Hematology Notes

Complete Blood Count

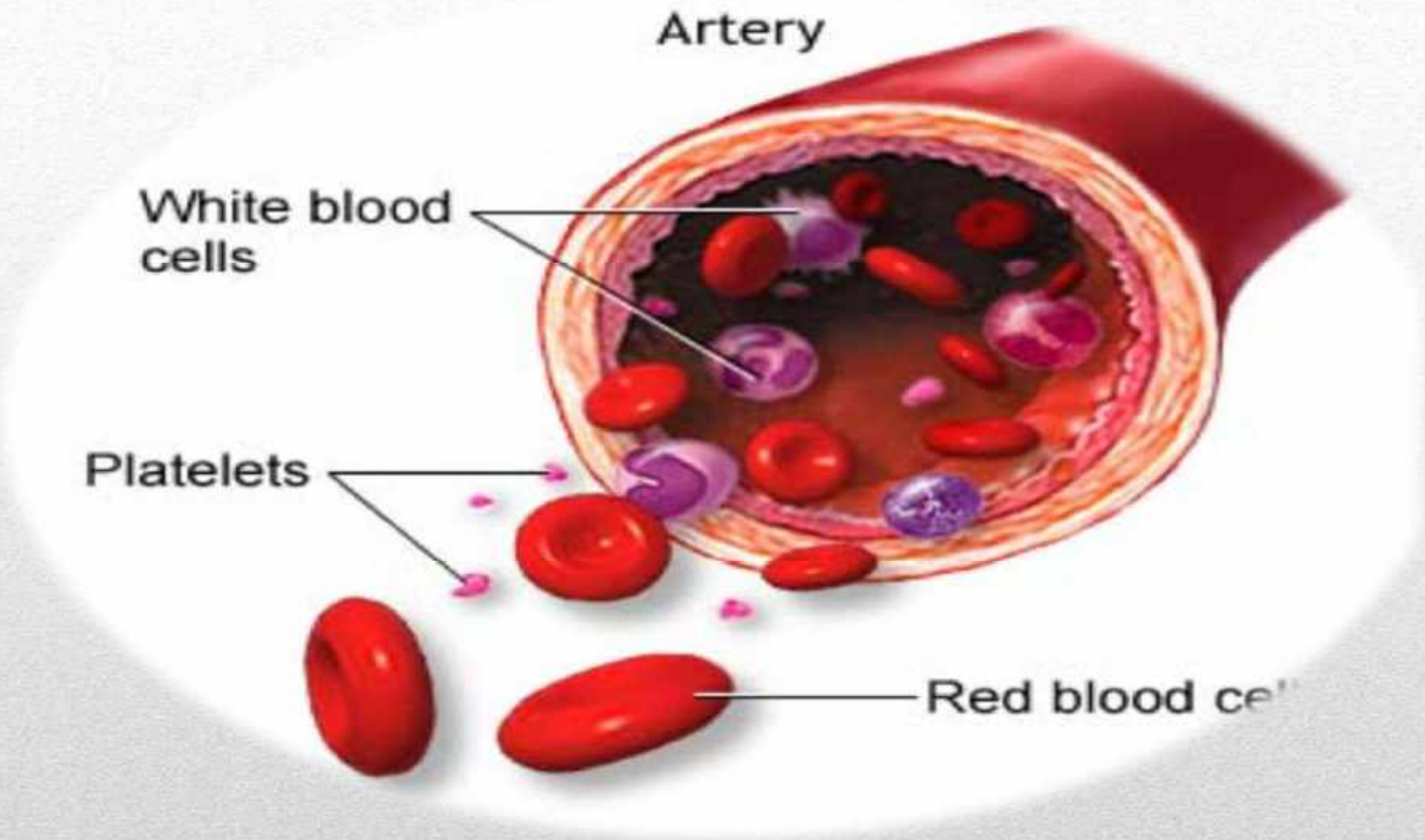
- CBC or Hemogram: one of the most commonly ordered lab tests. It assesses:
- White blood cells (WBC)
- Red blood cells (RBC)
- Platelets (PLT)
- WBC Differential

The Complete Blood Cell Count

TABLE 1
The Complete Blood Cell Count

Parameter	Normal adult range	Indications
Hemoglobin	*Male: 14.0 – 16 mg/dL* *Female: 12.0 – 14.0 mg/dL*	*Low: Anemia* *High: Polycythemia*
Hematocrit	*Male: 46% – 52%* *Female: 35% – 42%*	*Low: Anemia* *High: Polycythemia*
RBC count	*Male: 4.5 – 5.5 x 10^6/μL* *Female: 4.0 – 5.0 x 10^6/μL*	*Low: Anemia* *High: Polycythemia*
WBC count	*4.0 – 11.0 x 10^3/μL*	*Low: Leukopenia* *High: Leukocytosis*
Platelet count	*150 – 400 x 10^3/μL*	*Low: Thrombocytopenia* *High: Thrombocytosis*
Reticulocyte count	*0.5% – 1.5%* *25 – 85 x 10^3/μL*	*Low in anemia: Low marrow output* *High: RBC loss*

RBC, red blood cell; WBC, white blood cell.



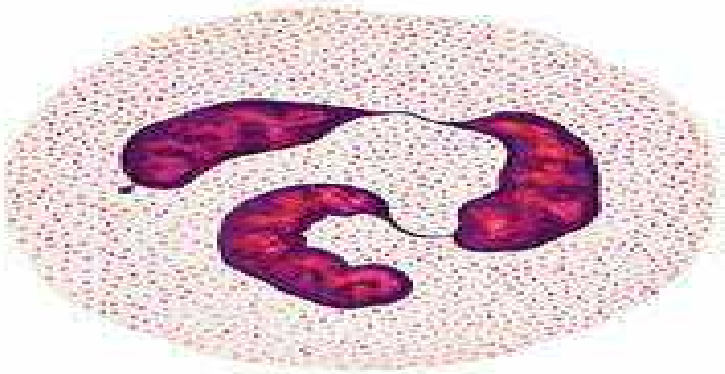
Blood cells

I. Blood makes up about 7% of a body's weight
II. An average adult has 14-18 pints of blood

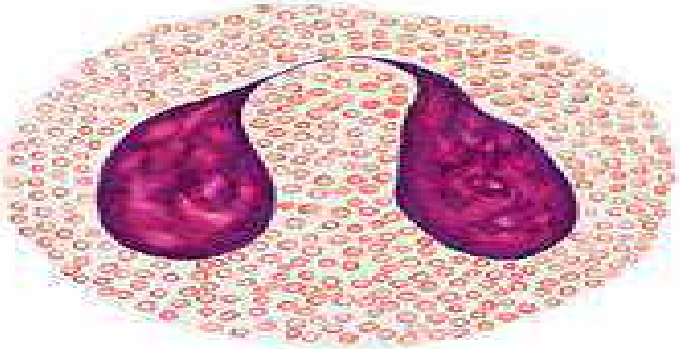
III. Four main blood types: A, O, B, AB
IV. Rh positive or negative

