Blood physiology

Tharunya Kurusanth MD4

Platelets & red blood cells

Platelets

- Function and origin
- Hemostasis
  - Primary hemostasis
  - Secondary hemostasis
  - Disorders of hemostasis
  - Drugs that affect hemostasis

Red blood cells

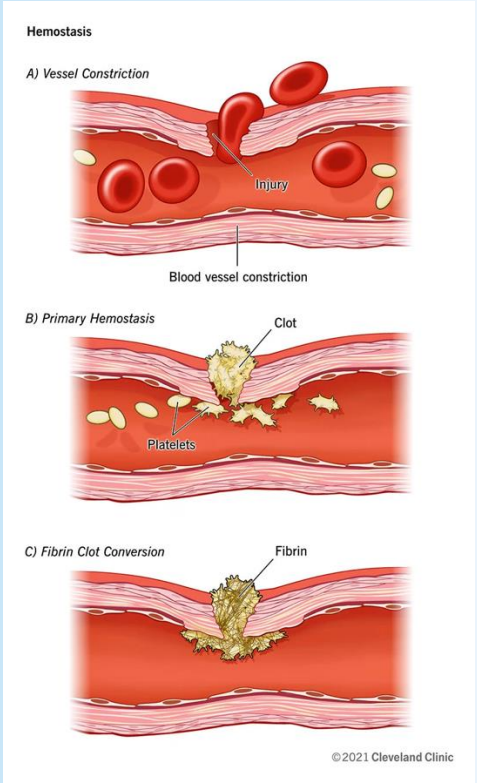
- Function and origin
- Blood type AB0 and Rh
- Serological conflict
- Hemoglobin

Platelets (PLT's)

- 150.000 - 400.000 cells/µL
- Small (2–3 µm), anuclear
- Cell membrane: phospholipids, glycoproteins
- **Thrombopoietin** from the **liver** (and kidney)
- Life span ≈ 10 days

Hemostasis

- Stopping of blood flow and prevention of blood loss



3 stages:

1. Vasoconstriction
2. Formation of temporary **«platelet plug»**
3. Activation of coagulation cascade and formation of **«fibrin plug»**

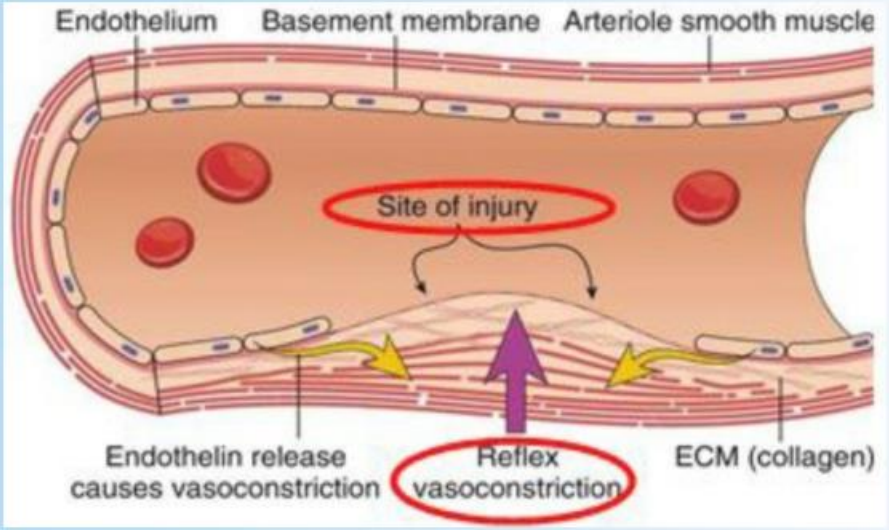
Hemostasis

	Primary	Secondary
Goal	Platelet plug	Fibrin plug
Mechanism	Vasoconstriction Platelet aggregation	Coagulation cascade
Clot characteristics	Unstable	Stable

Primary hemostasis

Vasoconstriction

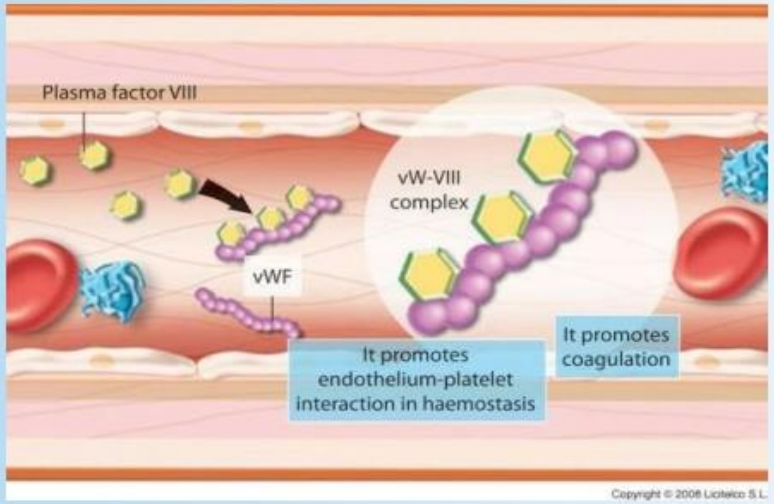
- *Damage to endothelium* →
- Sympathetic reflex
  - Arteriolar smooth muscle contraction
- Vasoconstrictors
  - Thromboxane A2
  - Serotonin

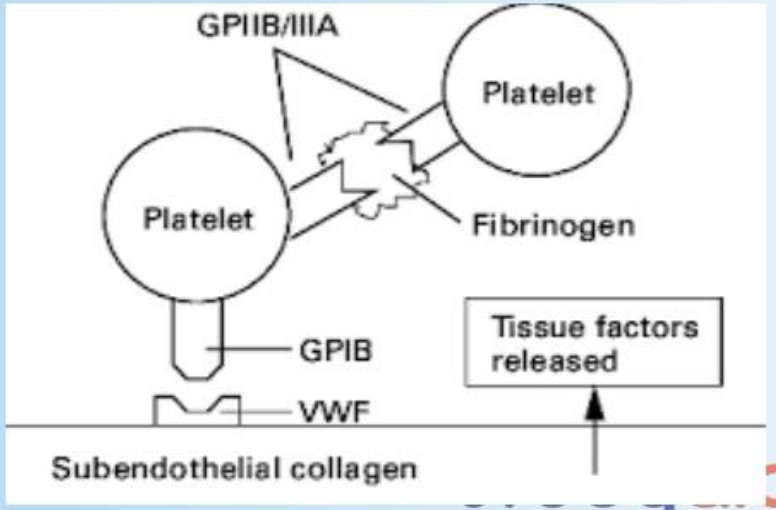


Primary hemostasis

PLT activation

- Subendothelial collagen – PLT activation
- Release of PLT granules:
  - *TXA_2, serotonin, ADP*
    - *Activate nearby PLT's*
  - *Von Willebrand factor (vWF)*
    - PLT adherence
    - GPIIB/IIIA
    - Clotting factor VIII

