MEDICINE 438's

GIT PHYSIOLOGY

LECTURE XI: Platelets Structure and Functions

EDITING FILE

IMPORTANT | MALE SLIDES | EXTRA | FEMALE SLIDES | LECTURER'S NOTES

1 PLATELETS STRUCTURE AND FUNCTIONS

Lecture Eleven

OBJECTIVES

- Describe formation and development of platelets.
- Understand platelet normal ultrastructure.
- Understand the functions of different platelets organelles and surface receptors.
- Understand the mechanisms of platelet functions.
- Relate membrane receptors and granule content to normal function in hemostasis and bleeding (platelet) disorders.

Recall... "HEMOSTASIS"

1. Vascular phase
2. Platelet phase
3. Coagulation phase
4. Fibrinolysis phase

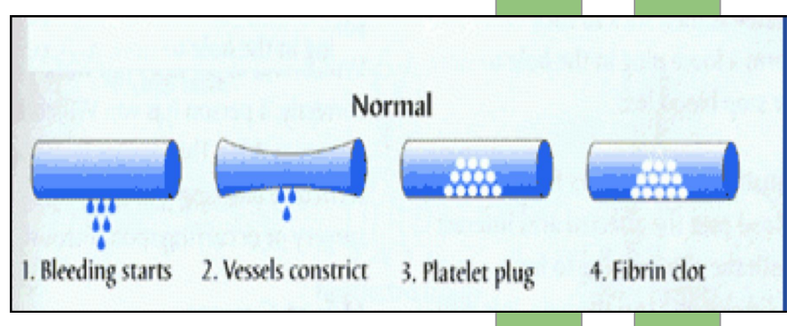
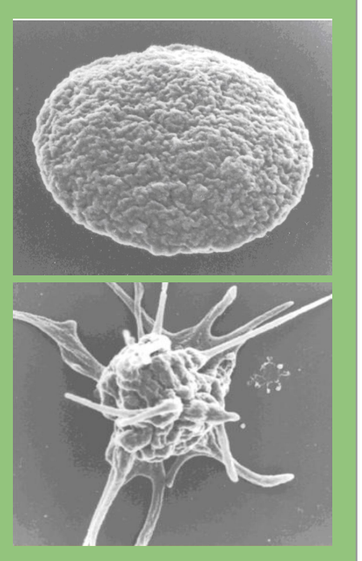


Figure 11-1

Thrombocytes

- Anuclear and discoid cell (oval disc shaped) spherical when activated.
- Platelet count = 150,000-300,000/ml.
- Size: 1.5–3.0 µm.
- Life span: 7–10 days.
- Sequestered in the spleen; hypersplenism may lead to low platelet counts.
- Location: 80% in the blood, and 20% in the spleen (hypersplenism may lead to low platelet count).
- Contractile, adhesive, cell fragments.
- Store coagulation factors and enzymes.
- Surface binding antigens glycoproteins.



Formation of Platelets

- Platelets formed by fragmentation of megakaryocytes.
- Formed in the bone marrow.

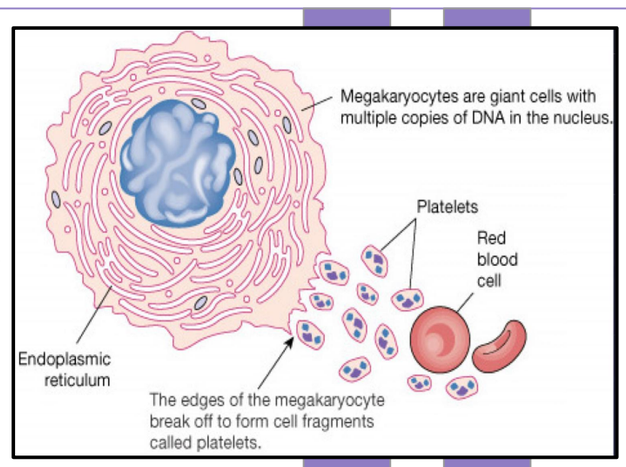


Figure 11-2

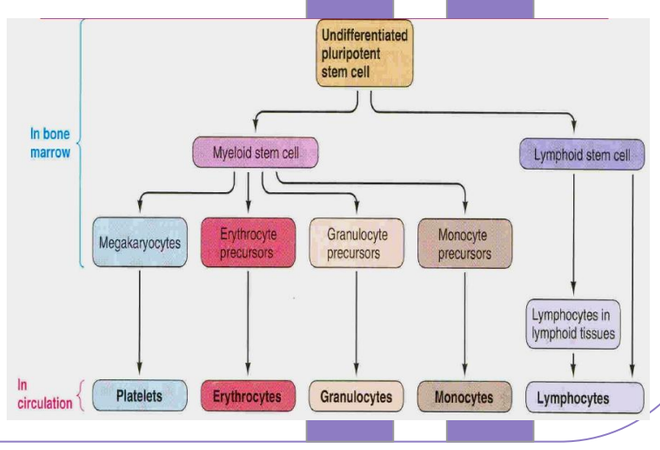


Figure 11-3

Platelet Ultrastructure

Showing presence of:

1-Two types of granules:

A- Alpha Granules, contains:

- von Willebrand Factor (vWF)
- Fibrinogen
- Chemokines (PF4,etc.)
- Thrombospondin
- P-selectin
- Platelet derived growth factor (PDGF)

B- Dense Granules (delta), contains:

- ADP/ATP
- Calcium
- Serotonin

2- Mitochondria

3- Open canalicular system

4- Microtubules

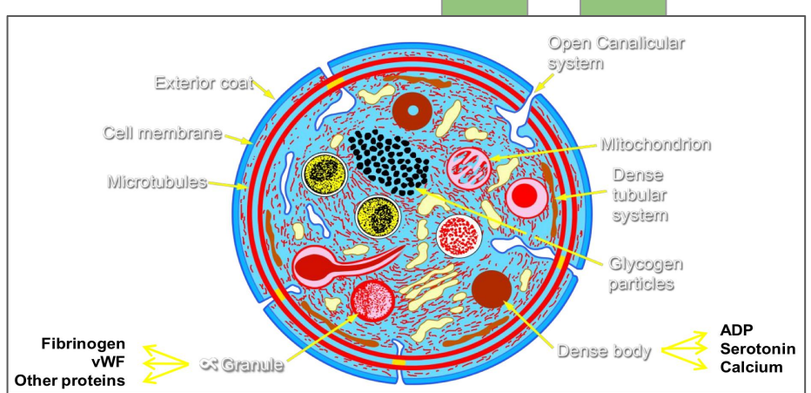


Figure 11-4

Functional Characteristics of Platelets

- **Motile:** Actin and myosin molecules.
- **Active** endoplasmic reticulum, golgi apparatus and mitochondria.
- **Enzymes** system such as for synthesis of prostaglandins.
- **Granules** (alpha and delta).