V. Universal Donor: O-

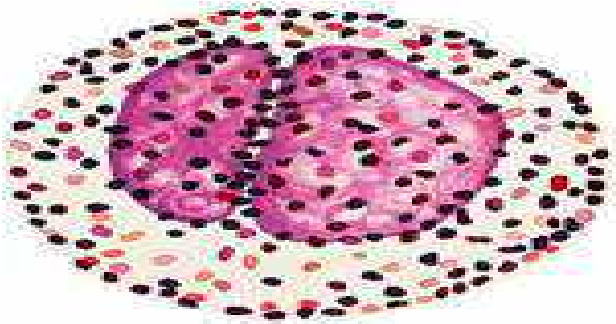
VI. Universal Recipient: AB +



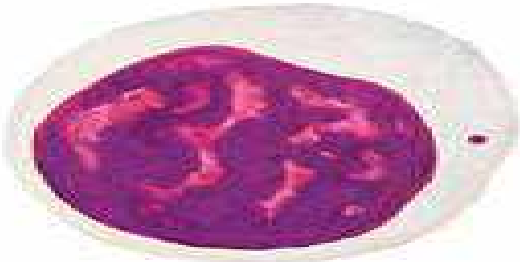
Neutrophilic granulocyte



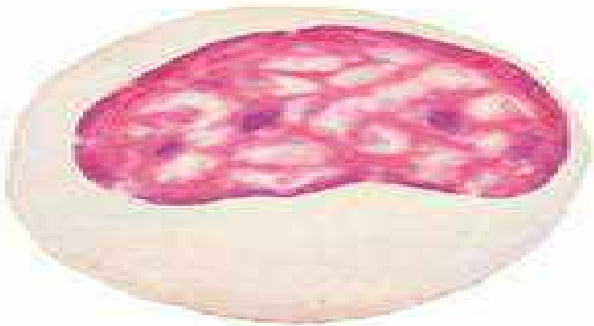
Eosinophilic granulocyte



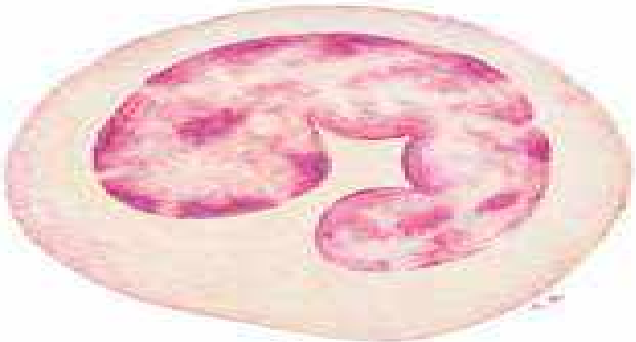
Basophilic granulocyte



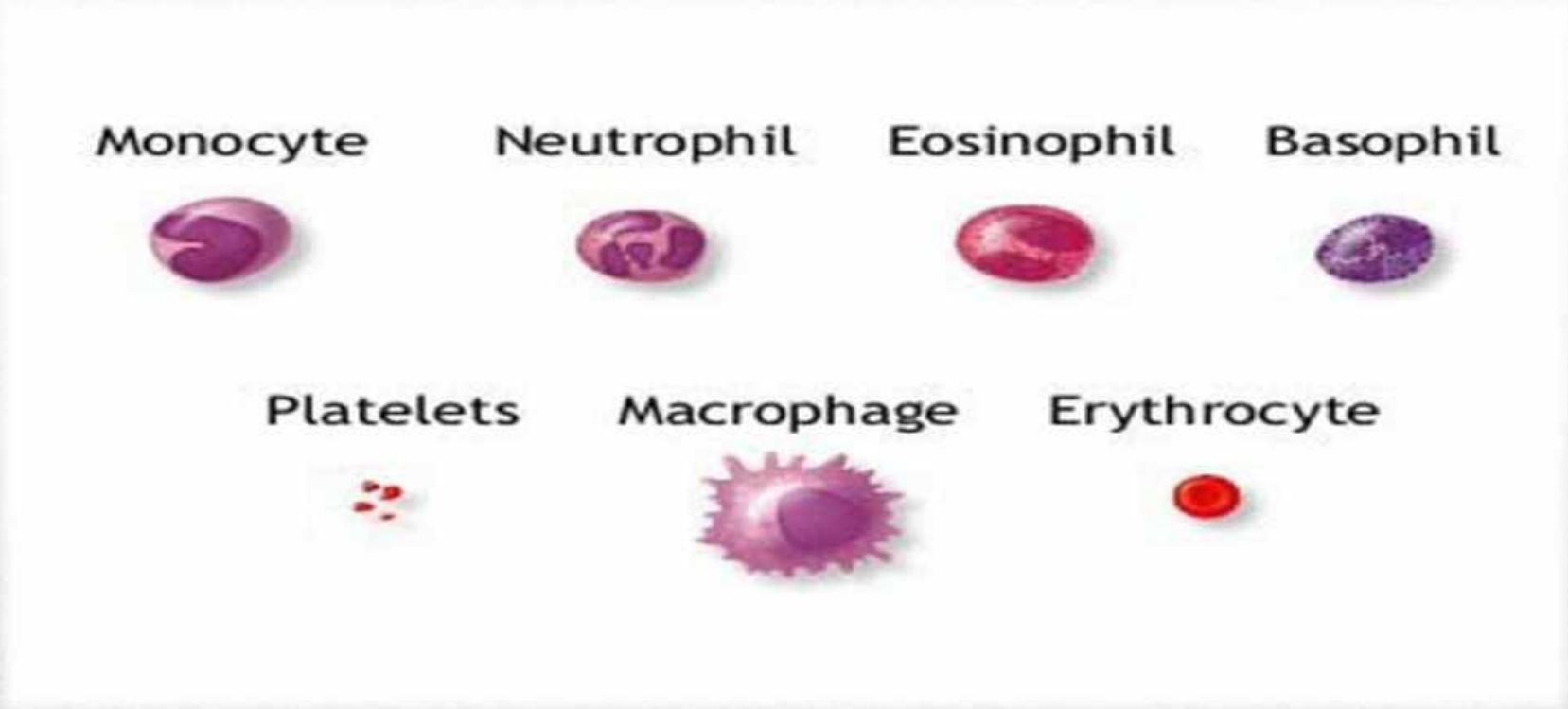
Lymphocyte



Monocyte



Monocyte


Monocyte
Neutrophil
Eosinophil
Basophil
Platelets
Macrophage
Erythrocyte

Red Blood Cells

- *Red blood cells transport oxygen from the lungs to the organs and peripheral tissues, then return to the lungs carrying carbon dioxide to be exhaled. RBCs are pliable and designed to traverse the small capillary beds. RBCs contain the oxygen carrying protein Hemoglobin (HGB). Hematocrit measures the % of RBC mass in 100ml blood.*

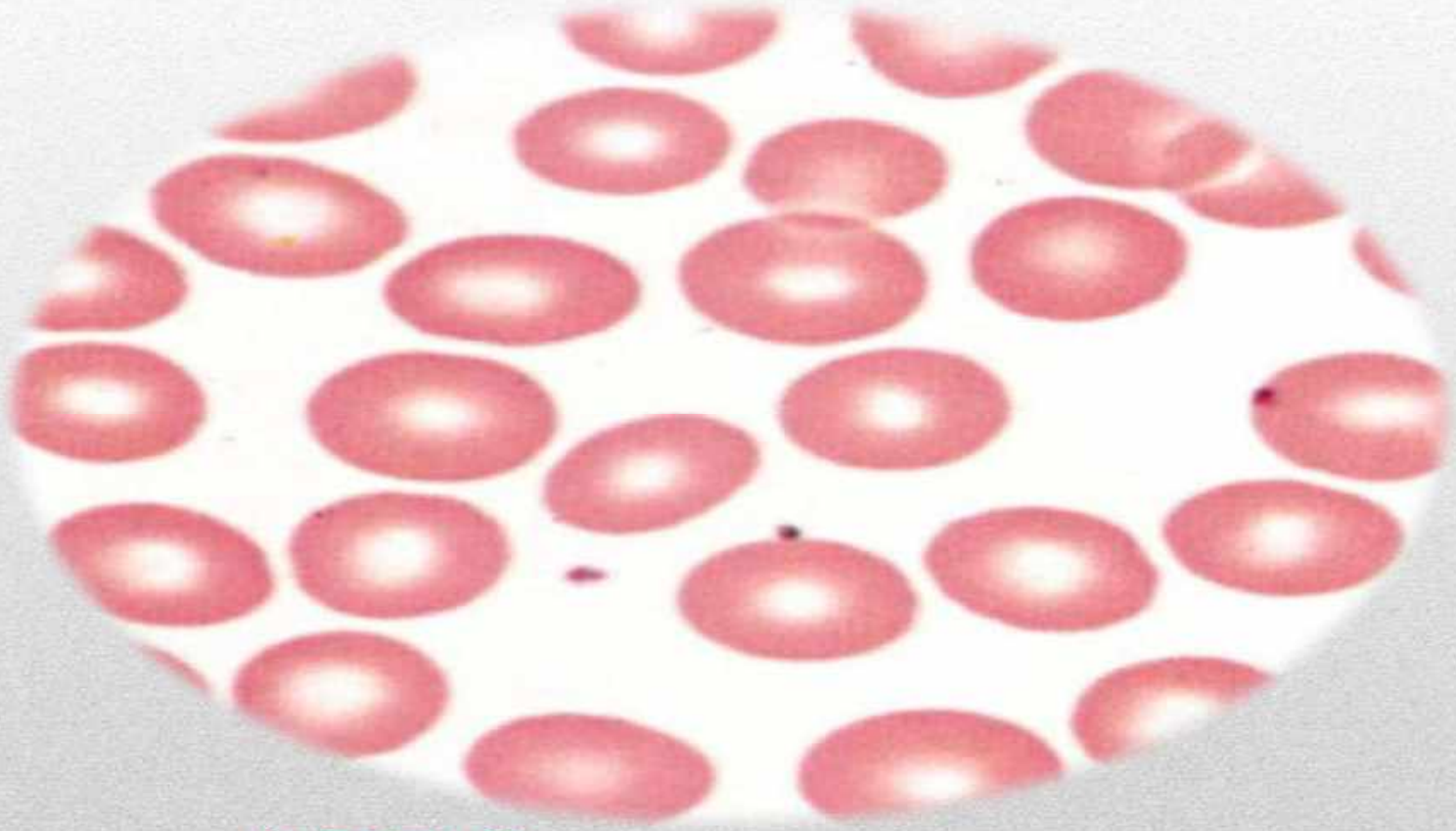
- *Normal RBC life span = 120 days*

I. Reticulocytes: immature RBCs

II. Number helps to determine causes of anemia. Normal retic count is 1.0-2.0%

III. Low retic <1%= decreased marrow production of RBCs causing anemia

IV. Elevated Retic > 2% = indicates anemia caused by RBC loss



Normal RBC

TABLE 2
Red Cell Morpholog

Possible findings	Significance
Burr cells	Uremia, low potassium, artifact, stomach cancer, peptic ulcer disease
Spur cells	Liver disease, abetalipoproteinemia
Stomatocyte	Hereditary condition, alcoholic liver disease
Spherocyte	Hereditary condition, immune hemolytic anemia, water dilution, posttransfusion
Schistocyte, helmet	Thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, vasculitis, myelophthisic glomerulonephritis, prosthetic heart valve
Elliptocyte, ovalocyte	Hereditary, iron deficiency, megaloblastic anemias
Teardrop cells	Iron deficiency, myelophthisic, megaloblastic anemias
Sickle cells	Sickle cell disease
Target cells	Postsplenectomy thalassemia, hemoglobinopathy
Parasites	Malaria, babesiosis
Basophilic stippling	Thalassemia, lead toxicity
Bite cells	G6PD deficiency

Hypoplastic Anemia:

- *When the marrow slows production due to insufficient erythropoietin (EPO), lack of other vital elements in RBC production including iron, folate, B12, or attack on the bone marrow by a virus, toxin or cancer.*

- *The mean corpuscular volume (MCV) is the most useful parameter to evaluate a low reticulocyte count anemia*

Microcytic Anemia

- Microcytic anemias –
- have low MCV (< 80)
- most common type of anemia encountered in primary care

- Differential diagnosis: Iron deficiency anemia, thalassemia, anemia of chronic disease/inflammation, sideroblastic anemia

Microcytic Anemia

Table : 3 Laboratory Findings in Microcytic Anemia

	Red cell morphology	*Serum iron level*	*Total iron-binding capacity*	*Percent of saturation*	*Serum ferritin level*
Iron deficiency anemia	***Microcytic, hypochromic***	***Decreased***	***Increased***	***< 16%***	***Decreased***
Anemia of chronic inflammation	***Normocytic, microcytic***	***Decreased***	***Decreased***	***10% – 20%***	***Increased***
Sideroblastic anemia	***Microcytic, hypochromic***	***Increased***	***Normal***	***50% – 100%***	***Increased***
Thalassemia	***Microcytic, target cells***	***Normal or increased***	***Normal***	***30% – 100%***	***Normal /increased***

Data extracted from: Massey. Med Clin North Am. 1992[9]; Adamson JW. Iron deficiency and other hypo proliferative anemia. *Harrison's Principles of Internal Medicine. 16th ed. New York, NY: McGraw-Hill Professional; 2004:660-666.*

Iron Deficiency Anemia

- Definition: anemia occurs when body iron stores are depleted by prolonged bleeding without replacement. Other causes can include inadequate iron stores due to poor dietary intake and or poor absorption or utilization
- Incidence: common, seen in up to 20% of women, 50% of pregnant women and 3% of men
- Lab findings: anemia, low retic, low MCV and low MCHC
- low ferritin, low % iron saturation, elevated TIBC, possible thrombocytosis
- Signs and Symptoms: fatigue, pallor, pica, blood loss
- Exam findings: pallor, pale conjunctiva, koilonychia, angular stomatitis, glossitis. More severe anemia may see tachycardia, tachypnea

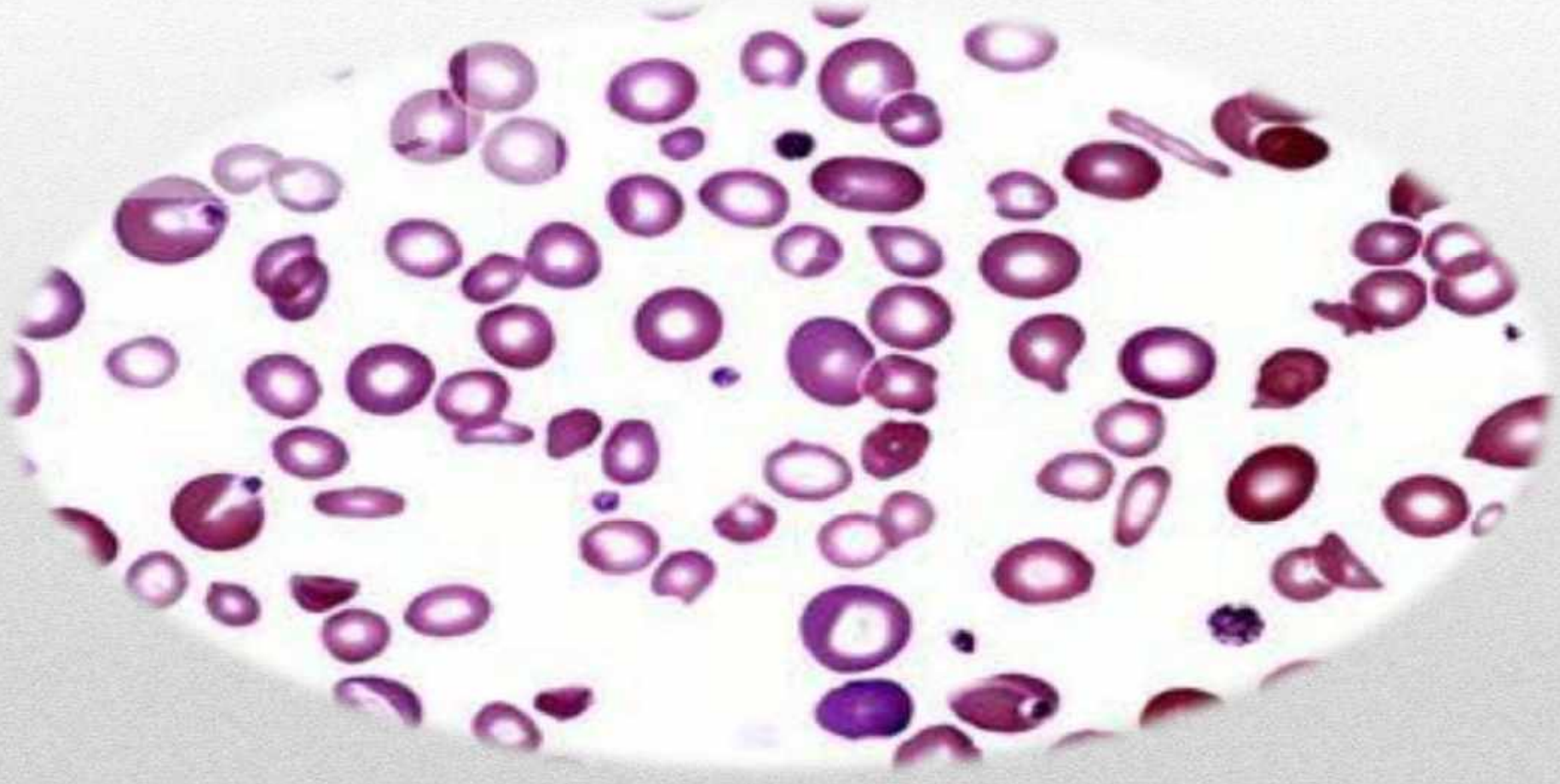
15

Management:

- first must identify etiology

- GI bleeding
- Menorrhagia
- Pregnancy
- Poor intake
- Lack of absorption

Iron deficiency anemia



Hemolytic anemia

- Hemolytic anemia – occurs when the bone marrow is unable to make up for premature destruction of red blood cells by increasing their production. Hemolysis can be triggered by infection, medications, auto-immune responses, inherited disorders (hemoglobinopathies)

- Treatment depends on cause

- Folate (folic acid) is used in all hemolytic anemias to help stabilize the RBC membrane and decrease destruction

Auto-immune hemolytic anemia –

Cause is often unknown

- *Signs and Symptoms: usually very acute and serious with sudden rapid drop in Hgb leading to fatigue, weakness, SOB. Patient is usually hospitalized*
- *Exam findings: pallor, tachycardia, tachypnea, jaundice, splenomegaly*
- *Labs: low Hb/Hct, +ve direct Coomb's, elevated bilirubin, elevated LDH, low serum haptoglobin, elevated reticulocyte count*
- *Diff Dx: anemia secondary to blood loss, hemoglobinopathy*

Auto-Immune Hemolytic anemia

- Treatment:
- Steroids, usually Prednisone at high dose (1mg/kg) to help suppress the immune system. Gradual taper over weeks to months. Splenectomy is often considered followed by other types of immune modulation if hemolysis is not improving. Blood transfusions can be used to off set severe anemia however there is increased risk for antibody development and reactions

- This can be a chronic relapsing disease

Hemoglobinopathies

- Hemoglobinopathy: defined as a genetic defect that results in an abnormal structure of one or both of the globin chains of the hemoglobin molecule
- These disorders are hereditary and some such as sickle cell trait and G6PD deficiency once offered an evolutionary advantage over time by providing immunity to malaria
- There are hundreds of types of hemoglobinopathies and most are not clinically apparent

Thalassemia Syndromes

- Definition: inherited genetic disorders that cause decreased production of normal Hgb A.
- Three types:
- Beta Thalassemia major
- Beta Thalassemia minor
- Alpha Thalassemia
- Incidence: In b thalassemia can be as high as 1 in 10 in certain Mediterranean populations. In the US approx 2 million people have some form of thalassemia trait or disease. Thalassemia is the most common genetic disorder worldwide.

