RED BLOOD CELLS AND BLEEDING DISORDERS

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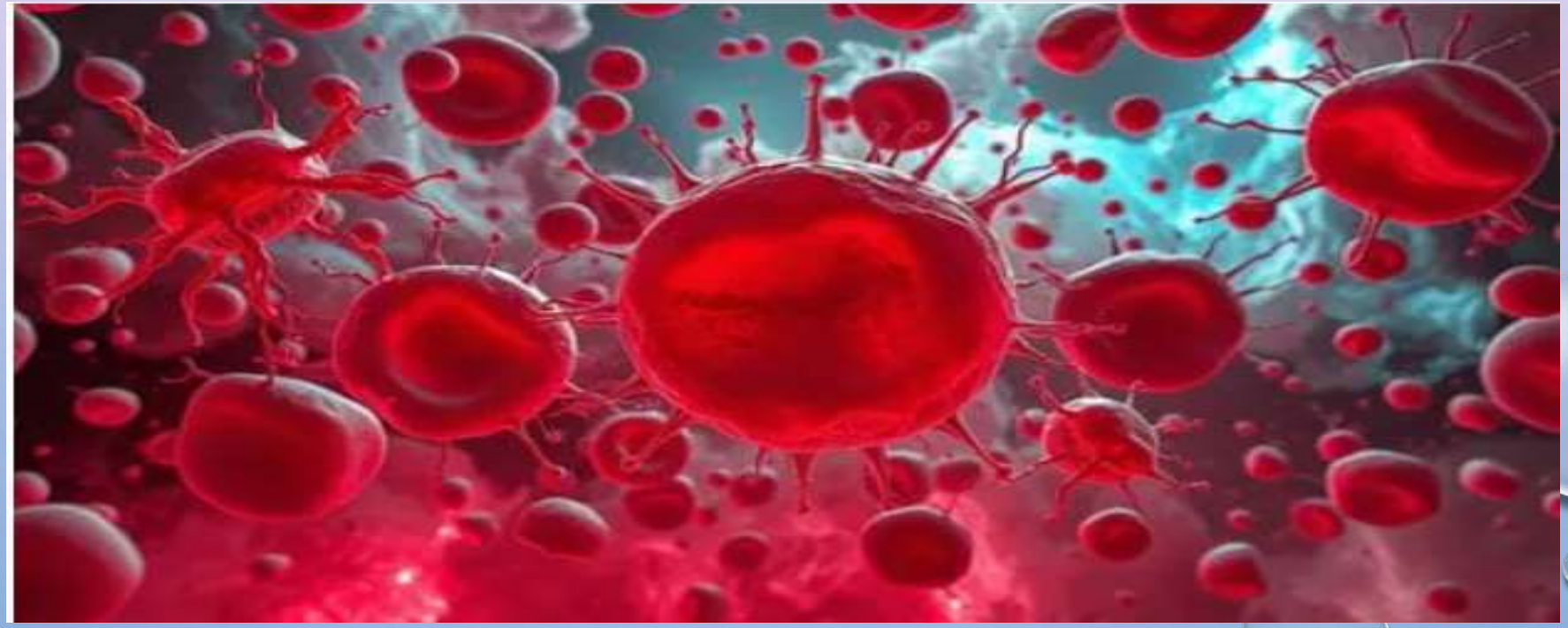


INTRODUCTION

- **Hematology: the study of various cells and components of the blood.**
- **Hematopoiesis:** the process of production of blood cells.
- Sites of hematopoiesis:
- **By birth:** the bone marrow in whole of the skeleton is haematopoietically active and is the chief source of blood cells and it remains so till puberty
- **After puberty:** the red marrow is present in vertebrae, ribs, sternum, skull, pelvis and proximal epiphyseal regions of humorous and femur.

❖ Classification of hematolymphoid disorders based on predominant involvement of:

1- red cells

2- white cells

3- the coagulation system, which includes platelets and clotting factors.

ANEMIAS

ANEMIAS

- Anemia is defined as a reduction in the oxygen-transporting capacity of blood, resulting from a decrease in the red cell mass to subnormal levels.

❖ **Definition : HB <13 g/dl Male, <12 g/dl Female**

❖ **Clinical features:**

- Fatigue
- Breathlessness
- Headache
- Pallor of skin and mucous membranes
- Palpitation (fast beating of heart)

❖ **Investigations:**

- CBC and Blood film
- Serum iron ferritin, vitamin B12 and Folate levels
- Hemoglobin electrophoresis

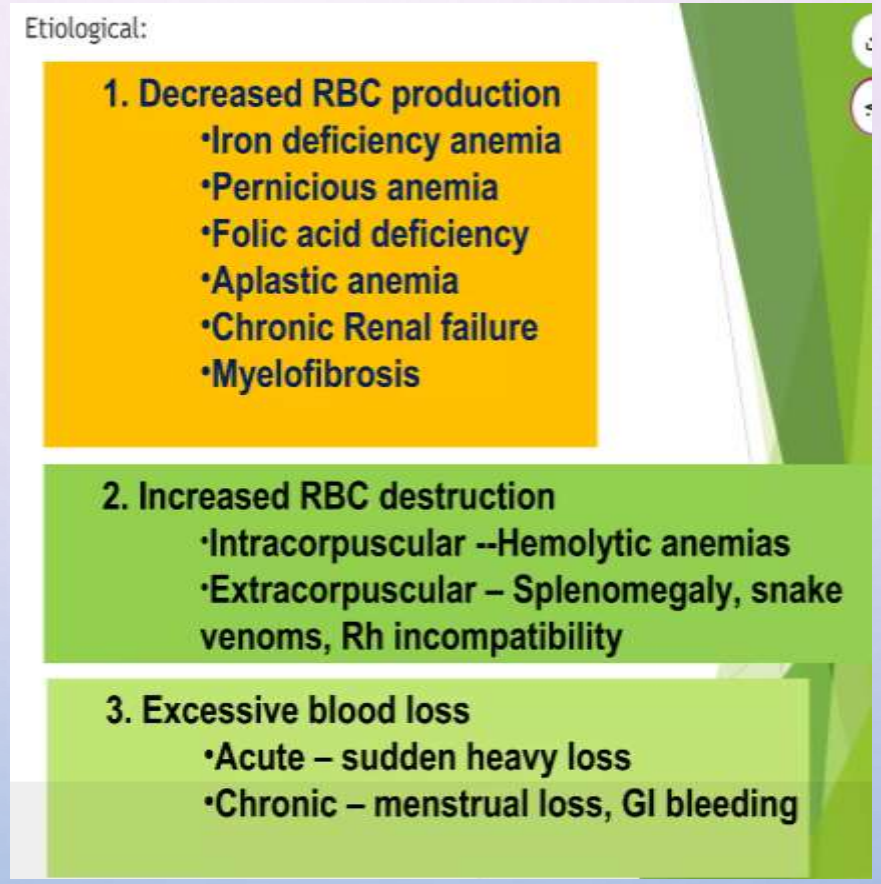
CLASSIFICATION OF ANEMIA

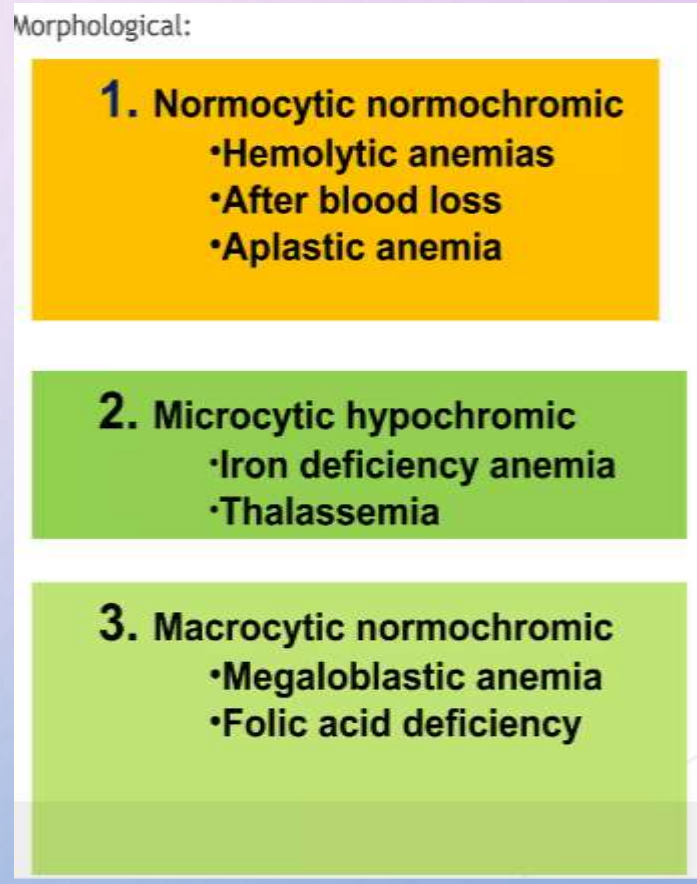
❖ **Etiological:** according to the cause.:

1. Decreased RBC production
2. Increased RBC destruction
3. Excessive blood loss

❖ **Morphologic classification**: according to the shape and amount of Hb

1. Normocytic (MCV 80-100 fl)
2. Microcystic (MCV < 80 fl)
3. Macrocystis (MCV > 100 fl)





COMPLETE BLOOD COUNT (CBC)

- The **CBC** offers a quantitative assessment of each of the blood's cellular elements.
- **Reticulocyte:** is a newly released RBC (< 36 hours). It contains residual RNA.
- Normal reticulocyte count: less than 1.5%
- In anemia one should correct the percentage of reticulocytes.

