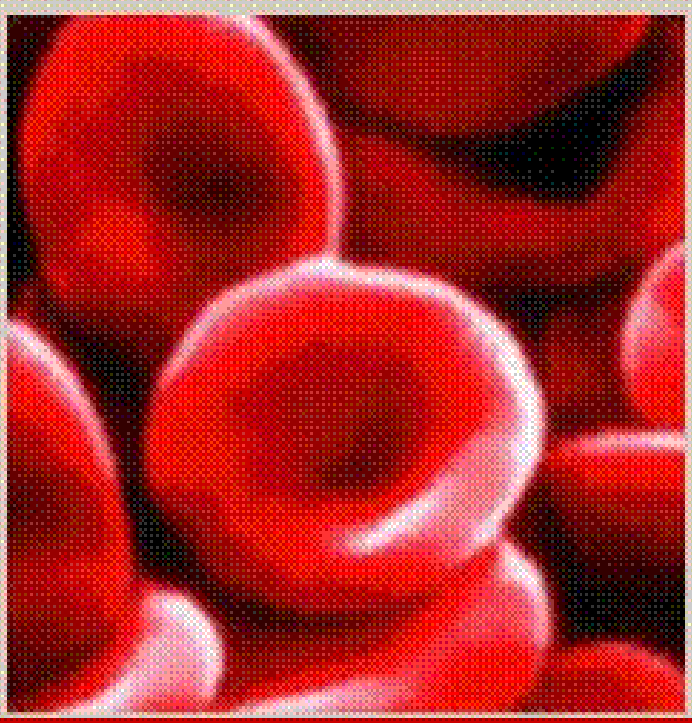
Physiology of BLOOD



Dr. Muhannad Shweash
PhD United Kingdom (UK)

PHYSIOLOGY OF BLOOD *Lec #2*

Q- Why don't you bleed to death from a minor injury?

- **Hemostasis** (stoppage of blood flow after damage).

Steps of hemostasis:

1. Vascular spasms (vasoconstriction at injured site)
2. Platelet plug formation (plugging the hole)
3. Coagulation (blood clotting - complex mechanism)

Vascular Spasms: first response to vascular injury - vasoconstriction is stimulated by:

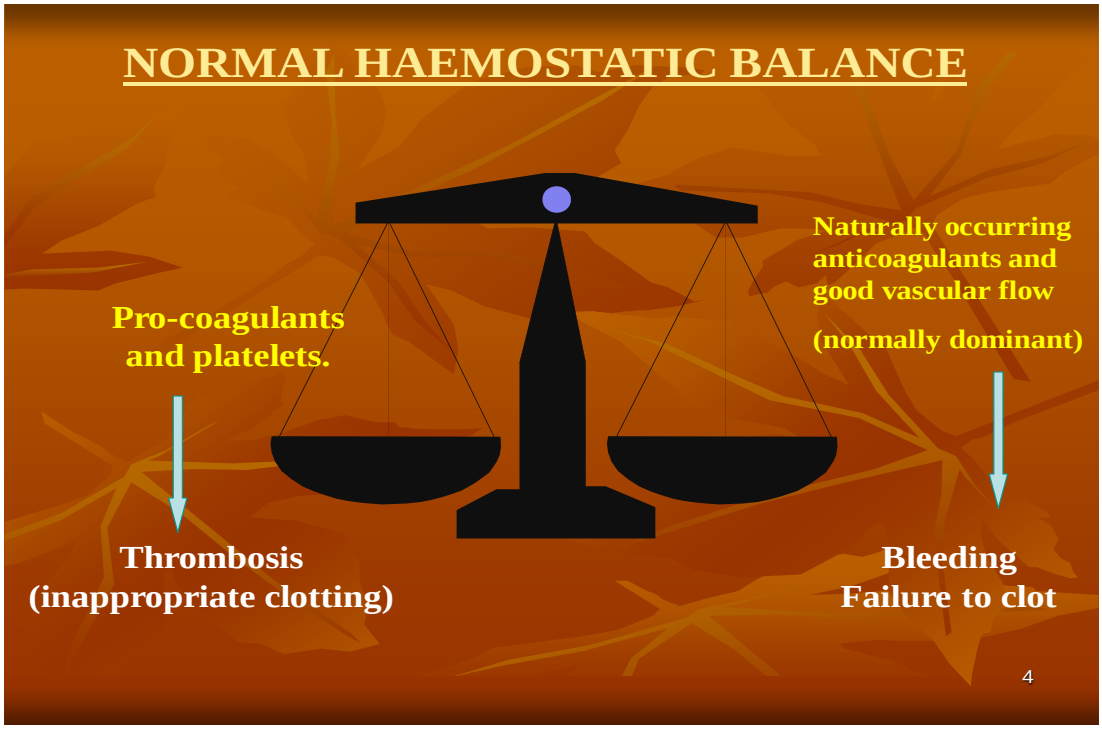
a. compression of vessel by escaping blood
b. injury "chemicals" released by injured cells
c. reflexes from adjacent pain receptors

