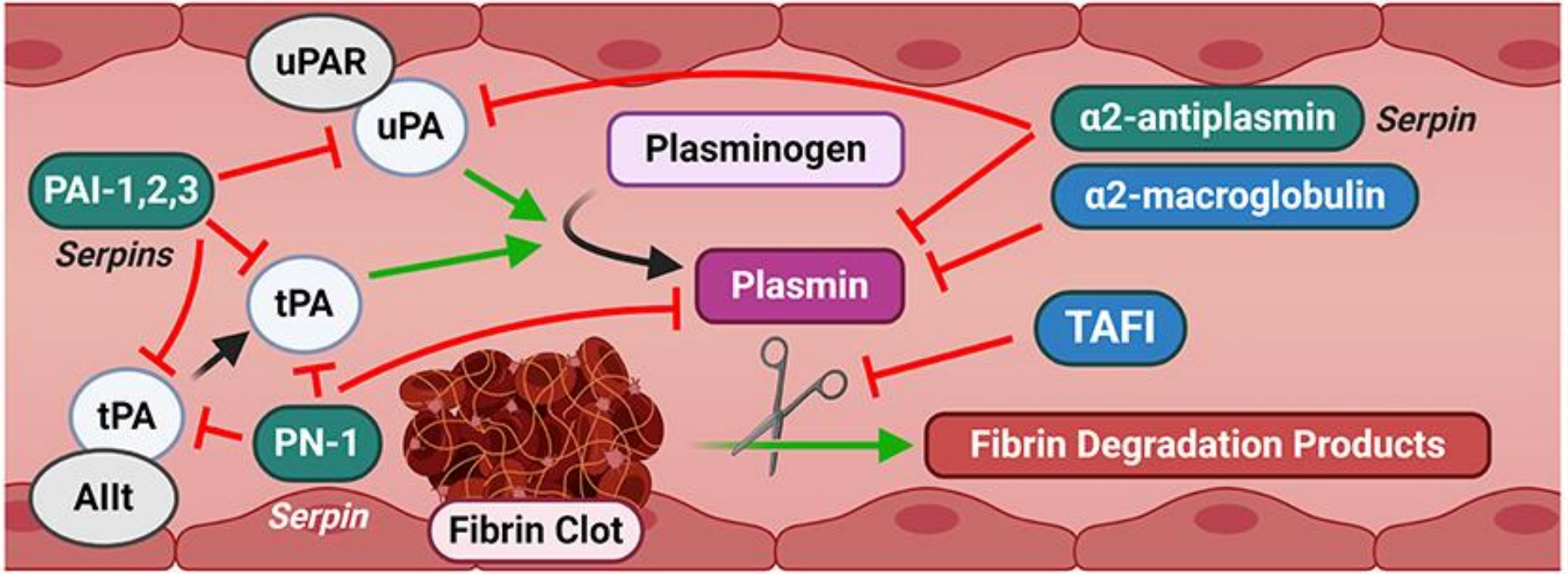


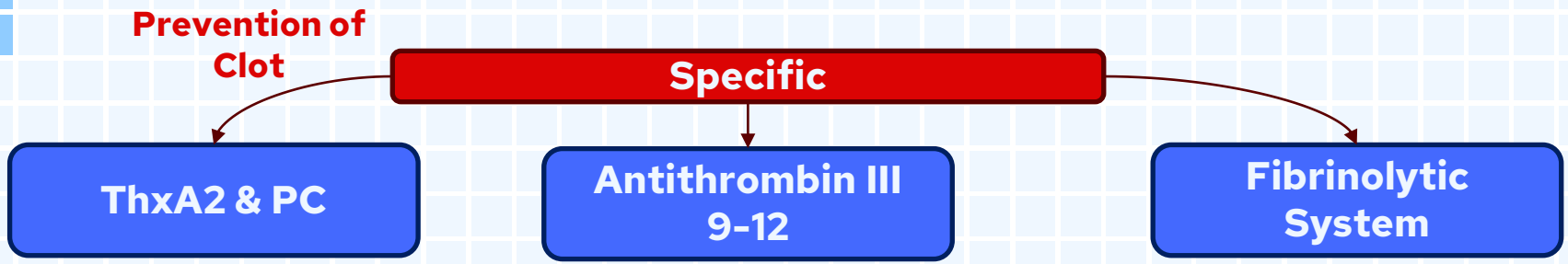
PLATELETS (THROMBOCYTES)