Differential white cell count

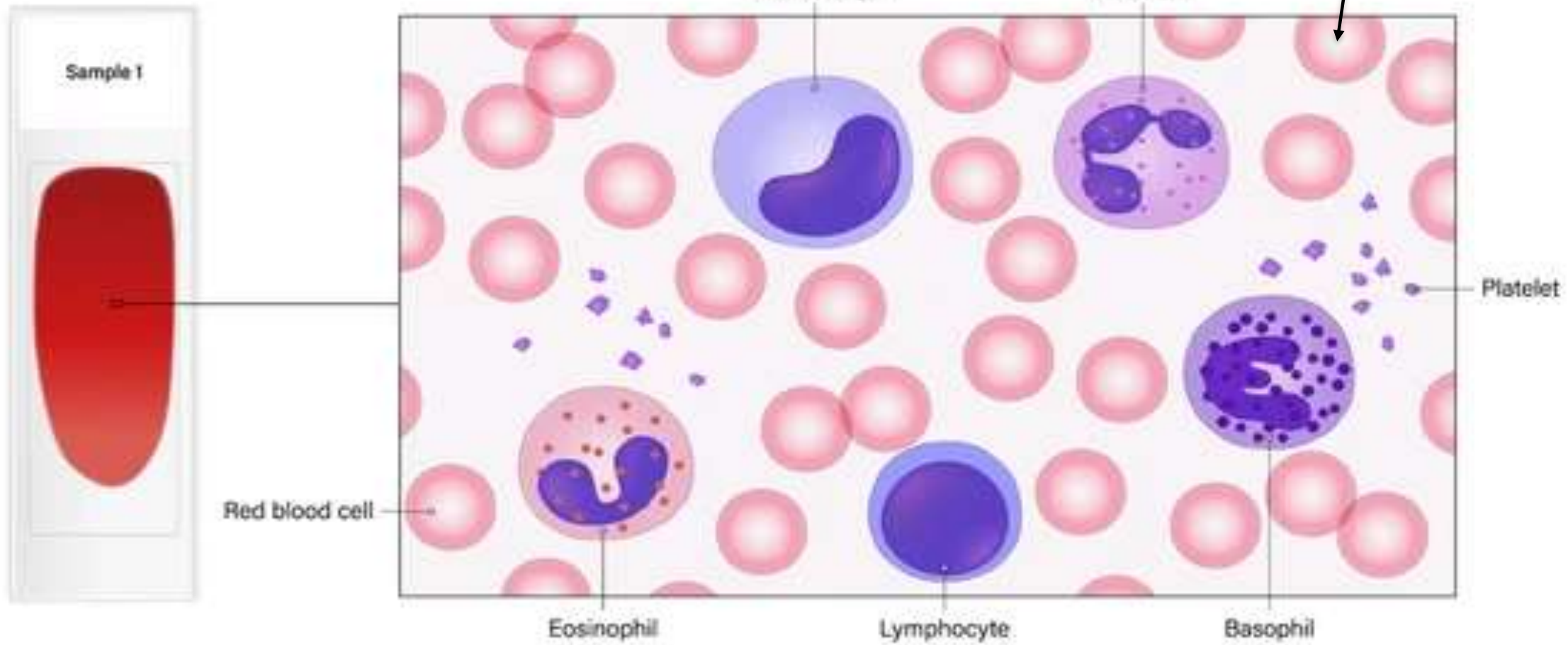
- Neutrophils 2.0–7.0 x 10^9 /l (40–80%)
- Lymphocytes 1.0–3.0 x 10^9 /l (20–40%)
- Monocytes 0.2–1.0 x 10^9 /l (2–10%)
- Eosinophils 0.02–0.5 x 10^9 /l (1–6%)
- Basophils 0.02–0.1 x 10^9 /l (<1–2%)

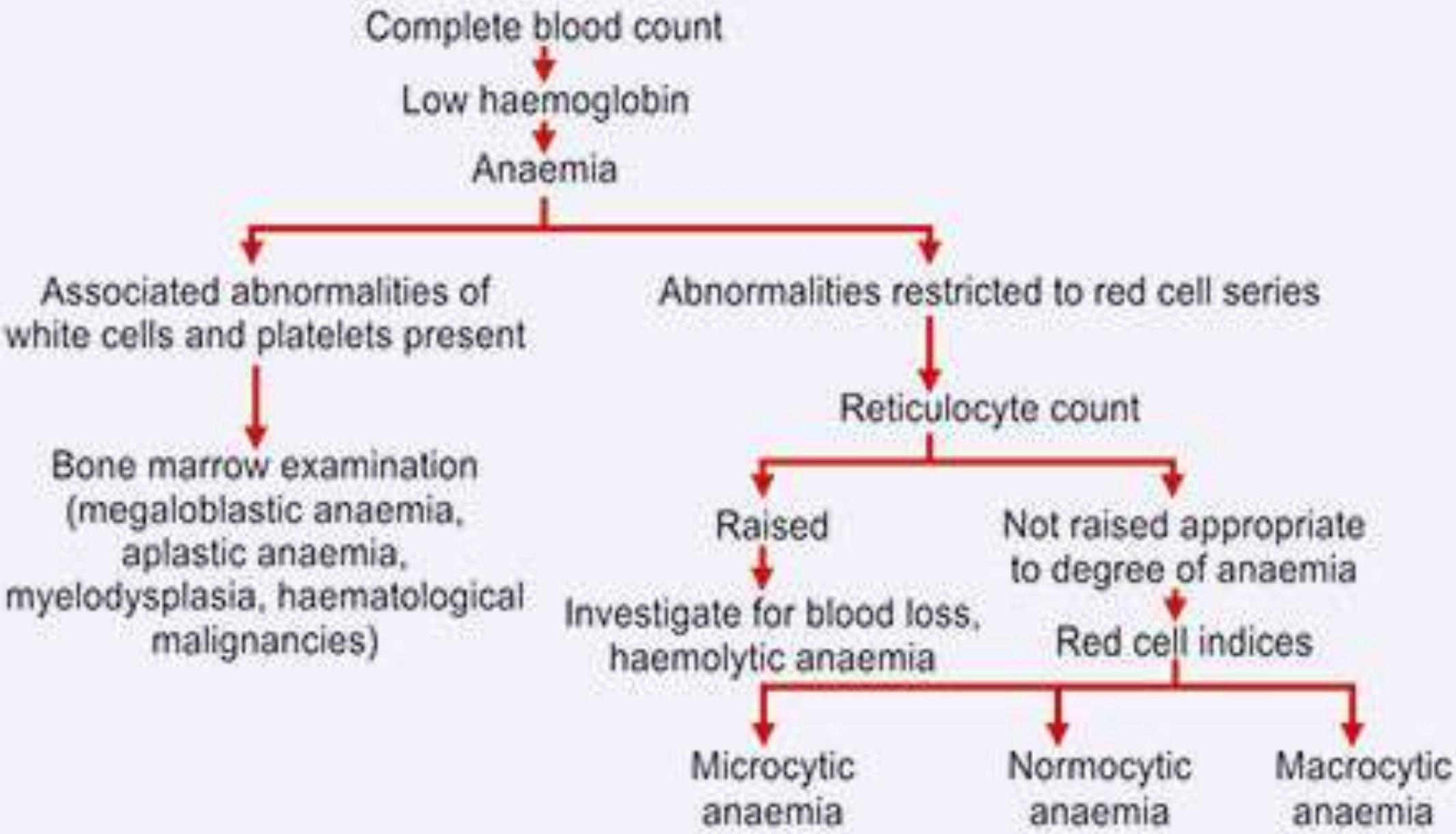
Adult Reference Ranges for Red Blood Cells[a]

	Units	Men	Women
Hemoglobin (Hb)	g/dL	13.2–16.7	11.9–15.0
Hematocrit (Hct)	%	38–48	35–44
Red cell count	$\times 10^6/\mu L$	4.2–5.6	3.8–5.0
Reticulocyte count	%	0.5–1.5	0.5–1.5
Mean cell volume (MCV)	fL	81–97	81–97
Mean cell Hb (MCH)	pg	28–34	28–34
Mean cell Hb concentration (MCHC)	g/dL	33–35	33–35
Red cell distribution width (RDW)		11.5–14.8	

PERIPHERAL BLOOD SMEAR/FILM

helps identify morphological abnormalities in red blood cells, white blood cells, and platelets




Complete blood count
Low haemoglobin
Anaemia
Associated abnormalities of white cells and platelets present
Bone marrow examination (megaloblastic anaemia, aplastic anaemia, myelodysplasia, haematological malignancies)
Abnormalities restricted to red cell series
Reticulocyte count
Raised
Investigate for blood loss, haemolytic anaemia
Not raised appropriate to degree of anaemia
Red cell indices
Microcytic anaemia
Normocytic anaemia
Macrocytic anaemia

IRON DEFICIENCY ANEMIA (IDA)

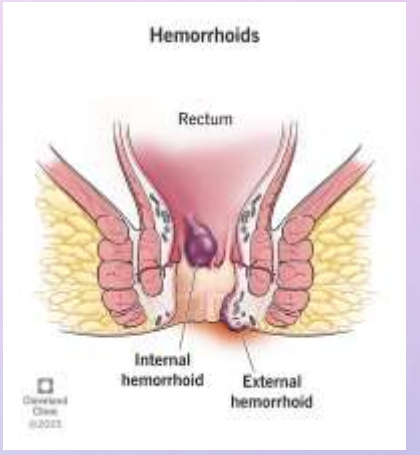
- Deficiency of iron is the most common nutritional disorder in the world.
- Particularly in toddlers, adolescent girls, and women of childbearing age.
- Approximately 80% of functional body iron is present in **hemoglobin, myoglobin and iron-containing enzymes** (Catalase, cytochromes).
- The storage pool represented by **hemosiderin** and **ferritin** contains about 15% to 20% of total body iron.

➢ Free iron is highly toxic, and storage iron must therefore be sequestered. This is achieved by the binding of storage iron to either ferritin or hemosiderin.

