BLOOD PHYSIOLOGY

- Lect-1:Blood Composition and Functions
- Lect-2:Erythropoeisis & its control
- Lect-3:Iron metabolism and hemoglobin

HANDOUTS
OCTOBER 2016

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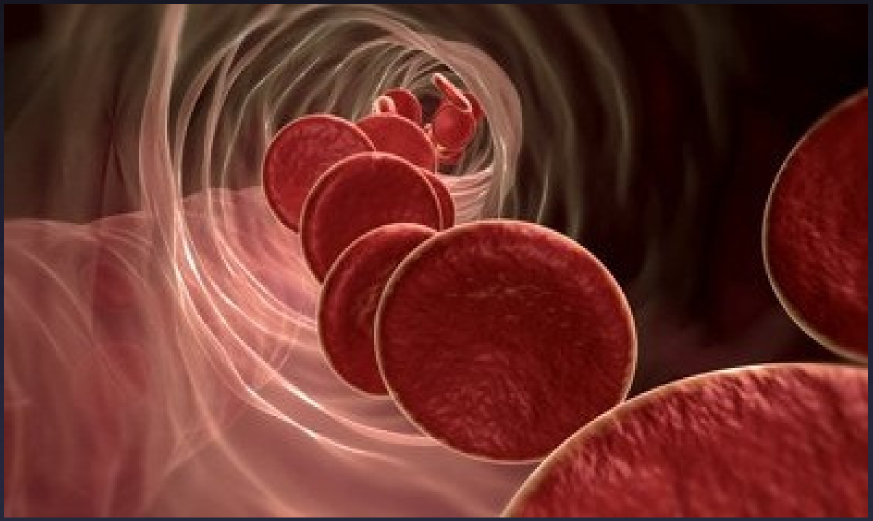
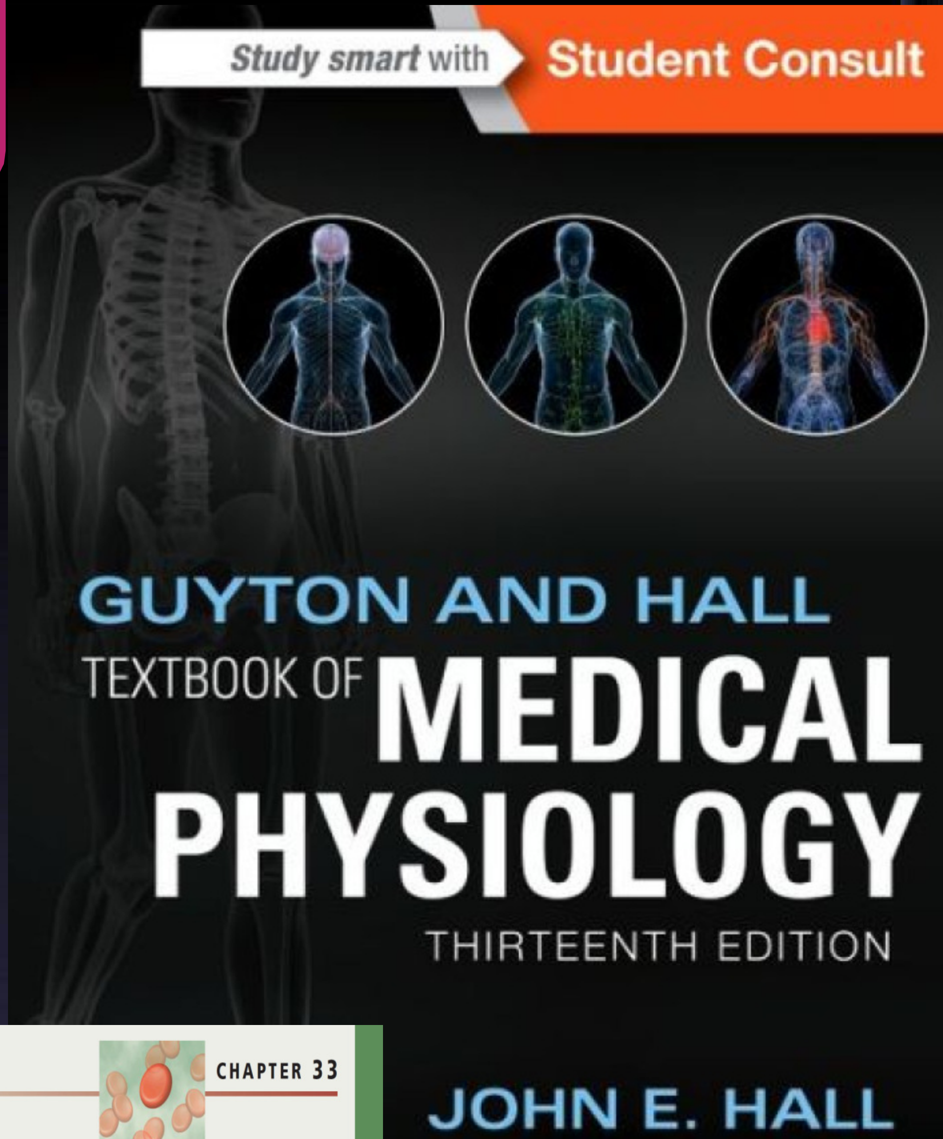
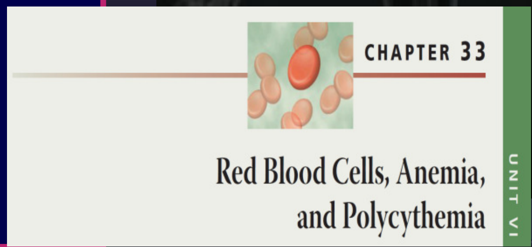


REMEMBER

- These handouts will facilitate what you have to study and are not an alternative to your text book.
- The main source of Lectures 1,2 & 3 is from Guyton & Hall 13th Edition
- Pages 423-431




CHAPTER 33

Red Blood Cells, Anemia, and Polycythemia

UNIT VI

Lect-1: Objectives

At the end of this lecture you should be able to:

1. Understand functions of blood
2. Describe composition of blood with important values
3. Differentiate between the terms formed elements, Packed Cell Volume, plasma and serum
4. Describe physical and chemical characteristics of blood
5. Describe RBC shape and its advantages

<u>Blood is a specialized type of liquid connective tissue that circulates in blood vessels.</u>

It is the largest Organ in the body

"Right now a medical doctor analyzing the blood of an ailing patient looks at something like 10 to 20 chemicals," said University of Alberta biochemist David Wishart. "We've identified 4,229 blood chemicals that doctors can potentially look at to diagnose and treat health problems."

ScienceDaily, 1 March 2011.

Characteristics of Blood

- Its **volume** is 5-6 L in males and 4-5 L in females (About 8% of body weight)
- **Viscosity** 3-4 times than Water
- **pH**: Slightly alkaline, with a pH of 7.35-7.45
- It has a salty metallic **taste** and is Sticky
- **Color:** Bright red = O_2 rich; Dull red = O_2 poor
- **Temperature** about 37^0C (slightly higher than normal body temp)
- Tremendous **regenerative** capacity

Characteristics of Blood

- **Viscosity:**

  Blood relative viscosity (4-5) mainly depends on the numbers of red blood cells.

  Plasma relative viscosity (1.6-2.4) is mainly involved in plasma protein

- **Plasma pH value is about 7.35-7.45 (Hb acts as blood buffer)**
- **Osmolality: Plasma osmolality is about 300 mmol/L (Equal to 0.9% NaCl Solution=Isotonic)**

Characteristics of Blood

- Plasma osmotic pressure is 300 mmol/L or 770kPa

  Crystal osmotic pressure results from NaCl and modulates water distribution between inside and outside of cells.

  Colloid osmotic pressure results from albumin and regulates water distribution between inside and outside of capillary.

- Specific gravity:

  Total blood (1.050-1.060) more influenced by red blood cells; plasma (1.025-1.030) more influenced by plasma protein; RBC (1.090-1.092) more influenced by Hb.

Functions Of the blood

Transport

–Respiration : oxygen and carbon dioxide are transported

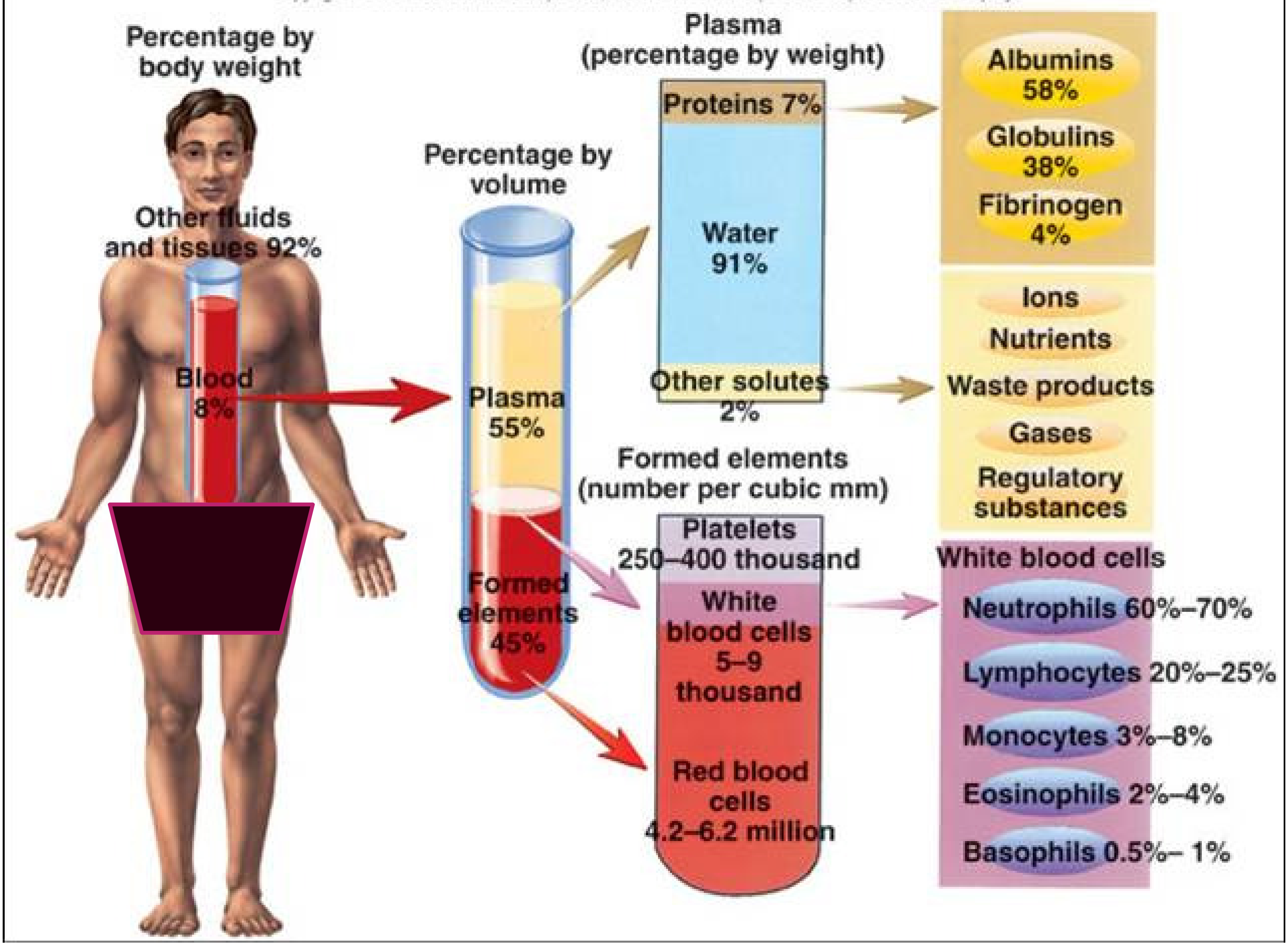
–Trophic : nutrients are delivered to the tissues

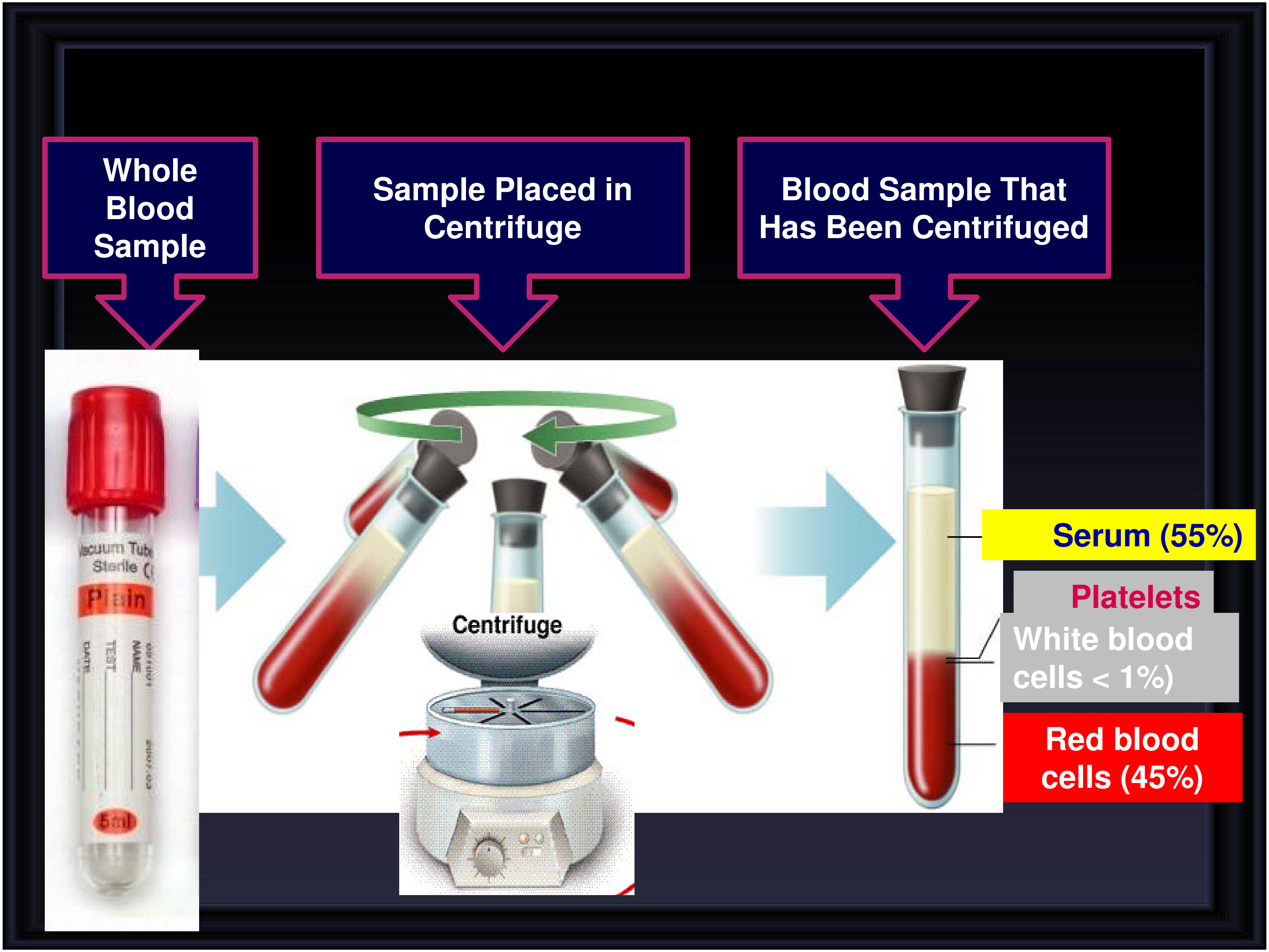
–Excretive : metabolites are delivered from tissues to excretory organs

–Regulative : hormones are transported

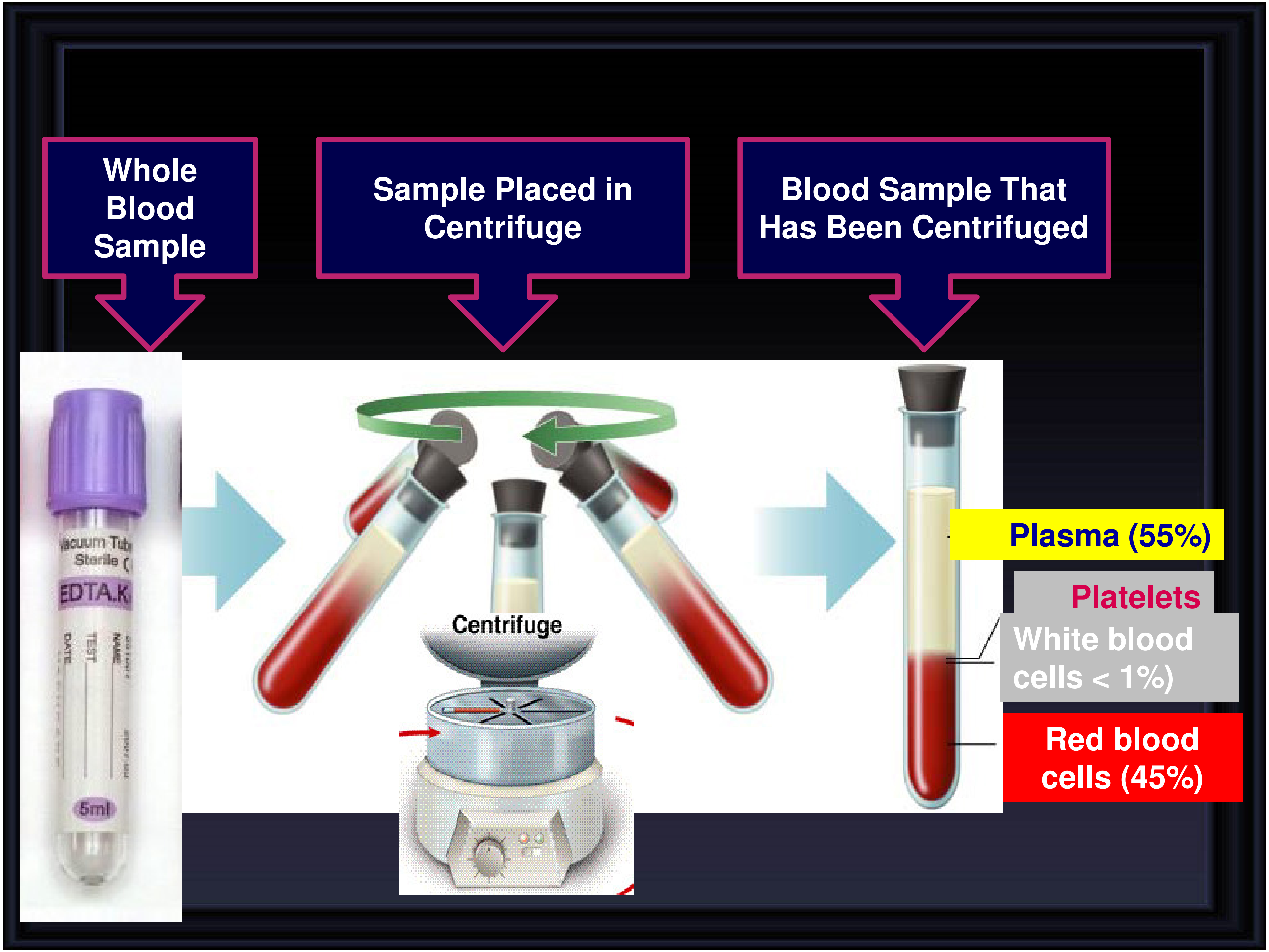
Protecting: the body against infections (White Blood Cells, Antibodies) & Hemostasis (preventing blood loss)

Homoeostasis: Regulation of body temperature by redistribution of blood volume between skin and internally, Regulation of ECF pH


Percentage by body weight
Other fluids and tissues 92%
Blood 8%
Percentage by volume
Plasma 55%
Formed elements 45%
Plasma (percentage by weight)
Proteins 7%
Water 91%
Other solutes 2%
Albumins 58%
Globulins 38%
Fibrinogen 4%
Ions
Nutrients
Waste products
Gases
Regulatory substances
Formed elements (number per cubic mm)
Platelets 250–400 thousand
White blood cells 5–9 thousand
Red blood cells 4.2–6.2 million
White blood cells
Neutrophils 60%–70%
Lymphocytes 20%–25%
Monocytes 3%–8%
Eosinophils 2%–4%
Basophils 0.5%– 1%



Whole Blood Sample
Sample Placed in Centrifuge
Blood Sample That Has Been Centrifuged
Vacuum Tube
Sterile
Plain
5ml
Centrifuge
Serum (55%)
Platelets
White blood cells < 1%)
Red blood cells (45%)


Whole Blood Sample
Sample Placed in Centrifuge
Blood Sample That Has Been Centrifuged
Centrifuge
5ml
Plasma (55%)
Platelets
White blood cells < 1%)
Red blood cells (45%)

Composition of Blood

Cells

45 %

RBCs
WBCs
Platelets

Plasma

55%

Electrolytes
Clotting Factors
Antibodies
Blood Gases
Nutrients
Wastes

The Plasma is a straw colored liquid (90-92% Water). It serves as a transport medium for blood cells and platelets.

