Erythrocytes

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Contents

- Abnormal Changes
- Production
- Life Cycle
- Structure and Morphology
- Definition

Red Blood Cells or Erythrocytes

Most abundant cells in the blood

- 40 - 45 %.

Shape: Biconcave disc which is round and flat

- Increases the surface area so more oxygen can be carried
- The surface area of an erythrocyte is calculated to be 128 μm^2
- The average person has 3840 m^2 of RBC membrane area

Acidophilic cell

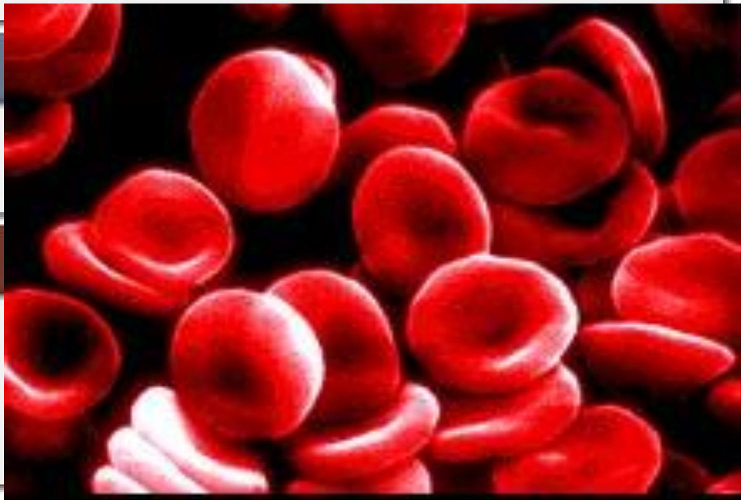
- The iron found in hemoglobin gives the blood its red color

Lack a nucleus

- Extra space inside

Contain hemoglobin(33%)

- Oxygen carrying molecule
- → 250million molecules / cell



Red Blood Cells or Erythrocytes

Diameter

- 7 – 8 microns

4-6 x 10 ^{6}/ mm^{3}

in a healthy individual

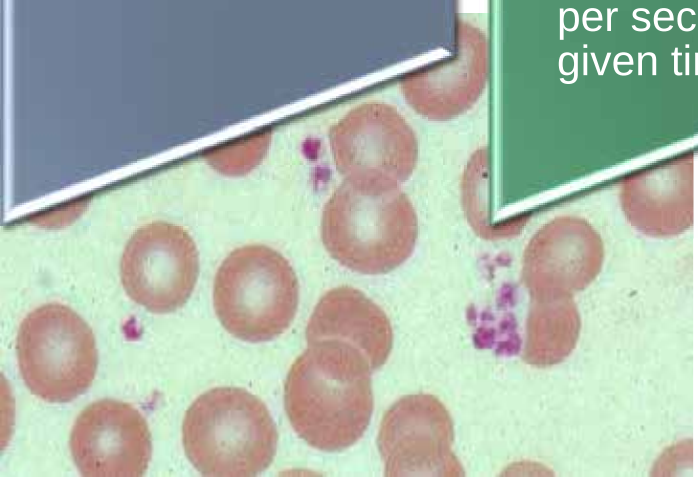
- 2.4 million new RBC are produced /s in human adults
- 20–30 trillion RBC per second at any given time

RBC Development

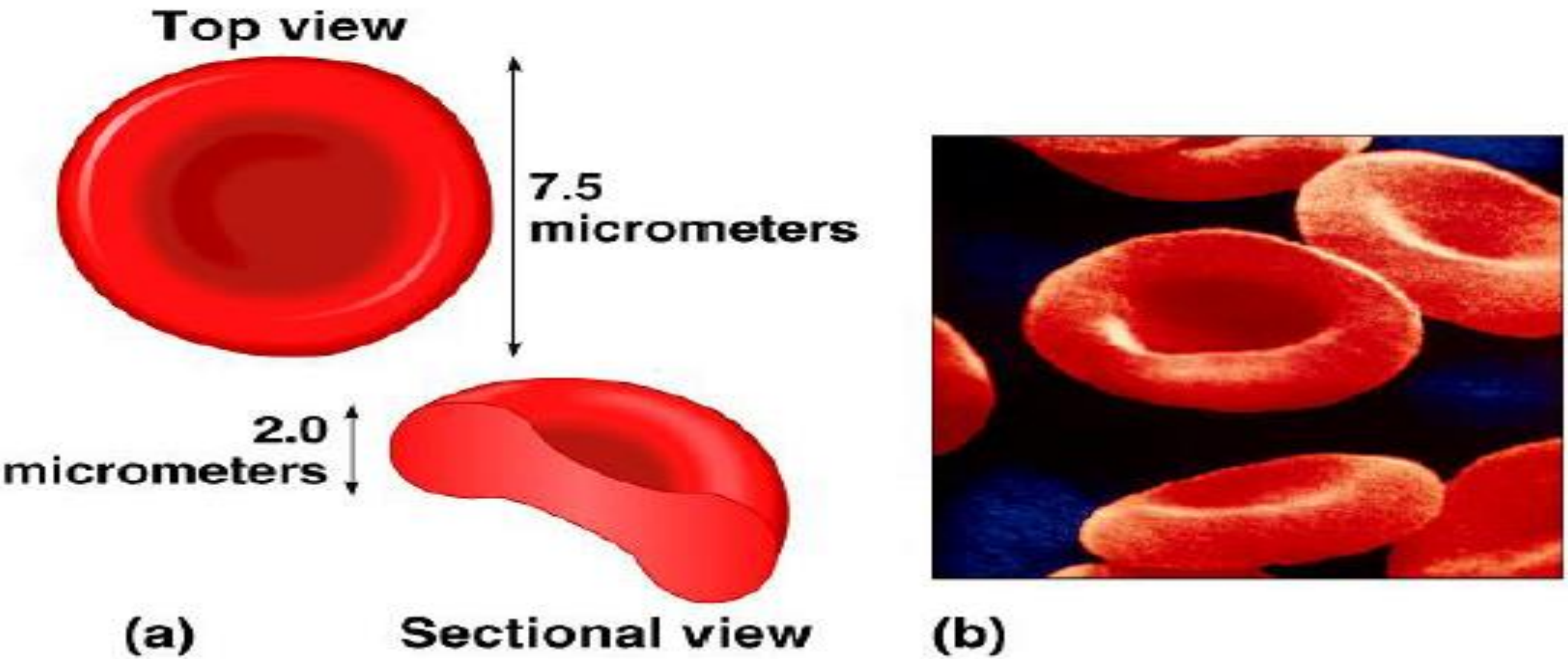
- Cannot repair themselves
- Discard their nuclei during development and so cannot reproduce or produce proteins
- The mature erythrocyte also loses its Golgi apparatus, centrioles, ER and most of its mitochondria

Life span of 120 days

- Under normal circumstances, red blood cells never leave the circulatory system



Erythrocytes



The biconcave shape also allows erythrocytes to form stacks, which facilitate flow through small capillaries, and also makes them flexible enough to pass through capillaries as narrow as 4 mm in diameter.

Erythrocytes (RBCs)

Biconcave discs

- Anucleate
- No organelles

Filled with Hemoglobin (Hb)

- Protein that functions in gas transport

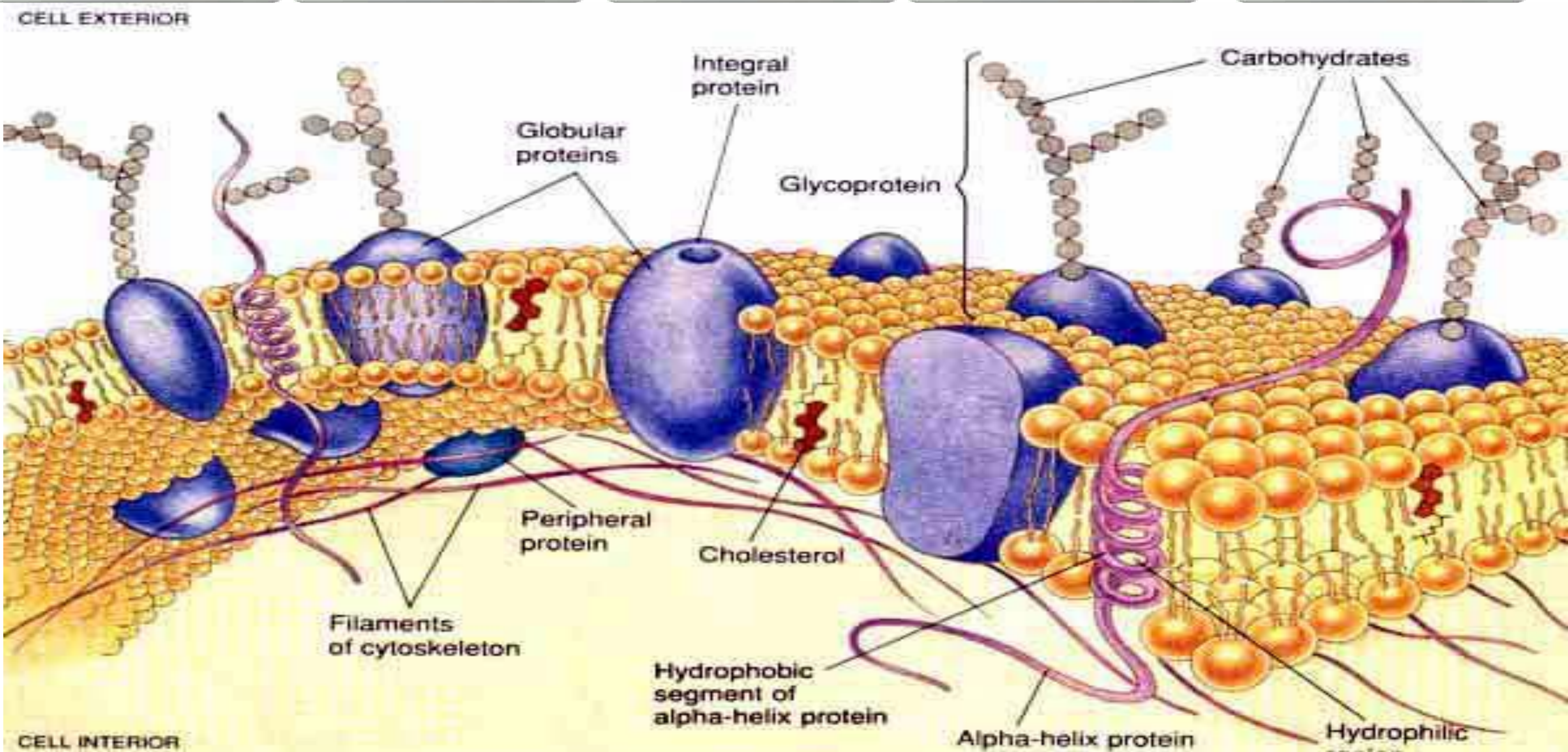
Bilayered Cell Membrane

- **Spectrin** and actin: cytoskeletal function
- RBC flexibility
- Move through capillaries
- Change shape as necessary
- Cup shape in capillaries

RBC Membrane

Trilaminar

Outermost layer		Central layer		Inner layer
Glycolipids	**Glycoproteins**	**Cholesterol**	**Phospholipids**	**Cytoskeleton**



Cytoskeleton of the RBC Membrane

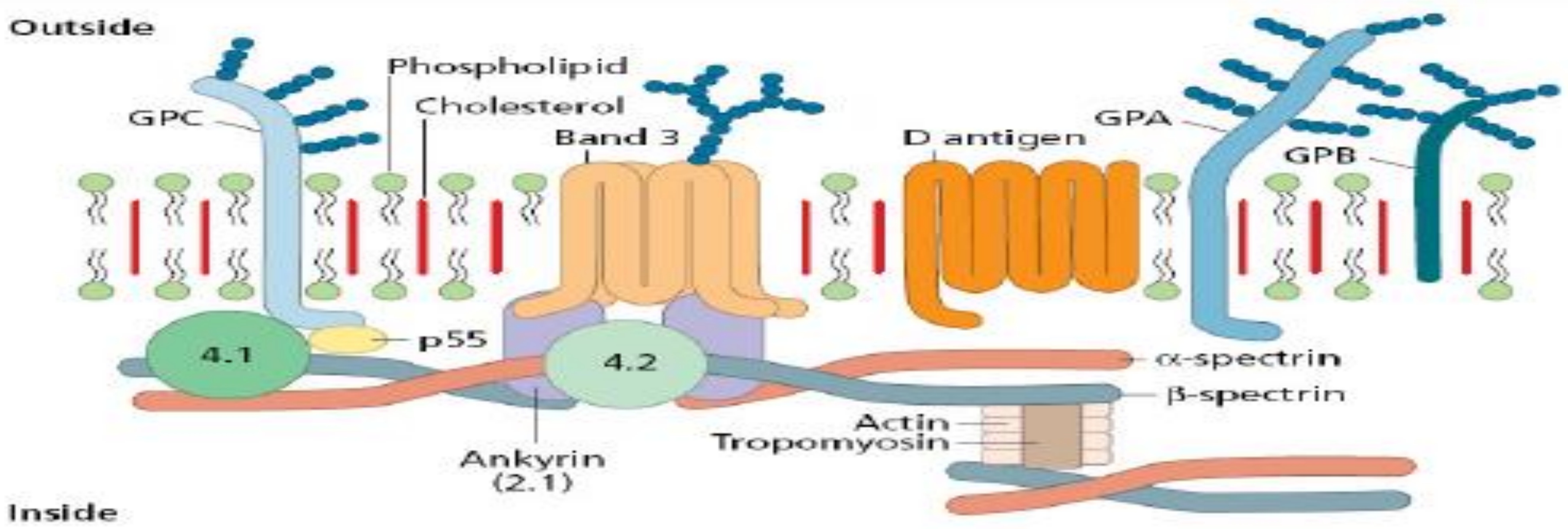
Spectrin

Composed of alpha & beta chains

Join to form a matrix which strengthens the membrane against sheer force and controls biconcave shape

