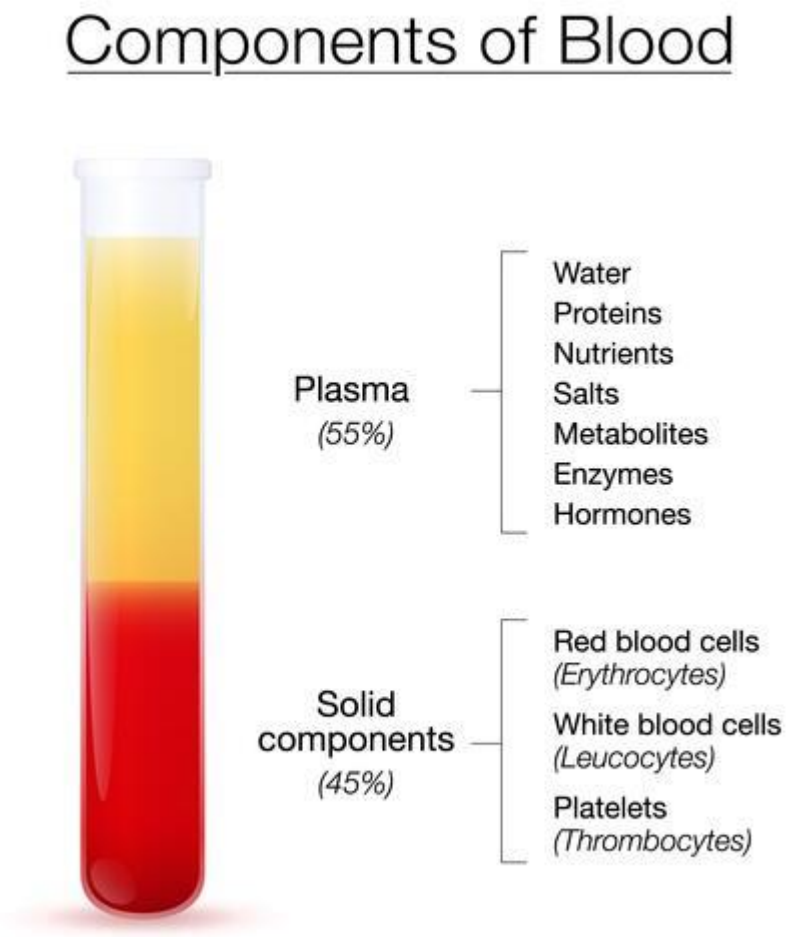
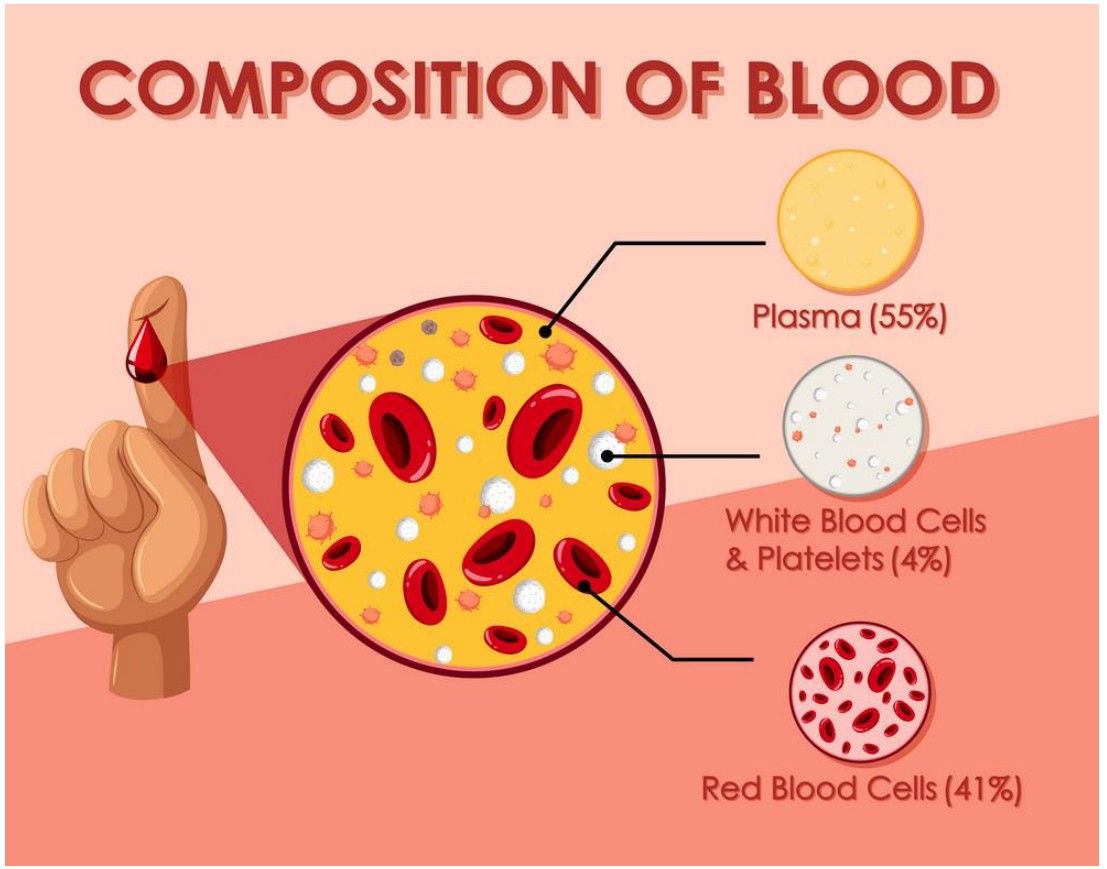
Hemato-Lymphoid System HLS

DR. DUA ABUQUTEISH

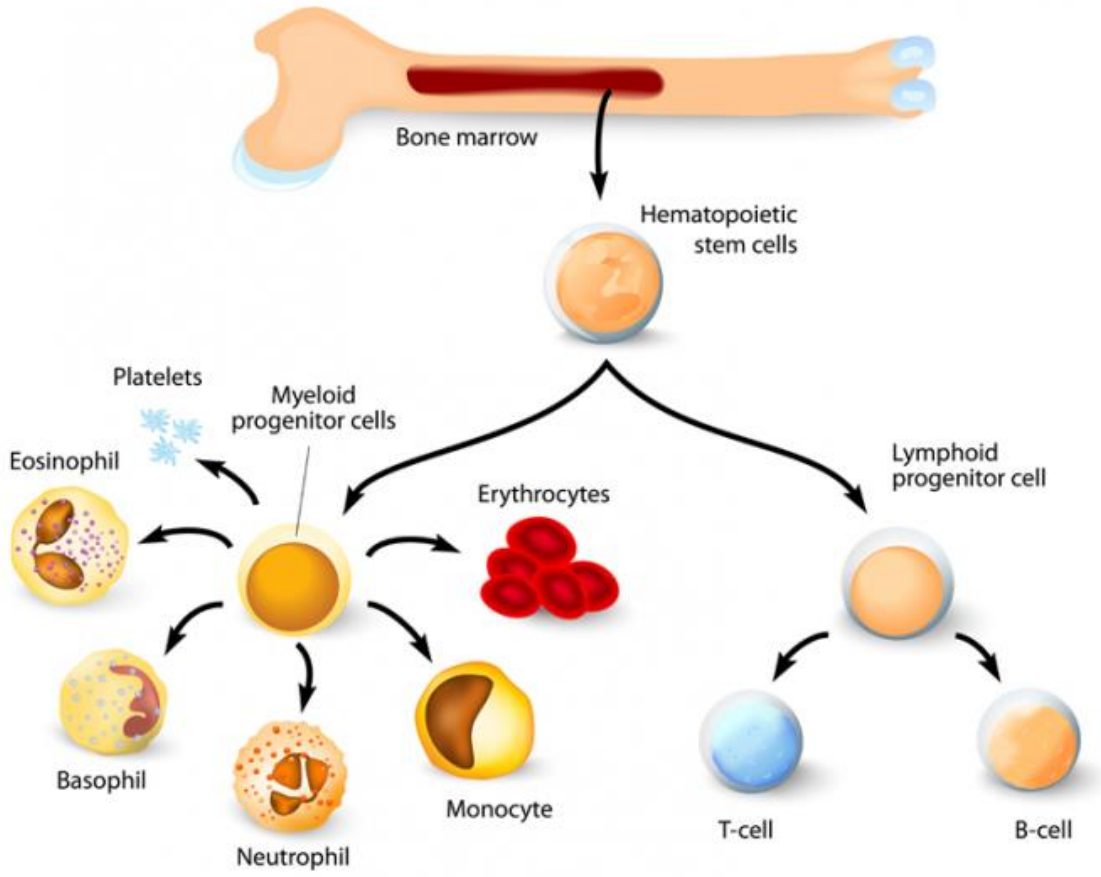
Composition of blood

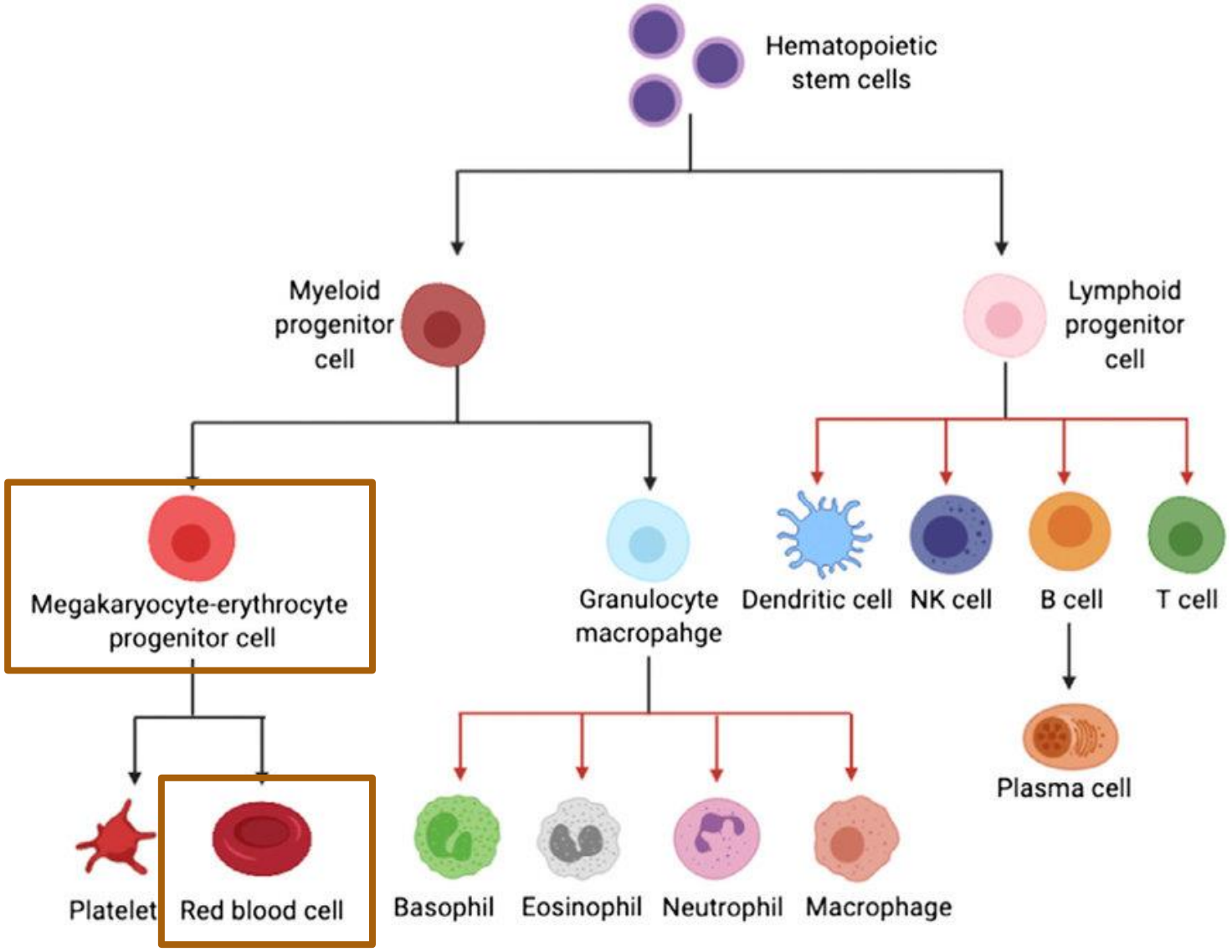


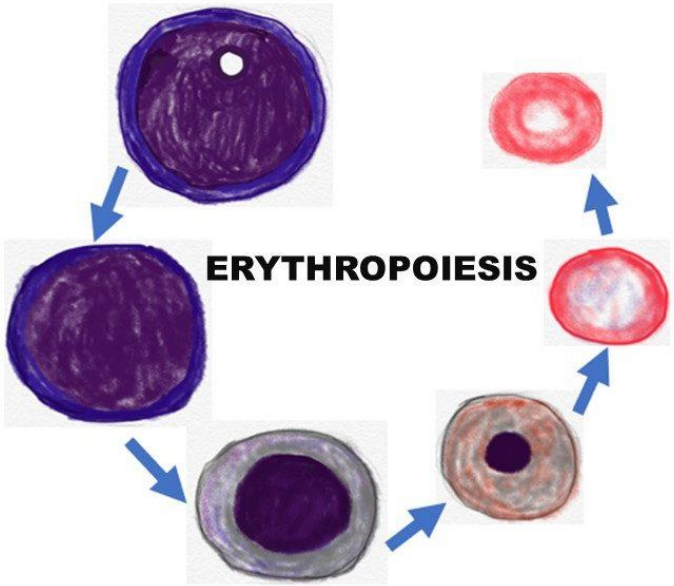


Hematopoiesis:
is the formation of blood cellular components

- All types of blood cells are derived from primitive cells (**stem cells**) that are **pluripotent.**
- Hematopoiesis in adults occurs mainly in the **bone marrow**
- However, in certain diseases it can also occur outside the bone marrow (**spleen & liver**). This is termed **extramedullary hematopoiesis**




Hematopoietic stem cells
Myeloid progenitor cell
Lymphoid progenitor cell
Megakaryocyte-erythrocyte progenitor cell
Granulocyte macropahge
Dendritic cell
NK cell
B cell
T cell
Plasma cell
Platelet
Red blood cell
Basophil
Eosinophil
Neutrophil
Macrophage



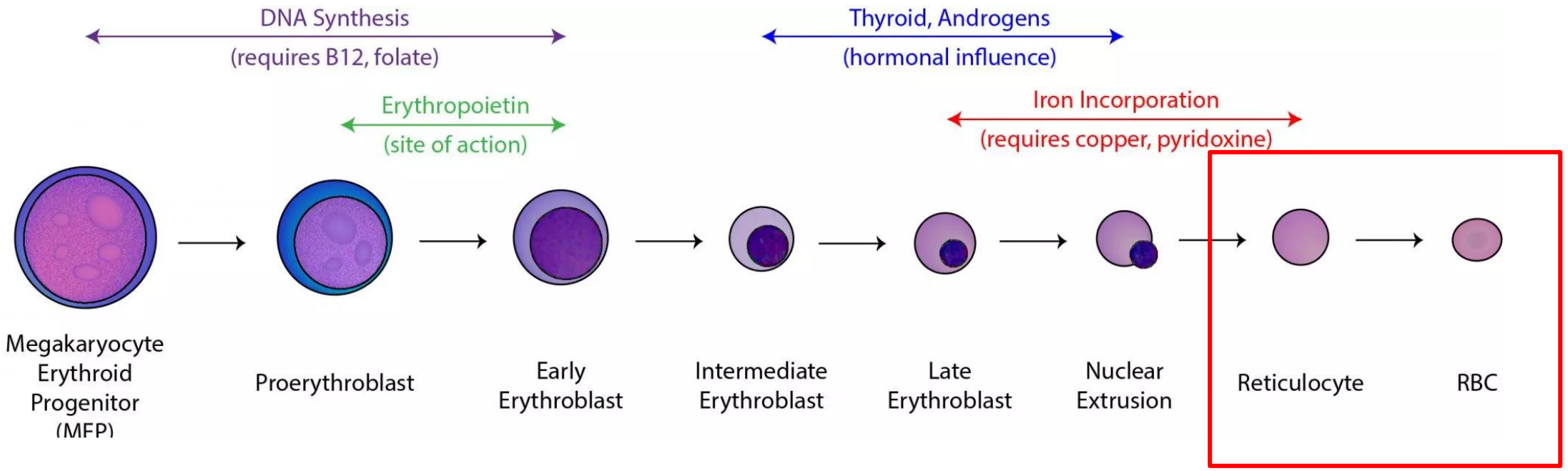
Erythropoiesis

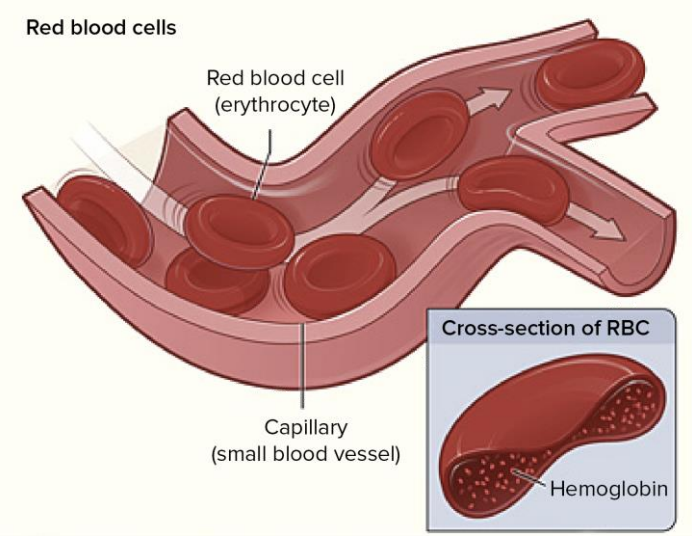
From Greek 'erythro' means "red" and 'poiesis' "to make“

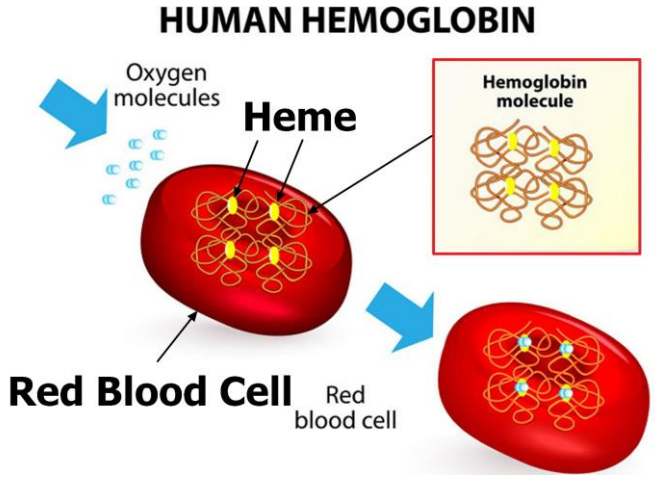
Erythropoiesis is the process which produces red blood cells (**erythrocytes**)

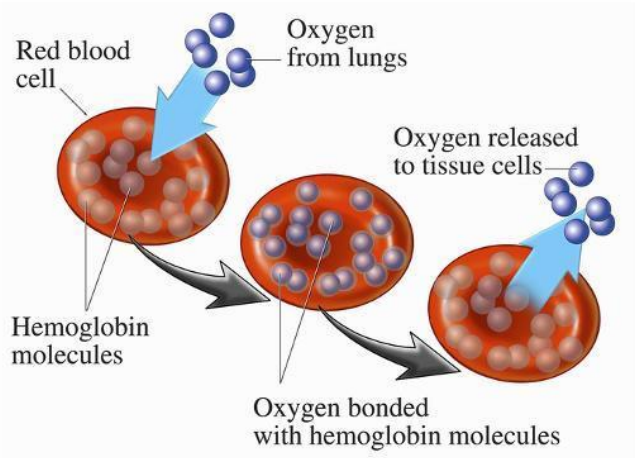
It is the development from erythropoietic stem cell to mature red blood cells

Erythropoiesis









Mature RBC's

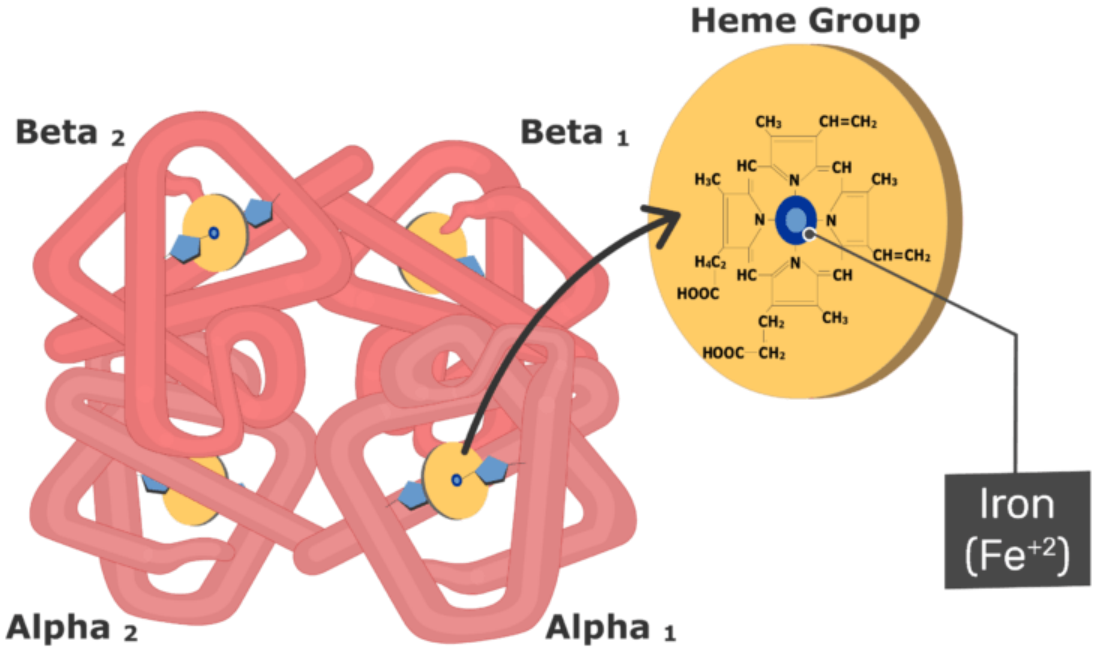
Each RBC contains around **270 million** hemoglobin molecules

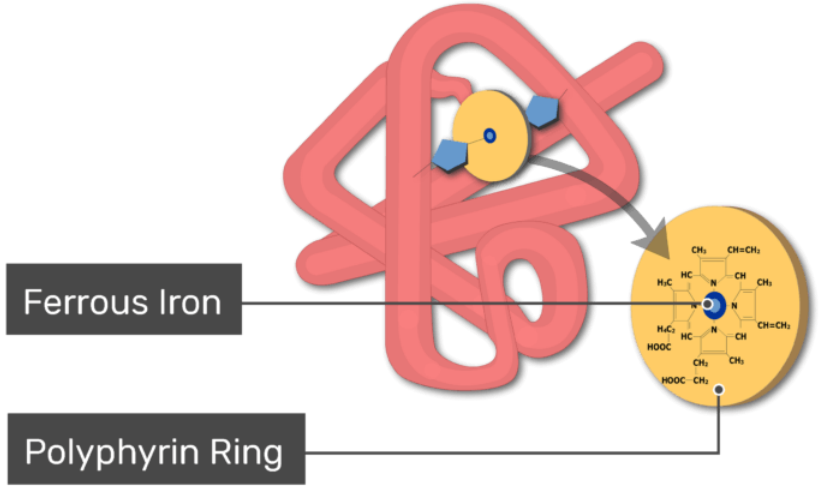
Hemoglobin is a tetramer composed of two parts:

Globin: 4 protein chains (subunits) (2α and 2β)

Heme: Porphyrin ring with central iron.

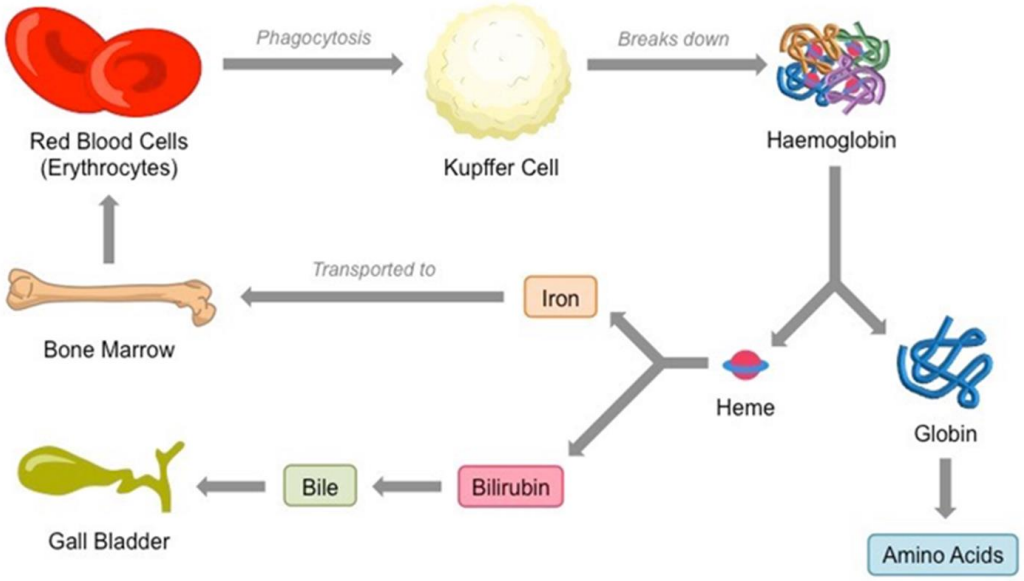
4 heme groups each attached to globin chain.

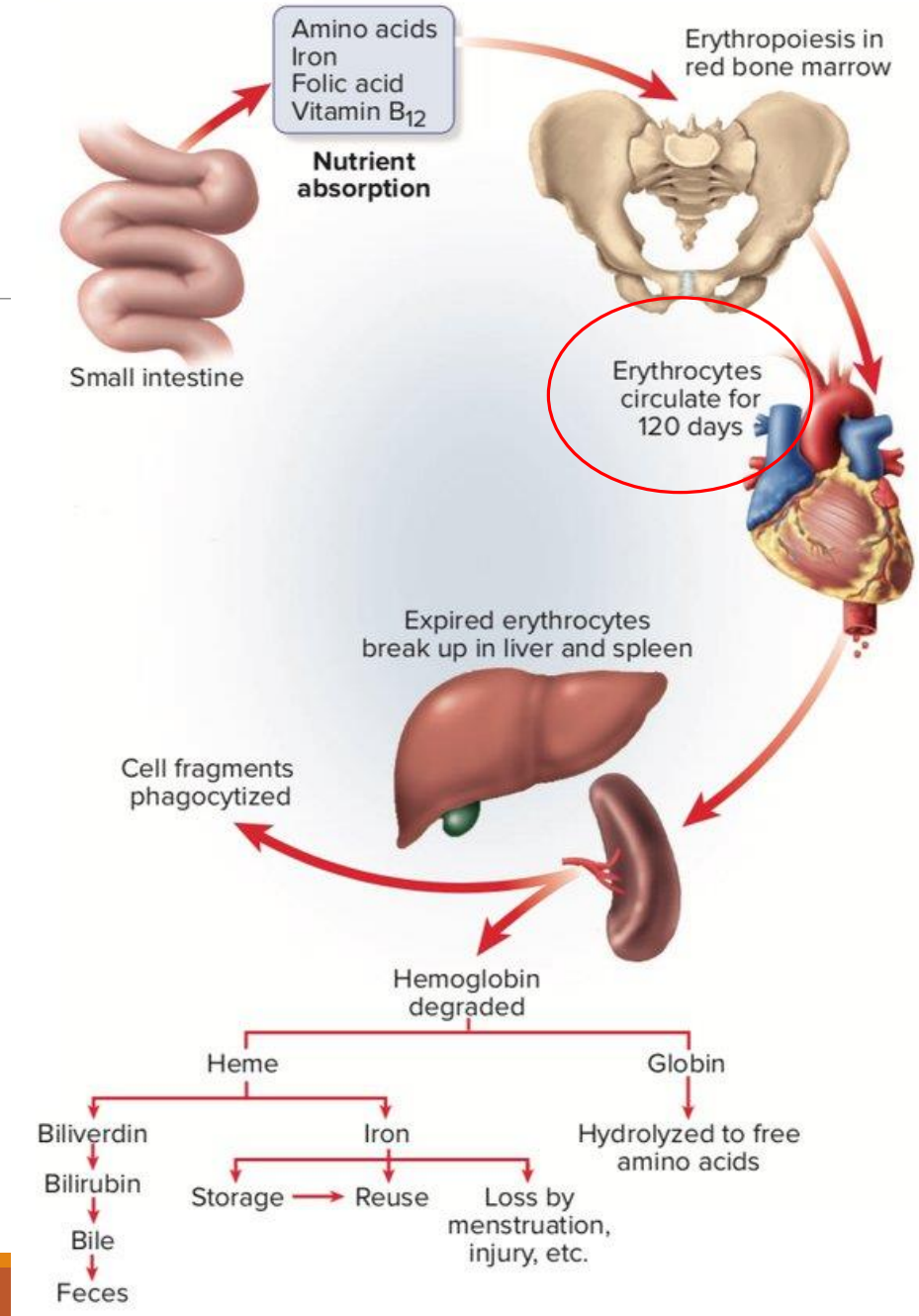


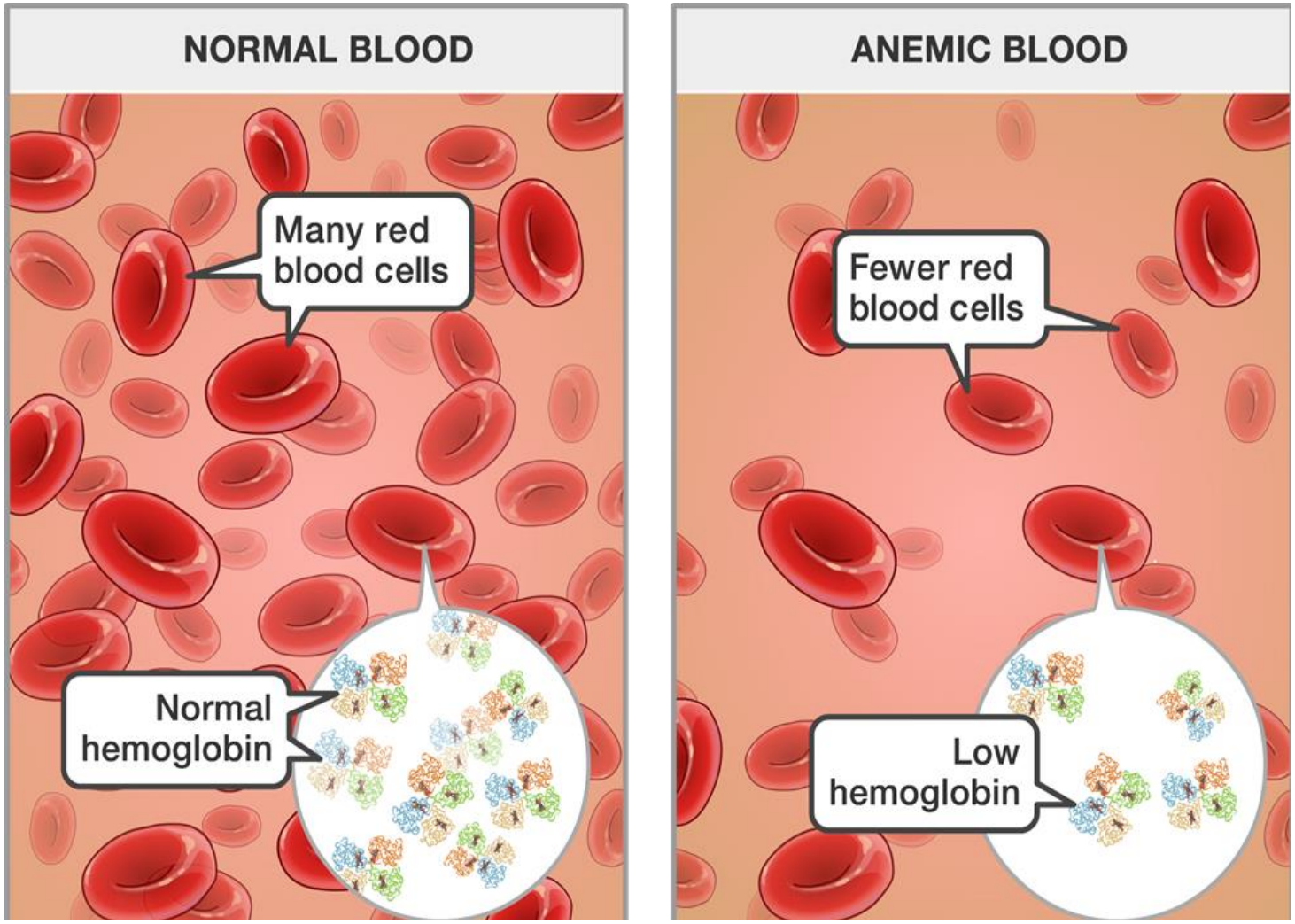


HEMOGLOBIN = HEME + GLOBIN

Life cycle of RBC






NORMAL BLOOD
Many red blood cells
Normal hemoglobin
ANEMIC BLOOD
Fewer red blood cells
Low hemoglobin