When clotting factors specially fibrinogen is removed from plasma as a result of coagulation, the remaining fluid is called serum.


EVACUATED TUBE
Clot Activator
4 mL
C.D.RICH
EVACUATED TUBE
3 mL
C.D.RICH
2 ML
KEDTA
3 ml
bincodear.ecvv.com

Vacuum Tube
Sterile
E.S.R.
Vacuum Tube
Sterile
Coagulation
Vacuum Tube
Sterile
Plain
Vacuum Tube
Sterile
EDTA.K
Vacuum Tube
Sterile
Glucose
Vacuum Tube
Sterile
Heparin Li
Vacuum Tube
Sterile
Gel Clot Activ
NAME
TEST
DATE
1.5ml
2.7ml
5ml
5ml
3ml
5ml
4ml

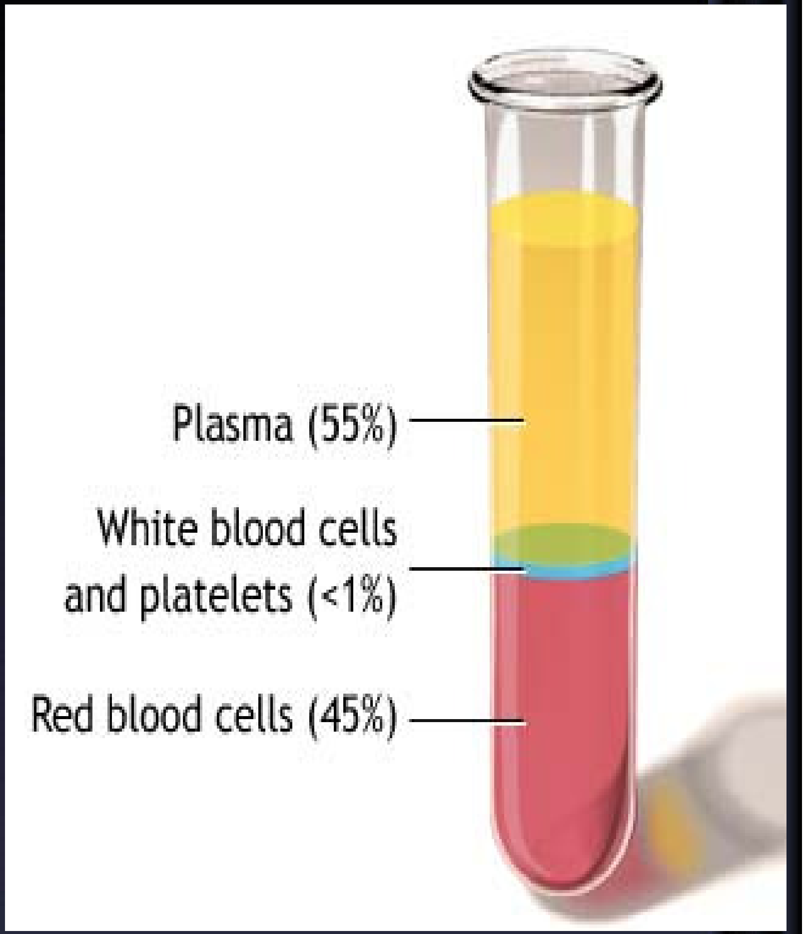
Blood Composition

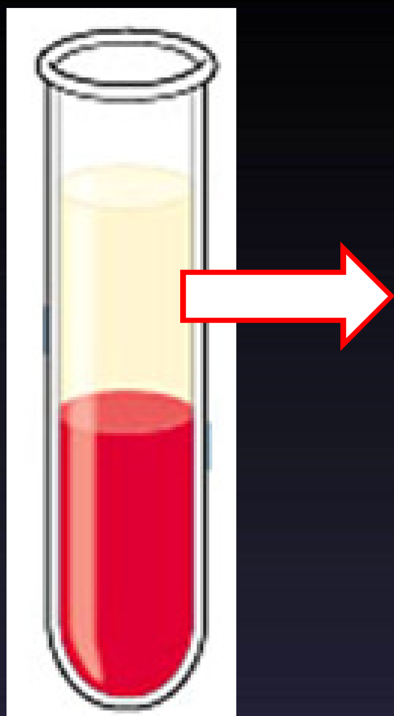
1. Cellular components

- ***Red Blood Cells 5,200,000 /Cubic mm (±300,000) in Males & 4,700,000 (±300,000) in Females***
- ***White Blood Cells 4000-11000/ul***
- ***Platelets 150000-400000/ul***

2. Plasma consist of:

- ***Water: 92%***
- ***Ions: Na, K, HCO3, PO4 ..etc***
- ***Plasma proteins (Albumin, globulin, Fibrinogen)***
- ***Same ionic composition as interstitial fluid***





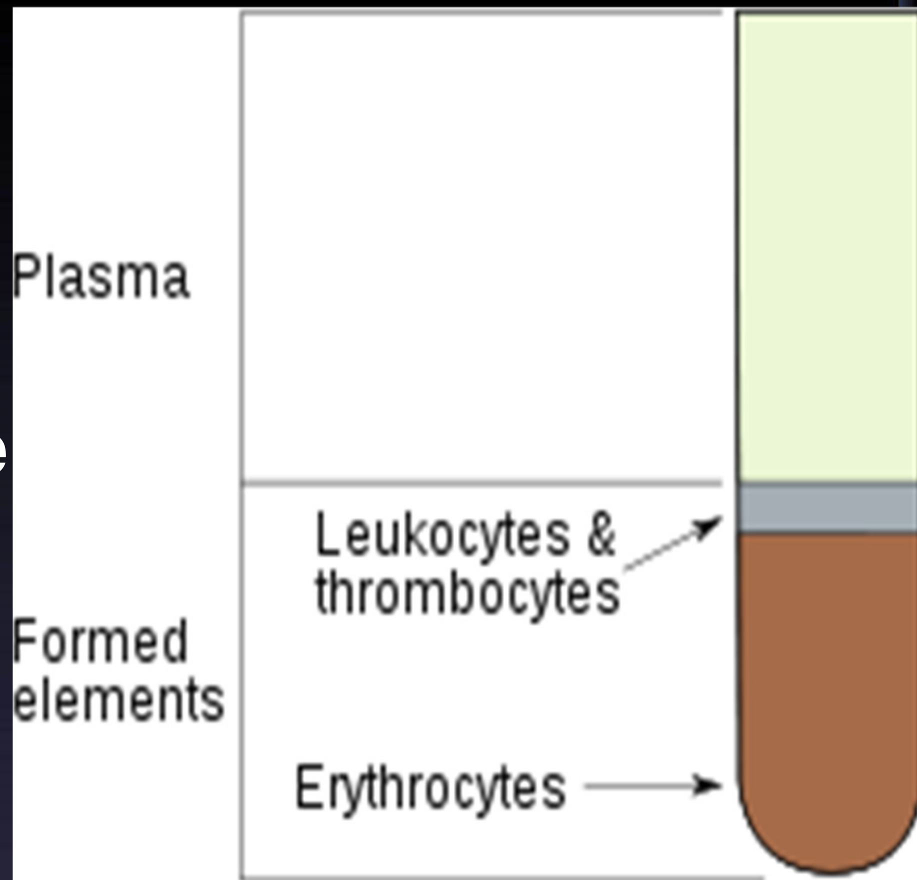
Constituents of PLASMA	Major Functions
Water	Solvent for carrying other substances
Salts Sodium Potassium Calcium Magnesium Chloride Hydrogen carbonate	Osmotic balance, pH buffering, Regulation of membrane permeability
Plasma Proteins Albumin Fibrinogen Antibodies	Osmotic balance, pH buffering, Clotting, Immunity Transportation (Binding Prot)
Substances transported by blood	

Hematocrit

The hematocrit , also known as **packed cell volume (PCV),** is the volume or percentage (%) of red blood cells **(formed elements)** in the blood. It is normally about

<u>47%</u>for men and

<u>42%</u> for women



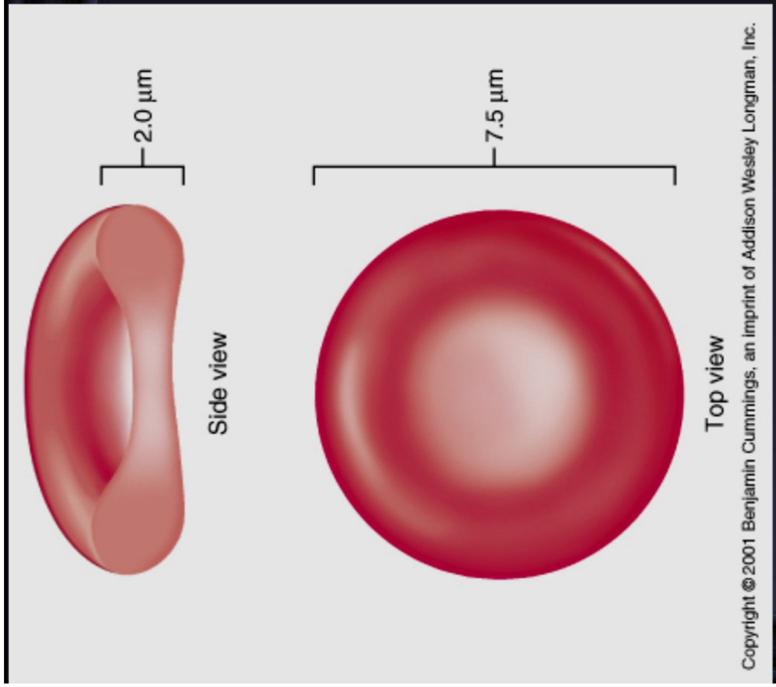
RED BLOOD CELLS

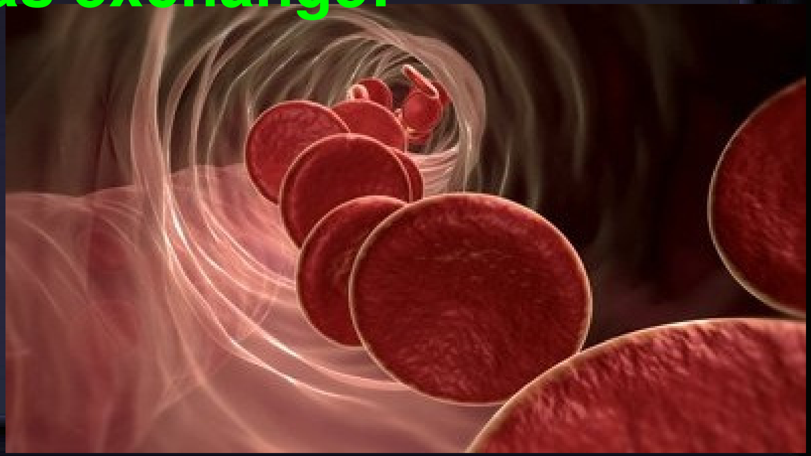
ERYTHROS MEANS : RED
KYTOS MEANS : CELL

Geometry of erythrocytes

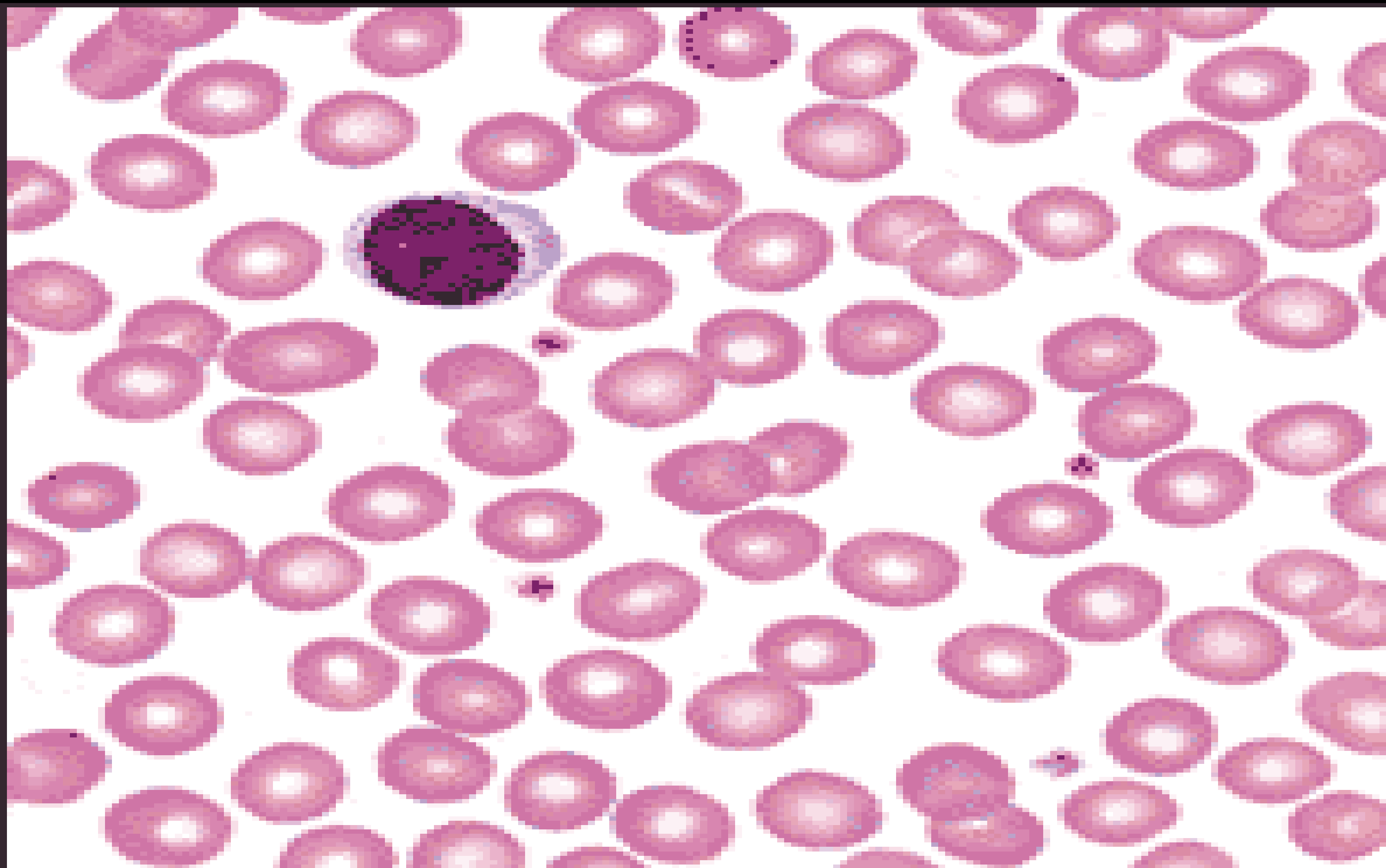
Biconcave Discs:
(7.5X2X1um)
Negative Charge
Life Span=120 days

- Biconcave-discoid shape provides an extra surface area
- Shape change requires significantly smaller forces
- Gas exchange!