Ankyrin

Binding site for spectrin



RBC Membrane: Function

Shape

Provides the optimum surface to volume ratio	Respiratory exchange and is essential to deformability

Provide Deformability, Elasticity

Allows for passage through microvessels

Provides permeability

Allows water and electrolytes to exchange via cation pumps	RBC controls volume and H_2O content primarily through control of sodium and potassium

Erythrocytes (RBCs)

Complementarity of structure and function

Structural characteristics contribute to its gas transport function

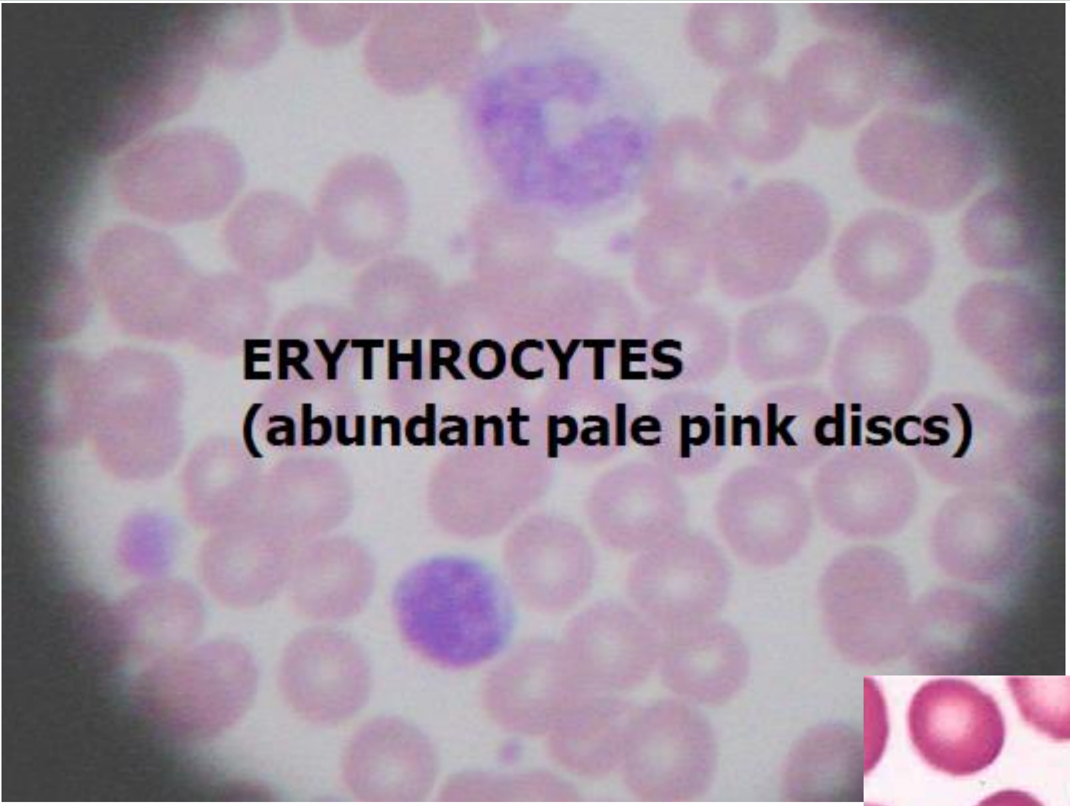
Biconcave shape that has a huge surface area relative to volume

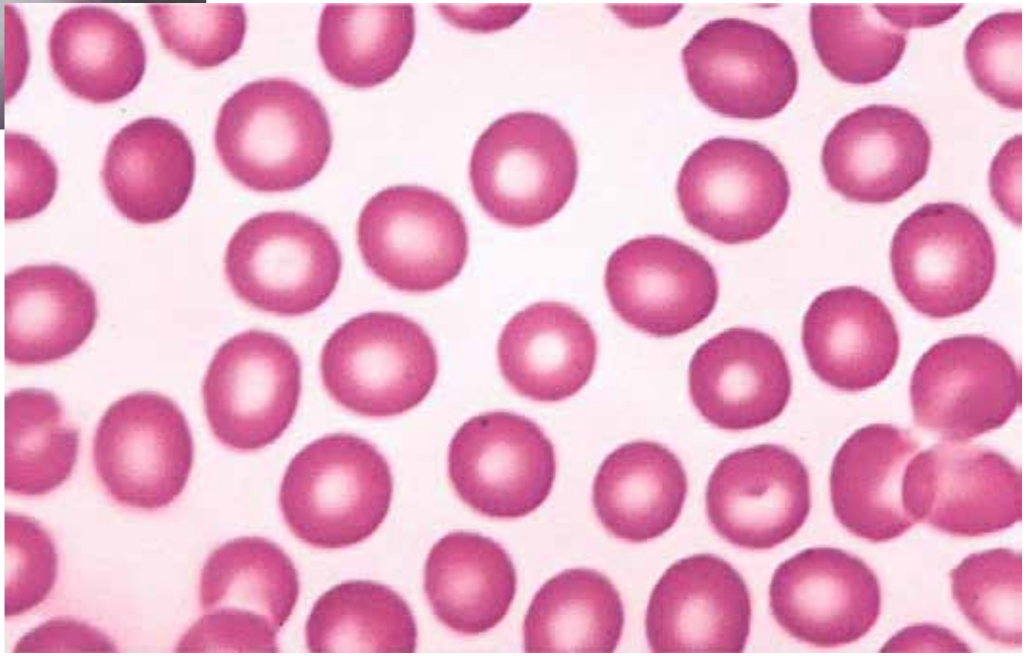
No mitochondria

ATP is generated anaerobically(through glycolysis alone)

Do not consume the oxygen they transport

RBC Erythrocytes





RBC
Erythrocytes

RBC's pass through capillary beds in single file

Erythrocyte Function

Hemoglobin reversibly binds with oxygen

Most oxygen in the blood is bound to hemoglobin

CO_2 , NO are also carried by hemoglobin

Hemoglobin: protein globin

two alpha and two beta chains

Each bound to a heme group

Respiratory gas transport

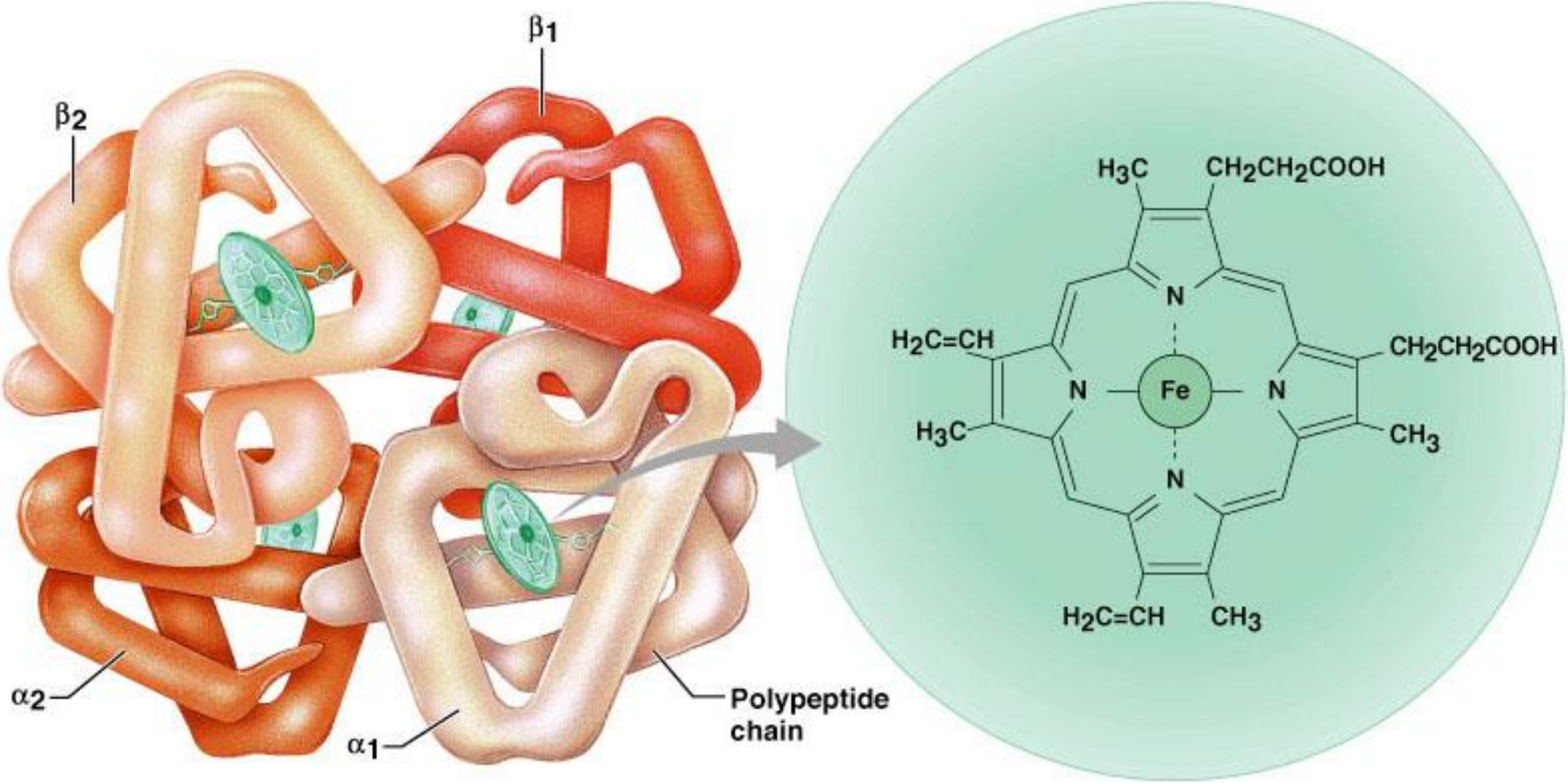
Each heme group bears an atom of iron

bind to one oxygen molecule

Each hemoglobin molecule can transport four molecules of oxygen

280 million hemoglobin molecules in each RBC

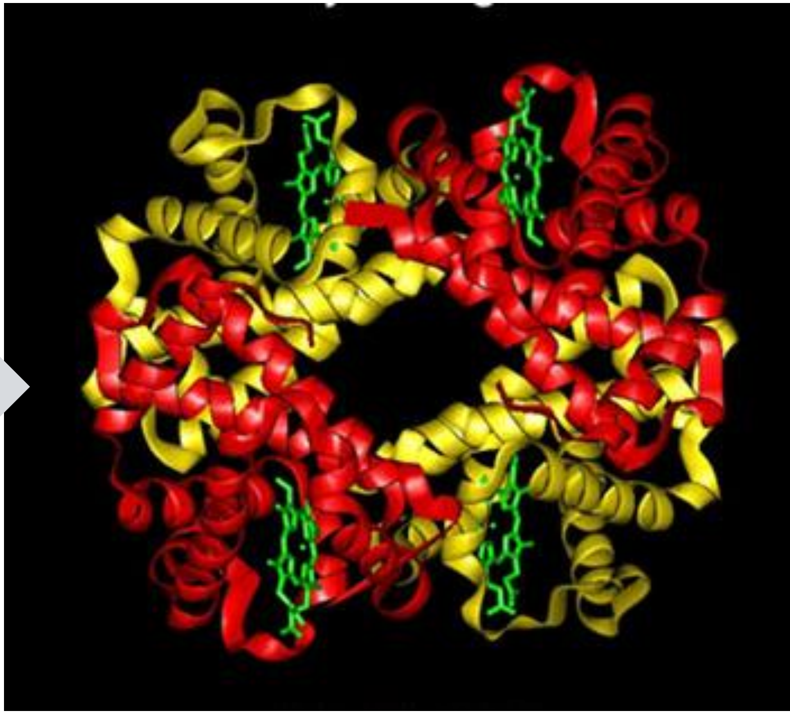
Structure of Hemoglobin



(a) Hemoglobin (b) Iron-containing heme group

Haemoglobin

- Gives RBC their color
- Can carry up to 4 molecules of O_2
- Associates and dissociates with O_2
- Contains iron



Properties of Hemoglobin

Stucture

Quaternary structure: (α2ß2)

Each subunit is: 1 Heme + 1 globin

Each heme contains 1 iron (2+ ↔ 3+)

