BLOOD

Prepared by

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Functions of Blood

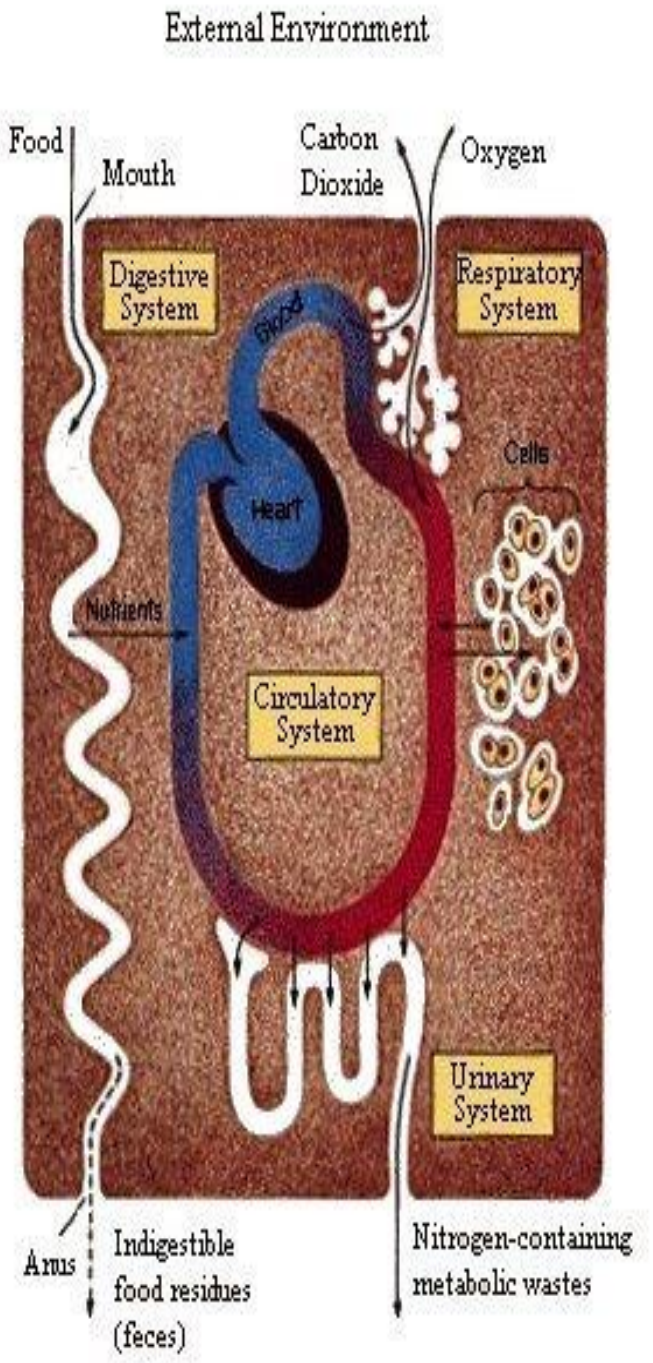
Functions of blood:

1- Distribution (Transport) functions:

- Transports gases between lung and all body cells (Respiratory function)
- Transports nutrients from the digestive tract to all body cells (Nutritive function)
- Transports metabolic waste products from cells to elimination sites (Excretory function)
- Transports hormones from endocrine organs to their target organs

2- Regulation functions:

- Maintains appropriate body temperature by absorbing, distributing, and dissipating body heat
- Maintains normal pH in body tissues
- Maintains adequate fluid volume in the circulatory system; removes excess water to kidneys and sweat glands (Water balance).



3- Protection functions:

- Prevents blood loss from injured blood vessels (Blood clotting)

- Prevents infection by bacteria and viruses (Antibody formation and phagocytosis)

Q:

Describe 3 major functions of blood?

GENERAL PROPERTIES OF BLOOD

(1) Relative volume of blood:

- Blood volume in most species of animals accounts for about
  = 7-8% of body weight.
  = 1/12th of the body weight

- This corresponds to 5-6 L in adult males and 4-5 L in adult females

Different methods are used for the determination of blood volume:

1- direct slaughter of the animal,
2- using radioactive isotopes or by using special stains.

(2) Colour:

- Arterial blood is bright red due to oxyhaemoglobin (HbO_2)

- Venous blood is **purplish (dark) red** due to **deoxyhemoglobin** (reduced haemoglobin "Hb")

(3) Blood temperature:

Blood temperature is always slightly higher than that of body temperature = 38^oC (100^oF)

(4) Osmotic pressure (OP) of blood:

Osmosis

= Diffusion (flow) of small molecules (e.g., water) through a semi-permeable membrane.

Osmotic pressure (OP)

= Pressure that stop or reverse osmosis and return to the initial condition.

(4) Osmotic pressure (OP) of blood:

	a- Crystalloid OP	b- Colloidal OP
Value	5000 mmHg (7 atmospheres)	25 – 35 mmHg
It is mainly due to:	Plasma NaCL	Plasma proteins
Physiological importance in regard to water diffusion across the capillary membrane:		
	Not physiologically effective	Highly effective
Comment:	Cystalloids distributes themselves equaly in both sides of the membrane to form two equal opposite osmotiic forces. So, the resultant osmotic force = zero	Plasma proteins are mainly present in one side

N.B: OP of plasma protein is greatly due to albumin because of its:

1- higher concentration (55% of plasma proteins)

2- low molecular weight (7000)

(5) Viscosity:

= Physical property by which fluids resist any changes in their shape

- Blood viscosity is due to:

a- Erythrocytes

b- plasma proteins

- Significance of blood viscosity

Maintain normal arterial blood pressure by preventing rapid flow of blood from arteries into veins

- Blood viscosity:

- ↓ in anemia and hypoproteinemia
- ↑ in polycythemia and haemoconcentration.

- Viscosity of blood is five times greater than that of water.

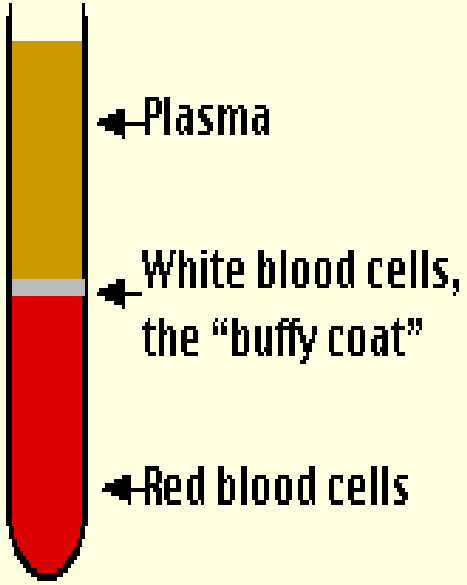
	Viscosity
Water	1
Plasma	2
Whole blood	5

(6) Specific gravity (Sp. gr):

- The specific gravity of whole blood in all species of animals is slightly lower or higher than 1.050 .

- The specific gravity of cells is greater than that of plasma.

	Sp. gr
Whole blood	1.05 - 1.06
Plasma	1.03
RBCs	1.09
WBCs	1.075
Platelets	Lower than WBCs



(7) Reaction of blood (pH):

- In most species of animals the pH ranges between 7.35 to 7.45 .

- Arterial blood is slightly more alkaline than venous blood.

- Plasma is more alkaline than the corpuscles. ***Comment?***

  Because of the great role played by plasma bicarbonates “alkali reserve”.

N.B.: Ratio of bicarbonate in plasma ($NaHCO_3$) to that in RBCs ($KHCO_3$) is 3:1

Composition Of Blood

BLOOD IS A CONNECTIVE TISSUE!

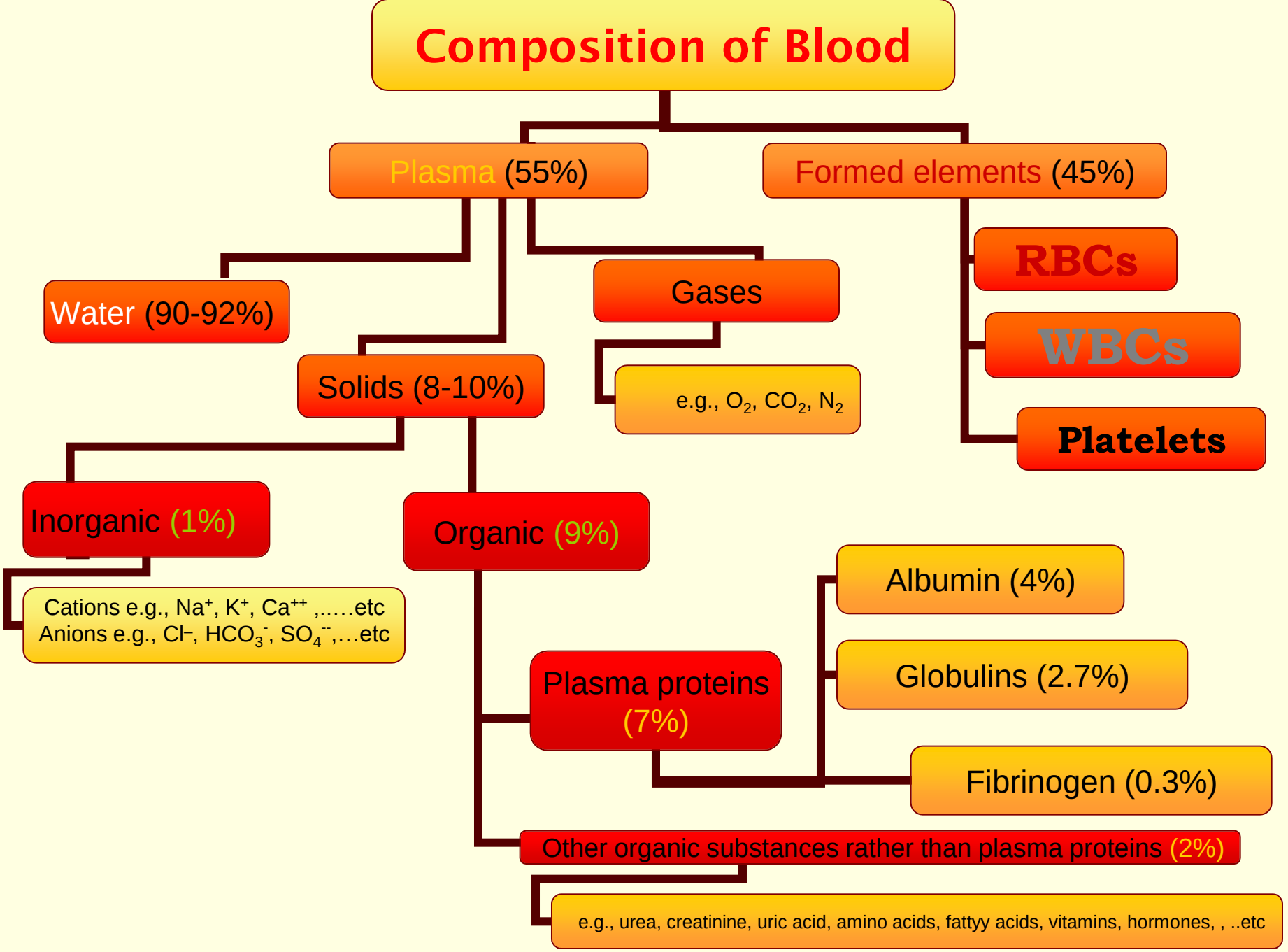
Blood is considered one of the connective tissues (C.T)!

Since, it has all of the three components which characterize C.T.:

1- **Fibers =** latent in normal blood, and is expressed only in response to injury.

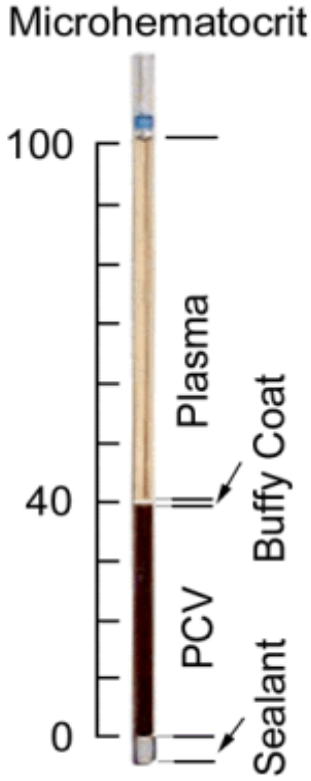
2- **Matrix (ground substance) = blood plasma**

3- **Cells = formed elements** of normal circulating blood, which in many cases the same cells found in loose CT's**.**


Composition of Blood
Plasma (55%)
Formed elements (45%)
Water (90-92%)
Solids (8-10%)
Gases
e.g., O_2, CO_2, N_2
RBCs
WBCs
Platelets
Inorganic (1%)
Organic (9%)
Cations e.g., Na^+, K^+, Ca^{++} ,.....etc
Anions e.g., Cl^-, HCO_3^-, SO_4^{--},...etc
Plasma proteins (7%)
Albumin (4%)
Globulins (2.7%)
Fibrinogen (0.3%)
Other organic substances rather than plasma proteins (2%)
e.g., urea, creatinine, uric acid, amino acids, fattyy acids, vitamins, hormones, , ..etc

Q:

Describe the major components of the blood



FORMED ELEMENTS OF BLOOD

Formed Elements

1- Erythrocytes (Red Blood Corpuscles “RBCs”)

2- Leukocytes (WBCs)

3- Platelets (thrombocytes)

Formed Elements in Blood

Red Blood Cells
(erythrocytes)

4 million–6 million per mm^3 blood

White Blood Cells
(leukocytes)

Granular leukocytes

20–50 per mm^3 blood

- Basophil

100–400 per mm^3 blood

- Eosinophil

3,000–7,000 per mm^3 blood

- Neutrophil

Agranular leukocytes

1,500–3,000 per mm^3 blood

- Lymphocyte

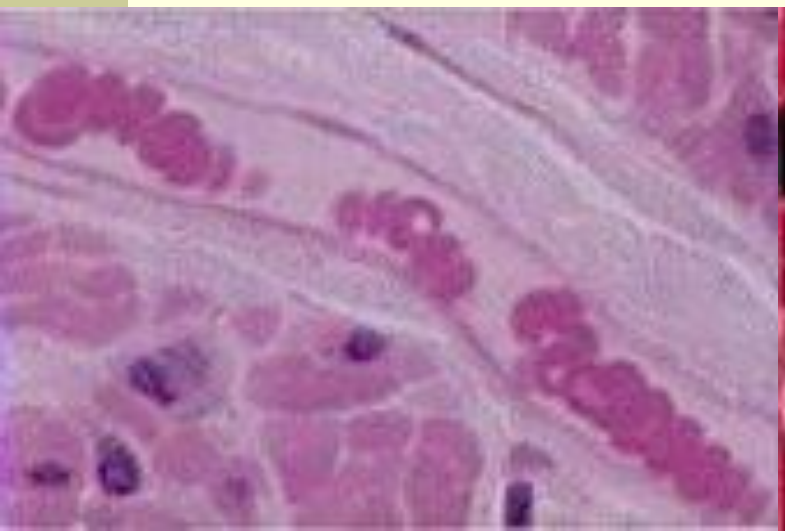
100–700 per mm^3 blood

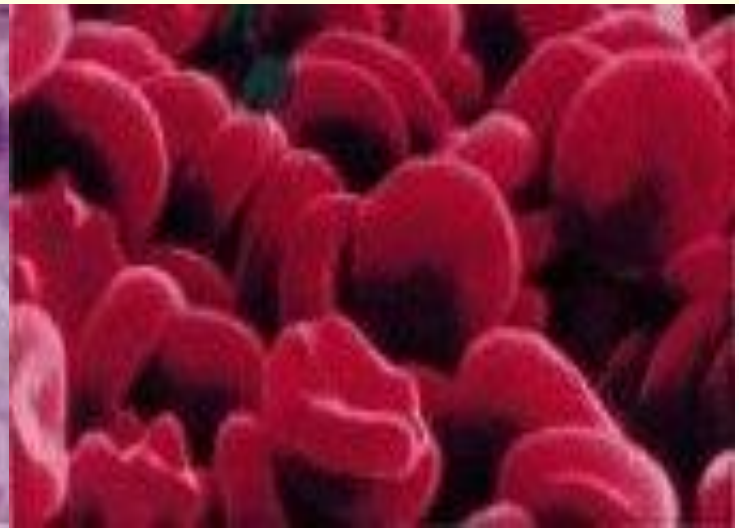
- Monocyte

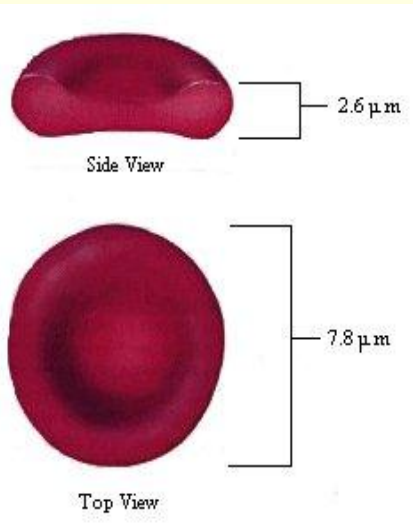
Platelets
(thrombocytes)

150,000–300,000 per mm^3 blood

Erythrocytes



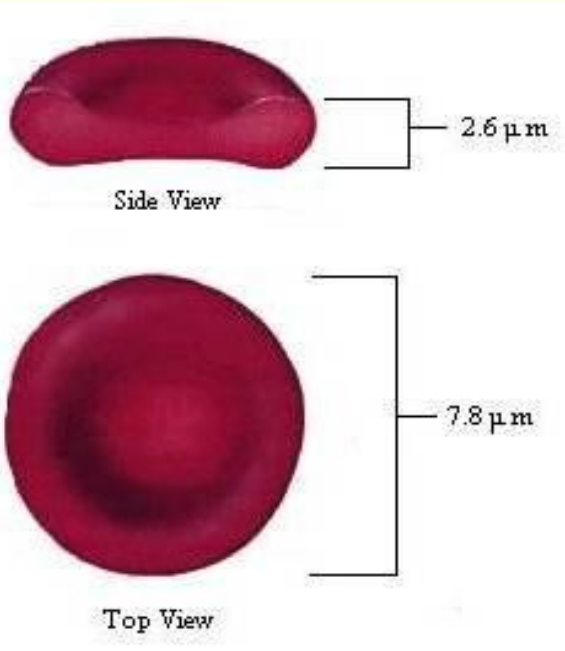




(1) Size:

The average diameter (microns) of erythrocyte in domestic animals are as follows:

Species	Diameter of RBC (micron)
Goat	**4.1**
Sheep	5.0
Horse and Cattle	5.6
Pig	6.2
Cat	6.5
Dog	**7.3**
Man	**7.5**



- The smallest RBC is present in goat; 4.1 microns

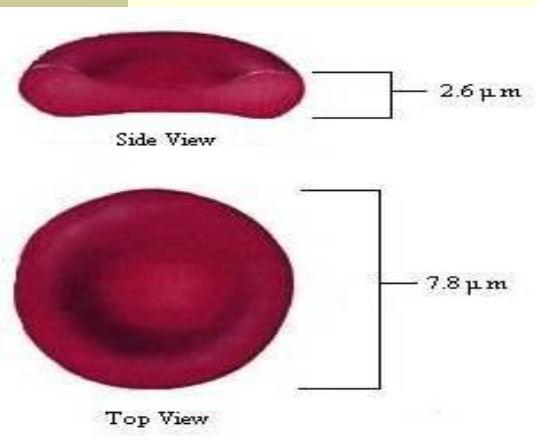
- The largest RBC is present in man and dog; 7.3 - 7.5 microns.

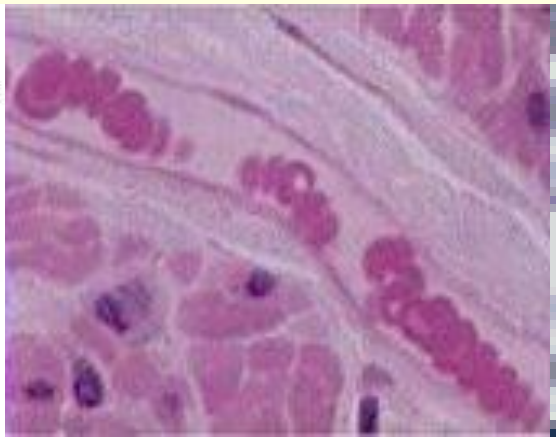
Erythrocytes (RBCs):

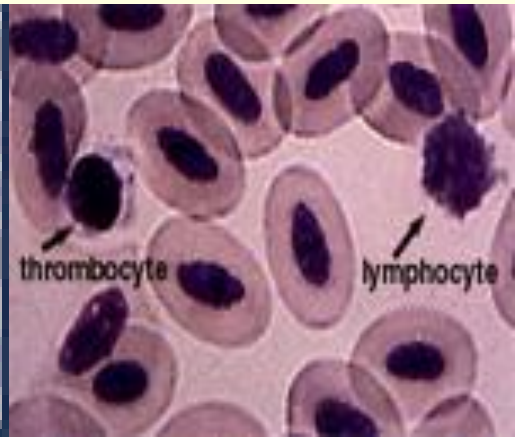
(2) Shape and Structural Characteristics of RBCs in most mammals:

A- Shape	Physiologic significance
1- Biconcave circular discs	Provides a maximum surface area (relative to its volume) for gas diffusion
2- Soft, flexible (but not elastic), easily compressed and non-motile cells.	Can pass through small capillaries whose diameter may be smaller than that of the red cell.

- In camels: RBCs are elliptical or oval in shape
- In fish, amphibia and fowls: RBCs are true nucleated cells, biconvex and elliptical in shape.







Erythrocytes (RBCs):

B- Structure of RBC:

	Physiologic significance
1- Circular disc = Not true cell as it lacks - Nucleus - Mitochondria - Centrioles - Other organelles	Just act as a "bags" of hemoglobin = on a dry weight basis, it is 97% hemoglobin
	- Genertate ATP anaerobically - Preserves the oxygen which are transporting.
	Do not divide but are renewed by the division of stem cells in the bone marrow

2- Consists of:

A) lipo-protein semi-permeable membrane:

- preserve Hb and other RBCs contents.
- allows passage of some ions e.g., HCO_3^- and Cl^- and prevent passage of others e.g., Na^+ and K^+.
- contains agglutinogens that determine blood groups

b) a sponge like elastic stroma:

- composed of proteins, lecithin, cholesterol, cephalin and inorganic substances
- in which hemoglobin deposited in it's interstices (small spaces).

(3) Chemical composition of RBCs:

1- Water (62-72 %)

2- Solids (28-38 %):

- Hemoglobin pigment constitutes about 95-97% of these solids
- Stroma constitutes 3-5 % of solids.

(4) Specific gravity (Sp.gr):

- Erythrocytes are the most heavier elements in the blood.

- The specific gravity of red cells ranges about 1.084-1.098 .

	Sp. gr
Whole blood	1.06
Plasma	1.03
RBCs	1.09
WBCs	1.075
Platelets	

-Therefore,

if a sample of anticoagulated blood is kept in a narrow tube and exposed to high speed centrifugation, each type of cell will packed together according to their specific gravity leaving the plasma clear at the top.

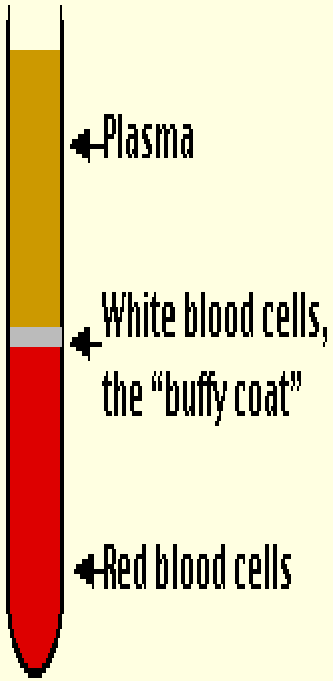
Q: What is difference between PCV and HV?

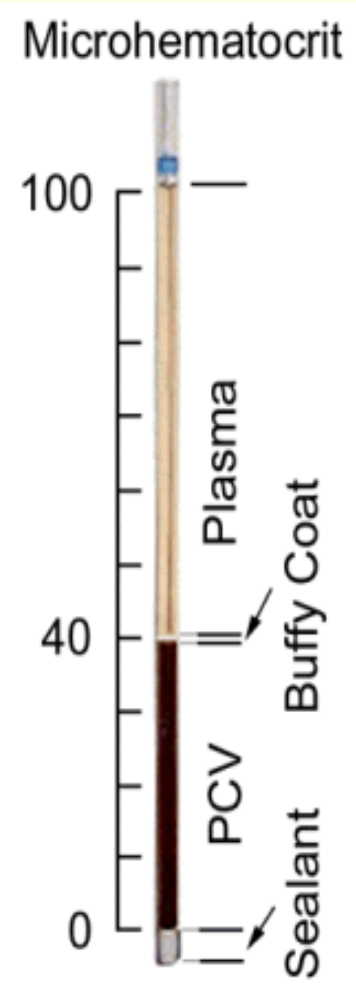
- Packed Cell Volume (PCV) = Volume of packed cells (WBCS, RBCs and Platelets)

- Hematocrite value (HV)= Volume of packed red cells only

The following are the hematocrite values for some animals and man:-

Species	H.V. (%)
Man	45
Cow, horse, pig and Rabbit	40-42
Dog	45
Sheep and goat	32-34



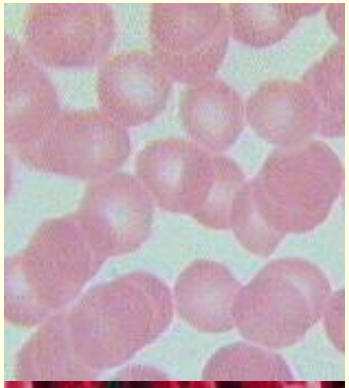


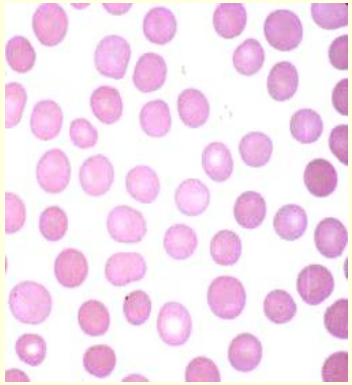
(5) Roleaux formation:

= It is the tendency of RBCs in fresh preparations of blood to adhere together at their broad surface giving the appearance of arranged chain of coins.

