Chapter 10 血 液

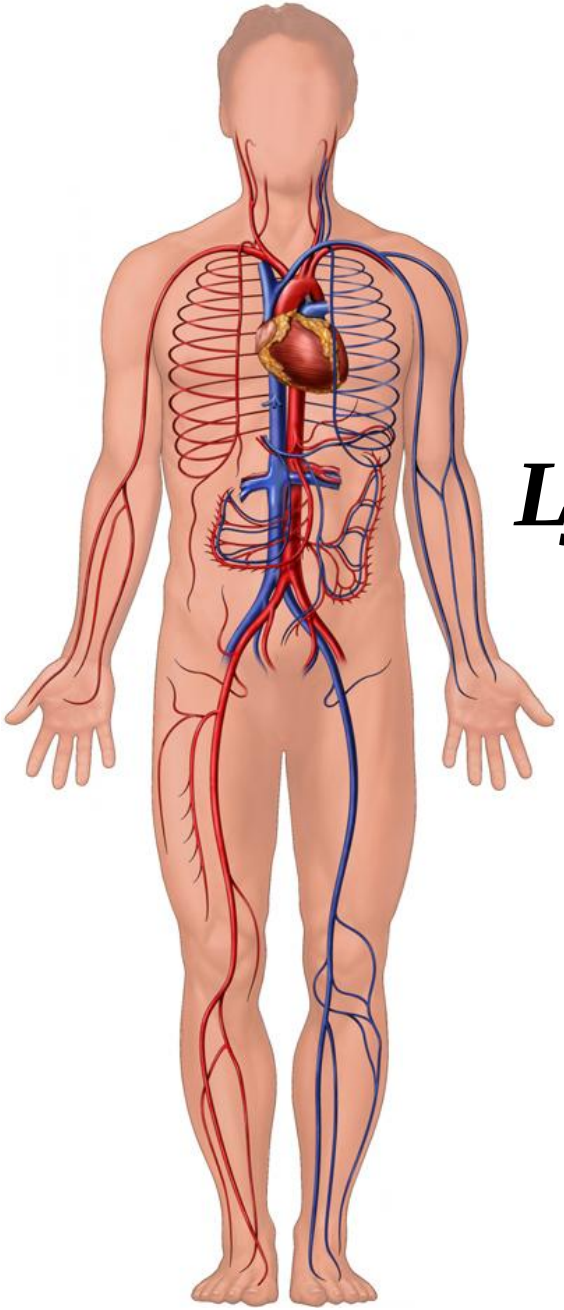
10-1 血液的特性

10-2 血液的組成

10-3 凝血及抗凝血

10-4 血型及輸血

Cardiovascular System (CVS)



Blood + Heart + Blood vessels

= CVS

Lymph + Lymph nodes+ lymph vessels

= Lymphatic System

CVS + Lymphatic System

= Circulatory System

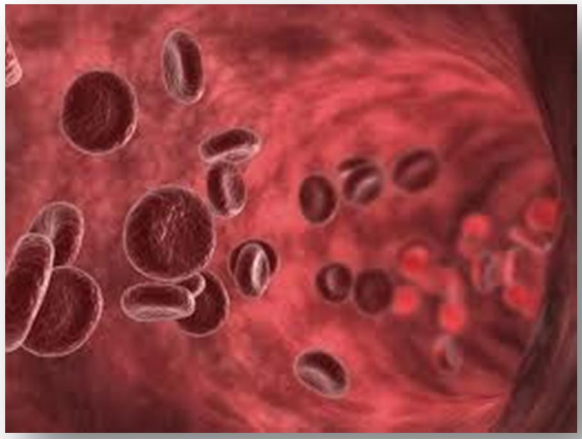
Functions of Cardiovascular System

1. Transportation

--Respiratory gases

--Delivery of oxygen and nutrients

--Waste removal



2. Regulation

--Temperature

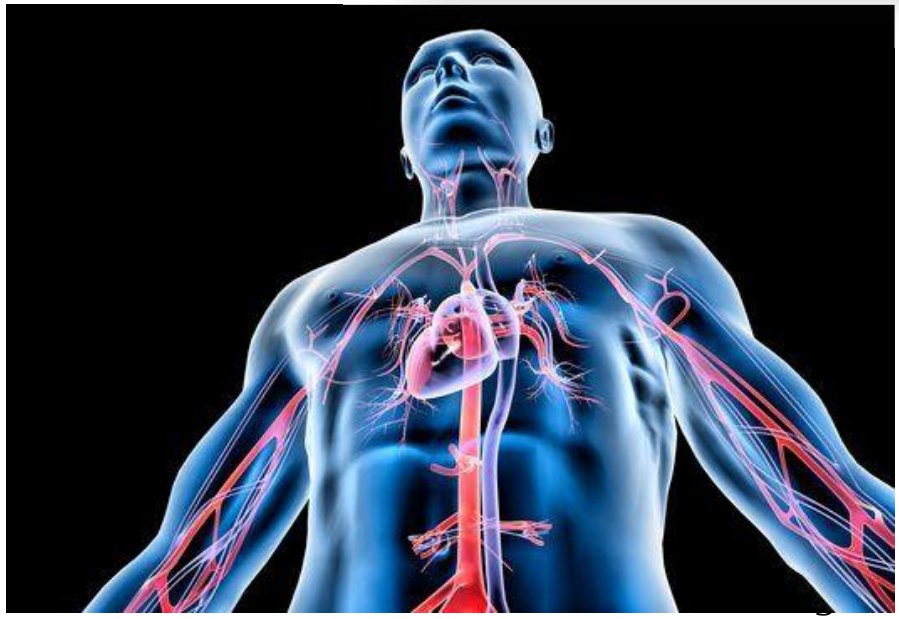
--Acid-base balance

--Hormones

3. Protection

--Clotting

--Immune function



Characteristics of Blood

血 量	體重的1/13或8%
比 重	男：1.059；女：1.056
顏 色	動脈：鮮紅色；靜脈：暗紅色
酸鹼值	7.35~7.45 (主要是依賴於 $NaHCO_3/H_2CO_3$)
黏稠度	男：4.7；女：4.4 (主要取決於血球數量)
滲透壓	280~300 mOsm (主要取決於溶質顆粒數目)

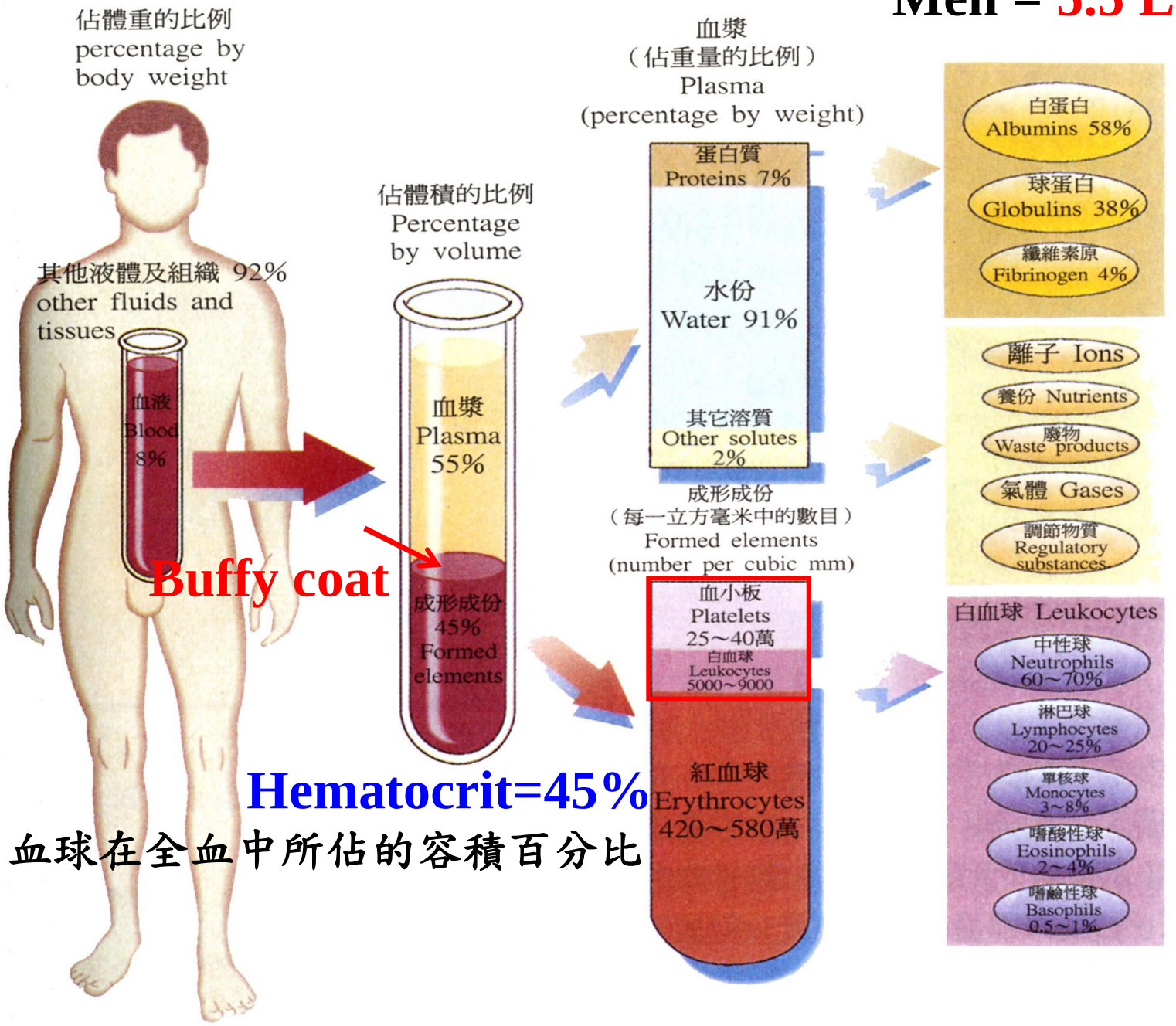
Crystal vs. Colloid Osmotic Pressure

比較項目	血漿晶體滲透壓	血漿膠體滲透壓
定 義	血漿內由晶體物質構成的滲透壓	血漿內由膠體物質構成的滲透壓
構成物	電解質（主要為 NaCl）	血漿蛋白（主要為白蛋白）
數 值	300 mOsm/kgH_2O	1.5 mOsm/kgH_2O
生理意義	維持紅血球內外水平衡和正常形態，避免細胞水腫	維持微血管內外水平衡，防止組織水腫
產生原因	電解質易通過血管壁，不易通過細胞膜	膠體物質不易通過血管壁。

例如：**營養不良的患者**，由於血漿蛋白減少，血漿膠體滲透壓下降，血管內的水分過多地滲入組織間隙，造成組織液滯留組織間隙，形成**組織水腫**

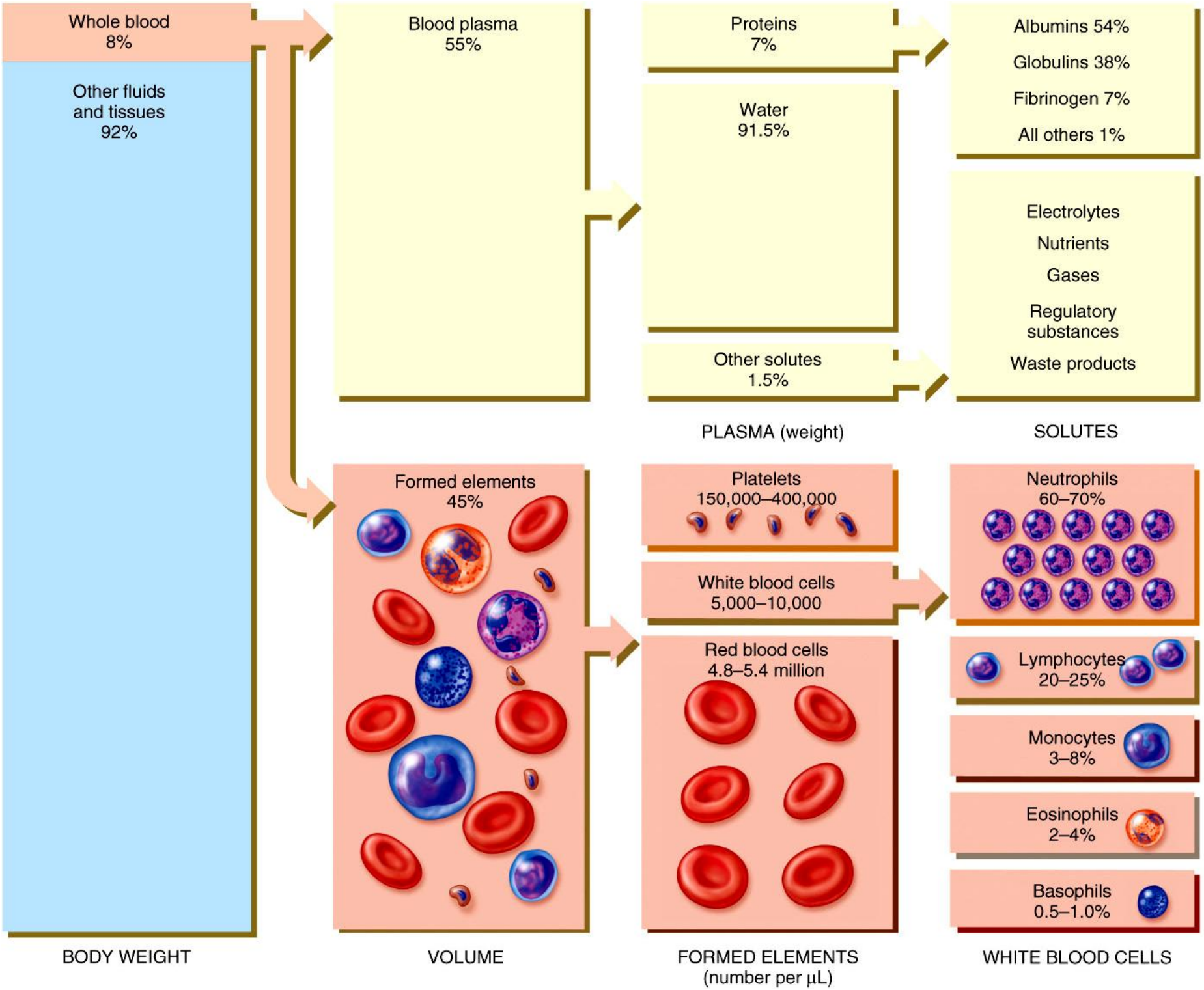
Components of Blood

Average blood volume
Women = 5.0 L
Men = 5.5 L

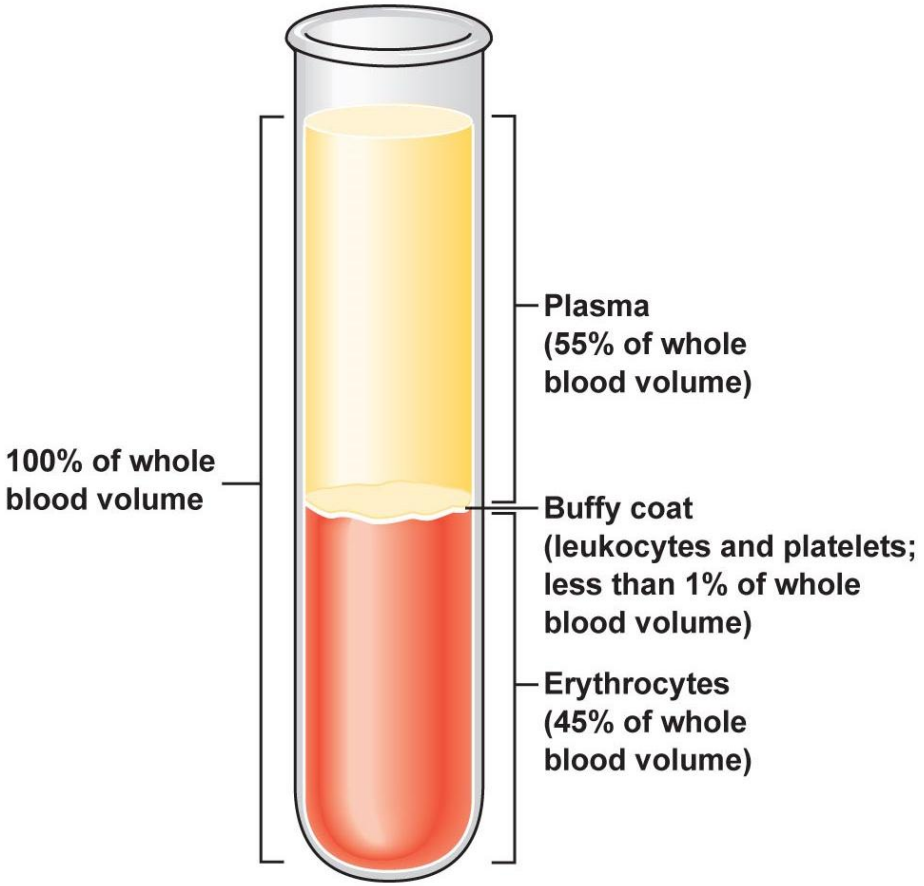


Hematocrit=45%

血球在全血中所佔的容積百分比


Whole blood
8%
Other fluids
and tissues
92%
BODY WEIGHT
Blood plasma
55%
Formed elements
45%
VOLUME
Proteins
7%
Water
91.5%
Other solutes
1.5%
PLASMA (weight)
Albumins 54%
Globulins 38%
Fibrinogen 7%
All others 1%
Electrolytes
Nutrients
Gases
Regulatory
substances
Waste products
SOLUTES
Platelets
150,000–400,000
White blood cells
5,000–10,000
Red blood cells
4.8–5.4 million
FORMED ELEMENTS
(number per μL)
Neutrophils
60–70%
Lymphocytes
20–25%
Monocytes
3–8%
Eosinophils
2–4%
Basophils
0.5–1.0%
WHITE BLOOD CELLS

Blood Plasma



Normal Hematocrit

Men = 42–52

Women = 37–47

- **Over 90% water**
- **7% plasma proteins: Albumin, Globulins and Fibrinogen**
  - --Synthesized in liver, except some globulins synthesized by lymphocytes
  - --Confined to bloodstream
  - --General functions: Colloid osmotic pressure, Buffer H^+, Increase blood viscosity and Fuel during starvation
- **2% other substances**
  - --Electrolytes, nutrients, hormones, gases, waste products

Functions of Plasma Proteins

●Albumins :

1. Major contributor to plasma oncotic osmotic pressure
2. Carriers

> ➢ 臨床上常檢查**Albumin-Globulin ratio (A/G ratio)** 作為肝功能的指標，A/G 正常值為 **1.5~2.5**，低於這個範圍代表肝功能異常

●Globulins :

1. **Alpha and Beta**
   --Carriers
   --Clotting factors
   --Enzymes
   --Precursor proteins (angiotensinogen)

   α-Angiotensinogen → ***Angiotensin***
2. **Gamma = immunoglobulins (Ig)**
   --Part of immune system

●Fibrinogen: Blood clotting

Components of Plasma

Component	Description and importance
Water	Makes up 90% of plasma volume; provides dissolving and suspending medium for solutes and formed elements
Solutes	
Proteins	Accounts for 8% of plasma (by weight); most are synthesized by liver
Albumin	60% of plasma proteins; largely responsible for plasma osmotic pressure
Globulins	36% of plasma proteins; include clotting proteins, antibodies secreted by certain leukocytes during the immune response, and proteins that bind to lipids, fat-soluble hormones, and metal ions to transport these substances in the blood
Fibrinogen	Important in the formation of blood clots
Others	Enzymes, hormones, and antibacterial proteins
Nitrogenous waste products	By-products of metabolism, such as urea, uric acid, and creatinine
Organic nutrients	Materials absorbed from the intestines and used by cells throughout the body; include glucose and other simple sugars, amino acids, fatty acids, glycerol, triglycerides, cholesterol, and vitamins
Electrolytes	
Cations	Sodium, potassium, calcium, magnesium (important in neuromuscular signaling), and trace metals (important in normal enzyme activity)
Anions	Chloride (important in neuromuscular signaling), bicarbonate, and phosphate (important in maintenance of normal plasma pH)
Respiratory gases	Oxygen and carbon dioxide; most oxygen and some carbon dioxide is bound to hemoglobin in erythrocytes; a significant fraction of carbon dioxide is found in the plasma in the form of bicarbonate

Plasma vs. Serum

比較項目	血漿	血清
定 義	從抗凝血液中分離出的液體	血液凝固後分離出的淺黃色液體
纖維蛋白原	含有	無
凝血因子	含有	無
血小板因子	無	含有

Hematocrit = volume of red cells (~45%)

Plasma = fluid in fresh blood

Serum = fluid after blood has clotted

Plasma = serum + fibrinogen (& other clotting factors)

Normal volumes:
blood ~5.5L, plasma ~3L, rbc's ~2.5L

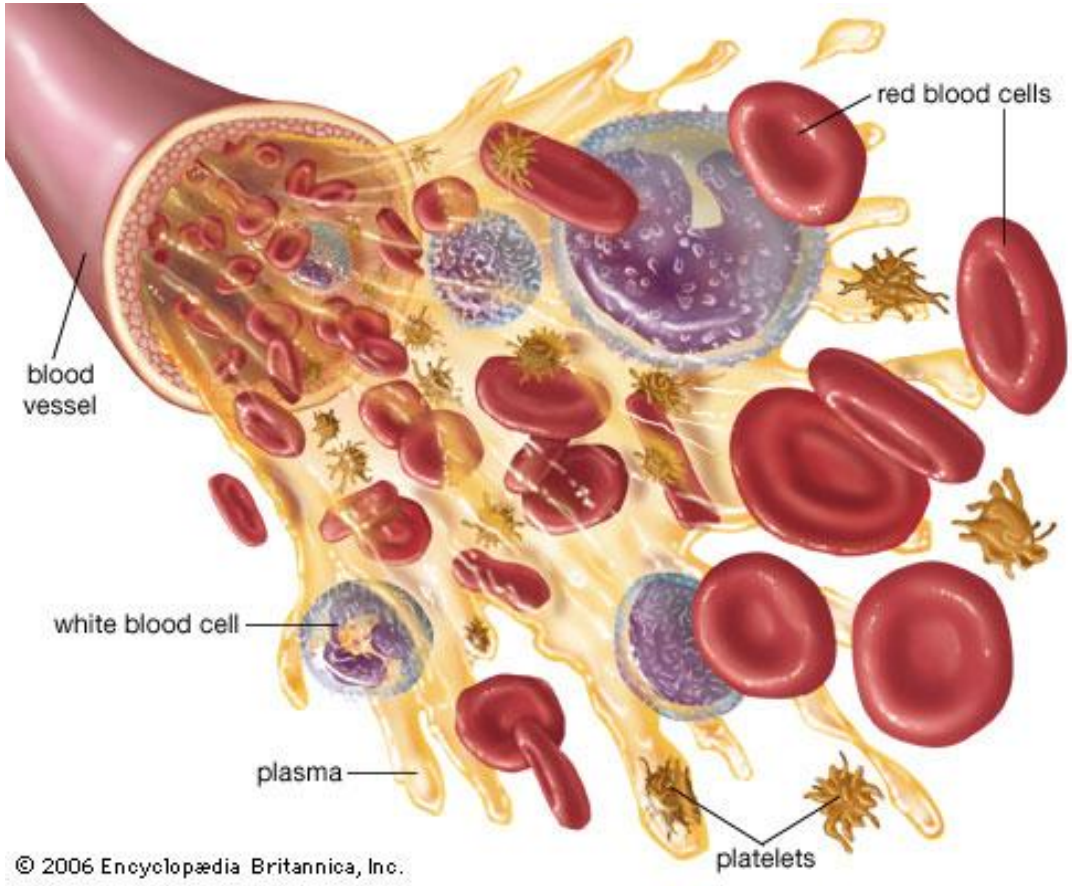
Normal Plasma Value

Test	Normal range
血液體積	80 – 85 ml/kg 體重
血液滲透值	280 – 300 mOsm
血液 pH 值	7.35 – 7.45
酵素	
肌酸磷酸酵素(CPK)	女性：10 – 79 U/L
	男性：17 – 148 U/L
乳酸去氫酵素(LDH)	40 – 90 U/L
磷酸酵素(phosphatase)	女性：0.01 – 0.56 Sigma U/ml
(酸性)(acid)	男性：0.13 – 0.63 Sigma U/ml
血液值	
血比溶	女性：37% – 48%
	男性：45% – 52%
血紅素	女性：12 – 16 g/100 ml
	男性：13 –18 g/100 ml
紅血球計數	4.2 – 5.9 million/mm^3
白血球計數	5000 – 10000 /mm^3

