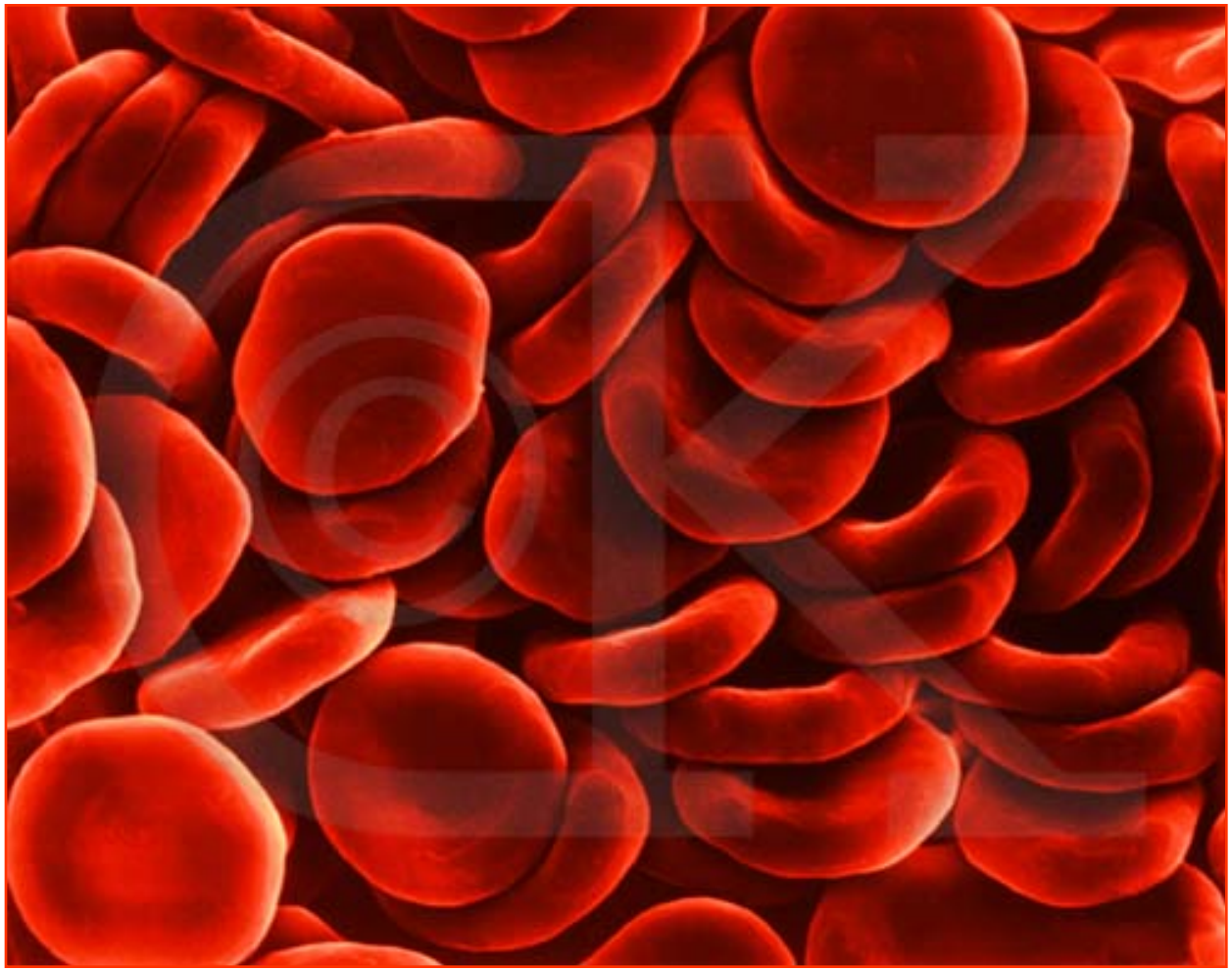
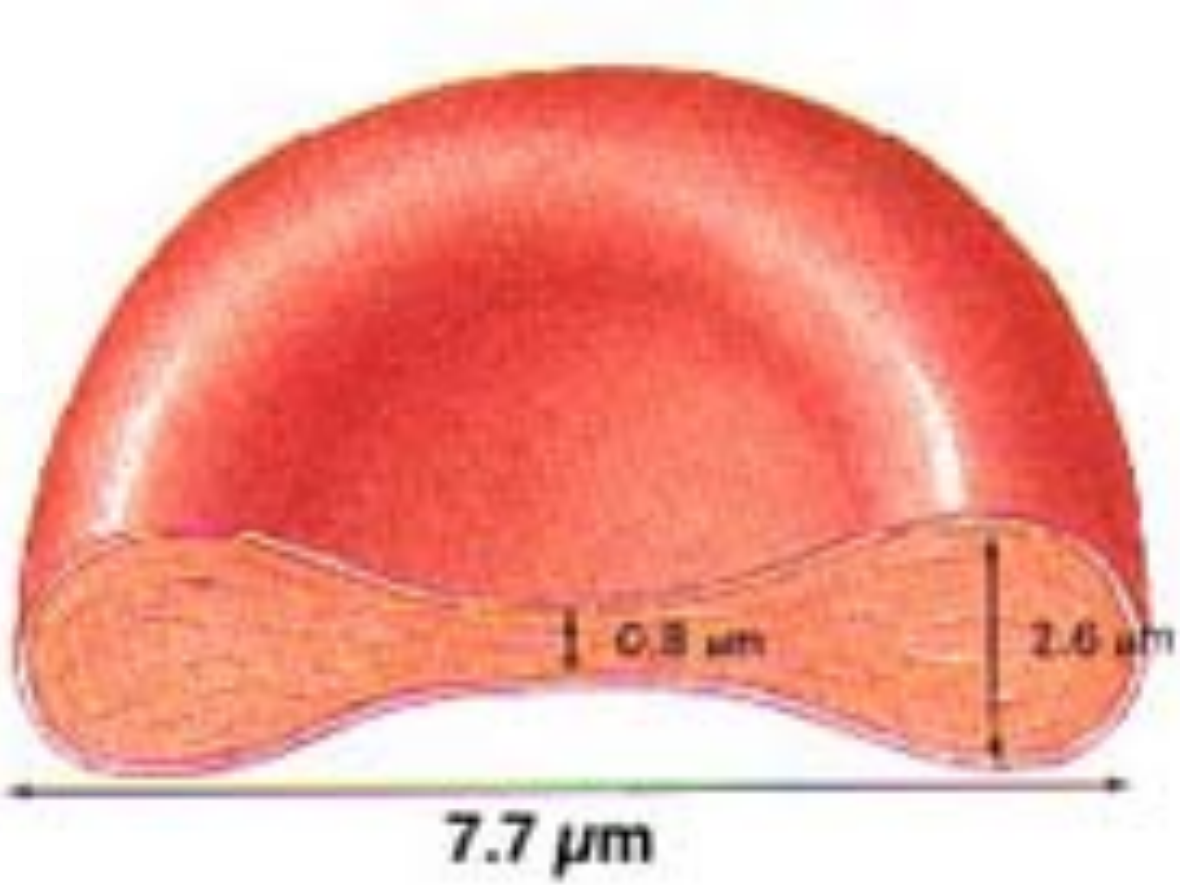
RBCs = ERYTHROCYTES



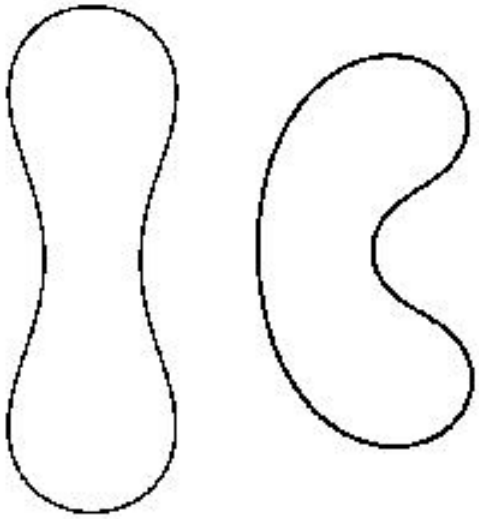
Function: facilitate transport of respiratory gases between lungs and cells

RBC SHAPE and DIMENSIONS

“biconcave” disk



ADVANTAGE of SHAPE



1. Maximal surface area and minimal diffusion distance for its volume (increases efficiency of O_2 & CO_2 diffusion)

2. High degree of flexibility (Alows cells to squeeze through narrow capillaries)

RBC STRUCTURE and NUMBERS

♂ 5.1 – 5.5 x 10^6/µL

♀ 4.5 - 4.8 x 10^6/µL

(25×10^{12} / 5L)

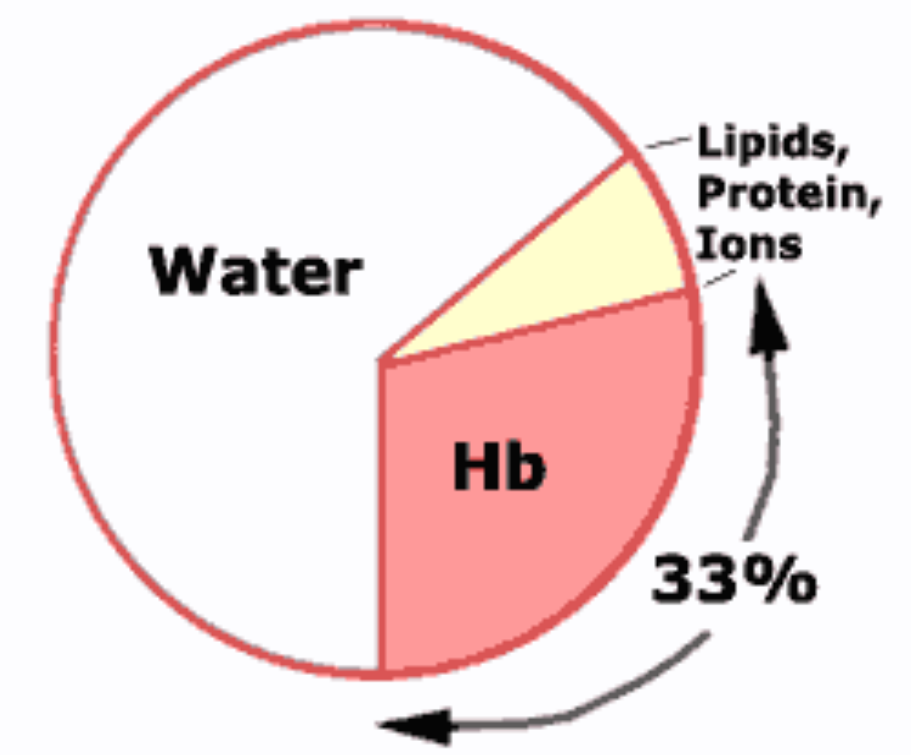
NOTE: No Subcellular Organelles

RBCs have important Enzyme Systems:

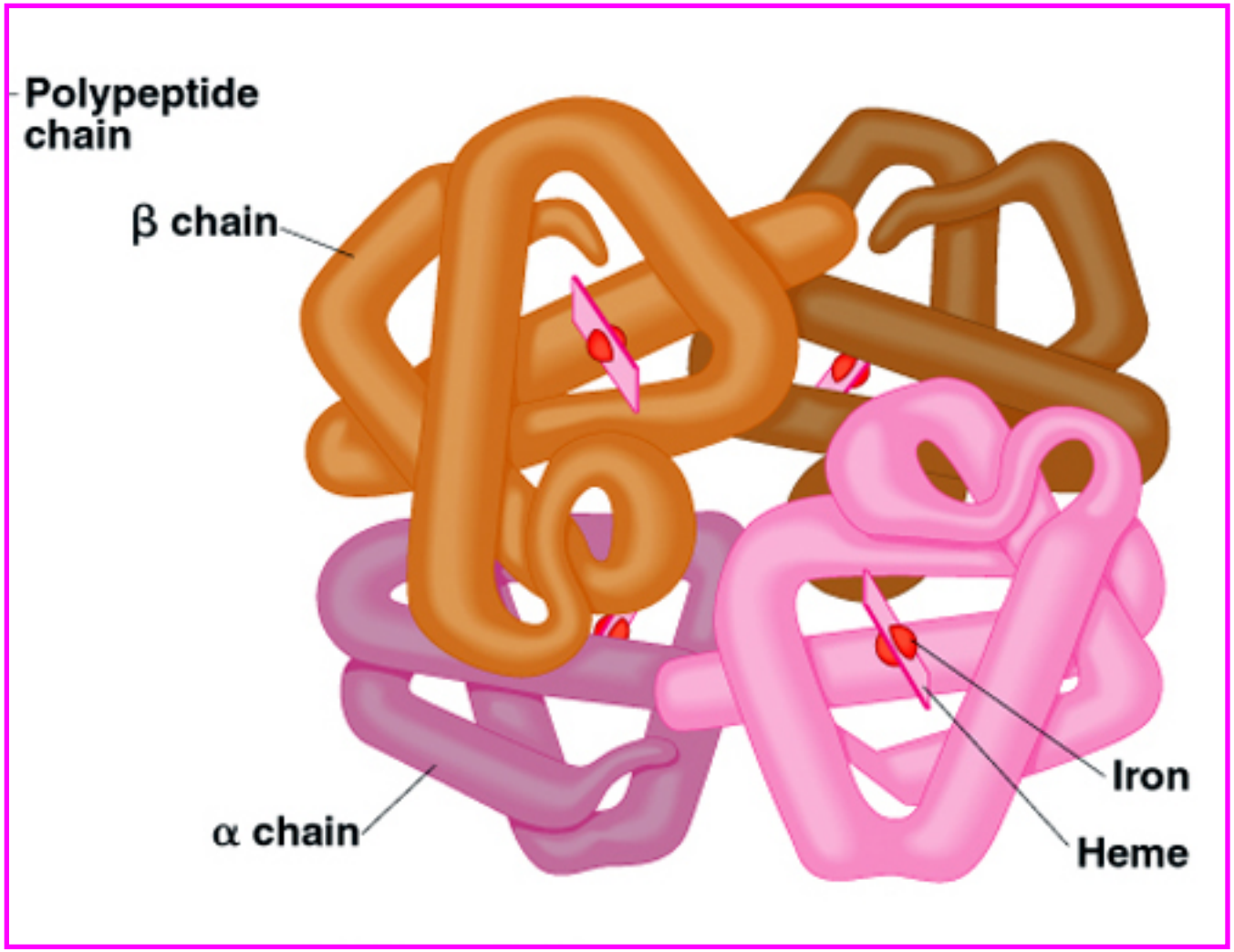
GLYCOLYTIC ENZYMES ⟶ Generate Energy

CARBONIC ANHYDRASE ⟶ CO_2 Transport

RBC Composition

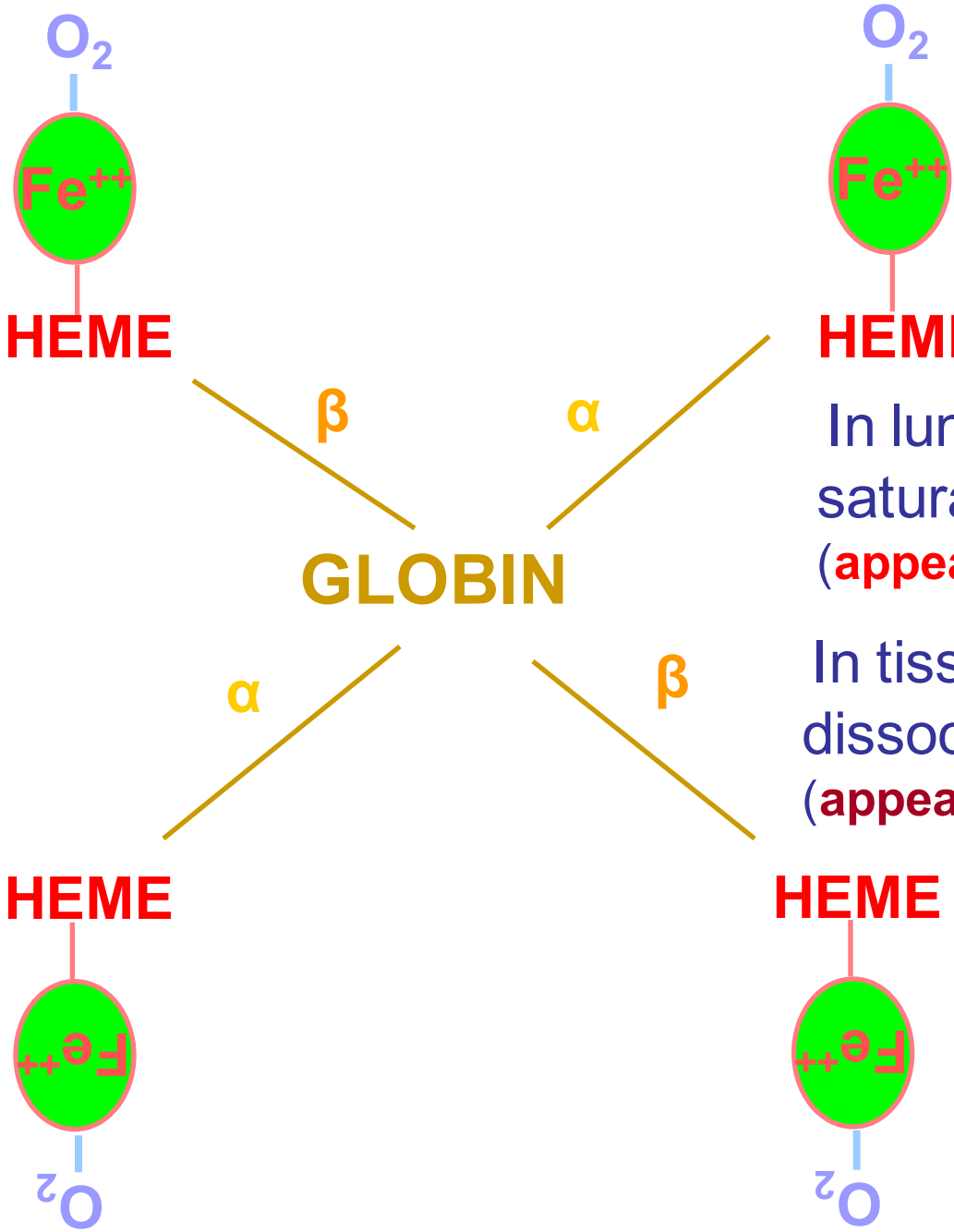


HEMOGLOBIN STRUCTURE p454[12]; 470-71[13] Vander



200-300 x 10^6 molecules/RBC

MW = 64K



In lungs, Hb becomes saturated with O_2 – (**appears bright red**)

In tissues, O_2 dissociates from Hb, (**appears dark red**)

HEMOGLOBIN FUNCTIONS p 462[12]; p467[13] Vander

Solubility of O_2 in plasma is very low:

0.3 ml O_2/100 ml plasma

In blood (because of **Hb**), carrying capacity is:

20 ml O_2/100 ml blood

Hb FUNCTIONS

1. Transport of O_2 $\quad Hb + O_2 \rightleftharpoons HbO_2$
2. Transport of CO_2
3. Act as a buffer

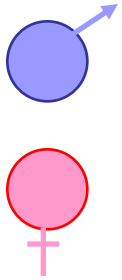
What are advantages of having **Hb** inside the cell (rather than dissolved in plasma)?