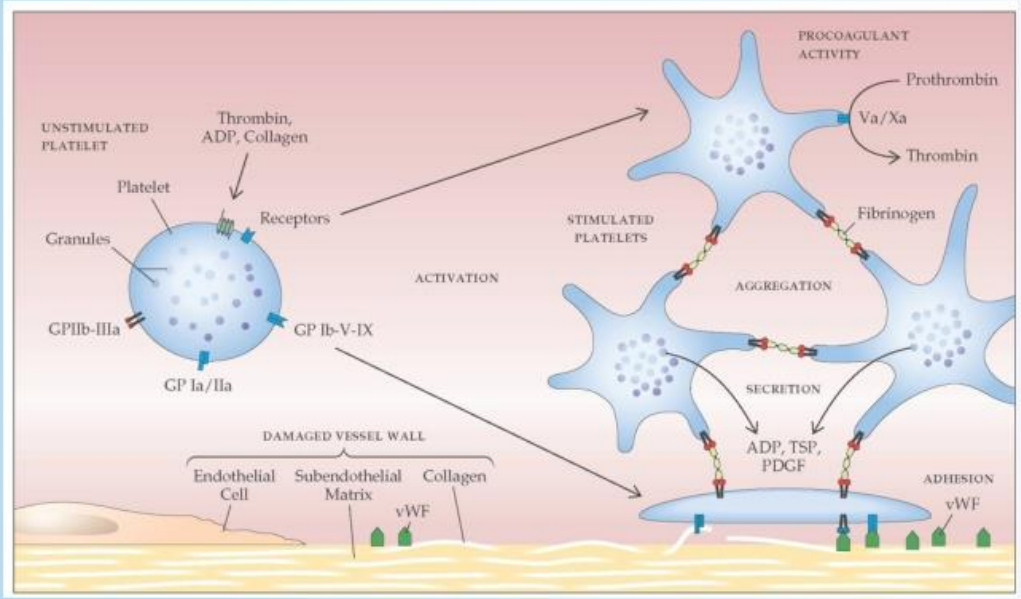


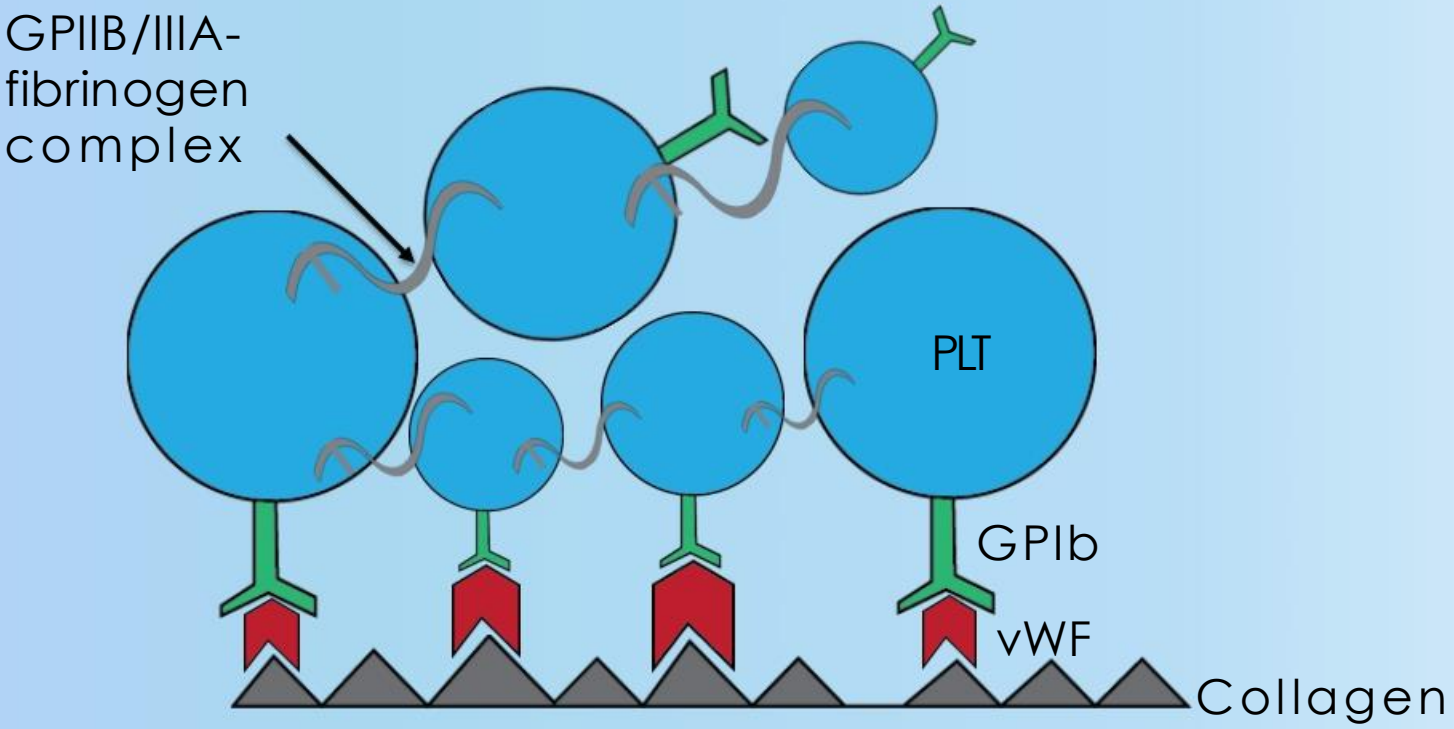


Primary hemostasis

PLT aggregation

- **ADP** - *change of PLT shape, GPIIB/IIIA expression*
- **Thromboxane A2** (TXA_2) - *PLT aggregation*
- **Fibrinogen** binds to GPIIB/IIIA, and ties platelets together





Platelets & red blood cells

Platelets

- ~~Function and origin~~
- ~~Hemostasis~~
  - ~~Primary hemostasis~~
  - Secondary hemostasis
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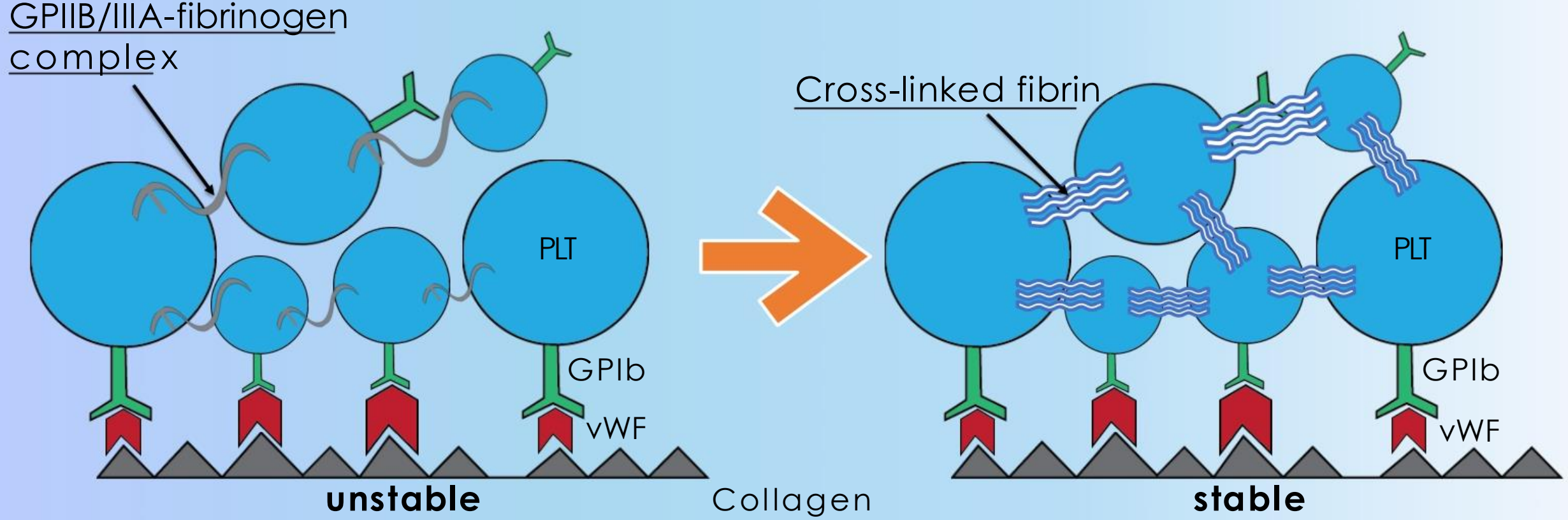
  - Drugs that affect hemostasis

Red blood cells

- Function and origin
- Blood type AB0 and Rh
- Serological conflict
- Hemoglobin

What is the goal?

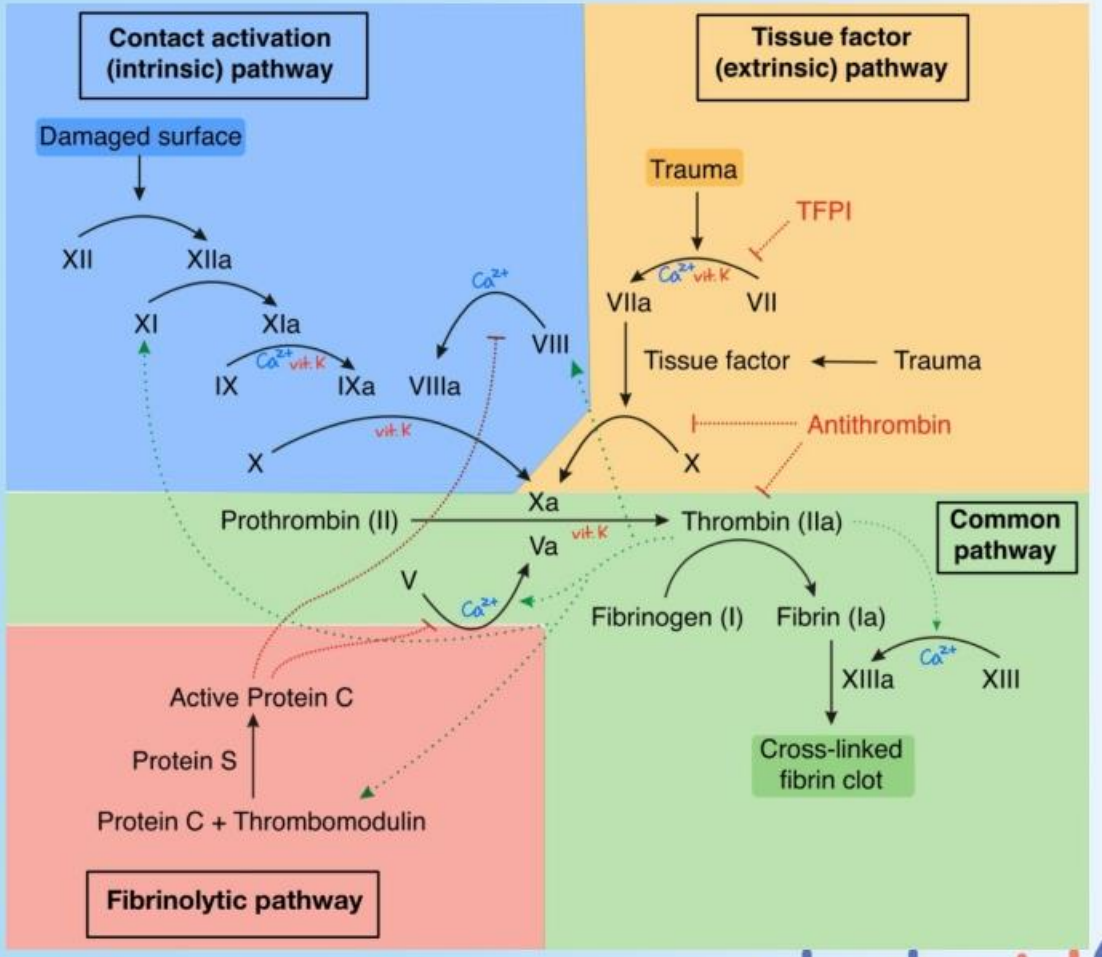


Secondary hemostasis

Coagulation cascade

4 pathways:

- Intrinsic pathway
- Extrinsic pathway
- Common pathway
- Fibrinolytic pathway



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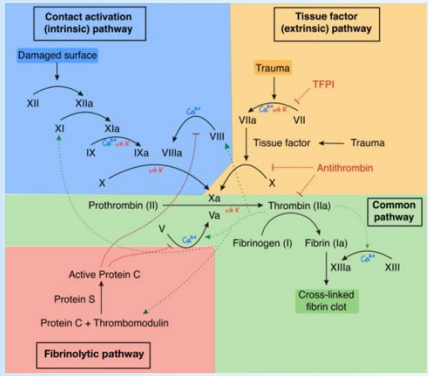
Coagulation cascade

Extrinsic pathway



external trauma

↓

tissue factor (thromboplastin)

↓

7 → **7a**

Ca^{2+}, vit. K

↘

common pathway

Unlucky with a papercut? Need LUCKY number **7** to fix that☺

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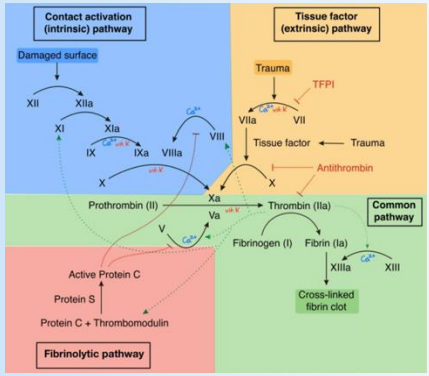
Coagulation cascade

Intrinsic pathway



Collagen

12 → **12a**

11 → **11a**

9 → **9a**

Ca^{2+}, vit. K, PL*

8

Activated by vWF!

common pathway

TENET! 12, 11, 9, 8, 10

**PL = platelet phospholipids*

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Coagulation cascade

Common pathway

8a
+
9a 7a

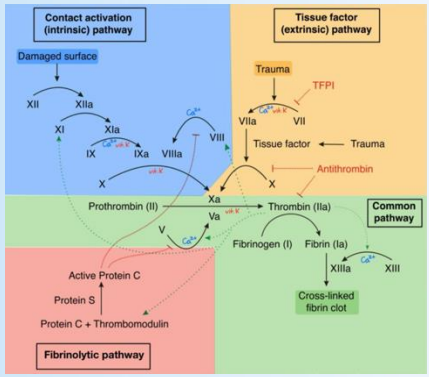
10 → 10a

5a
Ca2+ PL

prothrombin (2) → thrombin (2a)
Vit. K

Ca2+
13 → 13a

fibrinogen → fibrin



10$ will buy **5** burgers for **2** friends!

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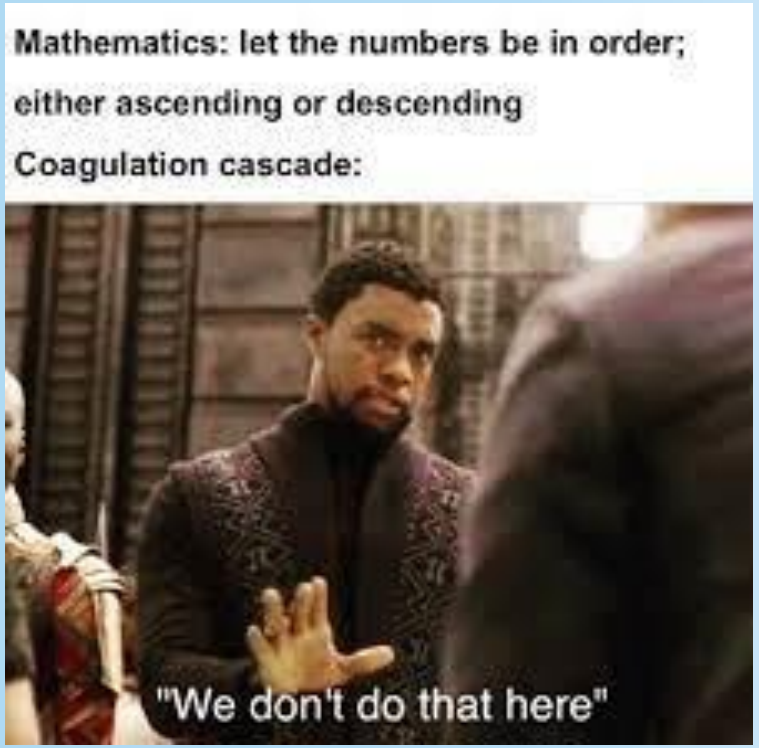
Clotting factors

1. ***F****ibrinogen*
2. ***P****rothrombin*
3. ***T****issue factor*
4. ***C****alcium*
5. **L**abile factor (proaccelarin)
7. **S**tabile factor
8. **A**nti-haemophilic factor
9. **C**hristmas factor
10. **S**tuart - Prower factor
11. **P**TA (plasma thromboplastin antecedent)
12. **H**ageman factor
13. **F**ibrin stabilizing factor

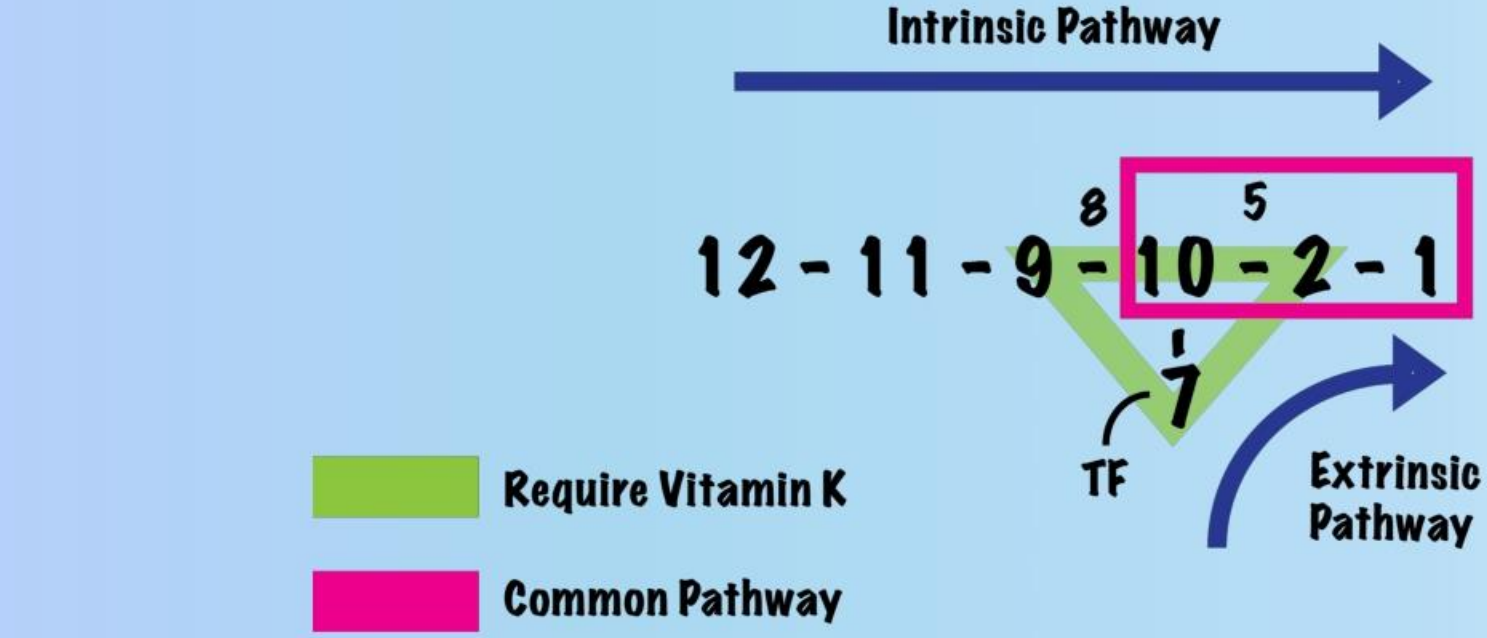


F*oolish* ***P****eople* ***T****ry* ***C****limbing* ***L****ong* ***S****lopes* ***A****fter* ***C****hristmas,* ***S****ome* ***P****eople* ***H****ave* ***F****allen*

Secondary hemostasis

Coagulation cascade

Vit. K dependent	Synthesized in liver	Ca^{2+} dependent
• 10, 9, 7 & 2 ▸ «1972»	• 1, 2, 5, 7, 8, 9, 10, 11, 12 • Protein C	• 5, 7, 8, 9 & 13