Normal Plasma Value

Test	Normal range
激素	
睪固酮	男性：300-1100 ng/100ml 女性：25-90 ng/100ml
腎上腺皮質刺激素(ACTH)	15-70 pg/ml
生長激素	小孩：高於10 ng/ml　成年男子：低於5 ng/ml
胰島素	6-26 μU/ml (禁食)
離子	
重碳酸鹽	24-30 mmol/l
鈣	2.1-2.6 mmol/l
氯	100-106 mmol/l
鉀	3.5-5.0 mmol/l
鈉	135-145 mmol/l
有機分子(其它)	
膽固醇	120-220 mg/100ml
葡萄糖	70-110 mg/100ml(禁食)
乳酸	0.6-1.8 mmol/l
蛋白質(全部)	6.0-8.4 g/100ml
三酸甘油脂	40-150 mg/100ml
尿素氮	8-25 mg/100ml
尿酸	3-7 mg/100ml

Functions of Blood Cells



❖**Transportation**

--O2, CO2, metabolic wastes, nutrients, heat & hormones

❖**Regulation**

--Helps regulate pH through buffers

--Helps regulate body temperature

--Helps regulate water content of cells by interactions with dissolved ions and proteins

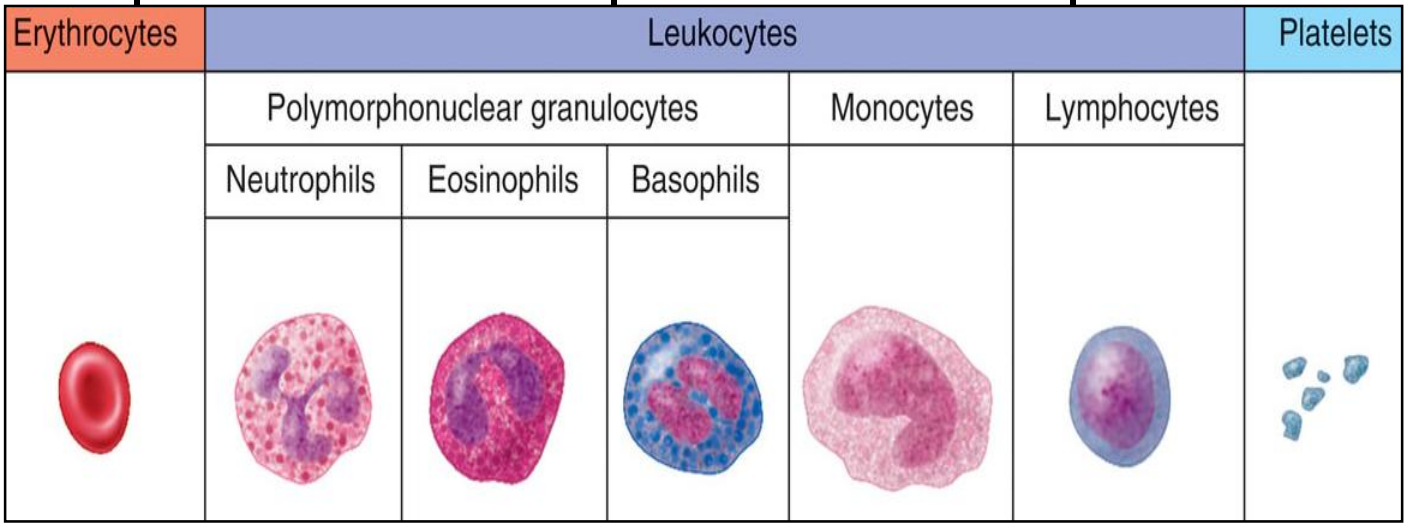
❖**Protection** from disease & loss of blood

Types of Blood Cells

Type	Describe	Number	Function
紅血球	雙凹圓盤狀無核，含有血紅素，可存活100到200天	4000000~~6000000/mm ^{3}	運輸氧和二氧化碳
白血球		5000~~10000/mm ^{3}	幫助防禦對抗微生物感染
I. 顆粒性細胞	大約是紅血球的兩倍大，細胞質中有顆粒存在，存活12小時到13天		
1. 嗜中性球	核分為2到5葉，細胞質中的顆粒可被輕微的染上粉紅色	佔白血球的54%到62%	具吞噬細胞的功能，急性感染時，嗜中性球會大量增生
2. 嗜酸性球	核分為2葉，細胞質中的顆粒在酸性染劑染成紅色	佔白血球的1%到3%	幫助將外來的物質解毒，分泌能溶解血塊的酵素，抵抗寄生蟲感染，與過敏反應有關
3. 嗜鹼性球	核分為多葉，細胞質中的顆粒在蘇木素染劑中染成藍色	佔白血球的1% 以下	轉變成肥大細胞分泌肝素(抗凝劑) Histamine及5-HT(與過敏及發炎有關)

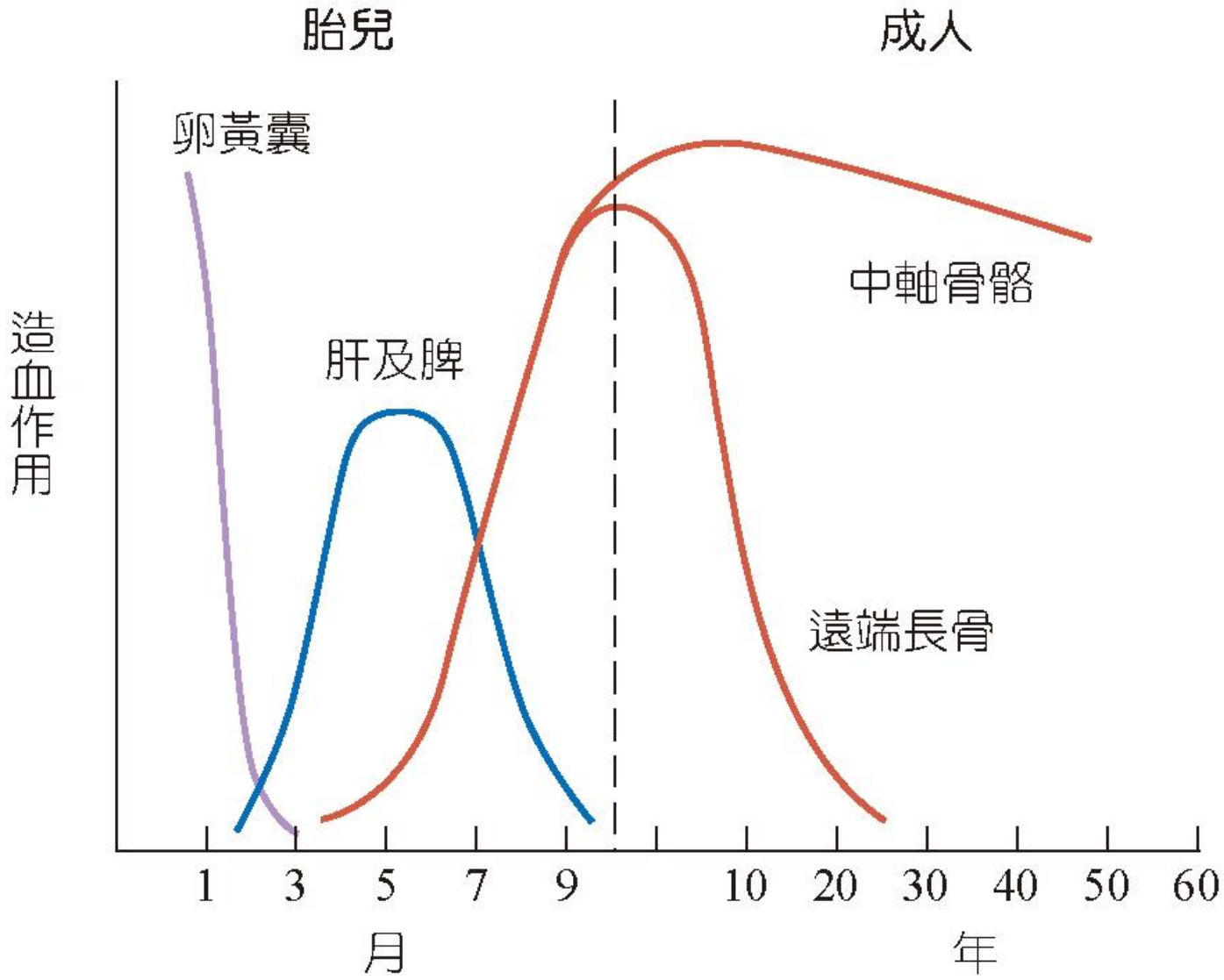
Types of Blood Cells

Type	Describe	Number	Function
II. 非顆粒性細胞	細胞質中沒有顆粒，存活100天到300天		
1. 單核球	比紅血球大2~~3倍，核的形狀多變化，有圓形的也有分葉的	佔白血球的3%到9%	轉變成巨噬細胞時，具吞噬細胞的功能
2. 淋巴球	只比紅血球大一點，核幾乎佔滿整個細胞	佔白血球的25%到33%	提供特定的免疫反應(包括抗體)
血小板	巨核細胞的碎片，存活5天到9天	250000~~450000/mm ^{3}	促進凝血，提供血管保護

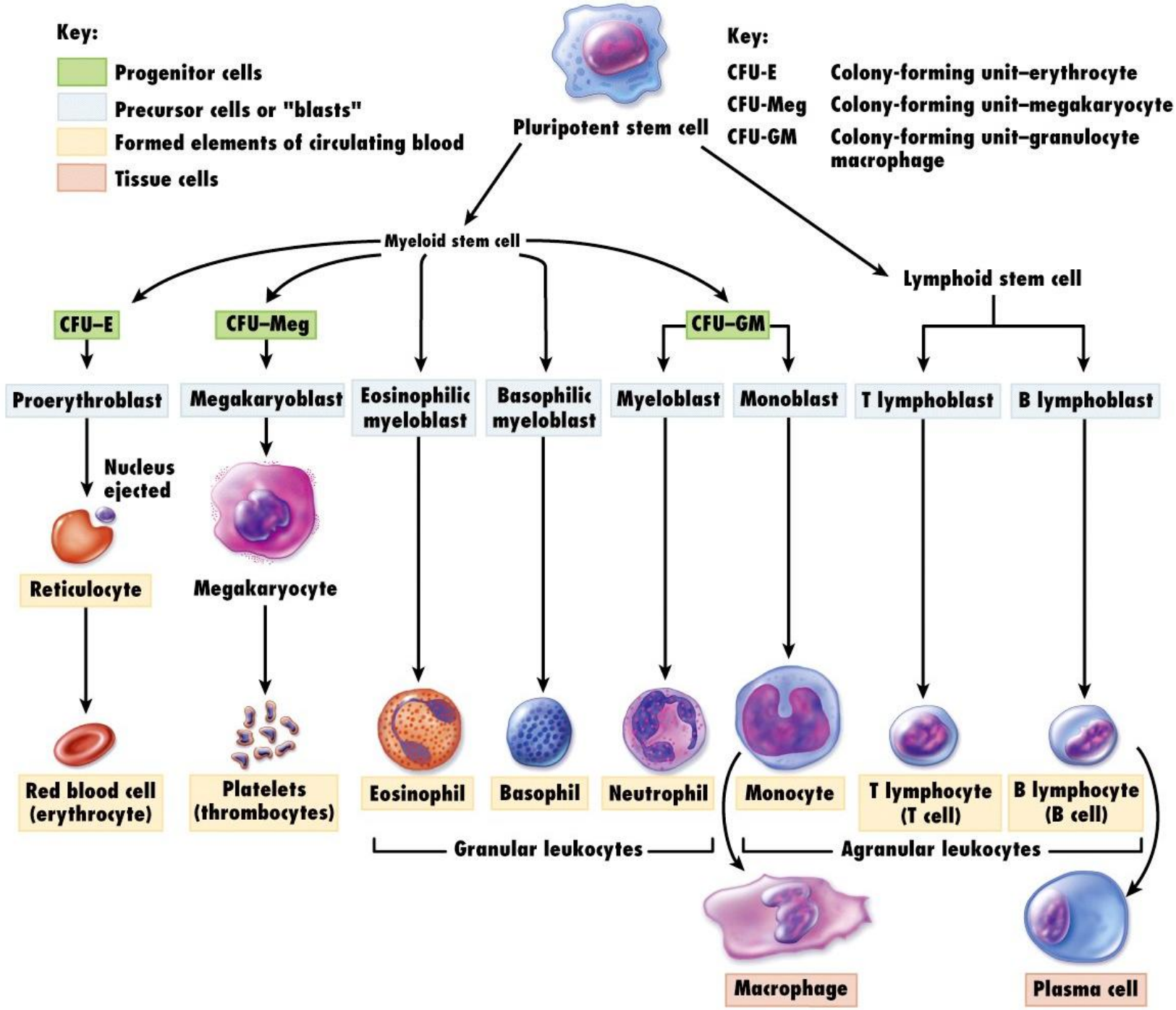


Hematopoiesis= Blood Cell Formation

- **In the embryo (occurs in yolk sac, liver, spleen, thymus, lymph nodes & red bone marrow)**
- **In adult (occurs only in red marrow of flat bones like sternum, ribs, skull & pelvis and ends of long bones)**



Hematopoiesis= Blood Cell Formation



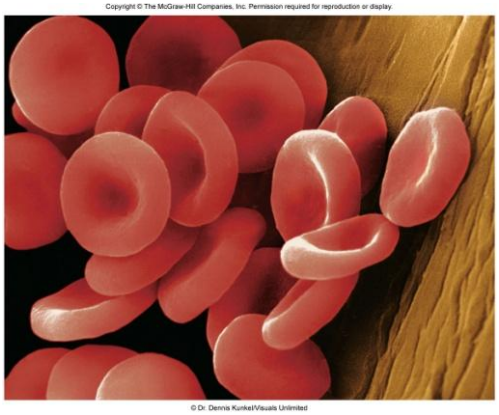
Stages of Blood Cell Formation

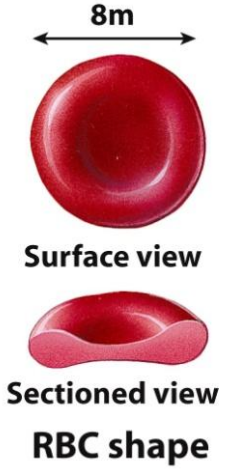
- **Pluripotent stem cells**
  - --1% of red marrow cells
  - --Replenish themselves as they differentiate into either myeloid or lymphoid stem cells
- **Myeloid stem cell line** of development continues:
  - --Progenitor cells (colony-forming units) no longer can divide and are specialized to form specific cell types
    - Example: CFU-E develops eventually into only red blood cells
  - --Next generation is blast cells (precursor cell)
    - Have recognizable histological characteristics
    - Develop within several divisions into mature cell types
- **Lymphoid stem cell line** of development
  - --Pre-B cells & prothymocytes finish their develop into B & T lymphocytes in the lymphatic tissue after leaving the red marrow

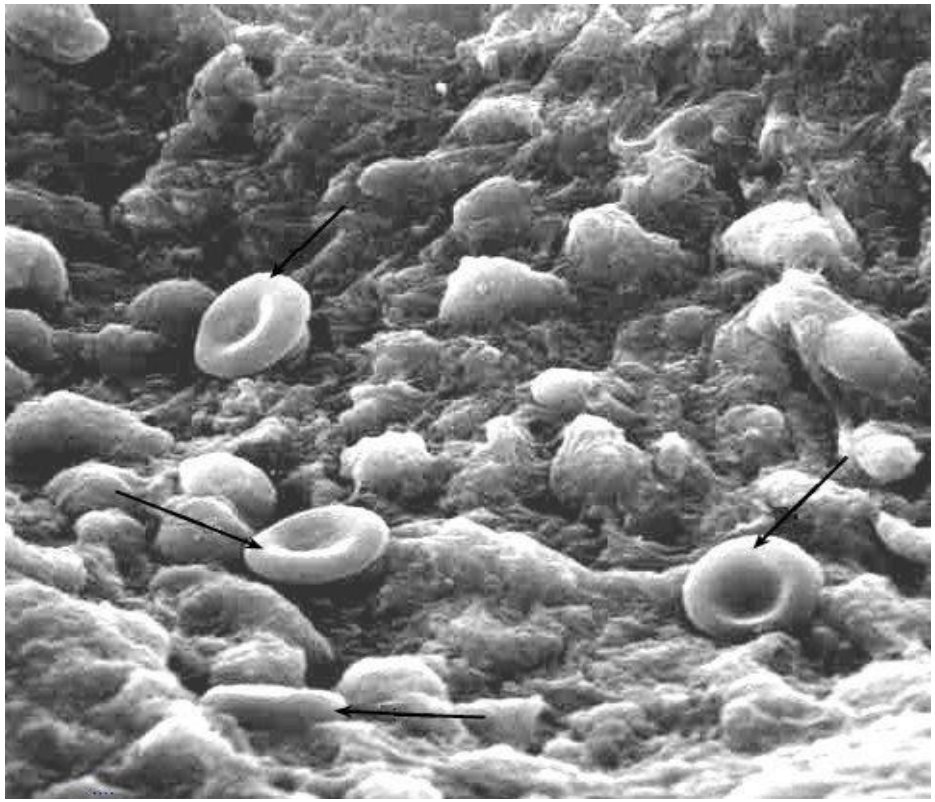
Hemopoietic Growth Factors

- Regulate differentiation & proliferation
- **Erythropoietin (EPO)**
  - --Produced by the kidneys increase RBC precursors
- **Thrombopoietin (TPO)**
  - --Hormone from liver stimulates platelet formation
- **Cytokines** are local hormones of bone marrow
  - --Produced by some marrow cells to stimulate proliferation in other marrow cells
  - --Colony-stimulating factor (CSF) & interleukin stimulate WBC production
- Available through recombinant DNA technology
  - --Recombinant EPO very effective in treating decreased RBC production of end-stage kidney disease
  - --Other products given to stimulate WBC formation in cancer patients receiving chemotherapy which kills bone marrow
    - Granulocyte-macrophage colony-stimulating factor
    - Granulocyte colony stimulating factor
  - --TPO helps prevent platelet depletion during chemotherapy

Red Blood Cells or Erythrocytes

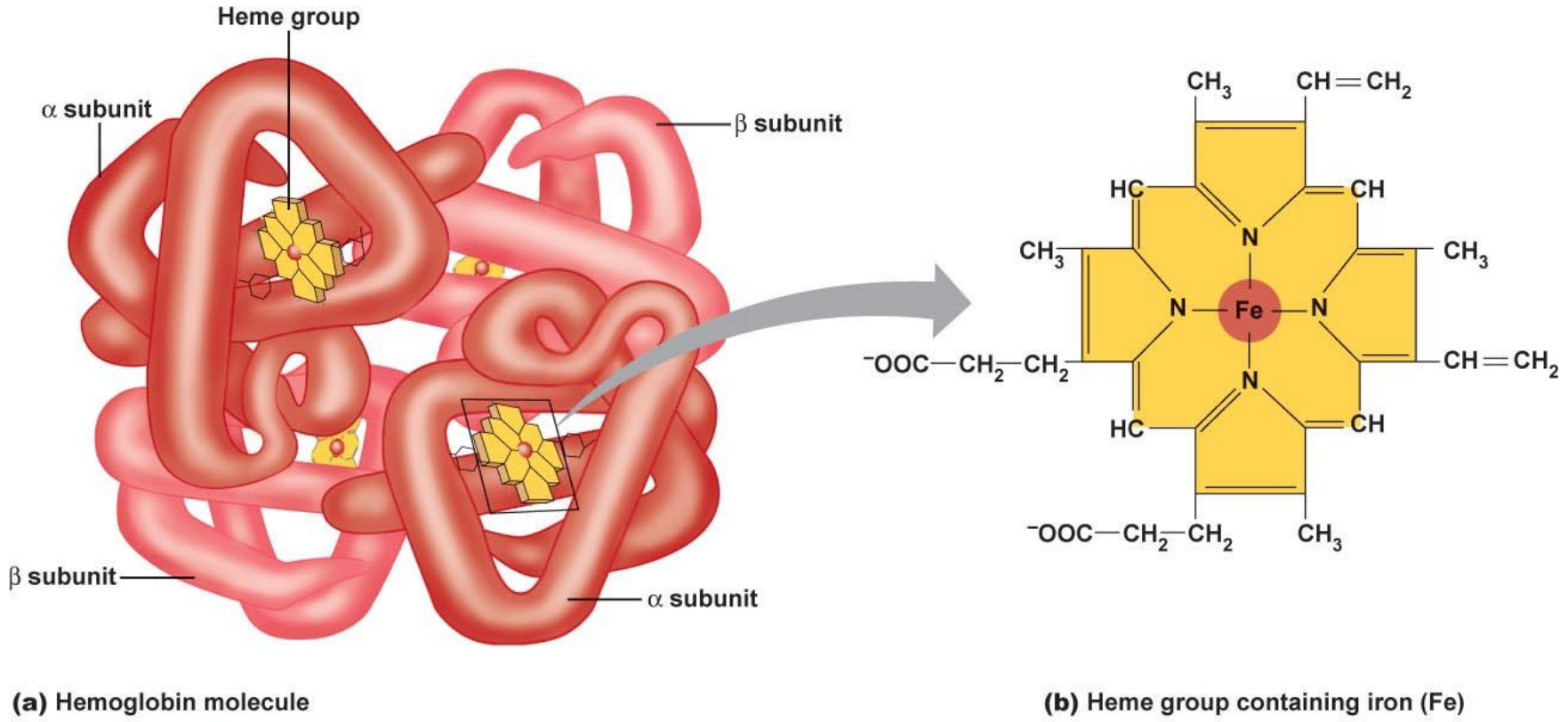






- Contain **oxygen-carrying protein hemoglobin (Hb)** that gives blood its red color
  - --1/3 of cell's weight is hemoglobin
- **Biconcave disk 8 microns in diameter**
  - --Increased surface area/volume ratio
  - --Flexible shape for narrow passages (**Spectrin**: cytosolic fibrous protein)
  - --No nucleus or other organelles
  - --No cell division or mitochondrial ATP formation
- Normal RBC count
  - --Male **5.4 million**/drop & female **4.8 million**/drop (mm^3)
  - --New RBCs enter circulation at 2 million/second (life cycle **120 days**)

Hemoglobin= 4Heme+Globin



- Globin protein consisting of 4 polypeptide chains
- One heme pigment attached to each polypeptide chain
  - --Each heme contains an iron ion (Fe^{+2}) that can combine reversibly with one oxygen molecule
- Enzymes: Glycolytic enzymes & Carbonic anhydrase

Hemoglobin Molecule

- Molecule = ***globin + 4 heme groups***
  - --Globin = ***4 chains of polypeptides***
  - --Heme = ***an iron containing group***
- Greatly increases O_2 transport
  - --**98.5%** of transported O_2 is bound to **Hb**
  - --**1.5%** of transported O_2 is dissolved in **plasma**
- Binding rate: $CO > O_2 > CO_2$
- Oxygenated Hb is **bright red**; Deoxygenated Hb is **dark red**

Characteristics of RBC

1. **Suspension stability**: negative charge of erythrocyte surface and plasma albumin

--**Erythrocyte Sedimentation rate (ESR**)

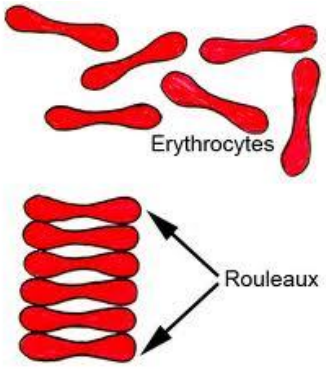
Men: 0~15 mm/h

Women: 0~20 mm/h

--When an inflammatory process is present, the high proportion of fibrinogen in the blood causes red blood cells to stick to each other. The red cells form stacks called '**rouleaux**,' which settle faster