Anemia

Anemia

- **Is the reduction in the oxygen transporting capacity of blood, which results from a reduction of the total circulating red blood cell mass to below normal levels .**

It can result from :

1- Excessive bleeding

2- Increased red cell destruction

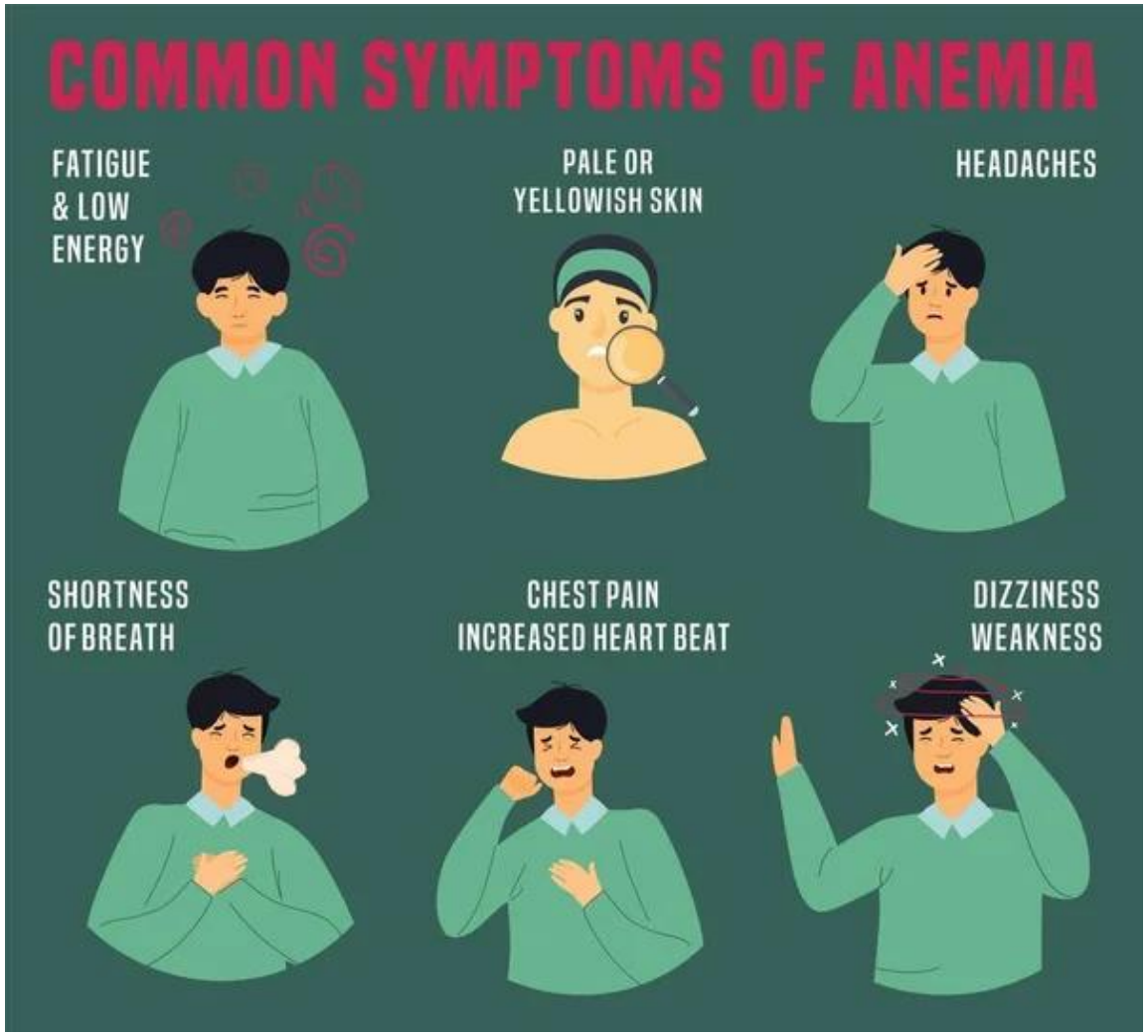
3- Decreased red cell production

Anemia

Definition

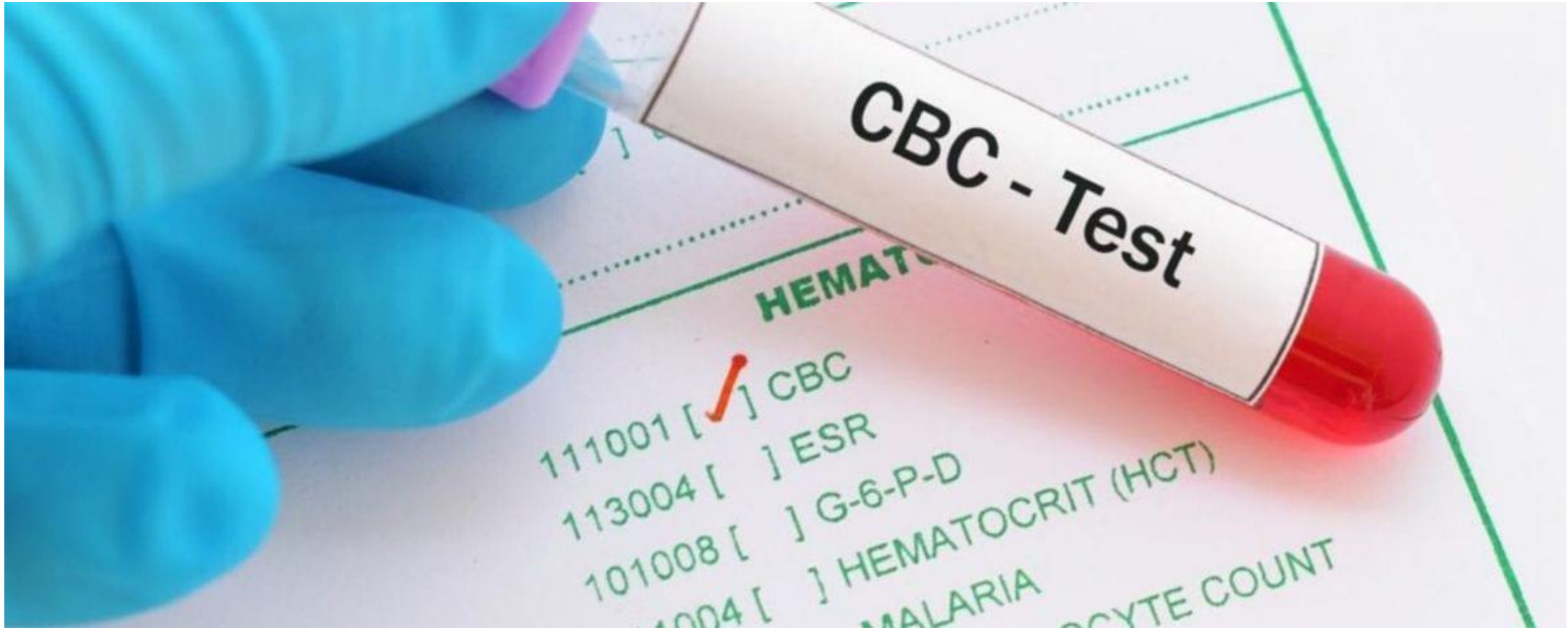
- In males: Hb<13 g/dl
- In females: Hb<12 g/dl

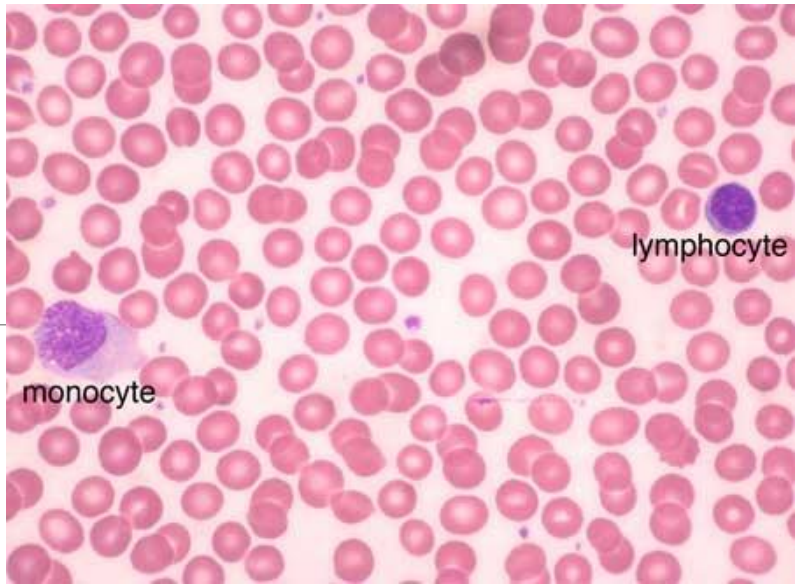
- **Anemia is not a diagnosis but a sign of disease**

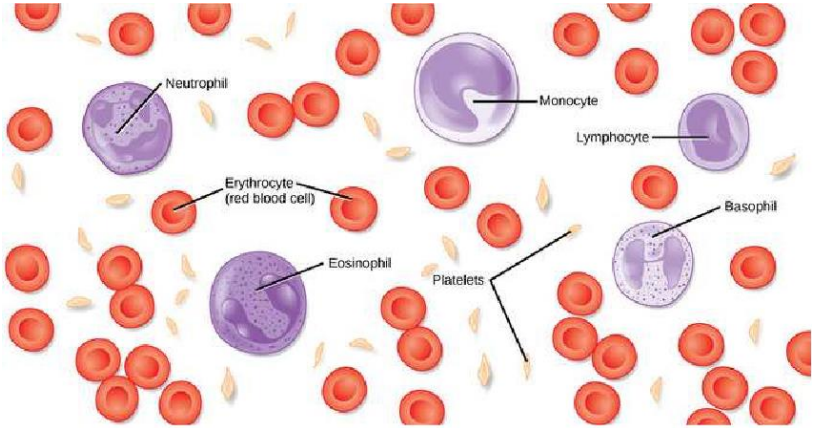


Anemia
Clinical cues

- Fainting, pallor, tachycardia…**anemia in general**
- Jaundice, gallbladder stones, red urine…**anemia due to hemolysis**
- Hx: Age of presentation, gender, past medical history, family history
- Anemia workup: **CBC and blood smear,….among others**


CBC - Test
111001 [ ] CBC
113004 [ ] ESR
101008 [ ] G-6-P-D
] HEMATOCRIT (HCT)
MALARIA


lymphocyte
monocyte

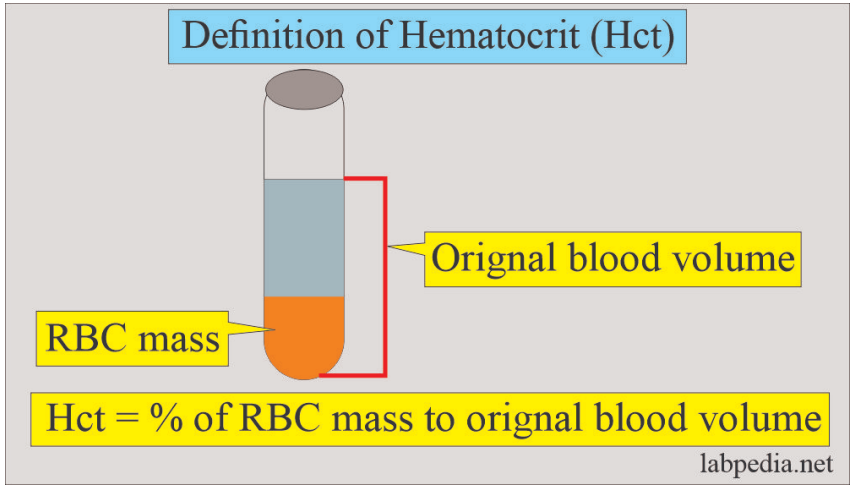

Neutrophil
Monocyte
Lymphocyte
Erythrocyte
(red blood cell)
Basophil
Eosinophil
Platelets

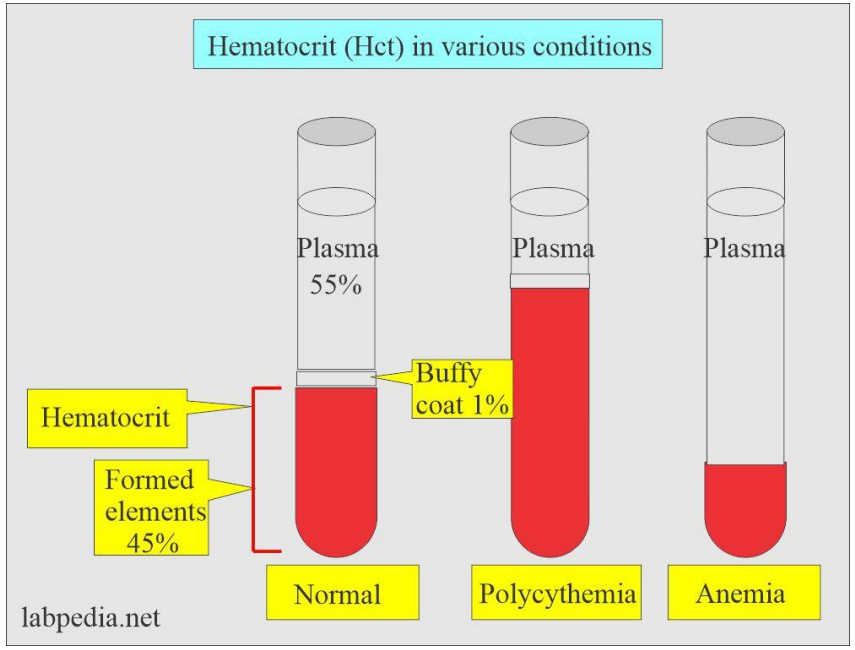
Blood smear

Components of CBC w/diff and Reference Ranges

Test	Reference Range
White blood count (WBC)	4000–11,000/μL
Red blood count (RBC)	4.20-5.4 M/μL
Hemoglobin	Female: 12–16 g/dL Male: 14–18 g/dL
Hematocrit	Female: 37%–47% Male: 42%–50%
Mean corpuscular volume (MCV)	80–98 fL
Mean corpuscular hemoglobin (MCH)	28–32 pg
Mean corpuscular hemoglobin concentration (MCHC)	33–36 g/dL
Red blood cell distribution width (RDW)	9.0–14.5
Platelet	150,000–450,000/μL
Neutrophils (%)	50%-70%
Lymphocytes (%)	30%-45%
Monocytes (%)	0%-6%
Eosinophils (%)	0%-3%
Basophils (%)	0%-1%%

CBC "Complete Blood Count"

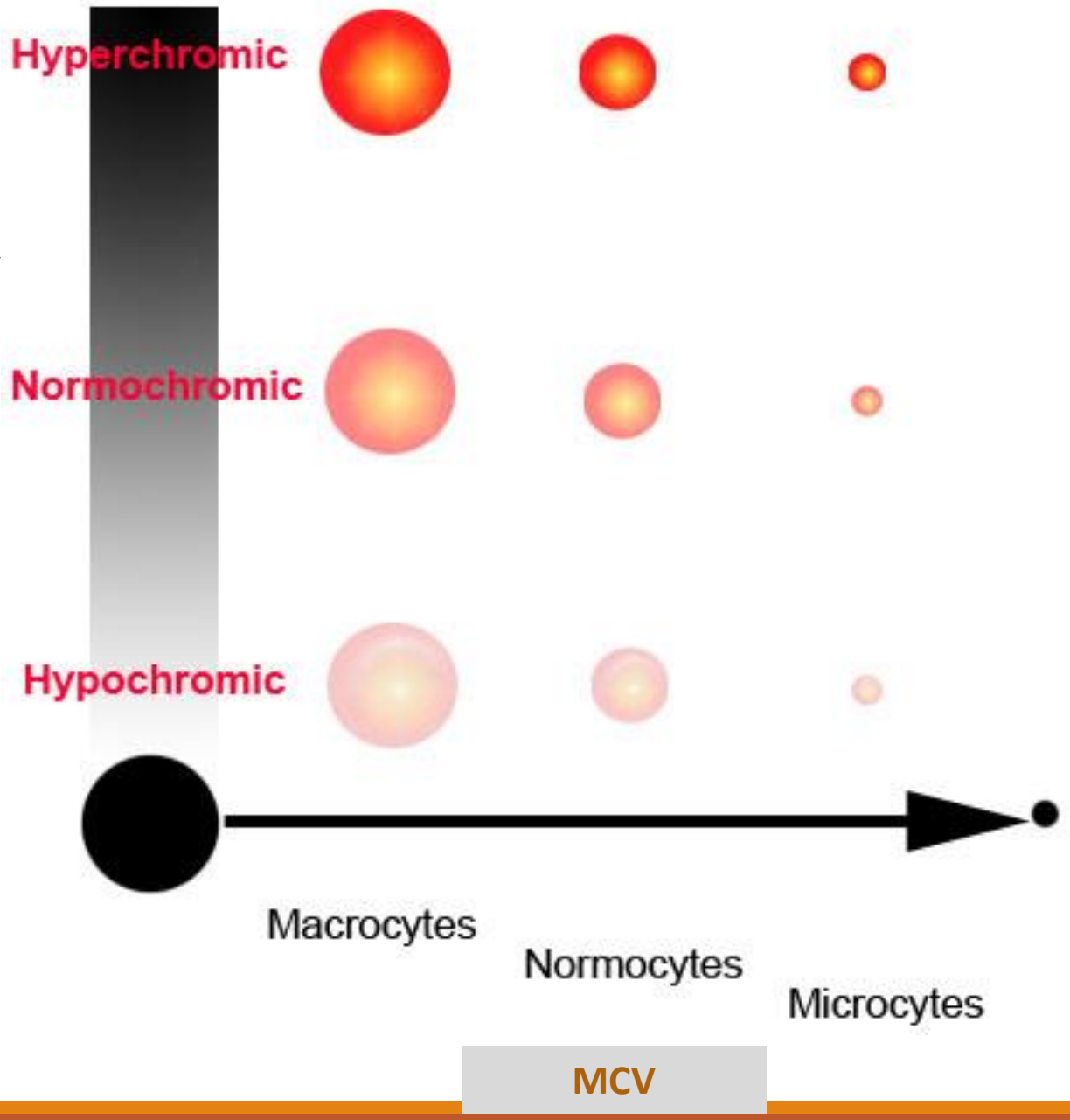




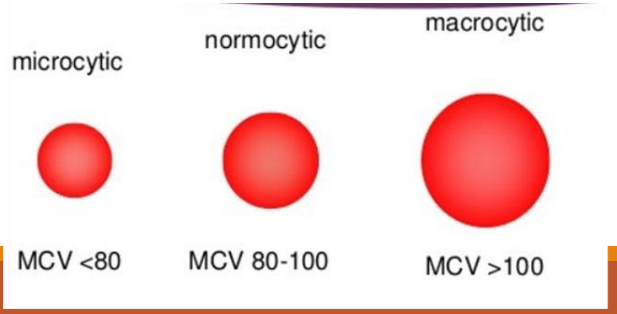
Complete Blood Count

- **RBC Count:** the number of RBCs per unit of volume
- **Hematocrit:** is a measure of the proportion of blood that is composed of red blood cells.
- **Mean Corpuscular Volume (MCV):** The average size of the red blood cells.
- **Mean Corpuscular Hemoglobin (MCH):** The average amount of hemoglobin per red blood cell
- **Mean Corpuscular Hemoglobin Concentration (MCHC):** The average amount of hemoglobin in a given volume of red blood cells.
- **Red Cell Distribution Width (RDW):** The variation in size of red blood cells in a sample

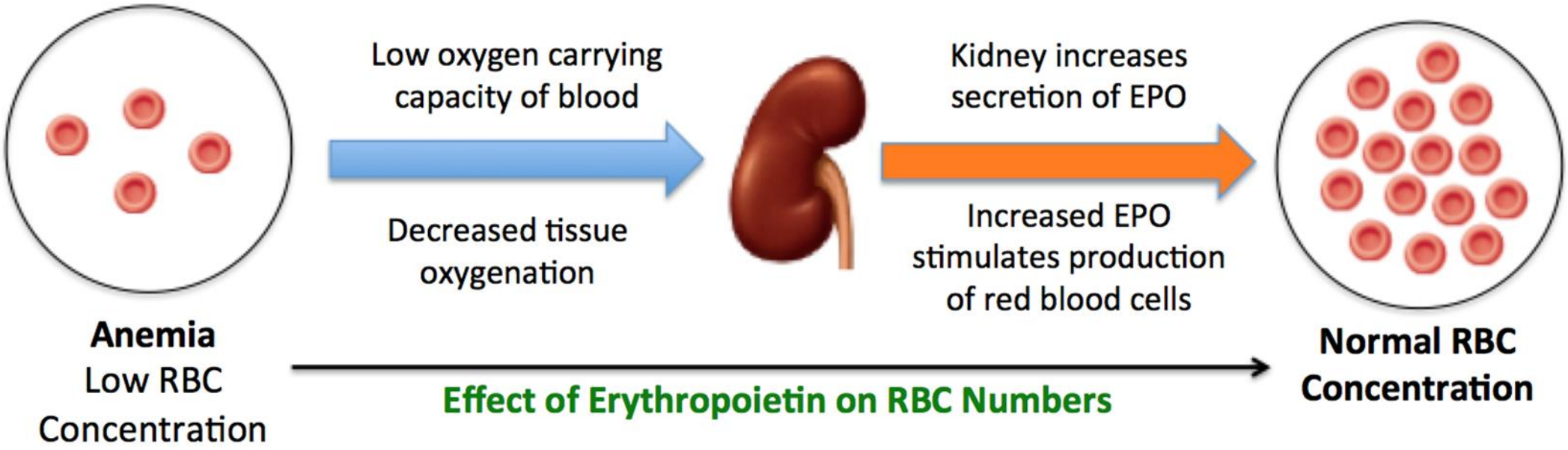
MCH


Hyperchromic
Normochromic
Hypochromic
Macrocytes
Normocytes
Microcytes

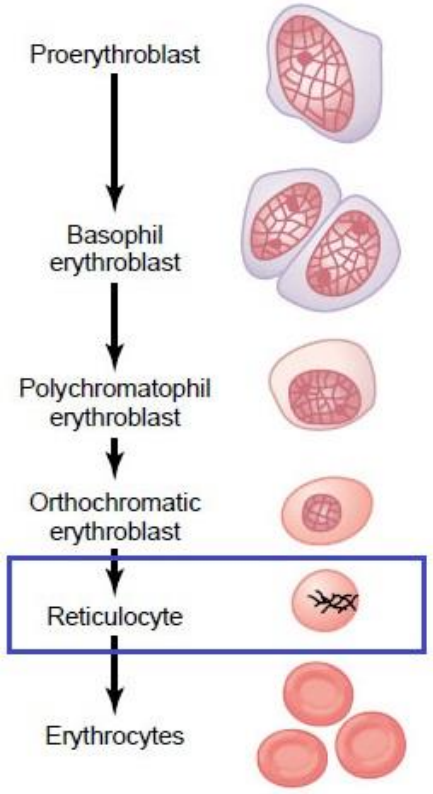
MCV

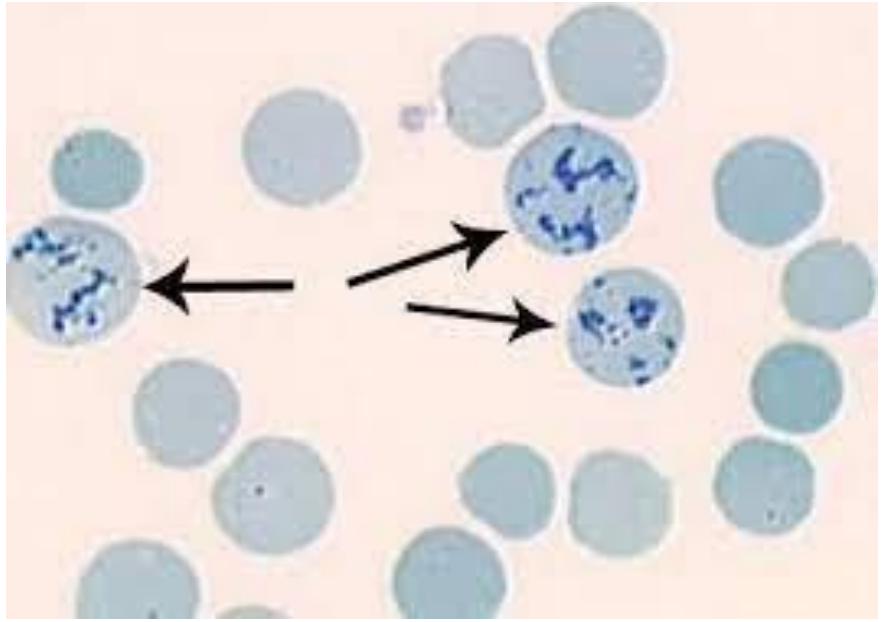

microcytic
normocytic
macrocytic
MCV <80
MCV 80-100
MCV >100

Body response to anemia



Reticulocytes





- **Reticulocyte** is an immature rc that has lost its nucleus and retains aggregates of **RNA** within its ribosomes
- RNA decreases as rc matures
- Reticulocytes remains in BM for 2 days and 1 day in peripheral blood

> **Reticulocyte count** – can be used to assess *BM erythropoietic activity*

Reticulocyte Count

- ✓Anemias are categorized on the basis of the adequacy of the reticulocyte response.
- ✓**An elevated reticulocyte count implies a bone marrow response** to either increased RBC destruction (hemolysis) or acute or chronic blood loss.
- ✓**In patients with moderate or severe anemia, the reticulocyte count may appear elevated, but in absolute terms, it may be insufficient for the degree of anemia.**

Reticulocyte Index (RI)

$$\text{Corrected Reticulocyte Count} = \text{Reticulocyte \%} \times \frac{\text{Actual Hct}}{\text{Normal Hct}}$$

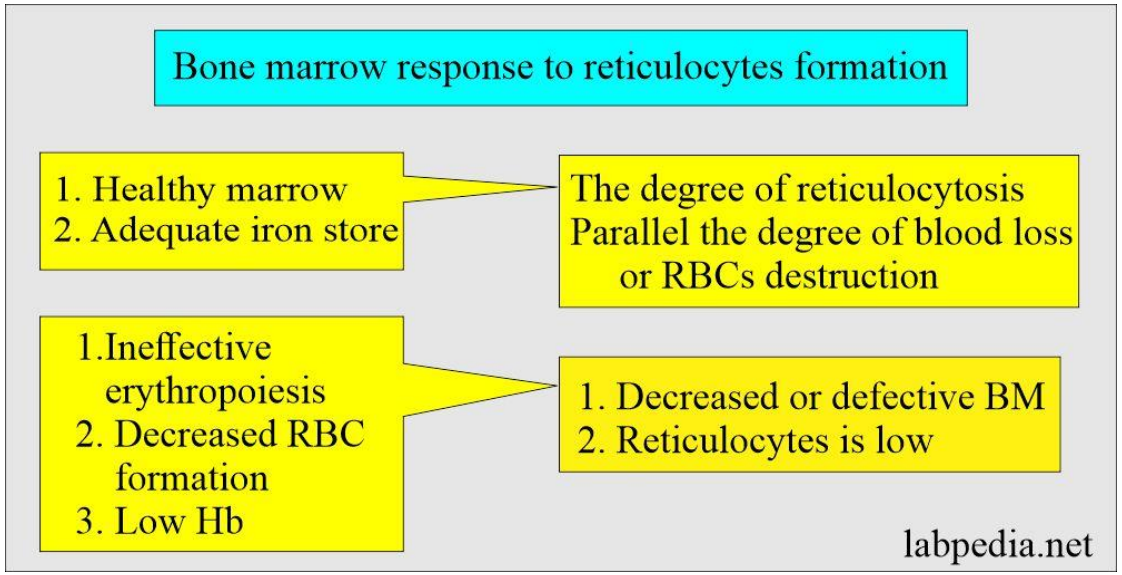
Normal Hct ≈ 45

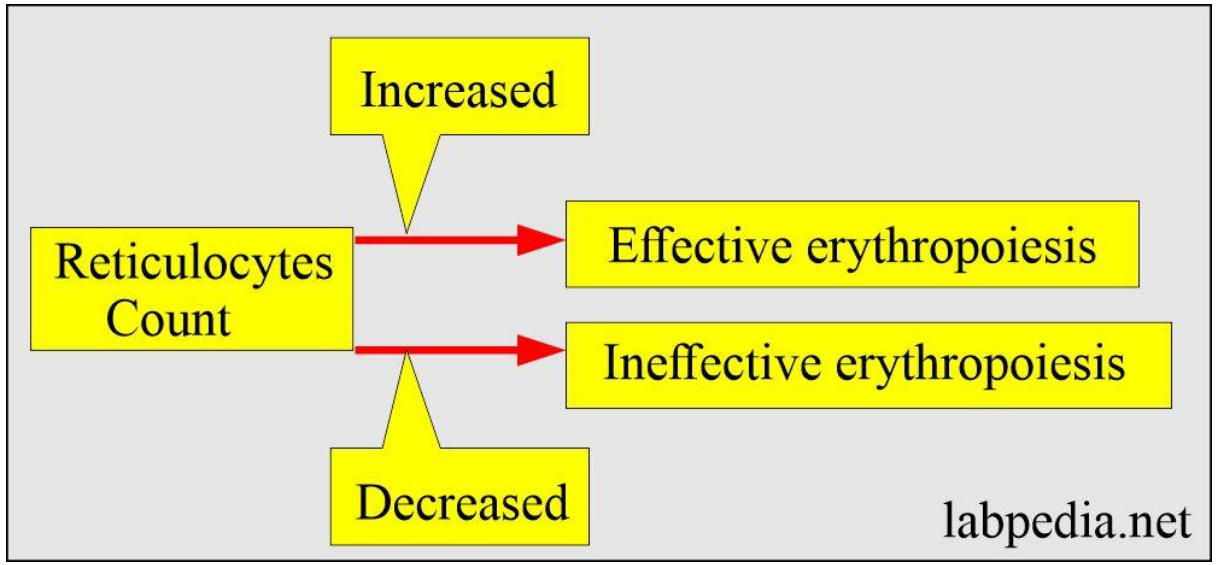
RI should be between 0.5-2.5% in healthy patients

