CHERYL KOVALSKI, DO FACOI

NO DISCLOSURES

ACOI BOARD REVIEW 2017

ANEMIA

- Hemoglobin <13 grams or
- Hematocrit<39%

IRON DEFICIENCY

- Most common nutritional problem in the world
- Absorbed in small bowel, enhanced by gastric acid
- Absorption inhibited by inflammation, phytates (bran) & tannins (tea)

CAUSES OF IRON DEFICIENCY

- Blood loss – most common etiology
- Decreased intake
- Increased utilization-EPO therapy, chronic hemolysis
- Malabsorption – gastrectomy, sprue

CLINICAL MANIFESTATIONS OF IRON DEFICIENCY

- Impaired psychomotor development
- Fatigue, Irritability
- PICA
- Koilonychiae, Glossitis, Angular stomatitis
- Dysphagia

ANEMIA

MCV

RETICULOCYTE COUNT

Corrected retic ct :

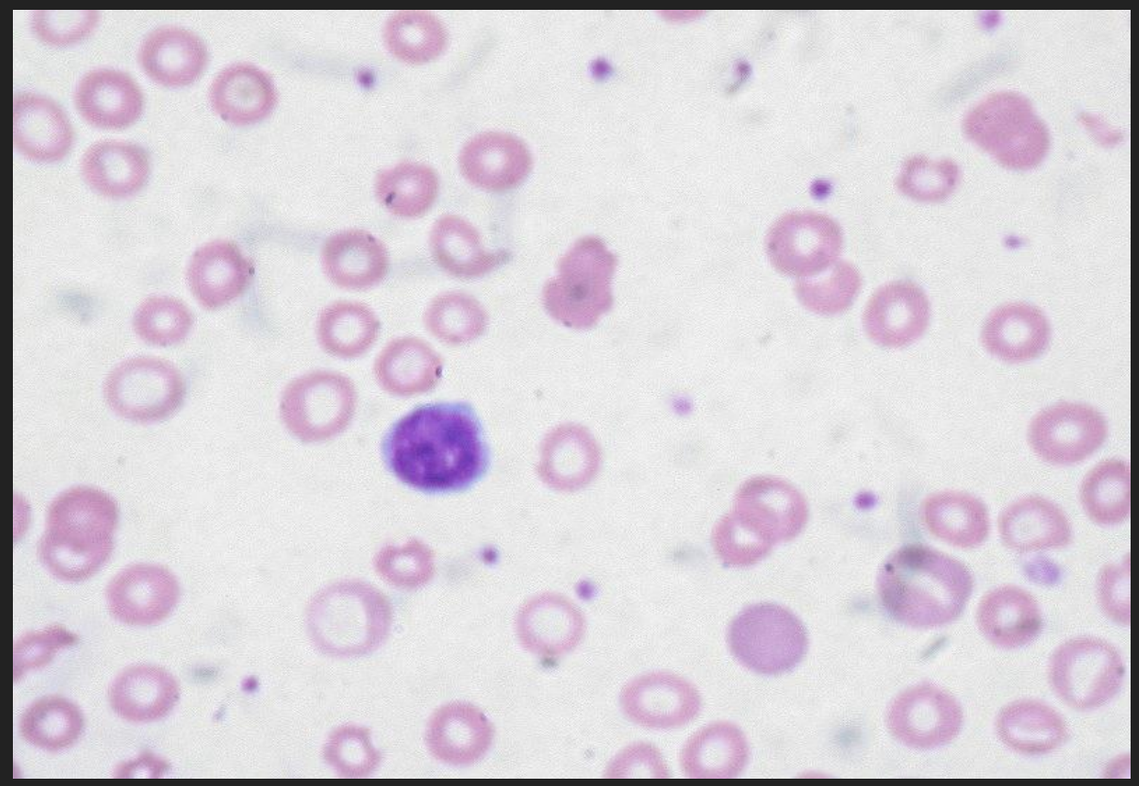
- >2%: blood loss or hemolysis
- <2%: hypoproliferative process

ANEMIA

- MICROCYTIC
- Obtain and interpret iron studies
- Serum iron
- Total iron binding capacity (TIBC)
- Transferrin saturation
- Ferritin-correlates with total iron stores
- can be nml or inc if co-existent inflammation

IRON DEFICIENCY LAB FINDINGS

- Low serum iron, increased TIBC
- % sat <20



MANAGEMENT OF IRON DEFICIENCY

- MUST LOOK FOR SOURCE OF BLEED: ie: GI, GU, Regular blood donor
- Replacement:

1. Oral: Ferrous sulfate 325 mg TID until serum iron, % sat, and ferritin mid-range normal, 6-12 months
2. IV

SIDEROBLASTIC ANEMIAS

Diverse group of disorders of RBC production characterized by:

1. Defect involving incorporation of iron into heme molecule
2. Ringed sideroblasts in bone marrow

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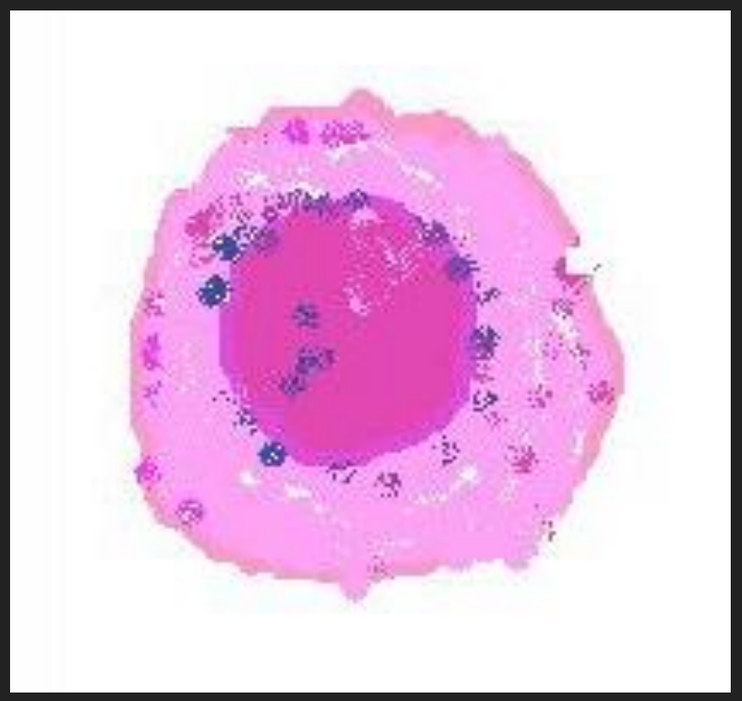


CLASSIFICATION OF SIDEROBLASTIC ANEMIA

- ACQUIRED IDIOPATHIC – now considered one of the MDS categories
- REVERSIBLE – alcohol, INH, chloramphenicol
- LEAD POISONING – autonomic & motor neuropathy, abdominal pain