- Transported in plasma by an iron-binding protein called **transferrin,**
- The absorption of dietary iron in the **proximal duodenum**

Causes of IDA

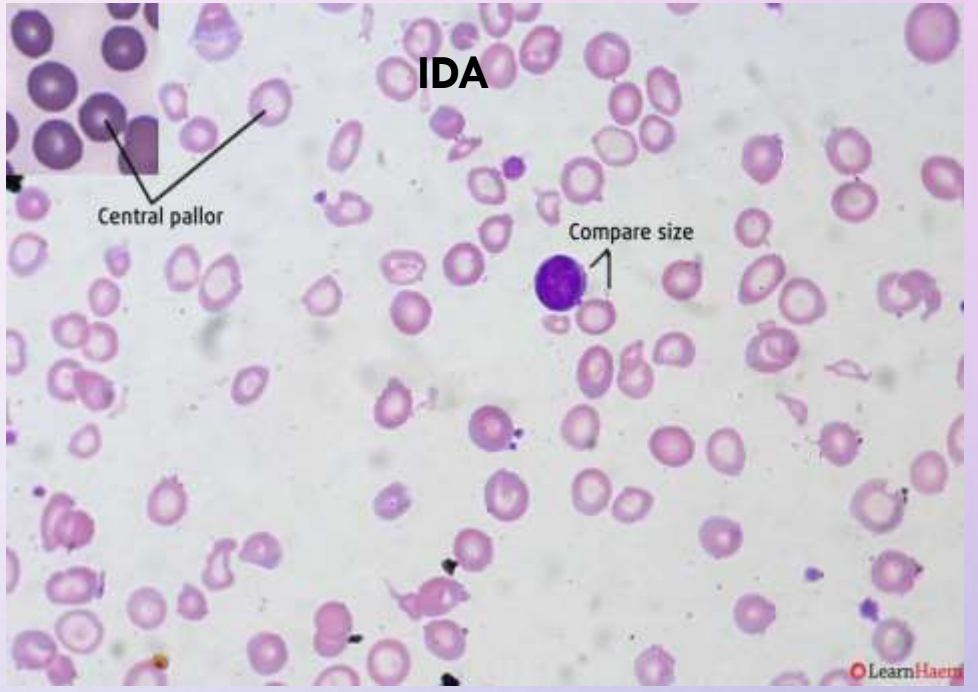
Dietary lack	Impaired absorption	Increased requirement	Chronic blood loss
- Infants - Children - Low socio-economic status - Elderly	- Steatorrhea - Sprue - Chronic diarrhea - Gastrectomy	- Growing infants and children - Pregnant females - Premenopausal women	- GIT (peptic ulcer, gastric cancer, hemorrhoids)- urinary tract (renal, pelvic or bladder cancers) - Genital tract (uterine cancer, menorrhagia)



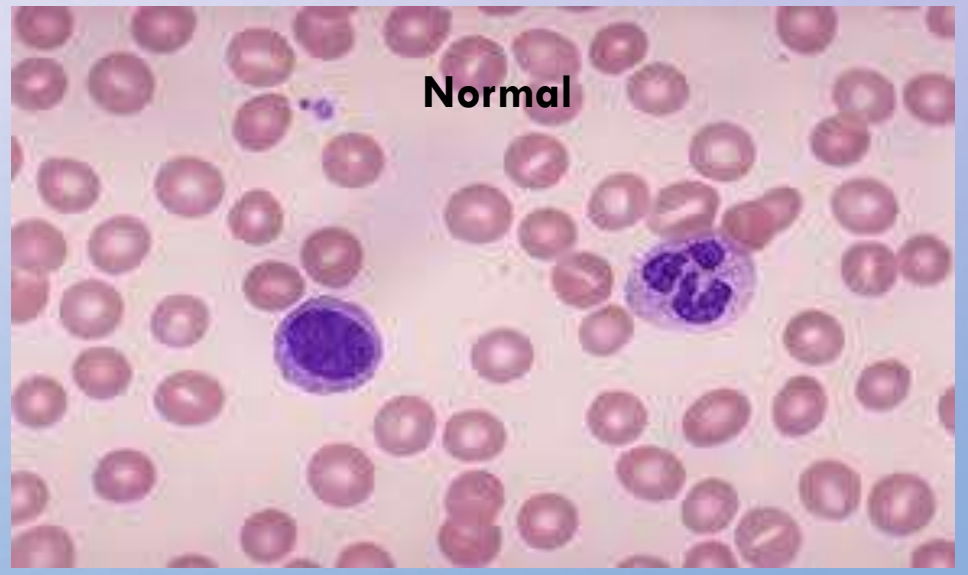
Clinical features:

- Fatigue
- Impaired growth and development
- Pica (eating mud in children)
- Koilonychia (spoon shaped nails)
- Angular stomatitis (ulceration at the angle of mouth)
- Palpitation

- **Findings on CBC and peripheral blood:**
- Microcytic and hypochromic RBCs
- Reduced MCV, MCH, and MCHC



- **Treatment:**
- Oral or parenteral iron therapy
- Response to treatment is clinically assessed by improvement in symptoms and increase in the reticulocyte count on about 8^{th}-9^{th} day



- **Importance of diagnosis**:

• It may be the earliest manifestation of a serious underlying diseases (10-20% of iron deficient patients have cancer, up to 50% have GER/PUD)

MEGALOBLASTIC ANEMIA

❖ Due to vitamin B12 and folate deficiency.

➢ Deficiency in either B12 or folic acid disrupts DNA formation and maturation

- Leads to slow red blood cell (RBC) reproduction
- Causes RBCs to be abnormally large, oddly shaped, and fragile
- Results in the formation of **megaloblasts**

❖ **Causes of deficiency:**

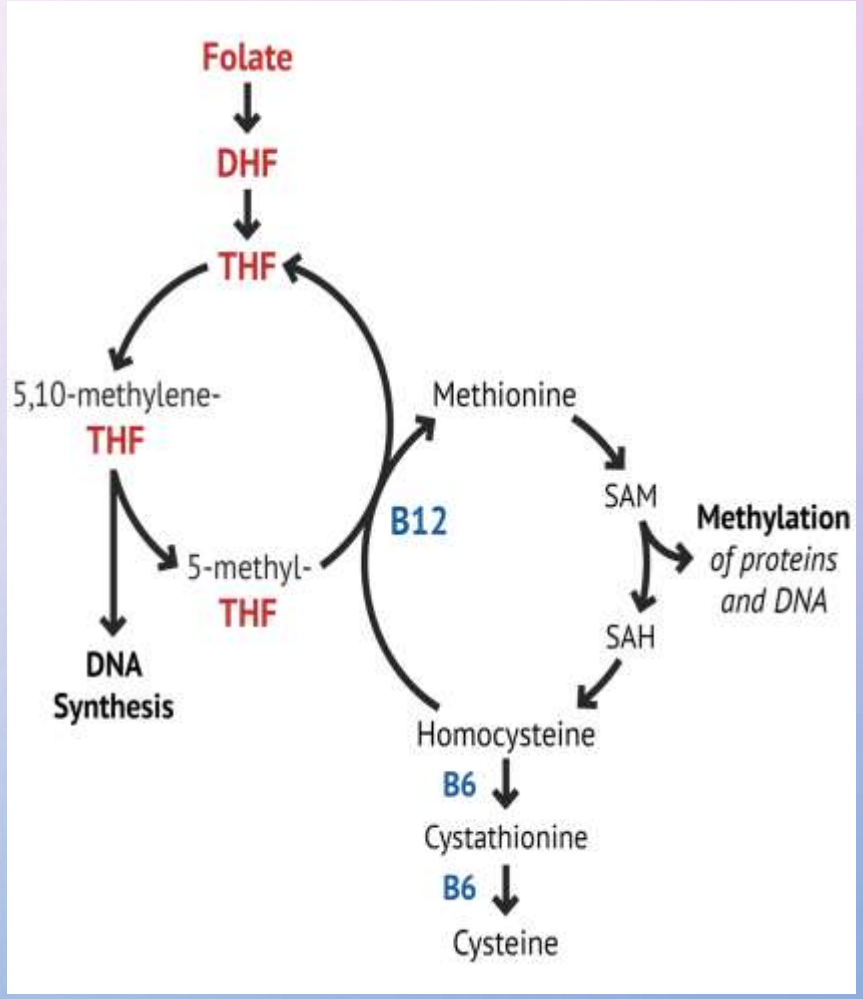
- **1) Decreased intake:** vegetarian
- **2) Impaired absorption:**

B12: intrinsic factor deficiency, gastrectomy, intestinal diseases, ilial resection.

Folate: intestinal diseases, anticonvulsant.

- **3) Increased requirement:**

Folate: Pregnancy infancy.



- **Vitamin B12 absorption mechanism:**
- Intrinsic factor produced in the stomach.
- It binds to vitamin b12, forming a complex that travels to the terminal ileum (the final section of the small intestine) where it is absorbed into the bloodstream
- Without sufficient intrinsic factor, vitamin B12 absorption is impaired, which can lead to **pernicious anemia**
- **Site of B12 absorption is terminal ilium**

- **Folate deficiency during pregnancy** causes neural tube defects in babies
- Folate supplementation is mandatory before and during pregnancy
- Iron tablets should be taken alongside folate supplements