HEMOSTASIS

The Hemostatic process consists of the following:

D. **Limitation Reaction to Dissolve Clot after wound healing.**

B. Specific limiting reactions:



PLATELETS (THROMBOCYTES)

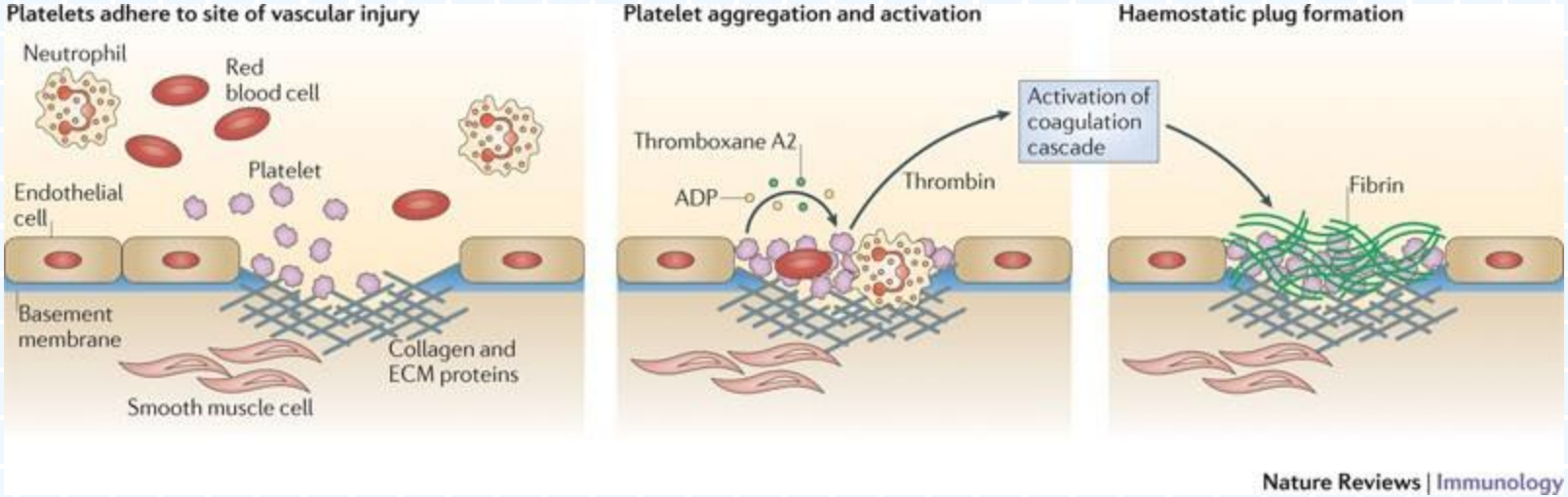
Anticoagulants:

B. In Vivo Anticoagulants:

They prevent Blood clotting inside the body.

	Heparin	Dicumarol
Origin	Mast Cells & Basophils.	Plants
Mode of Action	Facilitates action of Antithrombin III (Inactivates II, IX, X, XI, XII)	Competitive Inhibition of Vitamin K on its receptors in the liver → inhibits the formation of II, VII, IX, X.
Site of Action	In Vivo and in Vitro	Only in Vivo
Onset	Rapid	Slow
Duration	Short	Long
Administration	Intravenous (IV) and Subcutaneously (SC)	Orally
Antidote	Protamine Sulfate 1% Fresh Blood transfusion	Vitamin K Fresh Blood transfusion

PLATELETS (THROMBOCYTES)



