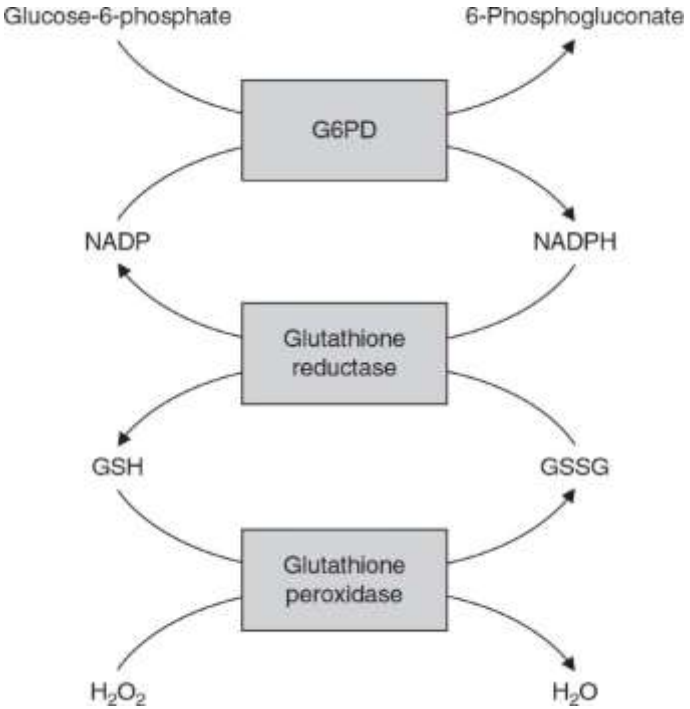
Red Cell Disorders

Hemolytic anemias

Ghadeer AlMuhaisen, M.D.
Consultant hematopathologist
Mutah University

Glucose-6-Phosphate Dehydrogenase Deficiency

- RBCs are constantly exposed to both endogenous & exogenous oxidants.
- Normally inactivated by reduced glutathione (GSH)
- Abnormalities affecting enzymes responsible for the synthesis of GSH leave RBCs vulnerable to oxidative injury and hemolysis.
- The most common of these conditions is glucose-6-phosphate dehydrogenase (G6PD) deficiency.



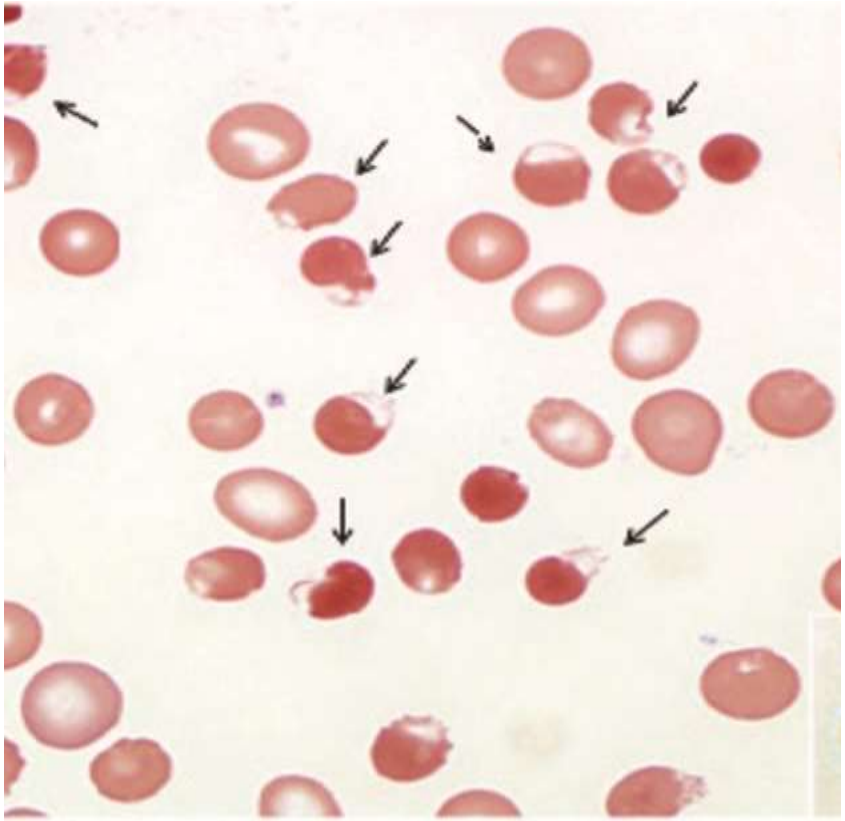
Glucose-6-Phosphate Dehydrogenase Deficiency