RI < 2% with anemia = inadequate response to correct anemia

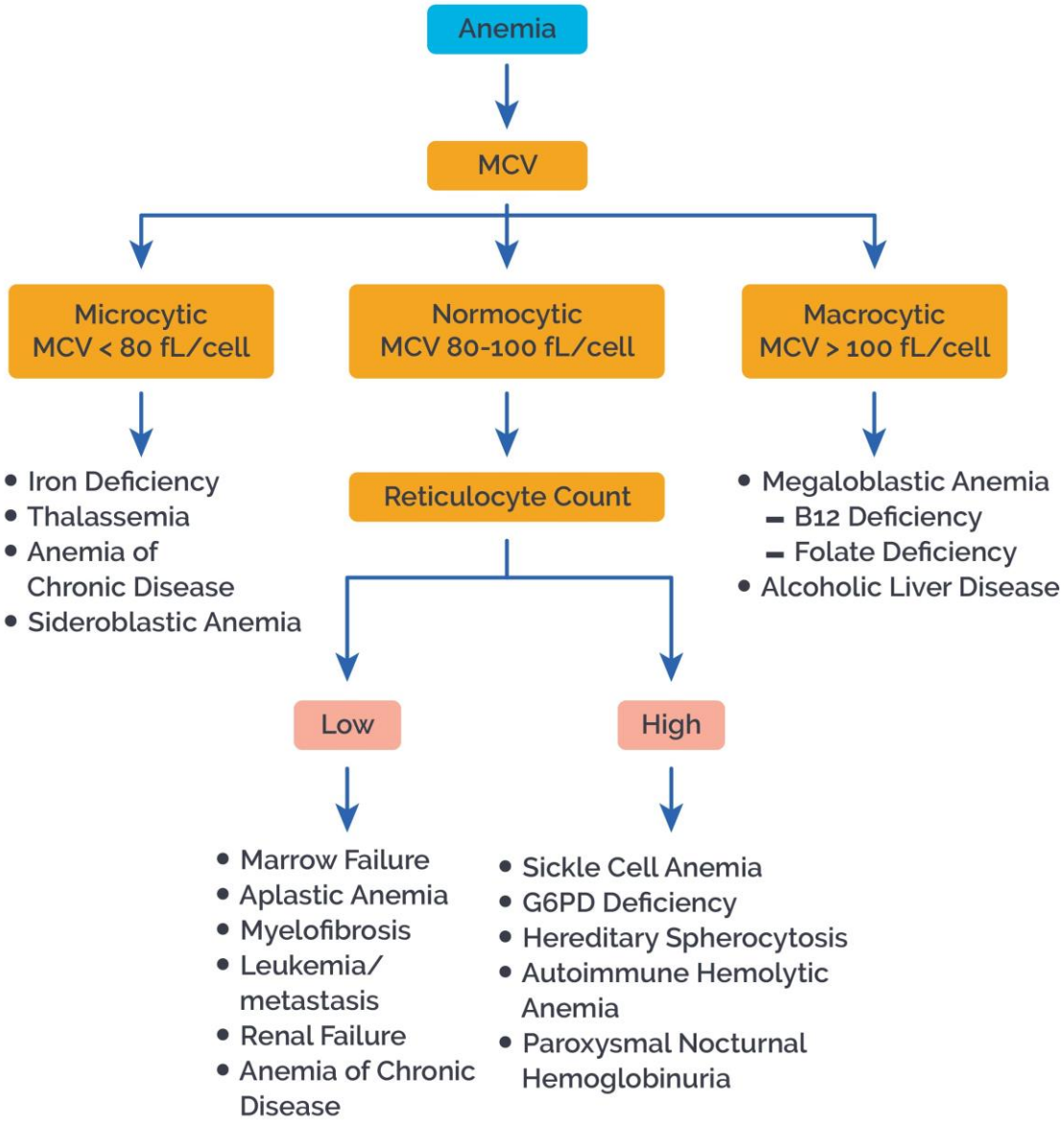
RI > 3% with anemia = compensatory production of reticulocytes

Reticulocytosis reflects marrow response to anemia

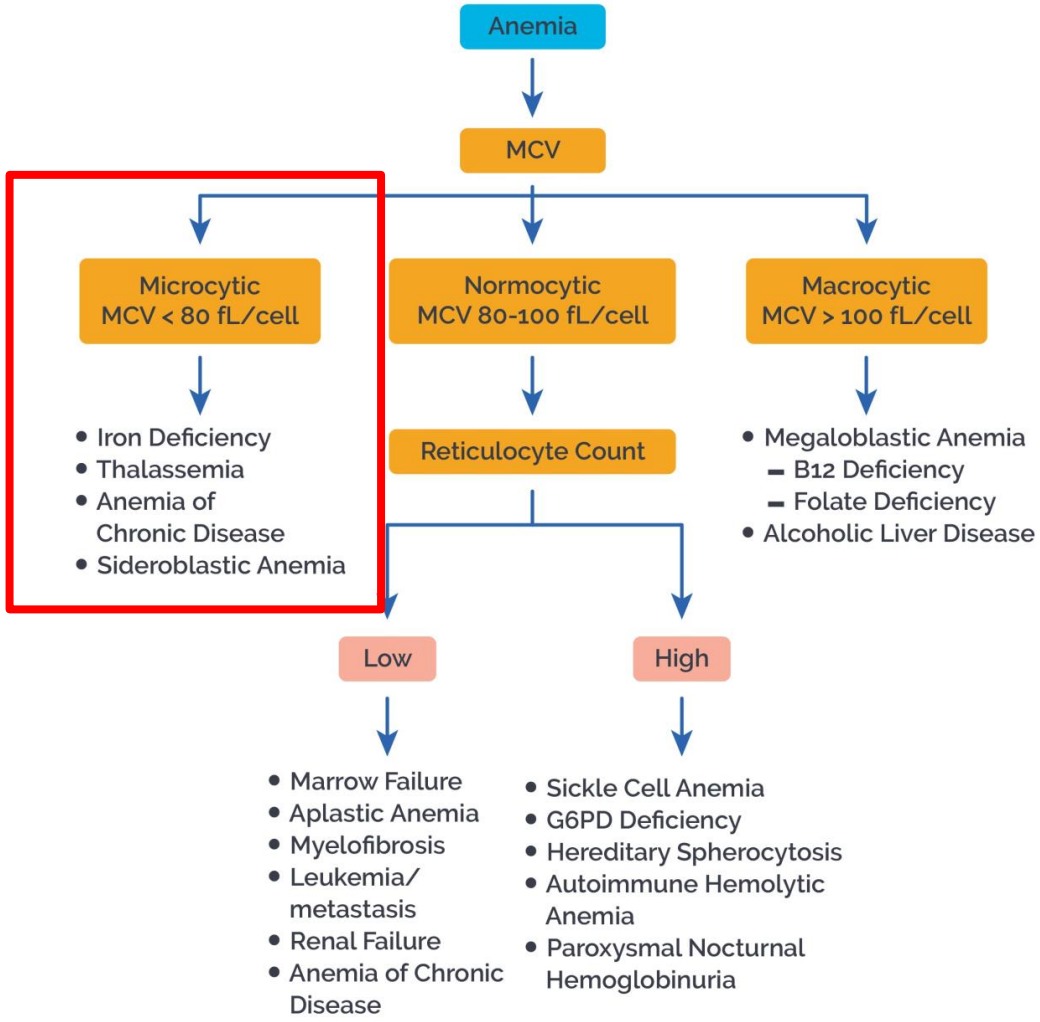




CLASSIFICATION OF ANEMIAS



CLASSIFICATION OF ANEMIAS



Microcytic anemia

- The main problem in microcytic anemia is **decreased production of Hb**

- RBC is produced from subsequent division of erythroblasts, and during Hb deficiency, erythroblasts divides too much. As a result, RBCs become small and microcytic anemia occurs.

THE RISK OF Iron Deficiency

IRON DEFICIENCY IS THE MOST COMMON NUTRIENT DEFICIENCY
IN THE WORLD[1]

4 TO 5 BILLION

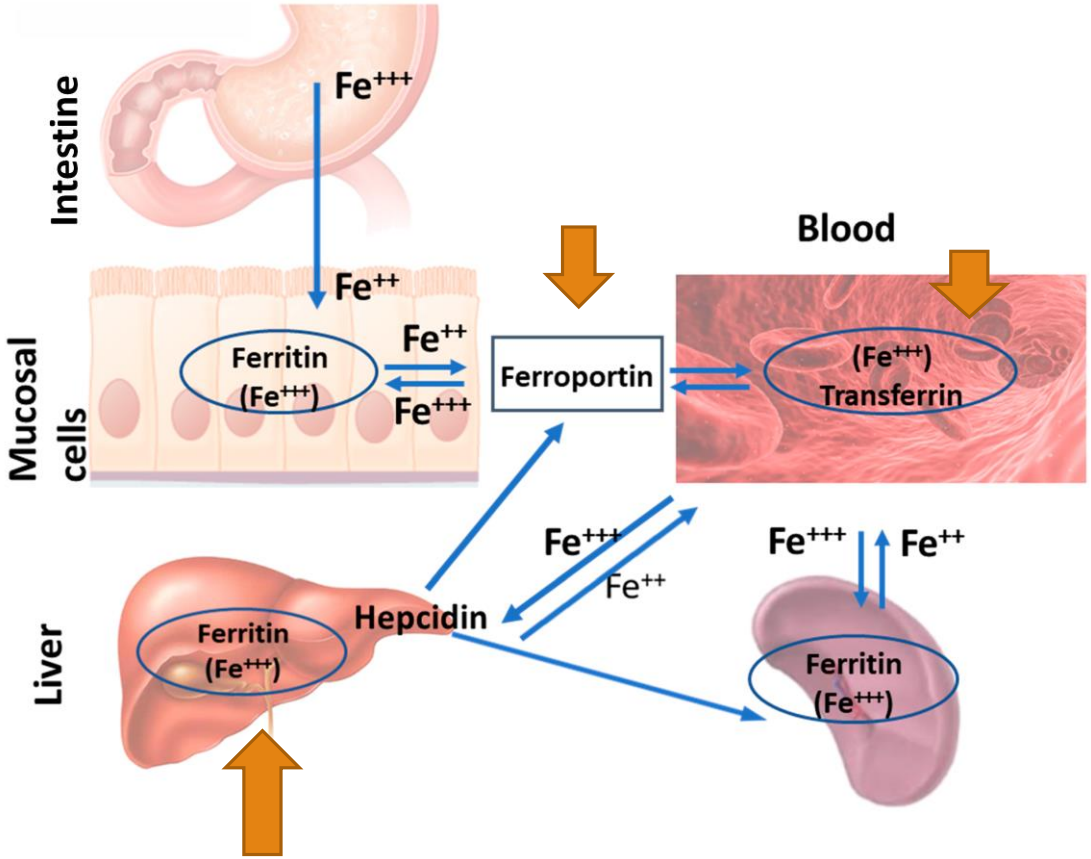
Up to 4 to 5 billion people may suffer from iron deficiency.[2]

Although prevalences can vary across communities, iron deficiency anaemia affects approximately 15% of the world population.[3]

111 MILLION

In the high developed countries, 9.1% of the population is affected resulting in 111 million affected people.[4]

Review of normal iron metabolism



➢Fe is absorbed in **duodenum**. Protein called **FERROPORTIN -** transports Fe from lumen to enterocyte to blood.

➢ **TRANSFERRIN** transports iron in blood and takes it to liver and bone marrow macrophages for storage

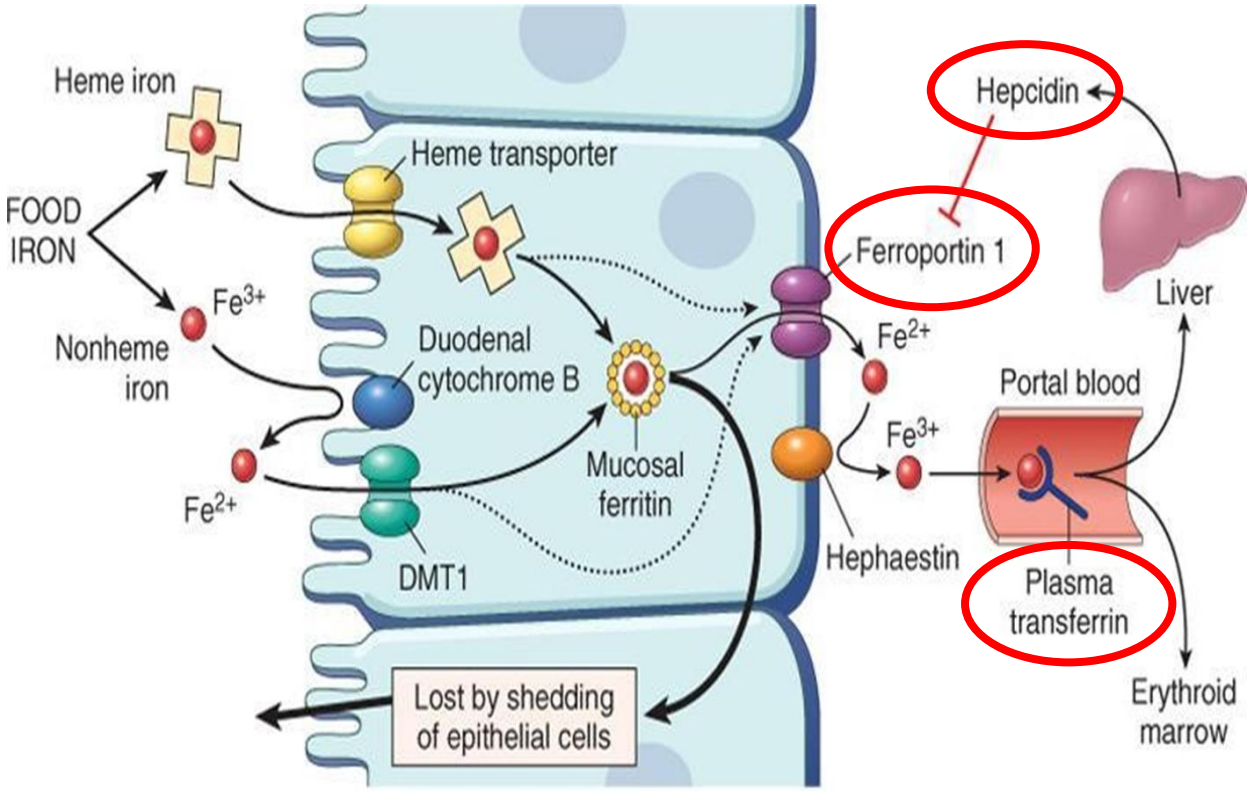
➢ Stored intracellular iron is bound to **FERRITIN (high is a good indicator of the adequacy of body iron stores)**

Review of normal iron metabolism

➢Normally, **1 in every 3 transferrin in blood is bound to Fe.**

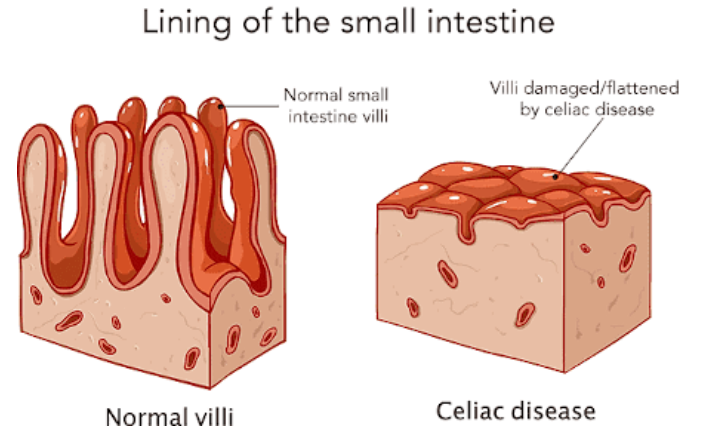
➢There is no real way to get rid of Iron from body. So, absorption by enterocytes is regulated (some by shedding and menstruation)

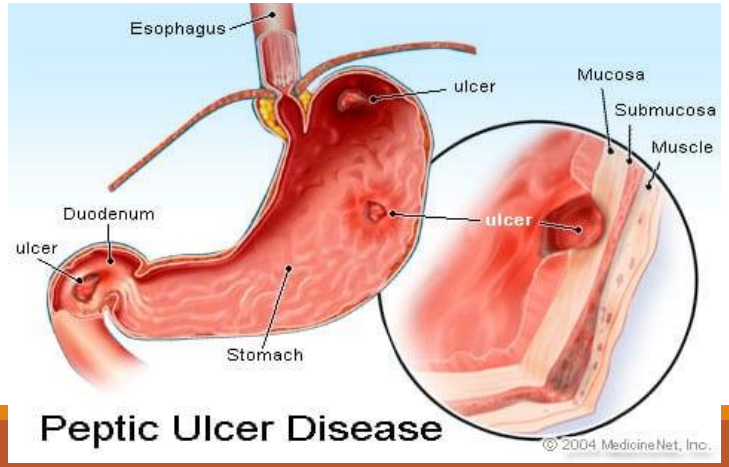
➢To regulate iron absorption, **Hepcidin** is produced from the liver, it interacts with ferroportin, and inhibits iron absorption from the gastrointestinal tract.



Causes of Iron deficiency anemia

- Malnutrition (vegetarian diet)
- Malabsorption as in celiac disease, or after gastrectomy (acid is needed for Fe absorption)
- Increased demands as in pregnancy & labor & infancy
- Chronic blood loss, such as gynecological bleeding (menorrhagia) and GIT bleeding (peptic ulcer, cancer, polyps, Inflammatory bowel disease and others)





Iron deficiency anemia Pathophysiology

- Iron is essential for hemoglobin synthesis during erythropoiesis
  - Impaired delivery of iron to erythroid precursors results in decreased erythropoiesis

- Iron deficiency leading to IDA is a chronic process
  - Initially normal RBCs are produced
  - Later, decreased iron transport to bone marrow results in microcytic hypochromic RBCs

Iron deficiency anemia

Fe lab measurement:

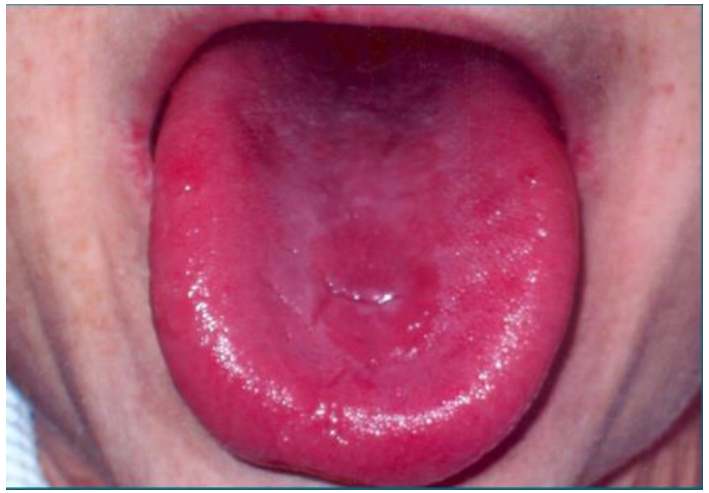
- **Serum Fe** – measures Fe in blood (most of it is bound to transferrin)
- **TIBC (total iron binding capacity)** – tells total transferrin in blood. Normally, 1 in every 3 transferrin in blood is bound to Fe.

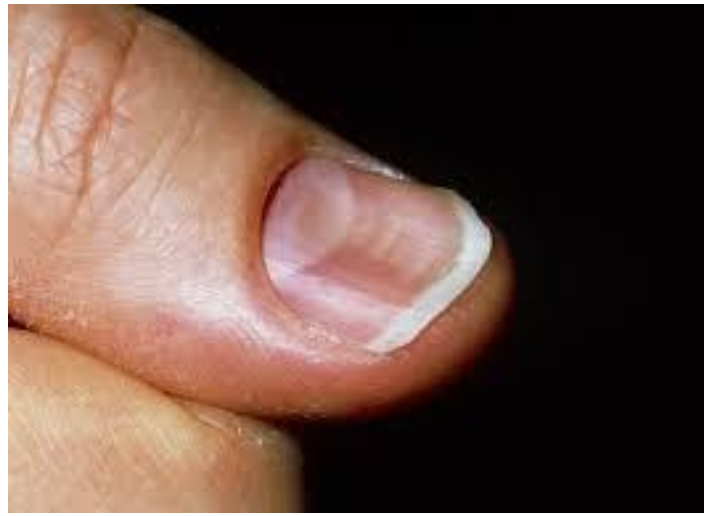
- **% saturation** – % saturation of transferrin by Fe
- **Serum ferritin** – indication of how much Fe is in storage sites

- **When ferritin↓, TIBC ↑ and vice versa**

Iron deficiency anemia
Clinical presentation

- In most cases iron deficiency anemia is asymptomatic.
- Anemia symptoms “**weakness** and **pallor"** may be present in severe cases
- With long-standing severe anemia, thinning, flattening, and eventually **"spooning" of the fingernails** sometimes appears. Also called **Koilonychia** (spoon shaped nails)
- Sometimes Pica (psychological drive to eat dirt – perhaps to get Fe) may develop with long standing anemia
- Glossitis and angular stomatitis (cheilitis)





Iron deficiency anemia
Clinical presentation

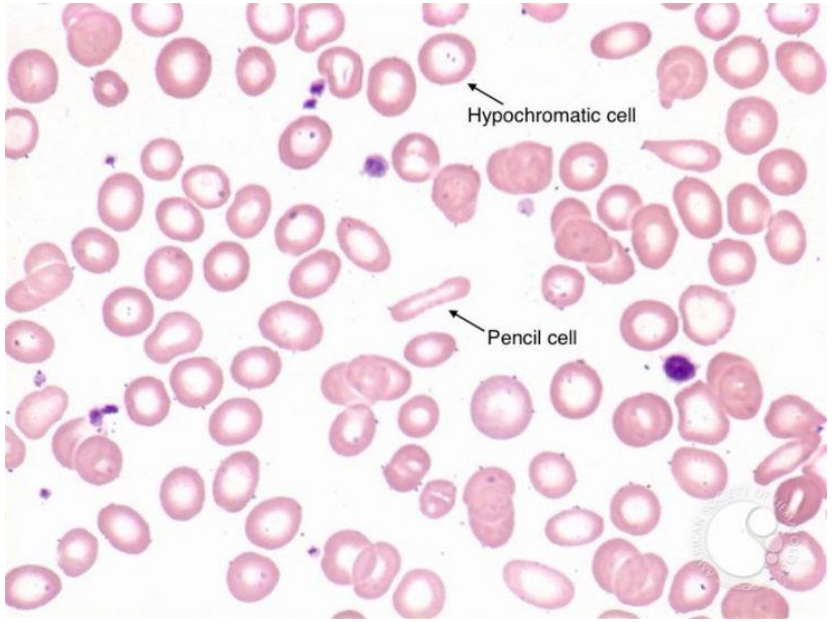
Iron deficiency anemia
Lab findings

- **Microcytic, hypochromic anemia** with ↑RDW

(RDW is like standard deviation of size of RBC; larger the variation in RBC sizes, larger the RDW)

- ↓ferritin, ↑TIBC
- ↓serum iron, ↓%saturation
- **Blood smear**: Microcytic anemia with:

Poikilocytosis (variable shapes), anisocytosis (variable size), cigarette-shaped RBC or pencil cell



Blood smear – Iron def. anemia

Iron deficiency anemia Treatment

- It is easy to treat (iron supplementation) and saves unnecessary tests/treatments.
- It may be the earliest manifestation of a serious underlying diseases (10-20% of iron deficient patients have cancer, up to 50% have PUD).

Anemia of chronic disease/anemia of inflammation (ACD/AI)

Anemia of chronic disease/anemia of inflammation (ACD/AI)

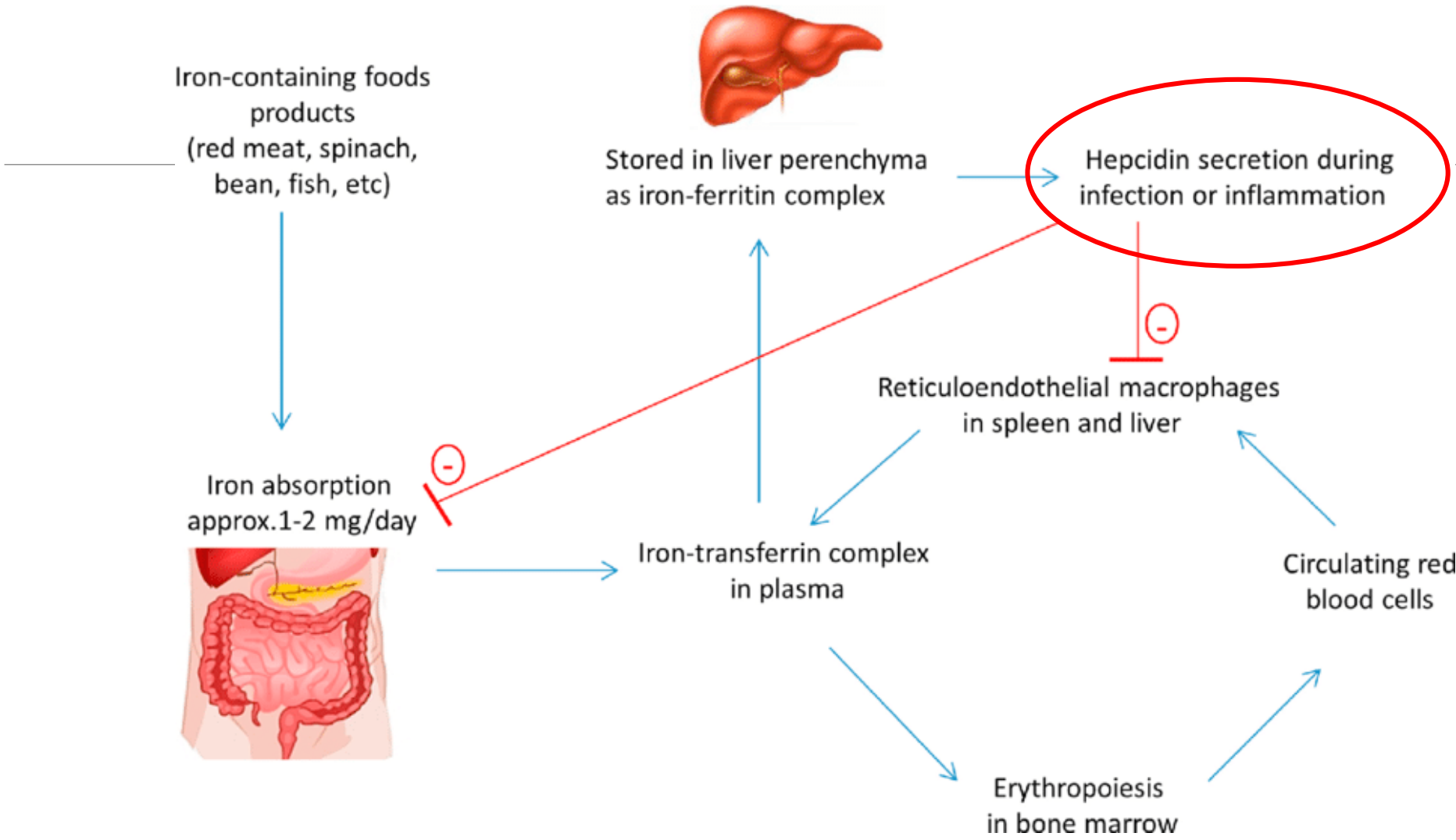
- Anemia of chronic disease (ACD) is the most common anemia in hospitalized patients

Pathophysiology: during acute/chronic inflammation, acute phase proteins are produced (an example is Hepcidin).

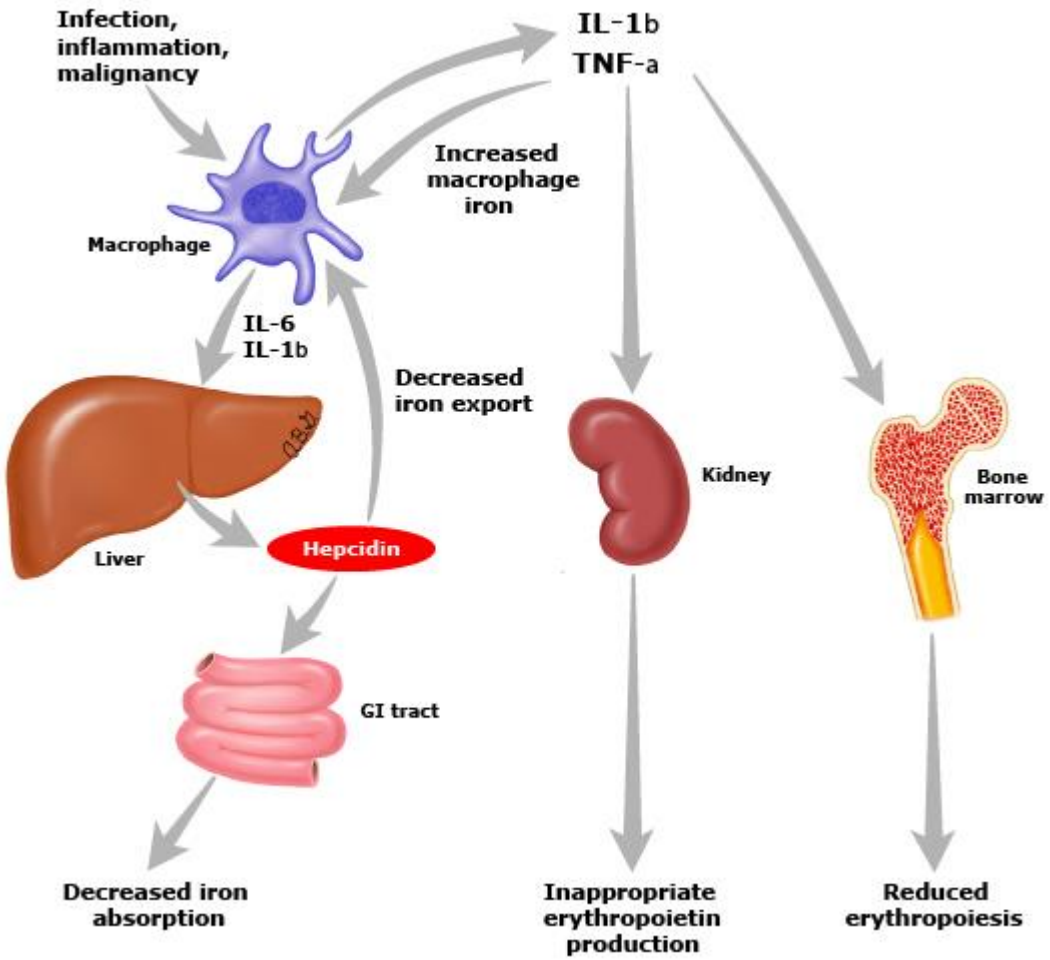
Hepcidin causes anemia by:

1. ↓Erythropoietin production (indirectly by IL-1b and TNF-a)
2. Hepcidin interacts with iron export protein ferroportin, thus inhibiting iron absorption from the gastrointestinal tract.
3. Decreases release of iron from macrophages.

