

# Physiology of Blood Blood Clotting

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# Blood Functions

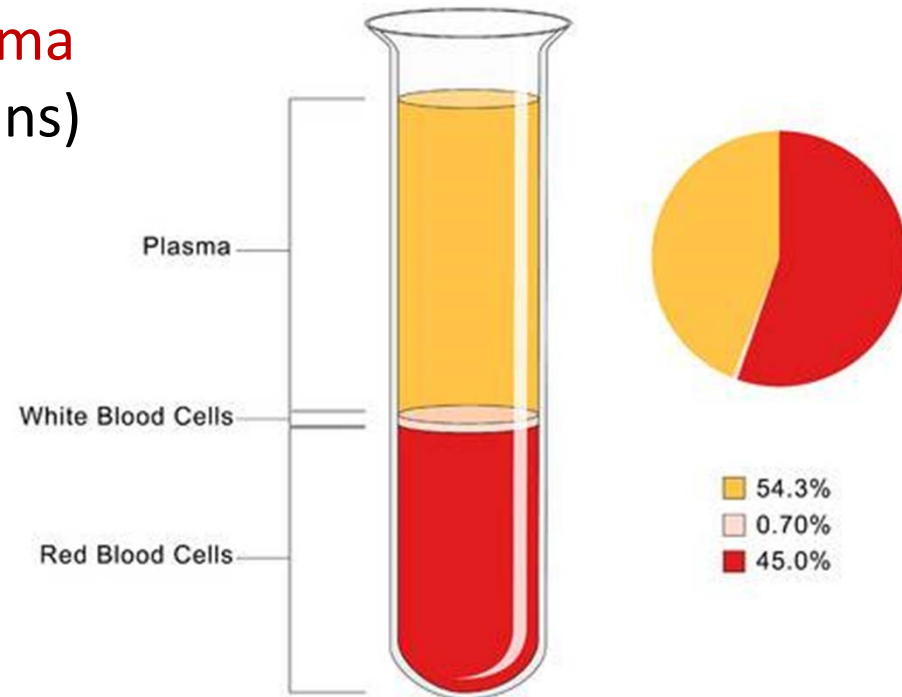
- **transport function**
  - blood gases
  - nutrients, metabolites, vitamins
  - hormones
  - heat, *etc.*
- **humoral regulation**
- **homeostatic function**
  - thermoregulation
  - buffering
- **immune defence**
- **blood clotting**



<https://www.rd.com/health/healthcare/why-is-blood-red/>

# Blood Composition








- total blood volume: - adult man ~80 ml/kg body weight (6-8% of total body mass) - adult woman ~70 ml/kg body weight
- suspension of formed elements in plasma
- complex fluid consisting of **plasma** (extracellular fluid rich in proteins) and of **formed elements** (RBCs, WBCs, platelets)
- **hematocrit** - fraction of the total column occupied by RBCs; **measure of concentration!**
  - adult man ~45%
  - adult woman ~40%
  - newborn ~55%, infant ~32%



[https://www.123rf.com/photo\\_39782091\\_blood-composition.html](https://www.123rf.com/photo_39782091_blood-composition.html)

# Blood Composition - Plasma

- **watery solution** composed of:
  - **water** (90-92%)
  - **electrolytes** (< 1%)
  - **plasma proteins** (7-8%)
  - **nutrients** (carbohydrates, lipids, aminoacids)
  - **gases** (O<sub>2</sub>, CO<sub>2</sub>)
  - **waste products** (urea, uric acid, etc.)
  - **others** (hormones, vitamins, etc.)
- **serum** – residual fluid after blood clotting

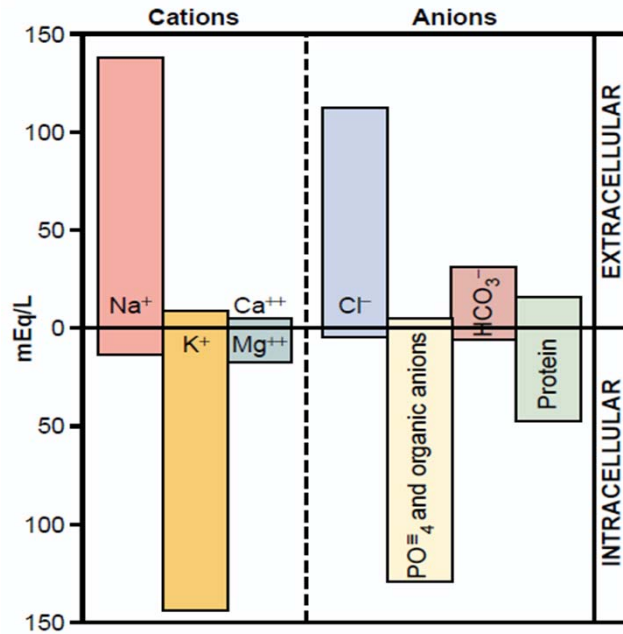
FORMED ELEMENTS	Function and Description	Source
<b>Red Blood Cells</b> (erythrocytes)  4 million–6 million per mm <sup>3</sup> blood	Transport O <sub>2</sub> and help transport CO <sub>2</sub>  7–8 μm in diameter; bright-red to dark-purple biconcave disks without nuclei	Red bone marrow
<b>White Blood Cells</b> (leukocytes) 5,000–11,000 per mm <sup>3</sup> blood <i>Granular leukocytes</i> <ul style="list-style-type: none"> <li>• Neutrophils  40–70%</li> <li>• Eosinophils  1–4%</li> <li>• Basophils  0–1%</li> </ul> <i>Agranular leukocytes</i> <ul style="list-style-type: none"> <li>• Lymphocytes  20–45%</li> <li>• Monocytes  4–8%</li> </ul>	Fight infection  Phagocytize pathogens. 10–14 μm in diameter; spherical cells with multilobed nuclei; fine, lilac granules in cytoplasm if Wright stained.  Phagocytize antigen-antibody complexes and allergens. 10–14 μm in diameter; spherical cells with bilobed nuclei; coarse, deep-red, uniformly sized granules in cytoplasm if Wright stained.  Release histamine and heparin, which promote blood flow to injured tissues. 10–12 μm in diameter; spherical cells with lobed nuclei; large, irregularly shaped, deep-blue granules in cytoplasm if Wright stained.  Responsible for specific immunity. 5–17 μm in diameter (average 9–10 μm); spherical cells with large, round nuclei.  Become macrophages that phagocytize pathogens and cellular debris. 10–24 μm in diameter; large, spherical cells with kidney-shaped, round, or lobed nuclei.	Red bone marrow
<b>Platelets</b> (thrombocytes)  150,000–300,000 per mm <sup>3</sup> blood	Aid hemostasis.  2–4 μm in diameter; disk-shaped cell fragments with no nuclei; purple granules in cytoplasm.	Red bone marrow



PLASMA	Function	Source
Water (90–92% of plasma)	Maintains blood volume; transports molecules	Absorbed from intestine
Plasma proteins (7–8% of plasma) Albumins Globulins Fibrinogen	Maintain blood osmotic pressure and pH Maintain blood volume and pressure Transport; fight infection Coagulation	Liver
Salts (less than 1% of plasma)	Maintain blood osmotic pressure and pH; aid metabolism	Absorbed from intestine
Gases		
Oxygen Carbon dioxide	Cellular respiration End product of metabolism	Lungs Tissues
Nutrients	Food for cells	Absorbed from intestine
Lipids Glucose Amino acids		
Nitrogenous wastes	Excretion by kidneys	Liver
Uric acid Urea		
Other	Aid metabolism	Varied
Hormones, vitamins, etc.		

[http://encyclopedia.lubopitko-bg.com/Composition\\_and\\_Functions\\_of\\_Blood.html](http://encyclopedia.lubopitko-bg.com/Composition_and_Functions_of_Blood.html)

# Blood Composition - Plasma



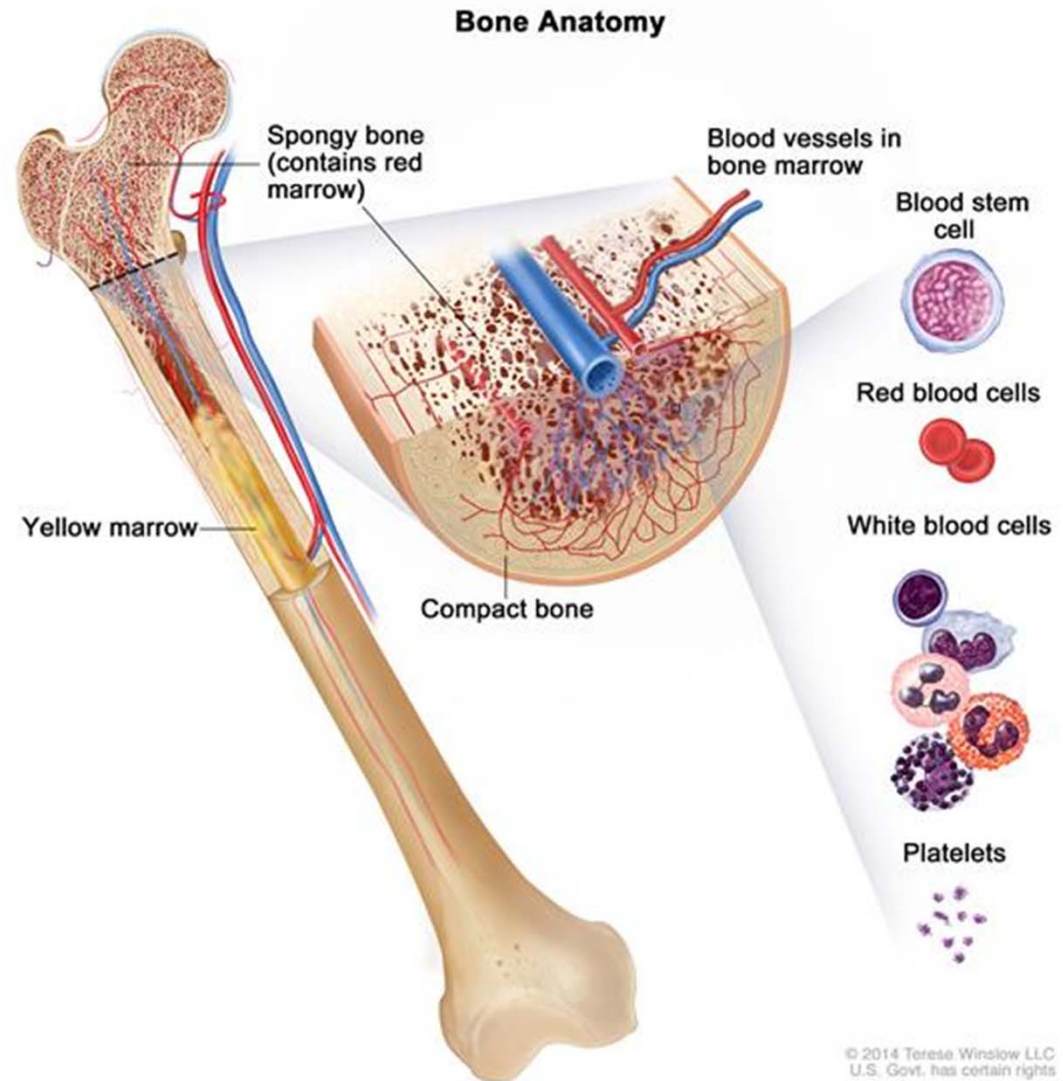
	Plasma (mOsm/L H <sub>2</sub> O)	Interstitial (mOsm/L H <sub>2</sub> O)
Na <sup>+</sup>	142	139
K <sup>+</sup>	4.2	4.0
Ca <sup>++</sup>	1.3	1.2
Mg <sup>+</sup>	0.8	0.7
Cl <sup>-</sup>	108	108
HCO <sub>3</sub> <sup>-</sup>	24	28.3
HPO <sub>4</sub> <sup>-</sup> , H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	2	2
SO <sub>4</sub> <sup>-</sup>	0.5	0.5
Phosphocreatine		
Carnosine		
Amino acids	2	2
Creatine	0.2	0.2
Lactate	1.2	1.2
Adenosine triphosphate		
Hexose monophosphate		
Glucose	5.6	5.6
<u>Protein</u>	<u>1.2</u>	<u>0.2</u>
Urea	4	4
Others	4.8	3.9

# Blood Composition – Formed Elements

	elements / $\mu\text{l}$	White Blood Cell Count	%
<b>LEUKOCYTES (WBCs)</b>	3600 - 9600		
GRANULOCYTES		GRANULOCYTES	
neutrophils	3000 - 6000	neutrophils	50 - 70
eosinophiles	150 - 300	eosinophiles	1 - 4
basophils	0 - 100	basophils	< 1
AGRANULOCYTES		AGRANULOCYTES	
lymphocytes	1200 - 3400	lymphocytes	20 - 40
monocytes	110 - 590	monocytes	2 - 8
<b>ERYTHROCYTES (RBCs)</b>			
man	$4.5 - 6.3 \cdot 10^6$		
woman	$4.2 - 5.4 \cdot 10^6$		
<b>THROMBOCYTES (platelets)</b>	140000 - 440000		