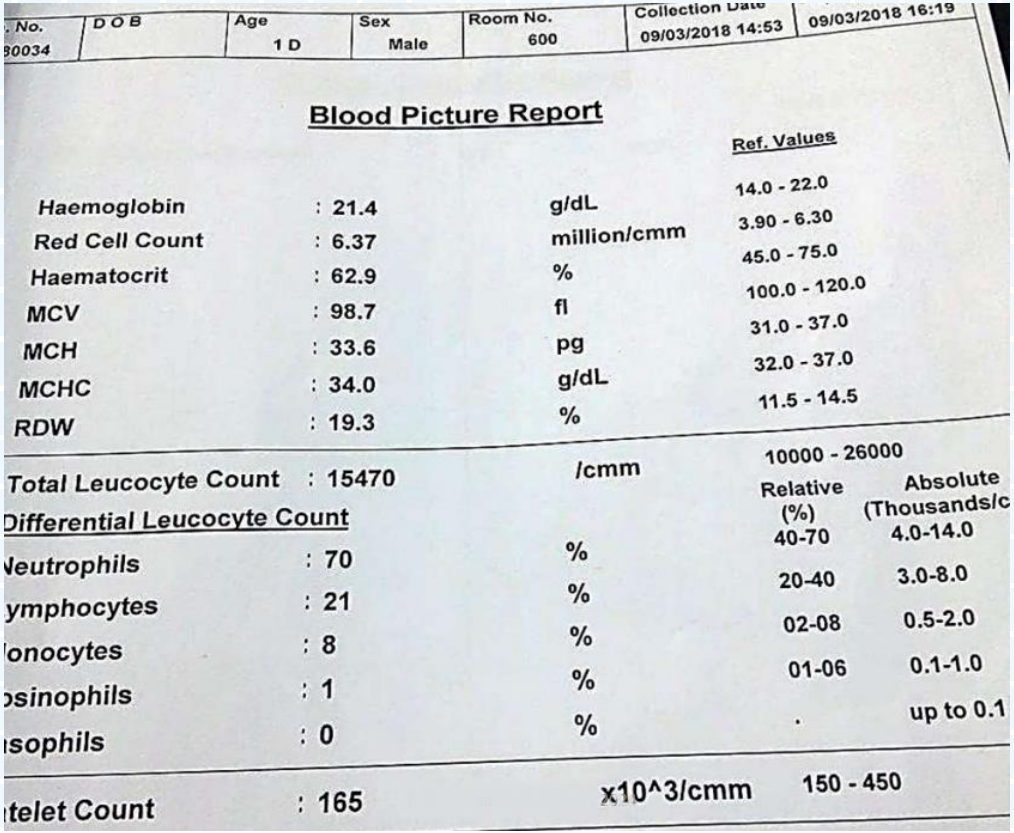
PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

- Complete Blood Count (CBC)
- Bleeding & Clotting Time
- Prothrombin Time (PT)
- International Normalised Ratio (INR)
- Active Partial Thrombin Time (aPTT)
- Platelet Count (PC)

PLATELETS (THROMBOCYTES)

Hemostatic Function Tests



No.	DOB	Age	Sex	Room No.	Collection Date	
90034		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	

PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

1. **Blood Count and Blood Film**

2. **Bleeding Time :**

   It is the Time needed for Bleeding to Stop without blood clotting. The normal bleeding time is 1-3 minutes, depending on platelet count and function. It is prolonged in Thrombocytopenic Purpura.

3. **Tests for Blood Coagulation**

   a. **Clotting time:** It is the Time needed for Blood to Clot. Normally, it is 3-10 minutes at 37° C. It is prolonged in disorders such as Vitamin K deficiency, Hemophilia and Liver Diseases.

PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

3. Tests for Blood Coagulation

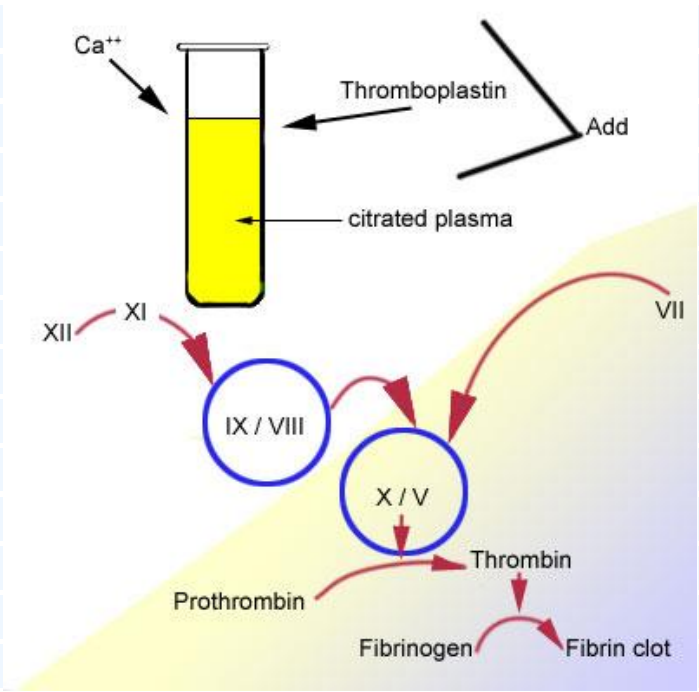
- **Prothrombin Time (PT):** A blood sample is collected in a tube containing Citrate or EDTA to chelate any Calcium and thus inhibit Coagulation, and then the cells are removed by Centrifugation. After the cells are removed, excess Calcium is added with an excess of Thromboplastin to Anticoagulated Plasma to initiate Coagulation. A normal PT is 11.0–12.5 seconds. A PT greater than 20 seconds is indicative of a Coagulation deficit. The result (in seconds) for a Prothrombin Time performed on a normal individual will vary according to the type of Analytical System employed. This is due to the variations between different batches of the manufacturer's tissue factor used in the reagent to perform the test.

PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

3. Tests for Blood Coagulation

b. Prothrombin Time (PT):



PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

3. Tests for Blood Coagulation

- **International Normalized Ratio (INR):**

The INR was devised to standardize the results.

Each manufacturer assigns an ISI Value (International Sensitivity Index) for any tissue factor they manufacture. The ISI value indicates how a particular batch of tissue factor compares to an international reference tissue factor. The ISI is usually between 1.0 and 2.0.

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

PT (pat)= Patient's prothrombin time

PT (n) = Normal reference range

ISI = International sensitivity index
(the optimal ISI is 1.3 to 1.5)

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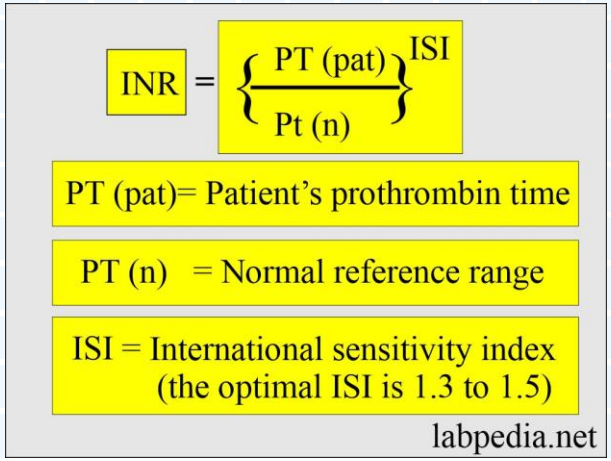
PLATELETS (THROMBOCYTES)

Hemostatic Function Tests

3. Tests for Blood Coagulation

- **International Normalized Ratio (INR):**

The INR is the ratio of a patient's Prothrombin Time (PT) to a normal (control) sample, Raised to the power of the ISI Value for the Analytical System used.



A high INR level, such as INR=5, indicates a high chance of bleeding, whereas if the INR=0.5, there is a high chance of having a clot. The Normal INR Range for a Healthy person is 0.9–1.3, and for people on Warfarin therapy, 2.0–3.0. However, the target INR may be higher in particular situations, such as those with a Mechanical Heart Valve

PLATELETS (THROMBOCYTES)