NORMAL PERIPHERAL FILM



A Mature RBC

DOES NOT HAVE

- Nucleus
- Mitochondria
- Ribosomes
- Endoplasmic Reticulum
- Golgi Apparatus

IT CONTAINS

- Haemoglobin
- Enzymes For Glucose Metabolism (Carbonic Anhydrase & 2,3 DPG Synthesis)
- Structural Proteins (cytoskeleton)

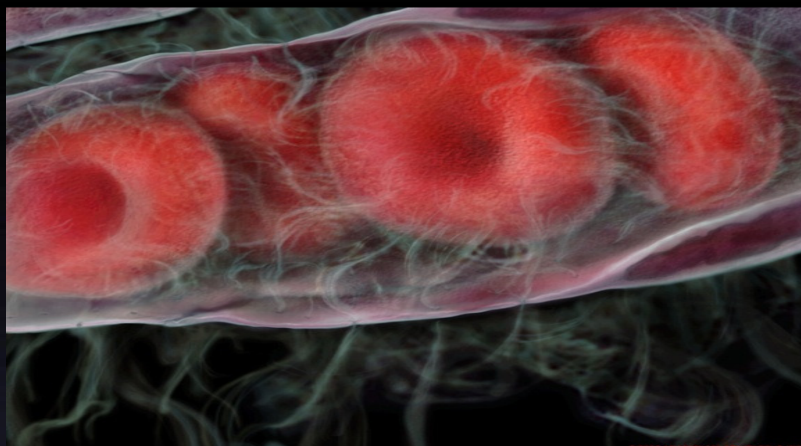
ENERGY METABOLISM OF RBC:

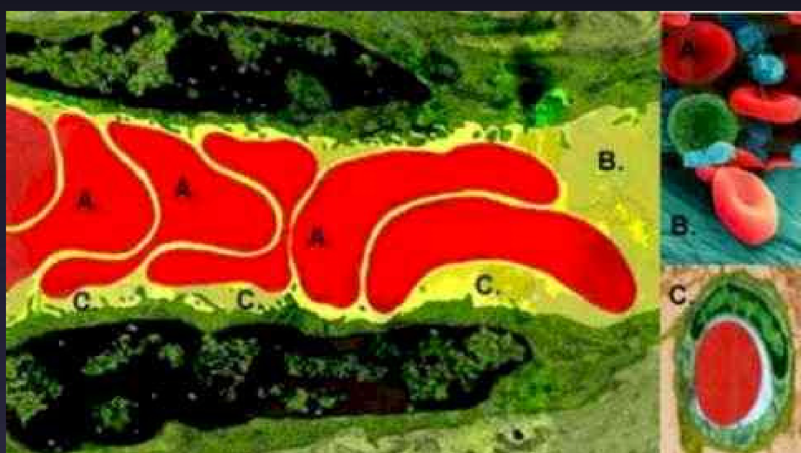
(1) GLYCOLYSIS 90%

(2) HMP SHUNT 10%

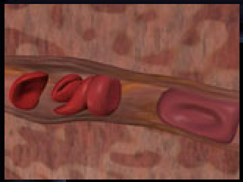
(GLUCOSE ENTERS INTO RBC BY CARRIER MEDIATED DIFFUSION)

Red Blood cells in capillaries





- Capillaries are very narrow.
- They **bend** as they pass through capillaries (Thimble / Parachute Shaped)
- This is an advantage, it keeps them in very close contact with the capillary walls; this **reduces the diffusion distance for gas** exchange with the surrounding tissues



RBC are flexible & elastic:

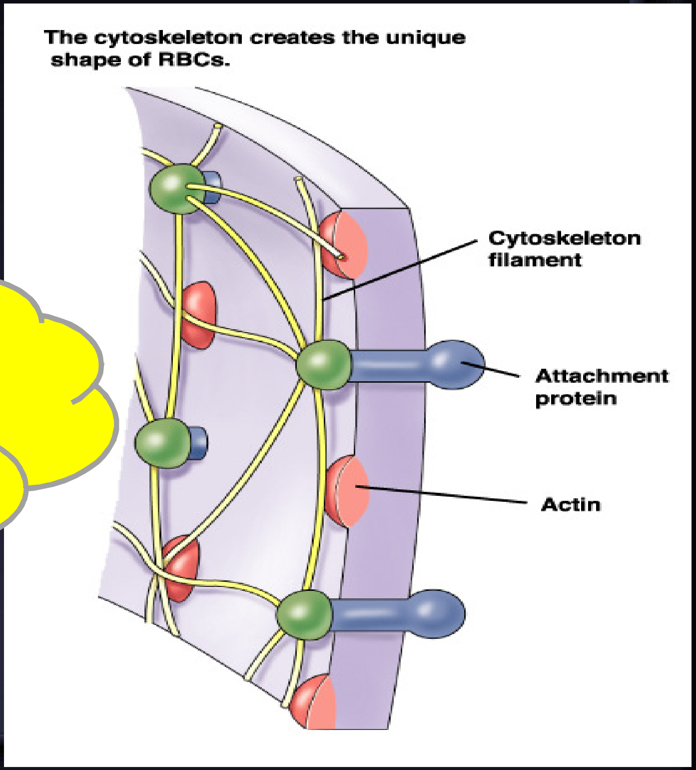
- to squeeze through narrow capillaries

Cardiac muscle and capillary

Erythrocytes in single file – capillary is so narrow about 5 um

RBC Cytoskeleton

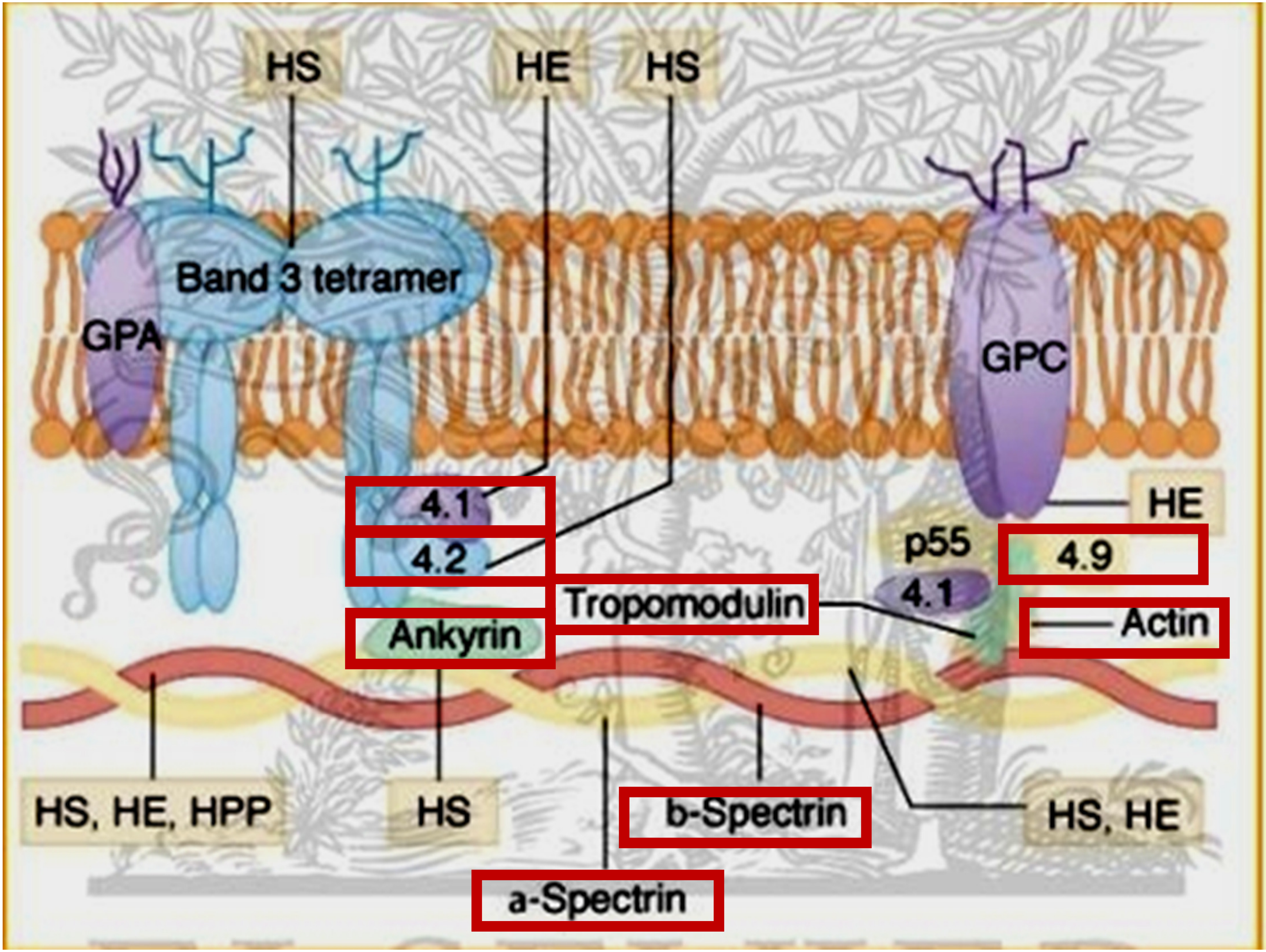
The red cell, as it continuously circulates, must be able to undergo extensive **passive deformation** and to **resist fragmentation**. These two essential qualities require a highly deformable yet remarkably stable membrane.



Skeletal protein network

- Spectrin
- Actin
- Ankyrin
- Tropomyosin
- Proteins 4.1 and 4.9

Hereditary spherocytosis?



HS
HE
HS
GPA
Band 3 tetramer
GPC
HE
4.1
4.2
p55
4.9
Tropomodulin
4.1
Actin
Ankyrin
HS, HE, HPP
HS
b-Spectrin
HS, HE
a-Spectrin

RBC lack mitochondria.
Give *two* advantages of this.

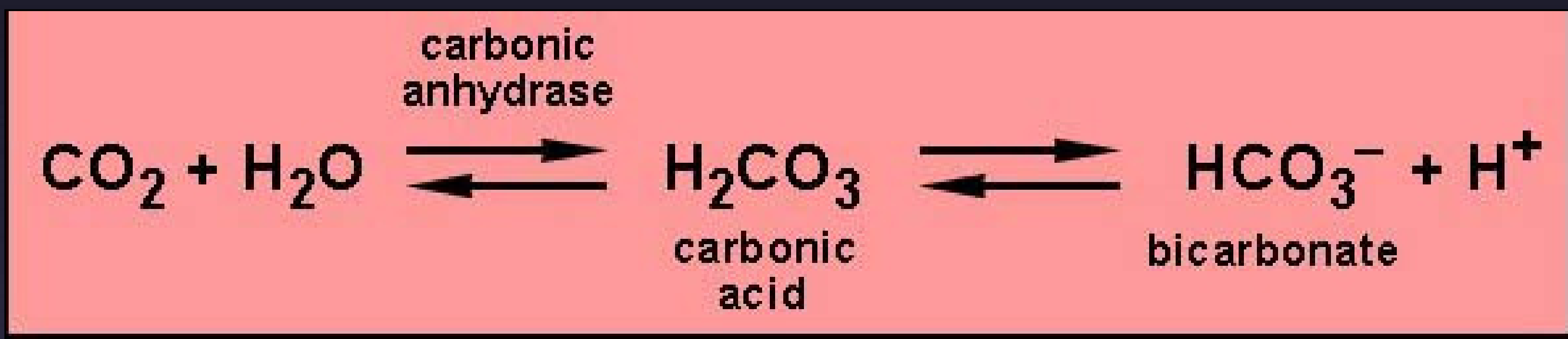
1. **More room for carrying hemoglobin**
2. **Respire anaerobically : do not use up any of the O_2 they carry**

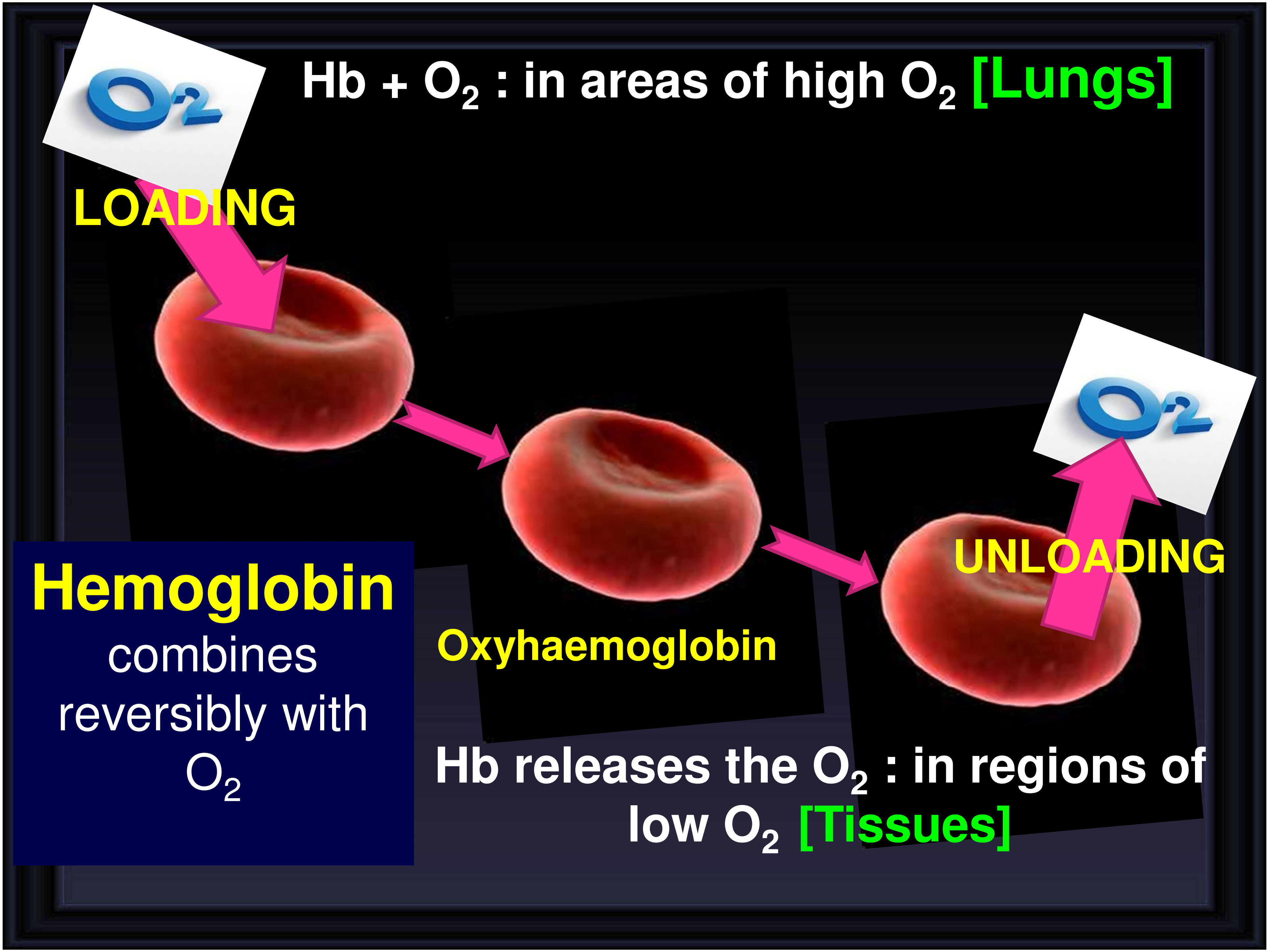
RBCs contain the enzyme:

Carbonic anhydrase

An enzyme that catalyzes the reversible reaction between carbon dioxide (CO2) and water to form carbonic acid (H2CO3), increasing the rate of this reaction several thousandfold.

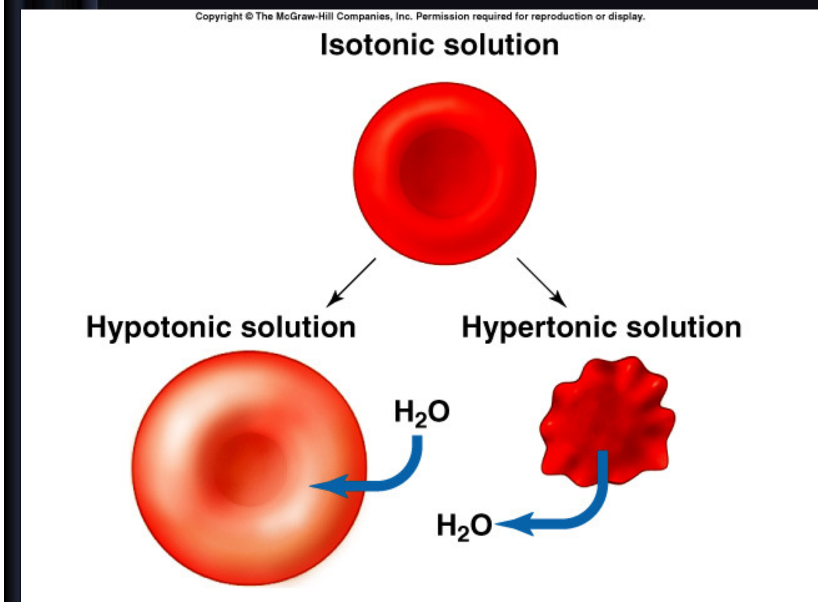
Plays a role in CO_2 transport




Hb + O_2 : in areas of high O_2 [Lungs]
LOADING
UNLOADING
Oxyhaemoglobin
Hemoglobin
combines reversibly with O_2
Hb releases the O_2 : in regions of low O_2 [Tissues]

Osmotic Fragility

Osmotic fragility: When RBCs are put in lower osmotic salty solution they swell and burst. Osmotic fragility of aged RBCs may increase in some diseases like HS.



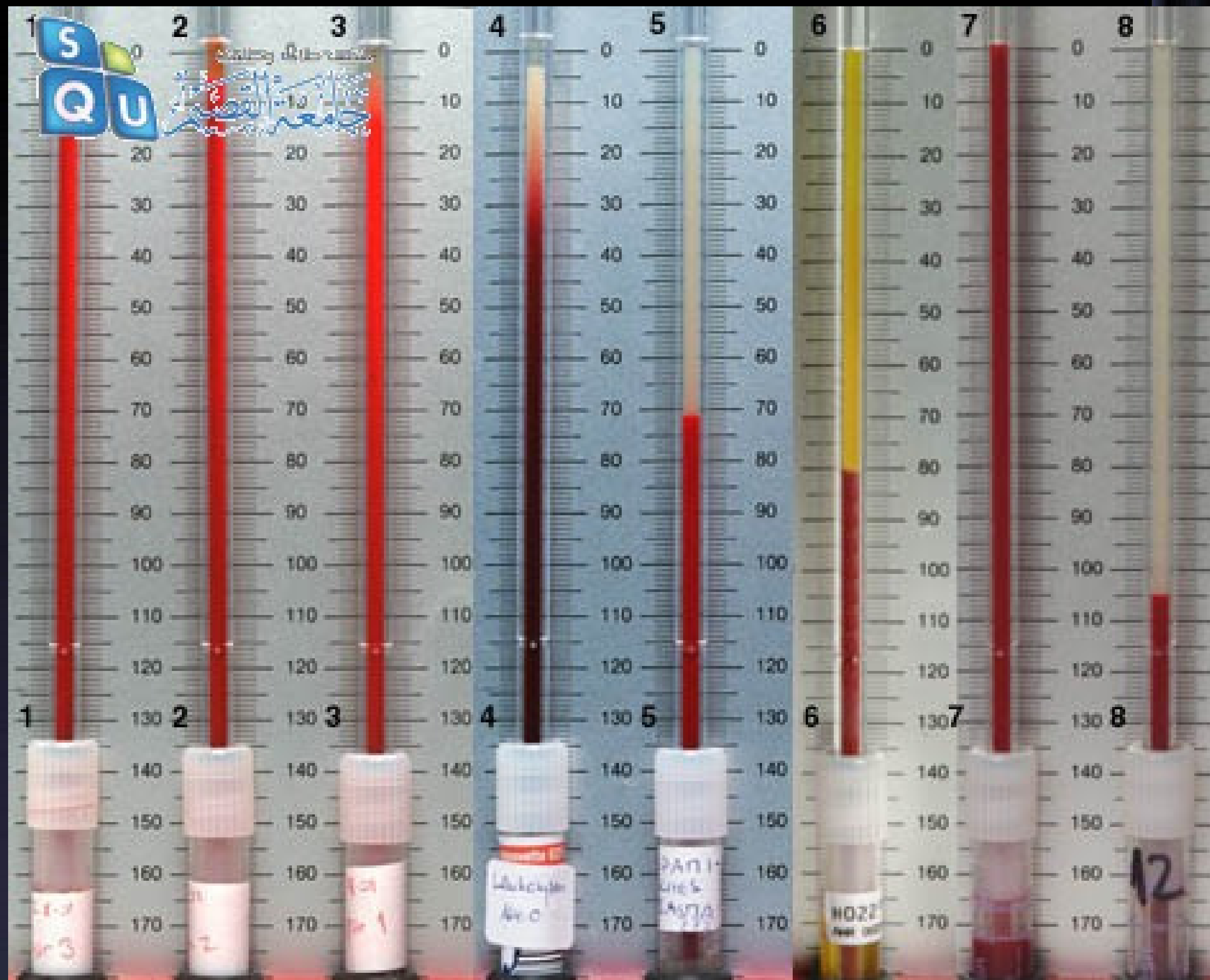
Normal

Abnormal

Hereditary Spherocytosis cells lyse more readily at low ionic strength

Erythrocyte sedimentation rate (ESR)

It can be described and measured by erythrocyte sedimentation rate (ESR) which is RBC descending distance per hour Normal value : male, 0~15 mm/h; female, 0~20 mm/h.