Platelet Receptors

- **Glycoprotein Ia and VI receptors for collagen.**
- **Glycoprotein Ib, IX and V receptors for Von willebrand factor.**
- **Glycoprotein IIb and IIIa receptors for Von willebrand factor and Fibrinogen.**
- **TPα receptor for Thromboxane A2.**
- **$P2Y_{12}$ receptor for ADP.**

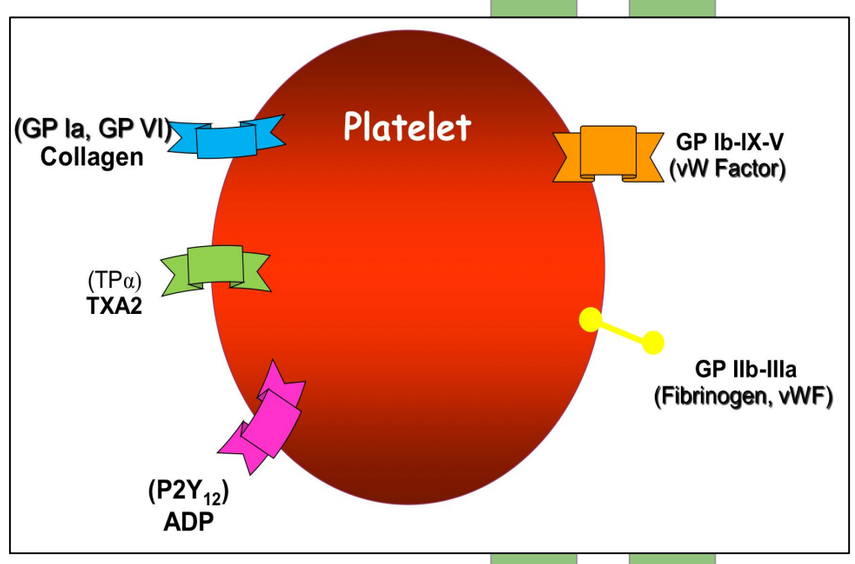


Figure 11-5

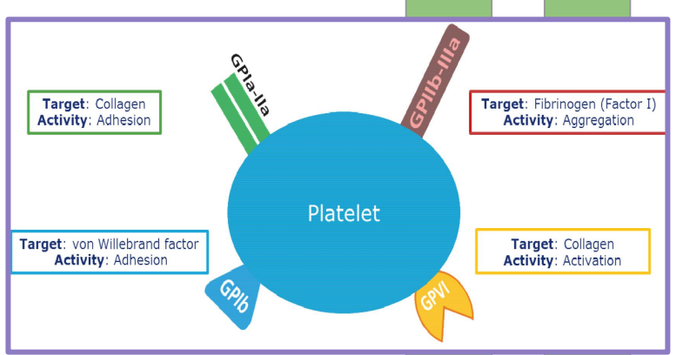
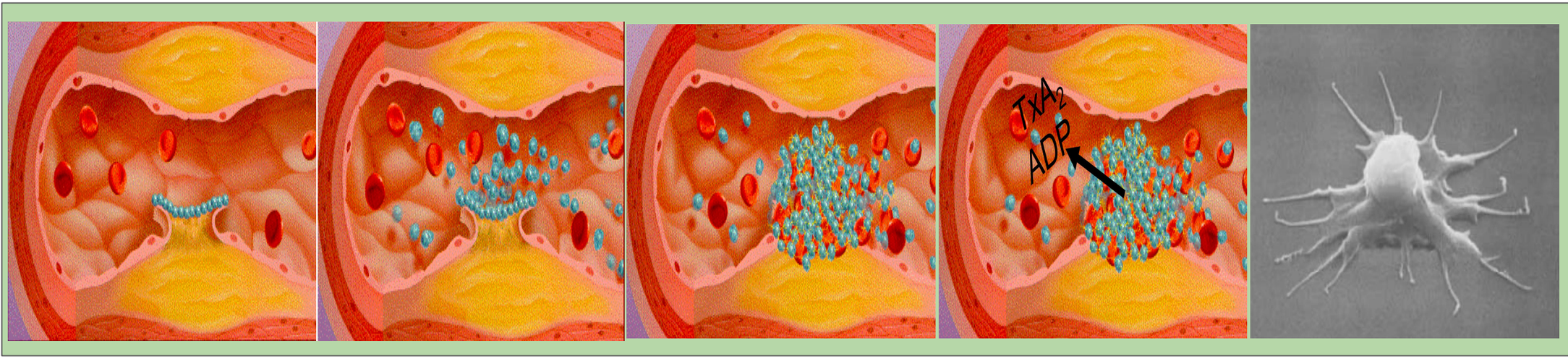


Figure 11-6 Showing the functions of different receptors

Platelet Plug Formation (Activation)



Adhesion | Shape change (Activation) | Aggregation | Release reaction | Clot retraction

Platelet Haemostatic Plug Formation

- Platelets activated by adhesion.
- Extend projections to make contact with each other.
- Release:
Thromboxane A2, serotonin & ADP >>> activating other platelets.
- Serotonin & thromboxane A2 are vasoconstrictors decreasing blood flow through the injured vessel.
- ADP causes stickiness and enhances aggregation.