- Roleaux formation is:
  - **found** in equines
  - **absent** in cattle, sheep and goat.

N.B: Roleaux hastens the acceleration of sedimentation





Cattle
Sheep
Goat

Equine

(6) Number:

The number of red cells/mm^3 of blood varies greatly due to several factors.

Q: What are the causes of physiological variations in RBCs number?

a- Speceis

b- Sex

c- Endocrine

d- Distance from sea level

e- Hot weather

f- Muscular exercise

g- During sleep

h- At birth

Erythrocytes (RBCs): Causes of physiological variations in RBCs number:

a) Species:

The number of red cells/mm^3 of blood varies greatly among:

- Different species.
- Individuals of the same species.
- Within the individual itself

Species	RBCs Number ($X10^6$/ mm^3)
Women	4.6
Man	5.4
Cow	6.3
Horse	6.9
Sheep:	
Lambs	10.1
Adults	8.1
Goat	13.9
Dog	6.2
Cat	7.2
Rabbit	5.9
Chicken:	
Cock	3.2
Hen	2.8
Rat	7.1

b) Sex:

The count in males is usually higher than that of females. **Comment?**

1- Androgens increase formation of RBCs, through:

- Stimulating Erythropoietin hormone production and release.
- direct stimulation of hemoglobin formation.

2- Estrogens in female interfere with copper absorption which is essential for the synthesis of hemoglobin.

c) Endocrine:

- Thyroid, adrenals and pituitary gland **have direct effects on the metabolic activities of all tissues** and organs.

- Therefore, the hypofunction of these endocrines results in a decreased erythrocyte count.

d) Distance from sea level:

At high altitude

↓

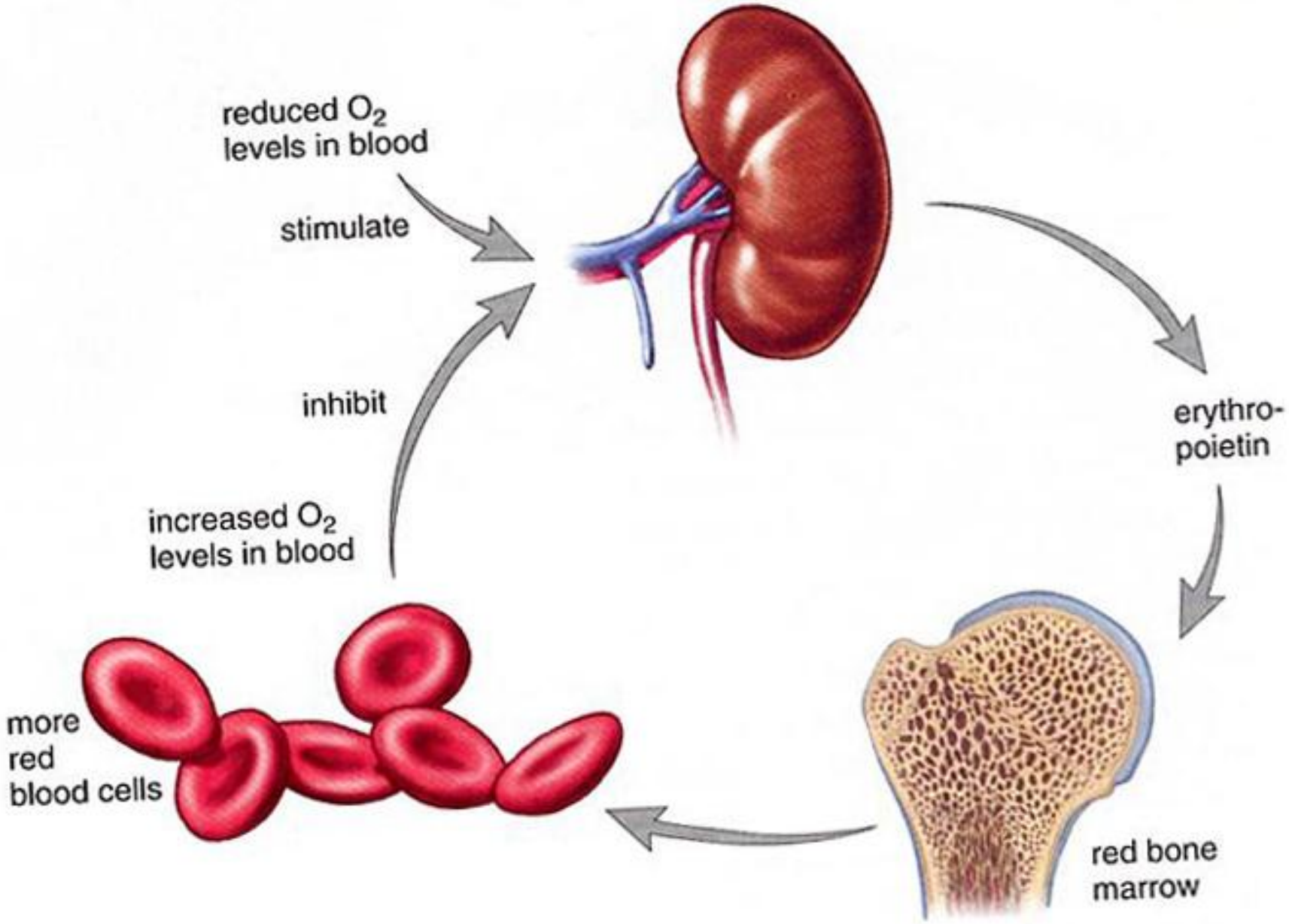
The partial tension of oxygen is reduced

↓

Stimulates production of large amounts of hemopoetin hormone from the kidneys.

↓

Activates red bone marrow to produce large numbers of erythrocytes


reduced O_2 levels in blood
stimulate
erythro-poietin
red bone marrow
more red blood cells
increased O_2 levels in blood
inhibit

e) Hot weather:

Despite the hypothyroidism noticed in hot seasons, the rise in environmental temperature is usually accompanied with increase in the count of red cells. Comment?

Due to Haemoconcentration

f) Muscular exercise:

Increase RBCs due to squeeze of spleen.

Erythrocytes (RBCs): Causes of physiological variations in RBCs number:

g) During sleep:

Decreases RBCs count.

h) At birth:

Increases RBCs due to hypoxaemia (O_2 lack in blood) in the foetus.

Erythrocytes (RBCs):

- Anaemia

  = Decrease in O_2 carrying capacity of blood that results from an abnormal decrease in the number of RBCs and/or Hb concentration.

- Polycythaemia

  = Abnormal increase in the number of RBCs that results in an increase in blood viscosity.

(5) Chemical analysis of RBCs:

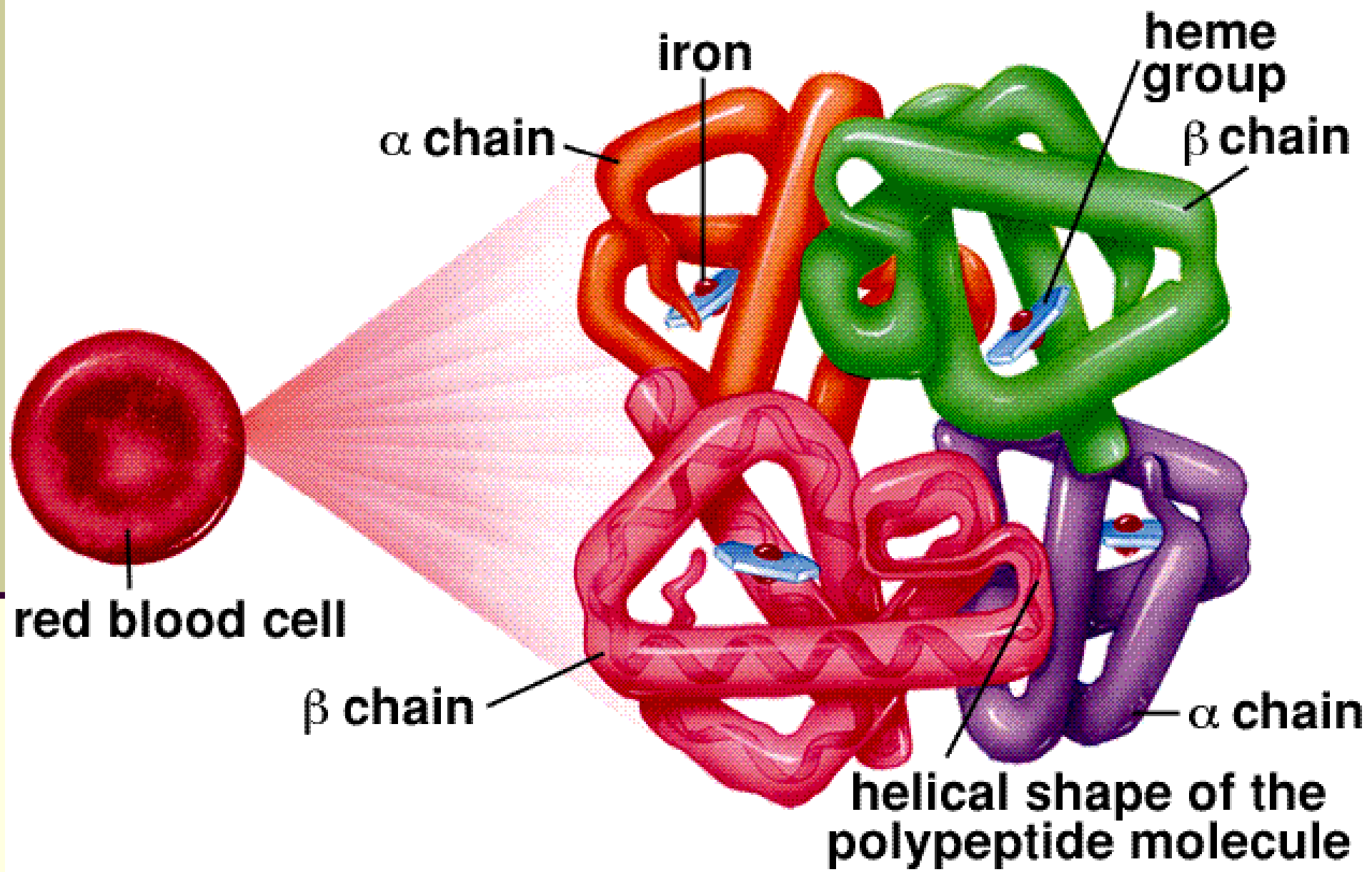
1- Water (62-72 %)

2- Solids (28-38 %):

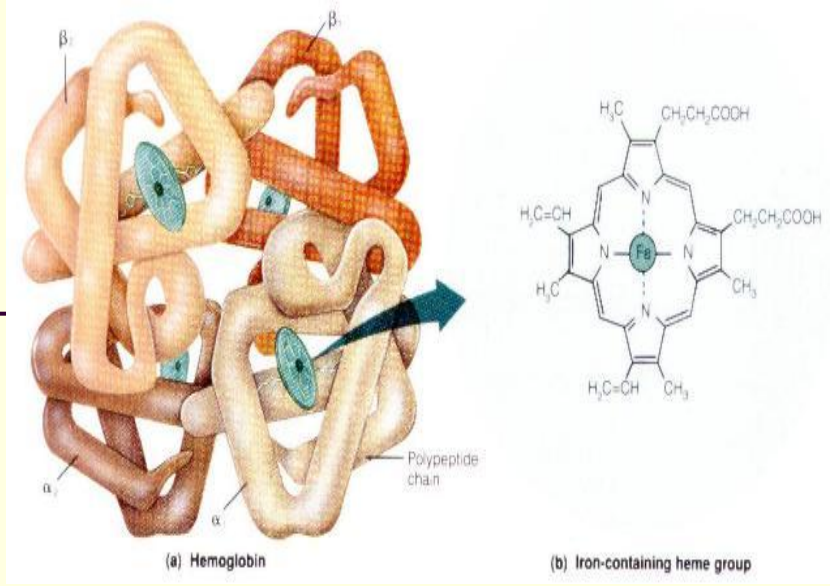
- Hemoglobin pigment constitutes about 95-97% of these solids
- Stroma constitutes 3-5 % of solids.

Hemoglobin molecule

Hemoglobin Molecule



Structure of Hb molecule:



1- One molecule of globin:

- 94% of Hb mol
- 4 polypeptide chains (2 alpha and 2 beta – chains)
- each chain binds a heme group

2- Four Heme groups:

- 5% of Hb mol
- protoporphyrine pigment= a non-protein pigment.
- Each heme group contains an iron atom in the ferrous (reduced) state (Fe^{++})
- Each iron atom can combine reversible with one molecule of oxygen

∴ each hemoglobin molecule can transport four molecules of oxygen.

3- Lipoid substance:

- 1% of Hb mol.

Hemoglobin of different animals are not identical. Comment?

Due to the difference in globin fraction among different species?

1- differences in amino acid content (number, sequence)

2- differences in the molecular ratios of methionine to cystine.

Hemoglobin concentration in different species:

Species	Hb Conc. (g%)
Equines	14
Cattle and sheep	12
Goat	11
Dog	13

Types of hemoglobin:

1- Oxyhemoglobin:

2- Myoglobin (Myohemoglobin or Muscle hemoglobin):

1- Oxyhemoglobin:

$$O_2 + Hb \longleftrightarrow HbO_2$$

O_2 combines loosely with hemoglobin to form oxyhemoglobin (HbO2; reversible compound). This is due to presence of iron in ferrous state

The aqueous solution of:

- Oxyhemoglobin in the arterial blood, is bright red in colour.
- Reduced Hb in the venous blood, is purplish (dark) red

2- Myoglobin (Myohemoglobin or Muscle hemoglobin):

(= Hemoglobin found in muscles)

- It is a true hemoglobin formed of heme and globin

- The only difference from blood hemoglobin is that it have only one heme group and consequently one ferrous atom.

-The amount of myoglobin increases with the advancement in age and activity.

Abnormal forms of hemoglobin:

1- Methemoglobin

2- Carboxyhemoglobin

3- Sulph-hemoglobin

1) Methemoglobin (ferrichemoglobin)

= True oxide of hemoglobin (ferrous iron of Hb mol. is converted into ferric)

- Results from:

exposure of Hb to oxidizing agent e.g., nitrate poisoning.

- ***The amount of methemoglobin in erythrocytes is negligible.*** *Comment?*

RBCS contains some reducing systems (e.g., NADH-methemoglobin reductase) which prevent the accumulation of methemoglobin.

Remember that:

Oxyhemoglobin is an oxygenated hemoglobin where:

- *O_2 combines loosely with hemoglobin molecule.*

- *Iron is present in ferrous (Fe^{++}) state.*

2) Carboxyhemoglobin:

Hb + CO → carboxyhemoglobin

Pollution of inspired air with CO is very poisoning. Comment?

1- The reaction is almost irreversible.
2- Affinity of hemoglobin for CO is more than 200 times greater than it's affinity to O_2.
3- CO does not only prevent the oxygenation of hemoglobin but also it
   - prevents O_2 of some hemoglobin molecules to be set free.
   - displaces O_2 of Hb molecule

The increased O_2 partial pressure as well as the presence of CO_2 hasten the oxygenation of carboxyhemoglobin and the driven out of CO.

The reaction will be as follow:

$$HbCO + O_2 \xrightarrow{CO_2} HbO_2 + CO$$

3) Sulph-hemoglobin:

- Results from:

exposure of Hb to H_2S gas.

Hemoglobin derivatives:

1) Hemin:

2) Hematoporphyrin:

Hemoglobin derivatives:

1) Hemin:

= Hydrochloride of ferriheme in which the iron atoms are in the ferric state.

2) Hematoporphyrin:

= Iron-free pigment formed when hemoglobin or even hemin is treated with strong mineral acids. Therefore, it is closely related chemically to bilirubin.

Functions of hemoglobin:

1- O_2 and CO_2 transportation:

See Respiration

2- Maintenance of the acid-base equilibrium.

Functions of hemoglobin:

1- O_2 and CO_2 transportation:

Oxygen transport:

- Hemoglobin can combines readily with O2 forming oxyhemoglobin
- one g. of Hb. can combines with 1.36 ml. of O2.
- The combination and dissociation of O2 with hemoglobin molecules depend mainly on:
- **The difference in O2 partial tensions inside and outside erythrocytes**

-In the pulmonary capillaries the O2 partial tension of alveolar air is greater than that of erythrocytes and thus combination of O2 and Hb. occurs.

- On the other hand, in the systemic capillaries, the partial tension of oxygen inside erythrocytes is greater than that of the surrounding tissue fluids and as a result O2 is set free.
- -The increased acidity in the tissues due to the accumulation of CO2 and lactic acid favors this dissociation of oxygen from Hb.

Functions of hemoglobin:

1- O_2 and CO_2 transportation:

CO_2 transport:

1. Dissolved CO2

Carbon dioxide is much more soluble in blood than oxygen. About 5 % of carbon dioxide is transported unchanged, simply dissolved in the plasma.

2. Bound to hemoglobin

- Carbon dioxide combines reversibly with hemoglobin to form **carbaminohaemoglobin.**
- Carbon dioxide bind to amino groups on the polypeptide chains of hemoglobin.
- About 10 % of carbon dioxide is transported bound to hemoglobin.

Functions of hemoglobin:

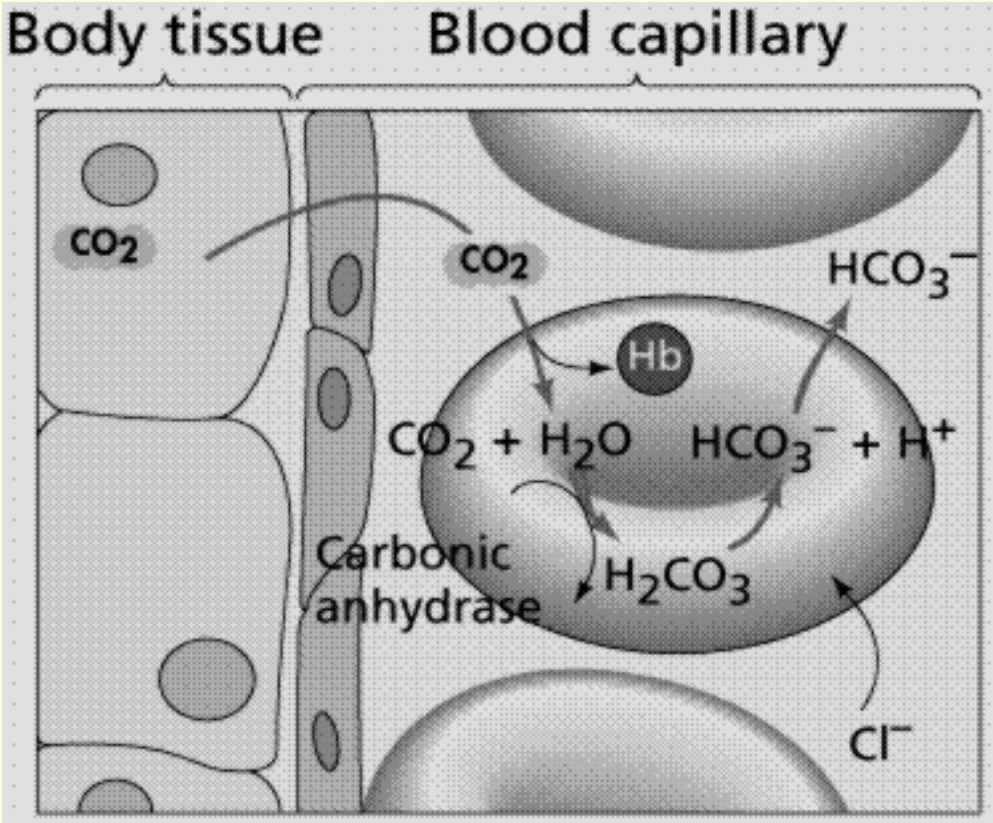
CO_2 transport:

3. Bicarbonate ions (HCO3-)

-Carbon dioxide enters red blood cells in the tissue capillaries where it combines with water to form carbonic acid (H2CO3).

-This reaction is catalyzed by the enzyme **carbonic anhydrase** which is found in the red blood cells.

- Carbonic acid then dissociates to form bicarbonate ions (HCO3-) and hydrogen ions (H+).



Functions of hemoglobin:

CO_2 transport:

3. Bicarbonate ions (HCO_3^-)

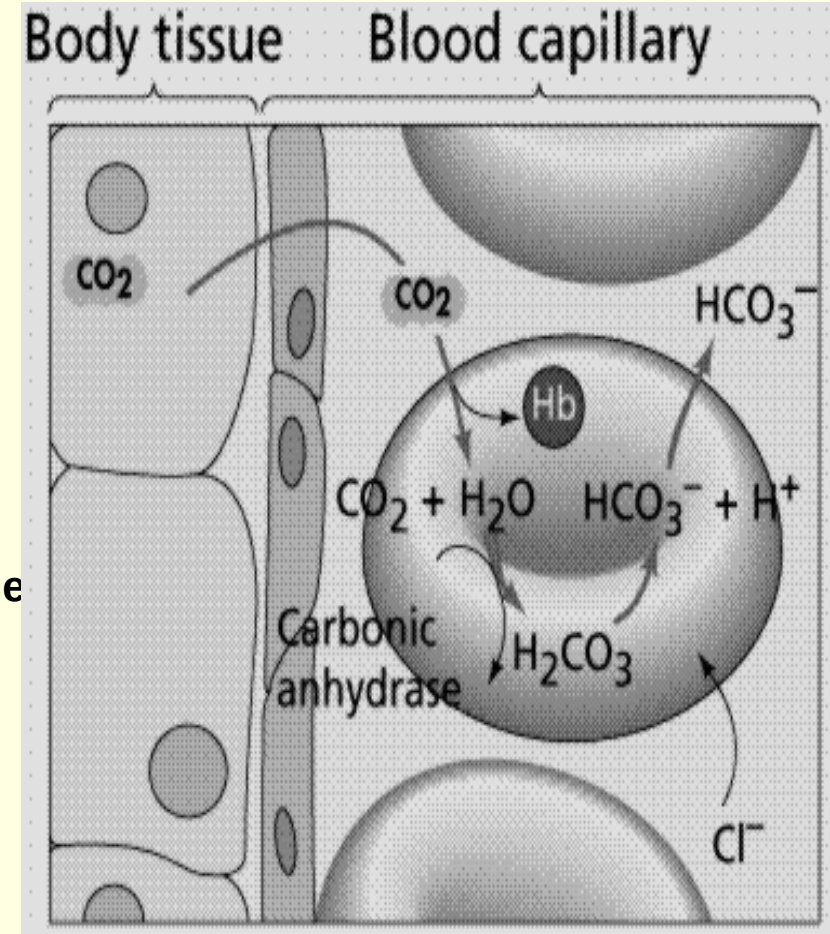
-Hydrogen ions produced in the red blood cell from the dissociation of carbonic acid are buffered primarily by haemoglobin.

-The corpuscular membrane is impermeable K^+ but not to HCO_3^- which contributes to accumulate in the erythrocytes

-The matter which upsets the ionic equilibrium between erythrocytes and plasma.

- In order to restore this equilibrium HCO_3^- diffuses from the red cells into the plasma. In the opposite direction, and as a mean of ionic exchange, Cl^- passes from plasma into erythrocytes.

-This is the bicarbonate-chloride shift.



Erythrocytes (RBCs):

Osmotic Properties of RBCs:

See practical notes

Hemolysis:

See practical notes

Erythropoiesis

Erythropoiesis:

= Continual formation of new erythrocytes .

Site of Erythropoiesis:

(a) In mammals

- Fetus:

- liver, spleen and lymph nodes

- Postnatal life:

- Bone marrow (flat bones) is the only organ of erythropoiesis
- ***Under certain pathological conditions***, liver, spleen and lymph nodes may assume again their fetal function of erythrpoiesis.