Function

Oxygen binding and transport

CO_2 binding and transport

Hemoglobin levels

infants: 140-200 g/l

Adult males:
140-180 g/l

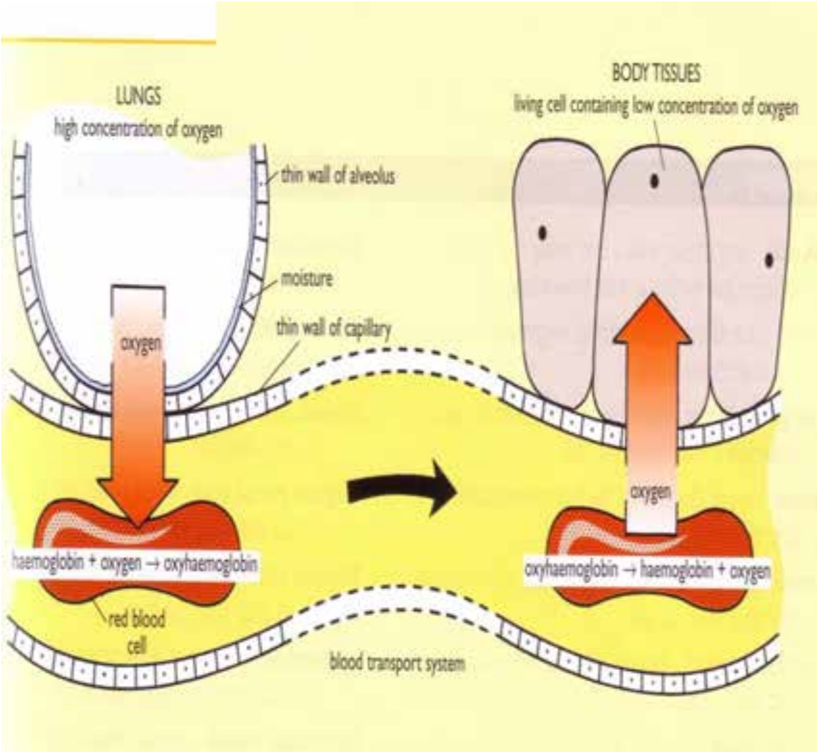
Adult females:
120-160 g/l

Function of Haemoglobin

Blood reaches the tissue

Tissue have low concentration of oxygen, hemolglobin separate

Oxygen is released into tissues

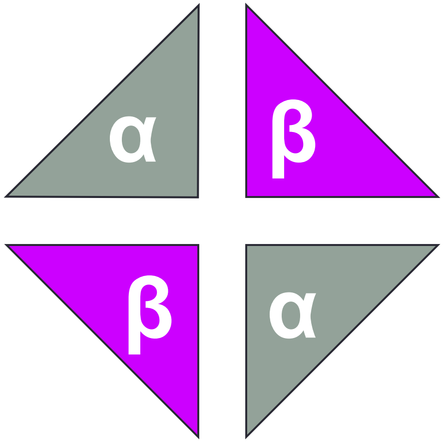


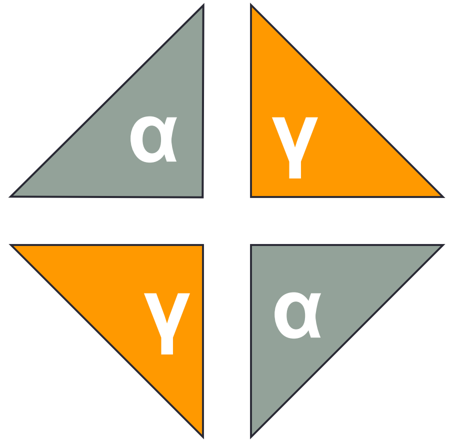
Haemoglobin: the key to successful gas carriage

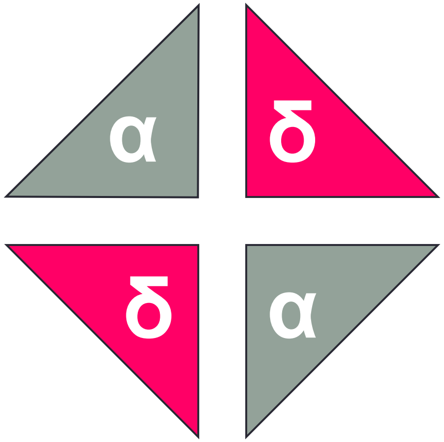
Four different globin chains: a, b, g and d

Adult haemoglobin A HbA	Fetal haemoglobin HbF	Haemoglobin A2 HbA2
a2b2	a2g2 greater affinity for oxygen than HbA	a2d2
	Facilitates the transfer of oxygen from the maternal blood to the fetal blood HbF greater oxygen saturation than adult haemoglobin for a given PO2	2-3% of adult

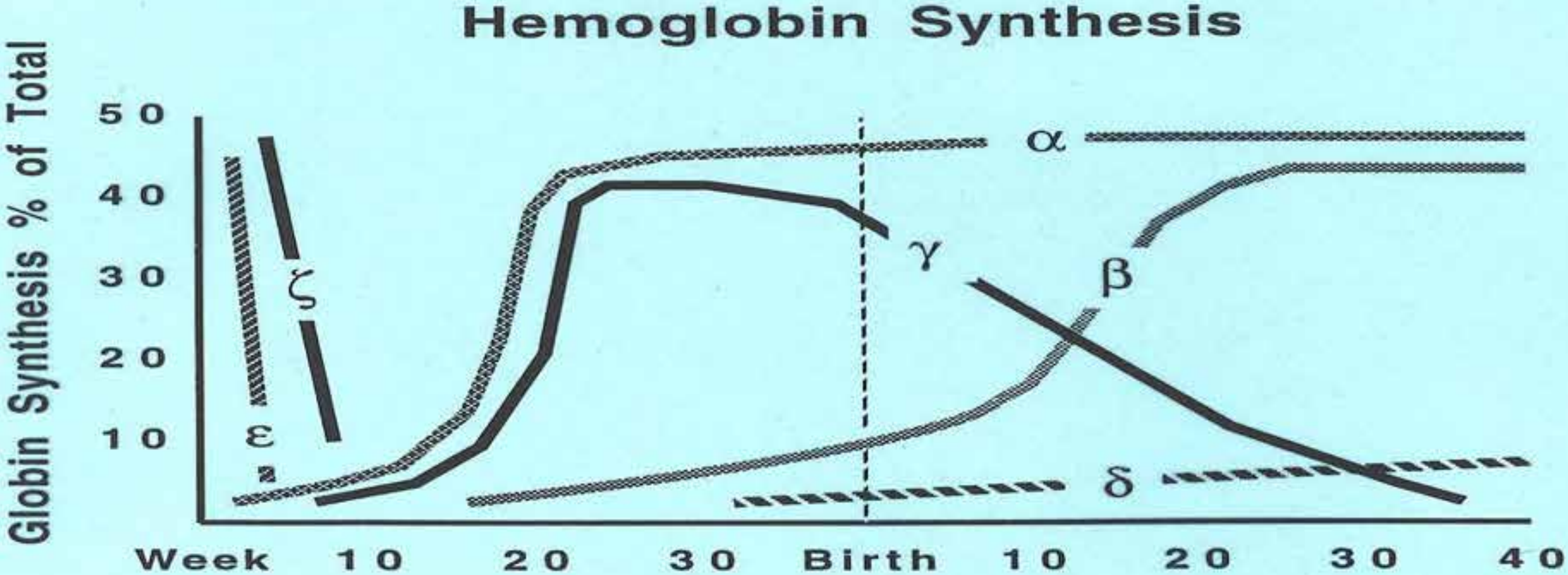
Hb in Adults







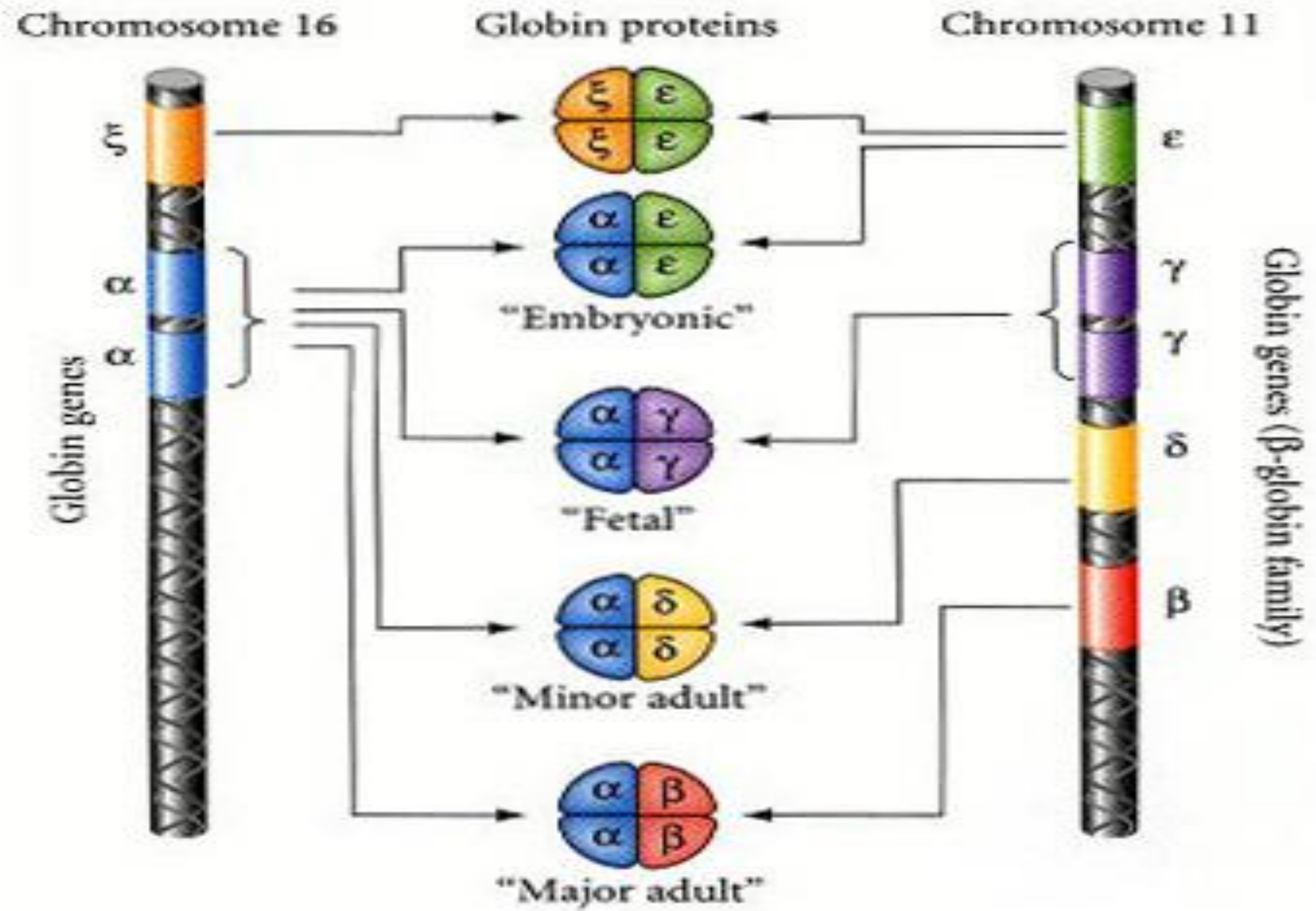
HbA	HbF	HbA_2
98%	~1%	<3.5%



		Adult	Newborn
α2β2	Hb A	97 %	20 %
α2δ2	Hb A2	2.5	<0.5
α2γ2	Hb F	<1	80

Embryonic:

ζ2ε2	Gower-1
α2ε2	Gower-2
ζ2γ2	Portland


Chromosome 16
Globin proteins
Chromosome 11
ξ
α
α
Globin genes
ε
γ
γ
δ
β
Globin genes (β-globin family)
ξ ε ξ ε
α ε α ε
"Embryonic"
α γ α γ
"Fetal"
α δ α δ
"Minor adult"
α β α β
"Major adult"

Metabolic Pathways

Energy required for maintenance of

Cation pumps	Hb in reduced state	RBC integrity and deformability

Limited

Production of Erythrocytes

Hematopoies

Red blood cell formation

Occurs in the red bone marrow of the :

- Epiphyses of the humerus and femur
- Axial skeleton and girdles

Hemocytoblasts

- give rise to all formed elements
- 100 billion blood cells/day

Production of Erythrocytes

Embryonic blood cells

- third week of gestation
- vessels of the yolk sac
- first 8 weeks

As organs develop

- Embryonic blood cells migrate to the liver, spleen, thymus and bone marrow
- where they differentiate into stem cells

From 2 to 5 months of gestation

- the liver and, to a lesser extent, the spleen are the primary sites of erythropoiesis

Production of Erythrocytes

As the skeleton matures

- Red bone marrow gradually takes over as the major site of erythrocyte production

In children

- Axial skeleton (skull, vertebrae, ribs, sternum, scapulae and pelvis)
- the bones of the extremities.