(i) re Plasma Viscosity

(ii) re Plasma C.O.P.

(i) re Loss via Kidney

HEMOGLOBIN VALUES



16 g/100 ml blood

14 g/100 ml blood

When Hb is fully saturated with O_2, each g of Hb holds 1.34 ml O_2

Therefore, the O_2 carrying capacity of blood is 15 x 1.34 = 20 ml O_2/100 ml blood

Factors affecting ability of Hb to bind and release O_2

1. Temperature
2. Ionic Composition
3. pH
4. pCO_2
5. Intracellular enzyme concentration

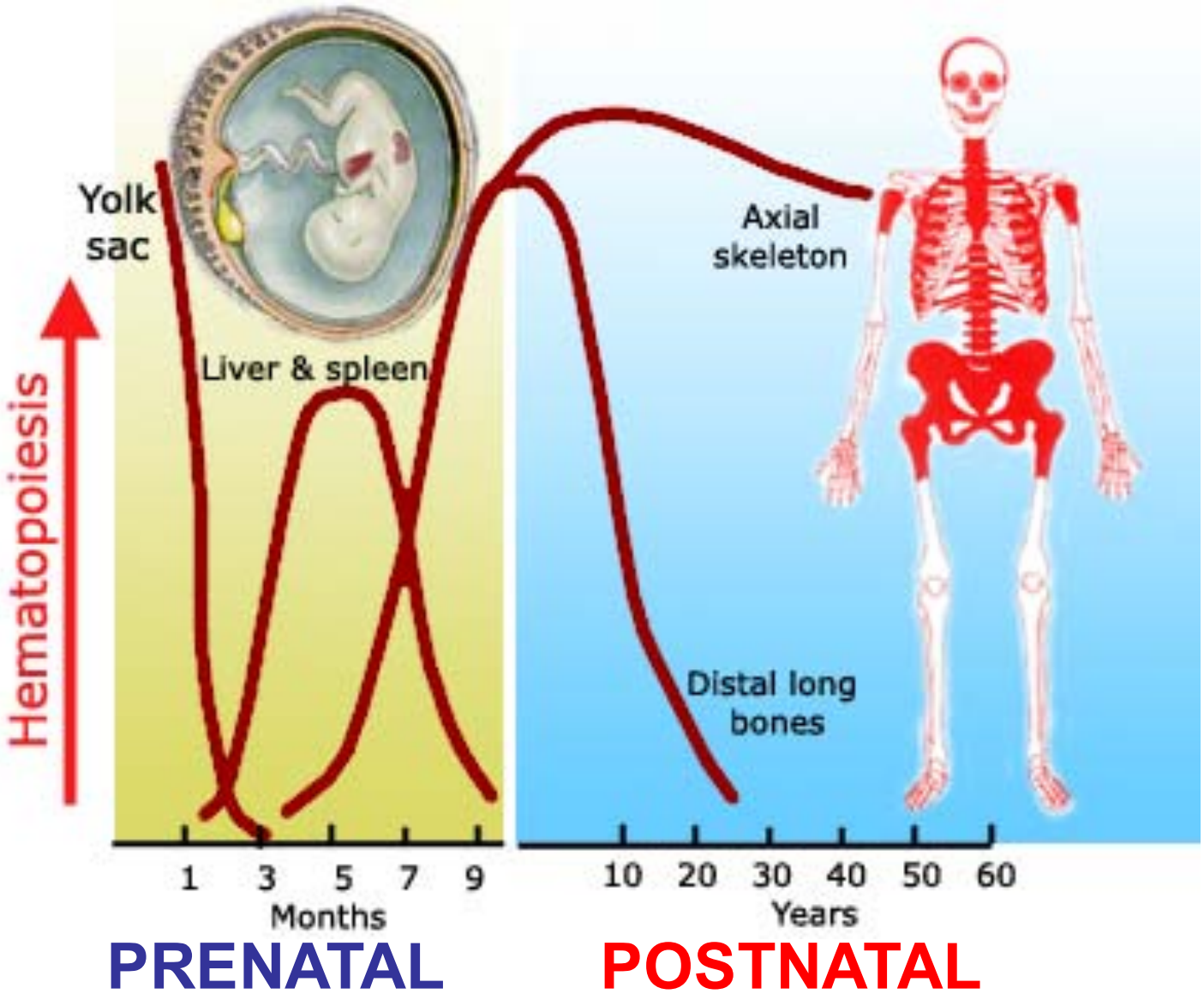
ERYTHROPOIESIS

1. WHERE?

2. HOW?

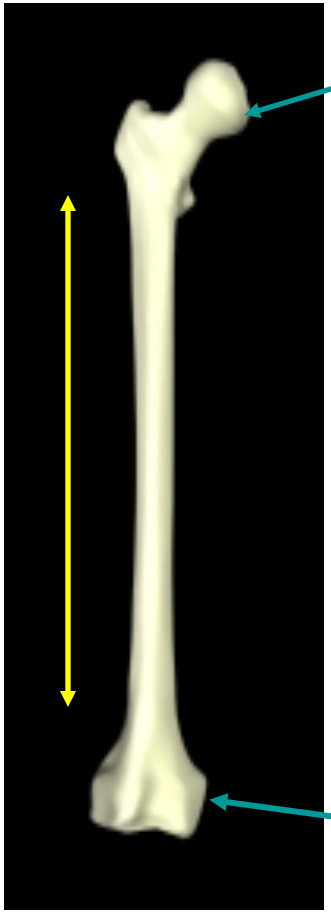
3. REGULATION?

SITES of HEMATOPOIESIS



Flat bones of skull, shoulder blades, pelvis, vertebrae, sternum, ribs, epiphyses of long bones

FEMUR

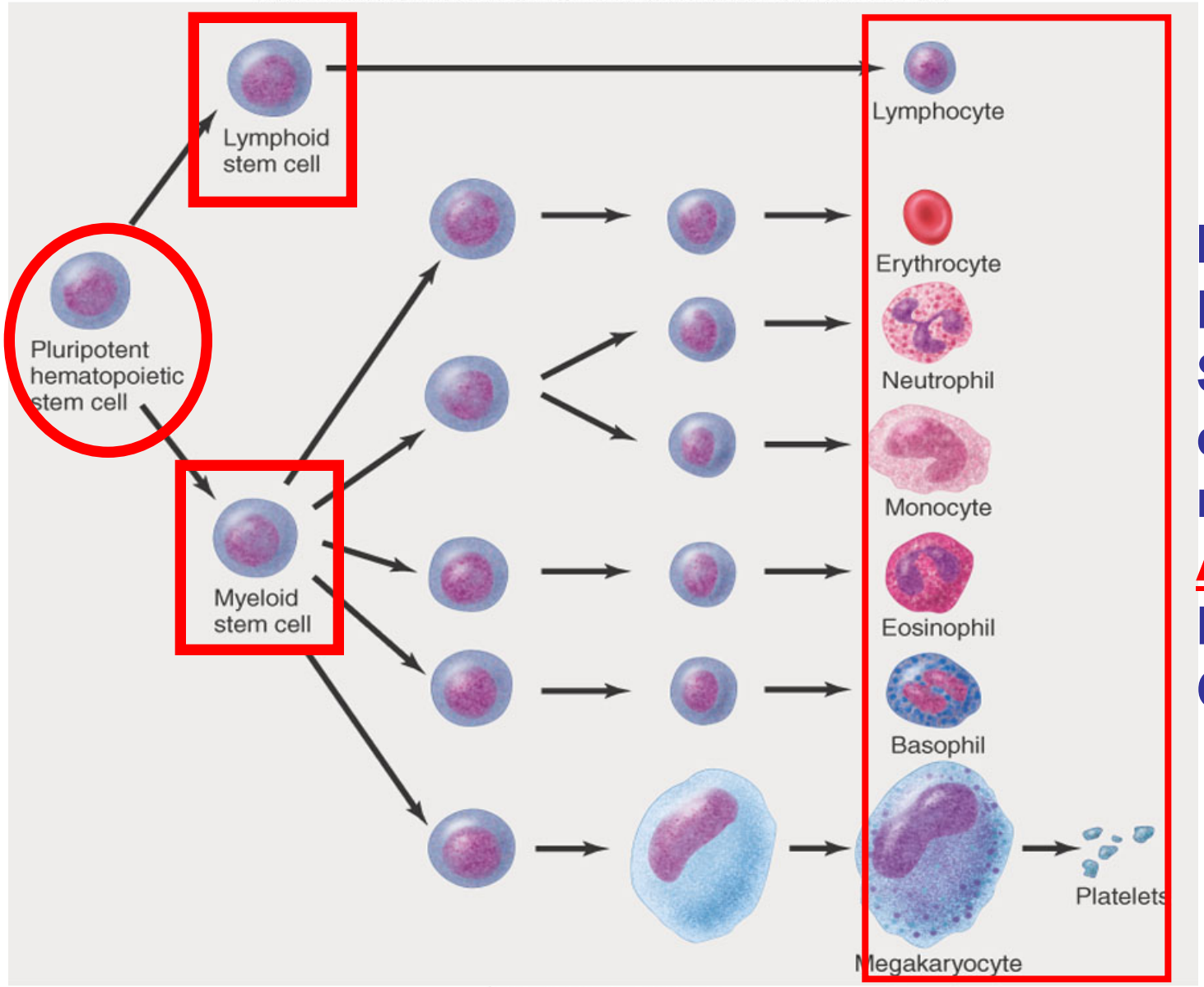


Epiphysis

Diaphysis

Epiphysis

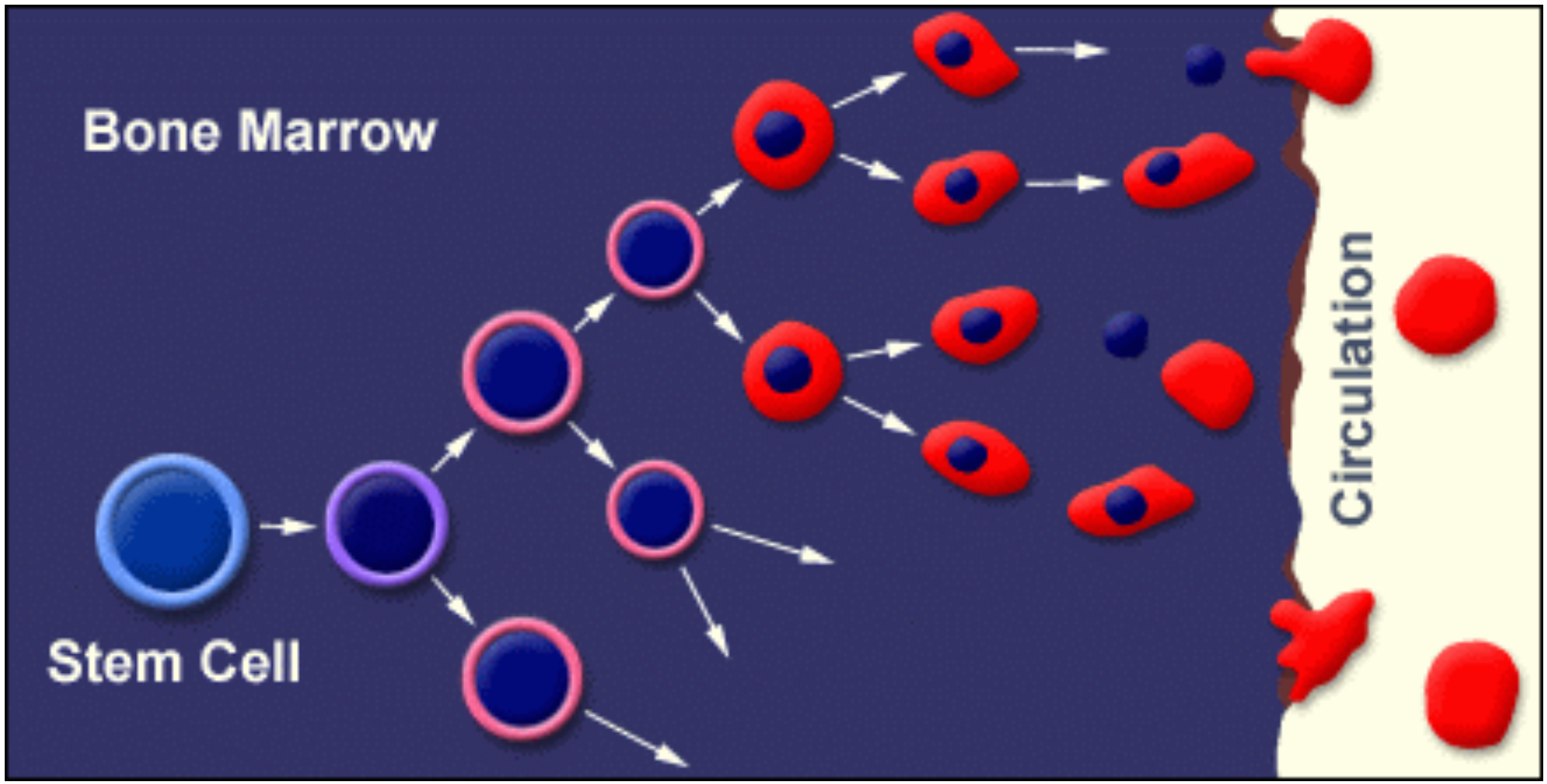
HEMATOPOIESIS–pp 421- 422[12] *(428- 429)*[13] *Vander*



Adapted form Golde and Gasson.

Injection of Bone Marrow Stem cells can reconstitute <u>ALL</u> hematopoietic Cell Types