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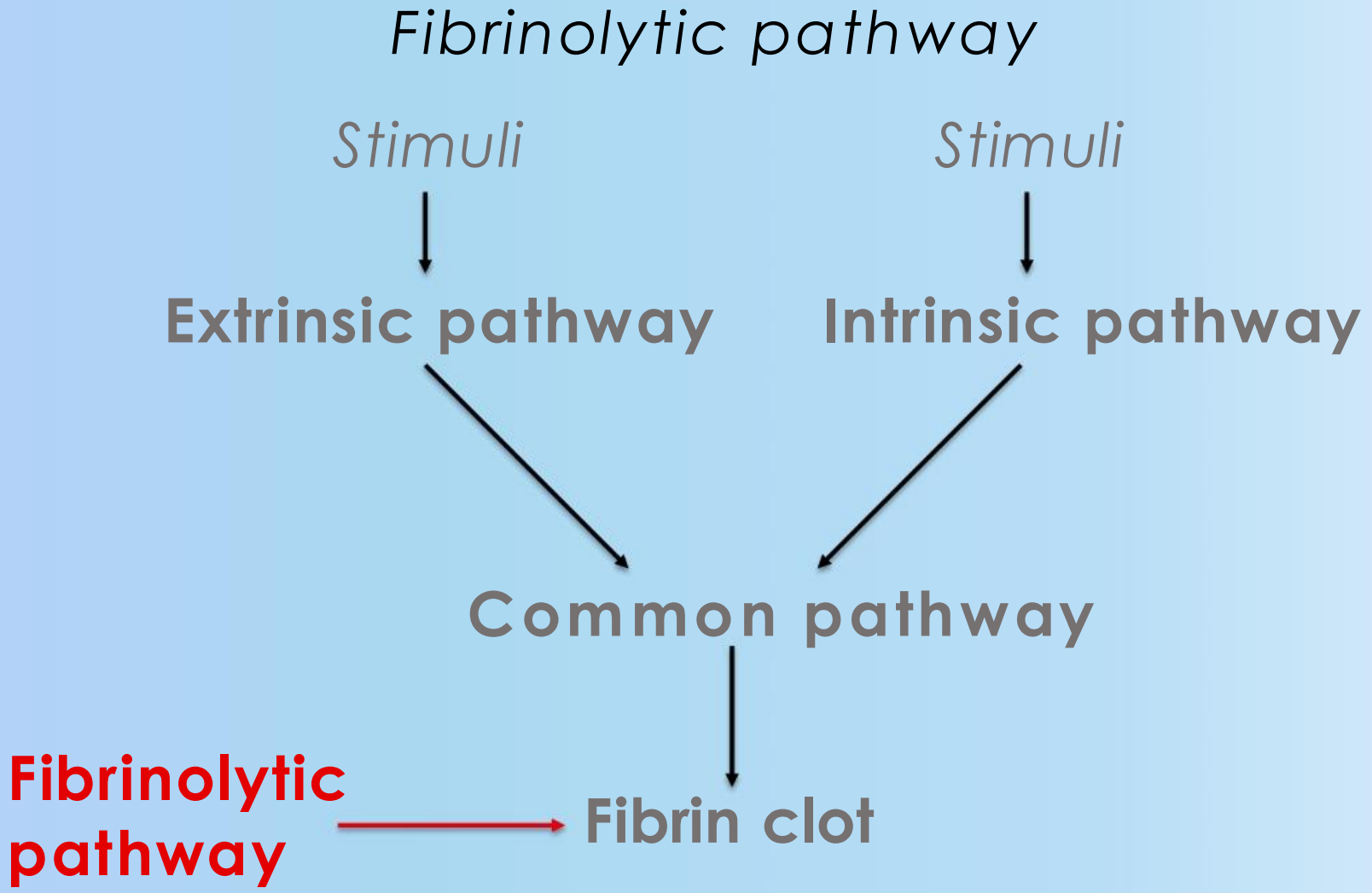
Coagulation cascade

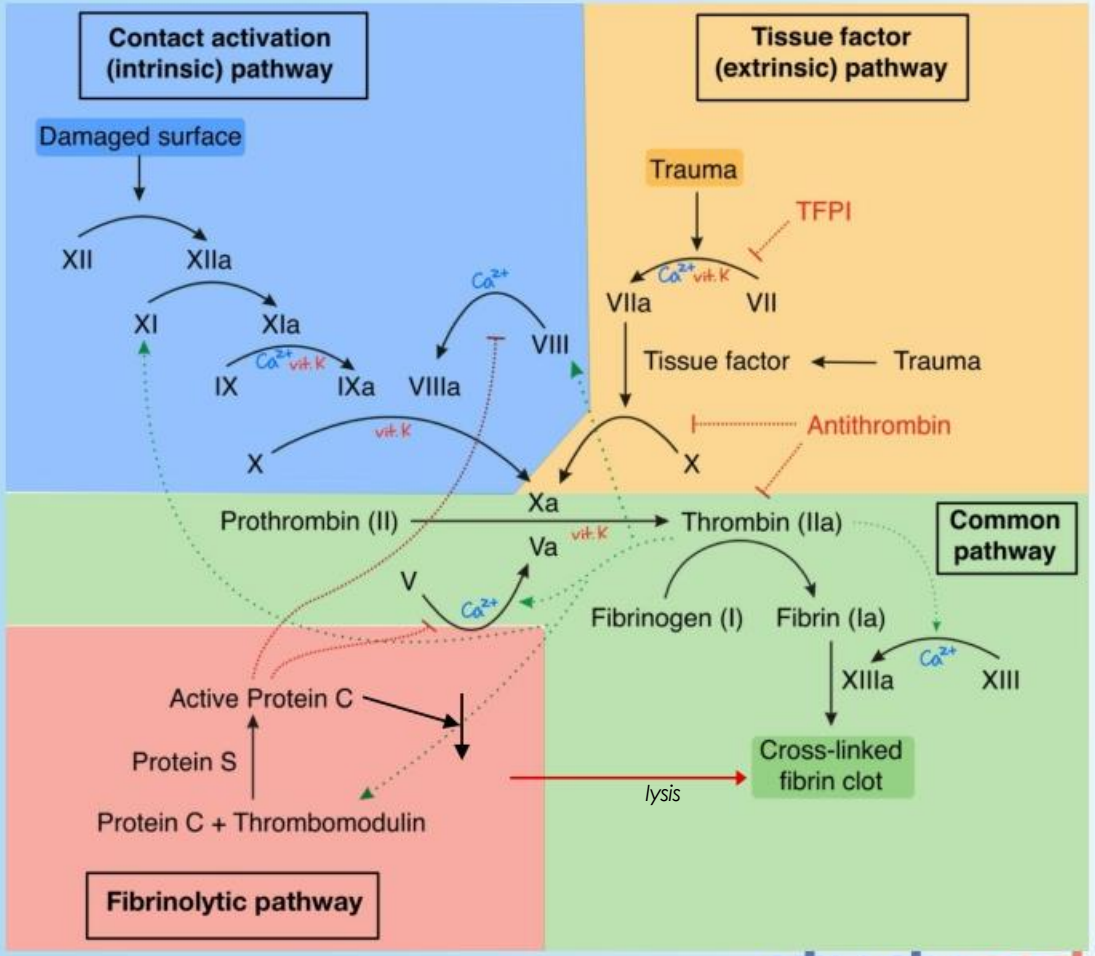


Coagulation cascade

Fibrinolytic pathway

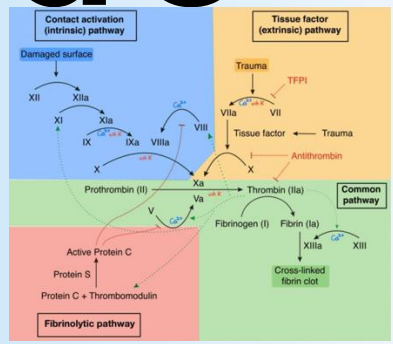
Goal:

- Destroy pre-existing clots: *thrombolysis*
- Stop new clots from forming: *anticoagulation*



Coagulation cascade

Fibrinolytic pathway



Thrombin (2a)