Note: advantage of Hepcidin is that bacteria need Fe to grow and flourish.


Iron-containing foods products (red meat, spinach, bean, fish, etc)
Stored in liver perenchyma as iron-ferritin complex
Hepcidin secretion during infection or inflammation
Reticuloendothelial macrophages in spleen and liver
Iron absorption approx.1-2 mg/day
Iron-transferrin complex in plasma
Circulating red blood cells
Erythropoiesis in bone marrow

Mechanism for anemia of chronic disease/anemia of inflammation (ACD/AI)



A proposed mechanism for ACD/AI is shown here. In the presence of infection, inflammation, or malignancy, the **macrophage is stimulated to produce IL-6 and IL-1b,** which **induce the production of hepcidin by the liver.**

Hepcidin reduces plasma iron levels characteristic of ACD/AI.

Inflammatory cytokines such as IL-1b and TNF-a reduce erythropoietin production

Anemia of chronic disease/anemia of inflammation (ACD/AI)

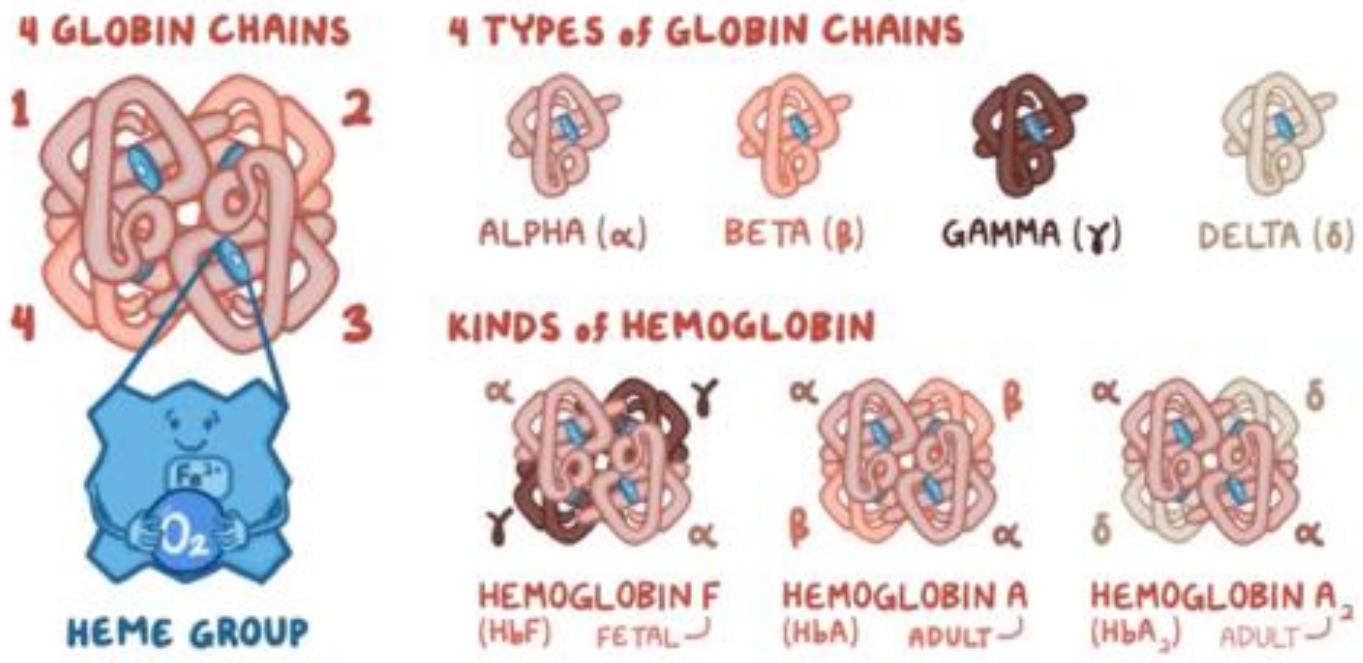
Lab findings in ACD:

- ↑ferritin, ↓TIBC
- ↓serum iron (bone marrow takes Fe from serum as macrophage isn't giving it)
- ↓% saturation

Treatment of ACD:

- Treat underlying cause of chronic disease (to reduce hepcidin)
- Exogenous erythropoietin (especially helpful in cancer patients)

Thalassemia



Normal globin molecule in hemoglobin

In adults, HbA is the major hemoglobin (97%), composed of ($\alpha_2\beta_2$) with minor amount of HbA2 (1.5 - 3.5%; α2δ2) and HbF (< 1%; α2γ2)

Thalassemia

A heterogeneous group of inherited disorders caused by mutations that decrease the rate of synthesis of α- or β-globin chains.

- Can be of two types :

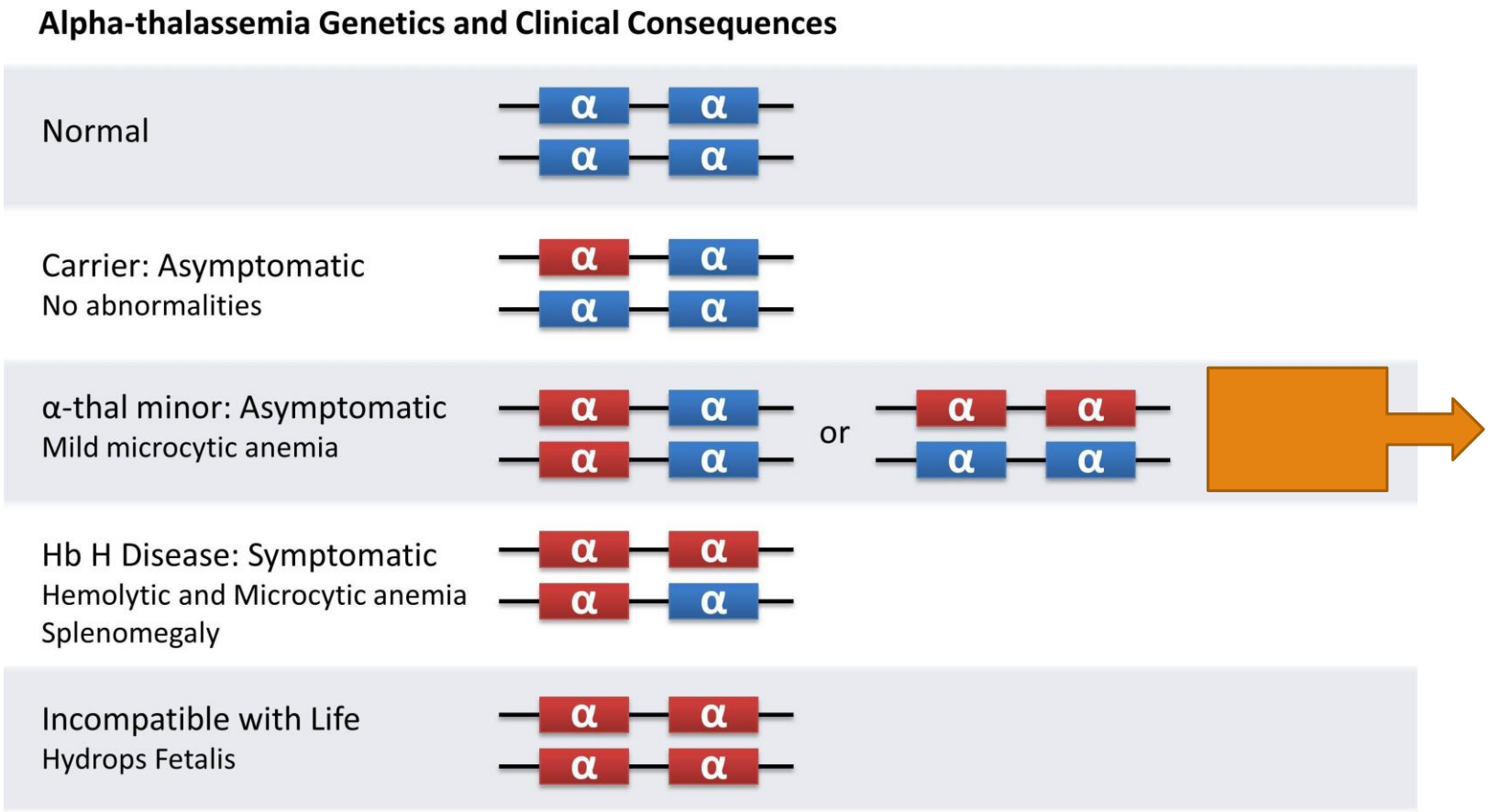
- **α-thalassemia** : characterized by deficient synthesis of **α-globin chains**
- **β-thalassemia** : caused by deficient synthesis of **β-globin chains**

So, there is a deficiency of hemoglobin, with additional secondary red cell abnormalities caused by the relative excess of the other unaffected globin chain.

α-thalassemia

- ✓ **α-thalassemia is caused due to gene deletion of alpha chain of hemoglobin.**
- ✓Two α-globin genes are located on each **chromosome 16**, resulting in **4 α-gene loci (αα/αα)**
- ✓**Severity of α-thalassemia depends** on the **number of deleted alpha loci**
- ✓**α-thalassemia is usually inherited in an autosomal recessive manner**
- ✓**It results in low levels of hemoglobin, decreased mean corpuscular volume (MCV) and decreased mean corpuscular hemoglobin (MCH)**

α-thalassemia: 4 types



Cys deletion (deletion of both allele on same chromome) is worse than trans deletion (deletion of two allele on different chromosome)

Because cys is associated with increased risk of severe thalassemia in offspring

α-thalassemia; 4 types

1. **Bart's hydrops fetalis syndrome:** complete absence of all 4 α chains (--/--)

   - Because of the absence of α chains, **no HbA or HbF is present**
   - There is excess production of gamma globin of the HbF which is called **Hb Barts (γ4)** .
   - Hb Bart's have an extremely high oxygen affinity and are incapable of effective oxygen delivery
   - **Incompatible with life**, fetuses are still born with severe anemia, marked edema and hepatosplenomegaly

α-thalassemia; 4 types

2. HbH disease: absence of 3 α chains (--/-α)

- There is excessive HbH (β4) hence called HbH disease .
- This HbH has a high affinity to oxygen (10 X the affinity of HbA) but it cannot transfer oxygen to the cells properly.
- RBC have precipitated HbH and damaged walls, so they are phagocytosed in the spleen.
- Chronic hemolytic anemia, mild jaundice and hepatosplenomegaly
- Most individuals clinically do well and survive; transfusion is rarely needed

α-thalassemia; 4 types

3. α-thalassemia trait: absence of 2 α chains either (--/αα) or (-α/-α)

- Benign condition with most patients diagnosed on routine screening
- Does not require treatment

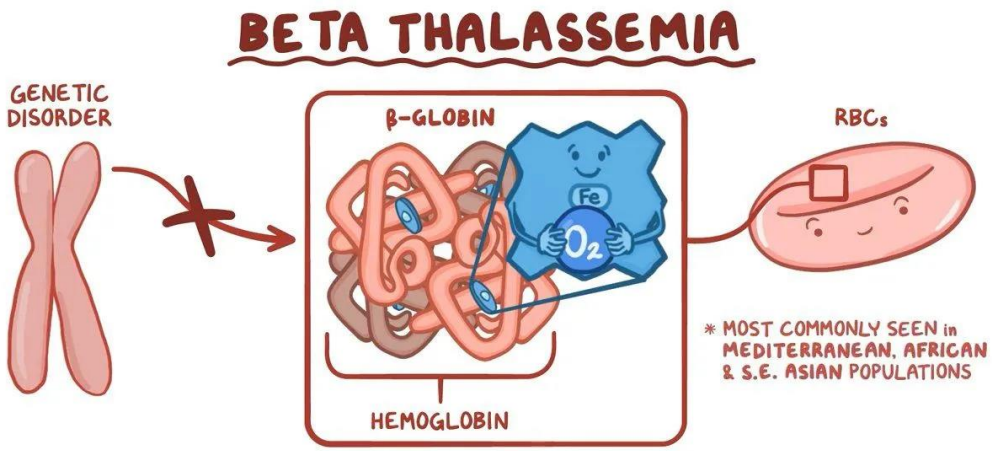
4. α-thalassemia silent carrier: absence of 1 α chain (αα/-α)

- No clinical abnormalities

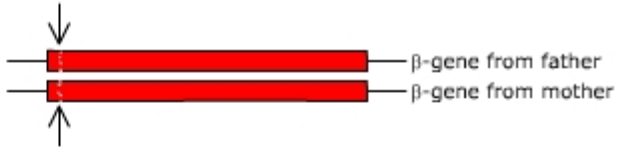
Diagnosis of thalassemia is done by CBC, electrophoresis, blood smear, family hx

α-thalassemia; lab findings

- **Hb Bart's hydrops fetalis syndrome:**
  - CBC: severe microcytic hypochromic anemia and reticulocytosis
  - Hb Bart’s > 80%
- **HbH disease:**
  - CBC: decreased MCV and MCH, and reticulocytosis
- **α-thalassemia trait:**
  - CBC: may show mild hypochromic (low MCH), microcytic (low MCV) anemia
- **α-thalassemia silent carrier:**
  - CBC: either normal or mild reduction of MCV and MCH



With a mutation on one of the two β-globin genes, a carrier is formed with lower protein production, but enough hemoglobin



Without a mutation enough Hemoglobin

No thalassemia carrier

With one mutation less Hemoglobin

β-thalassemia carrier without illness, but less hemoglobin (slight aneamia)

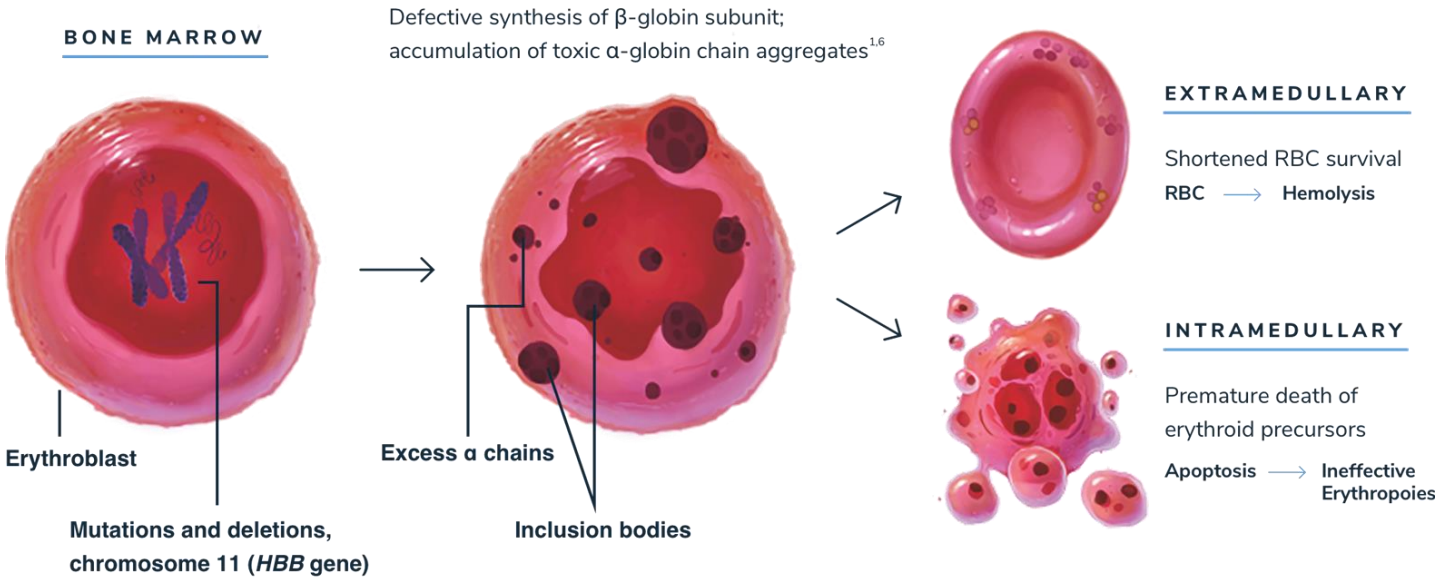
With two mutations no β-globin

β-thalassemia major patient with severe aneamia

β-Thalassemia

β-Thalassemia

- Inherited in an **autosomal recessive manner**
- Beta thalassemia is caused due to **gene mutation of beta chain of hemoglobin**. Mutations result in absent (aka **B0**) or diminished (aka **B+**) production of B-globin chain.
- Normally, 2 beta alleles are present on chromosome 11 (1 allele per chromosome)



β-Thalassemia; types

Types	Alleles	Description
Thalassemia minor	β^+/β β^o/β	Only one of β globin alleles has a mutation. Patients will have microcytic anemia (MCV <80 fL)
Thalassemia intermedia	β^+/β^+ β^o/β^+	Patients can have a normal life, but may need occasional transfusions, example at times of increase demand (illness or pregnancy)
Thalassemia major	β^o/β^o	Severe microcytic, hypochromic anemia. Untreated, causes anemia, splenomegaly and severe bone deformities, and death before age 20. Treatment is blood transfusion; splenectomy for splenomegaly and chelation for iron overload

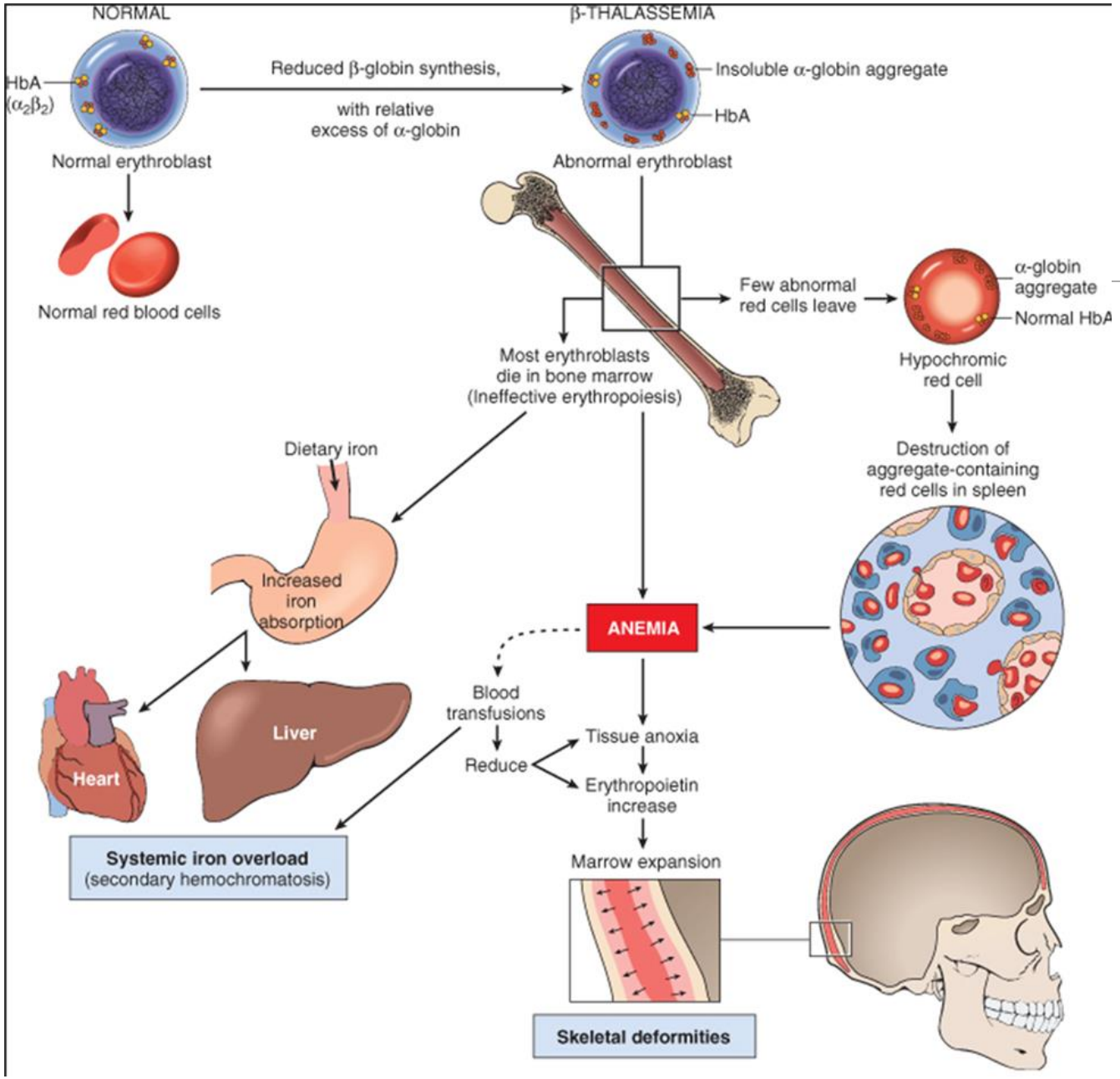
Mutations as (βo) means no formation of β globin - mutations (β+) means some β globin chain is formed

β Thalassemia Minor

- ✓ Is much more common form of thalassemia , also affects most commonly individuals in Mediterranean countries and parts of Southeast Asia & Africa .
- ✓ The patients are heterozygous therefore asymptomatic & anemia is mild if it is present .
- ✓ The abnormalities are confined to peripheral blood and CBC.
- ✓ Peripheral blood smear show hypochromic microcytic anemia.
- ✓ There is increased Hb A2, while Hb F may be normal or increased .

β-Thalassemia Major

- ✓ Affects individuals in Mediterranean countries and parts of Southeast Asia & Africa .
- ✓ Most individuals inheriting any two βo have β-thalassemia major .
- ✓ The patients are homozygous .
- ✓ The anemia manifests at 6th-9th months after birth as Hb synthesis switches from HbF to HbA
- ✓ Affected children fail to develop normally and their growth is retarded .
- ✓ With transfusions alone the survival into the second & third decades is possible, but gradually they develop iron overload , hemochromatosis & heart failure .



β-Thalassemia Pathogenesis

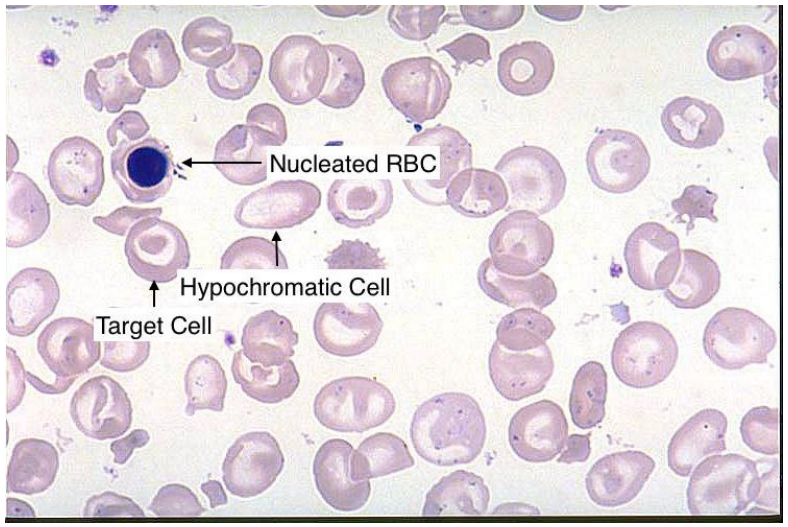
Pathogenesis of β thalassemia

- β chains not produced →α chains accumulate in normoblasts → destruction of normoblasts in bone marrow → ineffective erythropoiesis ↓
- Anemia → → Hypoxia in tissues
- ↓
- ↓ →↑erythropoietin production by renal cells .
- ↓ ↓
- Extramedullary hematopoiesis
- ↓ ↓
- Bone changes + cardiac failure & ↓ death.
- Repeated blood transfusions.
- ↓
- Iron overload “Secondary Hemochromatosis”

β-Thalassemia Major

Morphology :

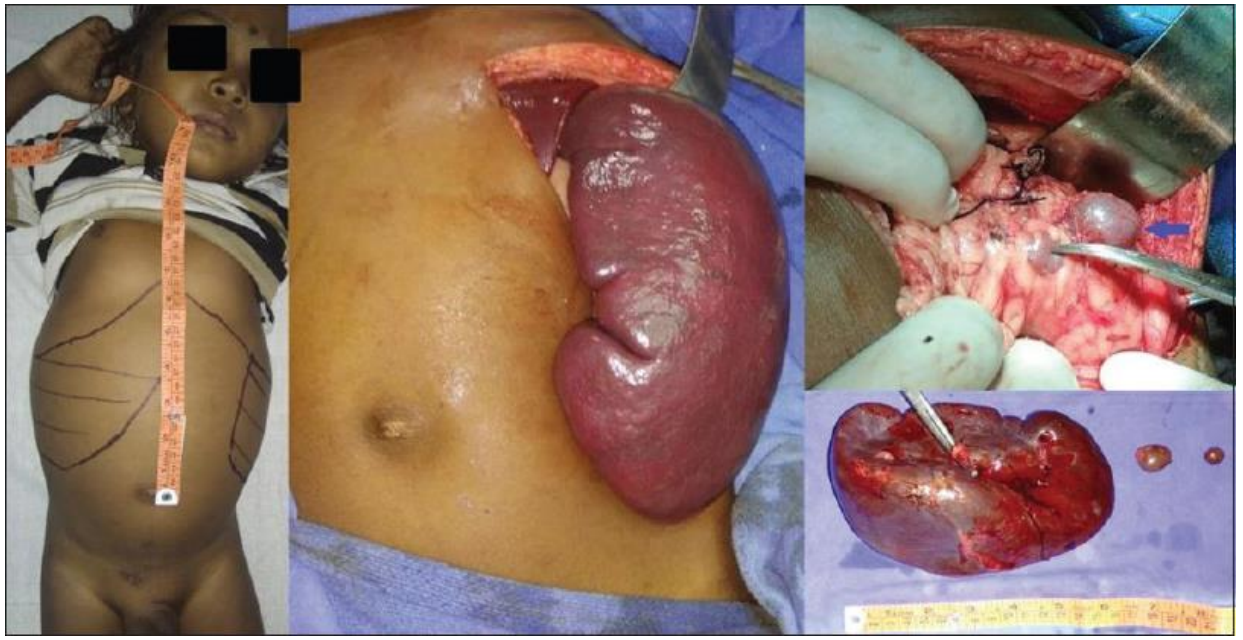
- **Peripheral blood** shows microcytic hypochromic red blood cells with variation in shape of RBCs called (poikylocytosis) & variation in size of cells called (anisocytosis) with **target cells**
- **Bone marrow** is hypercellular with erythroid hyperplasia .



Peripheral blood

β thalassemia major “splenomegaly”

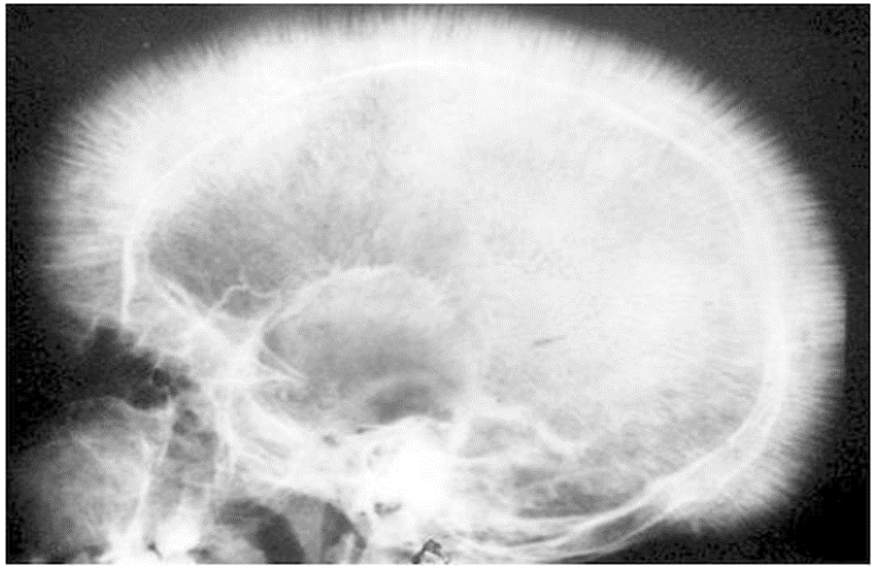
Extramedullary hematopoiesis occurs in the liver & spleen causing prominent splenomegaly (up to 1500 grams) & hepatomegaly.

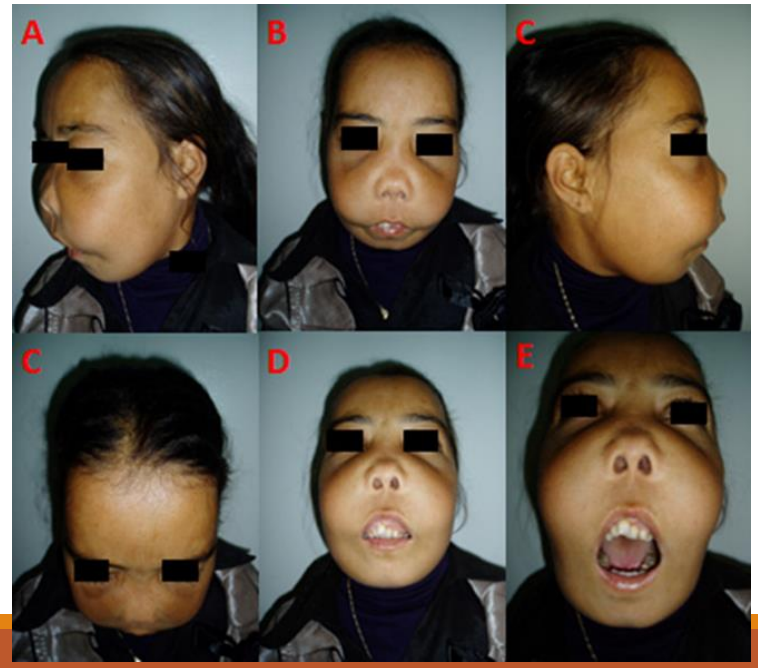


β thalassemia

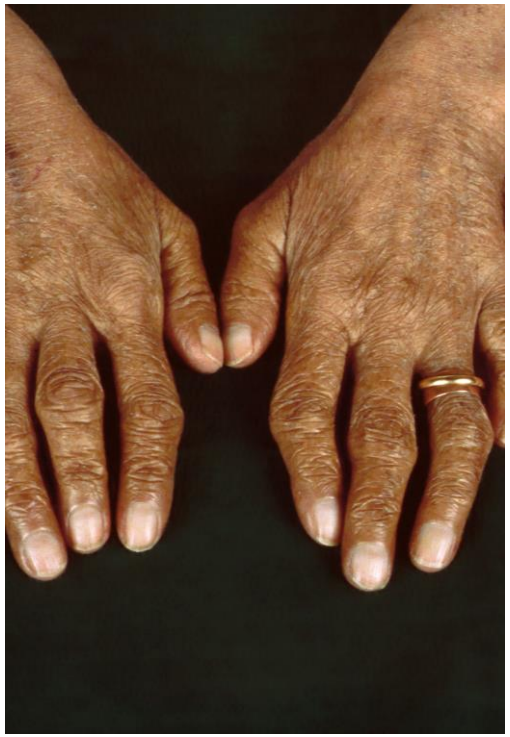
The ineffective erythropoiesis & red cell hemolysis stimulates erythropoietin secretion.