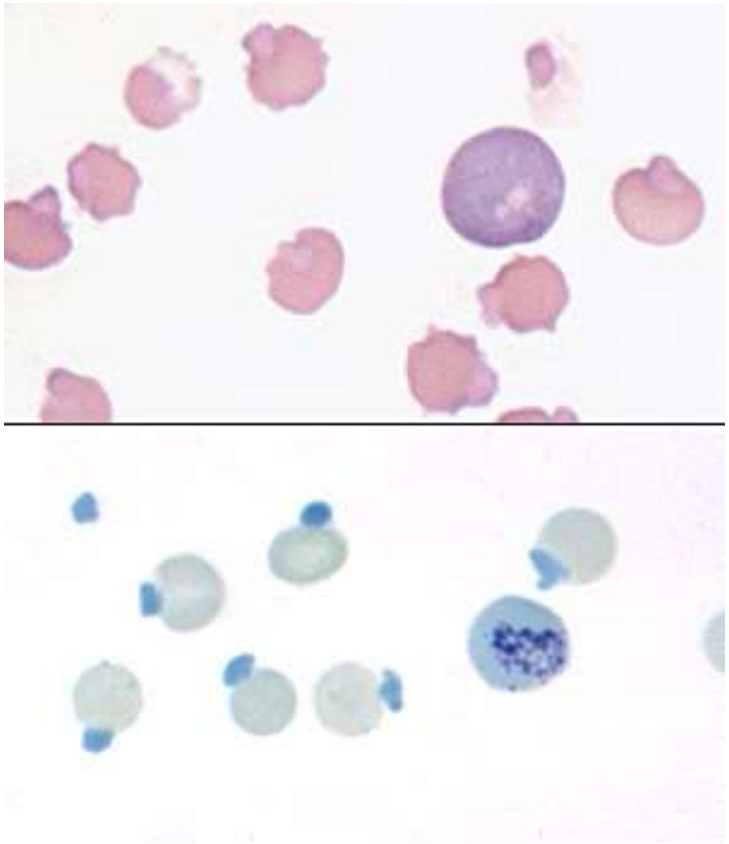
- G6PD gene is on the X chromosome.
- Males more vulnerable than female
- So many variants of G6PD, only few associated with disease:
  - A− variant, 10% of black males in the US. A normal enzymatic activity but a decreased half-life → older G6PD A− red cells become progressively deficient in enzyme activity and GSH (more sensitive)→ coz RBCs do not synthesize proteins.
  - G6PD Mediterranean, mainly in the Middle East, the enzyme deficiency and the hemolysis that occur on exposure to oxidants are more severe.

- **Patients are asymptomatic and have transient episodes of intravascular hemolysis caused by exposure to an environmental that produces oxidant stress.**
    1. Drugs: include antimalarials (e.g., primaquine), sulfonamides, nitrofurantoin, phenacetin, aspirin (in large doses), and vitamin K derivatives.
    2. Infection (more common) → induce phagocytes to generate oxidants as part of the host response.
    3. Favism
- Hemolysis typically 2-3 days after exposure with variable severity
- Regeneration of GSH is impaired in G6PD-def.cells → oxidants are free to “attack” other red cell components including globin chains.