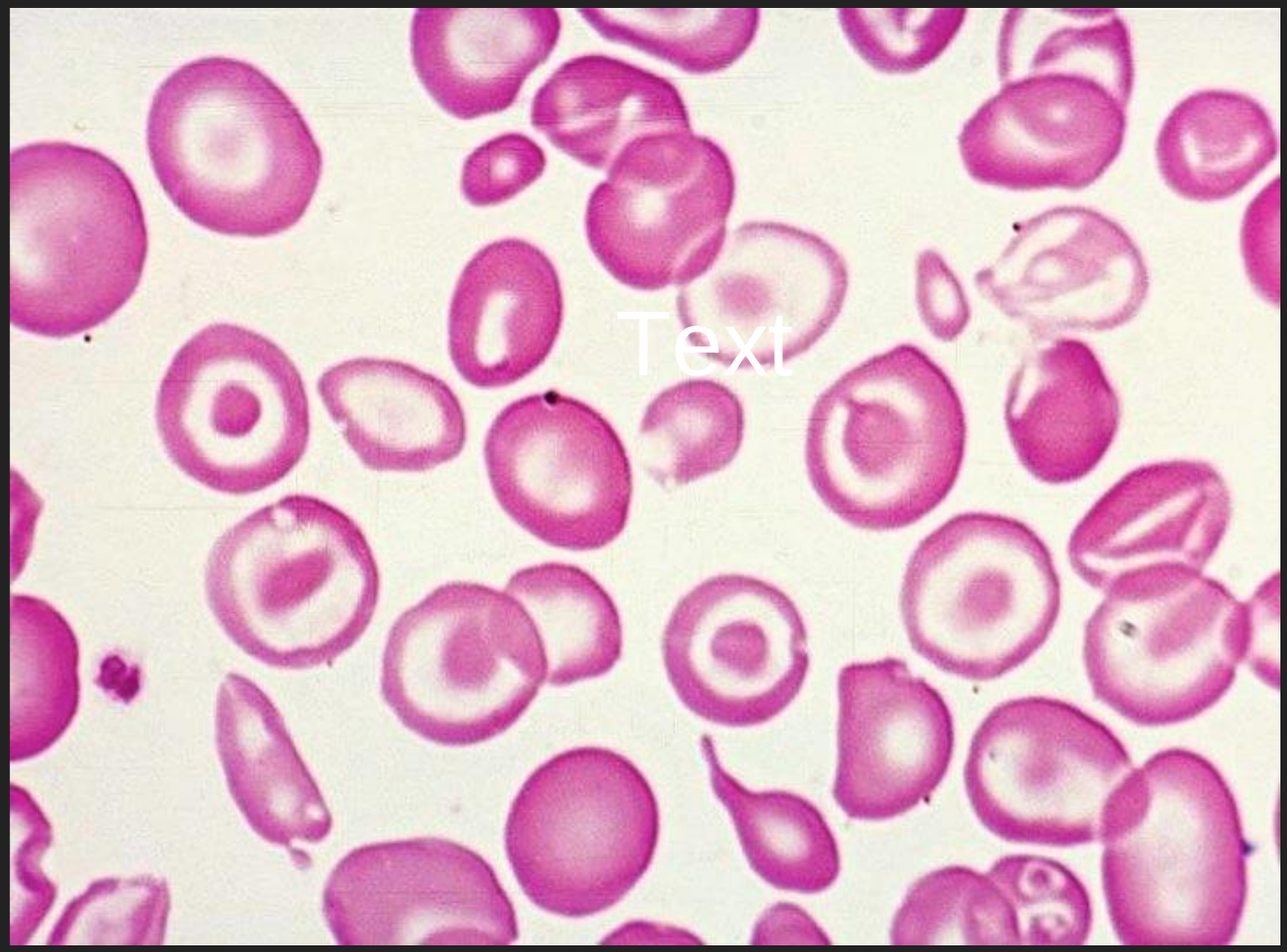
THERAPY OF SIDEROBLASTIC ANEMIA

- SUPPORTIVE
- PYRIDOXINE
- ALLO BMT
- EPO

THALASSEMIA

- Perhaps man's most common genetic disorder
- Beta Thal – decreased synthesis of beta globin chain mostly caused by point mutations, resulting in relative excess of alpha globin chains, dx-Hg electropheresis
- Alpha Thal – decreased synthesis of alpha globin chains mostly caused by gene deletion resulting in relative excess of beta globin chains, dx-Alpha thal gene probe

THALASSEMIA



CLINICAL CLASSIFICATION OF B-THALASSEMIA

- B-Thalassemia trait (B-thalassemia minor): uncomplicated heterozygous B-Thal
- B-Thalassemia intermedia: many different genotypes
- B-Thalassemia major (Cooley's anemia): homozygous or compound heterozygous B-thal
- genotype-phenotype correlations often difficult to make: 100s of mutations, frequent interactions, role of other modifying genes and environment

CLINICAL DIAGNOSIS OF B-THALASSEMIA

- B-Thalassemia trait

  -microcytosis, hypochromia, +/- mild anemia

  -elevated level of HbA2 (>3.5%)

- B-Thalassemia intermedia

  -microcytic anemia, may need treatment

  -many different genotypes, high Hb F

  -bone disease, iron overload, splenomegaly, pulm hypertension

CLINICAL DIAGNOSIS OF B-THALASSEMIA

- B-Thalassemia major

  -transfusion-dependent microcytic anemia

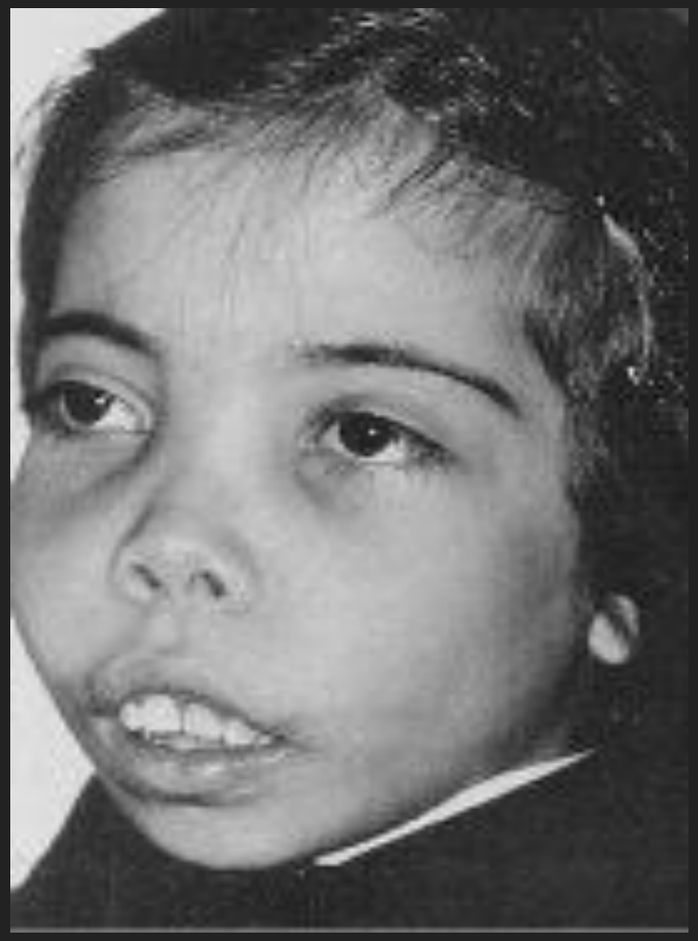
  -very high Hb F (approaching 100%)

  -bone disease, iron overload, splenomegaly, pulmonary hypertension

BETA THALASSEMIA: COMPLICATIONS

If transfusion dependent, best if managed in thalassemia center

- Pulmonary hypertension
- Thromboembolism
- Heart Disease
- Endocrinopathies
- Bone Disease
- Liver Disease
- Growth Retardation/Skeletal changes



ALPHA THALASSEMIA

- Silent carrier: heterozygous a+ thal; 3 of 4 alpha genes present and functional; +/- mild microcytic anemia
- Trait: 2 of 4 alpha genes present and functional; +/- mild microcytic anemia; Hb Barts (gamma 4) in 2-10% newborns
- Hemoglobin H Disease: genotype a-/- -; 20-40% Hb Barts in newborns; 5-40% Hg H(Beta 4) in adults