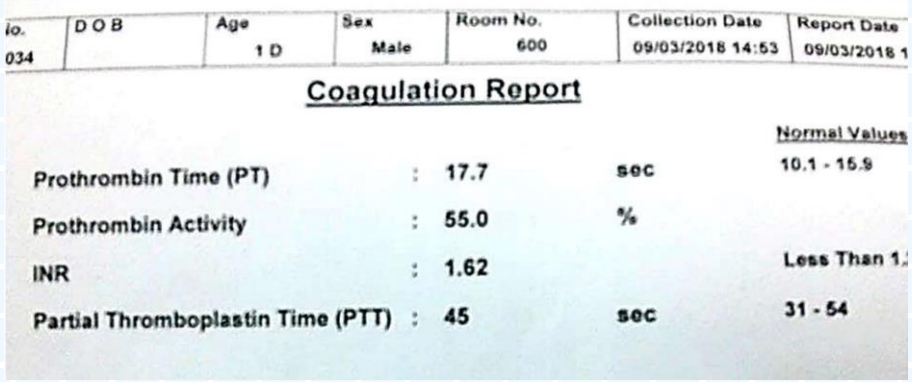
Hemostatic Function Tests

3. Tests for Blood Coagulation

- **Activated Partial Thromboplastin Time Test (aPTT):** a test performed to **investigate bleeding disorders** and **to monitor patients taking an anticlotting drug** such as Heparin which inhibits factors X and Thrombin, while activating Anti-Thrombin.

  The Partial Thromboplastin time is the time it takes for a clot to form, measured in seconds. **Normally, the sample will clot in 35 seconds.**

- **Prothrombin Concentration:** **Normally > 70 %.**



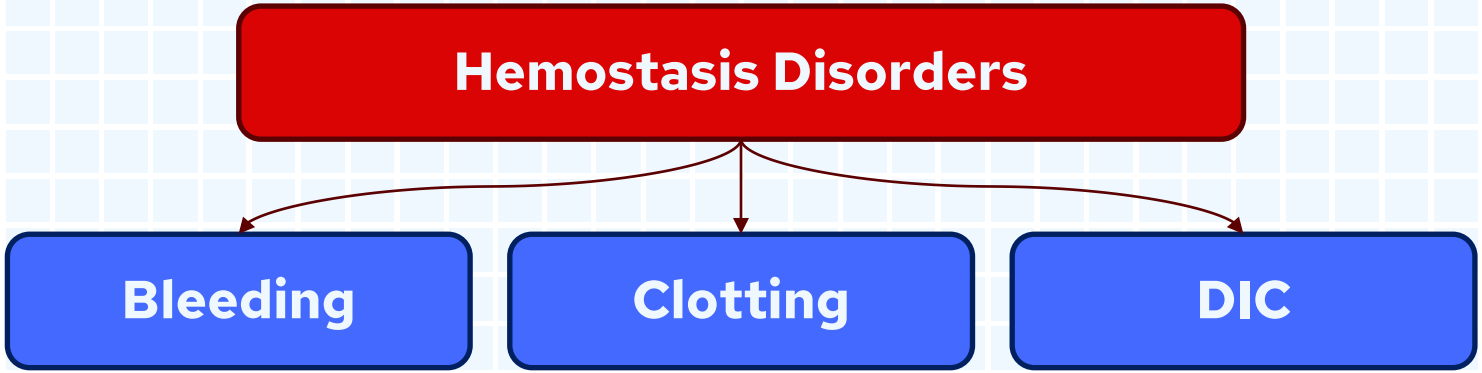
io.	D O B	Age	Sex	Room No.	Collection Date	Report Date
034		1 D	Male	600	09/03/2018 14:53	09/03/2018 1

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

PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:



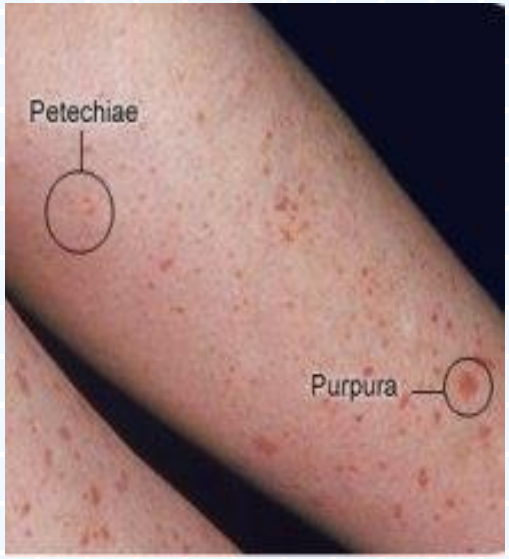
PLATELETS (THROMBOCYTES)

