بِسْمِ اللهِ الرَّحْمٰنِ الرَّحِيمِ

رَبِّ زِدْنِي عِلْمًا

- اللَّهُمَّ أرِنِى حَقِيقَةَ الْاَشْيَآءَ كَمَا هِىَ

"O Allah! Show me the reality of all things as it (really) is.."

PREVENTION IS BETTER THAN CURE

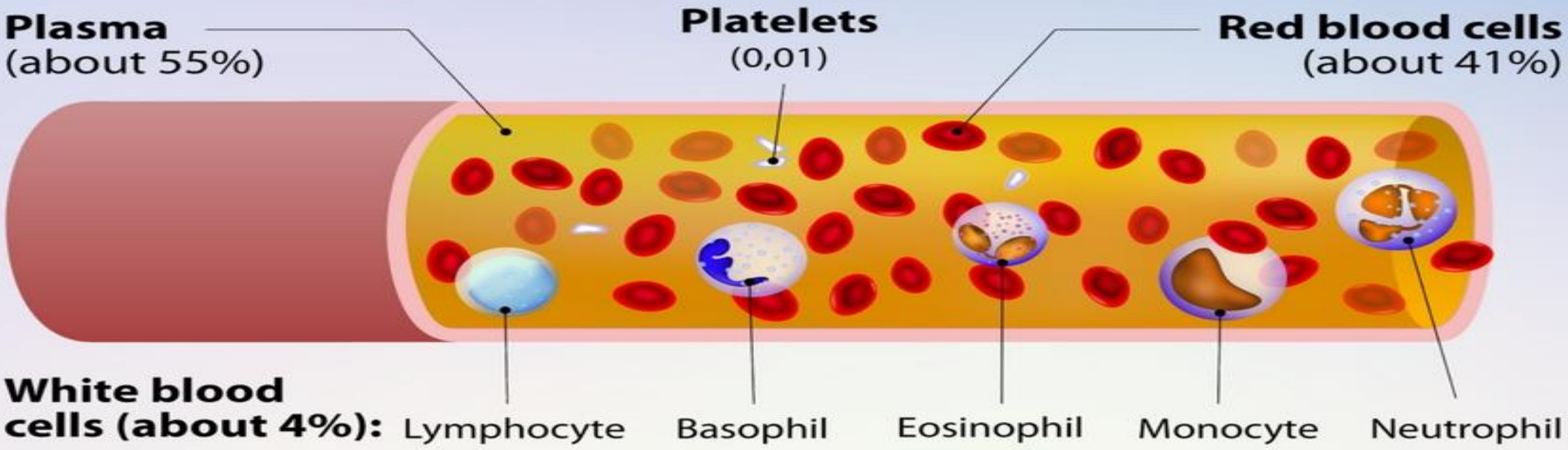
BLOOD Physiology

Tayyab Hamid (MBBS, PhD)
LECTURER in Physiology

Contents

WHAT IS BLOOD?

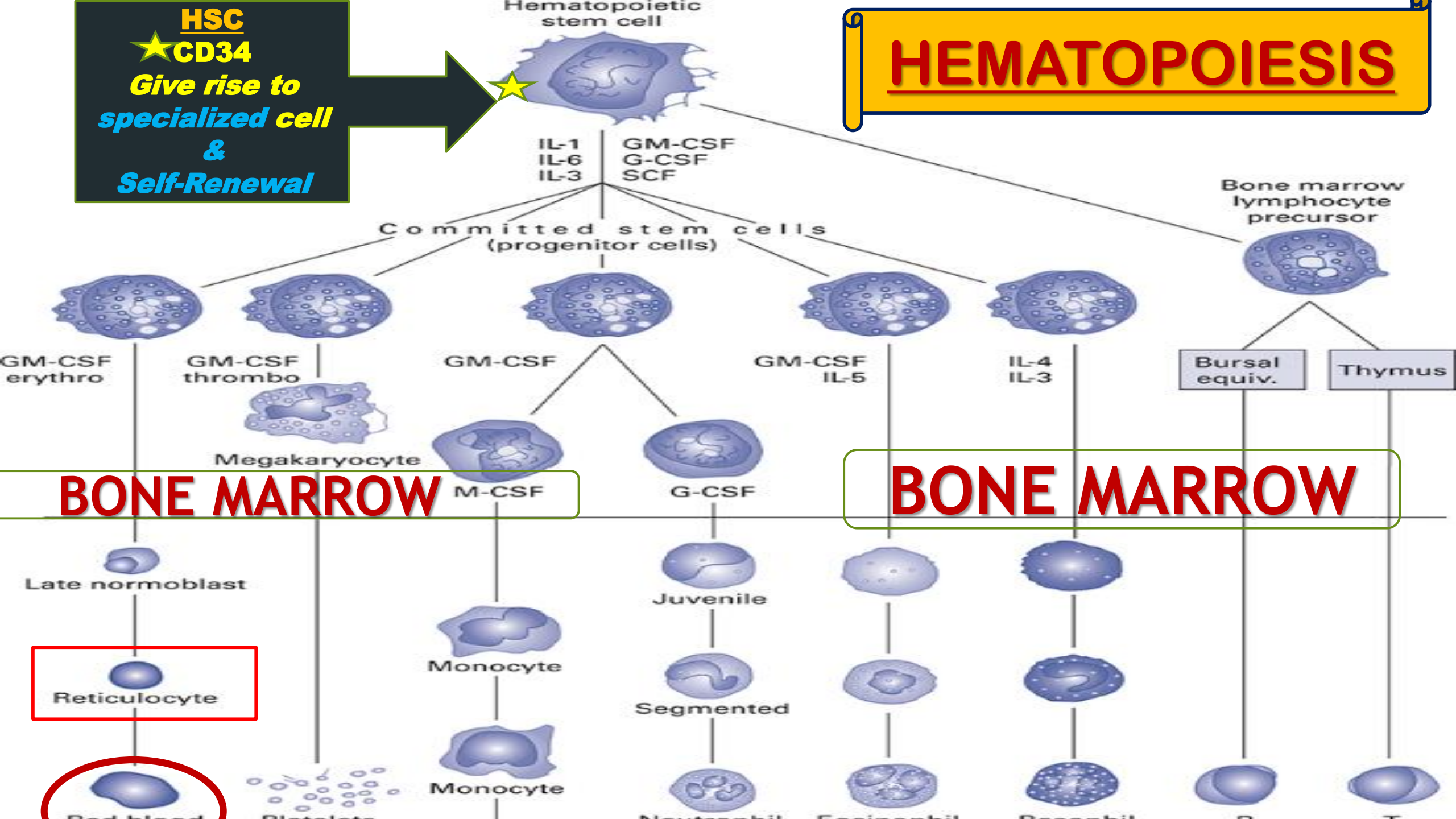
BLOOD & ITS COMPONENTS



BLOOD IS THE **ORIGINAL** HEALER

HEMATOPOIESIS

HSC
★**CD34**
Give rise to specialized cell & Self-Renewal



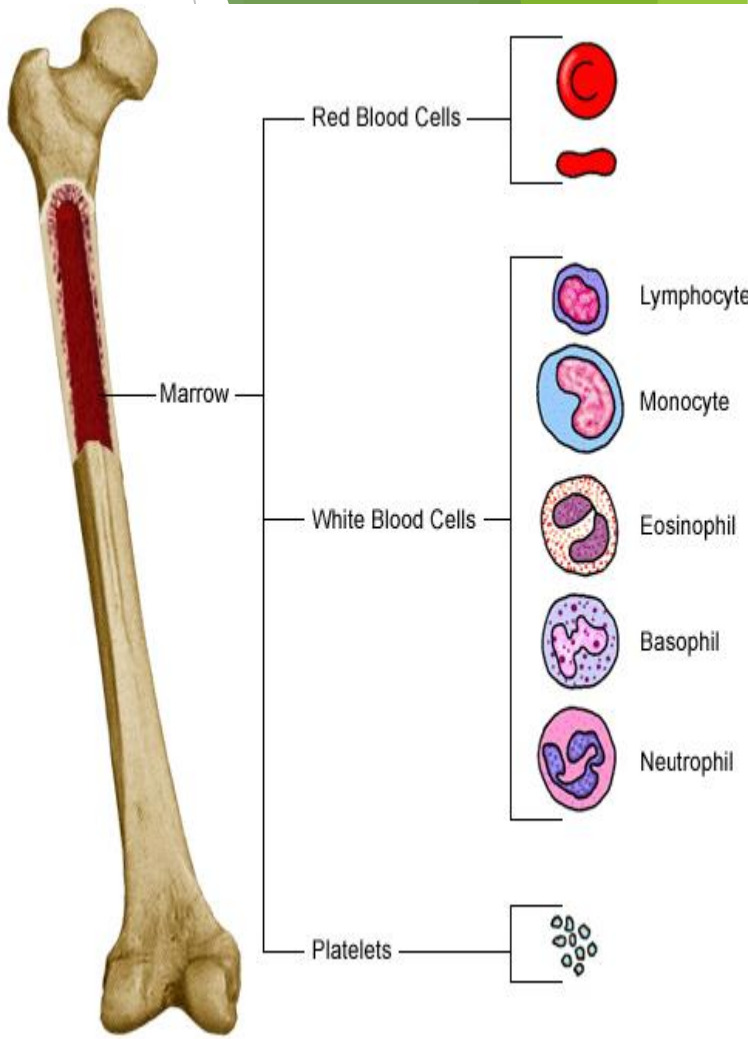
HEMATOPOIESIS, ERYTHROPOIESIS & ERYTHROPOIETIN