ALPHA THALASSEMIA

- Hemoglobin H Disease: hemolysis of varying degrees, microcytosis, splenomegaly ineffective erythrocytosis, iron overload
- Hemoglobin Bart’s Hydrops Fetalis: Homozygous alpha 0 (- -/- -); no functional alpha globulin genes: Hb Barts, eclampsia in mother, stillbirth, erythroblastosis in infant

ALPHA THALASSEMIA TRAIT

- 2 of 4 alpha genes present and functional
- +/- mild anemia
- MCV <80
- Usually diagnosis of exclusion

ALPHA THALASSEMIA

- SCREENING: in populations at high risk for Hb Bart's or hydrops fetalis
- Hg H Disease: Regular medical follow-up
- Diagnosis of the very mild alpha thalassemias, carrier & trait is important only for counseling and avoiding misguided treatments like iron
- Diagnosed by Alpha Thal gene probe

THALASSEMIA

BIGGEST MISTAKE:

Treated with iron without benefit of iron studies

NORMOCHROMIC NORMOCYTIC ANEMIA

ANEMIA OF CHRONIC DISEASE

Hypoproliferative anemia

- Decreased red cell survival
- Impaired EPO production
- Impaired marrow response to EPO
- Impaired mobilization of iron
- Inflammatory response to underlying disorder

ANEMIA OF CHRONIC DISEASE

- Chronic nonhematologic conditions:

  Infectious

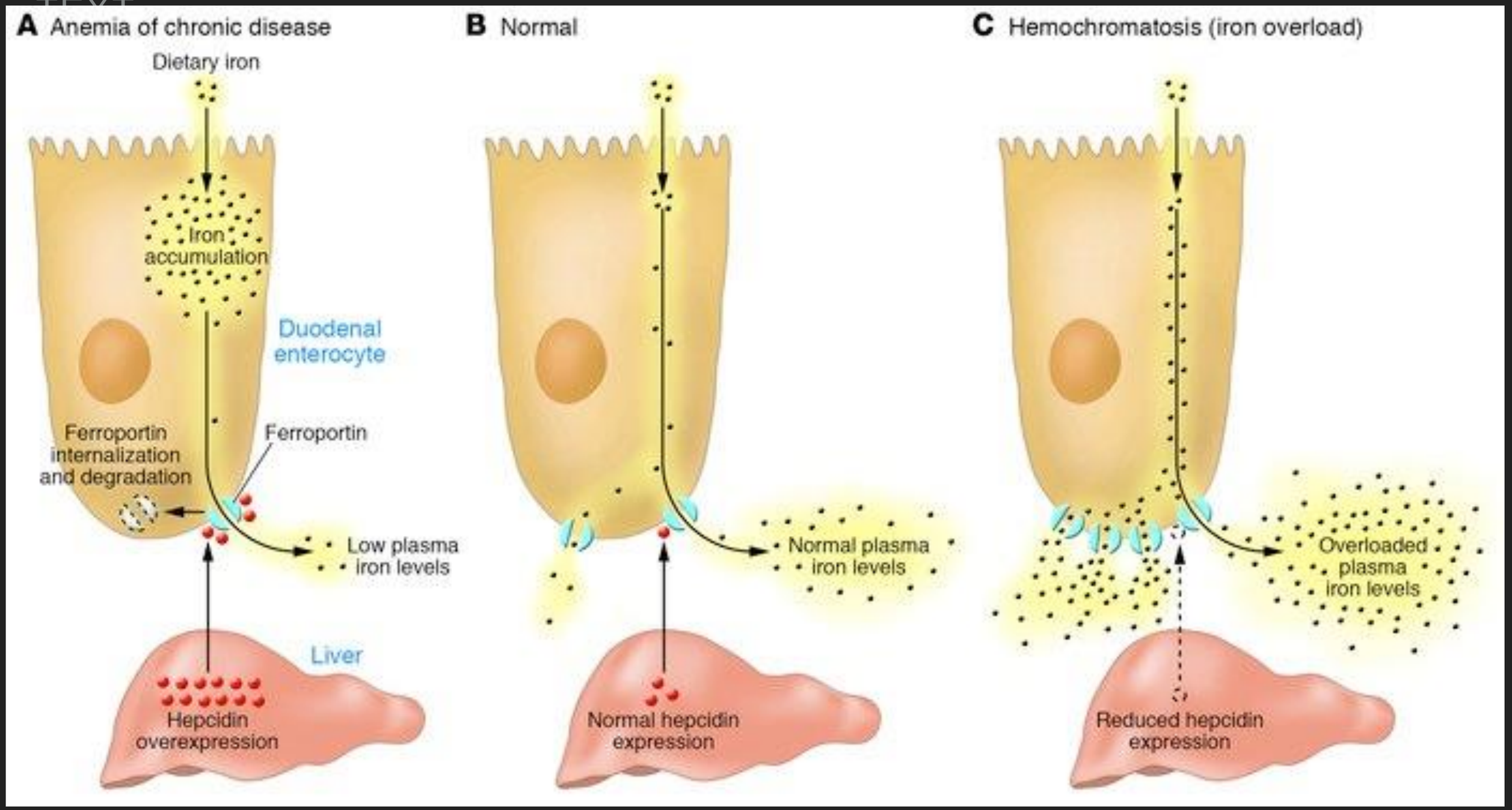
  Malignant

  Inflammatory

  Traumatic

ANEMIA OF CHRONIC DISEASE: DIAGNOSIS

- Exclude other etiologies of anemia
- Confirm hypoproliferative anemia
- Low serum iron despite increased iron stores in bone marrow & macrophages



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ANEMIA OF CHRONIC DISEASE: THERAPY

- Most are self-limiting and need no specific treatment
- Treat the underlying disorder
- Correct any coexistent deficiency
- Selected patients may benefit from EPO

MACROCYTIC ANEMIA

- Characterized by abnormal nuclear maturation of red cell precursors
- B12 Deficiency
- Folic Acid Deficiency
- Chemotherapy
- MDS
- Monoclonal protein

- Monoclonal protein

B12 ABSORPTION

- STOMACH: Acid, pepsin

  Parietal cells

  Intrinsic factor
- DUODENUM
- TERMINAL ILEUM

CAUSES OF B12 DEFICIENCY

- Dietary lack
- Inadequate proteolysis of B12

    - H2 Blockers, PPIs

- Deficiency of intrinsic factor

    - Gastrectomy, H2 Blockers

    - Pernicious Anemia

- Associated autoimmune disorders: hypothyroidism , Hashimoto’s, vitiligo, diabetes, Addison’s disease

CAUSES OF B12 DEFICIENCY

- Metformin
- Pancreatic insufficiency
- Blind loop
- Diphyllobothrium latum
- Intestinal malabsorption
- Congenital disorders
- Nitrous Oxide inhalation
- Infections: HIV, H. pylori