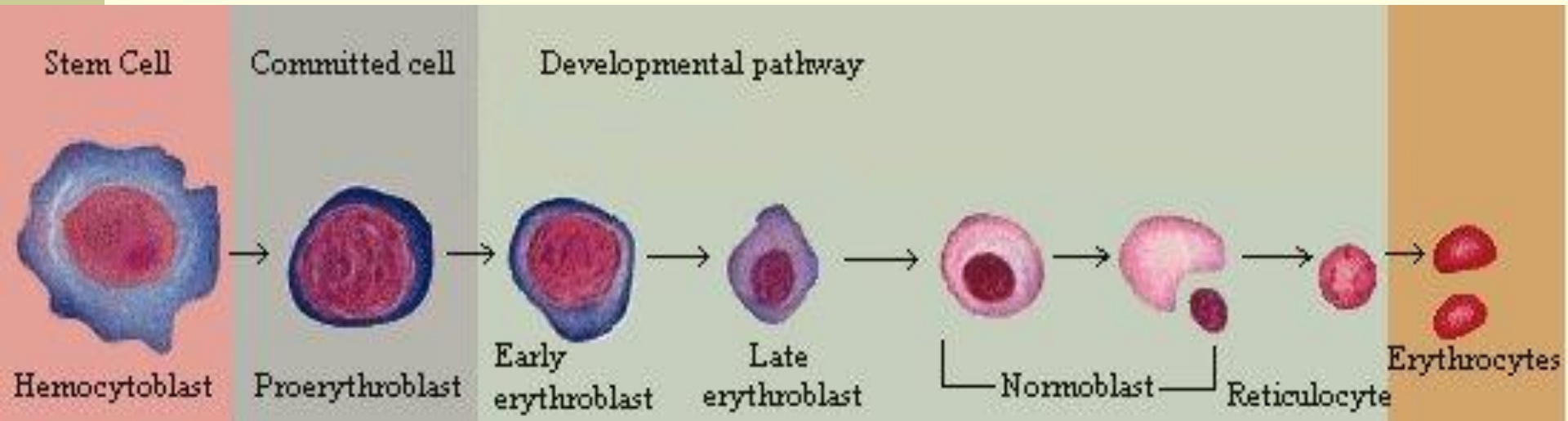
(b) In birds:

- Bone marrow is the main site of red cell formation
- Spleen also shares to a limited extent.

Stages of erythropoiesis:

1- Hemocytobalst (Stem cell):

- Originates from a mother cell.
- Nucleus: True nucleated cell:
- Cytoplasm:
    - basophilic.
    - devoids of granules.
- It divides **mitotically** giving rise to Proerythroblast**.**

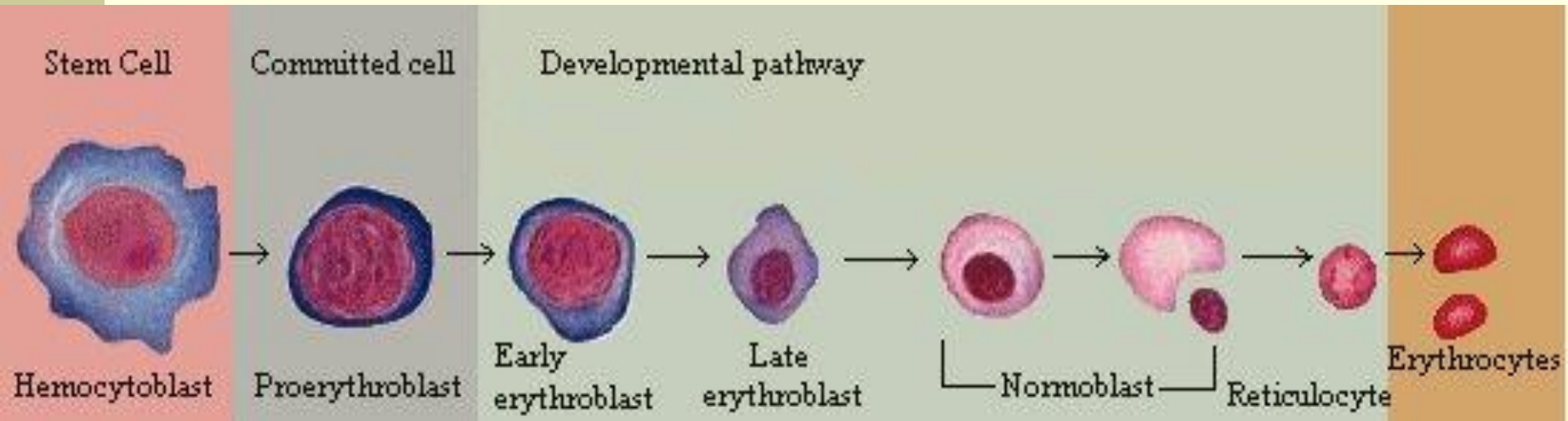


Stages of erythropoiesis:

2- Immature Erythroblast:

Proerythroblast
↓
Early erythroblast (Basophilic normoblast)
↓
Late erythroblast (Polychromatic normoblast)

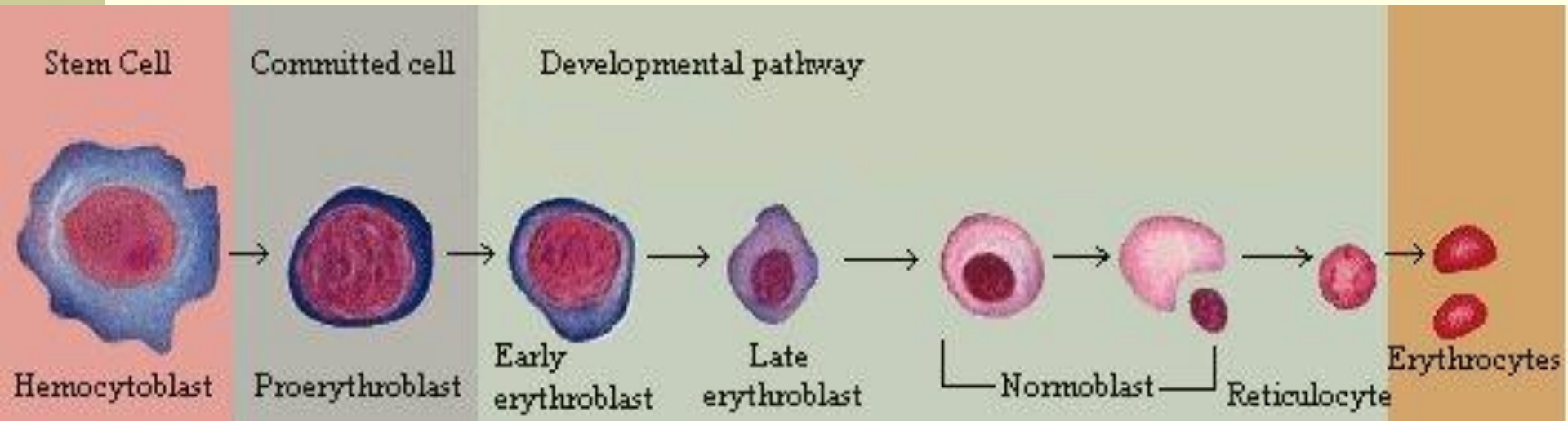
- Cytoplasm changes from blue **(basophilic)** to orange (polychromatic), reflecting:
  - Decrease in RNA and protein
  - Increase in hemoglobin



Stages of erythropoiesis:

3- Erythroblast or Normoblast (Orthochromatic Erythroblast) :

- Smaller in size
- Cytoplasm becomes acidophilic, reflecting that it is completely replaced by hemoglobin
- Nucleus becomes compact and:
    - Undergoes pyknotic changes.
    - situated near the membrane prior to its expulsion (together with other organelles) out of the cell



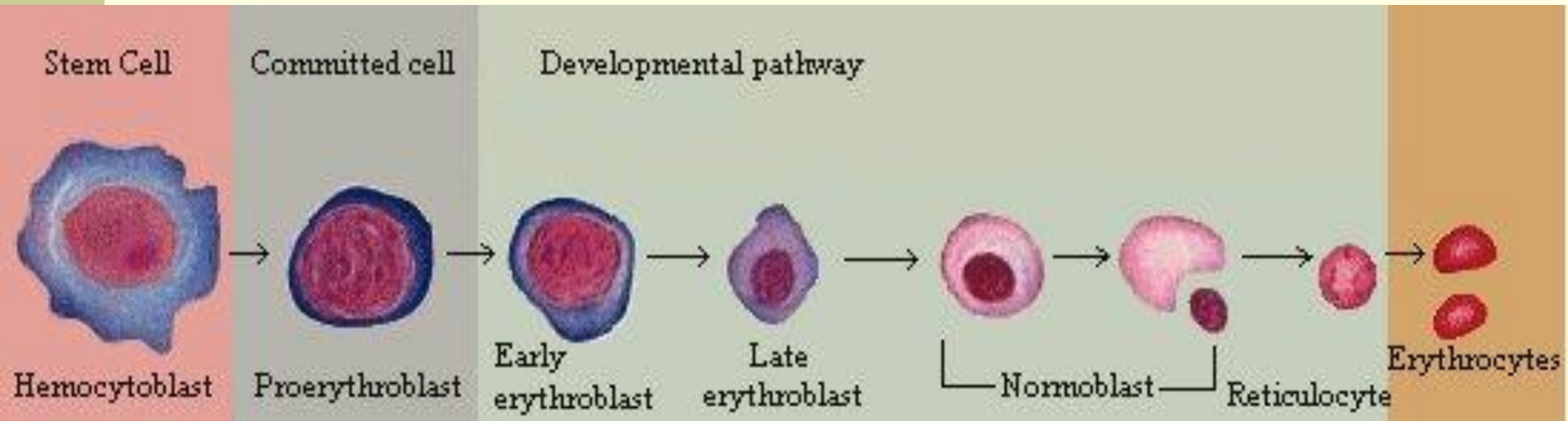
Stages of erythropoiesis:

4- Reticulocyte:

- **Young erythrocyte** = nearly similar to erythrocyte, but using a supervital stain a fine reticulum can be demonstrated and hence the name reticulocyte is applied.

- Reticulocytes are present at a rate of 1-3% in normal blood ($60.000x10^6/L = 60.000x/\mu l$)

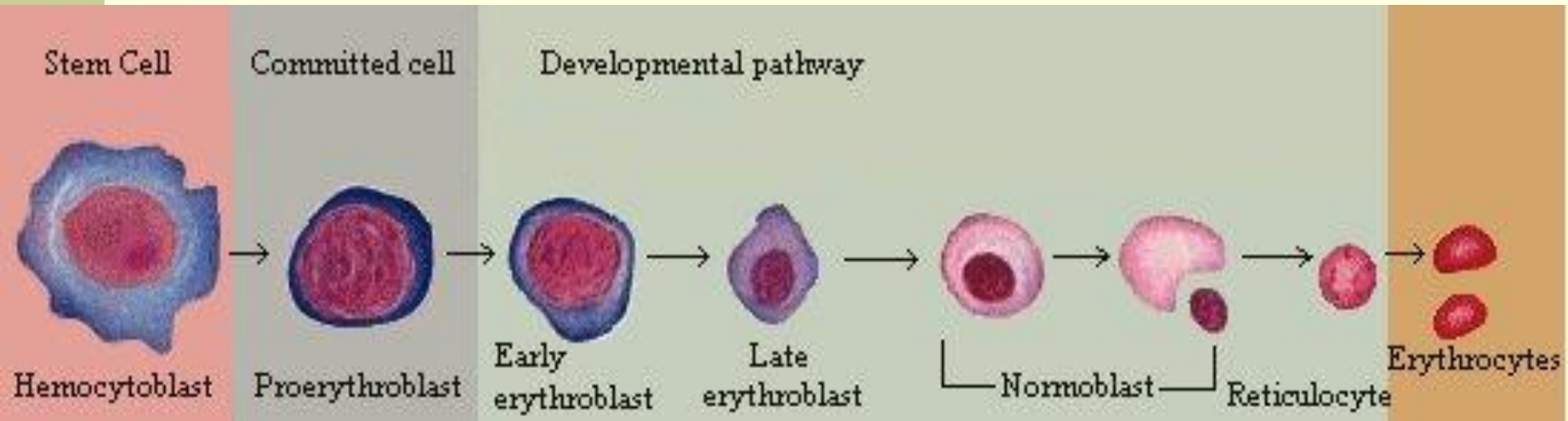
- **Reticulocytosis** frequently occurs after hemolysis or acute blood loss



Stages of erythropoiesis:

5- Erythrocyte or normocyte:

= Normal mature red cells present normally in blood.



General features on the process of Erythropoiesis:

* The entire process from **Hemocytoblast** to Reticulocyte:

1- takes 3 to 5 days

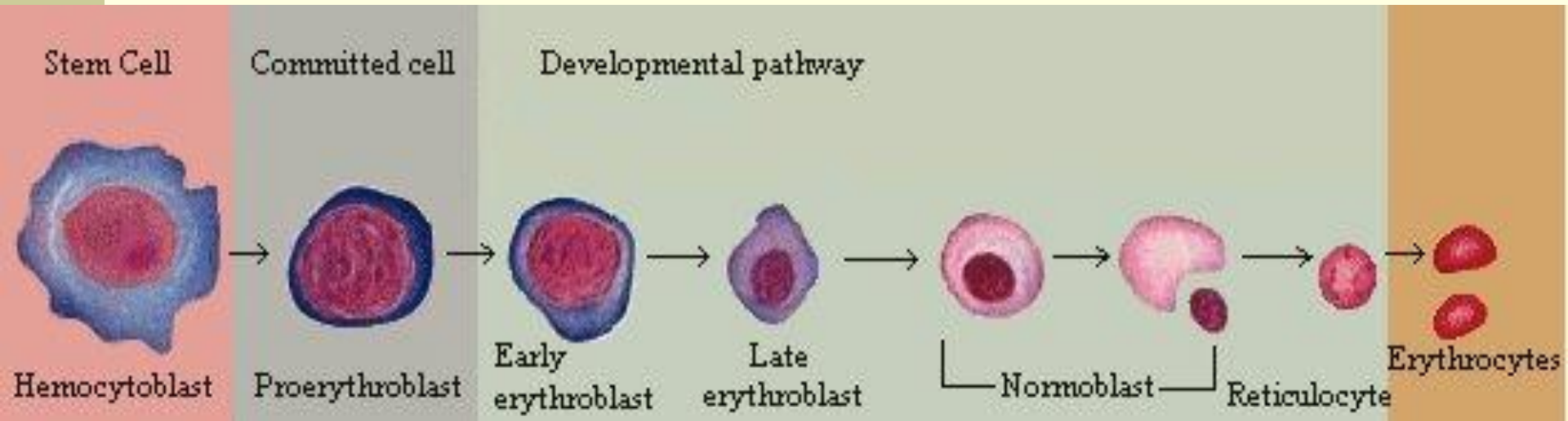
2- involves:

- Cytoplasmic changes from blue to orange due to:

  decrease in RNA and increase in Hb

- Nuclear changes:

  nucleus becomes smaller till extruded (together with other cytoplasmic organelles) out of the cell



General features on the process of Erythropoiesis:

* Reticulocytes enter the blood stream and become fully mature erythrocytes within 2 days

* New erythrocytes enter the bloodstream and function for about 120 days (Life span of RBC)

* The number of circulating erythrocytes in a given individual is remarkably constant

* this balance in maintained by the production and destruction of > 2 million cells per second

Life span
and
Fate of RBCs

derived from stem cells in bone marrow

destroyed in liver and spleen

- macrophages
- 8,000,000 destroyed every second
  - globin broken down and reused
  - iron saved for reuse
  - heme excreted as bile pigments

Life span of erythrocytes:

= is the time elapsing between the entrance of new red cell into the circulation and their disintegration.

Species	Life span (Days)
Dog and Man	124
Horse	140-145
Ruminants	50
Hen	28

N.B:

Nucleated cells tend to have the shortest life span.

Fate of erythrocytes:

- Aged and damaged RBCs are engulfed by macrophages of reticuloendothelial system (RES) e.g., liver, spleen, and bone marrow,

- In the macrophage cell, Hemoglobin is broken down into:

A- globin (Protein fraction), which breaks down into:
amino acids → released to the circulation (amino acid pool) for reuse

B- Heme (iron –containing fraction), which splits into:

1-Iron → stored in liver, spleen and bone marrow as ferritin and hemosidrin for reuse

2- Hematoidin pigment → Biliverdin

↓ Biliverdin reductase

Free bilirubin

↓

Carried in plasma in loose combination with albumin and α globulin

↓

liver →…….. → Bile pigments

RBCs: Disorders of Erythrocyte Recycling

Jaundice

= Yellowish color caused by deposition of bilirubin in skin due to **hyperbilirubinemia**

Causes:

- liver dysfunction (fails to process bilirubin properly)
- blockage of bile ducts
- excessive rupture of RBCs (e.g., neonatal jaundice or transfusion reaction)

Factors necessary for erythropoiesis:

1- Hormones:

e.g., Erythropoietin, testosterone, glucocorticoids, thyroid hormones and pituitary hormones

2- Food factors:

a) Proteins

b) Minerals e.g., Iron, copper and cobalt

c) Vitamins e.g., Vit C, Folic acid, B_{12}

Factors necessary for erythropoiesis:

1- Hormones:

(a) Erythropoietin (EPO):

- Nature: glycoprotein hormone
- Action: direct stimulus of erythrocyte formation
- Source: Produced and released by the kidneys (Juxtaglomerular apparatus)
- Factors affecting its secretion:

1- hypoxia stimulates its production and release

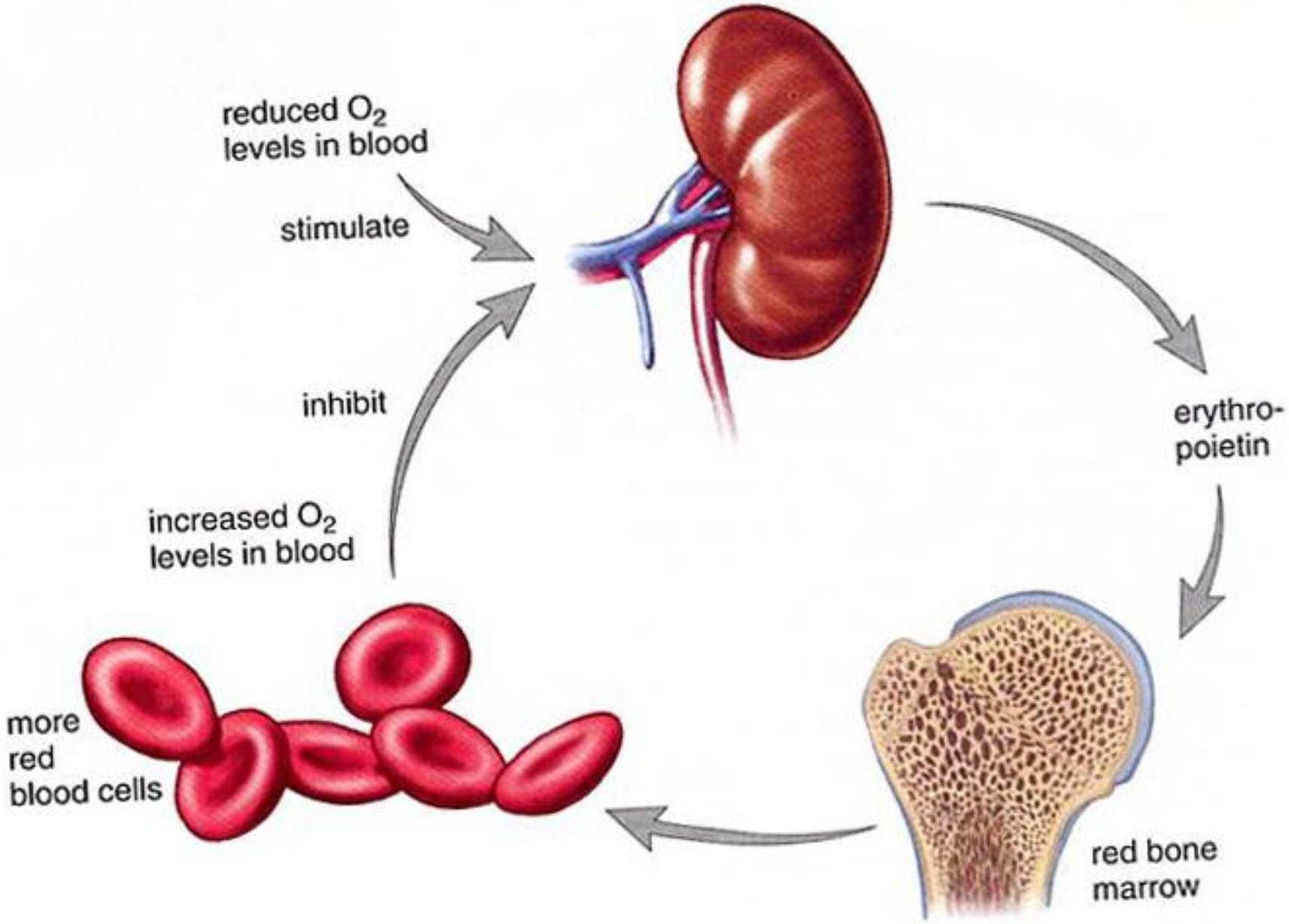
Hypoxia may result from

1- reduced numbers of RBCs caused by hemorrhage or excess RBC destruction

2- reduced availability of oxygen to the blood, e.g. high altitude or pulmonary diseases

3- increased tissue demands for oxygen, e.g. increased aerobic exercise

2- Testosterone enhances EPO production by the kidneys and may be partially responsible for the RBC counts seen in males


reduced O_2 levels in blood
stimulate
erythro-poietin
red bone marrow
more red blood cells
increased O_2 levels in blood
inhibit

(b) Other hormones:

Testosterone:

enhances EPO production by the kidneys and may be partially responsible for the RBC counts seen in males

Thyroid, adrenals and pituitary gland hormones:

have direct effects on the metabolic activities of all tissues and organs.

Therefore,

hypofunction of these endocrines results in

a decreased erythrocyte count.

2- Food factors:

(a) Proteins:

- Diets deficient in protein result in decrease in both the number of erythrocyte and hemoglobin content and the incidence of anemia. ***Comment?***

1- The non-pigment fraction of hemoglobin is the protein globin.

2- Animal proteins is a source of vit. B_{12} which is very necessary for normal erythropoiesis

2- Food factors:

(b) Minerals

- Iron, Copper and Cobalt:

are essential elements for erythropoiesis?

- Iron: enter in the structure of Hb molecule

- Copper : act as a catalysts for iron mobilization for Hb synthesis (but do not enter in the structure of Hb mol.)

- Cobalt: enter in the structure of Vit. B_{12}.

- Molybdenum and Magnesium:

are also necessary, particularly in birds.

Nutrional anemia

(Iron-deficiency anemia)

Characterized by:

RBC of smaller size (microcytic) and low Hb content (hyporchromic)

Cause:

1- Iron and/or copper deficiency:

- Inadequate intake
- Impaired absorption

2- Prolonged blood loss

Treatment:

Supply source of iron

2- Food factors:

(c) Vitamins:

- Vit. C:

  Essential for iron absorption from gastrintestinal tract

- Folic acid and Vit. B_{12} (Cyanocobalamine)

  Essential for maturation of red cells in the bone marrow.

Some remarks on Vit. B_{12} :

- It is called extrinsic factor

- Absorption:

To be absorbed by the intestinal cells in the ileum, it requires intrinsic factor:

- HCL or glycoprotein.
- produced by the parietal cells of stomach mucosa.

- Deficiency:

leads to Pernicious anemia

Pernicious anemia

Characterized by:

RBC of larger size (macrocytic) and higher Hb content (hyperchromic)

Cause:

1- Vit. B_{12} deficiency.

2- Deficiency of intrinsic factor e.g., atrophy of gastric mucosa

3- Feeding low quality protein or deficiency of animal protein which is a source of Vit. B_{12}.

Treatment:

Intramuscular injections of B_{12}

Iron cycle

Physiological significance of Iron:

- Each hemoglobin molecule contains four atoms of iron.

- About 65% of the iron content of the body is found in the hemoglobin.

Sources of Iron:

1) Animal products.

N.B.: milk is poor in iron,

2) Plant:

- Dried beans, wheat and legumes.
- some green vegetables e.g. clover and spinach.

Daily requirements of Iron:

= 12 mg/ day/ adult man.

N.B:

Daily requirements of iron (Under normal conditions) are traces. Comment?

(1) Iron content in the body seems to be traces (5 g. in the body of a mature man).

(2) Iron excretion or loss/ day from the body is also traces:

- 1.7 mg in women
- 0.9 mg in men

Factors increase daily requirements of iron:

- Pregnancy and lactation in mammals
- Egg laying
- Suckling animals, as milk is poor in iron.I

Iron absorption:

- Diet:

Iron consumed is usually in the form of ferric (Fe^{+++}).

- In the stomach:

Fe^{+++}

↓ ← Reduction by HCl and other acids; folic and lactic acids

Ferrous (Fe^{++}).

↓

Diffuses into the intestinal mucosa (duodenum and jejunum) by simple diffusion

Iron absorption:

- In the intestinal mucosa:

Fe^{++} ⟹ Small part diffuses directly to the submucosal blood vessels

⇓

Main Part is oxidized into

Fe^{+++}

⇓ ← protein apoferritin (in the 1st ½ of the mucosal cells)

Ferritin (Iron-apoferritin complex = Stored form)

⇓

moves to the opposite half of the mucosal cell where it is splitted into:

* Fe^{+++} → reduced into Fe^{++} → diffuses directly to the submucosal blood vessels

and

* Apoferritin → return again to the first half of the mucosal cell to combine with other Fe^{+++} and so on

Iron absorption:

- In the blood stream: Fe^{++}

↓ Oxidation (in the presence of adequate oxygen tension)

Fe^{+++}

↓ ← transferrin protein= apoferritin like substance (B2 globulin)

Ferritin (Iron-transferrin complex = Stored form)

↓

- Reach bone marrow and bind to cell membrane receptor on bone marrow cells
- splitted into:

⇨ 1- Fe^{+++} → Which is :

a- reduced into Fe^{++} and incorporated into heme mol (in the mitochondria of BM cells).

