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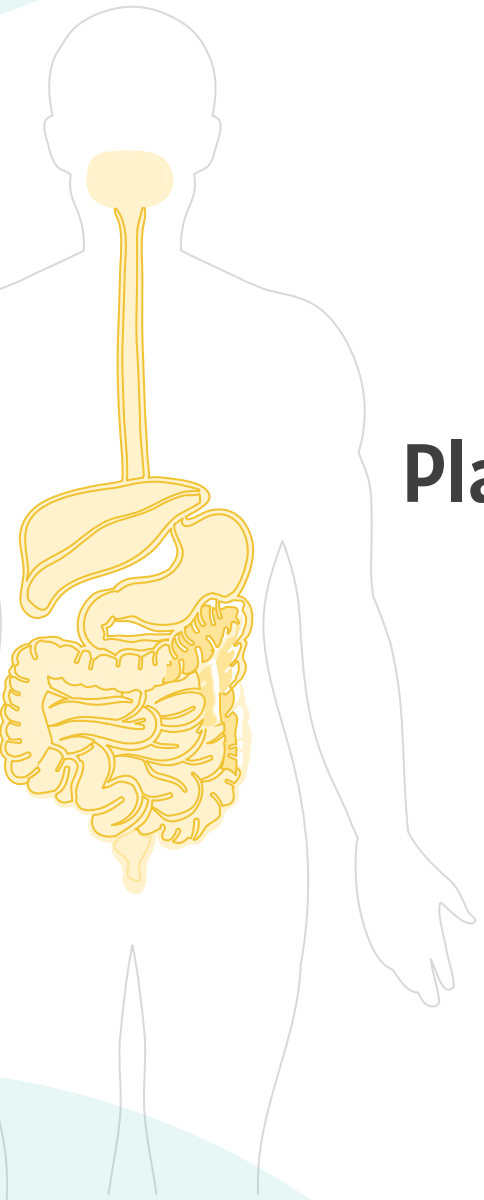


Platelet Structure & Functions

GNT Physiology

This lecture was presented by:
Dr. Shahid & Dr. Abeer Alghumlas

Color Index:

- Main text
- Important
- Female Slides
- Male Slides
- Notes
- Extra

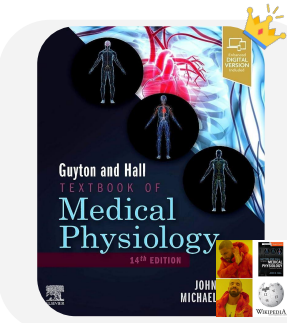
Editing File

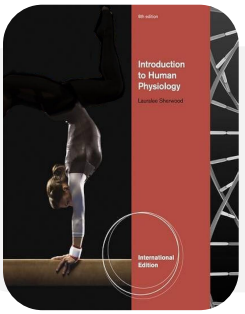
Objectives

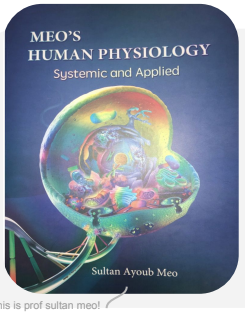
- **Describe formation and development of platelets**
- **Understand platelet normal ultrastructure.**
- **Understand the functions of different platelet organelles and surface receptors.**
- **Understand the mechanisms of platelet functions**
- **Relate the membrane receptors and granule content to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

Resources

Only GI chapters included







This is prof sultan meo!

Click here for a helpful channel by the team!

Helpful video to understand.

{ وَقُلْ رَبِّ زِدْنِي عِلْمًا }

Platelet Formation:

Female slides

Site of formation: Bone marrow → **Regulation of thrombopoiesis by Thrombopoietin**

Stem cell → megakaryoblast → megakaryocytes → platelets

Platelet Formation

• **Formed by**	fragmentation from megakaryocytes Possible MCQ
• **Shape:**	Anuclear and discoid cell minute round or oval discs, spherical when activated
• **Platelet count:**	$150x10^3$-$300x10^3$/mL / 150,000 – 300,000/ microliter
• **Size:**	1.5–3.0 µm in diameter
• **Life span:**	7–10 days
• **Sequestered in the spleen:**	• 80% (circulating) in the blood, and 20% in the spleen (for emergency) • **Hypersplenism** (over functioning spleen) may lead to → **low platelet count**

Male slides

Functional Characteristics

Possible SAQ ↴ What are the characteristics of platelets?