SYMPTOMS OF B12 DEFICIENCY

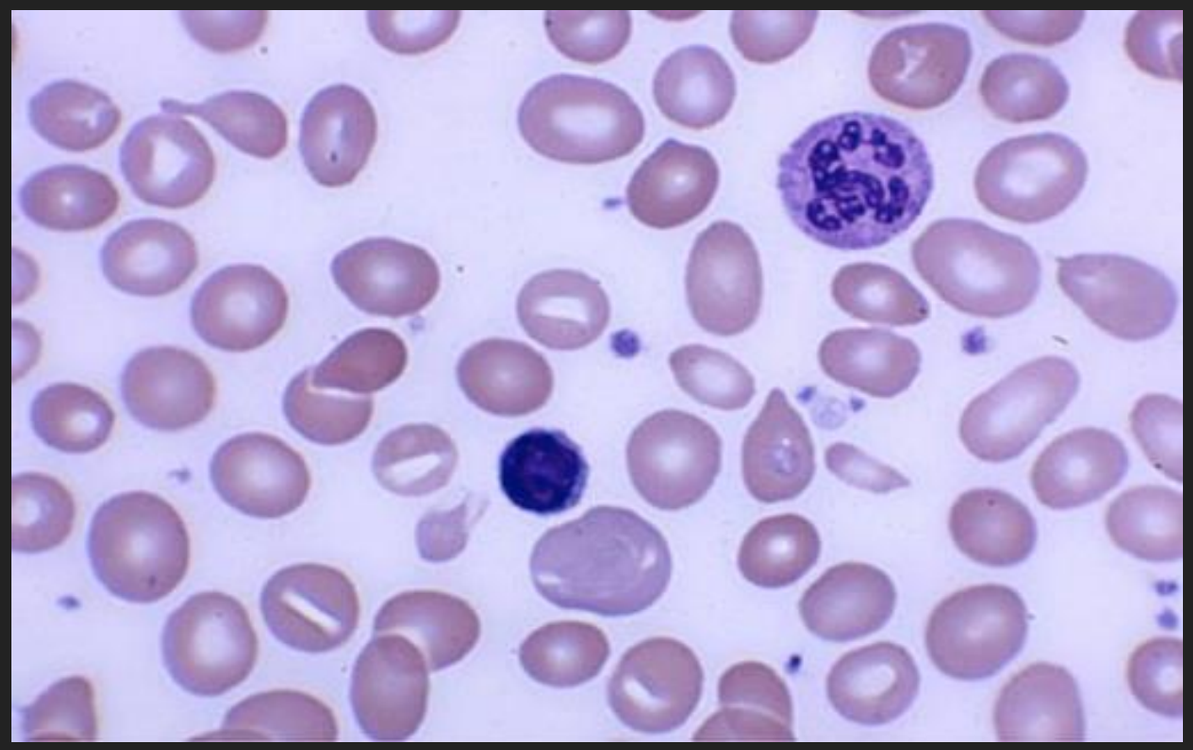
- Brain and cranial nerves-dementia, personality changes, psychiatric disorders, disturbances in taste & smell, optic nerve abnormalities
- Peripheral neuropathy-parethesias, sensory disturbances, diminished vibration and position senseAutonomic dysfunction
- Myelopathy affecting:

  posterior columns: acroparesthesias, sensory disturbances, incoordination, ataxia, diminished vibration, position

  lateral columns: weakness, spasticity

DIAGNOSIS

- Neuropsych symptoms can predate hematological changes.
- Serum B12 level <300 is standard diagnostic test but may not accurately reflect tissue levels
- Hyperlobated WBCs



B 12 DEFICIENCY

- Methylmalonic acid and homocysteine levels elevated
- Antibody testing to diagnose PA:

  anti-parietal cell ab

  anti-intrinsic factor ab

TREATMENT

- Oral- becoming the replacement mode of choice; includes SL
- IM or SQ
- Nasal, expensive
- Prophylactic for gastric or ileal resection

CAUSES OF FOLATE DEFICIENCY

- Dietary deficiency, can evolve in months
- Increased requirements
- Intestinal malabsorption
- Drugs that interfere with folate metabolism

DIAGNOSIS OF FOLATE DEFICIENCY

- SERUM FOLATE

  -May normalize after 1 meal

  -May be low normal with true folate deficiency

- RBC FOLATE

  -Normal or borderline in 60% pregnant pts

  and 30% alcoholics with true folate deficiency

TREATMENT

- Folic acid 1 mg po daily is usually adequate

-Maintenance Rx: depends on underlying disorder

-Prophylactic Rx: Pregnancy, prematurity, hemolysis, dialysis

HEMOLYTIC ANEMIA

PREMATURE DESTRUCTION OF RBC'S

Occurs by 2 different mechanisms

- Extra vascular hemolysis: RBCs prematurely removed from circulation by liver or spleen
- Intravascular hemolysis: RBCs lyse in the circulation

HEMOLYTIC ANEMIA

2 MAIN CAUSES

- Intrinsic RBC defects (inherited)
- Extra-corpuscular causes (acquired)

HEMOLYTIC ANEMIA

HEREDITARY HEMOLYTIC DISORDERS

- RBC Enzyme Defects
- RBC Membrane Defects
- Hemoglobinopathies
- Thalassemias

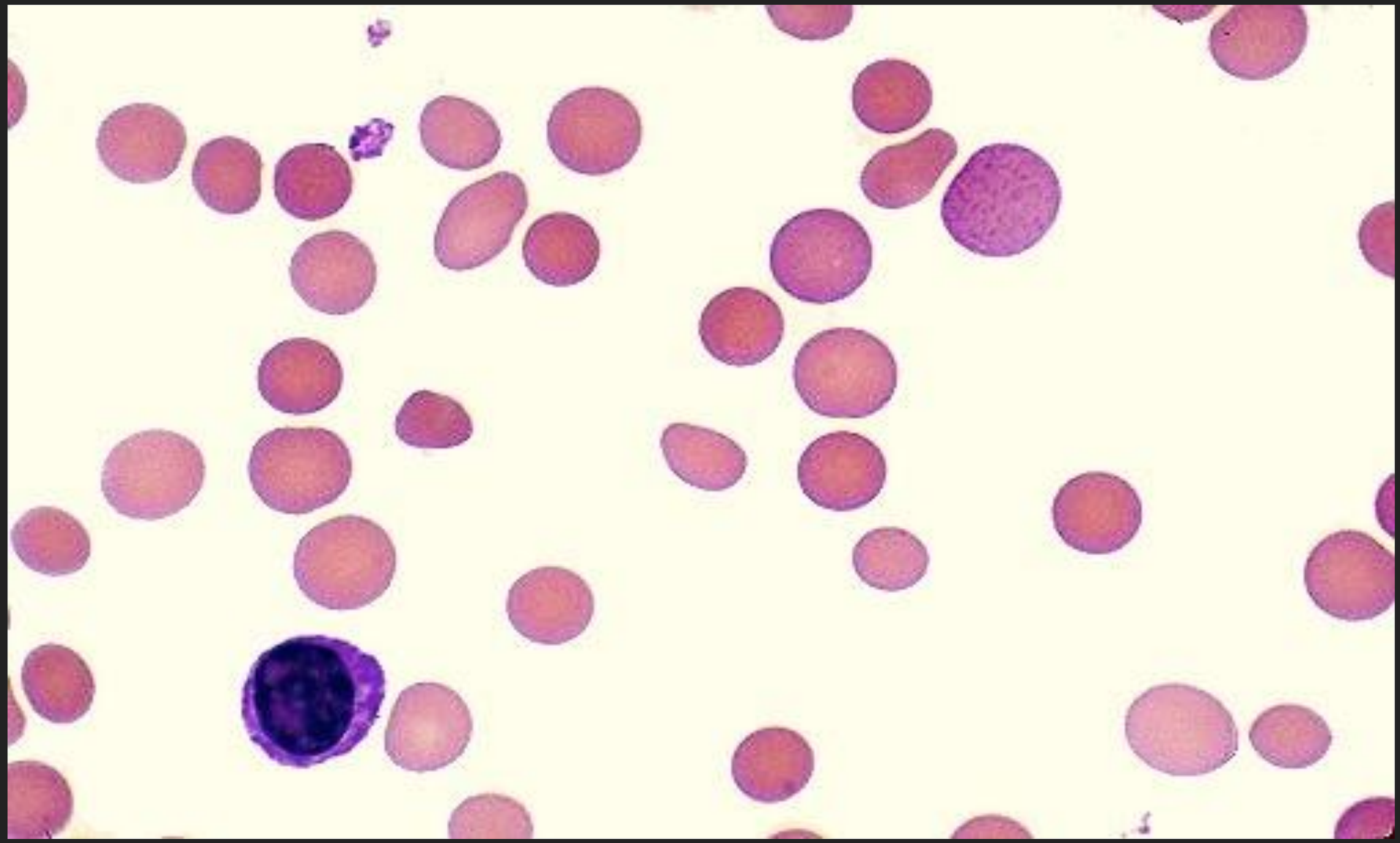
HEMOLYTIC ANEMIAS

- ACQUIRED HEMOLYTIC DISORDERS
- Immune Hemolytic Anemias
- Splenomegaly
- Microangiopathic Hemolytic Anemia
- PNH
- Direct toxic effect (malaria, clostridia)
- Spur Cell Anemia