G6PD deficiency

- Oxidized hemoglobin denatures→ precipitates intracellular inclusions called **Heinz bodies.**
- → damage the RBC membrane → intravascular hemolysis
- Lesser damaged cells lose their deformability and splenic phagocytes attempt to “pluck out” the Heinz bodies, creating **bite cells.**
- → trapped on recirculation to the spleen & destroyed by phagocytes (extravascular hemolysis)

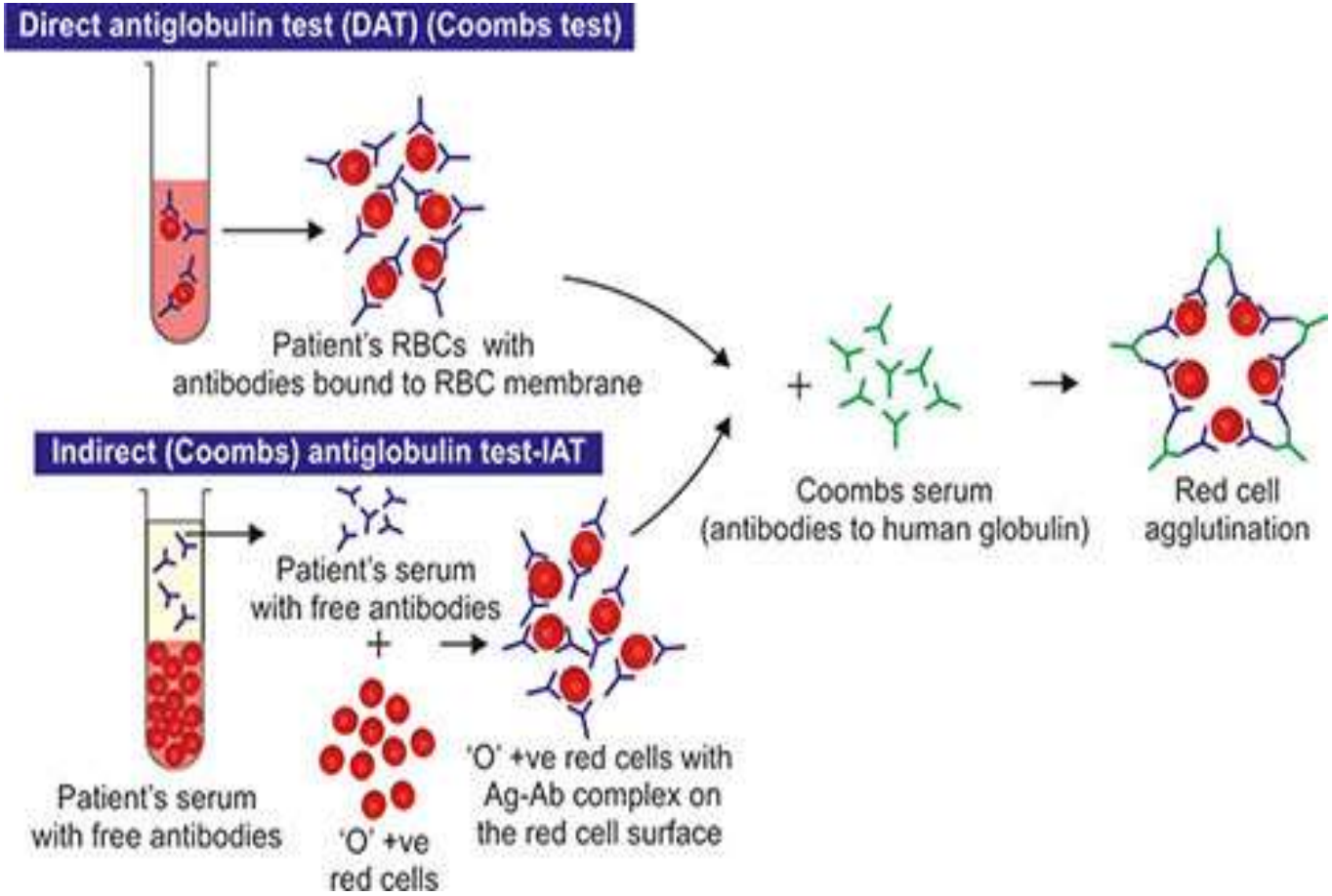