Motile: Actin and myosin molecules (which means it's able to contract)

Active: Endoplasmic reticulum, Golgi apparatus & mitochondria not found in RBCs

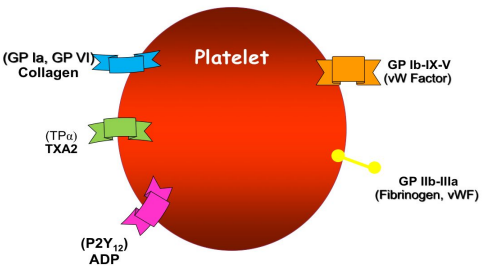
Enzymes system: such as for synthesis of prostaglandins

Contractile, adhesive, cell fragments (Not full cells)

Store coagulation factors & enzymes

Surface binding antigens glycoproteins

Granules (α & δ)



Platelet ultrastructure:

Doctor said:focus on the red colour.

1. **Mitochondrion**
2. **Open canalicular system**
3. **Microtubules:**(responsible for shape and structural support)
4. **Dense Granules (delta)**Contains:
   - Serotonin
   - ADP/ATP
   - Ca^{++}

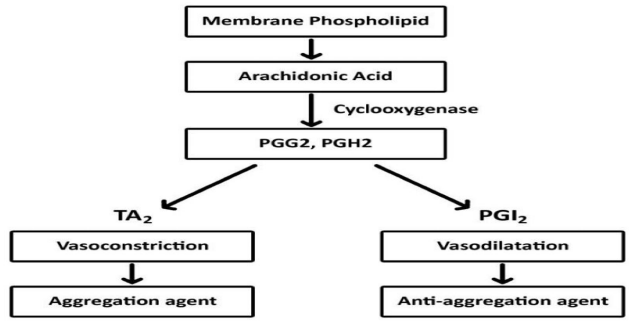
   Mnemonic: SAC
5. **Alpha Granules** Contains:
   - Von Willebrand Factor
   - Fibrinogen
   - PDGF
   - Thrombospondin
   - P-selectin
   - Chemokines (PF4,etc.) PF4: Platelet factor 4

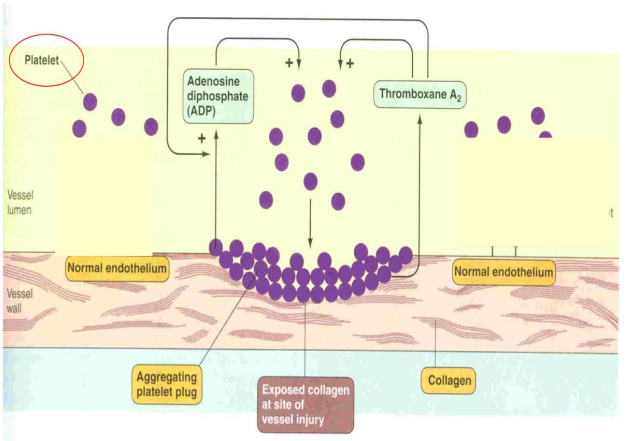
Both granules are major source of platelet content

Male slides

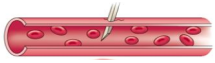
Normal endothelium secret:

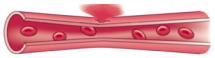
1. I-Prostacyclin (PGI2) **(oppose Thromboxane A2)**
2. 2-Nitric oxide (NO)
3. 3-ADP phosphatase (inhibit ADP phosphate)





Bleeding starts → **Vascular phase** → **Platelets Phase** → **Coagulation Phase** → **Fibrinolytic Phase**





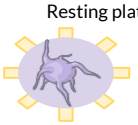
Vessels spasm

Platelets plug

Fibrin strands form fibrin clot and coagulate

Platelet function :