DIAGNOSIS OF HEMOLYTIC ANEMIA

- Corrected Retic ct >2%
- Elevated indirect bilirubin
- Elevated LDH
- Haptoglobin low or absent
- Urine hemosiderin: present in intravascular hemolysis only
- Urine hemoglobin: present in severe intravascular hemolysis- urine dipstick positive for blood but no RBCs seen on micro

AUTOIMMUNE HEMOLYTIC ANEMIA



DIAGNOSIS: DIRECT ANTIGLOBULIN TEST-COOMBS

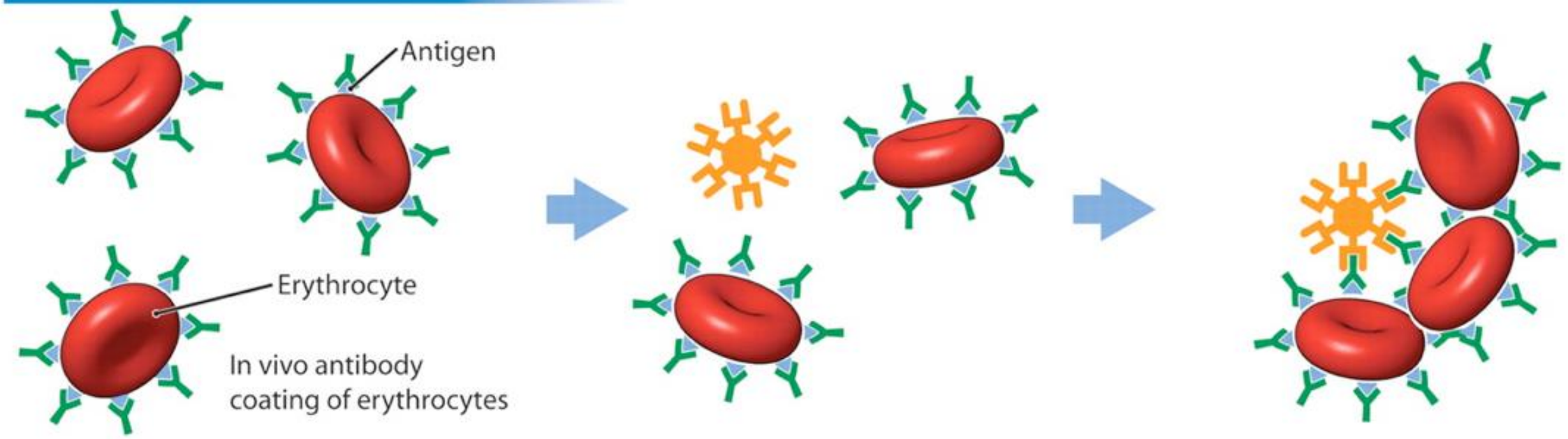
- Useful in diagnosing immune hemolytic anemia where there is antibody coating a patients red blood cells
- Done by mixing patients erythrocytes with antihuman globulin containing antibody to IgG and C3
- Test positive if agglutination occurs

TEXT

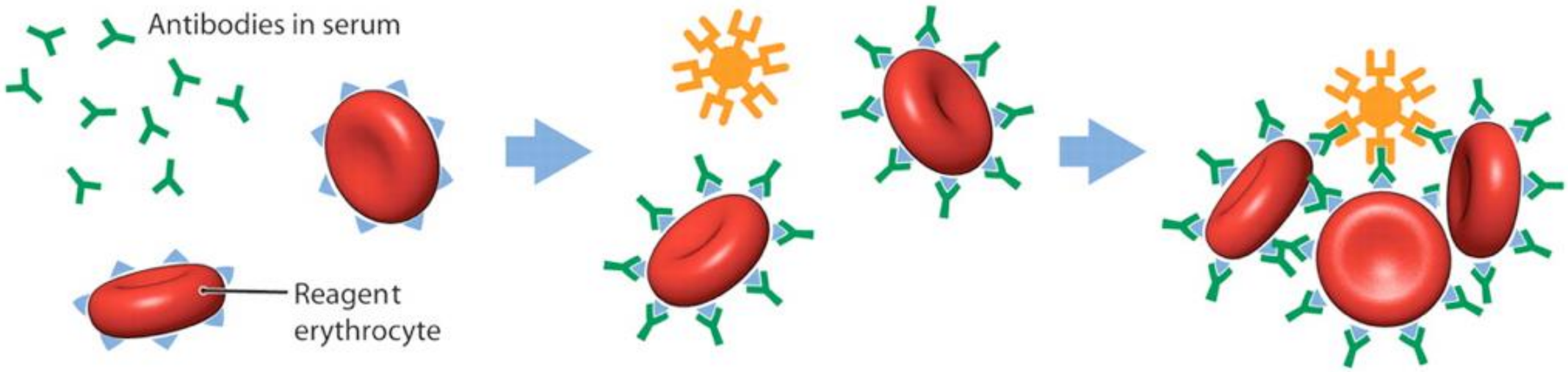
INDIRECT ANTIGLOBULIN TEST (INDIRECT COOMBS)

- Useful to detect antibodies present in patient’s serum
- Helpful in detecting alloantibodies induced by prior transfusion or by fetal transfer to mother

Direct Antiglobulin Test



Indirect Antiglobulin Test



IMMUNE HEMOLYTIC ANEMIA

- 40-50% Idiopathic
- Induced by binding of antibody &/or complement to RBC membrane
- Caused by autoantibody directed against patients own RBCs or acquired alloantibody directed against transfused RBCs
- Coombs is only test that provides definitive evidence of immune hemolysis.

IMMUNE HEMOLYTIC ANEMIA

Warm-antibody Autoimmune Hemolytic Anemia

- Autoantibodies optimally reactive at 37C
- IgG present on RBC surface
- May also have C3
- Most cases idiopathic
- Can be a complication of underlying disease

IMMUNE HEMOLYTIC ANEMIA

Warm Antibody Related Diseases

- Chronic lymphocytic leukemia
- Collagen vascular diseases
- Ulcerative colitis
- Congenital immunodeficiency

TREATMENT OF WARM-REACTIVE AIHA

- Prednisone 1 mg/kg/d
- Folic acid
- Splenectomy if refractory to prednisone
- Immunosuppressive drugs
- IVIg, Rituximab
- TRANSFUSE LEAST INCOMPATIBLE BLOOD

IMMUNE HEMOLYTIC ANEMIA

- COLD ANTIBODY

  -Cold Agglutinin disease

    idiopathic

    chronic lymphocytic anemia

    mycoplasma infection

    infectious mononucleosis

  -Paroxysmal Cold Hemoglobinuria

TREATMENT OF COLD ANTIBODY AIHA

- Avoid cold exposure
- Folic acid therapy
- Treatment of underlying disorder
- Immunosuppressive agents
- Splenectomy of little value
- Rituximab
- Plasmapheresis

