Red Blood Cell Disorders II:

Increased RBC destruction/hemolytic anemias

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Features of hemolytic anemias

- Destruction of RBCs
- Shortened RBC survival (<120 days)
- Increased erythropoietin
- Increased bone marrow RBC production
  - Marrow may be unable to compensate for increased destruction
- Accumulation of breakdown products from RBCs
  - Jaundice
  - Pigment gallstones

Increased RBC destruction

- Hemolytic anemias
  - Intravascular
  - Extravascular

Laboratory evidence of hemolysis

INTRAVASCULAR	EXTRAVASCULAR
+/- Schistocytes (if microangiopathic)	Microspherocytes
↑ ↑ ↑ LDH	↑ LDH
↓ ↓ ↓ haptoglobin	↓ haptoglobin
↑ free hemoglobin	↑ indirect bilirubin
↑ urine hemoglobin, hemosiderin	↑ urine & fecal urobilinogen
No splenomegaly	Splenomegaly

Hemolytic anemias

- Normal hemoglobin produced in normal quantities
  - Intravascular/Non-Autoimmune Hemolytic Anemias
    - Mechanical Damage
    - Microangiopathic Hemolytic Anemias
      - Disseminated Intravascular Coagulation
      - Thrombotic Thrombocytopenic Purpura
      - Hemolytic Uremic Syndrome
    - Paroxysmal Nocturnal Hemoglobinuria
    - Glucose-6-Phosphatase (G6PD) Deficiency
    - Malaria
  - Autoimmune Hemolytic Anemia
    - Warm autoimmune hemolytic anemia
    - Cold autoimmune hemolytic anemia
  - RBC membrane defects
    - Hereditary spherocytosis and elliptocytosis
- Abnormal hemoglobins
  - Hemoglobinopathies
    - Hemoglobin S
    - Hemoglobin C
    - Hemoglobin SC
- Normal hemoglobin produced in insufficient quantities
  - Thalassemias

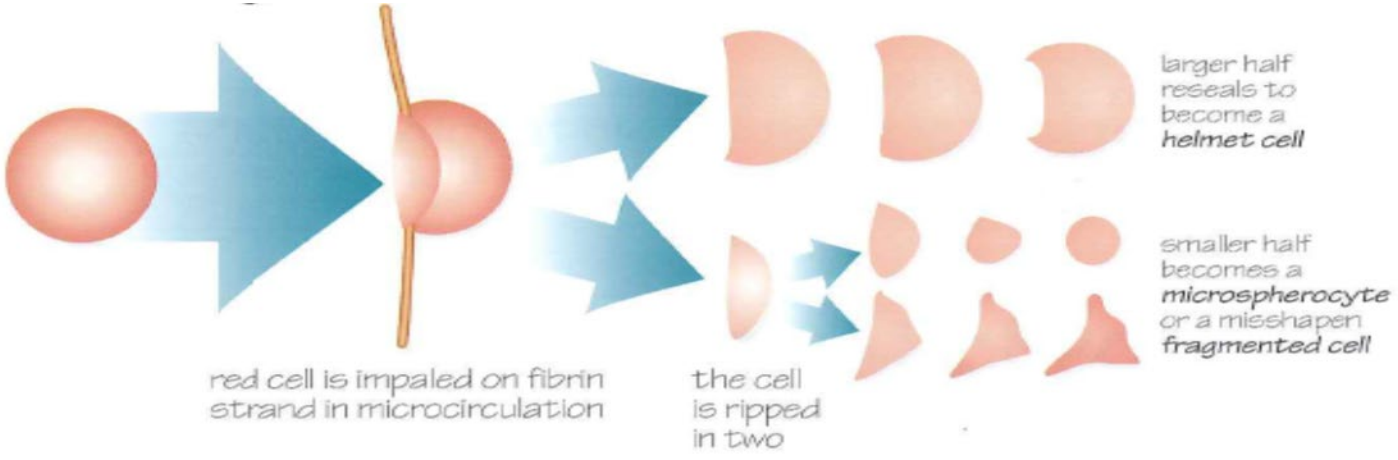
Mechanical trauma to RBCs

- Implanted devices
  - Artificial heart valves
  - Extracorporeal membrane oxygenation (ECMO)

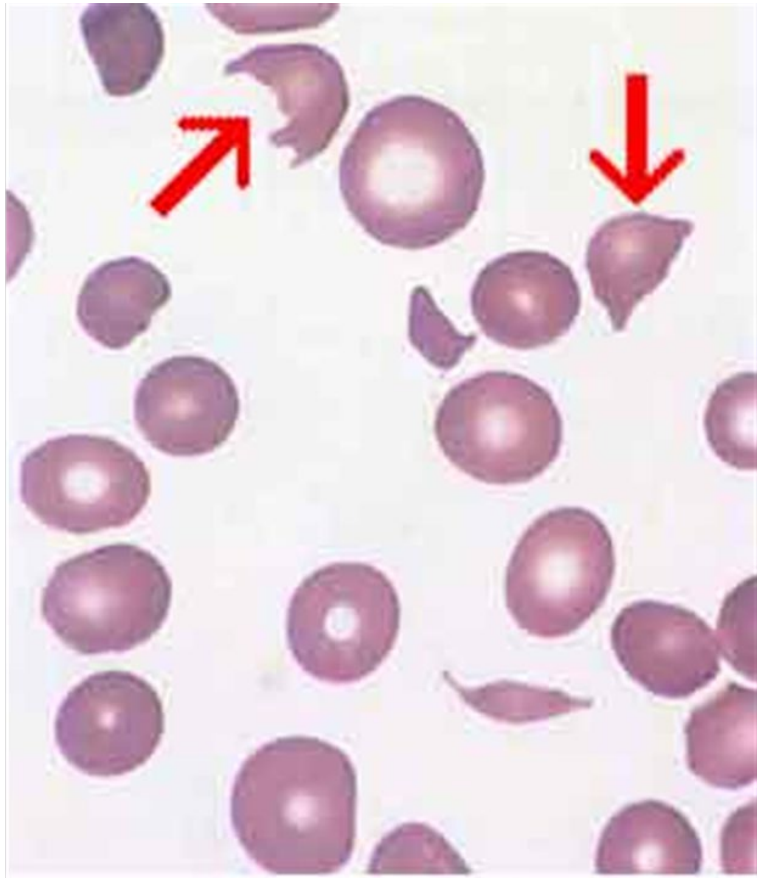
- Microangiopathic hemolytic anemias
  - Disseminated intravascular coagulation (DIC)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Hemolytic uremic syndrome (HUS)

Microangiopathic hemolytic anemia

- RBCs destroyed while circulating → release hemoglobin, lactate dehydrogenase (LDH)
- Free hemoglobin bound by haptoglobin
  - Haptoglobin-hemoglobin complex metabolized by the reticuloendothelial system
  - Decreased haptoglobin level
- Schistocytes in peripheral blood