HEMATOPOIESIS : production of all of the cellular components of blood)

ERYTHRPPOIESIS: erythrocyte/RBC production

LEUCOPOIESIS: leucocyte production

THROMBOPOIESIS: platelet/thrombocyte production



HEMATOPOIESIS, ERYTHROPOIESIS & ERYTHROPOIETIN

ERYTHROPOIESIS: erythrocyte/RBC production

Mature RBCs result from finely regulated process (differentiation and maturation) called **ERYTHROPOIESIS** that produces 2 million RBCs in healthy human adults (Palis, 2014)

In Fetus : Liver and Spleen
In Adults: Bone marrow

With Increasing Age Bones become less productive

M E N
1. Marrow
2. Erythropoietin
3. Nutrients (Iron, B12 and Folic Acid)

HEMATOPOIESIS, ERYTHROPOIETIN

Erythop

- Epo is a horm … ell production
- renal erythro …) are interstitia … cortex and ou …
- Epo is assisted by testosterone and cortisol in stimulating eryhthropoiesis

Kidney

↓

☆Epo

↓

Receptors on eryhtroid progenitor cells

↓

RBC production

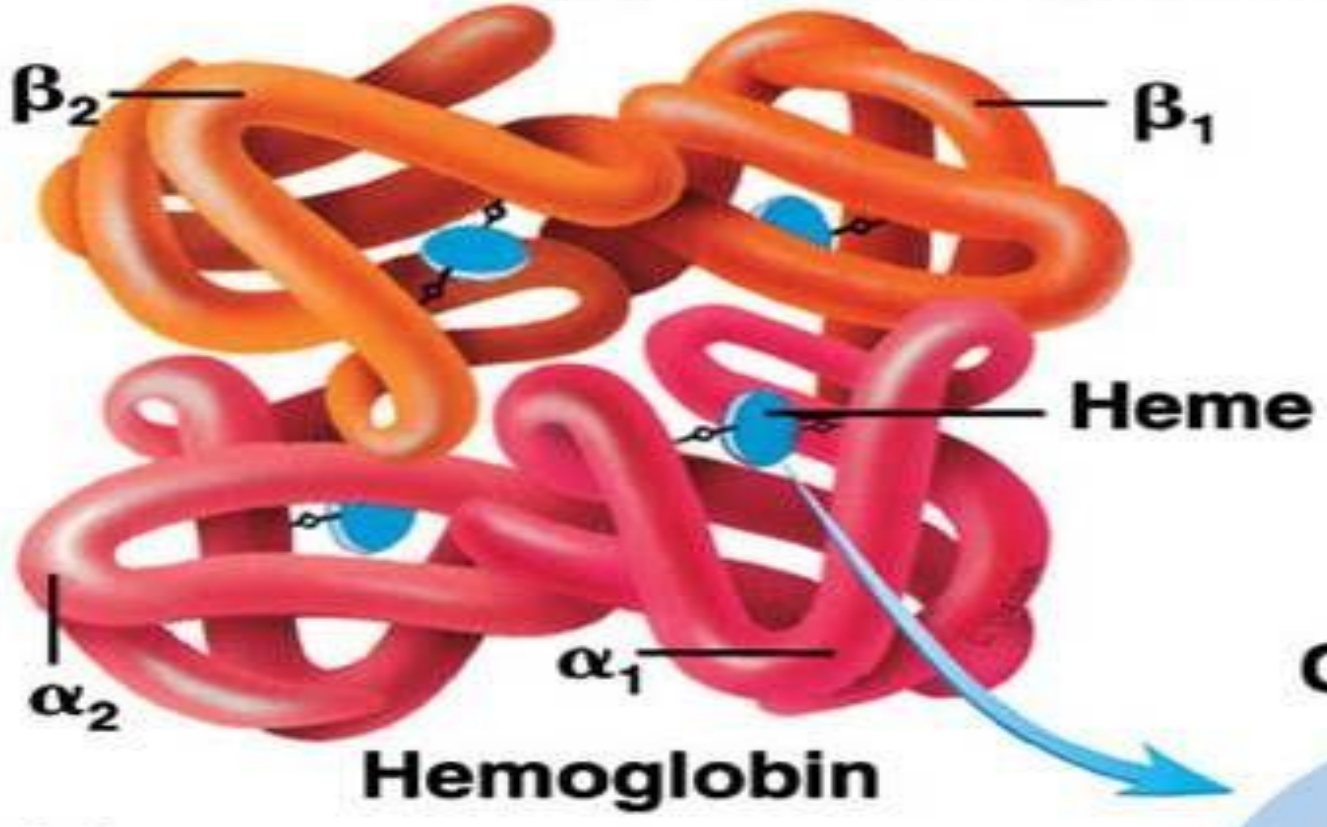
☆concentration is dynamically altered by the presence of hypoxia or anemia

HEMATOPOIESIS, ERYTHROPOIESIS & ERYTHROPOIETIN

Primary requirements for ***Effective Erythopoiesis***

1. Marrow (normal functioning factory – Hb synthesis
2. Erythropoietin
3. Nutrients (Iron, B12 and Folic Acid)

HEMOGLOBIN & Hemoglobinopathies



- Oxygen-carrying protein contained in RBCs.
- FOUR Subunits – Heme bound to polypeptide

Oxygen binds to Ferrous in Heme

HEMOGLOBIN & Hemoglobinopathies

- Uptake of iron by developing normoblast is partially controlled by intracellular heme – which has negative feedback on ALA synthase
- Heme synthesis partially occurs in mitochondria and partially in cytosol
- ***Transferrin*** transports iron; some stored as ***ferritin*** while most enters mitochondria to combine with protoporphyrin to perform Heme, using enzyme ***ferrocheltase*** to enhance reaction
- Globin chains synthesis occurs in ribosomes ***HbA - $\alpha_2\beta_2$***;
  HbA2 - $\alpha_2\delta_2$; **HbF -** $\alpha_2\gamma_2$

- **HbA_{1c}** - Glycated hemoglobin (glc attached to valine of beta chain)

Clinically important as it is increased in DM and may serve as a tool to monitor progression of disease or treatment effectiveness/compliance

Thalassemia:

2 pair of alpha genes (chromosome 16)

Single beta gene on each chromosome 11

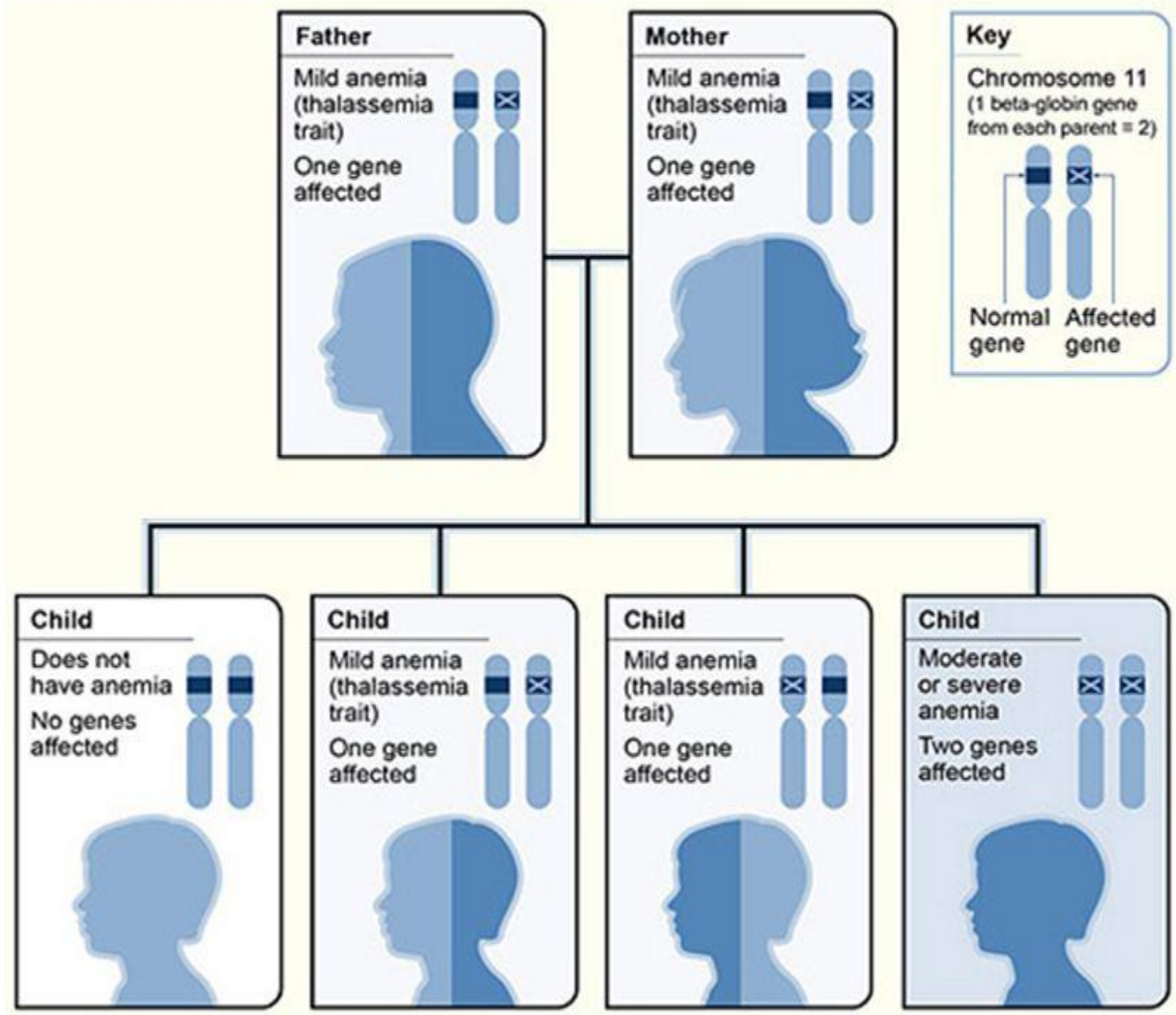
Beta thalassemia major: Two genes affected.
Decreased chains or absent.