OR

b- combines with apoferritin to be stored as ferritin

⇨ 2- transferrin → return again to blood

Factors influencing iron absorption:

1- Degree of acidity in stomach.

2- Amount of apoferritin in the mucosal cells and blood.

3- O_2 tension in the blood stream.

4- Increased requirements for iron as it occurs following sever hemorrhage and in cases of anemias.

General notes on iron cycle:

- Since free iron is toxic, iron is loosely bind to carrier protein forming protein-iron complexes which is the stored form e.g.,

	Binding protein	Stored form
Stomach	Apoferritin	Ferritin
Blood	Transferrin (B2 globulin)	
BM cells	Apoferritin	
liver and spleen		ferritin and hemosiderin.

-Iron to be absorbed must be in the reduced (Ferrous, Fe^{++}) state.

- Iron to be transported and bind with a carrier protein must be in an oxidized (Ferric, Fe^{+++}) state.

Q: What is the effect of iron deficiency?

Copper:

* Physiological importance in regard to erythropoiesis:

Copper acts as a catalyst for iron mobilization for synthesis of hemoglobin.

* Daily requirement:

Copper is continually excreted through bile in the feces. Therefore, there must be daily compensation of copper.

* **Copper absorption:**

- Site of absorption:

Intestinal mucosa of the jejunum.

- Factors affecting Cu^{++} absorption:

1- a normal pH in the stomach.

2- high intakes of molybdenum reduces copper absorption. This influence of molybdenum may be due to that it fixes copper in a form that is not utilized by the tissues.

Copper deficiency:

Nutritional anaemia

Copper poisoning:

Excessive intake of copper or lower intake of molybdenum in sheep results in

1- hemolytic anemia

2- weight loss

3- finally death due to copper poisoning.

This condition is also reported in calves, swines and chickens.

Cobalt:

* Physiological importance in regard to erythropoiesis:

enter in the structure of Vit. B_{12} which is essential for erythropoiesis.

** Source:*

- Plants. - Animals proteins

**** Cobalt absorption:***

Like iron and copper, cobalt requires the normal gastric pH in order to be absorbed from the upper part of the small intestine.

**** Cobalt deficiency:***

Cobalt deficiency is not dangerous as such

but

the deleterious effects are due to vit. B_{12} deficiency, resulting in

Pernicious anemia

(Macrocytic hyperchromic RBC)

Cobalt deficiency:

(1) In Carnivores and Omnivores:

Seldom suffer from cobalt deficiency. Comment?

They obtain animal proteins which are rich in vit. B12.

(2) Herbivores:

Suffer from cobalt deficiency. Comment?

1- Herbivores diet is poor in vit. B_{12}.

2- Ruminants synthesize vit. B_{12} in the rumen by **ruminal** micro-organisms utilizing the cobalt of the soil

(3) In non-ruminant herbivores e.g., rabbit:

Like herbivores. However,

Synthesis of vit. B_{12} occurs in the **caecum** and large intestine.

Thus, it passes in feces before adequate amounts are being absorbed. Therefore, these animals tend to have its requirements of vit. B_{12} from their feces; coprophagy.

Anti-Prnicious Anemia Factor (APAF)

= Factor which prevent or relief the pernicious anemia.

Source:

1- Animal protein:

- Feeding animal protein to patients suffering from pernicious anemia was an effective treatment. Comment?

  Animal protein is rich in Vit. B_{12}

- Therefore, APAF was formerly termed Animal Protein Factor (APF).

2- Extrinsic factor (Vit. B_{12} or cyanocobalamin):

- Supplied in the diet

3- Intrinsic factor (glycoprotein or HCl):

- Produced by the parietal cells of stomach mucosa.
- Required for absorption of Vit B_{12}.

The importance of APAF for erythropoiesis:

1- Responsible for RBCs maturation during their formation.

Therefore,

absence of APAF

↓

Stages of erythropoiesis stop at the megaloplastic stage
(before transformation of hemocytoblast to erythroblast).

↓

Pernicious anemia

(Macrocytic hyperchromic RBC)

2- Enables the mature erythrocytes to penetrate the collapsed capillaries and reach the blood stream.

Requirements of the extrinsic factor (Vit. B_{12}):

(1) Carnivores and Omnivores:

- **Seldom** suffer from Vit. B_{12} deficiency. Comment?

They feed animal proteins which are rich in vit. B_{12}.

(2) Herbivores:

- Synthesizes vit. B_{12} in the rumen by **ruminal** micro-organisms utilizing the cobalt of the soil

(3) Non-ruminant herbivores e.g., rabbit:

- Synthesizes Vit. B_{12} in the **caecum** and large intestine. *Therefore, these animals tend to have its requirements of vit. B_{12} from their feces;* coprophagy

General functions of cyanocobalamin:

1- Essential for erythropoiesis.

2- Improves the growth in growing animals.

3- Hastens the hatchability rate.

4- Lipotropic effect = helps mobilization and distribution of fats→ prevents their storage in the liver.

Folic acid:

Source:

Green leaves of plants (foliage).

Forms of Folic acid:

1- Pteroglutamic acid.

2- Pteroyltriglutamic acid

3- Pteroylheptaglutamic acid.

Chemical structure of Folic acid mol:

Folic acid Mol. consists of 3 parts

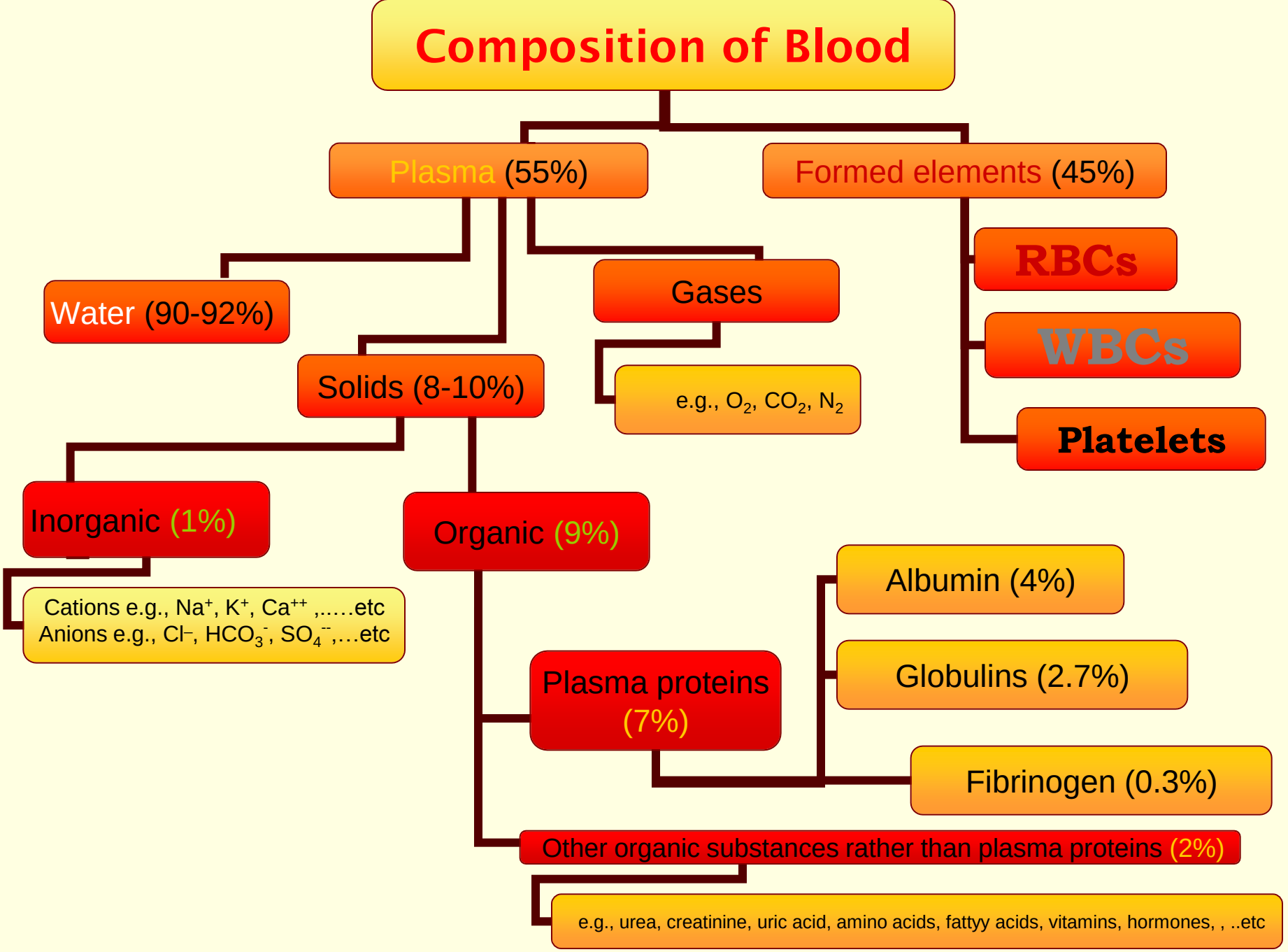
1- Pterin (a yellow pigment).

2- Glutamic acid.

3- Para-amino-benzoic acid.

Function:

Essential for normal cell development. Thus, it has a great importance in erythropoiesis.


Composition of Blood
Plasma (55%)
Formed elements (45%)
Water (90-92%)
Solids (8-10%)
Gases
e.g., O_2, CO_2, N_2
RBCs
WBCs
Platelets
Inorganic (1%)
Organic (9%)
Cations e.g., Na^+, K^+, Ca^{++} ,.....etc
Anions e.g., Cl^-, HCO_3^-, SO_4^{--},...etc
Plasma proteins (7%)
Albumin (4%)
Globulins (2.7%)
Fibrinogen (0.3%)
Other organic substances rather than plasma proteins (2%)
e.g., urea, creatinine, uric acid, amino acids, fattyy acids, vitamins, hormones, , ..etc

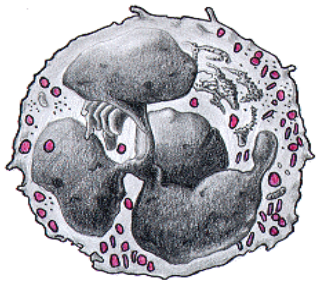


Fig. 8 - Neutrophil

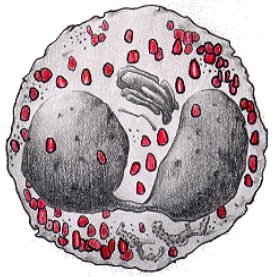


Fig. 9 - Eosinophil

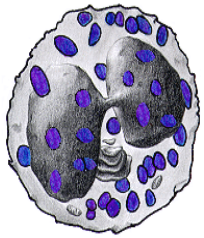


fig. 10 - Basophil

Fig. 11 - Lymphocyte

Fig. 12 - Monocyte

Leukocytes (WBCs)

General Structural and Functional Characteristics :

1- **Structure:** WBCs are the only formed elements that are complete cells with nuclei and the usual organelles.

2- **Total Number:** Account for <1% (Buffy coat) of total blood volume = 4000 - 11,000 WBCs/mm^3

3- **Leukocytosis:** number of WBCs can double (>11,000 WBCs/mm^3) within a few hours in response to bacterial or viral invasion of the body

4- **Primary function:** is the defense against disease

5- **Diapedesis:** able to slip out of the capillary blood vessels into loose connective tissue or lymphoid tissue where they participate in inflammatory or immune responses

6- **Chemotaxis:** move in extravascular tissue spaces by amoeboid motion and follow chemotaxic agents released by damaged cells. .

Classification of WBCs:

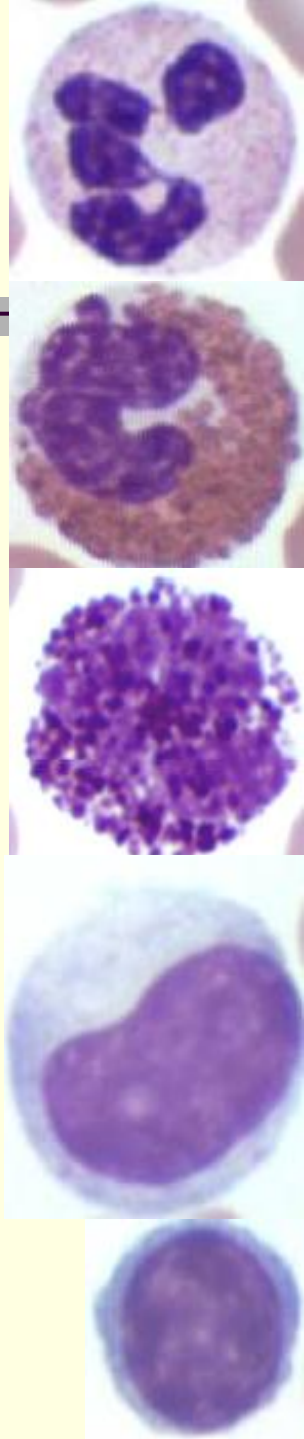
WBCs are grouped based on the presence or absence of membrane-bound cytoplasmic granules, as follow:

(I) Granulocytes:

- Neurtophil
- Eosinophil
- Basophil

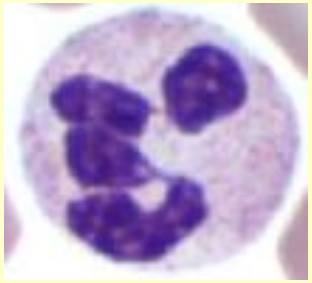
(II) Agranulocytes:

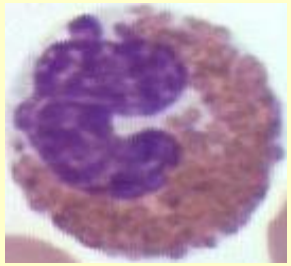
- Lymphocyte
- Monocyte

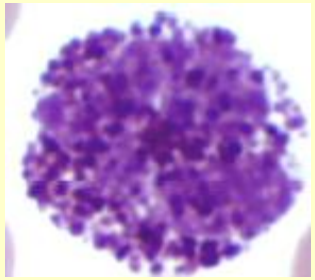


Granulocytes

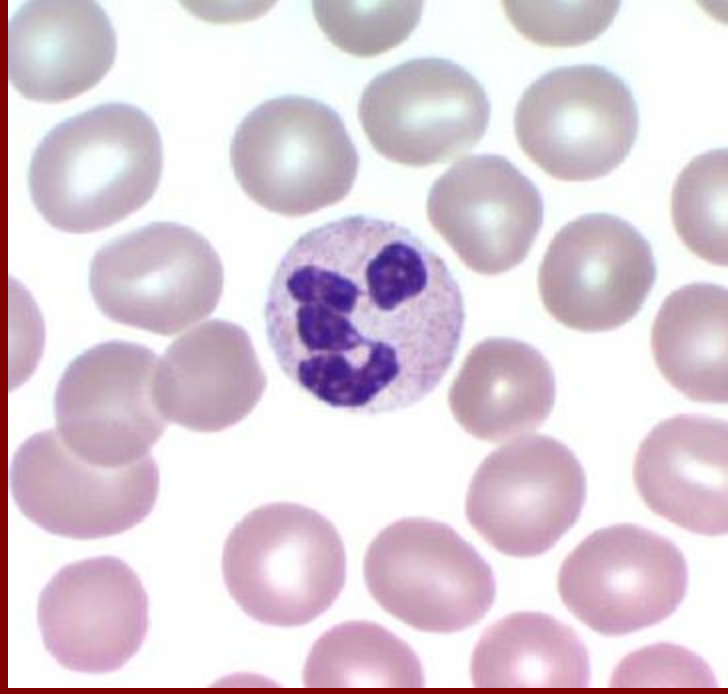
- Neutrophils
- Eosinophils
- Basophils







Neutrophils



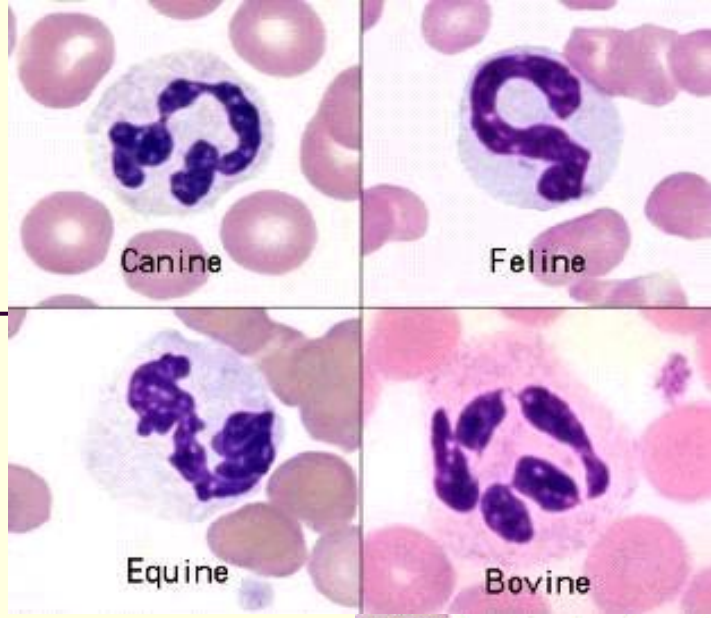
= Heterophils

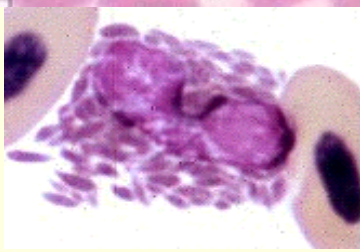
= Polys or "PMNs

=

Polymorphonuclear

Neutrophils





Birds

Percentage:

50-70% of WBC:

- Man, dogs and cats (60-70%)
- Chicken, ducks and pigeons (60%)
- Horses (50%).

Size:

About 9 to 12 microns diameter

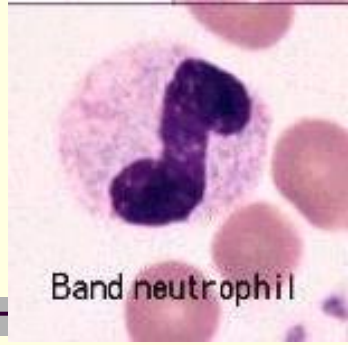
Shape:

- Cytoplasmic granules: neutral, staining with both basic (blue) and acidic (red) dye, so it is called heterophils

In rabbit, guinea pig and birds the granules are somewhat coarse and of eosinic reaction.

- Nucleus:

- Mature neutrophils: have 3 to 5 lobes, connected together with fine threads of nuclear material, and so it is called polys" or "PMNs" = polymorphonuclear leukocyte



Immature neutrophils:

nucleus is not segmented and appears as band-like, therefore, it is termed **Band cells.**

N.B: *Normal blood contains few numbers of band cells*

Shift to left:

Abnormal increase in the number band cells and those of 2 lobules in blood e.g., acute bacterial infection.

Shift to right:

Abnormal increase in the number of neutrophils having 4 and 5 lobules in blood

Drum sticks or sex chromatin:

In rabbits and guinea pigs, some neutrophils possess small nuclear expansion characteristic to the sex (females).

Life span of neutrophil:

Short life spans (~ 10 hrs; less if highly active)

Functions:

(1st line of defense)

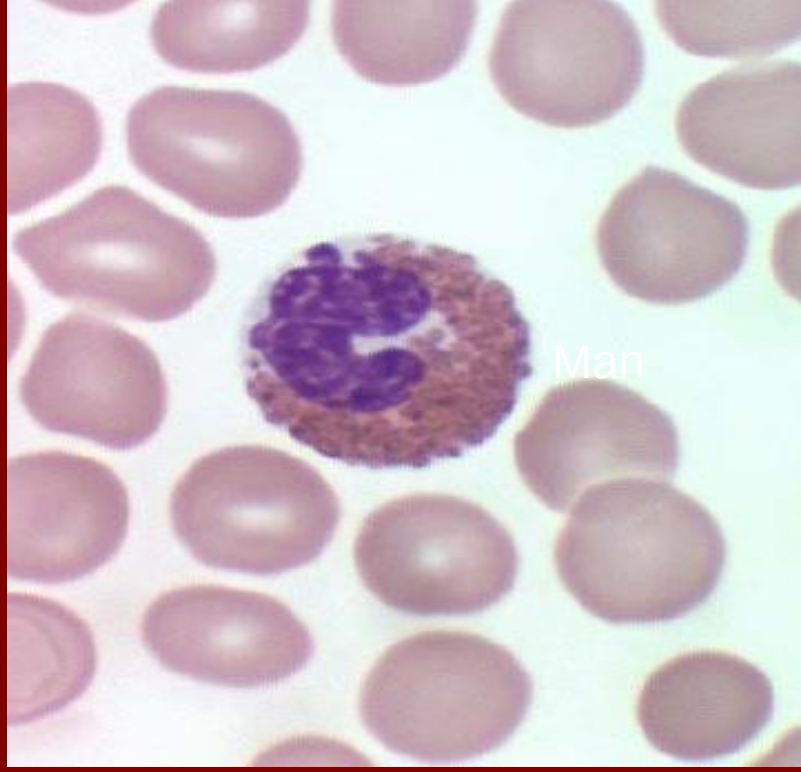
Neutrophils are actively motile and phagocytic i.e., tend to migrate (chemically attracted) to sites of inflammation?

1- Their numbers increase explosively during acute bacterial infections

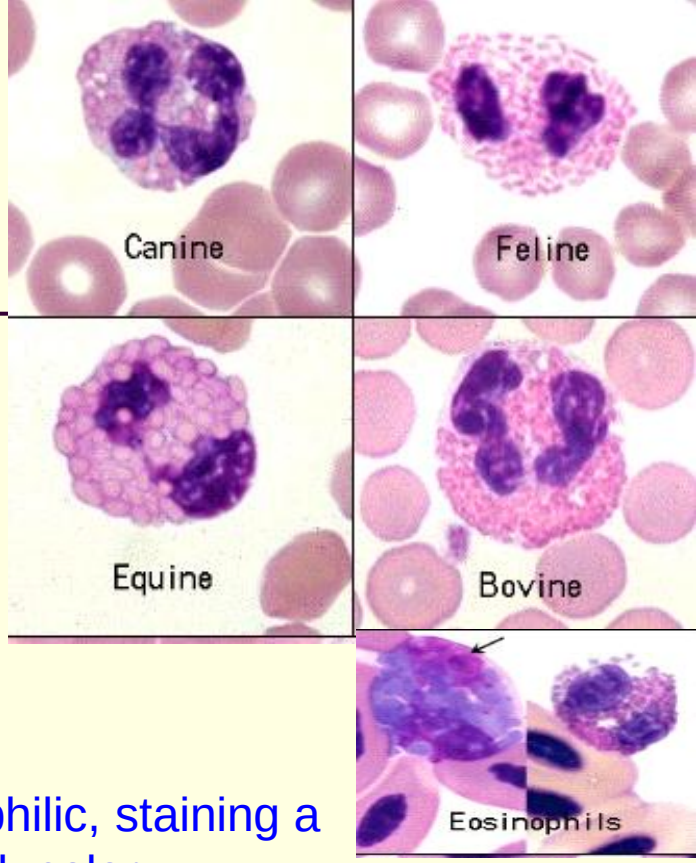
2- The granules in the neutrophil are lysosomes= contain peroxidases and hydrolytic enzymes and antibiotic-like proteins (defensins).

3- At these sites, they engulf and destroy invading bacteria, and then die; their dead and lysed bodies constitute the bulk of *pus* at sites of suppurating wounds

Eosinophil



Eosinophils



Birds

- Percentage:
  - 2-4% of WBCs
  - except in cattle, the percent of eosinophils is 12%.

- Size:
  same size or even slightly larger (10 to 14 microns) than neutrophil
- Shape:

- Cytoplasmic granules: are strongly eosinophilic, staining a bright orange-pink color

In horse the cytoplasmic granules are exceptionally large

- Nucleus:
  typically bi-lobed

Functions:

(3rd line of defense)

1- Main function:

Decrease the severity of allergy. Comment?