Red Cell Precursors Proliferation



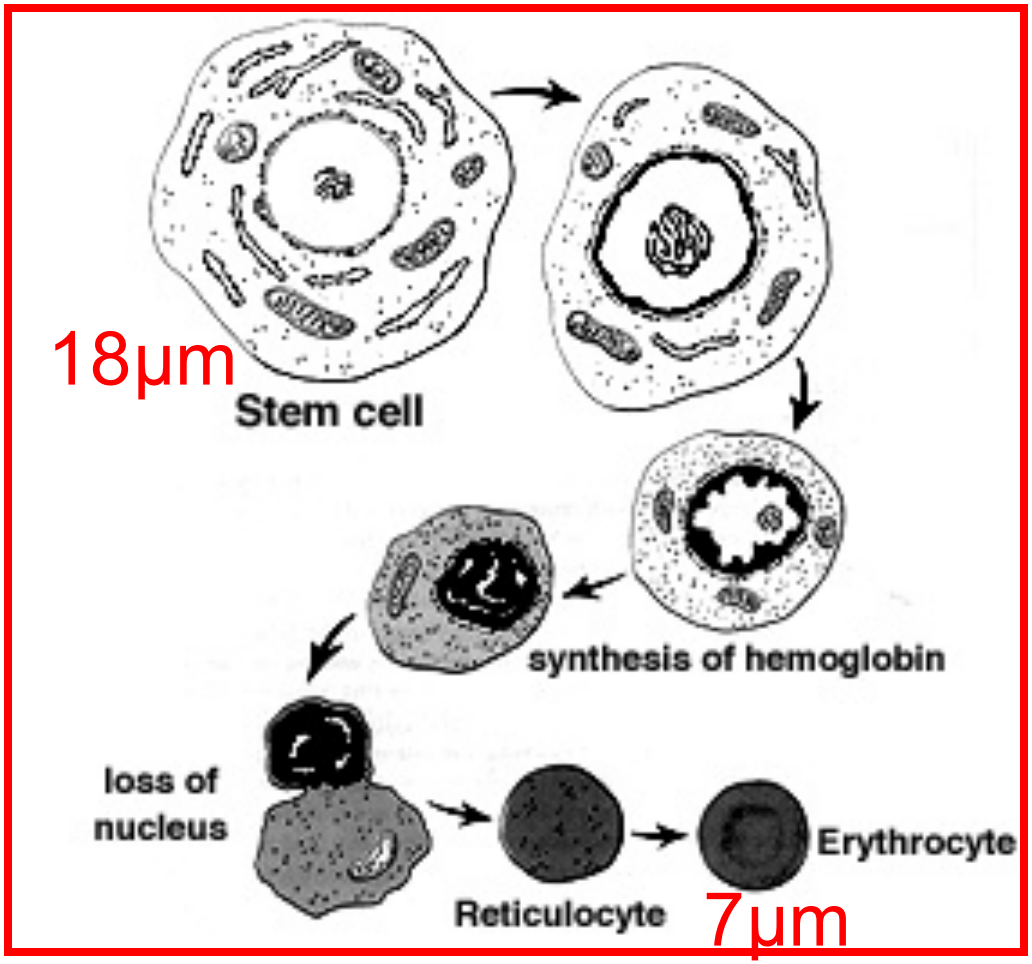
Divison and Differentiation

3 – 5 days

24 hours

Reticulocyte→RBC

Red Cell Precursors Differentiation

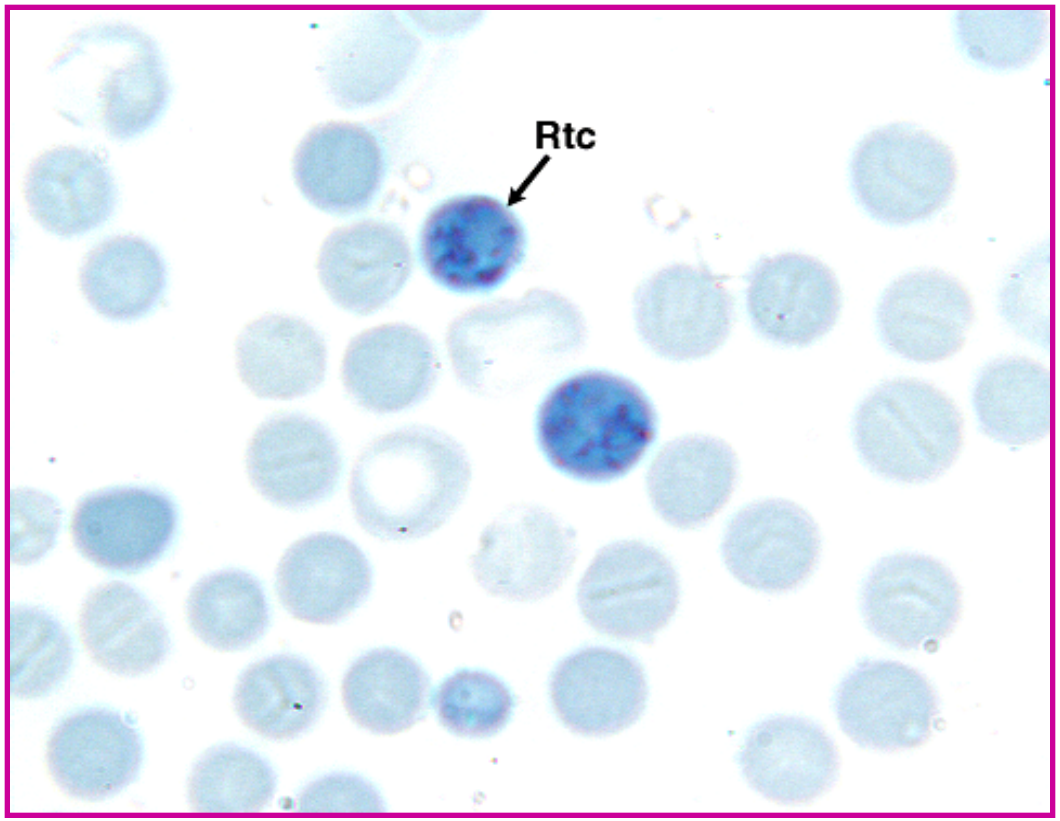


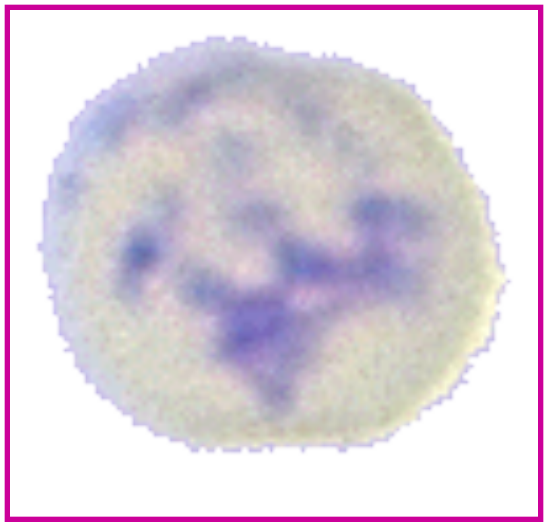
1. Decrease in size

2. Loss of nucleus

3. Accumulation of Hb

RETICULOCYTES





Normal Reticulocyte Count < 1 %

(reflects the amount of effective erythropoiesis in bone marrow)

Factors determining # of RBCs

1. O_2 requirements

2. O_2 availability

Variations in RBC counts at different altitudes

ALTITUDE (1000's feet)	pO_2 (mmHg)	RBC (x 10^6/µL)
0.7	150	4.5
4.4	120	5.2
12.0	100	6.8
15.6	90	7.8
18.2	85	8.3

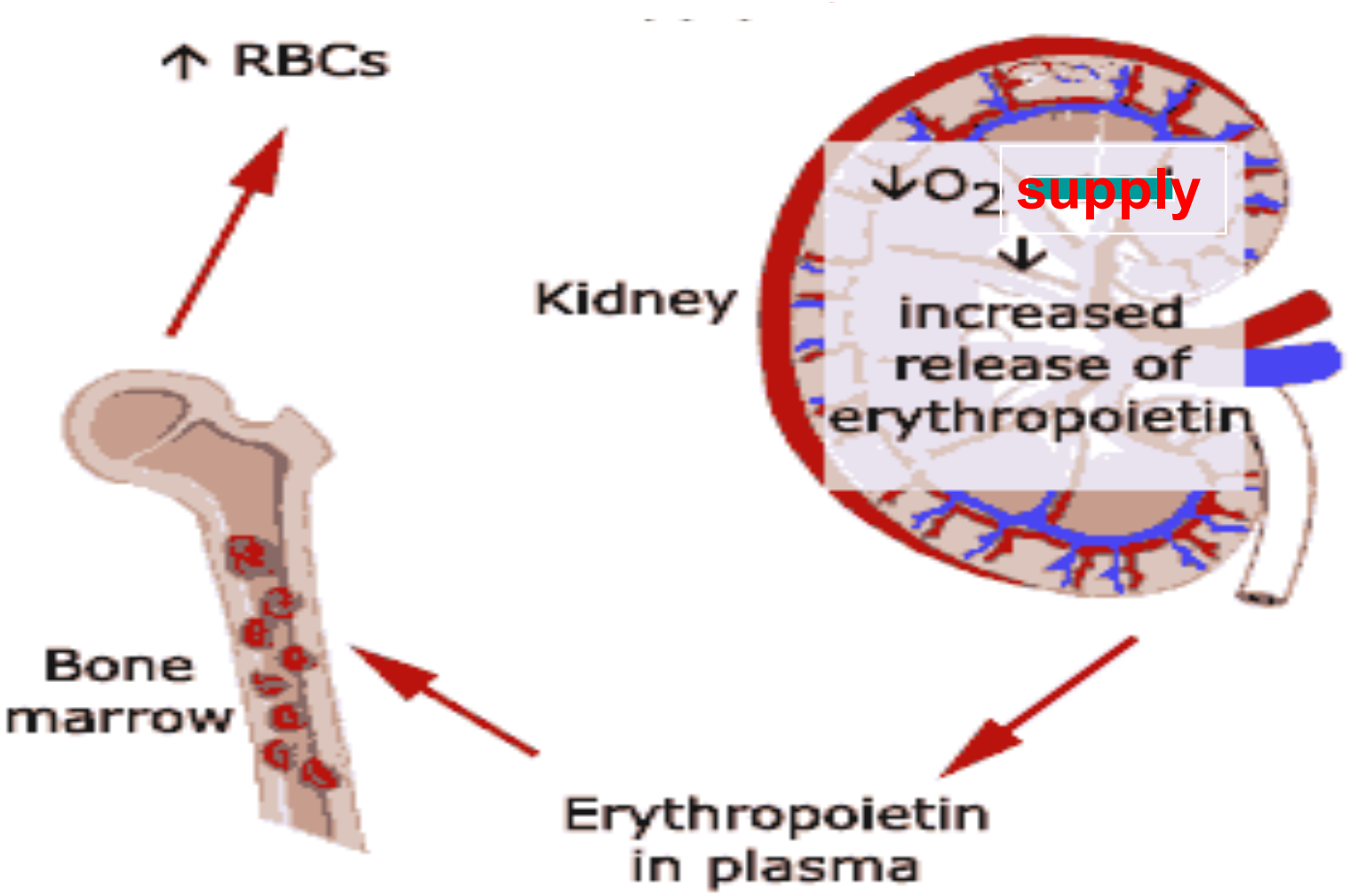
ERYTHROPOIETIN

A glycoprotein hormone/cytokine produced largely by the **kidney**

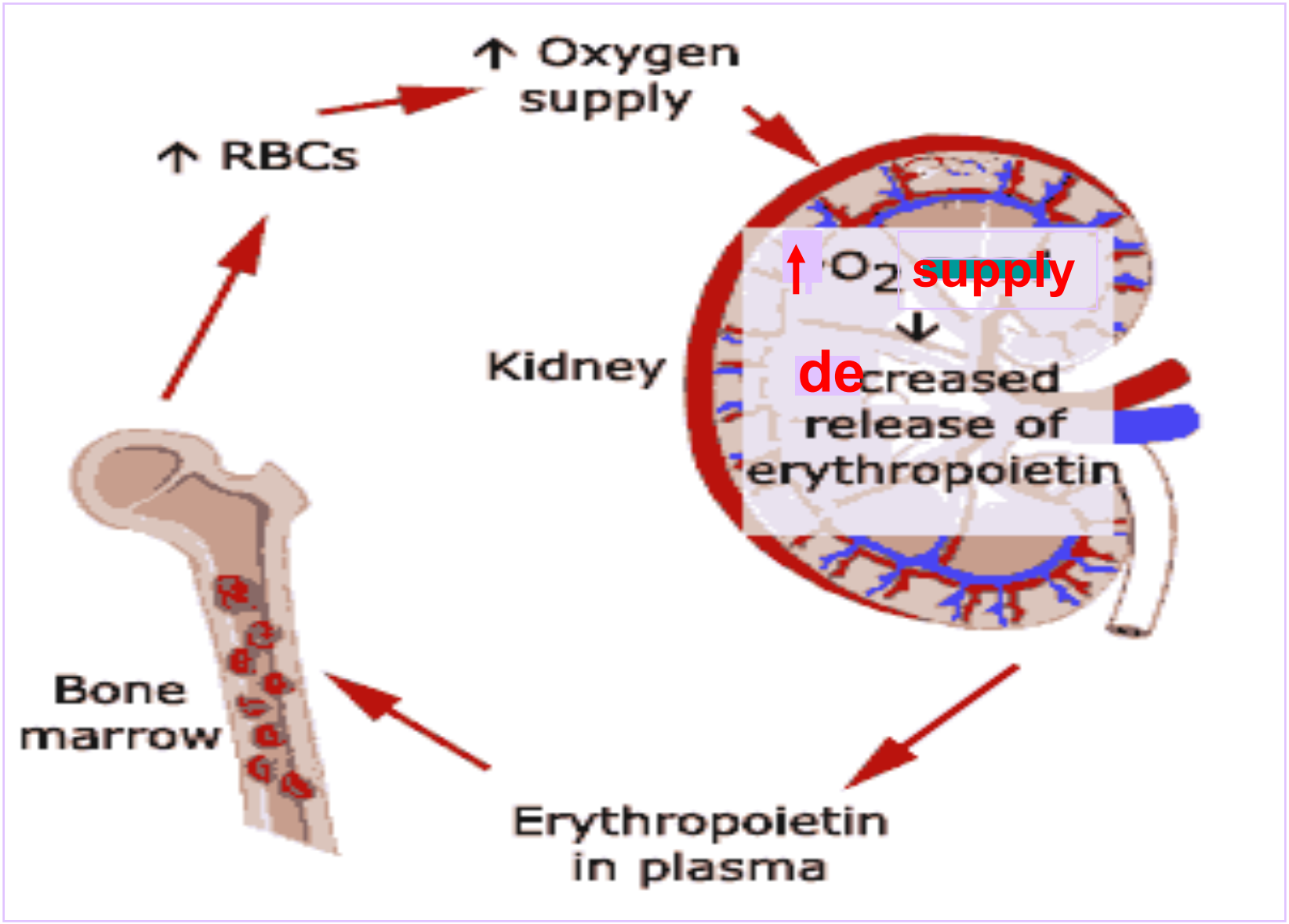
Stimulus for its release is **Hypoxia** **(which may result from decreased RBC count, or decreased availability of O_2 to blood, or increased tissue demand for O_2)**

It has been purified, sequenced, gene has been cloned, and **EPO** has been produced by recombinant DNA technology

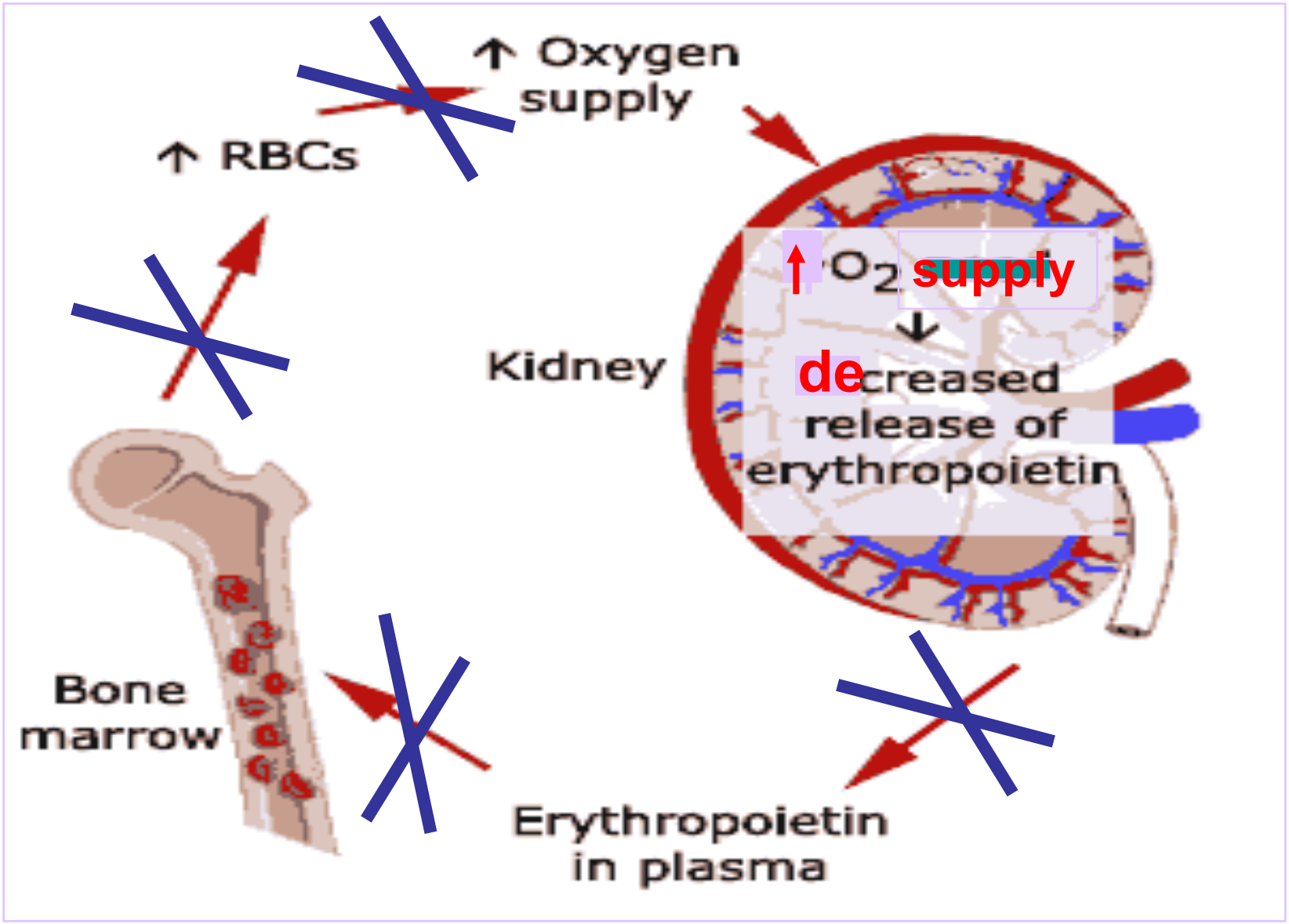
REGULATION OF ERYTHROPOIESIS



REGULATION OF ERYTHROPOIESIS

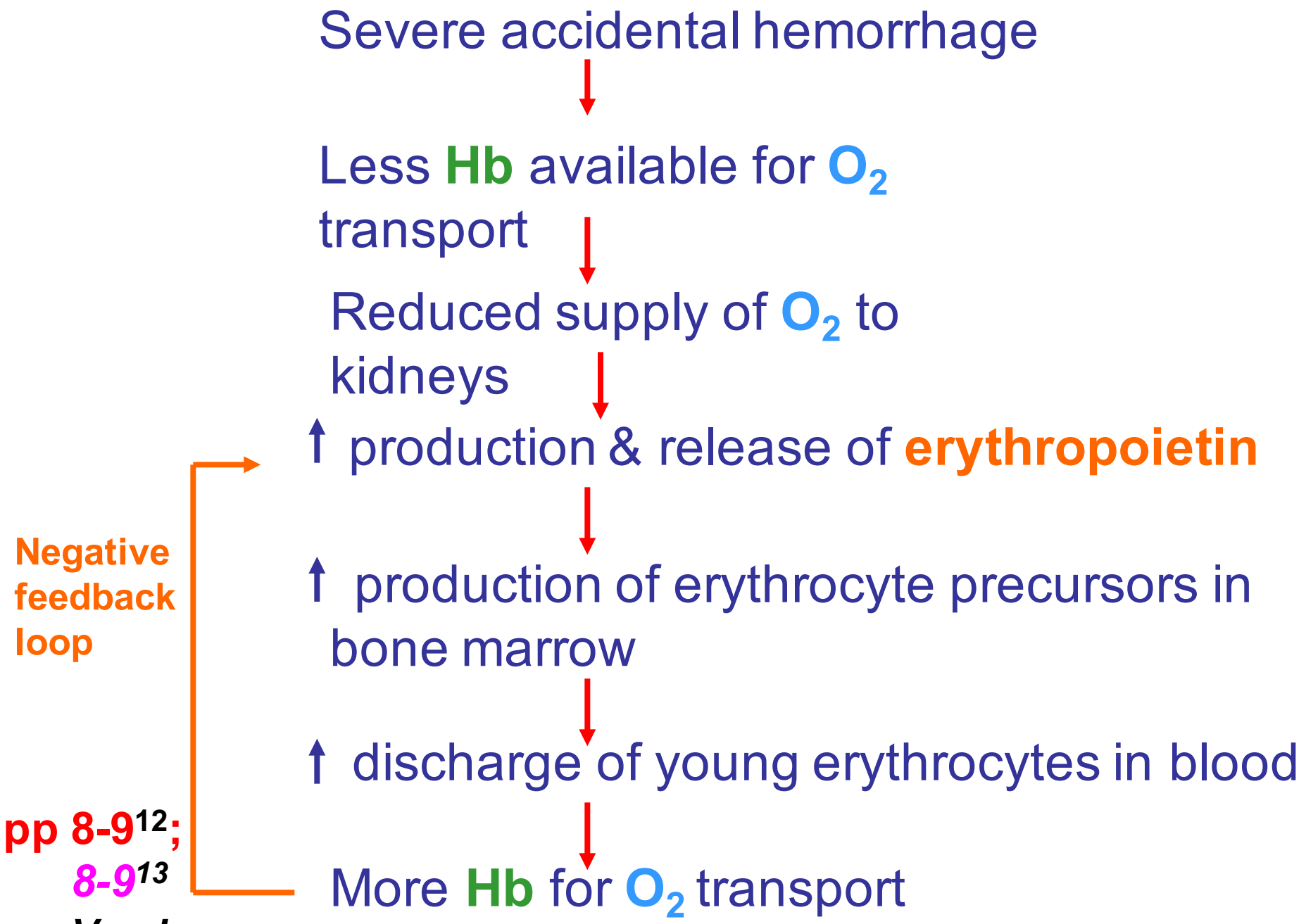


REGULATION OF ERYTHROPOIESIS



Regulation of Erythropoiesis

Erythropoietin, released from the kidney in presence of hypoxia, stimulates the bone marrow to produce more RBCs