Objectives For Lect2 & Lect3

At the end of these lectures you should be able to:

1. Understand steps of erythropoeisis& its regulation
2. Describe essential substances needed for RBC formation.
3. Recognize haemaglobin structure and its functions
4. Discuss iron metabolism (absorption, storage and transport) and vitamin B12 absorption.
5. Describe the fate of old RBC.
6. Describe anemia & polycythemia and its causes.

Classification of RBCs by Size & Color

- **ACCORDING TO SIZE :**

Normocytes - Normal sized RBCs

Microcytes - Small sized RBCs

Macrocytes - Large sized RBCs

- **ACCORDING TO COLOUR :**

Normochromia - Normal coloured RBCs

Hypochromia - Paler, due to decreased Hb

Hyperchromia- Darker,due to increased Hb

RBC Indices

- Mean corpuscular Volume

  (MCV= 80 TO 90 fl OR 83 Cubic um)
- Mean corpuscular hemoglobin

  (MCH= 27 – 32 picogram)
- Mean corpuscular hemoglobin conc.
  (MCHC= 30 – 36 gm/dl)

TABLE 31–2 Characteristics of human red cells.[a]

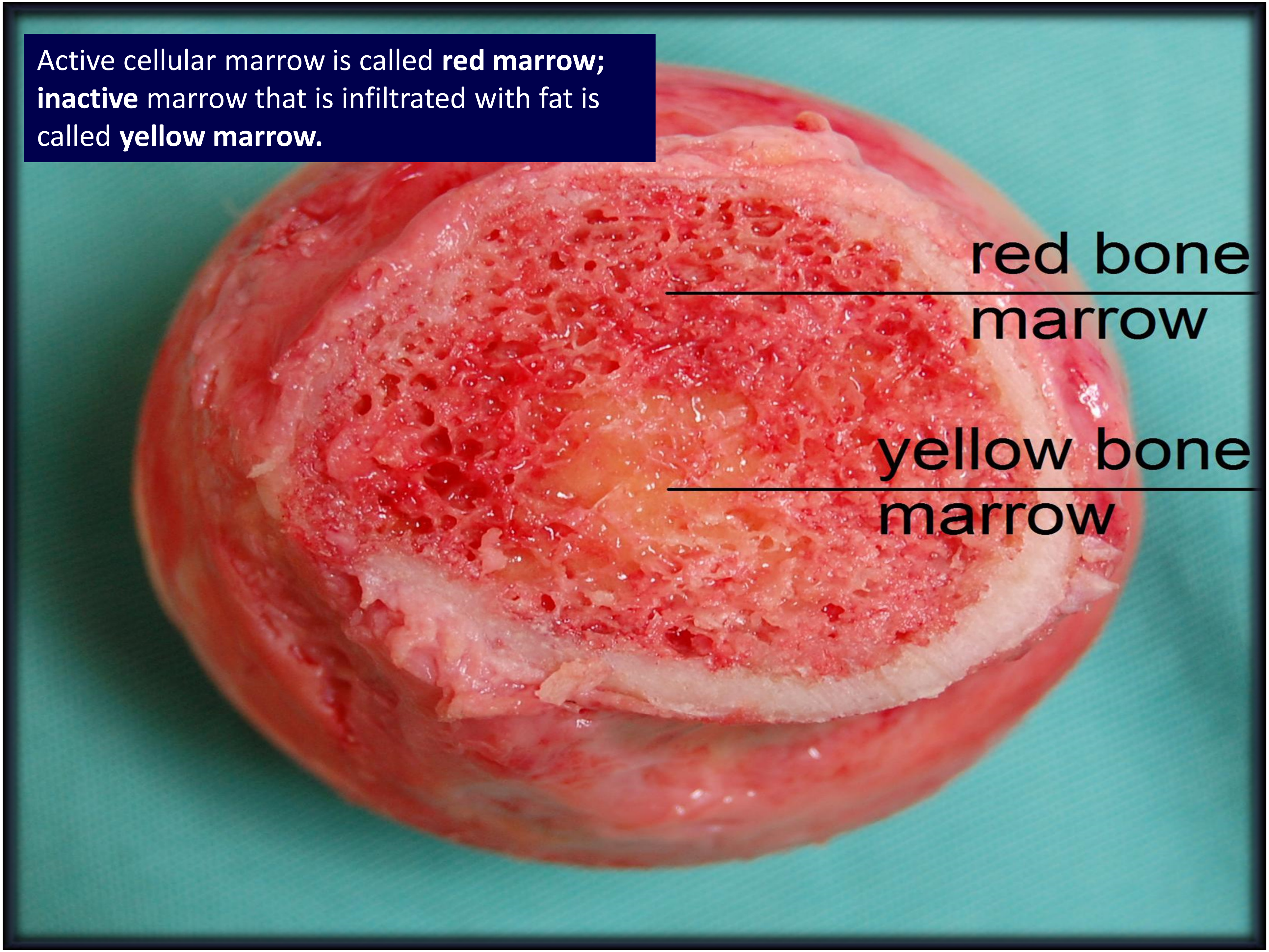
		Male	Female
Hematocrit (Hct) (%)		47	42
Red blood cells (RBC) ($10^6/\mu L$)		5.4	4.8
Hemoglobin (Hb) (g/dL)		16	14
Mean corpuscular volume (MCV) (fL)	$= \frac{Hct \times 10}{RBC\ (10^6/\mu L)}$	87	87
Mean corpuscular hemoglobin (MCH) (pg)	$= \frac{Hb \times 10}{RBC\ (10^6/\mu L)}$	29	29
Mean corpuscular hemoglobin concentration (MCHC) (g/dL)	$= \frac{Hb \times 100}{Hct}$	34	34
Mean cell diameter (MCD) μm)	= Mean diameter of 500 cells in smear	7.5	7.5

[a]Cells with MCVs > 95 fL are called macrocytes; cells with MCVs < 80 fL are called microcytes; cells with MCHCs < 25 g/dL are called hypochromic.

Blood Cells Formation

- Formation of blood
  - ► Haematopoiesis.
- Formation of erythrocytes (RBC)
  - ►Erythropoiesis
- Formation of leucocytes (WBC)
  - ► Leucopoiesis
- Formation of thrombocytes (platelets)
  - ► Thrombopiesis

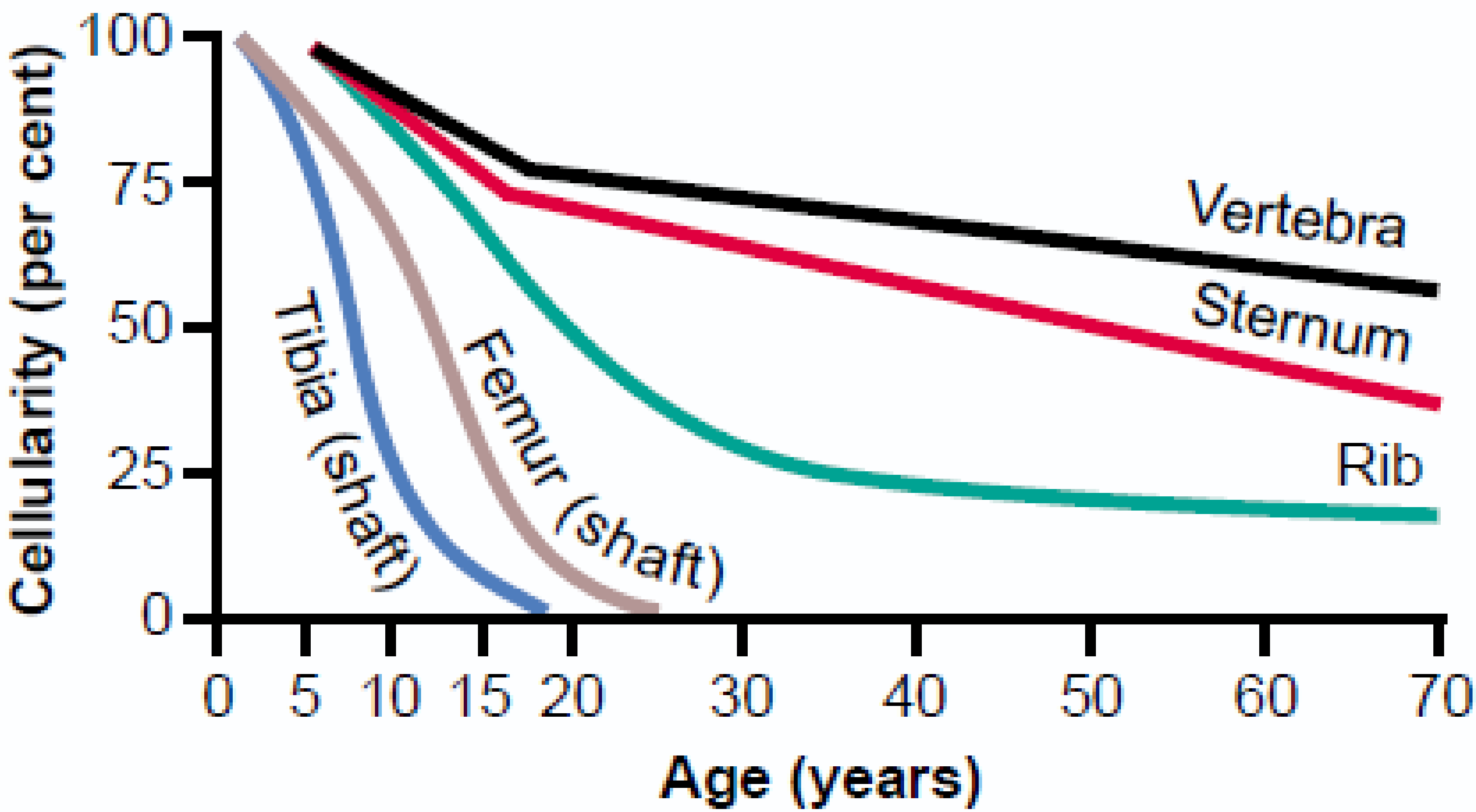
Active cellular marrow is called **red marrow; inactive** marrow that is infiltrated with fat is called **yellow marrow.**



Sites of blood formation

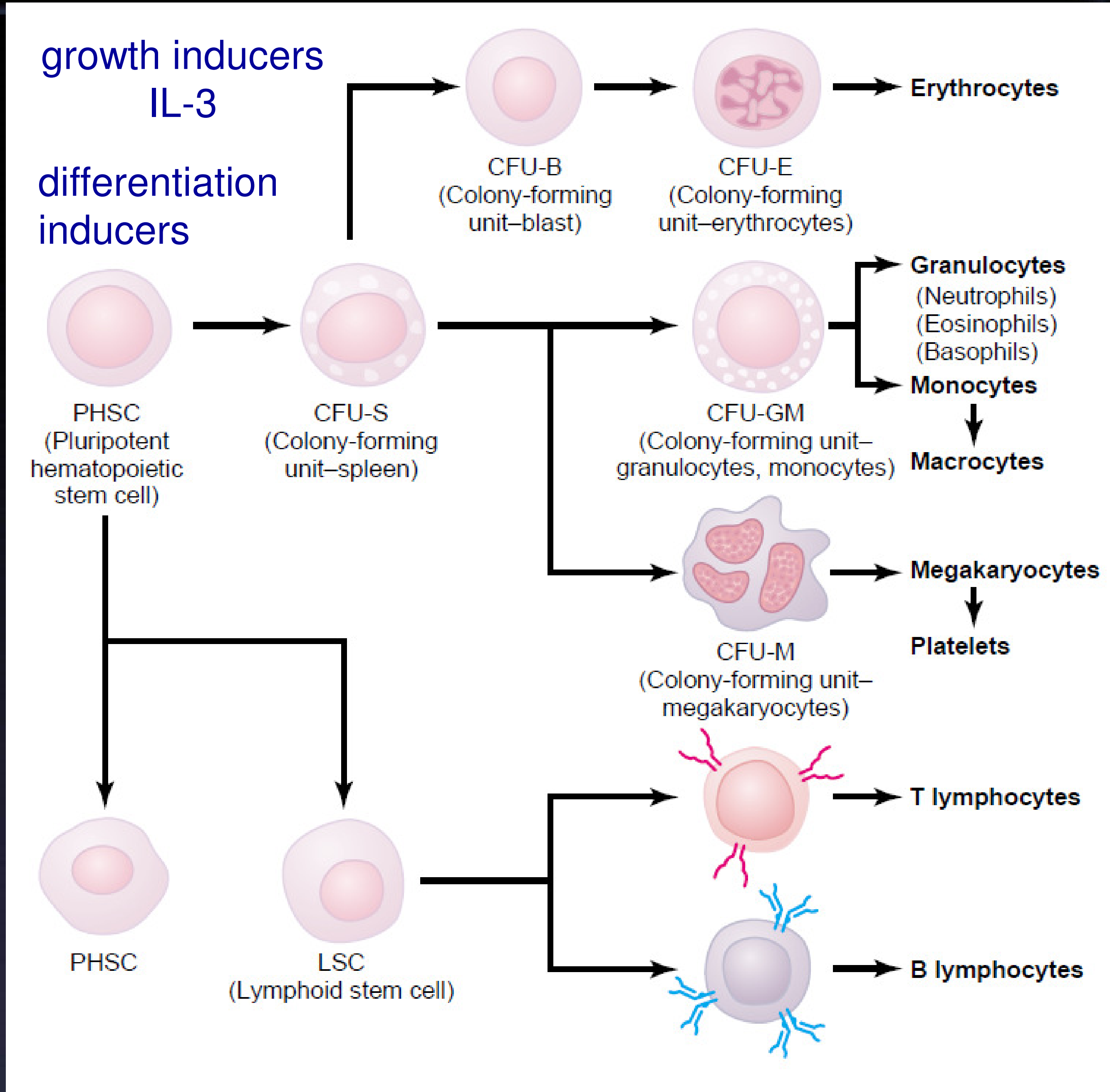
- Before Birth (In Fetus)
  - 1st 4 months ▶ Yalk Sac
  - Sec Trim ▶ Liver, spleen, lymph nodes
- Third Trim ▶ Bone Marrow
- Children ▶ Bone Marrow (Essentially all bones produces RBCs until a person is 5 years old)
- Adults ▶Bone Marrow (After the age of 20 years RBCs are produced in marrow of the membranous bones, such as the vertebrae, sternum, ribs, and ilia)

Sites of blood formation



Formation of the multiple different blood cells from the original pluripotent hematopoietic stem cell (PHSC) in the bone marrow

75% - white blood cell-producing myeloid series only 25% - are maturing red cells

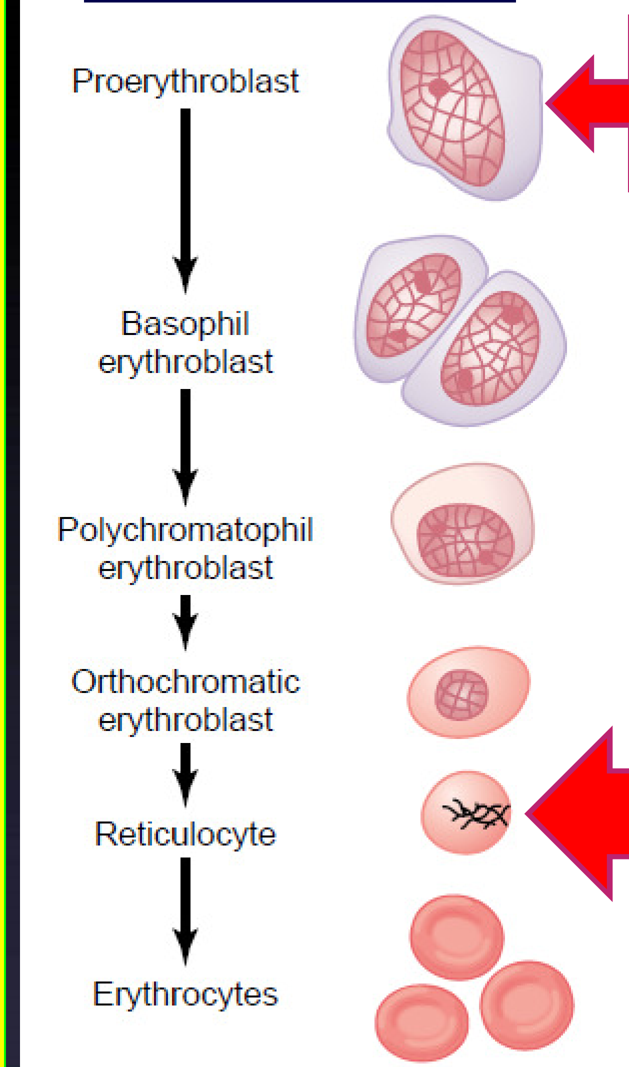


Steps of Erythropoiesis

PHSC

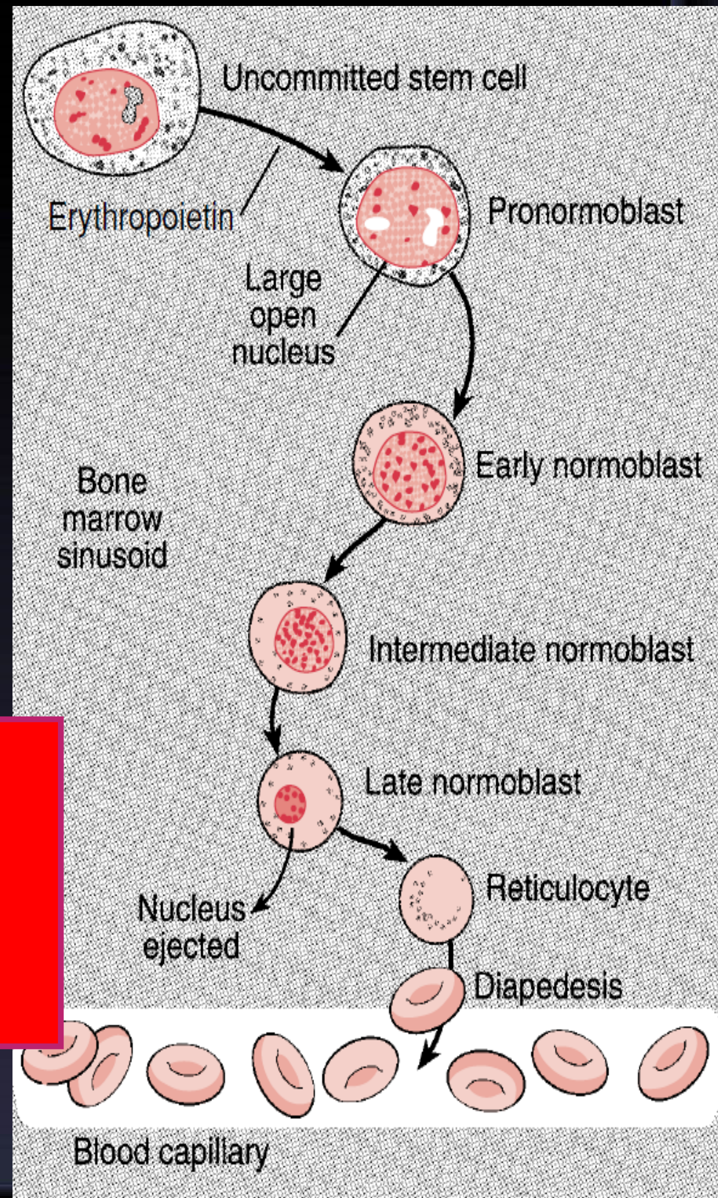
CFU-E

Stages of RBC development (7 days)