# Blood Composition – Formed Elements

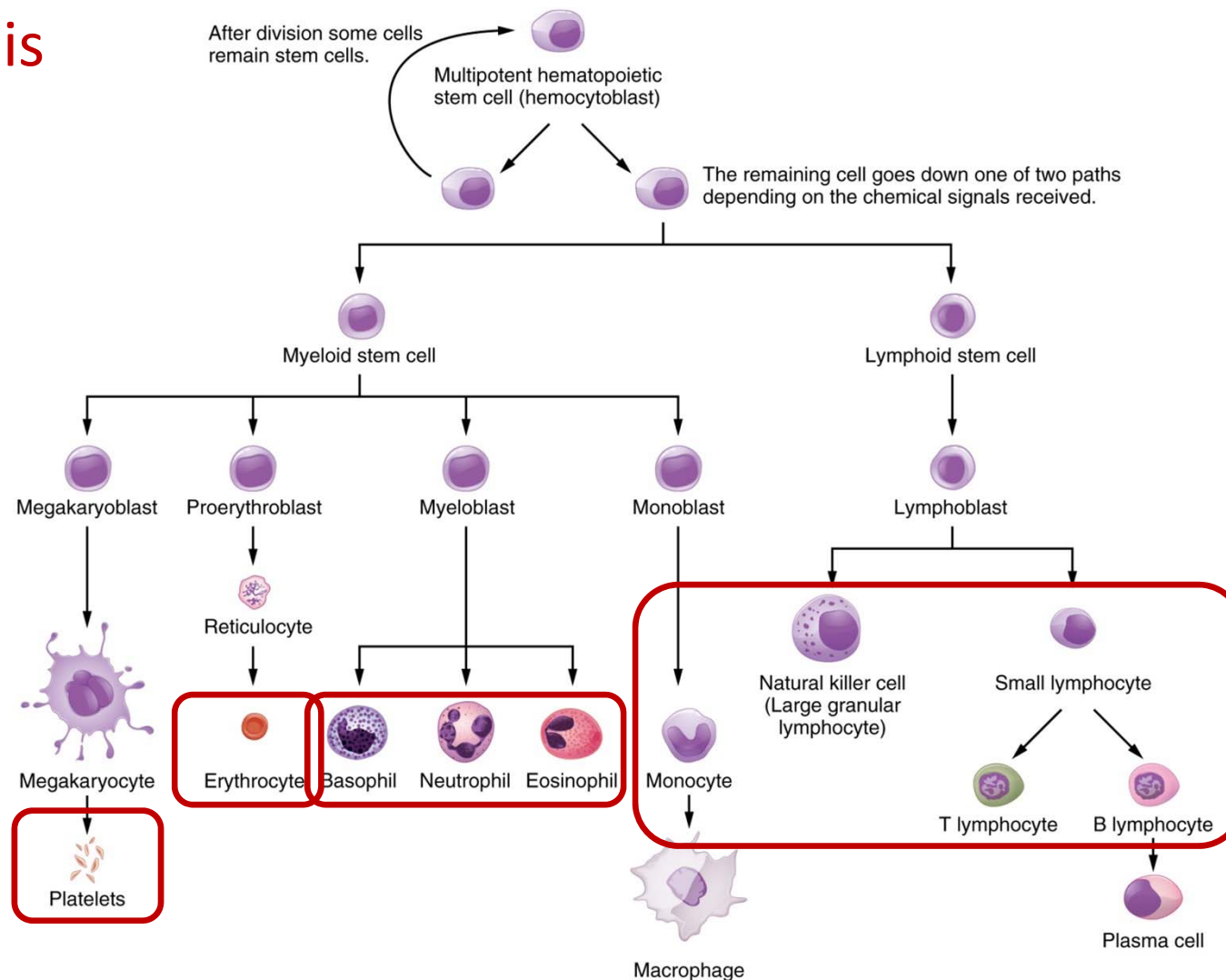
- Hematopoiesis
  - medullar  
adult – bone marrow
  - extramedullar  
children – liver, spleen



<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/bone-marrow>

# Blood Composition – Formed Elements

## ■ Hematopoiesis





# Blood Composition – Formed Elements

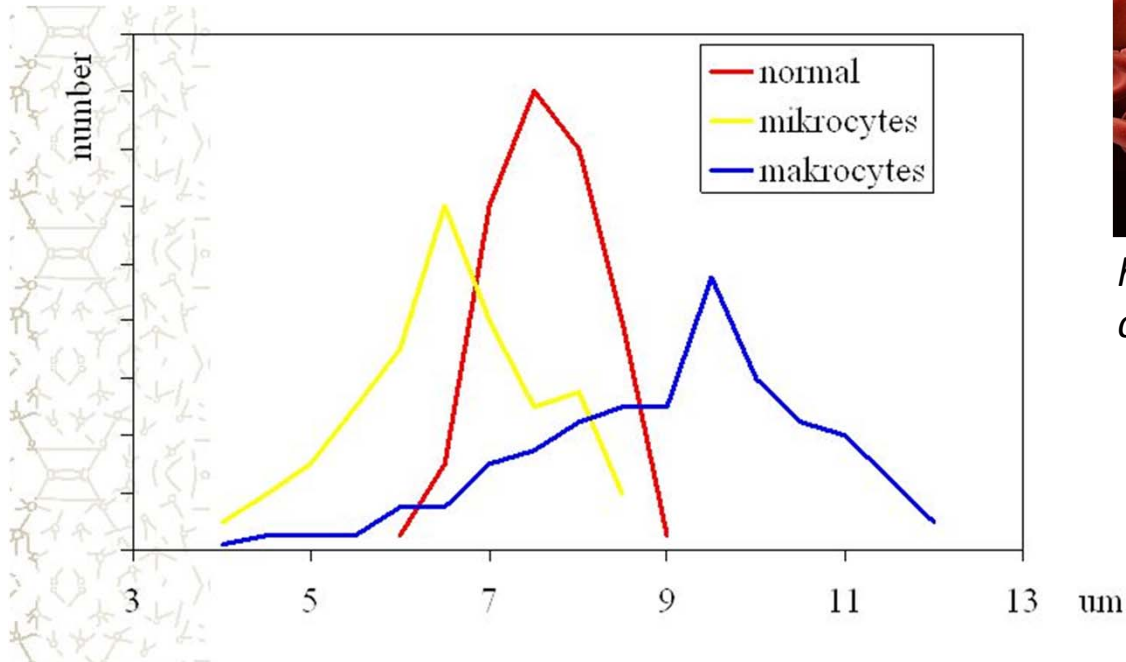
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White Blood Cell Count	%
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neutrophils	50 - 70
eosinophiles	1 - 4
basophils	< 1
AGRANULOCYTES	
lymphocytes	20 - 40
monocytes	2 – 8

# Red Blood Cells (Erythrocytes)

- lack of organelles
- diameter  $\sim 7.5 \mu\text{m}$ , thickness  $\sim 2 \mu\text{m}$ ; volume  $\sim 90 \text{ fl}$  (normocytes)  
microcytes (-osis)  $< 6 \mu\text{m}$ ,  $< 80 \text{ fl}$ ; macrocytes (-osis)  $> 8.2 \mu\text{m}$ ,  $> 95 \text{ fl}$   
anizocytosis (physiological vs. pathological)

## Price-Jones curve



<https://www.rd.com/health/health-care/why-is-blood-red/>

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**anizocytosis (physiological vs. pathological)**

- biconcave discs

**OPTIMAL SURFACE TO VOLUME RATIO**

**DEFORMATION IN CAPILLARIES  
(Fahraeus-Lindqvist effect)**



**poikilocytosis – abnormal shape of erythrocytes**

spherocytes – spheric erythrocytes

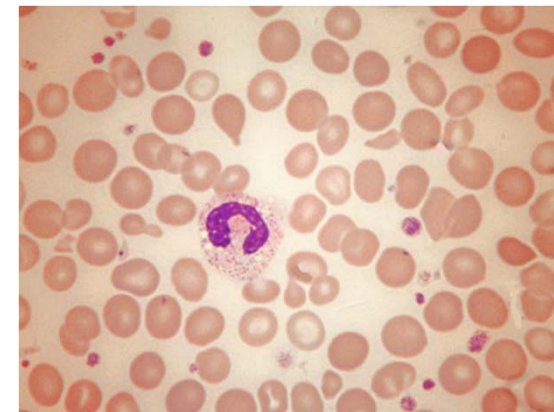
eliptocytes – eliptic erythrocytes

schizocytes – fragmented erythrocytes

*etc.*



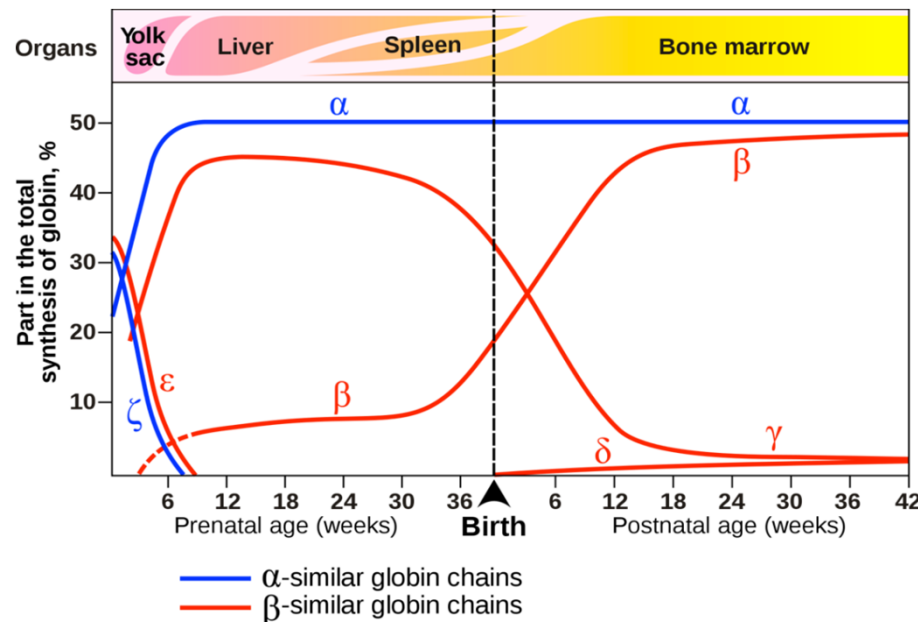
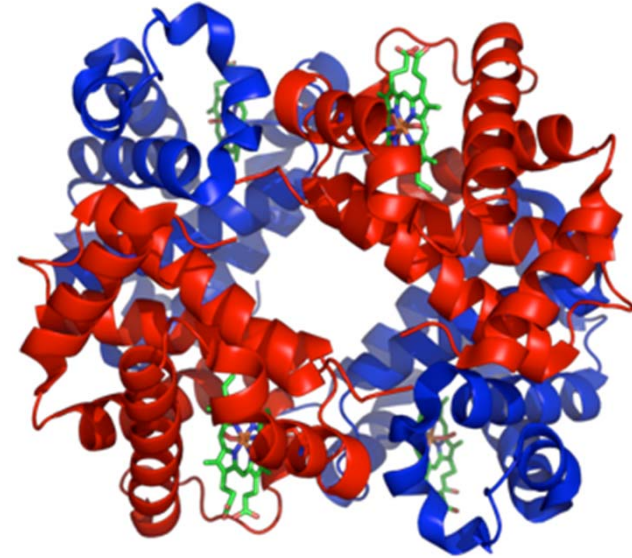
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# Red Blood Cells (Erythrocytes)

## ■ Hemoglobin

- red pigment transporting oxygen
- 4 protein subunits (**globin**)
- **hem** – derivative of porphyrine containing iron, conjugated with globin



■ HbA (adult;  $\alpha_2\beta_2$ )

■ HbF (fetal;  $\beta_2\gamma_2$ )

weaker binding of 2,3-DPG, thus, higher affinity to oxygen

# Red Blood Cells (Erythrocytes)

## ■ Hemoglobin derivatives

- oxyhemoglobin ( $O_2$ )
- carbaminohemoglobin ( $CO_2$ )
- carboxyhemoglobin (CO)
- methemoglobin ( $Fe^{3+}$  in hem)
- glycosylated hemoglobin ( $HbA_1$ ) – physiologically < 5%

**$HbA_1$  level proportional to glucose plasma concentrations in previous weeks - monitoring of diabetes in clinical practise**

# Red Blood Cells (Erythrocytes)

parameter		man	woman
hematocrit (Hct; %)		42 - 52	37 - 47
erythrocytes (RBC; $10^6/\mu\text{l}$ )		4.5 – 6.3	4.2 – 5.4
<b>hemoglobin (Hb; g/l)</b>		<b>140 - 180</b>	<b>120 - 160</b>

parameter		man	woman
mean corpuscular volume (MCV; fl)	= HCT / RBC	80 - 95	80 - 95
mean content of hemoglobin (MCH; pg)	= Hb / RBC	27 - 32	27 - 32
mean corpuscular hemoglobin concentration (MCHC; g/1 ml)	= Hb / Hct	310 - 360	310 - 360

**erythrocytopenia (oligocytopenia) - normocytemia – polyglobulia (polycytemia)**

**anemia**

**hypochromia – euchromia - hyperchromia**

# Red Blood Cells (Erythrocytes)

## ■ Anemia

- disease characterized by a decreased amount of hemoglobin
- Hct and RBC are usually lower as well but not in all cases!

## Morphological classification

- |              |                 |                    |                    |
|--------------|-----------------|--------------------|--------------------|
| A) RBC size: | 1. Normocyte a. | B) RBC Hb content: | 1. Normochromic a. |
|              | 2. Microcyte a. |                    | 2. Hypochromic a.  |
|              | 3. Macrocyte a. |                    | 3. Hyperchromic a. |

## Pathophysiological classification

- A) anemia caused by inefficient hemopoiesis:
1. sideropenic a. (lack of iron)
  2. megaloblastic a. (lack of vitamin B12 or folic acid)
  3. a. due to suppression of hemopoiesis
  4. symptomatic a. (secondary to a primary disease)
  5. thalasemia

# Red Blood Cells (Erythrocytes)

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## Pathophysiological classification

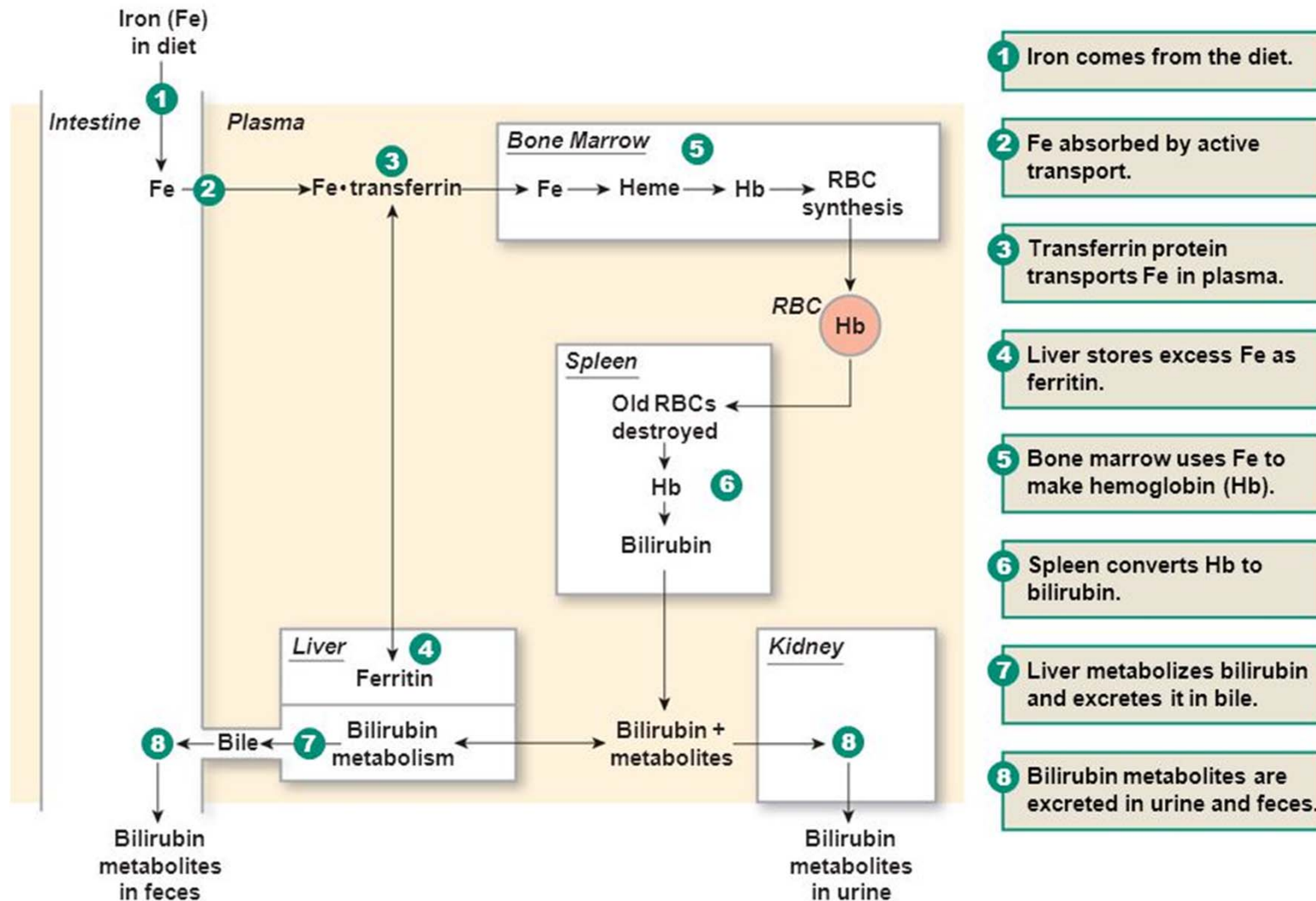
- A) anemia caused by inefficient hemopoiesis:
- B) anemia caused by an increased loss
  - 1. acute and chronic posthemorrhagic a.
  - 2. hemolytic a.