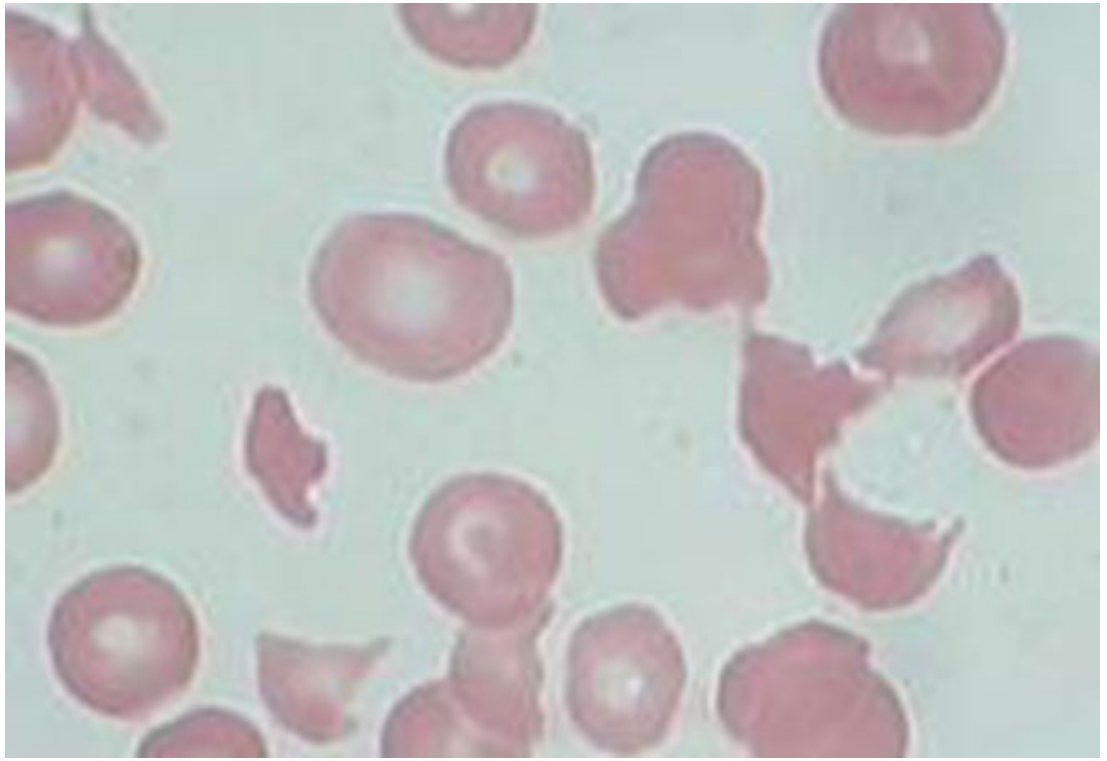


Microangiopathic hemolytic anemia



Schistocytes / Helmet Cells

Robbins Pathologic Basis Of Disease: 6th Edition. 1999.
Fig. 14-17 p. 621.



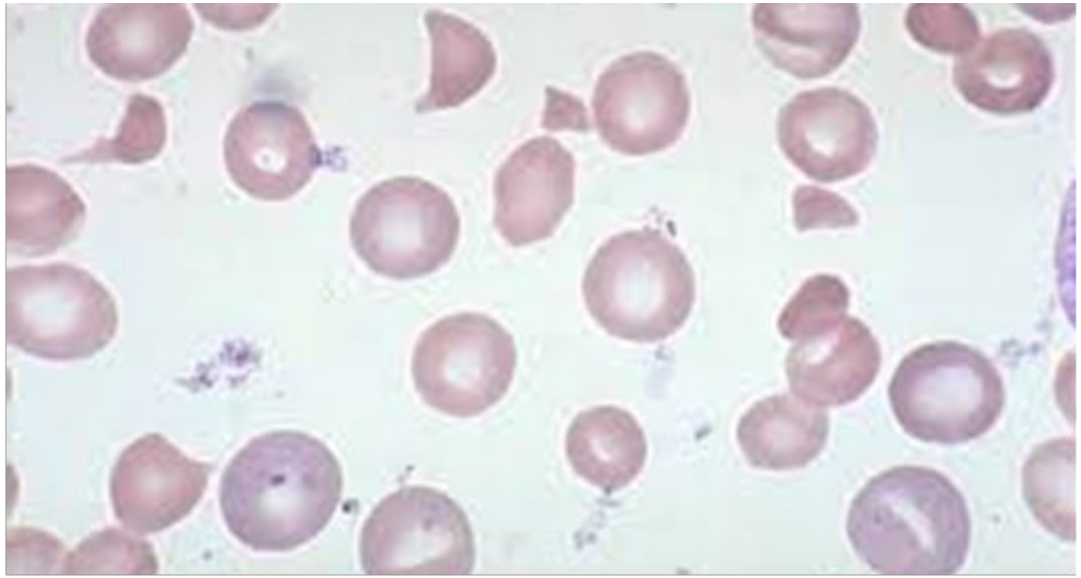
Disseminated intravascular coagulation (DIC)

- Pathologic activation of coagulation cascade leading to formation of microthrombi throughout circulation
  - Thrombotic: microthrombi formation within microcirculation
  - Hemorrhagic: consumption of coagulation factors required for hemostasis
- Two major mechanisms of coagulation cascade activation:
  - Release of thromboplastic substances into circulation
  - Widespread endothelial injury
- Causes: pregnancy, malignancy, sepsis/bacterial infections, major trauma

Disseminated intravascular coagulation (DIC)

- Laboratory findings:
  - Peripheral smear:
    - Schistocytes
    - Decreased platelets
    - Anemia
  - Prolonged PT, PTT
  - Hypofibrinogenemia
  - ↑ D-dimer: reflects fibrin formation
- Treatment:

  Treat underlying cause

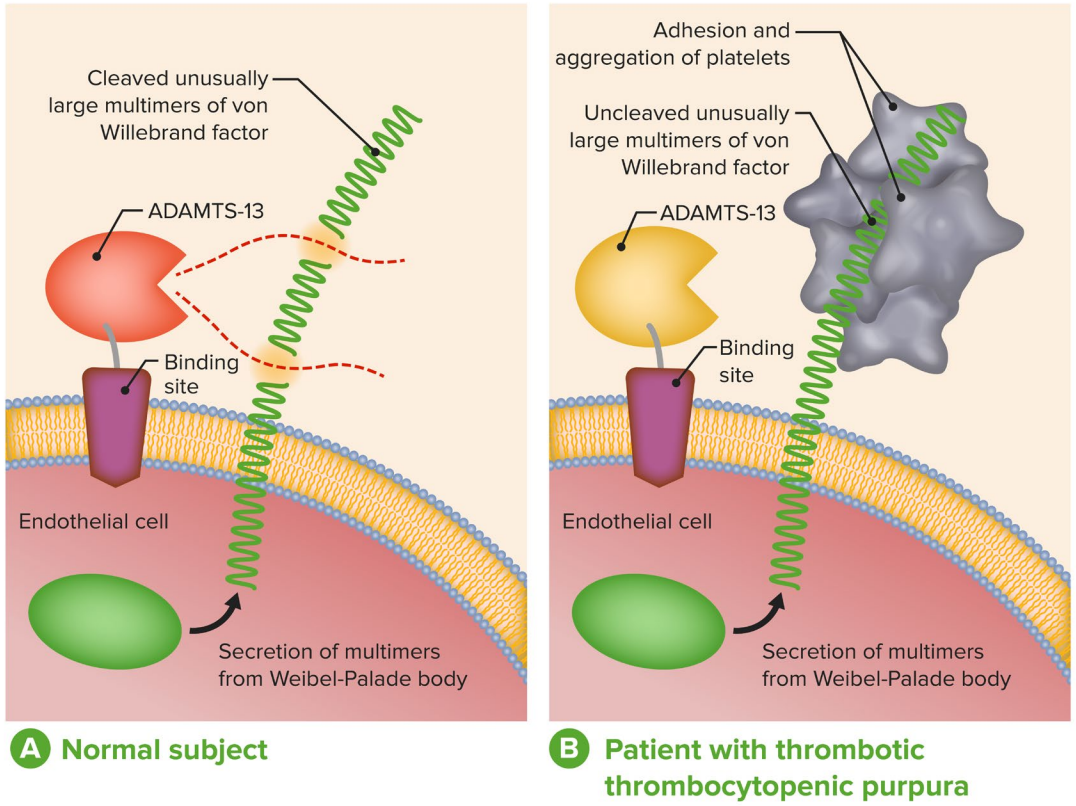


Peripheral smear: schistocytes due to shearing by microthrombi, low platelets due to consumption, polychromasia due to compensatory efforts

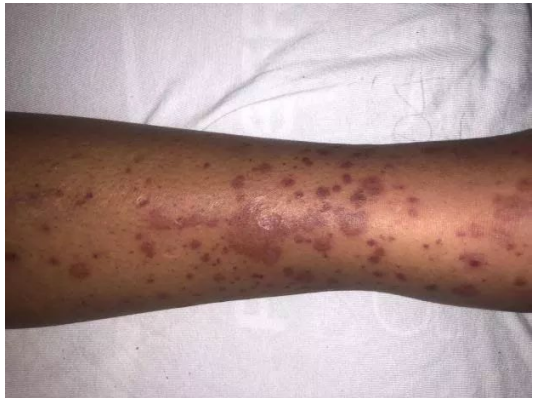
Thrombotic thrombocytopenic purpura (TTP)