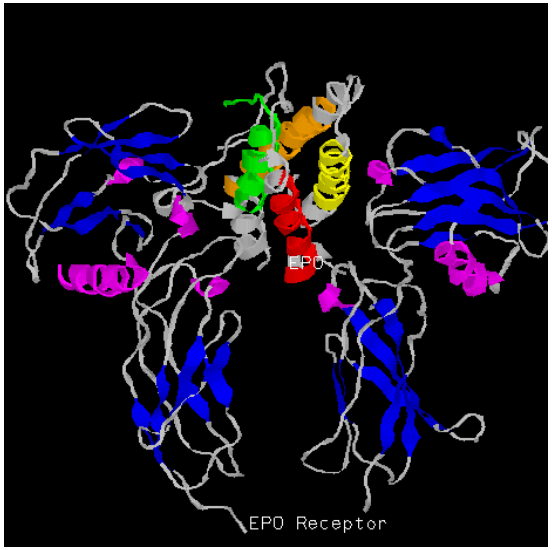


pp 8-9[12]; *8-9*[13]

Vander

p 419[12]; *430*[13]*Vander*

ERYTHROPOIETIN ACTION

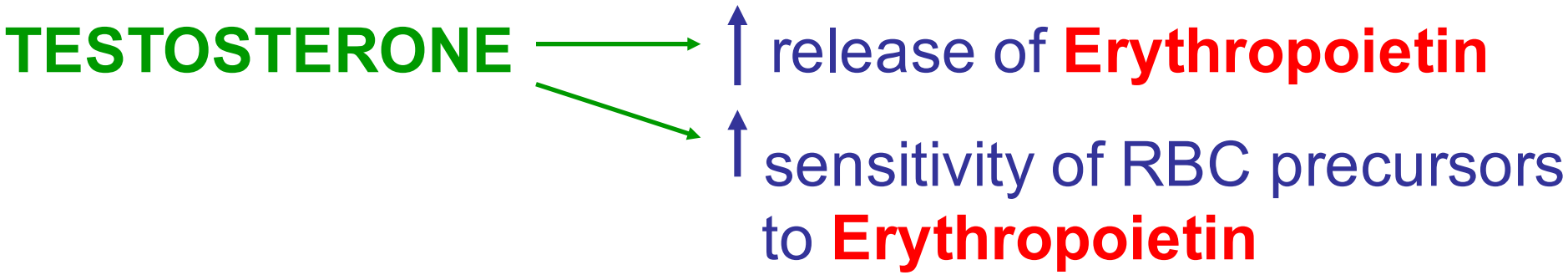


EPO Accelerates Maturation

Pluripotent Stem Cell → Committed Stem Cell → Reticulocytes → Mature RBC

EPO Stimulates Proliferation

HORMONAL EFFECTS ON ERYTHROPOIETIN



ESTROGEN has the opposite effects

Destruction of RBCs

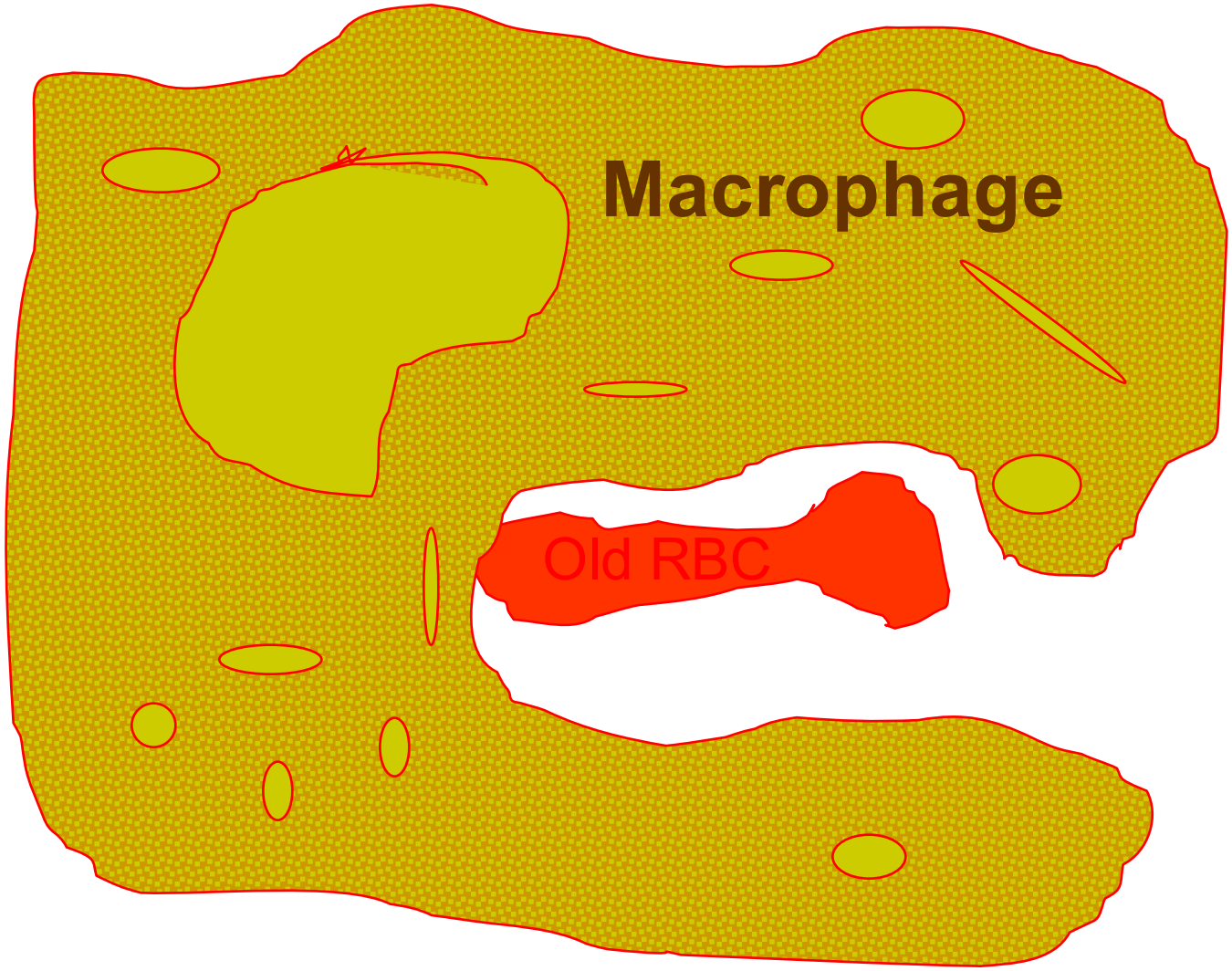
Life Span of **RBCs** **120 days**

(during that time, each RBC travels the equivalent of 300 miles!)

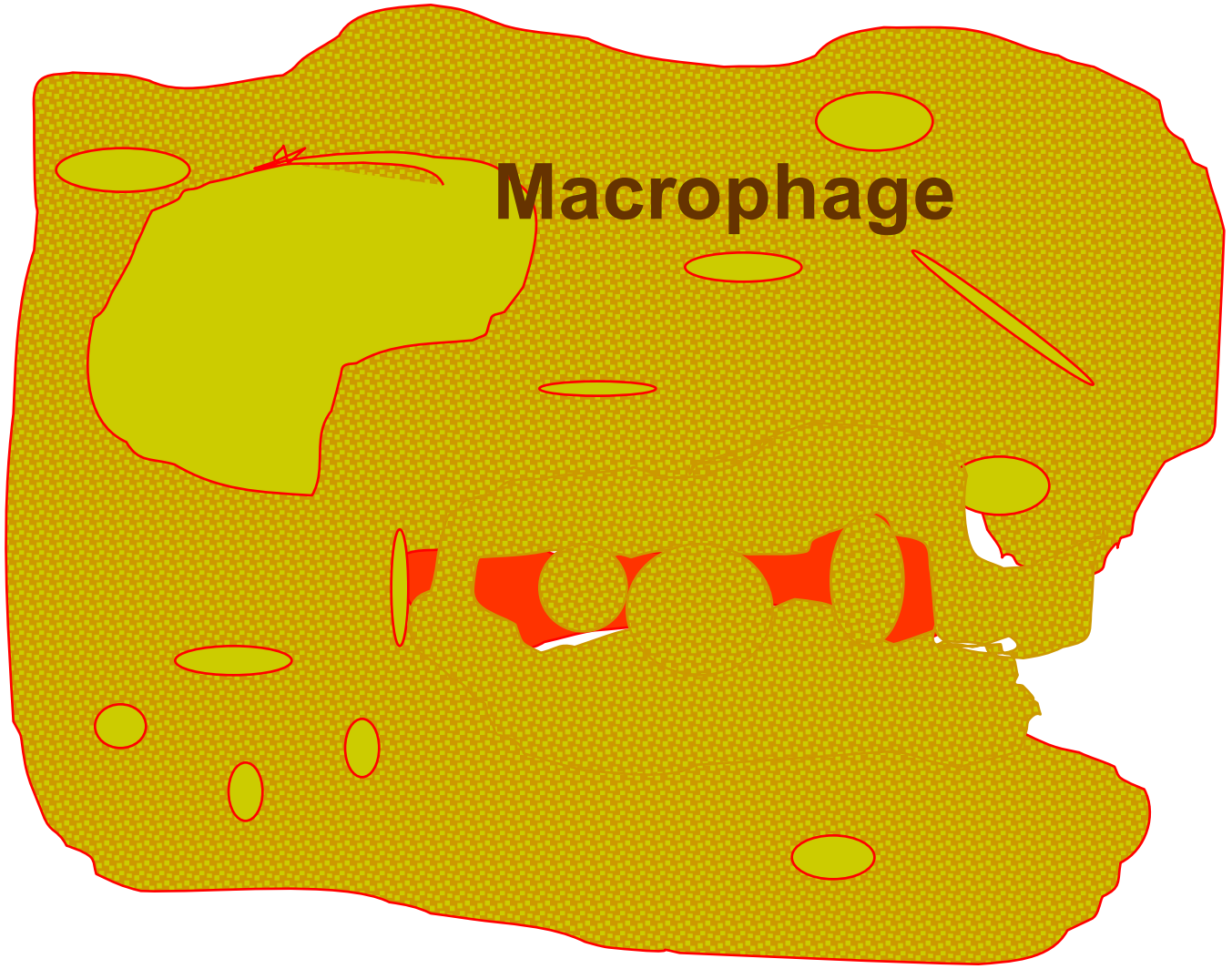
NOTHING prolongs RBC lifespan!

Old **RBCs** are recognized as such and are removed from the circulation by a system of highly phagocytic cells known as **MACROPHAGES**

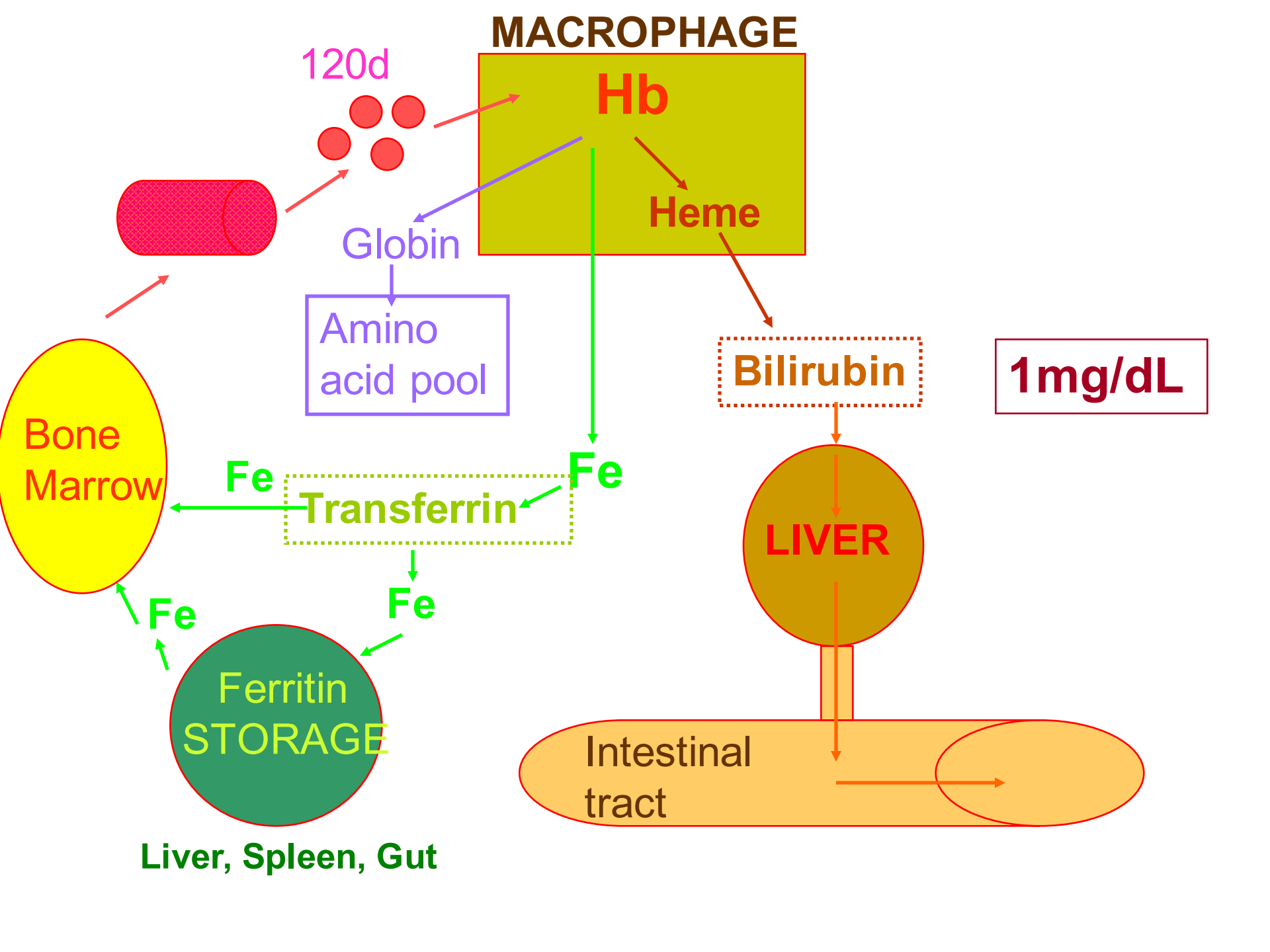
Phagocytosis of old RBC by Macrophage

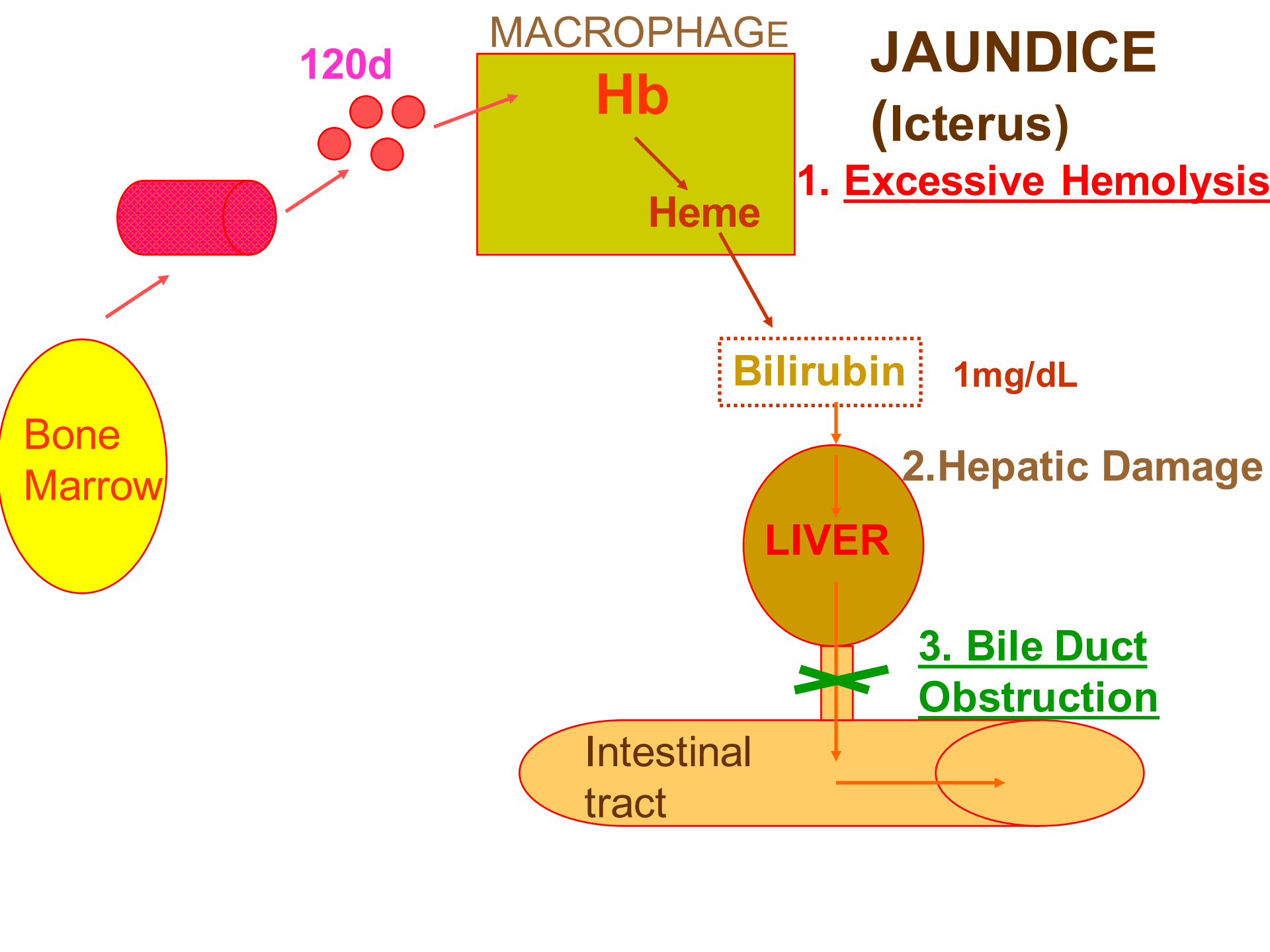


Phagocytosis of old RBC by Macrophage



RBC membrane “digested”, contents released


MACROPHAGE
120d
Hb
Heme
Globin
Amino acid pool
Bilirubin
1mg/dL
Bone Marrow
Fe
Transferrin
Fe
LIVER
Fe
Fe
Ferritin STORAGE
Intestinal tract
Liver, Spleen, Gut