# Red Blood Cells (Erythrocytes)

## ■ Hemoglobin

erythrocyte life span: 120 days



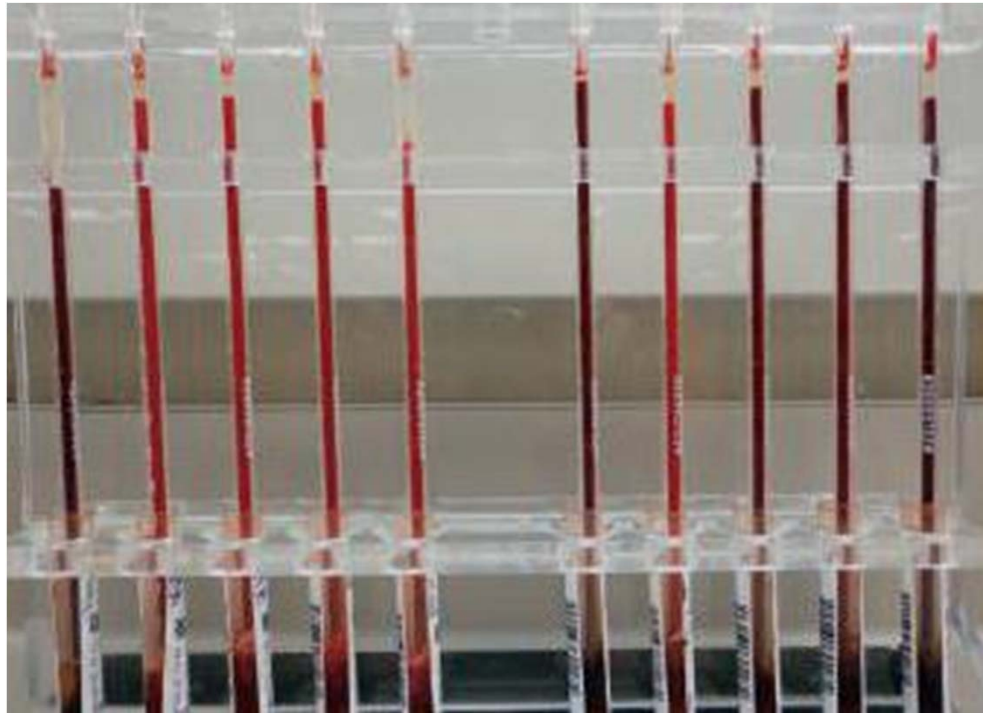
# Red Blood Cells (Erythrocytes)

## ■ Hemolysis

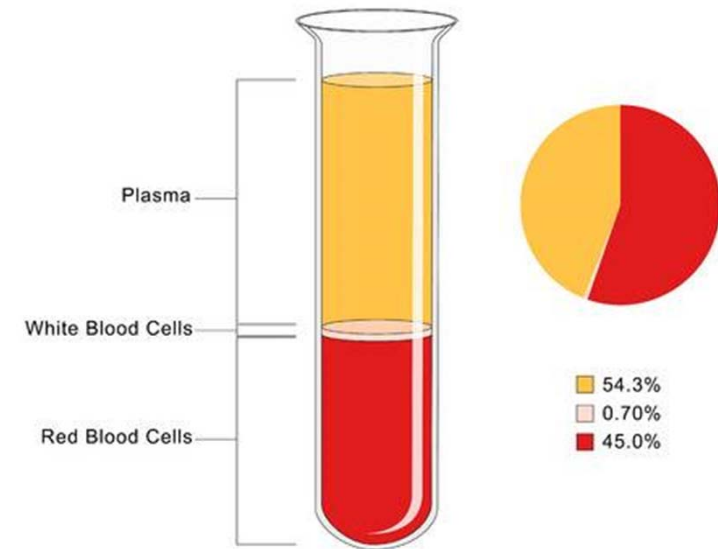
- destruction of membrane of erythrocyte
- physical
- chemical
- osmotic
- toxic (biological)
- immunological

# Red Blood Cells (Erythrocytes)

- Erythrocyte sedimentation rate



[https://www.syl.ru/article/170503/new\\_skorost-osedaniya-eritrotsitov-norma-cto-oznachaet-skorost-osedaniya-eritrotsitov](https://www.syl.ru/article/170503/new_skorost-osedaniya-eritrotsitov-norma-cto-oznachaet-skorost-osedaniya-eritrotsitov)

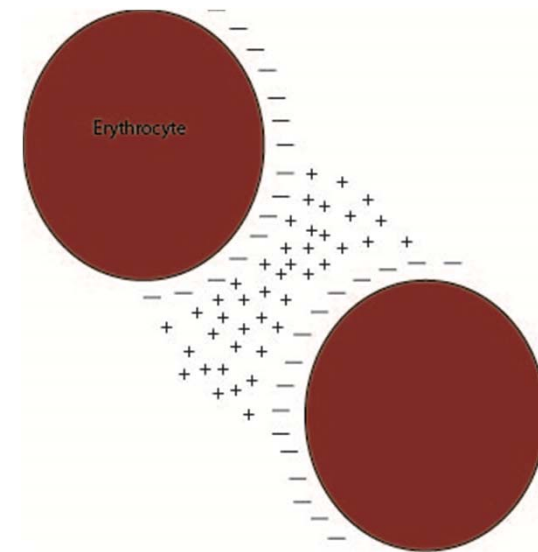
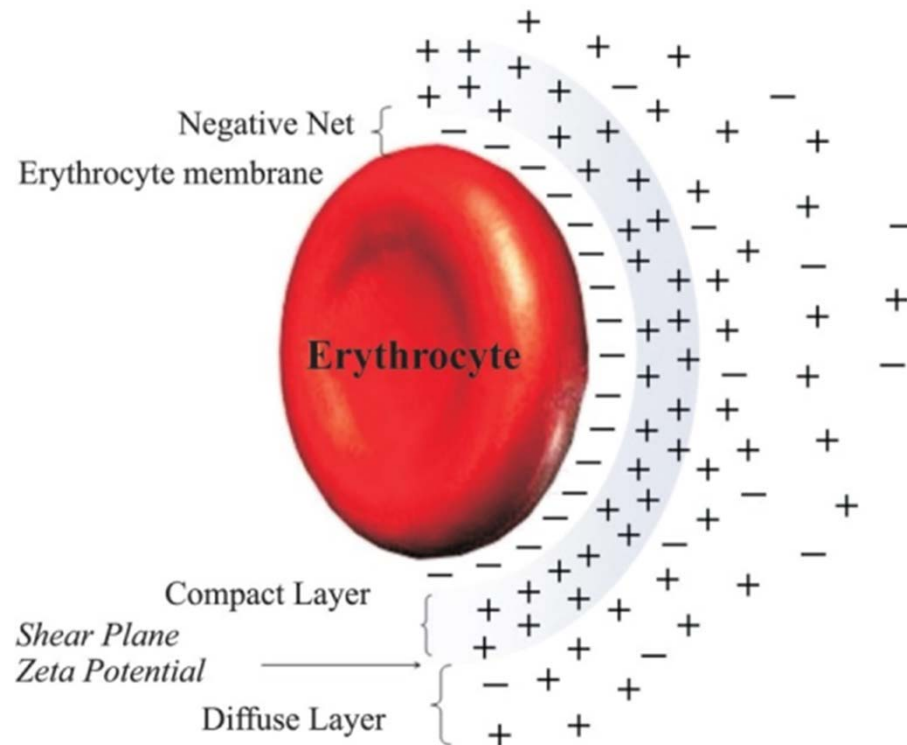


[https://www.123rf.com/photo\\_39782091\\_blood-composition.html](https://www.123rf.com/photo_39782091_blood-composition.html)

# Red Blood Cells (Erythrocytes)

## ■ Erythrocyte sedimentation rate

- indirectly proportional to the suspension stability of erythrocytes (Helmholtz bilayer, zeta potential)



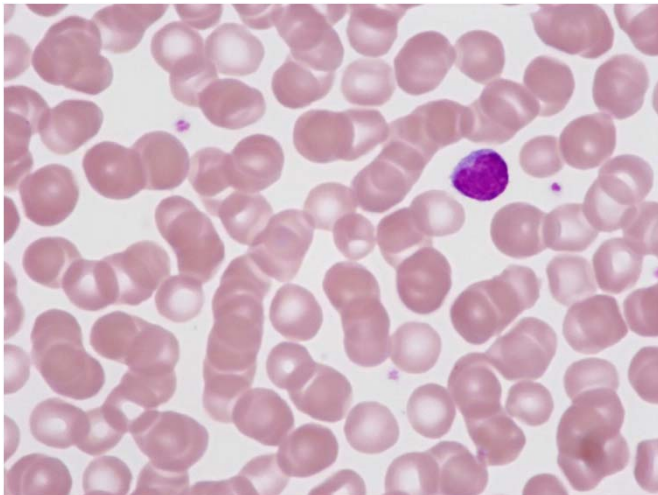
[https://openi.nlm.nih.gov/detailedresult.php?img=P\\_MC3415751\\_rbhh-33-297-g05&req=4](https://openi.nlm.nih.gov/detailedresult.php?img=P_MC3415751_rbhh-33-297-g05&req=4)

[https://www.labce.com/spg8\\_13211\\_zeta\\_potential\\_and\\_van\\_der\\_waals\\_forces.aspx](https://www.labce.com/spg8_13211_zeta_potential_and_van_der_waals_forces.aspx)

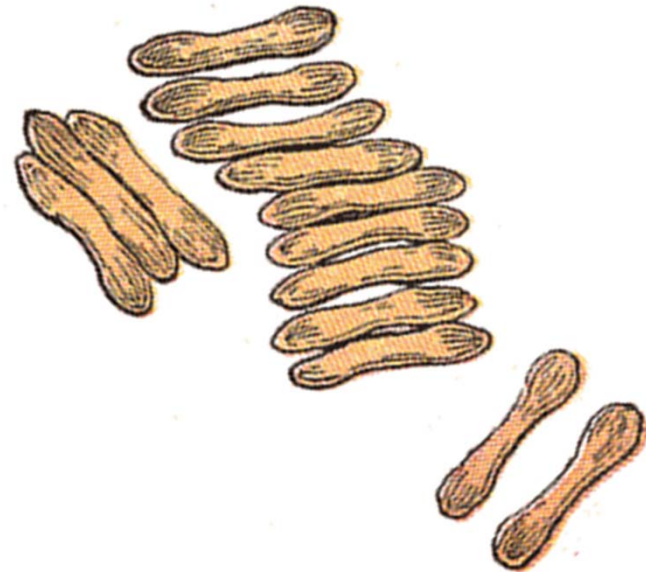
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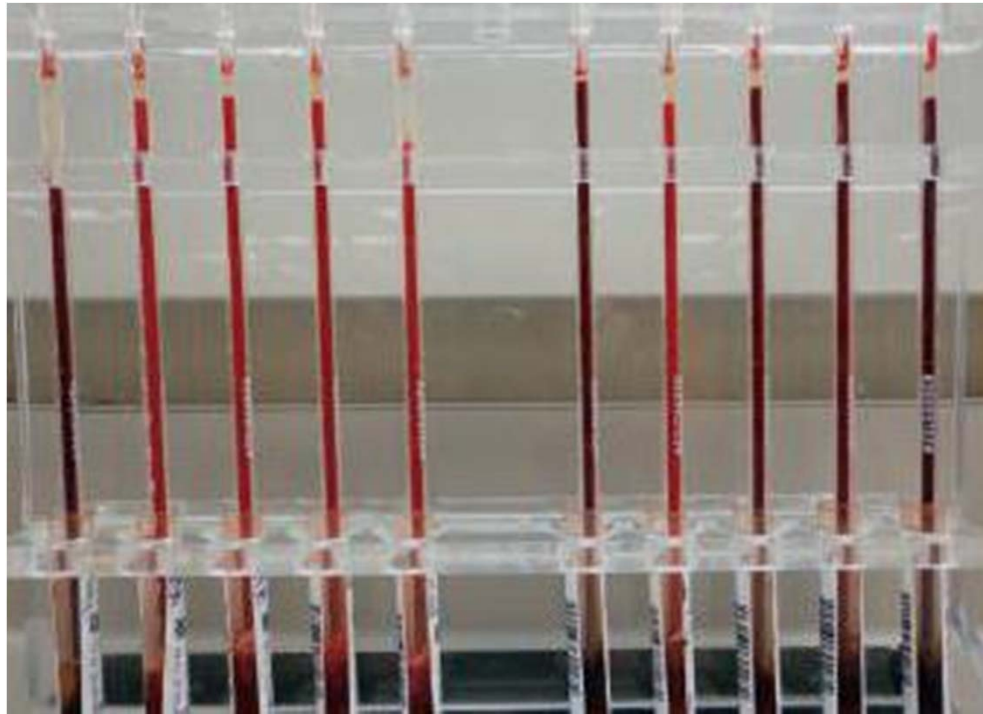
<https://www.sysmex.cz/media-center/rouleaux-formation-5493.html>