Thrombin-thrombomodulin complex

Thrombomodulin

Protein C

APC

8

5

t-P A

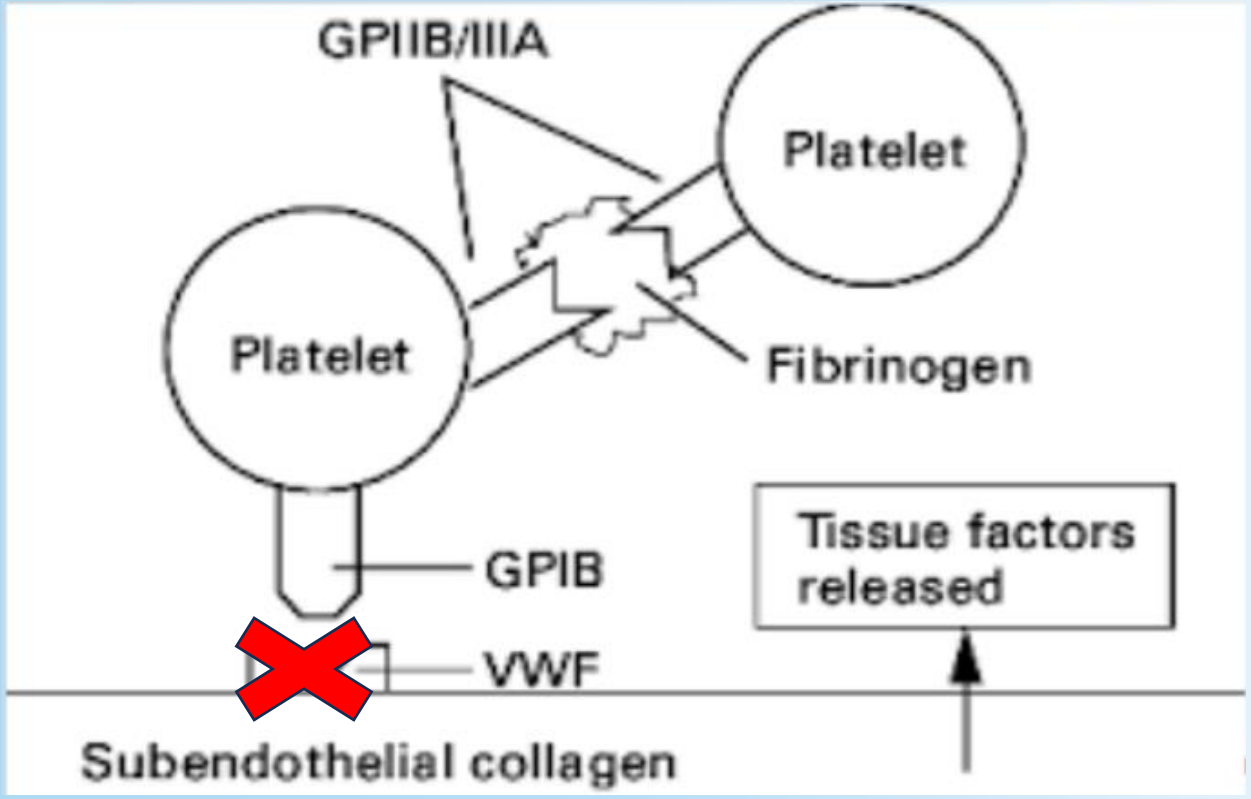
Plasminogen

Plasmin

lyses fibrin

Clotting disorders – von Willebrand disease

- ↓vWf or no vWf
- Primary hemostasis



Clotting disorders – secondary hemostasis

Hemophilia A

- Deficiency of **clotting factor 8**

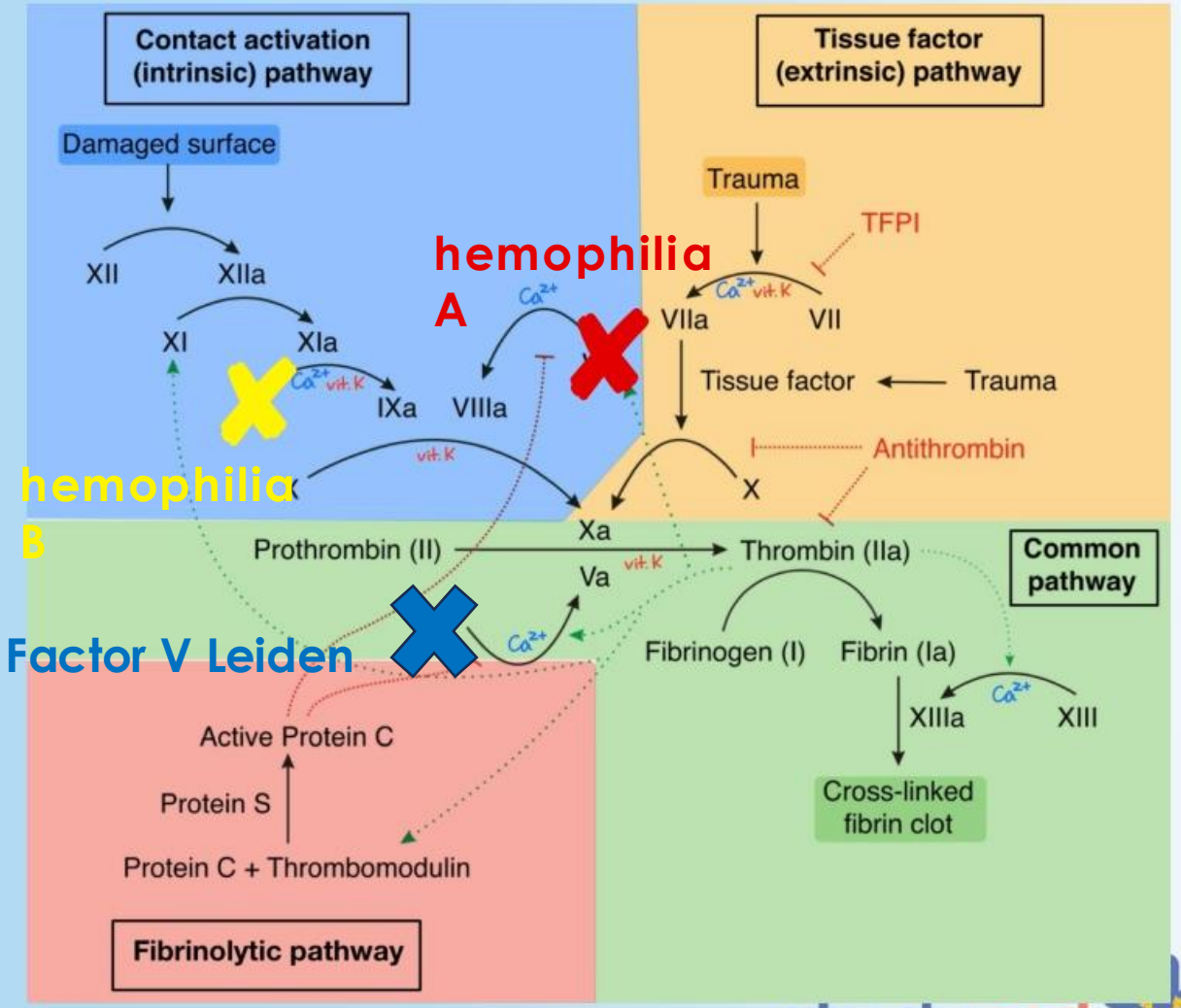
«hemophilia Aight»

Hemophilia B

- Deficiency of **clotting factor 9**

Factor V Leiden

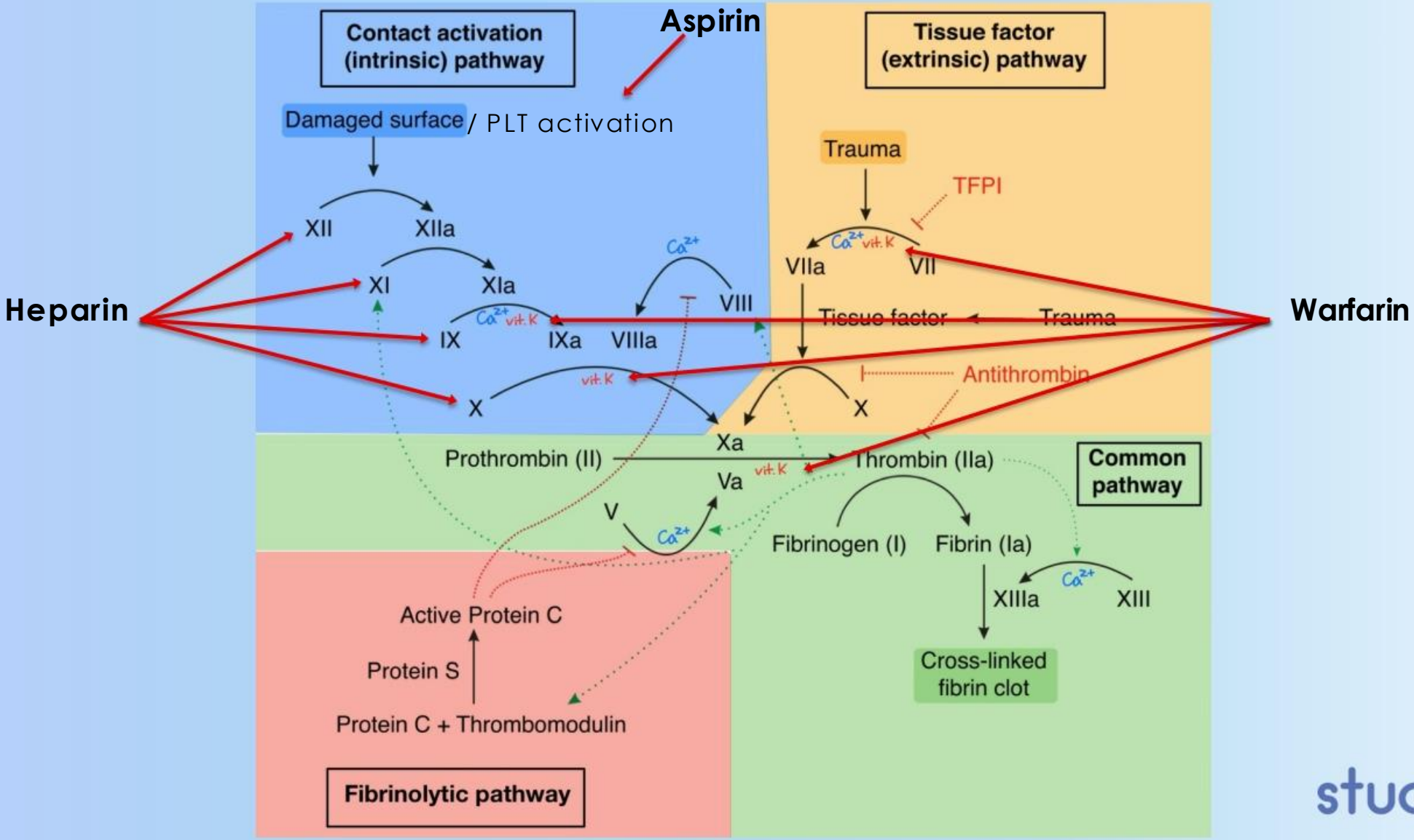
- Mutation of **clotting factor 5**



Clotting disorders

	Haemophilia	Von Willebrand disease	Factor V leiden	Vitamin K deficiency
Disorder type	Hypocoagulative state of secondary hemostasis	Hypocoagulative state of primary hemostasis	Hypercoagulative state of secondary hemostasis	Hypocoagulative state of secondary hemostasis
Pathophysiology	**Hemophilia A:** Deficiency of factor VIII **Hemophilia B:** deficiency of factor IX	Deficiency of vWF	Mutation of factor V	Insufficient activation of clotting factors 2, 7, 9 & 10
Mechanism	X-linked recessive inheritance	Autosomal dominant inheritance	Inherited	Liver disease Malabsorption Warfarin overdose