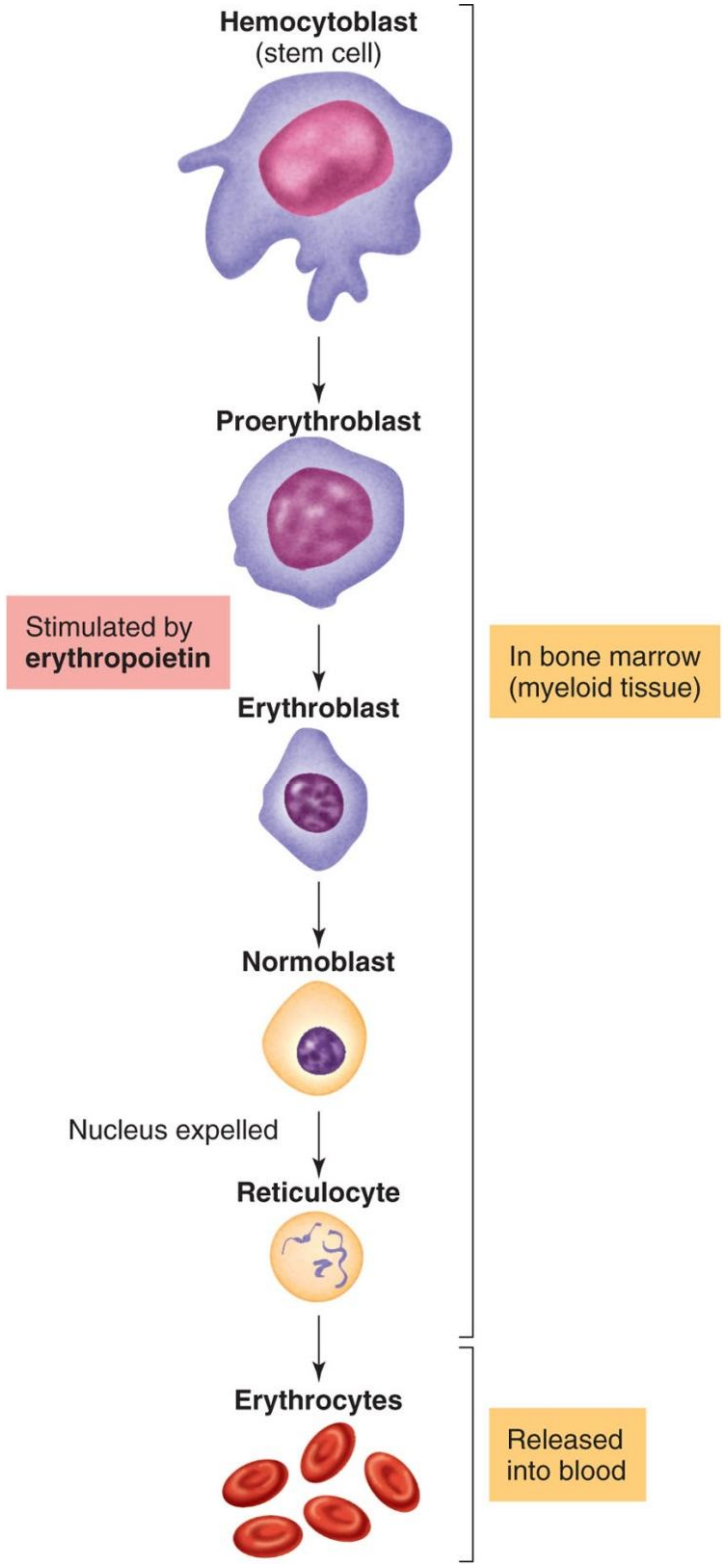
2. **Osmotic fragility**

3. **Plastic deformation**



RBC Production

- RBCs are synthesized in red bone marrow by the process called **Erythropoiesis**
- Erythrocytes and leukocytes develop from same stem cells in bone marrow
  - ***--Hematopoietic stem cells***
- Erythrocyte synthesis stimulated by **erythropoietin (EPO)**

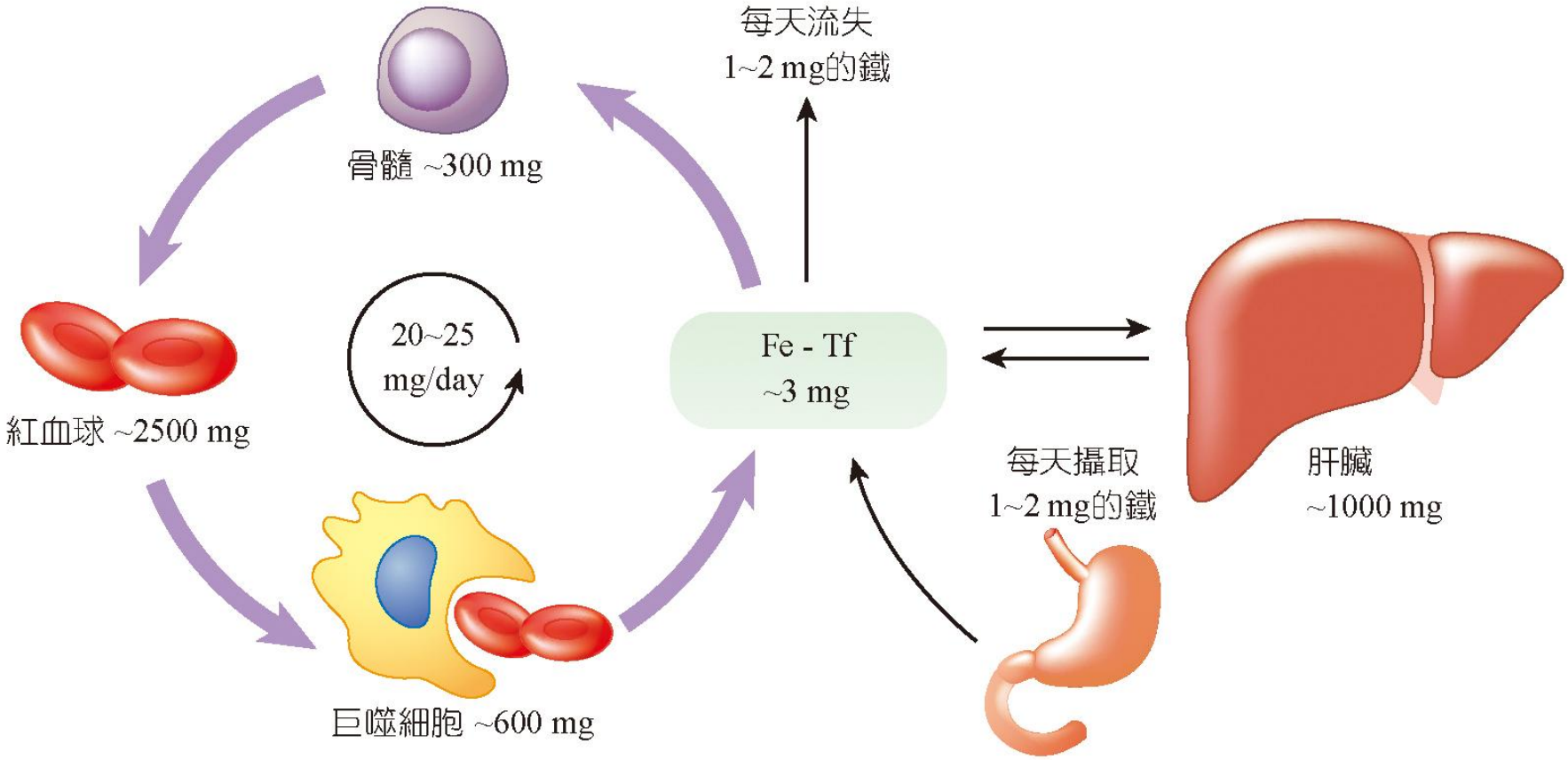


Requirements for RBC Production

- **Iron**
  - --Component of hemoglobin (**heme portion**)
  - --Normal hemoglobin content of blood
    - ***Men: 13–18 gram / dL***
    - ***Women: 12–16 gram / dL***
- **Folic acid**
  - --Necessary for DNA replication, thus cell proliferation
- **Vitamin B_{12}**
  - --Necessary for DNA replication, thus cell proliferation

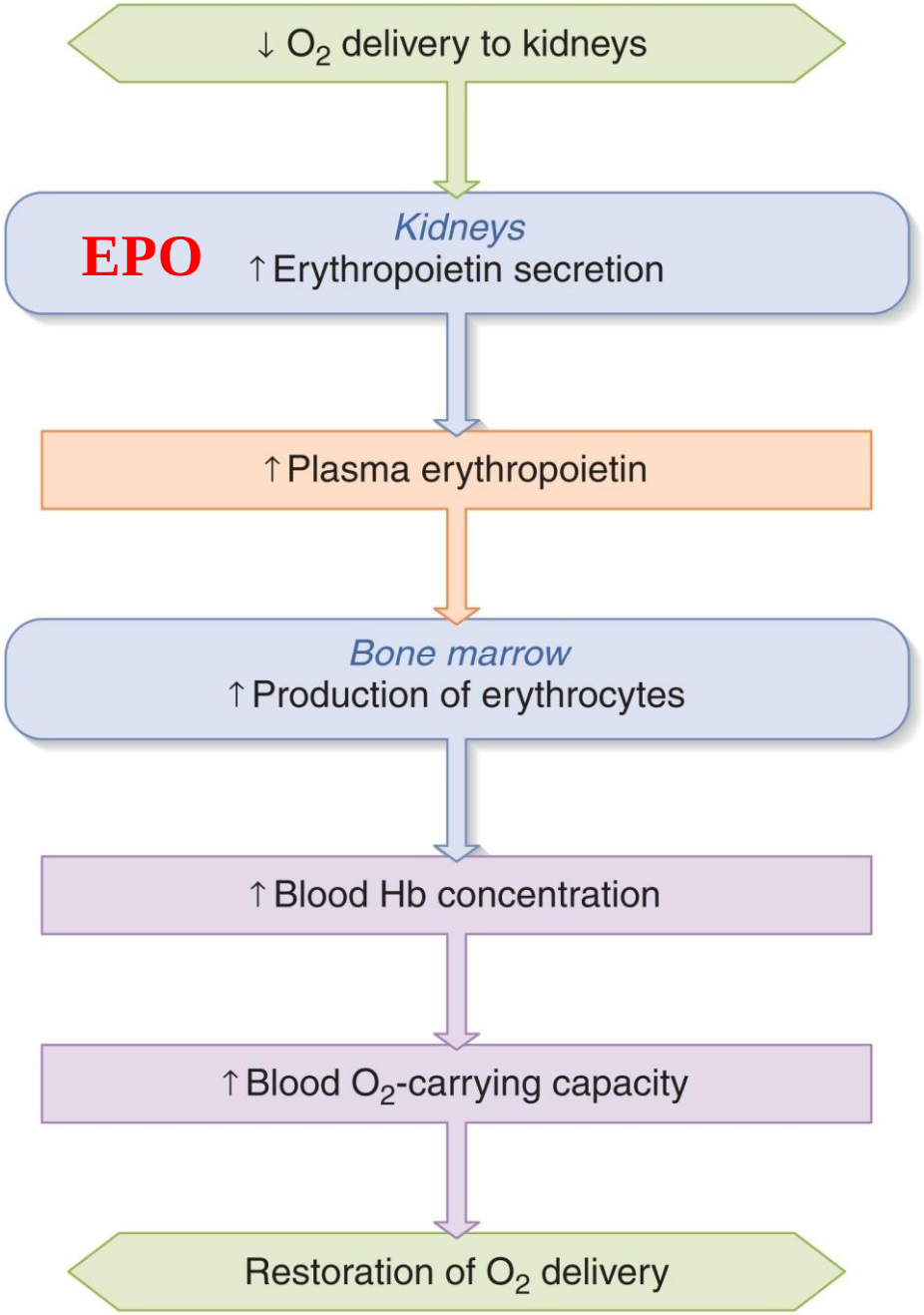
項目		作用
造血 (Hb) 原料	蛋白質	合成血球蛋白
	鐵	合成血基質
紅血球成熟因子	葉酸	促進 DNA 合成
	維生素 B_{12}	促進葉酸利用

- **鐵**是合成血紅素的必需原料，每天用於合成血紅素的鐵含量約為20~25 mg，其中 95% 的鐵來自於體內鐵的再利用，另一部分是從食物中吸收，約 1 mg。
- 食物中的鐵多以 Fe^{3+} 形式存在，經胃酸的作用，將其還原為 Fe^{2+}，進入血漿後與**運鐵蛋白(transferrin)**結合，運至骨髓供血紅素合成



• 圖 10-7　鐵的代謝途徑，以及鐵在各部位的最大利用量或最大儲存量。正常人體內鐵的總量約 3~5 克，其中近 2/3 為血紅素鐵，其餘為在肌紅素、各種酶和輔酶因子中的鐵，以及在血漿中運輸的鐵。

Feedback Control of RBC Production



- **Tissue hypoxia**
  - --High altitude since air has less O2
  - --Anemia
    - RBC production < RBC destruction
  - --Circulatory problems
- **Kidney** response to hypoxia
  - --Release **erythropoietin**
  - --Speeds up development of proerythroblasts into reticulocytes

Clinical Application

- **Renal dialysis** patients whose kidneys have failed have **too little erythropoietin** and need to have synthetic forms administered to maintain normal RBC counts

- **Athletes** who abuse this synthetic form (to increase stamina) can die from the blood becoming **too viscous** which results in clotting, stroke and heart failure

- **Testosterone** also enhances RBC production by increasing EPO production (hence **men have higher hematocrit than women**) so people on hormone replacement need to be very careful with dosing

Filtering and Destruction of Erythrocytes

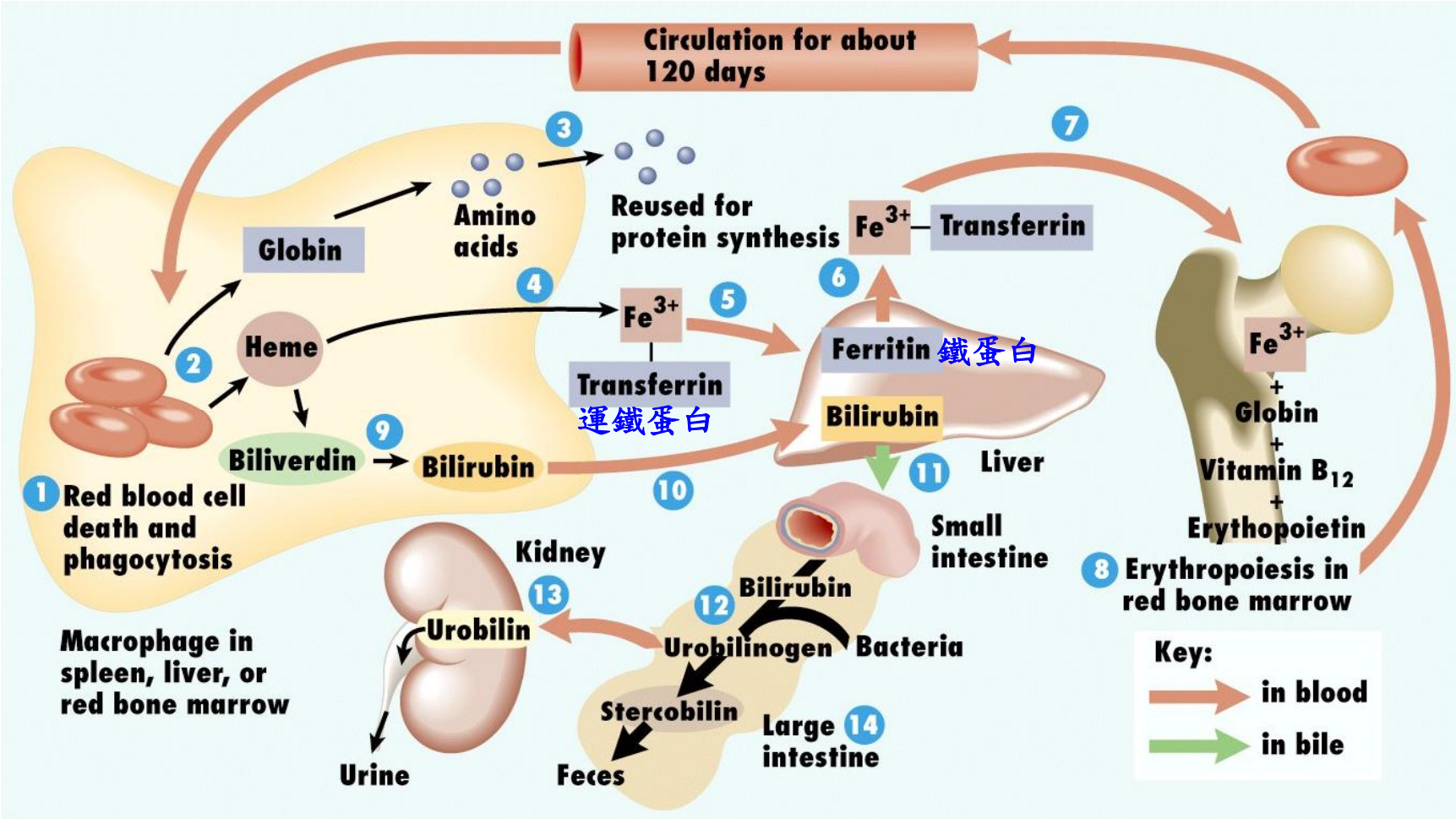
- The **spleen** filters and removes old erythrocytes, and the **liver** metabolizes byproducts from breakdown of erythrocytes ***(globin + heme)***

- **Iron** is recycled for the synthesis of new hemoglobin

- Iron is transported in the blood bound to **transferrin** 運鐵蛋白 to the red bone marrow

- Iron is stored bound to **ferritin** 鐵蛋白 in the liver, spleen and small intestines

Erythrocyte Life Cycle



- **In macrophages of liver or spleen** ***(After iron removed, heme → Bilirubin)***
  - --Globin portion broken down into amino acids & recycled
  - --Heme portion split into iron (Fe^{+3}) and biliverdin (green pigment)
- Biliverdin (green) converted to **bilirubin (yellow)**
  - --Bilirubin secreted by liver into bile

Types of Anemia

Type	Cause	Defect
Aplastic anemia	Toxic chemicals, radiation	Damaged bone marrow
Hemolytic anemia	Toxic chemicals, Malaria	RBC destroyed
Iron deficiency anemia	Dietary lack of iron	Hemoglobin deficient
Pernicious anemia	Inability to absorb vitamin B_{12}	Excess of immature cells
Sickle cell disease	Defective gene	RBC abnormally shaped
Thalassemia	Defective gene	Hemoglobin deficient, RBC short-lived
Hemorrhagic	Bleeding (ulcer)	Loss of RBCs
Renal anemia	Kidney disease	EPO deficient

- The blood test, ***hemoglobin A1c(HbA1c糖化血色素)***, can be used to monitor blood glucose levels in diabetics

貧 血 (Anemia) *Decrease in the oxygen-carrying capacity of blood*

貧血是指各種原因導致的周邊血液紅血球總量低於正常值以下的臨床症狀。臨床上一般以血紅素濃度 (Hb)、紅血球計數 (RBC)、血比容 (Hct) 等指標來檢測貧血的存在和貧血程度。一般標準認為，成年男性 Hb < 14 g/dl，RBC < 4.5×10^6/mm^3、Hct < 0.42/L；女性 Hb < 12 g/dl，RBC < $4.0\times10^6/mm^3$、Hct < 0.37/L 就可診斷為貧血。貧血的臨床表現為臉色蒼白，伴有頭暈、疲倦、心悸等症狀。

貧血具有不同的分類方法，根據紅血球形態可分成：**大細胞性貧血** (macrocytic anemia)、**正常細胞性貧血** (normocytic anemia) 和**小細胞低色素性貧血** (microcytic hypochromic anemia)（表 10-4）；依血紅素濃度可分成：輕度、中度、重度和極重度貧血（表 10-5）。

貧血是臨床上常見的疾病，有許多因素都可能引起貧血。在診斷貧血時，所謂的正常值標準僅僅是相對而言的。貧血患者紅血球計數的降低與血紅素濃度的降低一般是成正比，但是小細胞低色素性貧血的紅血球計數減少比血紅素的減少相對較少，以致貧血較輕時紅血球計數可以不低於正常；而巨母紅血球性貧血 (megaloblastic anemia) 時，血紅素濃度相對地偏高，而紅血球計數偏低。

當失水、水滯留或急性大量失血後，血液總量尚未恢復到正常時，血紅素的濃度不能準確反映貧血的真實程度，因此臨床上要考慮這些因素對貧血的影響。此外，在急性大量血管內溶血時，血漿內含有較高濃度的游離血紅素，這時血紅素測定的結果高於貧血的實際程度。在這種特殊情況下，血比容和紅血球計數更能反映貧血的程度。

表 10-4　貧血的紅血球形態分類

類 型	MCV (fl)	MCH	常見疾病
大細胞性貧血	> 100	32 ~ 35	主要為維生素 B_{12} 和葉酸缺乏或抗癌藥物引起。如：巨母紅血球性貧血 (megaloblastic anemia)，伴網狀紅血球大量增生的溶血性貧血，骨髓增生性異常症候群 (myeloproliferative syndrome abnormalities)， 肝臟疾病等
正常細胞性貧血	80~100	32 ~ 35	病因種類繁多，如：急性失血、慢性疾病引起之貧血，再生不良性貧血 (aplastic anemia)，純紅血球再生不良症 (pure red cell aplasia)，骨髓疾病性貧血等
小細胞低色素性貧血	< 80	< 32	如：缺鐵性貧血，海洋性貧血、鐵粒母紅血球性貧血 (sideroblastic anemia)，血球蛋白生成障礙性貧血等

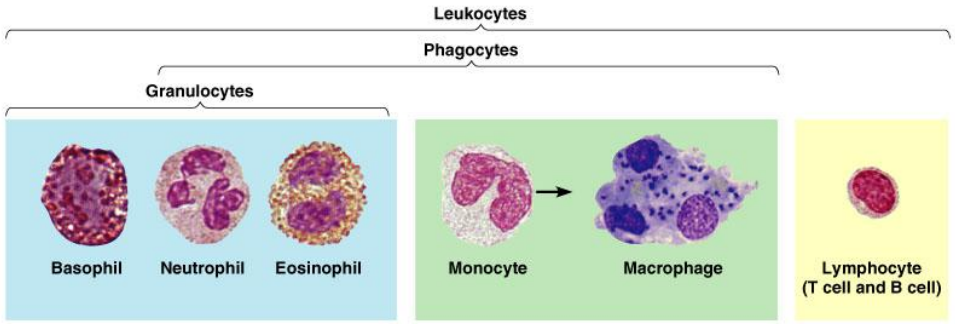
註：MCV ＝血球平均體積 (mean cell volume)；MCH ＝血球平均血紅素含量 (mean cell hemoglobin)。

表 10-5　貧血的嚴重度劃分標準

血紅素濃度 (g/dl)	< 3	3~	6~	9~
貧血嚴重程度	極重度	重度	中度	輕度

WBCs (Leukocytes)