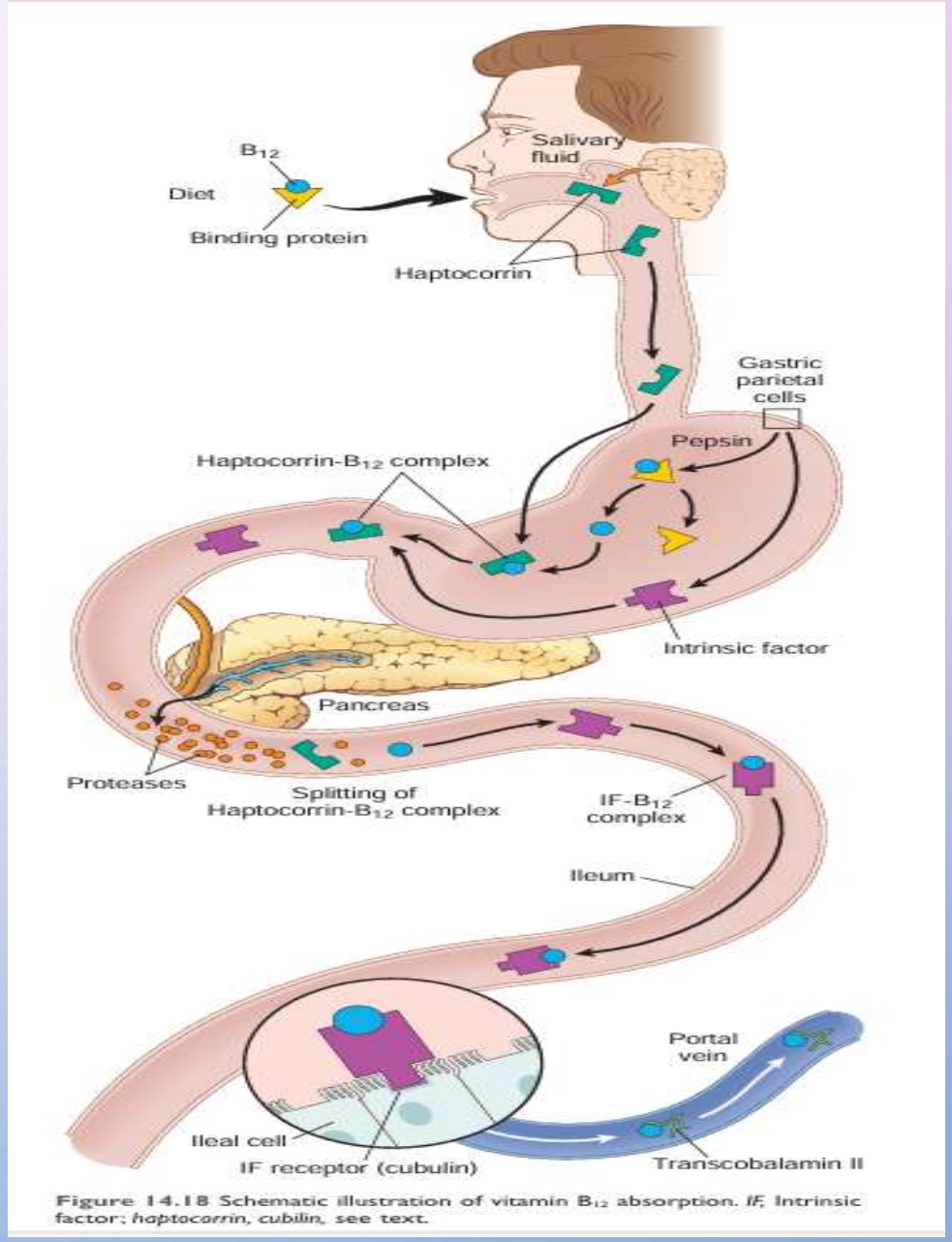
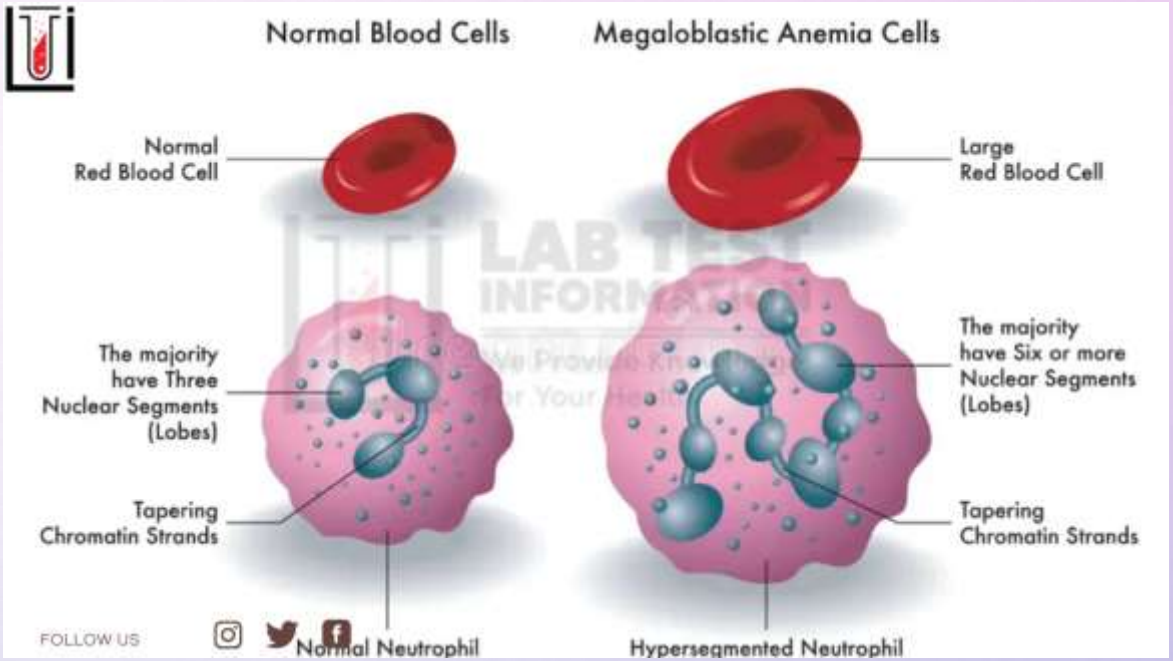
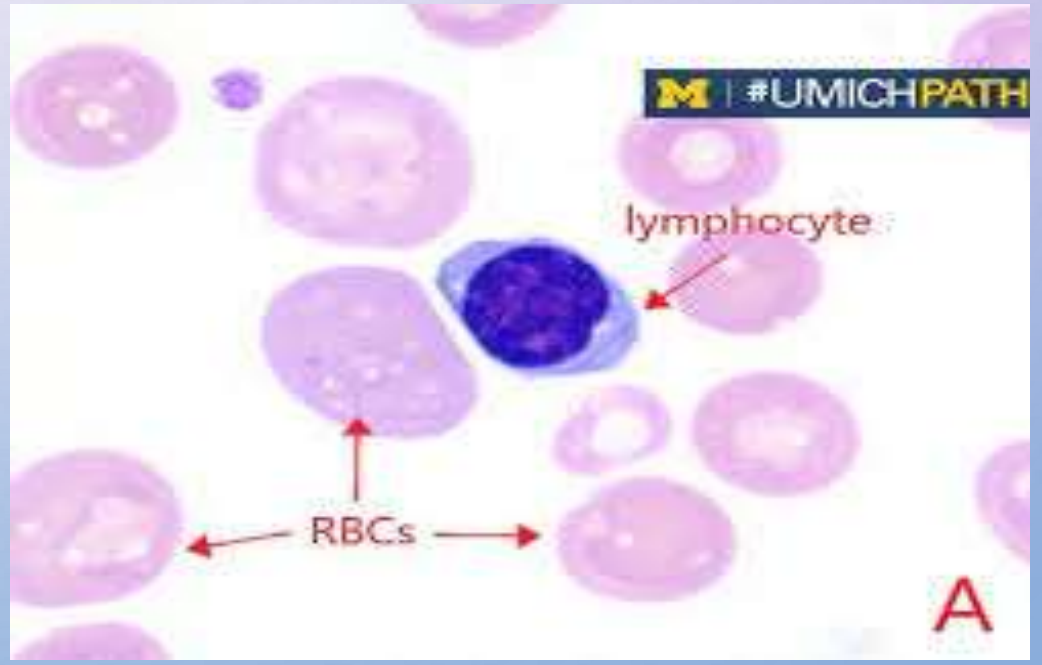


Figure 14.18 Schematic illustration of vitamin B_{12} absorption. *IF*, Intrinsic factor; *haptocorrin, cubilin,* see text.

- **Findings on CBC and peripheral blood:**
- Macrocytic, normochromic RBCs
- MCV, MCH increased.
- Hypersegmented neutrophils



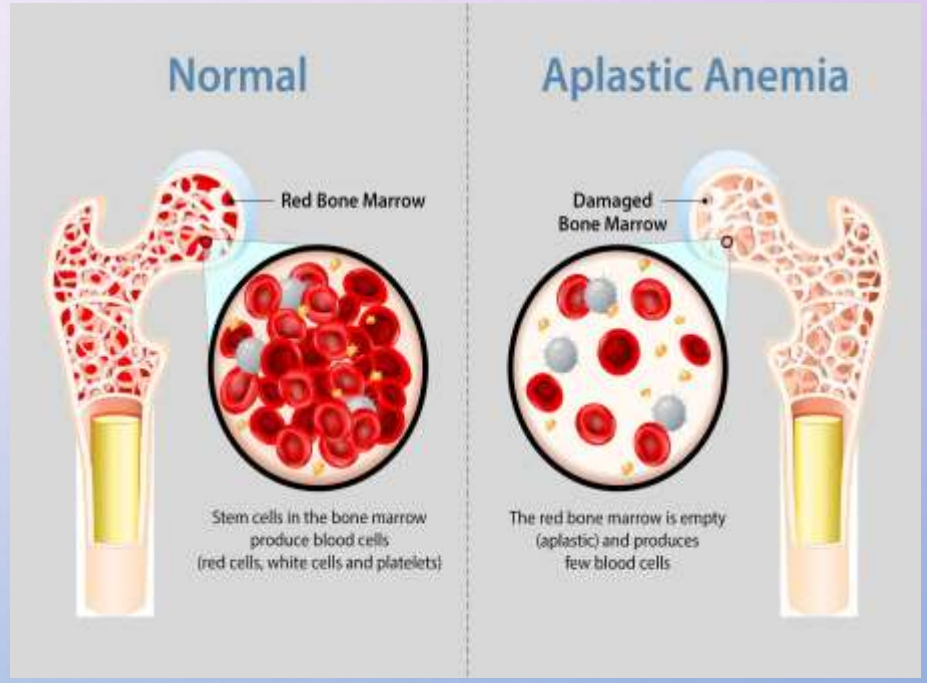
- **Clinical features of megaloblastic anemia**:
  - Fatigue and breathlessness
  - Soreness of the tongue
  - Glossitis and angular stomatitis
  - Tingling in hands and feet from peripheral neuropathy
  - Severe cases may lead to subacute combined degeneration of the spinal cord (SACD)
- **Treatment options:**
  - Folic acid (FA) tablets
  - Vitamin B12 injections



APLASTIC ANEMIA

- A syndrome of chronic primary hematopoietic failure and attendant pancytopenia (anemia, neutropenia, and thrombocytopenia).
- **Causes**:

- Drugs: chemotherapy, chloramphenicol
- Viral infection: viral hepatitis
- Whole body irradiation: therapeutic or nuclear accidents (Chernobyl)



❖ **Findings on CBC, Blood film and Bone marrow:**

- Pancytopenia: meaning there are low numbers of red blood cells, white blood cells, and platelets. A reticulocyte count is also low.
- Normocytic, Normochromic RBCs
- Dry tap bone marrow aspirate
- Bone Marrow biopsy: markedly hypocellular bone marrow is largely devoid of hematopoietic cells; often only fat cells, fibrous stroma, and scattered lymphocytes and plasma cells remain