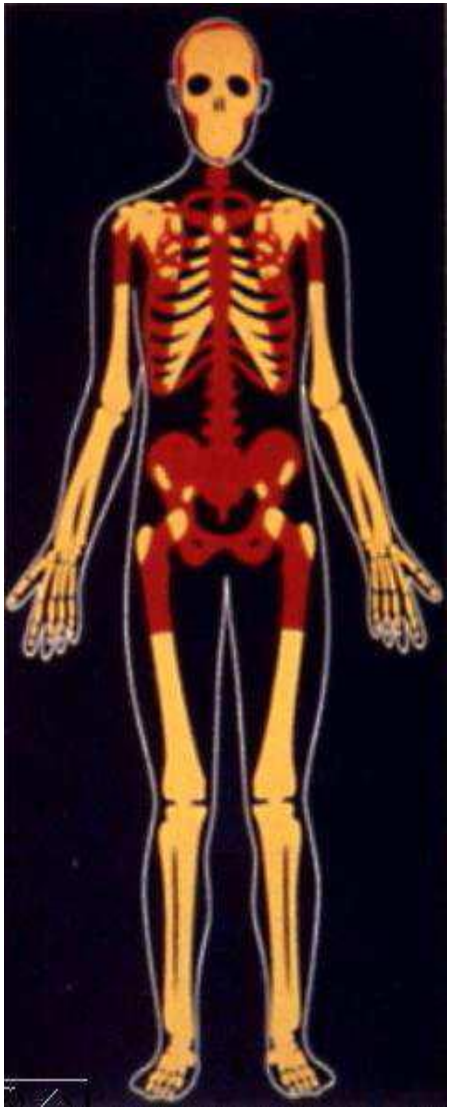
In adults

- Axial skeleton
- Proximal ends of the femur and humerus

Originate from red bone marrow

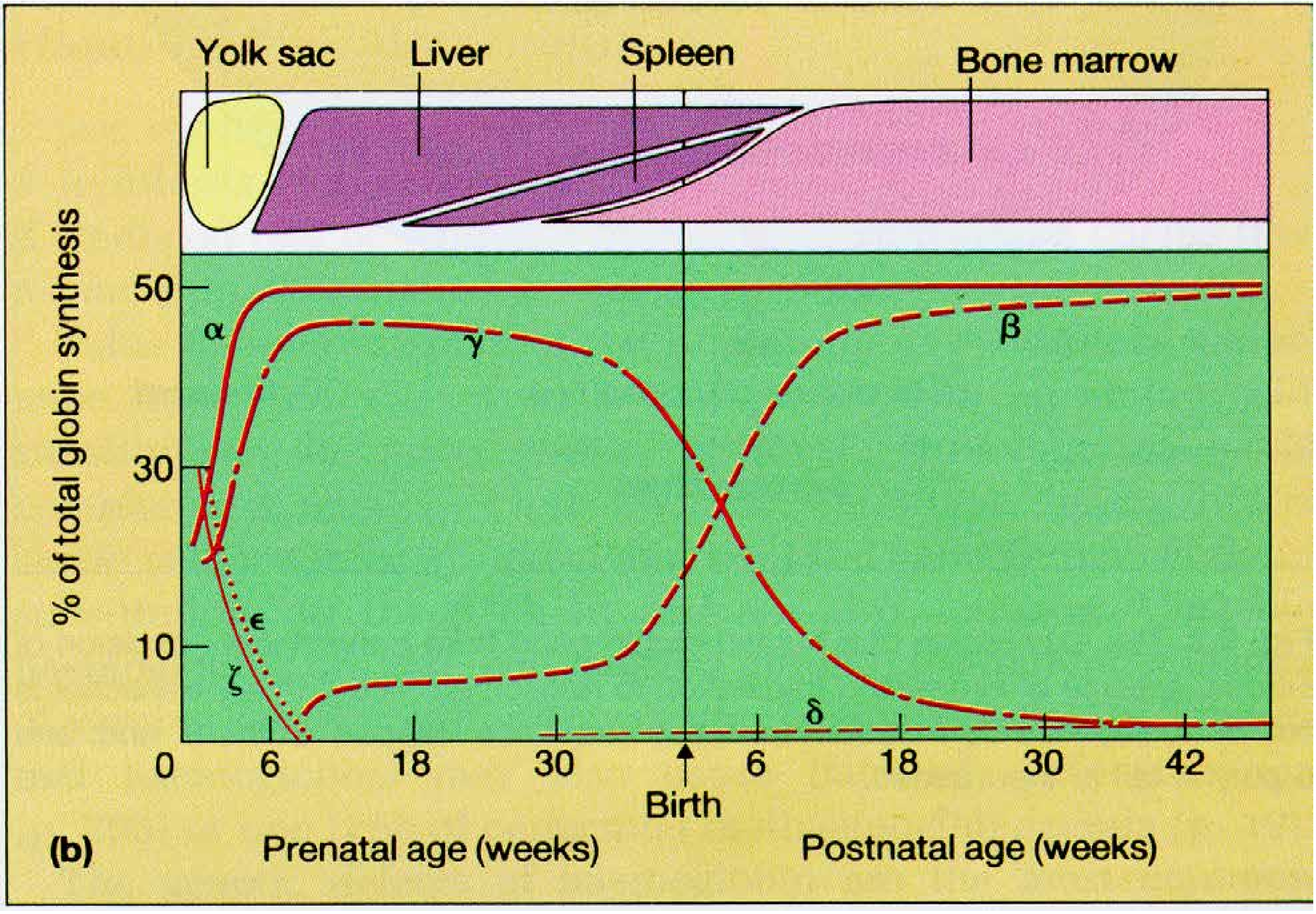
Emryo

- yolk sac
- liver



Adults

- **Flat bones:** hip bone, breast bone, skull, ribs, vertebrae and shoulder blades
- **"Spongy" material** at the proximal ends of the long bones **femur and humerus.**


Yolk sac
Liver
Spleen
Bone marrow
% of total globin synthesis
50
30
10
0
α
γ
β
ε
ζ
δ
6
18
30
6
18
30
42
Birth
(b)
Prenatal age (weeks)
Postnatal age (weeks)

Production of Erythrocytes

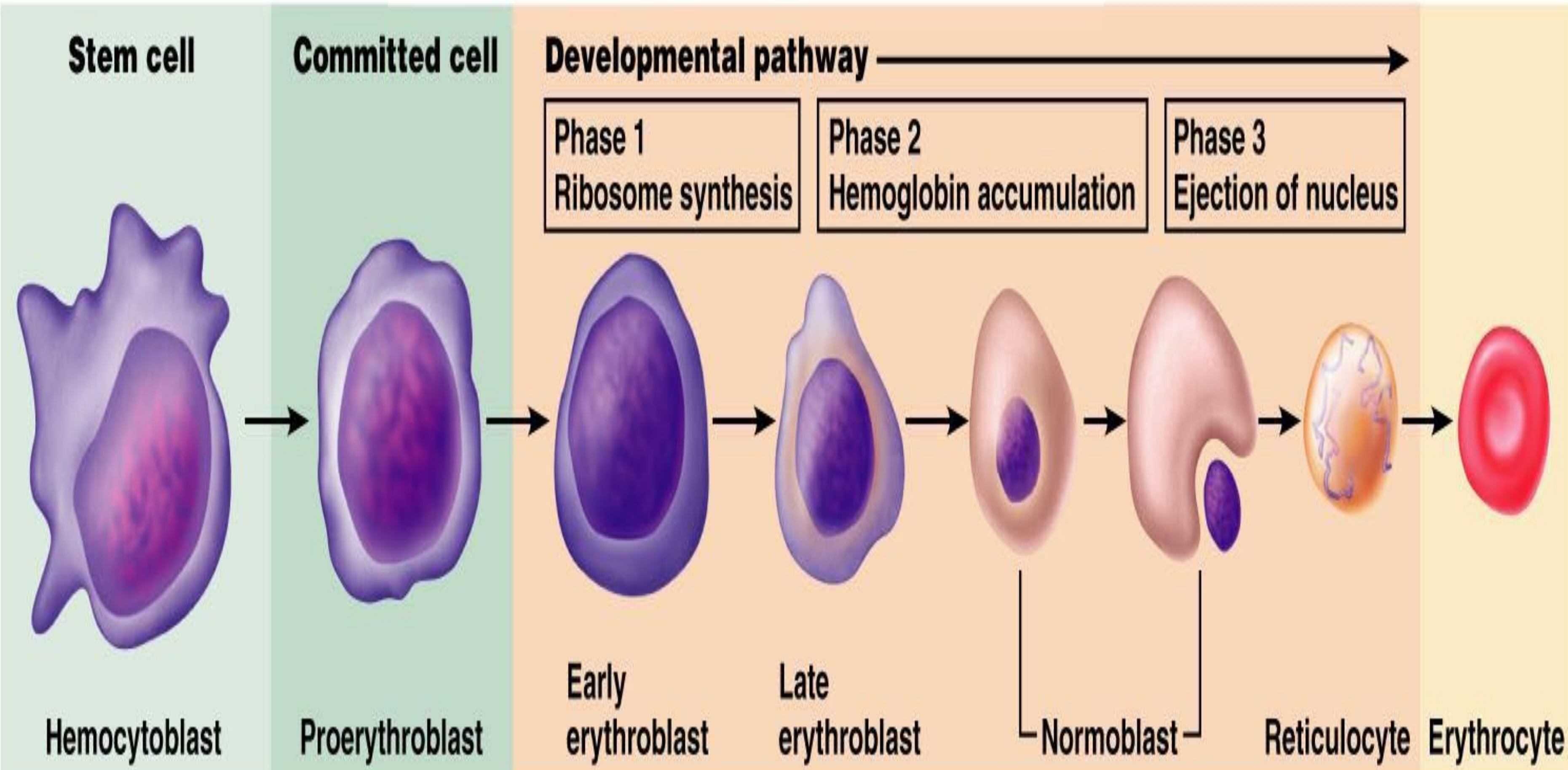
Erythropoiesis

- **Stimulated by** the hormone erythropoietin
- Produced by the kidney in response to a reduction in PO2

Under conditions of severe blood loss

- Yellow bone marrow found in other bones may convert to red marrow in order to increase erythrocyte production

Production of Erythrocytes: Erythropoiesis



7 days process
2.5 million RBC/s

Reticulocytes

Less Mature Erythrocytes

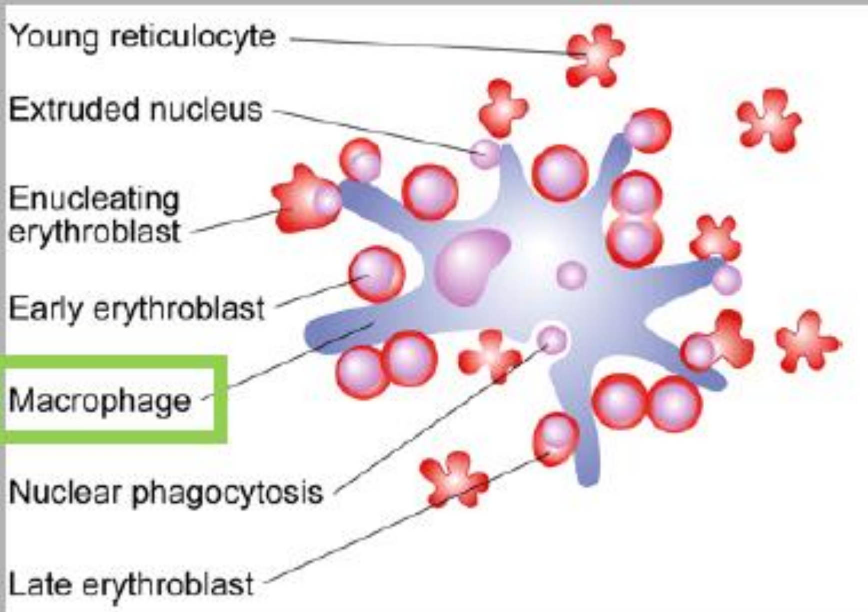
1-2 days in the circulation

Cytology

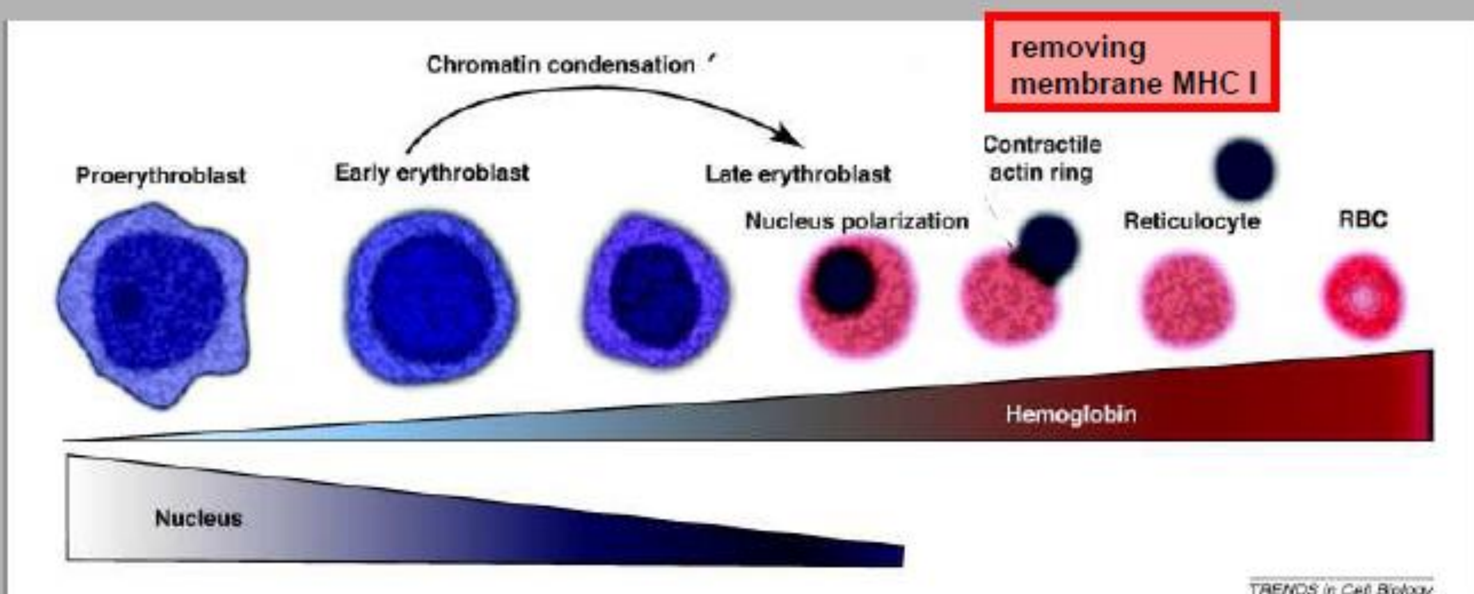
- Slightly larger than the older RBCs
- Have slightly more RNA
- Slightly bluish staining (polychromasia).
- Staining with a supravital dye (stains RNA)