MACROPHAGE
120d
Hb
Heme
JAUNDICE
(Icterus)
1. Excessive Hemolysis
Bone Marrow
Bilirubin
1mg/dL
2.Hepatic Damage
LIVER
3. Bile Duct Obstruction
Intestinal tract

NORMAL DYNAMICS FOR RBCs

PRODUCTION = DESTRUCTION

ABNORMAL DYNAMICS

PRODUCTION > DESTRUCTION → **POLYCYTHEMIA**

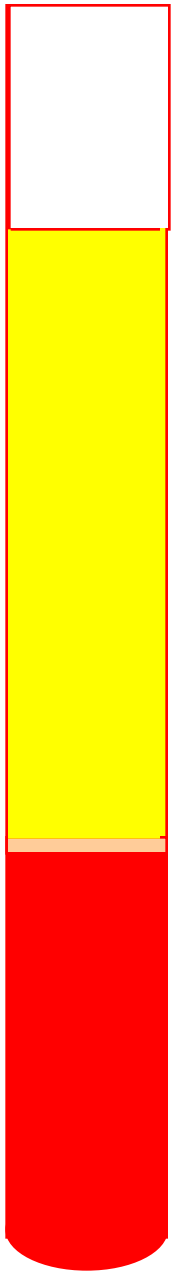
PRODUCTION < DESTRUCTION → **ANEMIA**

Clinical Indices

- Number of RBCs

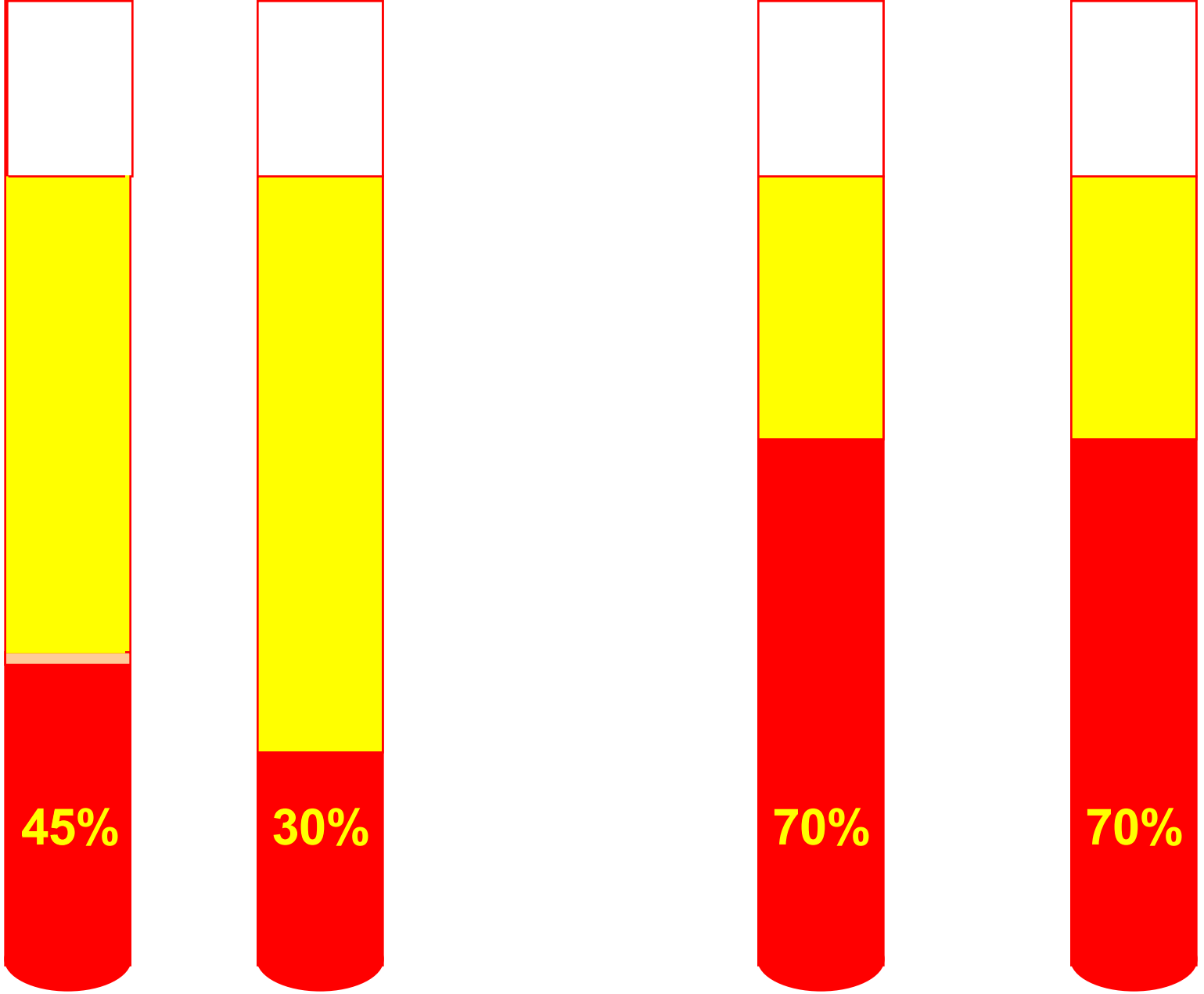
- Amount of Hb

- Hematocrit



HEMATOCRIT

That percentage of Blood Volume occupied by Red Blood Cells



Normal

Anemia

Fluid Retention ?

Polycythemia

Dehydration ?

POLYCYTHEMIA

p.420[12]; 431[13] Vander

Polycythemia:

>18g% Hb

> 6 x 10^6 RBC/uL

Normal:

16 g%

5-5.5 x 10^6 RBC/uL

Relative - due to ↓ plasma volume

Absolute

1. Physiological
2. Pathological

Physiological Polycythemia

(secondary to ↑O_2 needs or ↓O_2 availability)

- at high altitudes

- increased physical activity

- chronic lung disease

- heavy smoking

Pathological Polycythemia

- Tumours of Cells producing **Erythropoietin**

- Unregulated Production by Bone Marrow

Polycythemia vera - 7-8 x 10^6 RBC/uL

- Ht ~70%

What is the problem in Polycythemia?

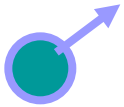
↑ blood viscosity

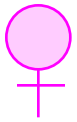
Sluggish blood flow ⟶ blood clots

ANEMIA pp. 419- 420[12]; 431[13] Vander

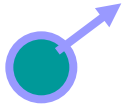
Decrease in the oxygen-carrying capacity of blood

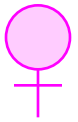
1. RBC count ↓

< 4 x 10^6/uL 

< 3.2 x 10^6/uL 

2. Hb content ↓

< 11g% 

< 9g% 

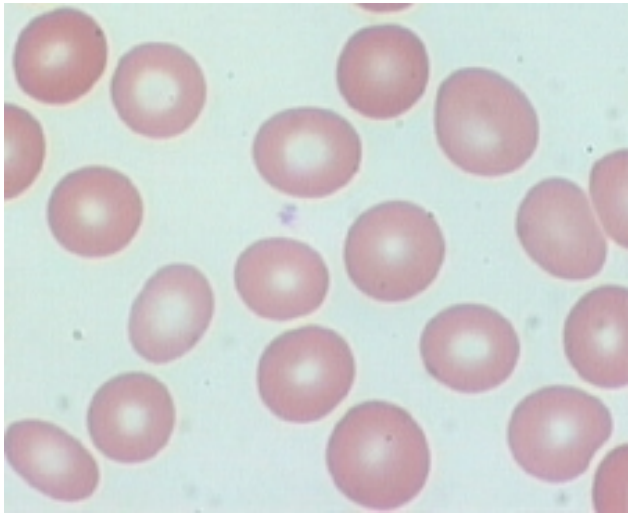
Classification of Anemias

MORPHOLOGIC

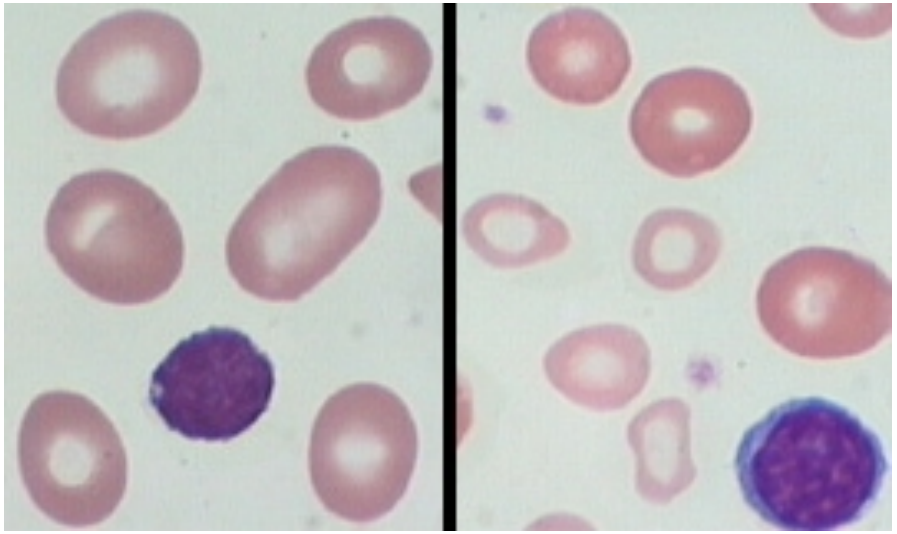
1. MICROCYTIC (<80u^3) NORMOCYTIC (80-94u^3) MACROCYTIC (>94u^3)

2. NORMOCHROMIC (~33%) HYPOCHROMIC (<33%)

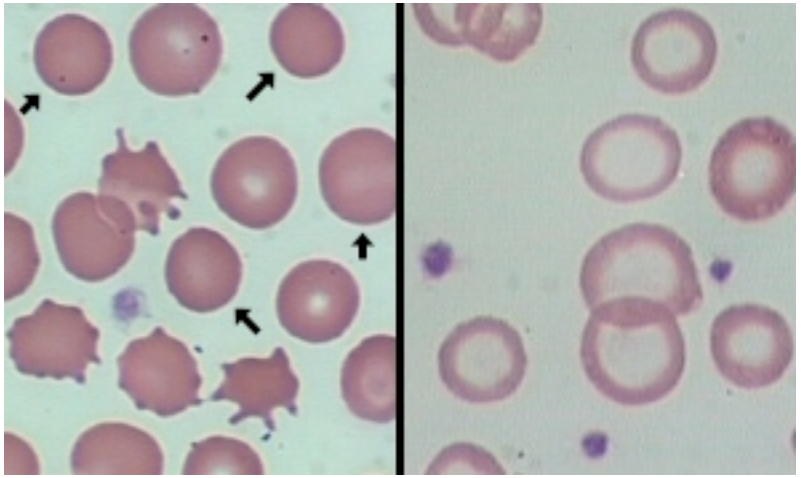
ANEMIAS



NORMOCYTIC



MACROCYTIC MICROCYTIC



NORMOCHROMIC HYPOCHROMIC

Classification of Anemias

ETIOLOGIC

1. Diminished Production

2. Ineffective Maturation

3. Increased Destruction

Etiologic Classification of Anemia

1. Diminished Production

(i) abnormal site
(ii) abnormal stimulus
(iii) inadequate raw materials

re (i) **APLASTIC (HYPOPLASTIC) ANEMIA**

ETIOLOGY : a. unknown

b. exposure to radiation

c. chemicals or drugs

CLASSIFICATION: **Normocytic, Normochromic**

re (ii) STIMULATION FAILURE

ETIOLOGY: renal disease

CLASSIFICATION: Normocytic, Normochromic

re (iii) inadequate raw materials

IRON DEFICIENCY ANEMIA (most common type)

ETIOLOGY: (i) ↑ requirements (infancy, adolescence, pregnancy)

(ii) inadequate supplies due to

- **Failure to absorb Fe**
- **Dietary deficiency**
- **Loss of Fe in hemorrhage**

CLASSIFICATION: Microcytic, Hypochromic

p.418[12]pp.430-31[13]Vander

IRON

Total Amount in Body **4g**

Daily Intake in Diet : ~15-20 mg

Daily absorption from gut (depending on need by body): ~1mg ♂

~2mg ♀

Normal erythropoiesis requires **25 mg Fe/d**

Normal RBC destruction ⟶ **25 mg Fe/d**

(1mg/d lost

24 mg/d recycled)


require 1mg/d


require 2mg/d

WHY?

1g **Hb** contains 3.5 mg **Fe**

15g **Hb**/100 ml of blood ⟶ ~50 mg **Fe**

Menstrual loss ~ 50 ml blood/month

Therefore, lose **~ 25 mg Fe**/month

+ 28 mg **Fe**/month (cf.  1mg/d)

~ 50 mg/month or 2 mg/d

Classification of Anemias

ETIOLOGIC

1. Diminished Production
2. Ineffective Maturation
3. Increased Destruction

2. INEFFECTIVE MATURATION (Maturation Failure Anemia)

ETIOLOGY: deficiencies of **Vitamin B12** and **Folic Acid**

(Both are required for normal synthesis of DNA)

CLASSIFICATION: Macrocytic, Normochromic

(i) Vitamin B_{12}

(usually failure to absorb)

(ii) Folic Acid

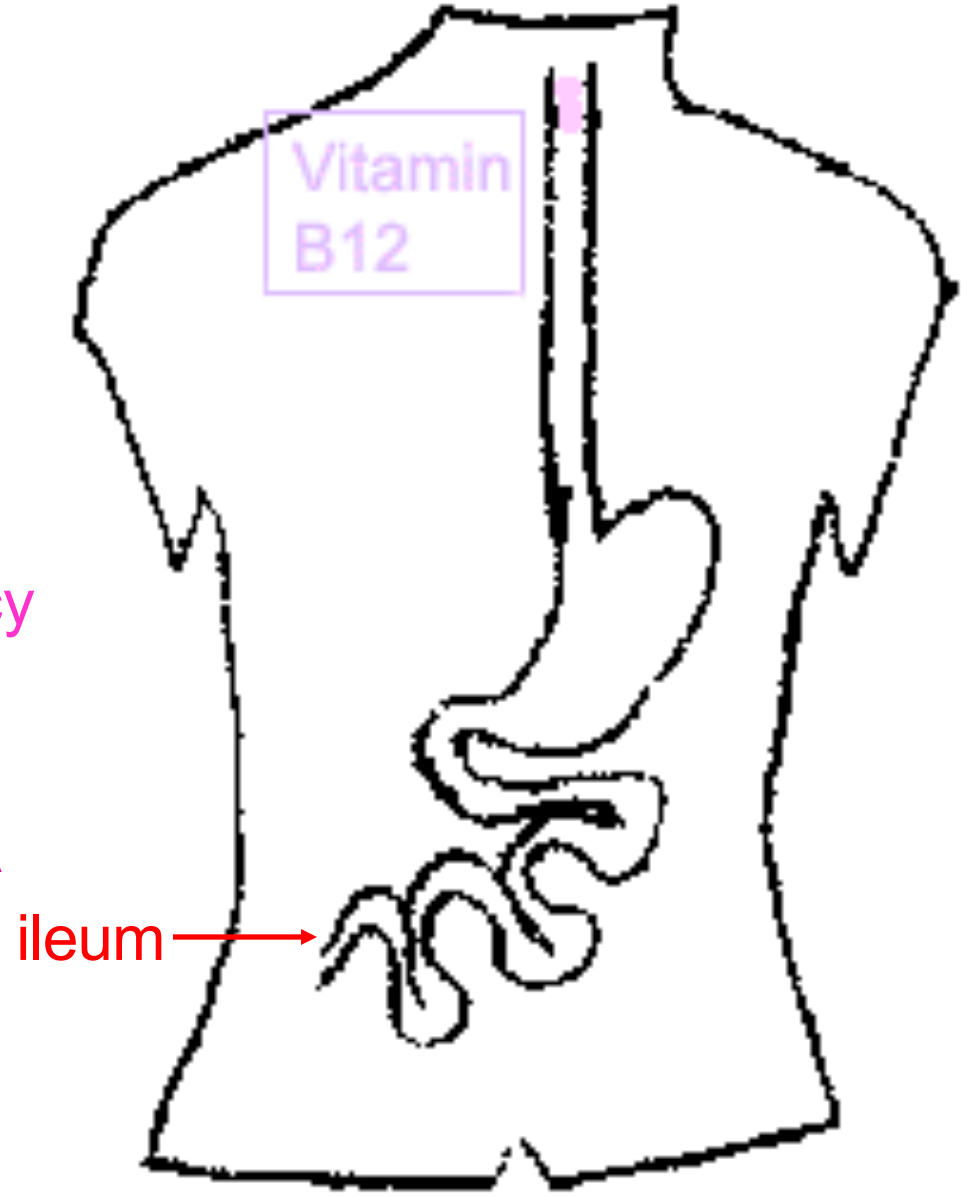
(usually dietary absence, overcooking vegetables)