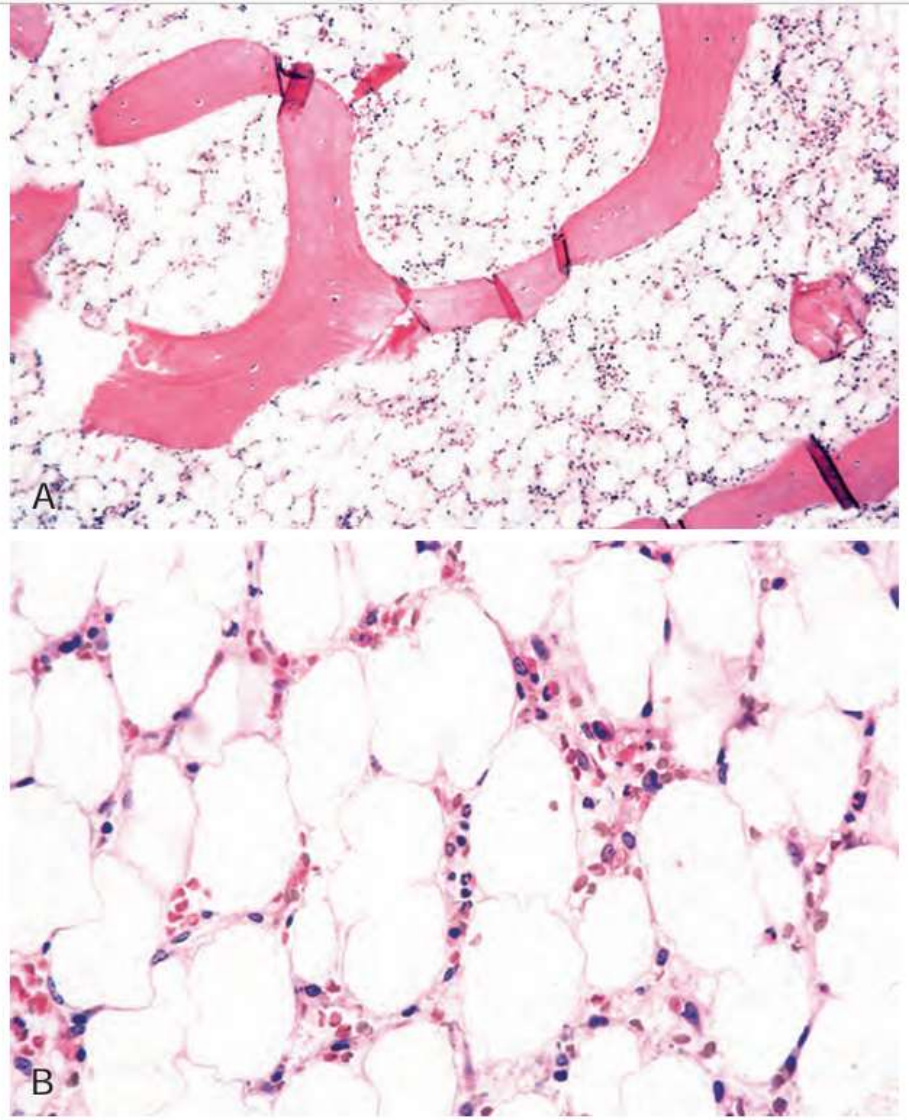
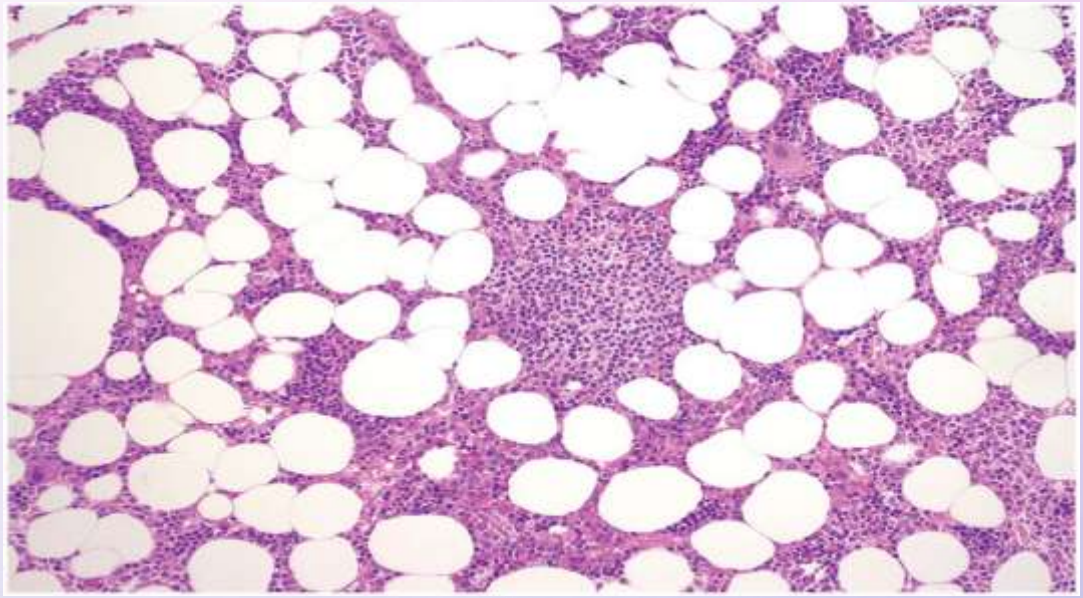
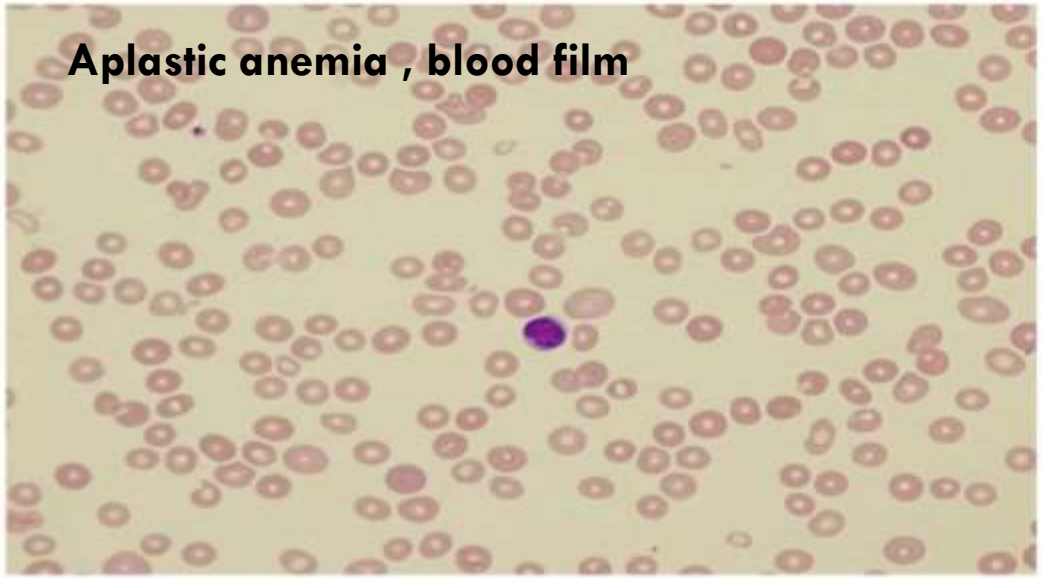


Figure 14.25 Aplastic anemia (bone marrow biopsy). Markedly hypocellular marrow contains mainly fat cells. (A) Low power. (B) High power. (Courtesy Dr. Steven Kroft, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Tex.)