β Thalassemia Major

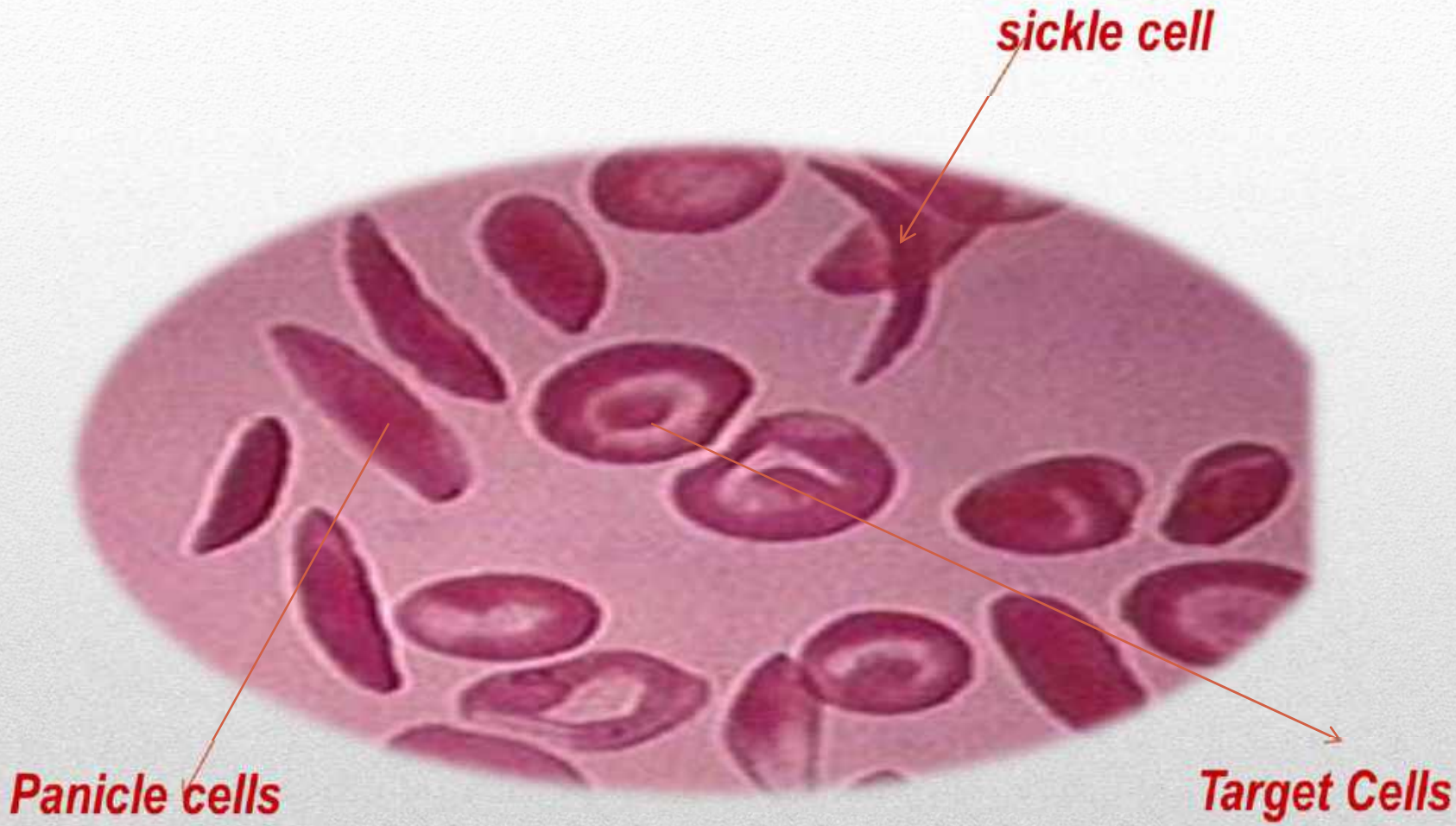
- *Most severe form. Also known as Cooley's anemia.*
- *Lab findings: Hgb electropheresis would show increase in Hgb A2 and F with no normal Hgb A*
- *Signs and symptoms usually present in infants prior to 6 months of age including irritability, poor feeding, pallor*
- *Physical findings: severe anemia, jaundice and hepatosplenomegaly, as well as growth retardation*
- *Management includes life long chronic blood transfusions to replace abnormal Hgb with normal Hgb. Chronic transfusions lead to iron overload which must be removed from the body with chelation therapy (Desferol, Exjade) to avoid liver and heart failure.*

β Thalassemia Minor

- Definition: less severe form of thalassemia whereby pt does produce some normal Hgb A
- Labs: Hgb electropheresis shows decreased Hgb A and increased Hgb A2 and F. Peripheral smear often shows target cells and basophilic stippling. Iron studies are normal
- Signs and Symptoms are usually absent
- Physical exam: normal or may have splenomegaly
- Management: no specific therapy is required. Iron supplements are not recommended unless iron studies confirm iron deficiency with low ferritin

α Thalassemia :

- **Definition:** Genetic disorder of the A-globin chain.
- 4 loci of alpha globin and severity of disease depends on number of alpha globin chains genetically affected.
- Incidence: Most common thalassemia with highest incidence in those of Southeast Asian, Mediterranean and African decent.
- Labs: Microcytic RBCs, with or without anemia. May have elevated RBC count. Hb electropheresis may be normal
- Signs and Symptoms: none to mild symptoms of anemia including pallor, fatigue to most severe form causing fetus with hydrops fetalis and stillbirth.


sickle cell
Panicle cells
Target Cells

Target Cells

Sickle cell anemia

- Sickle cell anemia – genetic disorder whereby red blood cells in a stressful environment become abnormally shaped like a sickle and cause hemolysis, anemia and veno-occlusion. This leads to end-organ damage in the spleen, kidneys and liver.
- Incidence: More than 70,000 Americans have sickle cell disease. About 2 million Americans, 1 in 12 African Americans - have sickle cell trait
- Ethnic groups with sickle cell anemia are usually African descendants although those of Mediterranean decent can also be affected.
- Labs: CBC shows anemia, adult sickle cell anemia patients usually have elevated WBC and platelet count, elevated retic, elevated bilirubin, Hgb electropheresis shows abnormal Hgb SS (more severe disease) or Hgb SC or S-beta thalassemia

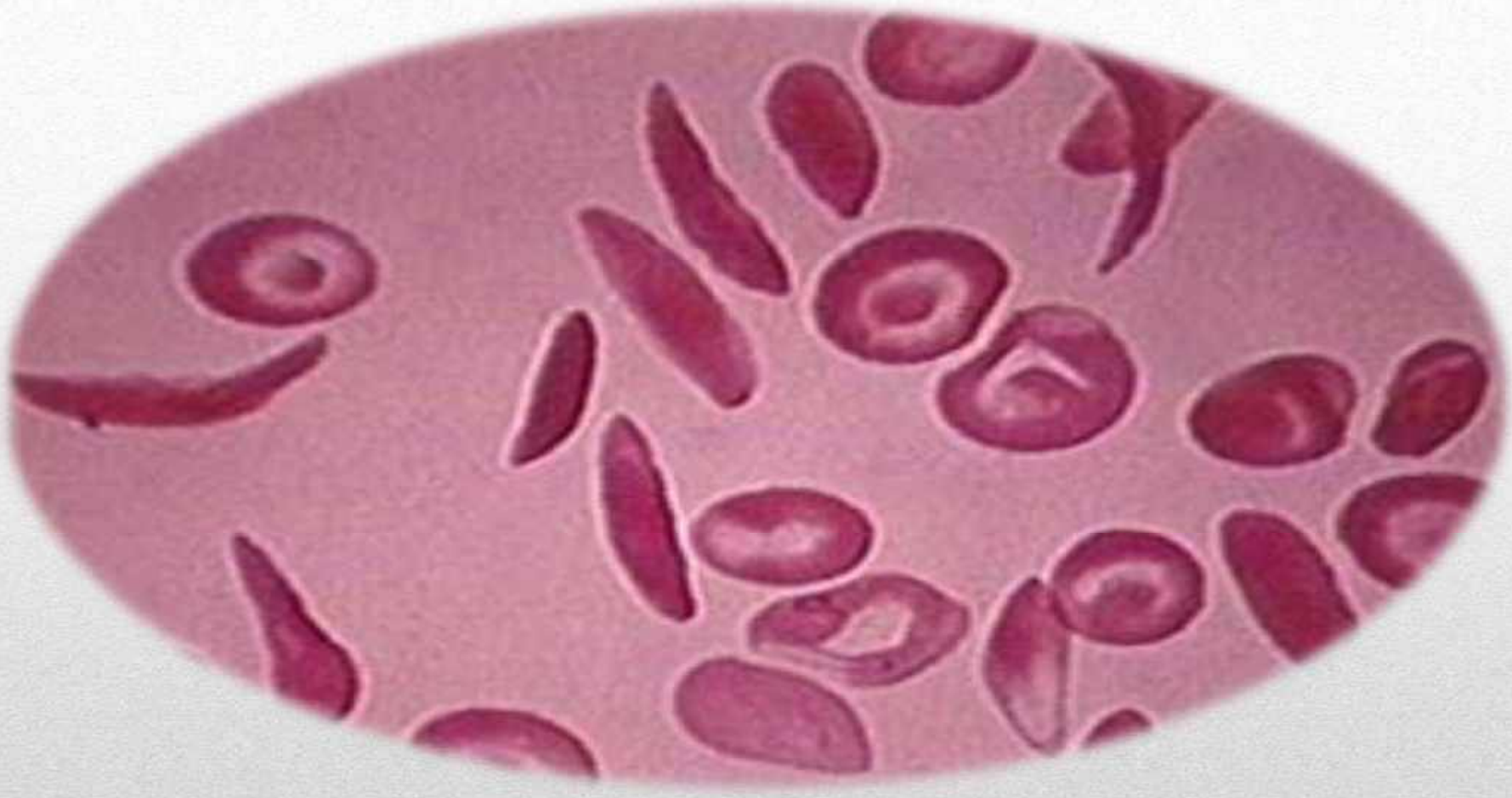
Sickle cell anemia

- *Signs and symptoms: anemia occurs as abnormal RBC have a shortened life span of only about 15 days compared to the usual 120 days. The RBCs are also fragile and lack flexibility leading to veno-occlusion and resulting pain crises, as well as risk for CVA and priapism. Sickle cell veno-occlusive crises can be triggered by infection, dehydration, temperature changes and other stressors to the body.*