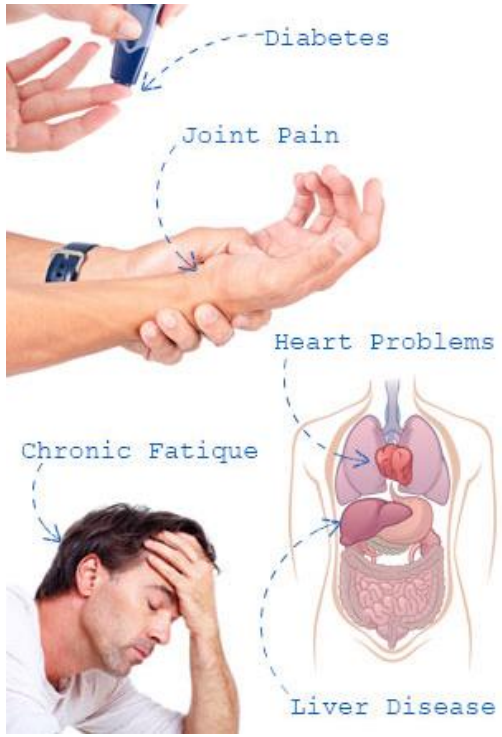
This causes severe erythroid hyperplasia and skeletal deformities due to expanded hyperplastic marrow invading the bone cortex giving an appearance of what is called "hair on end" as in the skull also there is a delay of bone growth.





β thalassemia





Another disastrous effect is the excessive absorption of iron together with frequent blood transfusions given to the patients will lead to **secondary hemochromatosis due to increased iron overload.**

Progressive hemochromatosis is an important cause of death.

Diagnosis of **β thalassemia**

- The diagnosis of β-thalassemia minor is made by **Hb electrophoresis**.
- In addition to reduced amounts of HbA (α2β2), the level of HbA2 (α2δ2) is increased.
- The diagnosis of β-thalassemia major can generally be made on clinical grounds.

Treatment: chronic blood transfusion; splenectomy and iron chelation to prevent secondary hemochromatosis

Thalassemia – extra notes

- **Parvovirus B19** is a virus that affects erythrocyte precursors and shuts down RBC production. In a normal person, shutting down RBC production for a week would not affect the person.

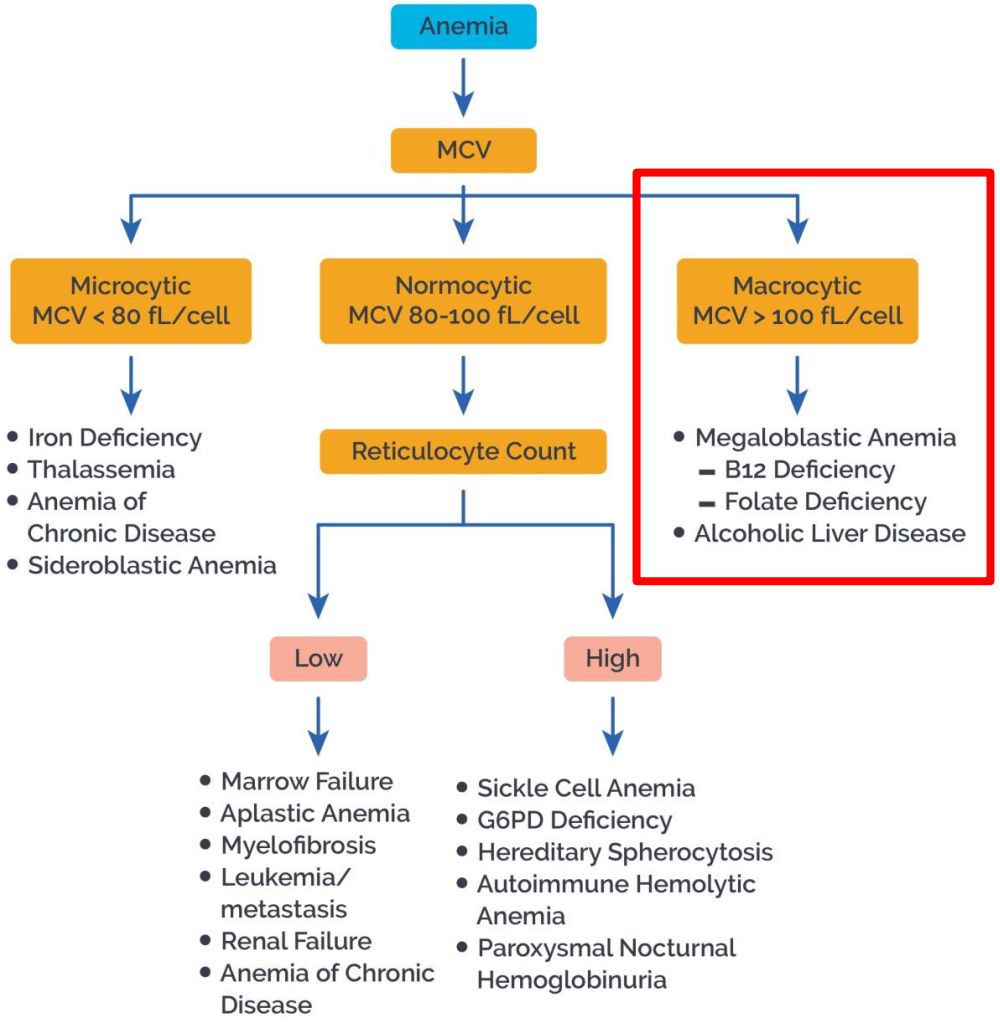
However, patients with β-thalassemia major cannot tolerate RBC production loss. So, they have a high risk of developing an aplastic crisis.

- It was found that patients with thalassemia are **protected against malaria infection by plasmodium falciparum.**

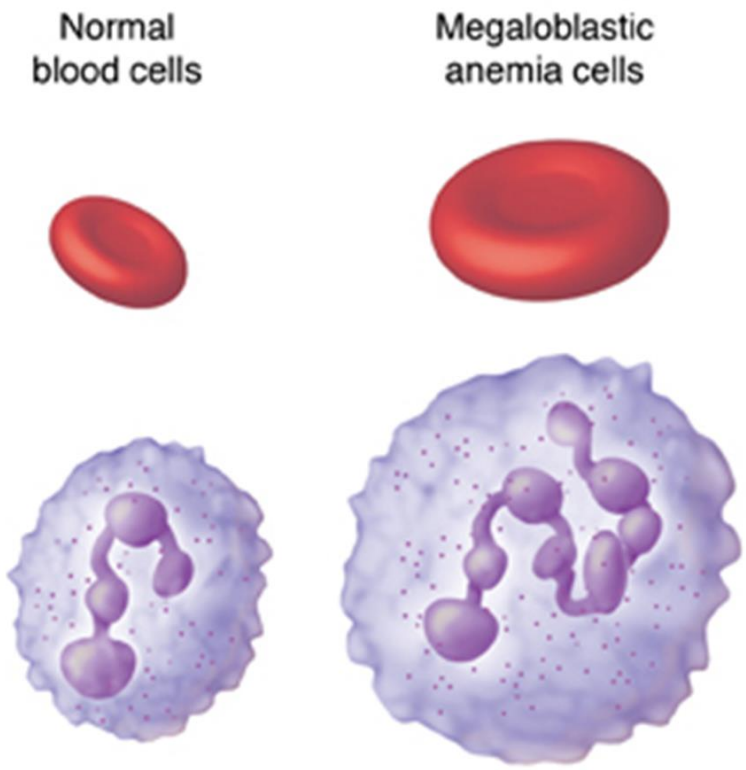
Iron panel for microcytic anemias

	Iron Deficiency	AOCD	Thalassemia Minor
Serum iron	↓	↓	Normal
TIBC	↑	↓	Normal
% saturation	↓	↓	Normal
Serum ferritin	↓	↑	Normal

CLASSIFICATION OF ANEMIAS



Macrocytic anemia



MACROCYTIC ANAEMIA

MEGALOBLAST

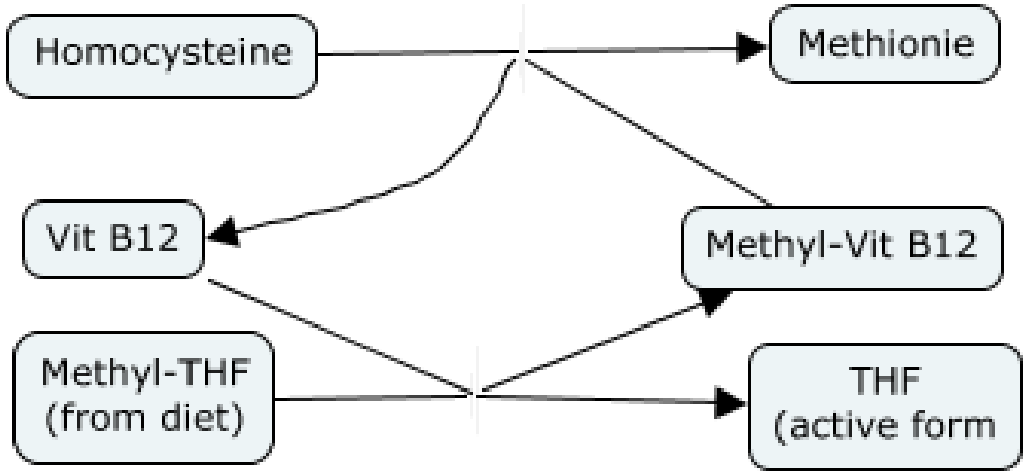
- **B12 deficiency** (e.g. pernicious anaemia)
- **Folate deficiency** (e.g. dietary insufficiency)

NON-MEGALOBLAST

- **Alcohol**
- **Reticulocytosis** (e.g. haemolysis)
- **Liver disease**
- **Hypothyroidism**

Folate and Vitamin B12

- Both **folate** and **Vit B12** are involved in DNA precursor synthesis
- Folate comes to body as methylated tetrahydrofolate (**M-THF**).
- **THF** is the active form. M-THF donates its methyl group to Vit B12. Vit B12 then gives methyl group to homocysteine.
- **Homocysteine** now becomes **methionine**.



Megaloblastic anemia

Megaloblast: abnormal erythroid precursors showing nuclear: cytoplasmic dyssynchrony (more immature nucleus for the degree of maturity of the cytoplasm)

Macrocyte: mature red blood cell with increased MCV (100 - 110 fL)

Megaloblastic anemia is a disorder of impaired DNA synthesis (with normal RNA synthesis).

Manifests with the presence of megaloblasts in the bone marrow resulting in **ineffective erythropoiesis**, and macrocytes in the peripheral blood and hypersegmented neutrophils

Disorder of impaired DNA synthesis → delayed nuclear maturation → nuclear: cytoplasmic dyssynchrony

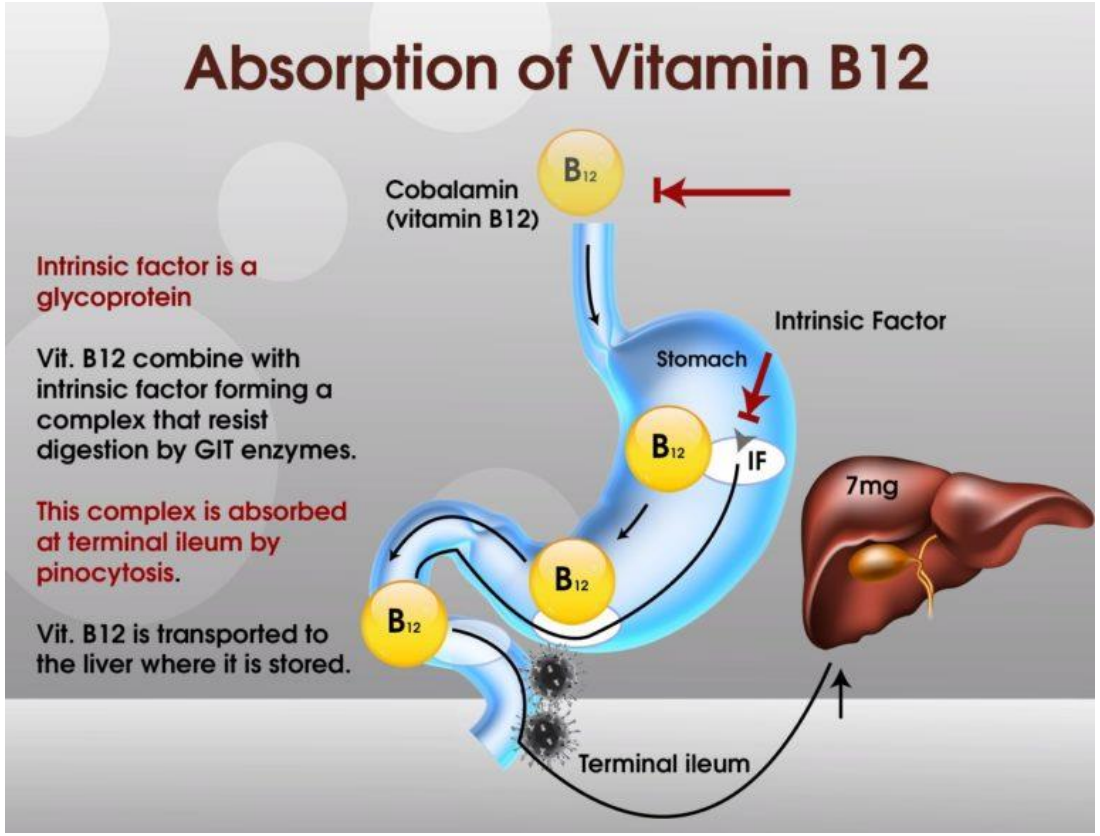
Vitamin B12

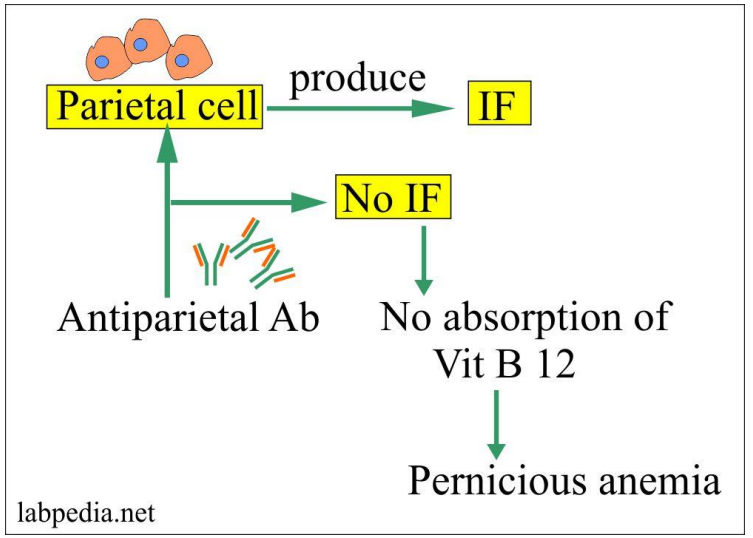
- Source of Vit b12 is mainly animal derived proteins
- Vitamin B12 is mainly absorbed in ileum
- Vitamin B12 deficiency takes years to develop due to large hepatic storage

Examples of vitamin B12 deficiency include:

- ✓ Dietary deficiency “especially in vegans”
- ✓ Pernicious anemia (autoimmune)
- ✓ Damage to terminal ileum (mainly in Crohn’s disease)

What is pernicious anemia?





Anti-parietal Ab
Ani-IF Ab

Vitamin B12 deficiency is caused by pernicious anemia when an **auto-antibody against the parietal cells & intrinsic factor** is seen in autoimmune gastritis. This interferes with vitamin B12 absorption. These autoantibodies can be detected in the patient's serum.

Folic acid

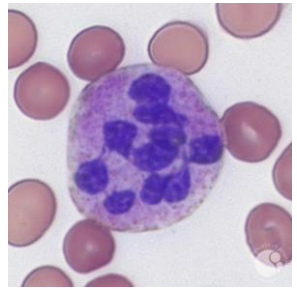
- Source of folic acid is mainly dark green vegetables and food
- Folic acid is mainly absorbed in jejunum
- Folic acid deficiency develops in months as body stores are minimum

Examples of vitamin Folic acid deficiency include:

- ✓ Dietary deficiency
- ✓ Increased demand “ex: pregnancy”

Megaloblastic Anemia
Clinical features

- Anemia (Macrocytic RBCs and hypersegmented neutrophils)
- Glossitis
- Serum low folate OR low Vitamin B12
- Increased serum homocysteine (causes an increased risk for thrombosis)

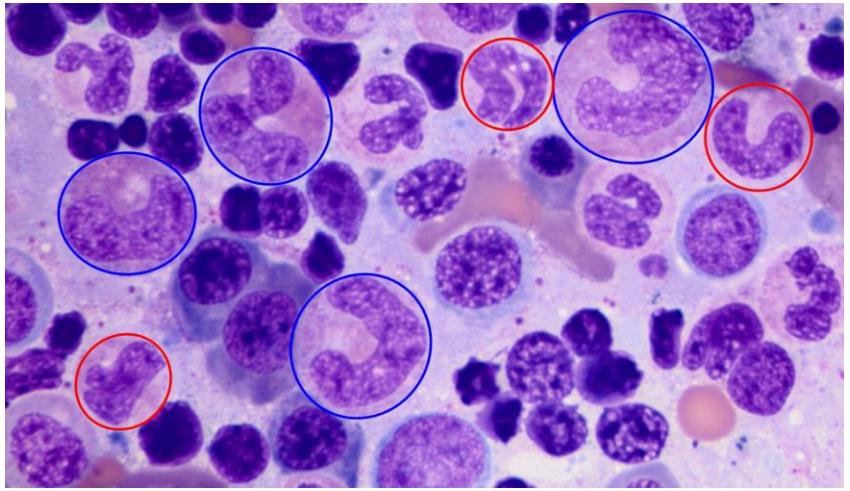


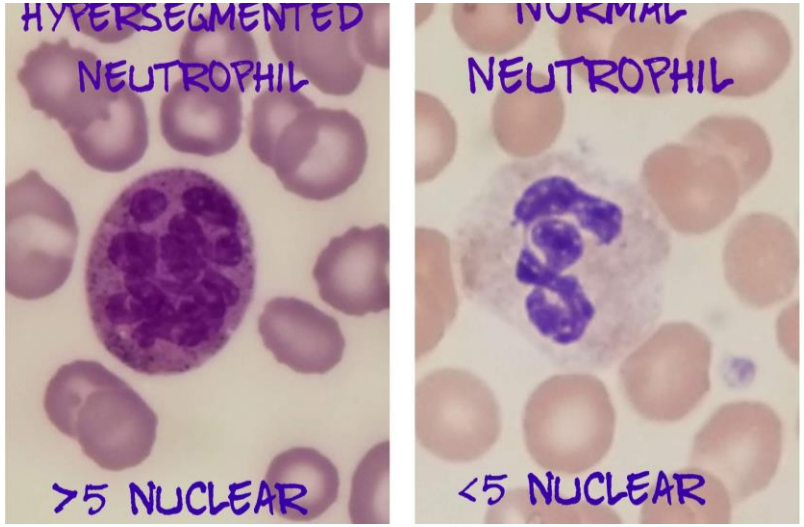
- **Subacute combined degeneration of the spinal cord** (only in Vit B12 deficiency); patients present with neurological manifestations, such as paresthesia, balance disorders, peripheral neuropathy, visual disturbances

Why does Vitamin B12 cause neurological symptoms?

✓Because Vit B12 is necessary to convert methylmalonic acid to succinyl Coenzyme A

✓Increased methylmalonic acid in myelin cells impairs spinal cord myelinization resulting in subacute combined degeneration of the spinal cord





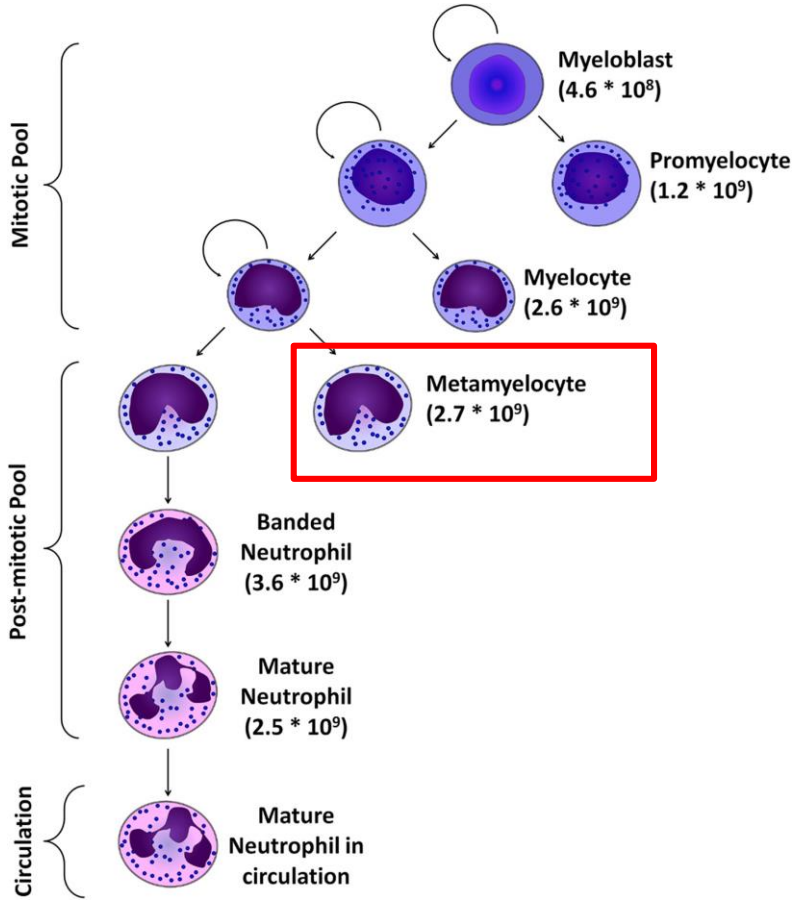
Megaloblastic Anemia Pathogenesis

- The morphologic hallmark of megaloblastic anemia is the enlargement of the erythrocytes precursors (**Megaloblasts**)
- The other myeloid lineage are affected; **the granulocytes precursors also enlarged (giant metamyelocytes**) and yield highly characteristic hypersegmented neutrophils
- Eventually, impaired DNA synthesis can lead to ineffective hematopoiesis in all 3 cell lines → **pancytopenia** “anemia , leukopenia & thrombocytopenia”

Megaloblastic Anemia
Diagnosis and morphology

CBC: anemia with high MCV. Also, might have leukopenia, and thrombocytopenia (pancytopenia). Low retic count (ineffective erythropoiesis)

Peripheral smear: Macrocytes. Anisocytosis (variation in RBC size) and poikilocytosis (variation in RBC shape). Nucleated red cells are seen with immature nucleus. Neutrophils show hypersegmentation.



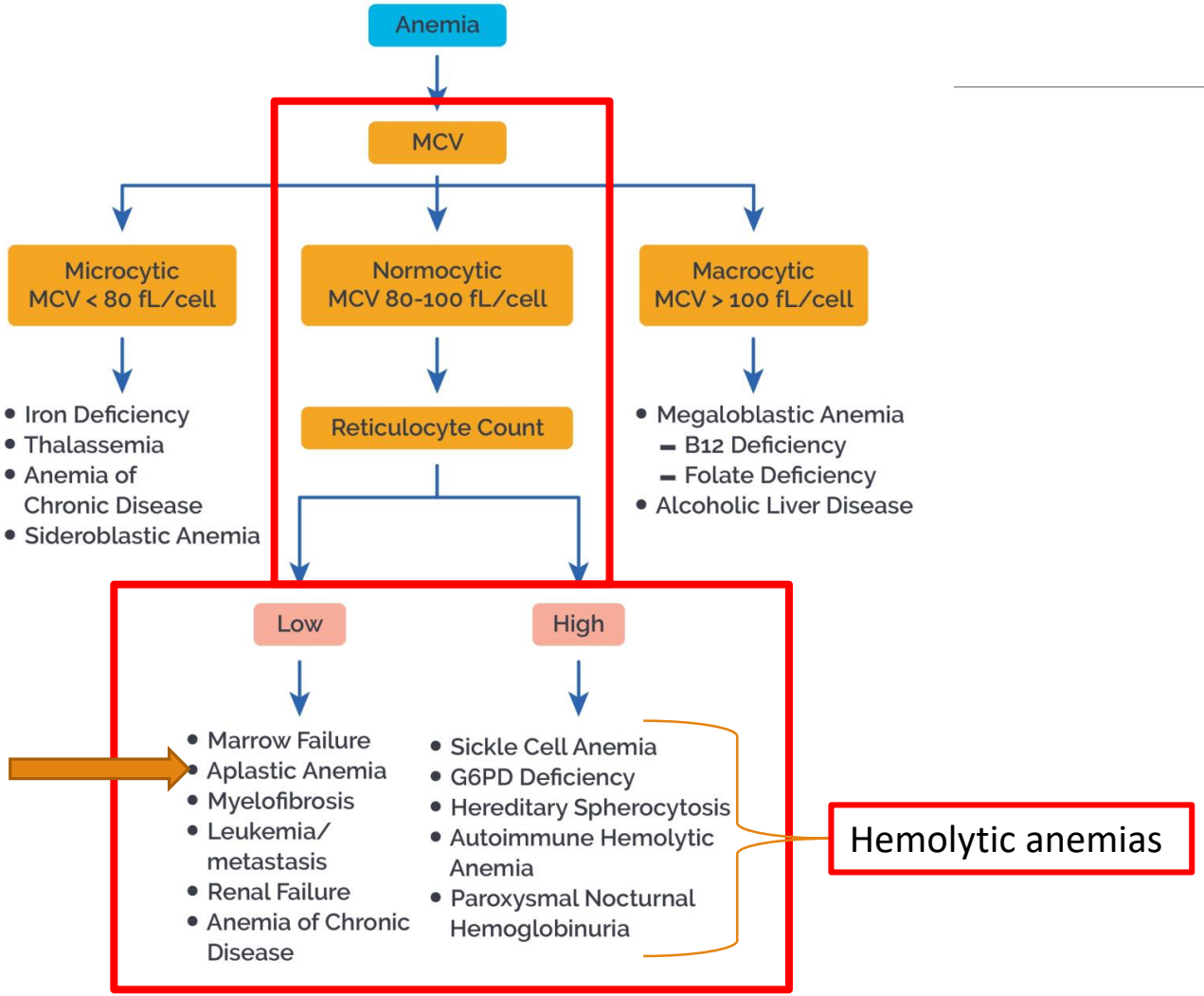
Megaloblastic Anemia

Presentation depends on the underlying cause of megaloblastic anemia;

- **General anemia symptoms:** weakness, shortness of breath, impaired concentration and exercise ability,…..
- **Clinical features specific to cobalamin (vit B12) deficiency**: neurological manifestations
- **Folic acid deficiency is less common**: it is characterized by similar clinical and hematological features but without neurological features**.**

Treatment: Supplementation of B12 and folate with dramatic increase of reticulocytes in blood 2-3 days after vit.B12 injection

CLASSIFICATION OF ANEMIAS



Normocytic Anemia

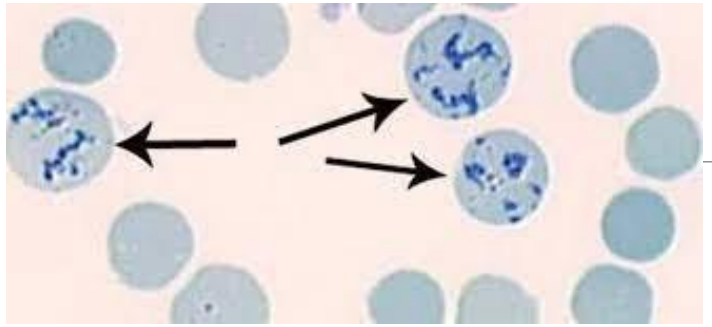
Normocytic anemia is decreased RBC mass with normal-sized RBC (MCV - 80-100 µm3)

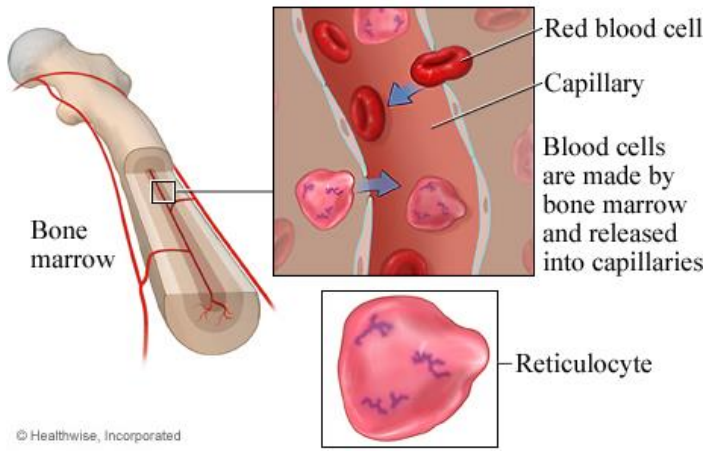
High retic count: Peripheral destruction of RBC (will have reticulocyte >3%)