Vitamin B12 Absorption

Intrinsic Factor Deficiency

↓

Pernicious Anemia



3. SURVIVAL DISORDERS

(Hemolytic Anemias – may be accompanied by jaundice)

ETIOLOGY:

(i) Congenital

(ii) Acquired

re (i)

a) Abnormal Membrane Structure (less flexible, more fragile) (e.g., hereditary spherocytosis)

b) Abnormal Enzyme Systems (abnormal metabolism)

c) Abnormal **Hb** structure (e.g., sickle cell anemia) (e.g., Thalassemia – deficient synthesis of globin amino acid chains)

re (ii)

a) Toxins

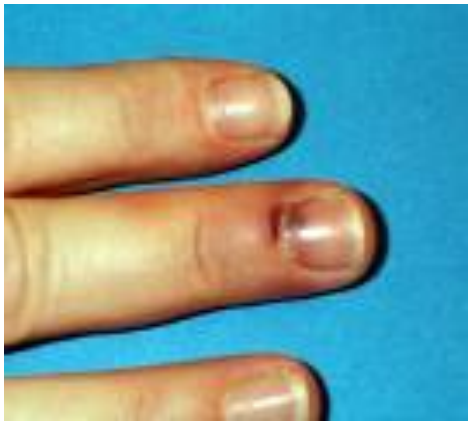
b) Drugs

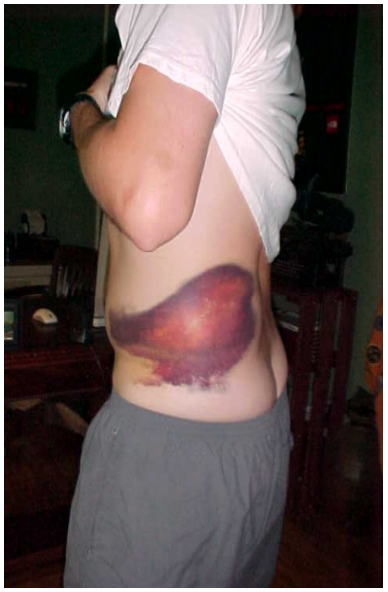
c) Antibodies

LOSS OF BLOOD - Hemorrhage

a) external

b) internal (into tissues)





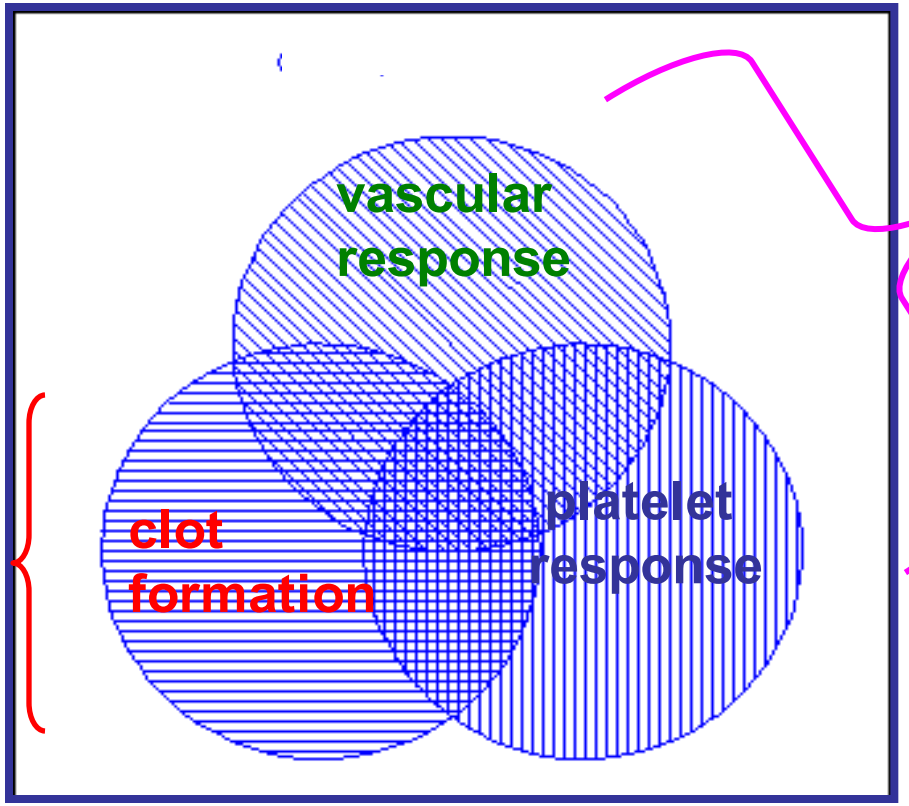
HEMATOMA = accumulation of blood in tissues

ARREST of BLEEDING- Hemostasis

pp.422- 427[12]; 432- 439[13] Vander

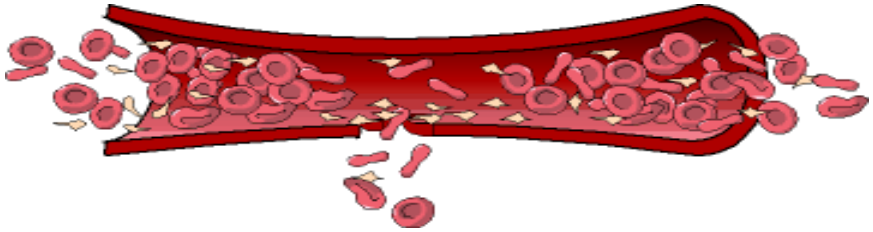
HEMOSTASIS - The arrest of bleeding following vascular injury

A number of interacting, overlapping mechanisms:



HEMOSTASIS

Vascular Injury



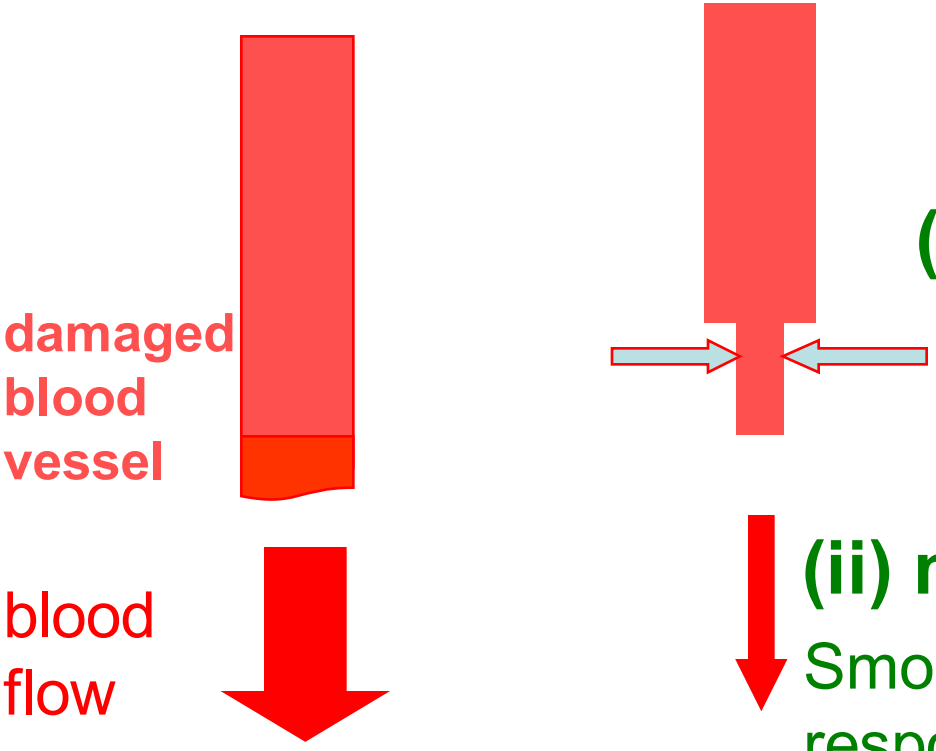
Vasoconstriction

Platelet Plug Formation

Blood Clot Formation

(i) Vascular Response

Vasoconstriction



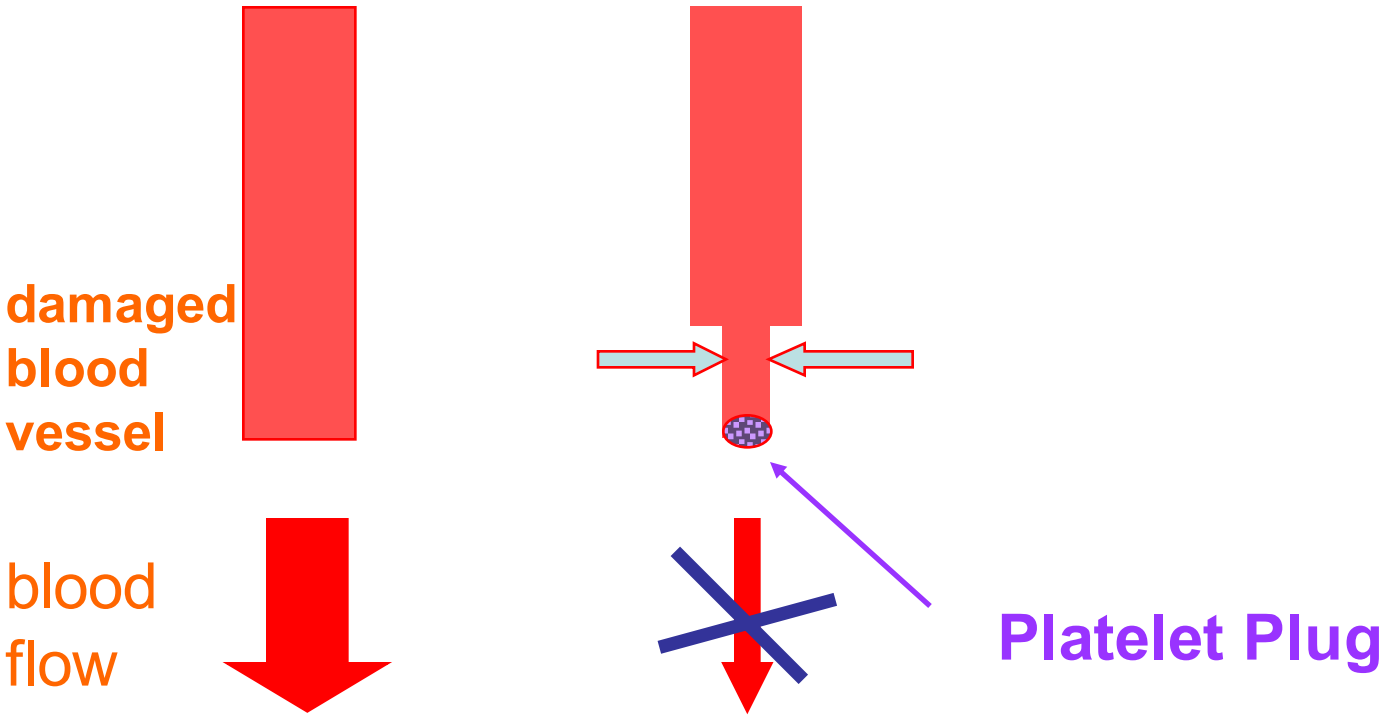
(i) nervous reflex

(ii) myogenic response

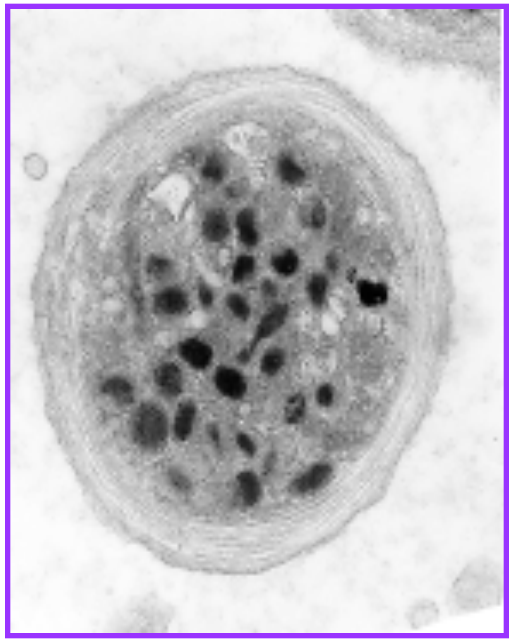
Smooth muscle cells in vessel wall respond to injury by contracting

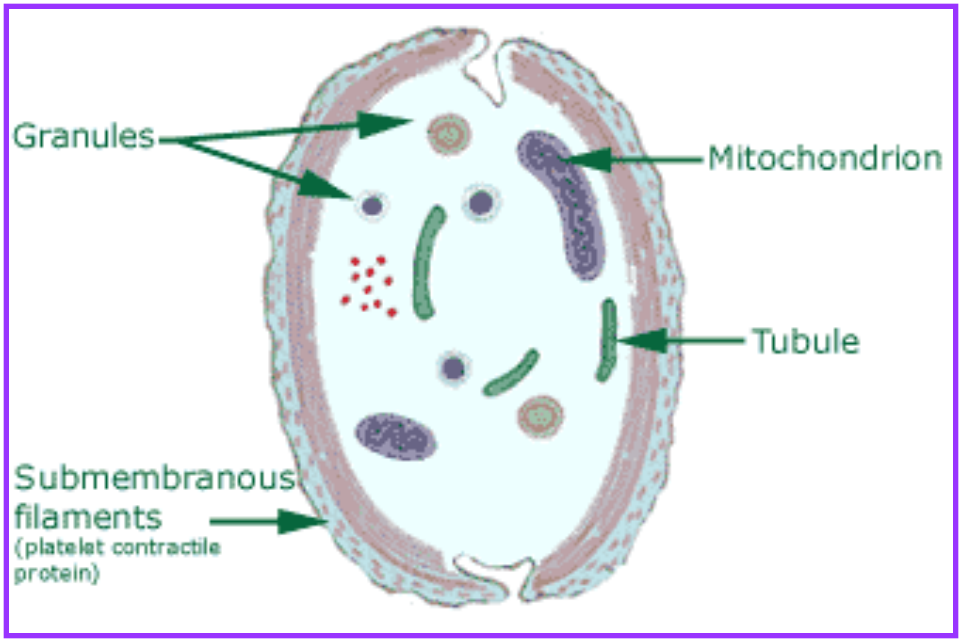
(iii) chemical vasoconstrictors

(ii) Platelet Response (white thrombus)



Platelet Structure





~ 2-4 um diameter

NO nucleus

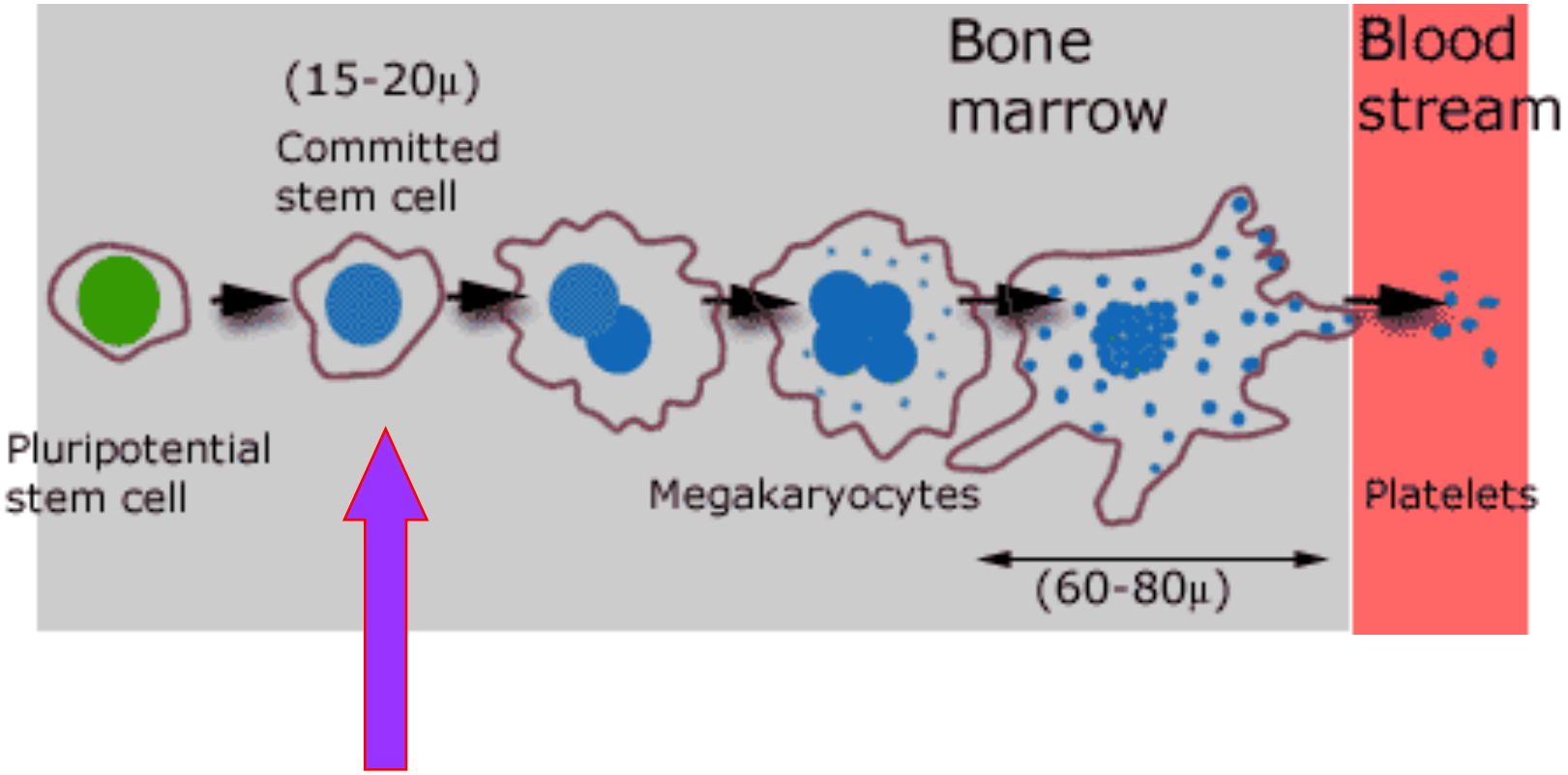
Many granules – factors for vasoconstriction, platelet aggregation, clotting, growth, etc..