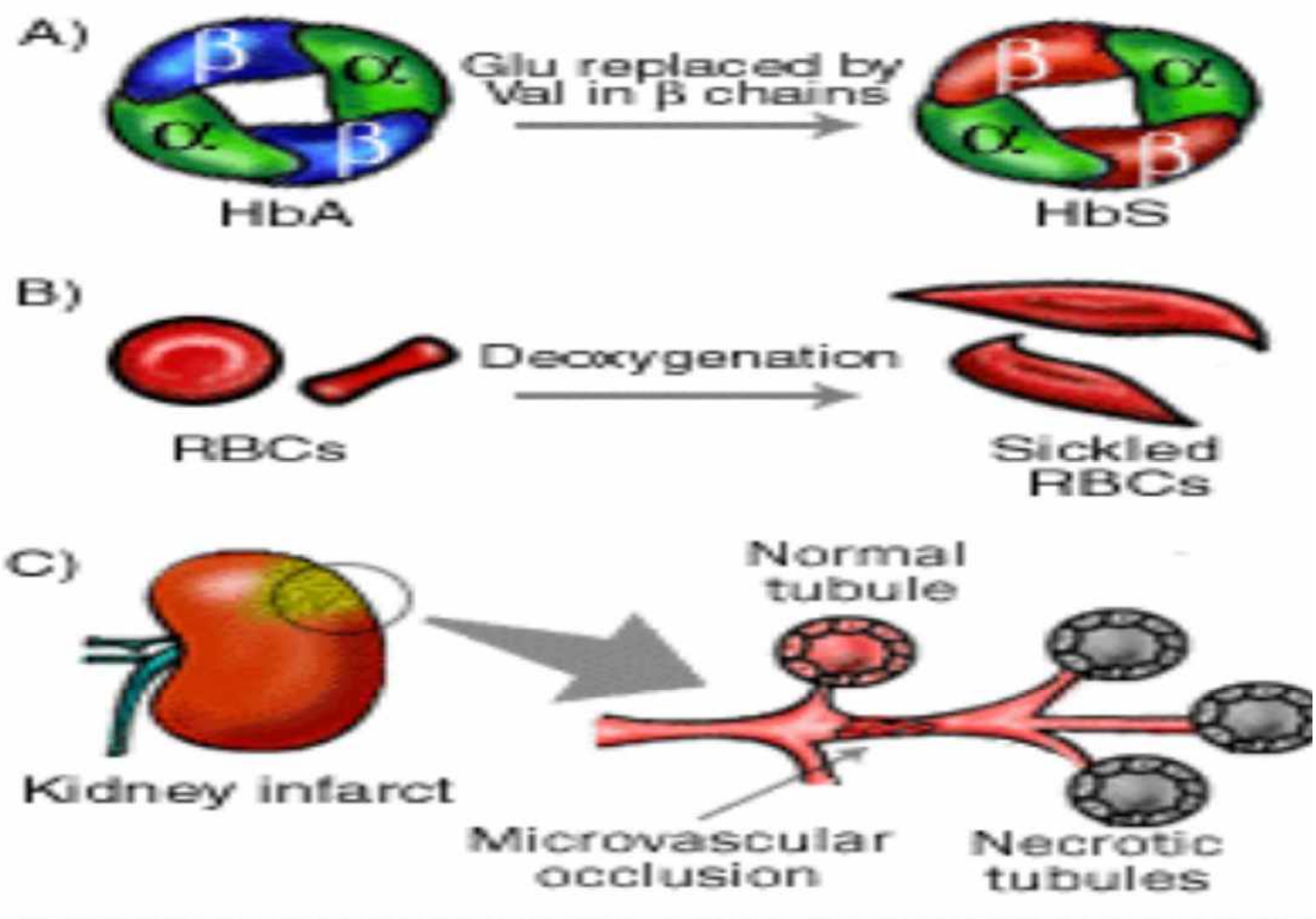
- *Exam findings: scleral icteris, jaundice, splenomegaly in children (adults usually have either required splenectomy in childhood or have infarcted the spleen causing loss of spleneic function by adult age).*

Sickle cell disease

- Normal adult spleen is 11cm
- A spleen that has infarcted due to sickle cell disease and shrunk to 4.5 cm in length.
- This spleen would not be functional.



Sickled red blood cells



Pathophysiology of sickle cell disease

Malaria

G6PD deficiency

- Glucose-6-phosphate dehydrogenase deficiency – a hereditary enzyme deficiency that leads to hemolysis when certain drugs are ingested that induce oxidant stress on RBCs.
-
- Incidence - Most common human enzyme deficiency affecting 400 million people worldwide. X-linked recessive disorder with more males affected than females. Occurs more often in blacks
- Signs and symptoms: none unless hemolysis occurs causing anemia with fatigue, SOB, dark urine

G6PD deficiency

- Exam findings: none specific unless having active hemolysis

- Drugs to be avoided with G6PD def:
- Pyridium, Sulfacetamide, Sulfasalazine, Isobutyl nitrite, Nitrofuratoin, Primaquine, Sulfamethoxazole (Bactrim), Toluidine blue

- *G6PD deficient patient are also to fava beans (favism)

- ***Lab:*** show evidence of hemolysis
- Elevated bilirubin levels
- Elevated serum LDH
- Low serum haptoglobin
- Hemoglobinuria
- Elevated retic count
- Low RBC count and hemoglobin
- Heinz bodies present on examination of the peripheral blood smear using special stains
- Methylene blue test
- Methemoglobin reduction test – used for diagnosis

Anemia of Chronic Disease

Definition: anemia caused by inflammatory processes

AE: occurring due to long-standing infection, neoplastic disease and other inflammatory disorders including rheumatoid arthritis, SLE.

Pathogensis: These processes block iron transportation from storage sites to the bone marrow factory. Can also be associated with renal failure and decreased erythropoietin production

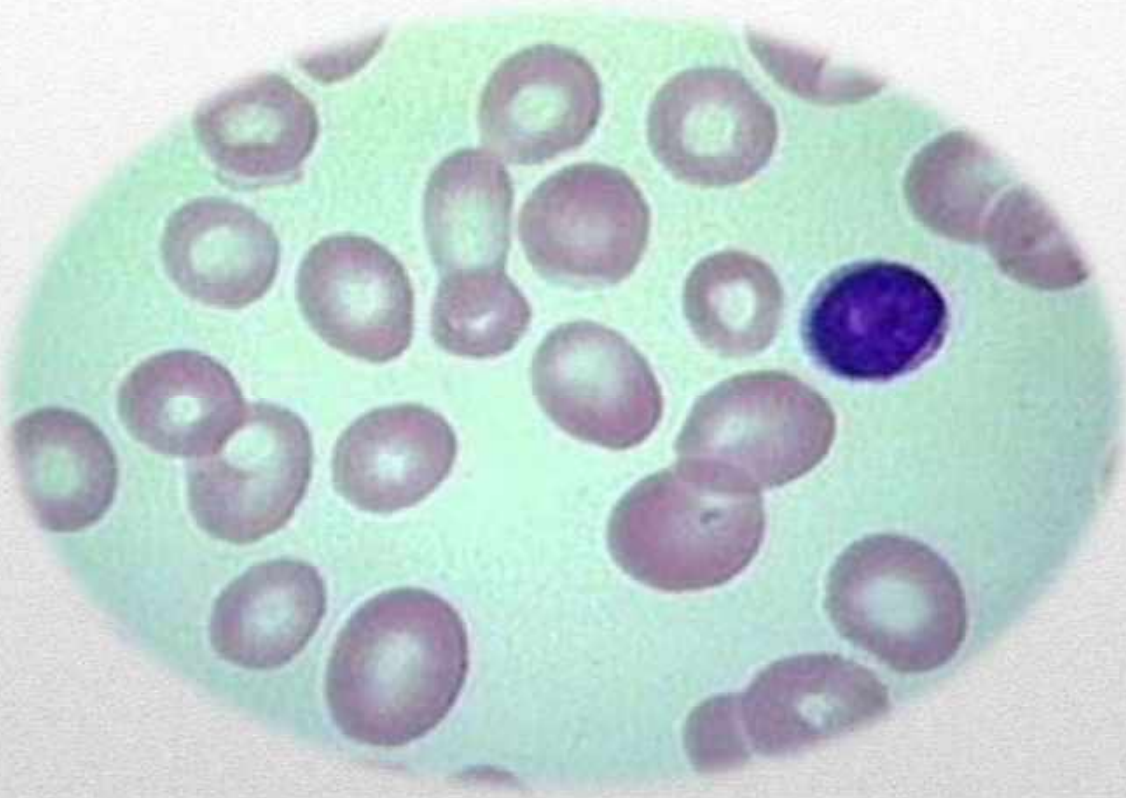
- Incidence: second most common anemia behind iron deficiency anemia
- *Lab findings*: CBC showing anemia, low or normal MCV, normal iron studies or low % iron saturation with normal to low TIBC, elevated CRP or sed rate,

Anemia of Chronic Disease

- Signs and Symptoms: fatigue, pallor or asymptomatic if patient has long standing history of RA, SLE, other inflammatory disease, chronic renal failure
- Physical findings: none specific
- Management: Treat underlying disease
- If unable to determine causative factor, refer to hematology for bone marrow biopsy

Macrocytic Anemias

- Definition: macrocytosis or megaloblastic anemia is characterized by anemia with elevated MCV
- Incidence: fairly common, seen more in the elderly and those with history of GI pathology or surgeries



Macrocytic RBC

B12 deficiency anemia

- Definition: anemia caused by inadequate B12. Can be due to inadequate dietary intake in vegans or more commonly as a result of loss of intrinsic factor which leads to inability to absorb B12 (pernicious anemia)