<https://en.wikipedia.org/wiki/File:Gray453-ab.png>

# Red Blood Cells (Erythrocytes)

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[https://www.syl.ru/article/170503/new\\_skorost-osedaniya-eritrotsitov-norma-cto-oznachaet-skorost-osedaniya-eritrotsitov](https://www.syl.ru/article/170503/new_skorost-osedaniya-eritrotsitov-norma-cto-oznachaet-skorost-osedaniya-eritrotsitov)

## Fahraeus-Westergren method (FW)

man ~2-8 mm/hour

woman ~ 7-12 mm/hour

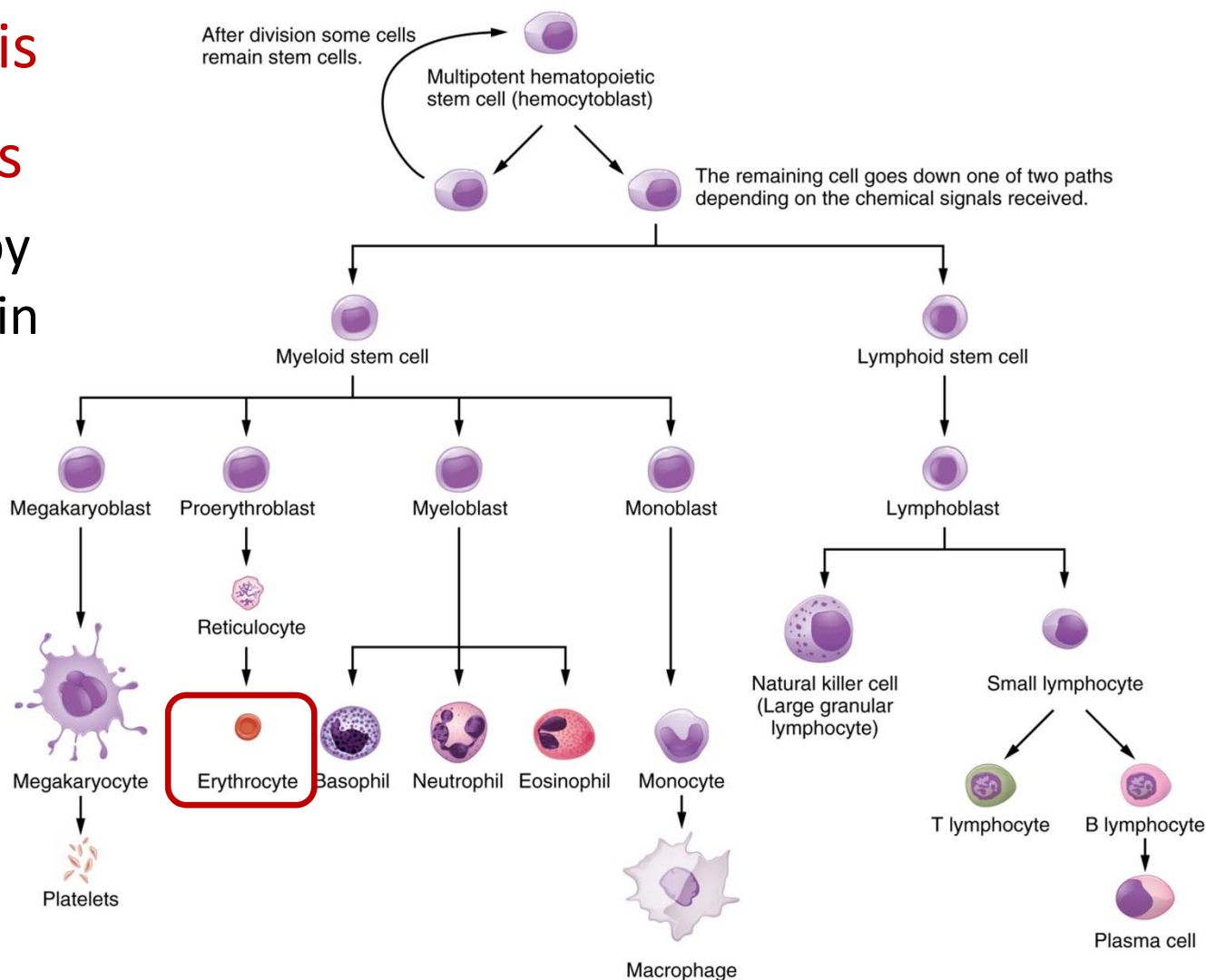
physiological vs. pathological increase

main factors affecting ESR:

- size and number of RBCs
- fibrinogen
- immunoglobulins

# Blood Composition – Formed Elements

- Hematopoiesis
- Erythropoiesis
  - stimulated by erythropoietin



# Erythropoiesis

## ■ Erythropoetin

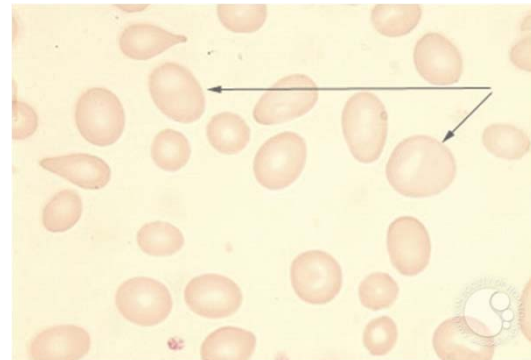
- glycoprotein,  $\alpha$ 2-globulin
- 85-90% originates in the kidney (endothelial cells of peritubular capillaries in the kidney medulla)
- 10-15 % originates in the liver
- synthesis and release stimulated by tissue hypoxia of any origin (adaptation to high altitude), alkalosis, androgens, catecholamines ( $\beta$ -rec.), *etc.*
- many other functions, such as regulation of bone formation and repair, muscle regeneration and hypertrophy, angiogenesis, neuroprotection (neurotrophic factor), *etc.*



# Erythropoiesis

## ■ Vitamin B12 (cyanocobalamin)

- produced by bacteria in **GIT**
- **ingested** - sources: liver, kidneys, meet, milk products, *etc.*
- the intrinsic factor (secreted by parietal cells of the stomach) is necessary for its resorption in the ileum
- transport in blood – bound to transcobalamin
- necessary for normal division and maturation of red blood cell line elements
- symptoms after long-term deficiency – **pernicious anemia**

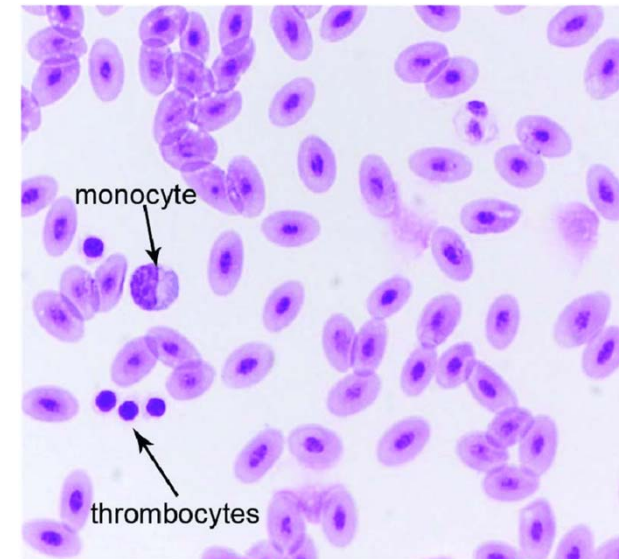


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# Thrombocytes (Platelets)

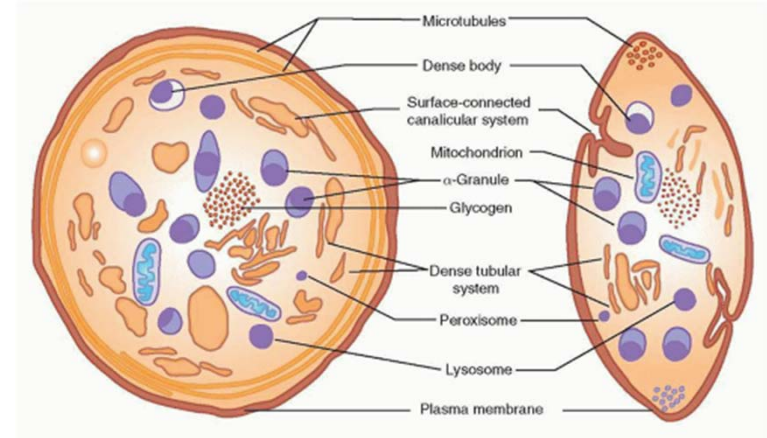
- the smallest formed elements  
(diameter 2-4  $\mu\text{m}$ , thickness 0.5-1  $\mu\text{m}$ , 4-8 fl)
- smooth, round discs
- nucleus-less, colorless, granulated
- fragments of megakaryocytes
  
- 1/3 in the spleen, 2/3 in the peripheral blood (thrombocytosis after splenectomy)
  
- life span: 9- 12 days, biological halftime ~4 days



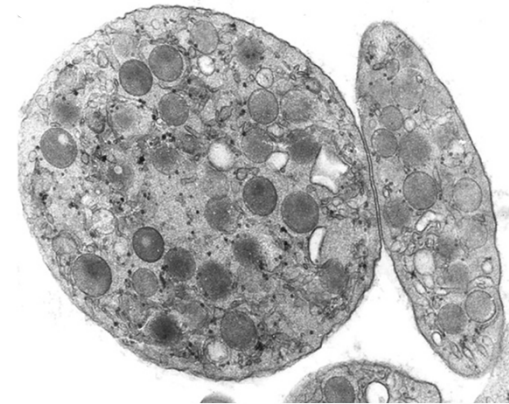
[https://www.researchgate.net/publication/283465115\\_Effects\\_of\\_Methadone\\_Exposure\\_during\\_Development\\_on\\_Avian\\_Brain\\_and\\_Blood\\_Cells/figures?lo=1](https://www.researchgate.net/publication/283465115_Effects_of_Methadone_Exposure_during_Development_on_Avian_Brain_and_Blood_Cells/figures?lo=1)

# Thrombocytes (Platelets)

- membrane contains glycoprotein **receptors** for adhesion to surfaces (collagen, fibrinogen, von Willebrand factor)
- cytoplasm contains **actin**, **myosin**, glycogen, lysosomes and **granules**
  - 1) dense granules ( $\delta$ -granules)  
(non-protein substances – calcium, serotonin, ADP, ...)
  - 2)  $\alpha$ -granules  
(protein substances – clotting factors such as vWF, factor V and XIII, PDGF, ...)
- glycocalyx – 10 – 50 nm, mixture of proteins and mucopolysaccharides (clotting factors, ions, histamin, ...)



<https://oncohemakey.com/platelet-structure-and-function-in-hemostasis-and-thrombosis/>

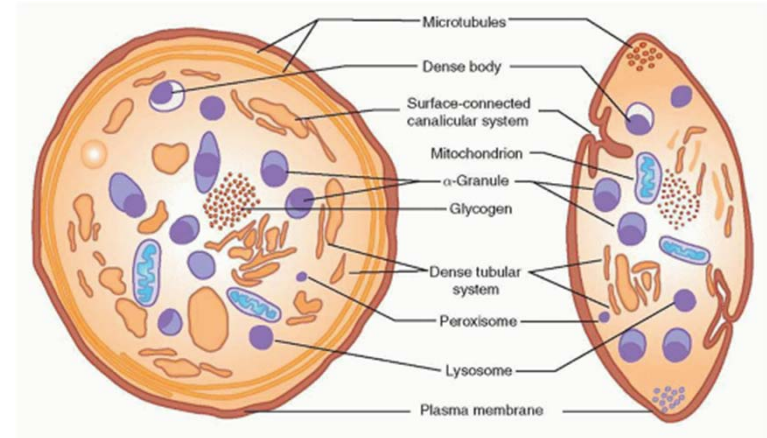


<http://www.bloodjournal.org/content/108/8/2587>

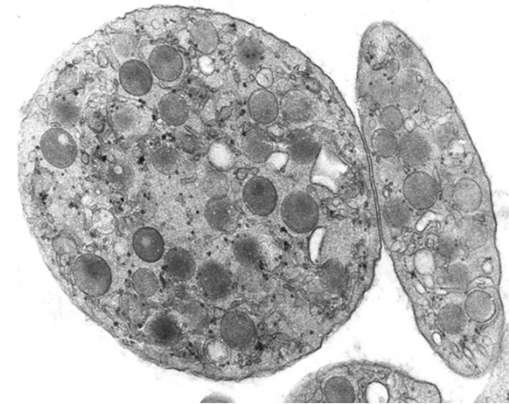
# Thrombocytes (Platelets)

## ■ Functions

- key players in hemostasis
- keeping integrity of the vessel wall and healing of a ruptured vessel wall (PDGF)
- inflammatory reaction, changes in permeability of capillary wall, graft rejection, ...
- carriers of many substances absorbed to their surface



<https://oncohemakey.com/platelet-structure-and-function-in-hemostasis-and-thrombosis/>



<http://www.bloodjournal.org/content/108/8/2587>

# Hemostasis

- set of mechanisms which prevent and stop bleeding
- three main processes:
  - reaction of vessels
  - actions of platelets
  - blood clotting



<https://www.firstaidforfree.com/what-are-the-different-types-of-bleeding-in-first-aid/>

- balance between procoagulant and anticoagulant factors to prevent/stop bleeding but also to prevent intravascular clotting! (thrombosis, risk of embolism)

# Hemostasis (white clot)

## ■ reaction of vessels - vasoconstriction

- myogenic contraction  
(direct damage)
- serotonin,  
thromboxan A2  
(platelets)
- endothelin 1  
(endothelial cells;  
thrombin, fibrinogen)
- epinephrine (pain)
- fibrinopeptides



<https://www.firstaidforfree.com/what-are-the-different-types-of-bleeding-in-first-aid/>

- the extent of vasoconstriction depends on the severity of vascular injury

# Hemostasis (white clot)

- **actions of platelets**

- vasoconstriction - serotonin, thromboxan A<sub>2</sub>
- formation of plug
- blood clotting (clotting factors in  $\alpha$ -granules)