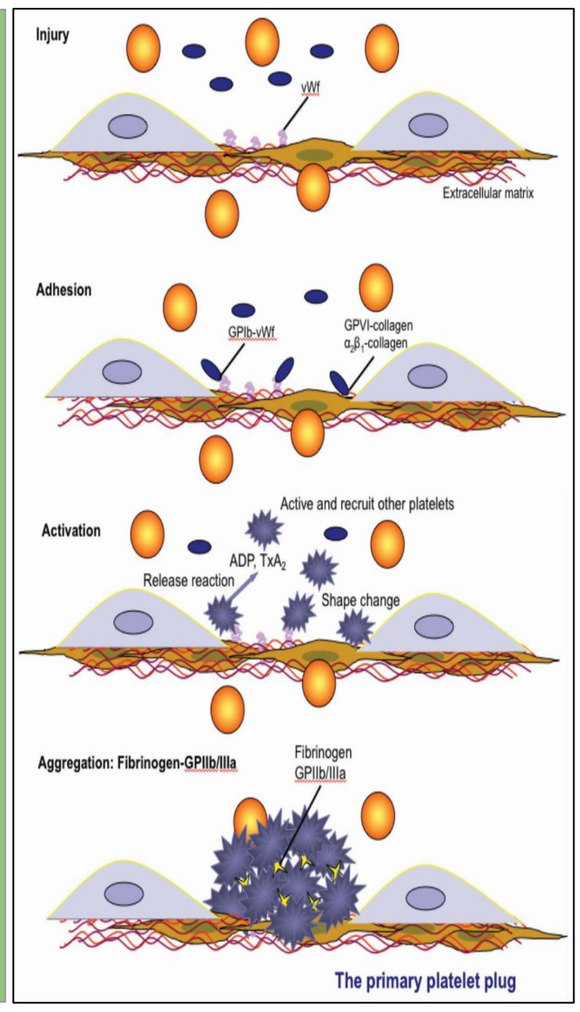


Figure 11-7

Platelet Aggregation

- Fibrinogen is needed to join platelets to each other via platelet fibrinogen receptors.

Figure 11-8

Normal endothelium secrete:
- Prostacyclin.
- ADP Phosphatase.
- NO.

TO PREVENT PLATELETS AGGREGATION

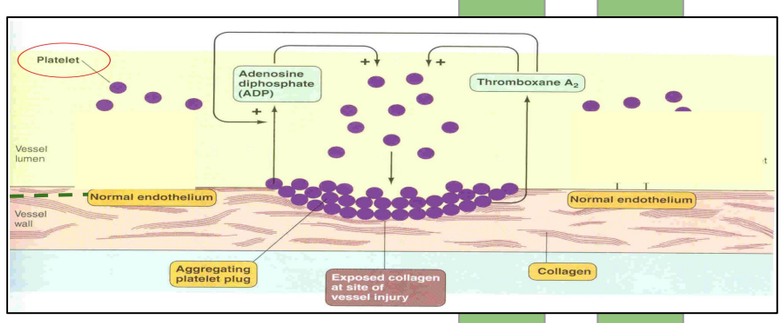


Figure 11-9

Release Reaction of the Platelets

- **Activated Platelets Secrete:**
  1. ADP

  2. 5HT (vasoconstriction)

  3. Platelet phospholipid (PF3) (clot formation)

  4. Thromboxane A2 (TXA2)
  is a prostaglandin formed from arachidonic acid, function:

  - Vasoconstriction. - Platelet aggregation.

  (TXA2 inhibited by aspirin)

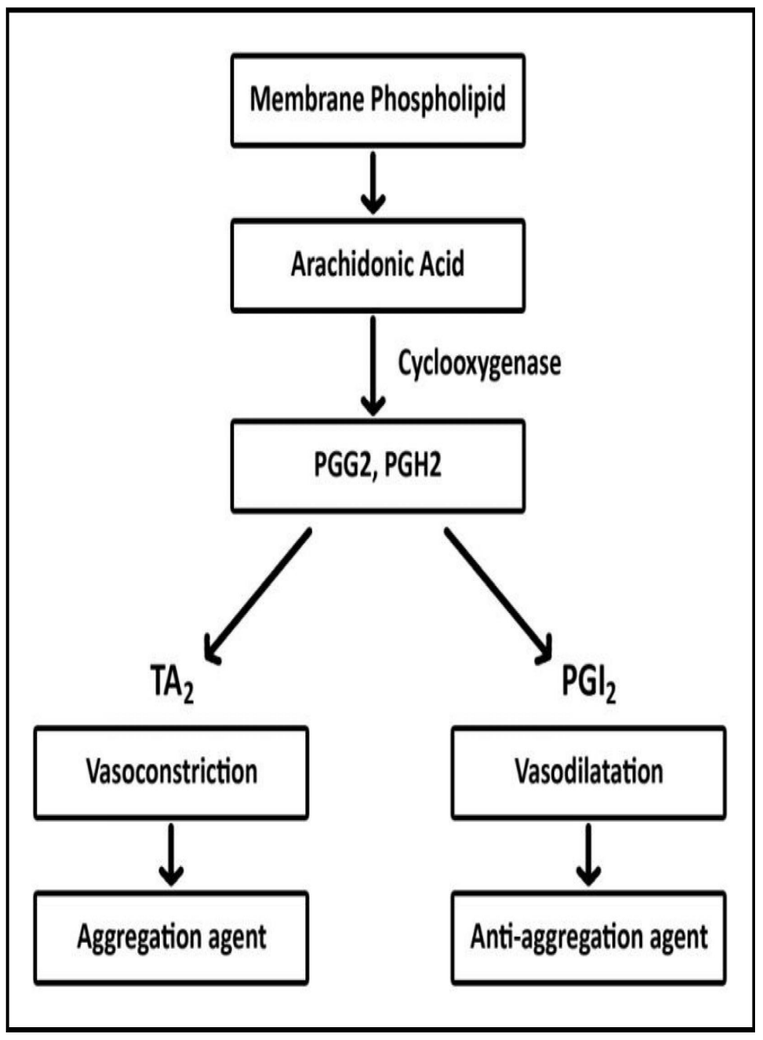


Figure 11-10

Platelet Retraction

- **Myosin and actin filaments in platelets are stimulated to contract during aggregation further reinforcing the plug and help release of granule contents.**

