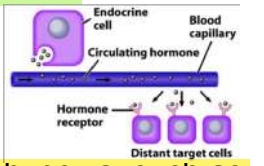
Stages of Differentiation of RBCs:

Pluripotential stem cells in the bone marrow can develop into any blood cells.

Pluripotential stem cells
Divide & develop
Colony-forming unit-erythrocytes (CFU-E)
(= *erythropoietin-sensitive stem cells*)
Erythropoietin
Erythroblasts
Erythrocytes

Reticulocytes are the immediate precursor of RBCs, following their release to the blood stream they mature within 1-2 days into RBCs. Contain a small amount of basophilic material, mainly remnants of the Golgi apparatus & mitochondria. They normally make less than1-2% of all RBCs. Used to estimate the degree of effective erythropoiesis. Their number increases in cases of bleeding and RBC hemolysis and decreases in cases of bone marrow failure.



Factors Affecting Erythropoiesis:

I. Role of Erythropoietin and Oxygen Supply to the Tissues:

There is an increased rate of production of RBCs in conditions associated with hypoxia, such as:

1. Hemorrhage: hypoxia is due to the loss of RBCs.
2. High altitude: hypoxia is due to decreased O_2 tension in atmospheric air.
3. Athletes: athletes have a relative oxygen deficiency since they have higher oxygen requirements than normal.
4. Heart failure: hypoxia is due to decreased blood flow in peripheral vessels.
5. Lung diseases: hypoxia is due to decreased oxygen diffusion from the lungs to the blood. Tissue hypoxia stimulates the release of a hormone called "erythropoietin."

Erythropoietin hormone: is a glycoprotein

Sources: In adults: 85% are produced in the kidneys and 15% in the liver. Therefore, anemia develops in kidney diseases and nephrectomy, as the liver cannot compensate for the erythropoietin deficiency.

-***Mechanism of action of erythropoietin:*** It accelerates all steps of erythropoiesis as it stimulates mRNA synthesis. It also shortens the maturation time of RBCs in the bone marrow.

-***Stimulation of secretion:***

-Hypoxia is the main stimulus.
-Conditions that increase Oxygen hemoglobin affinity increase Erythropoietin secretion.
-Alkalosis (increased oxygen affinity to oxygen).
-Cobalt salts and androgens.
-Beta-adrenergic agonists and adenosine.

II. Diet: other factors that affect erythropoietin synthesis

A. Proteins: High-biological value proteins (containing all essential amino acids) of animal origin are needed for normal erythropoiesis.

B. Iron:

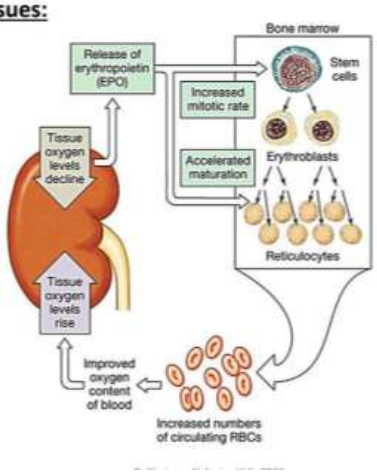
Functions of iron:

1-Formation of Hb in RBCs and myoglobin in muscles.
2-Co-factor for some oxidation enzymes, e.g., catalase, peroxidase, and cytochrome oxidase.

Total body iron: about 4 g.

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

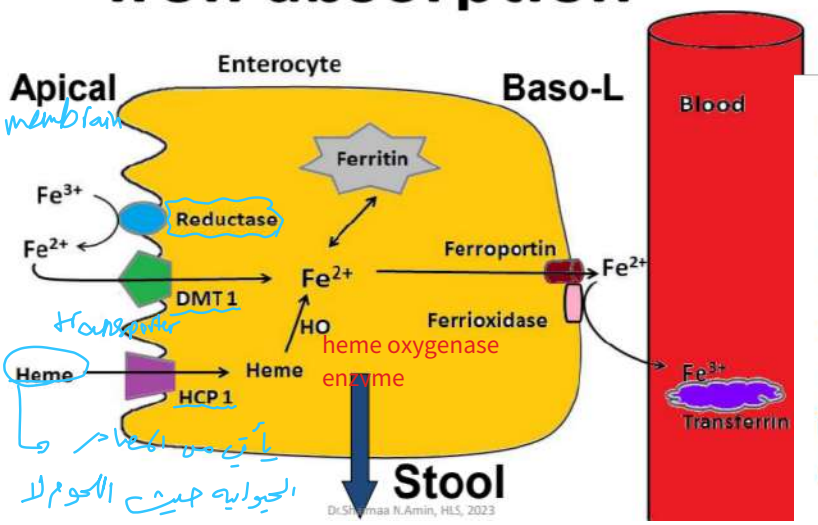
E) Copper and Cobalt

Factors Affecting Erythropoiesis:

(3) Hormones

(4) Healthy Liver and Bone Marrow:

Iron absorption



* Reductase يحول الحديد الذي وصل الاصعادق شكل Fe+2 إلى Fe+3

يدخل الحديد الى داخل خليه entrocyte وهي خليه من الخلايا المبطنه ل deudenum وليستطيع الدخول يجب ان يكون في الحاله المختزله fe+2 وان لم يكن كذلك يتم استعمال انزيم reductase لاختزاله ليدخل الخليه عن طريق DMT1 CARRIER ثم انه ان اراد الخروج من هذه الخليه يجب ان يتحول الى الحاله المؤكسده حيث يكون fe+3 وذلك باستعمال انزيم ferrioxidase ليخرج عن طريق بروتين يسمى ferroportin.

يأتي من الطعام والحيوانيه حيث الهيم free iron تشمل

Iron absorption, transport, and storage:

-Most dietary iron is ferric (Fe^{3+}), which is reduced by **stomach HCl** & **vitamin C** (ascorbic acid) to ferrous (Fe^{2+})→ more readily absorbed.

-Phytic acid (in cereals), oxalates, & phosphates prevent iron absorption as they form insoluble complexes.

-Iron absorption occurs in the **upper part of the small intestine** by an active process→ carried by **Transferrin** in blood and transported to the bone marrow to form Hb and to the muscles to form myoglobin.

-Excess iron is stored in the **liver & spleen** as **ferritin**.

-Ferrous iron is transported into the enterocytes by divalent metal transporter 1 (DMT1) present at the apical membrane of these cells. The iron that is not reduced in the stomach and reaches the duodenum in the F3+ form will still be reduced by a reductase enzyme associated with DMT1 before it can be transported by DMT1 into the enterocyte.

-Heme can be transported into the enterocytes by the specific heme carrier protein (HCP1) present in the apical membrane of the enterocytes. Iron is released from heme by the action of the heme oxygenase enzyme inside the enterocytes.

-Inside the enterocyte, iron transported by DMT1 and HCP1 has one of two fates, ***depending on body requirements:*** If the body stores of iron are replete, and there is no increased rate of erythropoiesis, most of the iron inside the enterocytes is stored in the form of ferritin. Because duodenal enterocytes' lifespan is very short (approximately 3-4 days), this intracellular ferritin iron is quickly lost into the intestinal lumen as the aging enterocytes are sloughed off and excreted in stools. If, on the other hand, there is increased demand by the body, then most of the iron inside the enterocytes is transported out of the cells at their basolateral border to reach the bloodstream. The export of iron out of the enterocytes at the basolateral border occurs through an iron export protein called ferroportin. While Fe2+ is transported out of the enterocytes, it is oxidized to Fe3+ form by the action of the ferrioxidase enzyme. This enzyme is present on the basolateral border of the enterocytes in association with ferroportin.