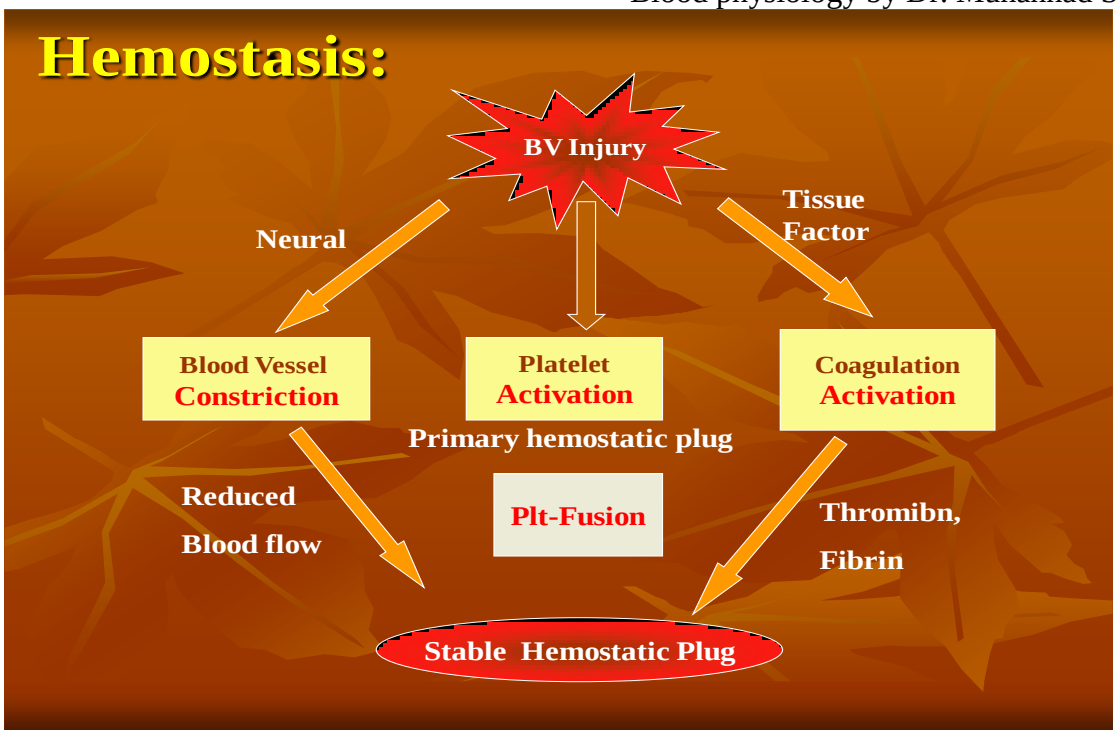
Formation of a Platelet Plug:

1. Damage to endothelium of vessel
2. Platelets become spiky and sticky in response
3. Platelets attach to damaged vessel wall to plug it
4. Platelets produce thromboxane A2 - granule release
5. Serotonin release enhances vascular spasm
6. ADP - attracts and stimulates platelets at site
7. Prostacylin - inhibits aggregation at other sites

Platelet aggregation: When a blood vessel wall is injured, platelets adhere to the exposed collagen and **von Willebrand factor** in the wall via the receptors on the platelet membrane. Binding produces platelet activations which release the

contents of their granules. The released ADP acts on the ADP receptors in the platelet membranes to produce further accumulation of more platelets.





- **Hemostasis system**

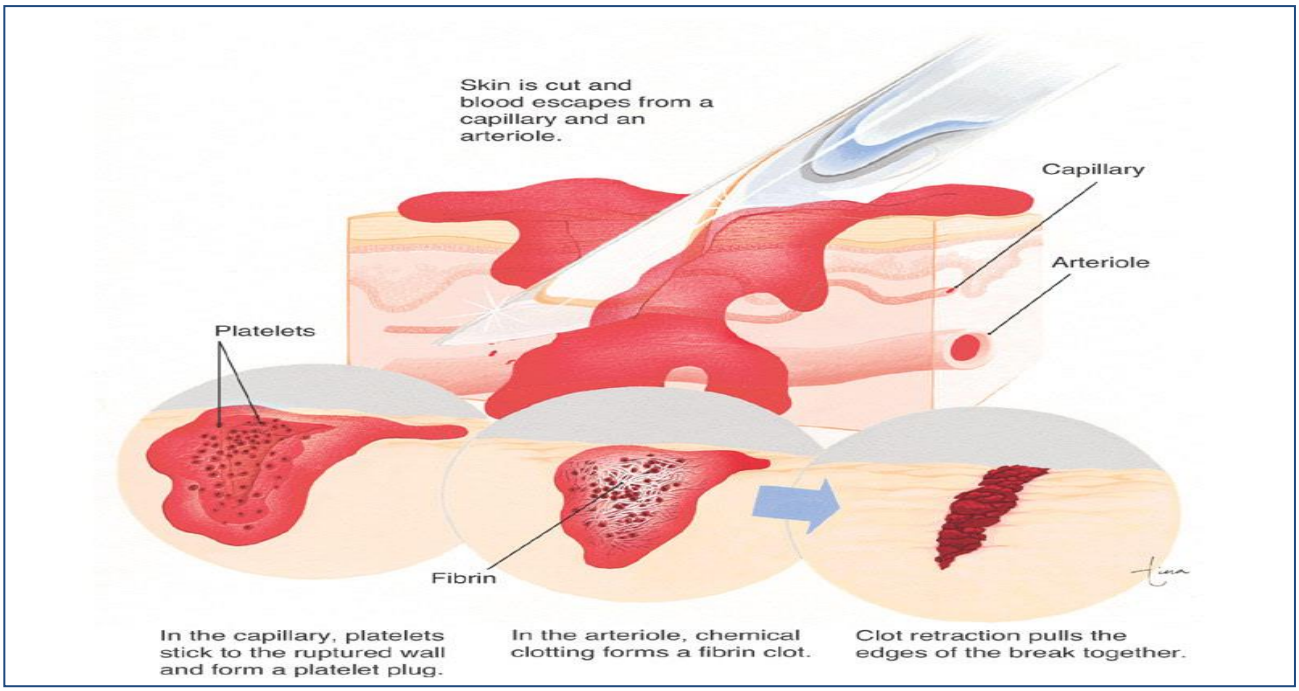
- Hemostasis is the physiologic system, which support the blood in the fluid condition and prevent bloodless.