TREATMENT OF COLD ANTIBODY AIHA

- Transfusions of packed red blood cells:
- Compatibility testing should be done at 37˚C
- Transfuse warm blood recommended but lacks proven efficacy

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

- Acquired clonal stem cell disorder-in which a mutation of PIG-A gene causes defective production of GPI Anchor Protein
- Only a portion of RBCs affected
- Defective platelets & WBCS
- Increased sensitivity of RBCS to complement mediated hemolysis

PNH: CLINICAL PRESENTATION

- May remain undiagnosed for a long period of time
- History of unexplained, chronic hemolysis, hemoglobinuria, pancytopenia & thrombotic events
- Intravascular hemolysis
- Absent haptoglobin, increased LDH, hemoglobinuria, & hemosidinuria

PNH: CLINICAL PRESENTATION

- Can be found in the setting of another specified bone marrow disorder:

  Aplastic Anemia

  Refractory Anemia-MDS

- Can be subclinical (no hemolysis)

PNH: DIAGNOSIS

Flow cytometry using antibodies directed against GPI-AP (glucosyl phosphatidylinositol-anchored proteins)

PNH: TREATMENT

- Folic acid
- Corticosteroids
- RBC Transfusions
- Iron (can precipitate hemolysis)
- Anticoagulation with warfarin
- Eculizumab (Solaris)
- Stem cell transplant

NONIMMUNE HEMOLYTIC ANEMIA

Inherited nonimmune hemolytic anemia

- RBC membrane disorders:
  - Hereditary spherocytosis
  - Hereditary elliptocytosis
  - Hereditary stomatocytosis
- G6PD deficiency

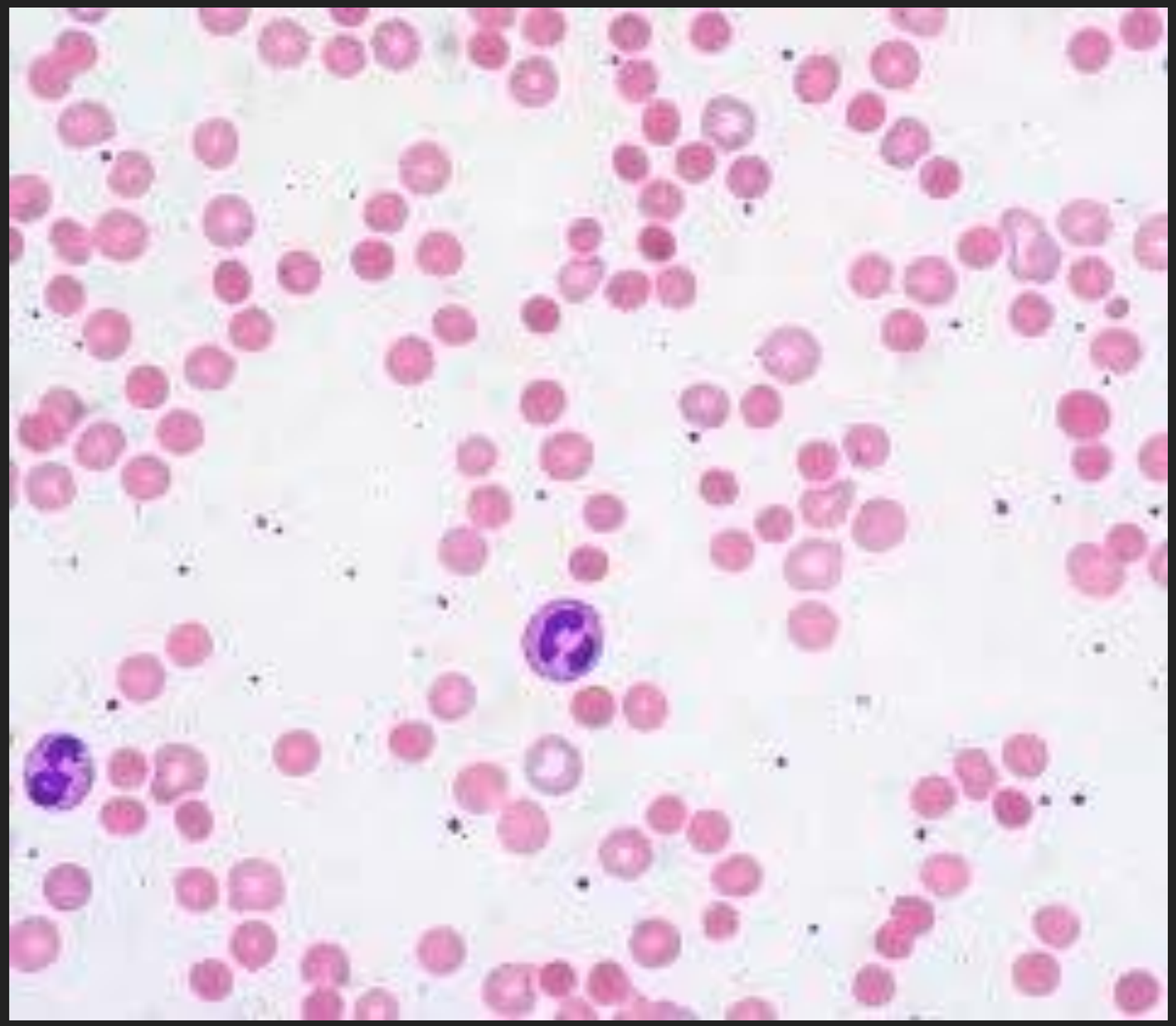
HEREDITARY SPHEROCYTOSIS

- Molecular defect in one or more of the proteins in the red blood cell cytoskeleton causing the cell to contract into a sphere shape. It has a high osmotic fragility and more prone to physical degradation.
- Osmotic fragility test

HEREDITARY SPHEROCYTOSIS

- Mild to severe hemolytic anemia
- Spherocytes on peripheral smear
- Increased osmotic fragility
- Negative direct antiglobulin test
- Aplastic crisis with viral infection
- Splenectomy is treatment of choice in severe cases