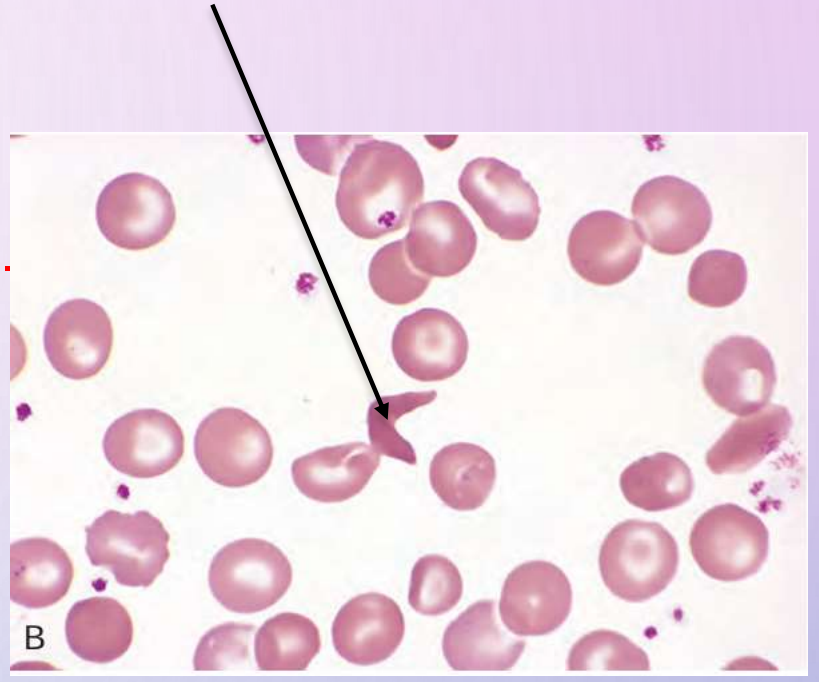
Normal bone marrow



Aplastic anemia , blood film



SICKLE CELL ANEMIA

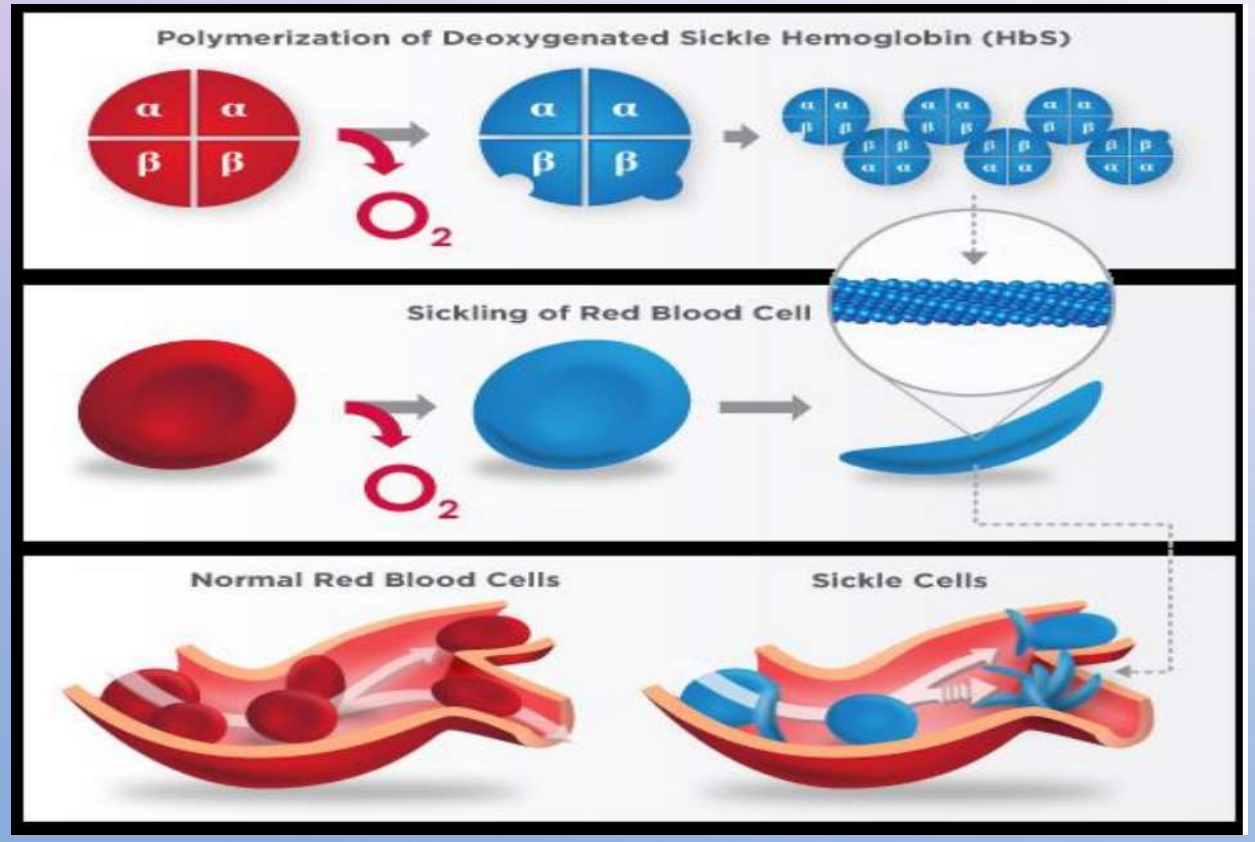


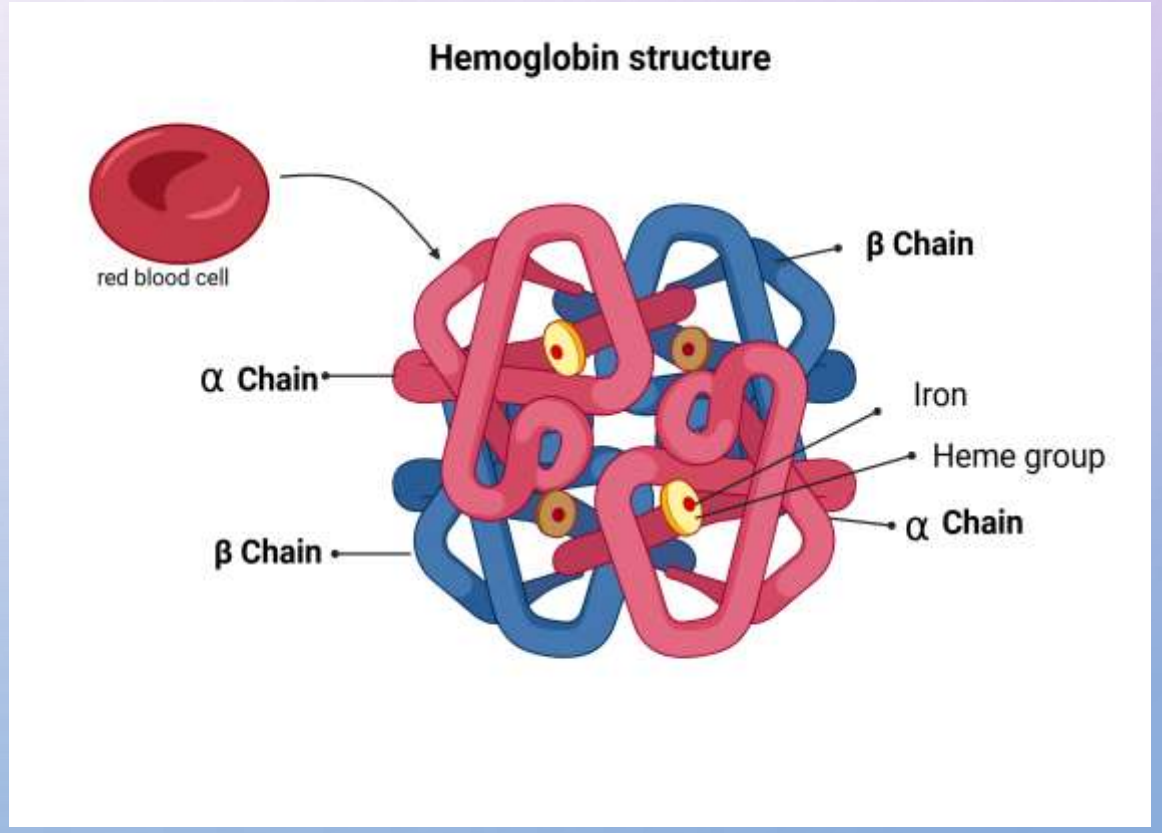
- Type of hemolytic anemia.
- Common hereditary hemoglobinopathy caused by a mutation in β-globin
- **Pathophysiology**: deoxygenated HbS polymerizes, causing sickle-cells that hemolyze and block blood vessels
- **Findings in CBC and peripheral blood**:
- Normocytic, Normochromic RBCs
- **Clinical features:**
- Autosplenectomy: in early childhood, the spleen is enlarged by red pulp congestion caused by the trapping of sickled red cells. With time, however, chronic erythrostasis leads to splenic infarction, fibrosis, and progressive shrinkage, so that by adolescence or early adulthood only a small amount of fibrous splenic tissue is left.
- Vaso-occlusive crises, also called pain crises, are episodes of hypoxic injury and infarction that cause severe pain in the affected region, mostly, lung, bone, skin, and others

❖ Normal adult red cells contain:

1) Mainly HbA (α2β2)
2) Small amounts of HbA2 (α2δ2)
3) Small amount of fetal hemoglobin (HbF; α2γ2).

❖ Sickle cell disease is caused by a missense mutation in the β-globin gene that leads to the replacement of a charged glutamate residue with a hydrophobic valine residue. The abnormal resulting sickle hemoglobin (HbS) are responsible for the disease.





THALASSEMIA

❖ Germline mutations that decrease the synthesis of either α-globin or β-globin

❖ α thalassemia: rare

- B thalassemia:
  - Major: complete absence of β chain
  - Minor: reduced β chain synthesis
- Compensatory increase in hbA2 and hbF

❖ **Mechanism**:

- Results in the body not producing enough functional hemoglobin to carry oxygen, causing red blood cells to be destroyed prematurely by the spleen.
- The process also includes the buildup of unstable, unpaired globin chains that damage red blood cell precursors in the bone marrow, leading to ineffective erythropoiesis.

❖**Findings on CBC and peripheral blood:**

- Microcytic Hypochromic anemia.

❖ **Clinical features**:

- failure to thrive
- Crewcut skull and distinct facial features: Wide forehead, prominent cheekbones, a flattened nasal bridge, and a protruding upper jaw, due to the expansion of bone marrow.

❖ **Treatments**:

- blood transfusion, splenectomy, bone marrow transplantation

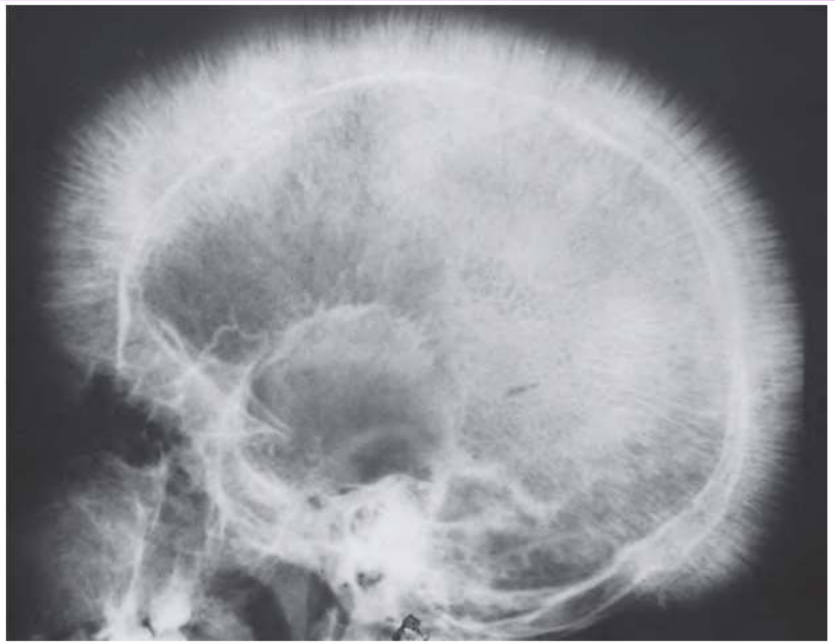


Figure 14.13 β-Thalassemia major. X-ray film of the skull showing new bone formation on the outer table, producing perpendicular radiations resembling a crewcut. (Courtesy Dr Jack Reynolds, Department of Radiology, University of Texas Sc

❖ Pre-marriage test:

- **Initial screening:** CBC to look for signs like a lower-than-normal MCV
- **Definitive test:** hemoglobin electrophoresis
- The hemoglobin electrophoresis with beta thalassemia trait usually has reduced or absent HbA, elevated levels of HbA2, and increased HbF