- Leukocytes (white blood cells) function in the **defense of the body**



  --Immune system

  --Defend against pathogens

  --Identify and destroy cancer cells

  --Phagocytosis of debris from dead or injured cells

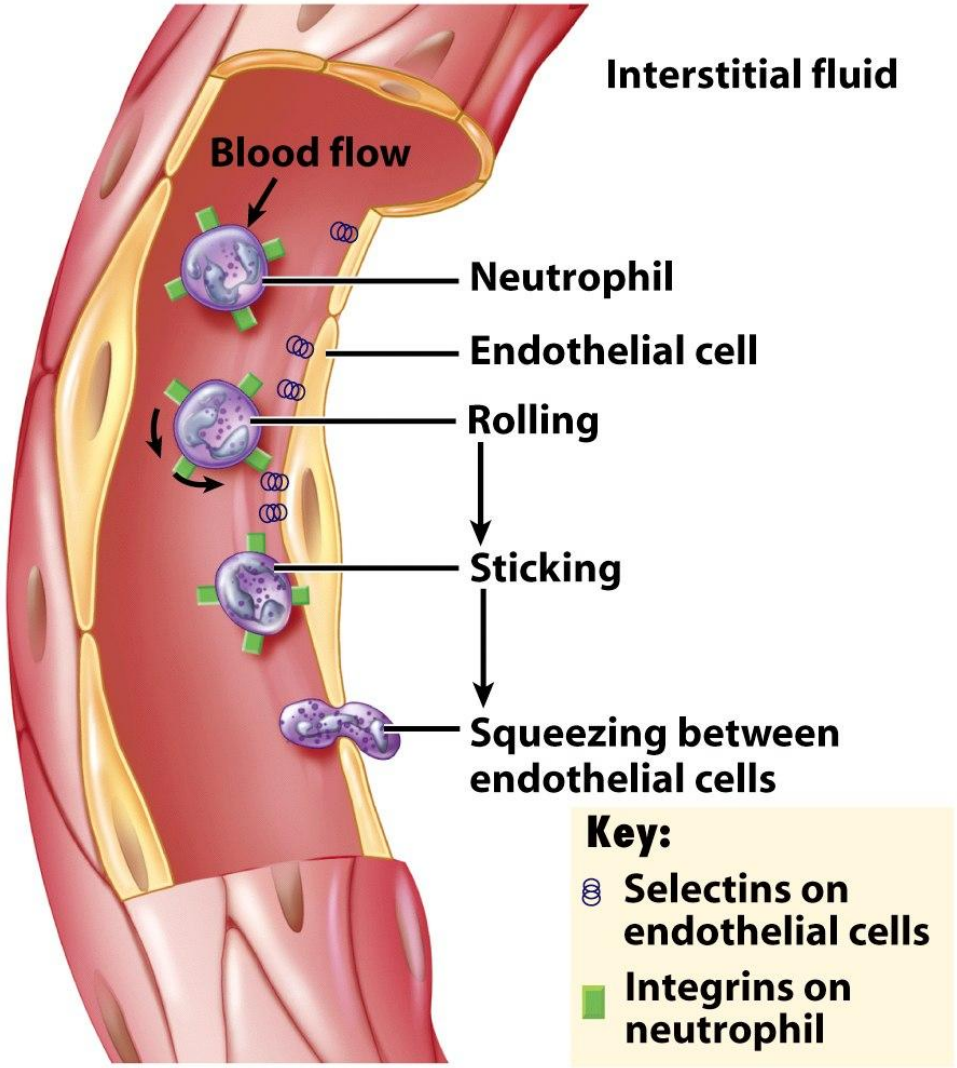
- They can be divided into **granulocytes** and **agranulocytes**

  --Granulocytes—cytoplasmic granules: Neutrophils, Eosinophils and Basophils

  --Agranulocytes—no cytoplasmic granules: Monocytes and Lymphocytes

Function of WBCs(Leukocytes)

Defense of the Body



- WBCs leave the blood stream by ***emigration***
- Some WBCs, particularly neutrophils and macrophages, are active in ***phagocytosis***
- The chemical attraction of WBCs to a disease or injury site is termed ***chemotaxis***

Neutrophil

Polymorphonuclear leukocytes (PMNs)

Leukocyte morphology	Functions in immunity
 Neutrophil	Engulf microorganisms, abnormal cells, and foreign particles by phagocytosis

Red and blue staining granules

- 50–80% of leukocytes in blood
- Phagocyte
- Circulate in blood 7–10 hours
- Migrate to tissues for a few days
- Numbers increase during infections

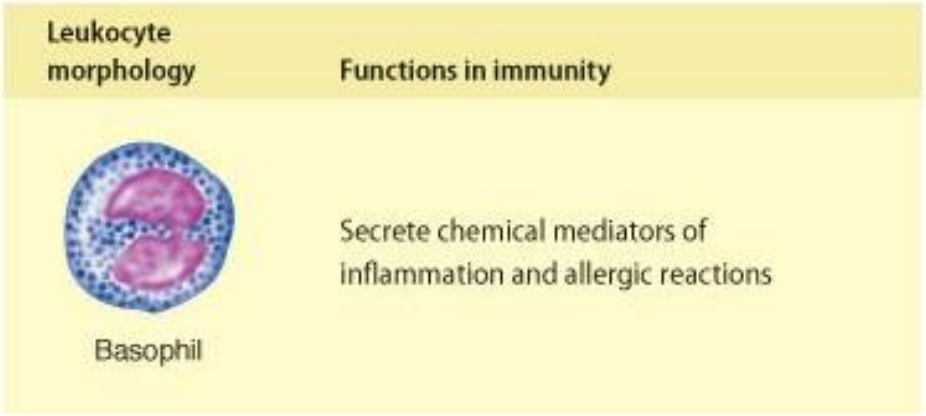
Eosinophil

Leukocyte morphology	Functions in immunity
 Eosinophil	Secrete enzymes that kill parasites; contribute to tissue damage in allergic reactions

Red staining granules

- 1–4% of leukocytes
- Phagocytes (but not main mechanism of action)
- Release histaminase, phagocytize antigen-antibody complexes
- Defend against parasitic invaders (e.g., parasitic worms)
- Granules contain toxic molecules that attack parasites

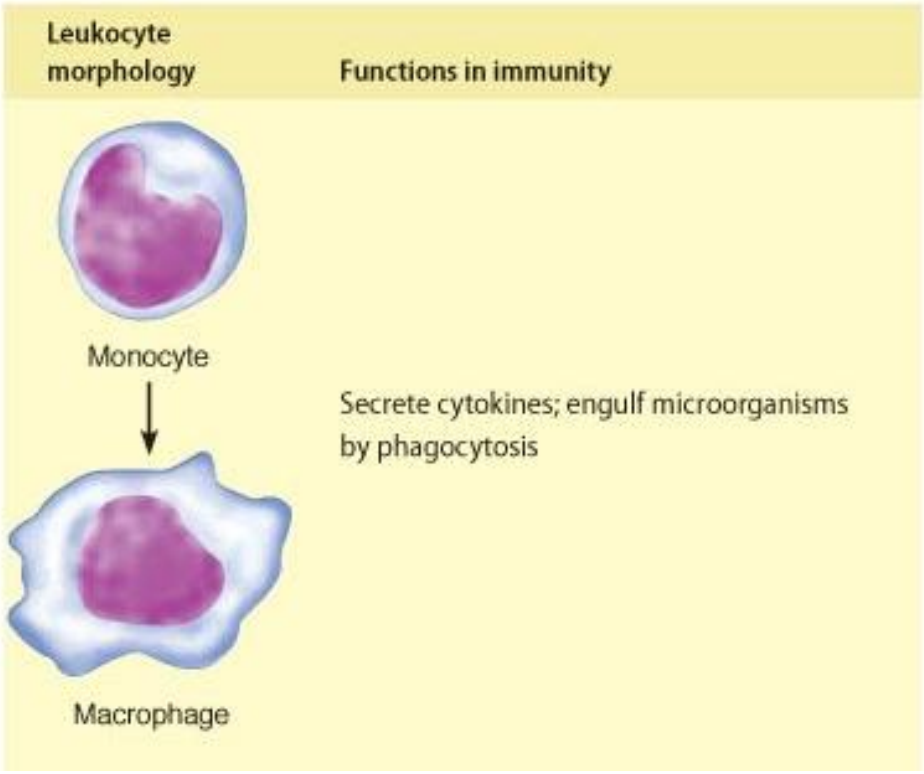
Basophil



Blue staining granules

- <1% of leukocytes
- Nonphagocytic
- May defend against large parasites by releasing toxic substances
- Contribute to allergic reactions
  - --Histamine
  - --Heparin
  - --5-HT

Monocyte



- 5% of leukocytes
- Phagocytes
- New monocytes circulate in blood few hours
- Migrate to tissues and become macrophages
  - --Wandering macrophages
  - --Fixed macrophages

Lymphocyte

Leukocyte morphology	Functions in immunity
 Lymphocyte	Plasma cells (mature form of B cells) secrete antibodies Helper T cells secrete cytokines that activate multiple cell types: cytotoxic T cells secrete factors that lead to the death of infected cells and tumor cells Null cells called natural killer cells secrete factors that lead to the death of infected cells and tumor cells

*Morphological features shown are characteristic of preparation with Wright's stain.

- 30% of leukocytes
- 99% of interstitial fluid cells
- Three types
  - --B lymphocytes (B cells)
  - --T lymphocytes (T cells)
  - --Null cells (NK cells)

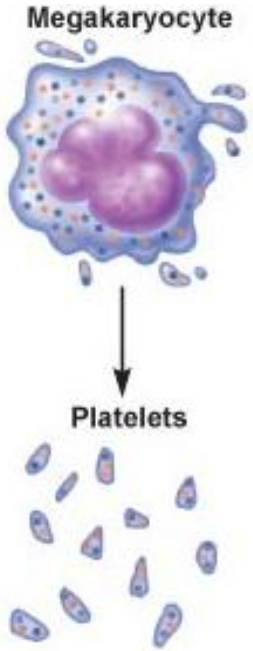
Differential WBC Count

- **Complete blood count(CBC)** is total RBC, WBC, platelet counts, differential WBC, hematocrit and hemoglobin measurements (screens for anemia and infection)
- **Differential WBC count** is detection of changes in numbers of circulating WBCs (percentages of each type)
  --Indicates infection, poisoning, leukemia, chemotherapy, parasites or allergy reaction
- **Normal WBC counts**
  --Neutrophils 60-70% (up if bacterial infection)
  --Lymphocyte 20-25% (up if viral infection)
  --Monocytes 3-8 % (up if fungal/viral infection)
  --Eosinophil 2-4 % (up if parasite or allergy reaction)
  --Basophil <1% (up if allergy reaction or hypothyroid)

表 10-6　白血球正常值及主要功能

白血球種類	絕對數 ($\times 10^9$/L)	百分比 (%)	主要功能
白血球	4.0~10.0		
嗜中性球（桿狀核）	0.04~0.5	1~5	1. 具有吞噬作用，參與急性炎症反應 2. 具有趨化作用
（分葉核）	2.0~7.0	50~70	
嗜酸性球	0.02~0.5	0.5~5	1. 參與免疫作用，吞噬被抗體標示的物質 2. 限制嗜鹼性球，限制立即型過敏反應 3. 參與寄生蟲免疫反應
嗜鹼性球	0.0~1.0	0.5~1	1. 釋放肝素，防止血液凝固 2. 釋放組織胺參與過敏反應
單核球	0.12~0.8	3~8	1. 具有極強的吞噬作用 2. 參與慢性炎症反應，釋放內生性致熱原，引起發熱
淋巴球	0.8~4.0	20~40	1. T 淋巴球參與細胞性免疫 2. B 淋巴球參與體液性免疫

Platelets (Thrombocytes)

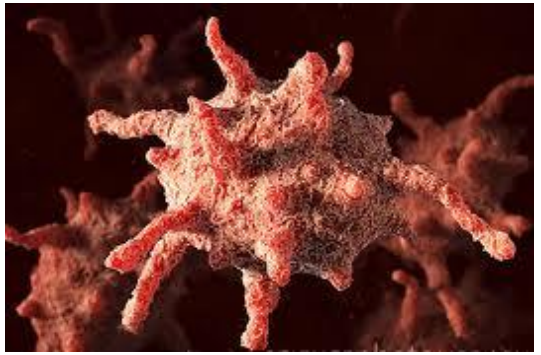


- **Platelets are cytoplasmic fragments derived from megakaryocytes, also called thrombocytes**

- **As cell fragments there are no organelles, but they do have granules and are important in blood clotting**
  --A ***clot*** is a gel consisting of a network of insoluble protein fibers (**fibrin**) in which blood cells are trapped
  --The chemicals involved in clotting are known as **coagulation (clotting) factors**; most are in blood plasma, some are released by platelets, and one is released from damaged tissue cells

- The granules contain secretory products: **ADP, Serotonin and Epinephrine, etc.**

Short life span: 5-9 days



Coagulation (clotting) Factors

編號	同義名	合成部位	主要活化物	主要抑制物	主要功能
I	纖維蛋白原 (fibrinogen)	肝細胞			形成纖維蛋白
II	凝血酶原 (prothrombin)	肝細胞（需維生素 K）	凝血酶原複合物	抗凝血酶 III	凝血酶促進生成纖維蛋白；啓動 V-VIII-XI-XIII-血小板
III	組織因子 (tissue factor, TP)；組織凝血質 (tissue thromboplastin)	內皮細胞			外源性凝血的啓動因子
IV	鈣離子 (Ca^{2+})	—			輔因子
V	前加速素 (proaccelerin)	內皮細胞、血小板	凝血酶 + Xa	活化蛋白質 C	加速 Xa
VII	前轉化素 (proconvertin)	肝細胞（需維生素 K）	Xa	組織因子途徑抑制物 (TFPI)、抗凝血酶 III	III-VII 啓動 X 和 XI
VIII	抗血友病因子 (antihemophilic factor, AHF)	肝細胞	凝血酶 + Xa	不穩定，自發失活；活化蛋白質 C	加速 IXa

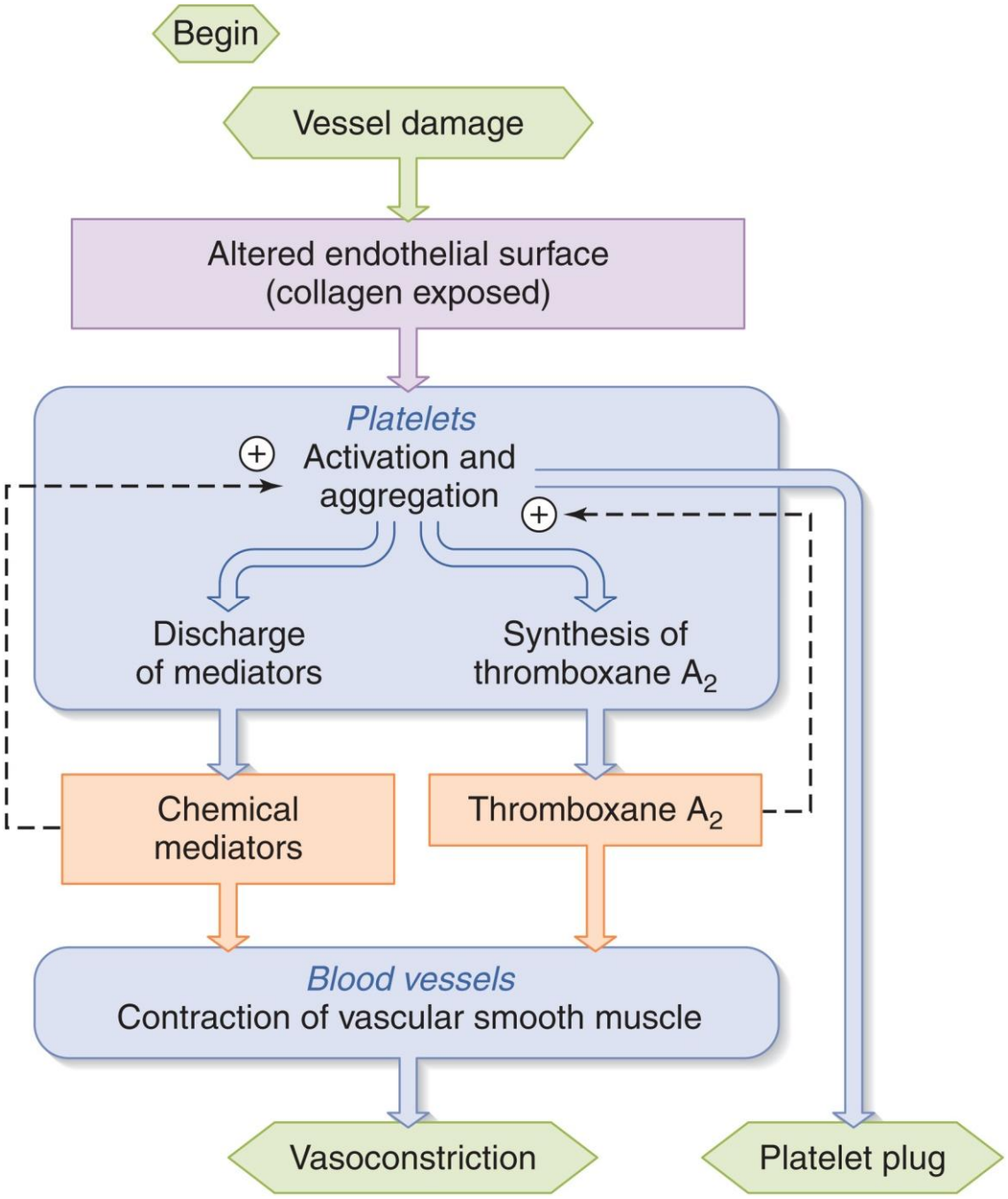
- 除 Ca^{2+} 與磷脂質外，其餘的因子全是**蛋白質**
- III因子(factor III) 只存在於血管外，其餘的凝血因子均存在於血漿中，多數在肝臟中合成，其中有些凝血因子如**II、VII、IX、X因子**的合成還需要**維生素K** 參與

編號	同義名	合成部位	主要活化物	主要抑制物	主要功能
IX	血漿凝血質成分 (plasma thromboplastin component, PTC)；耶誕因子 (Christmas factor)	肝細胞（需維生素 K）	XI+VIIa- 組織因子複合物	抗凝血酶 III	啓動 Xa
X	Stuart-Prower 因子	肝細胞（需維生素 K）	VIIa-III 複合物、IXa-VIIIa 複合物	抗凝血酶 III，TFPI	形成凝血酶原活化物
XI	血漿凝血質前質 (plasma thromboplastin antecedent, PTA)	肝細胞	XIIa、凝血酶	α 抗胰蛋白酶 抗凝血酶 III	啓動 IXa
XII	Hageman 因子；接觸因子 (contact factor)	肝細胞	膠原蛋白、帶負電異物表面	抗凝血酶 III	啓動 XIa
XIII	纖維蛋白穩定因子 (fibrin stabilizing factor)	肝細胞、血小板	凝血酶		使纖維蛋白單體聚合成纖維蛋白網
	高分子量激肽原 (HWMK)	肝細胞			促進 XIIa
	前激肽釋放酶 (prekallikrein)	肝細胞	XIIIa	抗凝血酶 III	啓動 XIIa

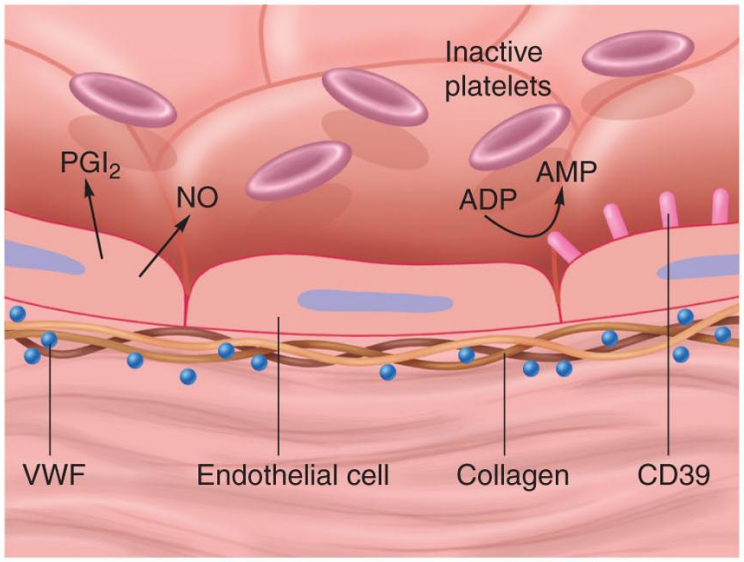
註：目前認為 VI 因子與活化的 V 因子是相同的物質，因此被除名。

Blood Clotting

- **Hemostasis = stop bleeding**
- **Hemostasis is a 3-step process:**
  1. ***Vascular spasm (Vasoconstriction)***
  2. ***Formation of platelet plug***
  3. ***Blood coagulation (Formation of fibrin protein web)***



1. Vascular Spasm



- Intact endothelium secretes **prostacyclin (PGI_2)** and **NO:** ***vasodilate and inhibit platelet aggregation***, and **CD39:** ***breaks down ADP into AMP and P_i to inhibit platelet aggregation further***
- Vascular spasm results from damage to the blood vessel. The damaged tissue secretes factors (**5-HT**, **TXA_2**) that cause contraction
- Vessels constrict to minimize blood loss (this is protective to maintain BP)
- Endothelial layer becomes **sticky** to aid in the clotting process

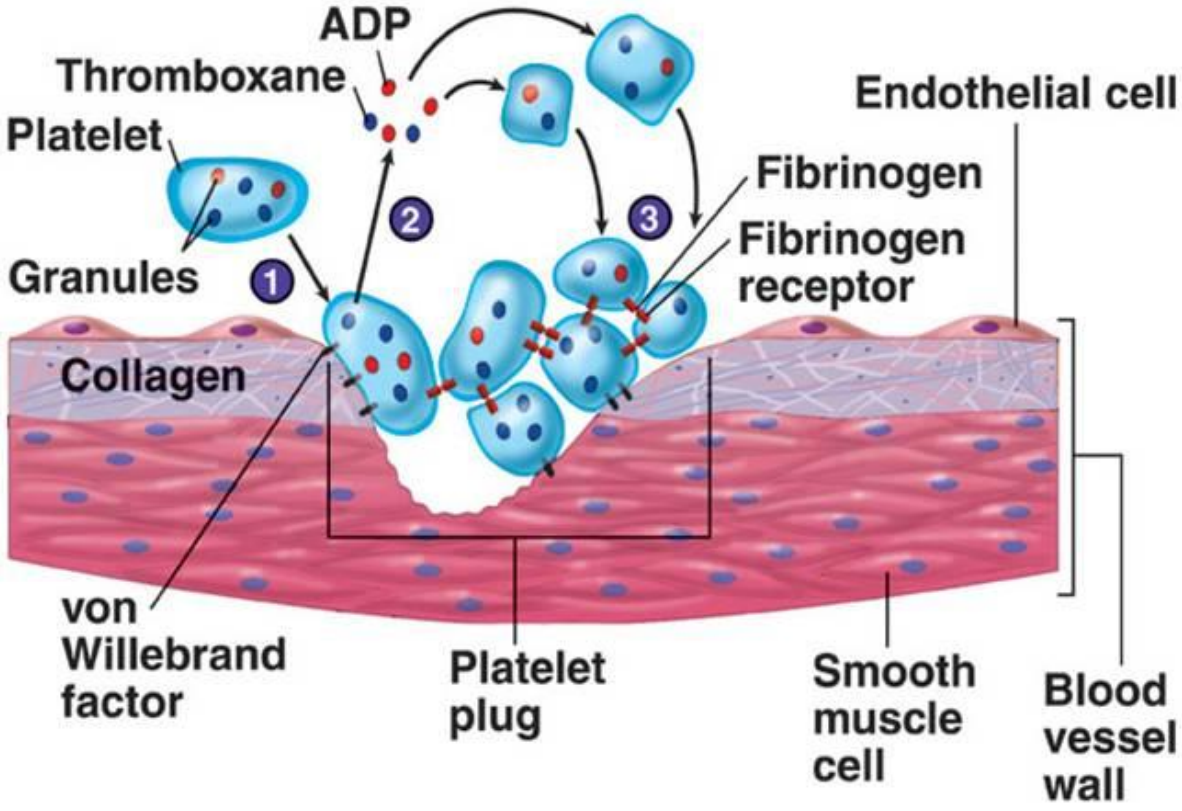
2. Platelet Plug Formation

- The platelet plug forms around site of vessel damage and is started by the **sticky endothelium** at the damaged site
- The plug results in a **decreased blood loss** (maintains BP)
- The plug formation is necessary for <u>production of a blood clot</u>