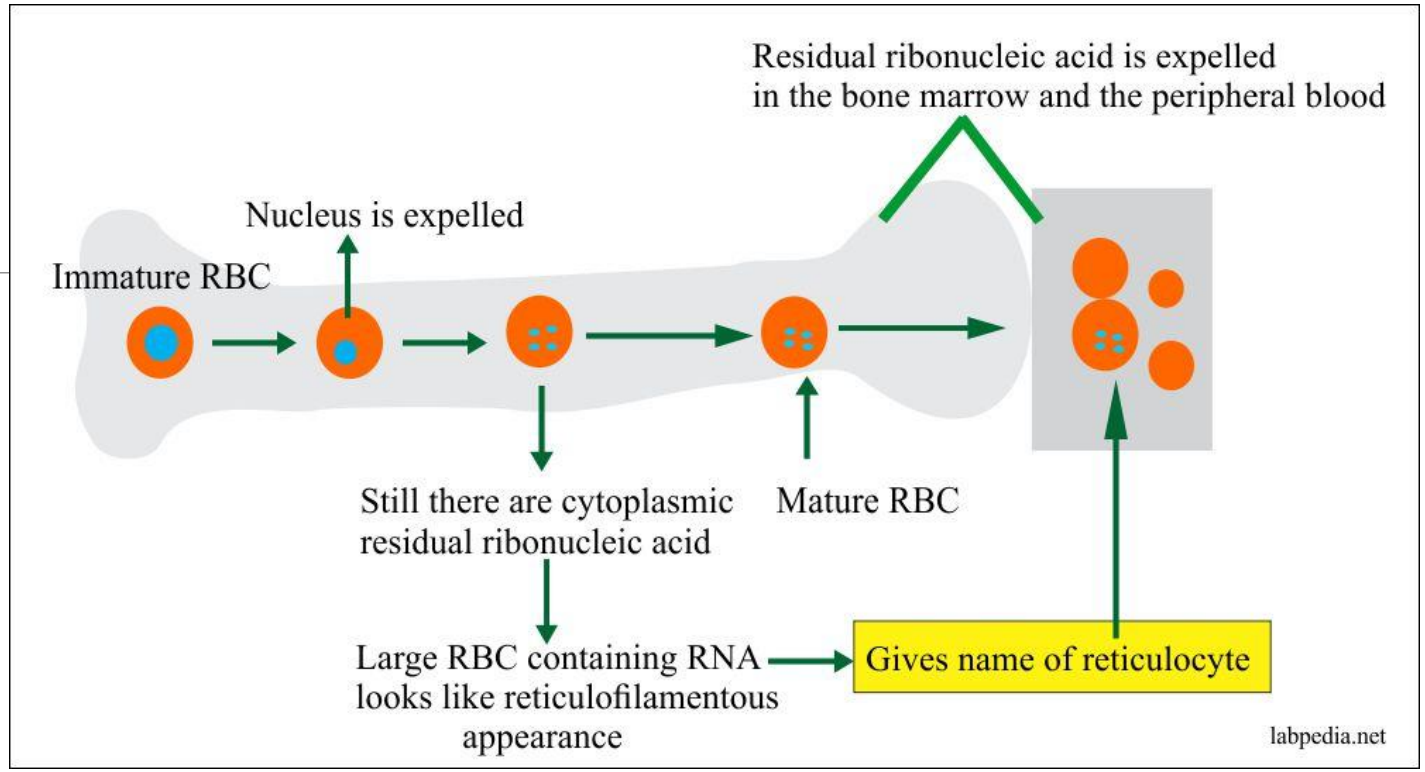
- Extravascular hemolysis (RBC destroyed by liver, spleen and lymph)
- Intravascular hemolysis (RBC destroyed within blood vessels)

Low retic count:

Underproduction of RBC (no increased reticulocytes)







Reticulocytes

Aplastic anemia

- Aplastic anemia is a bone marrow disorder characterized by pancytopenia due to ineffective hematopoiesis **in the absence** of any underlying neoplasia or fibrosis

- Mostly sporadic but can be constitutional (congenital)

- Bimodal age distribution: first peak at 10 - 25 years; second peak at > 60 years

Aplastic anemia; etiology

Acquired aplastic anemia (most common)

- Infectious agents: parvovirus B19, HIV, EBV, Hepatitis C virus
- Toxins such as benzene
- Drugs, chemicals, or radiations (example of drugs: chloramphenicol)
- Autoimmune disease - most common SLE
- Idiopathic

Constitutional "congenital" aplastic anemia; example "Fanconi anemia"

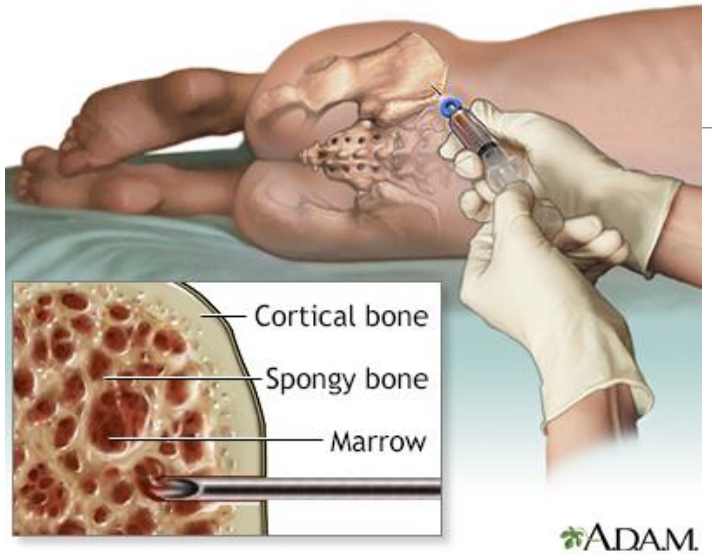
Aplastic anemia; morphology

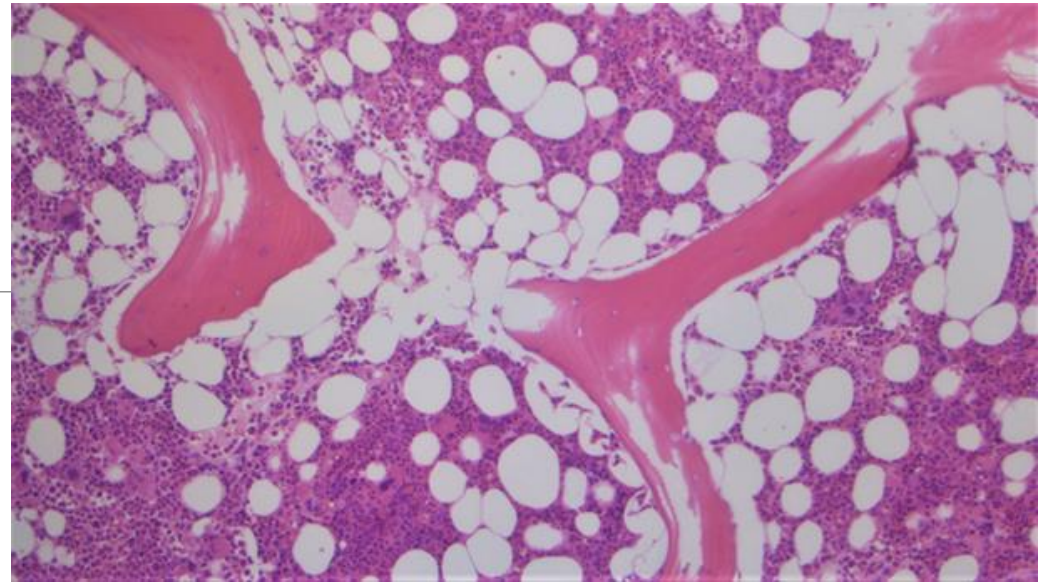
- CBC: shows pancytopenia (including normochromic normocytic anemia)
- Low reticulocyte count (< 30 x 10^9/L)
- Normal vitamin B12, folate and iron (to exclude vitamin deficiency anemias)

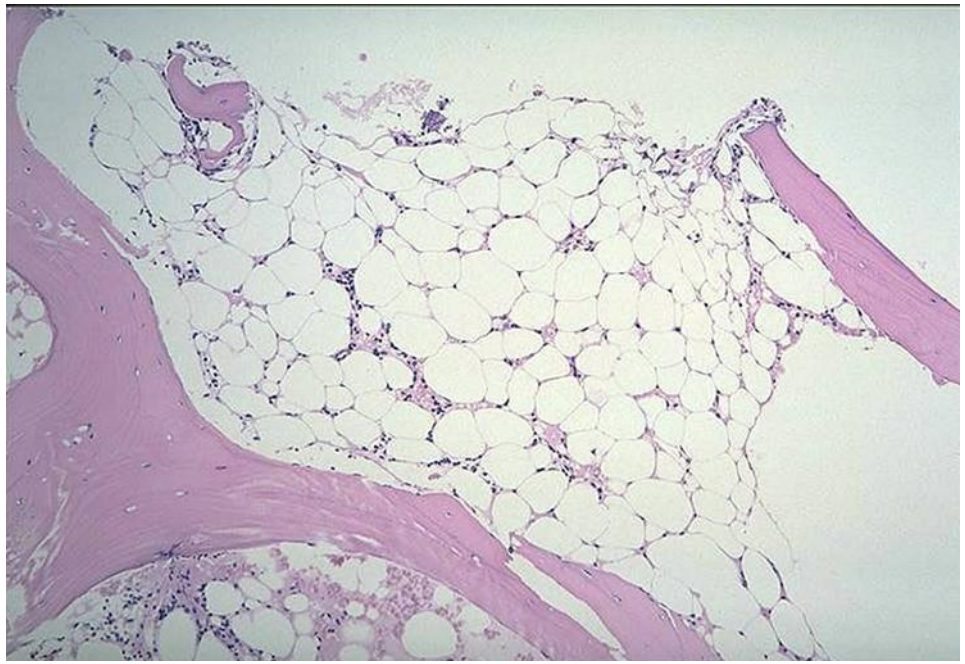
Bone marrow biopsy:

- Bone marrow markedly hypocellular (cellularity < 5%)
- Lacunar spaces replaced by fatty cells
- Residual nucleated cells include mostly lymphocytes, plasma cells, macrophages, mast cells

Normal bone marrow biopsy







Bone marrow biopsy in aplastic anemia:
Marrow lacunar spaces are replaced by fat, and very scant hematopoietic cells

Aplastic anemia; clinical features and treatment

Signs and symptoms related to severity of pancytopenia:

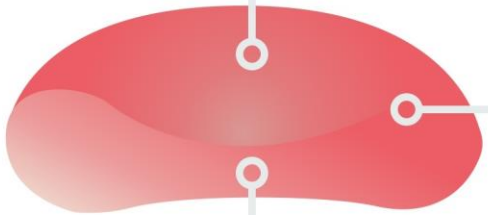
Anemia: most common are fatigue, shortness of breath, …..

Thrombocytopenia: bleeding and bruising

Leukopenia: frequent or prolonged infections

Treatment:

- ✓Bone marrow transplant is the only curative treatment
- ✓Treat underlying cause if present (toxic, drugs, infections)
- ✓Immunosuppression for cases with abnormal T-cell activation
- ✓Transfusion support only to relieve symptoms



METABOLIC ABNORMALITIES

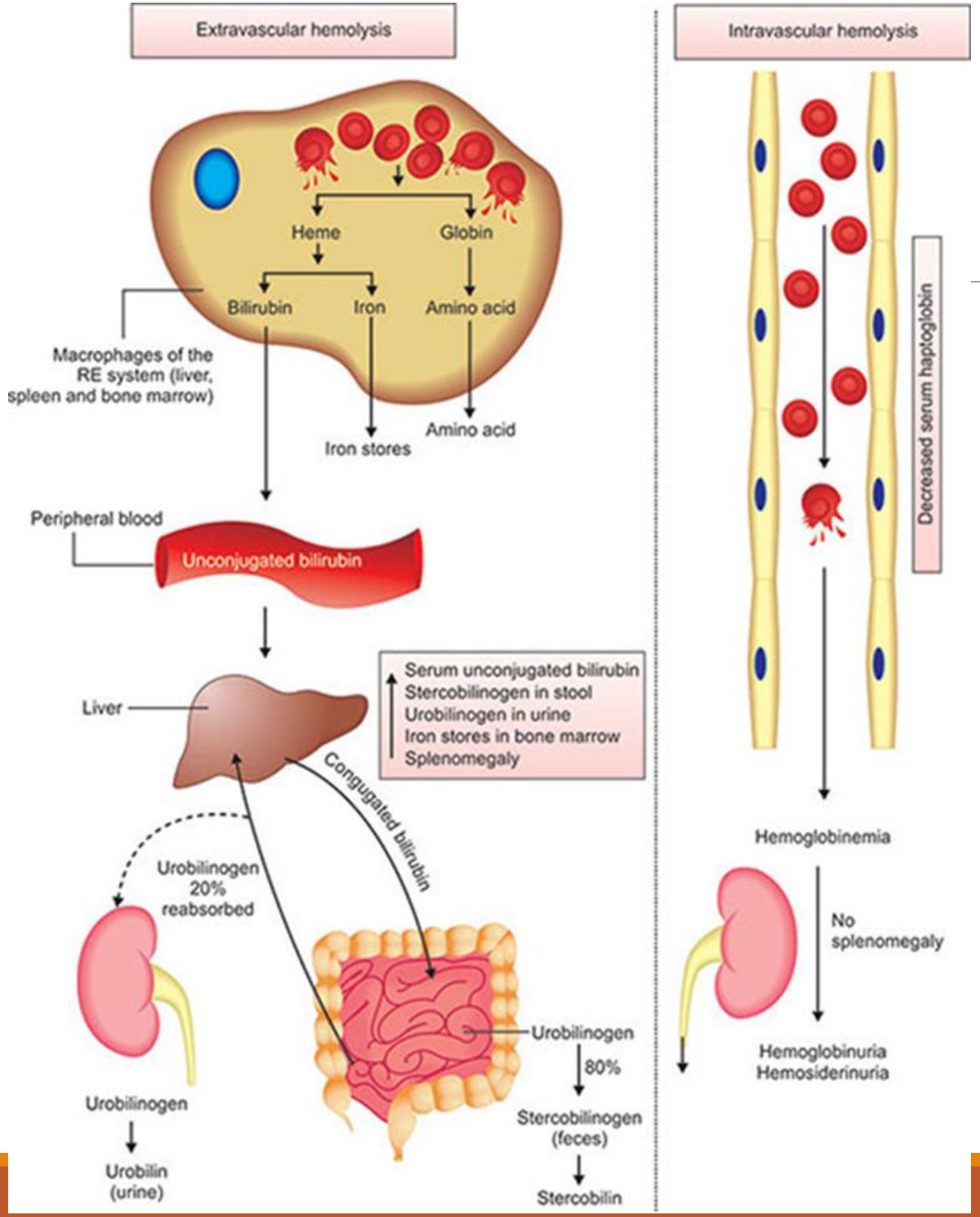
- **G6PD deficiency** (protects RBC from oxidative stress)

HAEMAGLOBIN ABNORMALITIES

- **Sickle cell** (RBCs sickle at low O2 tensions)
- **Thalassaemia** (impaired production of alpha or beta Hb chains)

MEMBRANE ABNORMALITIES

- **Hereditary spherocytosis** (results in premature removal by splenic macrophages)



Features of Hemolytic Anemia (Intra- and Extravascular)

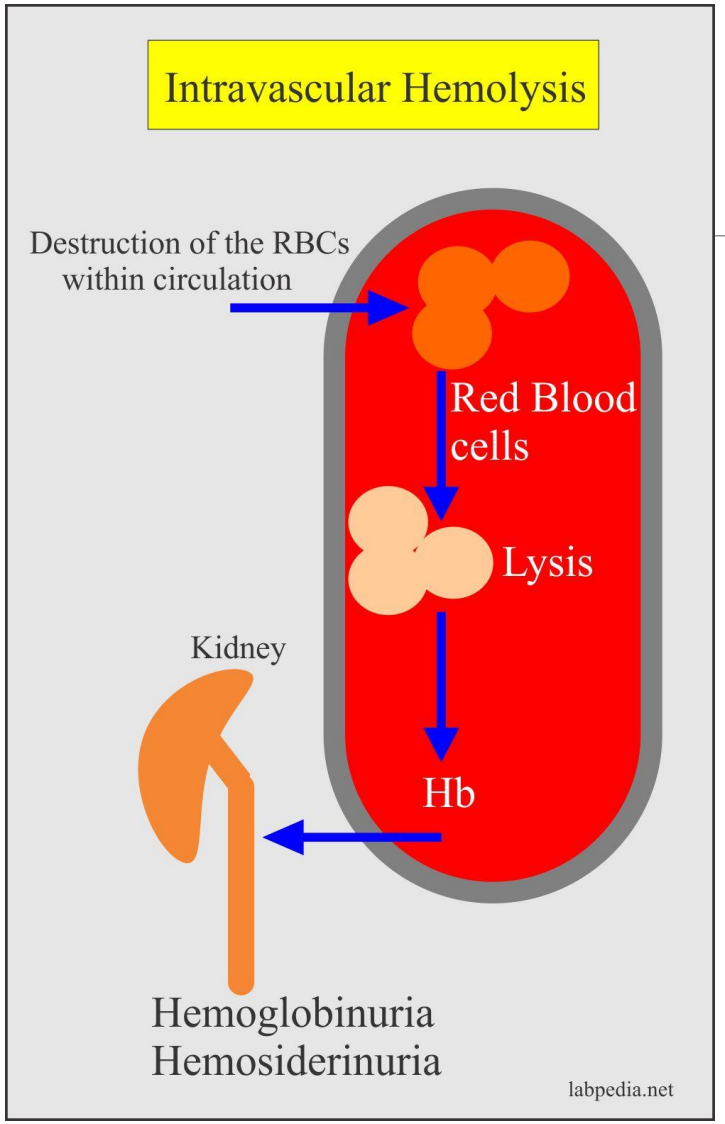
- Shortened RBCs survival
- Elevated erythropoietin level leading to increased erythropoiesis and early release of RBCs from marrow
- Reticulocytosis
- Elevation in unconjugated Bilirubin (indirect) and LDH

Extravascular hemolysis

- Hemolysis done by reticuloendothelial system (macrophage in liver, spleen and lymph nodes)
- Globin is broken to AA; Iron is recycled
- Unconjugated (indirect) bilirubin is carried by albumin to liver and then conjugated in liver and excreted to bile.

Extravascular hemolysis clinically present with:

- Anemia with splenomegaly
- Jaundice due to unconjugated bilirubin (too much bilirubin to be conjugated by liver)
- High risk for bilirubin gallstones
- Marrow hyperplasia with corrected reticulocyte >3%



Intravascular hemolysis

- ✓RBC is destroyed in blood vessels. Unlike macrophage breaking down hemoglobin to bilirubin, **hemoglobin simply leaks out to blood.**
- ✓Patients will have **hemoglobinemia** and **hemoglobinuria** (hemoglobin water soluble)
- ✓Then, **hemosiderinuria** occurs after few days - Hemoglobin in urine is picked up by renal tubular cells. Iron is recycled back and stored as hemosiderin. Renal tubular cells slough off and hemosiderin will be seen in urine.

Intravascular hemolysis

- Hemoglobin is carried by haptoglobin. Haptoglobin is not enough to bind all Hgb. So, patients will quickly have hemoglobinemia and hemoglobinuria

- Also, patients will show marked decrease in Haptoglobin “almost absent”

Immediate	After few days
- Decreased serum haptoglobin	- Hemosiderinuria
- Hemoglobinemia	
- Hemoglobinuria	

Marrow Response To Hemolysis

- Erythroid hyperplasia with decreased Myeloid :Erythroid ratio
- In chronic cases, extramedullary hematopoiesis may take place.
- Erythropoiesis can increase up to 8 times its normal level. Thus, hemolysis may take place without development of anemia.

Anemia develops if:

- Rate of hemolysis increases beyond the compensatory rate (hemolytic crisis).
- The bone marrow stops producing RBCs (aplastic crisis)

Hemolytic anemia

Test	Intravascular hemolysis	Extravascular hemolysis
Serum Haptoglobin	↓ ↓	Normal or ↓
Plasma Hb	Present	Absent
Hemoglobinuria	Present	Absent
Hemosiderinuria	Present	Absent
Serum lactate dehydrogenase LDH	↑	↑
Serum unconjugated bilirubin	Normal or ↑	↑

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V. Infections

VI. Snake bites/venoms

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- B. Membrane defects
  - i. Hereditary spherocytosis
  - ii. Hereditary elliptocytosis
- C. Enzyme deficiencies
  - i. G6PD deficiency
  - ii. Pyruvate kinase deficiency

II. Extracorpuscular defects
- A. Immune-mediated hemolytic anemia
  - i. Autoimmune
  - ii. Drug-induced
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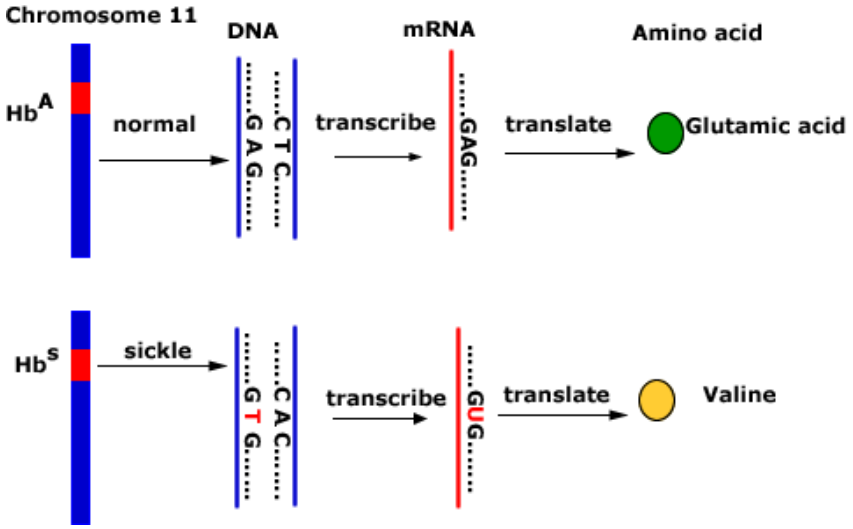
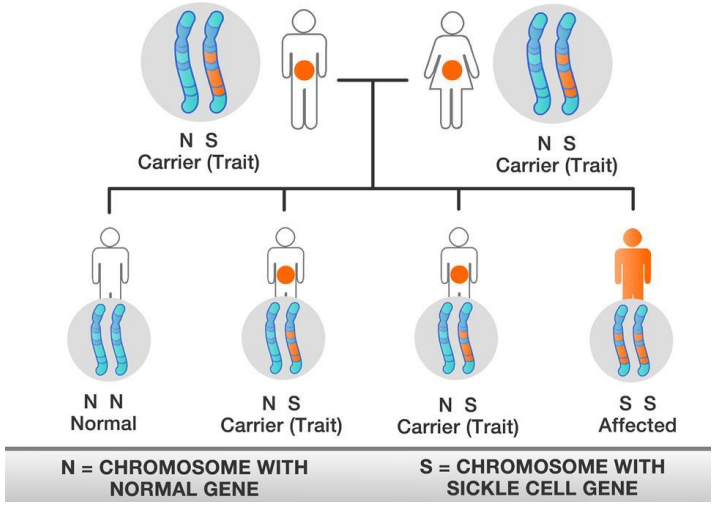




SICKLE CELL DISEASE

- Most common familial hemolytic hemoglobinopathy
- Molecular basis: single point mutation (A to T substitution) in the first exon of the β globin gene, converting glutamic acid into valine
- It is an **autosomal recessive** inheritance

SICKLE CELL DISEASE

Phenotype	Hemoglobin composition
Sickle cell disease (homozygous mutation)	90% HbS, 8% HbF, 2%HbA_2, **no HbA**
Trait (one mutated and one normal B chain)	**55% HbA**, 43% HbS, 2% HbA_2

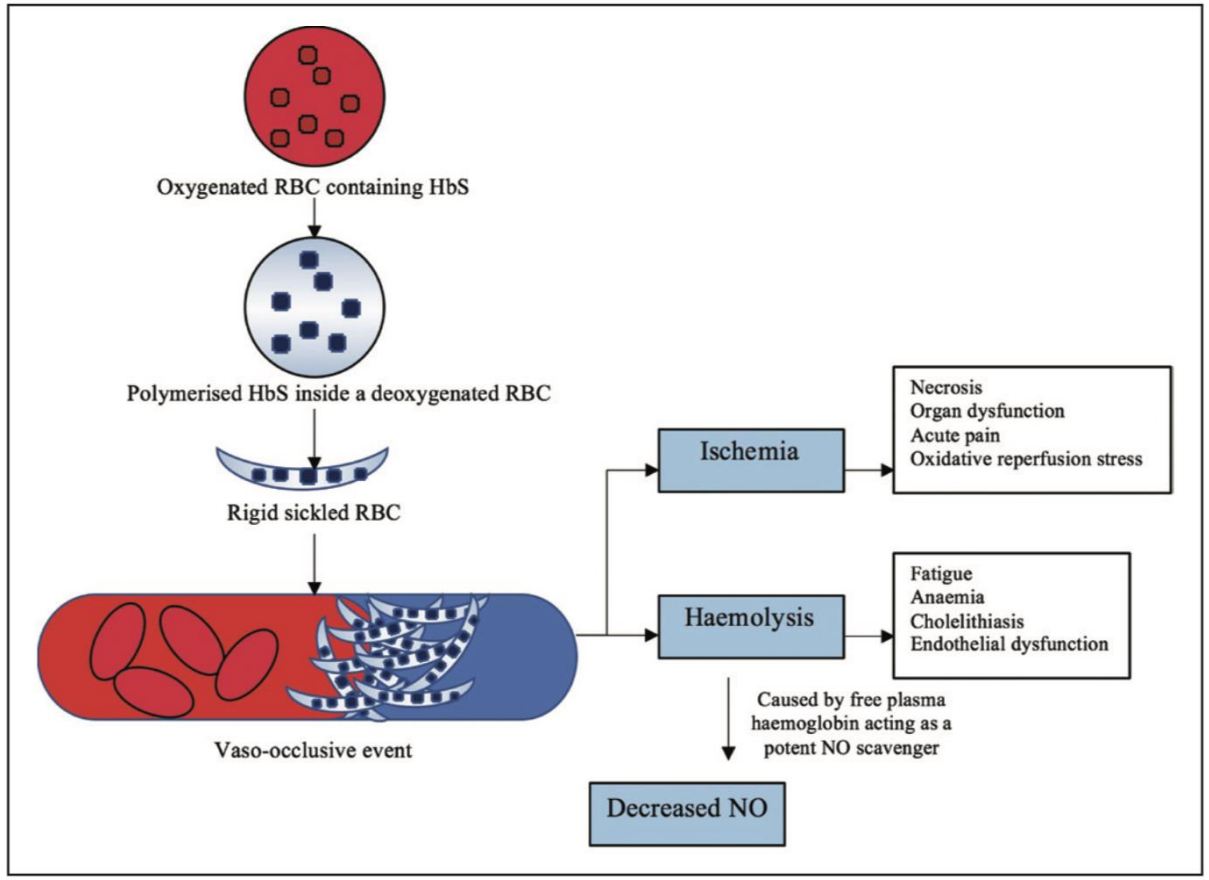
- *HbS – sickle cell hemoglobin (in $\alpha 2 \beta 2$ protein, both copies of β are mutated)*

SICKLE CELL DISEASE

Incidence :

- It is more common among African & Asian population
- It was found that HbS has a protective effect against Plasmodium Falciparum malaria infection.

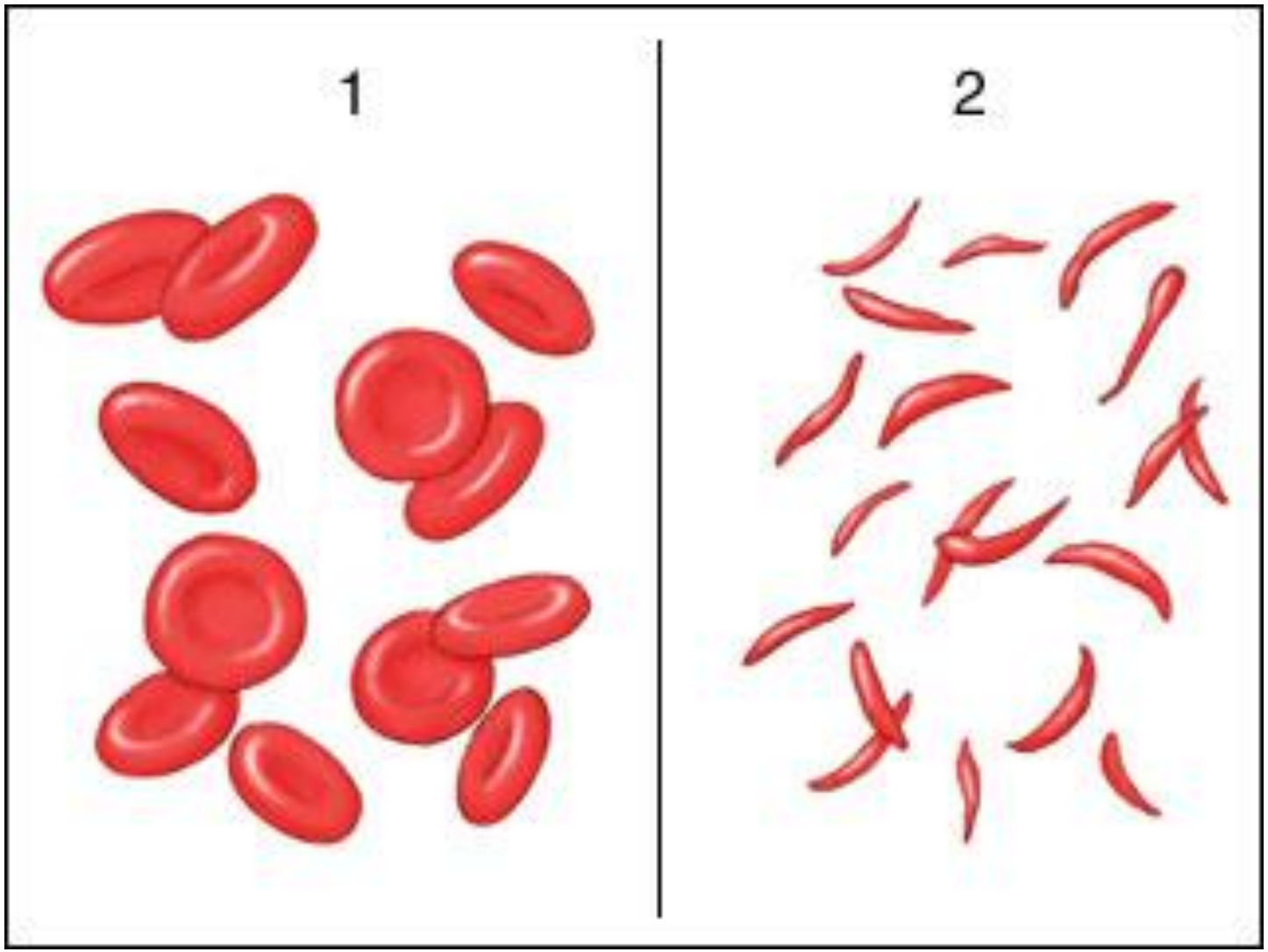
Pathogenesis of sickle cell anemia



- **HbS polymerizes when deoxygenated** (reversible). The polymers accumulate into needle shaped structures and make RBC sickle cell.
- Sickling increases with **hypoxemia, dehydration** and **acidosis**.
- **Note:** HbF protects against sickling. Kids protected for first few months of life.

Sickling and de-sickling damages membrane leading to both intravascular and extravascular hemolysis (spleen eats damaged RBC); sickled RBC cause **vaso-occlusion.**

Massive erythroid hyperplasia occur in BM to replace RBC.