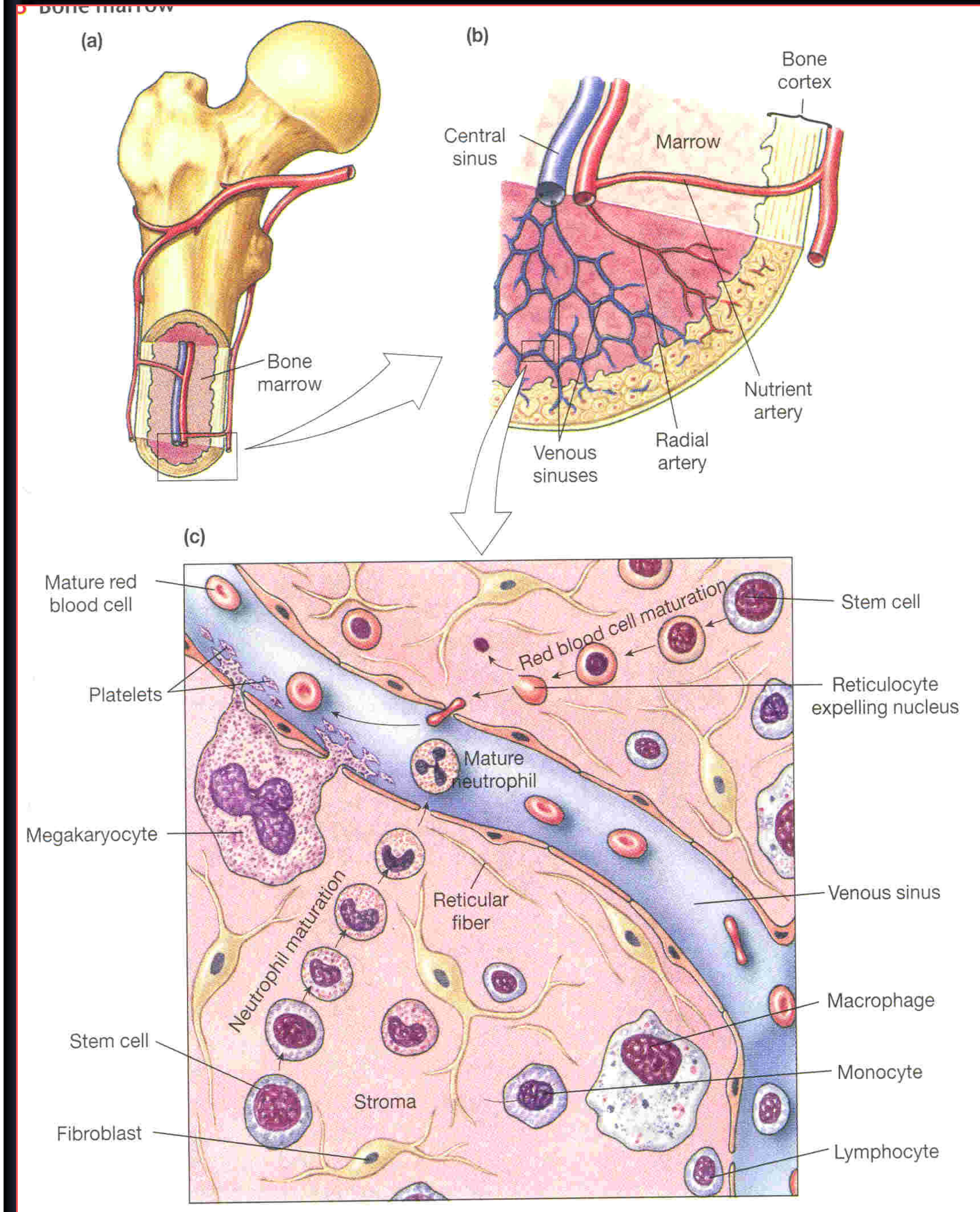


First Identifiable cell

First cell to appear in Circulation Matures in 24-48 Hours



Reticulocytes Contain remnants of the Golgi apparatus & mitochondria,



Features of RBC maturation

1. Reduction in size
2. Disappearance of the nucleus
3. Acquisition of haemoglobin

Nutritional requirements for Erythropoiesis

Nutirents/Requirements	Functions	Result of Deficiency
Amino acids	Protein Synthesis (Globin Chains)	Hemoglobinopathies & Anemia
Iron	Heme Synthesis	Microcytic and hyochromic anaemia
Vit B12 and Folic acid	Synthesis of DNA & Cell division	Megaloblastic anemia
Vit C	Iron absorption	Iron Deficiency
Vit B6	RBC Synthesis	normochromic

Erythropoietin

- **Chemistry:** Glycoprotein
- **Site of Synthesis:** 90% from renal cortex 10% liver
- Does not affect maturation process
- Can be measured in plasma & urine
- High level of erythropoietin are seen in;
  - anemia
  - High altitude
  - Heart failure

- Stimulate the production of proerythroblasts from hematopoietic stem cells in the bone marrow
- once the proerythroblasts are formed, the erythropoietin causes these cells to pass more rapidly through the different erythroblastic stages and can increase it to perhaps 10 or more times normal

Control of Erythropoiesis

Tissue Hypoxia

↓

↓ Blood O2 levels

↓

Tissue (kidney) hypoxia

↓

↑ Production of erythropoietin

↓

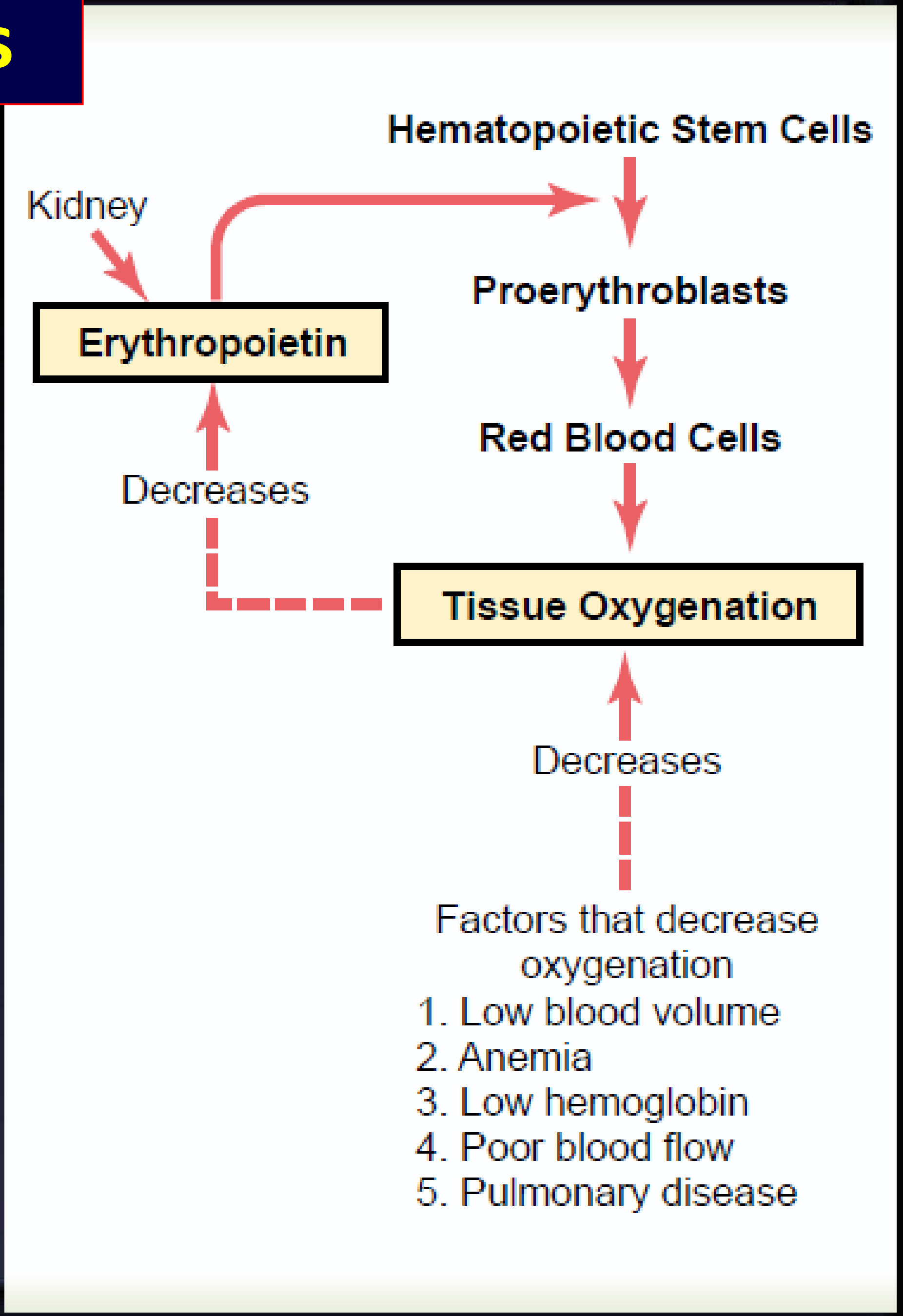
↑ plasma erythropoietin

↓

Stimulation of erythrocytes production

↓

↑ Erythrocyte production



Destruction of Erythrocytes

- At the end of RBC life (About 120 days) ….. Cell membrane ruptures during passage in sinusoidal capillaries of the spleen, bone marrow & liver.
- Haemoglobin
  - Polypeptide → amino acids → amino acid pool
  - Heme:
    - Iron → recycled (reused)→ iron storage
    - porphryn → biliverdin → bilirubin (excreted in bile)

Quantity of Hemoglobin in Blood

- The concentration of Hemoglobin in whole blood is about 15 gm/dl (13-16 females, 14-18 males, New Born 18-19)
- RBCs have the maximum ability to concentrate hemoglobin in the cell fluid up to about 34 grams in each 100 milliliters of cells
- Each gram of hemoglobin can combine with 1.34 ml of oxygen if Hb is 100% saturated with O_2.

O_2 Carrying Capacity of Blood

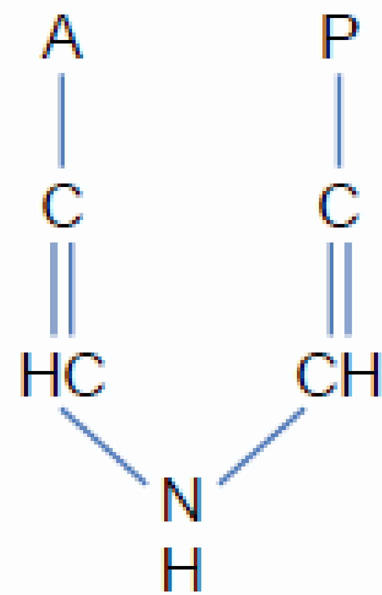
It is the amount of O_2 carried by 100 ml of blood

Calculated by: Hb conc x 1.34

Example: 16 x 1.34 = 21.4 ml

HAEMOGLOBIN SYNTHESIS

I. 2 succinyl-CoA + 2 glycine →



(pyrrole)

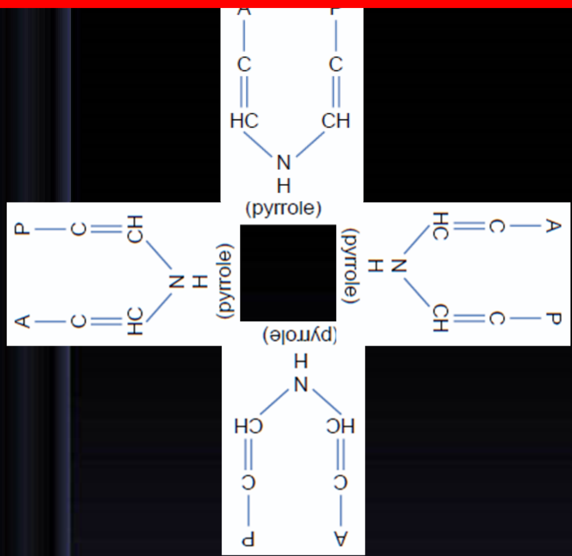
II. 4 pyrrole → protoporphyrin IX

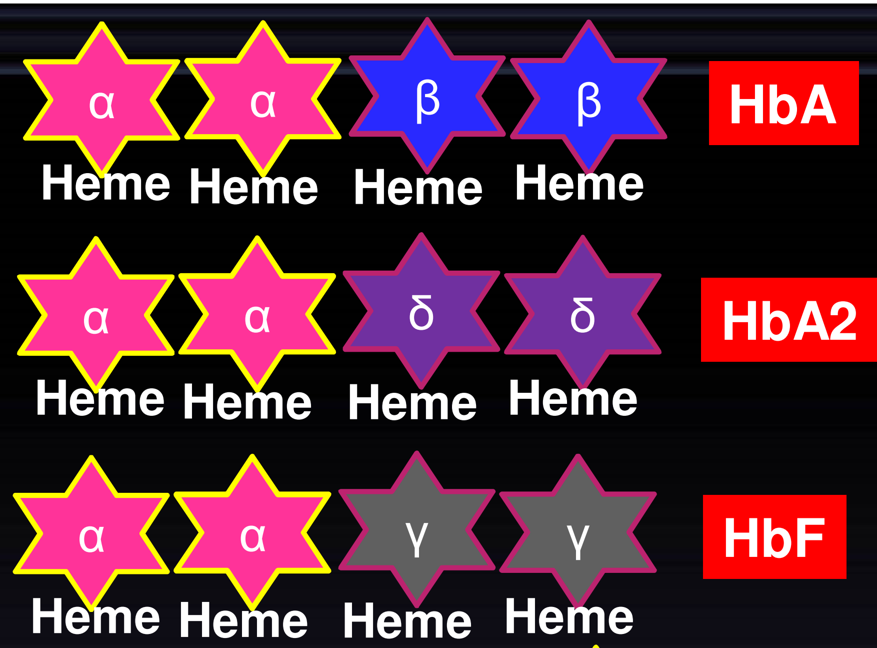
III. protoporphyrin IX + Fe^{++} → heme

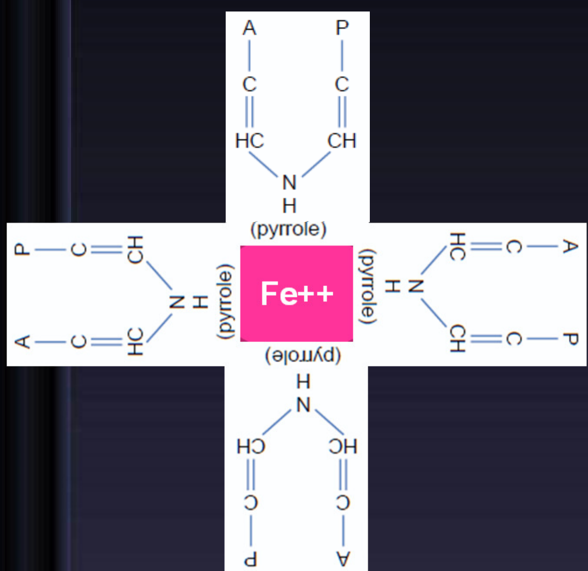
IV. heme + polypeptide → hemoglobin chain (α or β)

V. 2 α chains + 2 β chains → hemoglobin A

4pyrrole→Protoporphyrin







Protoporphyrin+Fe^{++}→ Heme

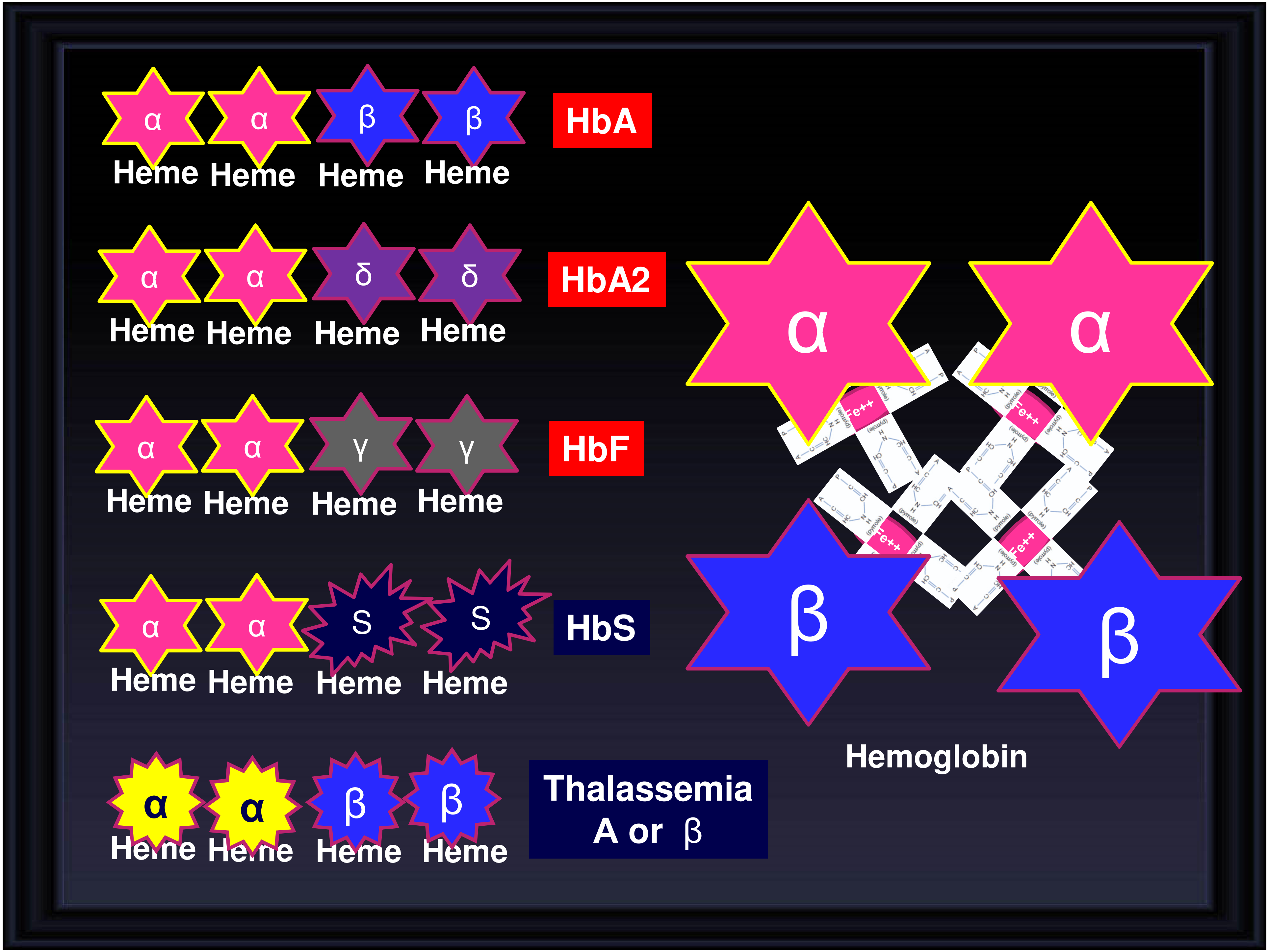
TYPES OF NORMAL HEMAGLOBIN

- HbA: 98% of adult Hb its polypeptide chains (2α & 2β)
- HbA2: 2.5% of adult Hb (2α & 2δ)
- HbF: 80-90% of fetal Hb at birth (2α & 2γ)