Resting platelets



GP IIb/IIa receptors

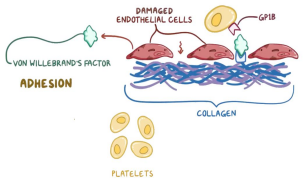
Activated platelets

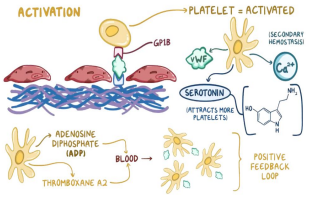
1- Adhesion:
Platelets get activated by adhesion to collagen in the injured blood vessel

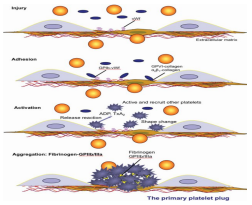
2- Activation:
when platelets get activated they release some chemicals → ↑platelets activation

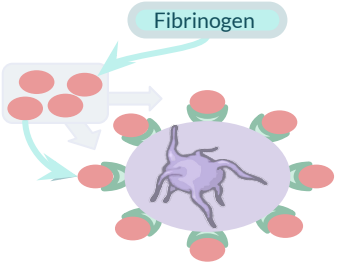
3- Secretion:
(The table below is extremely important)

4- Aggregation:
Fibrinogen is needed to join platelets to each other via platelet fibrinogen receptors.
↑ platelets activation →↑ platelets aggregation →stronger platelets plug









important:

Secretion	Thromboxane A2 (TXA2)	ADP	5-HT	(PF3) Platelet phospholipid

Effect	• Prostaglandin
	• **Formed from:** arachidonic acid.
	• **Inhibited by aspirin.**
	• **Functions:**
	  ○ Vasoconstriction
	  ○ Platelet aggregation
		Adhesion	Vasoconstriction	Clot formation

Platelet activation:

Adhesion → Shape Change → Aggregation (Needs Fibrinogen) → Release Reaction → Clot Retraction

Platelet activation :

Adhesion

Collagen has a strong attractive feature that attracts the platelets, but the endothelial cells prevent their adhesion ***in normal states.***
In case of injury, the platelet immediately adheres to the collagen, Platelets either **bind to collagen *"GP Ia/6"*** directly, or indirectly by **binding to vWF *"GP Ib/9/5"*** which is normally circulating, once the collagen exposure occurs, it binds to collagen.

Shape changes

Then the platelet changes its shape **"extend projections to make contact with each other"platelets becomes activated by adhesion** and sticky to bind and activate other platelets.

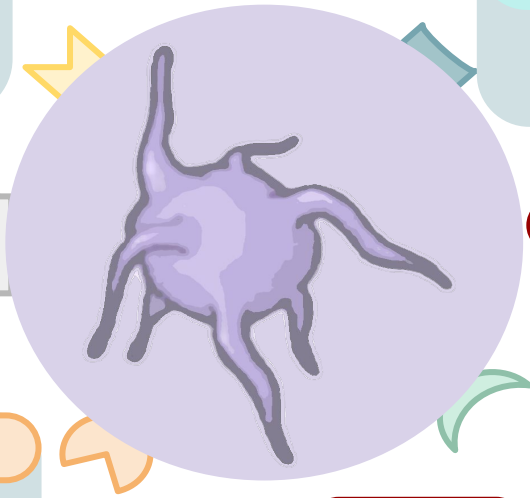
GP = glycoprotein
"16 to make it easy to memorize"

Important:
Affected in Bernard-Soulier syndrome

"195 to make it easy to memorize"

GP Ia, GP VI
For collagen binding

GP Ib - IX - V
For Von Willebrand factor binding
Adhesion



TPα
For **Thromboxane A2** (TXA2) binding

Important:
GP IIb-IIIa
For **Fibrinogen & vWF**
Aggregation

$P2Y_{12}$
For **ADP** binding

Important:
Affected in Glanzmann thrombasthenia

Any activated platelets release **ADP** and **TXA2** activate **more platelets aggregation to form** primary **hemostatic plug"**
example of **positive feedback**

Secretion reaction

- This is the time for secretion of platelets contact "from alpha granules & dense body"
- **They will release: thromboxane A2, serotonin & ADP** that activating other platelets then they will bind to their receptor in platelets ***"TPa for TXA2, $P2Y_{12}$ for ADP"***
- ***5-HT & TXA2 are vasoconstrictors*** decreasing blood flow through the injured vessels

Aggregation

Then aggregation starts, but aggregation **needs fibrinogen** that is normally circulating in the bloodstream **to join platelets to each other via platelet fibrinogen receptors.**
ADP causes stickiness and enhances aggregation.