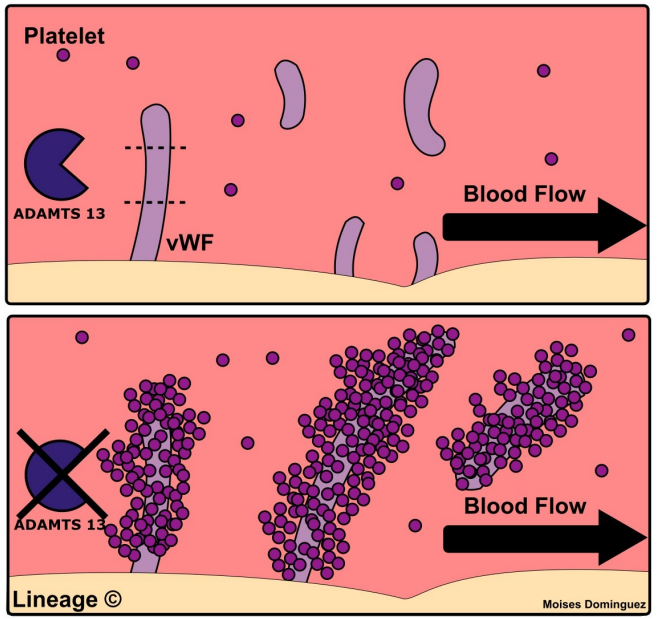
- Formation and deposition of “hyaline thrombi” within microcirculation
  - Platelet consumption
  - Intravascular thrombi damage RBCs, leading to anemia

- Pathophysiology
  - Deficiency in **ADAMTS13**
  - Genetic: inherited mutations
  - Acquired: antibodies to ADAMTS13



Thrombotic thrombocytopenic purpura (TTP)

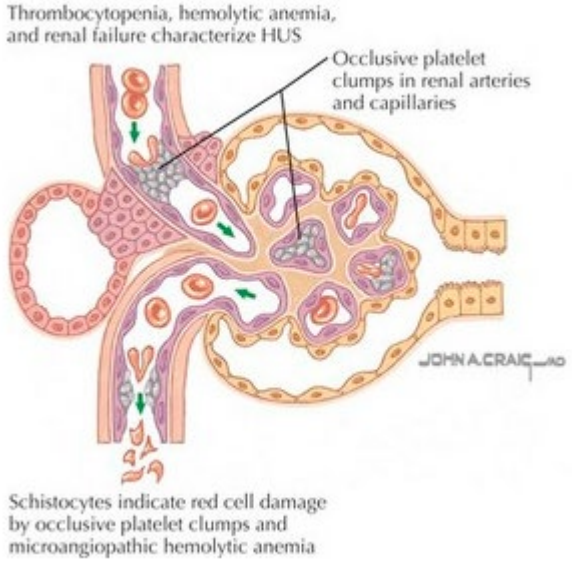


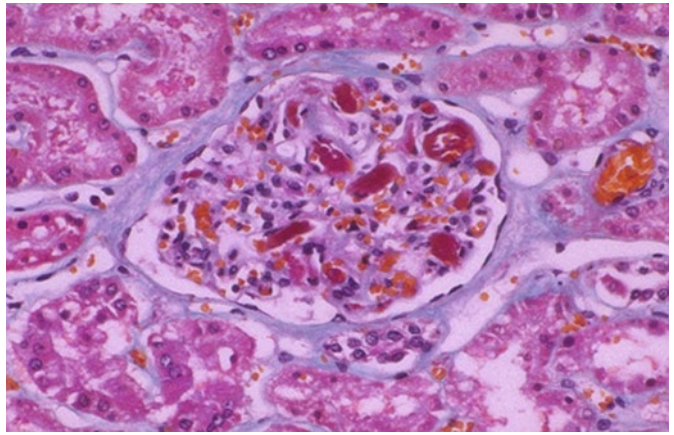


- Clinical findings
  - Fever
  - Microangiopathic hemolytic anemia
  - Thrombocytopenia
  - Renal failure
  - Neurologic deficits
  - Petechial rash
- Peripheral smear findings:
  - Low platelets
  - Fragmented RBCs
- Test for ADAMTS13 activity
- Treatment
  - Plasma exchange
  - Medication (steroids, rituximab/antibody-based)

Hemolytic uremic syndrome (HUS)

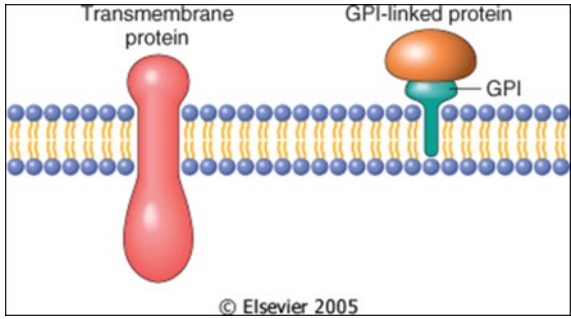
- Pathogenesis distinct from TTP: normal levels of ADAMTS 13
- Most cases due to *E. coli* O157:H7 strain → gastroenteritis mediated by Shiga-like toxin
  - Toxin binds to and damages glomerular endothelium, making them thrombogenic
- Other causes include: drugs, radiation therapy, complement abnormalities
- Peripheral smear findings: similar to DIC and TTP
- Diagnosis is based on clinical findings
  - Can serotype looking for *E. coli*
- Clinical findings
  - Bloody diarrhea
  - Acute renal failure
  - Microangiopathic hemolytic anemia



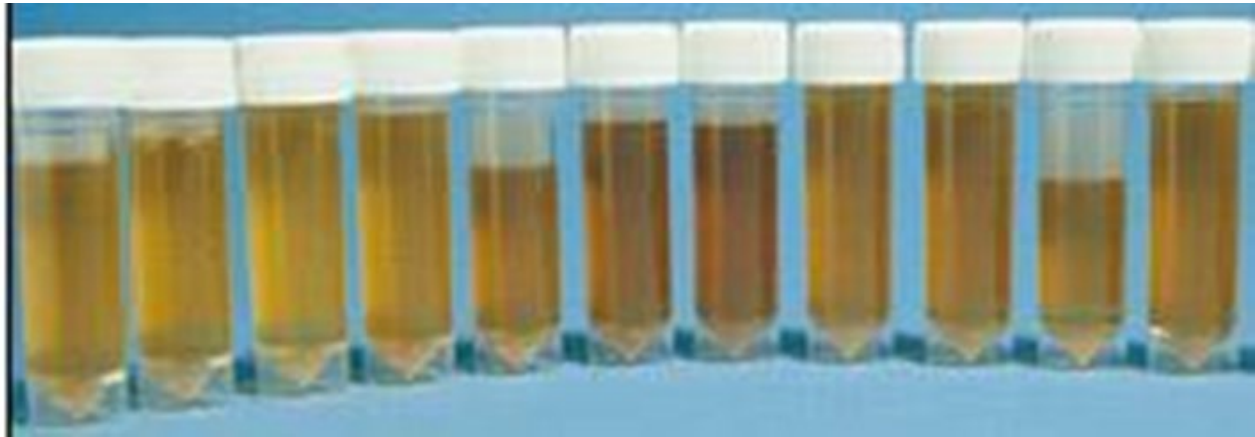


http://library.med.utah.edu/WebPath/RENAHTML/RENAL176.html

Paroxysmal nocturnal hemoglobinuria (PNH)



- Acquired membrane defect secondary to an acquired mutation that affects hematopoietic stem cells
- PIGA – phosphatidylinositol glycan anchor
  - Normal RBCs have PIGA, protecting from complement mediated lysis
  - RBCs lacking PIGA are more prone to destruction by complement
- Signs and symptoms
  - Episodic discolored urine
  - Thrombosis (can be deadly)