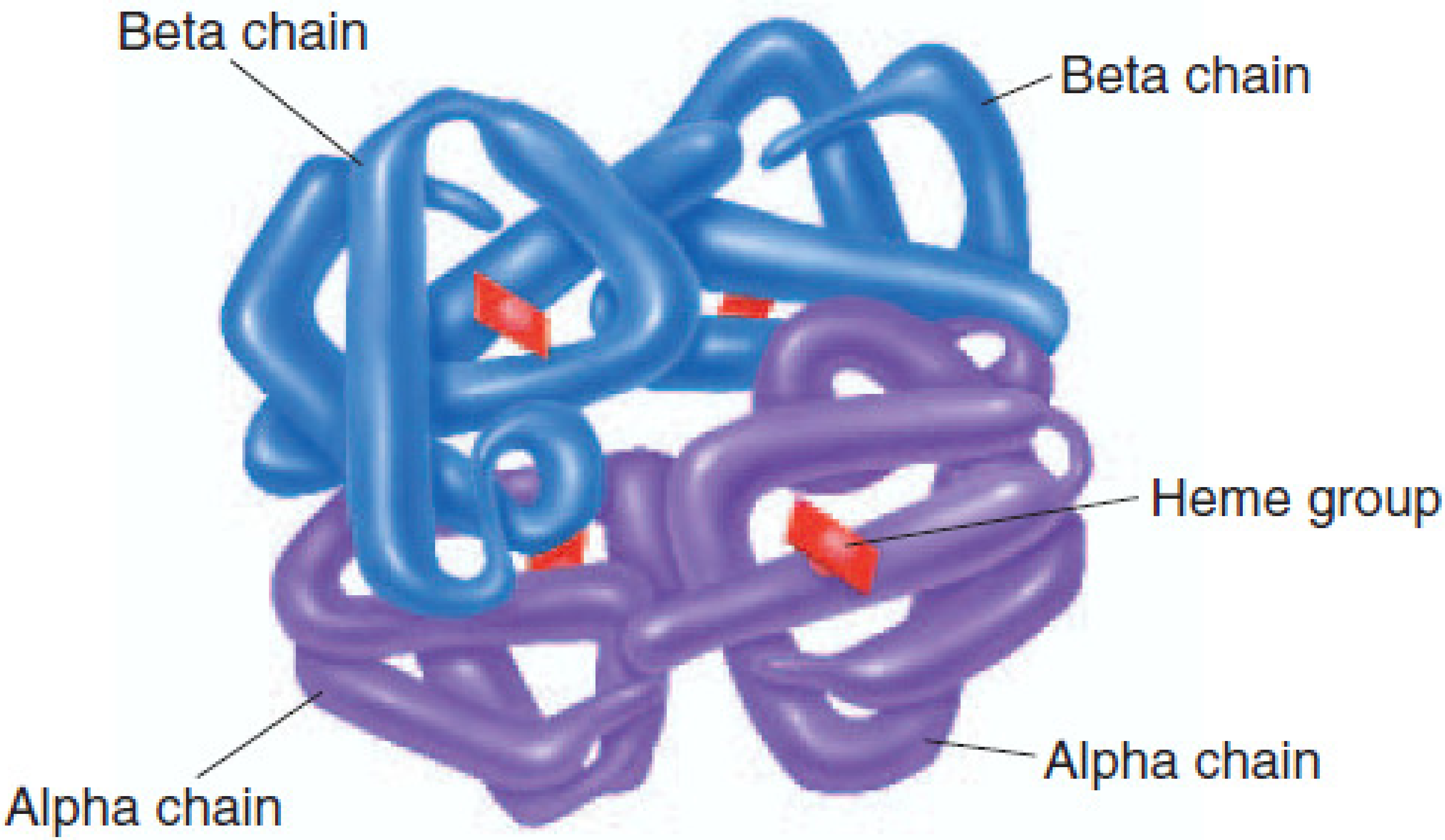
Abnormality in the polypeptide chain α & β results in abnormal Hb (hemoglobinopathies) e.g thalassemias, sickle cell

Functions of Hb

- Carriage of O_2 and CO_2
- Buffer
- (Bind CO in Smokers)


α α β β
Heme Heme Heme Heme
HbA
α α δ δ
Heme Heme Heme Heme
HbA2
α α γ γ
Heme Heme Heme Heme
HbF
α α S S
Heme Heme Heme Heme
HbS
α α β β
Heme Heme Heme Heme
Thalassemia
A or β
α α
Fe++
β β
Hemoglobin

Hemoglobin



a)

What is Anaemia?

Anemia is reduced amount/concentration of Haemoglobin or RBC count in blood less than the amount appropriate for that age, sex, race and physiological status.

Normal ranges of Hb

Men: Hb 13.5 to 17.5 g/dL

Women: Hb 12.0 to 15.5 g/dL

Infants : Hb 14 – 19 g/dL

Greek word (an-haîma) meaning "without blood"

Symptoms & Signs: Tiredness, Fatigue, Dyspnea (shortness of breathing), pallor, tachycardia

Etiologic Classification of Anaemia

1. Blood Loss
   - acute→ accident
   - Chronic → ulcer, worms (Parasitic Infections)
2. Decrease RBC production
   - Nutritional causes
     - Iron → microcytic anaemia
     - VB12 & Folic acid → megaloblastic anaemia
   - Bone marrow destruction by cancer, radiation, drugs → Aplastic anaemia.
3. Excessive destruction → Haemolytic
   - Abnormal Hb (sickle cells)
   - Incompatible blood transfusion

On the basis of morphology and color of RBC (Indices)

	Microcytic Hypochromic	Normocytic Normochromic	Macrocytic
Hb & RBC Count	↓	↓	↓
MCV	↓(MCV<80 fl)	N(MCV=80-100 fl)	↑(MCV=>100 fl)
MCH	↓(MCH<27pg)	N(MCH>27pg)	N (MCH>27pg)
	• Iron deficiency anemia • Thalassemia	• Endocrine diseases • Hypothyroidism • Hemolysis • Chronic infections	• Vit. B12 deficiency • Folic acid deficiency

Polycythemia

↑ number of RBC or high conc. of Hb

Types:

- True or absolute
  - Primary (polycythemia rubra vera): uncontrolled RBC production
  - Secondary to hypoxia: high altitude, chronic respiratory or cardiac disease
- Relative
  - Haemoconcentration:
    - loss of body fluid in vomiting, diarrhea, sweating

Iron metabolism

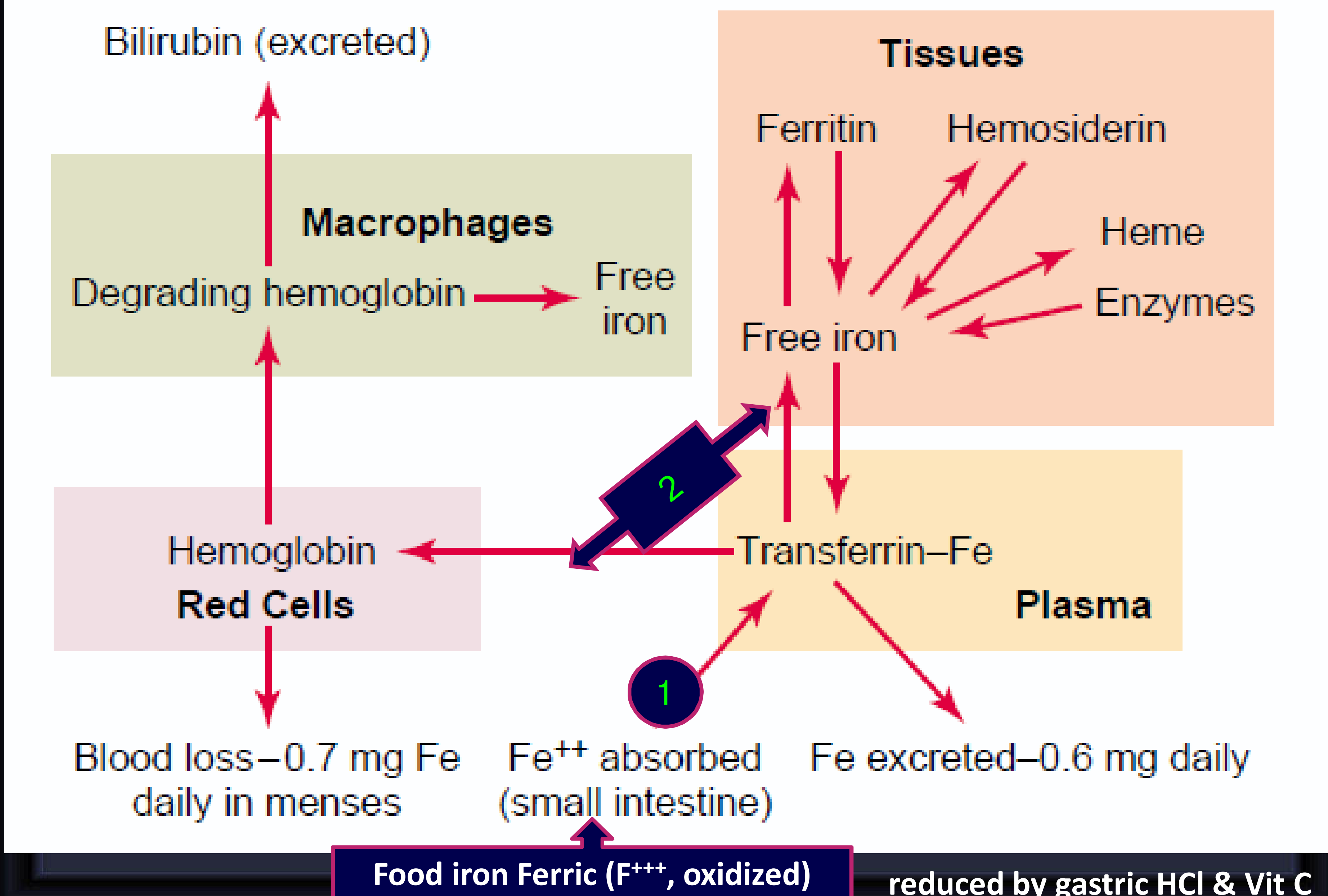
Total Iron in the body = 3-5g

1. Haemoglobin: ………. 65-75% (3g)
2. Stored iron…………. 15-30%
3. Muscle Hb (myoglobin) ….. 4%
4. Enzymes (cytochrome) …….. 1%
5. Plasma iron: (transferrin) …. 0.1%

(Serum ferritin $\rightarrow$ indication of the amount of iron stores)

Diet provides 10-20 mg iron per day

Iron transport and metabolism



reduced by gastric HCl & Vit C

Iron absorption

- Rate of iron absorption deceases when iron stores are saturated (When all the apoferritin is saturated).

Iron in plasma:

- Transporting protein: TRANSFERRIN
- Normally 30-40 saturated with Fe: (plasma iron 100-130ug/100ml)
- When transferrin is 100% saturated >> plasma iron: 300ug/100ml

(Total Iron Binding Capacity)

Iron stores

- **Sites:** liver, spleen & bone marrow
- Storage forms: Ferritin (loose bond) and haemosiderin (firm bond)

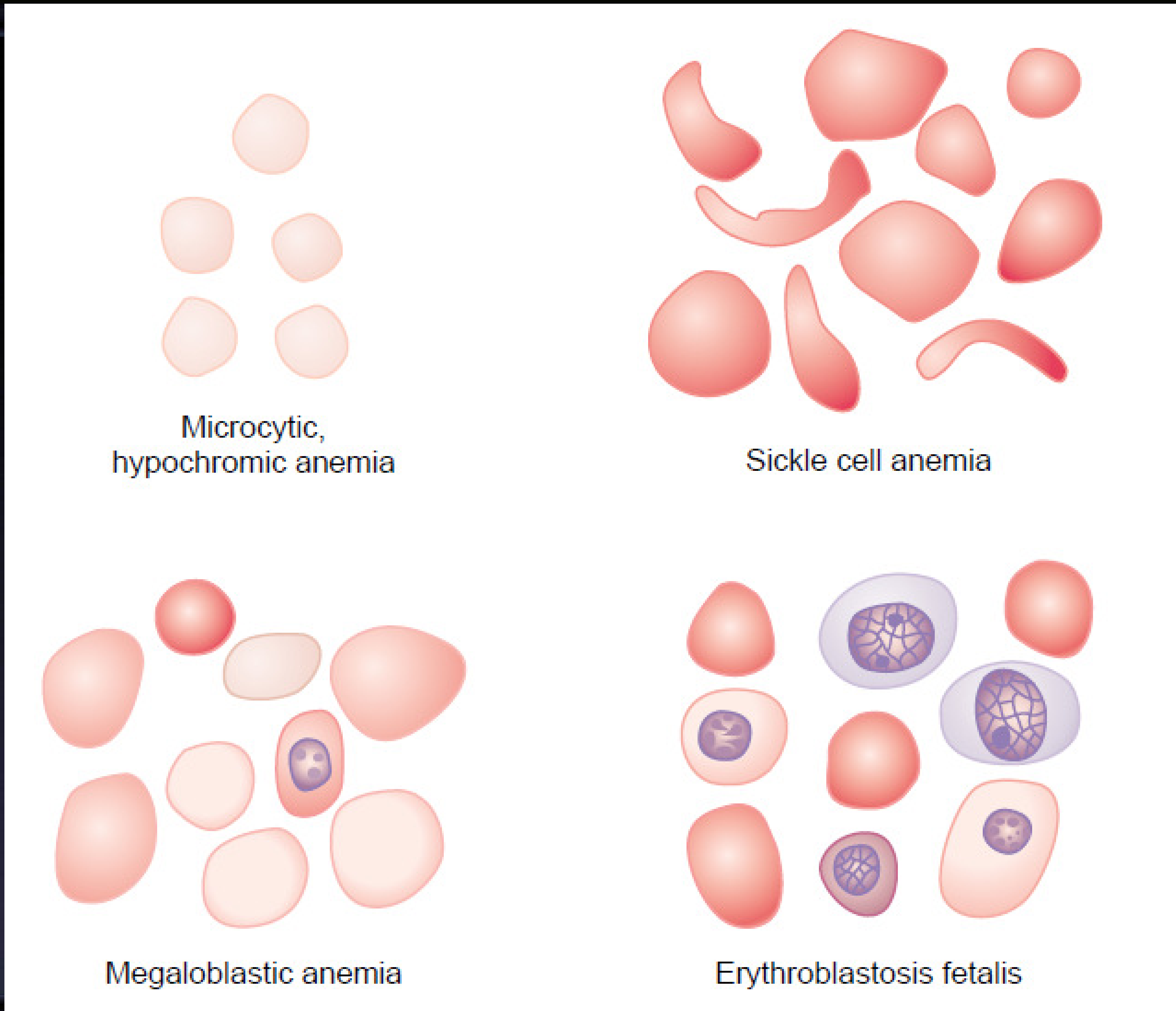
Apoferretin + iron = Ferritin

Ferritin + Ferritin = Haemosiderin

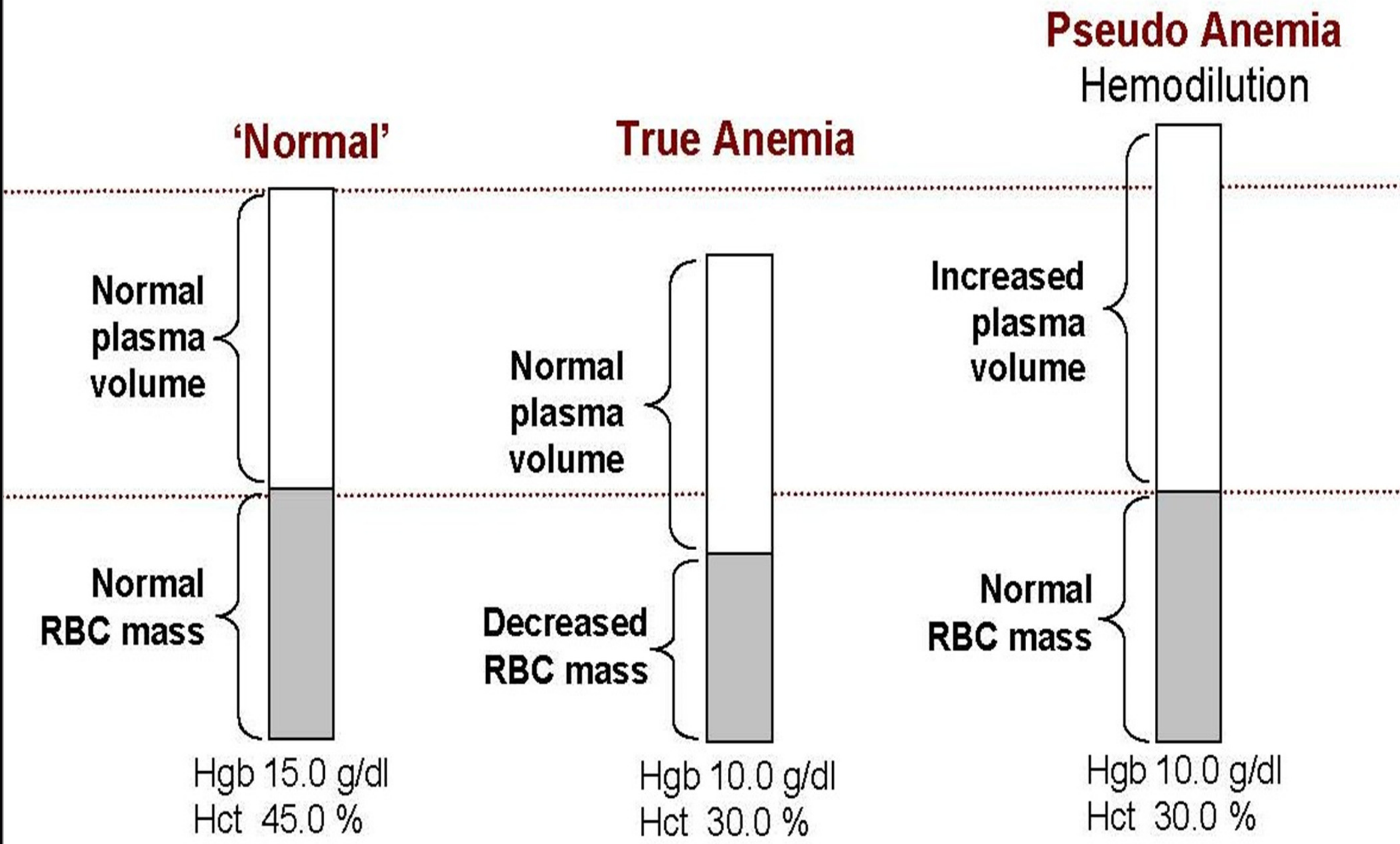
Hemosiderosis

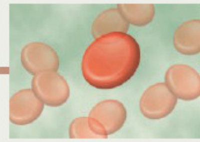
Iron excretion and daily requirement

- Iron losses
  - feces: unabsorbed, dead epithelial cells
  - bile and saliva.
  - Skin: cell, hair, nail, in sweat.
  - Urine
  - Menstruation, pregnancy and child birth


Microcytic, hypochromic anemia
Sickle cell anemia
Megaloblastic anemia
Erythroblastosis fetalis

RBC Mass and Plasma Volume Relationship





CHAPTER 33

Red Blood Cells, Anemia, and Polycythemia

In this chapter we begin discussing the *blood cells* and cells of the *macrophage system* and *lymphatic system.* We first present the functions of red blood cells (RBCs), which are the most abundant cells of the blood and are necessary for the delivery of oxygen to the tissues.