Many filaments, microtubules, mitochondria, sER

~250,000/uL

Life Span: 7-10d

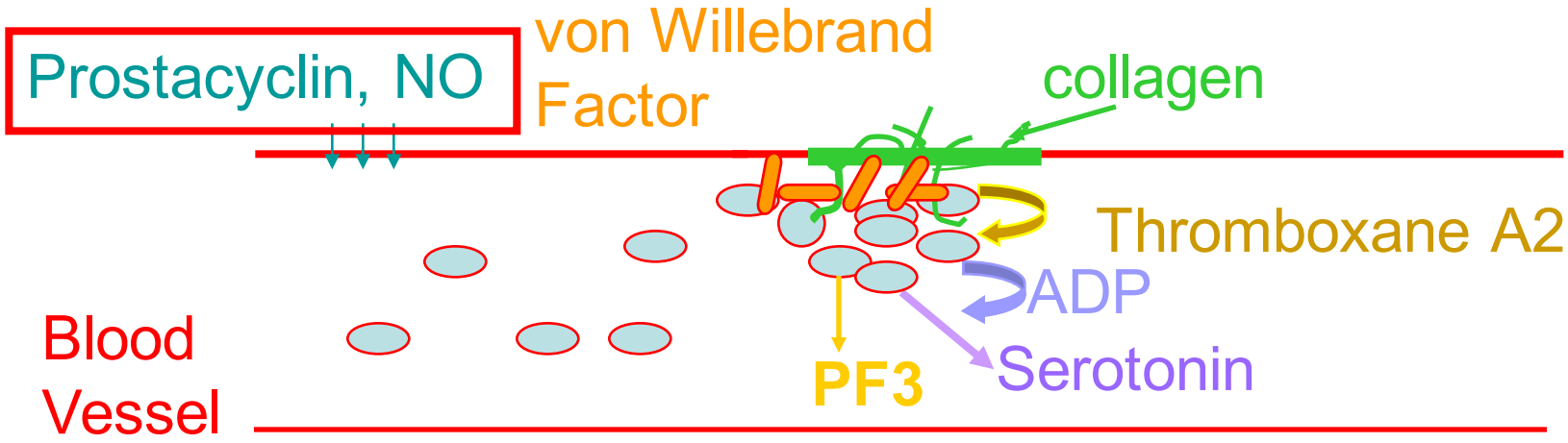
Platelet Production



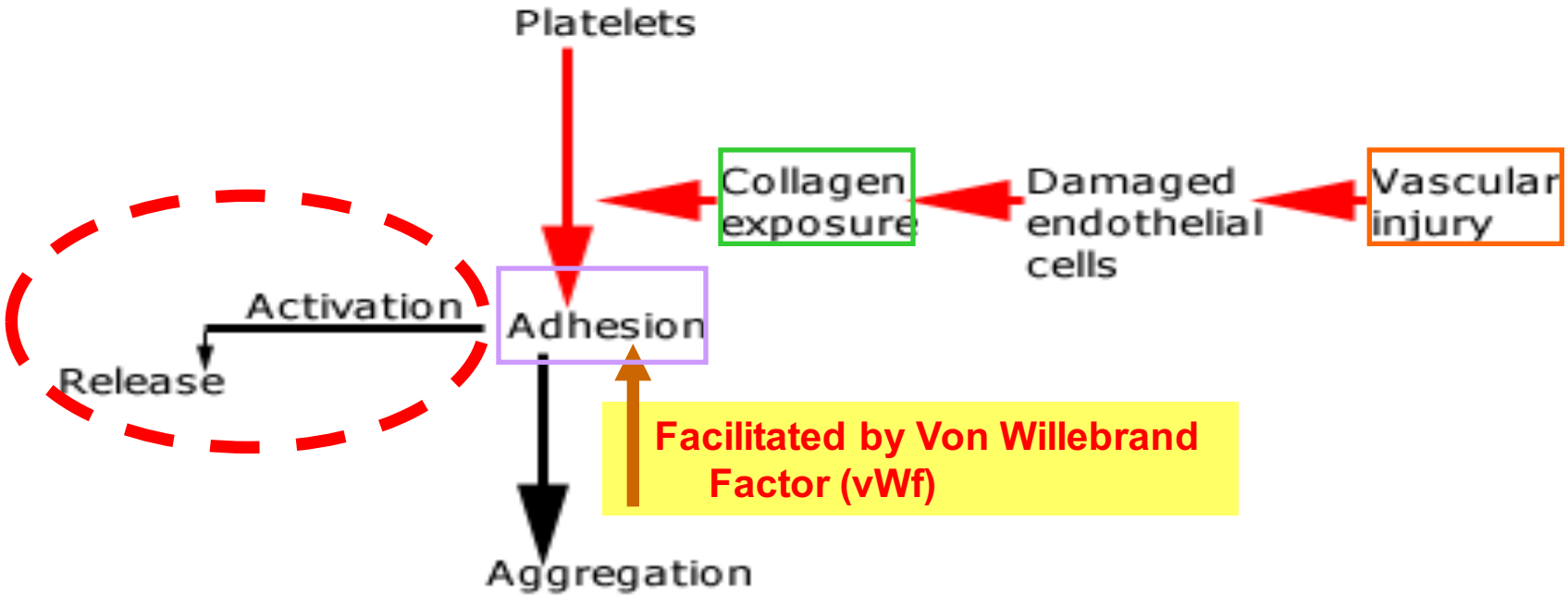
Thrombopoietin (mostly from liver)

Platelet Plug Formation

1. **Adhesion**
2. **Activation and release of cytokines**
3. **Aggregation**
4. **Consolidation**

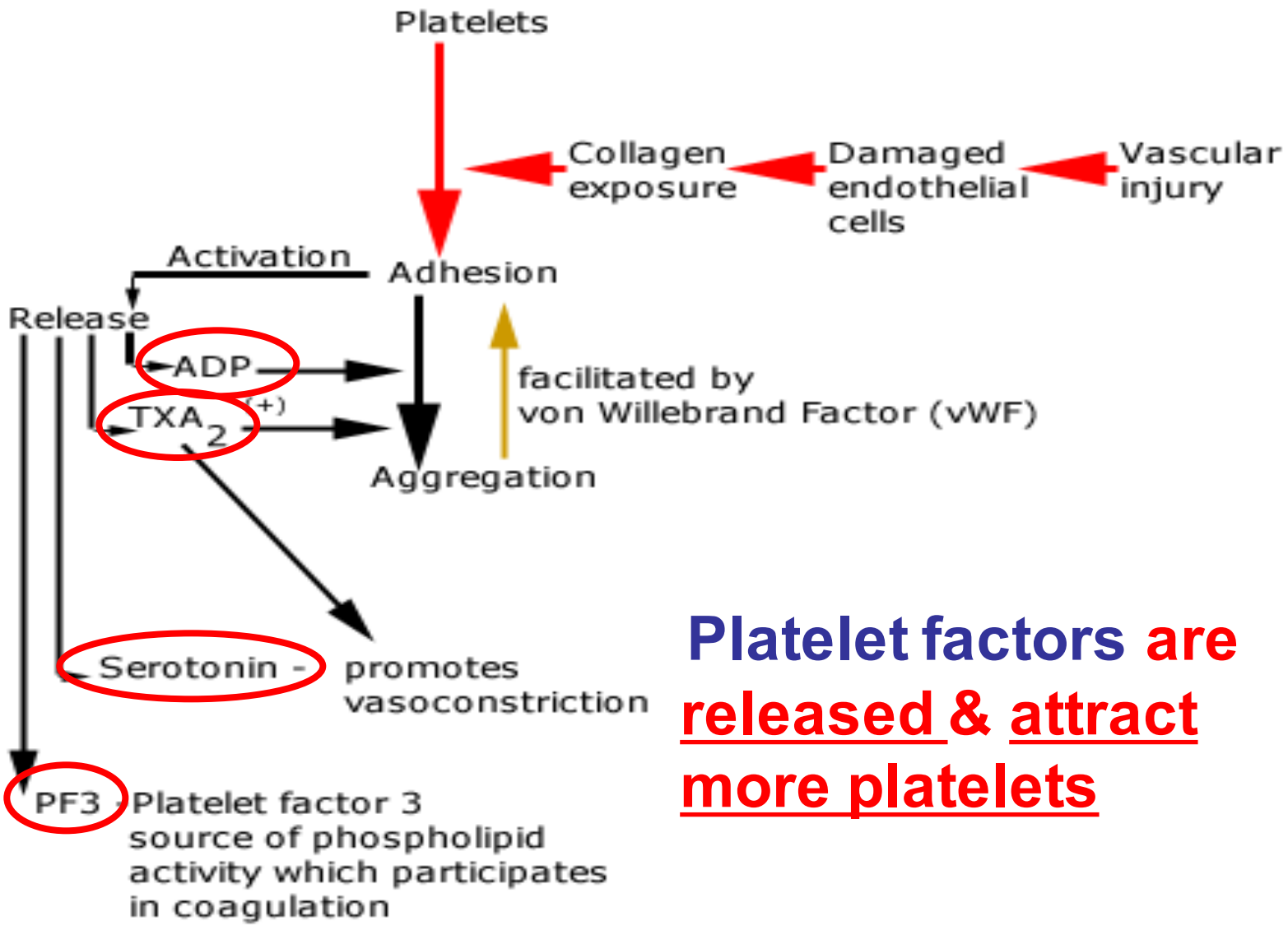


Platelet Plug Formation



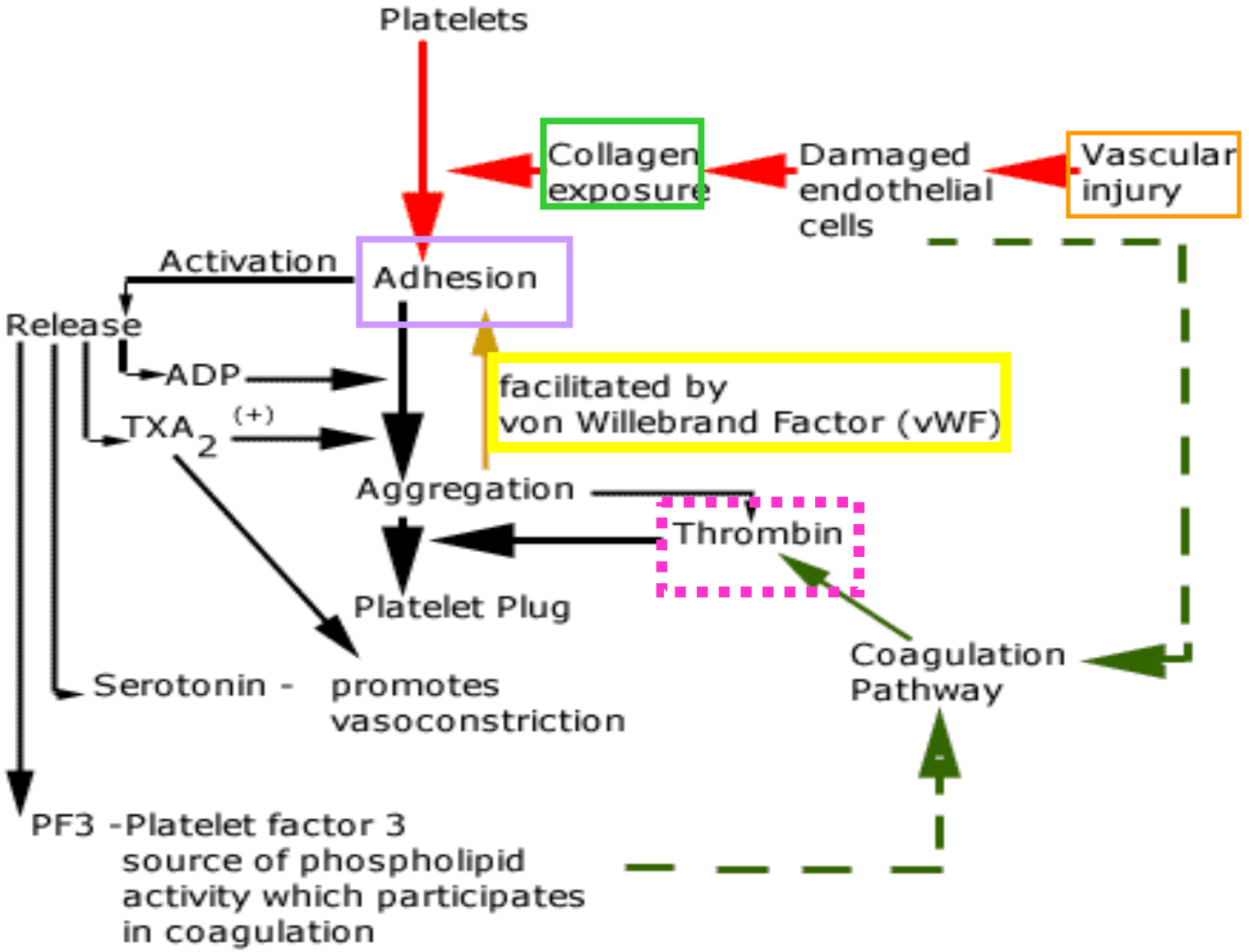
Exposed collagen binds & activates platelets

Platelet Plug Formation



Platelet factors are released & attract more platelets

Platelet Plug Formation



Platelet factors also promote coagulation scheme

Platelet Functions

- (a) Release vasoconstricting agents
- (b) Form Platelet Plug
- (c) Release Clotting Factors
- (d) Participate in Clot Retraction
- (e) Promote Maintenance of Endothelial Integrity

ABNORMAL PRIMARY HEMOSTATIC RESPONSE → **Prolonged Bleeding**

1. Failure of Blood Vessel to constrict

2. Platelet deficiencies

a) Numerical **< 75,000/uL**

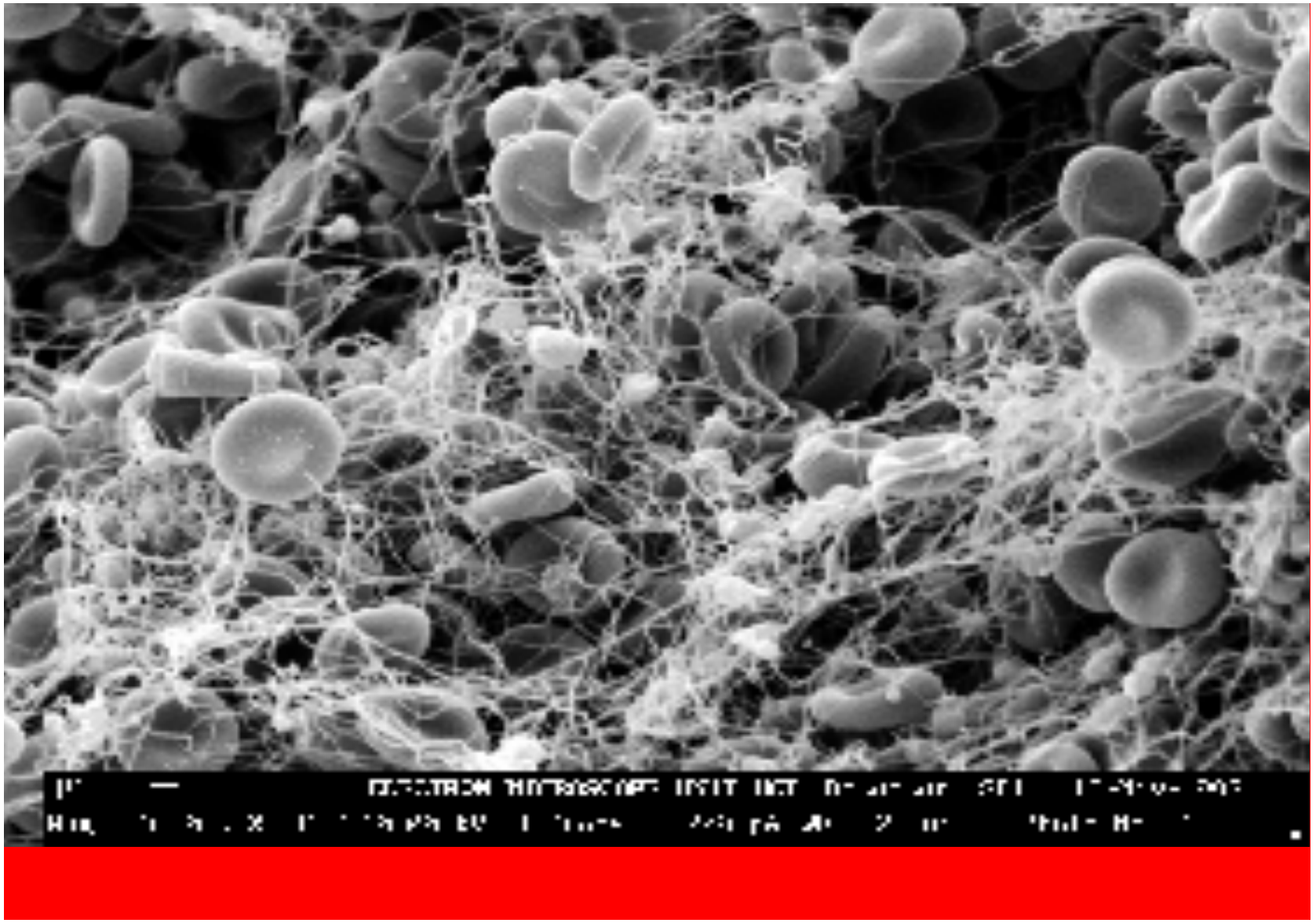
b) Functional → **congenital**

acquired

(Drugs, Toxins, Antibodies)

Aspirin (in small doses) inhibits synthesis and release of TXA2

Blood Clot = THROMBUS



Clot Formation is a function of PLASMA (RBCs are "innocent bystanders", NOT necessary for the process!!!)