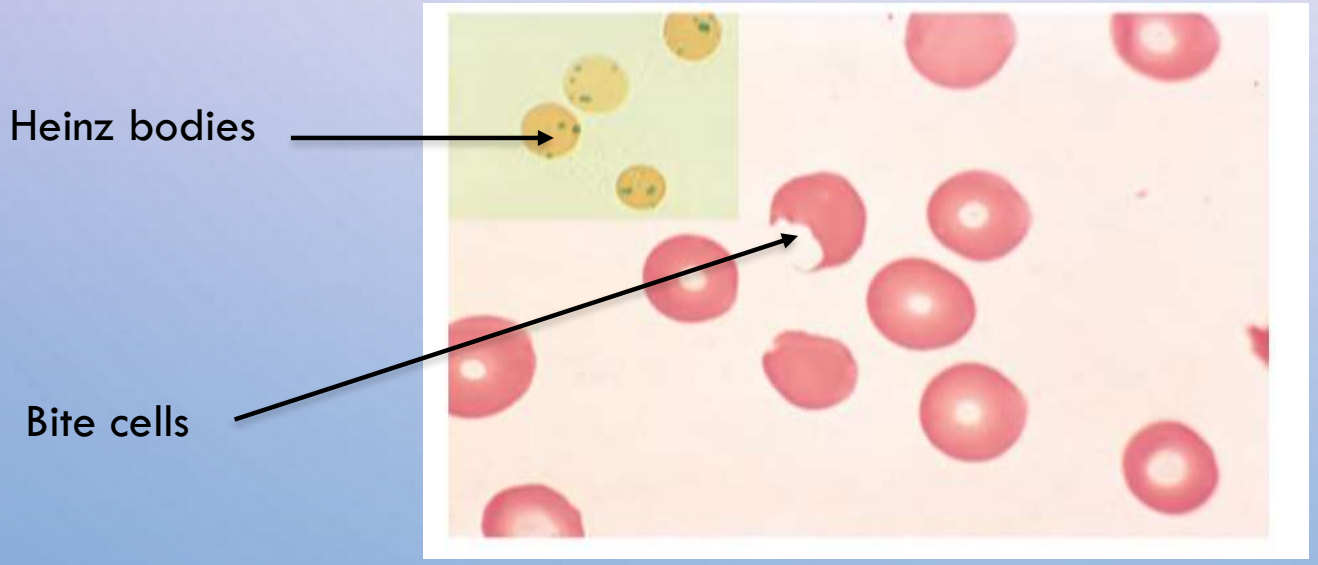
GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

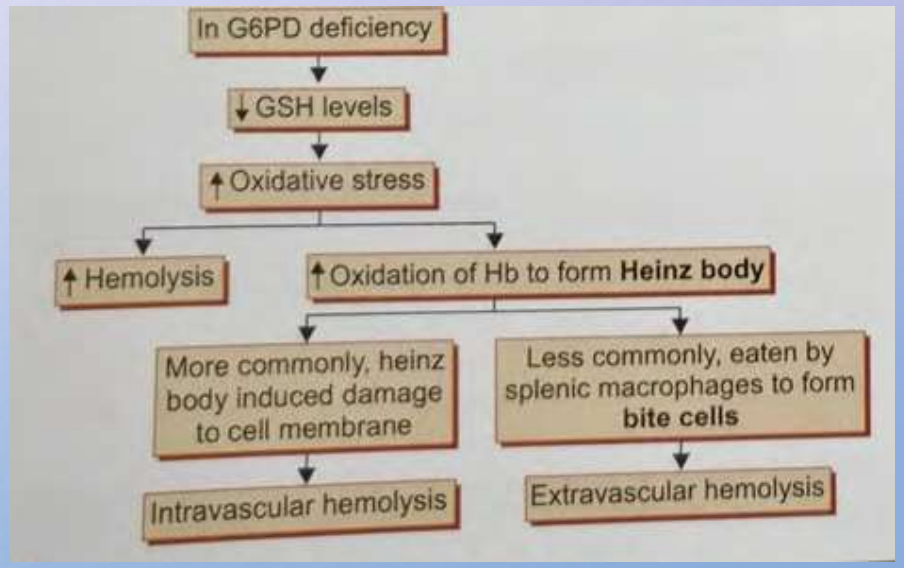
❖ Recessive x-linked trait, placing males at much higher risk for symptomatic disease

❖ The episodic hemolysis that is characteristic of G6PD deficiency is caused by exposures that generate oxidant stress:

- The most common triggers are infections, in which oxygen-derived free radicals are produced by activated leukocytes

- The other important initiators are drugs and certain foods (fava beans)





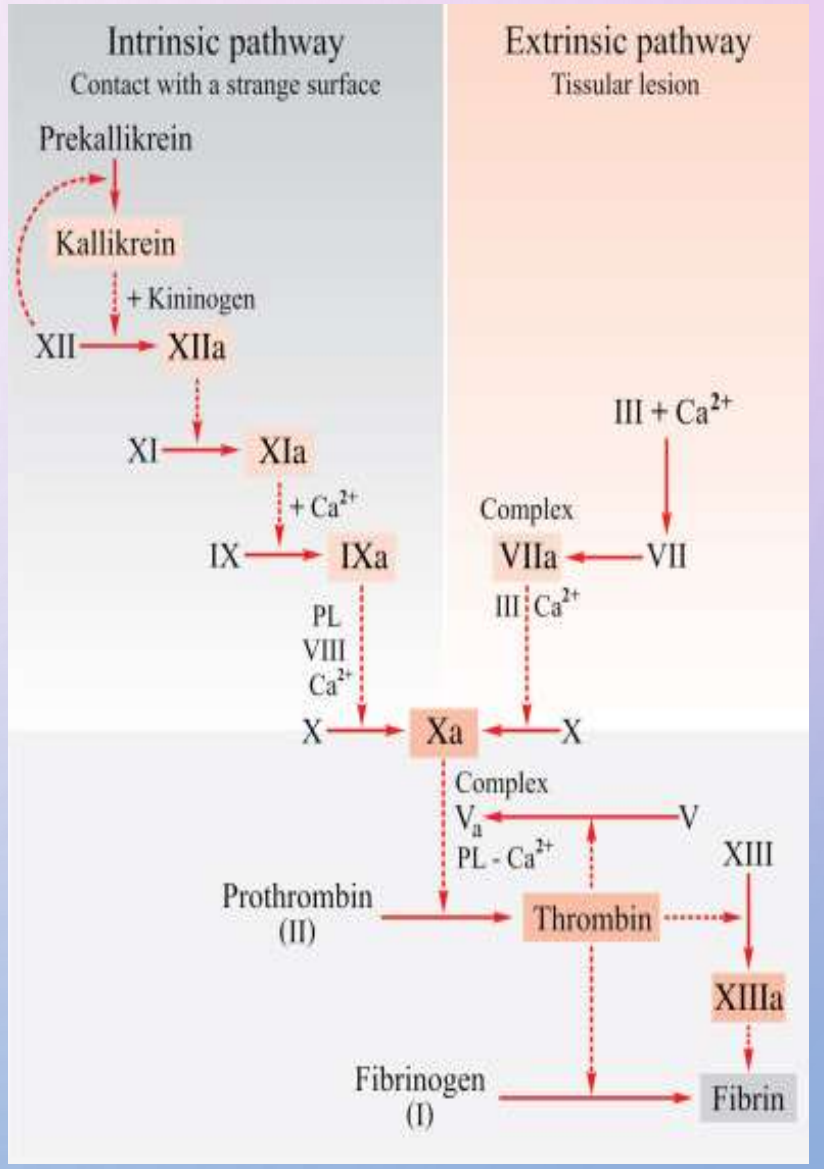
BLEEDING DISORDERS

- **Hemostasis** depends on the integrity of – blood vessels – platelets

– coagulation factors – anticoagulation factors

- **Bleeding disorders:** diseases characterized by a tendency to bleeding with deficient hemostasis either spontaneously or due to trauma.

- The most important test to evaluate bleeding disorder:
- 1) PT (Prothrombin Time): assess extrinsic and common coagulation pathway
- It measures the time in seconds needed for plasma to clot.
- 2) PTT (Partial Thromboplastin Time): assess intrinsic and common coagulation pathway
- 3) platelets count: the reference range 150,000-450,000.



CAUSES OF ABNORMAL BLEEDING

- VASCULAR DISORDERS
- THROMBOCYTOPENIA
- PLATELET FUNCTION DEFECT
- DEFECTIVE COAGULATION

DEFECTIVE COAGULATION

- Result from either congenital or acquired deficiency in clotting factors
- **Acquired:**
- Vitamin K is required for the synthesis of prothrombin and clotting factors VII, IX, and X, and its deficiency causes a severe coagulation defect
- The liver synthesizes several coagulation factors and also removes many activated coagulation factors from the circulation; thus, hepatic parenchymal diseases are common causes of complex hemorrhagic diatheses.
- DIC also may lead to multiple concomitant factor deficiencies
- **Hereditary**:
- Hemophilia A (a deficiency of factor VIII) and hemophilia B (Christmas disease, a deficiency of factor IX) are x-linked traits.
- Von Willebrand disease.

- **Hemophilia A**

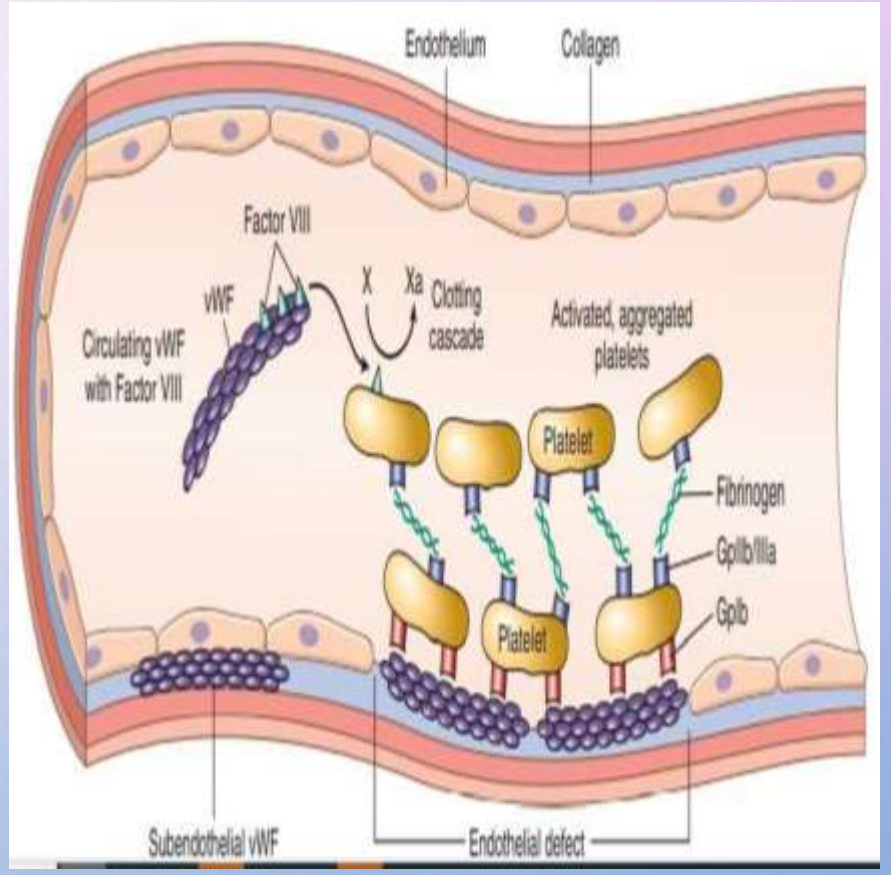
- Caused by absolute reduction of factor VIII or normal amount but defective factor VIII.
- Clinically :

- Easy bruising - massive hemorrhage after trauma or operative procedure.