RED BLOOD CELLS (ERYTHROCYTES)

A major function of RBCs, also known as *erythrocytes,* is to transport *hemoglobin,* which, in turn, carries oxygen from the lungs to the tissues. In some animals, hemoglobin circulates as free protein in the plasma and is not enclosed in RBCs. When it is free in the plasma of the human being, about 3 percent of it leaks through the capillary membrane into the tissue spaces or through the glomerular membrane of the kidney into the glomerular filtrate each time the blood passes through the capillaries. Therefore, hemoglobin must remain inside RBCs to effectively perform its functions in humans.

The RBCs have other functions besides transport of hemoglobin. For instance, they contain a large quantity of *carbonic anhydrase,* an enzyme that catalyzes the reversible reaction between carbon dioxide (CO_2) and water to form carbonic acid (H_2CO_3), increasing the rate of this reaction several thousandfold. The rapidity of this reaction makes it possible for the water of the blood to transport enormous quantities of CO_2 in the form of bicarbonate ion (HCO_3^-) from the tissues to the lungs, where it is reconverted to CO_2 and expelled into the atmosphere as a body waste product. The hemoglobin in the cells is an excellent *acid-base buffer* (as is true of most proteins), so the RBCs are responsible for most of the acid-base buffering power of whole blood.

Shape and Size of Red Blood Cells. Normal RBCs, shown in Figure 33-3, are biconcave disks having a mean diameter of about 7.8 micrometers and a thickness of 2.5 micrometers at the thickest point and 1 micrometer or less in the center. The average volume of the RBC is 90 to 95 cubic micrometers.

The shapes of RBCs can change remarkably as the cells squeeze through capillaries. Actually, the RBC is a "bag" that can be deformed into almost any shape. Furthermore, because the normal cell has a great excess of cell membrane for the quantity of material inside, deformation does not stretch the membrane greatly and, consequently, does not rupture the cell, as would be the case with many other cells.

Concentration of Red Blood Cells in the Blood. In healthy men, the average number of RBCs per cubic millimeter is 5,200,000 (±300,000); in women, it is 4,700,000 (±300,000). Persons living at high altitudes have greater numbers of RBCs, as discussed later.

Quantity of Hemoglobin in the Cells. RBCs have the ability to concentrate hemoglobin in the cell fluid up to about 34 grams in each 100 milliliters of cells. The concentration does not rise above this value because this is the metabolic limit of the cell's hemoglobin-forming mechanism. Furthermore, in normal people, the percentage of hemoglobin is almost always near the maximum in each cell. However, when hemoglobin formation is deficient, the percentage of hemoglobin in the cells may fall considerably below this value, and the volume of the RBC may also decrease because of diminished hemoglobin to fill the cell.

When the hematocrit (the percentage of blood that is in cells—normally, 40 to 45 percent) and the quantity of hemoglobin in each respective cell are normal, the whole blood of men contains an average of 15 grams of hemoglobin per 100 milliliters; for women, it contains an average of 14 grams per 100 milliliters.

As discussed in connection with blood transport of oxygen in Chapter 41, each gram of hemoglobin can combine with 1.34 ml of oxygen if the hemoglobin is 100 percent saturated. Therefore, in a normal man a maximum of about 20 milliliters of oxygen can be carried in combination with hemoglobin in each 100 milliliters of blood, and in a normal woman 19 milliliters of oxygen can be carried.

PRODUCTION OF RED BLOOD CELLS

Areas of the Body That Produce Red Blood Cells. In the early weeks of embryonic life, primitive, nucleated RBCs are produced in the *yolk sac.* During the middle trimester of gestation, the *liver* is the main organ for

production of RBCs, but reasonable numbers are also produced in the *spleen* and *lymph nodes.* Then, during the last month or so of gestation and after birth, RBCs are produced exclusively in the *bone marrow.*

As demonstrated in Figure 33-1, the bone marrow of essentially all bones produces RBCs until a person is 5 years old. The marrow of the long bones, except for the proximal portions of the humeri and tibiae, becomes quite fatty and produces no more RBCs after about age 20 years. Beyond this age, most RBCs continue to be produced in the marrow of the membranous bones, such as the vertebrae, sternum, ribs, and ilia. Even in these bones, the marrow becomes less productive as age increases.

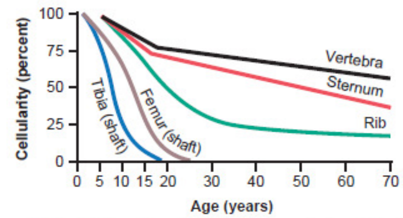


Figure 33-1. Relative rates of red blood cell production in the bone marrow of different bones at different ages.

Genesis of Blood Cells

Pluripotential Hematopoietic Stem Cells, Growth Inducers, and Differentiation Inducers. The blood cells begin their lives in the bone marrow from a single type of cell called the *pluripotential hematopoietic stem cell,* from which all the cells of the circulating blood are eventually derived. Figure 33-2 shows the successive divisions of the pluripotential cells to form the different circulating blood cells. As these cells reproduce, a small portion of them remains exactly like the original pluripotential cells and is retained in the bone marrow to maintain a supply of these, although their numbers diminish with age. Most of the reproduced cells, however, differentiate to form the other cell types shown to the right in Figure 33-2. The intermediate-stage cells are very much like the pluripotential stem cells, even though they have already become committed to a particular line of cells and are called *committed stem cells.*

The different committed stem cells, when grown in culture, will produce colonies of specific types of blood cells. A committed stem cell that produces erythrocytes is called a *colony-forming unit–erythrocyte,* and the abbreviation *CFU-E* is used to designate this type of stem cell. Likewise, colony-forming units that form

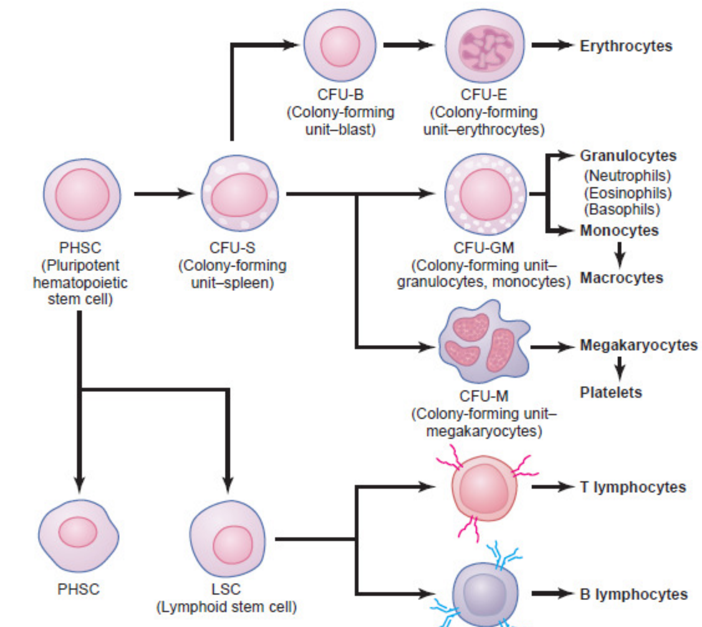


Figure 33-2. Formation of the multiple different blood cells from the original pluripotent hematopoietic stem cell in the bone marrow.

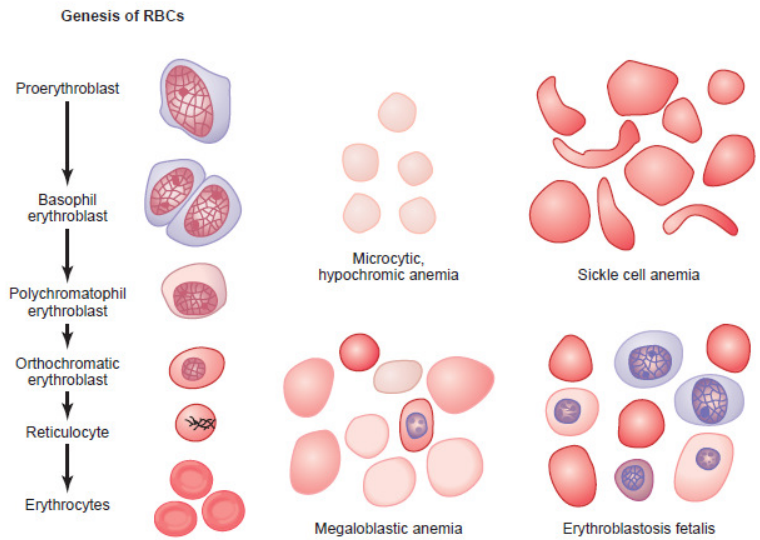


Figure 33-3. Genesis of normal red blood cells *(RBCs)* and characteristics of RBCs in different types of anemias.

granulocytes and monocytes have the designation *CFU-GM* and so forth.

Growth and reproduction of the different stem cells are controlled by multiple proteins called *growth inducers.* At least four major growth inducers have been described, each having different characteristics. One of these, *interleukin-3,* promotes growth and reproduction of virtually all the different types of committed stem cells, whereas the others induce growth of only specific types of cells.

The growth inducers promote growth but not differentiation of the cells, which is the function of another set of proteins called *differentiation inducers.* Each of these differentiation inducers causes one type of committed stem cell to differentiate one or more steps toward a final adult blood cell.

Formation of the growth inducers and differentiation inducers is controlled by factors outside the bone marrow. For instance, in the case of RBCs, exposure of the blood to low oxygen for a long time causes growth induction, differentiation, and production of greatly increased numbers of RBCs, as discussed later in the chapter. In the case of some of the white blood cells, infectious diseases cause growth, differentiation, and eventual formation of specific types of white blood cells that are needed to combat each infection.

Stages of Differentiation of Red Blood Cells

The first cell that can be identified as belonging to the RBC series is the *proerythroblast,* shown at the starting point in Figure 33-3. Under appropriate stimulation, large numbers of these cells are formed from the CFU-E stem cells.

Once the proerythroblast has been formed, it divides multiple times, eventually forming many mature RBCs. The first-generation cells are called *basophil erythroblasts* because they stain with basic dyes; the cell at this time has accumulated very little hemoglobin. In the succeeding generations, as shown in Figure 33-3, the cells become filled with hemoglobin to a concentration of about 34 percent, the nucleus condenses to a small size, and its final remnant is absorbed or extruded from the cell. At the same time, the endoplasmic reticulum is also reabsorbed. The cell at this stage is called a *reticulocyte* because it still contains a small amount of basophilic material, consisting of remnants of the Golgi apparatus, mitochondria, and a few other cytoplasmic organelles. During this reticulocyte stage, the cells pass from the bone marrow into the blood capillaries by *diapedesis* (squeezing through the pores of the capillary membrane).

The remaining basophilic material in the reticulocyte normally disappears within 1 to 2 days, and the cell is then a *mature erythrocyte.* Because of the short life of the reticulocytes, their concentration among all the RBCs is normally slightly less than 1 percent.

Erythropoietin Regulates Red Blood Cell Production

The total mass of RBCs in the circulatory system is regulated within narrow limits, and thus (1) an adequate number of RBCs are always available to provide sufficient

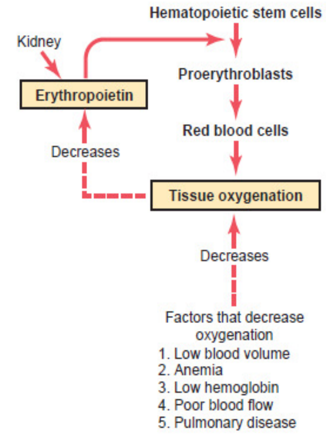


Figure 33-4. Function of the erythropoietin mechanism to increase production of red blood cells when tissue oxygenation decreases.

transport of oxygen from the lungs to the tissues, yet (2) the cells do not become so numerous that they impede blood flow. This control mechanism is diagrammed in Figure 33-4 and is described in the following sections.

Tissue Oxygenation Is the Most Essential Regulator of Red Blood Cell Production. Conditions that decrease the quantity of oxygen transported to the tissues ordinarily increase the rate of RBC production. Thus, when a person becomes extremely *anemic* as a result of hemorrhage or any other condition, the bone marrow begins to produce large quantities of RBCs. Also, destruction of major portions of the bone marrow, especially by x-ray therapy, causes hyperplasia of the remaining bone marrow, in an attempt to supply the demand for RBCs in the body.

At very *high altitudes,* where the quantity of oxygen in the air is greatly decreased, insufficient oxygen is transported to the tissues and RBC production is greatly increased. In this case, it is not the concentration of RBCs in the blood that controls RBC production but the amount of oxygen transported to the tissues in relation to tissue demand for oxygen.

Various diseases of the circulation that decrease tissue blood flow, particularly those that cause failure of oxygen absorption by the blood as it passes through the lungs, can also increase the rate of RBC production. This result is especially apparent in prolonged *cardiac failure* and in many *lung diseases* because the tissue hypoxia resulting from these conditions increases RBC production, with a resultant increase in hematocrit and usually total blood volume as well.

Erythropoietin Stimulates Red Blood Cell Production, and Its Formation Increases in Response to Hypoxia. The principal stimulus for RBC production in low oxygen states is a circulating hormone called *erythropoietin,* a glycoprotein with a molecular weight of about 34,000. In the absence of erythropoietin, hypoxia has little or no effect to stimulate RBC production. However, when the erythropoietin system is functional, hypoxia causes a marked increase in erythropoietin production and the erythropoietin, in turn, enhances RBC production until the hypoxia is relieved.

Erythropoietin Is Formed Mainly in the Kidneys. Normally, about 90 percent of all erythropoietin is formed in the kidneys, and the remainder is formed mainly in the liver. It is not known exactly where in the kidneys the erythropoietin is formed. Some studies suggest that erythropoietin is secreted mainly by fibroblast-like interstitial cells surrounding the tubules in the cortex and outer medulla, where much of the kidney's oxygen consumption occurs. It is likely that other cells, including the renal epithelial cells, also secrete the erythropoietin in response to hypoxia.

Renal tissue hypoxia leads to increased tissue levels of *hypoxia-inducible factor–1* (HIF-1), which serves as a transcription factor for a large number of hypoxia-inducible genes, including the erythropoietin gene. HIF-1 binds to a *hypoxia response element* residing in the erythropoietin gene, inducing transcription of messenger RNA and, ultimately, increased erythropoietin synthesis.

At times, hypoxia in other parts of the body, but not in the kidneys, stimulates kidney erythropoietin secretion, which suggests that there might be some non-renal sensor that sends an additional signal to the kidneys to produce this hormone. In particular, both norepinephrine and epinephrine and several of the prostaglandins stimulate erythropoietin production.

When both kidneys are removed from a person or when the kidneys are destroyed by renal disease, the person invariably becomes very anemic because the 10 percent of the normal erythropoietin formed in other tissues (mainly in the liver) is sufficient to cause only one third to one half the RBC formation needed by the body.

Erythropoietin Stimulates Production of Proerythroblasts from Hematopoietic Stem Cells. When an animal or a person is placed in an atmosphere of low oxygen, erythropoietin begins to be formed within minutes to hours, and it reaches maximum production within 24 hours. Yet almost no new RBCs appear in the circulating blood until about 5 days later. From this fact, as well as from other studies, it has been determined that the important effect of erythropoietin is to stimulate the production of proerythroblasts from hematopoietic stem cells in the bone marrow. In addition, once the proerythroblasts are formed, the erythropoietin causes these cells to pass more rapidly through the different erythroblastic stages than they normally do, further speeding up the production of new RBCs. The rapid production of cells continues as long as the person remains in a low oxygen state or until enough RBCs have been produced to carry adequate amounts of oxygen to the tissues despite the low level of oxygen; at this time, the rate of erythropoietin production decreases to a level that will maintain the required number of RBCs but not an excess.

In the absence of erythropoietin, few RBCs are formed by the bone marrow. At the other extreme, when large quantities of erythropoietin are formed and if plenty of iron and other required nutrients are available, the rate of RBC production can rise to perhaps 10 or more times normal. Therefore, the erythropoietin mechanism for controlling RBC production is a powerful one.

Maturation of Red Blood Cells Requires Vitamin B_{12} (Cyanocobalamin) and Folic Acid

Because of the continuing need to replenish RBCs, the erythropoietic cells of the bone marrow are among the most rapidly growing and reproducing cells in the entire body. Therefore, as would be expected, their maturation and rate of production are affected greatly by a person's nutritional status.

Especially important for final maturation of the RBCs are two vitamins, *vitamin B_{12}* and *folic acid.* Both of these vitamins are essential for the synthesis of DNA because each, in a different way, is required for the formation of thymidine triphosphate, one of the essential building blocks of DNA. Therefore, lack of either vitamin B_{12} or folic acid causes abnormal and diminished DNA and, consequently, failure of nuclear maturation and cell division. Furthermore, the erythroblastic cells of the bone marrow, in addition to failing to proliferate rapidly, produce mainly larger than normal RBCs called *macrocytes,* and the cell itself has a flimsy membrane and is often irregular, large, and oval instead of the usual biconcave disk. These poorly formed cells, after entering the circulating blood, are capable of carrying oxygen normally, but their fragility causes them to have a short life, one-half to one-third normal. Therefore, deficiency of either vitamin B_{12} or folic acid causes *maturation failure* in the process of erythropoiesis.

Maturation Failure Caused by Poor Absorption of Vitamin B_{12} from the Gastrointestinal Tract—Pernicious Anemia. A common cause of RBC maturation failure is failure to absorb vitamin B_{12} from the gastrointestinal tract. This situation often occurs in the disease *pernicious anemia,* in which the basic abnormality is an *atrophic gastric mucosa* that fails to produce normal gastric secretions. The parietal cells of the gastric glands secrete a glycoprotein called *intrinsic factor,* which combines with vitamin B_{12} in food and makes the B_{12} available for absorption by the gut. It does this in the following way:

1. Intrinsic factor binds tightly with the vitamin B_{12}. In this bound state, the B_{12} is protected from digestion by the gastrointestinal secretions.
2. Still in the bound state, intrinsic factor binds to specific receptor sites on the brush border membranes of the mucosal cells in the ileum.
3. Vitamin B_{12} is then transported into the blood during the next few hours by the process of pinocytosis, carrying intrinsic factor and the vitamin together through the membrane.

Lack of intrinsic factor, therefore, decreases availability of vitamin B_{12} because of faulty absorption of the vitamin.

Once vitamin B_{12} has been absorbed from the gastrointestinal tract, it is first stored in large quantities in the liver and then is released slowly as needed by the bone marrow. The minimum amount of vitamin B_{12} required each day to maintain normal RBC maturation is only 1 to 3 micrograms, and the normal storage in the liver and other body tissues is about 1000 times this amount. Therefore, 3 to 4 years of defective B_{12} absorption are usually required to cause maturation failure anemia.

Maturation Failure Caused by Folic Acid (Pteroylglutamic Acid) Deficiency. Folic acid is a normal constituent of green vegetables, some fruits, and meats (especially liver). However, it is easily destroyed during cooking. Also, people with gastrointestinal absorption abnormalities, such as the frequently occurring small intestinal disease called *sprue,* often have serious difficulty absorbing both folic acid and vitamin B_{12}. Therefore, in many instances of maturation failure, the cause is deficiency of intestinal absorption of both folic acid and vitamin B_{12}.