Clot retraction

- Myosin and actin filaments in platelets are stimulated to contract during aggregation → further **reinforcing the plug** and **help release of granule contents,** this occurs with the help of microtubules
- **When clot retracts (contracts), it expresses most of the fluid from the clot within 20-60 min and it's called Serum (cannot clot).**

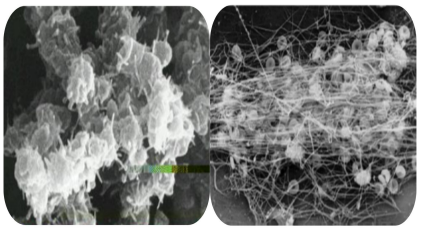
The fate of Clot: is lysis or fibrous tissue formation (platelet-derived growth factor)

Platelet function Cont.

Maintenance of vascular integrity

Female slides

1. Initial arrest of bleeding by platelet plug formation
2. Stabilization of hemostatic plug by contributing to fibrin formation
   - Adequate number and function of platelet is essential to participate optimally in haemostasis.



Cell-based Model:

(Wasn't explained by the Dr)

The cell-Based Model proposes three overlapping phases of coagulation

- **Initiation:**

Exposition of tissue factor to blood leads to activation of factor VII and other factors.

- **Amplification:**

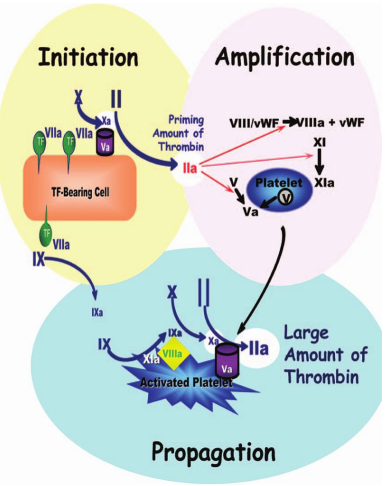
The resulting small amounts of thrombin activate platelets which bind factors Va, VIIIa, and IXa at their surface.

- **Propagation:**

Bound to the activated platelets' surface ("cell-based"), these coagulation factors are able to convert large amounts of prothrombin into thrombin.

The resulting thrombin burst then accounts for sufficient conversion of fibrinogen to fibrin and activation of factor XIII.

Females' Dr: This reaction occurs on the platelets surface. If the platelet is absent or deficient, the reaction will be affected



Male slides

Factors affecting blood platelets count:

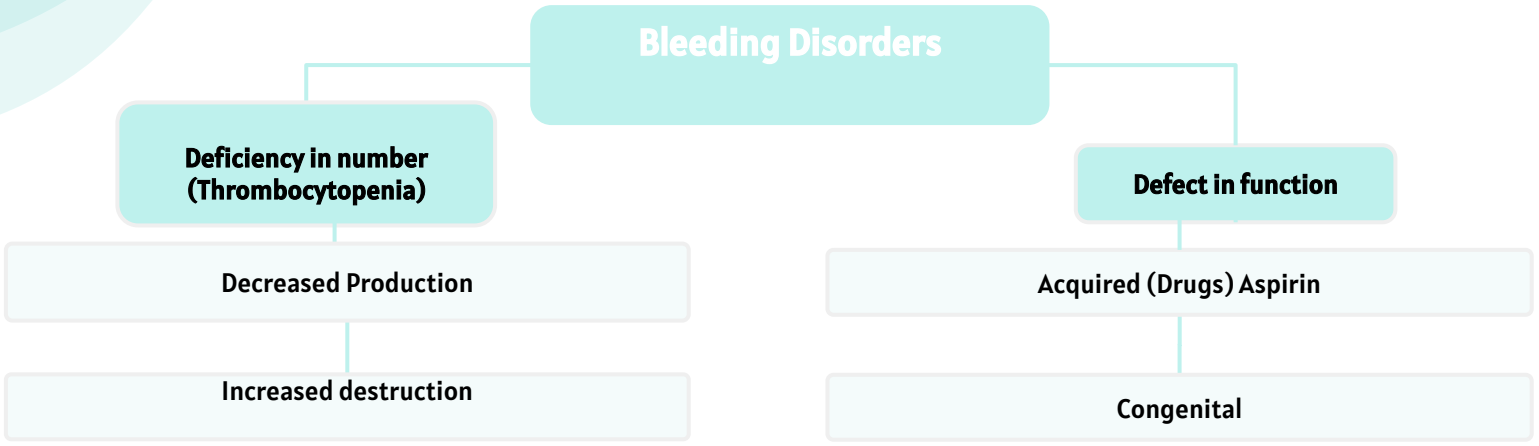
↓

- Prior menstruation
- In newborn
- In pregnancy
- With smoking
- With nutritional deficiencies. Eg: vitamin B12, folic acid & iron.

↑

- In injury
- With adrenaline
- With hypoxia
- After menstruation

Bleeding Disorders



Dr: don't memorize it

Abnormal distribution → **Splenomegaly with sequestration in the spleen**

Decreased Production	Increased destruction
Various anemias	Autoimmune diseases : **Idiopathic (immune) thrombocytopenic purpura**
Leukemia or lymphoma	Pregnancy:about 5 % of pregnant women develop mild decrease Thrombotic thrombocytopenic purpura.
Cancer treatments such as radiation or **chemotherapy**	Surgery: man - made heart valves , blood vessel grafts , bypass machines
Medications : diuretics , chloramphenicol	Medications: quinine , antibiotics containing sulfa , Dilantin® , vancomycin , rifampin , heparin - induced thrombocytopenia
Infections (Viruses) : chickenpox , mumps , Epstein - Barr , parvovirus , AIDS	Infections : septicemia
Toxic chemicals	Disseminated intravascular coagulation
Alcohol in excess	Pseudothrombocytopenia
Genetic conditions: Wiskott-Aldrich, May-Hegglin.	Partial clotting of specimen
	EDTA-platelet clumping
	Platelet satellitism around WBCs
	Cold agglutinins
	Giant platelets

Congenital Platelet Disorders

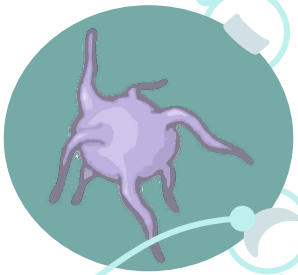
Dr:Important to know the diff between adhesion and aggregation

Bernard-Soulier

Deficiency of vW factor receptors:
GP Ib, V, IX

Glanzmann thrombasthenia

Deficiency of fibrinogen receptors:
GP IIb, IIIa



Adhesion

Aggregation

Grey Platelet Syndrome

Storage Pool deficiency

Hermansky - Pudlak syndrome

Chediak - Higashi syndrome

Granules

Dr: not important

Wiskott Aldrich syndrome → **Cytoskeleton**

Receptor defects TXA2 , collagen ADP , epinephrine) → **Primary secretion**

Congenital amegakaryocytic thrombocytopenia

MYH9 related disorders

Thrombocytopenia with absent radii (TAR)

Paris - Trousseau/Jacobsen

Production

Testing of Platelet Function

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

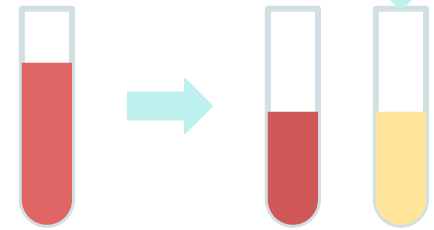
Platelet Aggregation in Platelet Rich Plasma (PRP)

Dr.Shahid:
We won't ask you in the exam.