-Iron (Fe3+) delivered by the enterocytes to plasma binds to a plasma transport protein called transferrin. Transferrin molecule has two binding sites for iron. Normally, transferrin in plasma is 35% saturated with iron.

-Transferrin delivers iron to different cells in the body.

Regulation of iron absorption: Human body does not have mechanisms to regulate iron excretion. Therefore, we depend on mechanisms that regulate iron absorption and regulate the release of recycled iron from macrophages to maintain iron homeostasis. These regulatory mechanisms for iron absorption and recycling involve the following:

Role of dietary iron: Excess iron in food decreases the DMT1 on enterocytes, thus decreasing iron absorption. This is sometimes referred to as *"the mucosal block*."

Role of Hepcidin: Hepcidin is a 25-amino acid hormone secreted by the liver. Hepcidin is a major regulator of intestinal iron absorption and iron release by macrophages.

Actions of hepcidin: Hepcidin binds to iron export protein ferroportin in duodenal enterocytes, macrophages, and liver cells. The degradation of ferroportin molecules follows such binding. This leads to the Inhibition of intestinal absorption of iron, the Inhibition of the release of recycled iron from macrophages, and the Inhibition of the release of iron from the liver and other store sites.

Factors affecting hepcidin secretion:

-Hypoxia and erythropoietin hormone decrease hepcidin secretion. In this way, iron absorption and release are increased to supply the increased demand by accelerated erythropoiesis for iron.

-Iron loading increases hepcidin secretion by the liver.

-Inflammation increases hepcidin secretion. This explains why anemia is a common complication of many inflammatory diseases.

Effect of iron deficiency: Iron deficiency anemia.

Causes of iron deficiency:

1-*Decreased iron intake in the diet*

2-*Failure of iron absorption,* which may be due to:

-Partial gastrectomy (insufficient HCl secretion)

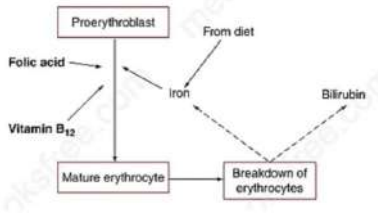
-Diseases of the upper small intestine

-Vitamin C deficiency

-Too much Phytic acid, oxalates, and phosphates in the diet

3-*Chronic blood loss:* It results in iron deficiency, as the iron stores are insufficient and dietary iron cannot compensate for the amount of iron lost. It occurs in:

- Excessive bleeding during menstruation in females
- Bleeding peptic ulcer and piles.
- Parasitic infestation.



C. Vitamins:

All vitamins are essential for erythropoiesis, esp. vitamin C, B_{12}, and folic acid.

Vitamin B_{12} (Cyanocobalamine = Extrinsic Factor)

Functions of vitamin B_{12}:

a. Vitamin B_{12} is essential for transforming mRNA into DNA, i.e., for the synthesis of DNA and nuclear maturation in RBCs. Therefore, vitamin B_{12} is also known as the *maturation factor*.

b. It is also essential for the metabolism of the myelin sheath of nerves.

Absorption of vitamin B_{12}:

- The parietal cells of the fundus of the stomach secrete a glycoprotein known as *intrinsic factor*. It unites with vitamin B_{12} (*extrinsic factor*) to be protected from digestion by the GIT enzymes.
- It is absorbed from the terminal ileum and passes to blood.

Causes of vitamin B_{12} deficiency:

a. absence of intrinsic factor due to atrophy of the gastric mucosa. The anemia, which develops due to the absence of intrinsic factors, is known as *pernicious anemia*.

b. Liver diseases: as they result in defective storage of the vitamin.

c. disease or surgical resection of the terminal ileum.

d. Very rarely, there is deficient vitamin B_{12} in the diet.

Effect of vitamin B12 deficiency:

a. failure of nuclear maturation and division of erythroblasts in the bone marrow. Therefore, erythroblasts increase in size and develop into *megaloblasts* and megalocytes. They are larger in size, contain a larger amount of hemoglobin, and have a shorter life span than erythrocytes. Therefore, the anemia, which develops due to vitamin B_{12} deficiency, is also called *megaloblastic* or *Macrocytic anemia*.

b. Neurological symptoms:

Since vitamin B_{12} is essential for the metabolism of the myelin sheath of nerves, its deficiency causes neurological manifestations.

2. Folic Acid: Folic acid is needed for DNA synthesis. Therefore, it is required for the division and maturation of RBCs.

Effect of folic acid deficiency:

Folic acid deficiency causes failure of maturation of RBCs and the development of macrocytes, resulting in Macrocytic anemia.

Causes of folic acid deficiency:

folic acid is present and vegetables more than animal sources

a.Dietary deficiency of folic acid due to over cooking of vegetables
b. GIT diseases interfere with folic acid absorption.
c. Cytotoxic drugs (antifolates) used in the treatment of cancer. with the course of the treatment they take a folate complement

D. Trace Elements:

Copper is a co-factor for Hb synthesis but does not enter into its formation.

Cobalt: It stimulates erythropoiesis and enters in vitamin B_{12} formation.

III. Hormones:

Several hormones increase the rate of erythropoiesis, including Thyroxin, Androgens, and Glucocorticoids.

*معدل افرازهم في الانثى أكبر من Female

IV. Healthy Bone Marrow:

- Since the bone marrow is the site of erythropoiesis, it must be healthy for normal RBCs production.
- Bone marrow may be destroyed by: X-rays, atomic radiation, drugs, and malignant tumors.
- Bone marrow destruction leads to a decrease in all types of blood cells, i.e., RBCs, WBCs, and platelets. This condition is called aplastic anemia. pancytopenia

V. Healthy Liver:

The liver is important for erythropoiesis because:

- It forms the globin part of hemoglobin
- It stores vitamin B_{12} and iron, which are essential for erythropoiesis
- It produces 15% of erythropoietin.

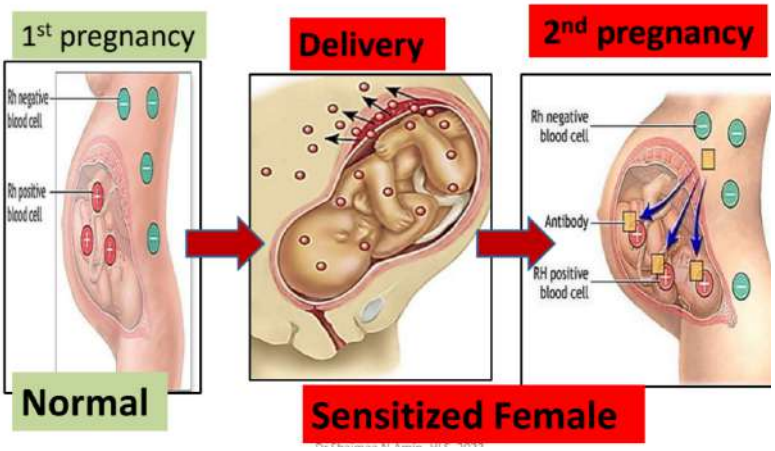
Blood Typing

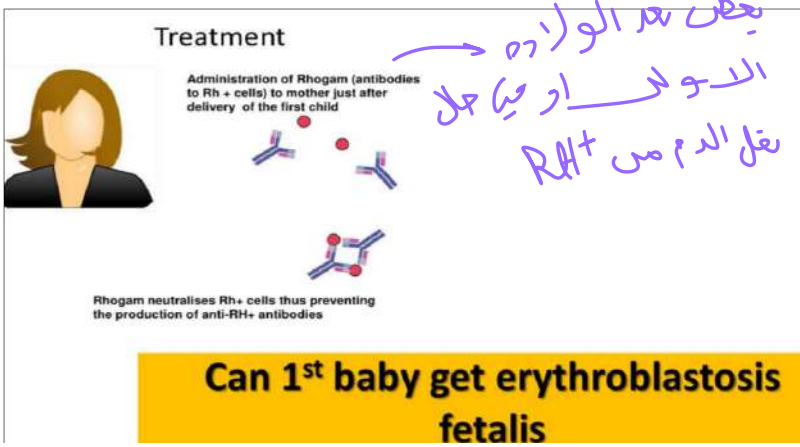
	Group A	Group B	Group AB	Group O
Red blood cell type	A	B	AB	O
Antibodies in plasma	Anti-B	Anti-A	None	Anti-A and Anti-B
Antigens in red blood cell	A antigen	B antigen	A and B antigens	None