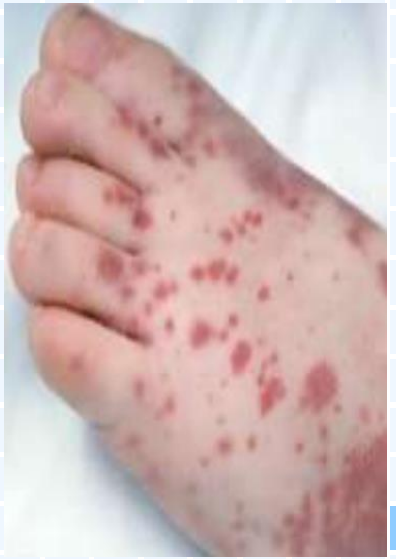
Abnormalities of Hemostasis:

A. **Bleeding:**

1. **Thrombocytopenic Purpura:**

It is due to a **Decreased Platelet Count below 50,000/mm3** . It is characterized by the presence of Subcutaneous Hemorrhages. The Bleeding Time is Prolonged.





PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:

A. Bleeding:

2. Vitamin K Deficiency:

- Vitamin K is essential for forming the Prothrombin group (II, VII, IX, and X) in the liver.
- Vitamin K is continuously Formed by the Intestinal Flora.
- Vitamin K is Fat-Soluble and requires Bile for its Absorption.
- Causes of Vitamin K Deficiency: (associated with prolonged clotting time)
  - ✓ Absence of Intestinal Flora: in newborns, Prolonged Oral Antibiotics.
  - ✓ Absence of Bile: in Obstructive Jaundice.
  - ✓ Block of its receptors in the liver by Dicumarol.

We can summarize the Causes of the Vitamin K Deficiency by:

- Inadequate Intake
- Inadequate Absorption
- Inadequate Utilization
- Vitamin K Antagonist, such as Warfarin

PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:

A. Bleeding:

3. Hemophilia:

This is a Congenital Sex-linked Disease carried on the X Chromosome. It is Recessive and is transmitted by Females to their Male sons.

It is characterized by Severe Bleeding, even after mild trauma. Joint Damage (Hemophilia Arthropathy) is the most common complication of bleeding in Hemophilia.

There are three types of hemophilia:

- Hemophilia A: due to the Absence of factor VIII (85% of cases)
- Hemophilia B: due to Deficiency of factor IX (10% of cases)
- Hemophilia C: due to Deficiency of factor XI (5% of cases).

There is prolonged clotting time.

PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:

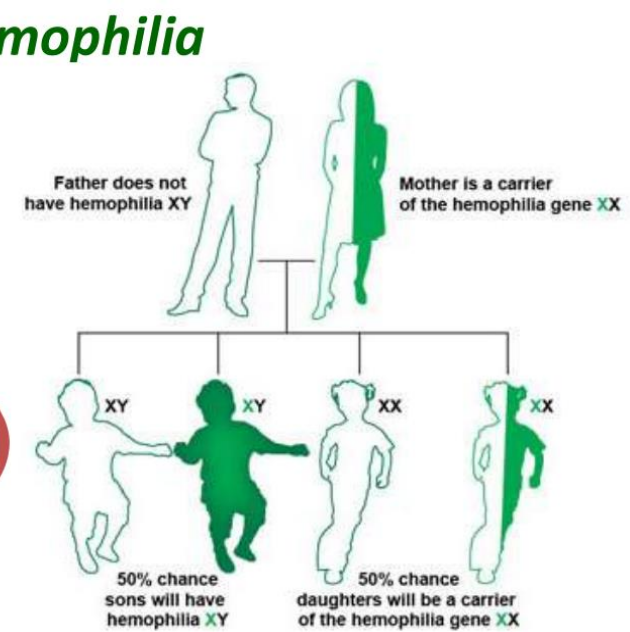
A. Bleeding:

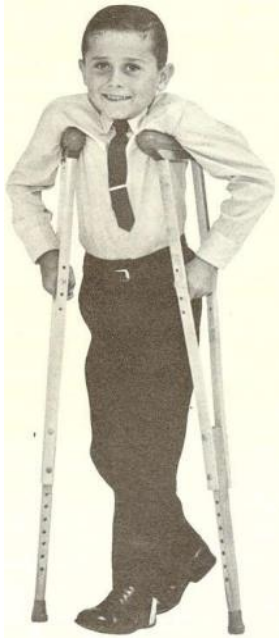
3. Hemophilia:

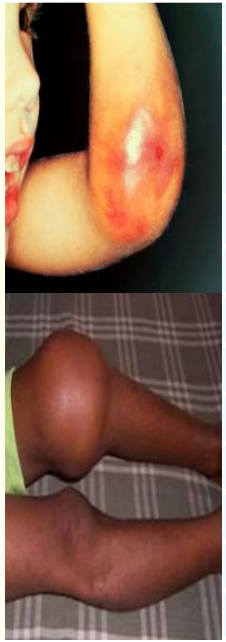
A (8)

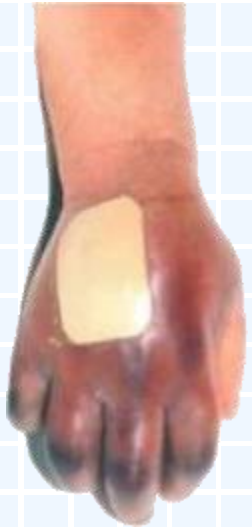
B (9)

C (11)









PLATELETS (THROMBOCYTES)

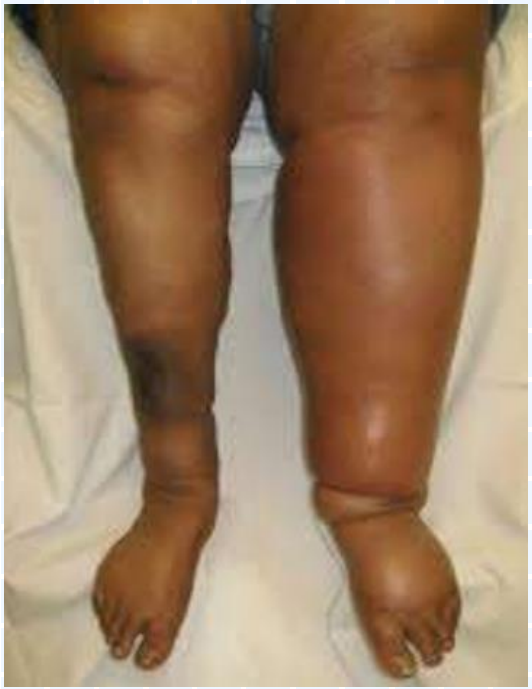
Abnormalities of Hemostasis:

A. **Bleeding:**

3. **Clotting (Thromboembolic Conditions):**

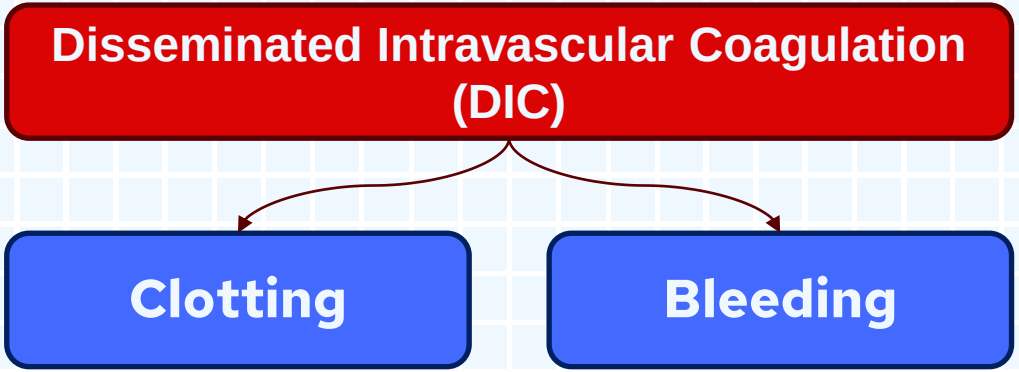
Slow Blood Flow :

- **Long Bed Rest**
- **Varicose Veins**
- **Atherosclerosis**



PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:



PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:

A. Bleeding:

4. 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.