Frequency

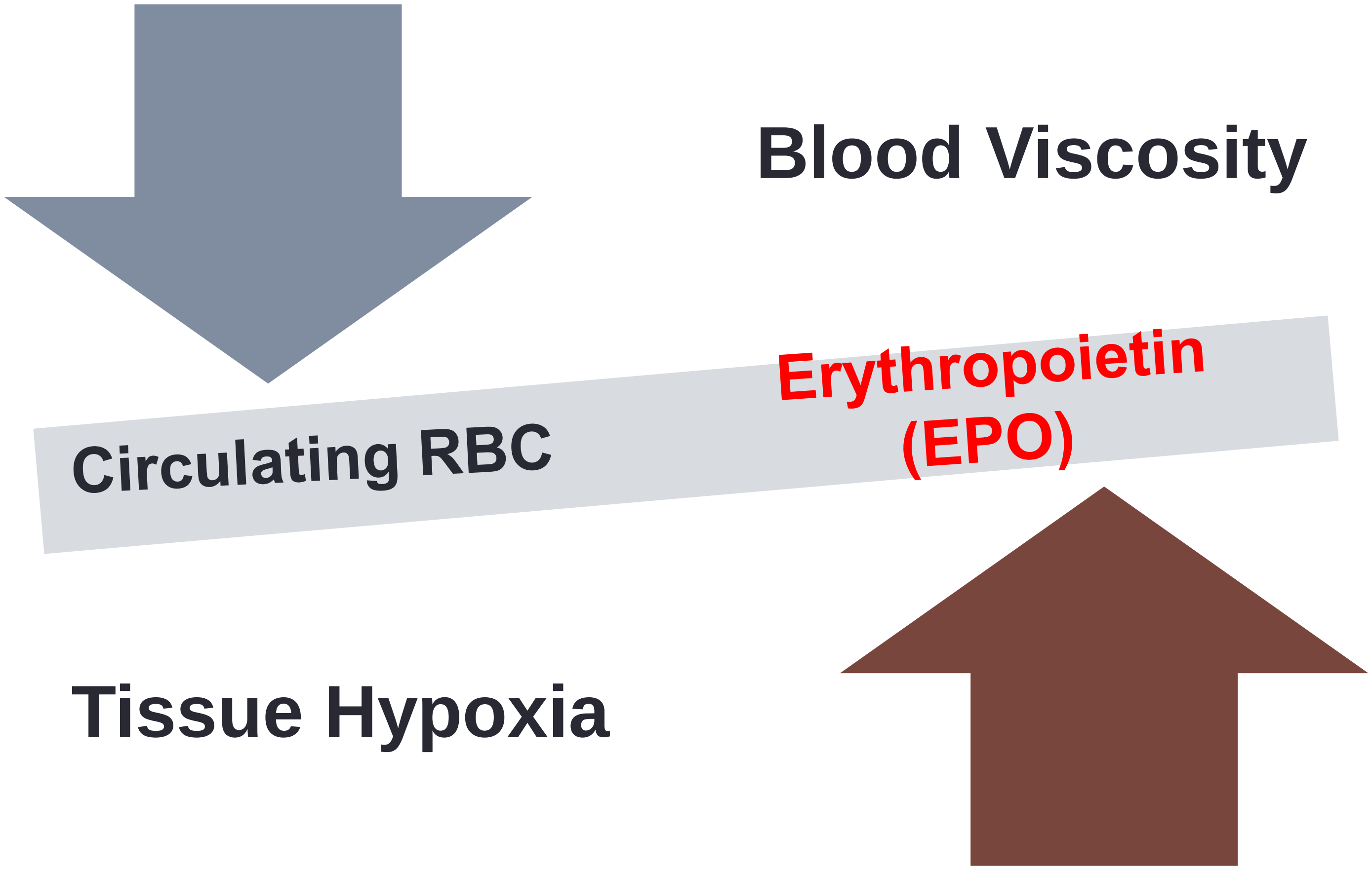
- 1-2% of RBCs
- increased : blood loss
- leukemia or metastatic cancer :bone marrow not be able to respond appropriately



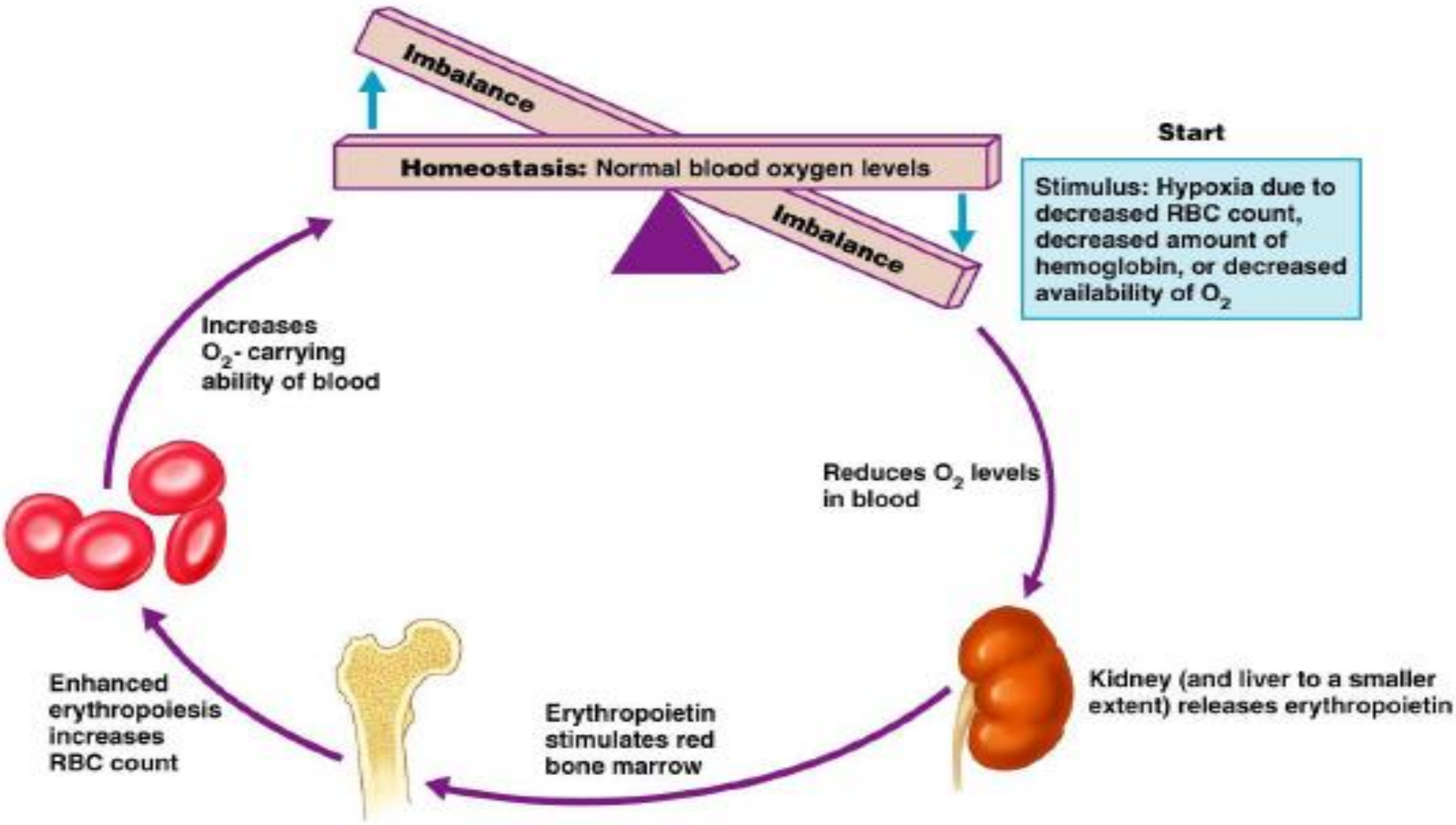
reticular (mesh-like) ribosomal RNS

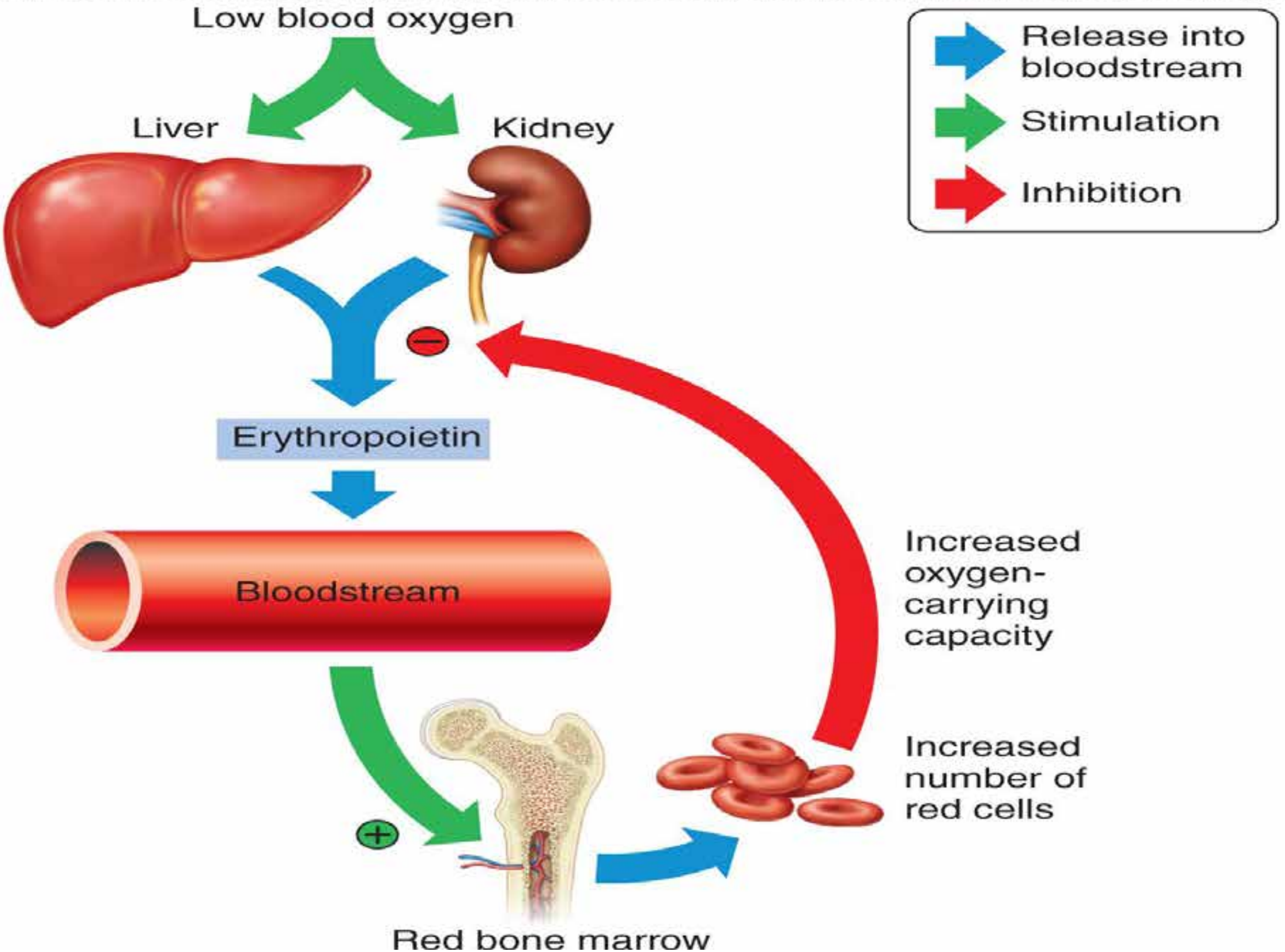


Erythropoiesis Regulation

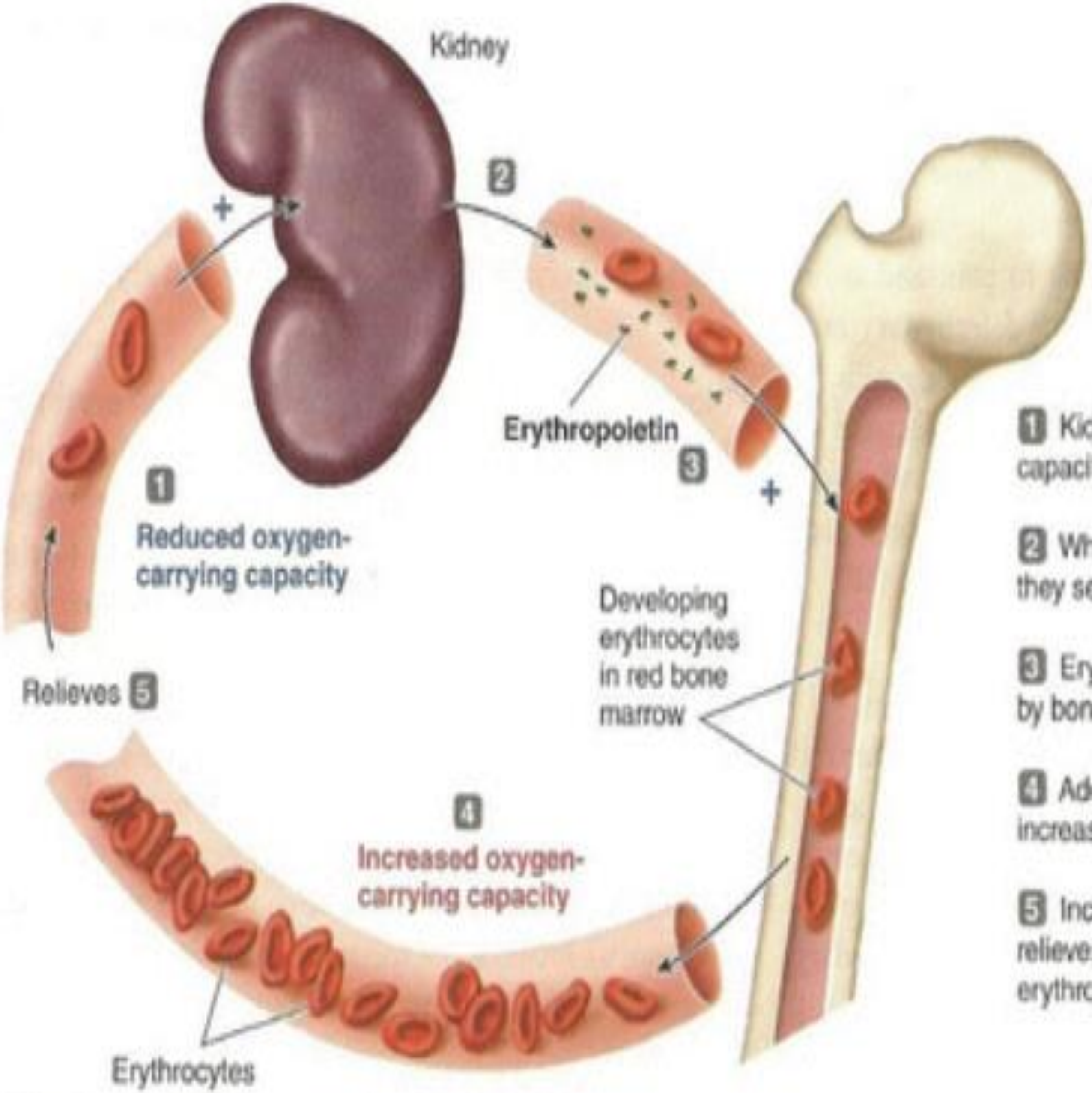


Erythropoietin Mechanism





Low blood oxygen
Liver
Kidney
Release into bloodstream
Stimulation
Inhibition
Erythropoietin
Bloodstream
Increased oxygen-carrying capacity
Increased number of red cells
Red bone marrow