Agonists:

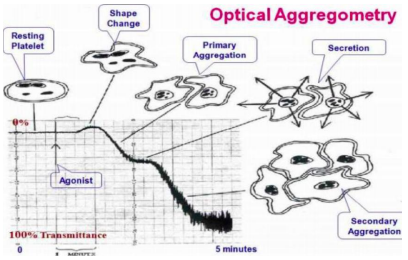
- ADP
- Adrenaline
- Collagen
- Arachidonic acid
- Thrombin
- **Ristocetin**

- <u>By Platelet Aggregation Method</u>: It provides information on time course of platelets activation.
- You need Platelet rich plasma Adrenaline (PRP)
- Reference ranges need to be determined for each agonist
- If we add those factors and we didn't get a response from any but ristocetin → VWf is normal, but agglutination is abnormal (no agglutination)
- If we add those factors and we get a response from all but ristocetin → VWf is abnormal (no adhesion)



Whole blood RBC PRP

Platelet aggregometry



Important:

Question from the slides: A 7 years girl complaining of severe bruising since birth and if she has injury she would bleed for days, she had epistaxis which lasts for days, her mother said "she just bruise more easily than her older sister".

- **Investigation:**

CBC: RBC, WBCs, platelets

- **Platelets morphology** → normal
- **Aggregometry:**

absent platelets aggregation in response to ADP, collagen, thrombin, epinephrine.

- **Diagnosis:**

Glanzmann's thrombasthenia

Lab tests in bleeding and clotting

Dr: Just have a general idea

Test	Normal value	Importance
Platelets 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** • **Warfarin** affect ext. pathway → PT is used to follow up
Partial thromboplastin time (PTT)	25-40 SECS	• **Measures effectiveness of the intrinsic pathway** • **Heparin** affect int. pathway → PTT is used to follow up
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

Dr: Not important

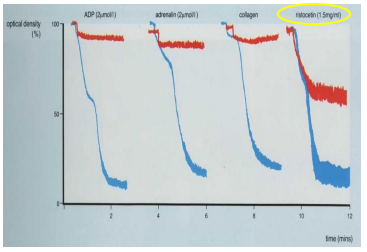
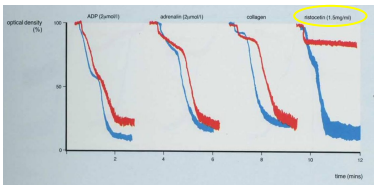
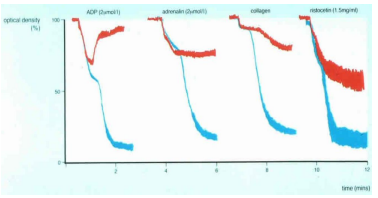
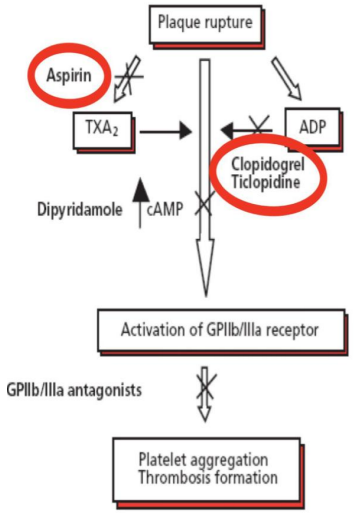
Platelet Functions beyond clotting

Dr: just for your information Except what in red.

- Platelets **sense invading pathogens** through their receptors, which results in platelet activation. Activated platelets release antimicrobial proteins and molecules limit the spread of the infection.
- The binding of viral pathogen with platelets not only result in clearance of platelets but also clearance of viral pathogens is caused by platelets
- Platelet have also **phagocytic function** during direct interaction of viral pathogens with human platelets, there is a phagocytosis of viral pathogens by platelets.
- Platelets and megakaryocytes express messenger ribonucleic acid (mRNA) and/or protein for the toll like receptors (TLR) that detect and bind viral components at the cell surface and viral nucleic acids.
- Platelets also **interact with other immune cells**; after activation platelets secrete a number of chemokines attracting neutrophils.
- The hemostatic function of platelets is to form the primary hemostatic plug.

Lab tests cont.

Dr: not important except first two .