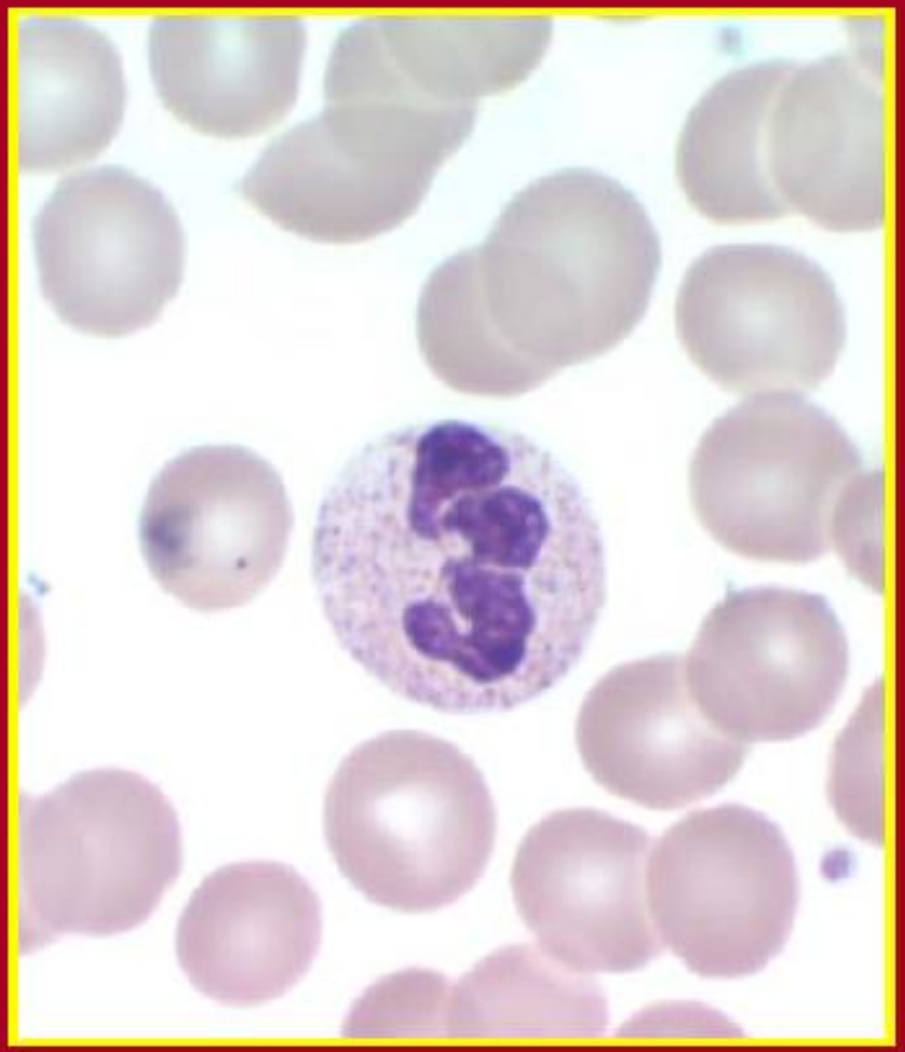
a- Their numbers increase during allergic attack
b- Detoxifies and inactivates histamine and histamine-like substances.
c- phagocytize antigen-antibody complexes involved in allergic attacks.

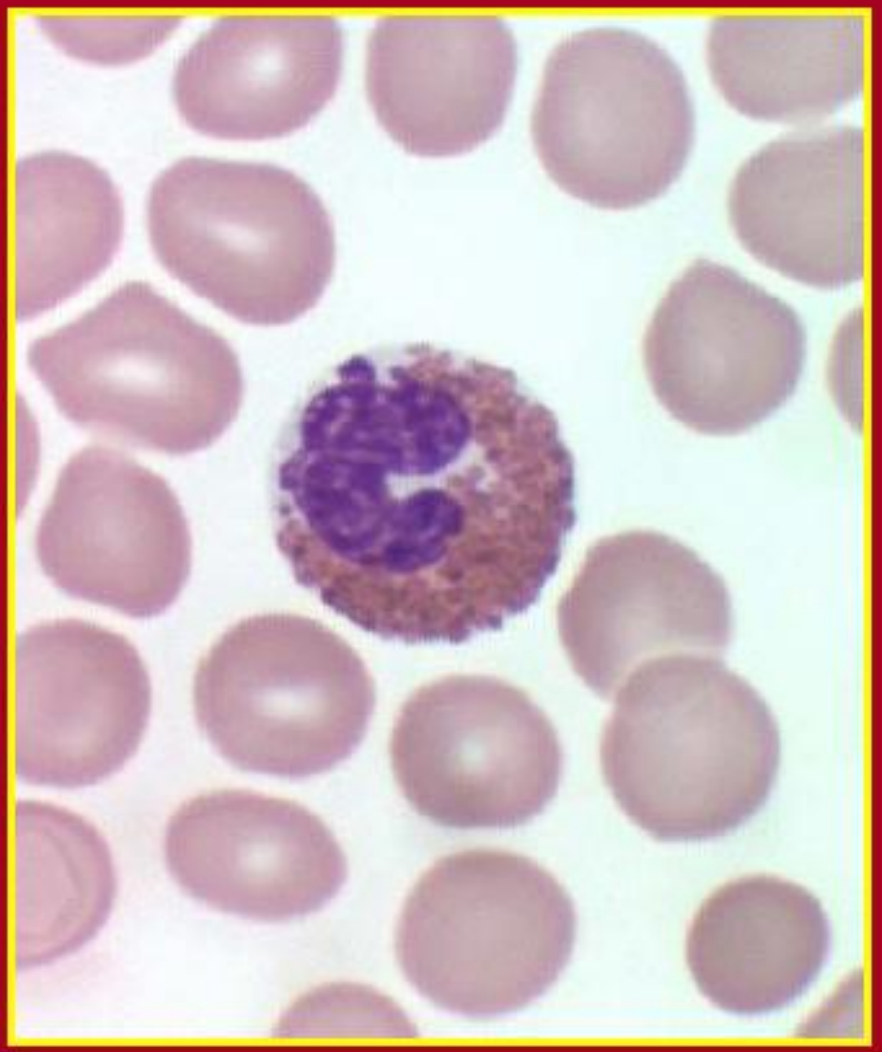
2- Kill parasitic worms:

e.g., flatworms (tapeworms and flukes) and roundworms (pinworms and hookworms).

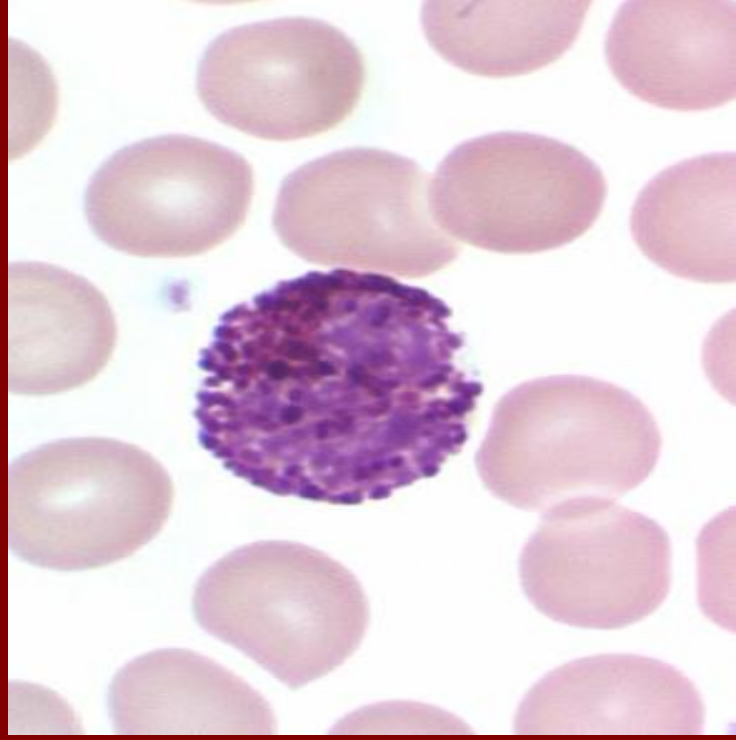
N. B.: Granules of eosinophils are lysosome-like but lack enzymes that specifically digest bacteria

NEUTROPHIL & EOSINOPHIL

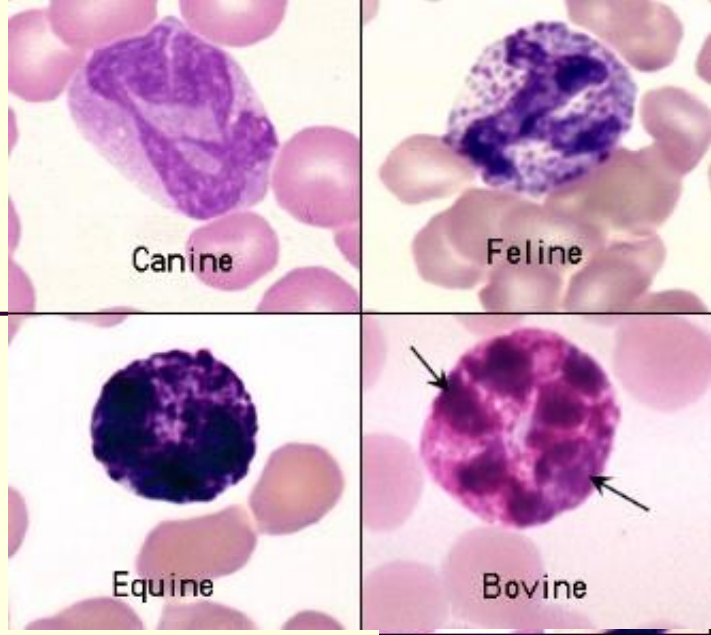


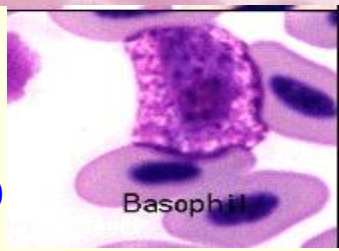


Basophil



Basophils





Birds

- Percentage:
  - <1% of WBCs
  - It is believed to be absent in cats, rats, and mice
- Size:
  same size as neutrophil
- Shape:
  - Cytoplasmic granules: are strongly basophilic, staining deep purple color, so often obscure the nucleus
  - Nucleus:
    bi-lobed

N.B.: histologically basophil is very similar to extravascular mast cells

Functions:

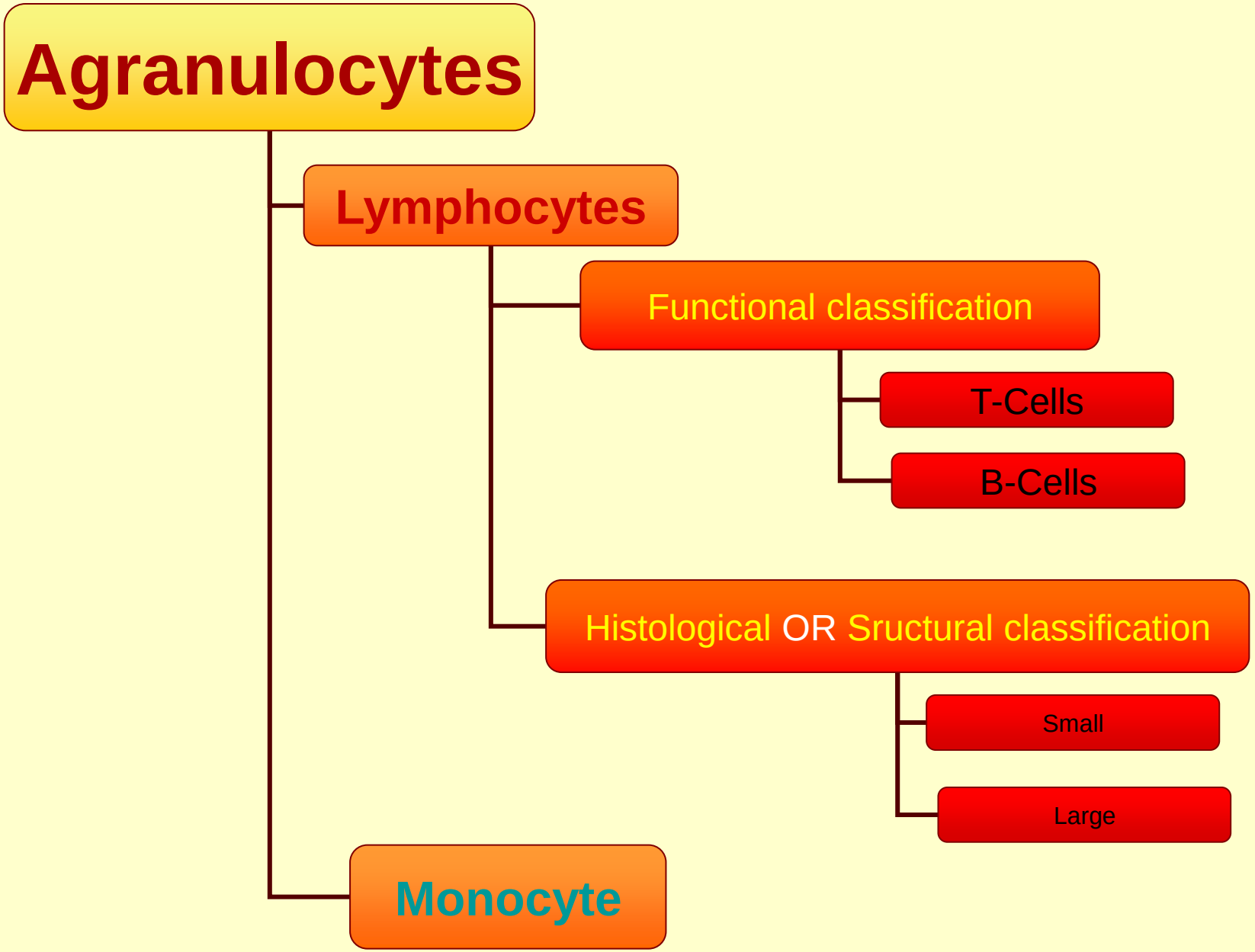
(5th line of defense)

1- Production of:

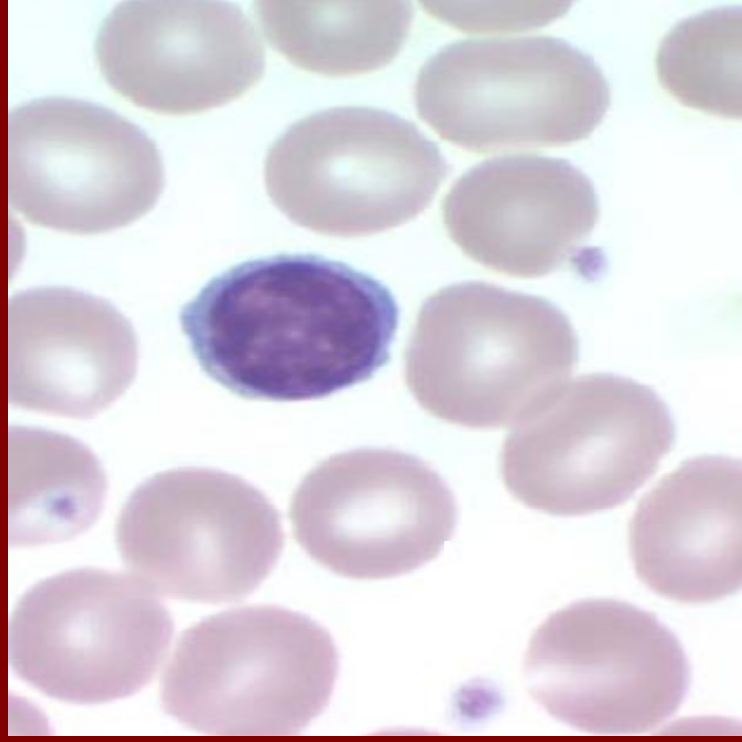
- heparin: Biological anticoagulant

- histamine: vasodilator substance (released at the site of local inflammation) → enables attraction of other WBCs to an inflamed site

N. B.: Granules of basophils contain histamine and heparin,


Agranulocytes
Lymphocytes
Functional classification
T-Cells
B-Cells
Histological OR Sructural classification
Small
Large
Monocyte

Lymphocyte



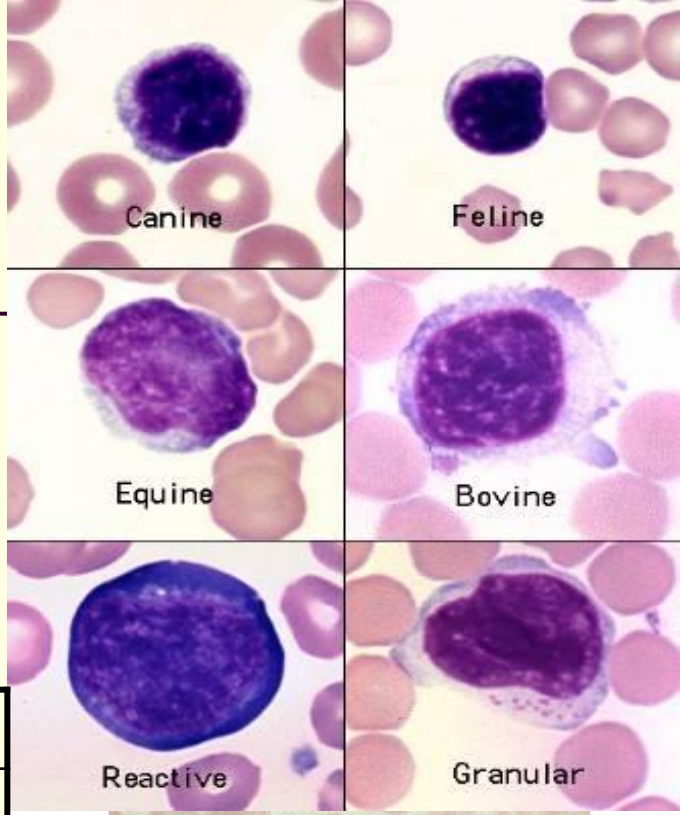
Lymphocytes

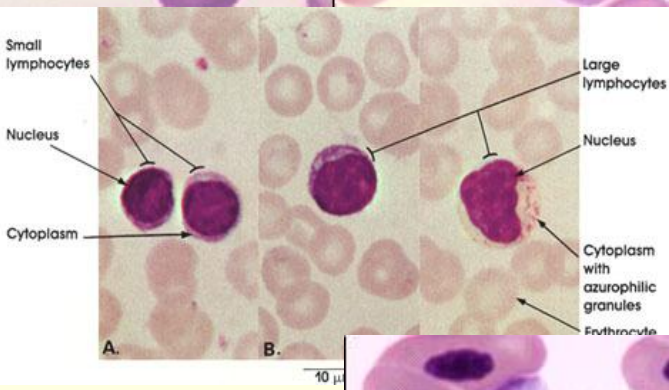
- Percentage:

  20-50 % of WBCs

- Morphological Structure:

	Small L	Large L
Diameter	6-10 microns	10-12 microns
Cytoplasm	thin band to one side of the nucleus, and is stained a dusky blue color	relatively abundant in amount.
Nucleus	very densely stained, and usually round	





Birds

Functions:

(4th line of defense)

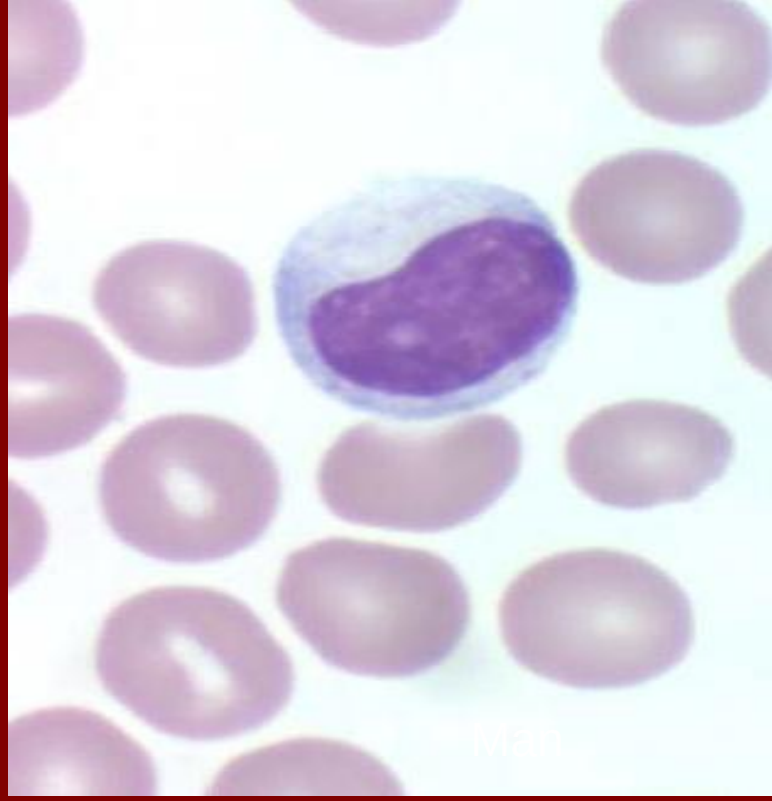
1- Immune response (Actual function):

T- cells	B- cells
Cellular immunity	Humoral immunity = Antibodies production (B lymphocytes give rise to plasma cells)

N.B.:

Both T- and B- cells are morphologically indistinguishable.

Monocyte



Monocytes

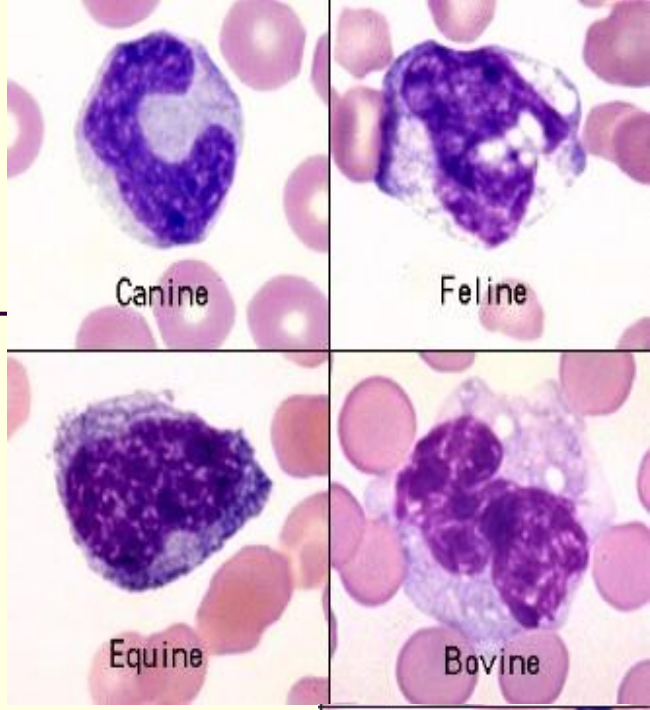
- Percentage:
  - Rarely exceeds 4% of WBCs
  - Some birds (e.g. chickens and ducks) they reach 10%.
- Size:

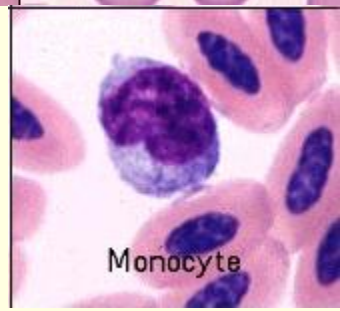
  16-25 microns (Largest WBC)
- Shape:

- Cytoplasm: stain a blue-gray color and is said to have a "ground glass" appearance due to the presence of fine granules in it.

- Nucleus:

  may be kidney, bean or classically horseshoe- shaped.