- Hemostasis system vital necessary and functionally connect with the cardiovascular, digestive, breathing, endocrine and other systems.

- **Successful haemostasis depends on:**

  - Vessel wall
  - Platelets
  - Coagulation system

- Fibrinolytic system



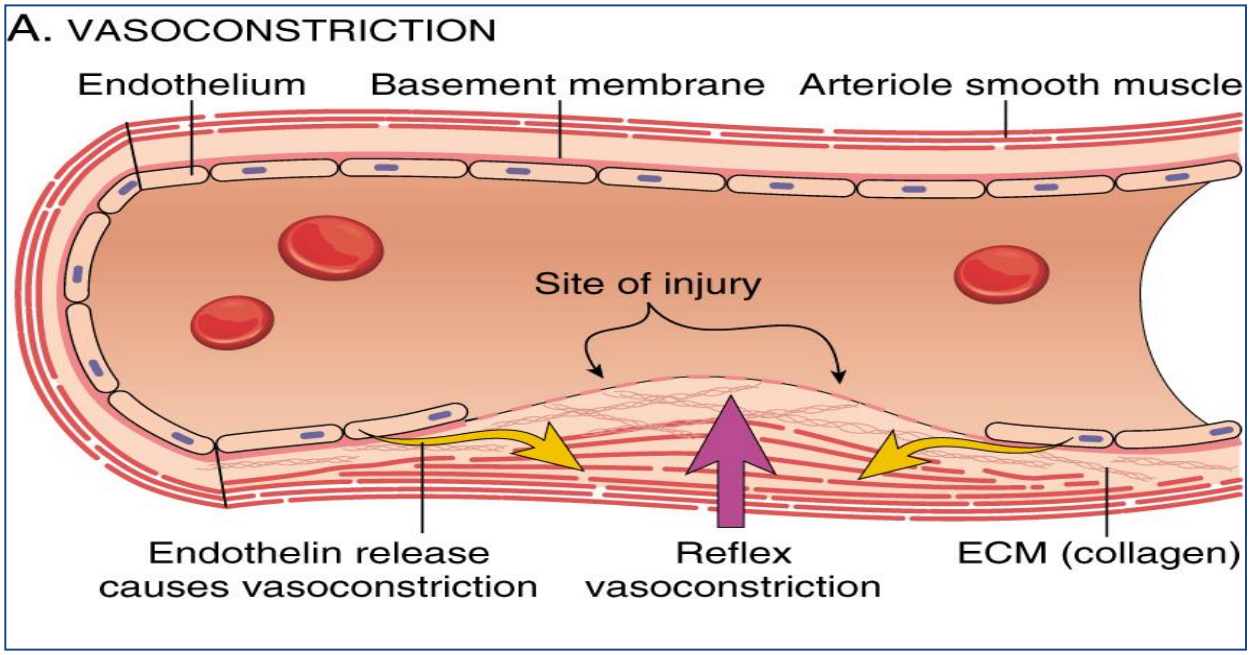
* The components of hemostasis system

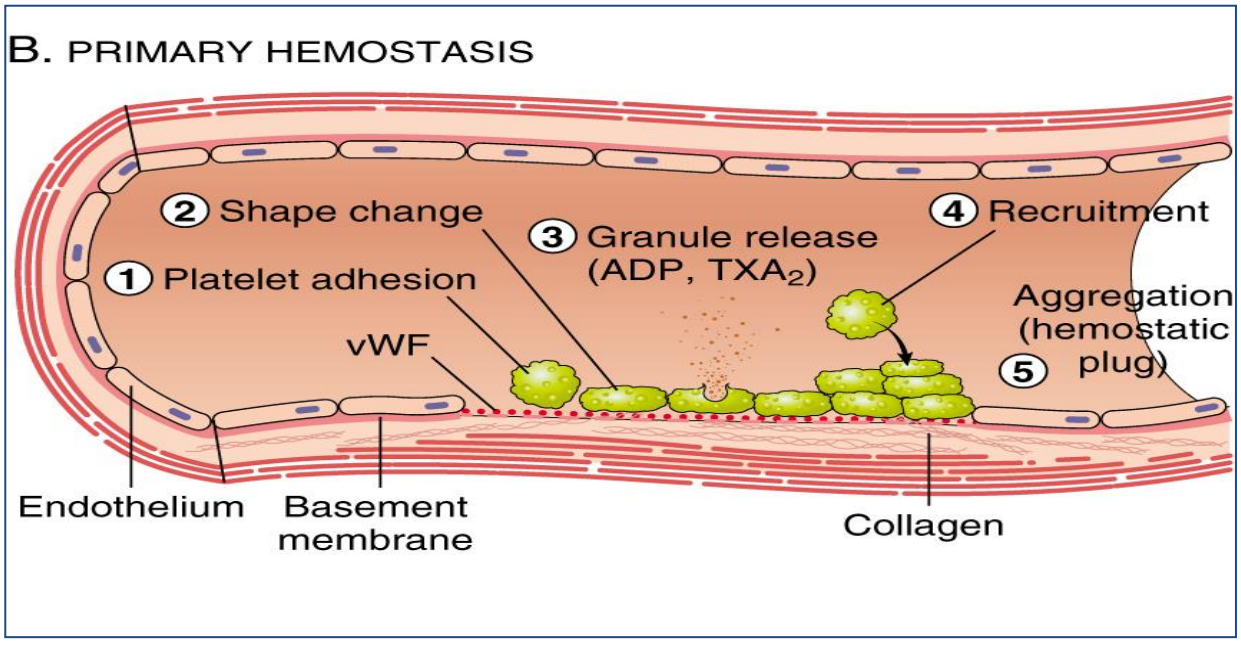
- **<u>The components of hemostasis are:</u>**
- - **Wall of the vessels**,
- - **Blood cells** – platelets, erythrocytes, leukocytes,
- - **Enzymes and nonenzymes components** of plasma – clotting and anticlotting substances, fibrinolytic components.
- **<u>There are 2 kinds of hemostasis</u>**: vessel-platelets (**primary**) and coagulative (**secondary**).