- **When clot retracts (contract), it expresses most of the fluid from the clot within 20-60 min called: serum.**

- **Serum cannot clot.**

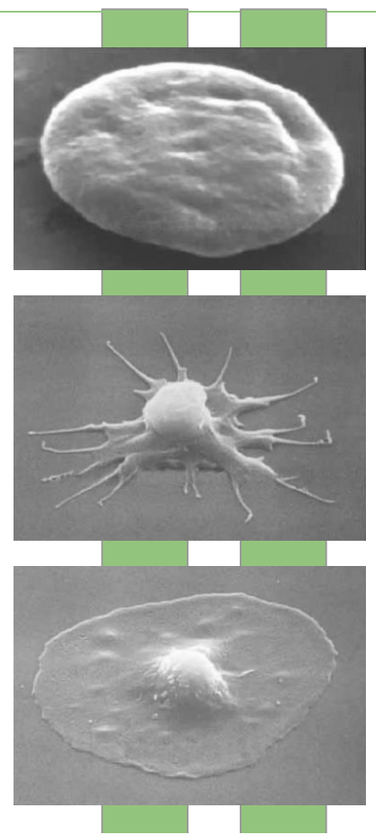


Figure 11-11

Role of Platelet in Blood Coagulation

(The cell based model of blood coagulation)

- Role of platelets in clot formation and retraction: **They are contractile.**

Fate of clot	**Lysis or fibrous tissue formation** (Platelet derived growth factor)

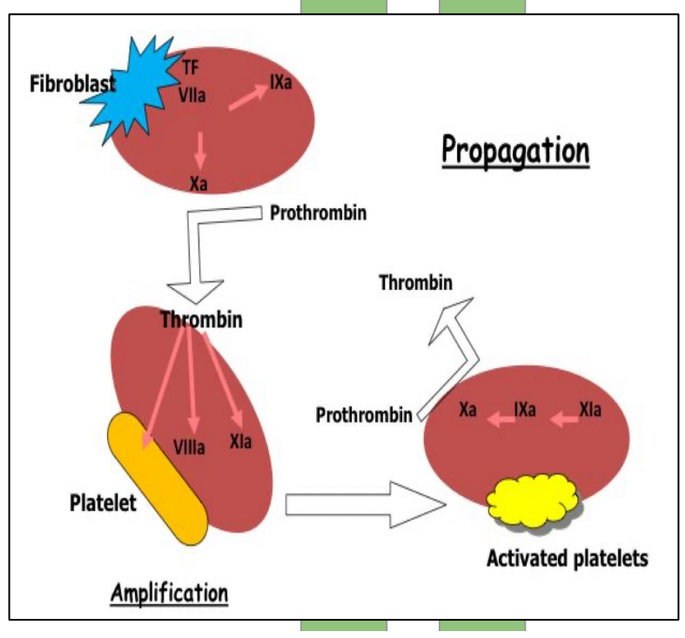
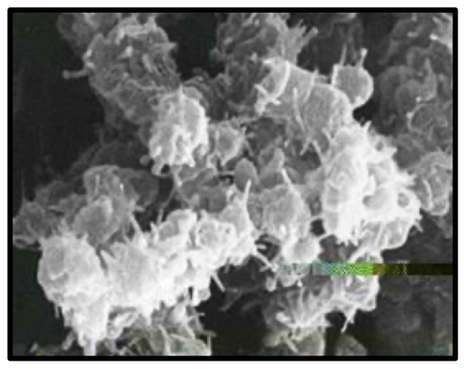
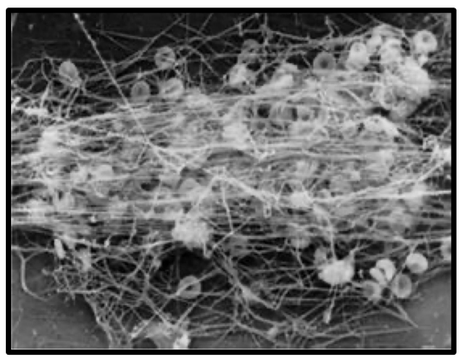


Figure 11-12

Platelet Function: Maintenance of Vascular Integrity

1- Initial arrest of bleeding by platelet plug formation





2- Stabilization of hemostatic plug by contributing to fibrin formation

An adequate number and function of platelets is essential to participate optimally in hemostasis.

Summary of Platelet Activation:

- **Platelets are activated when brought into contact with collagen exposed when the endothelial blood vessel lining is damaged.**
- **Activated platelets release a number of different coagulation and platelet activating factors.**
- **Transport of negatively charged phospholipids to the platelet surface; provide a catalytic surface for coagulation cascade to occur.**
- **Platelets adhesion receptors (integrins): Platelets adhere to each other via adhesion receptors forming a hemostatic plug with fibrin.**
- **Myosin and actin filaments in platelets are stimulated to contract during aggregation further reinforcing the plug and help release of granule contents.**
- **GPIIb/IIIa: the most common platelet adhesion receptor for fibrinogen and von Willebrand factor (vWF).**

Bleeding Disorders

- **Bleeding can result from:**
  1. Deficiency in number (thrombocytopenia).

→ Count < 50,000 ul may cause spontaneous bleeding.

→ Less than 10,000 (Fatal).

  2. Defect in function.
  3. Liver diseases & Vitamin-K deficiency.

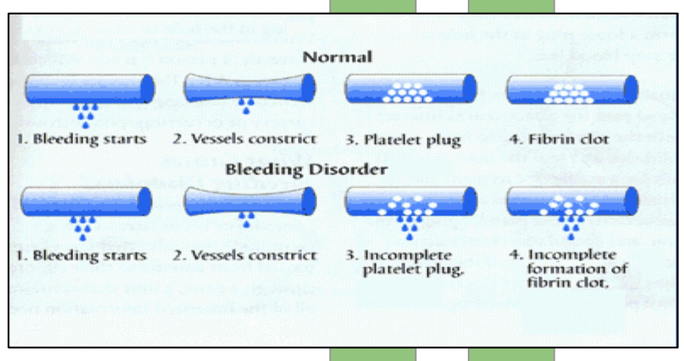


Figure 11-13

1- Thrombocytopenia

1- Decreased Production

- **Leukemia or lymphoma**
- **Cancer treatments** such as radiation or chemotherapy
- **Various anemias (Aplastic anemia)**
- **Toxic chemicals**
- **Medications**: diuretics, chloramphenicol
- **Infections (Viruses)**: chickenpox, mumps, Epstein-Barr, parvovirus, AIDS HIV, Measles
- **Alcohol** in excess
- **Genetic conditions**: Wiskott-Aldrich, May-Hegglin.