- Lab findings: anemia on CBC, MCV elevated usually > 95. Normal or low serum B12 with elevated methylmalonic acid, normal or elevated homocysteine, anti-intrinsic factor antibodies

B12 deficiency

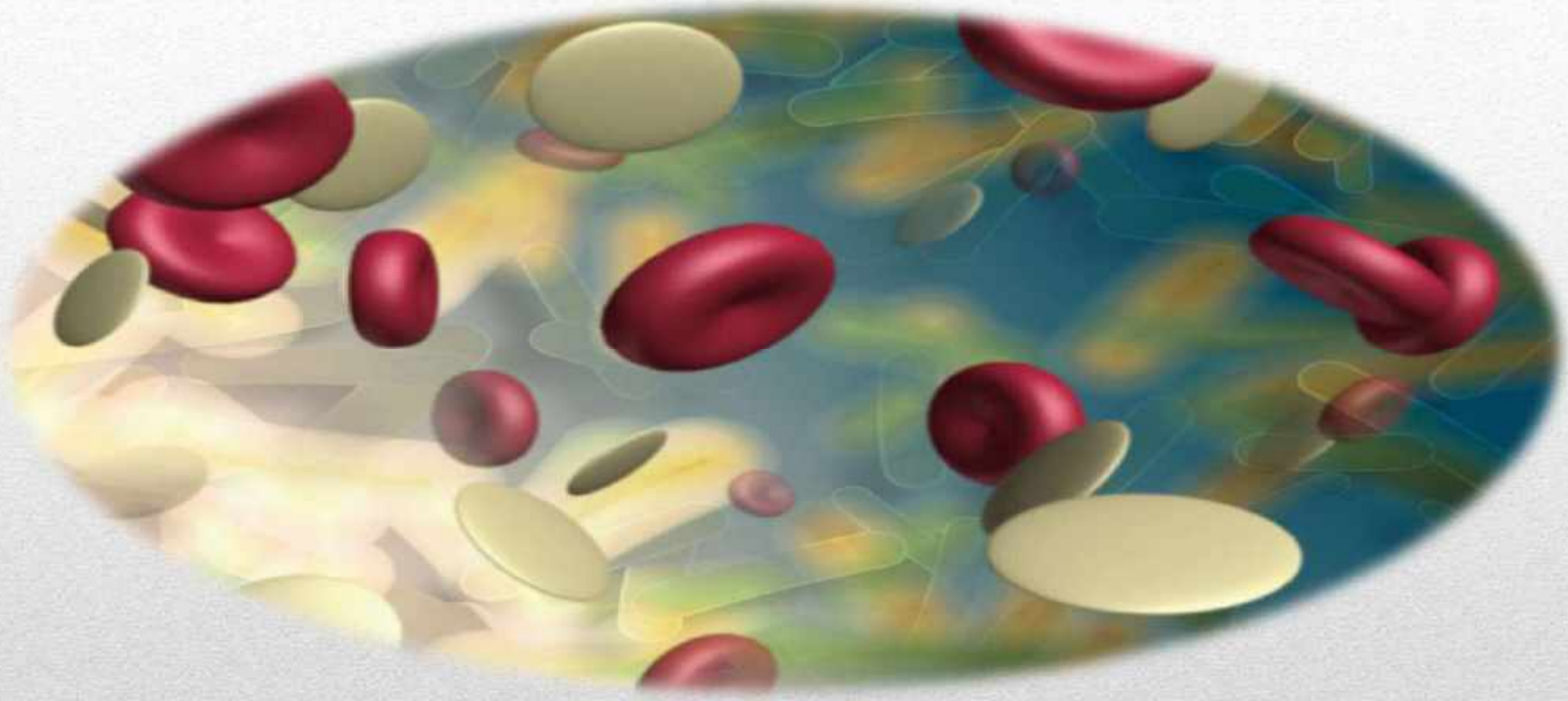
- Signs and Symptoms: fatigue, pallor, neuropathy, dizziness, hair loss, memory loss/dementia in elderly, history including chronic gastritis, bariatric surgery, auto-immune disorder.

- Physical findings: pallor, tachycardia, abnormal sensory neuro exam, tachypnea

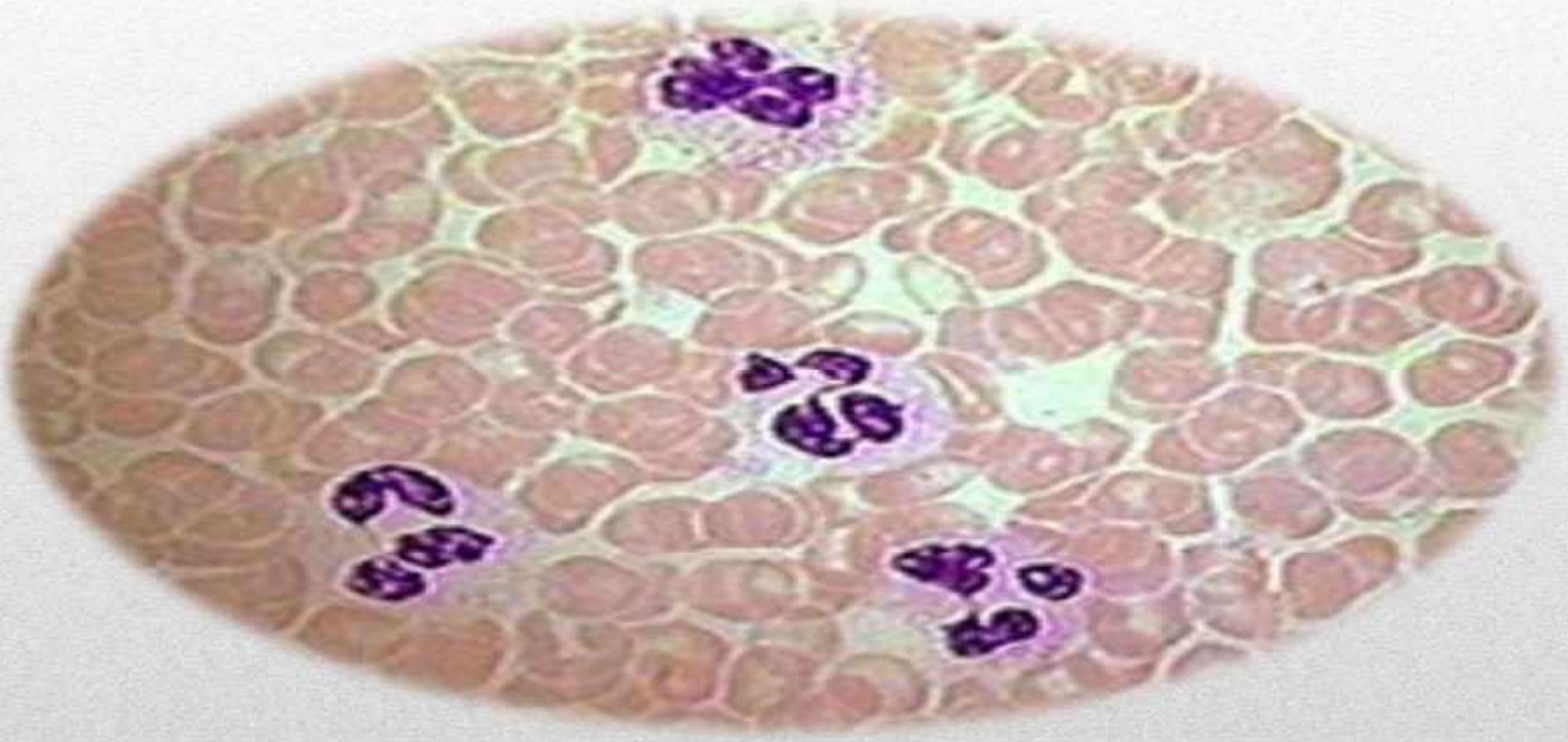
Folate Deficiency anemia

- Definition: macrocytic anemia caused by lack of folic acid. Common in alcoholics
- Lab findings: CBC with anemia, macrocytic with MCV > 95. Elevated homocysteine with low or normal serum folate
- Signs and Symptoms: fatigue, pallor, unusual diet (no uncooked fruits and vegetables), alcoholism
- Physical exam: none specific

Increased marrow production



- *Elevated blood cells due to over production in the marrow. Can see overproduction of RBC, WBC, Platelets*