Severe anemia.

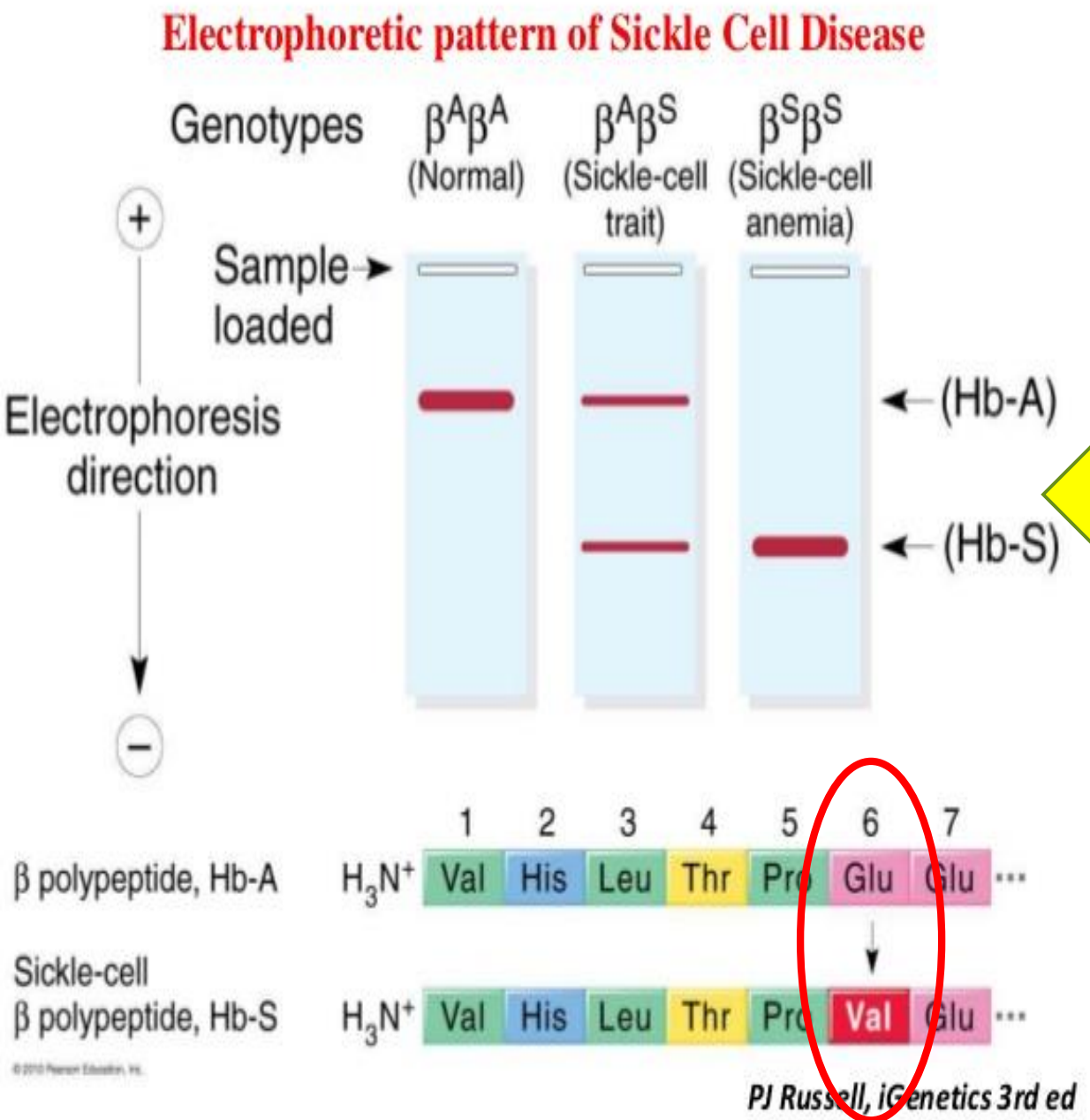
Transfusion required life-long. Risk of iron overload.

PUNJAB THALASSAEMIA PREVENTION PROGRAMME

Inheritance Pattern for Beta Thalassemia

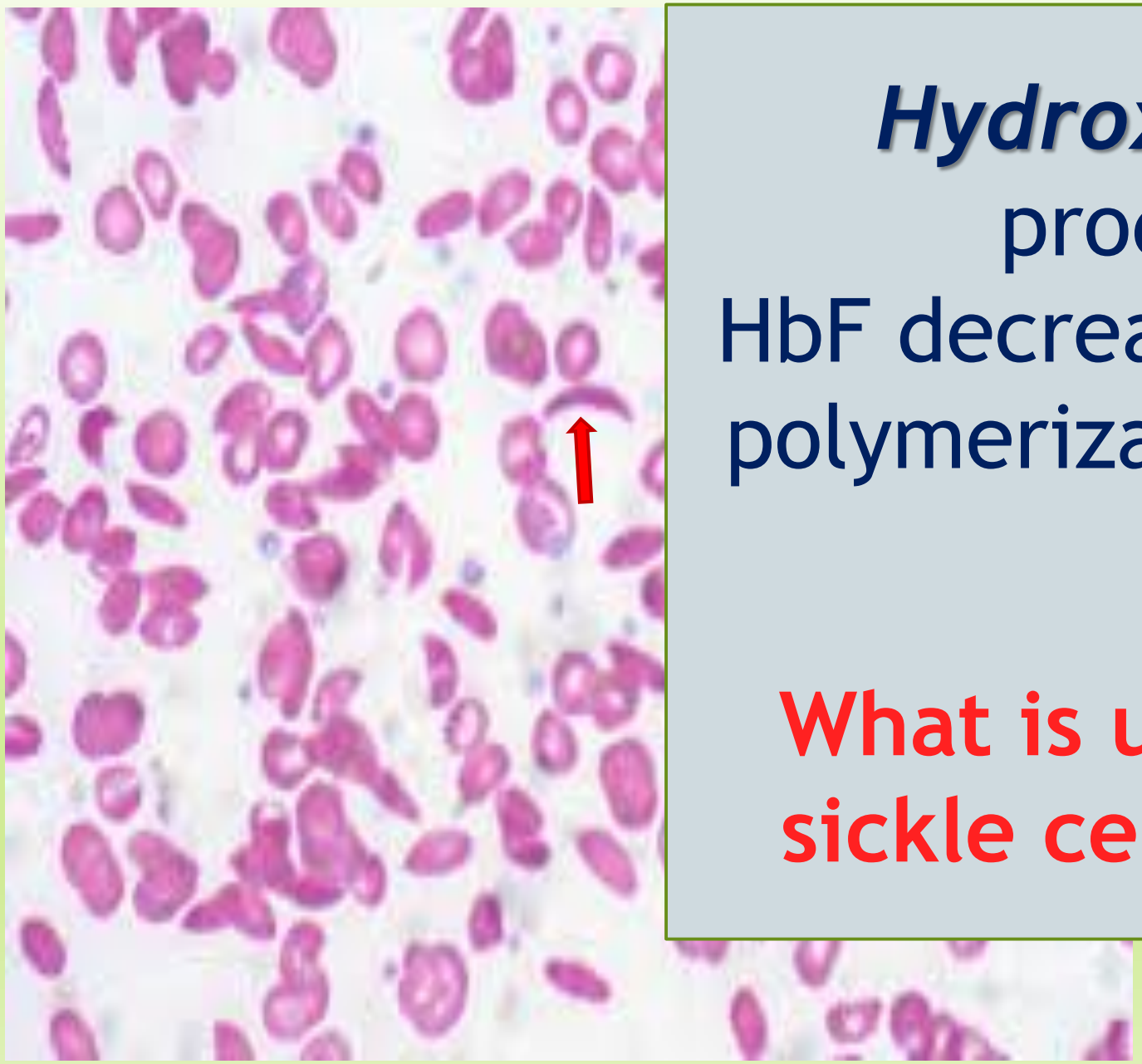


HEMOGLOBIN & Hemoglobinopathies



- Autosomal recessive
- one in ten in African American is a carrier ; also common in ME and SouthAsia
- Point mutation in beta globin gene
- Peripheral smear best initial;electrophoresis is diagnostic
- Sickle cell trait - identified as a major human malaria resistance factor