Drugs that inhibit clotting



Drugs that inhibit clotting

	LMW Heparin	Aspirin	Warfarin
Effect	Anticoagulant	Antiplatelet	Anticoagulant
Mechanism of action	When conjugated with antithrombin-III, inhibits factor IX, X, XI, XII	Inhibits synthesis of TXA_2	Inhibits vitamin K
Used in	- Always present in blood - Thromboembolism	- Heart attack - Cardiovascular diseases	Hypercoagulative disorders

Platelets & red blood cells

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  - ~~Drugs that affect hemostasis~~

Red blood cells

- Function and origin
- Blood type AB0 and Rh
- Serological conflict
- Hemoglobin

Red blood cells (RBC's)

- 4 - 6 million cells per microliter
- 6–8 µm, anuclear
- Stimulated by **erythropoietin** from the **kidney**
- Life span ≈ 120 days
- Function: **oxygen transport**

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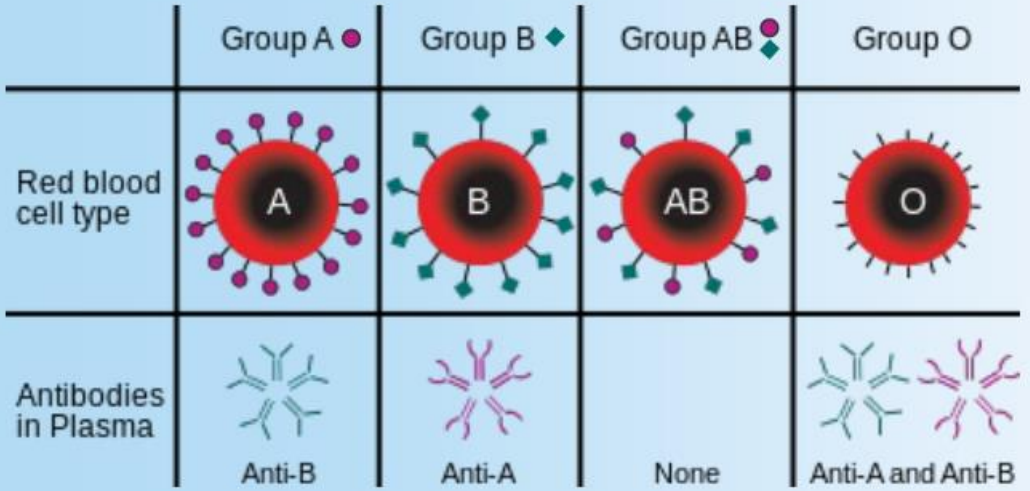
Blood types

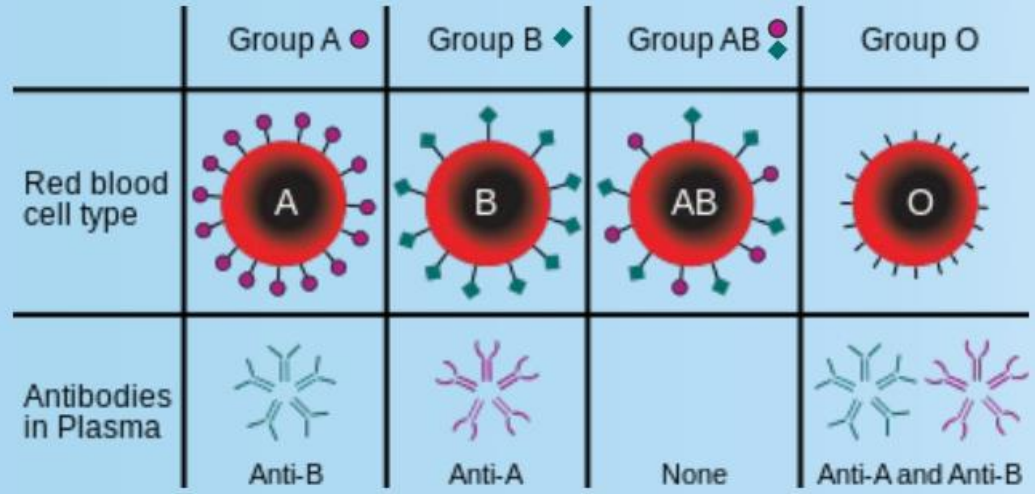
- Blood type **A**, **B**, **AB** or **0 -** proteins are present/absent RBC surface
- Antibodies against the proteins that are **absent**
  - Type A = antibody B
  - Type B = antibody A
  - Type 0 = antibody A and B
- Rhesus proteins: **+ or –**
  - Rh- = Rh antibody



Blood types

Blood transfusion

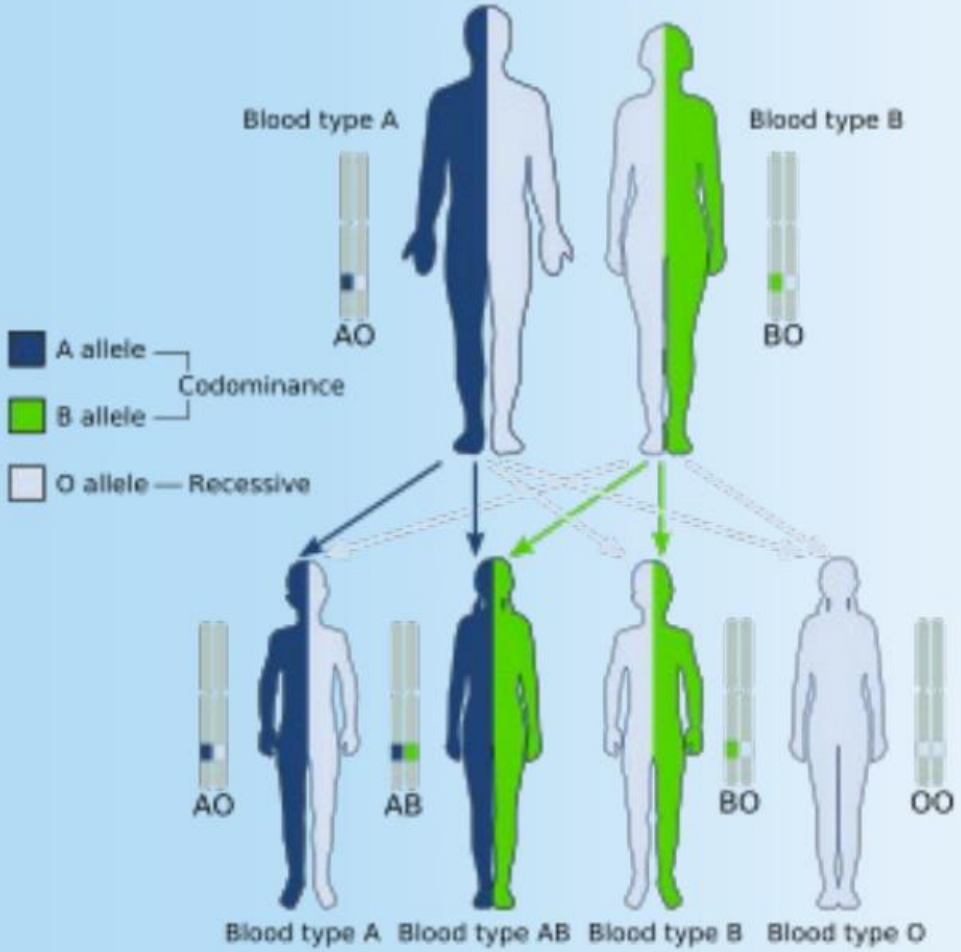
- Blood type AB+ = universal recipient
- Blood type 0- = universal donor



Blood type - inheritance

A = dominant
B = dominant } *Codominant*
0 = recessive

ABO genotype in the offspring		ABO alleles inherited from the mother		
		A	B	O
ABO alleles inherited from the father	A	A	AB	A
	B	AB	B	B
	O	A	B	O



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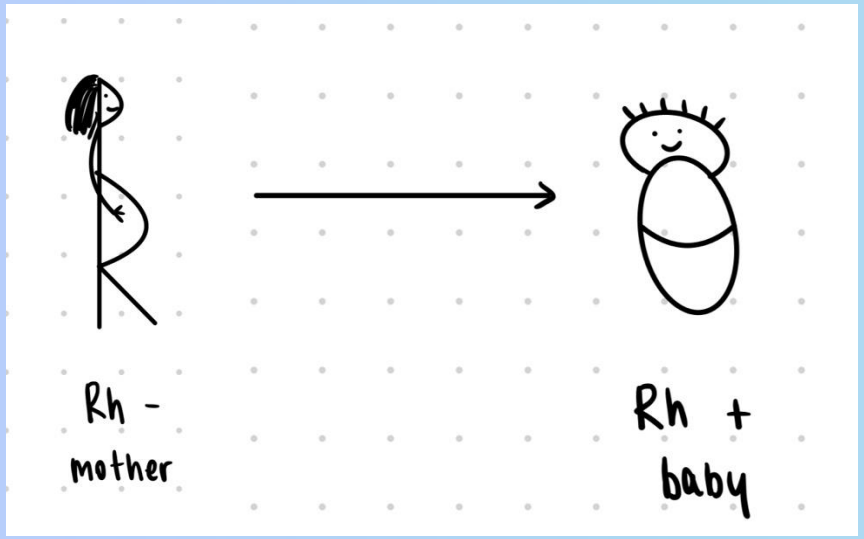
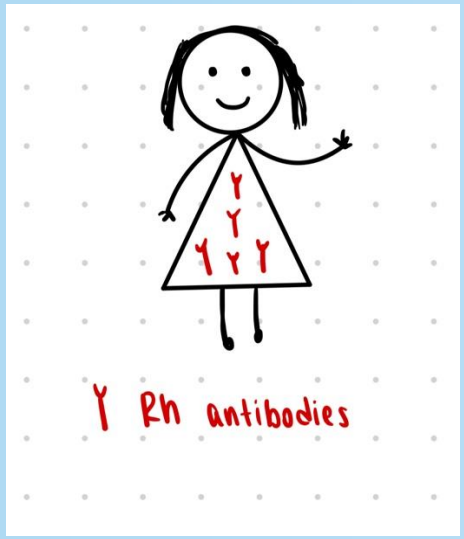
Serological conflict