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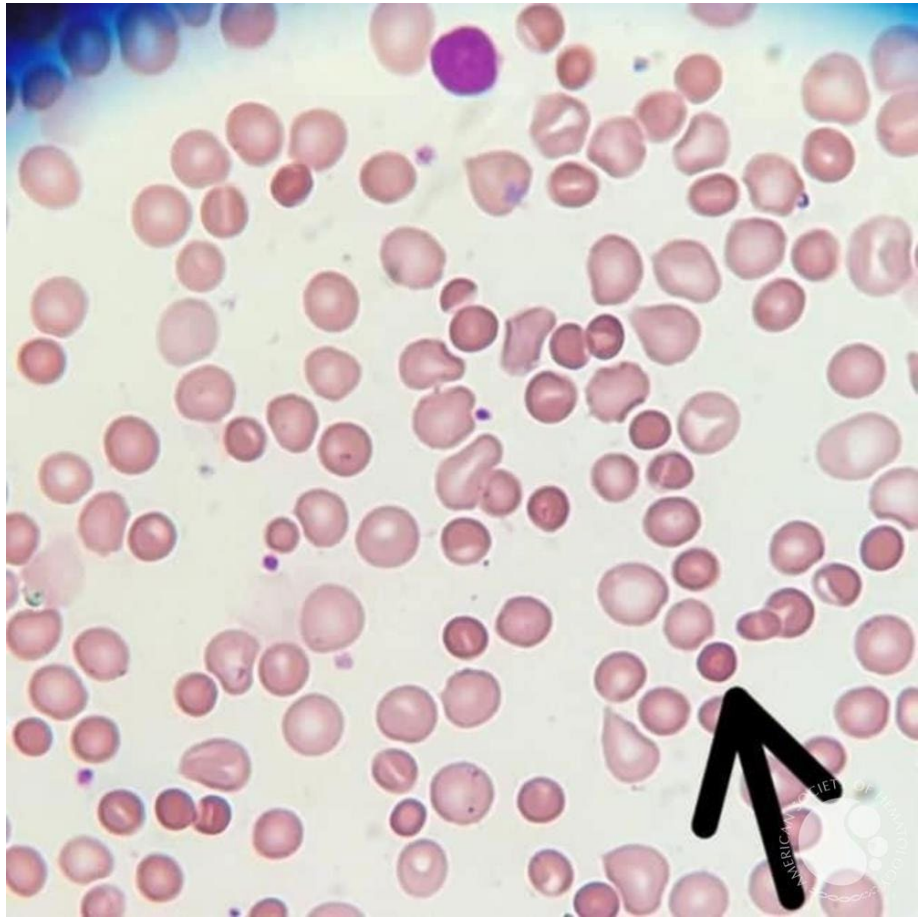
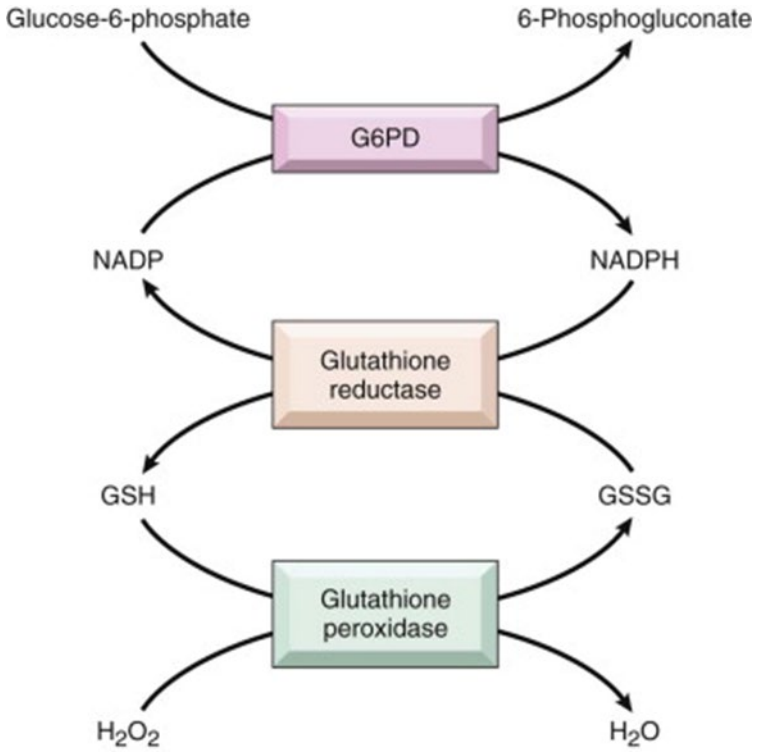


- Peripheral blood:
  - Microspherocytes (not schistocytes)
- Diagnosis:
  - Flow cytometry to identify WBCs and RBCs that lack GPI
    - CD59, CD55, FLAER
  - Older tests: sucrose (screen), acidified serum test
- Treatment is bone marrow transplant
  - Eculizumab-monoclonal antibody (>$400,000/yr)
- Can develop into aplastic anemia and/or subsequent leukemia

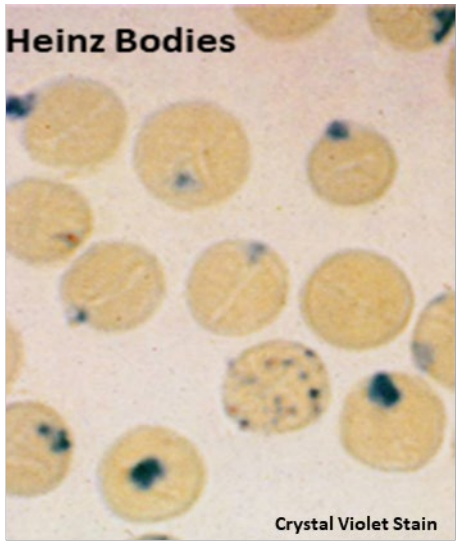
Glucose-6-phosphate dehydrogenase (G6PD) deficiency

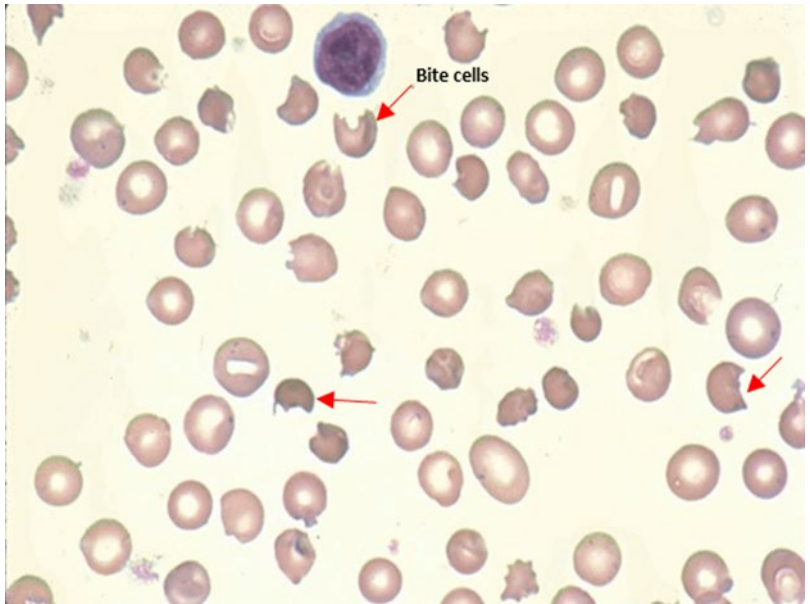
- X-linked recessive enzyme deficiency
  - African (mild)
  - Mediterranean (moderate/severe)
- G6PD is important in glutathione metabolism
  - In normal RBCs, reduced glutathione (GSH) protects RBCs from oxidative injury
  - G6PD deficiency:
    - RBCs more prone to oxidative injury
    - Hemolysis (intravascular and extravascular)