1 Kidneys detect reduced O_2-carrying capacity of blood.

2 When less O_2 is delivered to the kidneys, they secrete erythropoietin into blood.

3 Erythropoietin stimulates erythropoiesis by bone marrow.

4 Additional circulating erythrocytes increase O_2-carrying capacity of blood.

5 Increased O_2-carrying capacity relieves initial stimulus that triggered erythropoietin secretion.

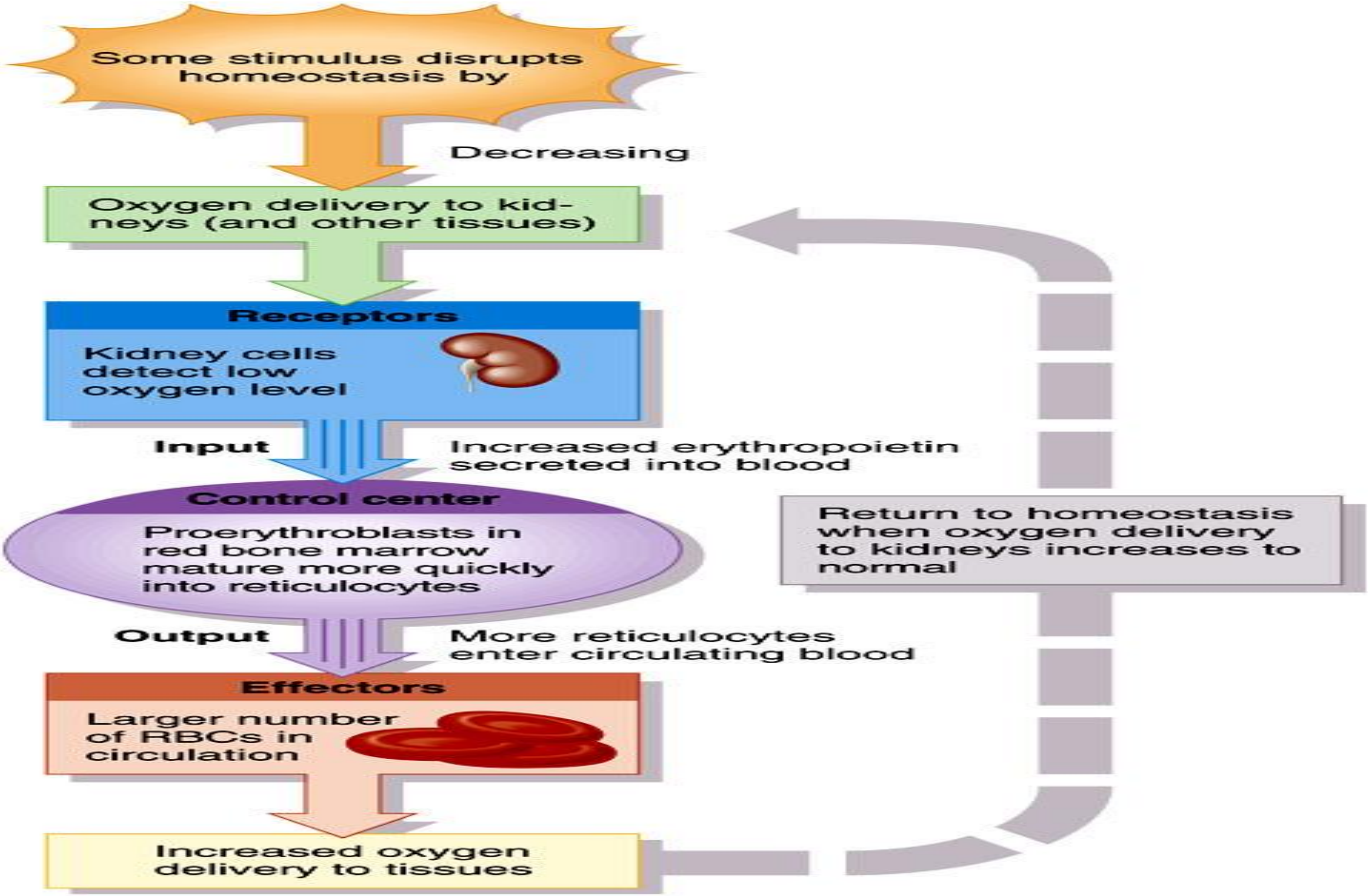


Figure 19.06 Tortora - PAP 12/e

Proteins

Lipids

Carbohydrates

Vitamins B12

Folic Acid

DNA Synthesis

Iron

Hemoglobin synthesis

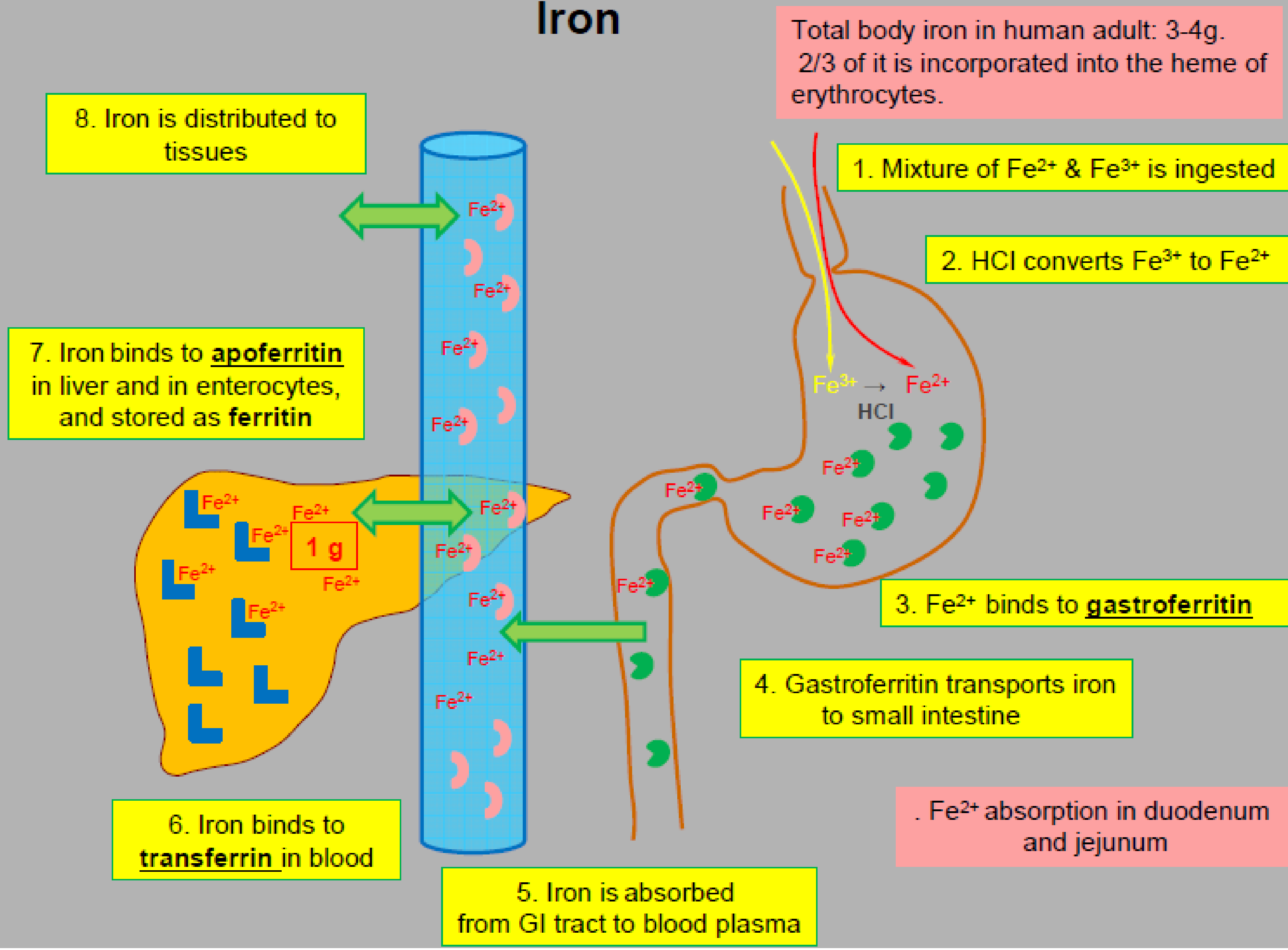
Most of the iron comes from recycling old RBC

The body stores iron in Hb (65%), the liver, spleen, and bone marrow

Intracellular iron is stored in protein-iron complexes such as **Ferritin** and **Hemosiderin**

Circulating iron is loosely bound to the transport protein **transferrin**

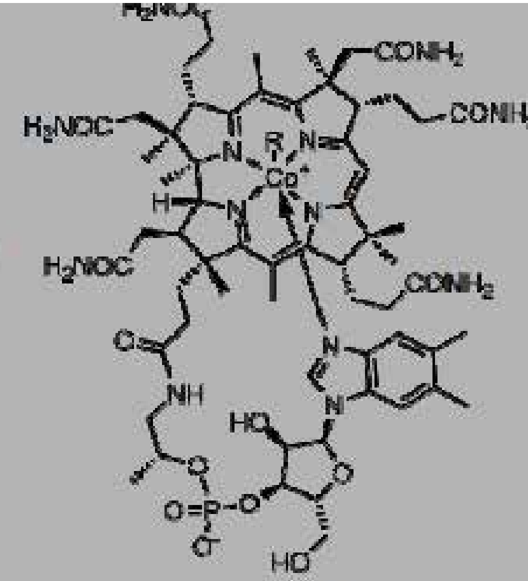
Erythropoietic factors 2: Iron



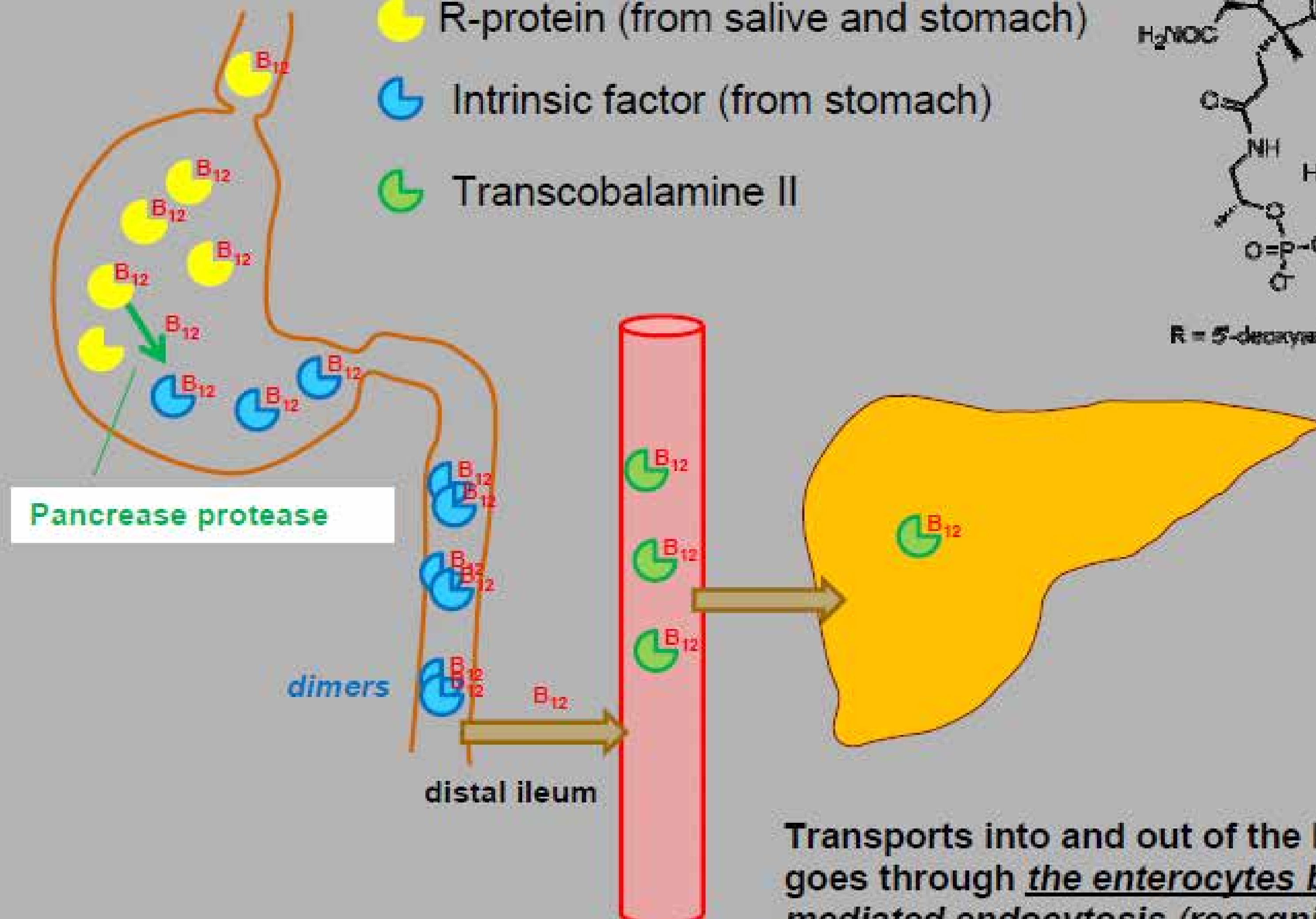
Vitamin B12 (cobalamine)