Birds

Functions:

(2nd line of defense)

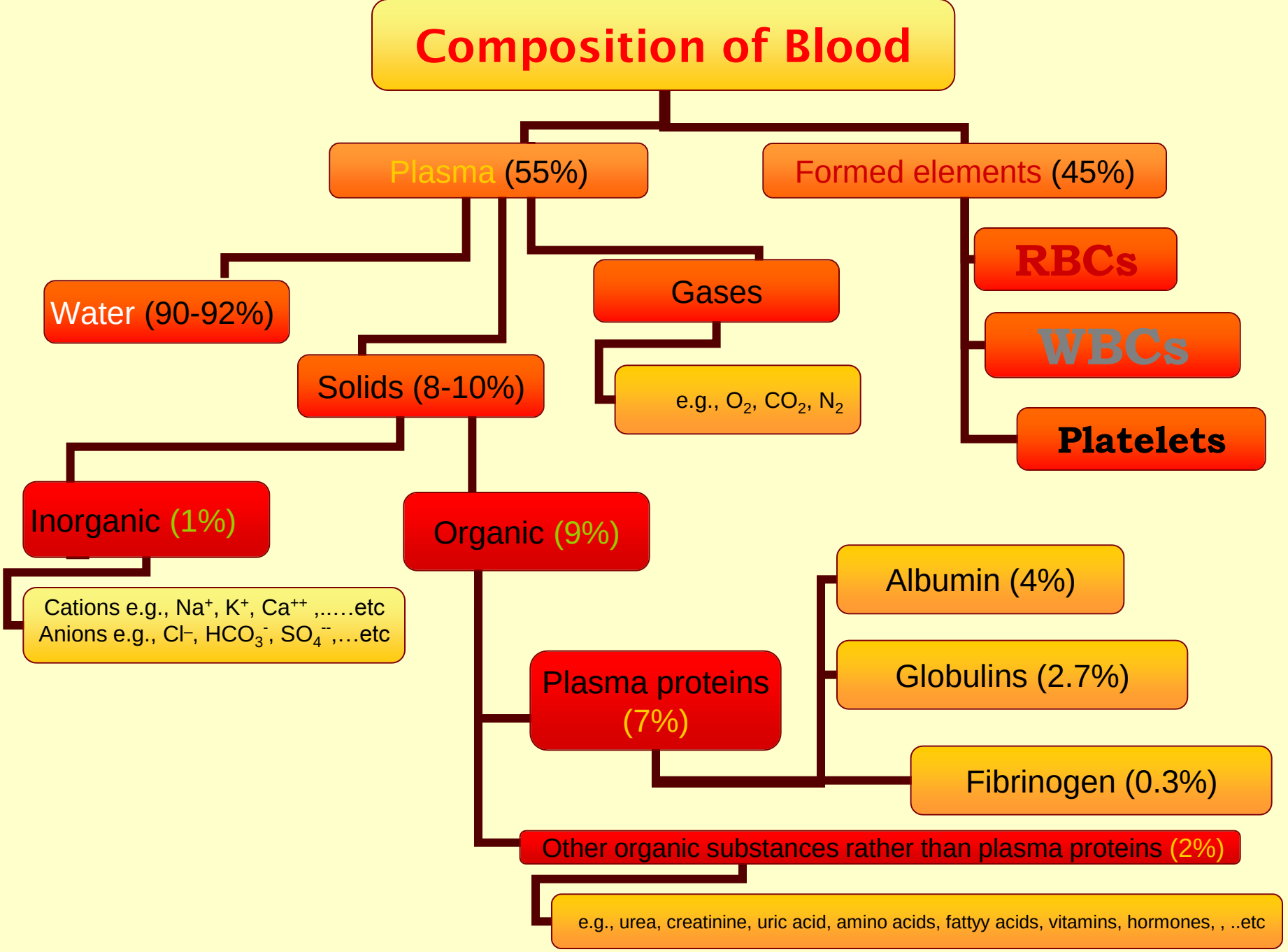
1- Actively motile and phagocytic:

- Number of active macrophages increases in chronic infections such as tuberculosis
- Precursor of macrophage in connective tissue

N.B: It is believed that monocytes are formerly large lymphocytes, then increased in size and acquired the phagocytic activity and become monocytes. Other believe that they produced from separate origin in the reticulo-endothelial system

Total WBCs count (10^3/mm.^{3}) and the percent of each type of leukocytes in man and some animal species:

	Total (10^3/mm^3)	Lymph.%	Mono. %	Neutro. %	Eosino. %	Baso. %
Man	10	24	4	70	1.5	0.5
Dog	11	19	6	71	4	0.0-1.0
Equine	5-14	44-53	2-4	35-50	4-8	1.0
Cattle	8-9	61-64	2-3	25-35	3-12	1.0-2.0
Camel	12	66	4	25	4	0.0-1.0
Sheep	9	70	2	30	5	0.5
Goat	9	55	3	35	5	0.5
Pig	10	37	5	37	4	1.0
Chicken	30	25	10	62	2	1.0-2.0
Duck	23	24	11	62	2	1.0


Composition of Blood
Plasma (55%)
Formed elements (45%)
Water (90-92%)
Solids (8-10%)
Gases
e.g., O_2, CO_2, N_2
RBCs
WBCs
Platelets
Inorganic (1%)
Organic (9%)
Cations e.g., Na^+, K^+, Ca^{++} ,.....etc
Anions e.g., Cl^-, HCO_3^-, SO_4^{--},...etc
Plasma proteins (7%)
Albumin (4%)
Globulins (2.7%)
Fibrinogen (0.3%)
Other organic substances rather than plasma proteins (2%)
e.g., urea, creatinine, uric acid, amino acids, fattyy acids, vitamins, hormones, , ..etc

Blood Platelets Thrombocytes

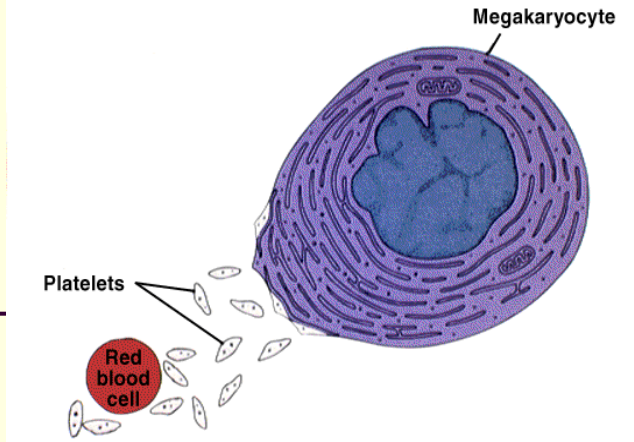
Thrombocytes = Blood Platelets:

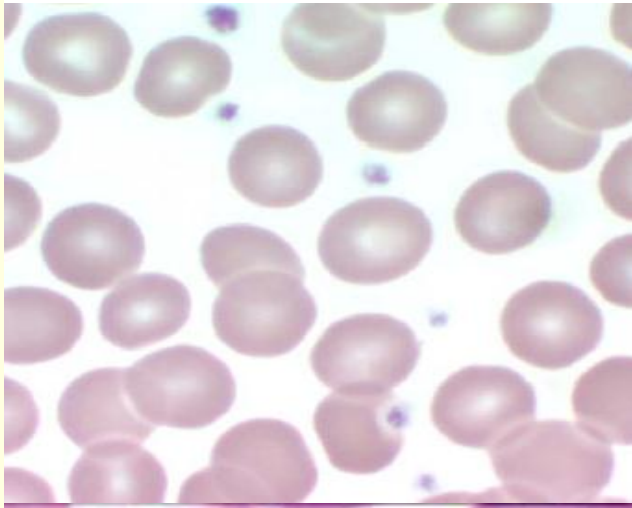
Number:

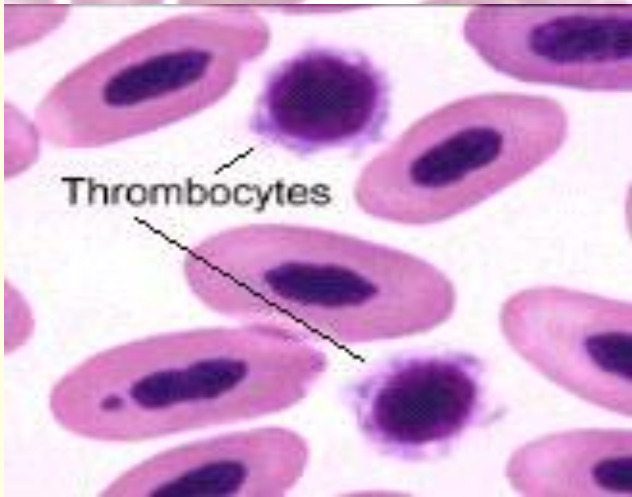
	Platelets count (10^3/ mm^3)
Man	200-500
Dog	267-432
Cow	74-740
sheep	620
Horse	210

Diameter:

- only 2 to 4 μm in diameter (Smallest formed elements).







Shape:

- Round to oval.
- Not true cell = Membrane- bound cytoplasmic fragments (containing granules and enzymes) .
- In birds and other submammalian: they are true nucleated cells

Origin:

Fragments of the very large (giant) cells called megakaryocytes of bone marrow. Explain?

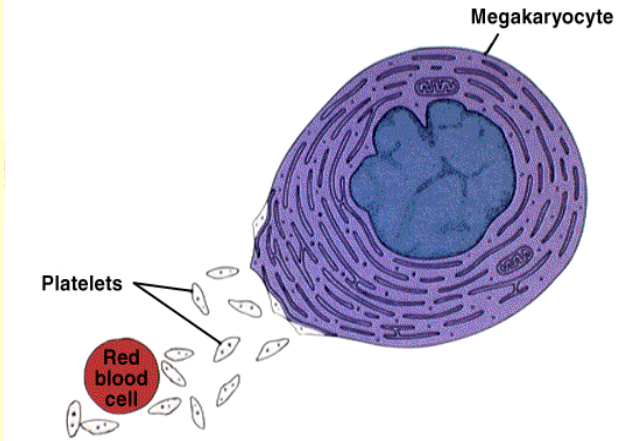
Megakaryocytes exhibit protoplasmic protrusions which while penetrating the blood sinuses of bone marrow fragment into platelets carried away in the blood current.

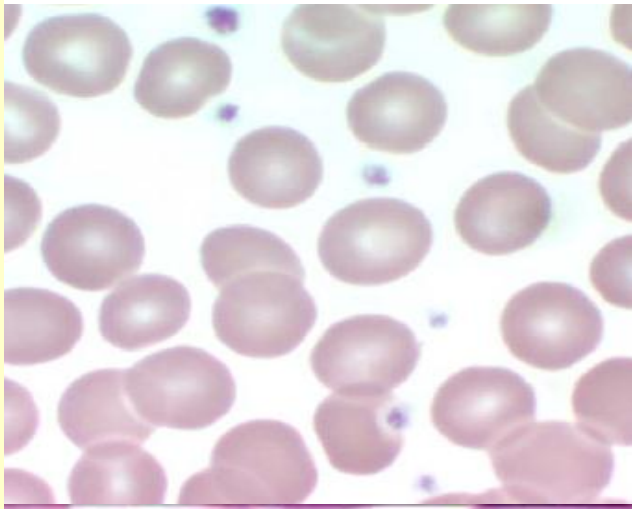
N.B.:

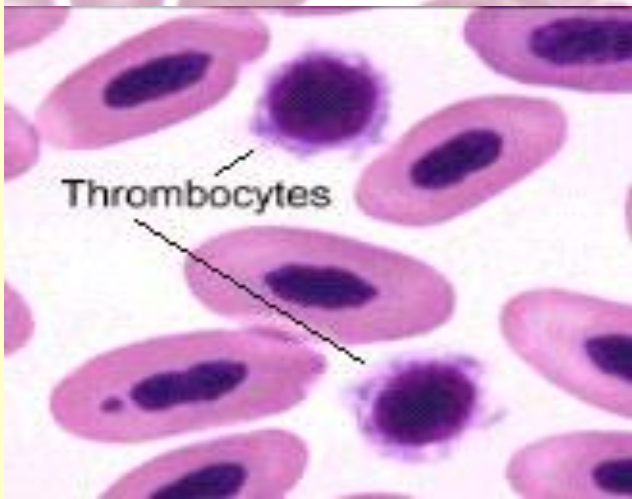
Thrombopoietin regulates the production of platelets by stimulating the hemocytoblast and myeloid stem cells

Life span:

degenerate in about 10 days if they are not involved in clotting







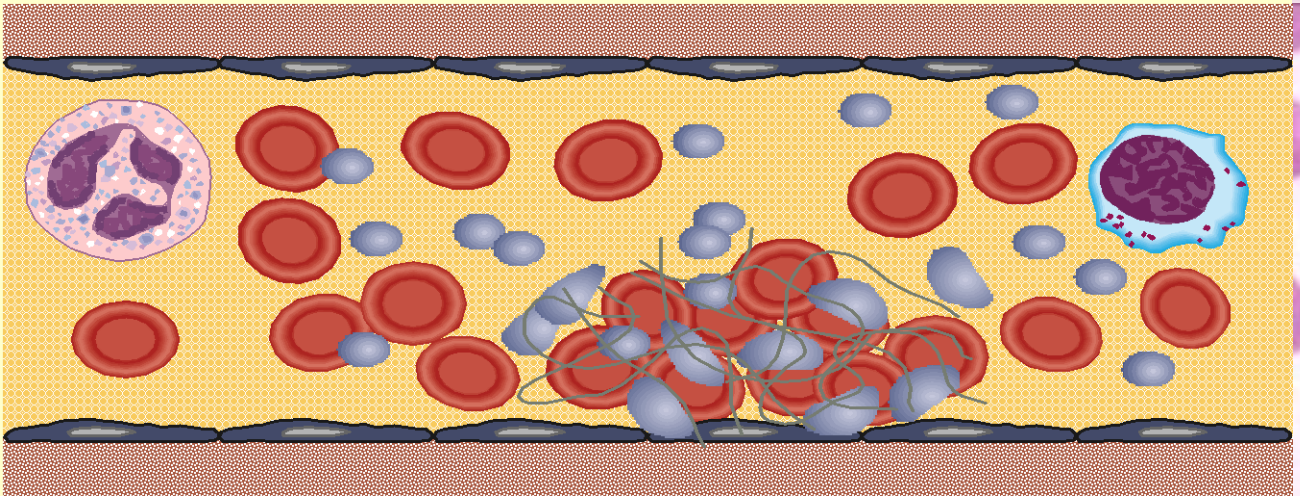
Function:

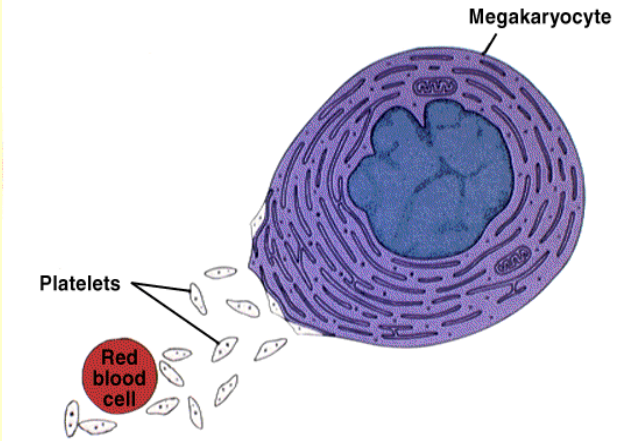
1- Formation of a temporary plug:

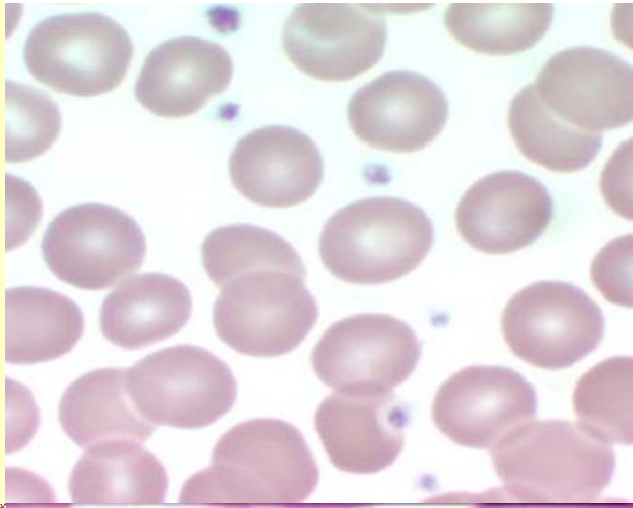
At the site of injury the platelets agglutinate very rapidly→ helps in sealing the break in the BV.

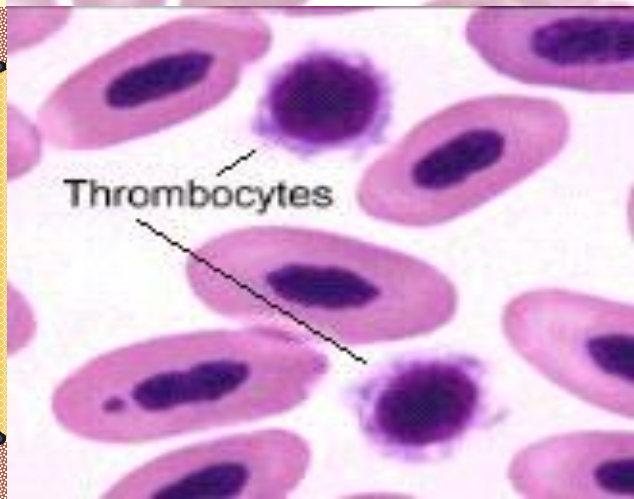
2- Granules contain many chemicals that act in the clotting process e.g

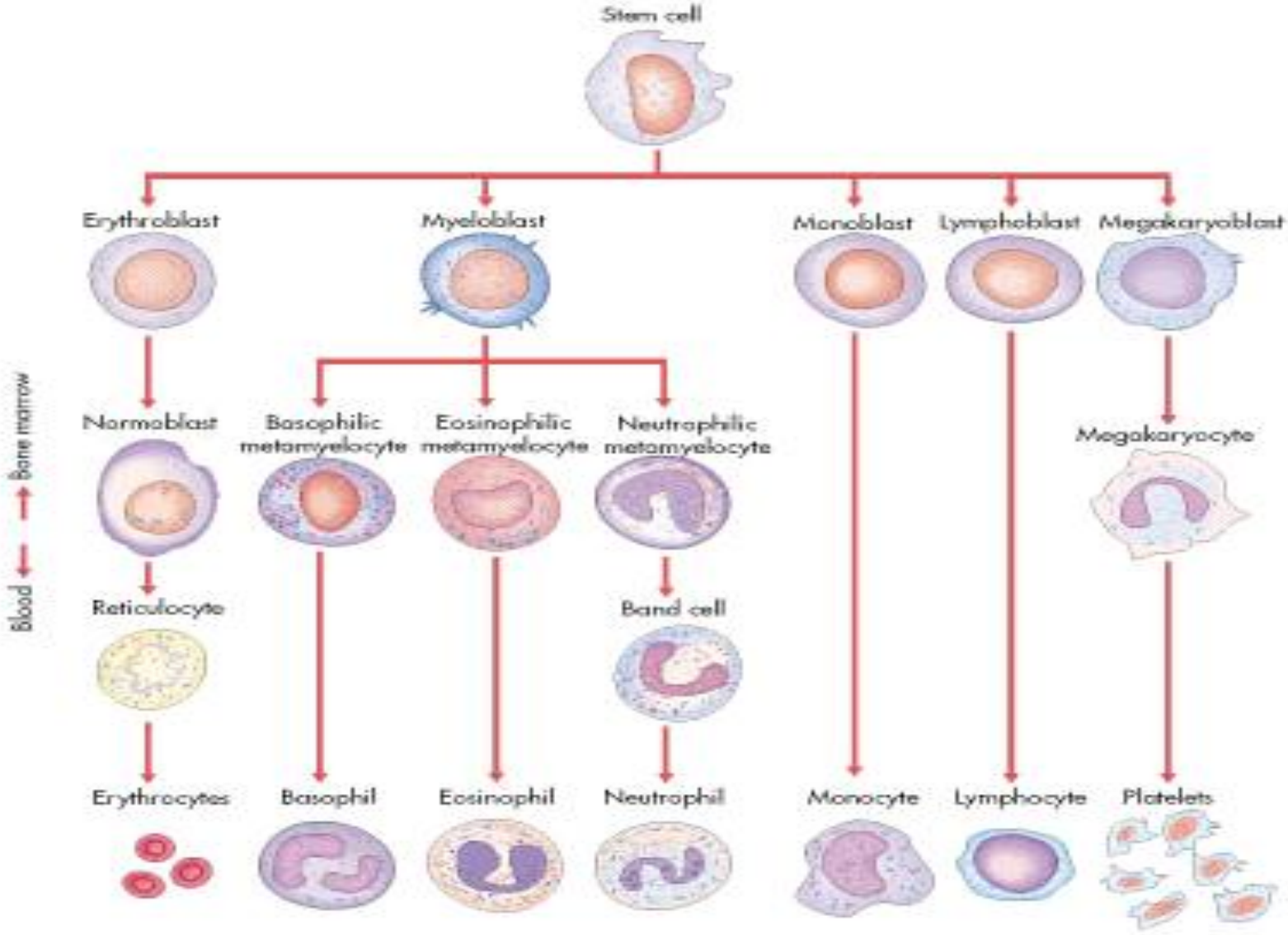
- serotonin → enhances vascular spasms
- ADP → attracts more platelets and causes them to degranulate (positive feedback)
- Prostaglandin derivatives " thromboxane (A2)" → stimulates both of the above
- Glycogen → source of energy utilized during the process of oagulation
- Ca^{++} → required for the coagulation cascade
- Phospholipids
- enzymes
- Platelet-derived growth factor.



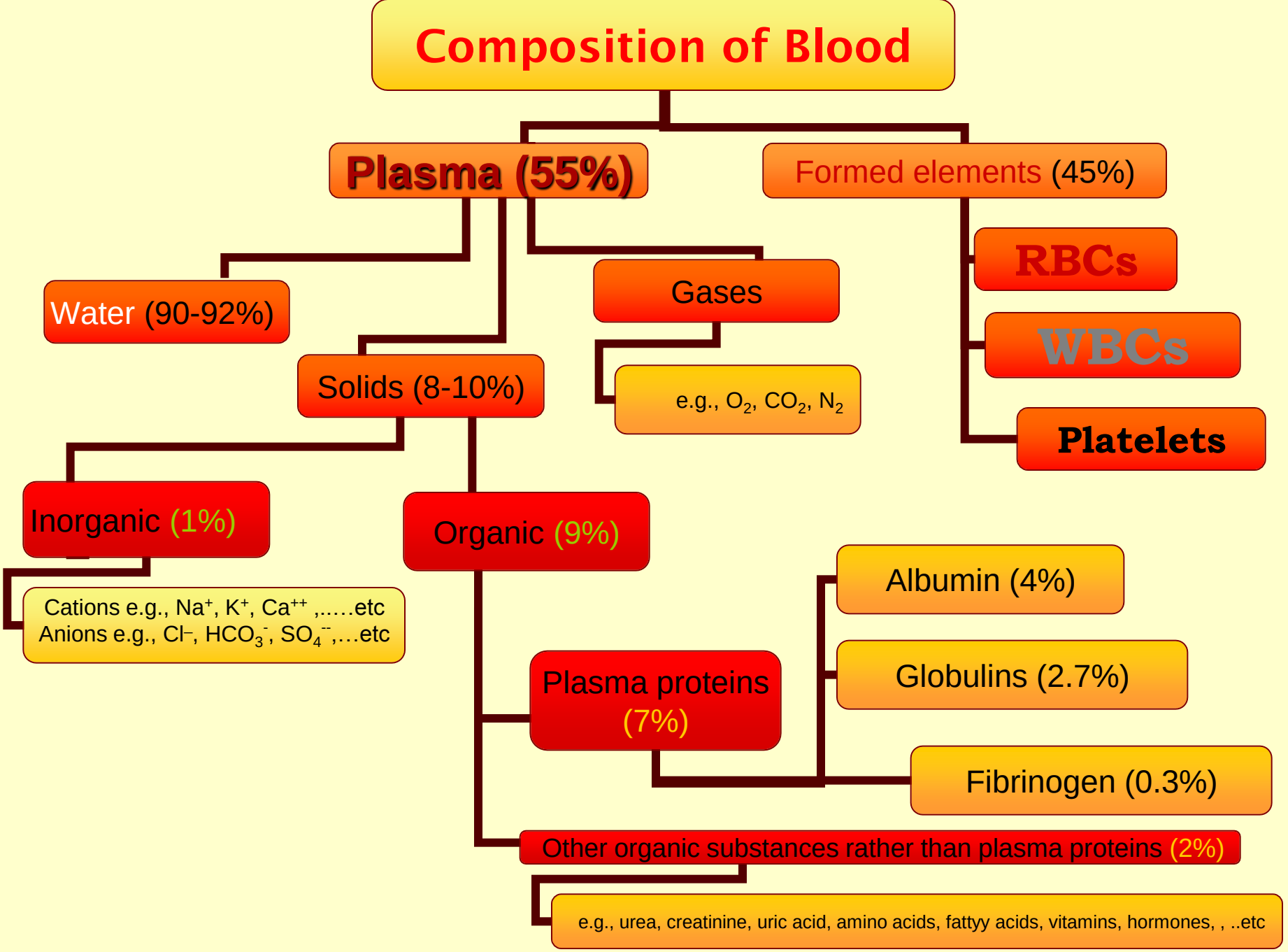




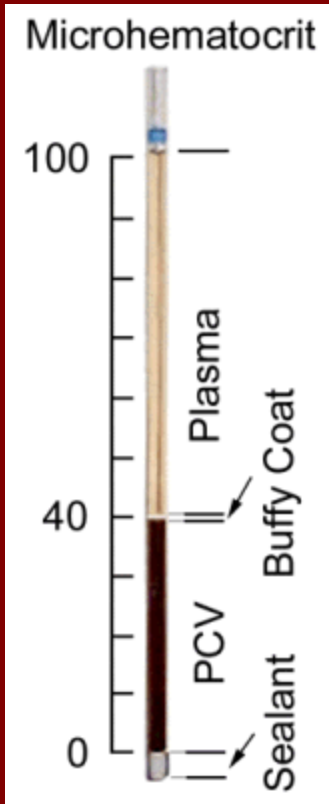




Development of blood cells


Composition of Blood
Plasma (55%)
Formed elements (45%)
Water (90-92%)
Gases
e.g., O_2, CO_2, N_2
Solids (8-10%)
RBCs
WBCs
Platelets
Inorganic (1%)
Organic (9%)
Cations e.g., Na^+, K^+, Ca^{++} ,.....etc
Anions e.g., Cl^-, HCO_3^-, SO_4^{--},...etc
Albumin (4%)
Plasma proteins (7%)
Globulins (2.7%)
Fibrinogen (0.3%)
Other organic substances rather than plasma proteins (2%)
e.g., urea, creatinine, uric acid, amino acids, fattyy acids, vitamins, hormones, , ..etc

Blood Plasma



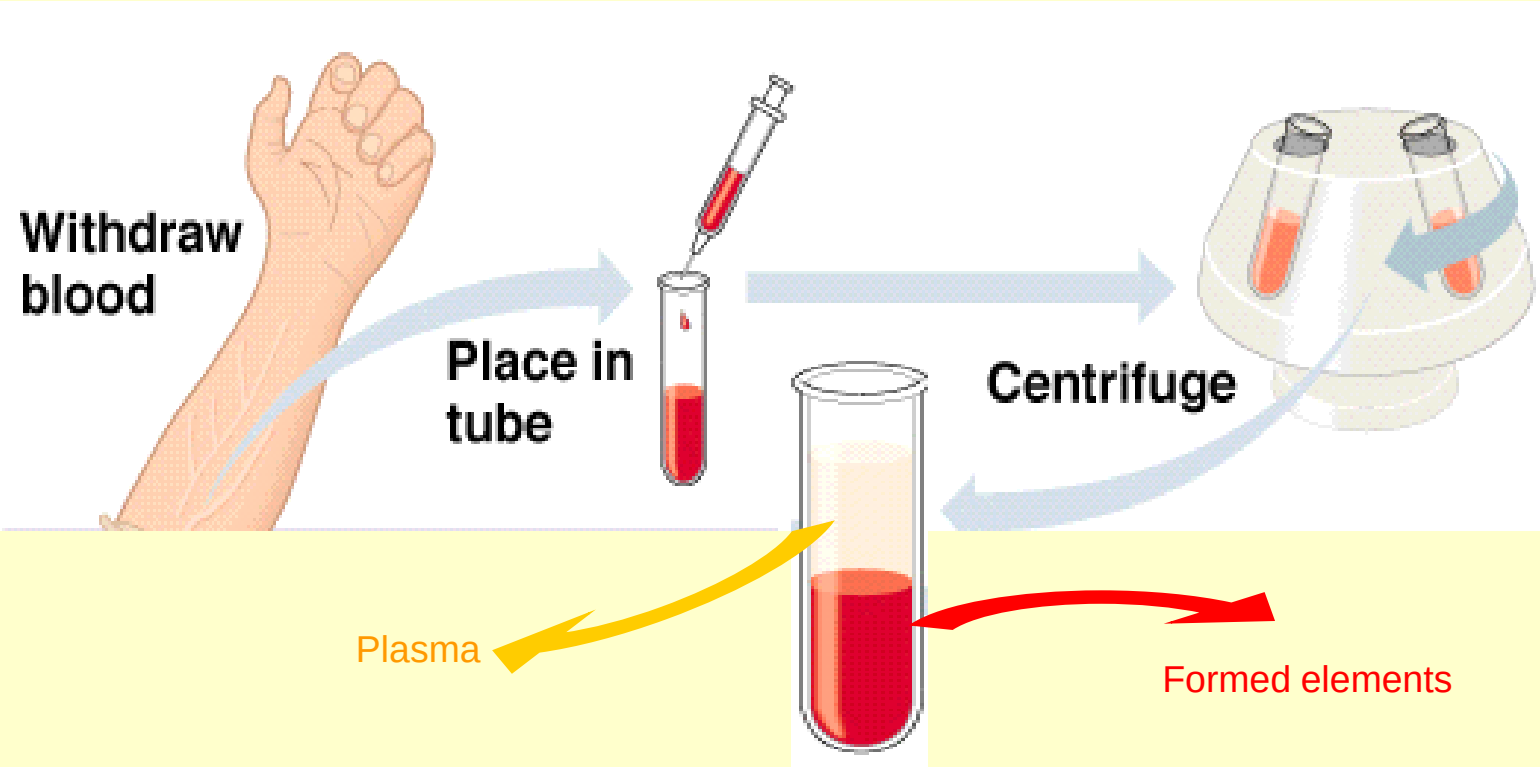
Plasma = Fluid part of uncoagulated blood

∴ Prepared by centrifugation of uncoagulated blood.