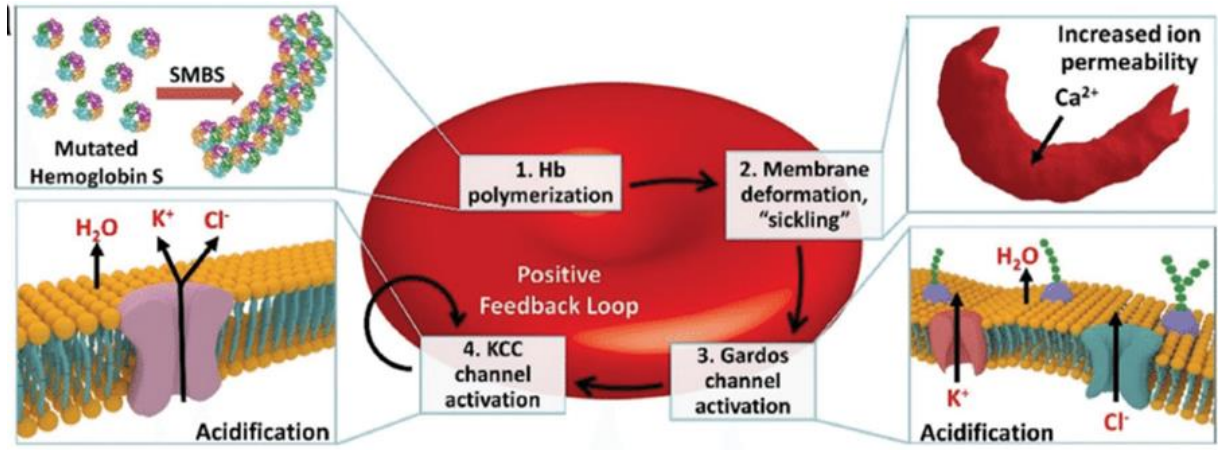
Normal RBCs

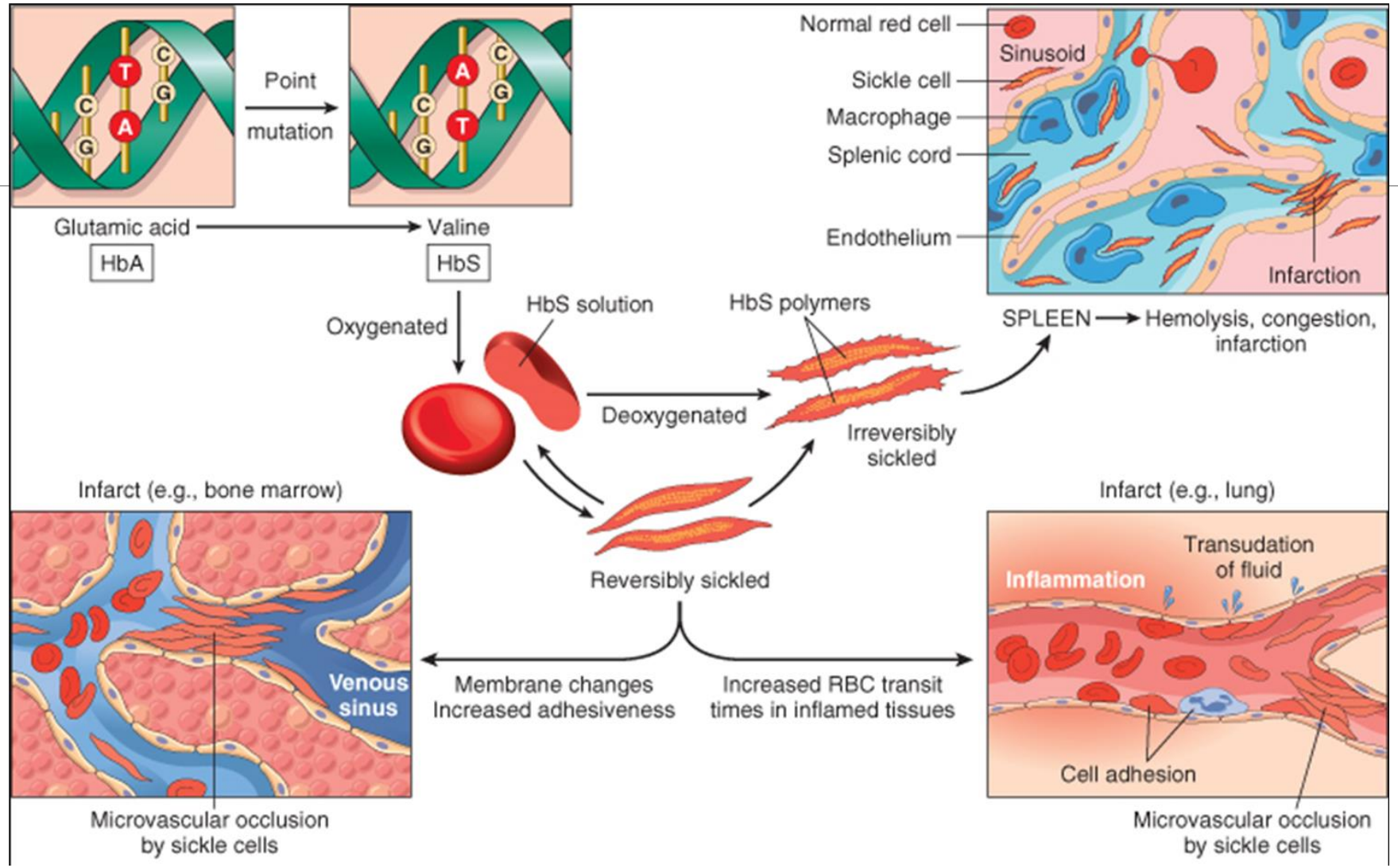
Sickled RBCs

Pathogenesis of sickle cell anemia

- Sickle RBCs are rigid, less deformable and have a shortened lifespan of 10 - 20 days

Note: repeated episodes of sickling cause cell membrane damage & then <u>becomes irreversibly sickled, retaining their abnormal shape even when fully oxygenated</u>




T
C
G
C
A
G
Point
mutation
A
C
G
C
T
G
Glutamic acid
HbA
Valine
HbS
Normal red cell
Sinusoid
Sickle cell
Macrophage
Splenic cord
Endothelium
Infarction
SPLEEN
Hemolysis, congestion, infarction
Oxygenated
HbS solution
HbS polymers
Deoxygenated
Irreversibly sickled
Reversibly sickled
Infarct (e.g., bone marrow)
Venous sinus
Microvascular occlusion by sickle cells
Membrane changes
Increased adhesiveness
Increased RBC transit times in inflamed tissues
Infarct (e.g., lung)
Inflammation
Transudation of fluid
Cell adhesion
Microvascular occlusion by sickle cells

FACTORS AFFECTING THE DEFGREE OF SICKLING

1. Type of Hb: Hemoglobin SC Disease ($\alpha_2\beta_2^{6\ Val}$, $\alpha_2\beta_2^{6\ Lys}$) shows a milder disease.
Also; homozygous vs. heterozygous

2. Hb. Concentration: red cell dehydration increases HbS concentration which will greatly facilitate sickling during deoxygenation and can trigger occlusion of small blood vessels .

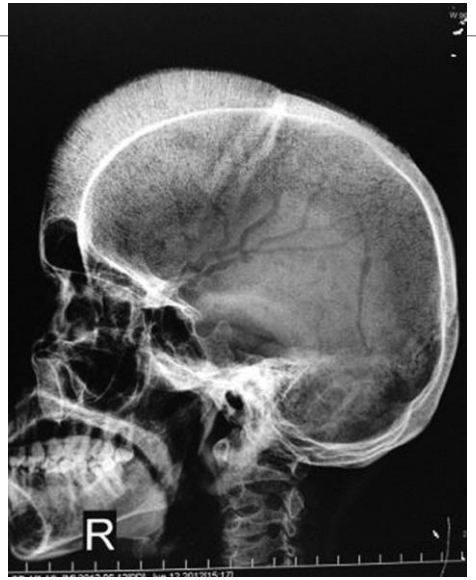
Also, coexistence of α thalassemia reduces the HbS concentration; due to low MCHC

3. Blood circulation: sickling is confined to microvascular beds where blood flow is sluggish - **bone marrow , spleen & possibly kidneys.**

Also, inflammation slows the flow by increasing the adhesion of leukocytes and RBC's

Sickle cell anemia; clinical consequences

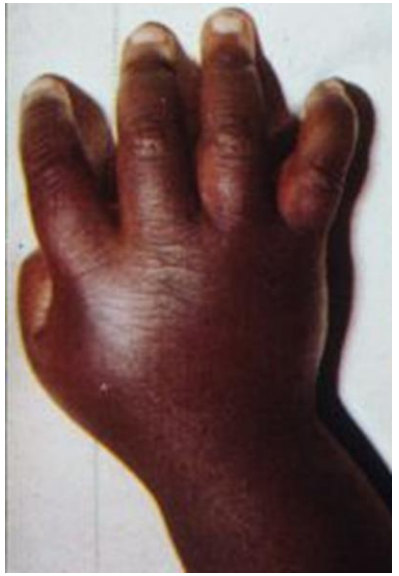
1. Chronic hemolysis: marked reticulocytosis and hyperbilirubinemia and gall stones formation. Expansion of the bone marrow due to increase erythropoiesis causes prominent cheek bones & changes in the skull. (“Hair on end” appearance on skull X-ray)



2. Ischemic manifestations (microvasculature obstruction): bones, liver, kidneys, skin, retina,…etc.

Examples

- Dactylitis is due to vasoocclusive infarcts in the bones of fingers in hands and feet, causing painful swelling
- Early common presentation in infants



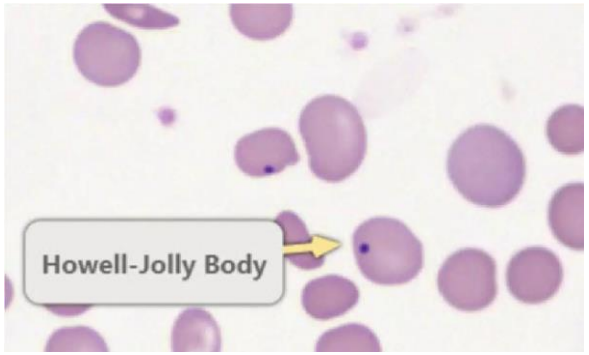
2. Ischemic manifestations Examples

- **Autosplenectomy (spleen autoinfarction),** which leads to shrunken, fibrotic and calcified spleen:

I. Increased risk of encapsulated organism infection (staph aureus, strep pneumo, haemophilus influenza)

II. Salmonella paratyphi osteomyelitis (encapsulated)

III. **Howel-Jolly bodies** on blood smear - nucleated RBC



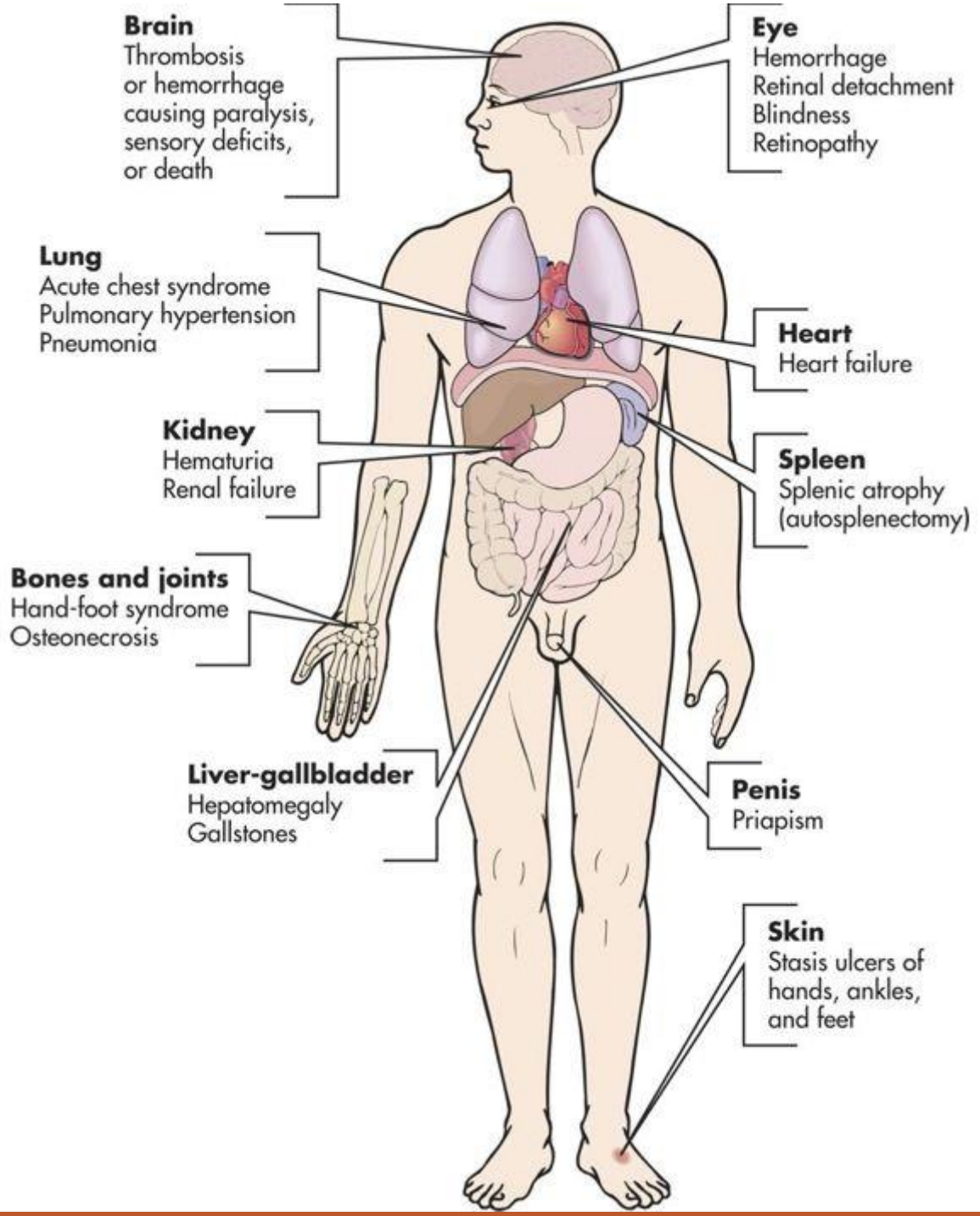
- **Acute chest syndrome** (vaso-occlusion of pulmonary microcirculation), often precipitated by pneumonia and presents with chest pain, SOB, lung infiltrates

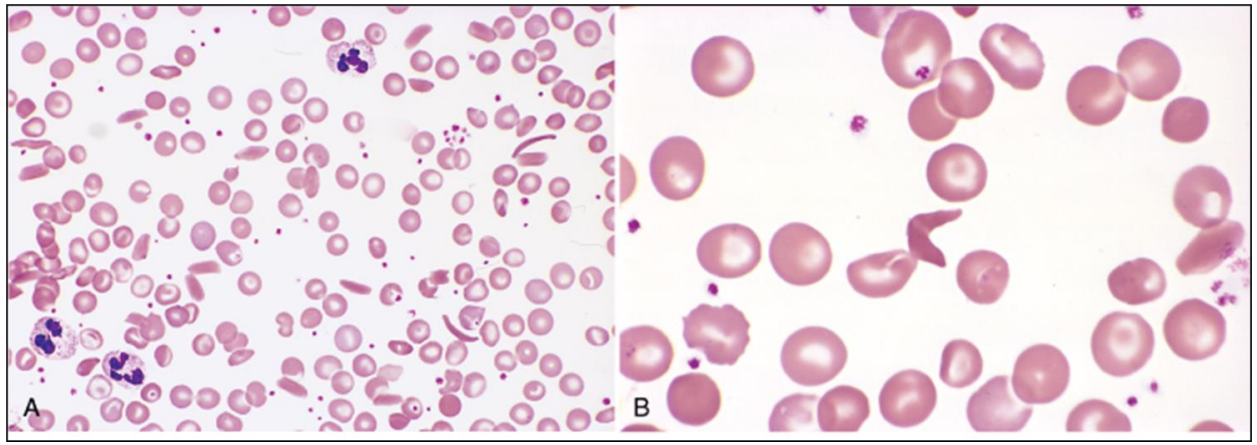
- **Renal papillary necrosis** – presents as gross hematuria and proteinuria

Sickle cell anemia; diagnosis and treatment

- Asymptomatic till 6 months of age.
- Moderate to severe anemia (6-8 g/dl).
- Unremitting course punctuated by sudden crises (pain crises, hemolytic crises).
- CBC and Hb electrophoresis (HcT is about 18% -30% - normal value 35 %-45%)

Sickle cell anemia





Treatment:

- ✓ Prophylactic treatment with penicillin to prevent pneumococcal infection .
- ✓ Adequate hydration and pain relief
- ✓ Use the hydroxyurea therapy “increase HbF”
- ✓ In severe cases, exchange transfusion to reduce the Hgb S

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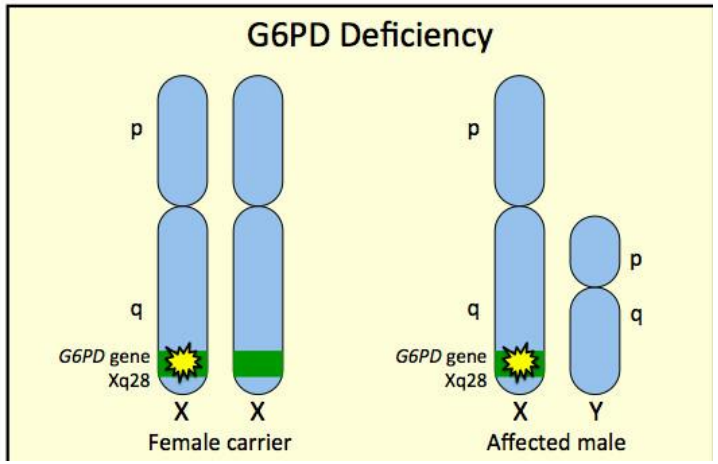
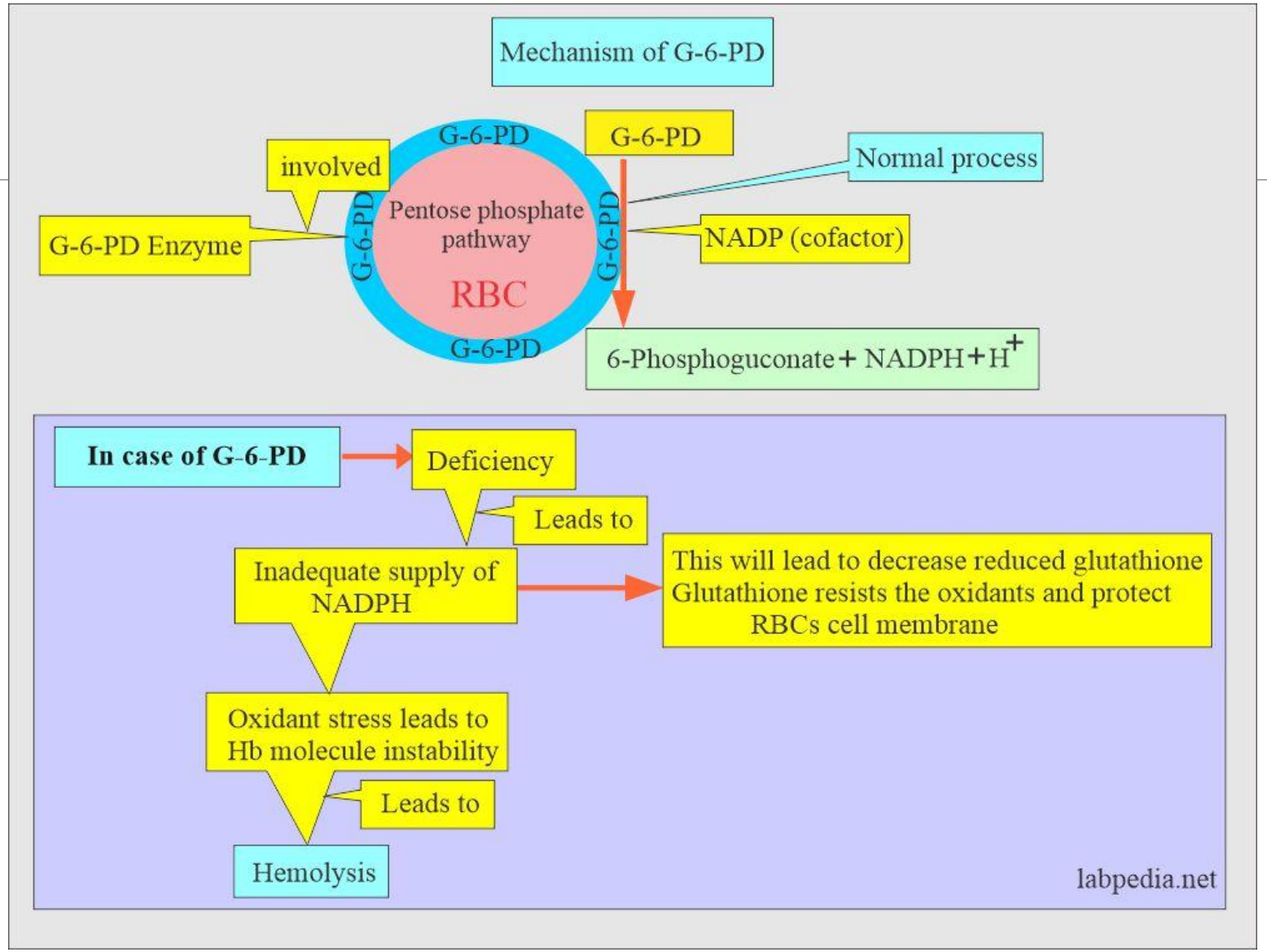
GDPD Deficiency aka “favism”

- X-linked recessive disorder
- G6PD is first enzyme in pentose phosphate pathway and is required to make NADPH. NADPH is important to reduce oxidative stress.
- **G6PD deficiency presents as increased oxidative stress including hemolytic anemia.**
- The majority of patients are asymptomatic most of the time and go through life without ever being aware of their genetic trait.
- Hemolysis occurs after a lag of 2-3 days
- Males more vulnerable than female (heterozygous)




Mechanism of G-6-PD
G-6-PD
G-6-PD
involved
Normal process
G-6-PD Enzyme
Pentose phosphate pathway
G-6-PD
G-6-PD
NADP (cofactor)
RBC
G-6-PD
6-Phosphoguconate + NADPH + H+
In case of G-6-PD
Deficiency
Leads to
Inadequate supply of NADPH
This will lead to decrease reduced glutathione
Glutathione resists the oxidants and protect RBCs cell membrane
Oxidant stress leads to Hb molecule instability
Leads to
Hemolysis
labpedia.net

GDPD Deficiency aka favism

Hemolysis due to oxidant stress:

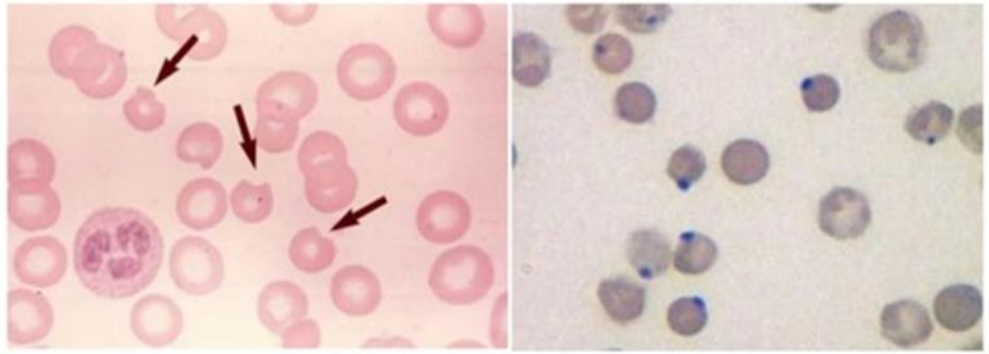
- **Drugs: eg. Antimalarials, sulfonamides, furantoins,…etc.**
- **Favism: chickpeas , green peas , all types of beans should be avoided**
- **Infections: produces free radicals**

Oxidation leads to denaturation of globin chains, and precipitation at membranes forming **Heinz bodies.**

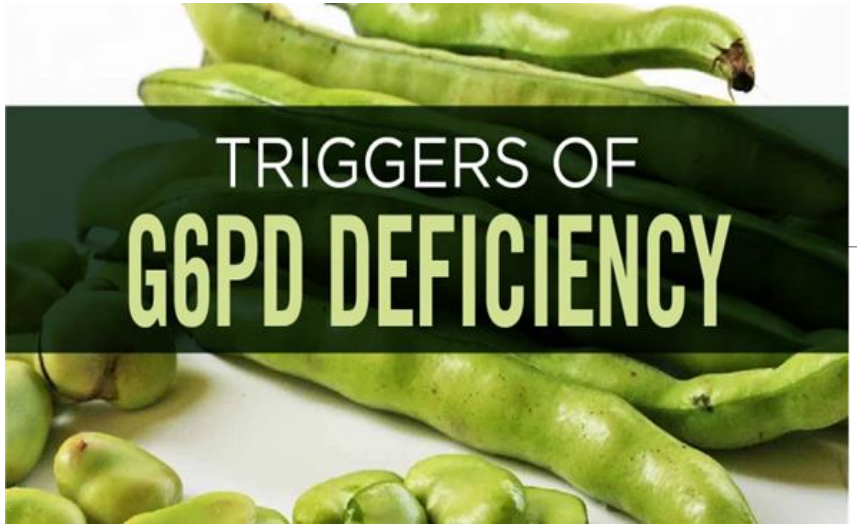
RBCs: Bite cells and Heinz bodies

Features of Extra/Intravascular hemolysis

Glucose 6-phosphate Dehydrogenase Deficiency



Bite cells | Heinz bodies

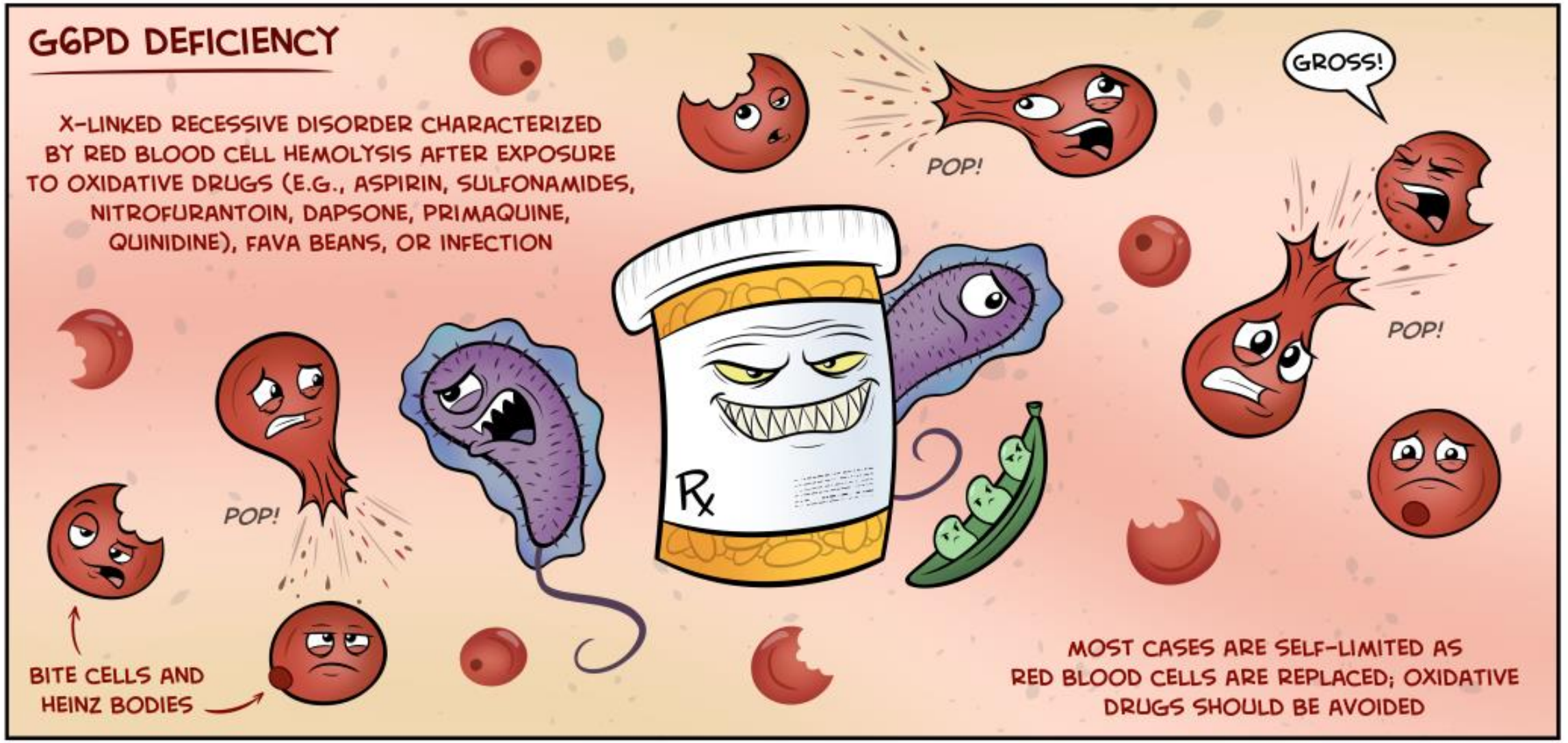


GDPD Deficiency

Diagnosis of G6PD deficiency:

- Screening - Heinz preparation – Blood smear will show Heinz bodies

- Confirm - enzymatic studies (however; in the acute phase, RBCs lacking G6PD are hemolyzed and dead, so they cannot be detected)


G6PD DEFICIENCY
X-LINKED RECESSIVE DISORDER CHARACTERIZED BY RED BLOOD CELL HEMOLYSIS AFTER EXPOSURE TO OXIDATIVE DRUGS (E.G., ASPIRIN, SULFONAMIDES, NITROFURANTOIN, DAPSONE, PRIMAQUINE, QUINIDINE), FAVA BEANS, OR INFECTION
POP!
GROSS!
POP!
POP!
Rx
BITE CELLS AND HEINZ BODIES
MOST CASES ARE SELF-LIMITED AS RED BLOOD CELLS ARE REPLACED; OXIDATIVE DRUGS SHOULD BE AVOIDED

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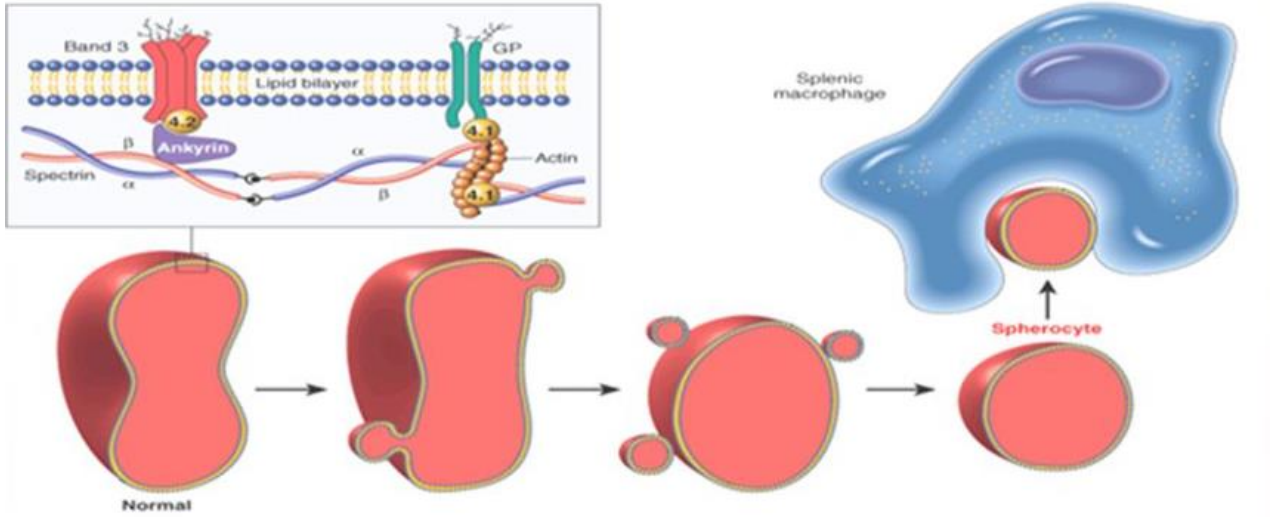
HEREDITARY SPHEROCYTOSIS



Spectrin and **ankyrin** are tethering proteins that attach RBC cytoskeleton

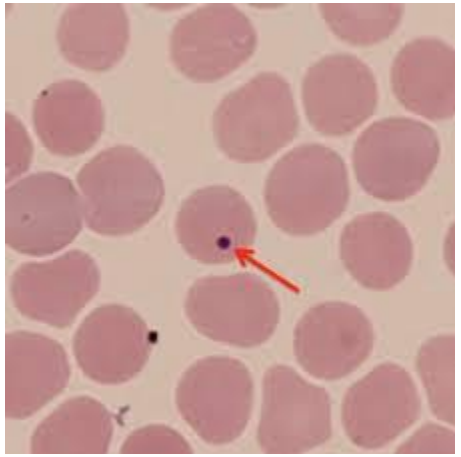
- ✓**Congenital hemolytic anemia (AD)** due to genetically determined **abnormal spectrin and ankyrin molecules**, leading to defects in red blood cell membrane
- ✓RBC membrane blebs and are lost over time. RBC becomes more spherical.
- ✓Red blood cells become trapped within spleen and have less than usual 120-day lifespan

HEREDITARY SPHEROCYTOSIS

✓Spherocytes are phagocytosed by splenic macrophages , leading to extravascular hemolysis characterized by anemia, jaundice, increased reticulocytes & splenomegaly.