HEMOGLOBIN & Hemoglobinopathies



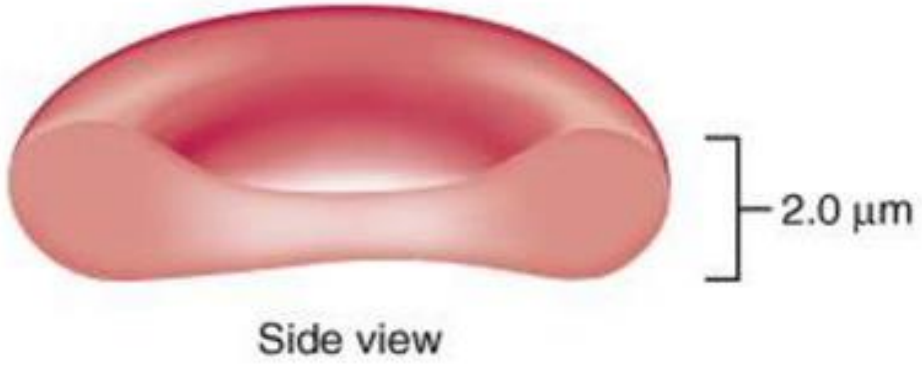
Hydroxyurea stimulates production of HbF.
HbF decreases polymerization of polymerization of deoxygenated HbS

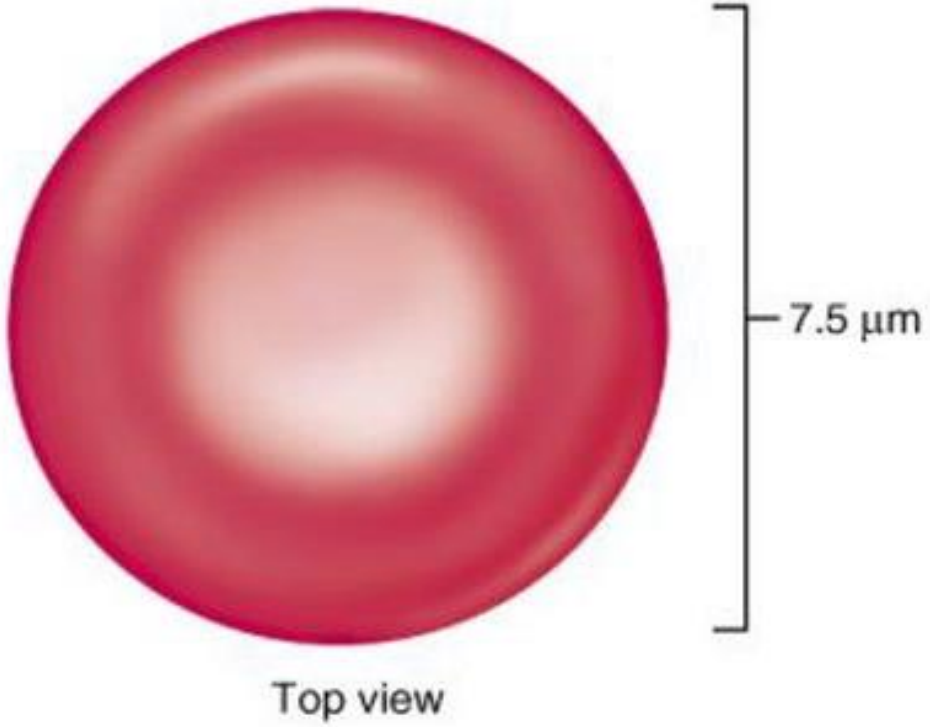
What is ultimate therapy for sickle cell Dz / Thalassemia?

- **IMPORTANCE OF** Glucose phposphate dehydrpgenase enzyme and *Glutathione reductase* in Red Blood Cell?

- What are Bite Cells (peripheral blood smear)?