2- Increased destruction

- **Autoimmune diseases:** Idiopathic (immune) thrombocytopenic purpura
- **Medications:** quinine, antibiotics containing sulfa, Dilantin, vancomycin, rifampin, heparin-induced thrombocytopenia.
- **Surgery:** man-made heart valves, blood vessel grafts, bypass machines
- **Infection:** septicemia, **HIV**
- **Pregnancy:** about 5% of pregnant women develop mild decrease Thrombotic thrombocytopenic purpura

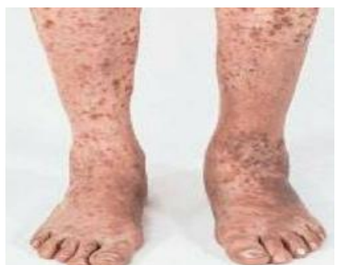
3- Abnormal distribution

- Splenomegaly with sequestration in the spleen

4-Pseudothrombocytopenia

- Partial clotting of specimen
- EDTA-platelet clumping
- Platelet satellitism around WBCs
- Cold agglutinins
- Giant platelets

Clinical Features



- Easy bruisability
- Epistaxis
- Gum bleeding
- Hemorrhage after minor trauma
- Petechiae/Ecchymosis

Diagnosis

- Platelet count decreased
- Bleeding time increased

Treatment

- Rx of the underlying cause
- platelet concentrates
- Fresh whole blood transfusion
- Splenectomy

Physiological Factors Affecting Platelet Count

- Increase in injury.
- Increase with adrenaline.
- Increase with hypoxia.
- **Age: decrease in newborn.**
- **Menstrual cycle:** decrease prior menstruation and increase after it.
- Decrease in pregnancy.
- Decrease with smoking.
- Decrease with nutritional deficiencies. Eg: vitamin B12, folic acid and iron.

2- Congenital Platelet Disorders

Recall... **(Platelets activation:**

Adhesion → **Shape change** → **Aggregation** → **Release** → **Clot Retraction**

1- Disorders of Adhesion:

- Bernard-Soulier

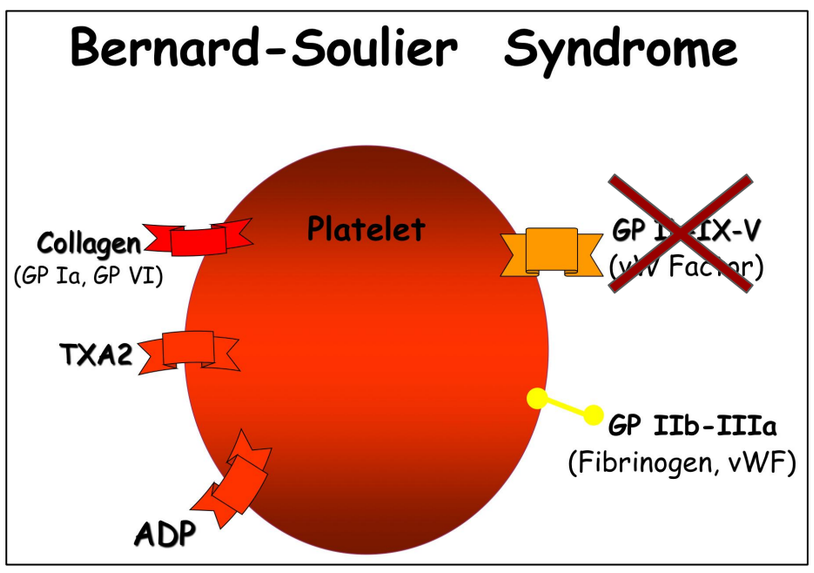


Figure 11-14
In Bernard-Soulier Syndrome, there is deficiency of vW factor receptors causing defects in **adhesion**.

2- Disorder of Aggregation:

- Glanzmann thrombasthenia

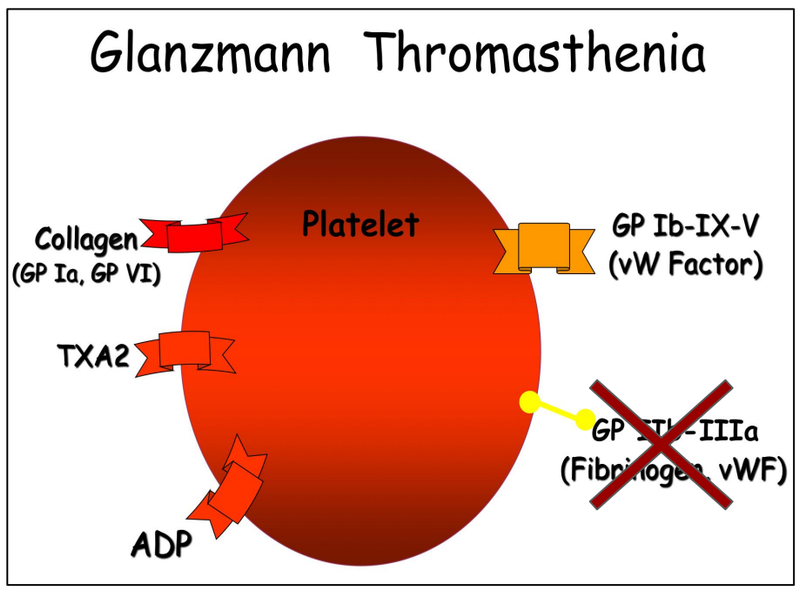


Figure 11-15
In Glanzmann Thrombasthenia, there is deficiency of fibrinogen receptors causing defects in **aggregation**.