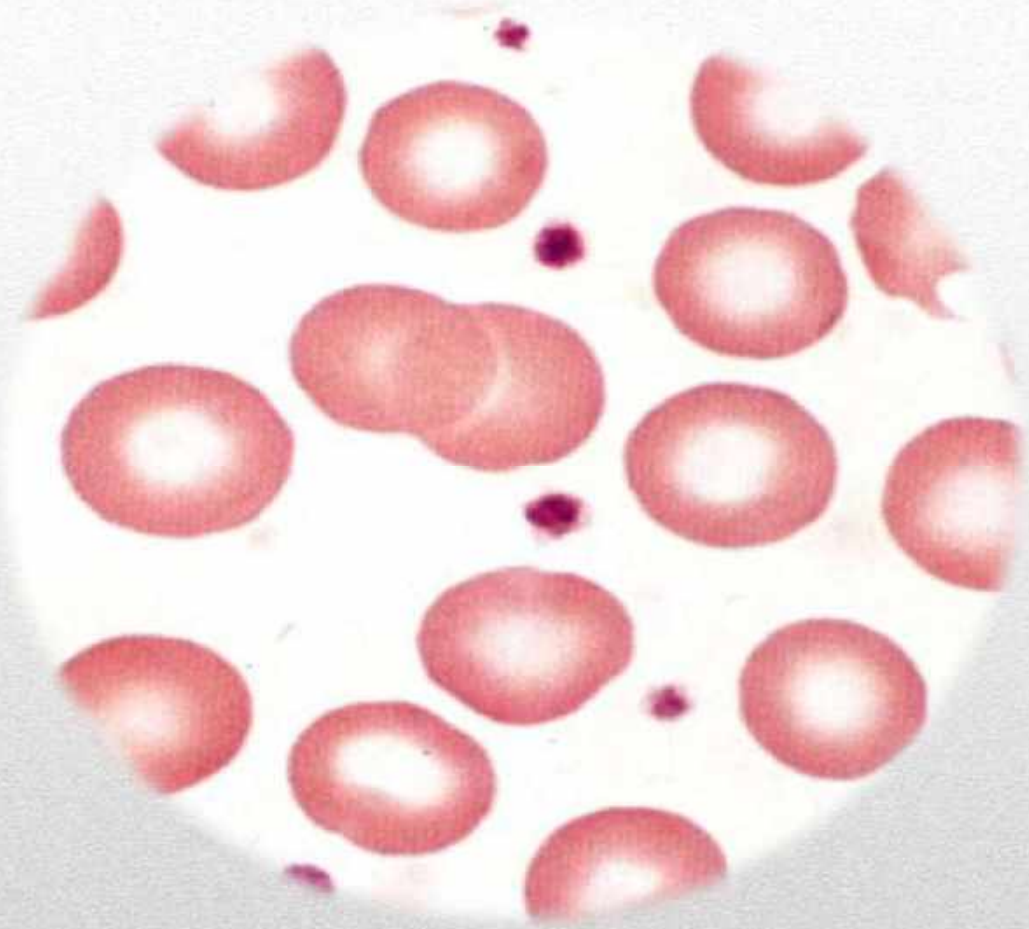
Polycythemia

Polycythemia Vera

- Lab tests would include RBC mass, serum erythropoietin levels (usually decreased), bone marrow biopsy usually performed, JAK 2 mutation analysis.
- History and Exam findings: splenomegaly, red complexion (plethora), fatigue, headache, dizziness, assess for clotting
- D.D.: elevated RBC from smoking, chronic cardiac or lung disease, high altitude, dehydration

Secondary Erythrocytosis

- Definition: elevated RBC count without other blood cell abnormality. Most common causes are smoking, dehydration and environment of chronic hypoxia
- Lab findings: Elevated RBC with otherwise normal WBC, platelet count. Bone marrow biopsy would show normal erythrocyte precursors, normal EPO level
- Diagnosis is often one of exclusion if polycythemia is ruled out
- Signs and symptoms depending on cause. May have symptoms of chronic hypoxia, oxygen requirement, current tobacco use. High altitude living
- Management: treat underlying cause



Platelets

Thrombocytosis

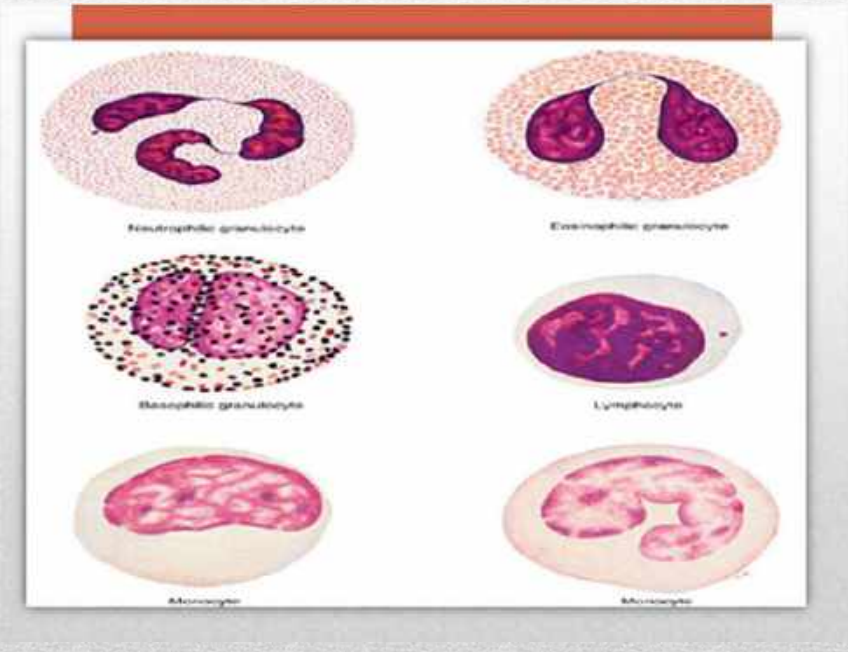
- Definition: elevated platelet count > 500,000
- D.D: includes: bone marrow myeloproliferative disorder as in essential thrombocythemia (ET) or secondary to iron deficiency, splenectomy, infection, malignancy or inflammatory disease
- Lab findings: CBC showing elevated platelet count. Iron studies may show iron deficiency. JAK 2 mutation analysis can be helpful
- Signs and Symptoms: often asymptomatic and found on routine CBC. ET patient may experience headaches, TIAs

Thrombocytopenia

- Definition: platelet count < 150,000.
- Differential Dx: bone marrow dysfunction, malignancy, auto-immune response, medication, chemotherapy, acute bleeding, acute thrombosis, DIC, HIT, lab error
- Incidence: ITP: 100 cases per million people per year with children accounting for half of those. Females more likely to be affected.
- Lab/diagnostic studies: CBC, BMA

White blood cells

- Definition: blood cells that fight infection. Produced in the bone marrow.
- Elevated = leukocytosis
- Decreased = leukopenia.



WBC Differential

- Five subtypes of WBC noted in differential include:
- Neutrophils (segments + bands) granulocytes
- Elevated neutrophils can be caused by acute infection, chemotherapy, stress reaction, burns, tissue necrosis, chronic inflammatory disorders. Decreased neutrophils = neutropenia. Increased risk for infection if neutrophils < 1000. Severe risk for infection if < 500.
- Lymphocytes – elevated or decreased levels can be caused by infection – TB or viral, most common cause of increased level >10,000 is CLL, ALL.
- Lymphopenia can be caused by acute illness (MI, pneumonia) as well as steroid therapy and lymphoma

WBC Differential

- Monocytes –
- Increased in infection, granulomatous disease (sarcoid), collagen vascular disease.
- Decreased in acute stress reaction, pt on steroids, leukemia, chemo and immunosuppressant therapies
- Eosinophils –
- Increased in allergic diseases, parasitic infections, collagen vascular diseases, from certain medications, leukemia. Decreased in acute stressful illness, steroids
- Basophils – Increased in allergic diseases, CML, chronic inflammatory disorders.

Leukopenia

- Definition: total WBC < 3000
- AE: Infection including bacterial or viral, chemotherapy, other medications (anti-epileptics, penicillins, sulfonamides, cephalosporins, thiazides, cimetidine, ethanol, immunosuppressants), hematologic malignancy, aplastic anemia, hypersplenism, auto-immune disorders, Felty's syndrome. Low WBC can be normal in certain populations
- Lab : CBC, differential, CMP, bone marrow biopsy

Leukocytosis

- Definition: WBC > 11,000
- AE: Infection, Chronic inflammation, Medications (steroids), Recovery post chemotherapy, WBC growth factors (Neupogen, Leukine, Neulasta) used in cancer therapies, hematologic malignancy (leukemia) or bone marrow dysfunction
- Lab: CBC with diff, UA/cx if urinary symptoms, blood cultures, LAP (leukocyte alkaline phosphotase – elevated in leukomoid reaction, decreased in leukemias)