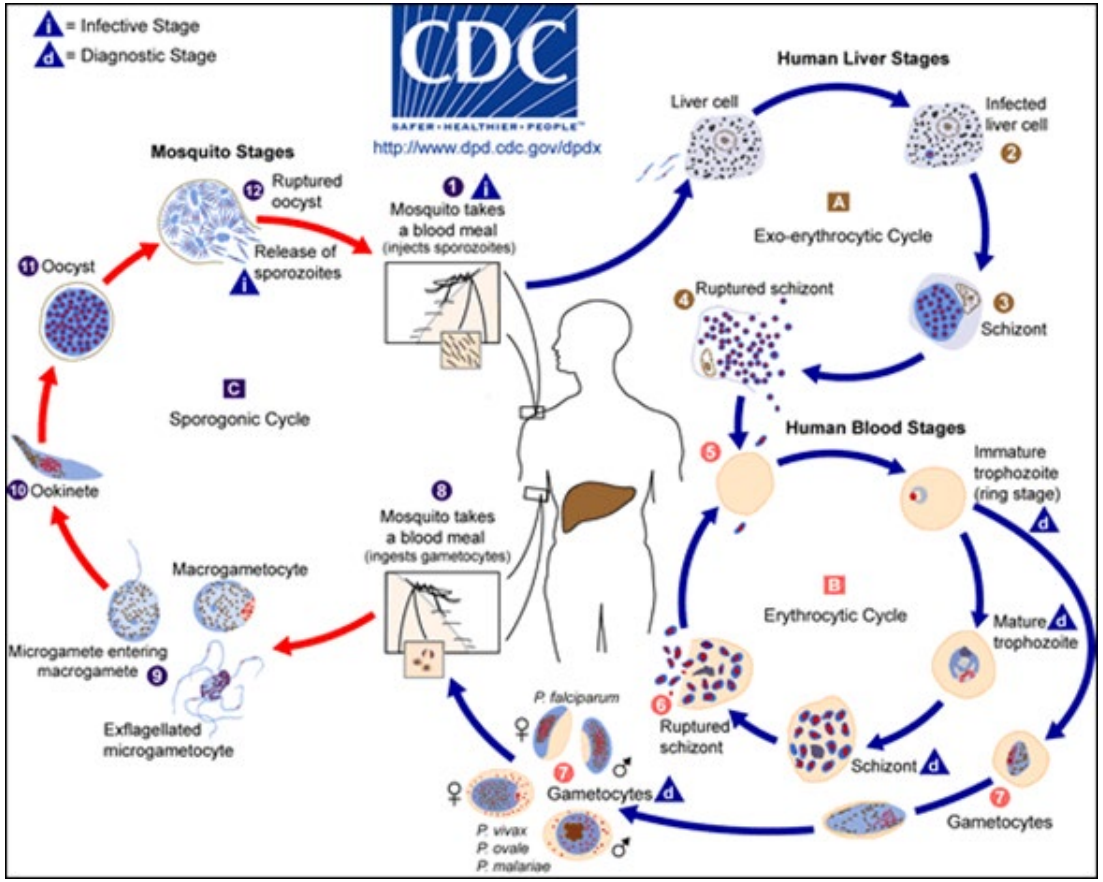
Glucose-6-phosphate dehydrogenase (G6PD) deficiency

- Episodic hemolytic anemia associated with drugs, toxins, foods (fava beans), and infections
  - Hemoglobinuria
  - Back pain
- Oxidative stress causes cross-linking of globin chains, which become denatured and form membrane-bound precipitates
  - Heinz bodies
  - Damage RBC membrane
- Macrophages in reticuloendothelial system remove Heinz bodies
  - Bite cells



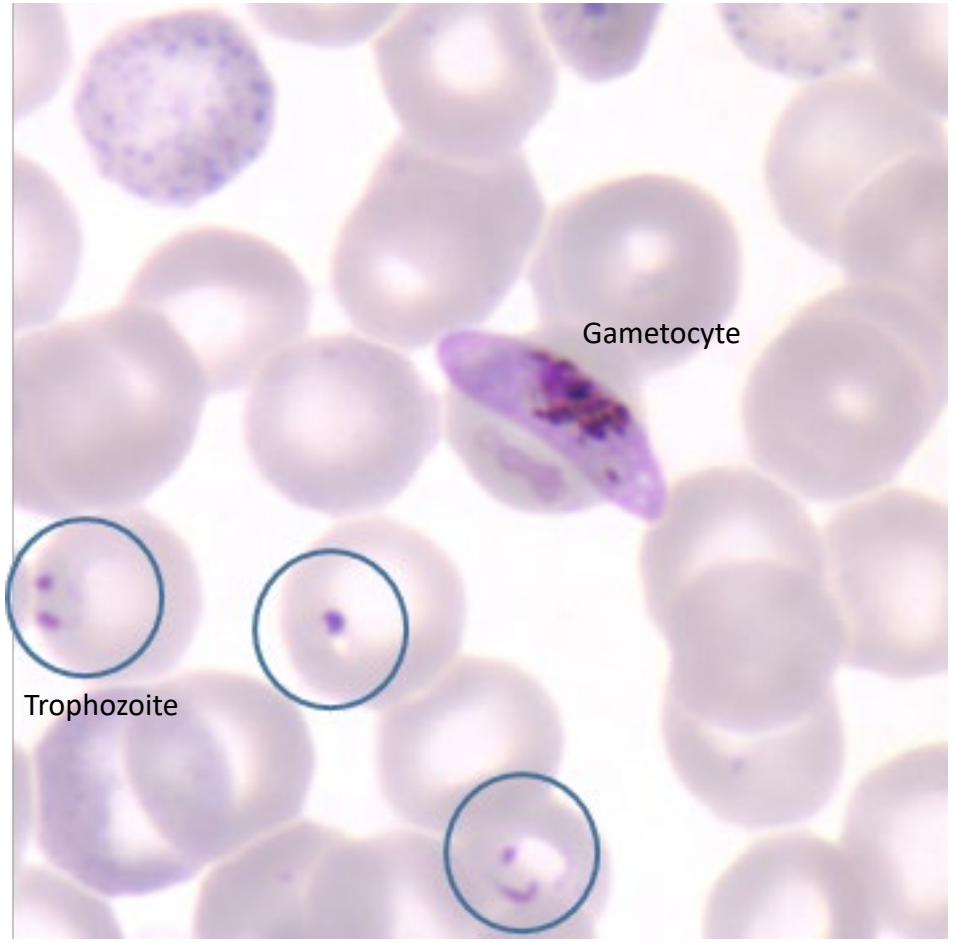


Malaria



- Major cause of hemolytic anemia worldwide
- Four types in humans
  - *Plasmodium falciparum*
  - *Plasmodium malariae*
  - *Plasmodium ovale*
  - *Plasmodium vivax*
- Clinical symptoms
  - Headache
  - Cyclic fevers
  - Joint pain
  - Hemolytic anemia
- Treatment
  - Quinines (primaquine)