Disorders	Findings in LTA	Test
Glanzmann's Thrombasthenia OR afibrinogenemia	• Absent or markedly impaired aggregation to all agonists (ADP, adrenaline or collagen) **except Ristocetin**. • Ristocetin-induced agglutination shows only primary wave • Aggregation cannot occur because fibrinogen cannot bind. Afibrinogenemia gives similar results.	Ristocetin is the only one working 
Bernard Soulier Syndrome OR Von Willebrand Disease	• Absent or markedly reduce platelet agglutination with Ristocetin.	Straight line = no agglutination 
Storage Pool Disorder OR Platelet Release Defect	• Primary aggregation with ADP, adrenaline and collagen • Only partial agglutination with Ristocetin • Suggesting a failure of granule release or a deficiency of platelet granules.	
Aspirin [or defects in the COX pathway]	• Aspirin inhibits platelet cyclooxygenase by irreversible acetylation, thereby preventing the formation of thromboxane A2 which is a powerful stimulant of platelet aggregation. • Absent aggregation to Arachidonic acid. • Primary wave aggregation only with ADP. • Decreased or absent aggregation with collagen.	
Clopidogrel	• Clopidogrel, a thienopyridine, acts by inhibiting adenosine receptors, which inhibits the early step of platelet activation. • Absent aggregation with ADP	

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.**

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)

Quiz

MCQ

Q1: Which of the following is related to platelets aggregation?

A- Exposed collagen
B- Activation of GB Ia/VI
C- Activation of GP IIb / IIIa
D- ADP phosphatase

Q2: A defect in platelets adhesion is referred to as:

A- Storage pool disorder
B- Glanzmann thrombasthenia
C- Bernard-Soulier syndrome
D- Grey Platelet Syndrome

Q3: The major source for platelets factors is?

A- Open canalicular system
B- Mitochondria
C- α & dense granules
D- Microtubules

Q4: Which of the following opposes the action of TXA2?

A- ADP phosphatase
B- Prostacyclin
C-Prothrombin
D- Cyclooxygenase

Q5: Aspirin inhibits platelet function by inhibiting the synthesis of:

A- Thromboxane A2
B- Plasmin
C- vWF
D- Thrombin

Q6: Von Willebrand factor is activated through which of the following?

A- Vasoconstriction
B- Adhesion of platelets to collagen
C- Secretion of TXA2 by platelets
D- Arachidonic acid degradation

Answers: Q1: **C** Q2: **C** Q3: **C** Q4: **B**Q5: **A** Q6: **B**

SAQ

Q: Name three platelets disorders.

A: slide 6

Q: mention two factors that Decreases and another two that increases the platelets count.

A: slide 4

TEST YOURSELF !

MCQ:

Q1) The regulation of Platelet production is done by

A) plasmin | B) thrombin | C)Fibrin | D) Thrombopoietin

Q2) Which of the following opposes the action of TXA2?

A) ADP phosphatase | B) Prostacyclin | C) Prothrombin | D) Cyclooxygenase

Q3) Aspirin inhibits platelet function by inhibiting the synthesis of

A) Thromboxane A2 | B) plasmin | C) thrombin | D) von willebrand factor

Q4) In Bernard-Soulier Syndrome there is defect in the receptor for which of the following?

A) von Willebrand Factor. | B) Fibrinogen | C) Collagen | D) TXA2

Answers: Q1:D | Q2:B | Q3A:| Q4:A

SAQ:

Q1) Enumerate (in order) the events of platelet Activation

Adhesion → Shape Change → Aggregation (Needs Fibrinogen) → Release Reaction → Clot Retraction

Q2) Mention 2 vasoconstrictors that will decrease blood flow through the injured vessel

-serotonin
-thromboxane A2

PHYSIOLOGY

GNT Block

Team 443

The BEST

Team Leaders

EVER..

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Fahad Almughaiseeb

Ghaida Aldossary

Faisal Alzuhairy

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- Layla Alfrhan
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- Nazmi M Alqutub
- khalid Alanezi
- Abdulaziz abahussain
- Yousof Badoghaish
- mansour Alotaibi
- Layan aldosary
- Norah alhazzani
- Jouri Almaymoni
- Salma Alkhlassi
- Shoug Alkhalifa