- adhesion

- activation

- aggregation

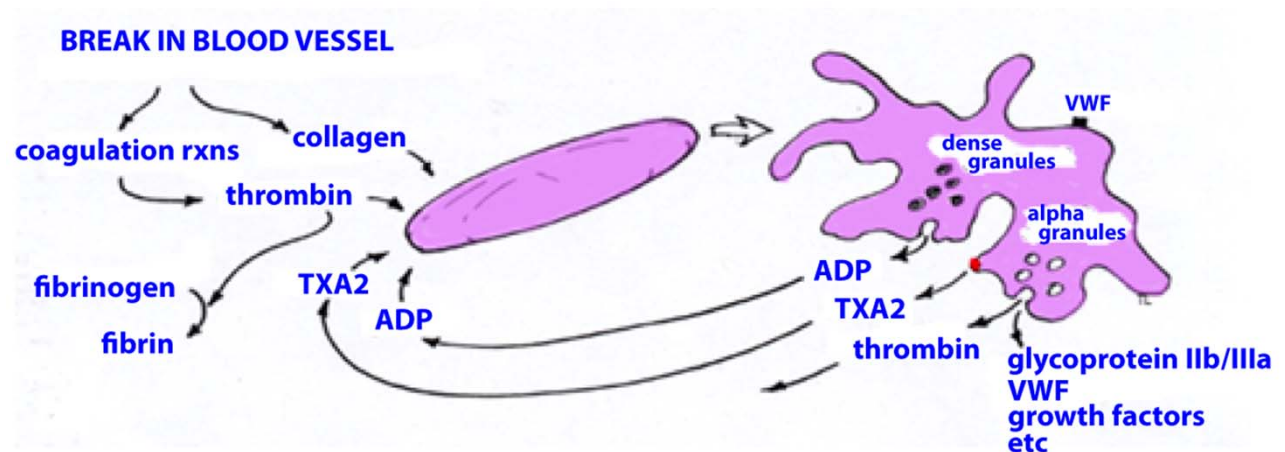


# Hemostasis (white clot)

- **actions of platelets**

- **adhesion**

- impaired endothelium – **collagen**, fibronectin, laminin (components of the subendothelial matrix) – platelet membrane receptors (glycoproteins, integrins)
- **von Willebrand factor (vWF)** released from endothelial cells and from  $\alpha$ -granules of thrombocytes (high shear stress, certain cytokines, hypoxia)



# Hemostasis (white clot)

- **actions of platelets**

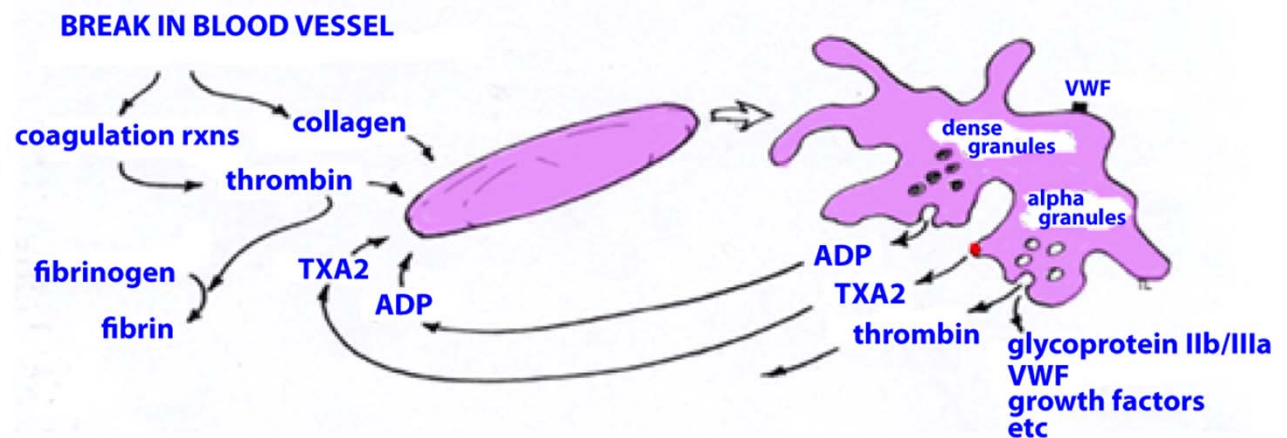
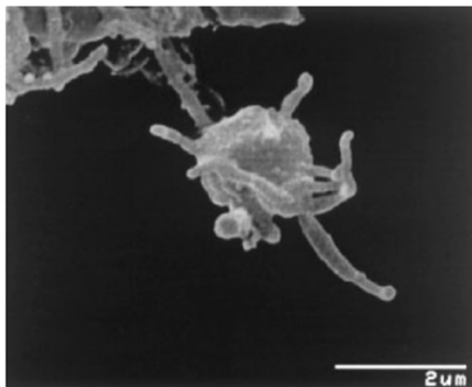
- **adhesion**

- **activation**

vasoconstriction (5-HT, TXA2)  
stimulation of adhesion (vWF),  
activation and aggregation (ADP, PAF)  
mitogenic effects (PDGF)

- degranulation: dense granules – serotonin (5-HT), Ca<sup>2+</sup>, ADP, ...  
α-granules – vWF, clotting factor V, fibrinogen,  
growth factors (PDGF), ...  
thromboxan A2 (TXA2; cyclooxygenase)

- morphological changes



<https://courses.washington.edu/conj/bloodcells/platelets.htm>

# Hemostasis (white clot)

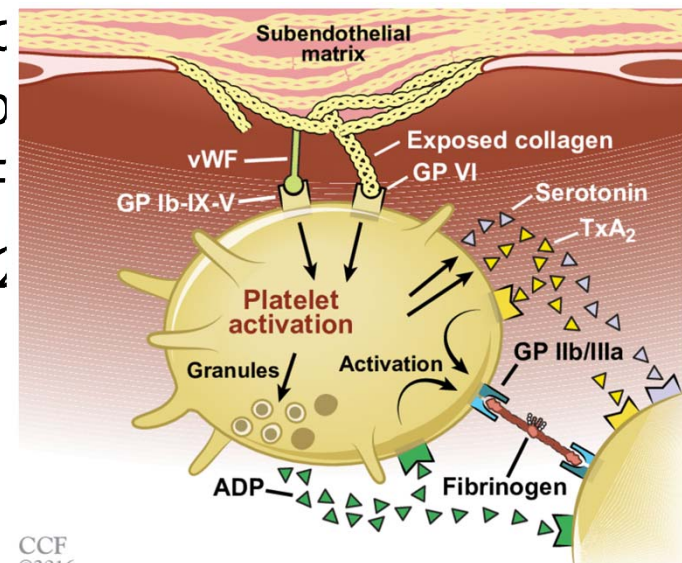
- **actions of platelets**

- **adhesion**

- **activation**

- degranulation: dense granules – serc  
α-granules – vWF, clo  
growth factors (PDGF  
thromboxan A2 (TXA<sub>2</sub>)
- morphological  
changes  
(pseudopodia)

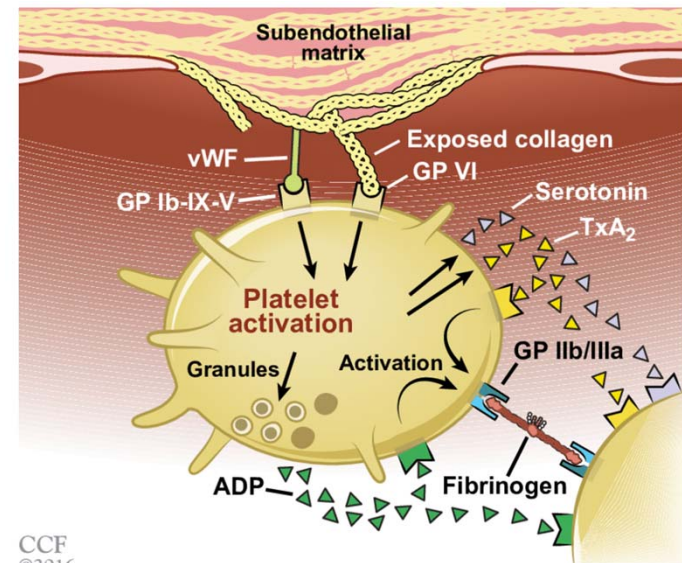
vasoconstriction (5-HT, TXA<sub>2</sub>)  
stimulation of adhesion (vWF),  
activation and aggregation (ADP, PAF)  
mitogenic effects (PDGF)



[https://www.researchgate.net/publication/308050751\\_Dual\\_antiplaquet\\_therapy\\_for\\_acute\\_coronary\\_syndromes\\_How\\_long\\_to\\_continue/figures?lo=1](https://www.researchgate.net/publication/308050751_Dual_antiplaquet_therapy_for_acute_coronary_syndromes_How_long_to_continue/figures?lo=1)

# Hemostasis (white clot)

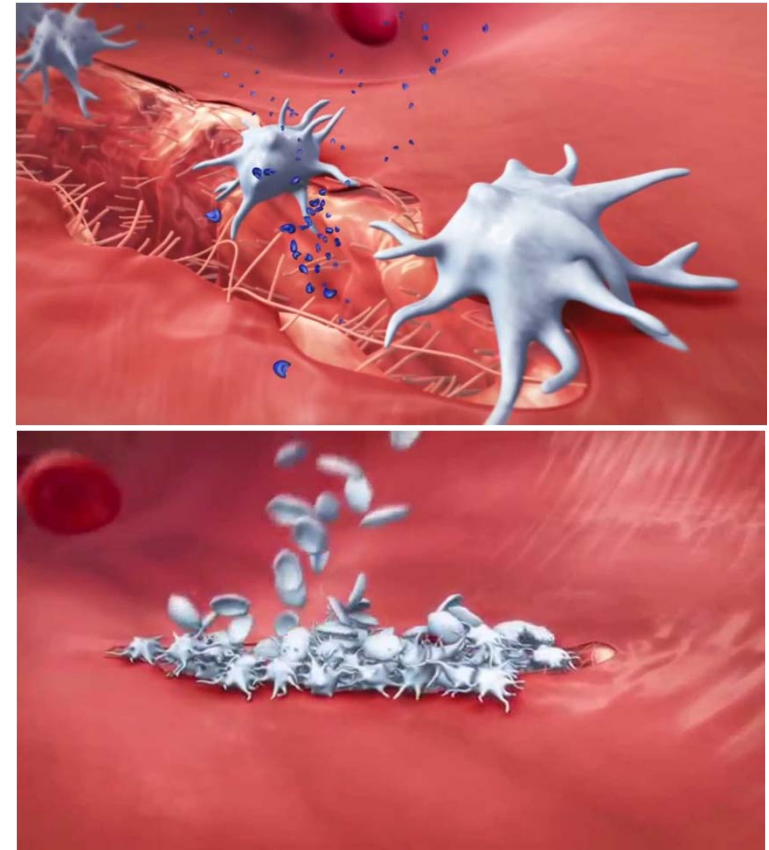
- actions of platelets
- adhesion
- activation
- aggregation
  - activation of additional platelets (ADP, 5-HT, TXA<sub>2</sub>) promotes their aggregation
  - molecular bridges between platelets: von Willebrand factor (vWF), fibrinogen



[https://www.researchgate.net/publication/308050751\\_Dual\\_antiplaquet\\_therapy\\_for\\_acute\\_coronary\\_syndromes\\_How\\_long\\_to\\_continue/figures?lo=1](https://www.researchgate.net/publication/308050751_Dual_antiplaquet_therapy_for_acute_coronary_syndromes_How_long_to_continue/figures?lo=1)

# Hemostasis (white clot)

- actions of platelets
- adhesion
- activation
- aggregation
  - activation of additional platelets (**ADP, 5-HT, TXA2**) promotes their aggregation
  - molecular bridges between platelets: **von Willebrand factor (vWF)**, fibrinogen



<https://www.youtube.com/watch?v=WFa1x6-ufTg>

- white clot

# Hemostasis

Factors Involved in Platelet Function				
Chemical Factor	Source	Activated by or Released in Response to	Role in Platelet Plug Formation	Other Roles and Comments
Collagen	Subendothelial extracellular matrix	Injury exposes platelets to collagen	Binds platelets to begin platelet plug	N/A
von Willebrand factor (vWF)	Endothelium, megakaryocytes	Exposure to collagen	Links platelets to collagen	Deficiency or defect causes prolonged bleeding
Serotonin	Secretory vesicles of platelets	Platelet activation	Platelet aggregation	Vasoconstrictor
Adenosine diphosphate (ADP)	Platelet mitochondria	Platelet activation, thrombin	Platelet aggregation	N/A
Platelet-activating factor (PAF)	Platelets, neutrophils, monocytes	Platelet activation	Platelet aggregation	Plays role in inflammation; increases capillary permeability
Thromboxane A <sub>2</sub>	Phospholipids in platelet membranes	Platelet-activating factor	Platelet aggregation	Vasoconstrictor; eicosanoid
Platelet-derived growth factor (PDGF)	Platelets	Platelet activation	N/A	Promotes wound healing by attracting fibroblasts and smooth muscle cells

Table 16.4

# Hemostasis (red clot)

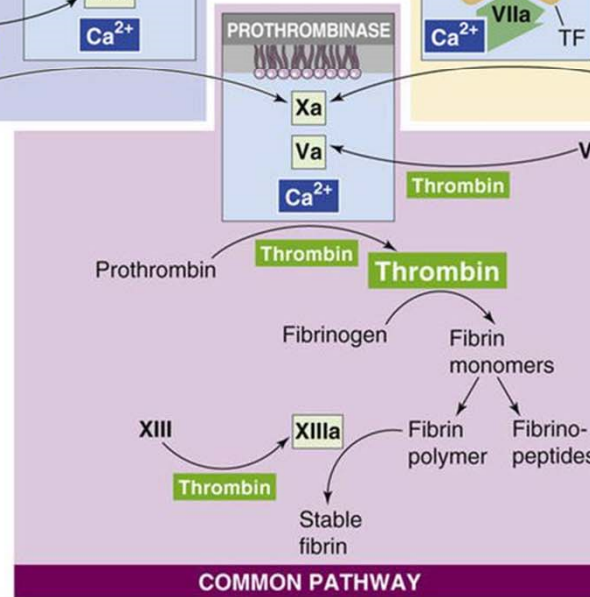
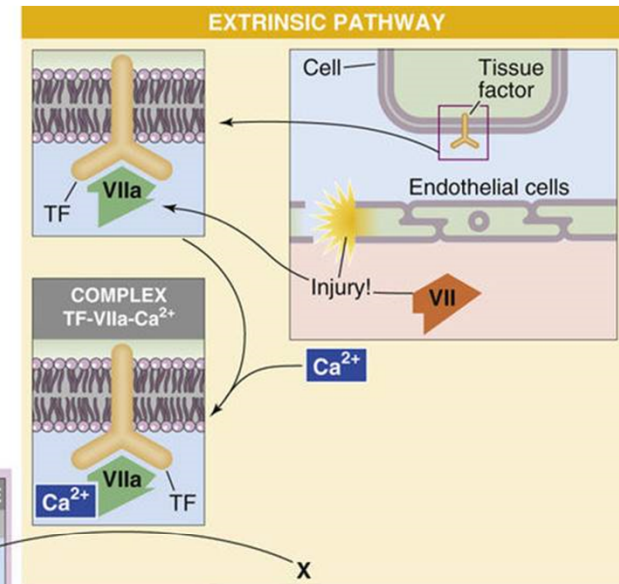
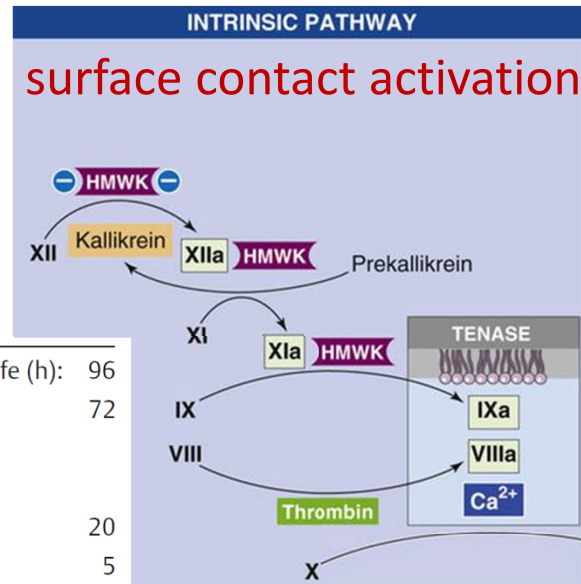
## ■ blood clotting