- **<u>Process- *primary haemostasis*</u>**

- In a normal individual, coagulation is initiated within 20 seconds after an injury occurs to the blood vessel damaging the endothelial cells.

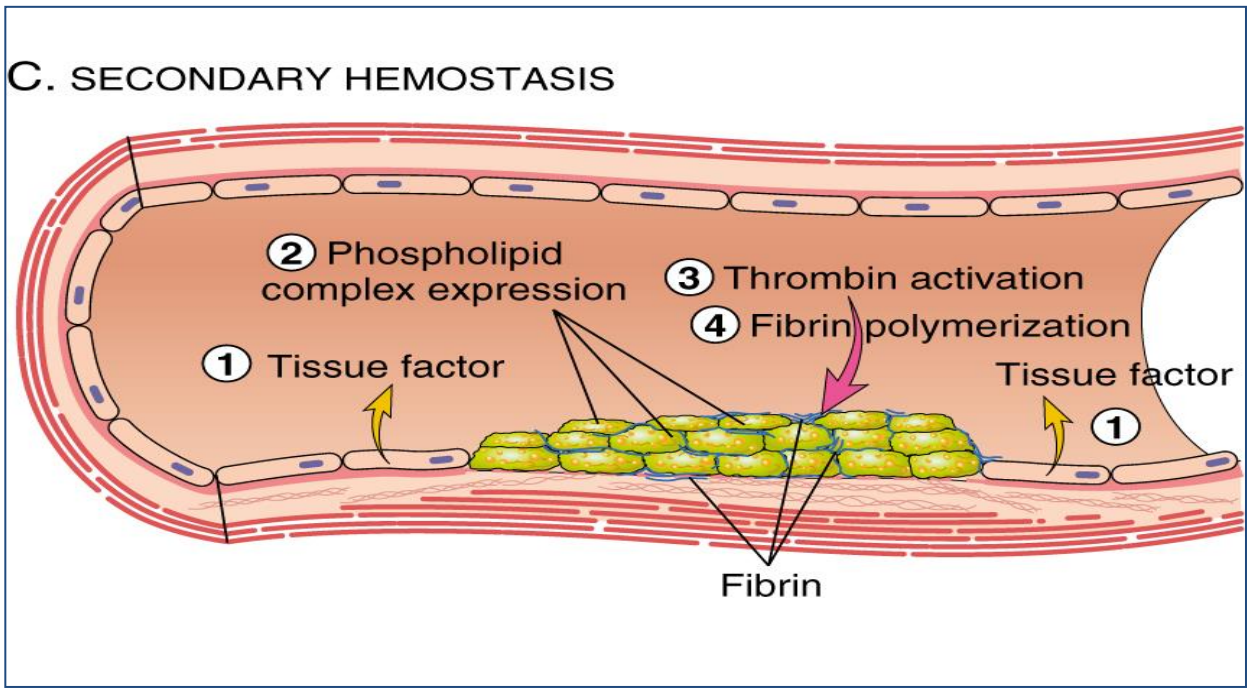
- Platelets immediately form a haemostatic plug at the site of injury. This is called *primary haemostasis*.





- **Secondary haemostasis**

- Secondary haemostasis then follows- **plasma** components called *coagulation factors* respond (in a complex cascade) to form **fibrin** strands which strengthen the platelet plug.
- Contrary to popular belief, coagulation from a cut on the skin is not initiated by air or drying out, but by platelets adhering to and activated by **collagen** in the blood vessel **endothelium**.
- The activated platelets then release the contents of their granules, these contain a variety of substances that stimulate further platelet activation and enhance the haemostatic process.



- **<u>PLETELET PHYSIOLOGY</u>**:

<u>Platelets Production:</u>

Hematopoietic stem cell

↓

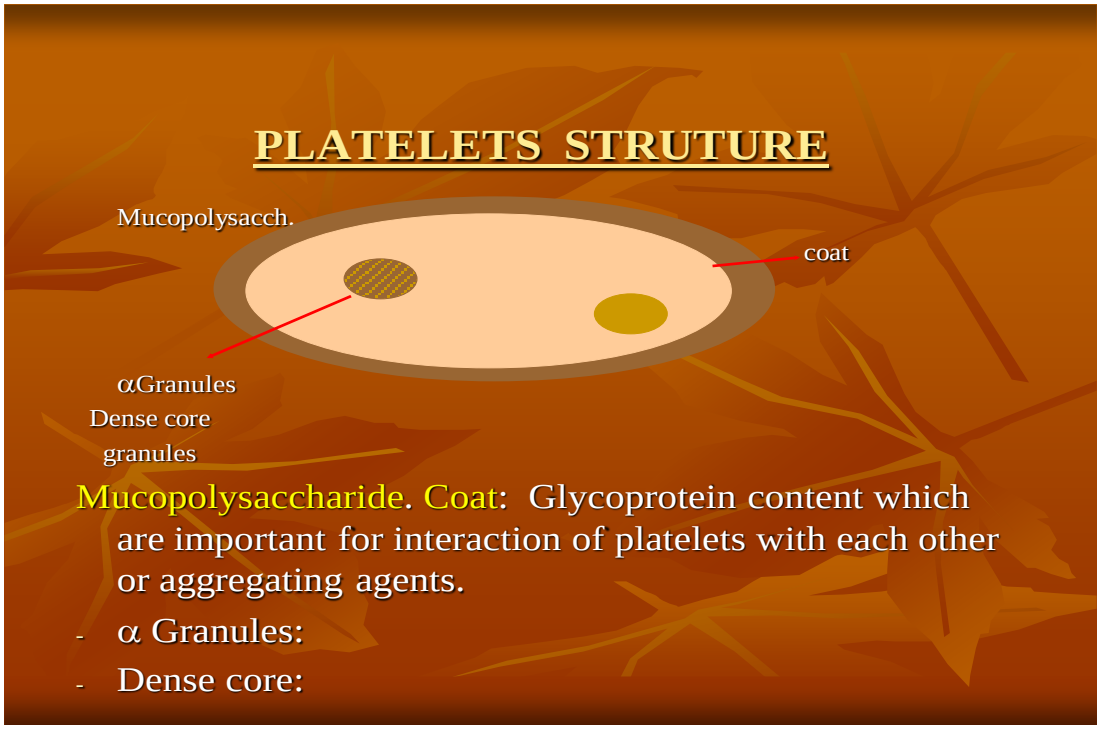
Megakaryoblast

↓

Megakaryocyte

↓ Fragmentation of cytoplasm

Platelets



Platelets (thrombocytes - "clotting")

The platelets are small, granulated bodies that aggregate at sites of vascular injury. They lack nuclei and are 2-4 um in diameter. There are about 300,000/uL of circulating blood, and they normally have a half-life of about 4 days. The megakaryocytes, giant cells in the bone marrow, form platelets by pinching off bits of cytoplasm and extruding them into the circulation. Between 60% and 75% of the platelets that have been extruded from the bone marrow are in the circulating blood, and the remainder are mostly in the spleen. Splenectomy causes an increase in the platelet count (thrombocytosis).

Platelets have a ring of microtubules around their periphery and an extensively invaginated membrane with an intricate canalicular system in contact with the ECF. Their membranes contain receptors for collagen, ADP, vessel wall von

Willebrand factor and fibrinogen. Their cytoplasm contains actin, myosin, glycogen, lysosomes, and **two types of granules**:

(1) Dense granules, which contain the nonprotein substances that are secreted in response to platelet activation, including serotonin, ADP and other adenine nucleotides,

(2) α-granules, which contain secreted proteins other than the hydrolases in lysosomes. These proteins include clotting factors and platelet-derived growth factor (PDGF).

PDGF is also produced by macrophages and endothelial cells. PDGF stimulates wound healing and is a potent mitogen for vascular smooth muscle.

* Platelet production is regulated by:

1. **Colony- stimulating factors** that control the production of megakaryocytes.
2. **Thrombopoietin**, a circulating protein factor. This factor, which facilitates megakaryocyte maturation

* Thrombocytopenic purpura:

When the platelet count is low, clot retraction is deficient and there is poor constriction of ruptured vessels. The resulting clinical syndrome (thrombocytopenic purpura) is characterized by easy bruise ability and multiple subcutaneous hemorrhages. Purpura may also occur when the platelet count is normal, and in some of these cases, the circulating platelets are abnormal (thrombasthenic purpura). Individuals with thrombocytosis (increased number of platelets) are predisposed to thrombotic events.

- **Function of platelets are:**

1. Haemostatic function – platelets produce substances, which are secure the hemostasis.

2. Angiotrophic function – provide trophy of endotheliocytes of vessel wall, support structure and functions of micro vessels. These function is realize by adhesion of platelets to endotheliocytes and injection the enzymes into the endotheliocytes.

3. Transport function – transfer the enzymes, ADP, serotonin and other.

4. Phagocytes function – the contain of platelets help to kill viruses and antigens bodies.

5. Regeneratory function – platelets have the growth factor, which help to grow the endothelial and muscles cells which are present in the vessel wall.

- **PLATELET PLUG**

- Platelets are normally **disc shaped**, but activated ones change shape and become **spiny all over**, exposing the receptors on them.
- **Von Willebrand factor** helps the platelet receptors anchor to the torn blood vessel.
- Inside the platelet, the **granules** release their contents, including **ADP**, which is dumped into the **plasma**. **ADP** is the #1 signal to recruit more platelets. Calcium, serotonin,
- **Thromboxane A2** is also released. As the platelets are activated and sticky, they will stick to exposed collagen and to each other in a platelet plug. It is not permanently fixed in place, that's the clotting phase.
- In this stage, the platelet plug is unstable, and **BP** could dislodge it.