immunoglobulin M

immunoglobulin M

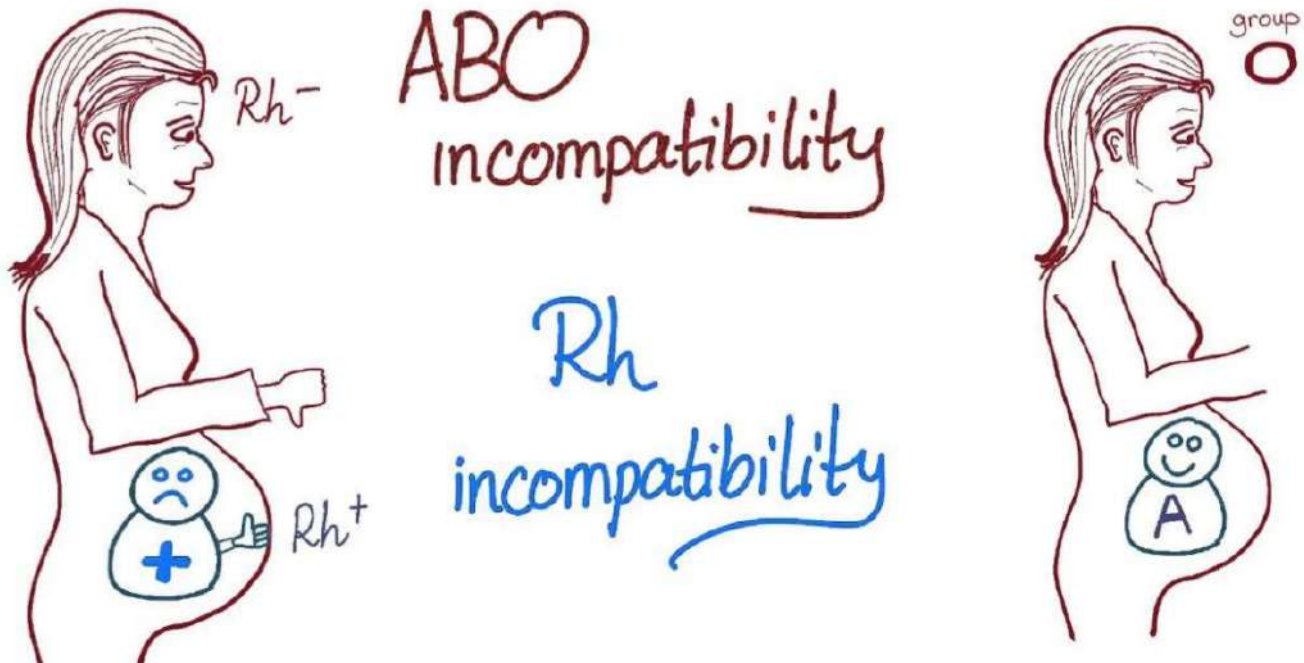
Erythroblastosis Fetalis





يعطى هذا الدواء للام بعد الولادة او بعد اي حمل ينقل الدم من Rh+

Can 1st baby get erythroblastosis fetalis



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.

كيف يكون الجسم اجسام مضاده ضد antigen غير الموجود على سطح خلايا الدم الحمراء؟يتعرض الجسم لمواد تشبه antigens الموجوده على سطح خلايا الدم الحمراء in intestinal bacteria& food particles لذلك تكون antibodies ضد (antigens) غير الموجود على سطح خليه الدم الحمراء

> 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

What is agglutination? Agglutination, which refers to the clumping of particles together, is an antigen-antibody reaction that occurs when an

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 (Antigen)	Agglutinin (antibodies)
AA.AO	A	A	Anti-B
BB.BO	B	B	Anti-A
AB	AB	AB	---
OO	O	O	Anti-A, anti-B

- O is a universal donor. - AB is a universal recipient.

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 an 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.

Importance of Rh factors: -

1- Erythroblastosis Fetalis: (hemolytic disease of the newly born). When an Rh-positive male marries an 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 an 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.*

Prevention:

1-Rh negative female should never receive Rh-positive blood

2-When an 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.

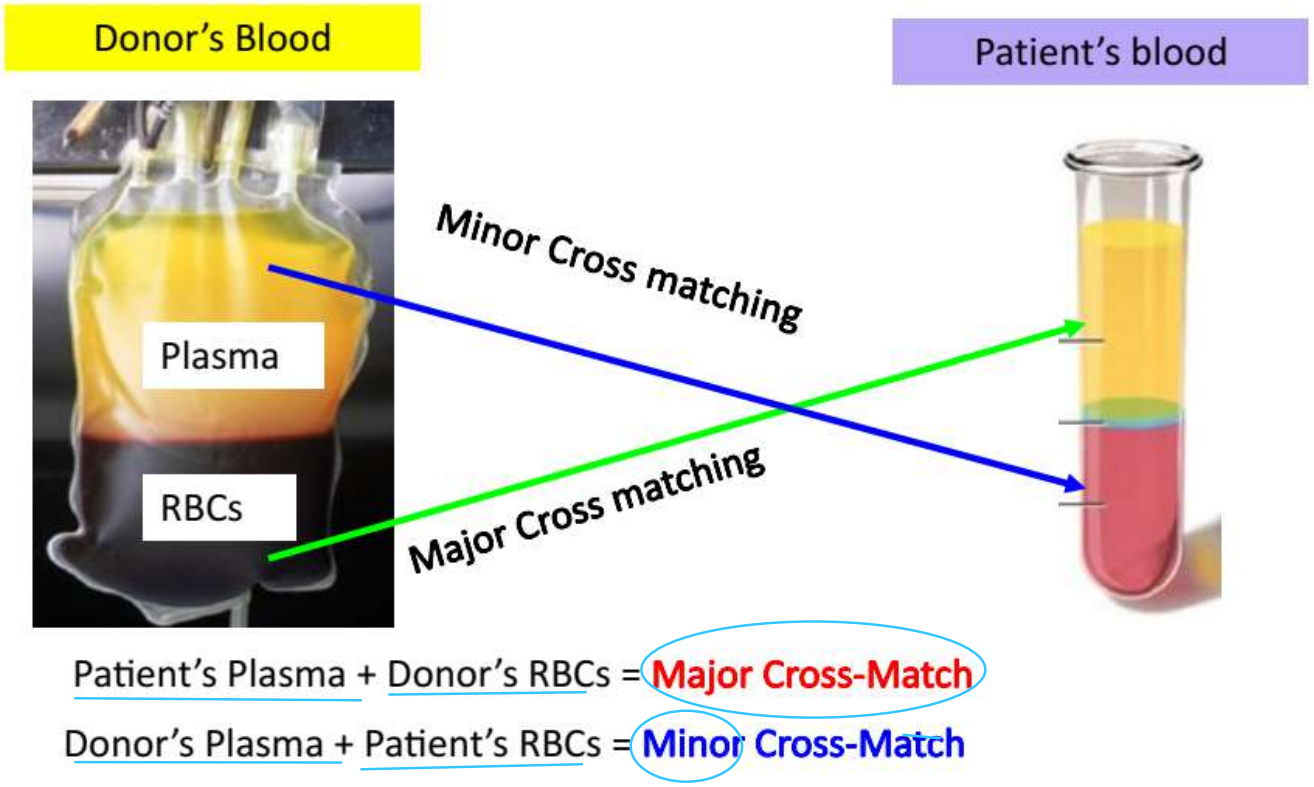
If an Rh-negative person is transferred with Rh-positive blood, he will produce agglutinins against the Rh factor (D antigen). If, after some time, this person is transfused again with Rh-positive blood, agglutination occurs.