(1) Platelet adhesion

(2) Platelet release reaction

(3) Platelet aggregation



2. Platelet Plug Formation

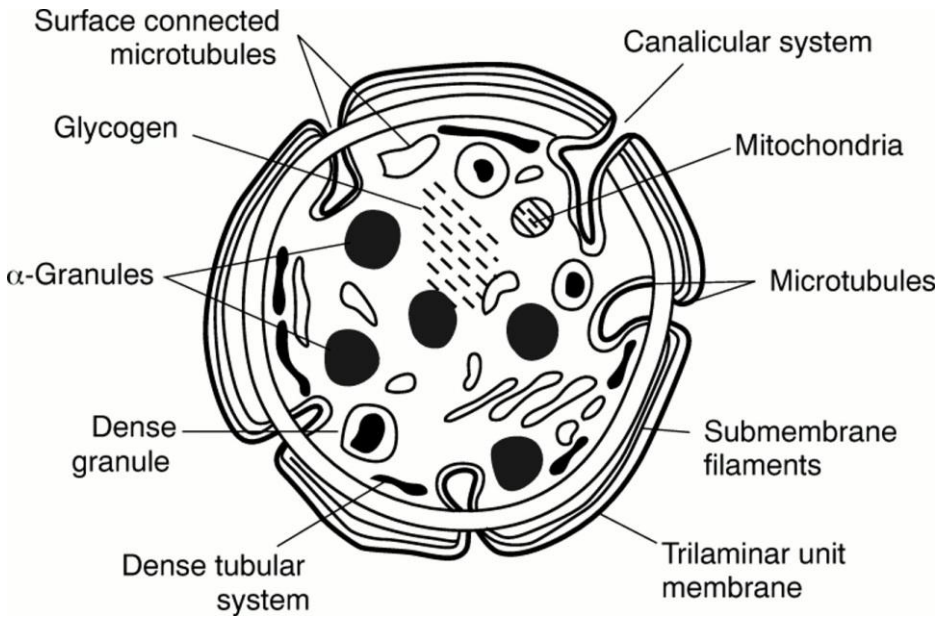
- Platelets store a lot of chemicals in granules needed for platelet plug formation

--Alpha granules

- ✓ **Clotting factors**
- ✓ **Platelet-derived growth factor (PDGF)**
  - – cause proliferation of vascular endothelial cells, smooth muscle & fibroblasts to repair damaged vessels

--Dense granules

- ✓ **ADP**, **ATP**, **Ca^{+2}**, **serotonin**, fibrin-stabilizing factor, & enzymes that produce **TXA_2**



- Steps in the process

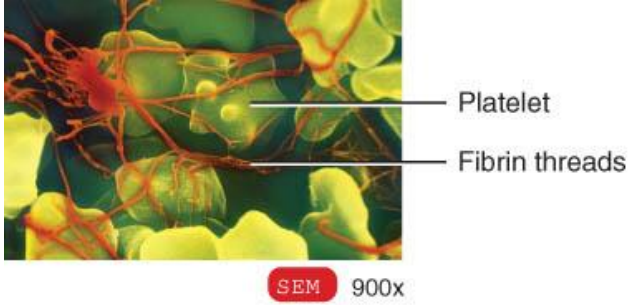
(1) Platelet adhesion

(2) Platelet release reaction

(3) Platelet aggregation

(1) Platelet Adhesion

- Platelets stick to exposed collagen underlying damaged endothelial cells in vessel wall

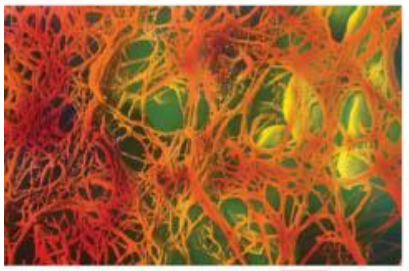


SEM 900x

(a) Early stage

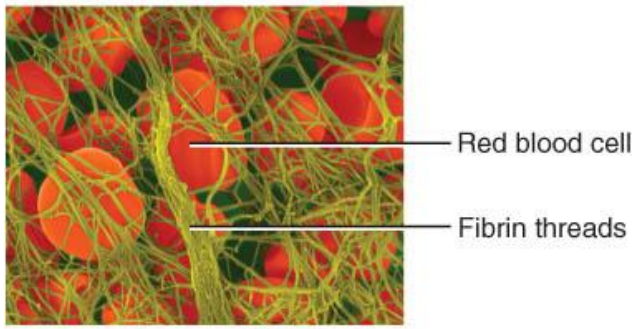
SEM 900x

(b) Intermediate stage



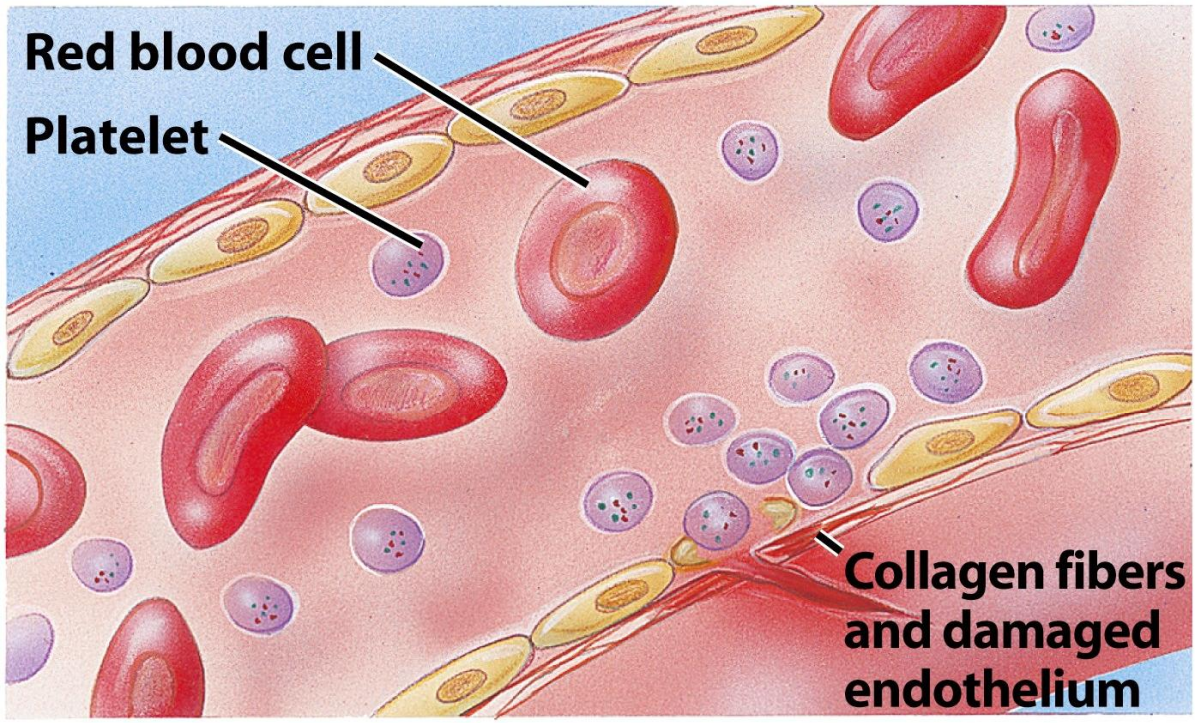
SEM 900x

(c) Late stage



SEM 1600x

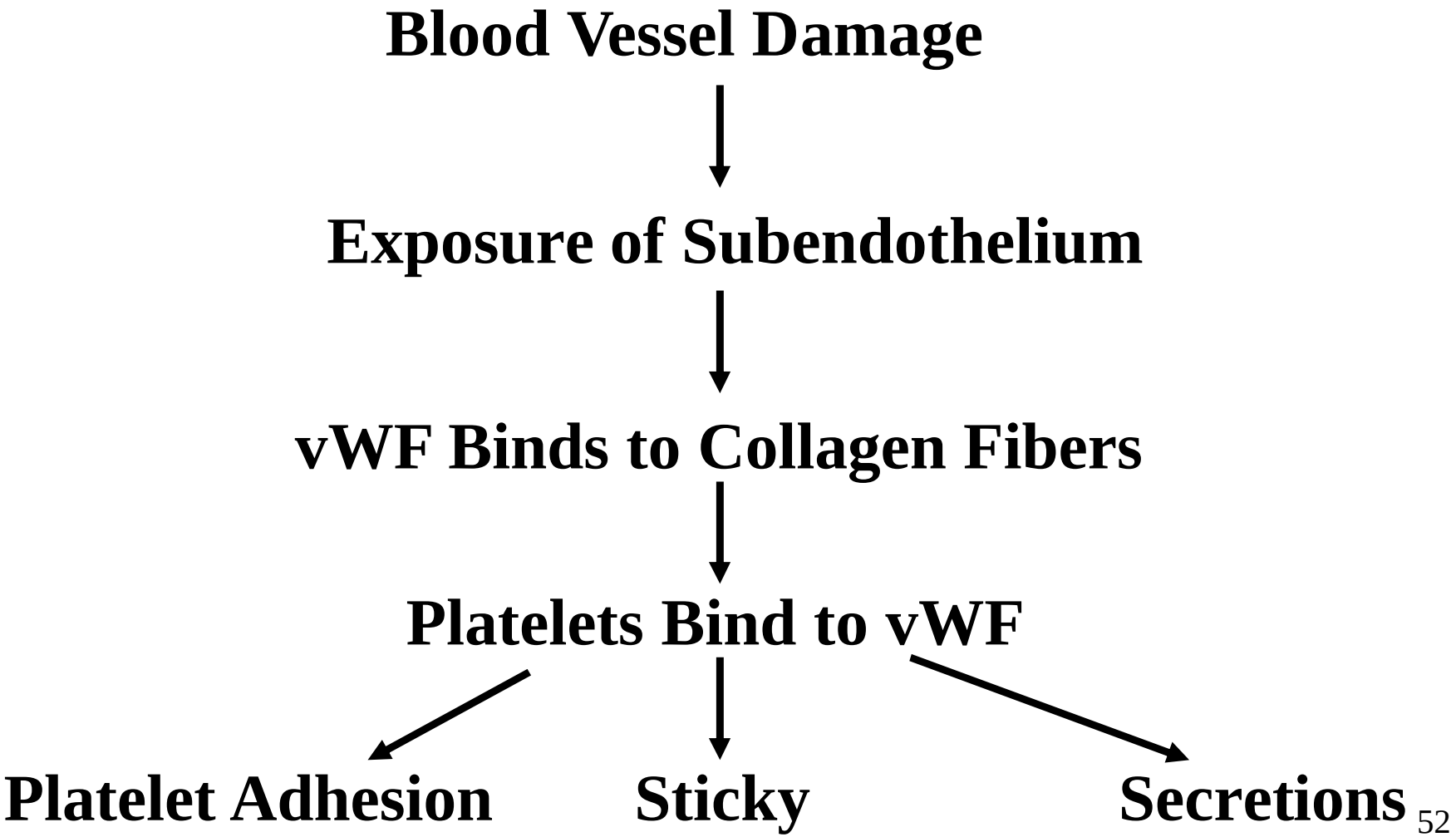
(d) Red blood cells trapped in fibrin threads



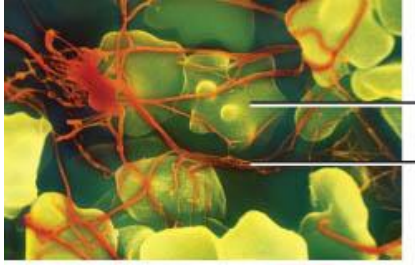
1 Platelet adhesion

(1) Platelet Adhesion

血小板黏著需要血小板膜上醣蛋白(glycoprotein)、內皮下膠原蛋白和血漿von Willebrand 因子(vWF) 的參與

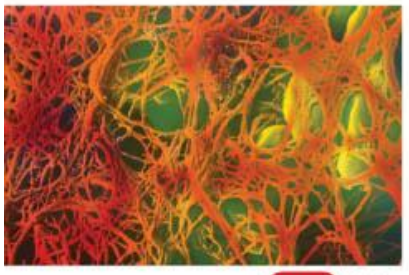


(2) Platelet Release Reaction

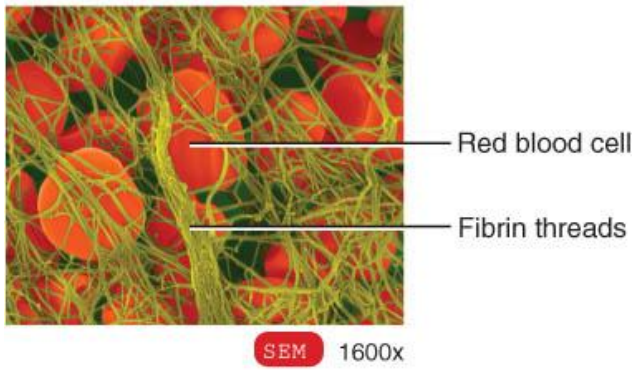


(a) Early stage

(b) Intermediate stage

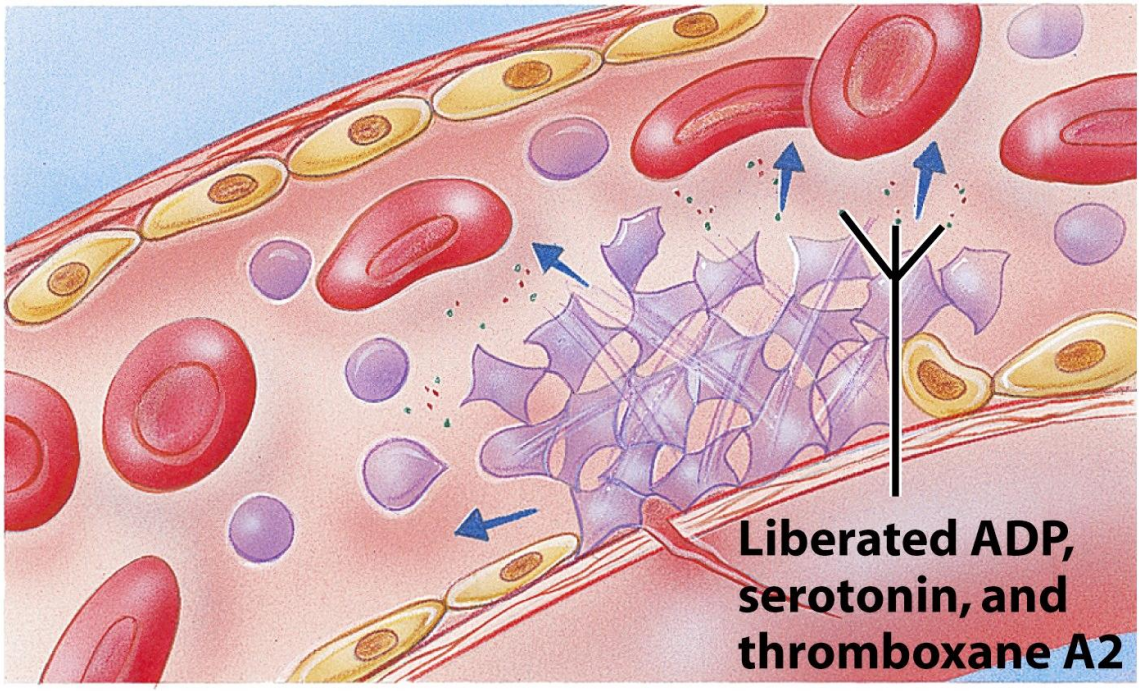


(c) Late stage



(d) Red blood cells trapped in fibrin threads

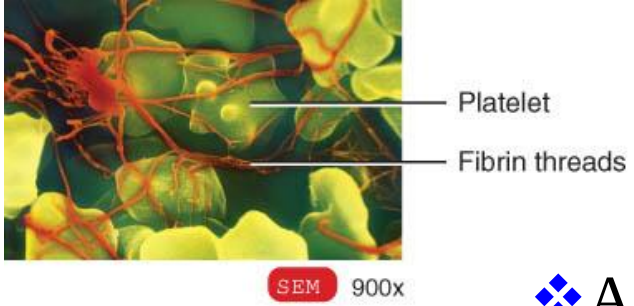
- Platelets activated by adhesion (platelet activation)
- Extend projections to make contact with each other
- Release **TXA_2 & ADP** activating platelets aggregation
- **5-HT, EPi & TXA_2** are vasoconstrictors decreasing blood flow through the injured vessel



2 Platelet release reaction

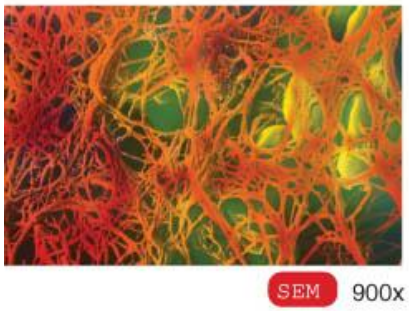
(3) Platelet Aggregation

- Activated platelets stick together and activate new platelets to form a mass called a platelet plug
- Plug reinforced by fibrin threads formed during clotting process

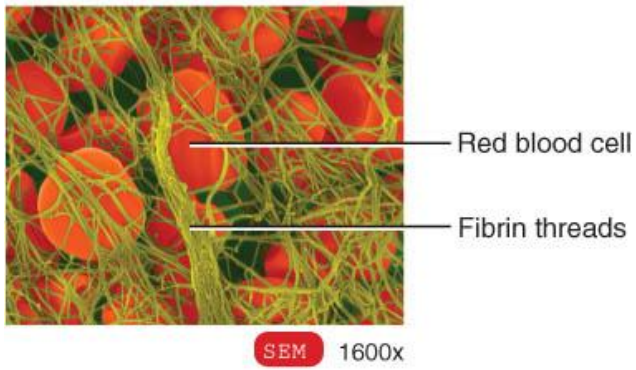


(a) Early stage

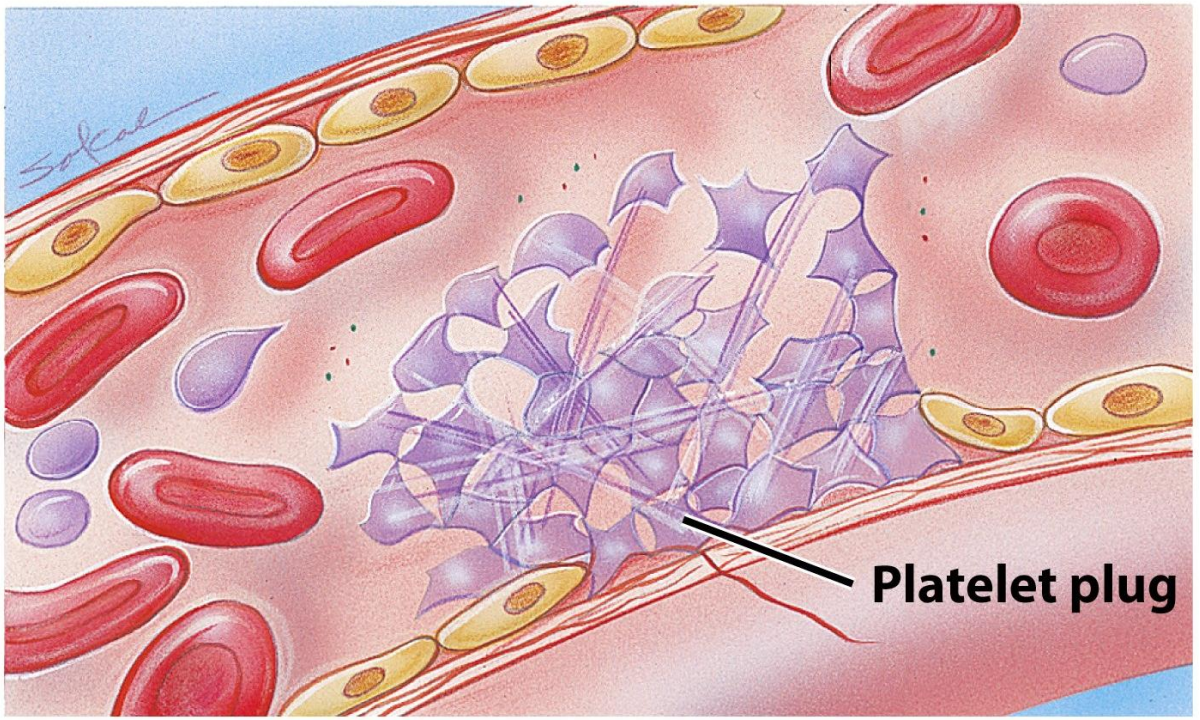
(b) Intermediate stage



(c) Late stage



(d) Red blood cells trapped in fibrin threads



3 Platelet aggregation

Role of Arachidonic Acid in Platelet Aggregation

Healthy Endothelial Cells

Arachidonic Acid/platelets

↓

Prostacyclin (Prostaglandin I_2)

cAMP ↓ & Ca ↑

Inhibits platelet aggregation

Adhered Platelets

Arachidonic Acid/platelets

↓

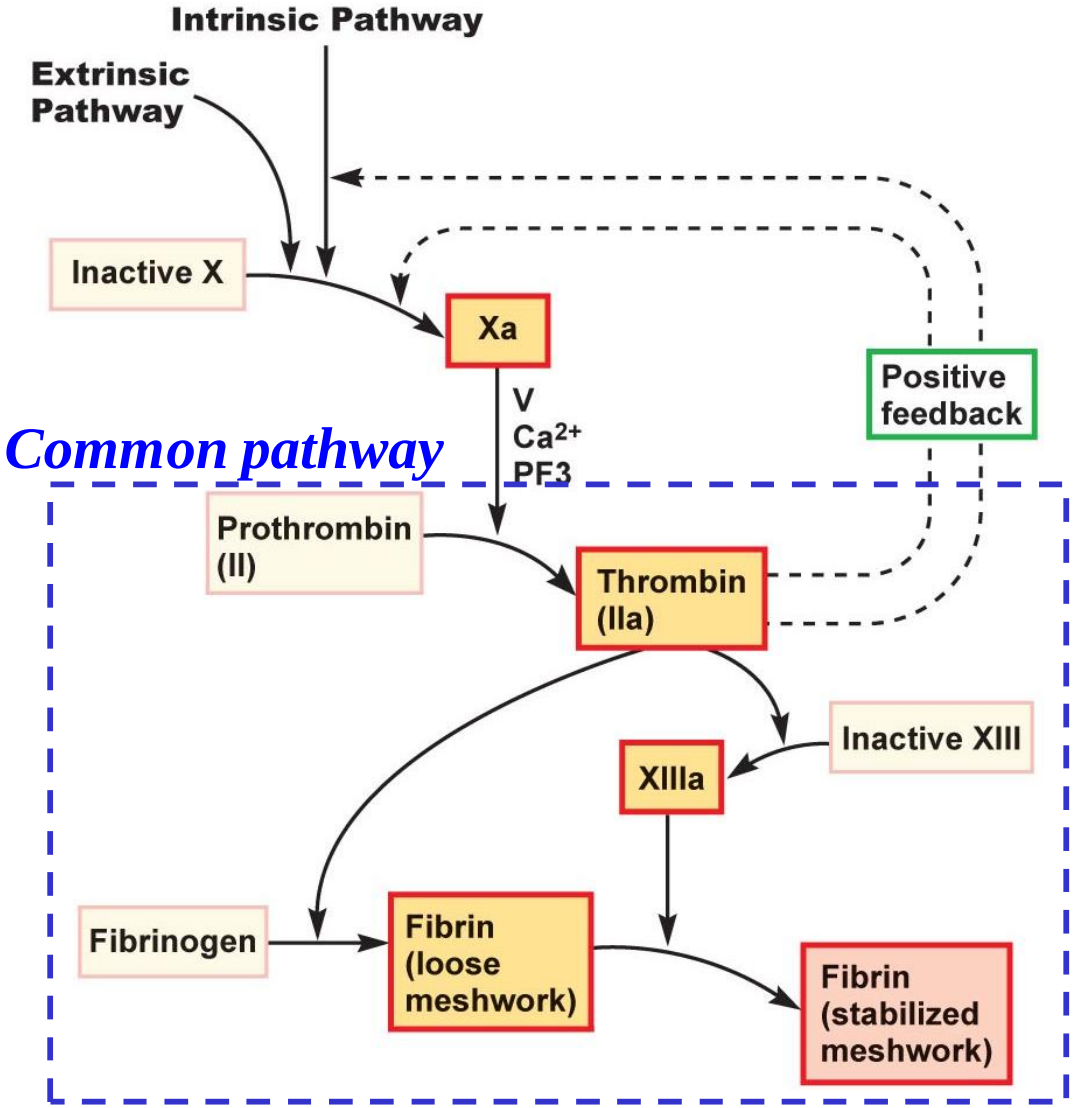
Thromboxane A_2 (TXA_2)