I	Fibrinogen	Half-life (h):	96
II <sup>K</sup>	Prothrombin		72
III	Tissue thromboplastin		
IV	Ionized calcium (Ca <sup>2+</sup> )		
V	Proaccelerin		20
VII <sup>K</sup>	Proconvertin		5
VIII	Antihemophilic factor A		12
IX <sup>K</sup>	Antihemophilic factor B; plasma thromboplastin component (PTC); Christmas factor		24
X <sup>K</sup>	Stuart–Prower factor		30
XI	Plasma thromboplastin antecedent (PTA)		48
XII	Hageman factor		50
XIII	Fibrin-stabilizing factor (FSF)		250
–	Prekallikrein (PKK); Fletcher factor		
–	High-molecular-weight kininogen (HMK); Fitzgerald factor		

# Hemostasis (red clot)

## ■ blood clotting

### tissue factor activation



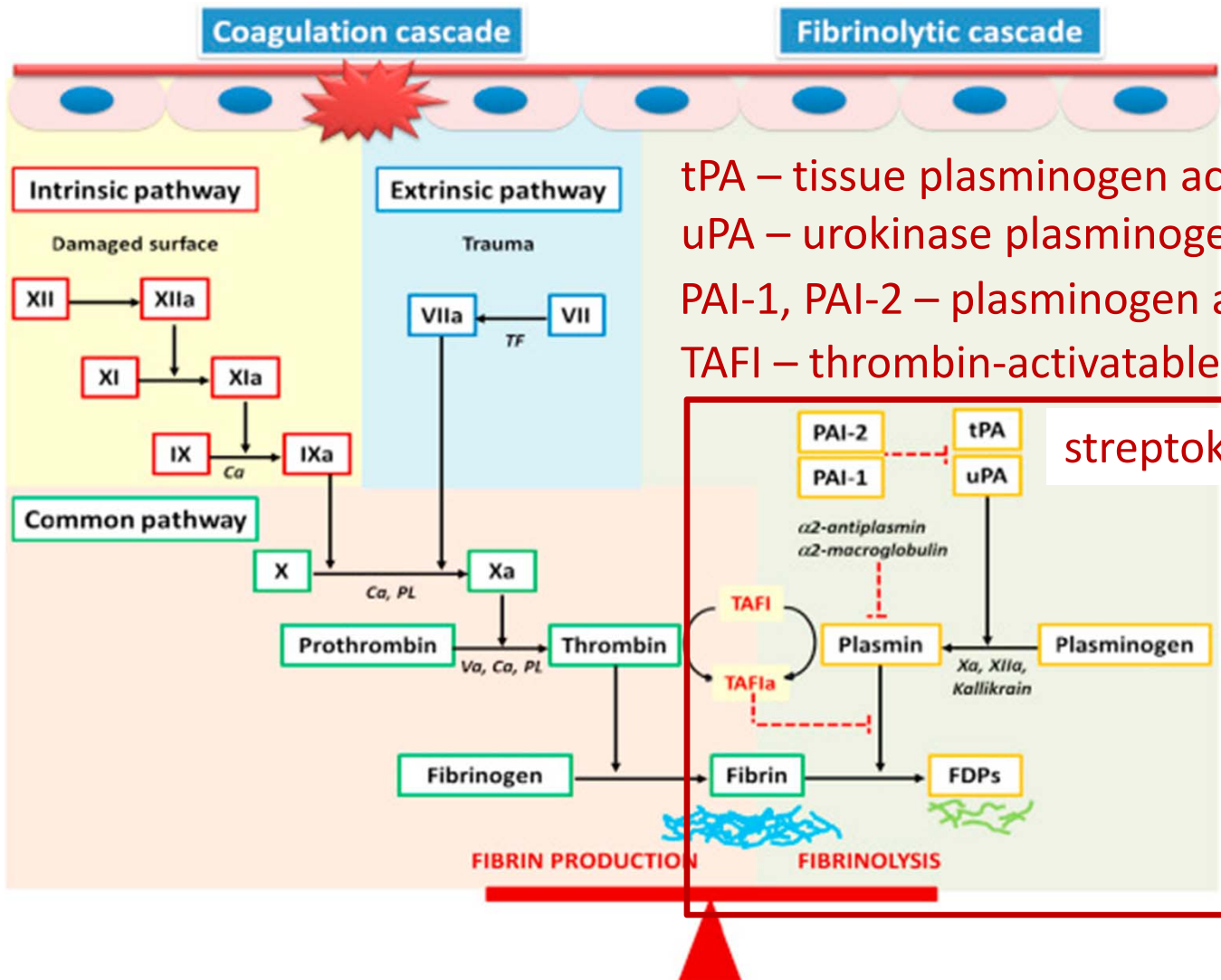
I	Fibrinogen	Half-life (h):	96
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<https://doctorlib.info/physiology/medical/101.html>



# Hemostasis (red clot)

## ■ fibrinolysis



tPA – tissue plasminogen activator

uPA – urokinase plasminogen activator

PAI-1, PAI-2 – plasminogen activator inhibitors

TAFI – thrombin-activatable fibrinolysis inhibitor

streptokinase

[https://www.researchgate.net/publication/284136686\\_Data\\_Supporting\\_the\\_Structural\\_and\\_Functional\\_Characterization\\_of\\_Thrombin-Activatable\\_Fibrinolysis\\_Inhibitor\\_in\\_Breast\\_Cancer/figures?lo=1](https://www.researchgate.net/publication/284136686_Data_Supporting_the_Structural_and_Functional_Characterization_of_Thrombin-Activatable_Fibrinolysis_Inhibitor_in_Breast_Cancer/figures?lo=1)

# Hemostasis (red clot)

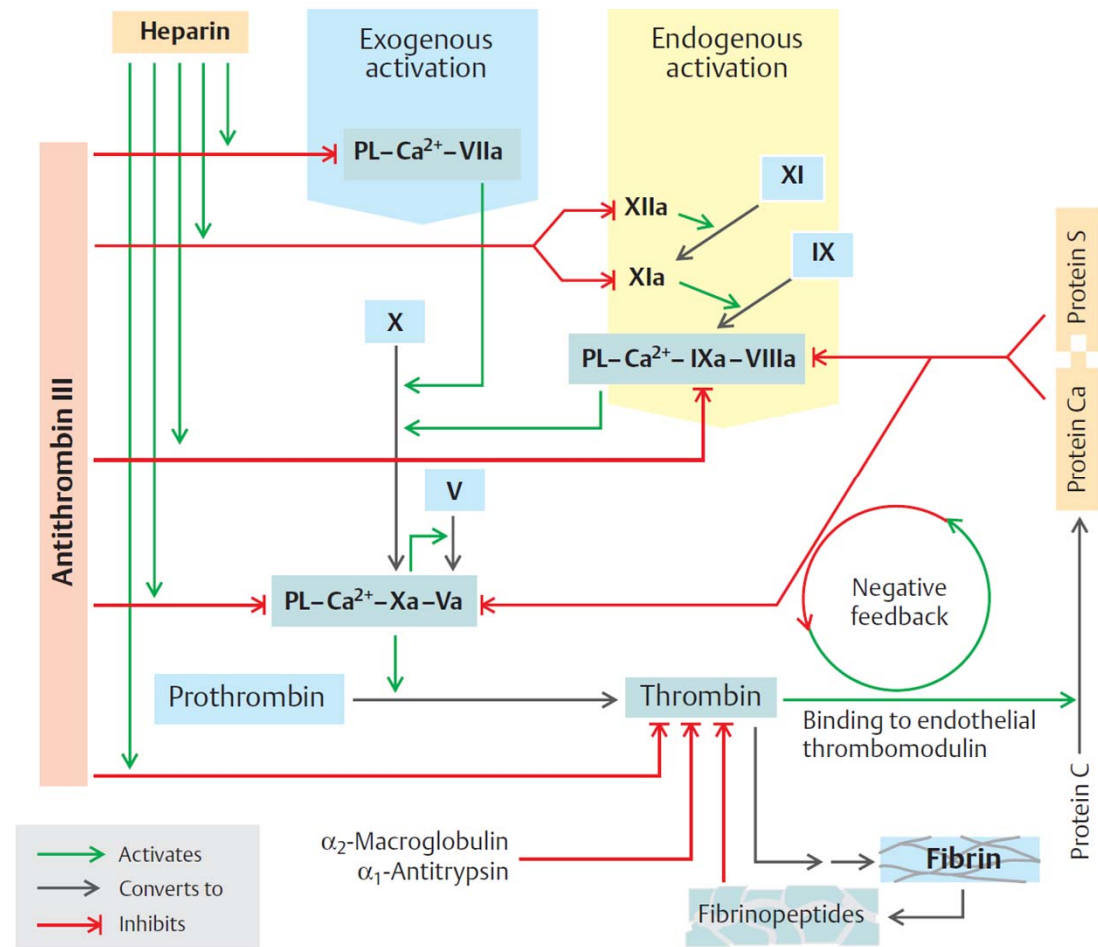
- clotting is counteracted by anticoagulating mechanisms

## a) non-humoral control

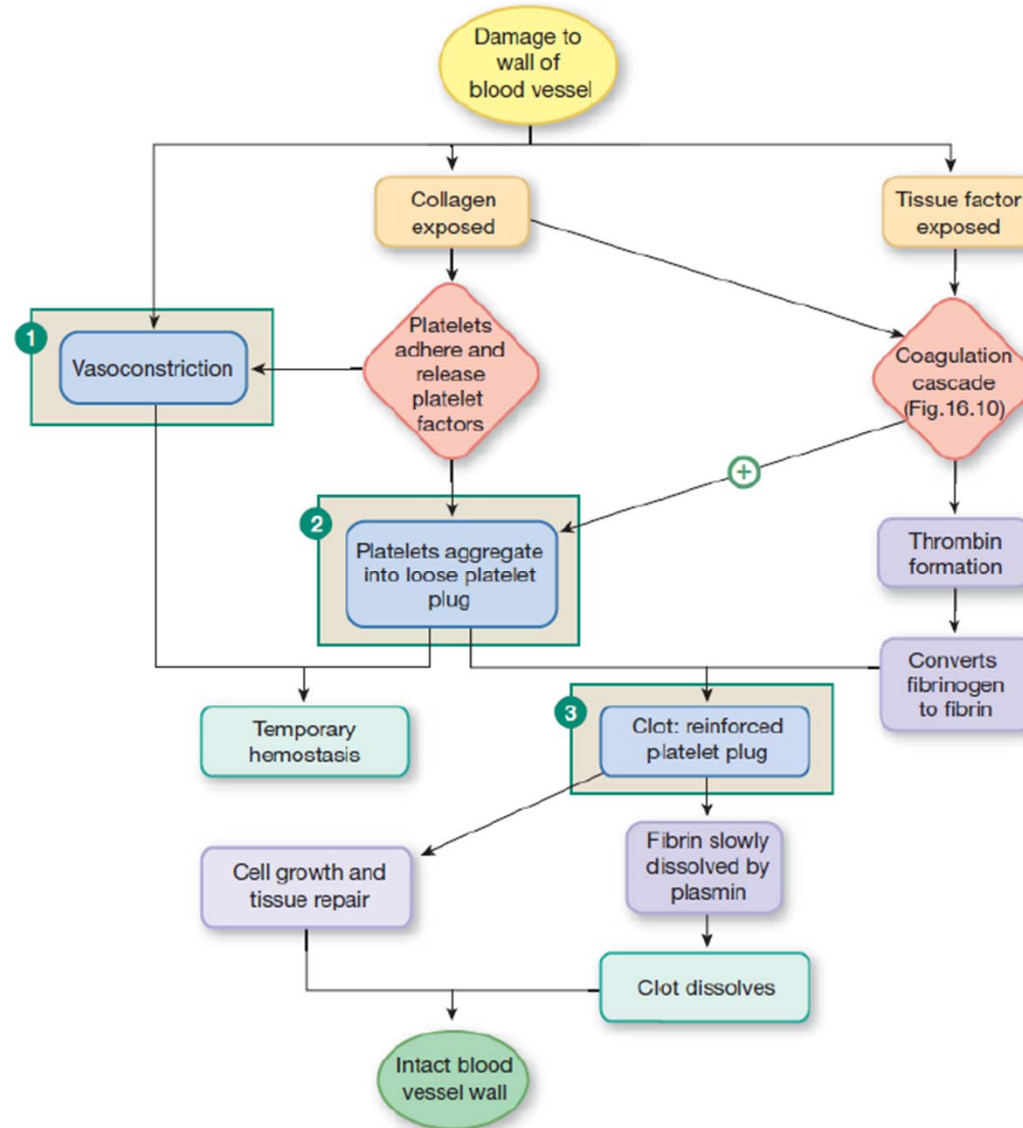
- endothelium
- blood stream
- TXA2 vs. prostacycline

## b) humoral control

- antithrombin III
- fibrin
- thrombomodulin
- protein C (Ca)
- protein S
- plasmin
- TFPI



# Hemostasis - Summary



Silverthorn, D. U. Human Physiology – an Integrated Approach. 6th. edition. Pearson Education, Inc. 2012.