HEREDITARY SPHEROCYTOSIS



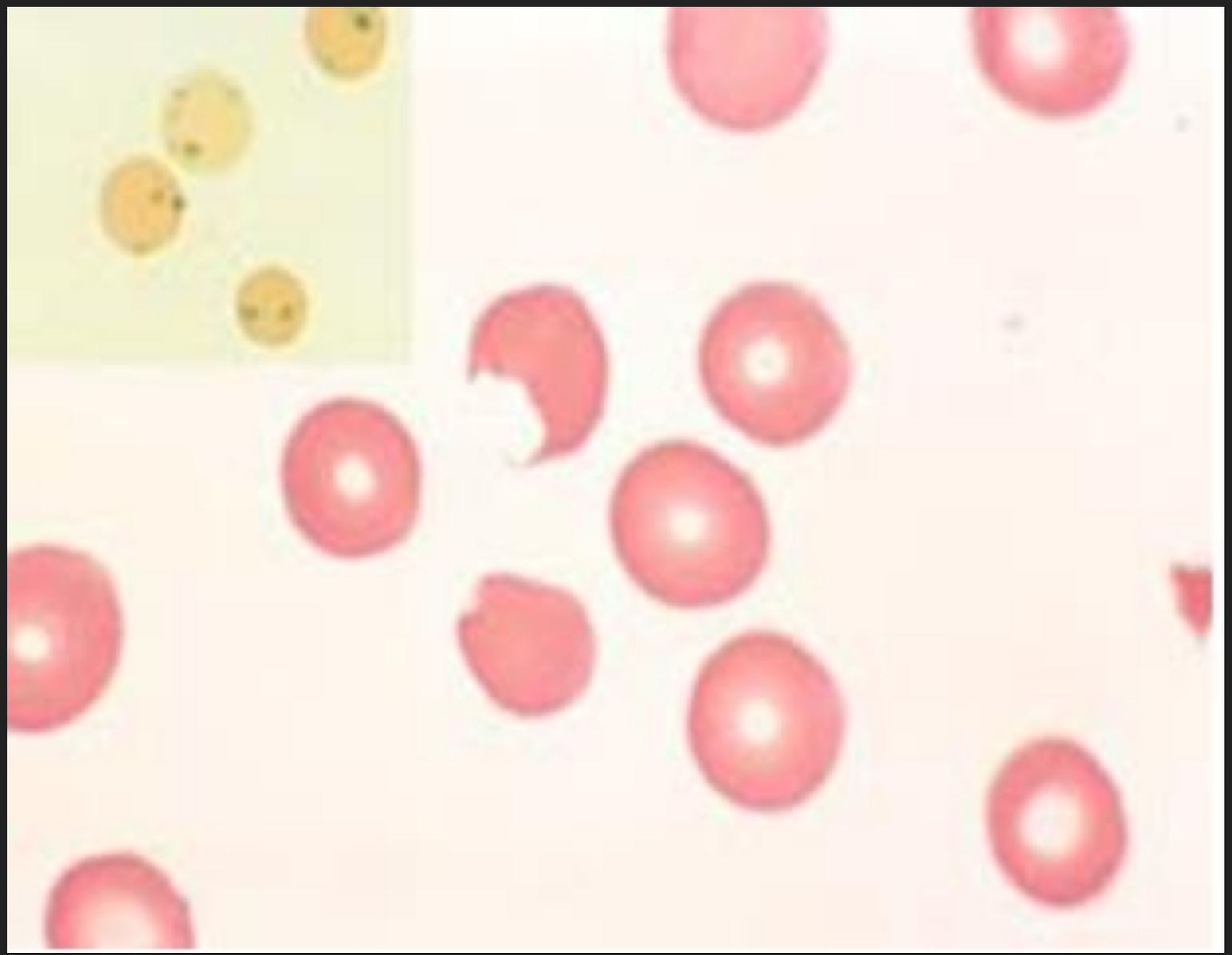
G6PD DEFICIENCY

- Most common enzyme deficiency worldwide.
- Different gene mutations cause different levels of enzyme deficiency and disease manifestationsG6PD helps protect hemoglobin from oxidation upon exposure to a drug or toxin that results in the generation of free radicals
- Drugs associated with hemolysis: primaquine, sulfa, dapsone, nitrofurantoin
- Fava beans will cause acute hemolysis shortly after ingestion

G6PD DEFICIENCY

- Acute hemolysis lasts 2-4 days, self-limiting, rarely requiring transfusion
- Infections and diabetic ketoacidosis can trigger hemolysis
- “Bite” cells on peripheral smear and Heinz bodies (precipitated hemoglobin)
- Diagnosis made by level of G6PD, but may be normal in active hemolysis

HEINZ BODIES & BITE CELLS



HEMOGLOBINOPATHIES

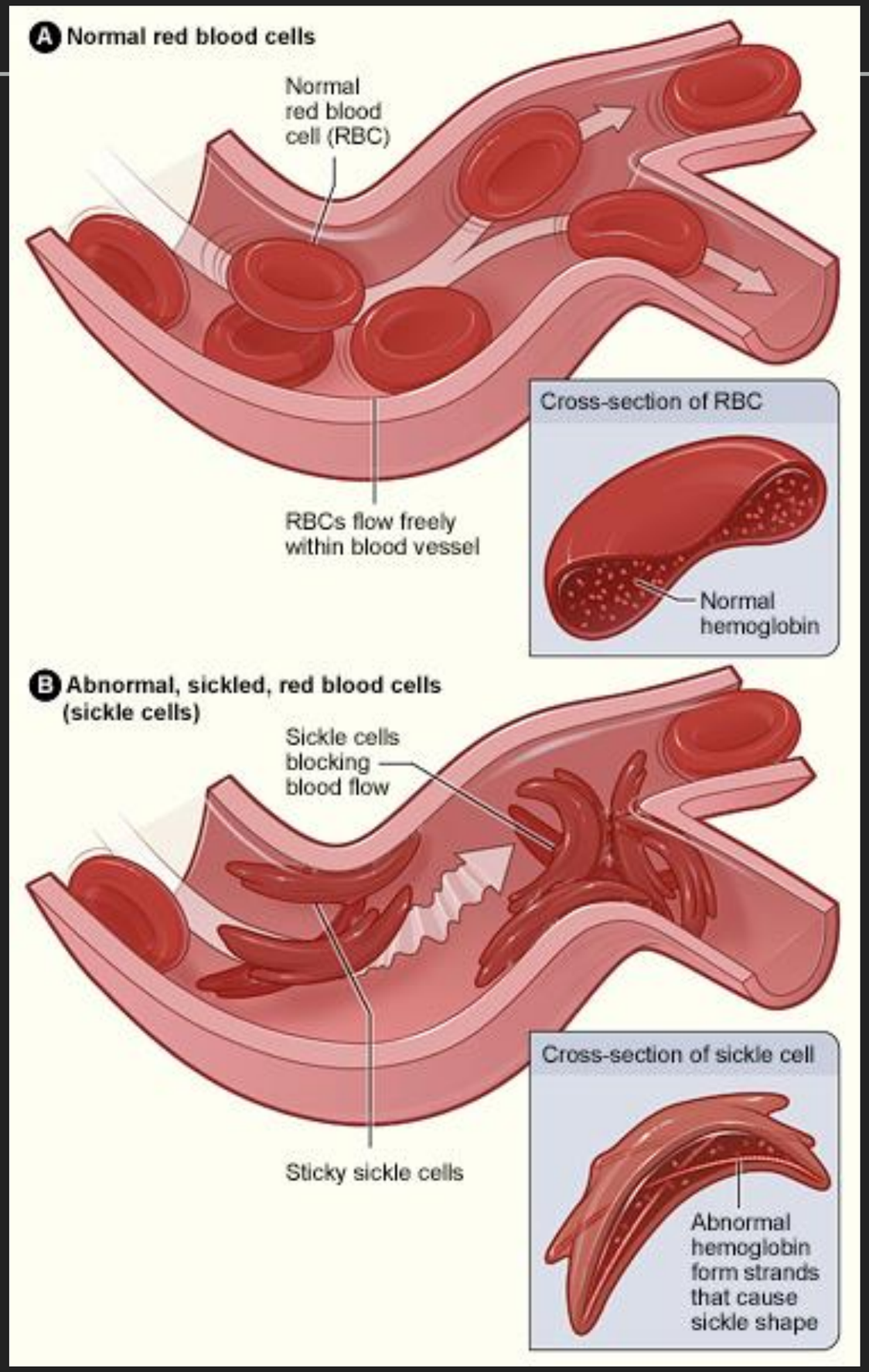
- SICKLE CELL DISEASE-the bone marrow makes sickle shaped red blood cells due to qualitative defects of globulin chain synthesis

-HbS >50%

-Multiple genotypes and phenotypes

-Sickle Cell Trait is not a disease

TEXT


A Normal red blood cells
Normal red blood cell (RBC)
RBCs flow freely within blood vessel
Cross-section of RBC
Normal hemoglobin
B Abnormal, sickled, red blood cells (sickle cells)
Sickle cells blocking blood flow
Sticky sickle cells
Cross-section of sickle cell
Abnormal hemoglobin form strands that cause sickle shape