- **Platelet Phase**

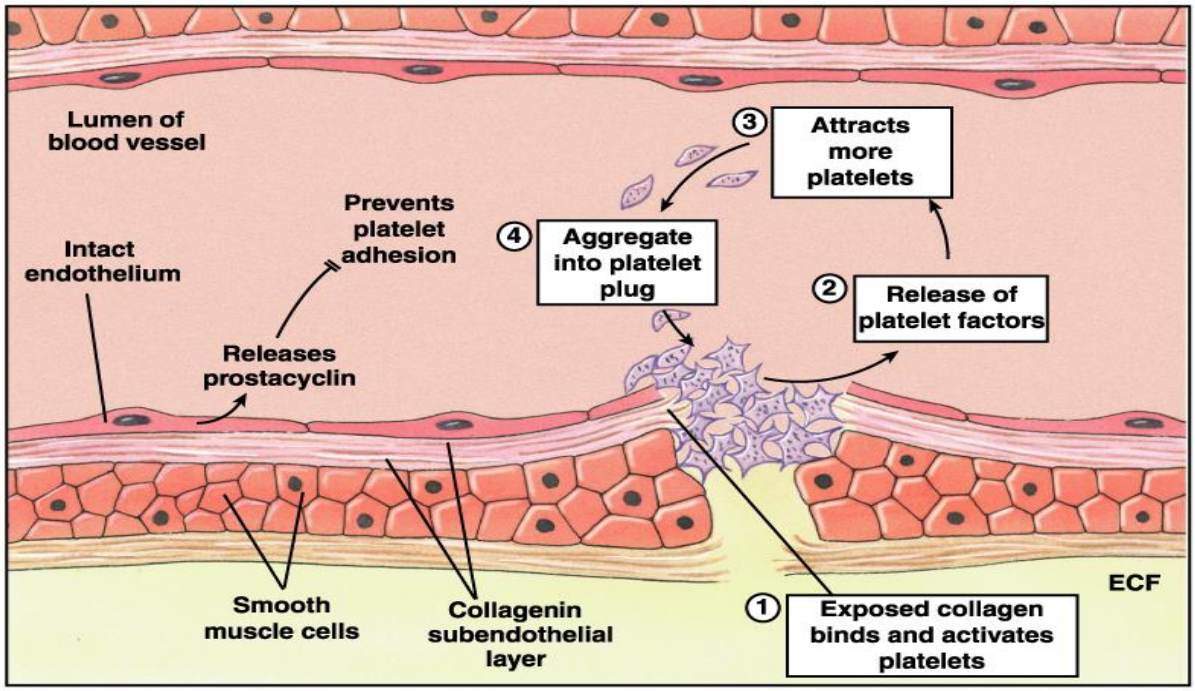
Platelets are normally repelled from the blood vessel endothelial lining

* **When** trauma occurs, traumatized platelets lyses and releases their granular contents ADP and thromboxane A_2. Occurs within 15sec of the injury

* **Platelets** attach to sticky endothelial cells, the basement membrane, and to exposed collagen fibers. The endothelial cells release Von Willebrand factor (vWF also is a carrier for VIII).

* **These** cause other platelet membranes to become "sticky", then release…. (Positive feedback) more release, more platelets… (Amplification effect)

- **ADP→→** the primary stimulus for platelet aggregation
- **Thromboxane A_2 →→** causes platelet aggregation and local vasoconstriction
- **Serotonin →→** causes local vasoconstriction
- **Calcium ions**



- **Factors that are against clotting**:

Endothelial cells also release a different prostaglandin called **prostacyclin and nitric oxide** help repel the platelets from the endothelial cells, so they cannot activate properly. These are anticoagulants.

- **Factors that promote clotting:**
- A tear in vessel, **collagen** fibers provide a place for **Von Willebrand** factors to allow platelets to bind.
- Just one platelet activated, releases **ADP Thromboxane A2,, serotonin, calcium**. These help clotting.

- **Platelet Facts**

- **Thromboxane** in platelets is formed from fatty acid precursor, arachidonic acid with the enzyme cyclooxygenase (COX-1 enzyme.)
- Aspirin is an irreversible COX enzyme inhibitor; blocks formation of thromboxane; platelets don't stick and plug is less likely to form.
- So, aspirin reduces tendency of those platelets to plug, and thus reduce blood clotting tendency.
- Often prescribe aspirin to those with greater tendency to clot, to reduce risk of heart attack and stroke, (baby aspirin)
- Must wait till exposed platelets are removed, turnover time, approx 1 wk-10 days

- **Defective Platelets Function**

  - A defect in function is suspected if there is prolonged bleeding time with or without skin or mucosal hemorrhage in the presence of normal platelet count.

- **Disorders of Platelets Function**

1- Congenital

- Glanzman's disease
- Bernard Soluier's
- Storage granules defect

2- Acquired

- Drugs
- Uremia
- Myeloproliferative disorders
- Multiple myeloma

- **Acquired Disorders of Platelet Function**

Causes:

- 1- Drugs e.g., Aspirin
- 2- Myeloproliferative disorder.
- 3- Paraproteinemias e.g., multiple myeloma.
- 4- Cardiopulmonary bypass.
- 5- Autoimmune diseases e.g., SLE (Systemic Lupus Erythromitosis)
- 6- Uremia (renal failure).

- **Coagulation (blood clotting)**

1. Blood coagulation is the most effective means of hemostasis.

2. Blood coagulation is very complex and uses *clotting factors*.

3. Damaged tissues release a chemical called *tissue thromboplastin*,which activates the first in a series of factors leading to the production of *prothrombin activator*.

4. *Prothrombin activator* converts prothrombin in the plasma into thrombin. This in turn, catalyzes a reaction that converts fibrinogen into fibrin.