RBC, RBC indices and Polycythemia



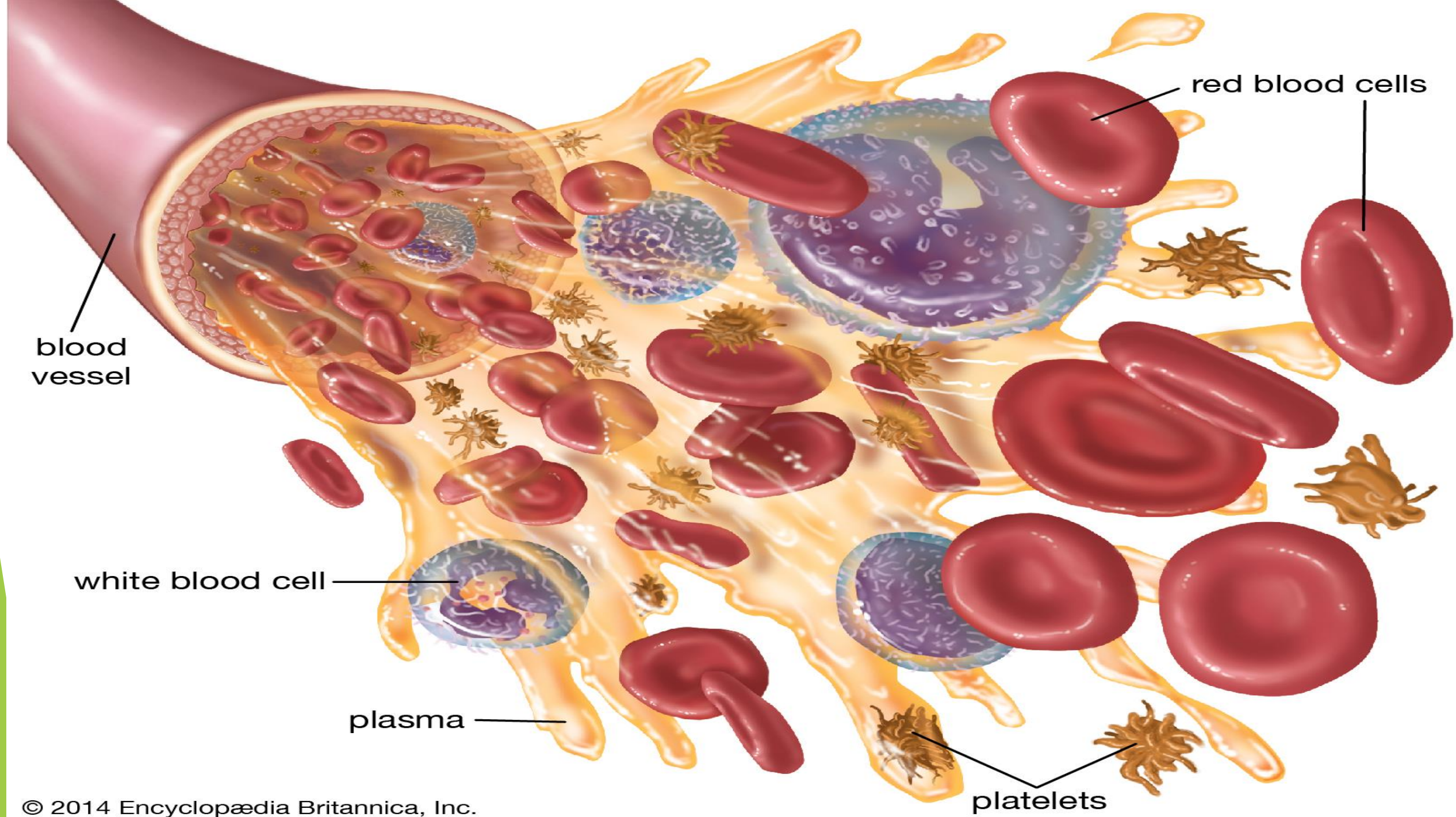


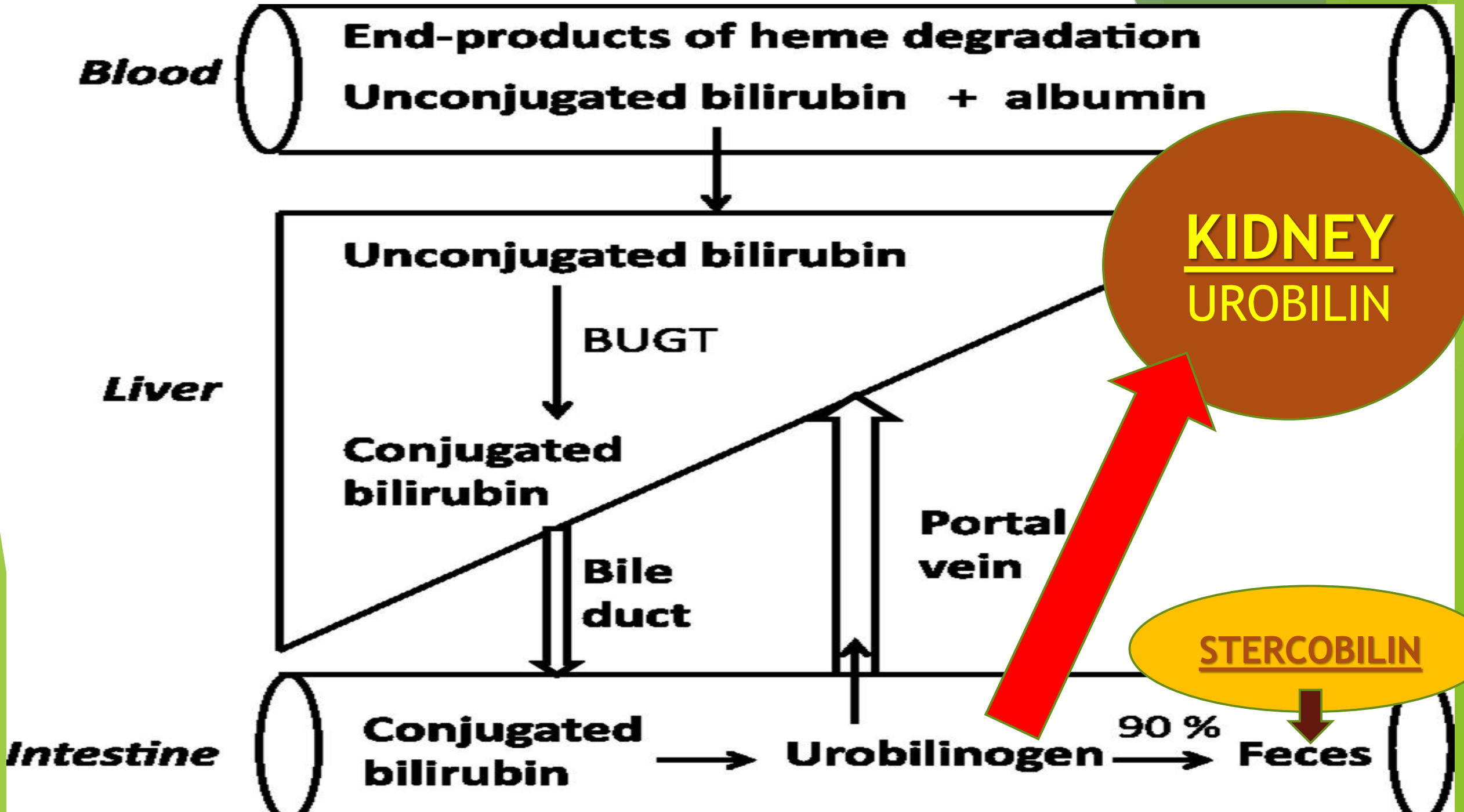
Biconcave shape that has a huge surface area to volume ratio. This is essential for gas exchange

Cytoskeletal protein (ankyrin ; spectrin)
prevent RBC deformity and resist fragmentation particularly when they transverse through micovasculature (spleen)

cytoplasm is filled with hemoglobin (Hb)

ATP is generated anaerobically, so the erythrocytes do not consume the oxygen they transport.




Blood
End-products of heme degradation
Unconjugated bilirubin + albumin
Liver
Unconjugated bilirubin
BUGT
Conjugated bilirubin
Bile duct
Portal vein
KIDNEY
UROBILIN
STERCOBILIN
Intestine
Conjugated bilirubin
Urobilinogen
90 %
Feces

RBC, RBC indices and Polycythemia

Mean Corpuscular Volume (MCV):

MCV refers to the average size of the RBCs constituting the sample and is expressed as femtoliters (10^{-15}; fl) (normal: 80-100 fL)

Mean Corpuscular Hb Concentration (MCHC):

MCHC correlates the hemoglobin content in the red blood cell contained within the sample. It is expressed as g/dl of red blood cells or as a percentage value. Reference interval for adults is typically 32 - 36 g/dL.

Red Cell Distribution Width (RDW):

RDW represents the coefficient of variation of the red blood cell volume distribution (size) and is expressed as a percentage.

Hematocrit: The hematocrit is a ratio of the volume of red blood cells to the whole blood (45% to 52% for men and 37% to 48% for women)

RBC, RBC indices and Polycythemia

The hemoglobin of red cells is located peripherally, leaving an area of central pallor equal to approximately 30 to 45% of the diameter of the cells. Cells of normal size and hemoglobin content (color) are termed *normocytic* and *normochromic*

Larger than normal erythrocytes are ***macrocytes*** (diameter greater than 9 μm); small red cells are ***microcytes*** (diameter less than 6 μm); and those with central pallor greater than 50% of the diameter are ***hypochromic***

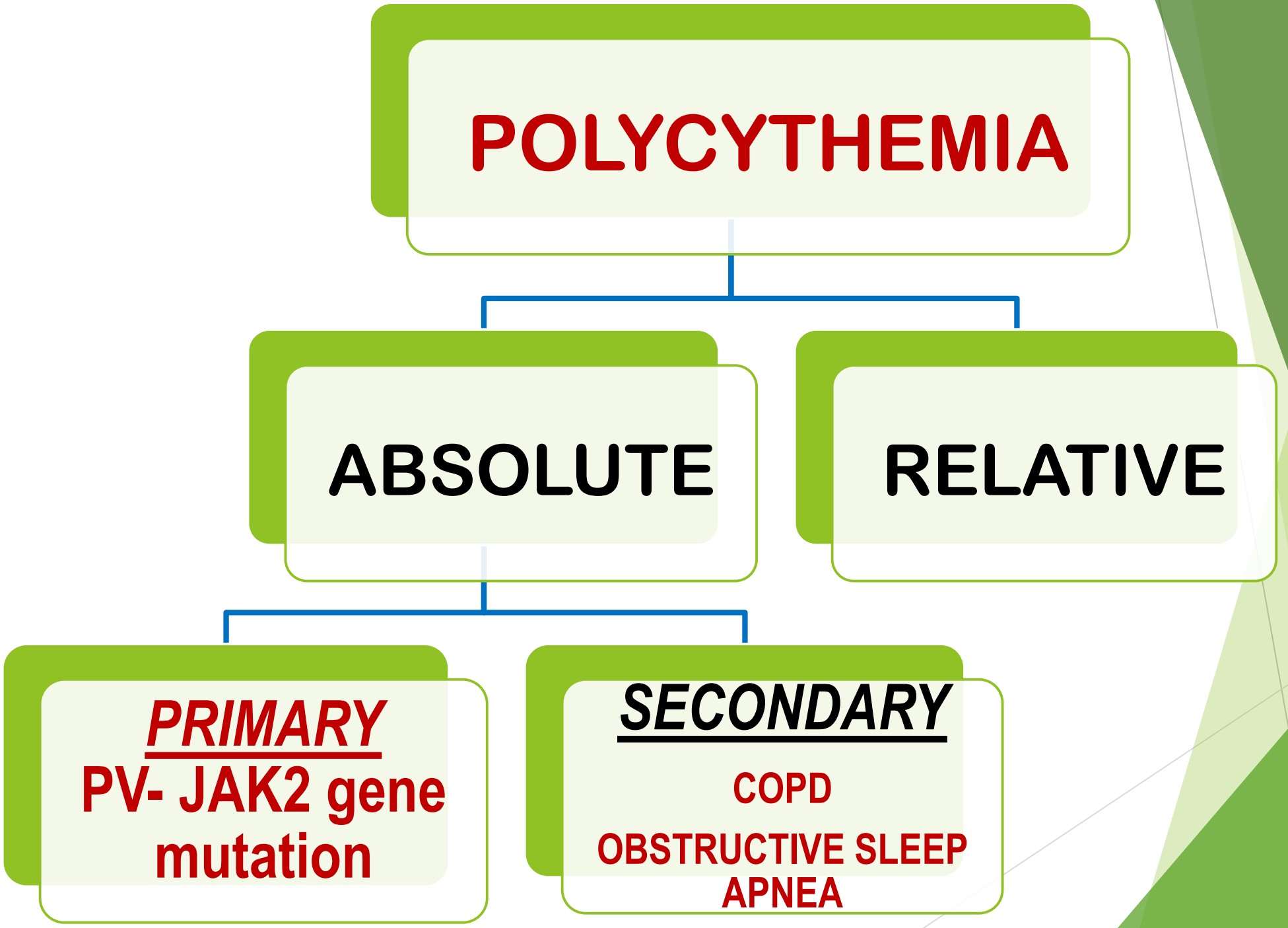
Abnormal variability in size is termed ***anisocytosis***
unusual variation in shape is called ***poikilocytosis***

A 32-year-old woman with type 1 diabetes mellitus has had progressive renal failure over the past 2 years. She has not yet started dialysis. Examination shows no abnormalities. Her hemoglobin is 9 g/dL, hematocrit is 28%, and mean corpuscular volume is 94 µm3 . A blood smear shows normochromic, normocytic cells. most likely cause of anemia?