1st pregnancy



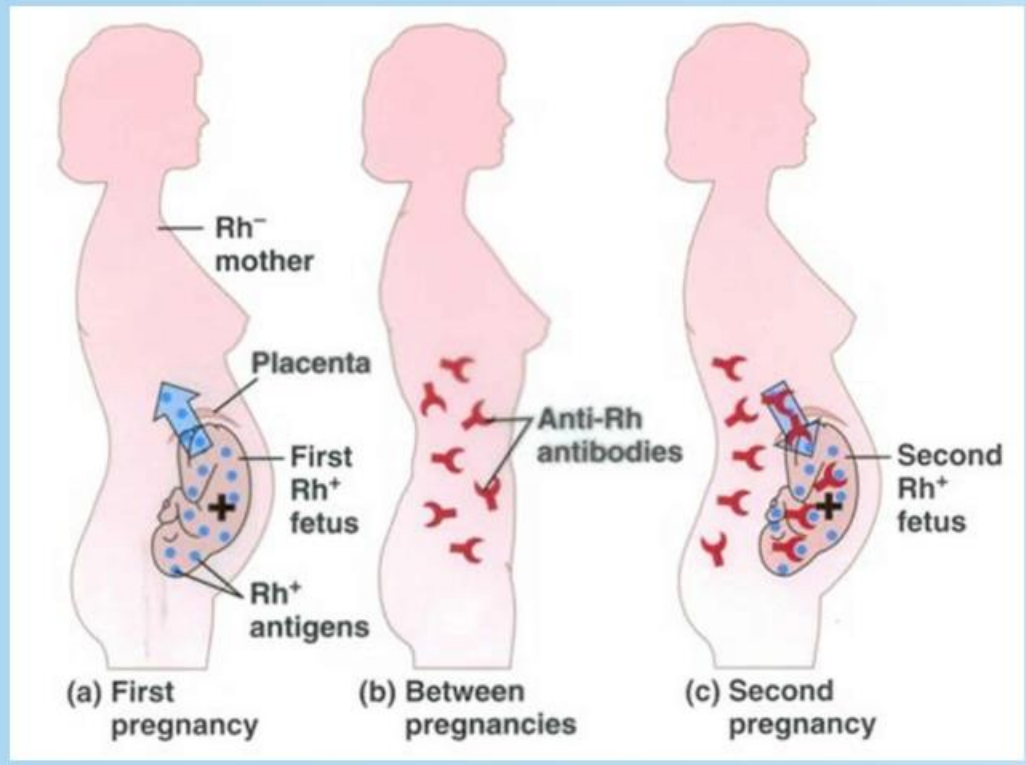
Between pregnancies



2nd pregnancy

Hemolysis → Jaundice, anemia

Serological conflict - prophylaxis



- Rh blood-typing
- Anti-D immunoglobulin within 72 hrs!

Platelets & red blood cells

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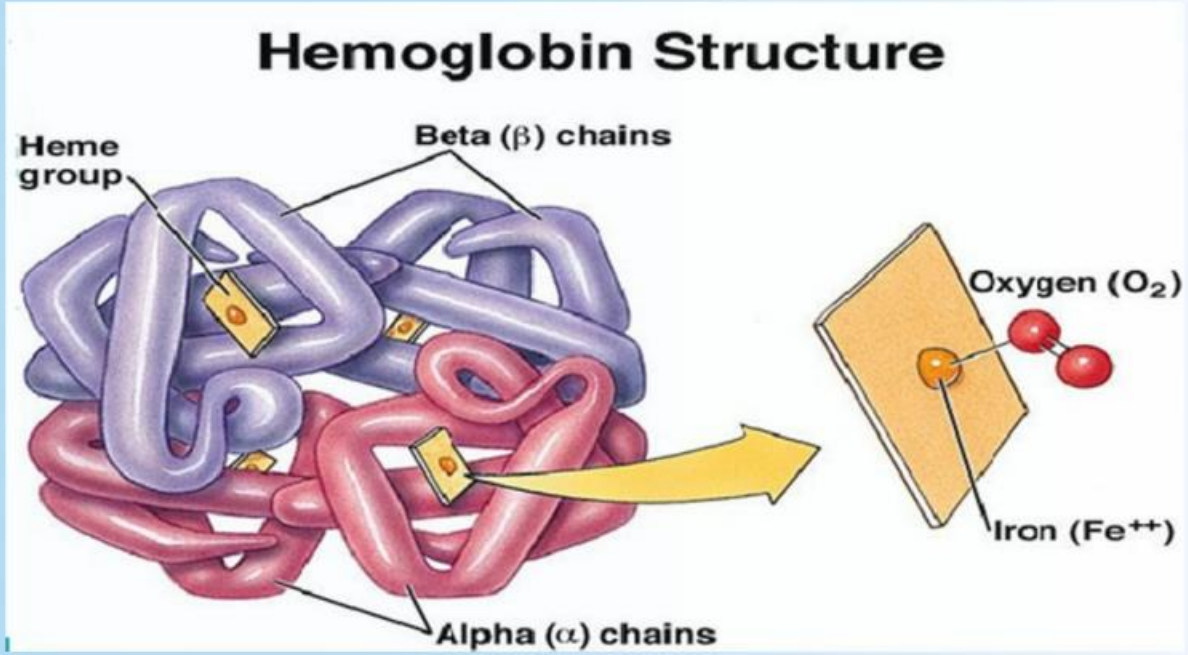
Red blood cells

- ~~Function and origin~~
- ~~Blood type ABO and Rh~~
- ~~Serological conflict~~
- Hemoglobin

Hemoglobin (Hb)

- A protein (globin): **4 subunits**
- Subunit: **1 heme** group
- Heme group: **1 Fe^{2+}**
- Fe^{2+} binds **1 O_2**

Quick maths: 1 Hb = 4 O_2



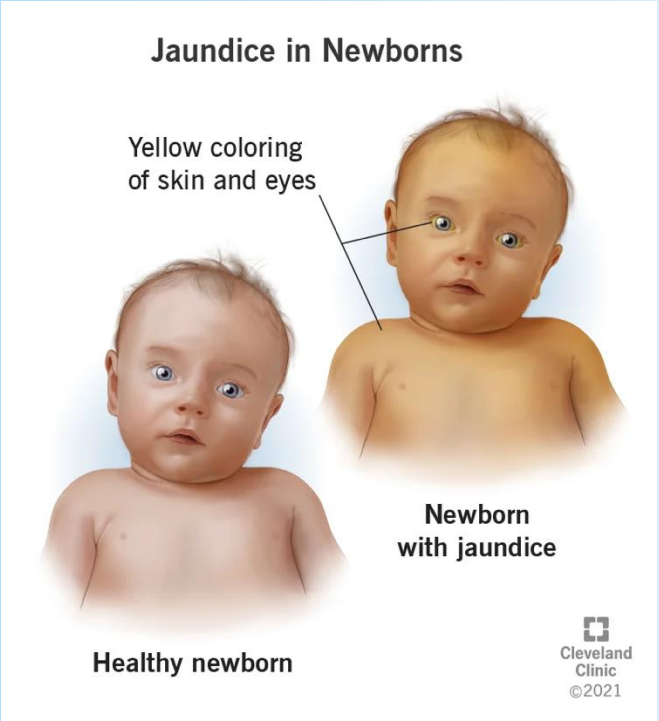
Hb - subunits

Adults

- HbA: $a_2\beta_2$

Fetus:

- HbF: $a_2\gamma_2$
- Higher affinity to oxygen

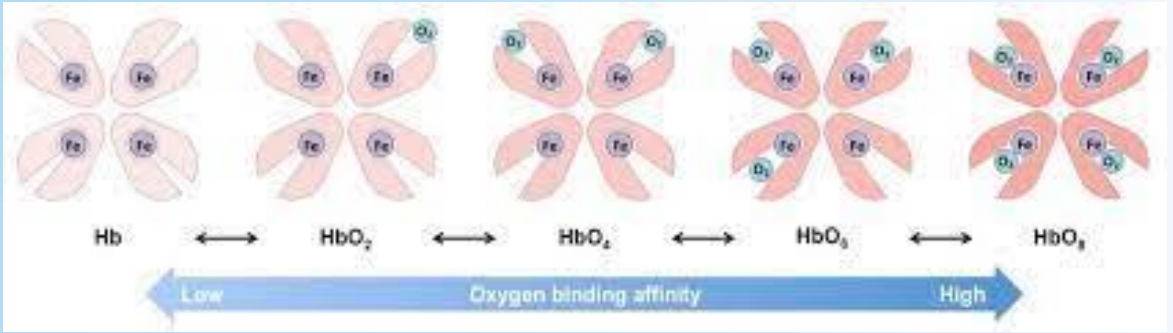


Clinical significance - fetal jaundice:
A normal process where fetal RBC's are removed from circulation to replace fetal hemoglobin with adult hemoglobin, causing jaundice. Bilirubin is the breakdown product of RBC´s, that why the skin is yellow!