HEMOGLOBIN FORMATION

Synthesis of hemoglobin begins in the proerythroblasts and continues even into the reticulocyte stage of the RBCs. Therefore, when reticulocytes leave the bone marrow and pass into the blood stream, they continue to form minute quantities of hemoglobin for another day or so until they become mature erythrocytes.

Figure 33-5 shows the basic chemical steps in the formation of hemoglobin. First, succinyl-CoA, which is formed in the Krebs metabolic cycle (as explained in Chapter 68), binds with glycine to form a pyrrole molecule. In turn, four pyrroles combine to form protoporphyrin IX, which then combines with iron to form the *heme*

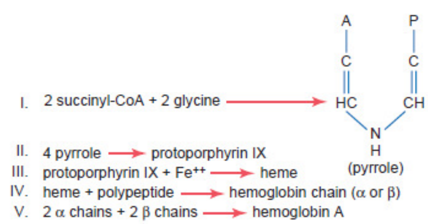


Figure 33-5. Formation of hemoglobin.

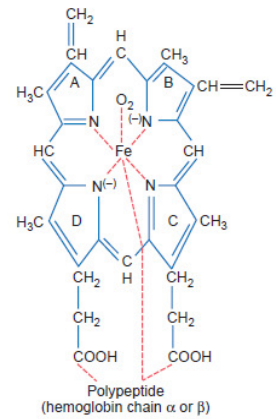


Figure 33-6. Basic structure of the heme moiety, showing one of the four heme chains that bind together, along with globin polypeptide, to form the hemoglobin molecule.

molecule. Finally, each heme molecule combines with a long polypeptide chain, a *globin* synthesized by ribosomes, forming a subunit of hemoglobin called a *hemoglobin chain* (Figure 33-6). Each chain has a molecular weight of about 16,000; four of these chains in turn bind together loosely to form the whole hemoglobin molecule.

There are several slight variations in the different subunit hemoglobin chains, depending on the amino acid composition of the polypeptide portion. The different types of chains are designated *alpha chains, beta chains, gamma chains,* and *delta chains.* The most common form of hemoglobin in the adult human being, *hemoglobin A,* is a combination of *two alpha chains* and *two beta chains.* Hemoglobin A has a molecular weight of 64,458.

Because each hemoglobin chain has a heme prosthetic group containing an atom of iron, and because there are four hemoglobin chains in each hemoglobin molecule, one finds four iron atoms in each hemoglobin molecule; each of these can bind loosely with one molecule of oxygen, making a total of four molecules of oxygen (or eight oxygen atoms) that can be transported by each hemoglobin molecule.

The types of hemoglobin chains in the hemoglobin molecule determine the binding affinity of the hemoglobin for oxygen. Abnormalities of the chains can alter the physical characteristics of the hemoglobin molecule as well. For instance, in *sickle cell anemia,* the amino acid *valine* is substituted for *glutamic acid* at one point in each of the two beta chains. When this type of hemoglobin is exposed to low oxygen, it forms elongated crystals inside the RBCs that are sometimes 15 micrometers in length. These crystals make it almost impossible for the cells to pass through many small capillaries, and the spiked ends of the crystals are likely to rupture the cell membranes, leading to sickle cell anemia.

Hemoglobin Combines Reversibly With Oxygen. The most important feature of the hemoglobin molecule is its ability to combine loosely and reversibly with oxygen. This ability is discussed in detail in Chapter 41 in relation to respiration because the primary function of hemoglobin in the body is to combine with oxygen in the lungs and then to release this oxygen readily in the peripheral tissue capillaries, where the gaseous tension of oxygen is much lower than in the lungs.

Oxygen *does not* combine with the two positive bonds of the iron in the hemoglobin molecule. Instead, it binds loosely with one of the so-called coordination bonds of the iron atom. This bond is extremely loose, so the combination is easily reversible. Furthermore, the oxygen does not become ionic oxygen but is carried as molecular oxygen (composed of two oxygen atoms) to the tissues, where, because of the loose, readily reversible combination, it is released into the tissue fluids still in the form of molecular oxygen rather than ionic oxygen.

IRON METABOLISM

Because iron is important for the formation not only of hemoglobin but also of other essential elements in the body (e.g., *myoglobin, cytochromes, cytochrome oxidase, peroxidase,* and *catalase*), it is important to understand the means by which iron is utilized in the body. The total quantity of iron in the body averages 4 to 5 grams, about 65 percent of which is in the form of hemoglobin. About 4 percent is in the form of myoglobin, 1 percent is in the form of the various heme compounds that promote intracellular oxidation, 0.1 percent is combined with the protein transferrin in the blood plasma, and 15 to 30 percent is stored for later use, mainly in the reticuloendothelial system and liver parenchymal cells, principally in the form of ferritin.

Transport and Storage of Iron. Transport, storage, and metabolism of iron in the body are diagrammed in Figure 33-7 and can be explained as follows: When iron is absorbed from the small intestine, it immediately combines in the blood plasma with a beta globulin, *apotransferrin,* to form *transferrin,* which is then transported in the plasma. The iron is loosely bound in the transferrin and, consequently, can be released to any tissue cell at any point in the body. Excess iron in the blood is deposited *especially* in the liver hepatocytes and less in the reticuloendothelial cells of the bone marrow.

In the cell cytoplasm, iron combines mainly with a protein, *apoferritin,* to form *ferritin.* Apoferritin has a molecular weight of about 460,000, and varying quantities of iron can combine in clusters of iron radicals with this large molecule; therefore, ferritin may contain only a

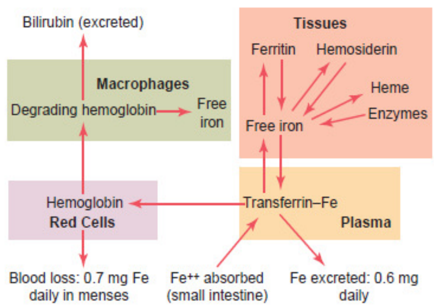


Figure 33-7. Iron transport and metabolism.

small amount of iron or a large amount. This iron stored as ferritin is called *storage iron.*

Smaller quantities of the iron in the storage pool are in an extremely insoluble form called *hemosiderin.* This is especially true when the total quantity of iron in the body is more than the apoferritin storage pool can accommodate. Hemosiderin collects in cells in the form of large clusters that can be observed microscopically as large particles. In contrast, ferritin particles are so small and dispersed that they usually can be seen in the cell cytoplasm only with an electron microscope.

When the quantity of iron in the plasma falls low, some of the iron in the ferritin storage pool is removed easily and transported in the form of transferrin in the plasma to the areas of the body where it is needed. A unique characteristic of the transferrin molecule is that it binds strongly with receptors in the cell membranes of erythroblasts in the bone marrow. Then, along with its bound iron, it is ingested into the erythroblasts by endocytosis. There the transferrin delivers the iron directly to the mitochondria, where heme is synthesized. In people who do not have adequate quantities of transferrin in their blood, failure to transport iron to the erythroblasts in this manner can cause severe *hypochromic anemia* (i.e., RBCs that contain much less hemoglobin than normal).

When RBCs have lived their life span of about 120 days and are destroyed, the hemoglobin released from the cells is ingested by monocyte-macrophage cells. There, iron is liberated and is stored mainly in the ferritin pool to be used as needed for the formation of new hemoglobin.

Daily Loss of Iron. A man excretes about 0.6 mg of iron each day, mainly into the feces. Additional quantities of iron are lost when bleeding occurs. For a woman, additional menstrual loss of blood brings long-term iron loss to an average of about 1.3 mg/day.

Absorption of Iron from the Intestinal Tract

Iron is absorbed from all parts of the small intestine, mostly by the following mechanism. The liver secretes moderate amounts of *apotransferrin* into the bile, which flows through the bile duct into the duodenum. Here, the apotransferrin binds with free iron and also with certain iron compounds, such as hemoglobin and myoglobin from meat, two of the most important sources of iron in the diet. This combination is called *transferrin.* It, in turn, is attracted to and binds with receptors in the membranes of the intestinal epithelial cells. Then, by pinocytosis, the transferrin molecule, carrying its iron store, is absorbed into the epithelial cells and later released into the blood capillaries beneath these cells in the form of *plasma transferrin.*

Iron absorption from the intestines is extremely slow, at a maximum rate of only a few milligrams per day. This slow rate of absorption means that even when tremendous quantities of iron are present in the food, only small proportions can be absorbed.

Regulation of Total Body Iron by Controlling Rate of Absorption. When the body has become saturated with iron so that essentially all apoferritin in the iron storage areas is already combined with iron, the rate of additional iron absorption from the intestinal tract becomes greatly decreased. Conversely, when the iron stores have become depleted, the rate of absorption can accelerate probably five or more times normal. Thus, total body iron is regulated mainly by altering the rate of absorption.

THE LIFE SPAN OF RED BLOOD CELLS IS ABOUT 120 DAYS

When RBCs are delivered from the bone marrow into the circulatory system, they normally circulate an average of 120 days before being destroyed. Even though mature RBCs do not have a nucleus, mitochondria, or endoplasmic reticulum, they do have cytoplasmic enzymes that are capable of metabolizing glucose and forming small amounts of adenosine triphosphate. These enzymes also (1) maintain pliability of the cell membrane, (2) maintain membrane transport of ions, (3) keep the iron of the cells' hemoglobin in the ferrous form rather than ferric form, and (4) prevent oxidation of the proteins in the RBCs. Even so, the metabolic systems of old RBCs become progressively less active and the cells become more and more fragile, presumably because their life processes wear out.

Once the RBC membrane becomes fragile, the cell ruptures during passage through some tight spot of the circulation. Many of the RBCs self-destruct in the spleen, where they squeeze through the red pulp of the spleen. There, the spaces between the structural trabeculae of the red pulp, through which most of the cells must pass, are only 3 micrometers wide, in comparison with the 8-micrometer diameter of the RBC. When the spleen is removed, the number of old abnormal RBCs circulating in the blood increases considerably.

Destruction of Hemoglobin by Macrophages. When RBCs burst and release their hemoglobin, the hemoglobin is phagocytized almost immediately by macrophages in many parts of the body, but especially by the Kupffer cells of the liver and macrophages of the spleen and bone marrow. During the next few hours to days, the macrophages release iron from the hemoglobin and pass it back into the blood, to be carried by transferrin either to the bone marrow for the production of new RBCs or to the liver and other tissues for storage in the form of ferritin. The porphyrin portion of the hemoglobin molecule is converted by the macrophages, through a series of stages, into the bile pigment *bilirubin,* which is released into the blood and later removed from the body by secretion through the liver into the bile; this process is discussed in relation to liver function in Chapter 71.

ANEMIAS

Anemia means deficiency of hemoglobin in the blood, which can be caused by either too few RBCs or too little hemoglobin in the cells. Some types of anemia and their physiological causes are described in the following sections.

Blood Loss Anemia. After rapid hemorrhage, the body replaces the fluid portion of the plasma in 1 to 3 days, but this response results in a low concentration of RBCs. If a second hemorrhage does not occur, RBC concentration usually returns to normal within 3 to 6 weeks.

When chronic blood loss occurs, a person frequently cannot absorb enough iron from the intestines to form hemoglobin as rapidly as it is lost. RBCs that are much smaller than normal and have too little hemoglobin inside them are then produced, giving rise to *microcytic, hypochromic anemia,* which is shown in Figure 33-3.

Aplastic Anemia Due to Bone Marrow Dysfunction. Bone marrow aplasia means lack of functioning bone marrow. For instance, exposure to high-dose radiation or chemotherapy for cancer treatment can damage stem cells of the bone marrow, followed in a few weeks by anemia. Likewise, high doses of certain toxic chemicals, such as insecticides or benzene in gasoline, may cause the same effect. In autoimmune disorders, such as lupus erythematosus, the immune system begins attacking healthy cells such as bone marrow stem cells, which may lead to aplastic anemia. In about half of aplastic anemia cases the cause is unknown, a condition called *idiopathic aplastic anemia.*

People with severe aplastic anemia usually die unless they are treated with blood transfusions—which can temporarily increase the numbers of RBCs—or by bone marrow transplantation.

Megaloblastic Anemia. Based on the earlier discussions of vitamin B_{12}, folic acid, and intrinsic factor from the stomach mucosa, one can readily understand that loss of any one of these can lead to slow reproduction of erythroblasts in the bone marrow. As a result, the RBCs grow too large, with odd shapes, and are called *megaloblasts.* Thus, atrophy of the stomach mucosa, as occurs in *pernicious anemia,* or loss of the entire stomach after surgical total gastrectomy can lead to megaloblastic anemia. Also, megaloblastic anemia often develops in patients who have intestinal sprue, in which folic acid, vitamin B_{12}, and other vitamin B compounds are poorly absorbed. Because in these states the erythroblasts cannot proliferate rapidly enough to form normal numbers of RBCs, the RBCs that are formed are mostly oversized, have bizarre shapes, and have fragile membranes. These cells rupture easily, leaving the person in dire need of an adequate number of RBCs.

Hemolytic Anemia. Different abnormalities of the RBCs, many of which are hereditarily acquired, make the cells fragile, so they rupture easily as they go through the capillaries, especially through the spleen. Even though the number of RBCs formed may be normal, or even much greater than normal in some hemolytic diseases, the life span of the fragile RBC is so short that the cells are destroyed faster than they can be formed, and serious anemia results.

In *hereditary spherocytosis,* the RBCs are very small and *spherical* rather than being biconcave disks. These cells cannot withstand compression forces because they do not have the normal loose, baglike cell membrane structure of the biconcave disks. Upon passing through the splenic pulp and some other tight vascular beds, they are easily ruptured by even slight compression.

In *sickle cell anemia,* which is present in 0.3 to 1.0 percent of West African and American blacks, the cells have an abnormal type of hemoglobin called *hemoglobin S,* containing faulty beta chains in the hemoglobin molecule, as explained earlier in the chapter. When this hemoglobin is exposed to low concentrations of oxygen, it precipitates into long crystals inside the RBC. These crystals elongate the cell and give it the appearance of a sickle rather than a biconcave disk. The precipitated hemoglobin also damages the cell membrane, so the cells become highly fragile, leading to serious anemia. Such patients frequently experience a vicious circle of events called a sickle cell disease "crisis," in which low oxygen tension in the tissues causes sickling, which leads to ruptured RBCs, which causes a further decrease in oxygen tension and still more sickling and RBC destruction. Once the process starts, it progresses rapidly, eventuating in a serious decrease in RBCs within a few hours and, in some cases, death.

In *erythroblastosis fetalis,* Rh-positive RBCs in the fetus are attacked by antibodies from an Rh-negative mother. These antibodies make the Rh-positive cells fragile, leading to rapid rupture and causing the child to be born with a serious case of anemia. This condition is discussed in Chapter 36 in relation to the Rh factor of blood. The extremely rapid formation of new RBCs to make up for the destroyed cells in erythroblastosis fetalis causes a large number of early *blast* forms of RBCs to be released from the bone marrow into the blood.

EFFECTS OF ANEMIA ON FUNCTION OF THE CIRCULATORY SYSTEM

The viscosity of the blood, which was discussed in Chapter 14, depends largely on the blood concentration of RBCs. In persons with severe anemia, the blood viscosity may fall to as low as 1.5 times that of water rather than the normal value of about 3. This change decreases the resistance to blood flow in the peripheral blood vessels, so far greater than normal quantities of blood flow through the tissues and return to the heart, thereby greatly increasing cardiac output. Moreover, hypoxia resulting from diminished transport of oxygen by the blood causes the peripheral tissue blood vessels to dilate, allowing a further increase in the return of blood to the heart and increasing the cardiac output to a still higher level—sometimes three to four times normal. Thus, one of the major effects of anemia is greatly *increased cardiac output*, as well as *increased pumping workload on the heart*.

The increased cardiac output in persons with anemia partially offsets the reduced oxygen-carrying effect of the anemia because even though each unit quantity of blood carries only small quantities of oxygen, the rate of blood flow may be increased enough that almost normal quantities of oxygen are actually delivered to the tissues. However, when a person with anemia begins to exercise, the heart is not capable of pumping much greater quantities of blood than it is already pumping. Consequently, during exercise, which greatly increases tissue demand for oxygen, extreme tissue hypoxia results and *acute cardiac failure* may ensue.

POLYCYTHEMIA

Secondary Polycythemia. Whenever the tissues become hypoxic because of too little oxygen in the breathed air, such as at high altitudes, or because of failure of oxygen delivery to the tissues, such as in cardiac failure, the blood-forming organs automatically produce large quantities of extra RBCs. This condition is called *secondary polycythemia*, and the RBC count commonly rises to 6 to 7 million/mm^3, about 30 percent above normal.

A common type of secondary polycythemia, called *physiological polycythemia*, occurs in natives who live at altitudes of 14,000 to 17,000 feet, where the atmospheric oxygen is very low. The blood count is generally 6 to 7 million/mm^3; this blood count allows these people to perform reasonably high levels of continuous work even in a rarefied atmosphere.

Polycythemia Vera (Erythremia). In addition to physiological polycythemia, a pathological condition known as *polycythemia vera* exists, in which the RBC count may be 7 to 8 million/mm^3 and the hematocrit may be 60 to 70 percent instead of the normal 40 to 45 percent. Polycythemia vera is caused by a genetic aberration in the hemocytoblastic cells that produce the blood cells. The blast cells no longer stop producing RBCs when too many cells are already present. This causes excess production of RBCs in the same manner that a breast tumor causes excess production of a specific type of breast cell. It usually causes excess production of white blood cells and platelets as well.

In polycythemia vera, not only does the hematocrit increase, but the total blood volume also increases, sometimes to almost twice normal. As a result, the entire vascular system becomes intensely engorged. Also, many blood capillaries become plugged by the viscous blood; the viscosity of the blood in polycythemia vera sometimes increases from the normal of 3 times the viscosity of water to 10 times that of water.

EFFECT OF POLYCYTHEMIA ON FUNCTION OF THE CIRCULATORY SYSTEM

Because of the greatly increased viscosity of the blood in polycythemia, blood flow through the peripheral blood vessels is often very sluggish. In accordance with the factors that regulate return of blood to the heart, as discussed in Chapter 20, increasing blood viscosity *decreases* the rate of venous return to the heart. Conversely, the blood volume is greatly increased in polycythemia, which tends to *increase* venous return. Actually, the cardiac output in polycythemia is not far from normal because these two factors more or less neutralize each other.

The arterial pressure is also normal in most people with polycythemia, although in about one third of them, the arterial pressure is elevated. This means that the blood pressure–regulating mechanisms can usually offset the tendency for increased blood viscosity to increase peripheral resistance and, thereby, increase arterial pressure. Beyond certain limits, however, these regulations fail and hypertension develops.

The color of the skin depends to a great extent on the quantity of blood in the skin subpapillary venous plexus. In polycythemia vera, the quantity of blood in this plexus is greatly increased. Further, because the blood passes sluggishly through the skin capillaries before entering the venous plexus, a larger than normal quantity of hemoglobin is deoxygenated. The blue color of all this deoxygenated hemoglobin masks the red color of the oxygenated hemoglobin. Therefore, a person with polycythemia vera ordinarily has a ruddy complexion with a bluish (cyanotic) tint to the skin.

Bibliography

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