(A)Acute blood loss (B) Erythrocyte enzyme deficiency

(C) Erythropoietin deficiency (D) Immunohemolysis

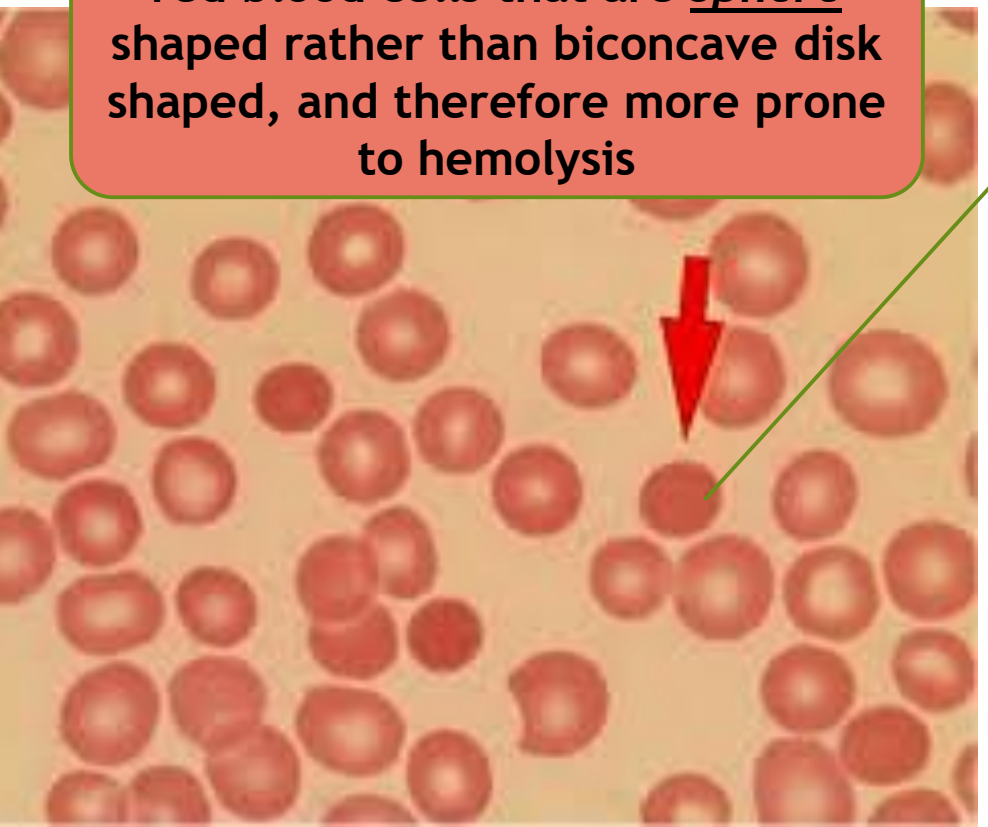
(E) Microangiopathic hemolysis (F) Sickle cell disease


POLYCYTHEMIA
ABSOLUTE
RELATIVE
PRIMARY
PV- JAK2 gene mutation
SECONDARY
COPD
OBSTRUCTIVE SLEEP APNEA

RBC, RBC indices and Polycythemia

Hereditary Spherocytosis

red blood cells that are *sphere* shaped rather than biconcave disk shaped, and therefore more prone to hemolysis



Defe

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Osmotic Fragility Test

Fragile Spherocytes do not tolerate the (hypotonic) saline solution well and will burst their membranes sooner than normal cells.

The eosin-5-maleimide (EMA) binding test performed by flow cytometry

decreased expression of red blood cell membrane proteins found in HS causes a reduced binding of EMA to band-3 protein and its fluorescence emission

A 55-yr old man with 1yr Hx of fatigue,daytime hypersomnolence. Hypertensive&smoking since 30years. BP 135/85, Pulse 84,RR 28/min. BMI 35. Lab Hct 58% (⇧), WBC normal, Plt⇧,EPO raised, JAK2 gene mutation negative. Why Hct elevated:

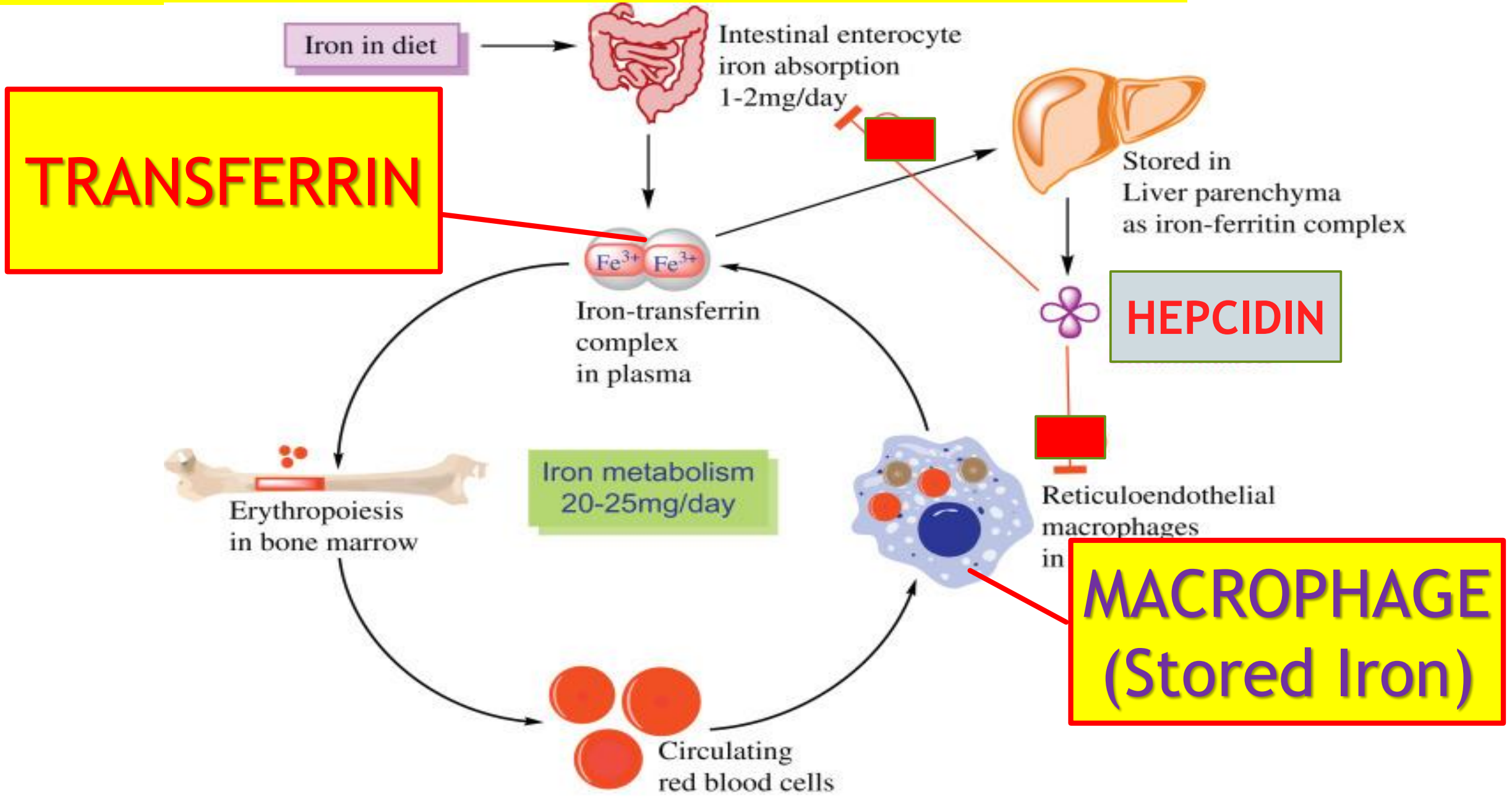
a. Relative polycthemia

b. High oxygen affinity Hb

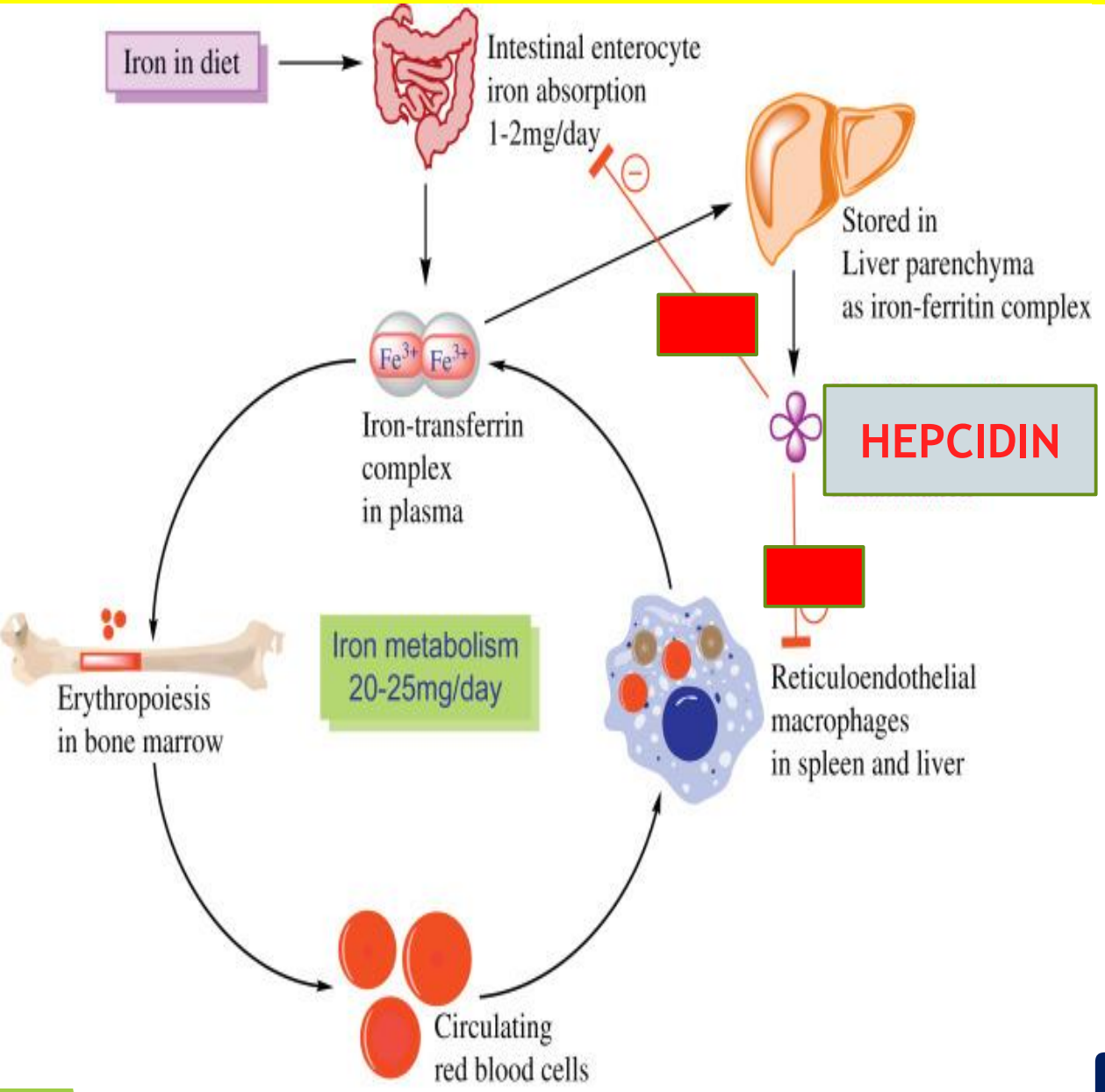
c. Secondary polycythemia

d. Polycythemia vera

IRON METABOLISM AND MICROCYTIC ANEMIA



IRON METABOLISM AND MICROCYTIC ANEMIA



Ferrous vs Ferric sources of iron?Which is better?

Transferrin vs Ferritin?

Hemosiderin?

TIBC vs Transferrin saturation?

Ferritin in Liver vs Ferritin in macrophages?

IRON METABOLISM AND MICROCYTIC ANEMIA

IRON DEFICIENCY ANEMIA

MCV	LOW
RDW	HIGH
FERRITIN	LOW
TIBC	HIGH
TRANS.SATU.	LOW

IRON METABOLISM AND MICROCYTIC ANEMIA

	IDA	ACD	THALASSEMIA
MCV	LOW	LOW	LOW
RDW	HIGH	NORMAL	NORMAL
FERRITIN	LOW	HIGH	NORMAL
TIBC	HIGH	LOW	NORMAL
TRANS.SATu.	LOW	HIGH	NORMAL

65YR OLD PRESENTS WITH FATIGUE & MALAISE. APPEARS PALE. BLOOD TEST SHOWS Hb 8.0g/dl, Hct 30%, MCV 65, Reticulocyte 0.5%. Iron studies results:

Ferritin – TIBC – Transferrin saturation

A. high – low – high

B. low - low – low

C. Low – high – low

D. low – high - high

- SERUM *FERRITIN* IS THE SINGLE BEST TEST IN DIFFERENTIATING BETWEEN IDA AND Anemia of Chronic Disease (Inflammatory anemia)

Source

transpo

Trans

AVOID SIMULTANEOUS INTAKE OF

IRON (SOURCE)

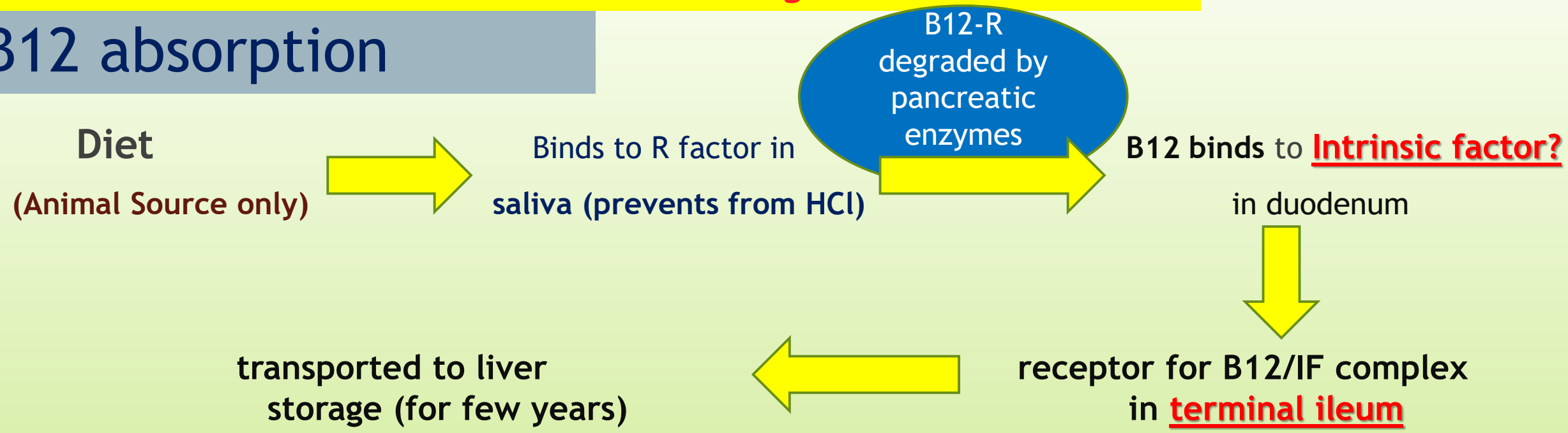
AND

CALCIUM (SOURCE)

(particularly in infants/children)

B12, Folic Acid and Macrocytic Anemia

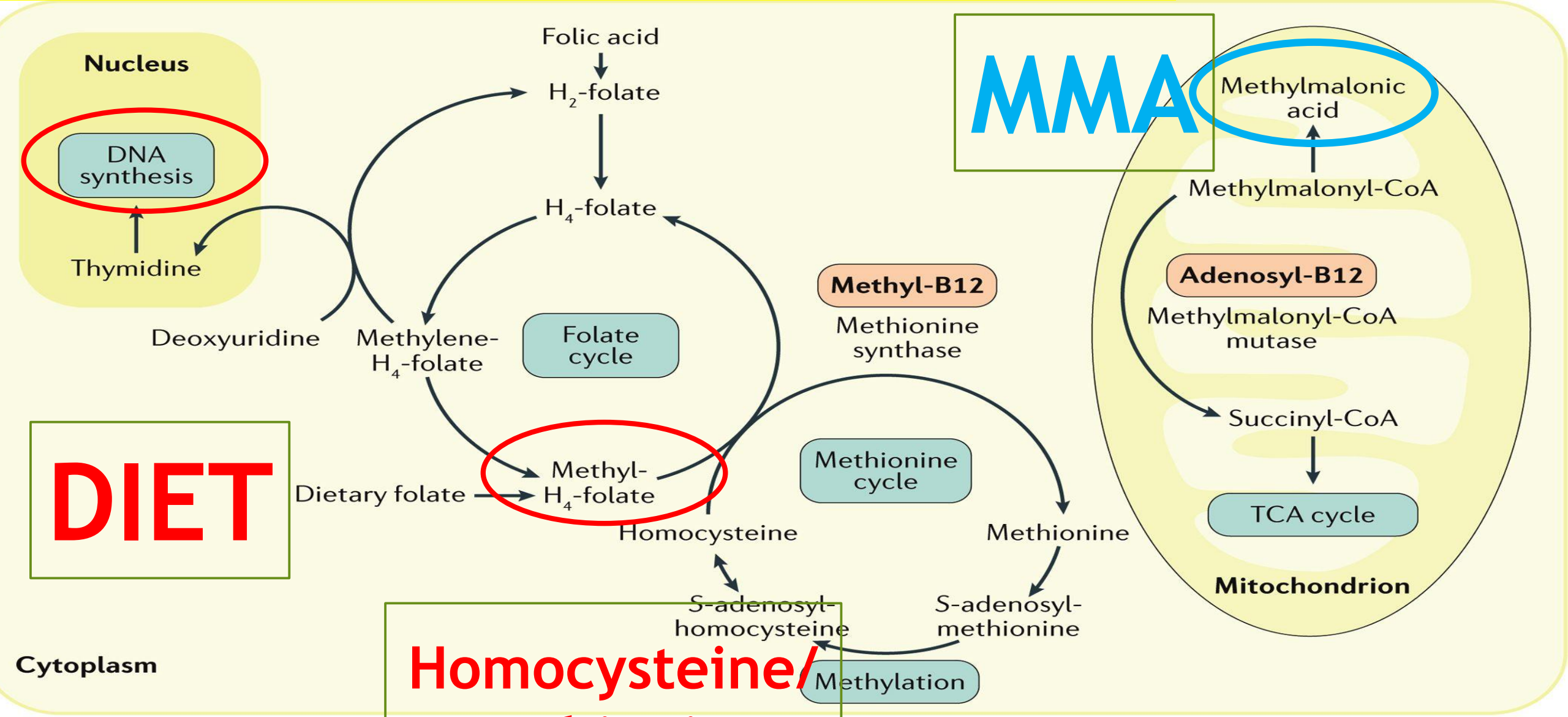
B12 absorption



Folic Acid is present in animal and plant products ; absorbed as monoglutamate in jejunum.