Hb - oxygen binding

Oxygen needs to be:

- Picked up in the lungs
- Released in peripheral tissues



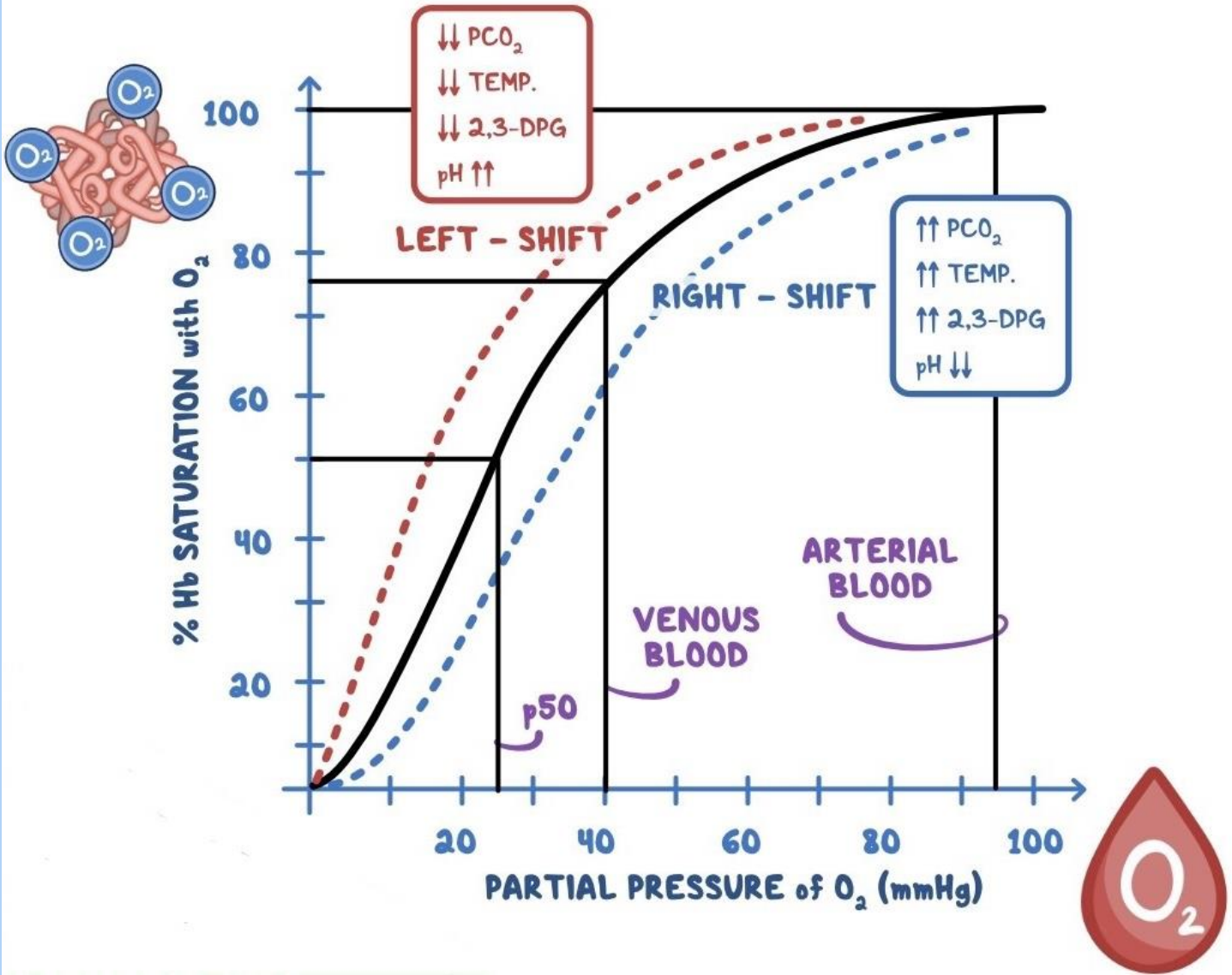
Arterial blood

- Oxyhemoglobin (≈ 97% O_2 saturation)
- R (relaxed) - configuration

Venous blood

- Deoxyhemoglobin (≈ 70% O_2 saturation)
- T (tense) - configuration

OXYGEN – HEMOGLOBIN DISSOCIATION CURVE



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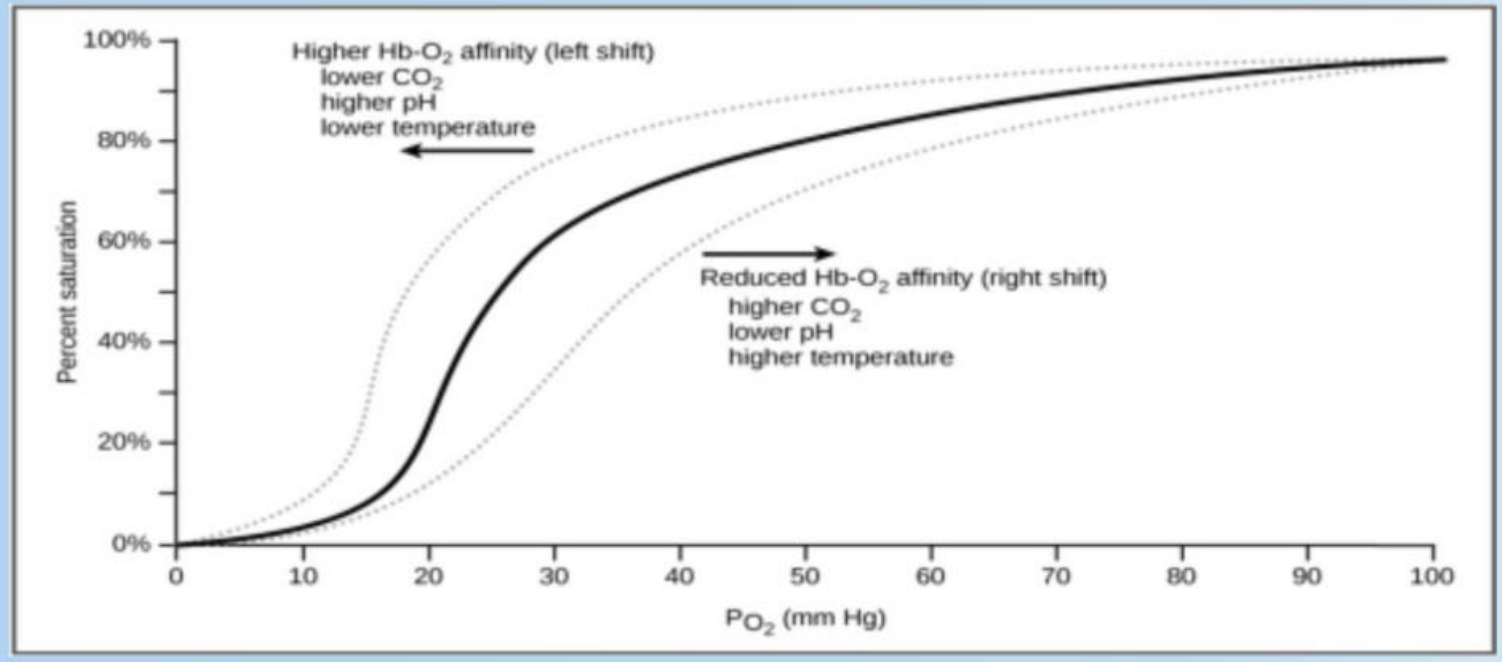


Left shift

↓O_2 unloading to tissues, ↑O_2-Hb affinity

- ↓H^+ (↑pH, base)
  - ↓CO_2 *(weak acid)*
- ↓ 2,3-BPG concentration
- ↓temperature
- HbF *(γ subunit)*
- R-state

Right shift

↑O_2 unloading to tissues, ↓ O_2-Hb affinity

Right = **ACE BATS** are **right** handed

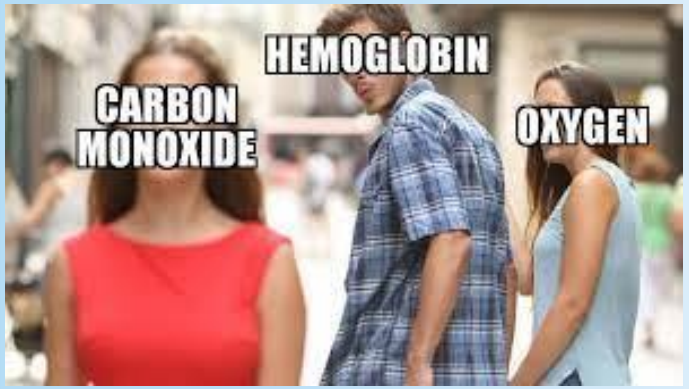
- ↑H^+ (↓pH, **A**cid)
  - ↑**C**O_2 *(weak acid)*
  - **E**xercise
- ↑2,3-**B**PG concentration
- High **A**ltitude
- ↑**T**emperature
- T-state

Hb - clinical significance

Carbon monoxide (CO) poisoning

- CO: **240 - fold greater affinity** to Hb than O_2
- Forms **carboxyhemoglobin**

  —> hypoxia



Methemoglobinemia

- Heme groups with Fe^{3+} in place of Fe^{2+}
- **Fe^{3+} doesn't bind O_2** —> decreased O_2-saturation (≈ 85%)
- Fe^{3+} induces conformational changes to hemoglobin that **increase O_2 affinity to Fe^{2+}**

  —> hypoxia

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