ABO incompatibility is the most common maternal-fetal blood group incompatibility and the most common cause of hemolytic disease of the newborn (HDN). ABO incompatibility is often seen in newborns with type A blood because of the higher frequency of type A compared to type B in most populations. ABO incompatibility in newborns generally presents as neonatal jaundice in contrast to the severe intrauterine or neonatal hemolytic anemia associated with Rh sensitization, clinically important neonatal anemia due to ABO incompatibility occurs infrequently. The major clinical issue with HDN due to ABO incompatibility is jaundice.

Several reasons have been proposed to account for the lack of intrauterine hemolysis due to ABO incompatibility. These include less well-developed A and B antigens on fetal red blood cells to stimulate maternal antibody production and the ubiquitous distribution of A and B antigens in other tissues resulting in fewer antibodies that cross the placenta to bind to antigens on fetal red cells. The most important reason that ABO incompatibility does not cause hydrops fetalis (intrauterine fetal death) is that the naturally occurring anti-A and anti-B antibodies are IgM and do not cross the placenta. Less than 1% of mothers with type O have clinically significant anti-A or anti-B antibodies, that is, IgG.

Importance of blood group determination: RBCs from donar + Antibody from recipient

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.



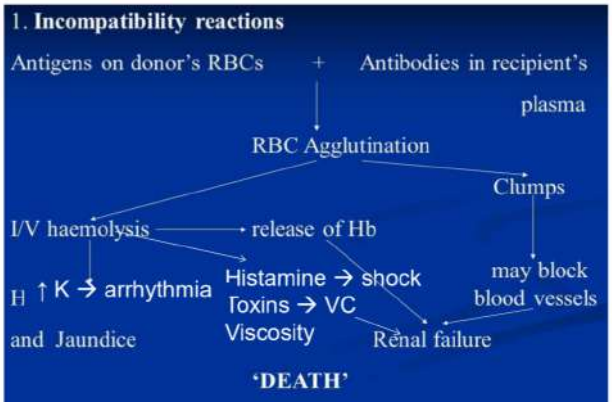
When incompatible blood is transfused, the mismatched transfusion reaction occurs immediately. The reaction is primarily due to the agglutination of the donor's red cells followed by their hemolysis. This is called acute hemolytic transfusion reaction. Usually, it occurs due to ABO incompatibility. The 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 hemoglobin will convert to bilirubin
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 vasoconstriction5.
5. Hyperkalemia (due to the release of potassium ions from red cells). This may cause cardiac arrest in diastole. in relaxed state

في الرسمة مجلس الارقام

Importance of blood group determination



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)**:

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.

2. Macrocytic Anemia (Megaloblastic Anemia):

In this type of anemia, the size of RBCs is larger than normal. It is caused by vitamin B_{12} or folic acid deficiency. hemoglobin content maybe normal and maybe not

3. Normocytic Normochromic Anemia:

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

-Causes of normocytic normochromic anemia:

1. *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.
2. *Bone Marrow Depression (Aplastic Anemia):* Depression of the bone marrow will decrease all blood elements (RBCs, WBCs, and platelets). It may be due to the following:
   - A- Exposure to X-rays and atomic irradiation,
   - B- Malignancy or viral infection.
   - C- Drugs
3. *Excessive Breakdown of RBCs (Hemolytic Anemia):* This may be due to intrinsic or extrinsic factors. have hemoglobin s
   - A *Intrinsic factors: as in sickle cell anemia and G6PD deficiency.*
   - B *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.