Malaria: Peripheral blood smear



- Intracellular trophozoites
- Extracellular gametocytes

Hemolytic anemias

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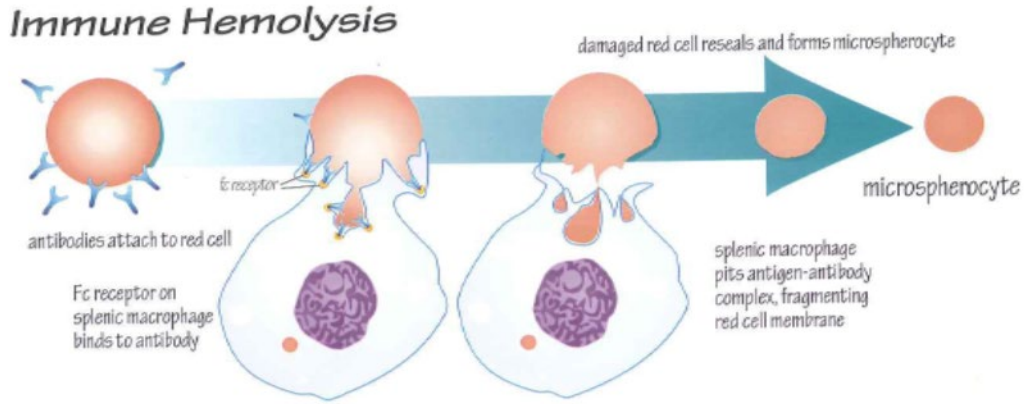
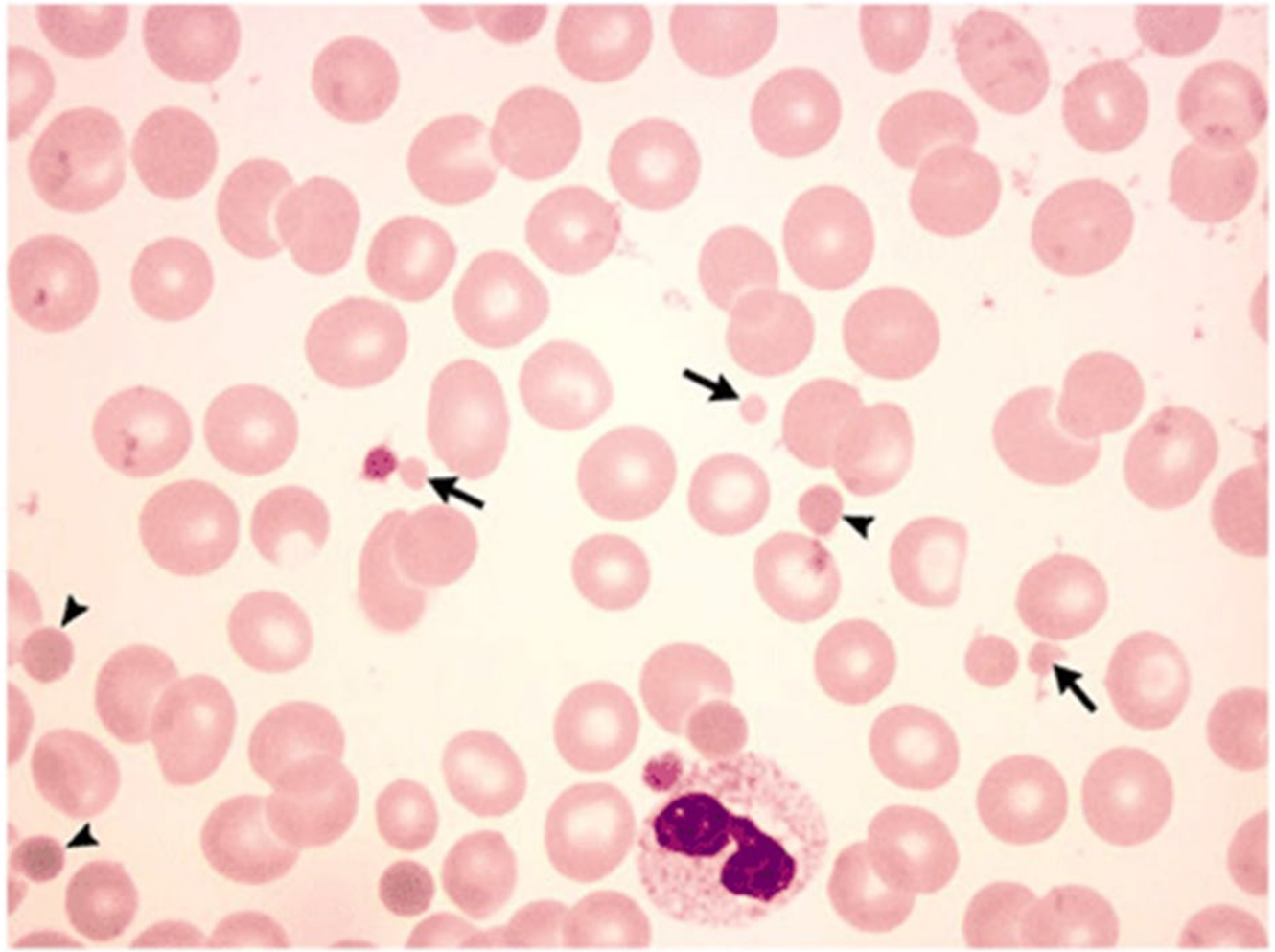
    - Hemoglobin SC
- Normal hemoglobin produced in insufficient quantities
  - Thalassemias

Autoimmune hemolytic anemia

- Phagocytosis of erythrocytes by macrophages within the reticuloendothelial system (spleen, liver, lymph nodes) and bone marrow
- Spleen breaks down heme into indirect/unconjugated bilirubin → gets to liver and is conjugated → excreted in urine and feces (dark)
- Peripheral blood: microspherocytes
- Direct antiglobulin test (DAT)/Coombs Test: positive

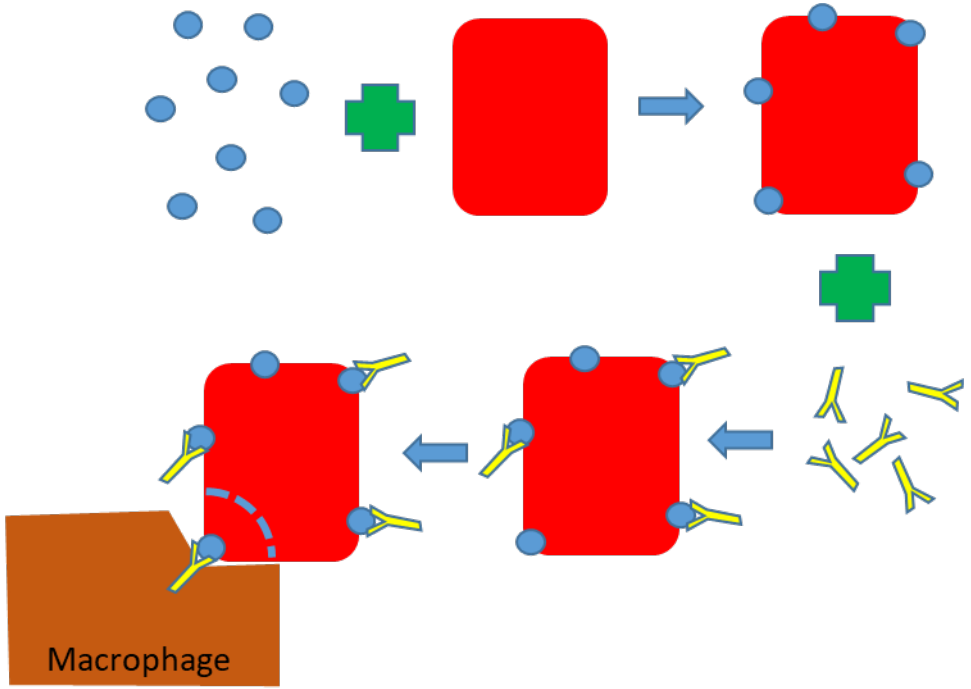


Autoimmune hemolytic anemia: microspherocytes



Warm autoimmune hemolytic anemia

- Anti-bodies (typically IgG) reacting to RBCs at room temperature
- Cells opsonized by autoantibodies and cleared by reticuloendothelial cells in the spleen (extravascular hemolysis)

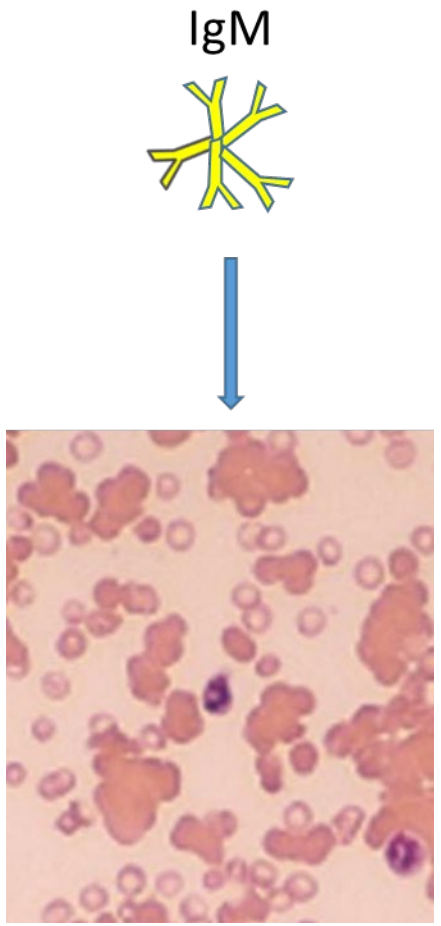


Warm autoimmune hemolytic anemia

- Causes
  - Idiopathic – most common
  - SLE
  - B-cell lymphomas (CLL)
  - Drug induced
    - Altered epitopes – alpha methyldopa
    - Drug acting as hapten – penicillin
    - Absorbed immune complexes – quinidine
- Peripheral Blood: Microspherocytes
- Clinical findings: Splenomegaly
- Positive DAT/Coombs