- Sites of bleeding: large joints and soft tissue /urinary tract and GI tract /brain /nose
- laboratory tests: prolonged PTT.
- **Hemophilia B**
- Caused by deficiency in blood clotting factor IX.
- Bleeding sites: similar to hemophilia A.
- Laboratory tests: – prolonged PTT.

➢ VON WILLEBRAND DISEASE

- Von Willebrand factor: a large glycoprotein that plays a crucial role in blood clotting by helping platelets stick to the site of an injury and to each other. Also carries and stabilizes the clotting protein factor VIII
- The disease result from: Quantitative or qualitative defects of plasma vWF.
- The most common hereditary bleeding disorder .
- Von Willebrand disease is transmitted as an autosomal dominant disorder.
- Clinically: mild bleeding problems / mucous membrane bleeding / easy bruising / menorrhagia / post-operative bleeding

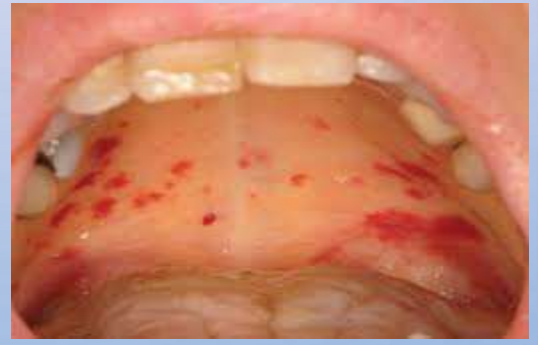


PLATELET DISORDERS

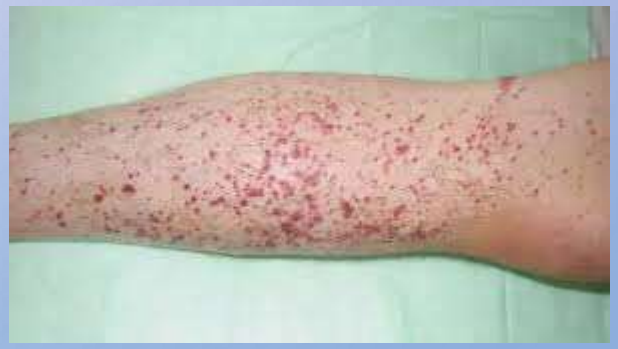
-Normal range 150-450 x 10^3 per µl.
-Levels above 60 x 10^3 will not cause bleeding under normal conditions.
-Levels below 20 x 10^3 will cause: petechiae, mucosal bleeding, Post-operative bleeding, CNS bleeding
-Levels around 5 x 10^3 can lead to fatal CNS or GI hemorrhage.

- **<u>Classification of thrombocytopenia:</u>**
- 1- Failure of production (aplastic anemia, radiation, chemo. treatment)
- 2- Increased platelet destruction (ITP)
- 3- Abnormal distribution (splenic sequestration)

Mucosal bleeding



petechiae



➢ **ITP (IMMUNE THROMBOCYTOPENIC PURPURA)** : INCREASED DESTRUCTION.

- primary or secondary
- Acute or chronic.

❖ **Acute ITP**

➢ Affects children.

➢ Develops acutely with 1-2 week duration.

➢ Bruising and petechia

➢ preceded by infection or vaccination in 75% of cases.

➢ Initial plt. Count < 20,000

➢ Self limited, Severe cases benefit from steroids or iv immunoglobulins

- **Chronic ITP**
- High incidence in women of child bearing age (20-50).
- No recent history of drug or recent infection.
- Mostly idiopathic, secondary causes include SLE, HIV, Hodgkin's disease, drugs (uncommon).
- Platelets lifespan reduced to hours.
- Megakaryocytes increased (in bone marrow)
- Petechial bleeding, easy bruising, menorrhagia

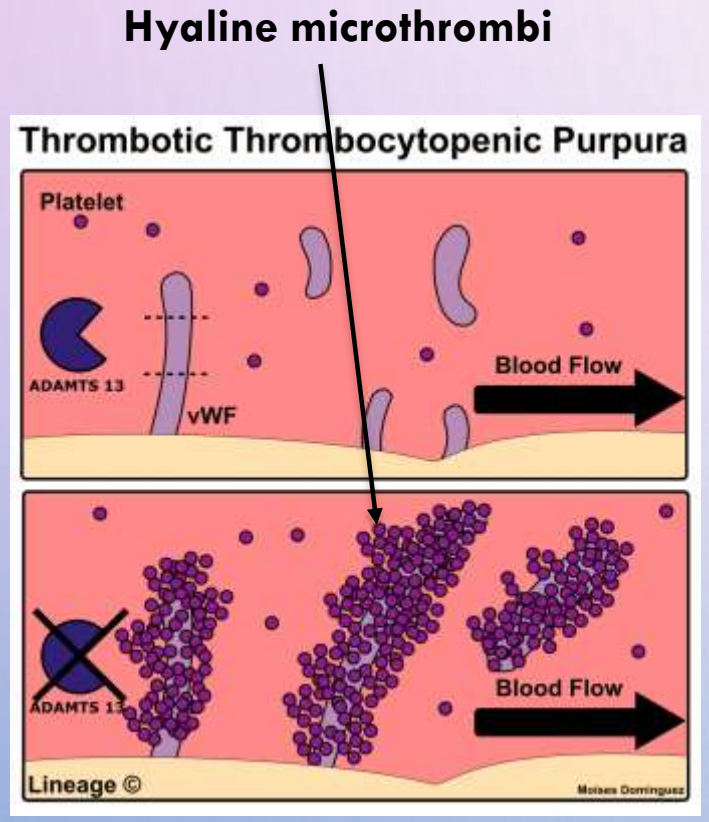
- **Lab findings of ITP:**
- Decreased platelet count (10-50x10^3 per µl).
- Hb And WBCs are normal.
- Blood film: large platelet.

Acute ITP	Chronic ITP
Mostly children	Mostly women
Preceded by infection	No recent history of infection
Self limited	Not self limited
	Megakaryocyte increased in bone marrow

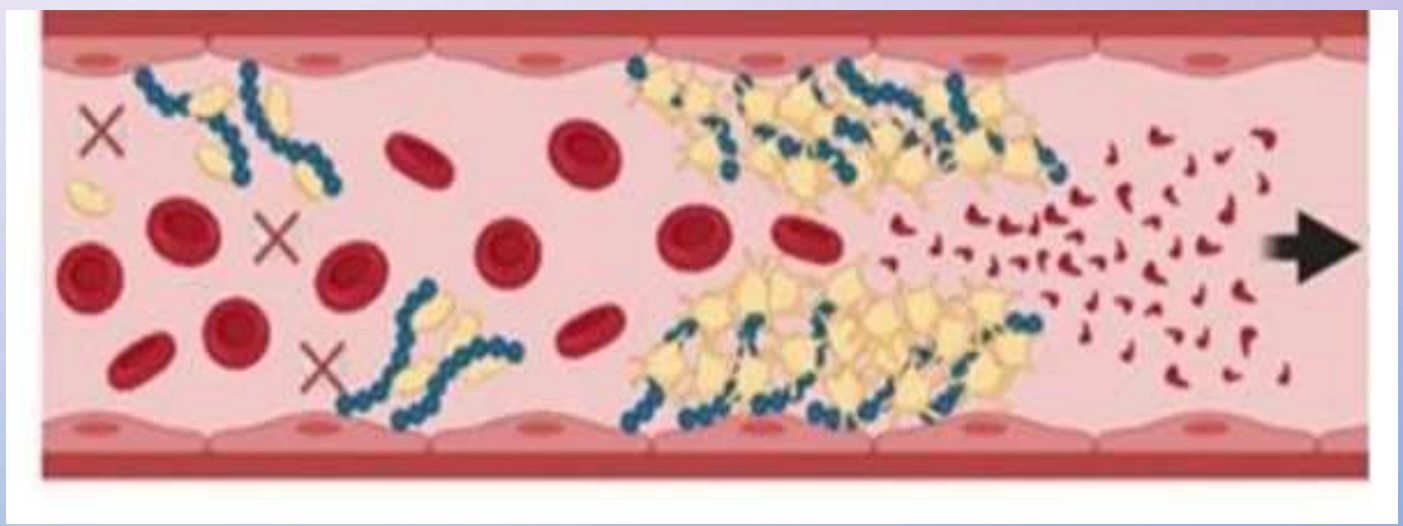
➢ **THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) :**INCREASED DESTRUCTION

- Female > males * 3rd-4th decade
- Characteristic pathologic feature: Hyaline microthrombi (platelet rich) in microcirculation (capillary of skin and gingiva)
- Clinically: Acute thrombocytopenia, fever, microangiopathic hemolytic anemia, neurologic abnormalities, renal dysfunction

- **Mechanism of hyaline microthrombi formation:** A deficiency in the ADAMTS13 enzyme leads to the accumulation of large vWF multimers, which spontaneously bind to platelets and cause aggregation in the microcirculation.



- **Microangiopathic hemolytic anemia:** red blood cells are fragmented as they are forced through the partially blocked and damaged microvasculature, creating characteristic schistocytes (fragmented red blood cells) visible on a blood film.



➢ **HEMOLYTIC UREMIC SYNDROME (HUS):** INCREASED DESTRUCTION

- More commonly seen in pediatric population.
- E. Coli O157:H7 (toxin induced endothelial damage)
- Clinically: Bloody diarrhea followed by acute renal failure., Platelet microaggregate (hyaline microthrombi) formation (usually limited to the glomerular capillaries), Acute thrombocytopenia, microangiopathic hemolytic anemia.

- **Mechanism of hyaline microthrombi formation**: after *E. Coli* infection, toxins damage endothelial cells, initiating platelet activation and the formation of hyaline microthrombi, primarily limited to the glomerular capillaries in the kidneys, causing acute renal FAILURE.

THE END

GOOD LUCK