3- Disorders of Granules:

- Grey Platelet Syndrome.
  (α granule deficiency)
- Storage Pool deficiency.
- Hermansky-Pudlak syndrome .
- Chediak-Higashi syndrome.

4- Disorders of Production:

- Congenital amegakaryocytic thrombocytopenia.
- MYH9 related disorders.
- Thrombocytopenia with absent radii (TAR).
- Paris-Trousseau/Jacobsen.

5- Disorders of Primary Secretion:

- Receptor defects (TXA2, collagen ADP, epinephrine)

6- Disorders of Cytoskeleton:

- Wiskott-Aldrich syndrome

3- Liver Diseases & Vitamin-K Deficiency

- Hepatitis & Cirrhosis: Decreased formation of clotting factors and Increased clotting time.
- Vitamin K dependent factors: Factors II, VII, IX & X.
- Vitamin-K is a fat soluble vitamin. It's required by liver for formation of four clotting factor: **II, VII, XI and X.**
- Sources: Diet, Synthesized in the intestinal tract by bacteria.
- Deficiency is caused by Malabsorption syndromes, Biliary obstruction, Broad spectrum antibiotics, Dietary deficiency (in Neonates).
- Treat the underlying cause → Vit K injections

Laboratory Testing of Platelet Functions

- Peripheral smear and platelet count (& shape)
- Electron-microscopy
- Bleeding time (Duke method)
- **Platelet Aggregation**
- Platelet Function Analyzer (PFA-100)
- Flow-cytometry
- Granule release products

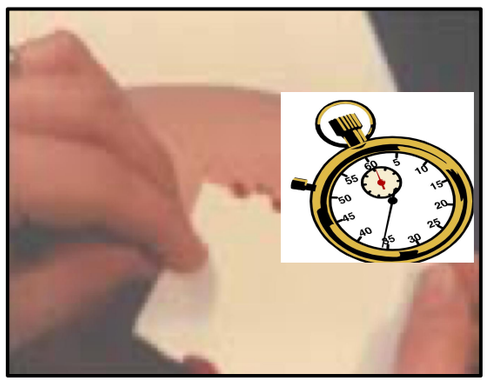


Figure 11-16
Bleeding time test

Figure 11-17
Platelet Aggregometry

Significance of lab tests

Test	Normal Value	Importance
PLATELET COUNT	100,000 - 400,000 CELLS/MM^3	Thrombocytopenia
PLATELET FUNCTIONS	Normal Aggregation	Thrombocytopathy (normal count) [Congenital or Acquired…Aspirin]
BLEEDING TIME (BT)	2-8 MINUTES	Bleeding disorders
PROTHROMBIN TIME (PT)	10-15 SECS	Measures Effectiveness of the Extrinsic Pathway
PARTIAL THROMBOPLASTIN TIME (PTT)	25-40 SECS	Measures Effectiveness of the Intrinsic Pathway
THROMBIN TIME (TT) $INR = \left(\frac{PT_{test}}{PT_{normal}}\right)^{ISI}$	9-13 SECS	A Measure of Fibrinolytic Pathway Time for Thrombin To Convert Fibrinogen ► Fibrin

Platelet Aggregation in Platelet Rich Plasma (PRP):

- It provides information on time course of platelets activation.
- **Agonists:**
  - ADP
  - Adrenaline
  - Collagen
  - Arachidonic acid
  - Ristocetin
  - Thrombin

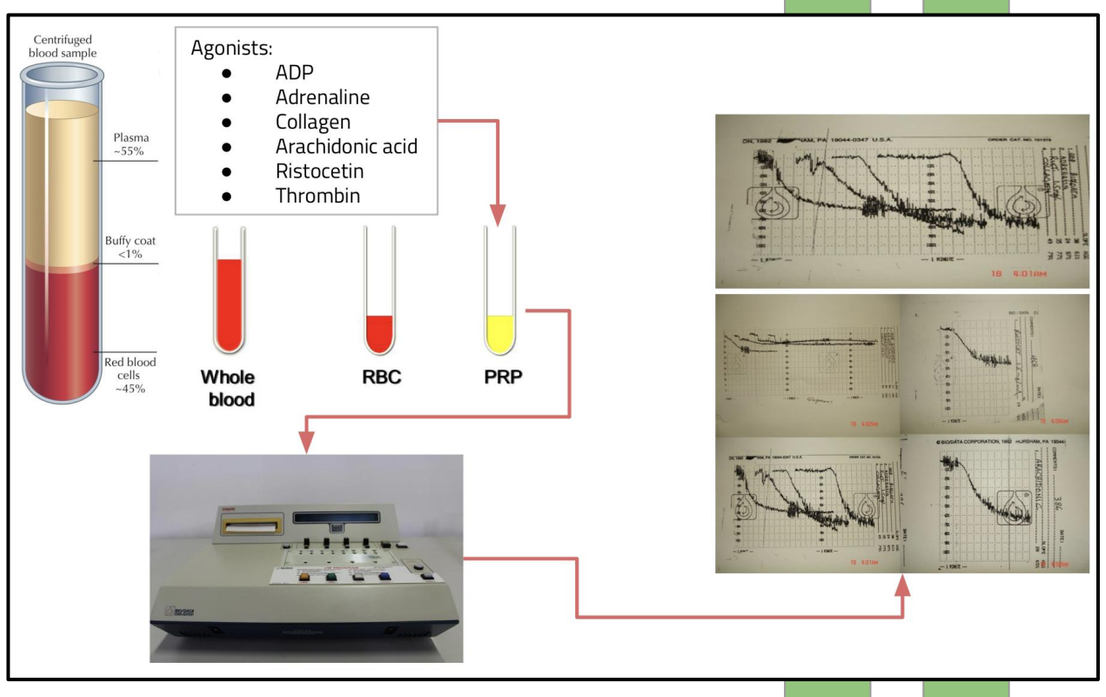


Figure 11-18

(Reference ranges need to be determined for each agonist)

Classic Biphasic Aggregation

1- Baseline.
2- Addition of an agonist.
(this results in change in platelet change and hence a drop in the baseline)
3- Primary wave aggregation.
4- Release of nucleotides.
5- Secondary wave aggregation.