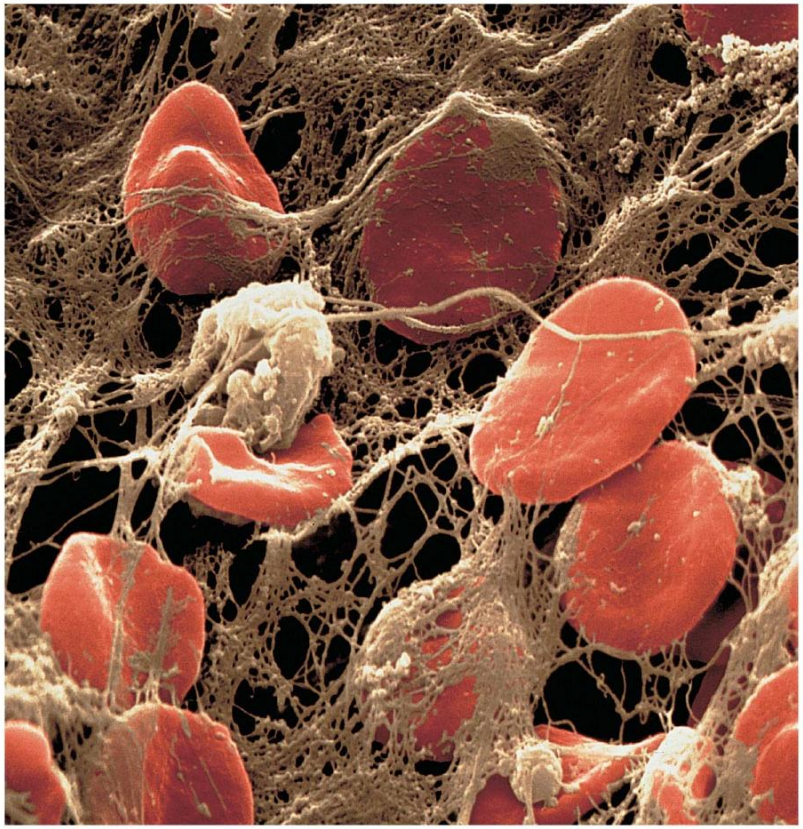
cAMP ↑ & Ca↓

Stimulates platelet aggregation and secretions

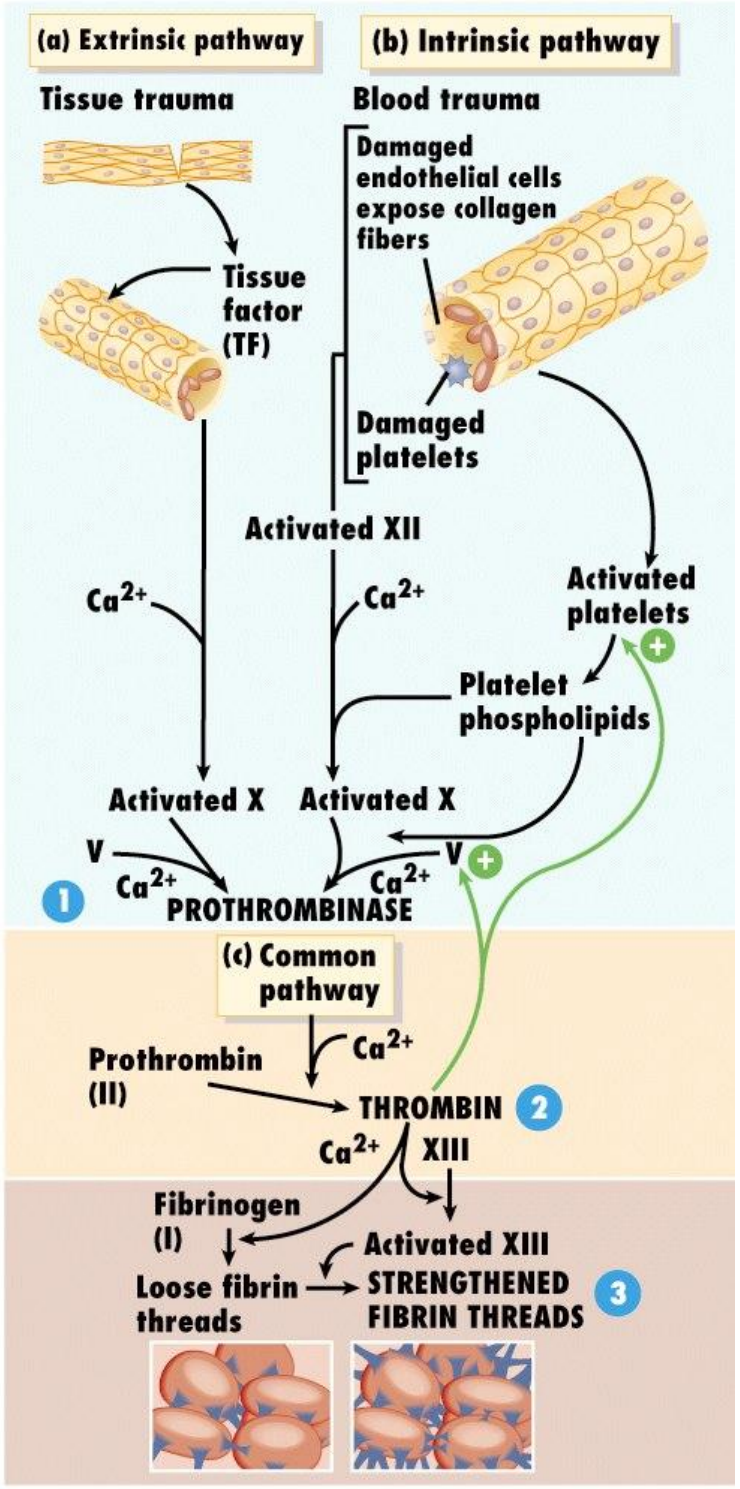
Blood Clotting = Coagulation

血液由流體狀態經一系列酶促反應轉變為不能流動的膠凍狀凝塊過程(clotting cascade)





Blood (Fibrin) Clot

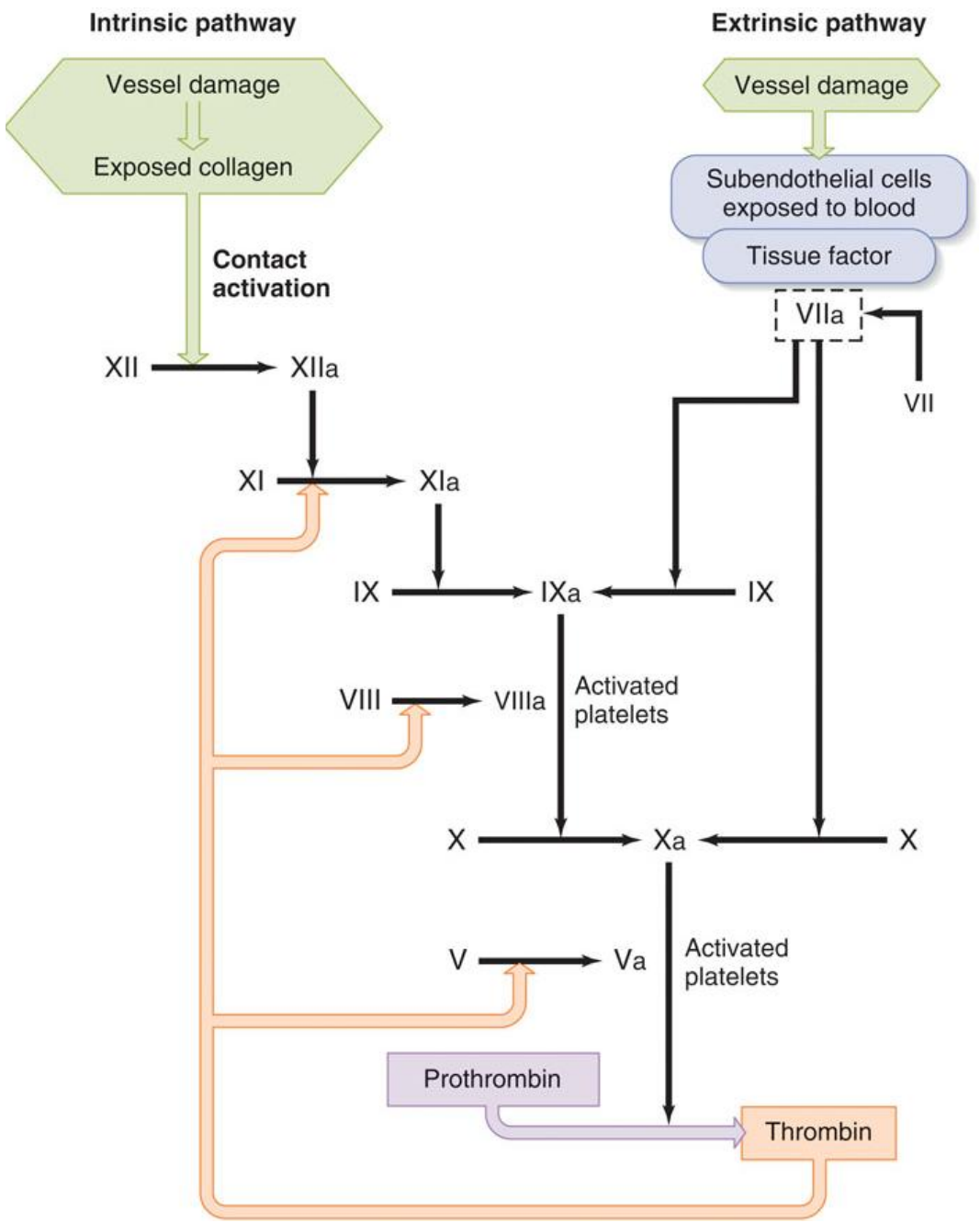


Clotting Cascade

- Prothrombinase is formed by either the **intrinsic** or **extrinsic pathway**
- Final common pathway produces **fibrin clot (blood clot)**

1. ***Formation of prothrombinase (prothrombin activator)***
2. ***Conversion of prothrombin (II) into thrombin (IIa)***
3. ***Conversion of soluble fibrinogen (I) into insoluble fibrin (Ia)***

Extrinsic & Intrinsic Pathway

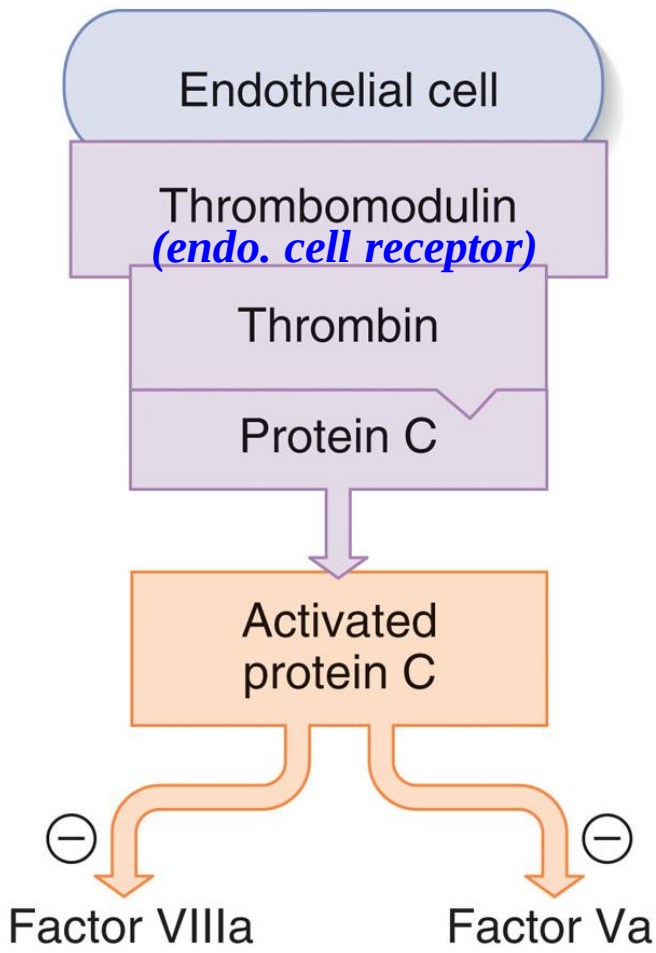


- **Extrinsic pathway:**
  - --Fewer steps then intrinsic and occurs rapidly
  - --Tissue factor (TF) or thromboplastin (III factor) leaks into the blood from cells ***outside (extrinsic to)*** blood vessels and initiates formation of prothrombinase
- **Intrinsic pathway:**
  - --More complex and slower than extrinsic
  - --Activators are either in direct contact with blood or contained ***within (intrinsic to)*** the blood
  - --Outside tissue damage not needed

Clotting Factors

Table 12–13	Official Designations for Clotting Factors, Along with Synonyms More Commonly Used
	Factor I (fibrinogen)
	Factor Ia (fibrin)
	Factor II (prothrombin)
	Factor IIa (thrombin)
	Factor III (tissue factor, tissue thromboplastin)
	Factor IV (Ca^{2+})
	Factors V, VII, VIII, IX, X, XI, XII, and XIII are the inactive forms of these factors; the active forms add an "a" (e.g., factor XIIa). There is no factor VI.
	Platelet factor (PF)

Table 12–14	Actions of Thrombin
Procoagulant	Cleaves fibrinogen to fibrin
	Activates clotting factors XI, VIII, V, and XIII
	Stimulates platelet activation
Anticoagulant	Activates protein C, which inactivates clotting factors VIIIa and Va

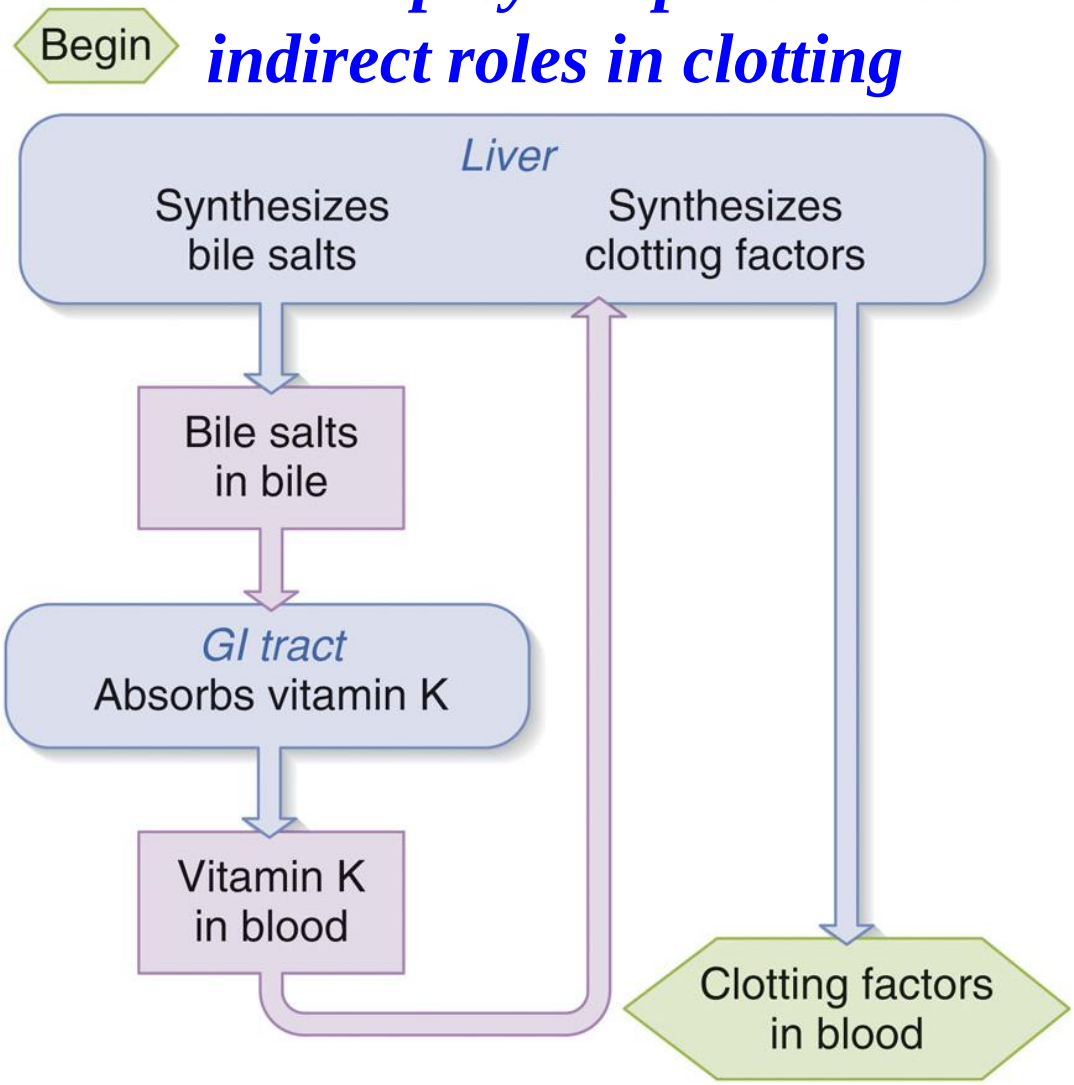


Anticoagulant action

In an uninjured vessel, thrombin bound to thrombomodulin activates protein C, which blocks the clotting response

Role of Vitamin K in Clotting

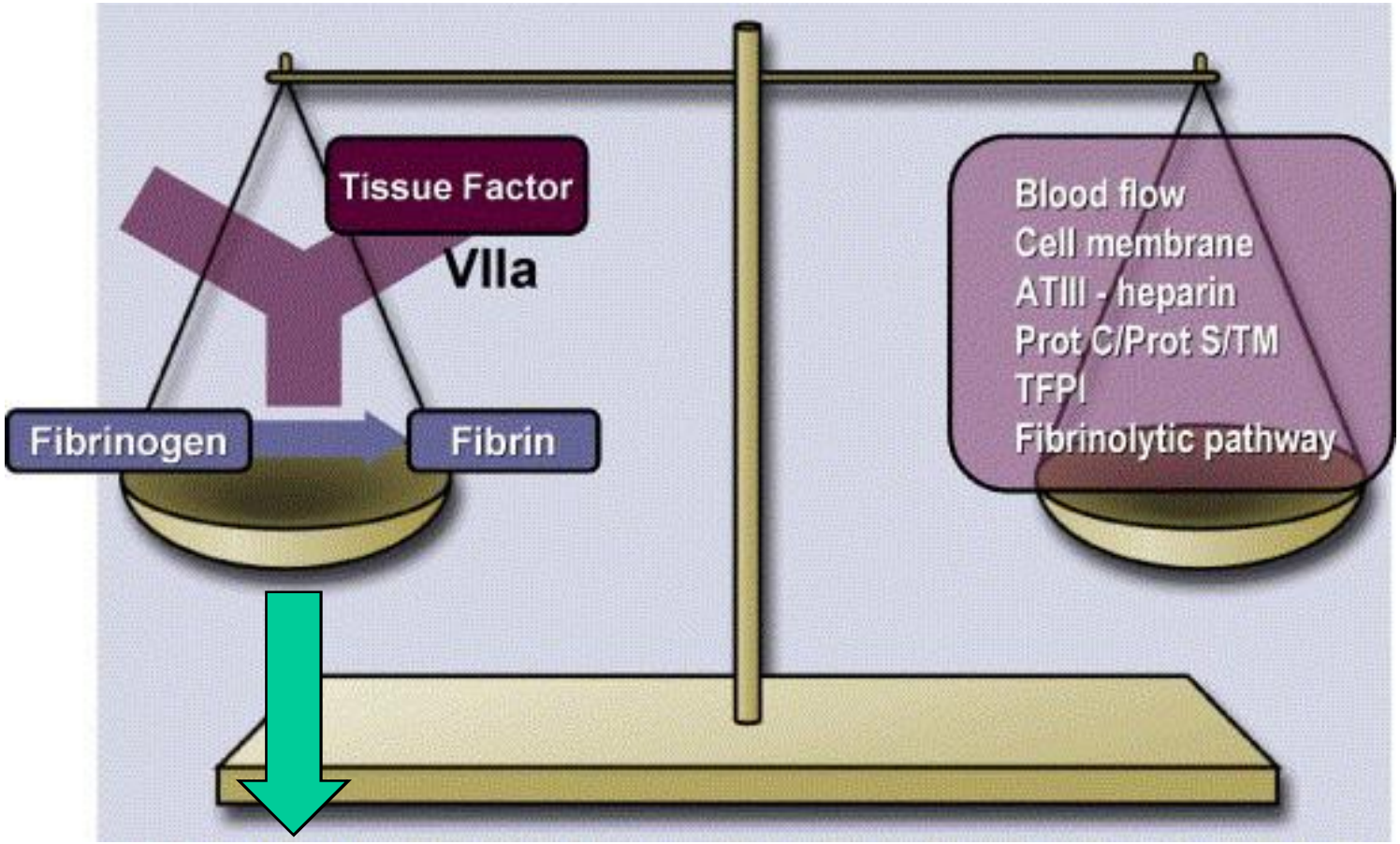
Liver plays important indirect roles in clotting



- Normal clotting requires adequate **vitamin K**
  - --Lipid-soluble vitamin absorbed if lipids are present
  - --Absorption slowed if bile release is insufficient
- Required for synthesis of 4 clotting factors by hepatocytes
  - --Factors **II (prothrombin), VII, IX and X**
- Produced by bacteria in large intestine
- **Liver disease** often have bleeding problems

Hemostatic Balance

Coagulation System ***Fibrinolytic System***



Hypercoagulability (Thrombosis)

formation of the clot

Fibrinolysis (Anticoagulant action)

dissolution of the clot

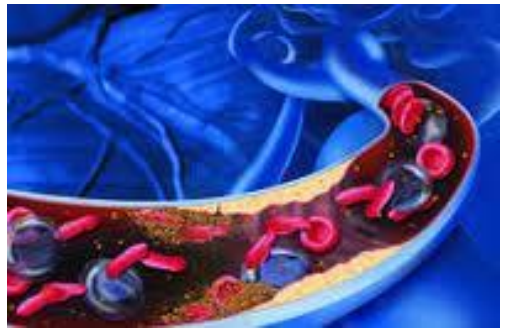
Anticoagulant Action

1. Cellular anticoagulant system

-- **Monocytes-macrophages** engulf clotting factors, tissue factors, prothrombin complex in blood

-- **Vascular endothelial cells** inhibit platelet adhesion and aggregation (PGI_2, NO), and activate protein C (inh. Factor Va and VIIIa)

2. Humoral anticoagulant system



Humoral Anticoagulant System

1. 抗凝血酶III (antithrombin III, AT III)：

--血漿中的AT III 是由肝細胞和血管內皮細胞分泌的醣蛋白(432 aa.)。

--它主要透過其精胺酸(arginine) 殘基與 IIa、IXa、Xa、XIa、XIIa 等凝血因子活性部位的絲胺酸(serine)殘基結合，從而達到抗凝作用(serine protease inhibitor)。