Cold autoimmune hemolytic anemia

- Also called “cold agglutinin disease”
- Low affinity IgM antibodies bind to RBCs at temperatures < 30°C (ears, hands, and toes)
  - IgM fixes complement
  - RBCs destroyed by further activation of complement (intravascular hemolysis) or C3b & C4b opsonization (extravascular hemolysis)
- Causes:
  - Primary: Idiopathic
  - Secondary: B-cell lymphomas, infection (Mycoplasma, infectious mononucleosis)
- Clinical findings: May have Reynaud phenomenon due to agglutination of RBCs
- Laboratory diagnosis: Positive DAT/Coombs



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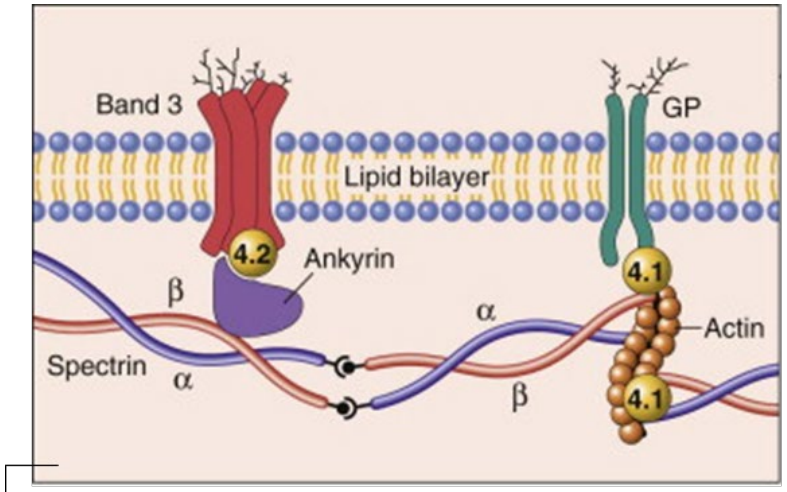
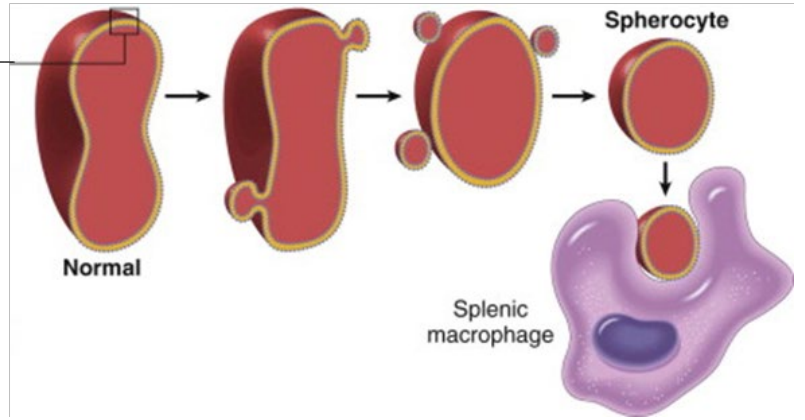
- Normal hemoglobin produced in insufficient quantities
  - Thalassemias

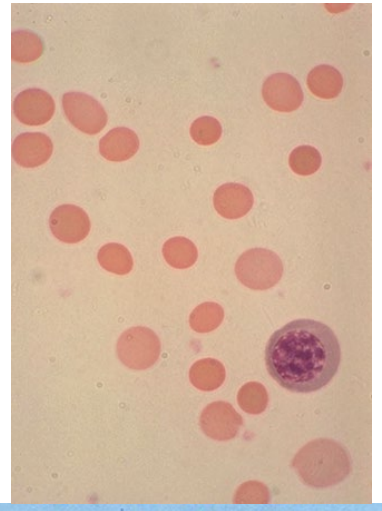
Hereditary spherocytosis

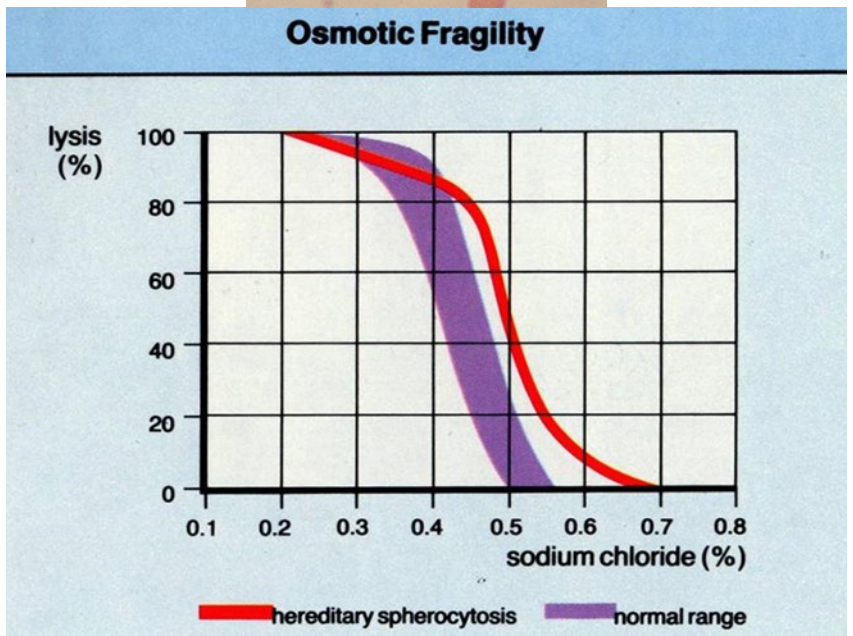
- Autosomal dominant
- Defects in RBC cytoskeletal proteins
  - Ankyrin
  - Spectrin
- Clinical signs and symptoms
  - Anemia, splenomegaly, jaundice, cholelithiasis
- Stable course punctuated by:
  - Hemolytic crises (infection)
  - Aplastic crises (parvovirus B19)