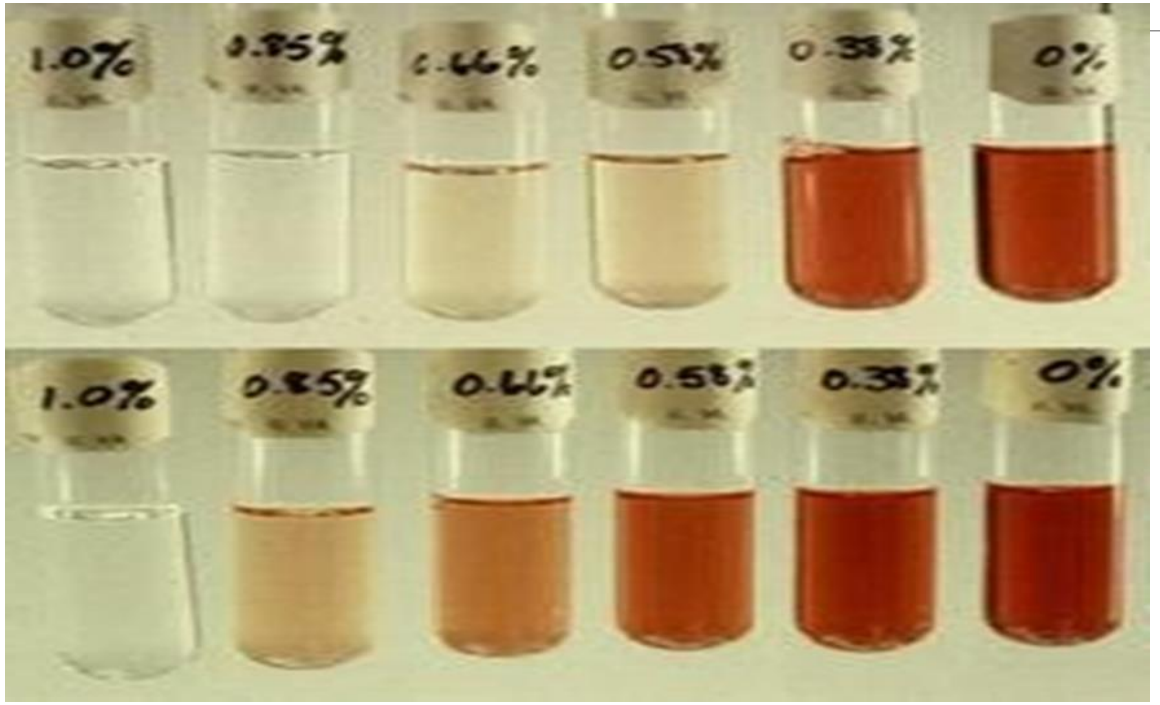
CBC and blood smear findings:

- RBC becomes round instead of disc shaped (loss of central pallor)
- High MCHC - high concentration of hemoglobin as cells are getting small
- Howell-Jolley bodies in peripheral blood RBCs . The Howell-Jolley body is anuclear DNA remnant



Howell-Jolley body

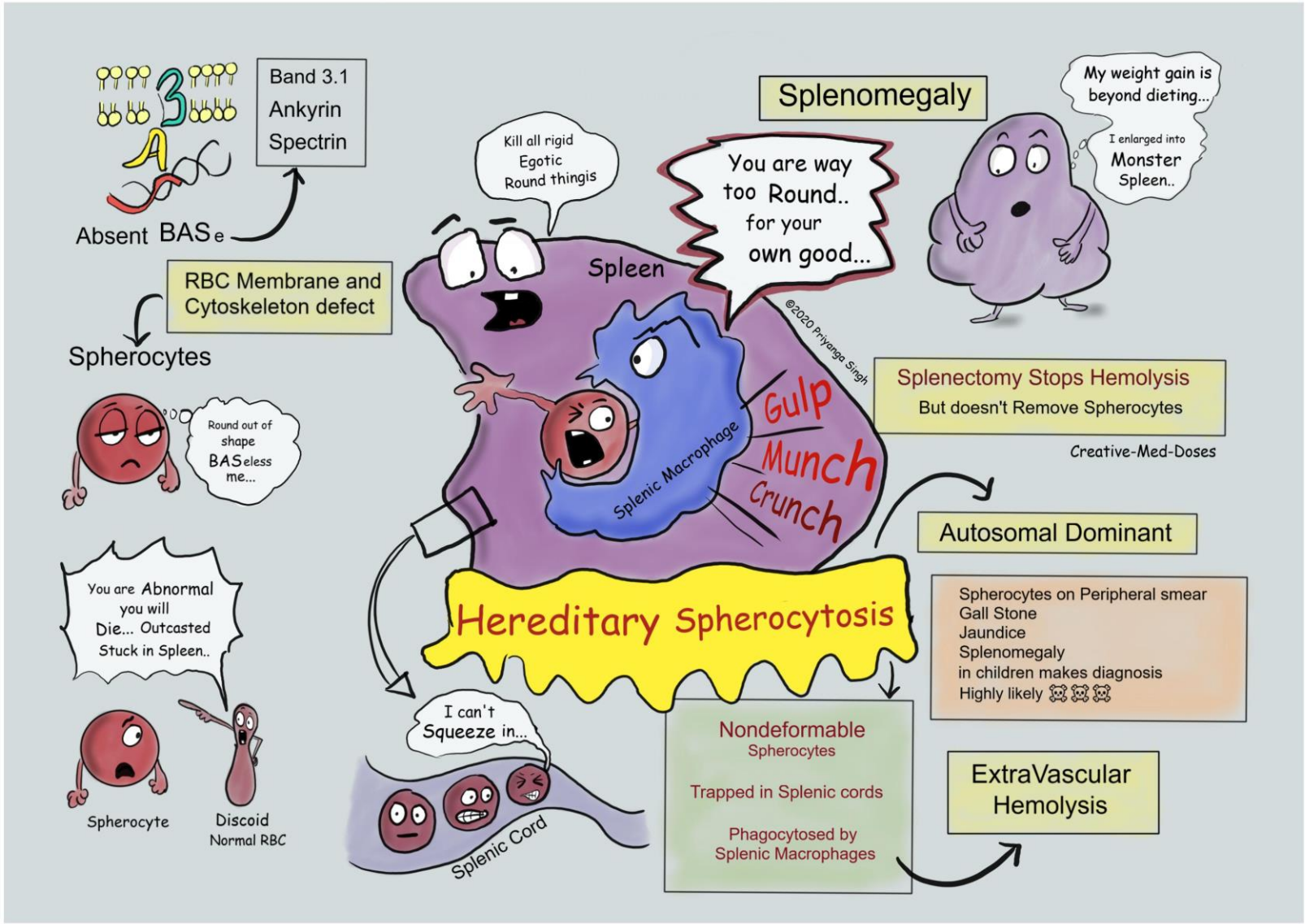
Treatment: Splenectomy (prolongs survival of red blood cells, although they still have membrane defects)



HEREDITARY SPHEROCYTOSIS

Osmotic fragility: increased; basis for diagnostic testing

- The osmotic fragility of red cells is increased i.e . the RBCs are easily hemolysed when kept in a hypotonic saline solution.
- The test consists of exposing RBC to varying strengths of hypotonic saline solutions and measuring the degree of hemolysis colorimetrically at room temperature .


Band 3.1
Ankyrin
Spectrin
Absent BASe
RBC Membrane and Cytoskeleton defect
Spherocytes
Round out of shape BASeless me...
You are Abnormal you will Die... Outcasted Stuck in Spleen..
Spherocyte
Discoid Normal RBC
Kill all rigid Egotic Round thingis
Spleen
You are way too Round.. for your own good...
Splenic Macrophage
Gulp
Munch
Crunch
©2020 Priyanga Singh
Splenomegaly
My weight gain is beyond dieting...
I enlarged into Monster Spleen..
Splenectomy Stops Hemolysis
But doesn't Remove Spherocytes
Creative-Med-Doses
Autosomal Dominant
Hereditary Spherocytosis
Spherocytes on Peripheral smear
Gall Stone
Jaundice
Splenomegaly
in children makes diagnosis
Highly likely
I can't Squeeze in...
Splenic Cord
Nondeformable
Spherocytes
Trapped in Splenic cords
Phagocytosed by Splenic Macrophages
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Immune Hemolytic Anemia
AIHA

Three broad categories:

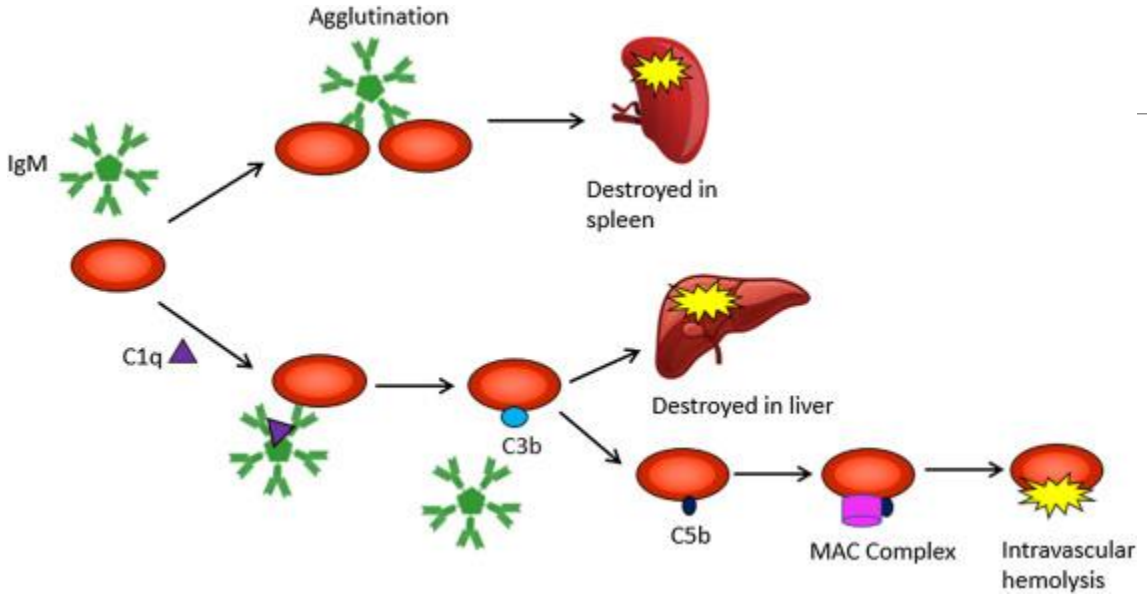
Alloimmune: The patient produces alloantibodies to foreign red cell antigens (transfusion, pregnancy, or organ transplant)

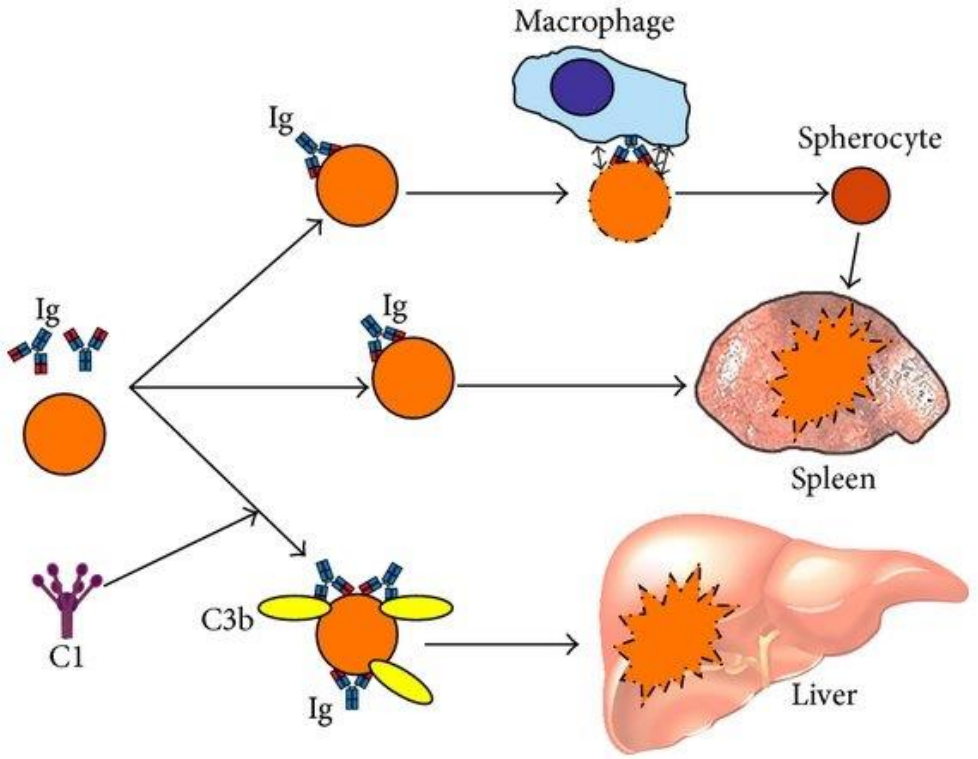
Autoimmune: Autoreactive antibodies (loss of self recognition of individual's own red cell antigen)

Drug-induced: Antibodies against red cells coated with drug or it is metabolites.

Causes of autoimmune-IHA
IgG or IgM mediated destruction of RBC

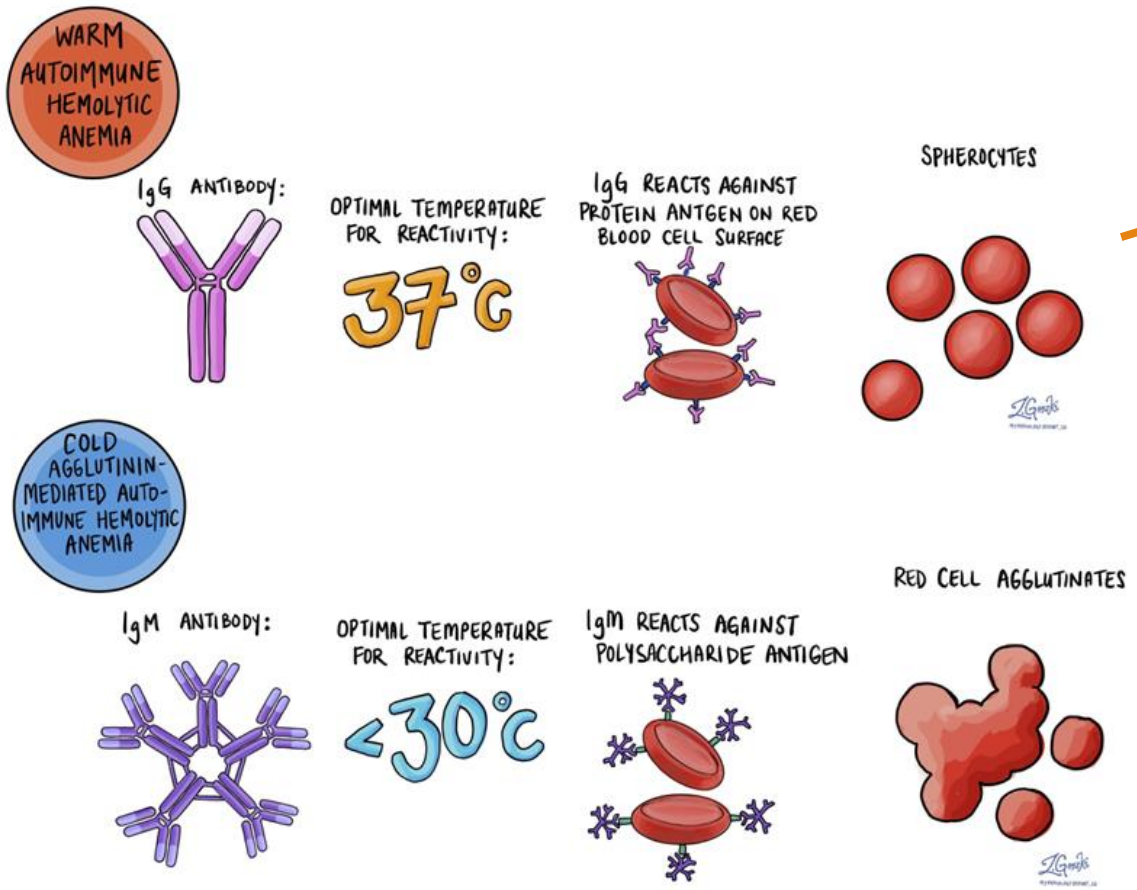
Warm Antibody: IgG/IgA type	Cold Antibody: IgM type
Activated at body temp. (37 c)	Active at 0-4°C IgM binds to RBC in cold temp (extremities)
IgG-coated RBC lysis in spleen (predominantly extravascular)	Clumping and complement fixation causes lysis in blood vessels and liver (intra- and extravascular)
Morphology: spherocytes (splenic macrophage phagocytose tagged RBC leading to formation of spherocytes)	IgM agglutination (hemolysis occurs in the hands & feet in cold weather)
80% of immune hemolytic anemias: Primary (50-70%) Secondary: - Lymphoproliferative disorders - Autoimmune diseases (SLE) - Drugs (penicillin and cephalosporins)	• Infectious mononucleosis (EBV) • Mycoplasma infection • Lymphoproliferative disorders

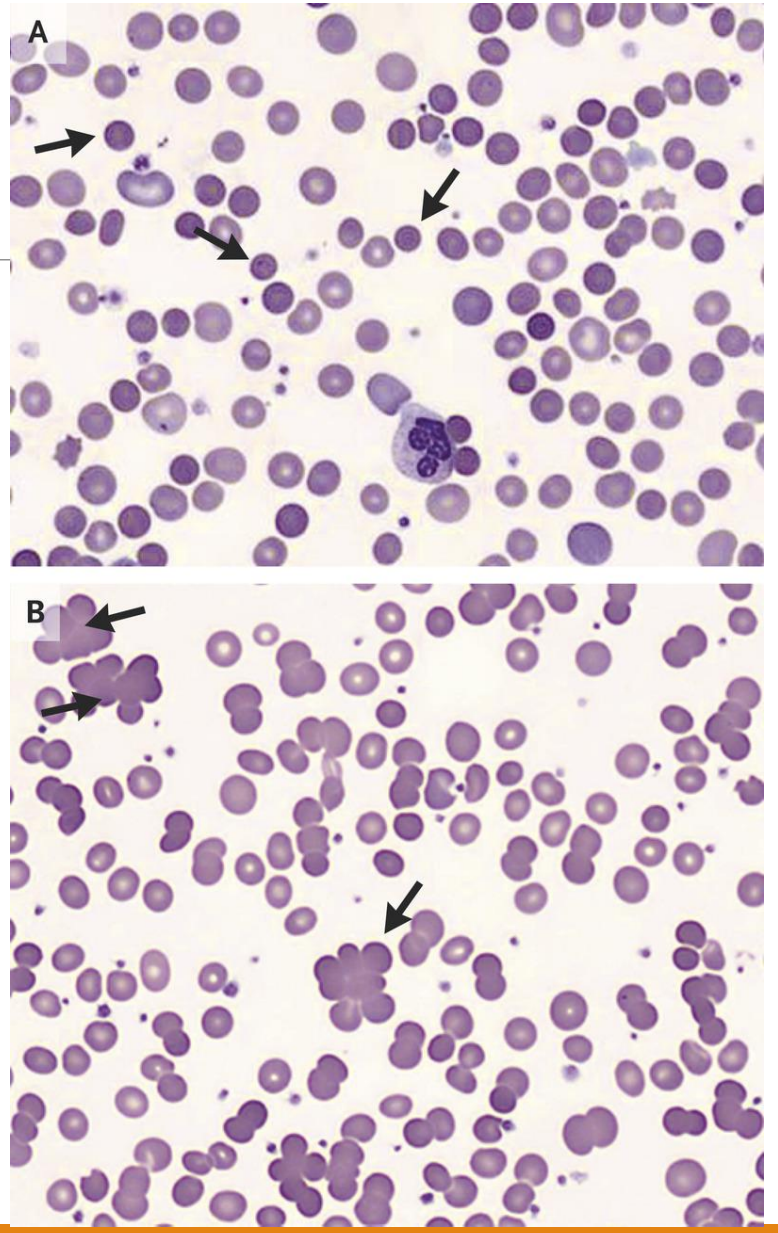




Cold Antibody: Clumping and complement fixation causes lysis in blood vessels and liver

Warm antibody: Opsonization, phagocytosis and spherocytosis


WARM AUTOIMMUNE HEMOLYTIC ANEMIA
IgG ANTIBODY:
OPTIMAL TEMPERATURE FOR REACTIVITY:
37°C
IgG REACTS AGAINST PROTEIN ANTGEN ON RED BLOOD CELL SURFACE
SPHEROCYTES
COLD AGGLUTININ-MEDIATED AUTO-IMMUNE HEMOLYTIC ANEMIA
IgM ANTIBODY:
OPTIMAL TEMPERATURE FOR REACTIVITY:
<30°C
IgM REACTS AGAINST POLYSACCHARIDE ANTIGEN
RED CELL AGGLUTINATES

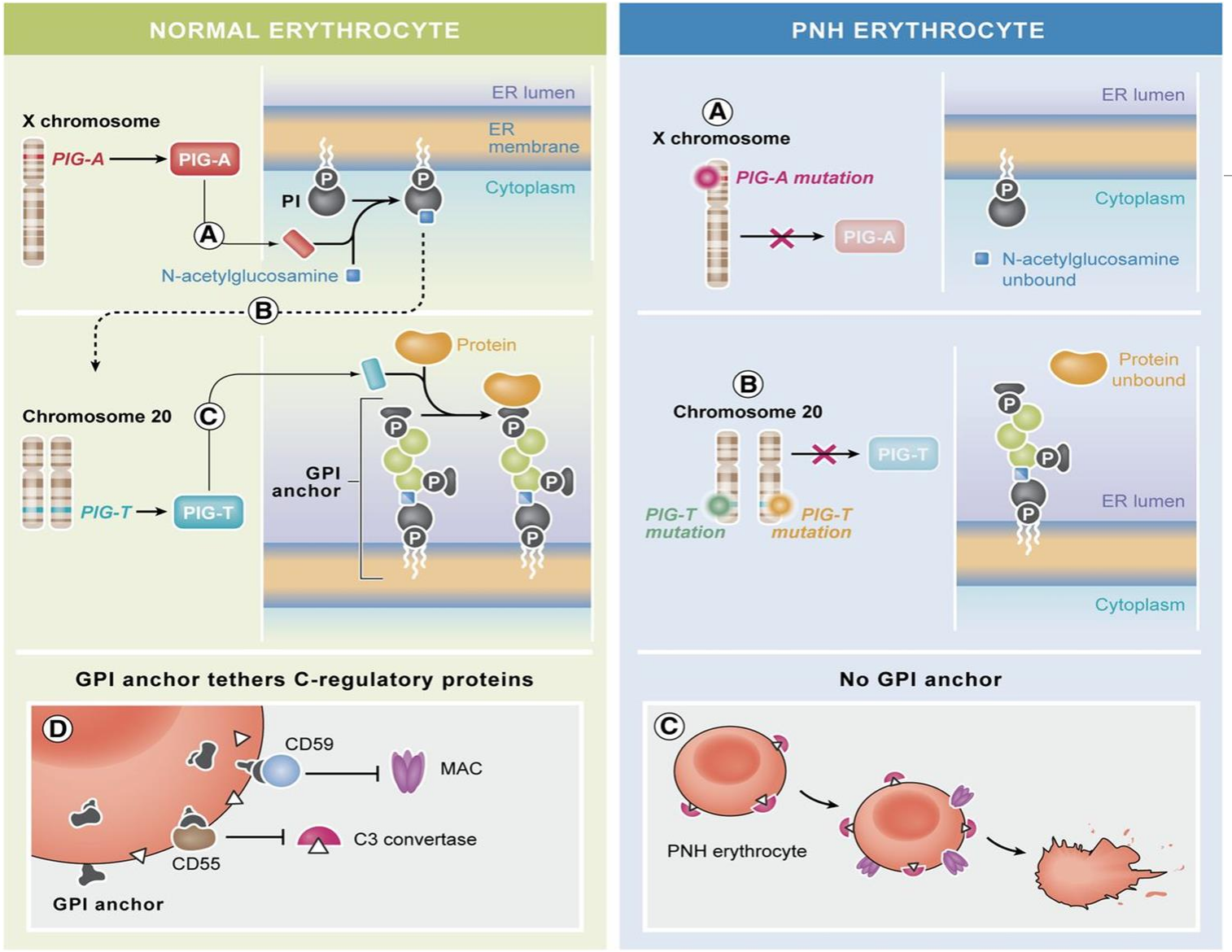

A
B

Paroxysmal nocturnal Hemoglobinuria(PNH)

- PNH is caused by an acquired somatic (non-germline) mutation in the X-linked phosphatidylinositol glycan class A (*PIGA*) gene;

- (*PIGA*) gene produces the glycosylphosphatidylinositol (GPI) anchor proteins (GPI-APs), that links cell surface proteins to cell membranes
- Hematopoietic cells containing *PIGA* mutations lack GPI anchored cell surface markers, including complement inhibitors (such as CD59 and CD55)

- **So, mature erythrocytes lacking GPI-APs are unprotected from the membrane attack complex (MAC or C5b9), leading to paroxysmal hemolysis**

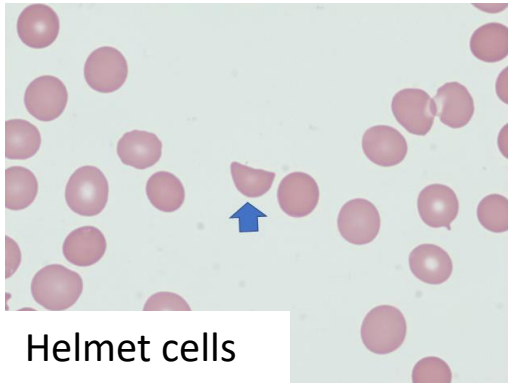


Hemolysis occurs mostly at night when there is fixation of complement which is enhanced by decrease of blood PH during sleep

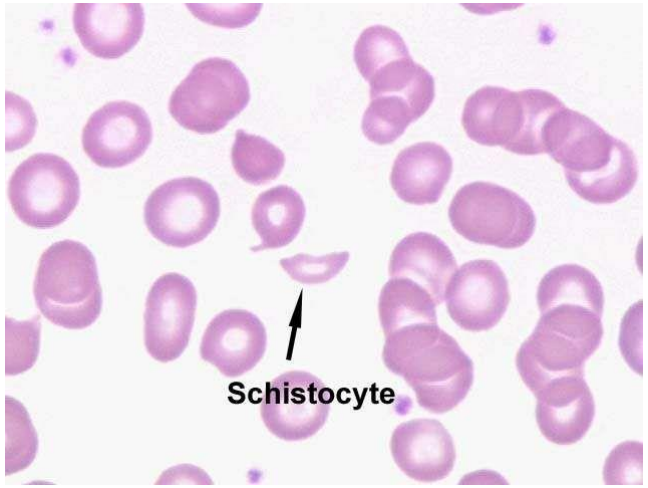
- ✓ Chronic intravascular hemolysis with hemoglobinemia, hemosiderinuria -/+ hemoglobinuria
- ✓ Reticulocytosis
- ✓ Venous thrombosis (hypercoagulability due to free Hb in blood)

Hemolytic anemias due to mechanical trauma to RBCs

Red cells are disrupted by **physical trauma**:



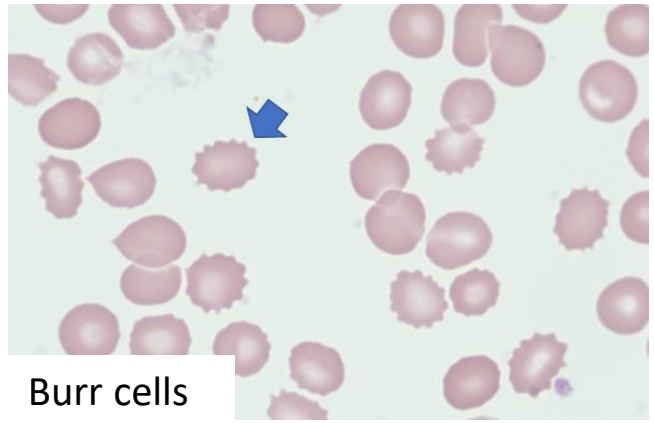
Helmet cells



I. Cardiac valve prostheses

II. Microangiopathic hemolytic anemia as in DIC , malignant hypertension, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS).

In all these conditions the circulating RBCs are mechanically traumatized , get the appearance of **Schistocytes , burr cells or helmet cells**



Burr cells