--正常情況下，AT III 作用非常緩慢而且很微弱，不能有效的抑制凝血，但當它與肝素結合後，其抗凝作用可增加上千倍。

Humoral Anticoagulant System

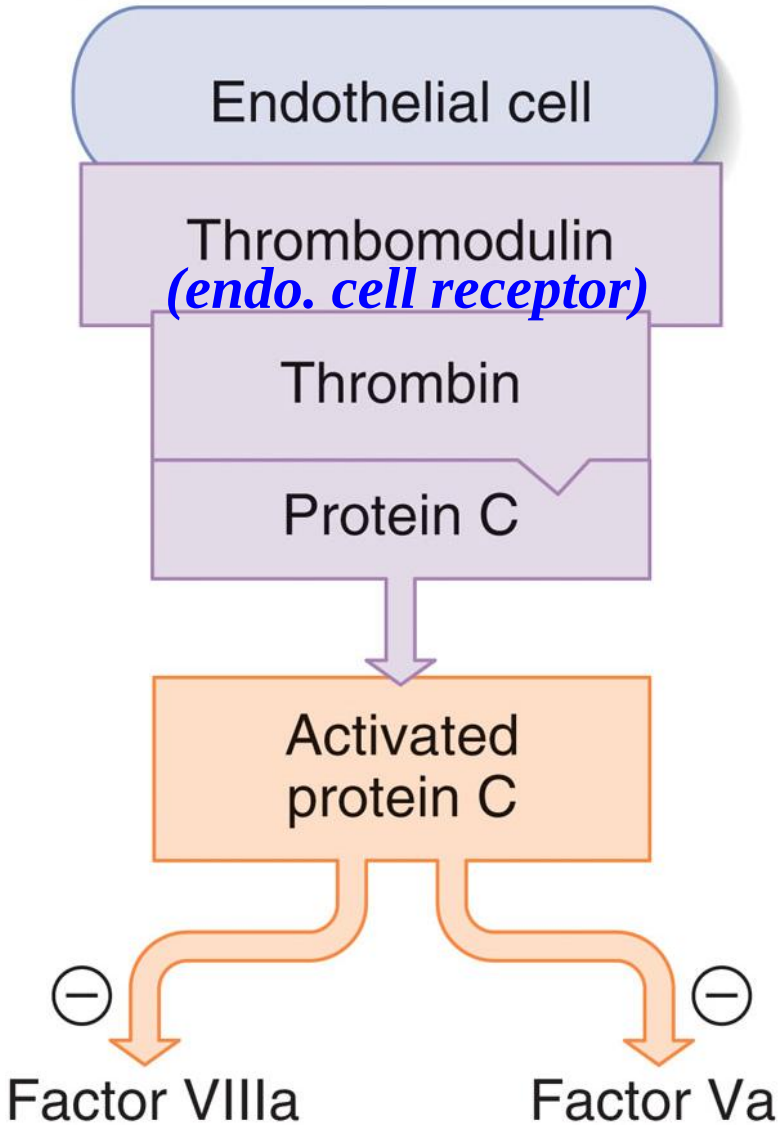
2. 蛋白質C 系統：

--包括蛋白質 C (protein C, PC)、蛋白質S (protein S, PS)、凝血酶調節蛋白(thrombomodulin, TM) 和蛋白質 C 抑制物。

--PC是一種由肝臟合成的維生素 K 依賴性血漿蛋白，平時以無活性的酶原形式存在於血漿中。

--在凝血過程中，當thrombin與血管內皮細胞上的TM結合後，PC 被活化，可以使Va 和VIIIa 去活化。

--阻礙Xa 與血小板上的膜磷脂結合，抑制prothrombin的啟動；促進纖維蛋白溶解(fibrinolysis)。



Humoral Anticoagulant System

3. 組織因子途徑抑制物 (tissue factor pathway inhibitor, TFPI)：

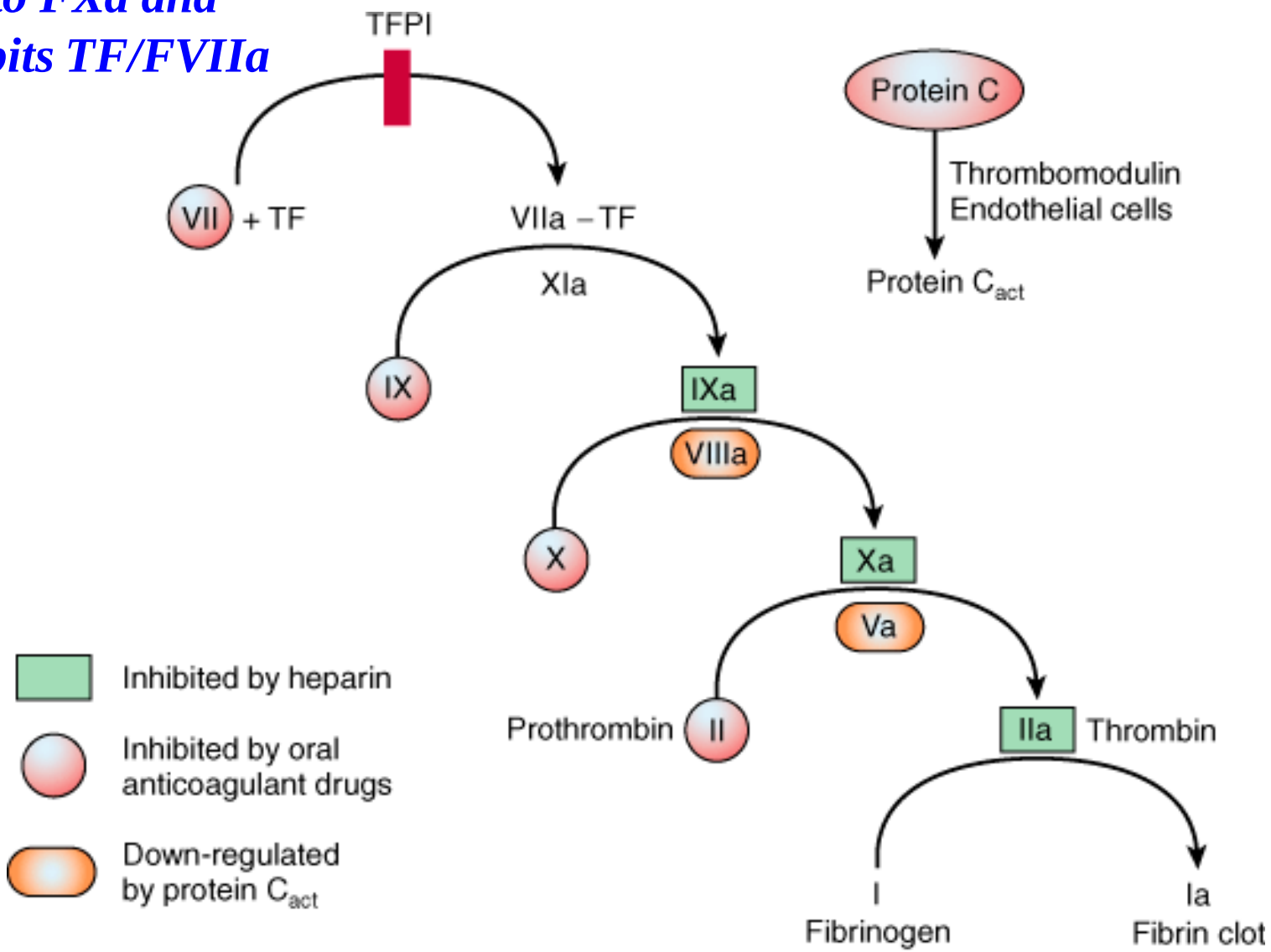
--是一種單鏈醣蛋白，主要由血管內皮細胞生成，是外源性凝血路徑的特異性抑制物(inhibitor of extrinsic pathways) 。

--TFPI 主要的作用是與 Xa 結合，並抑制其活性。

--在 Ca^{2+} 的存在下，TFPI 與 VIIa-組織因子複合物(VIIa-TF complex)結合，形成TF-VIIa-TFPI-Xa 四合體，進而抑制TFVIIa 的活性，對外源性凝血途徑發揮負迴饋抑制的作用 。

Tissue Factor Pathway Inhibitor (TFPI)

- ***TFPI is the endogenous inhibitor of TF activity***
- ***TFPI binds to FXa and thereby inhibits TF/FVIIa activity***



Humoral Anticoagulant System

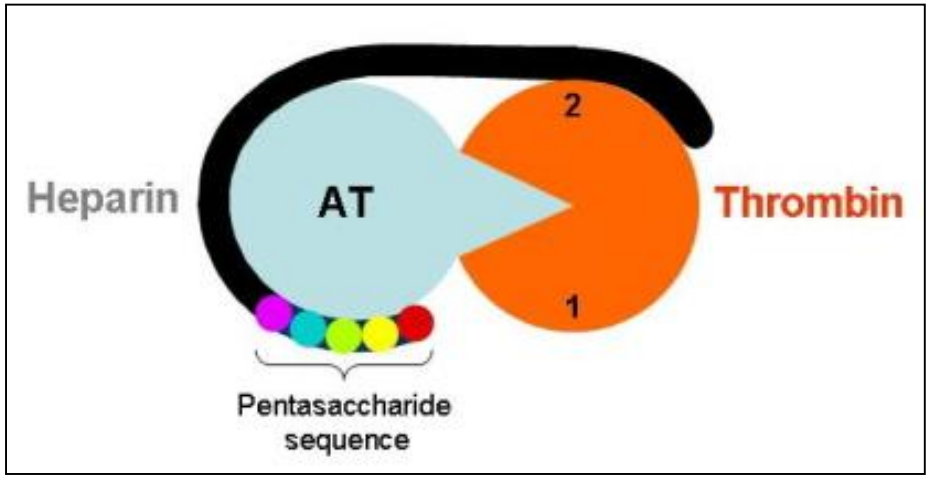
4. 肝素(heparin)：

--是一種酸性黏多醣(sulfated glycosaminoglycan)，主要由肥大細胞(mast cell)和嗜鹼性球產生。

--肝素能與血漿中的一些抗凝蛋白質結合，可增強抗凝蛋白質的活性。

--當肝素和抗凝血酶 III (AT III) 結合時，可使其與thrombin的親和力增加上百倍，進而抑制其活性。

--肝素可刺激血管內皮細胞大量釋放TFPI及其他抗凝物質，從而抑制凝血過程。



--肝素能增強蛋白質 C (PC)活性，刺激血管內皮細胞釋放胞漿素原活化物 (plasminogen activator)，以增強纖維蛋白溶解。

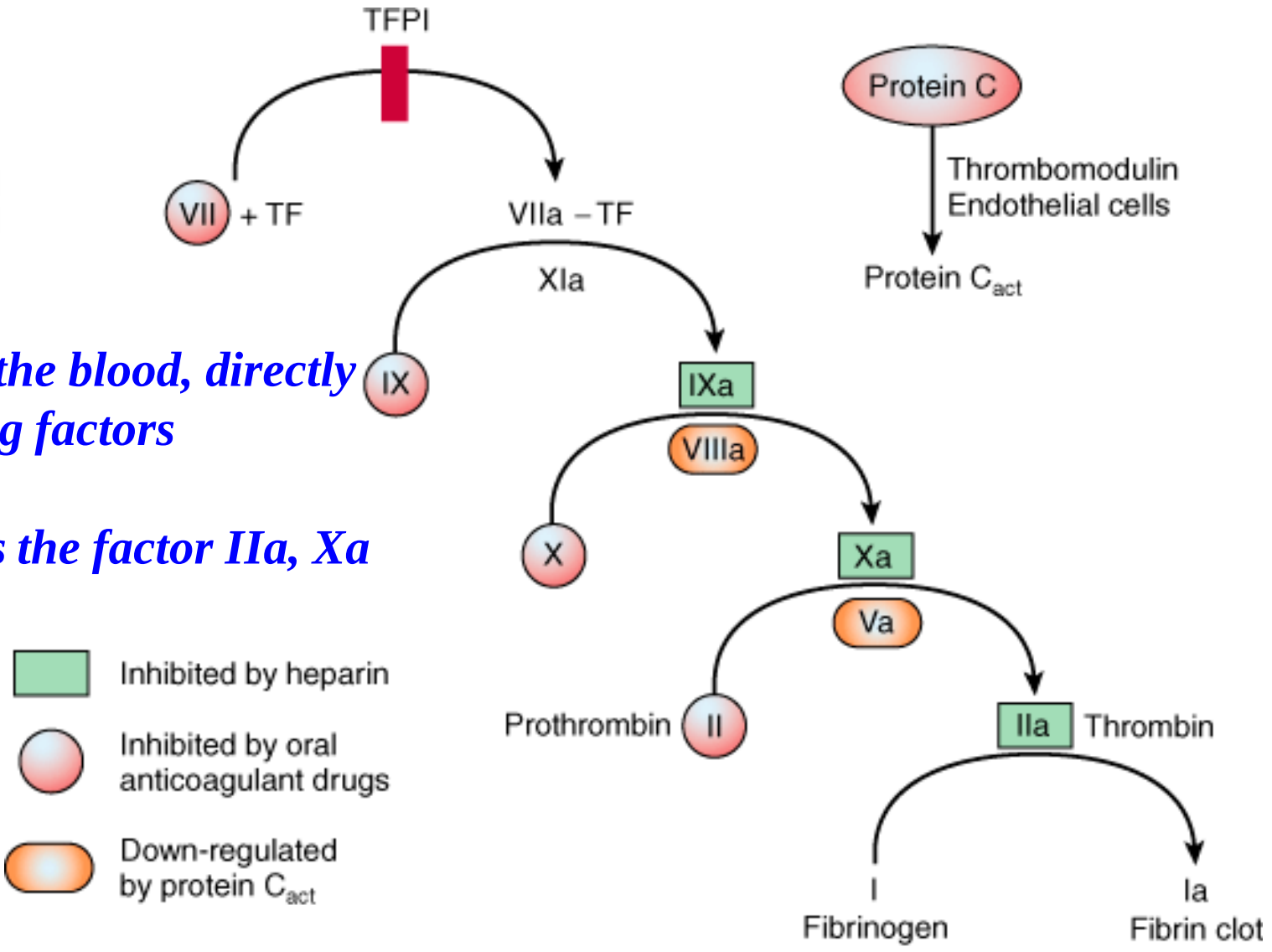
--肝素在臨床上常作為注射用抗凝劑。

Heparin

A Serious Side-Effect of Heparin is

Heparin-Induced Thrombocytopenia (induce an immune reaction)

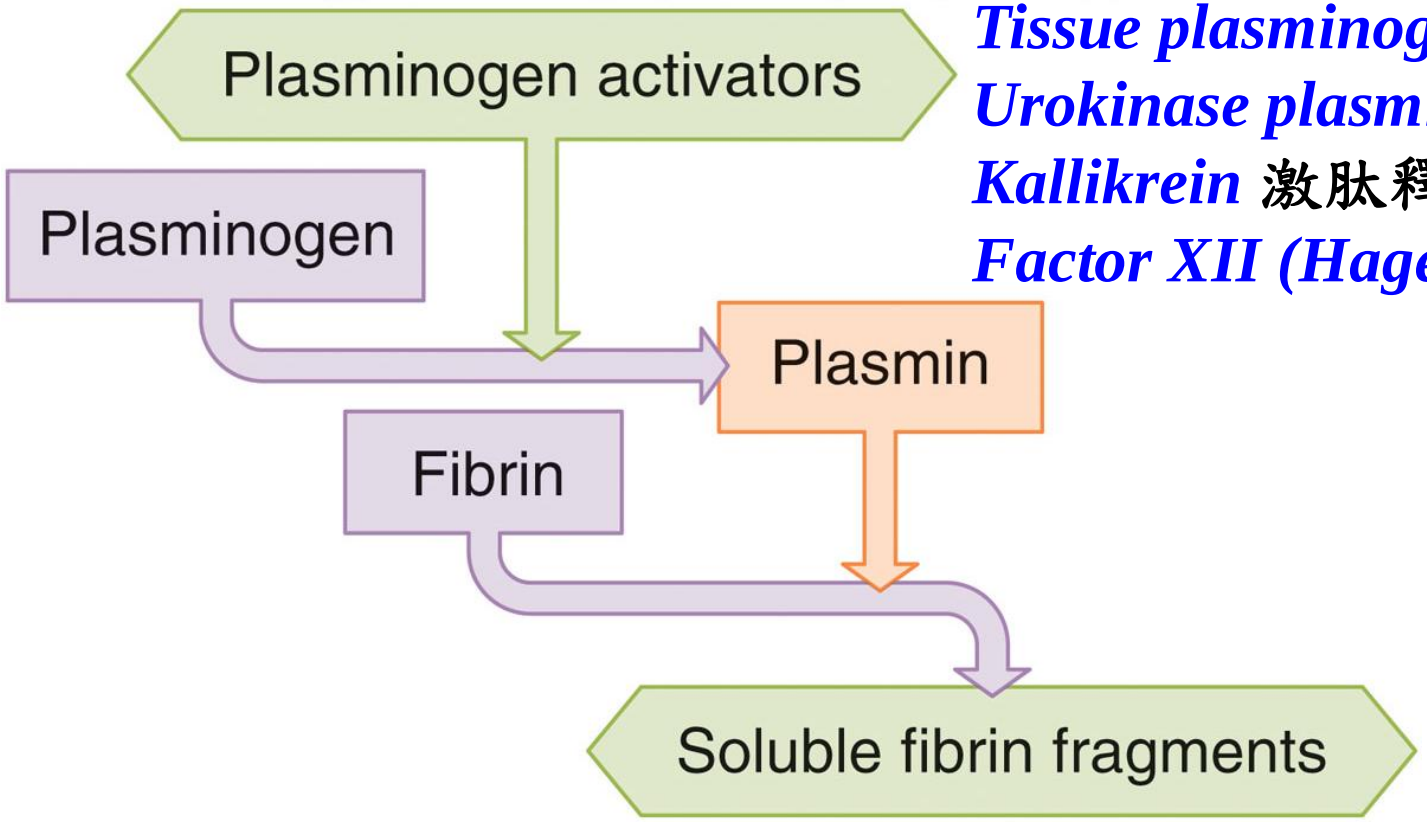
- ***Heparin, acting in the blood, directly activates anticlotting factors (antithrombin III)***
- ***Heparin inactivates the factor IIa, Xa and IXa***



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. (Extrinsic pathways)
Synthesize and release PGI_2 and nitric oxide	These inhibit platelet activation and aggregation.
Secrete tissue factor pathway inhibitor **(TFPI)**	This 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 **(t-PA)**	Tissue plasminogen activator catalyzes the formation of plasmin, which dissolves clots.

Fibrinolytic System
(Hemostatic Control Mechanisms)



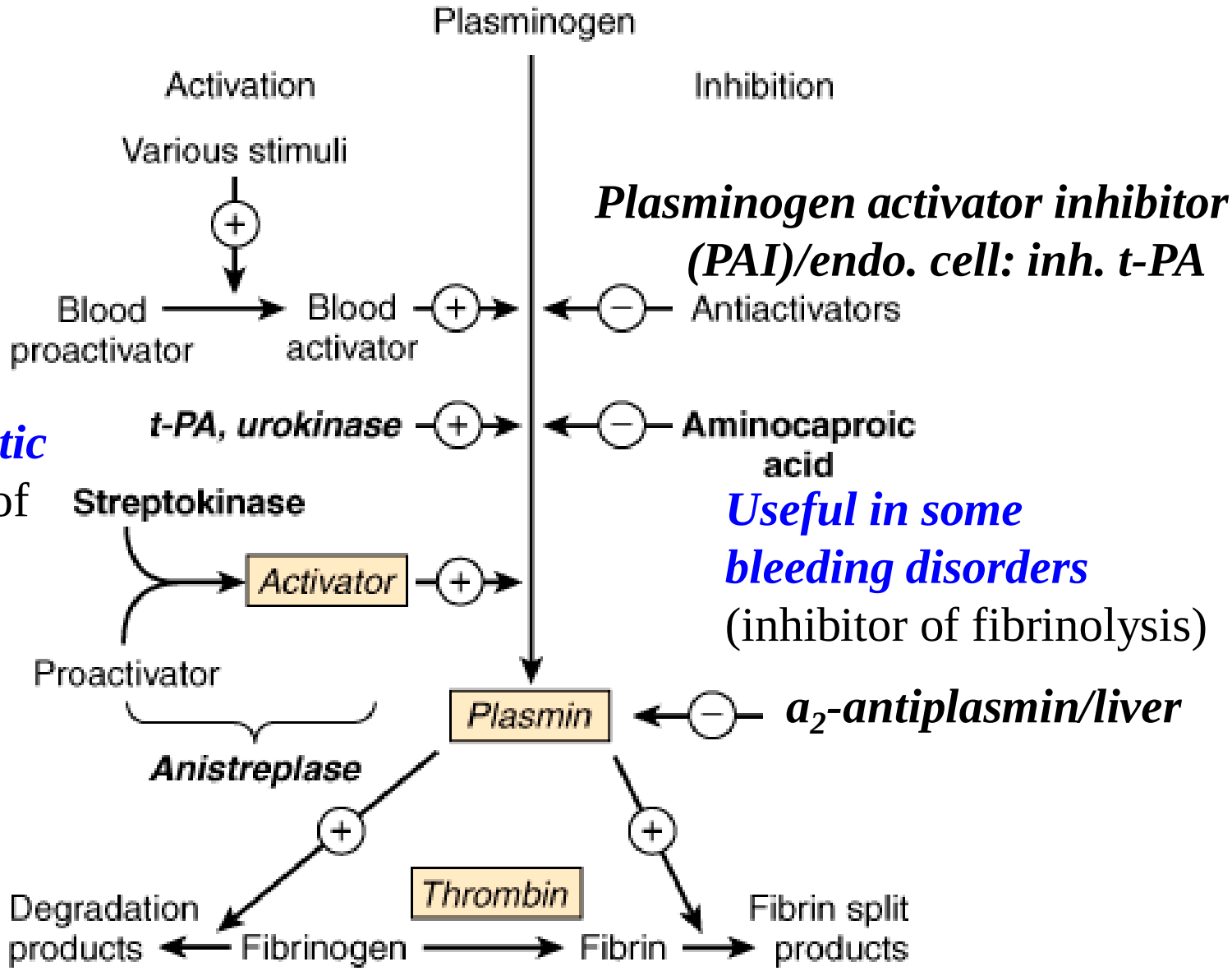
Tissue plasminogen activator (t-PA)
Urokinase plasminogen activator (uPA)
Kallikrein 激肽釋放酶
Factor XII (Hageman factor)

- ***Plasmin*** (fibrinolysin) is a **serine protease** that acts to dissolve fibrin blood clots= ***active fibrinolytic enzyme***
- ***Plasmin*** acts as an anticoagulant and clot disperser inside the body
- **PA** is secreted by endothelial cells during clot formation and activated by fibrin

Plasminogen Activators

- 除了激肽釋放酶(Kallikrein)外，某些**胞漿素原活化物 (plasminogen activators)**，在臨床上被使用來促進血塊溶解如吸血蝙蝠唾液。
- 最近在基因工程技術方面，發展出一種商業化內生性化合物**組織胞漿素原活化物 (tissue plasminogen activators，t-PA)**，它是將人類基因安插到細菌之內所製造的產物。
- **鏈球菌激酶 (streptokinase，SK)**，一種天然的細菌產物，是一強效且被廣泛使用的胞漿素原活化物(PA)。
- **SK** 和**t-PA**可注射到體循環或特別注射到因血栓(血塊)阻塞的冠狀動脈血管中。

Activator and Inhibitor of Fibrinolytic System



Plasminogen activator inhibitor (PAI)/endo. cell: inh. t-PA

Used in thrombolytic therapy (activator of fibrinolysis)

Useful in some bleeding disorders (inhibitor of fibrinolysis)