(Adrenaline and low dose ADP classically give a biphasic aggregation)

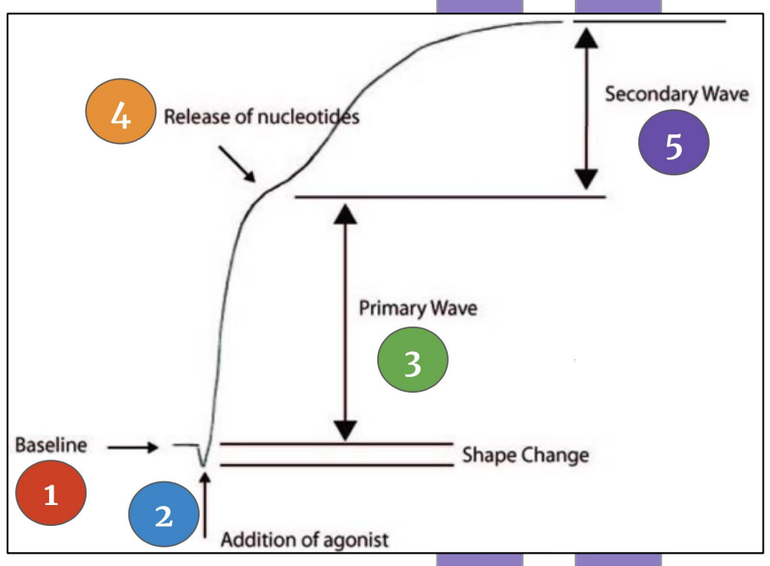
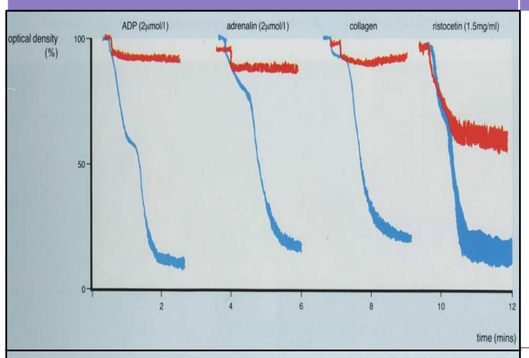
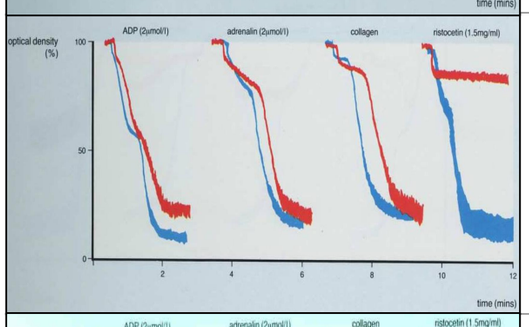
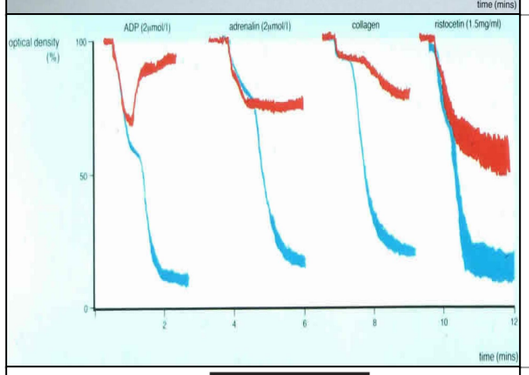
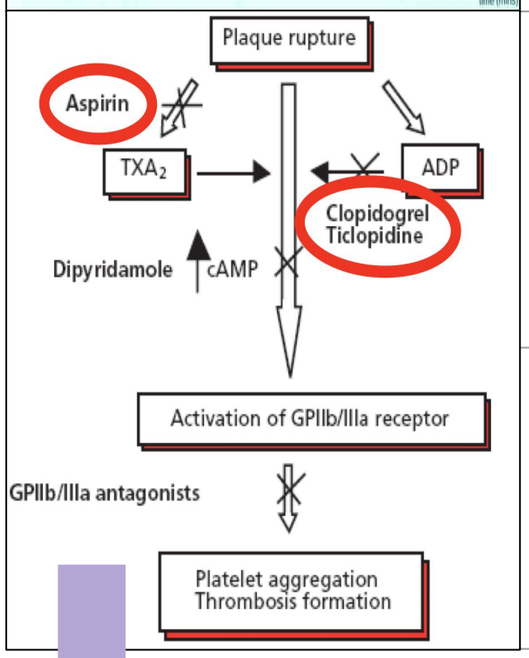


Figure 11-19

Aggregometry Results and Diagnosis

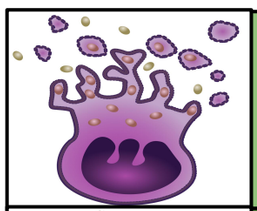
Figure	Characteristic of findings on LTA	Diagnosis
	Absent or markedly impaired aggregation to **all agonists** except ristocetin. (Ristocetin-induced agglutination shows only primary wave aggregation, aggregation cannot occur because **fibrinogen cannot bind**)	• **Glanzmann's thrombasthenia** • **Afibrinogenemia**
	Absent or markedly reduced platelet agglutination with Ristocetin.	• **Bernard soulier syndrome** • **Von willebrand disease**
	Primary aggregation only with ADP, Adrenaline and collagen and only partial agglutination with ristocetin suggesting failure of **granule** release or a deficiency of platelet **granules**.	• **Storage pool Disorder.** • **Platelet release defects.**
	Absent aggregation to Arachidonic acid. Primary wave aggregation only with ADP. Decreased or absent aggregation with collagen.	• **Aspirin** (or defects on COX pathway)
	Absent aggregation with ADP.	• **Clopidogrel** (ADP inhibitor.

- Aspirin inhibits platelet cyclooxygenase by irreversible acetylation, therapy preventing the formation of thromboxane A2, which is powerful stimulant of platelet aggregation.
- Clopidogrel, a thienopyridine, acts by inhibiting adenosine receptors, which inhibits the early step of platelet activation.