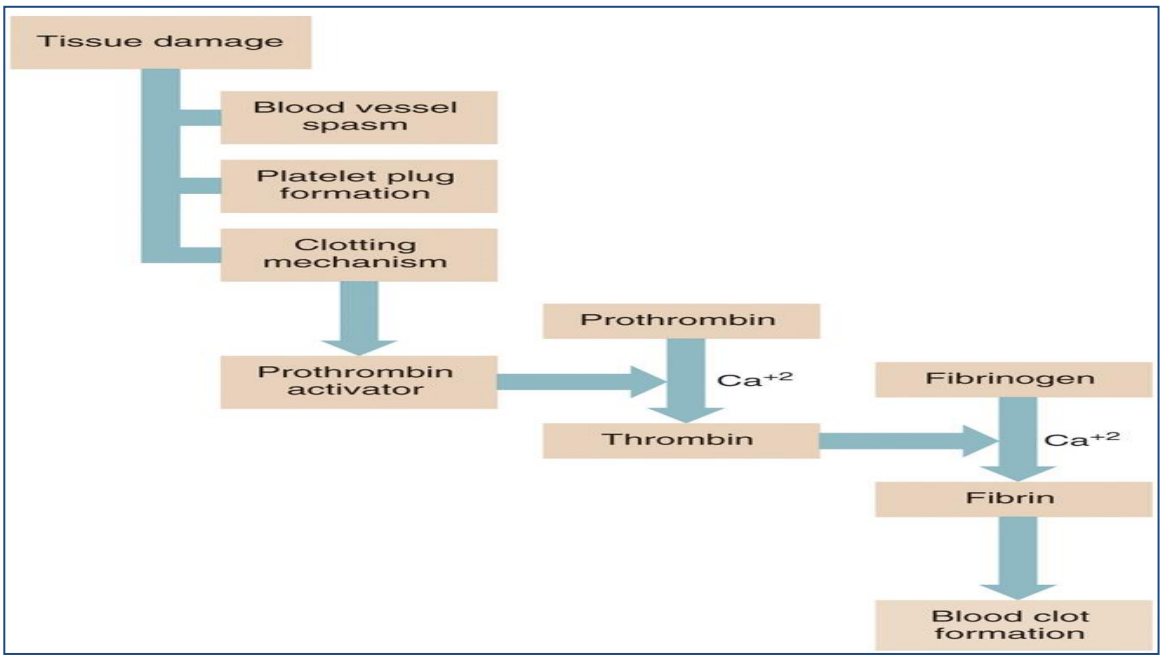
5. The major event in blood clot formation is the conversion of soluble *fibrinogen* into net like insoluble *fibrin* causing the blood cells to catch.

6. The amount of prothrombin activator formed is proportional to the amount of tissue damage.

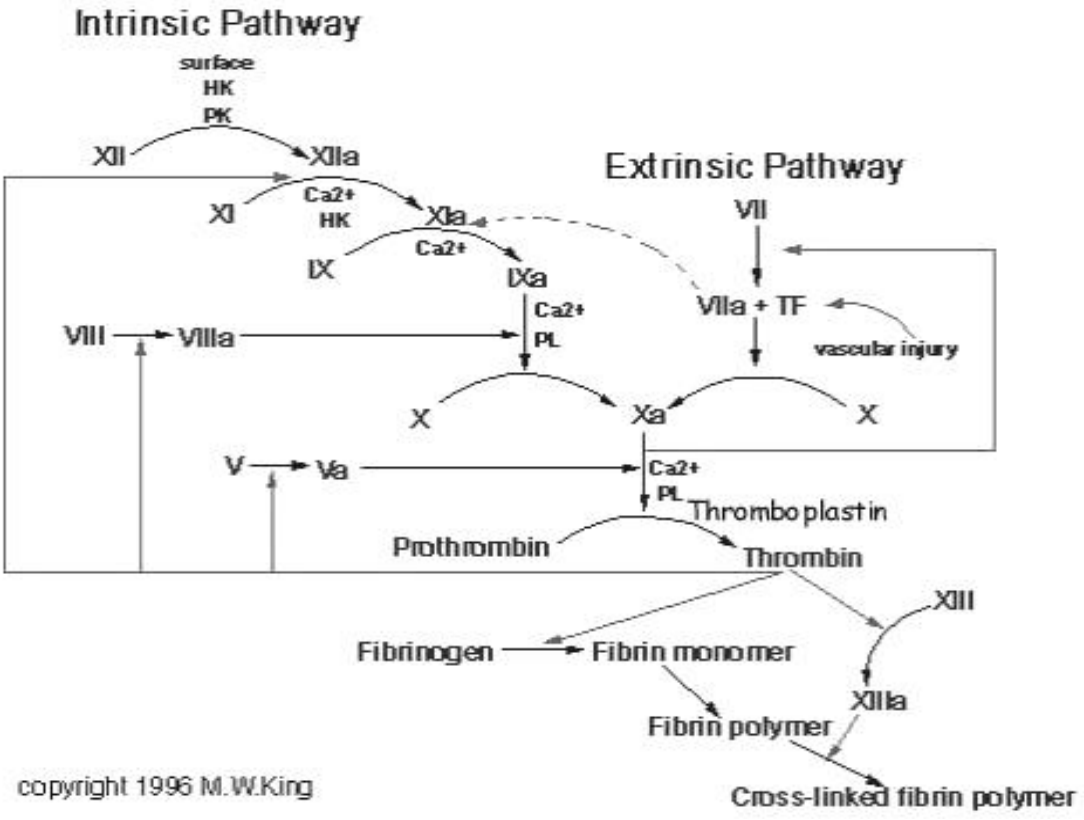
7. Once a blood clot forms, it promotes still more clotting through a positive feedback system.