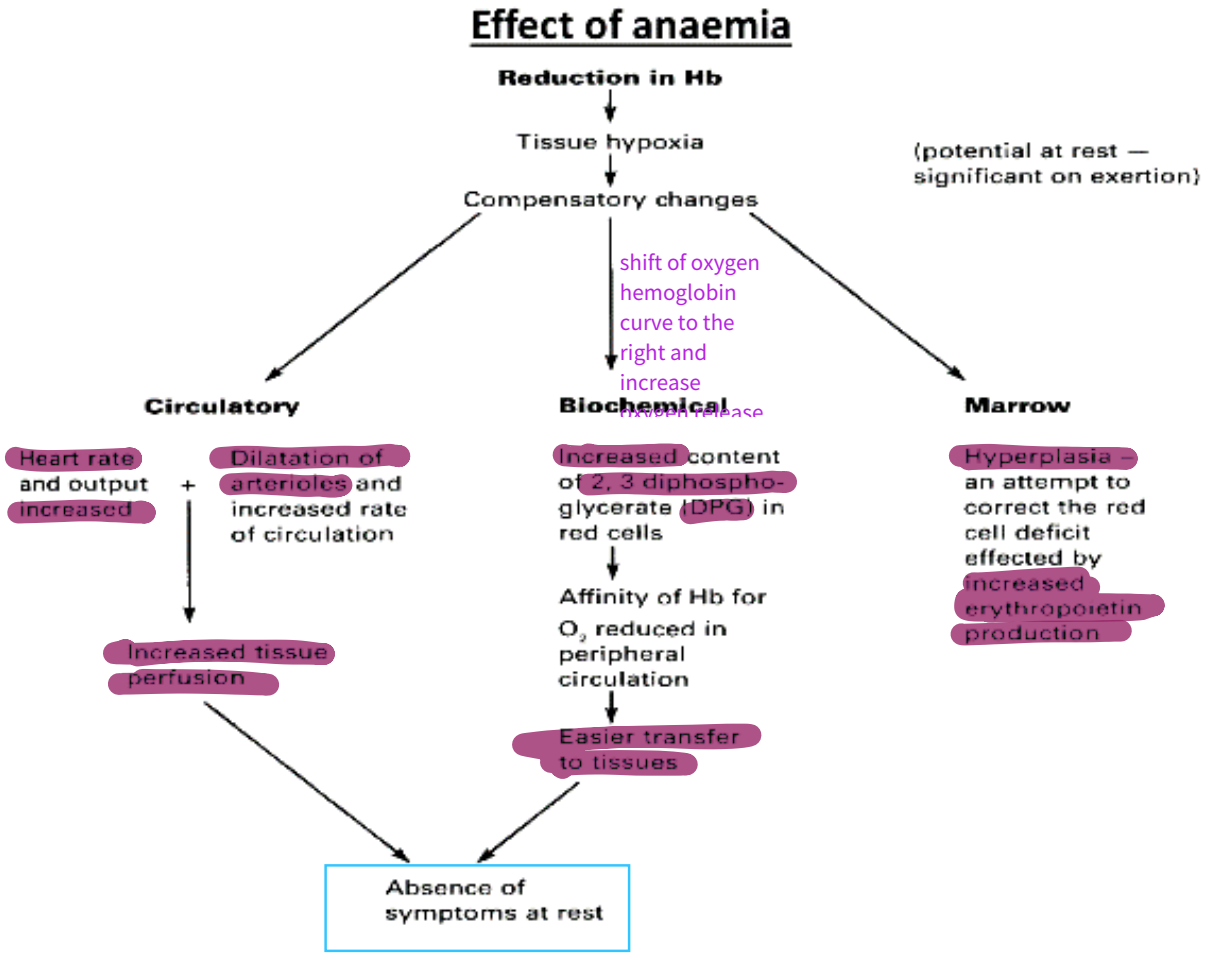
NB/

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



POLYCYTHEMIA: زياده في عدد الخلايا الحمراء او in the cell mass

It represents an increase in the number of red cells. It exists in two main forms:

A-Absolute Polycythemis:

1. ***The primary form***, also called polycythemia vera, is a clonal neoplastic disorder of hematopoietic stem cells. disorders in bone marrow and increase in RBCs WBC and platelets
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: فعليا عدد RBCs ممتاز ولكن تعرض الشخص لجفاف فقلت نسبه plasmaو زادت ال viscosity

The relative or apparent polycythemia is not true polycythemia but a spurious increase in red cells due to dehydration. والحل هنا هو اخذ IV fluids and water

==========

increase in viscosity of the blood and that will cause stagnant hypoxia

hypoxia و حدوث erythropoietin secretion يزداد بزياده

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.

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
4. Enzymes for the synthesis of prostaglandins from phospholipids of platelet membrane. Prostaglandins are local mediators 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)

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 platelet plug formation by platelet reactions.
C. Blood clot formation to stabilize the temporary platelet plug.
D. Limitation reaction to dissolve clot after wound healing.

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.

Transient (VC) تقليل تدفق الدم المكان → Neuronal reflex → endothelin → from damaged endothelial cells

تقلص عضلي محلي

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 A_2 liberated from platelets cause vasoconstriction.

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: 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.

2-Platelet 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.

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 A_2 synthase converts prostaglandin to thromboxane A_2, which causes vasoconstriction, and helps the release reaction and platelet aggregation.

thromboxane A2

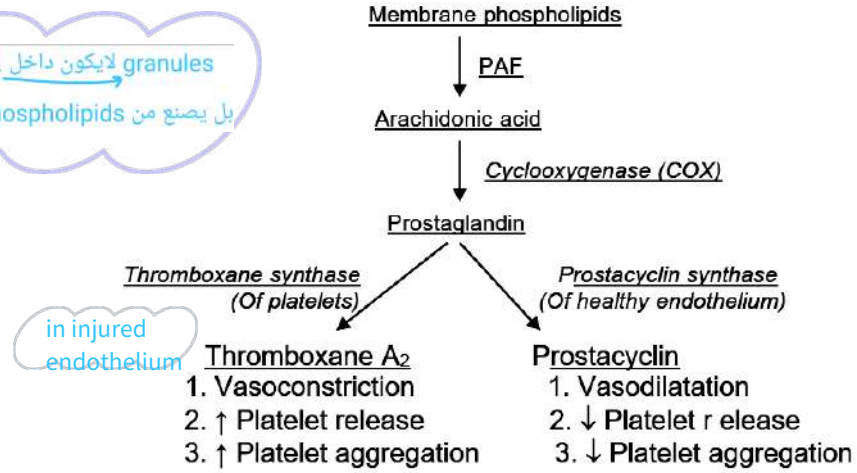
seratonin

① Seratonin ② TXA_2 ③ smooth muscles

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 A_2, prostacyclin keeps the platelet plug localized to the injury site.

thromboxane A2. لايكون داخل granules

cell membrane phospholipids بل يصنع من



NB Aspirin inhibits cyclooxygenase. It, therefore, decreases the synthesis of both thromboxane A_2 and prostacyclin. The endothelial cells can start to produce new cyclooxygenase within a few hours, while platelets cannot. Therefore, the daily intake of small amounts of aspirin reduces clot formation and prevents myocardial infarctions.

4-Platelet aggregation: Released ADP and thromboxane A_2 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 A_2. This self-propagating process forms a

مراجعه من ماده الباثو

* hemostasis هي عملية تكون كتلة صلبة من الدم الهدف منها هو سد ثقب في Blood vessel لحين ترميم ال (BV) ثم يحدث تذويب لها Thrombus

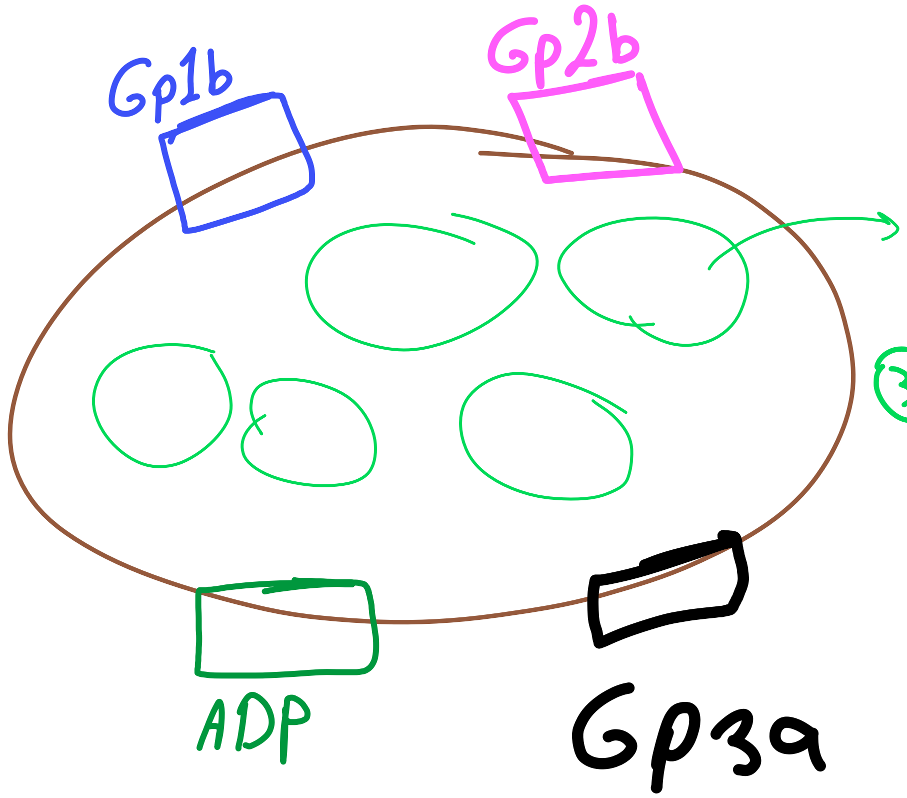
* تتكون ال hemostasis من ① fibrin ② platlets