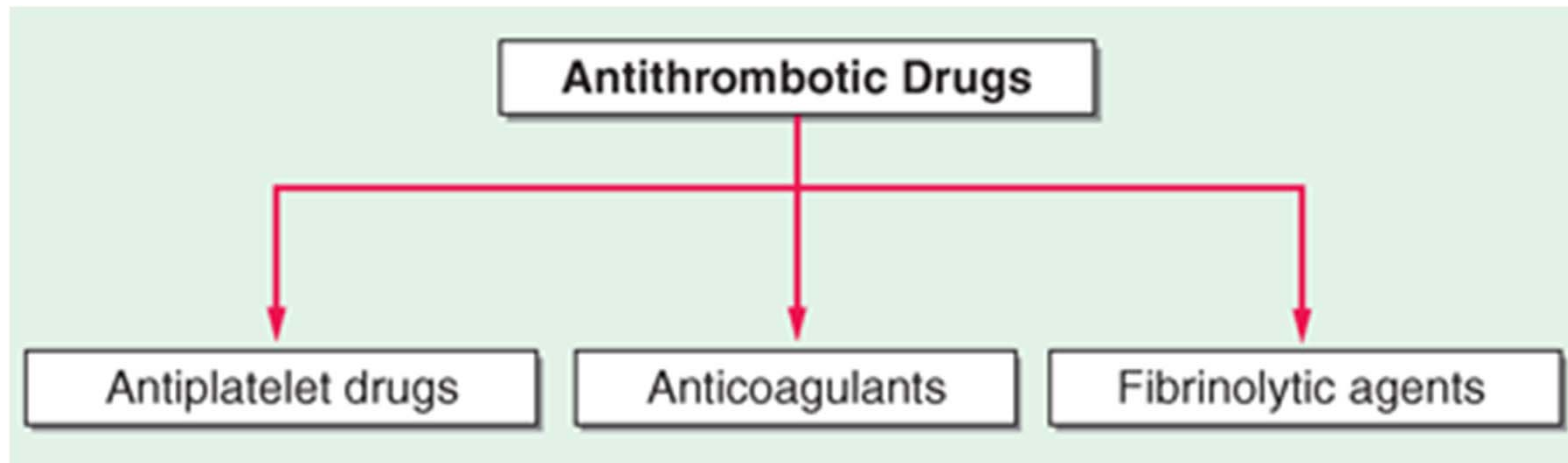
# Hemostasis – Endothelial Cells

**TABLE 14–16 Anticlotting Roles of Endothelial Cells**

Action	Result
Normally provide an intact barrier between the blood and subendothelial connective tissue	Platelet aggregation and the formation of tissue factor–factor VIIa complexes are not triggered
Synthesize and release PGI <sub>2</sub> and nitric oxide	These inhibit platelet activation and aggregation
Secrete tissue factor pathway inhibitor	Inhibits the ability of tissue factor–factor VIIa complexes to generate factor Xa
Bind thrombin (via thrombomodulin), which then activates protein C	Active protein C inactivates clotting factors VIIIa and Va
Display heparin molecules on the surfaces of their plasma membranes	Heparin binds antithrombin III, and this molecule then inactivates thrombin and several other clotting factors
Secrete tissue plasminogen activator	Tissue plasminogen activator catalyzes the formation of plasmin, which dissolves clots

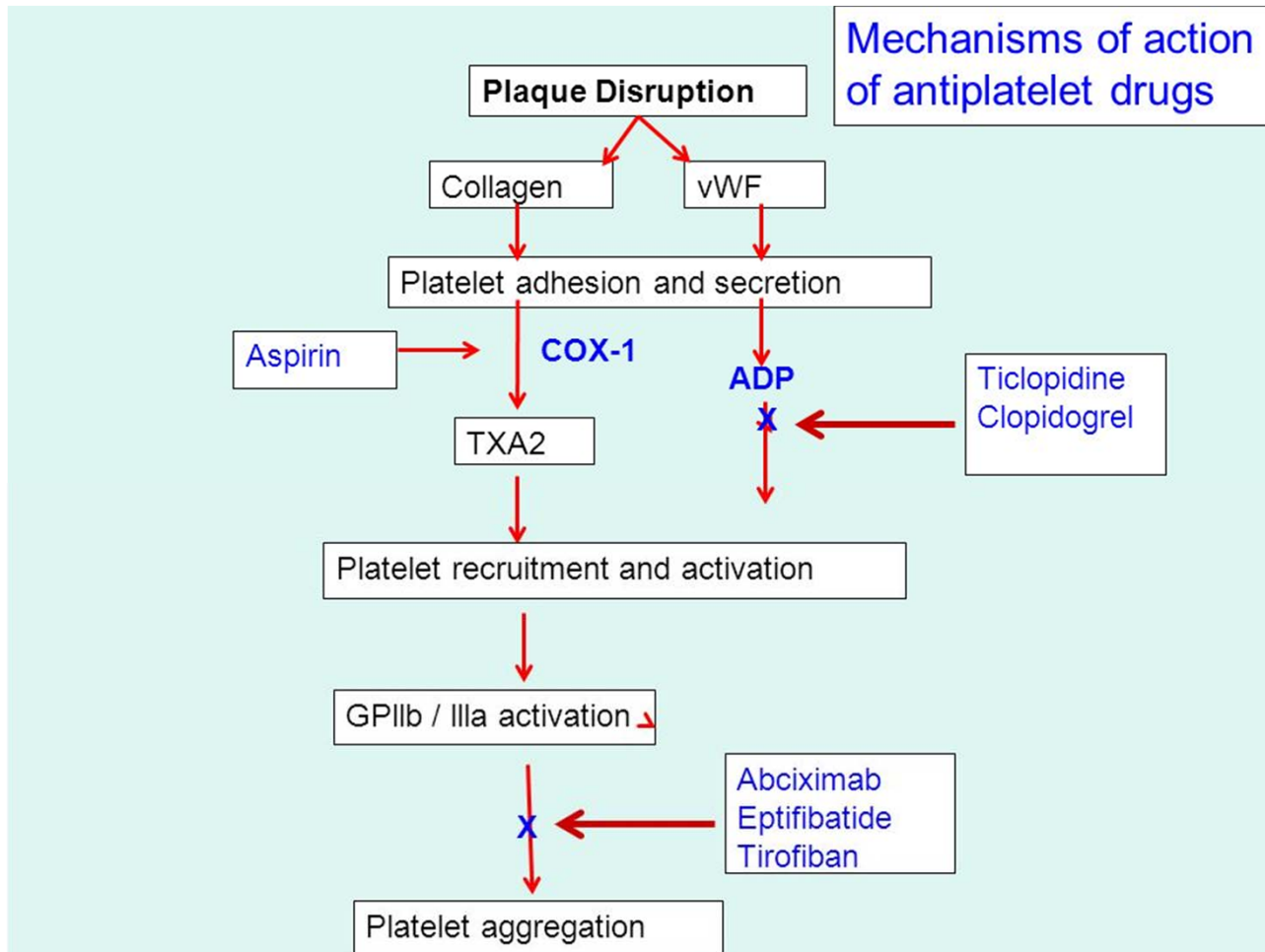
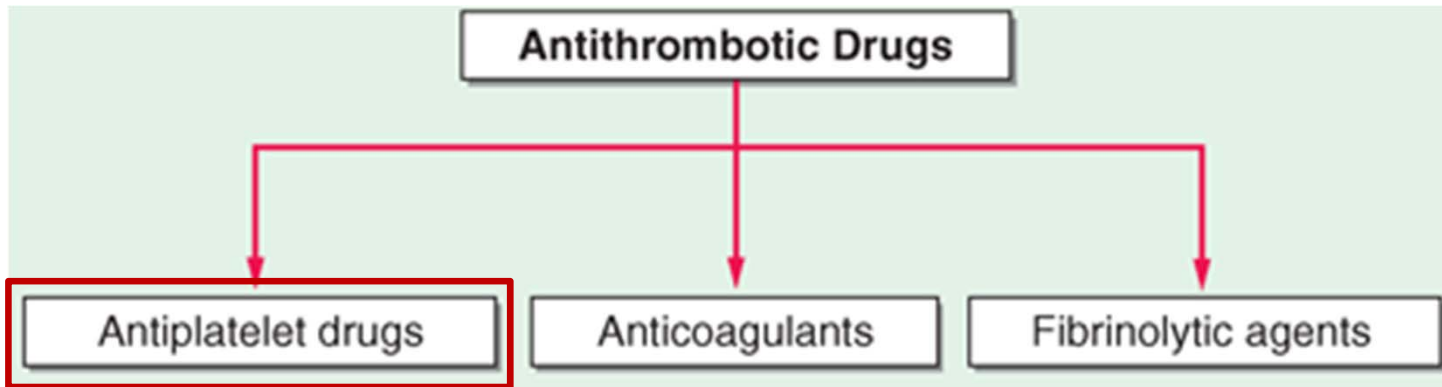
# Intravascular Coagulation

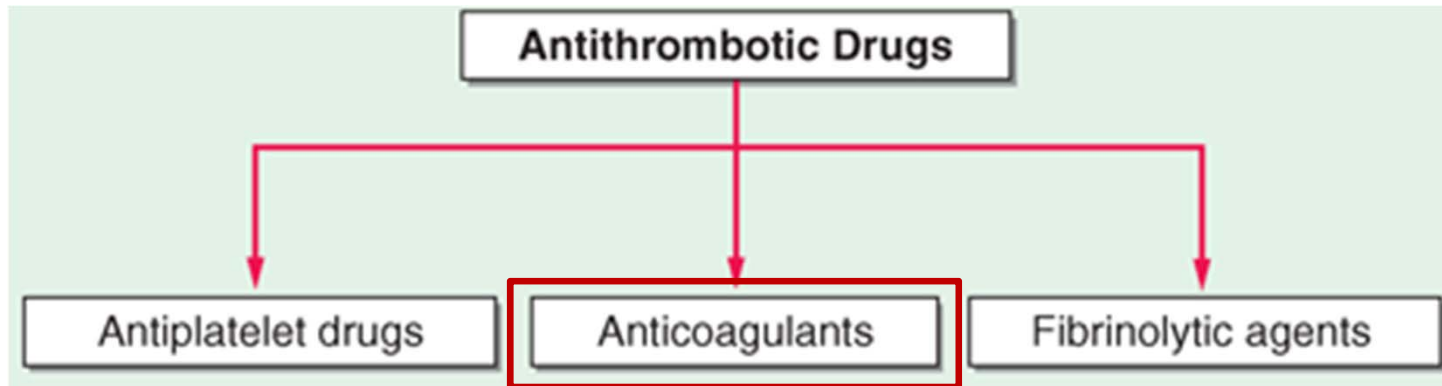
- caused by damage of endothelium due to:
  - atherosclerosis (myocardial infarction, stroke)
  - inflammation (venous thrombosis, pulmonary embolism)
- antithrombotic drugs



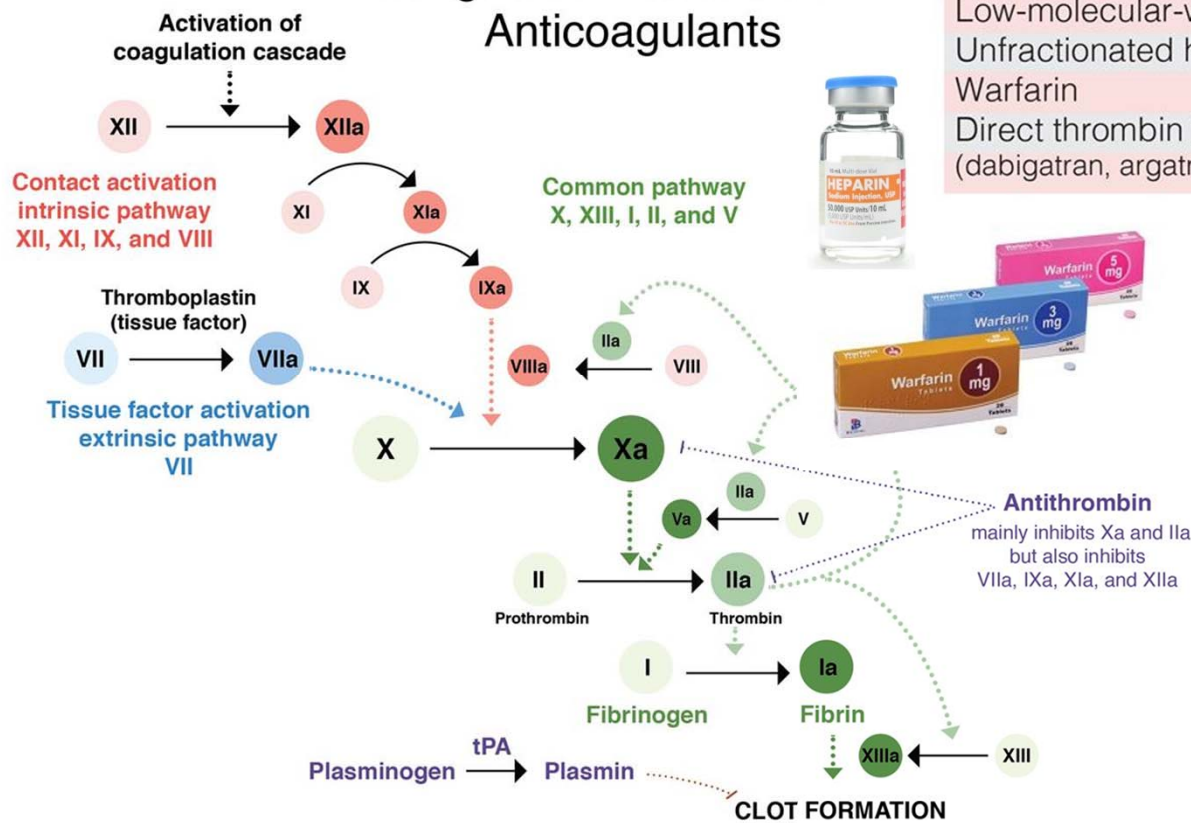
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: [www.accessmedicine.com](http://www.accessmedicine.com)