Serum = Fluid part of coagulated blood

∴ Prepared by centrifugation of coagulated blood.

(Serum = Plasma – Fibrinogen)



Q: What is the composition of Blood Plasma?

BLOOD PLASMA

= 55% of total blood volume

- Water (90-92%)
- Solids (8-10%)
  - Inorganic (1%)
    - Cations e.g., Na^+, K^+, Ca^{++} ,.....etc
      Anions e.g., Cl^-, HCO_3^-, SO_4^{--},…etc
  - Organic (9%)
    - Plasma proteins (7%)
      - Albumin (4%)
      - Globulins (2.7%)
      - Fibrinogen (0.3%)
    - Other organic substances rather than plasma proteins (2%)
      - * Lipids: fat, lecithin, cholesterol, …etc.,
      - * CHO: glucose, pyruvate, lactate, ..etc,
      - * NPN substances: amino acids, urea, uric acid, creatine, Creatinine, …etc,
      - * Enzymes, hormones, vitamins and pigments
- Gases
  - e.g., O_2, CO_2, N_2

General Features of blood plasma:

Water:-

- constitutes about 90-92 % of plasma.
- contains over 100 different dissolved solutes

Plasma proteins:

- are the most abundant plasma solutes
- are not taken up by cells to be used as nutrients

Albumins:

Amount:

constitute about 50-60%% of total plasma proteins
= 3.5 -4 g/ 100 ml. blood plasma.

Source:

Liver.

Functions:

1- Major contributor to the colloid osmotic pressure of blood plasma. Comment?

Albumins account for about 80% of the colloid osmotic of blood plasma, as it

- have a smaller molecular weight
- constitute the higher conc. (50-60%% of total plasma proteins)

Type	% of plasma	Molcular wt.
Albumin	3.5-4	69.000
α globulin	1.0	300.000
βglobulin	1.5	500.000
γ globulin	0.8	300.000
Fibrinogen	0.2-0.4	400.000

Albumins:

2- Carrier for certain molecules in the circulation:

- Bile pigments
- Some hormones e.g., thyroxine, cortisol, FSH and LH

3- Buffering action:

Proteins have free acidic (-COOH) and basic ($-NH_2$) groups which allows them to act as weak acid or alkalies according pH of the medium e.g.,

Lactic acid + Na proteinate $\rightarrow$ Na lactate + Proteinc acid

4- Carriage of CO_2:

- CO_2 + Plasma proteins (NH_2 group) $\rightarrow$ carbamino-proteins

- **Proteins (Na proteinate** "basic") **+** $H_2CO_3 \rightarrow$ $NaHCO_3$ + H Proteinate (Proteinic acid)

Q: *What are the effects of hypoalbuminemia?*

1- ↓↓ in the osmotic pressure→ oedema (accumulation of water in the different tissues). Comment?

2- Hormonal imbalance. Comment?

Globulins:

Amount:

constitute about 36- 45% of total plasma proteins

= 2.7 g/ 100 ml. blood plasma.

Types of Globulins:

Electrophoretic studies revealed that globulins are of three main classes;

1- alpha (α) globulin (15%): subfractionated into α_1 and α_2

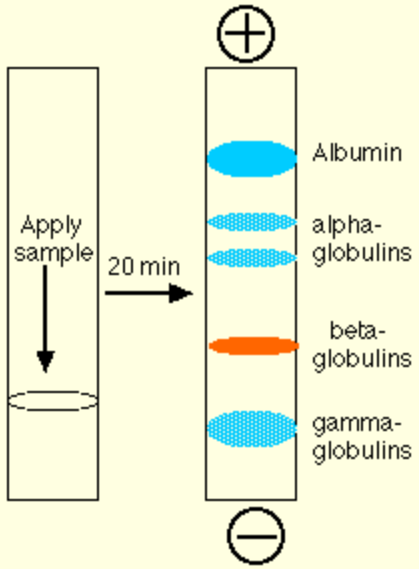
2- beta (β) globulin (19%): subfractionated into β_1 and β_2

3- gamma globulin (11%)

Source:

1- α and β globulins are formed in liver

2- γ are formed in lymphoid tissues (Plasma cells)



Separating serum proteins by electrophoresis

Functions:

1- α and β globulins

acts as transport proteins for various substances e.g.,

- pigments, lipids, metal ions, and fat-soluble vitamins
- Some hormones : transcortin for corticosteroids, thyroxine binding globulin

3- α_2 globulin (Hypertensinogen):

renin produced by the kidneys

↓

hypertensin

(vasodilator substance)

2- **γ globulins:**

consist of antibodies produced by plasma cells during the immune response.

Fibrinogen:

Amount:

constitute about 4% of total plasma proteins

= 0.3 g/ 100 ml. blood plasma.

Source:

Liver

Function:

1- **Blood coagulation:**

It is converted into insoluble fibrin.

2- Main plasma protein responsible for **blood viscosity** which are necessary for maintaining arterial blood pressure at normal level**.**

Q: What are the functions of blood plasma?

HEMOSTASIS

Hemostasis :

= Stoppage of bleeding **in response to injury of B.V.**

- Phases of hemostasis:

1- Vascular phase (vascular spasm)

2- Platelet phase (platelet plug formation)

3- Coagulation (clotting)

1st Phase

Vascular Phase

(i) Vascular Phase:

- Very rapid response
- Triggered by:
    1- Smooth muscle fibers of BV:
        Contract (vascular spasm) → pull vessel walls closer together
    2- Endothelial cells:
        - contract → pull vessel walls closer together
        - release chemicals that stimulate:
            a- vascular spasm
            b- division of endothelial cells, smooth muscle cells and fibroblasts

Significance:

Walls of damaged BV become closer together →Reduces blood loss and allows:

- platelet plug to form
- blood to clot

2nd Phase

Platelet Phase

(Platelet Plug Formation)

(ii) Platelet phase (platelet plug formation):

1- Platelet adhesion:

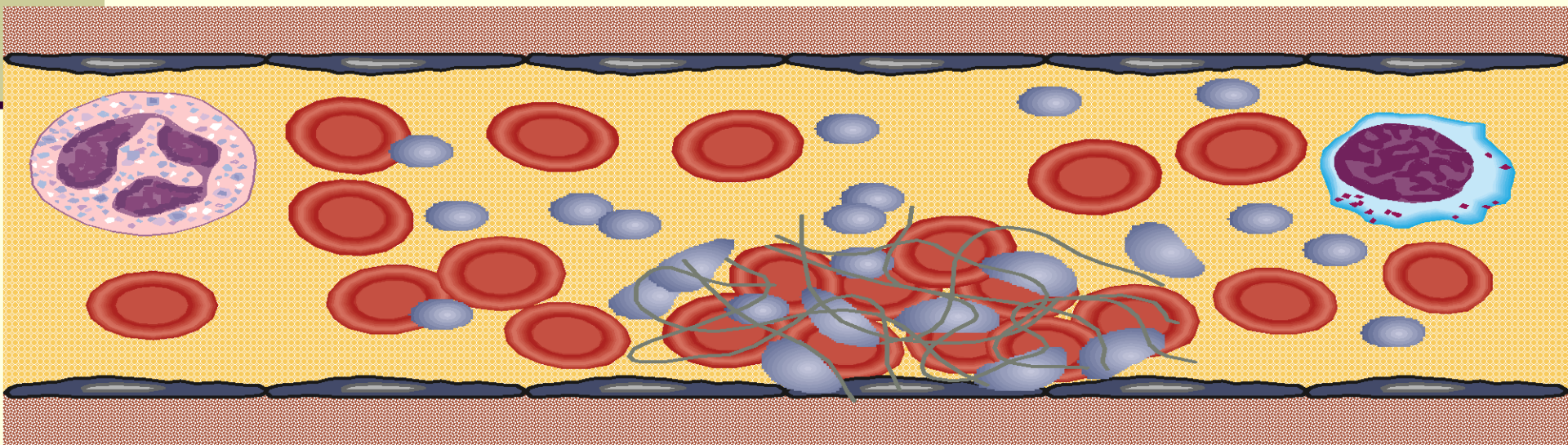
= Platelets stick to exposed collagen fibers of the injured BVs and extracelluar matrix.

Aided by von Willebrand factor (VWF) from endothelial cells

2- Platelet aggregation:

= Platelets change their shape (swell and develop spiked processes) to encounter other platelets and fibers

N.B: Aggregation of platelets forms the primary hemostatic plug



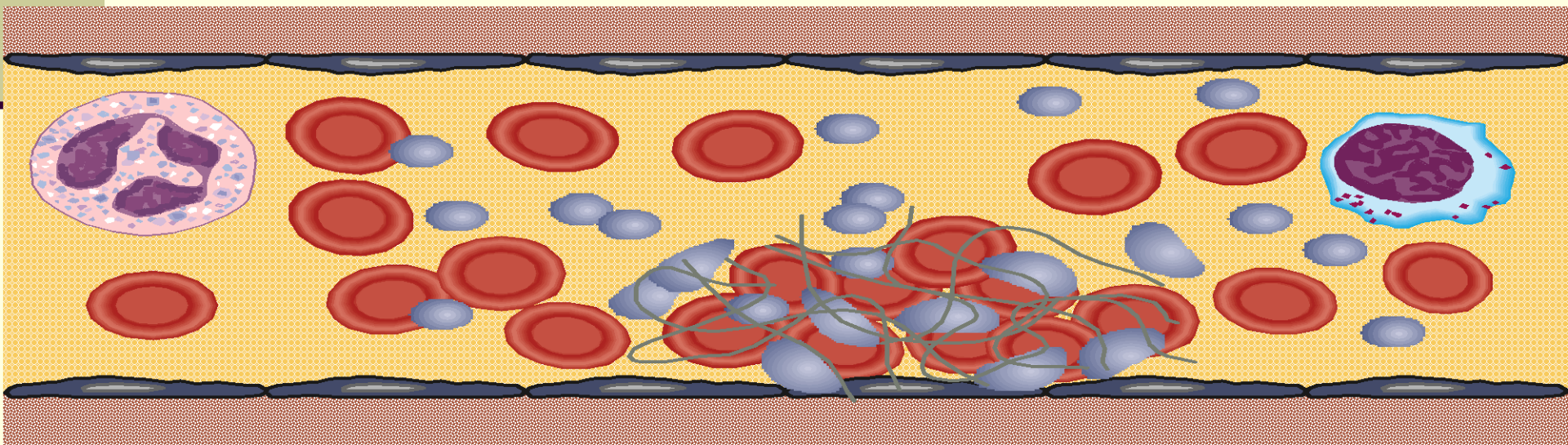
(ii) Platelet phase (platelet plug formation):

3- Platelets degranulate and release chemicals that enhance hemostasis:-

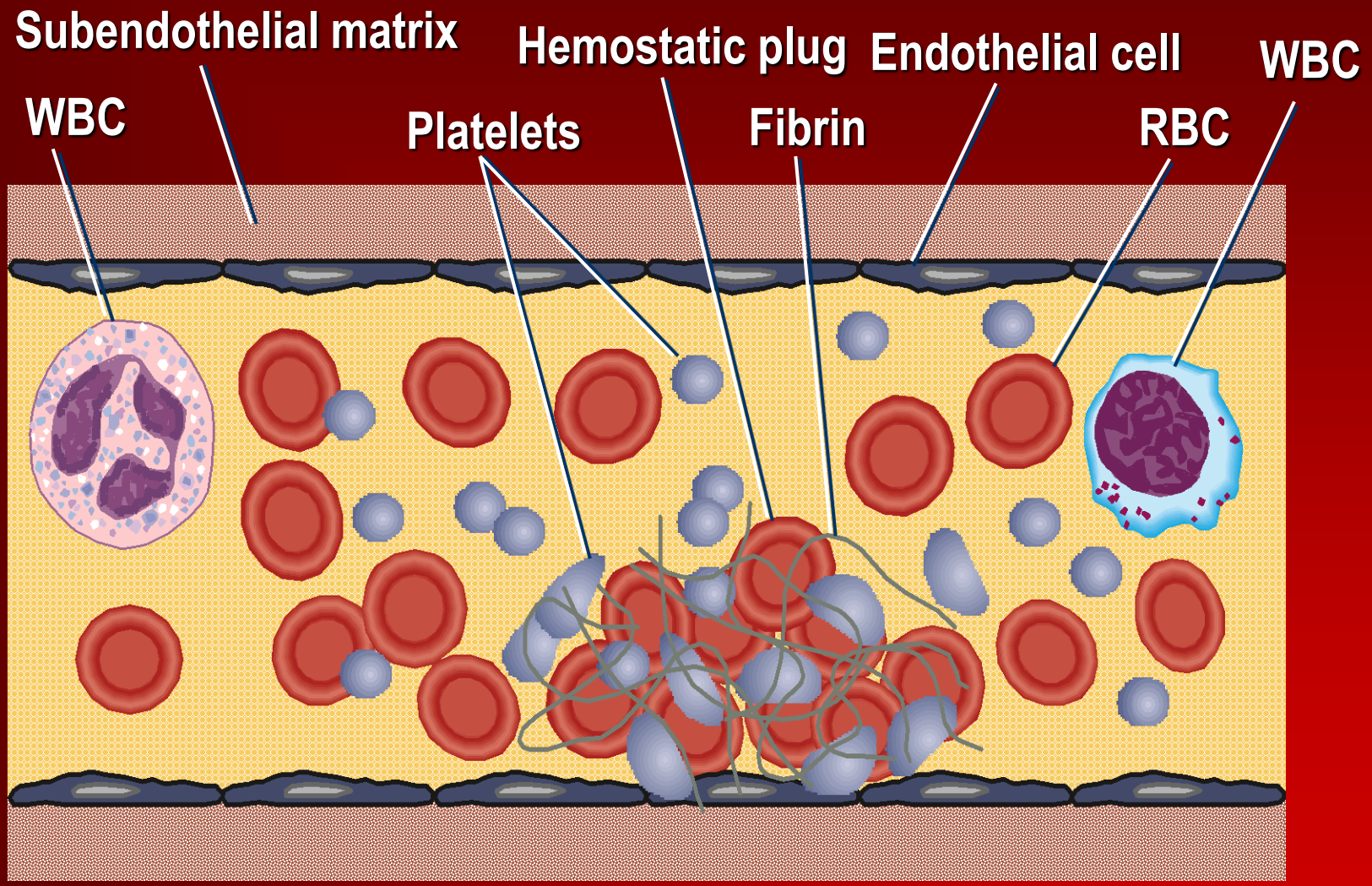
- serotonin→ enhances vascular spasms
- ADP → attracts more platelets and causes them to degranulate (positive feedback)
- Prostaglandin thromboxane (A2) → stimulates both of the above
- Ca^{++} (clotting factor IV) → required for the coagulation cascade
- protein clotting factors
- platelet-derived growth factor

Significance:

within a minute, a secondary, irreversible plug is formed. Fibrin cements the plug.



Platelet Plug Formation



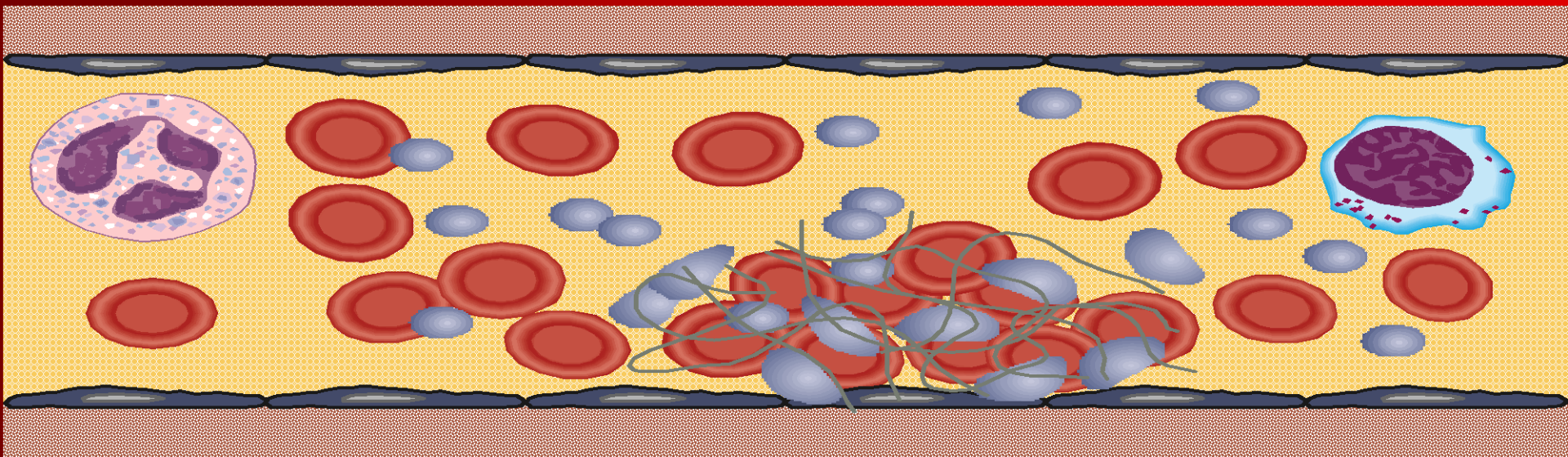
Platelet plug formation - Summary

= when a vessel is damaged, the **platelets**:

1- Stick to collagen of the exposed injured BV

2- Swell and from spiked processes →encounter with other platelets and fibers

3- Degranulate and release chemicals that enhances hemostasis



Natural Limits to Platelet Plug Formation

1- Prostacyclin (PGI_2; local prostaglandin) that inhibits platelet aggregation

2- Inhibiting compounds secreted by WBCs

3- Clotting (isolates platelet plug from circulation)

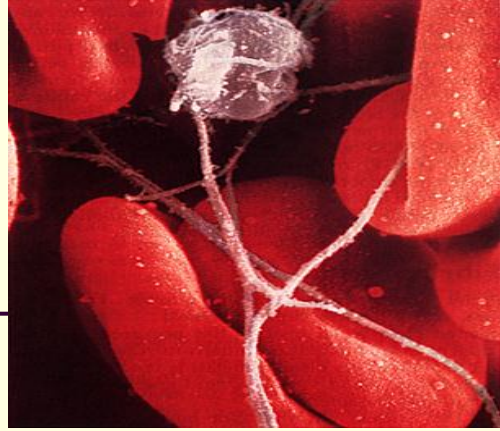
4- Antithrombin (inhibits action of thrombin)

3rd Phase

COAGULATION

(Clotting Phase)

Coagulation (Clotting) Phase



Clotting:

= Complex process by which liquid blood becomes solid clots.
= Transformation of fluid consistency of blood into jelly like mass

Very simply, coagulation is described as

Transformation of soluble fibrinogen into insoluble fibrin threads

↓

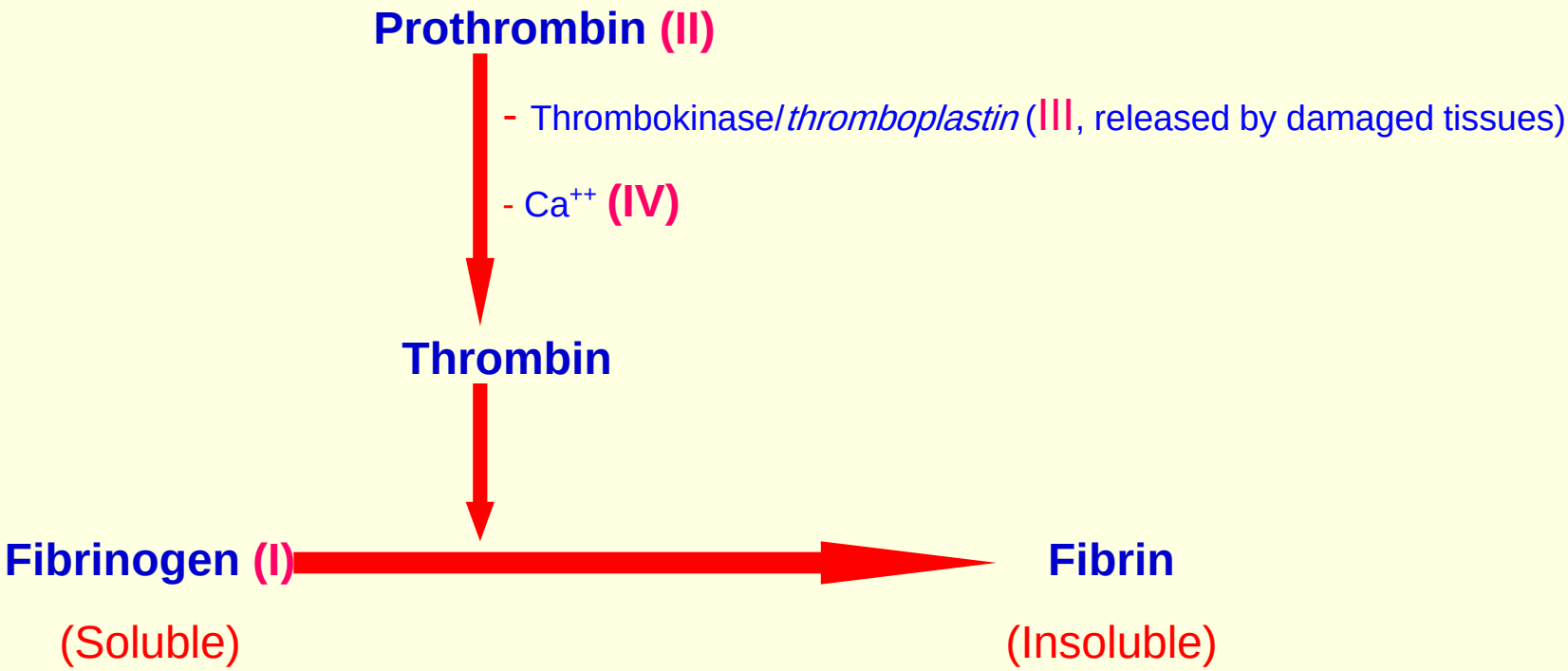
fine network in which the red cells as well as white cells are entangled

MECHANISMS OF COAGULATION

1- Simple (Classic theory):

At the end of the 19th century:

It was presumed that the coagulation system consisted of four factors



2) Advanced Theory:

In the 20th Century:

- Over 30 different **proteins** called **clotting factors** are involved in coagulation.