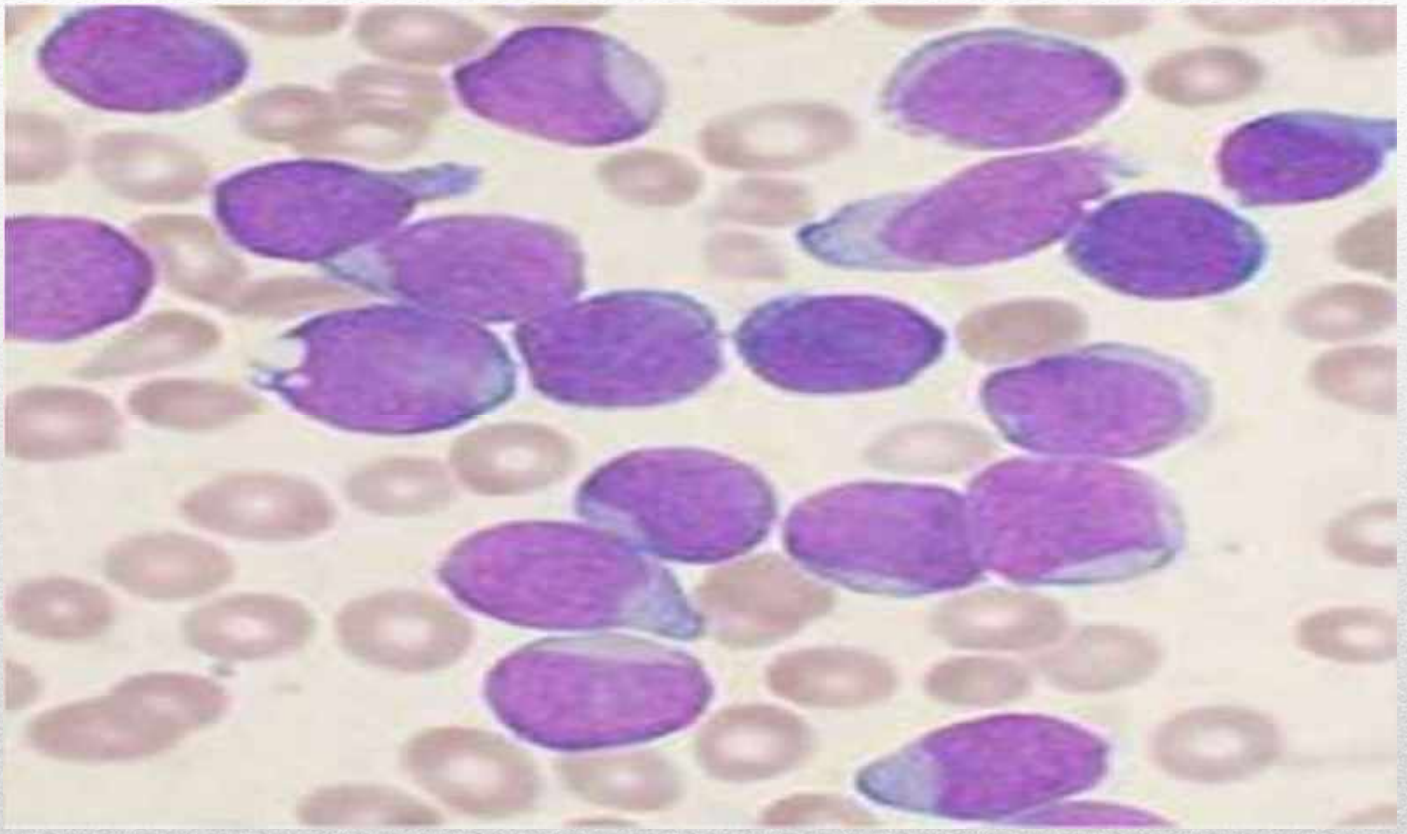
Leukocytosis

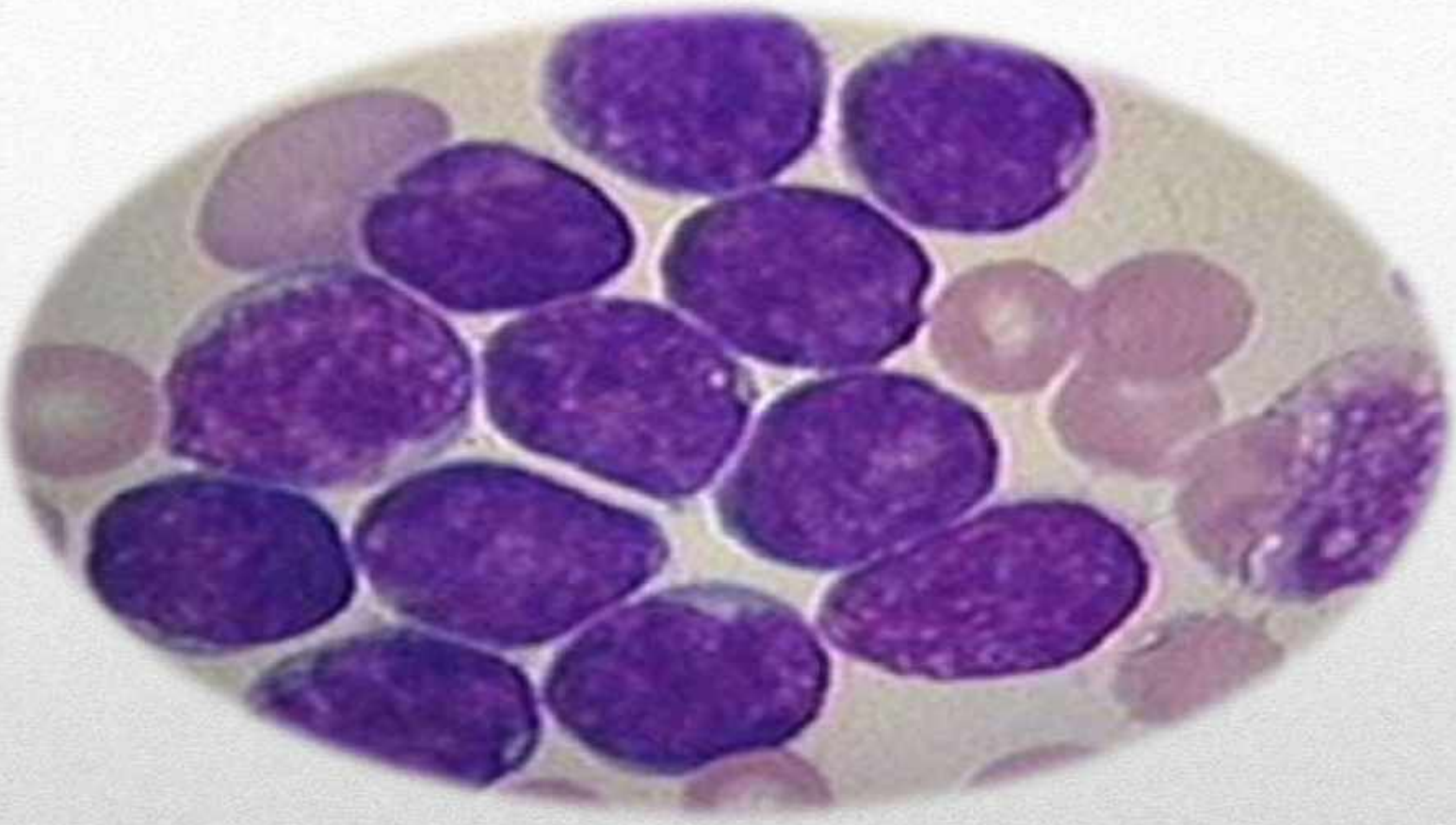
- Signs and Symptoms: may be asymptomatic, fever, infectious symptoms, cough, SOB, dysuria, skin infection/abcess, rash, weight loss, fatigue, night sweats
- Physical findings: may be none. Erythema, edema, skin rash, lymphadenopathy, cachexia, hepatosplenomegaly, abnormal heart sounds, adventitious lung sounds
- Management: determine underlying cause.

- If unable to determine cause or if leukocytosis persists or is rising after treating for infection, for bone marrow biopsy

Acute Leukemia

- Etiology is unknown for the most part. Risk factors include exposure to benzene, radiation exposure and prior treatment with cytotoxic chemotherapy
- Lab findings: CBC can show elevated, normal or low WBC count. Often see anemia at presentation as well as thrombocytopenia. Differential often shows circulating blasts (very immature WBCs). Elevated LDH usually seen. Bone marrow biopsy diagnostic
- Signs and Symptoms: pallor, fatigue, fever, anorexia,bpne pain weight loss, weakness, palpitations, dyspnea on exertion, infection, rash, bleeding, bruising





Acute Leukemia

Chronic Leukemia

- Definition:
- differs from acute leukemia in that symptoms have lasted more than 3 months.
- For CML, the natural history of the disease usually includes a chronic phase lasting 2-4 yrs.
- Accelerated phase can then occur leading to progressive leukocytosis, anemia and thrombocytopenia.
- Eventually a blast crisis may ensue in which the disease may behave more like AML requiring aggressive therapy and having a poor prognosis

Lymphoma

- Definition: Hematologic malignancy involving lymphadenopathy as well as possible bone marrow and other solid organ involvement.
- Types: Hodgkin's Lymphoma and Non-Hodgkin's Lymphoma (NHL)
-
- AE: infections causing lymphadenopathy, cat scratch fever, viral infections (HIV), auto-immune disorders, endocrine disorders, sarcoidosis
- Lab/diagnosis: CBC with diff, CMP, LDH, Beta 2 microglobulin, lymph node biopsy, bone marrow biopsy, CT scans, PET scan

Lymphoma

- Risk factors for development of lymphoma: EBV, HHV-8, HTLV-1 viruses have a strong association with development of lymphoid tumors. h.Pylori is a risk factor for development of gastric MALT (mucosa associated lymphoid tissue) lymphoma. Inherited or acquired immunodeficiency disorders also predispose individuals to lymphoma. Increase incidence of NHL in farmers and meat workers. Increased Hodgkin's disease in wood workers.

- Signs and symptoms: Painless adenopathy, fever, night sweats, weight loss, fatigue (B-symptoms)
- Physical findings: lymphadenopathy in one or more lymph node chains, hepatosplenomegaly, pallor

Lymphoma

- Staging: based on number of lymph node chains involved and location above and or below diaphragm, bone marrow status, extra nodal sites of disease, absence or presence of B-symptoms
- Stages from IA-IVB
- Histiologic subtypes also important in determining aggressiveness of disease which guides treatment plan offered to patient
- Less aggressive NHL: follicular center cell
- More aggressive NHL: diffuse large cell

Lymphoma

- Management:
- Based on stage, and subtype for Hodgkin's disease usually IV chemotherapy +/- radiation therapy

- NHL treatment can range from watch and wait approach to very strong IV chemotherapy for the aggressive subtypes. Bone marrow transplant is sometimes needed if patient fails initial chemotherapy for aggressive NHL.

Bone Marrow Biopsy


THANK YOU