- water soluble
- Only some bacteria and protozoa are able to synthesize (importance of colon bacteria!)
- Plants do not contain (VEGETARIANS!)
- Meat, liver, egg, milk
- Nicotine reduces the absorpion (smoking!)
- Daily requirement:1-2ug
- Stored in liver (3-6 years)

Erythropoietic factors 3: Vitamin B_{12} (cobalamine)



R = 5'-deoxyadenosyl, Me, OH, CN



Transports into and out of the blood stream goes through *<u>the enterocytes by receptor-mediated endocytosis (recognizes dimers!)</u>*

Fate and Destruction of Erythrocytes

RBC Life span

- **100–120 days**

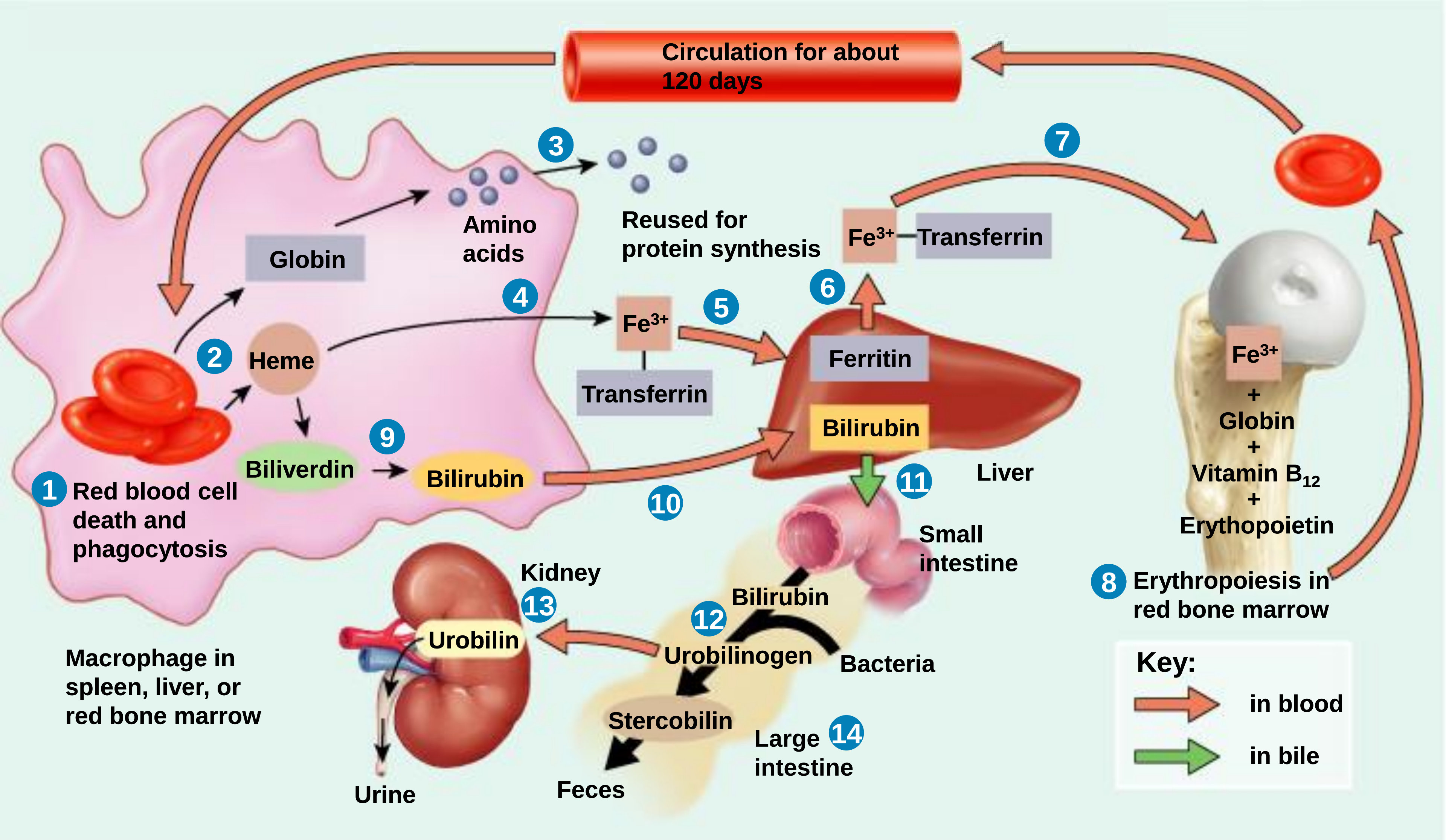
Turnover of RBC is high

- **1% replaced per day**

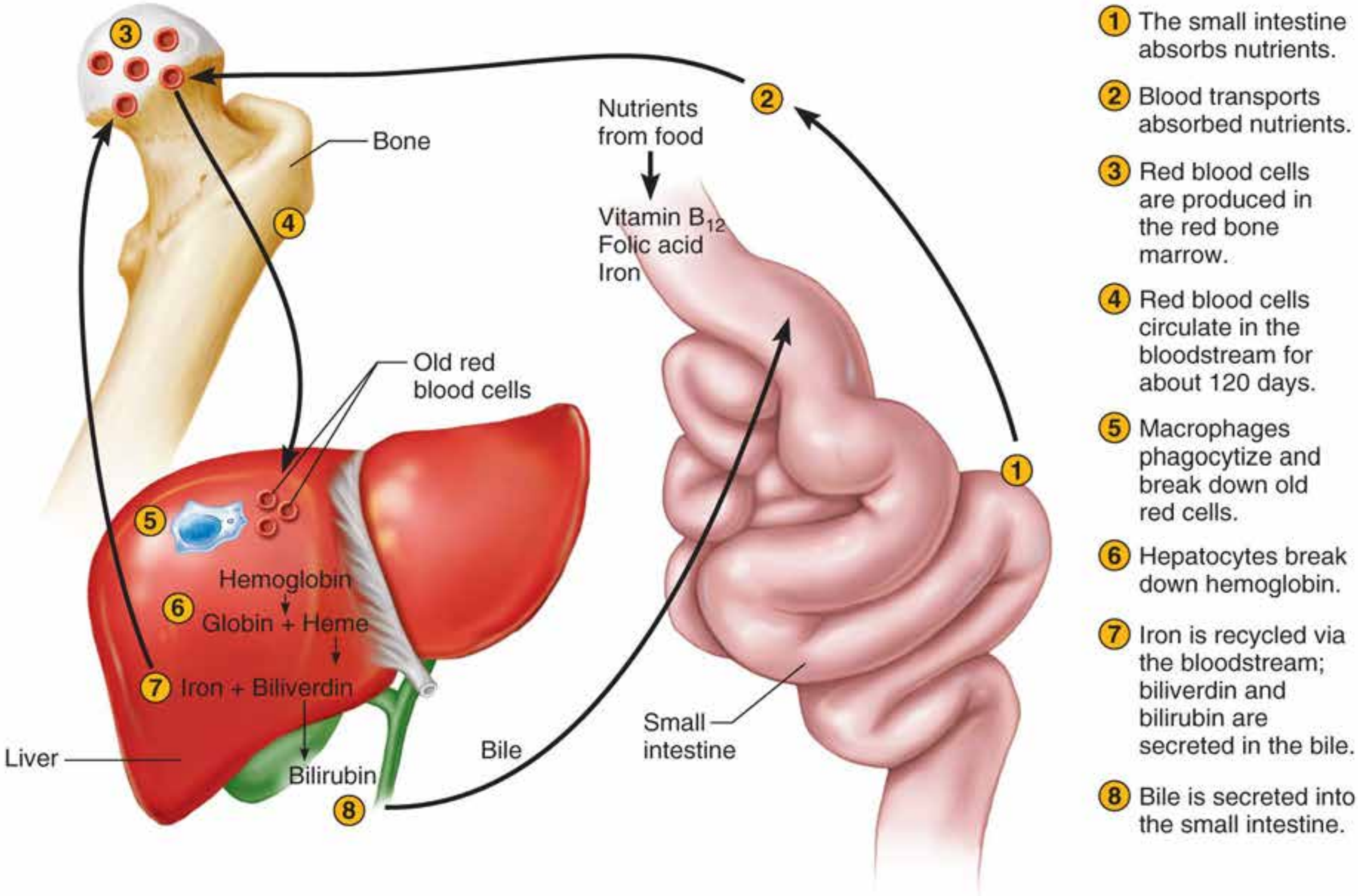
With age

- RBC become increasingly fragile
- Damaged by passing through narrow capillaries
- Macrophages in the liver and spleen phagocytize damaged RBC

Formation and Destruction of RBC's



Formation and Destruction of RBC's



Major Events in RBC Destruction

1. Squeezing through the capillaries of active tissues damages red blood cells.
2. Macrophages in the spleen and liver phagocytize damaged red blood cells.
3. Hemoglobin from the red blood cells is decomposed into heme and globin.
4. Heme is decomposed into iron and biliverdin.
5. Iron is made available for reuse in the synthesis of new hemoglobin or is stored in the liver as ferritin.
6. Some biliverdin is converted into bilirubin.
7. Biliverdin and bilirubin are excreted in bile as bile pigments.
8. The globin is broken down into amino acids metabolized by macrophages or released into the plasma.

Properties of RBC (Erythrocytes)

Concentration in blood is 4-6 million/cubic mm (4-6 T/l)

- Gender differences
- High individual variability

Morphoplogy: biconcave discs

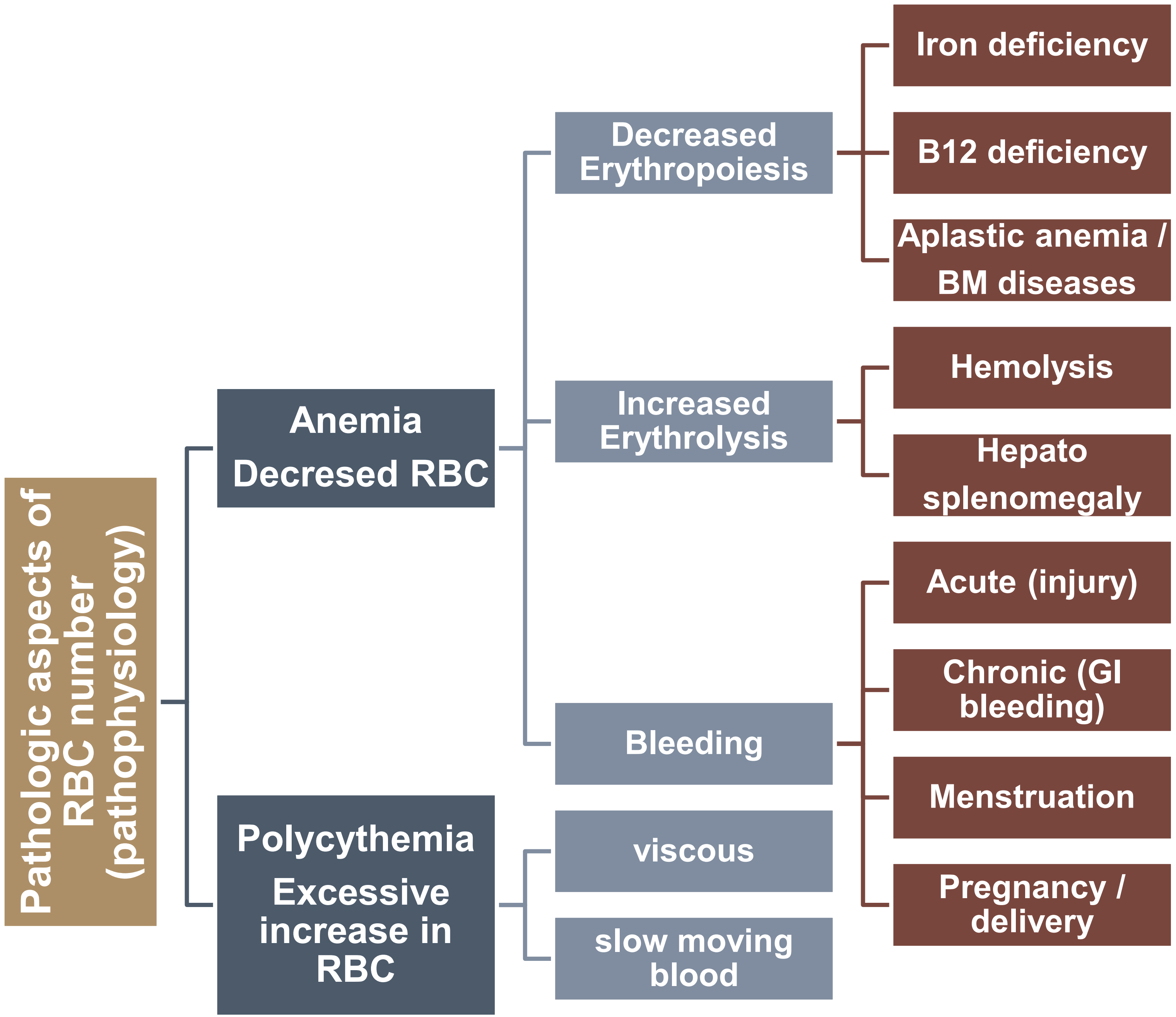
- Large surface area
- Enables cells to bend in small capillaries