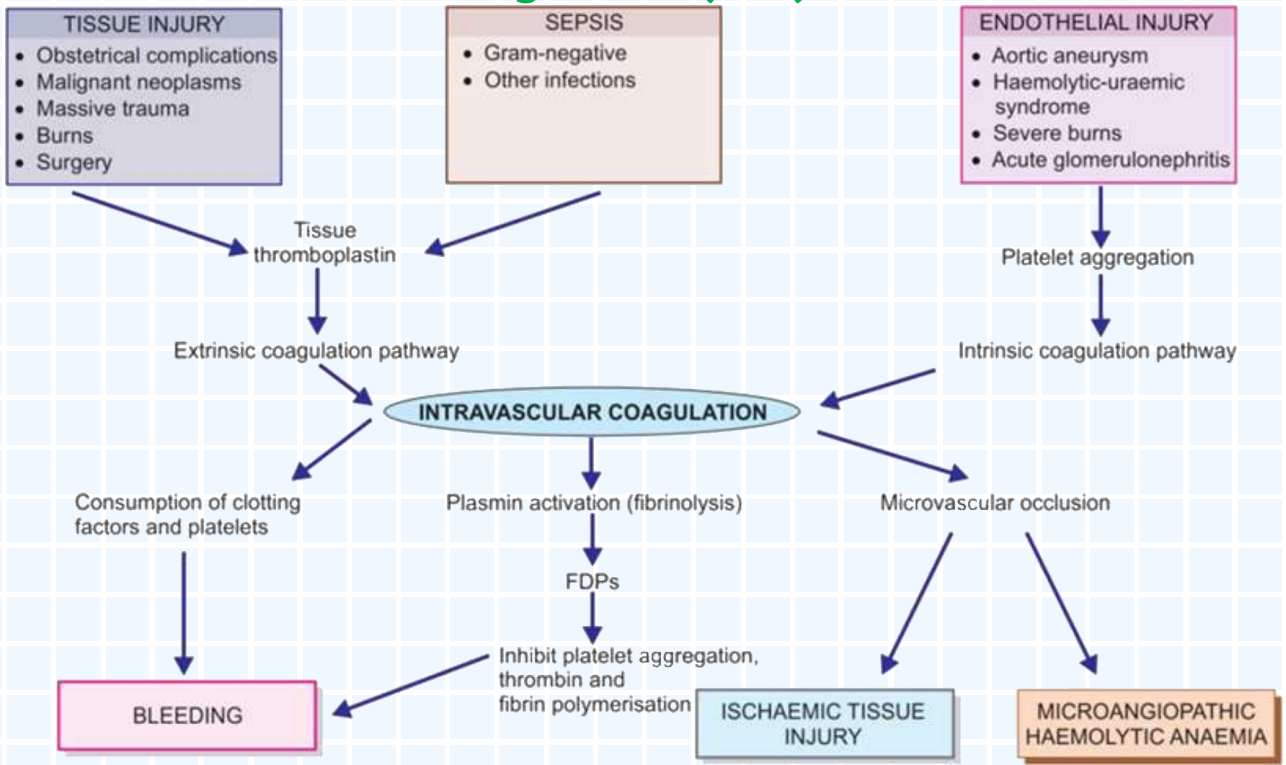
1. The Procoagulant activity overcomes the natural Anti-Coagulant mechanisms. This is also called Consumption Coagulopathy or Defibrination Syndrome.
2. This is a Hemorrhagic Disorder in which diffused Intravascular Coagulation results in defects of Hemostasis.
3. In this Disease, Coagulation factors 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

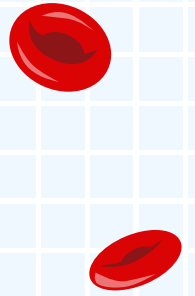
PLATELETS (THROMBOCYTES)

Abnormalities of Hemostasis:

A. Bleeding:

4. Disseminated Intravascular Coagulation (DIC):






THANK
YOU
النادي الطبي