SICKLE CELL ANEMIA: COMPLICATIONS

- Painful episode-most common
- Acute chest syndrome
- Stroke (10% children)
- Osteonecrosis
- Proliferative retinopathy
- Venooclusive complications
- Infectious complications

SICKLE CELL ANEMIA COMPLICATIONS

- HEMOLYSIS

  -Gallstones

  -Aplastic crisis

  -Osteopenia

  -Anemia

  -Nutritional deficiencies

SICKLE CELL ANEMIA: TREATMENT

- General medical care
- Pain management: AVOID MEPERIDINE!!
- Hydroxyurea
- Transfusion-limited, maintaining at baseline
- Stem cell transplant

APLASTIC ANEMIA

- Pure red cell aplasia
- Bicytopenia, pancytopenia
- Bone marrow failure

TEXT

RED CELL APLASIA: CLASSIFICATION

- Congenital: Diamond Blackfan Syndrome
- Acquired: Idiopathic & Secondary
- Secondary:

-Hematologic malignancies

-Solid tumors

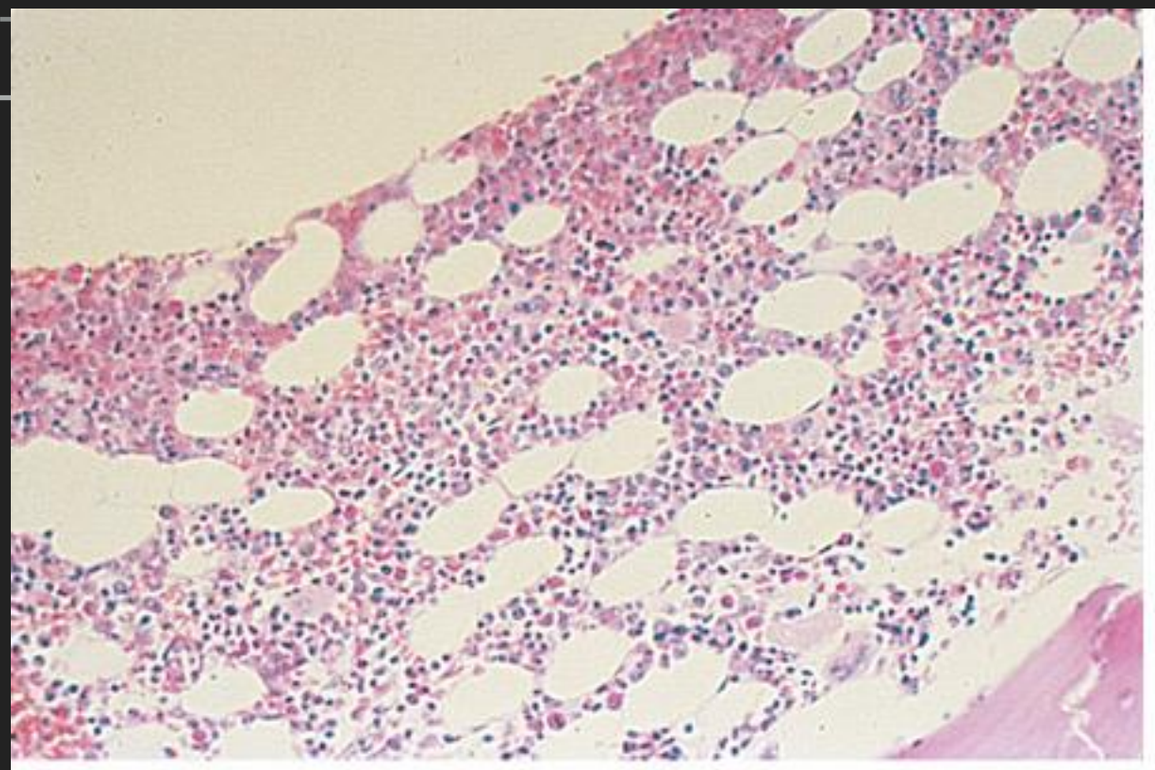
-Immunologic disorders

-Infectious diseases

-Drugs

APLASTIC ANEMIA: DIAGNOSIS

- BONE MARROW BIOPSY: 4-5 cores showing cellularity of <30%
- Flow cytometry & cytogenetics to r/o the rarer varient - hypocellular MDS



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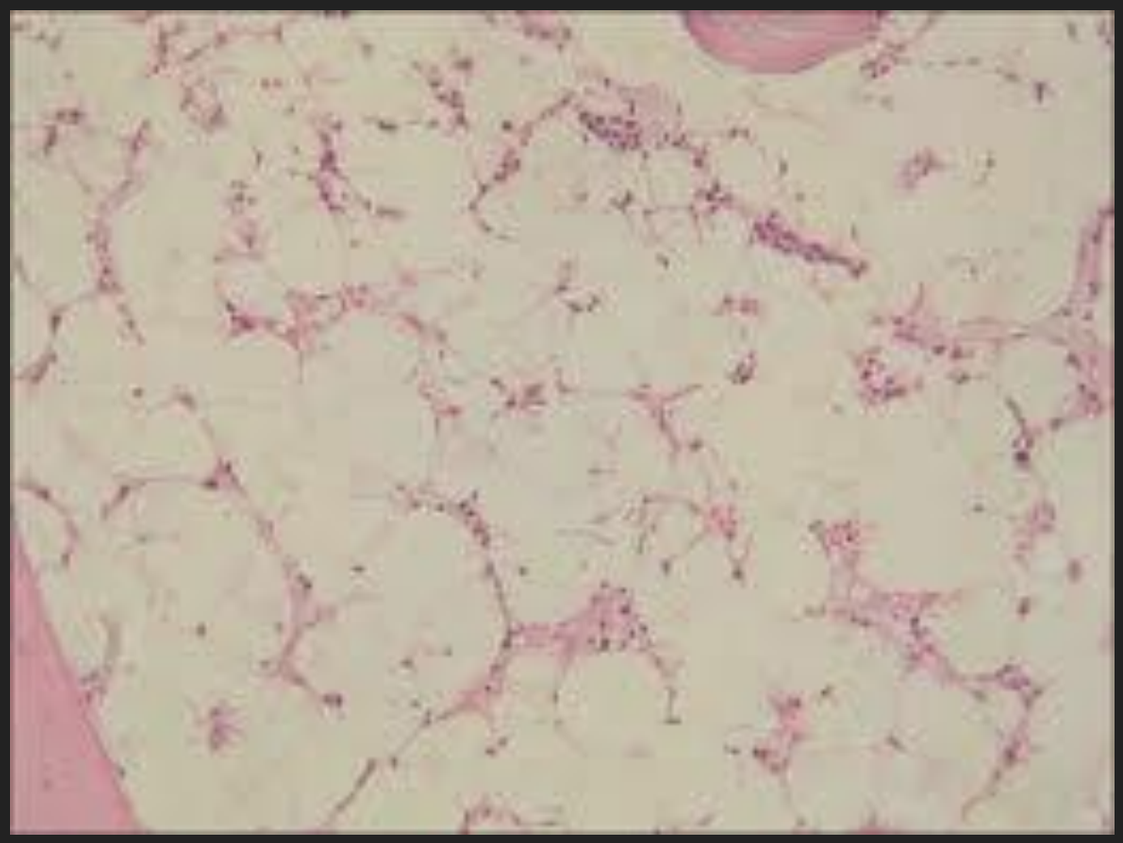
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com



APLASTIC ANEMIA: TREATMENT

- Antithymocyte globulin (ATG) & Cyclosporin (CSA)
- Transplant: Cord blood

  Stem cell