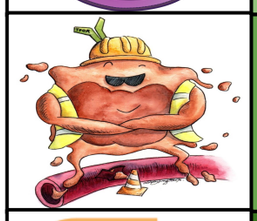
10 PLATELETS STRUCTURE AND FUNCTIONS

Lecture Eleven

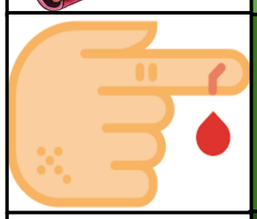
Summary



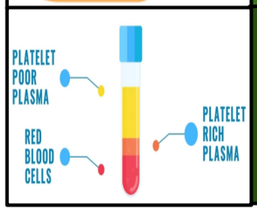
-Platelets are cell fragments derived from megakaryocyte in the bone marrow.



-Platelets play a pivotal role in haemostasis by arresting bleeding from an injured blood vessels



-Bleeding can result from: Platelet defects acquired or congenital.



-Platelet function tests are used to detect abnormal platelet function.

Case Study:

- **A 7 years old girl complaining of:**
  - severe bruising since birth and if she had injury she would bleed for days.
  - She had epistaxis which lasted for days.
  - Her mother said “she just bruise more easily than her older sister”.
- **Investigation:**
  - **CBC:** RBC, WBC, Platelets. (All normal)
  - **Platelet morphology**: normal.
  - **Aggregometry**: Absent platelet aggregation in response to ADP, collagen, thrombin, and epinephrine.

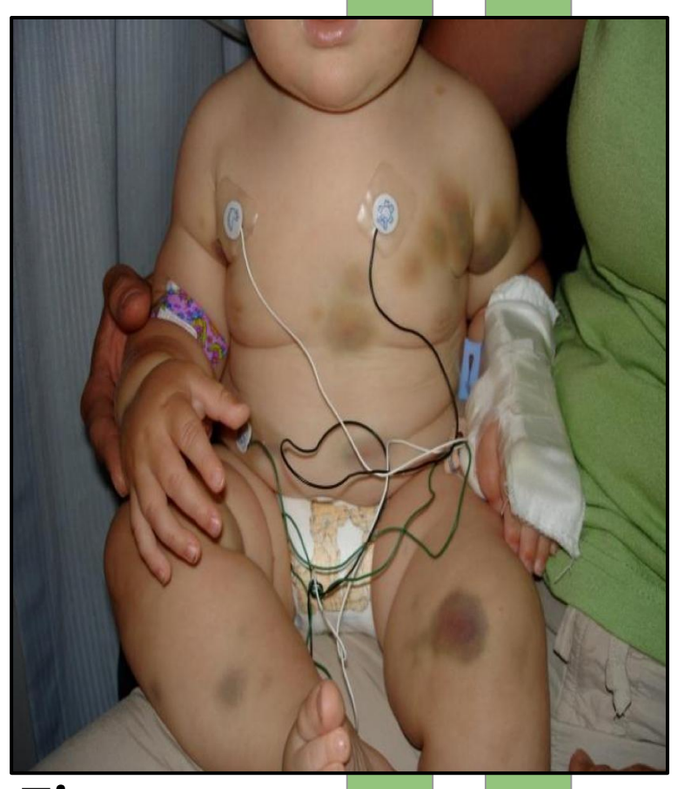


Figure 11-20
Notice the bruises

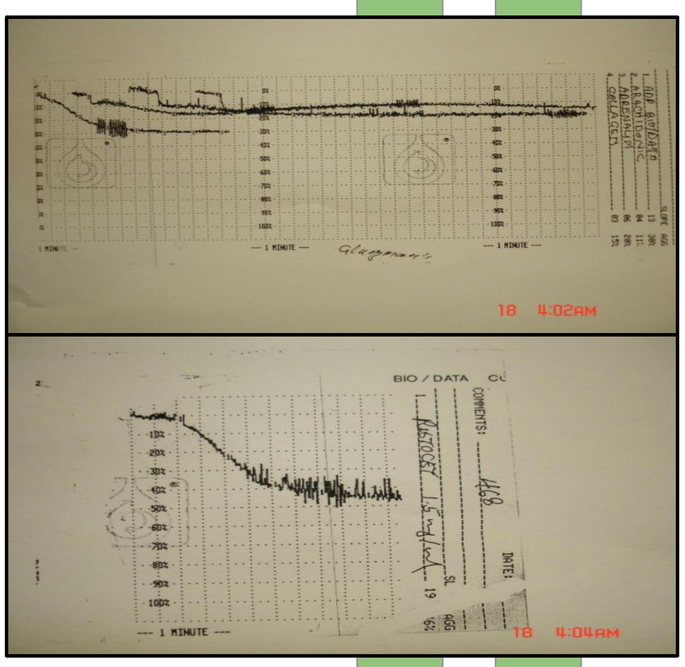


Figure 11-21

Diagnosis **Glanzmann's Thrombasthenia**
(Defects in aggregation)

QUIZ

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1. Which of the following is stored inside the platelets by the alpha granules?
A) ADP.
B) Serotonin.
C) Fibrinogen.
D) Calcium.

2. What is the first event happens during platelet activation?
A) Shape change.
B) Adhesion.
C) Release reaction.
D) Aggregation.

3. Which one of the following is essential for platelet aggregation?
A) von Willebrand Factor.
B) Fibrinogen.
C) Collagen.
D) Haemoglobin.

4. In Bernard-Soulier Syndrome there is defect in the receptor for which of the following?
A) von Willebrand Factor.
B) Fibrinogen.
C) Collagen.
D) Thromboxane A2

SHORT ANSWER QUESTIONS

Enumerate (in order) the four events of platelet activation.

ANSWERS

- Adhesion.
- Shape Change. (if they consider them 5 events)
- Agregation.
- Release reaction.
- Clot retraction

ANSWER KEY: C, B, B, A

THIS LECTURE WAS DONE BY

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REFERENCES

- Guyton and Hall Textbook of Medical Physiology
- Ganong's Review of Medical Physiology