* حضرت شرح د حمزه مراد
* حسيت احسن الملخص

Hemostasis

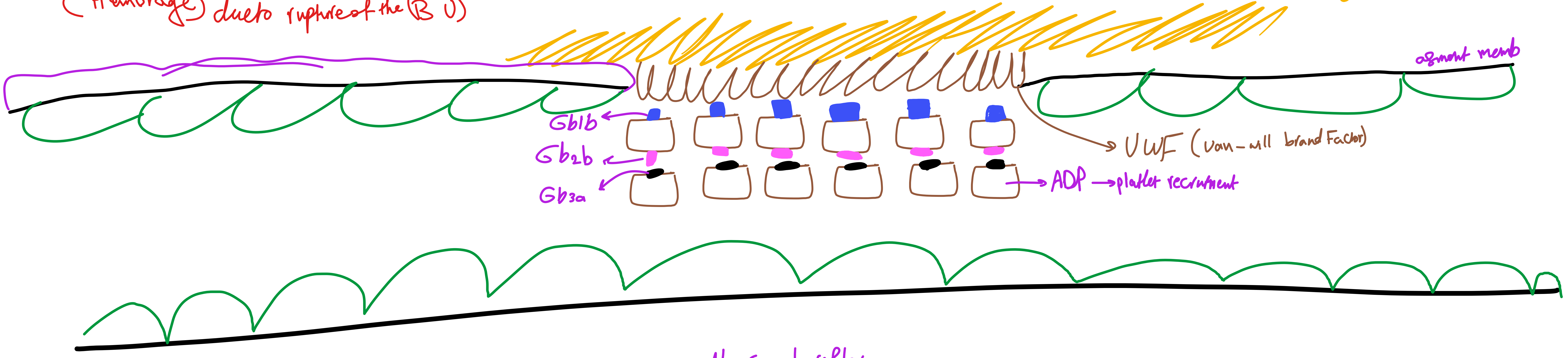
- Transient (VC)
  مسؤول عنها Blood vessels
- ② Primary hemostasis
  مسؤول عنها ال platlets
- ③ secondary hemostasis
  مسؤول عنها بروتينات تسمى clotting factor

* Structure of platlets



Granules consist of ① fibrinogen ② PDGV (platlet derived growth factor) ③ Ca^{+2} ④ PL (phospho lipids) ⑤ Seratonin ⑥ TXA_2 ⑦ ADP

لا حدوث نزف في (BV) نتيجة تدمير جروح
(Hemorage) due to rupture of the (BV)



① Transient (VC) تقليل تدفق الدم للمكان
- → Neuronal reflex
- → endothelin → from damaged endothelial cells

② Primary hemostasis

Ⓐ platlet adhesion — Between platlets (Gp1b) → CT VWF

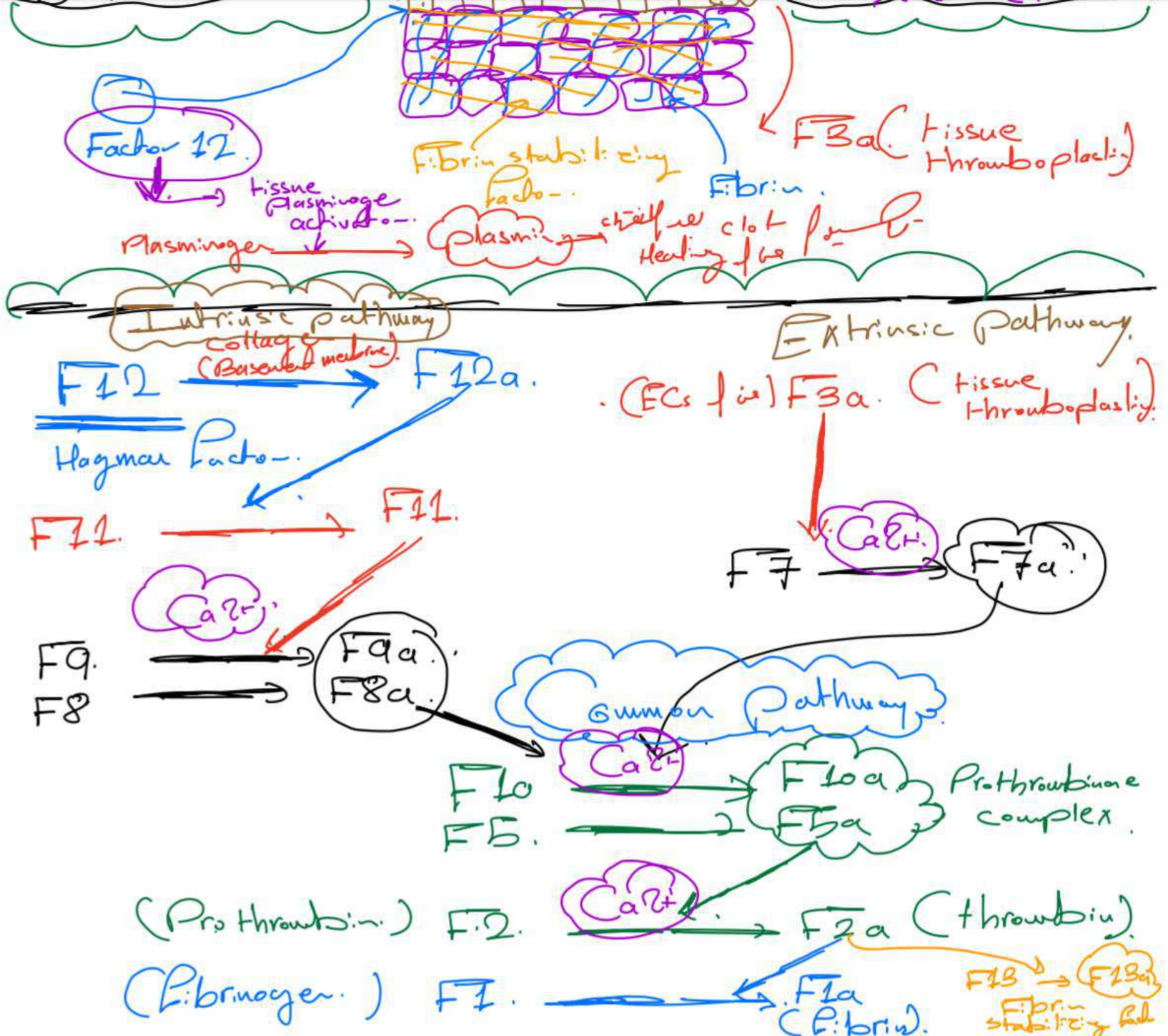
Ⓑ platlet activation (degranulation)
- TXA2 → VC
- seratonin → VC
- ADP → platlet recruitment
- fibrinogen
- Ca^{+2}/PL — دور في secondary hemostasis

Ⓒ platlet aggregation — Gb2b → Gb3a بيرسل يعمل & fibrinogen بأثير ال

Ⓓ formation of platlet plug — (BV) هدفها اغلاق مؤقت للتقني (platlets) من كتلة صغيرة من

③ Secondary hemostasis — هدفها تقوية ال (platlet plug) ووصول بما بروتينات تسمى clotting factor يتم ايتامهم من الكبد بتواجدوا داخل البلازما على شكل (Inactive) & يطلق عليهم اسم (Zymogens) & عددهم (13)

* نهاية Secondary hemostasis يتم تكوين (fibrin clot)
- platlets
- fibrin
- fibrin stabilizing factor


Factor 12.
Tissue plasminogen activator.
Plasminogen
Plasmin
Fibrin stabilizing factor.
Fibrin.
F3a (tissue thromboplastin)
Intrinsic pathway
(Basement membrane)
F12
F12a.
Hagman factor.
F11.
F11.
Ca2+.
F9.
F8
F9a.
F8a.
Extrinsic pathway.
(ECs) F3a. (tissue thromboplastin)
F7
Ca2+.
F7a.
Common pathway.
Ca2+
F10
F5.
F10a
F5a
Prothrombinase complex.
(Prothrombin) F2.
Ca2+
F2a (thrombin)
(Fibrinogen.) F1.
F1a (Fibrin).
F13
F13a
Fibrin stabilizing factor

platelet plug that closes the blood vessel.