- The **primary factors** involved in coagulation cascade are given the Roman figures from I to XIII

- Coagulation can be initiated by two pathways (intrinsic and extrinsic), share a common pathway at the end

Primary factors involved in coagulation:

Factor	Common Name	Pathway	Function
I	Fibrinogen	Common	Form fibrin clot
II	Prothrombin	Common	activates I, V, VII, XIII, protein C, platelets
III	Tissue Factor (Thromboplastin)	**Extrinsic**	*unassigned*
IV	Calcium ions	All	Cofactor
V	Proaccelarin (Labile factor)	Common	supports X, activates II
VI	Accelarin	Common	*Transformed form of factor V = Old name of factor Va*
VII	Procenvertin (Stable factor)	**Extrinsic**	
VIII	Antihemophilic factor	Intrinsic	supports IX, activates X
IX	Christmas factor	Intrinsic	activates X
X	Stuart Power factor	Common	activates Prothrombin and V II
XI	Plasma thrombin antecedent	Intrinsic	activates IX
XII	Hageman factor	Intrinsic	activates XI
XIII	Fibrin-stabilizing factor	Common	crosslinks fibrin
	Von Willebrand factor	Platelet	Platelet activation and adhesion
	Prekallikrein	Intrinsic	activates XII
	High Molecular Weight Kininogen (HMWK)	Intrinsic	supports reciprocal activation of XII, XI, and prekallikrein

PATHWAYS OF COAGULATION

Two pathways, share a common pathway at the end;

(1) Intrinsic pathway:

- Intrinsic = Only blood-borne substances are involved

- Requires surface of contact on which blood platelets agglutinate and release the platelet factors→ initiates activation of factor XII in blood

- Long pathway = many steps= slower (Fibrin formation occurs within 3-6 minutes)

N. B.: It may occur within an unbroken BVs.

(2) Extrinsic pathway:

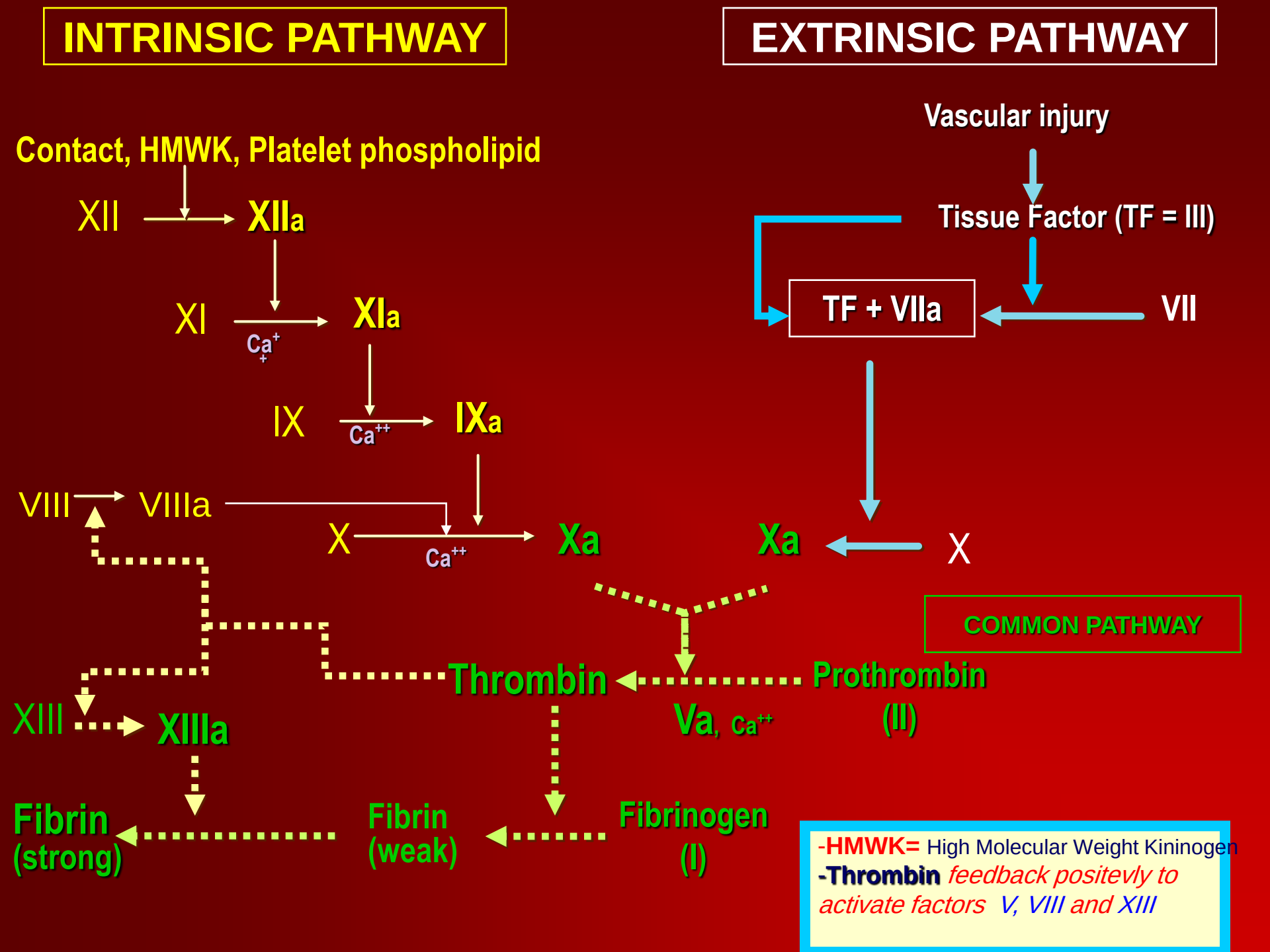
- Extrinsic = initiated by tissue factor which is not in the blood

- Requires tissue damage → tissue factor (factor III)

- Short pathway = fewer steps= faster (Fibrin formation occurs within ~ 15 seconds)

(3) Common pathway:

Start from formation of prothrombin activator (Xa) to formation of fibrin


INTRINSIC PATHWAY
EXTRINSIC PATHWAY
Contact, HMWK, Platelet phospholipid
XII
XIIa
XI
Ca+
XIa
IX
Ca++
IXa
VIII
VIIIa
X
Ca++
Xa
Vascular injury
Tissue Factor (TF = III)
TF + VIIa
VII
Xa
X
COMMON PATHWAY
Thrombin
Prothrombin
(II)
Va, Ca++
XIII
XIIIa
Fibrin
(strong)
Fibrin
(weak)
Fibrinogen
(I)
-HMWK= High Molecular Weight Kininogen
-Thrombin feedback positevly to activate factors V, VIII and XIII

Q: Diagram the intrinsic, extrinsic, and common pathways of blood coagulation

Prothrombin (Factor II)

Nature:

Carbohydrate-containing protein occurs in the globulin fraction of plasma proteins.

Origin:

- produced by the liver
- Vit. K is necessary for its synthesis. However, vit. K is not a part of prothrombin molecule.

Form in circulation:

Prothrombin is found normally in blood in an **inactive form** as it combines with antiprothrombin forming **prothrombin-antiprothrombin** combination.

Action:

See pathway of coagulation

Clot Retraction

= 30 – 60 minutes after the clot is being formed, the disintegrated platelets release Retractozymes (contractile protein) which lead to

Retraction of fibrin threads

↓

Clot becomes shrunken and more firmer

↓

Pulls torn edges of vessel together

↓

Reduces size of damaged area

N.B.: Serum (plasma minus clotting proteins) is squeezed from the clot during this contraction

Fibrinolysis

= If the clotted blood is left for a long time, in vitro, a process of proteolytic fermentation occurs and results in clot dissolution (liquefaction of the clot)

Plasminogen
(Inactive precursor)

Activation

Extrinsic: Tissue plasminogen activator (TPA) - produced by damaged tissues

Intrinsic: XIIa, HMWK, kallikrein.

Common: thrombin produced by common pathway of clotting

PLASMIN
(= active enzyme)
(= fibrin-digesting enzyme)

Fibrin (Insoluble)

Fibrin (Soluble)
= Degradation products

Natural Control of Clotting

1- Dilution of procoagulants (inactive clotting factors).

2- Plasma anticoagulants

a) antithrombin III:

Source: platelets
Action: inactivates thrombin

b) Heparin

Source: basophils and mast cells as well as endothelial cells.
Action: accelerates activity of antithrombin III

c) Prostacyclin (PGI_2; local prostaglandin):

Source: endothelial cells normally

Action: prevent platelet aggregation

3- Intact endothelium:

Surface of the endothelium is smooth→ prevent platelets adherance and aggregation

4- Activity of fibrinolysis:

Factors affecting Coagulation

Factors which hasten coagulation:

(i) Physical factors:

1- Warming blood to 37ºC:

2- ↑↑Surface of contact e.g.,

- presence of cotton or guze (wettable surface)
- Burns, inflammation

3- Gentle agitation of blood:

Factors which hasten coagulation:

(ii) Physiological factors:

1- - Ingestion of saturated fatty acids or cholesterol → Arteriosclerosis
↓
Roughening of the endothelium

N.B: consumption of unsaturated fatty acids prolong the coagulation time.

2- Pain stimuli.

3- Experimental stimulation of the superior cervical ganglion (SCG).

N.B.: Surgical removal of SCG extends coagulation time.

Factors which hasten coagulation:

(iii) Chemical factors:

1- Addition of few amount of calcium ions. Comment?

N.B: addition of huge amount of calcium ions blocks coagulation.

2- Local application of adrenaline, thrombin or thromboplastin. Comment?

3- Some snake venomes contain thrombin.

4- Vit. K injection. Comment?

Factors which Retard coagulation:

1- Lower temperature:

Action:

Decreases optimum environment for coagulation reactions

2- ↓↓ Surface of contact e.g.,

- Preventing blood from being in direct contact with wettable surface
- Smooth, intact endothelium of BVs
- Action:

Prevents platelet aggregation and degranulation

3- Decalcification of blood:

- addition of some anticoagulants e.g.,sodium citrate, sodium fluoride and EDTA
- Action:

Precipitates Ca^{++}

4- Defibrination of blood:

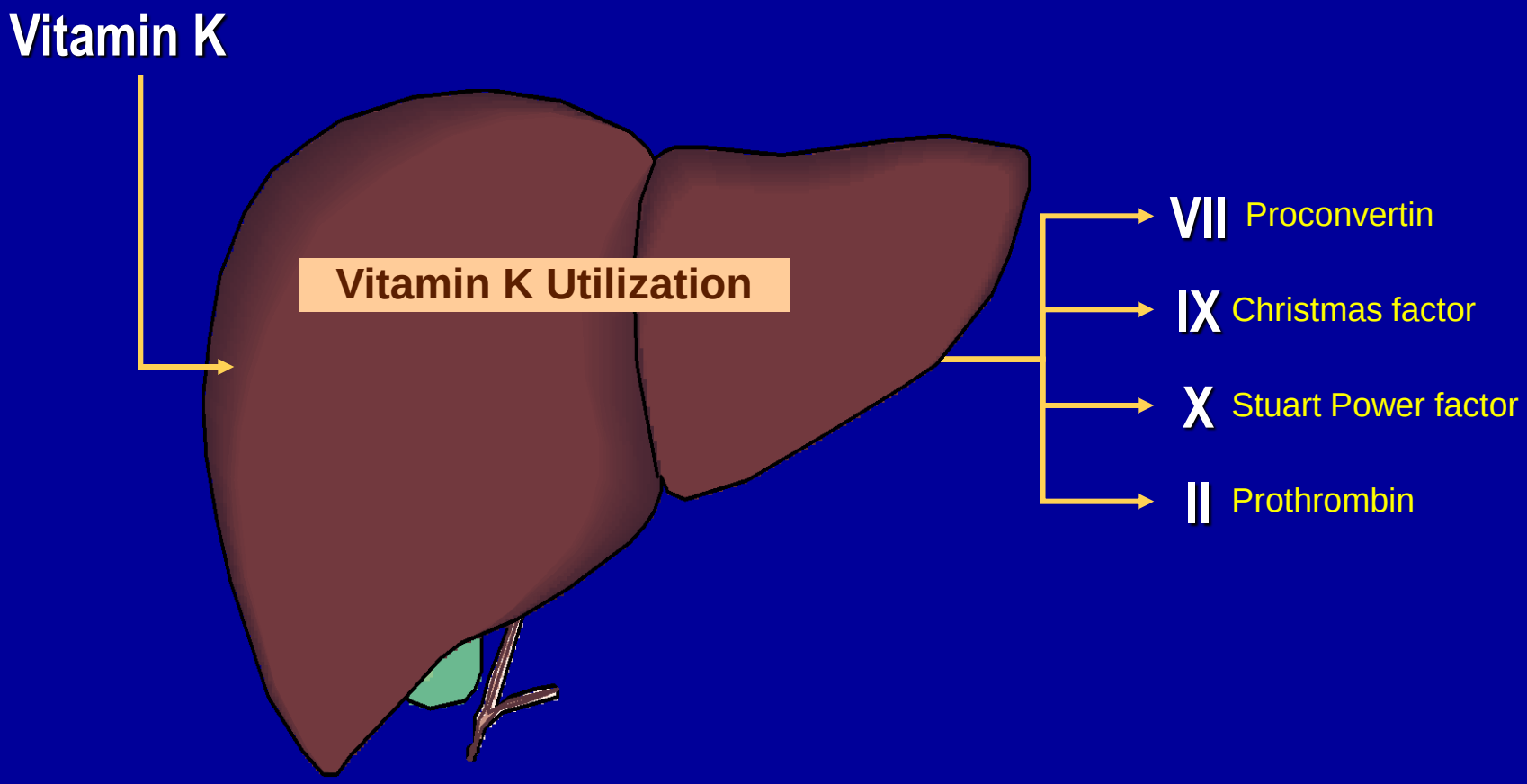
Factors which Retard coagulation:

5- Vit. K deficiency:

- Causes of Vit. K deficiency:
  - 1- Impaired fat absorption:
    - vitamin K is a fat-soluble vitamin,
  - 2- liver disease
    - - cells fail to produce bile which is required for fat and vit. K absorption
  - 3- Vit. K antagonists:
    - - Dicumarol
    - - Warfarine
- Effect:
  - Interferences with synthesis of *clotting factors; II, VII, IX and X* by liver cells

N.B: vitamin K is required by the liver cells to produce the clotting factors; II, VII, IX and X

Vit. K- Coagulation factors:



Factors which Retard coagulation:

6- Some drugs:

A- Aspirin

- Action:

inhibits thromboxane A2 formation → inhibits platelet aggregation and plug formation

N.B: low doses have been shown to reduce heart attacks by 50%

B- Heparin (natural anticoagulant):

- Action:

antiprothrombin agent

- Source: basophils (mast cells) and endothelial cells

C- Warfarin (Coumadin):

- Action:

interferes with utilization of Vit. K by liver cells → interfers with production clotting factors that require vit. K for their synthesis

Q: Mention the clinical control of clotting?

Factors which Retard coagulation:

7- Dicumarol:

- Action:

  anti-vit. K

- Found in: Spoiled sweet clover.
- Toxic effect:

  Sweet clover disease

  Sheep and cattle fed on this type of clover suffer from internal hemorrhage till die even from minor wound

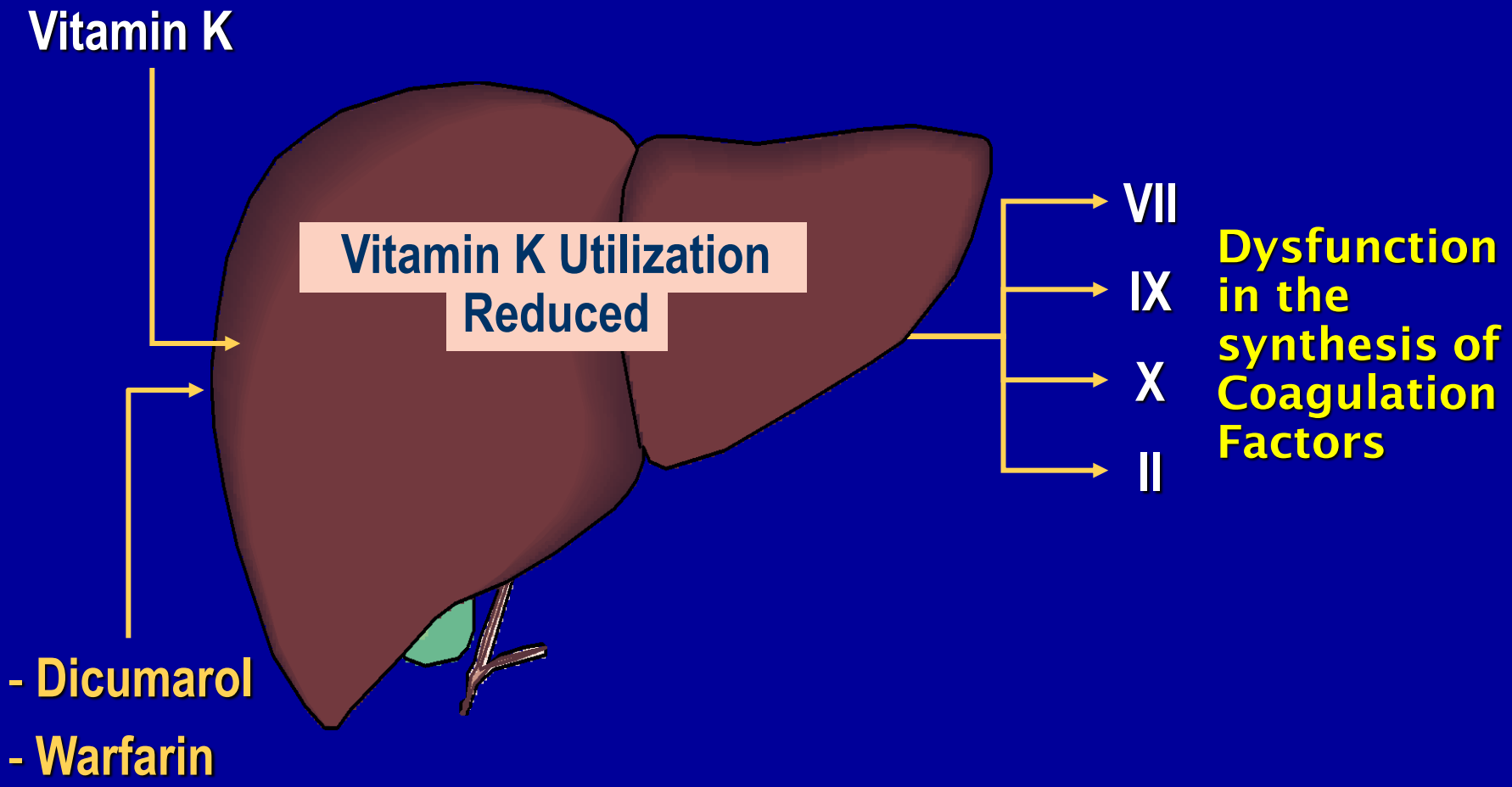
8- Hirudin:

- Action:

  antithrombin activity

- Found in: Salivary glands of some blood leech

Dicumarol and Warfarin- Mechanism of Action



Factors which Retard coagulation:

9- Some snake venoms (e.g., cobra)

Action:

1- Prevent the transformation of prothrombin to thrombin.

2- Prevent transformation of fibrinogen to fibrin.

10- Some basic dyes, peptone injections and concentrated salt solutions:

Action:

Prevent blood coagulation

Love = HEMOSTASIS

Everybody talks about it, nobody understands it.

JH Levy 2000

Professor of Anesthesiology
Emory University School of Medicine
Atlanta, Georgia

RBCs:
Blood Typing

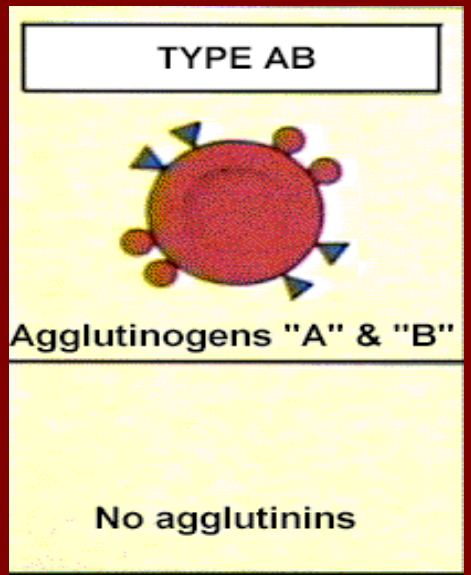
RBCs: Blood Typing

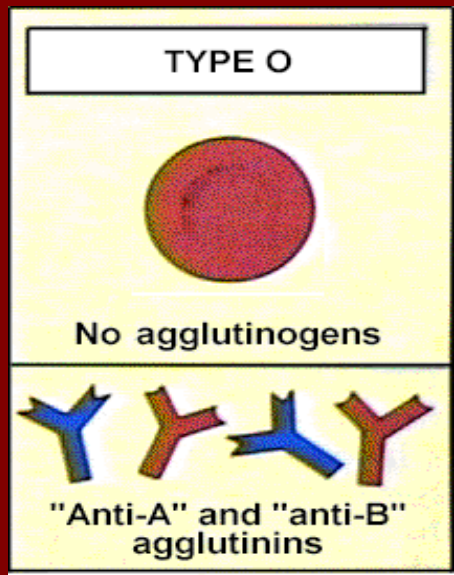
Based on the surface protein (agglutinogens = antigens “Ags”), the most common blood types are:

- ABO blood group
- Rh factor (D)

N.B.:

- At least 50 kinds of proteins used
- Antigen (Ag) = anything that cause antibodies (Ab) to be produced



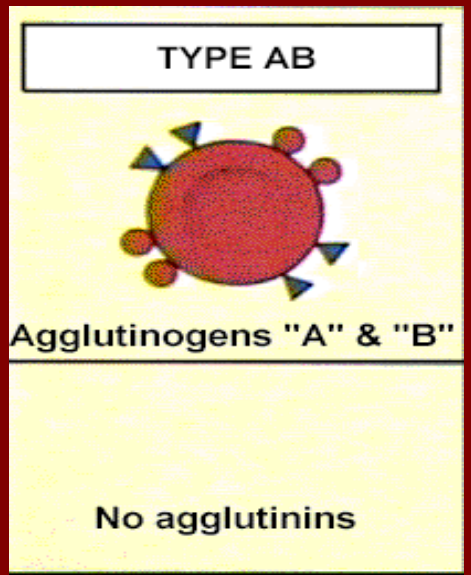


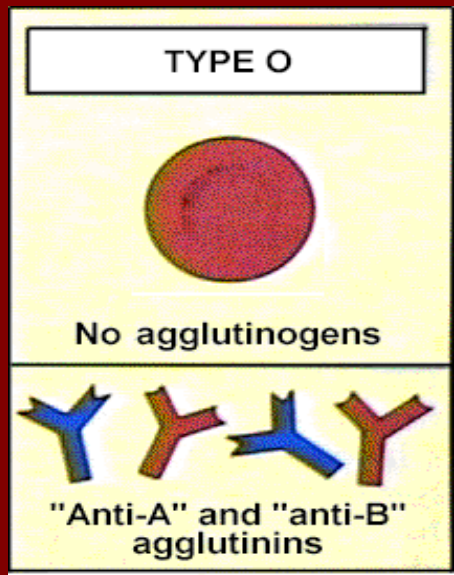
ABO Types:

Blood Type	A	B	AB[1]	O[2]
Surface Ag Present:	A	B	A & B	neither
Antibody present in plasma:	Anti-B	Anti-A	neither	Anti-A Anti-B
May Receive Blood From:	A, O	B, O	A, B, AB, O	O
May Give Blood To:	A, AB	B, AB	AB	A, B, AB, O

[1] Universal Recipient

[2] Universal Donor (as, it has no RBCS surface Ag)





Rhesus Factor (Rh)

- Rh is an agglutinogen (antigen).
- First demonstrated in Rhesus monkey, then known in human.
- Types:
  - (1) Rh^+
  - (2) Rh^-

Rh Blood Types

Blood Type	Rh^+	Rh^-
Rh Antigen (D)	**Present**	Absent
Makes anti-Rh Antibodies (anti-D):	No	Yes [1]
May *Receive* Blood From:	Rh^+ or Rh^-	Rh^- [2]
May *Give* Blood To Without Reaction[2]:	Rh^+	Rh^+ or Rh^-

[1] Only makes antibodies (agglutinins) ***after exposure*** to Rh+ blood cells (via transfusion or during birth process)
[2] Transfusion of Rh^- individual with Rh^+ blood results in production of anti-D agglutinins; sensitizes person to Rh factor and may result in anaphylaxis if exposed a second time.

Rh and pregnancy

If Rh^- (Makes Anti-Rh) women are carrying Rh^+ fetus:

Fetal blood cells (Rh+) pass to mother's blood

↓

Sensitization

= Antibodies against fetal blood are generated

↓

Erythroblastosis fetalis

(Damage to fetal blood cells→Sever anaemia and icteru)

- 1st Pregnancy:

  Titer of Anti-Rh in maternal blood is low → child is born normal

- 2nd Pregnancy:

  Titer of Anti-Rh in maternal blood increases progressively → Child suffer from Erythroblastosis fetalis

Treatment:

- Injection of mother with antibodies against Rh-agglutinins (Anti-RH) that neutralizes Rh-agglutinins (Anti-Rh)
- *Injection o RhoGam* to destroy any fetal blood cells in mother's Blood

Cross Matching Test

- Very simple and rapid technique.
- Performed if blood grouping is not available

Method:

- One drop of recipient’s plasma + One drop of dononr’s RBCs
- One drop of recipient’s RBCs + One drop of dononr’s plasma

Result:

If no agglutination occurs in either of the two samples, blood can be transfused safely

Thanks