Hereditary spherocytosis

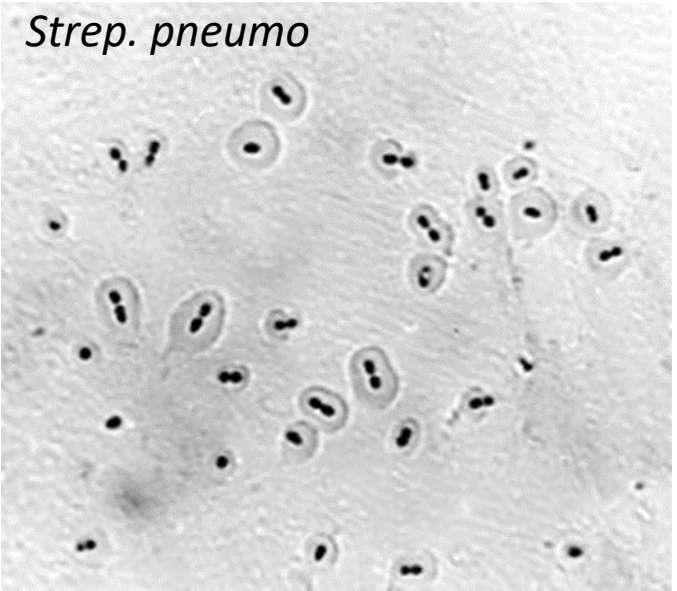


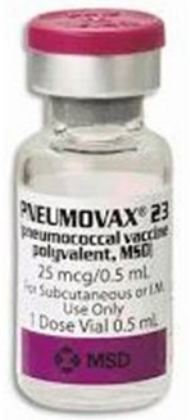


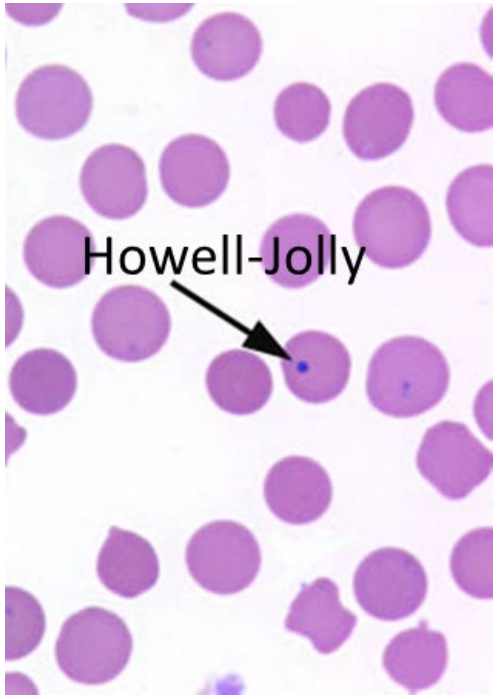
- Peripheral smear
  - Spherocytes
    - No central pallor
    - ↑ MCHC
- Laboratory diagnosis: osmotic fragility test
  - Spherocytes are more prone to rupture in hypotonic solutions

Hereditary spherocytosis

- Treatment: splenectomy
  - Howell-Jolly bodies
  - Prone to infections with encapsulated bacteria
    - Anti-pneumococcal vaccine

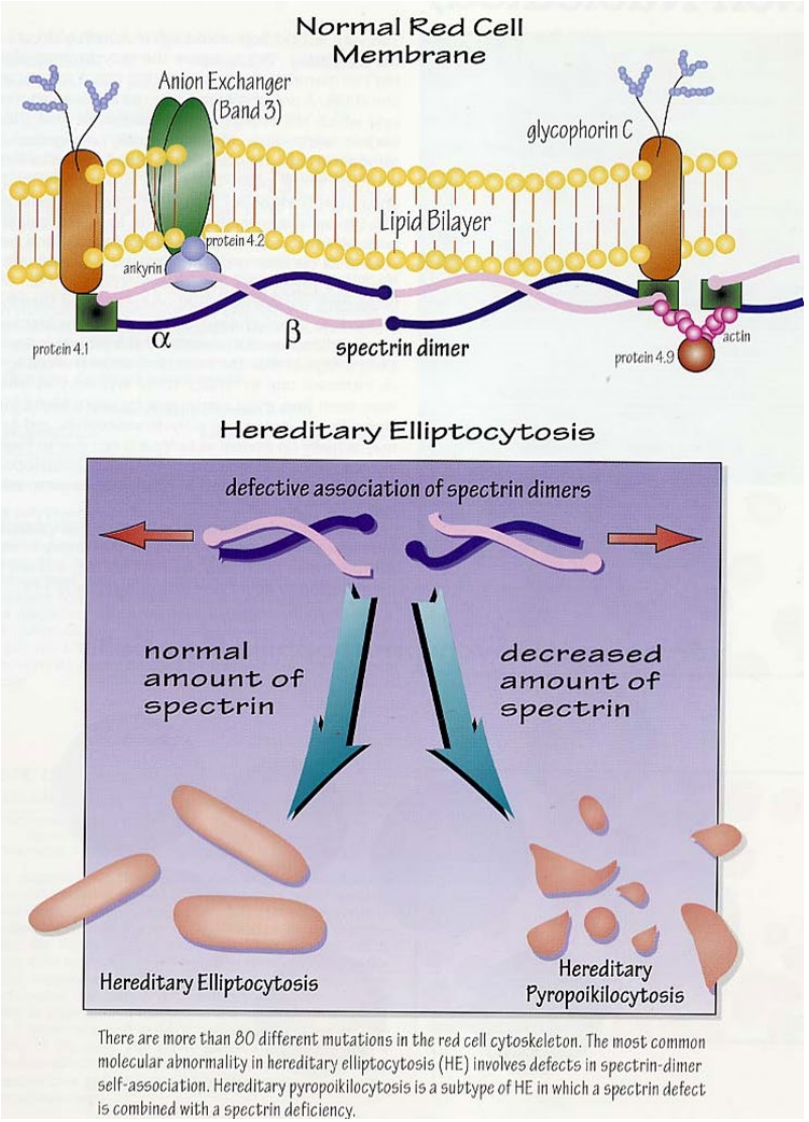




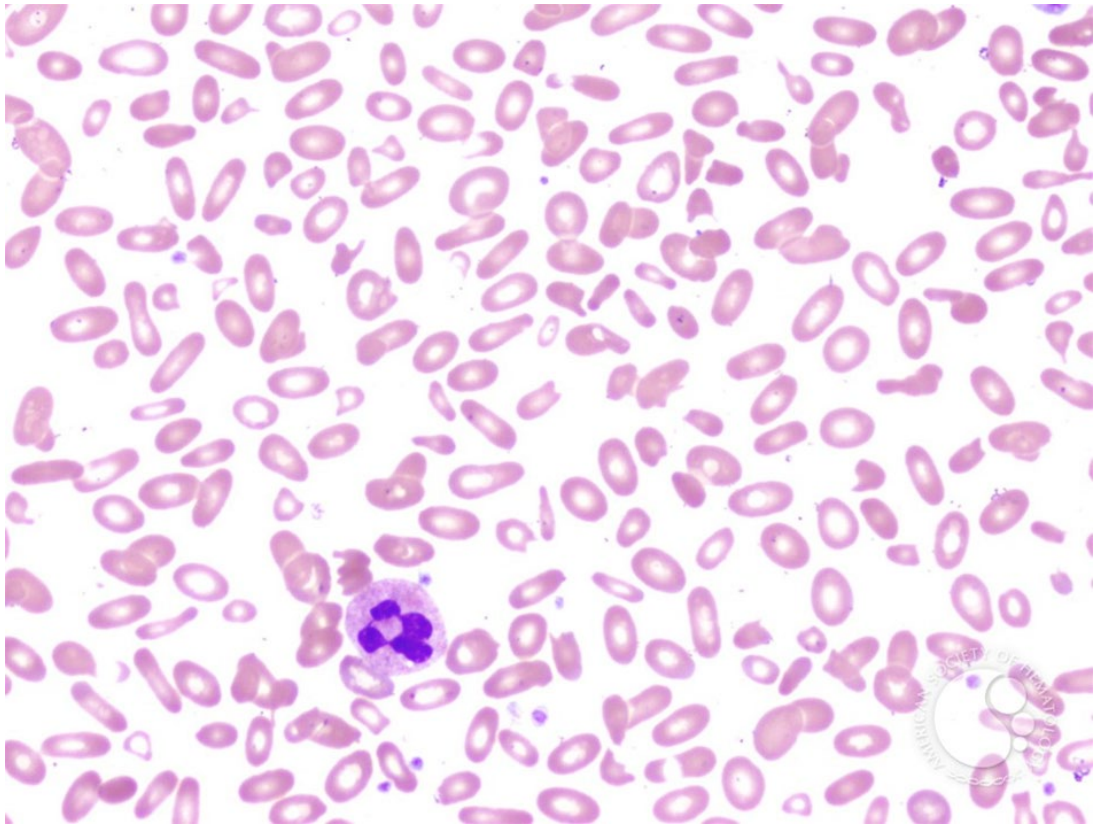


Hereditary elliptocytosis

- Defects in spectrin
  - Weakening of membrane skeleton
  - Defective association of proteins holding skeletons together
- Autosomal dominant inheritance
  - 3-5/10,000 individuals
- Hemolytic anemia of variable severity



Hereditary pyropoikilocytosis



- Spectrin defect + deficiency
- Peripheral blood smear:
  - Marked poikilocytosis
  - Unusual thermal sensitivity

Questions?