5-Platelet procoagulant activity: 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.

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

III. Blood Coagulation (Blood Clotting): The clotting factors are plasma proteins, mostly (β-globulins). They are proteolytic enzymes, which are present in blood in an inactive form. When activated, they activate other inactive enzymes in cascade reactions, which end in clot formation. Clotting factors were given numbers to simplify the description of the clotting mechanisms. They are given an "a" when they are activated.

Clotting factors are categorized into three groups:

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

Factor 7, Factor 9 and factor of 10 is a present in the serum

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+}.

fibrin stabilizing Factor

- Fibrinogen ⟶ fibrin monomer + 2 pairs of polypeptide chains

- Fibrin monomers polymerize ⟶ loose mesh of fibrin

- Fibrin $\xrightarrow[\text{XIII + } Ca^{2+}]{\text{Cross linkages}}$ tight fibrin clot

The conversion of fibrinogen to fibrin is catalyzed by thrombin, which is formed from prothrombin in the presence of active factor X.

- Prothrombin $\xrightarrow{\text{Xa}}$ thrombin

Either intrinsic or extrinsic pathways activate factor X.

A. Intrinsic Pathway

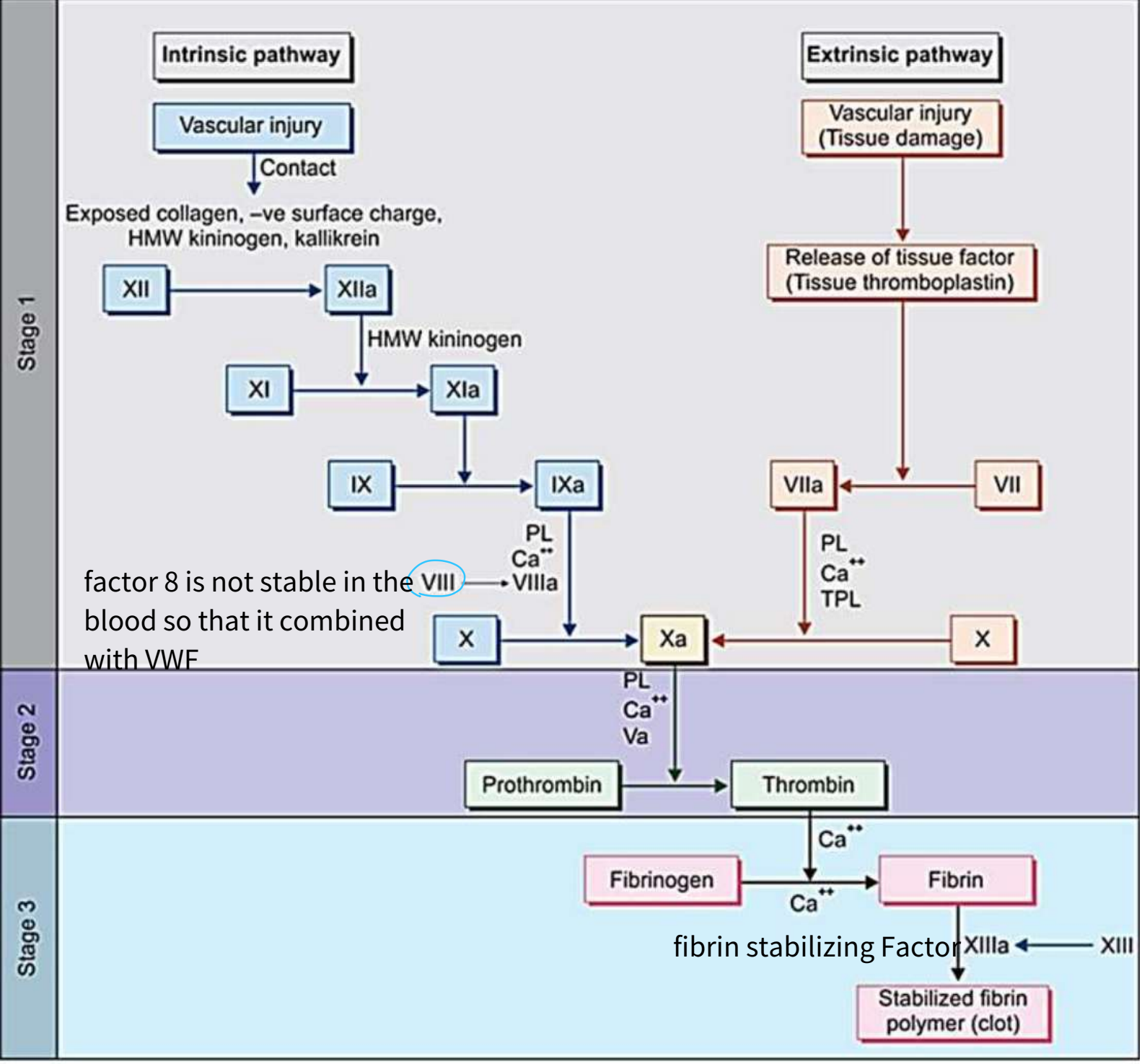
- This system is called intrinsic, as the phospholipids involved in the reactions arise from platelets (PF3), i.e., it is present in plasma.
- Initiation of the pathway may occur either:

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

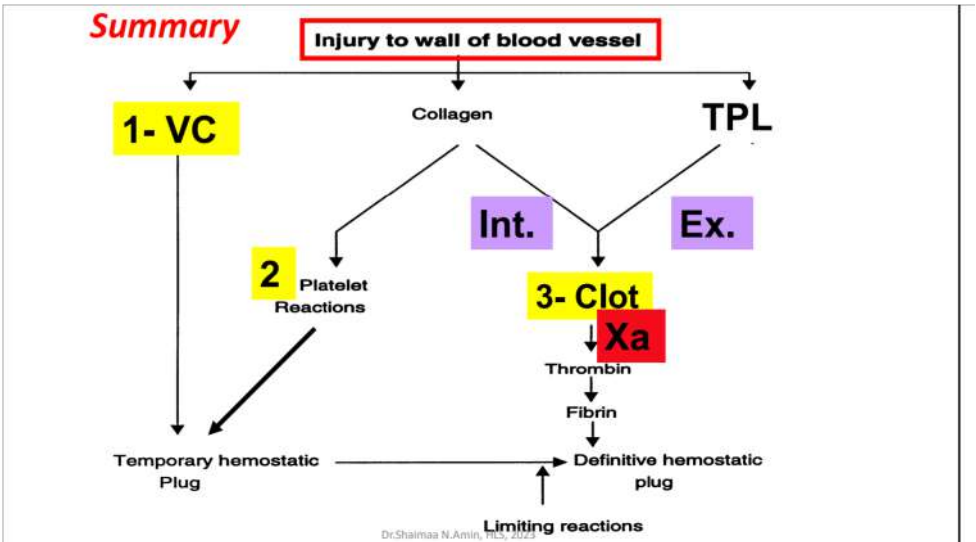
1. Any of the previously mentioned factors activates factor XII.
2. XIIa activates factor XI, which in turn activates IX.
3. IXa forms a complex with VIIIa and activates factor X in the presence of phospholipids (PL) and Ca^{2+}.