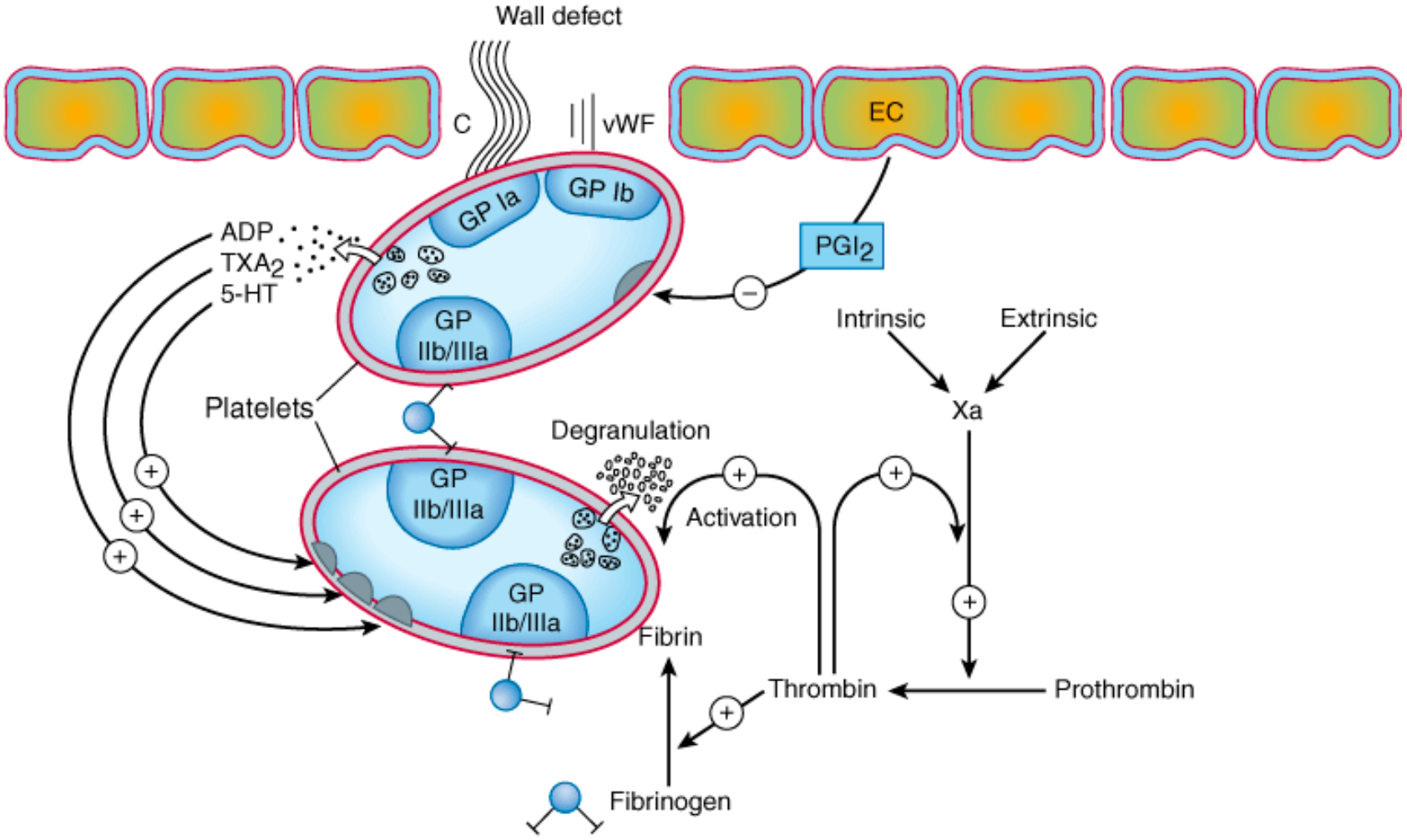
a_2-antiplasmin/liver

Intravascular Clotting

- **Thrombosis**
  - --Thrombus (clot) forming in an unbroken blood vessel
    - Forms on rough inner lining of BV
    - If blood flows too slowly (stasis) allowing clotting factors to build up locally & cause coagulation
  - --May dissolve spontaneously or dislodge & travel
- **Embolus**
  - --Clot, air bubble or fat from broken bone in the blood
    - Pulmonary embolus is found in lungs
- **Low dose aspirin** blocks synthesis of **TXA_2** & reduces inappropriate clot formation (anticoagulant)
  - --Strokes, transient ischemic attacks (TIAs=mini stroke) and myocardial infarctions
  - **--High dose aspirin** blocks synthesis of **PGI_2** (clot formation)

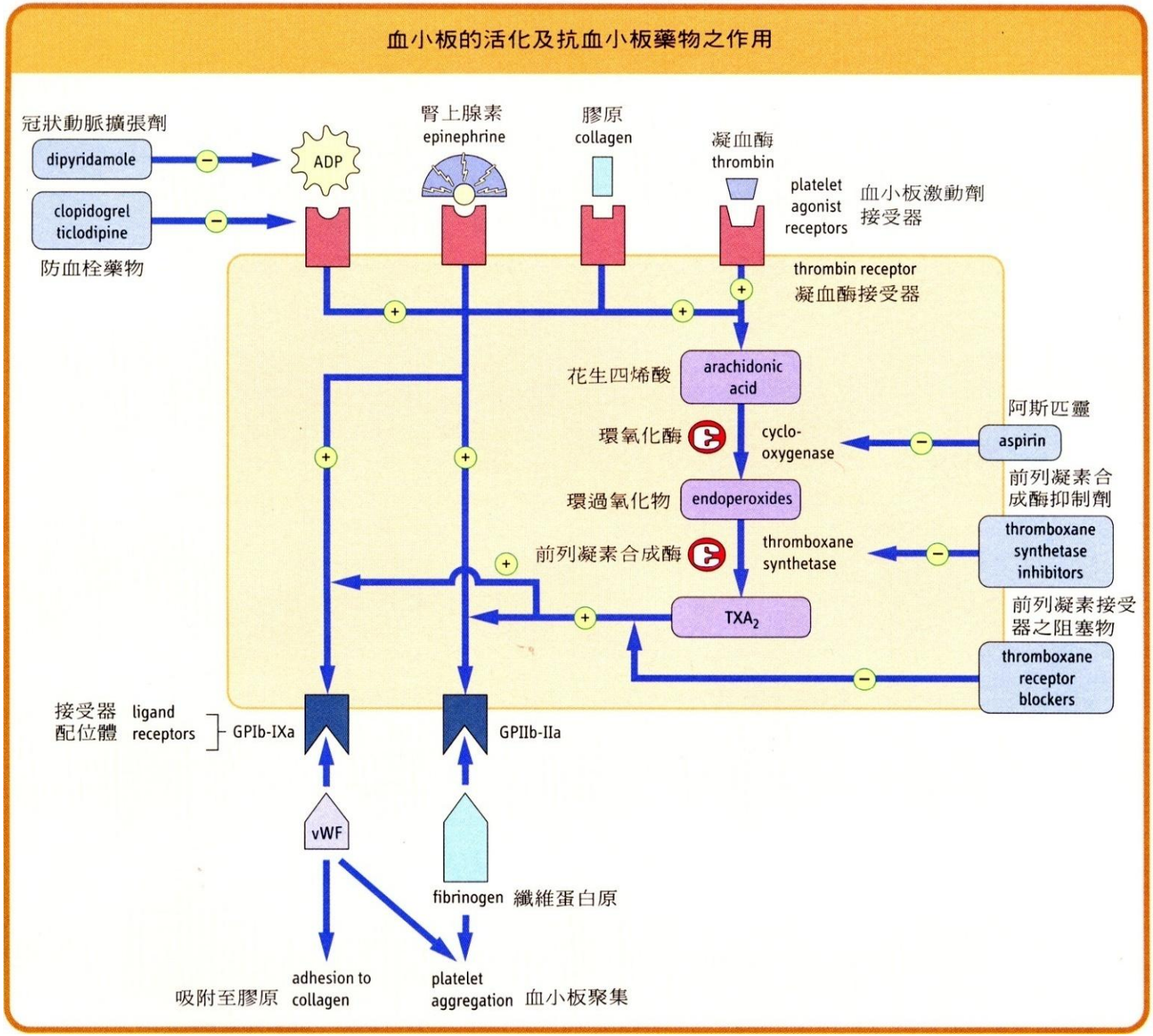
Thrombus Formation in Damaged Vascular Wall

- Platelet membrane receptors include the **glycoprotein (GP) Ia receptor**, binding to collagen (C)
- **GP Ib receptor**, binding von Willebrand factor (vWF), and **GP IIb/IIIa**, which binds fibrinogen and other macromolecules



Anticoagulants and Thrombolytic Agents

- **Anticoagulants suppress or prevent blood clotting**
  - **--Heparin** (present in blood)
    - Binds antithrombin III (ATIII) and then inactivates thrombin
    - Administered during hemodialysis and surgery
  - **--Warfarin (Coumadin)**
    - Antagonist to vitamin K so blocks synthesis of clotting factors
    - Slower than heparin
  - --Stored blood in blood banks treated with **citrate phosphate dextrose (CPD) or EDTA** that removes Ca^{+2}
- **Thrombolytic agents are injected to dissolve clots**
  - --Directly or indirectly activate plasminogen
  - --Streptokinase (SK) or tissue plasminogen activator (t-PA)


血小板的活化及抗血小板藥物之作用
冠狀動脈擴張劑
dipyridamole
clopidogrel
ticlodipine
防血栓藥物
ADP
腎上腺素
epinephrine
膠原
collagen
凝血酶
thrombin
platelet
agonist
receptors
血小板激動劑
接受器
thrombin receptor
凝血酶接受器
花生四烯酸
arachidonic
acid
環氧化酶
cyclo-
oxygenase
阿斯匹靈
aspirin
環過氧化物
endoperoxides
前列凝素合
成酶抑制劑
前列凝素合成酶
thromboxane
synthetase
thromboxane
synthetase
inhibitors
TXA2
前列凝素接受
器之阻塞物
thromboxane
receptor
blockers
接受器
配位體
ligand
receptors
GPIb-IXa
GPIIb-IIa
vWF
fibrinogen
纖維蛋白原
吸附至膠原
adhesion to
collagen
platelet
aggregation
血小板聚集

Clotting Disorders and Anticoagulants

種類	病因	說明
後天凝血障礙 (acquired clotting disorders)	缺乏維生素 K	肝臟中凝血酶原和其他凝血因子的形成不足
先天凝血障礙 (inherited clotting disorders)	A 型血友病 (第 $VIII_{AHF}$ 因子缺陷)	X 染色體所攜帶的隱性表徵；延緩血纖維蛋白的形成
	馮維布蘭德氏病 (第 $VIII_{VWF}$ 因子缺陷)	體染色體所攜帶的顯性基因表徵；能力受損的血小板附著於內皮下結締組織的膠原蛋白
	B 型血友病 (第九因子缺陷)，也稱為克里斯馬斯病 (Christmas disease)	X 染色體所攜帶的隱性基因表徵；延緩血纖維蛋白的形成
抗凝血劑 (anticoagulants)		
阿斯匹靈 (aspirin)	抑制前列腺素產生，導致血小板釋放反應不全	
香豆素 (coumarin)	抑制維生素 K 的活化	
肝素 (heparin)	抑制凝血酶的活性	
檸檬酸鹽 (citrate)	與鈣離子結合，因而抑制許多凝血因子的活性	

一位三歲大的血友病患，因輕微跌倒所造成之嚴重瘀傷

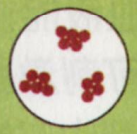
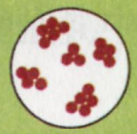
Clinical Application: Leeches and Bloodleting

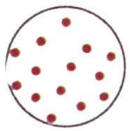
- Leeches have been used for **bloodletting** since the age of Hippocrates. Surgeons have currently used medicinal leeches *(Hirudo medicinalis)* to **prevent thrombosis** and **increase blood flow** in treatments of ischemia, pain and inflammation
- Leech saliva contains **an anesthetic , a vasodilator, and an anticoagulant**
- **Hirudin** is a specific, **irreversible thrombin inhibitor** from leech saliva that is now available in recombinant form as **lepirudin** (administered parenterally).
- Lepirudin has little effect on platelets or the bleeding time. Lepirudin is excreted by the kidney and should be used with great caution in patients with **renal insufficiency** as no antidote exists

Blood Types

血球表面特異性抗原的類型

- **凝集原(agglutinogen)** 的特異性取決於紅血球膜上的特異性蛋白質、醣蛋白或醣脂質，在凝集反應中產生抗原作用
- **凝集素(agglutinin)**是能與凝集原發生特異性反應的抗體(γ球蛋白)

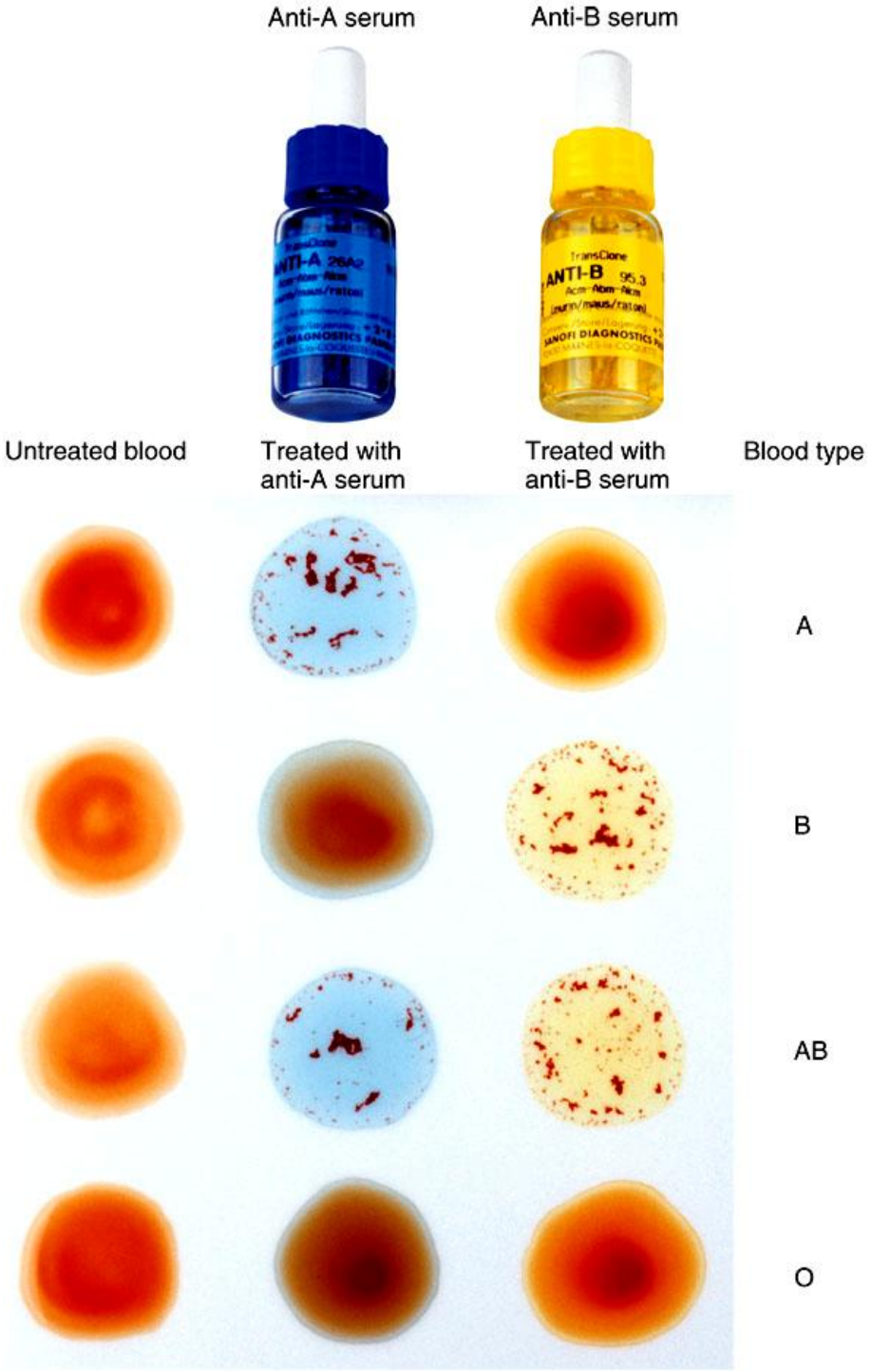
受血者之血液		與捐血者血液之反應			
紅血球抗原 RBCs antigens	血漿抗體 Plasma antibodies	捐血者血型 O	捐血者血型 A	捐血者血型 B	捐血者血型 AB
無（O型）	抗A抗B				
A（A型）	抗B				
B（B型）	抗A				
AB（AB型）	無				

 正常血

 凝集血

Typing Blood

- Single drops of blood are mixed with different antisera
- Agglutination with an antisera indicates the presence of that antigen on the RBC



Blood Transfusion

- 輸血原則：
  1. 在輸血前，必須進行**血型鑑定**，以確保供血者和受血者的血型相同。
  2. 每次輸血前必須做**交叉配對試驗(cross match test)**，可排除 ABO 血型的亞型、Rh 陰性血型產生抗 Rh 抗體可能引起的輸血反應。

     --將供血者的紅血球與受血者的血清混合(主要配對)，同時將受血者的紅血球與供血者的血清混合(次要配對)的試驗。

交叉配對試驗		配對結果	輸血可行性判斷
主要配對	次要配對		
凝集	凝集	不合	不可輸血
凝集	不凝集	不合	不可輸血
不凝集	凝集	基本相合	原則上不輸血， 但在緊急時，可考慮緩慢、少量輸血
不凝集	不凝集	成功	可以輸血

Blood Component Therapy in Blood Transfusion

血液成分輸血是把血液中的各種成分分別
製成高純度或高濃度的製品
按照不同疾病患者對輸血的不同需求進行輸血

- **嚴重貧血**，主要是紅血球數量不足，血液總量不一定少，適合輸入紅血球的濃縮懸液。
- **缺乏凝血因子**引起的凝血功能障礙的患者，適合輸注血漿。
- **大面積燒傷患者**或**大創傷**，血容量減少，可輸血漿補充血容量。
- **血小板缺乏患者**，可輸入濃縮的血小板懸液。
- 在緊急狀況時，**O 型血**(無A、B 抗原)可輸給 A 型、B 型、AB 型或 O 型的人，稱為**全能供血者**。
- **AB 型**(無抗A、抗B抗體)的人可接受A 型、B 型、AB 型或O型血，稱為**全能受血者**。
- 若輸血量太大時，仍可能發生輸血反應，因此在臨床上並不建議。

表 10-10　ABO 血型遺傳規律

子女血型 \ 父親血型	A	B	AB	O
A	A, O	A, B, AB, O	A, B, AB	A, O
B	A, B, AB, O	B, O	A, B, AB	B, O
AB	A, B, AB	A, B, AB	A, B, AB	A, B
O	A, O	B, O	A, B	O

Antibodies of ABO Blood Types

- 人類 ABO 血型抗原是由**第 9 號染色體**上的 ABO 基因控制，是鑲嵌在紅血球膜上的醣脂分子。
- 血型抗體有兩類：**天然抗體**和**免疫抗體**

  --ABO 血型存在天然抗體。

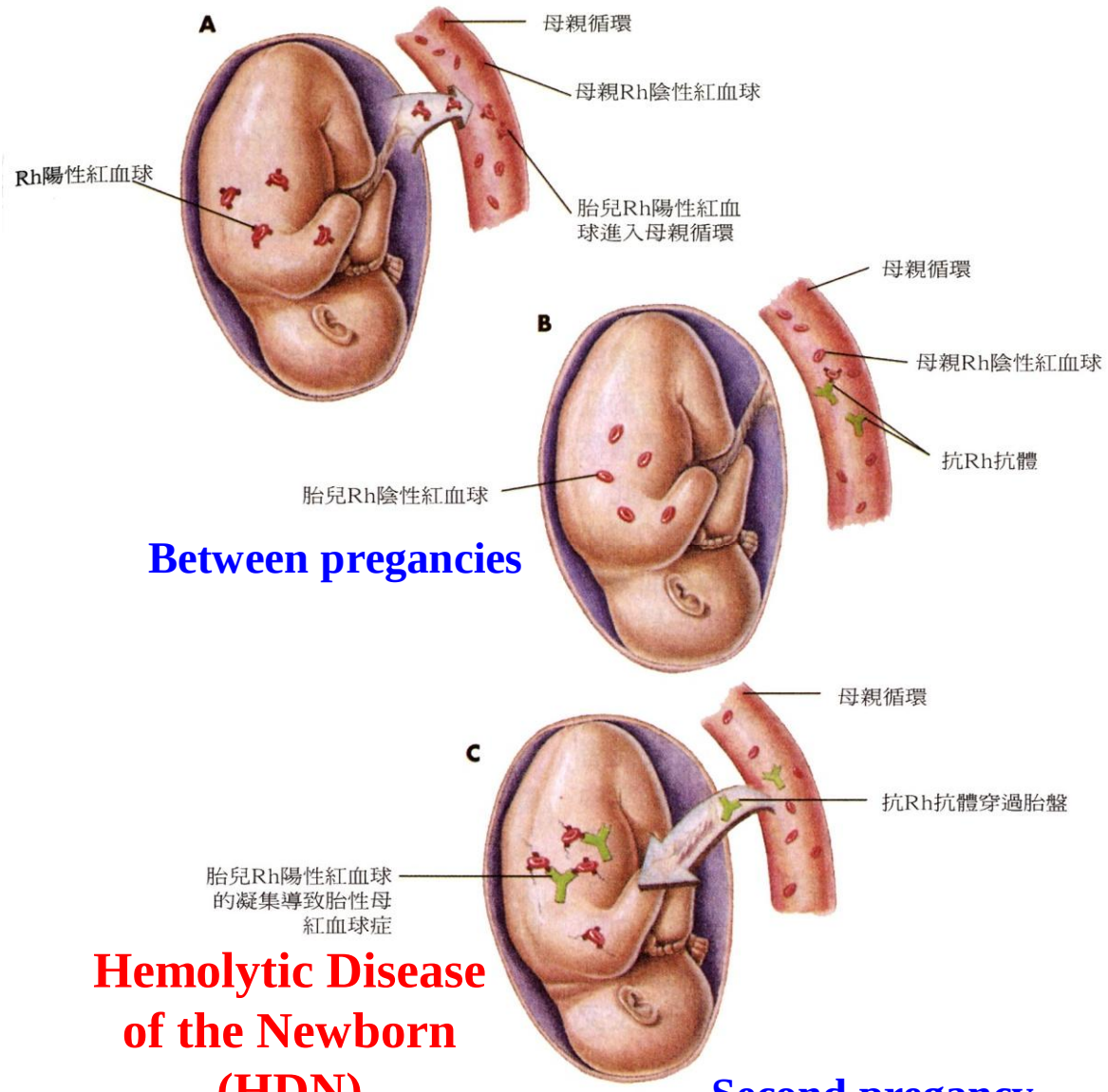
  --ABO 血型抗體在出生後 2~8 個月開始產生，8~10 歲時達到高峰。

  --**天然抗體**多屬 **IgM**，分子量大，不能通過胎盤。即使孕婦與胎兒血型不合，也不會使胎兒的紅血球發生凝集破壞。

  --**免疫抗體**是人體接受自身不具有的紅血球抗原後產生的抗體，它屬於 **IgG** 抗體，分子量小，能夠通過胎盤進入胎兒體內。

Erythroblastosis Fetalis

First pregancy



Between pregancies

Hemolytic Disease of the Newborn (HDN)

Second pregancy

- Antigen was discovered in blood of *Rhesus* monkey (Rh blood group)
- People with Rh agglutinogens on RBC surface are **Rh^+**. Normal plasma contains **no anti-Rh Ab**
- Antibodies develop only in Rh^- blood type & only with exposure to the antigen
  - **--Transfusion** of positive blood
  - --During a **pregnancy** with a positive blood type fetus
- Transfusion reaction upon **2nd exposure** to the antigen results in **hemolysis of the RBCs** in the donated blood

表 10-13　ABO 血型與 Rh 血型的比較

比較項目	ABO 血型	Rh 血型
血型分型	四種：A、B、AB、O	兩種：Rh 陽性、Rh 陰性
抗原	A、B、H 抗原	D、E、C、c、e 抗原
血型的天然抗體	有	無
抗體特徵	完全抗體 IgM，不能通過胎盤	不完全抗體 IgG，能通過胎盤
人群比例	A、B、O 各約 30%，AB 約 10%	Rh 陽性約 99%、Rh 陰性約 1%
輸血反應	發生快（立即輸血反應）	發生慢（延遲性輸血反應）
溶血反應	直接溶血：由抗原、抗體直接引起的血管內溶血，以血尿症為主	間接溶血：由凝集紅血球逐漸被巨噬系統破壞的血管外溶血，以高膽紅素血症為主

- **急性溶血性輸血反應：**
  --受血者在輸血後 24 小時內發生的溶血。
  --常出現發燒、噁心嘔吐、呼吸困難、低血壓、心慌、多處疼痛、血尿(hematuria)、急性腎衰竭等症狀。

- **延遲性溶血性輸血反應：**
  --受血者在輸血後數天後發生的溶血。
  --常表現為發熱、寒顫、貧血、黃疸(jaundice)、血漿膽紅素升高等症狀。
  --多見於稀有血型不合如新生兒溶血性疾病。