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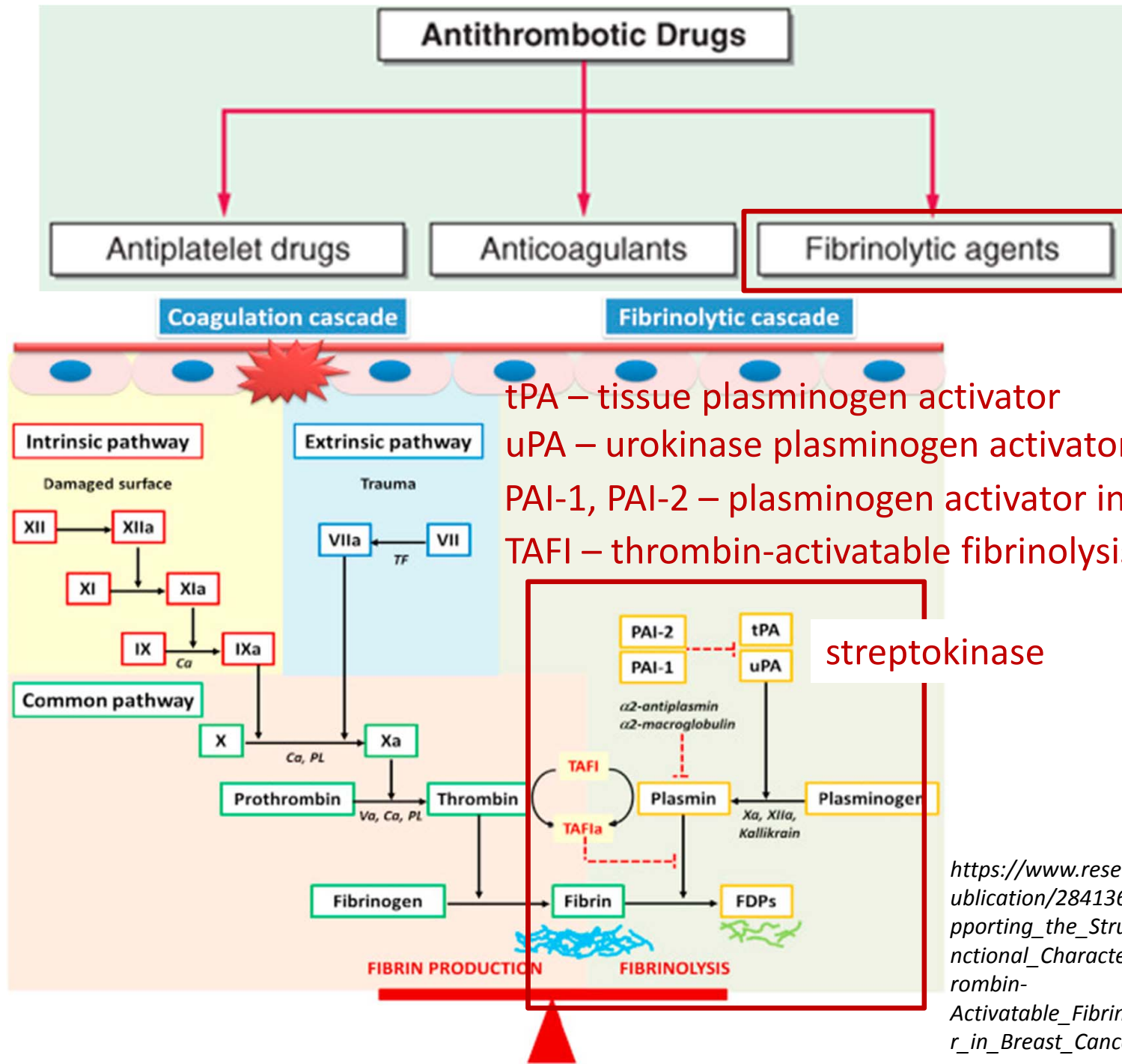
### Coagulation Cascade and Anticoagulants



Anticoagulant	Factors inhibited
Low-molecular-weight heparin	Xa
Unfractionated heparin	IIa, Xa
Warfarin	IIa, VIIa, IXa, Xa
Direct thrombin inhibitor (dabigatran, argatroban, lepirudin)	IIa

Factor	Name	Half-life (h):
I	Fibrinogen	96
II <sup>K</sup>	Prothrombin	72
III	Tissue thromboplastin	
IV	Ionized calcium (Ca <sup>2+</sup> )	
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<https://step2.medbullets.com/heme/121681/anticoagulants>



tPA – tissue plasminogen activator  
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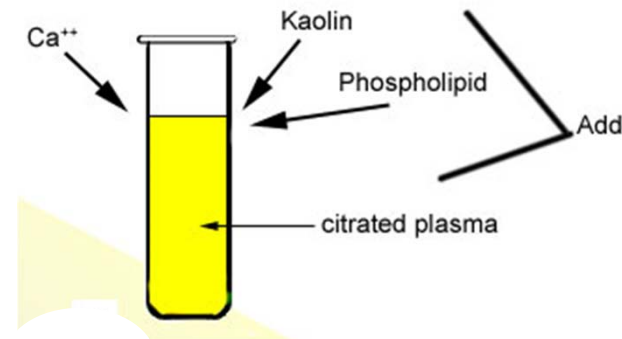
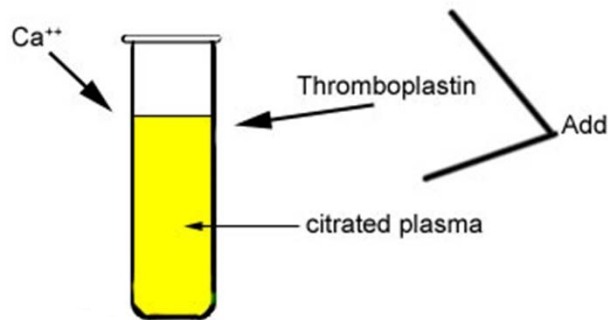
streptokinase

[https://www.researchgate.net/publication/284136686\\_Data\\_Supporting\\_the\\_Structural\\_and\\_Functional\\_Characterization\\_of\\_Thrombin-Activatable\\_Fibrinolysis\\_Inhibitor\\_in\\_Breast\\_Cancer/figures?lo=1](https://www.researchgate.net/publication/284136686_Data_Supporting_the_Structural_and_Functional_Characterization_of_Thrombin-Activatable_Fibrinolysis_Inhibitor_in_Breast_Cancer/figures?lo=1)



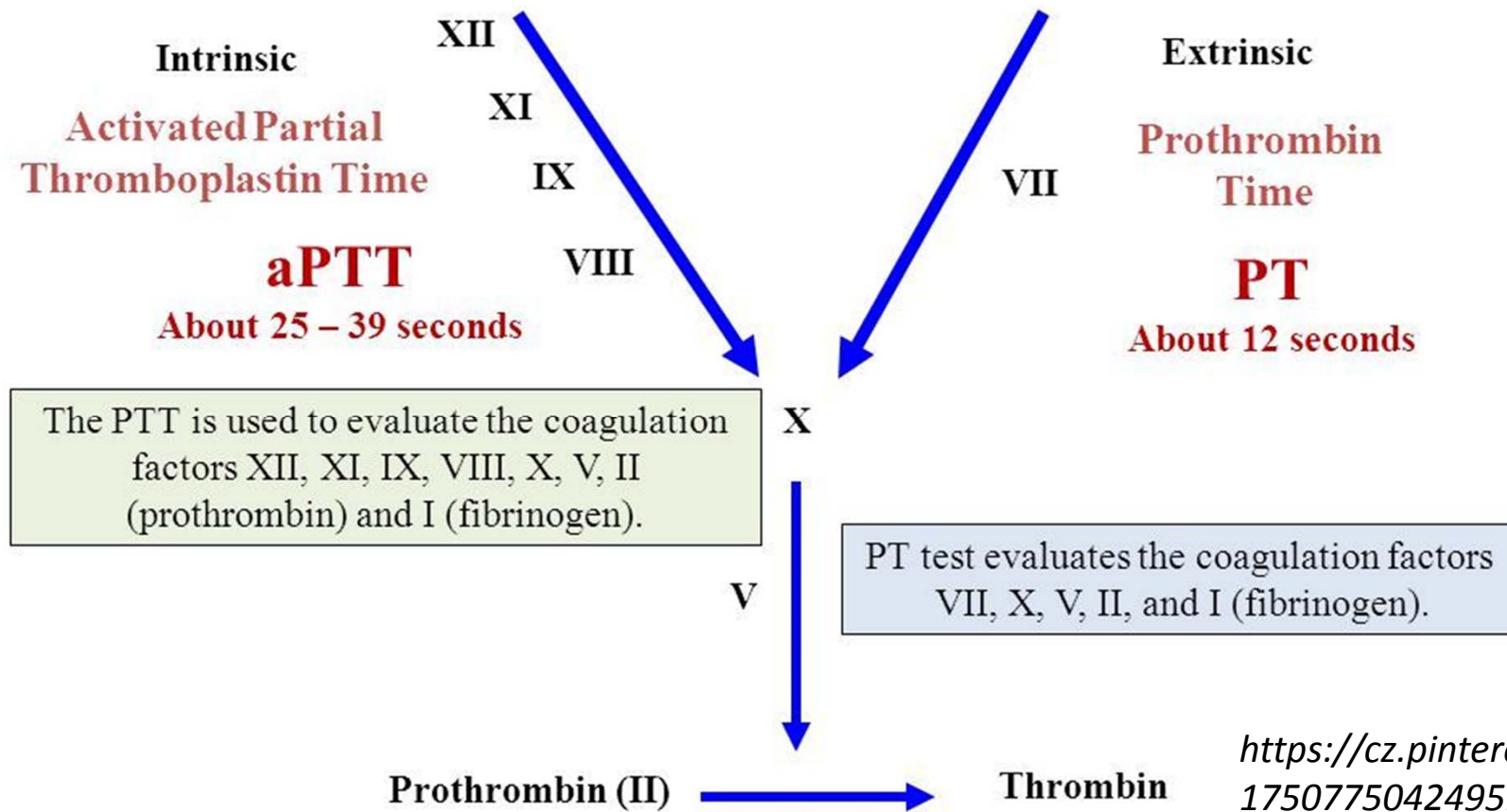
# Blood Clotting Testing

- bleeding time, clotting time
- prothrombin time
- activation partial thromboplastin time



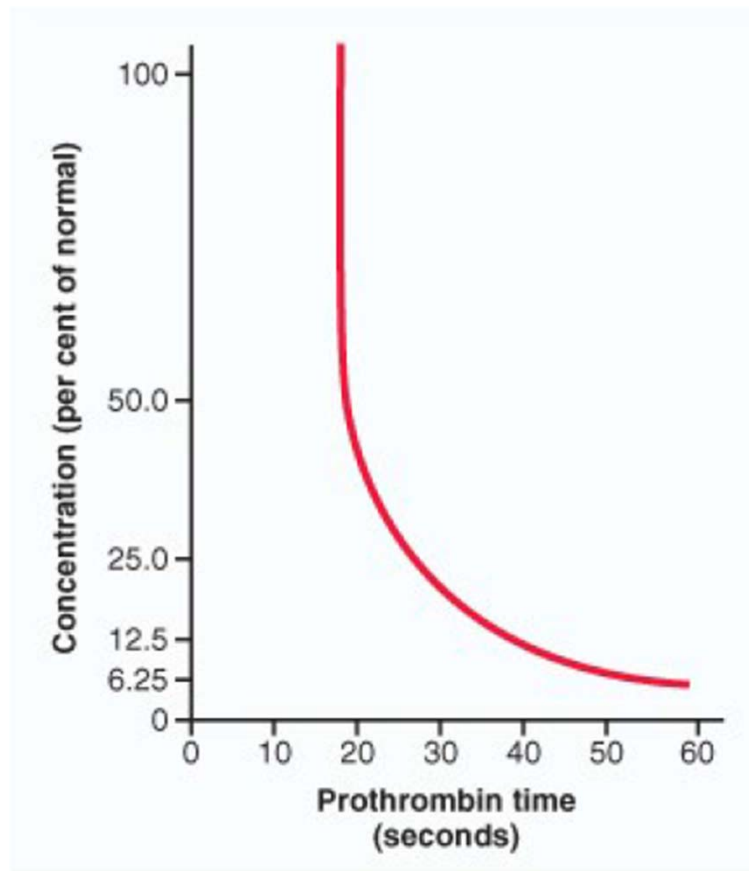
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# Blood Clotting Testing

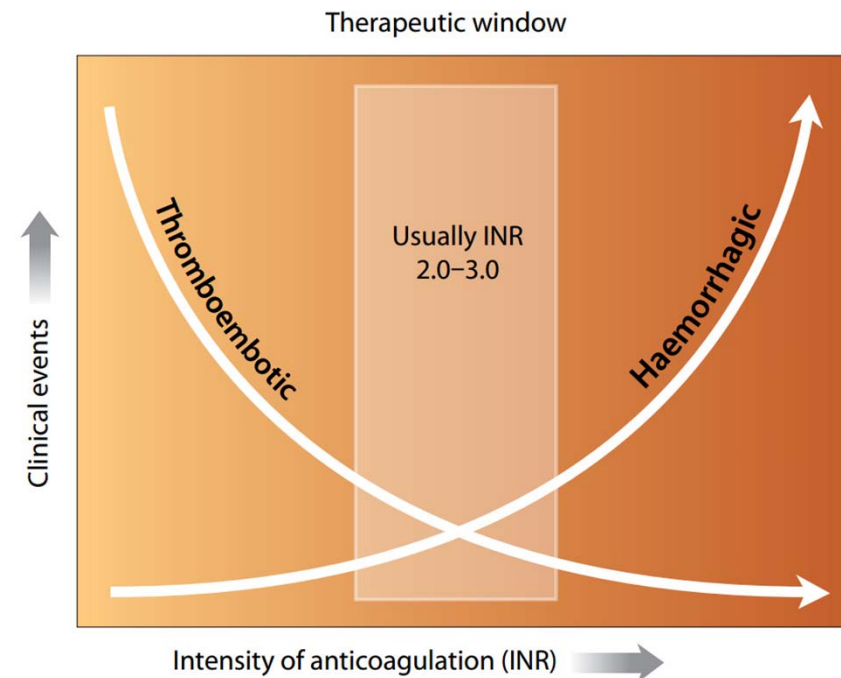
- bleeding time, clotting time
- prothrombin time



Guyton & Hall: Textbook of Medical Physiology 11e

International Normalized Ratio (INR) Calculation

$$INR = \left( \frac{PT_{\text{patient}}}{PT_{\text{normal}}} \right)^{ISI}$$



<https://bpac.org.nz/BT/2010/November/inr.aspx>

# Coagulation Disorders

- blood clotting starts either spontaneously or after inadequately small stimulus, or blood clotting blunted
  - diseases of **vessels**
  - **platelet** disorders (thrombocytopenia, thrombocytopathy)
  - **coagulopathies**
    - a) disorders of synthesis of clotting factors (*e.g.* hemophilia, hypovitaminosis K, therapy with coumarin derivatives)
    - b) disorders of metabolism of clotting factors (*e.g.* consumptive coagulopathy, hyperfibrinolysis, therapy by heparin, repeated transfusions)