CLOTTING: initiated by injury to blood vessel wall, results in sequential activation and interaction of a group of plasma proteins or clotting factors (some acting as enzymes, others as co-factors) , in the presence of Ca^{++} and some phospholipid agents

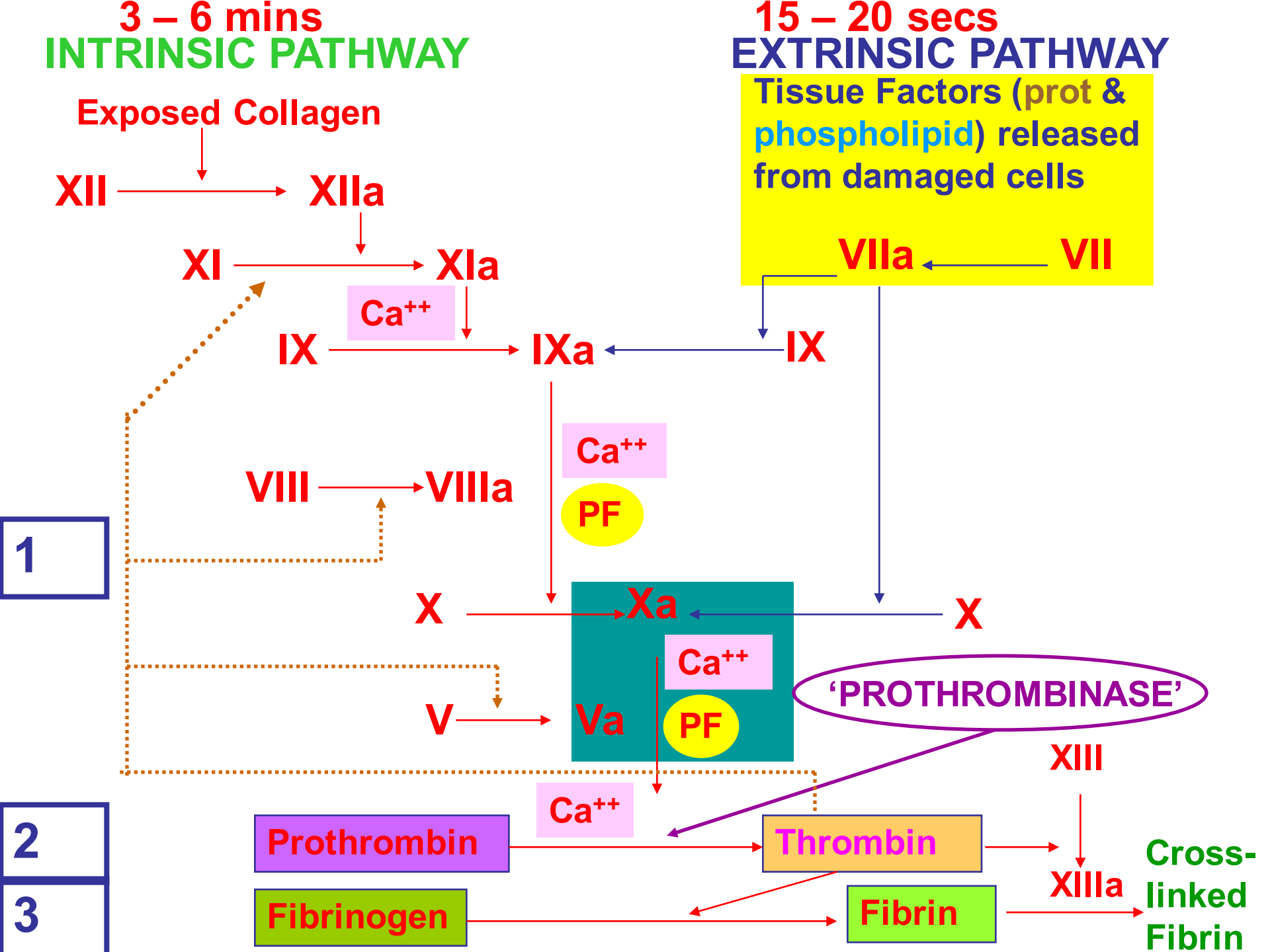
3 STAGES:

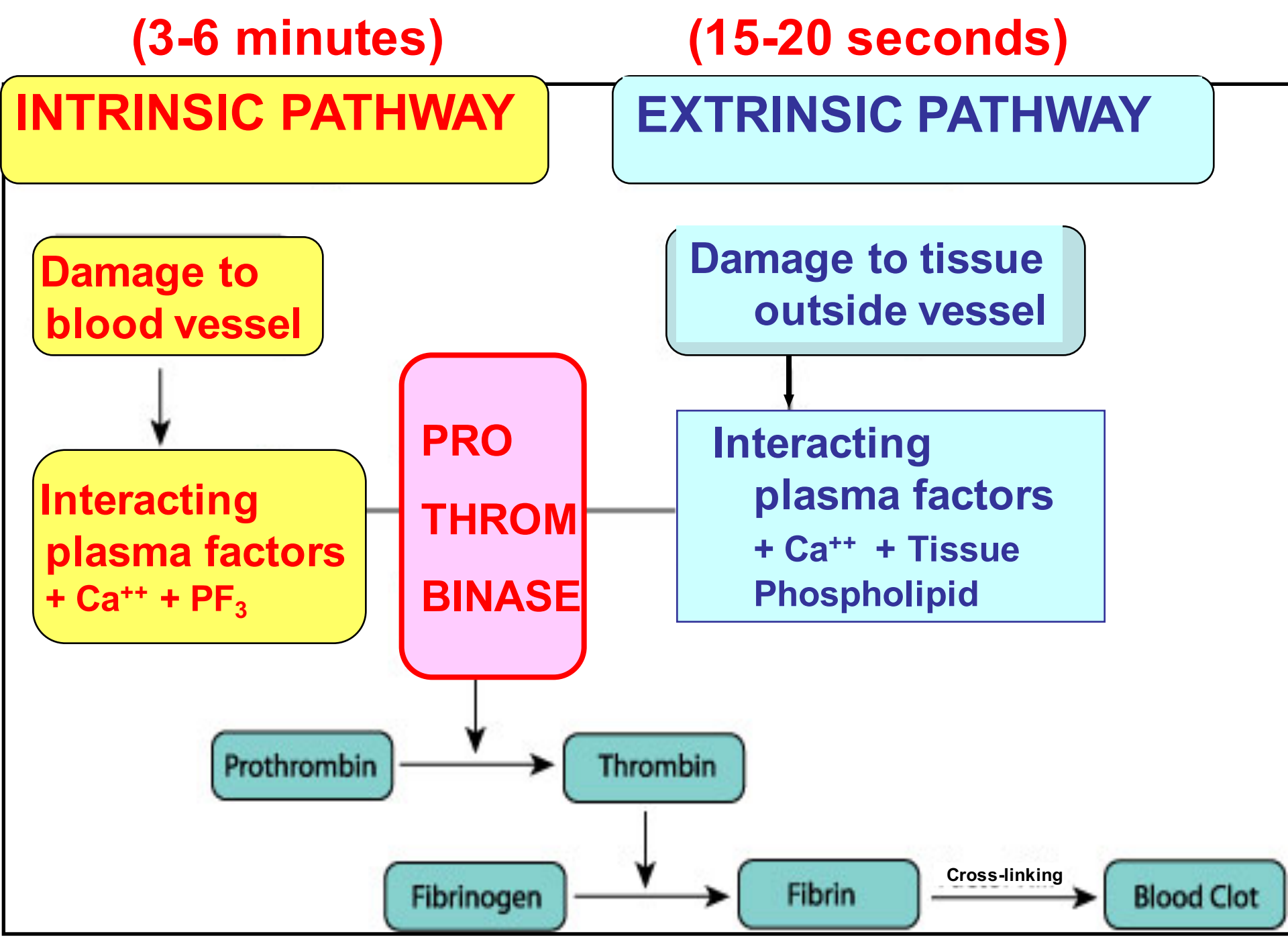
1

2

3

Protein factors named as Roman Numerals I - XIII (in order in which they were discovered)


3 – 6 mins
INTRINSIC PATHWAY
15 – 20 secs
EXTRINSIC PATHWAY
Exposed Collagen
Tissue Factors (prot & phospholipid) released from damaged cells
XII
XIIa
XI
XIa
VIIa
VII
Ca++
IX
IXa
IX
Ca++
PF
VIII
VIIIa
1
X
Xa
X
Ca++
'PROTHROMBINASE'
V
Va
PF
XIII
Ca++
2
Prothrombin
Thrombin
XIIIa
Cross-linked Fibrin
3
Fibrinogen
Fibrin


(3-6 minutes)
(15-20 seconds)
INTRINSIC PATHWAY
EXTRINSIC PATHWAY
Damage to blood vessel
Damage to tissue outside vessel
Interacting plasma factors
+ Ca++ + PF3
PRO THROM BINASE
Interacting plasma factors
+ Ca++ + Tissue Phospholipid
Prothrombin
Thrombin
Fibrinogen
Fibrin
Cross-linking
Blood Clot

INTRINSIC PATHWAY
(3-6 minutes)

EXTRINSIC PATHWAY
(15-20 seconds)

The small amounts of THROMBIN generated rapidly by the Extrinsic Scheme, are sufficient to trigger its strongly positive feedback effects on the Intrinsic Scheme to generate larger quantities of THROMBIN

Clotting is kept in check by INHIBITORS (of platelet adhesion) and ANTICOAGULANTS (naturally occurring chemicals which block one or more of the reactions of the coagulation scheme).

Please read Vander pp. 425-426[12]; 437- 439[13]

ANTICOAGULANTS:

- Heparin and antithrombin III work together to block IX, X, XI, XII
- Protein C inhibits Factors V and Viii

FACTORS IN COAGULATION

Ca^{++}

PHOSPHOLIPID

PROTEIN PLASMA FACTORS

CLOTTING FACTOR DEFICIENCIES

CONGENITAL

Hereditary deficiencies of (usually) a single factor

e.g. VIII (Hemophilia)

ACQUIRED

Usually multifactor deficiencies (e.g.,

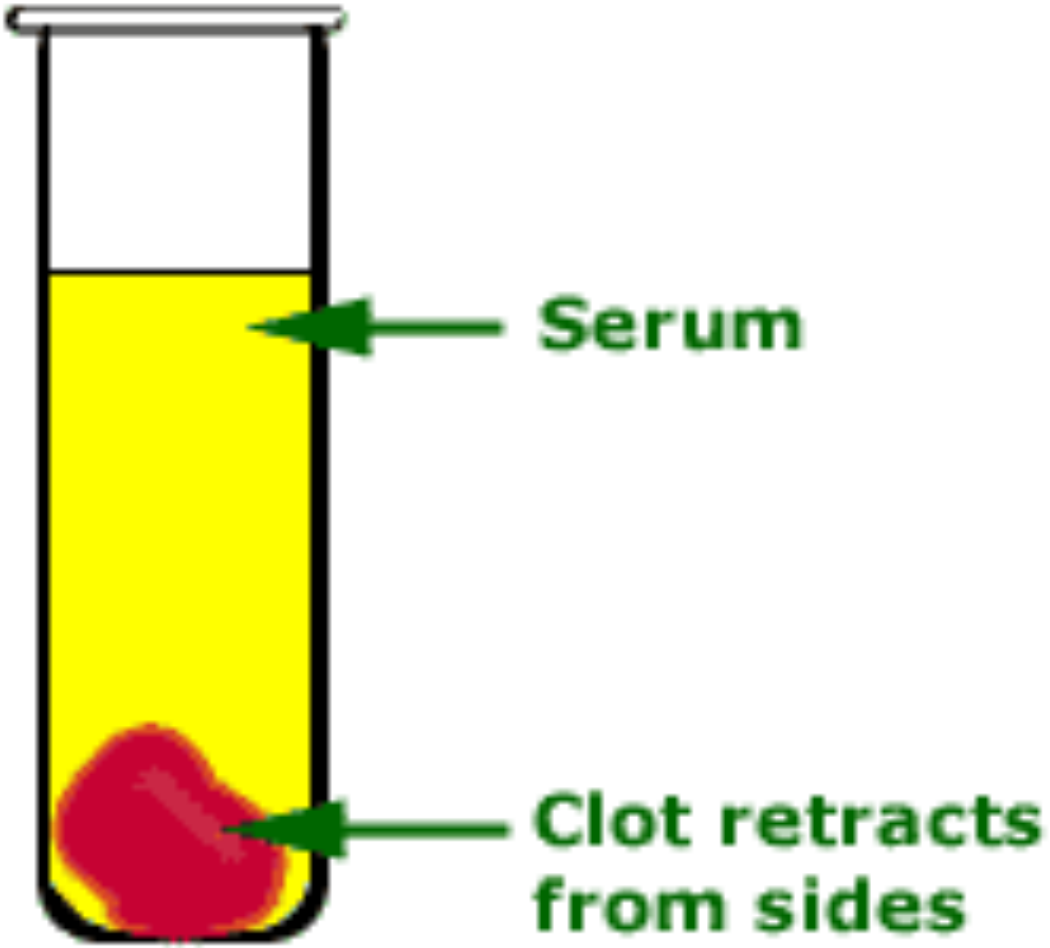
(i) liver disease

(ii) Vitamin K deficiency

(Vit. K is cofactor in synthesis of Prothrombin, VII, IX, X)

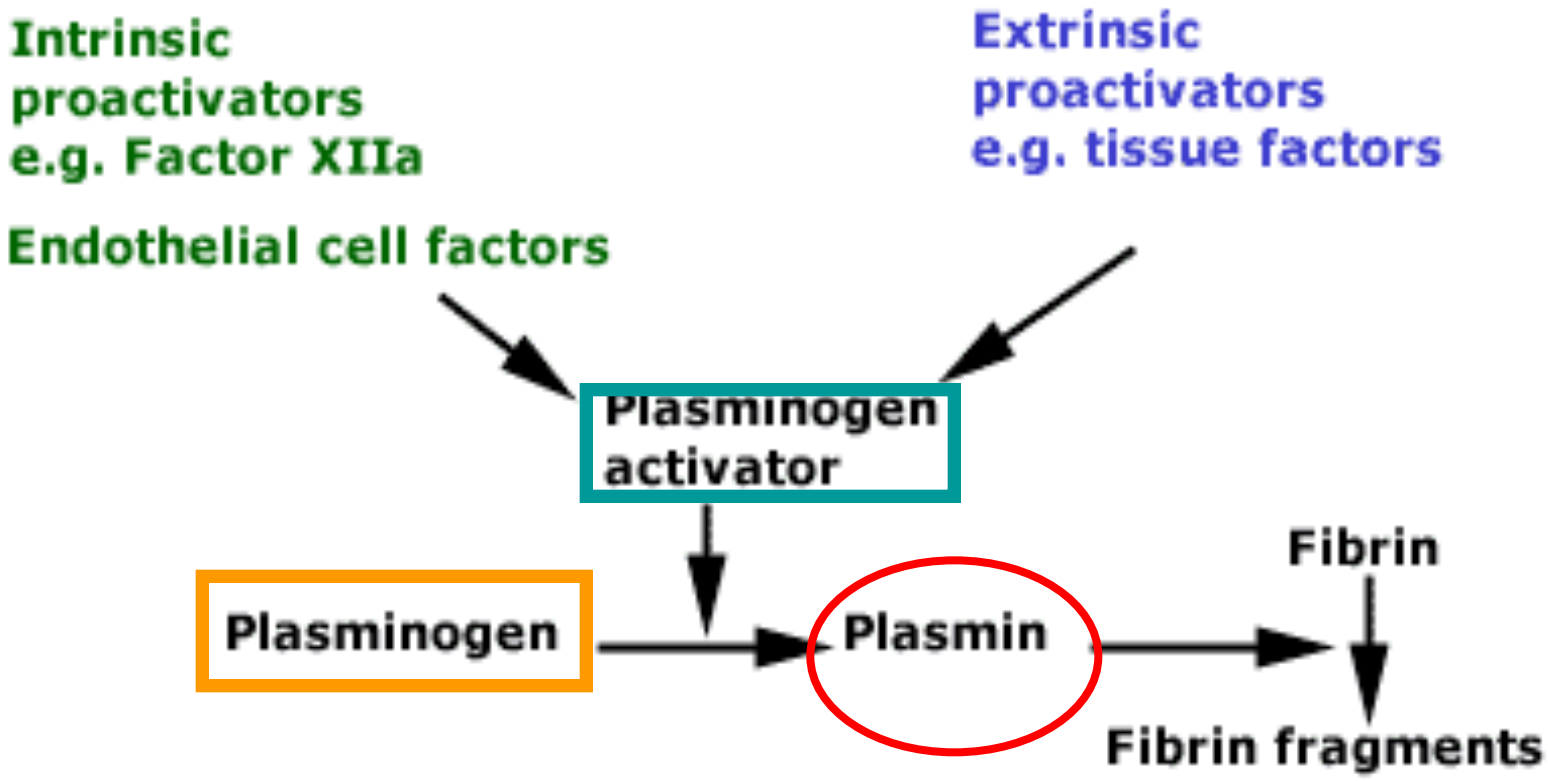
p. 422[12]; 433[13] Vander

Clot Retraction



Retraction depends on the presence of a contractile protein (thrombosthenin) released by platelets.

Clot Lysis (Fibrinolysis)



1. INHIBITORS of PLATELET ADHESION (e.g.,aspirin)

2. ANTICOAGULANT DRUGS (interfere with clot formation)

(i) COUMARIN – blocks synthesis of functional Prothrombin, VII, IX, X

(ii) HEPARIN – promotes inhibition of THROMBIN activation and action

3. THROMBOLYTIC DRUGS (promote clot lysis)

(i) TISSUE PLASMINOGEN ACTIVATOR (t-PA)

(ii) STREPTOKINASE

Please read Vander p.427[12]; 438-439[13]