- **In intestinal cells , monoglutamates are converted to N^5 - methyl-FH4, which is primary circulating form of folate in blood (for3-4 months).**
- **Phenytoin, Alcohol, OCP may interfere with folate (monoglutamates) absorption.**
- **Is b12 synthesized by intestinal bacteria?why cannot it be absorbed?**

B12, Folic Acid and Macrocytic Anemia

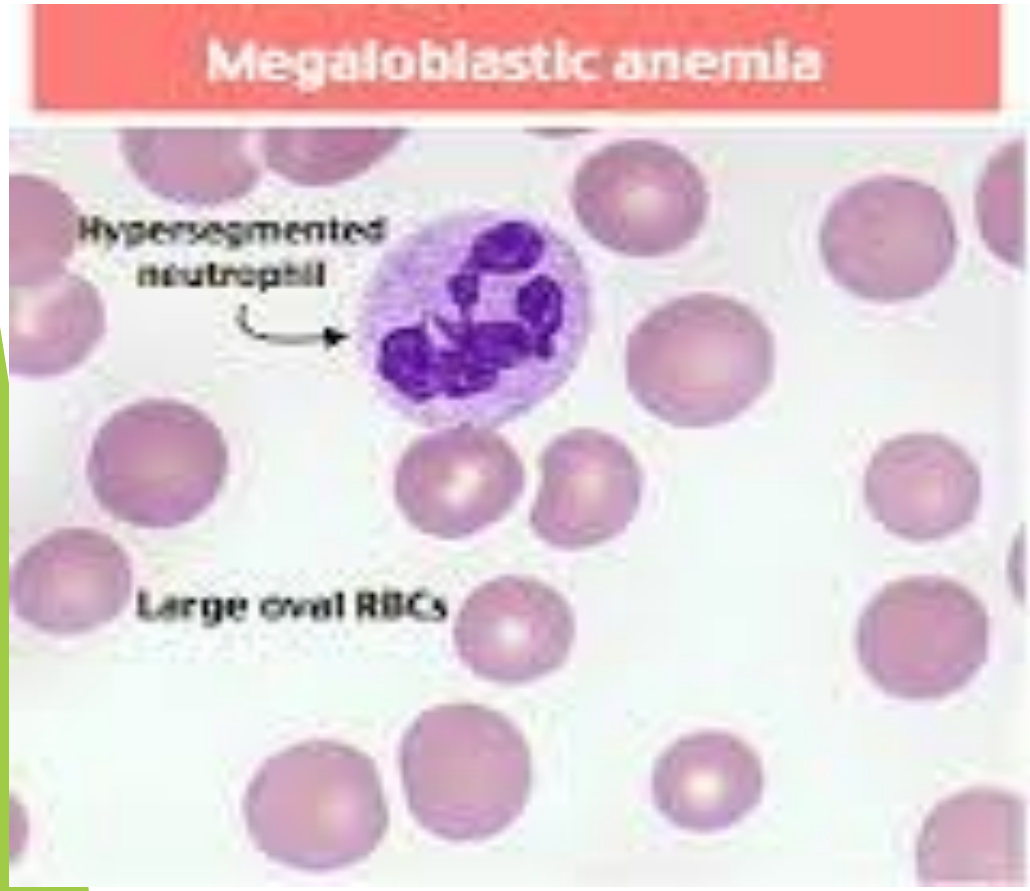


DIET

Homocysteine/ Methionine

B12, Folic Acid and Macrocytic Anemia

Ineffective Erythrocytosis



B12/Folic acid deficiency

↓

Impaired DNA synthesis

↓

remature death of immature appearing erythoblast cells

↓

Maturation Failure

↓

Ineffective Erythrocytosis

1 YR old child PRESENTS WITH pallor and irritability. Stool Negative for occult bood, parasites and ova. Lab reveals Hb: 6.5mg/dl WBC 6000;Platelets 200,000. MCV: 68. Peripheral smear shows anisocytosis, poikilocytosis, microcytosis. Cause?

A. Iron Deficiency Anemia

B. Macrocytic anemia

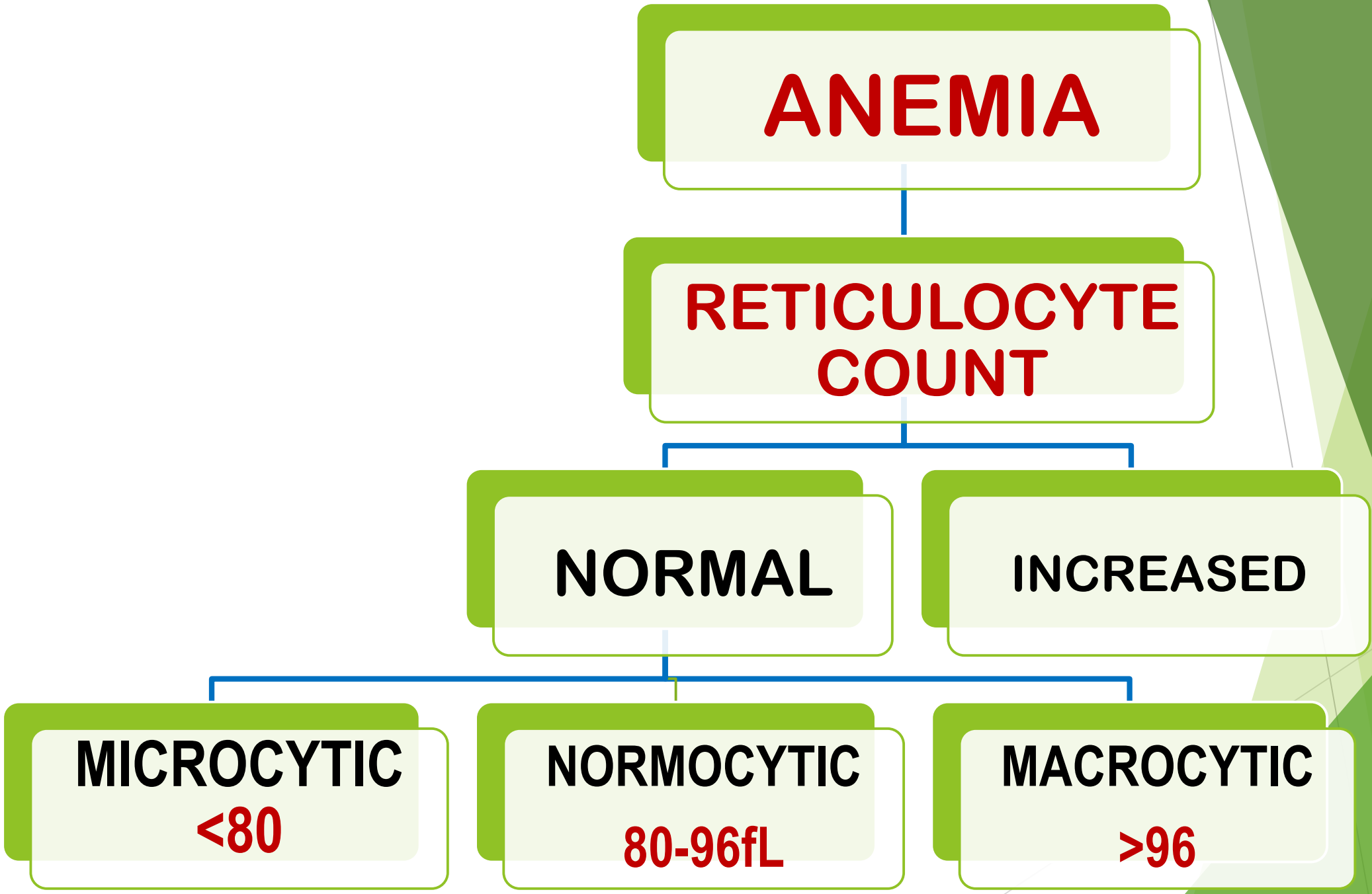
C. Folate deficiency

D. Normocytic anemia

CLASSIFICATION OF ANEMIA

MCV

- **LOW**
  - MICROCYTIC <80
- **NORMAL**
  - NORMOCYTIC 80-96fL (Observe Reticulocyte count)
- **INCREASED**
  - MACROCYTIC >96


ANEMIA
RETICULOCYTE COUNT
NORMAL
INCREASED
MICROCYTIC
<80
NORMOCYTIC
80-96fL
MACROCYTIC
>96