#VWF is it present in subendothelial collagen, platelet granules and endothelium

#trauma stimulates intrinsic and extrinsic pathway at the same time

#contractile protein in platelets couse plug retraction



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.

Important Notes #VWF is it present in subendothelial collagen, platelet granules and endothelium

-Von Willebrand factor (vWF) is 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, and storage granules within endothelial cells and 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.

- 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) tissue thromboplastin
- 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: factor 2

- activates fibrinogen to fibrin.
- activates the other factors of the fibrinogen group (V, VIII, and XIII) 5 8 13
- accelerates the actions of factors IX, X, and XI
- accelerates the formation of more thrombin from prothrombin.
- Accelerates platelet aggregation.

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.

Prevention of Blood Clotting and Lysis of Blood Clots

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. produced by mast cells

B. Specific limiting reactions:

1. Thromboxane A_2 and prostacyclin: The formation of thromboxane A_2 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 IX, X, XI, and XII, blocking their activity. This binding is facilitated by heparin.
3. The Fibrinolytic System:

-Thrombomodulin is produced by all endothelial cells (except those of the cerebral microcirculation). 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) increases the formation of plasmin.

-Plasmin (fibrinolysin) lyses fibrin and fibrinogen, forming fibrinogen degradation products (FDP), inhibiting thrombin.

Anticoagulants: These are substances used to prevent blood clotting.

A. In vitro anticoagulants: They prevent blood coagulation outside the body.

1. Removal of Ca^{2+} ions:
   - Oxalates precipitate Ca^{2+} ions as calcium salts,
   - Citrates (used in blood transfusions) bind Ca^{2+} ions by deionizing them.
2. Silicon-coated tubes prevent the activation of factor XII.
3. Addition of heparin.

B. In vivo anticoagulants: They prevent blood clotting inside the body.

	Heparin	*Dicumarol*
Origin	Mast cells and basophils	**Plant**
Mode of Action	Facilitates the action of Antithrombin III which inhibit Factor 9 ,10, 11 ,12	**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	**in vivo**
Onset	Rapid	**Slow**
Duration	Short	**Long**
Administration	intravenous (IV) and subcutaneously (SC)	**Orally**
Antidote	**Protamine sulfate 1%** ويزيد heparin يعمل عكس عمل the viscosity of the blood **Fresh blood transfusion**	**Vitamin K** **Fresh blood transfusion**

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^{O}C. *It is prolonged in* disorders such as vitamin K deficiency, hemophilia, and liver diseases.

b-Prothrombin time: PT assessment for extrinsic pathway

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.

c-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.

$$\mathrm{INR} = \left(\frac{\mathrm{PT_{test}}}{\mathrm{PT_{normal}}}\right)^{\mathrm{ISI}}$$

The INR is the ratio of a patient's prothrombin time 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 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.

d- 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.

e-Prothrombin concentration: normally > 70 %.

Abnormalities of Hemostasis:

A-Bleeding:

1. Thrombocytopenic purpura:

- It is due to decreased platelet count below 50,000/mm^3.
- It is characterized by the presence of subcutaneous hemorrhages.
- The bleeding time is prolonged.
-

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 that 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.

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 arthopathy) 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.

B-Clotting (Thromboembolic Conditions):

Slow blood flow [long bed rest, varicose veins, atherosclerosis]

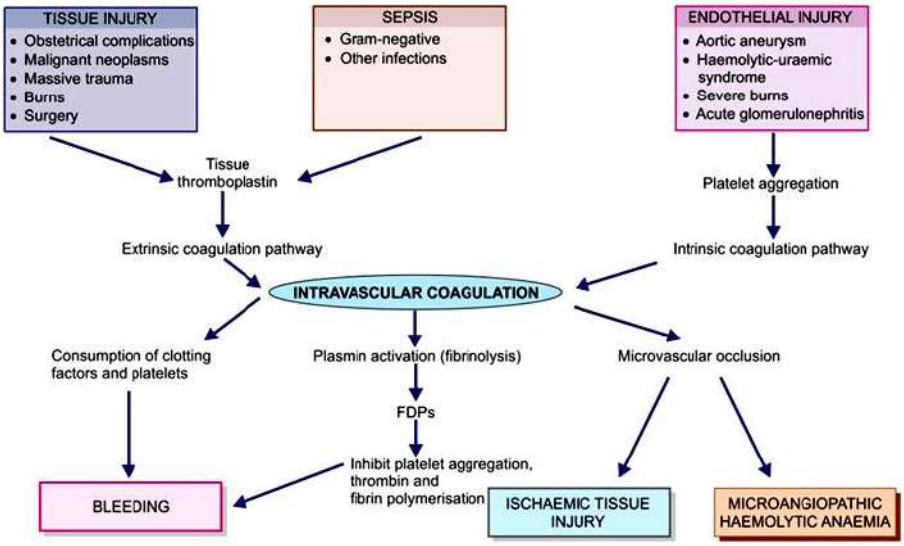
C. Disseminated Intravascular coagulation (DIC):

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



WHITE BLOOD CELLS (WBCs)
LEUKOCYTES

The total leukocytic count is 4,000–11,000/mm^3 of blood.

Functions of Leukocytes

Leukocytes are responsible for the body's defense against pathogenic organisms and their toxins.

The matured cells are released into circulation and remain in circulation for a few hours before they enter the tissues (circulation pool): At rest, many leucocytes, especially neutrophils, adhere to the endothelial lining of blood vessels, which is ***called the margination pool of leucocytes***. In addition, leucocytes circulate in the blood ***(the active circulation pool)***.

Disruption of margination causes leucocytosis: Leucocytes adhere to the inner lining of the blood vessel, called margination. In exercise and other conditions of increased hemodynamics, leukocytosis occurs mainly due to the disruption of the margination of leucocytes.

TYPES OF LEUKOCYTES:

A. Granular Leukocytes:

1. *Neutrophils:* (60-70% of WBCs)

-They represent the first line of defense against invading organisms.

- They perform their function by:

a. Margination: Neutrophils attach to the walls of capillaries.

b. Diapedesis: Neutrophils squeeze themselves through the pores of capillaries and pass into tissue spaces.

c. Amoeboid movement: This movement allows neutrophils to reach invading organisms.

d. Chemotaxis: Breakdown products of inflamed tissues and bacterial toxins attract neutrophils to the infected area.

e. Phagocytosis: This is the most important property of neutrophils. They can ingest invading bacteria and necrotic tissue by engulfing them (endocytosis). It results in the formation of a phagocytic vacuole. The neutrophil granules release their contents into the phagocytic vacuoles, killing the bacteria.

- In more severe infections, pus is formed. It consists of necrotic tissue, dead neutrophils, and dead macrophages.

2. Eosinophils: (2-6% of WBCs)

Eosinophils increase in parasitic infestations. They kill too large parasites to be engulfed by releasing toxic substances.

-They also increase during allergic conditions.

-Eosinophils are weakly phagocytic and show chemotaxis.

3. Basophils: (0-1% of WBCs)

- Basophils are similar to mast cells. They contain histamine (increases capillary permeability) and heparin (naturally occurring anticoagulant).

B. Agranular Leukocytes:

1. Monocytes: (2-8% of WBCs)

-They are the largest type of leukocytes.

-They enter the blood from the bone marrow and circulate for 72 hours. Then they enter the tissues & become ***tissue macrophages***. The tissue macrophage system was earlier known as the reticuloendothelial system.