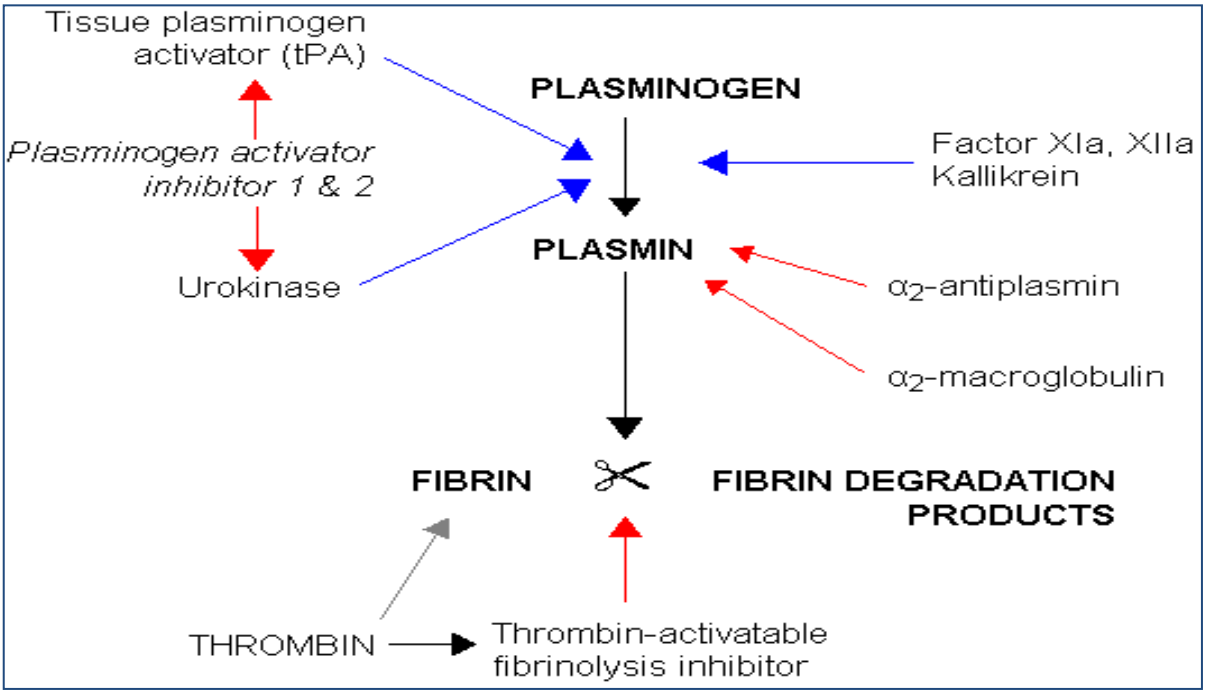
8. After a clot forms, *fibroblasts* invade the area and produce fibers throughout the clots.

9. A clot that forms abnormally in a vessel is a thrombus; if it dislodges, it is an embolus.



- **<u>General Events in Clotting is shown in the diagram below:</u>**





Fibrinolysis Blue arrows = stimulation; red arrows = inhibition. tPA is released by damaged endothelium**.**

* Summary:

1. Anticoagulant - chemical that inhibits clotting
2. Procoagulant - chemical that promotes clotting
3. Intrinsic pathway - within the damaged vessel
    a. more procoagulants needed (I-XIII) toward PF3 and Factor X
    b. allows more "scrutiny" before clotting occurs
4. Extrinsic pathway - in outer tissues around vessel
    a. tissue thromboplastin (Tissue Factor) - skips intrinsic steps straight to PF3 and Fac X
    b. allows rapid response to bleeding out of vessel (clot can form in 10 to 15 seconds)
5. After activation of Factor X, common pathway:
    Factor X, PF3 (thromboplastin), Factor V, Ca^{++} -->
    prothrombin activator ->
    prothrombin converted -> thrombin (active enzyme)
    thrombin stimulates: fibrinogen -> fibrin (meshwork)
    Ca^{++} & thrombin -> Factor XIII (fibrin stabilizer)

- **Clot Retraction (shrinking of clot):**

1. Actomyosin - causes contraction of platelets
2. Blood serum - plasma WITHOUT clotting Factors
3. Platelet-derived growth factor (PDGF) - stimulates fibroblast migration and endothelial growth

* Clot Eradication (Fibrinolysis):

1. Healing occurs over 2 - 10 days
2. Tissue plasminogen activator (TPA) - causes the activation of plasminogen
3. Plasminogen--> plasmin
4. Plasmin degrades proteins within the clot

* Factors Limiting Growth and Formation of Clots:

1. Limiting Normal Clot Growth
a. Blood moves too fast to allow procoagulants
b. Factors interfere with normal clotting
i. Prothrombin III - deactivates thrombin
ii. Protein C - inhibits clotting Factors
iii. Heparin - inhibits thrombin; prevents adherence of platelets to injured site

- **Disorders of Hemostasis:**

A. Thromboembolytic Disorders (undesirable clotting)

1. Thrombus - blood clot in normal blood vessel
2. Embolus -blood clot/gas bubble floating in blood
a.TPA, streptokinase - can dissolve a clot
b. Aspirin - inhibits Thromboxane formation
c. Heparin - inhibits thrombin & platelet deposit
d. Dicumarol - anticoagulant, blocks Vitamin K

B. Bleeding Disorders

1. Thrombocytopenia - reduced platelet count; generally below 50,000 per cubic millimeter; can cause excessive bleeding from vascular injury.

2. Impaired liver function - lack of procoagulants (Clotting Factors) that are made in liver a. vitamin K - essential for liver to make Clotting Factors for coagulation

3. Hemophilias - hereditary bleeding disorders that occur almost exclusively in males

a. Hemophilia A - defective Factor VIII (83%)
b. Hemophilia B - defective Factor IX (10%)
c. Now genetically engineered TPA and Factor VIII are produced so patients do not need transfusions as often.

Dr. Muhannad Shweash