Main characteristics: reduced cell

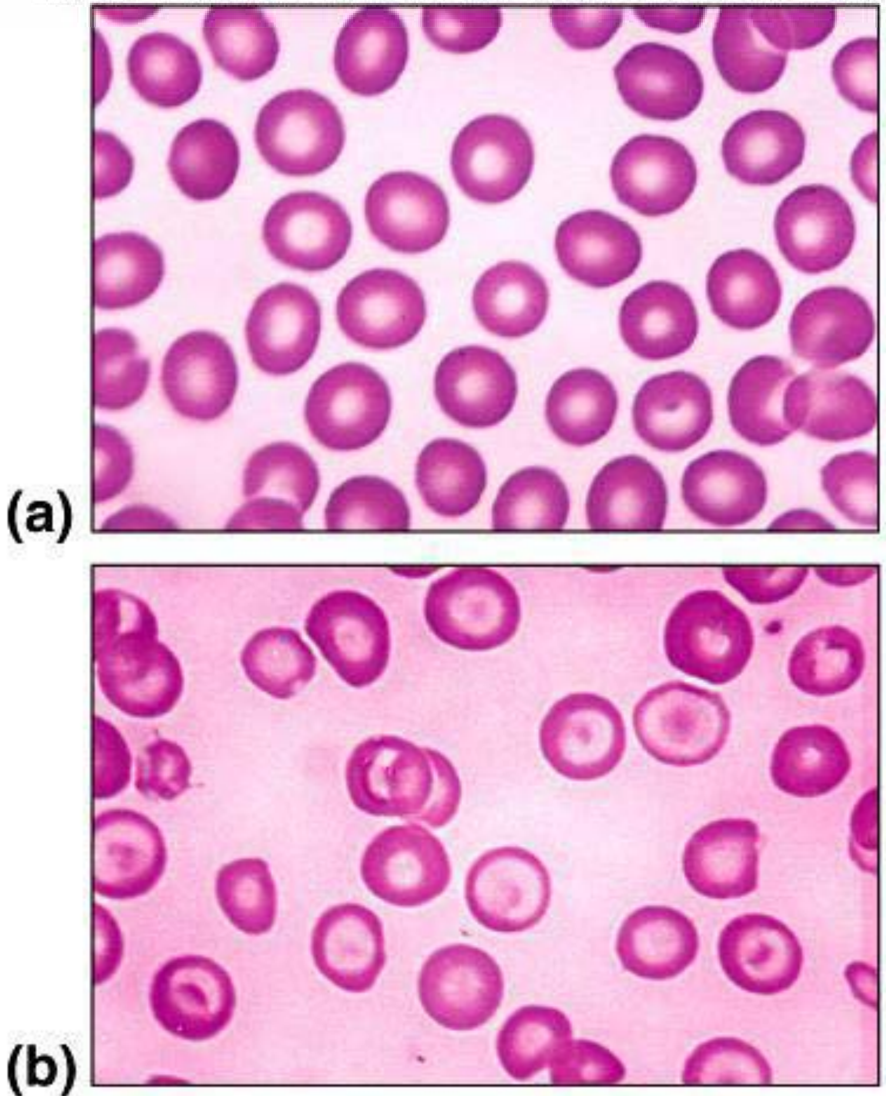
- No nucleus → cannot reproduce
- No mitochondria → no metabolism
- No ribosomes → no protein synthesis

Function

- Transport hemoglobin
- 280 million hemoglobin molecules/cell


Pathologic aspects of RBC number (pathophysiology)
Anemia
Decresed RBC
Polycythemia
Excessive increase in RBC
Decreased Erythropoiesis
Increased Erythrolysis
Bleeding
viscous
slow moving blood
Iron deficiency
B12 deficiency
Aplastic anemia / BM diseases
Hemolysis
Hepato splenomegaly
Acute (injury)
Chronic (GI bleeding)
Menstruation
Pregnancy / delivery

Normal Erythrocytes vs. Hypochromic Anemia



Anemia

Definition	• Significant reduction in the total body RBC mass • Measured as a reduction in the RBC count, the hemoglobin, and the hematocrit • Anemia exists when the hemoglobin is less than 12 g/dL or the hematocrit is less than 37%. • A deficiency of RBCs, which can be caused by either too rapid loss or slow production
Classification **Cytometric schemes**	• Microcytic • Macrocytic • Normocytic
Classification **Erythrokinetic schemes**	• Rates of RBC production and destruction
Classification **biochemical/molecular schemes**	• Etiology of the anemia at the molecular level

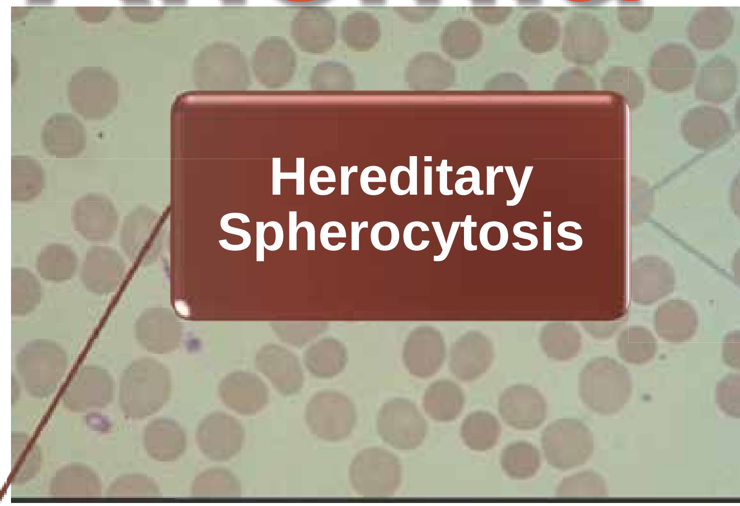
Anemia

Blood loss Anemia	• Due to hemorrhage, plasma is replaced in 1-3 days, but, RBC replacement takes longer
Microcytic Hypochromic Anemia	• Low levels of hemoglobin in RBCs due to chronic blood loss resulting in low Fe^{3+} levels in newly produced RBCs
Aplastic Anemia	• Decreased RBC production in bone marrow due to chemical, drug, or radiation exposure
Pernicious Anemia	• Chronic illness caused by impaired absorption of Vitamin B-12 because of a lack of intrinsic factor (IF) in gastric secretions. Vitamin B12, in turn, is necessary for the formation of red blood cells.

Anemia

Hemolytic Anemia

Different abnormalities of RBCs that make RBCs fragile and rupture easily



Hereditary Spherocytosis

- RBC develop as small spherical cells rather than being biconcave.
- These spherical cells easily rupture by slight compression

Sickle-cell Anemia

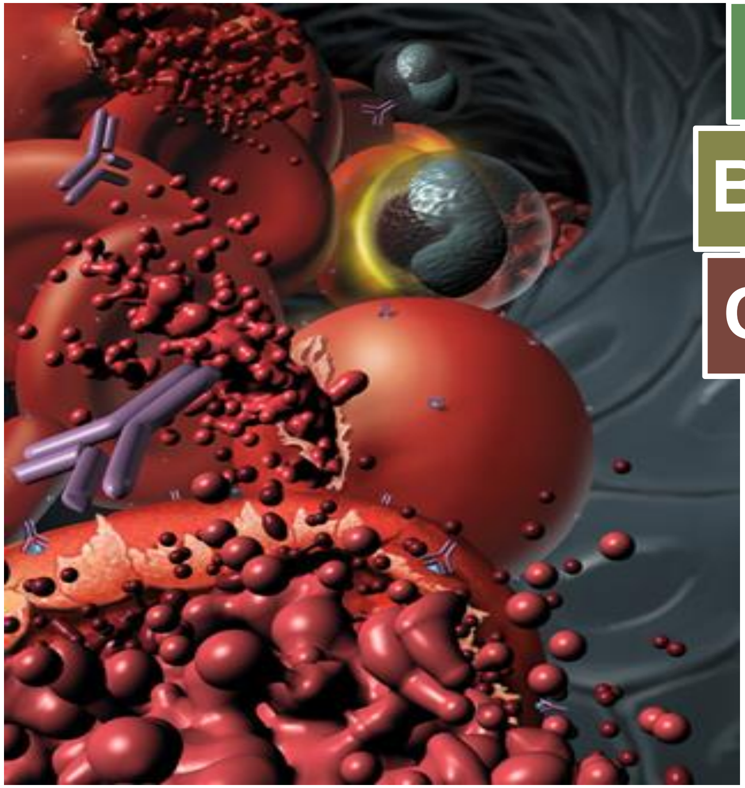
- Genetic mutation causing abnormal beta chains
- When this hemoglobin is exposed to low O2 concentrations

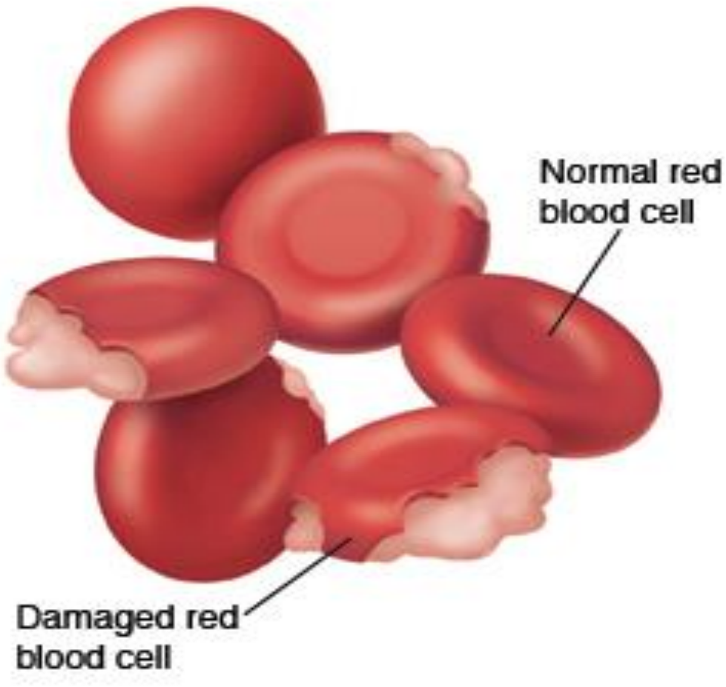
  precipitates into long crystals

  cause the cells to become sickle-shaped

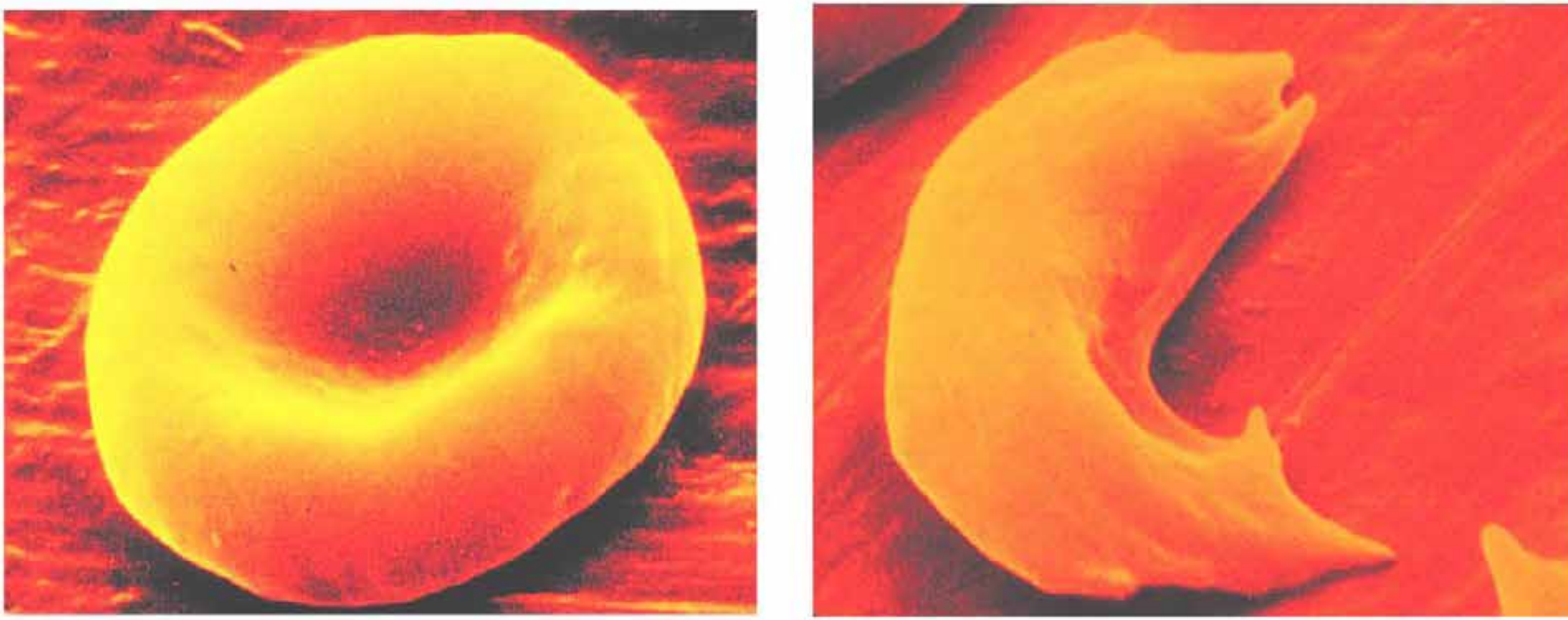
Types of Hemolysis of Erythrocytes

- Osmotic
- Mechanical
- Thermal
- Biological
- Chemical





Normal versus sickled erythrocyte



(a) (b)

Some Types of Anemia

Type	Cause	Defect
Aplastic anemia	Toxic chemicals, radiation	Damaged bone marrow
Hemolytic anemia	Toxic chemicals	Red blood cells destroyed
Iron deficiency anemia	Dietary lack of iron	Hemoglobin deficient
Pernicious anemia	Inability to absorb vitamin B_{12}	Excess of large, fragile cells
Sickle cell disease	Defective gene	Red blood cells abnormally shaped
Thalassemia	Defective gene	Hemoglobin deficient; red blood cells short-lived

Haemoglobin: the key to successful gas carriage

α chains : chromosome 16(4 α genes)

Non-α genes: chromosome 11

Defects in globin chain synthesis(deletions or mutations) = Thalassaemia

α thalassaemia: deletion of one to four of the a genes

Deletion of all four a genes is fatal

Non-α thalassaemias : gene deletion or transcription failures.

Outcome: Reduction in oxygen-carrying capacity of the haemoglobin