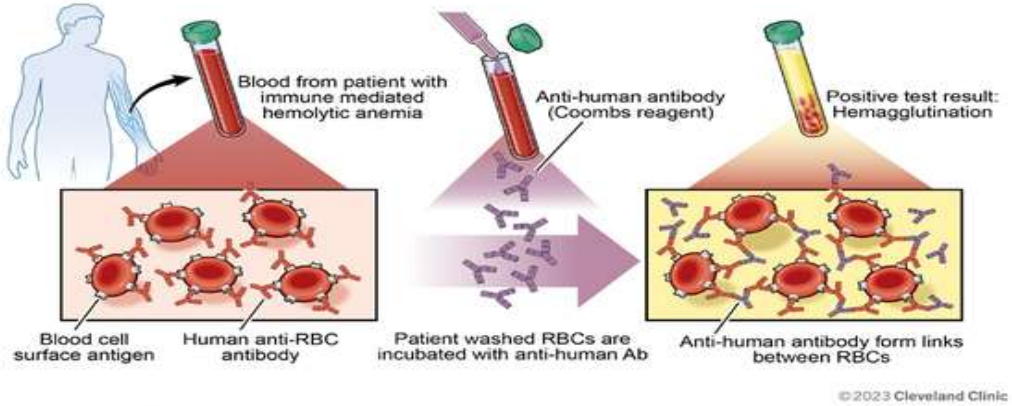


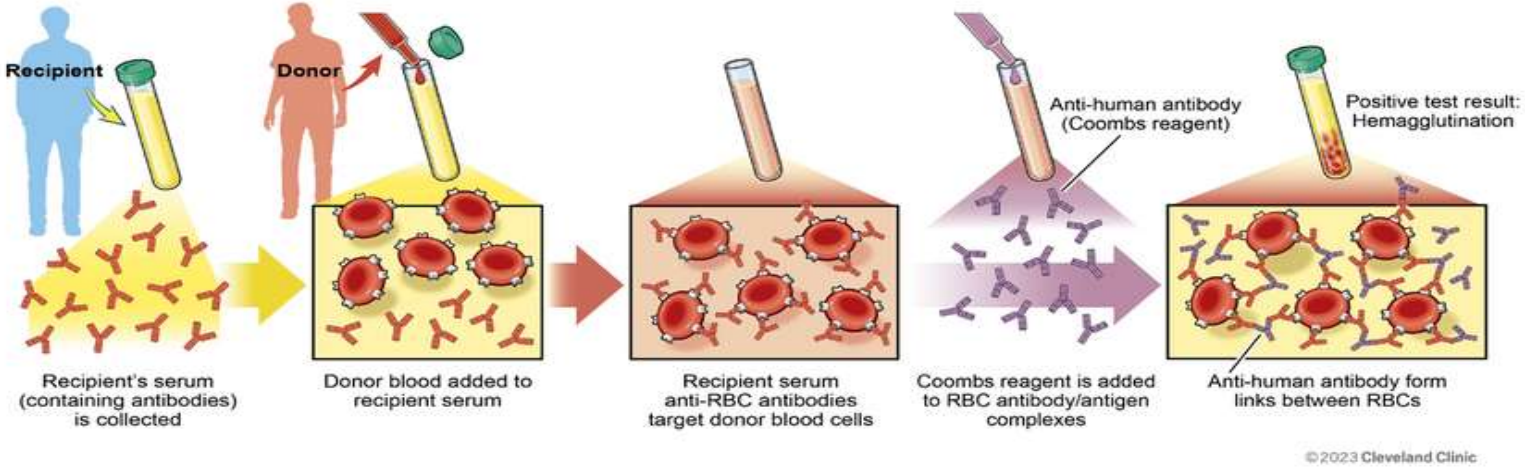
https://www.klimud.org/public/atlas

Immunohemolytic Anemia

- Caused by antibodies that bind to antigen on red cell membranes.
- These antibodies may arise:
  1. Spontaneously, or
  2. induced by exogenous agents: drugs or chemicals.
- Uncommon and is classified based on:
  1. the nature of the antibody
  2. the presence of predisposing conditions
- The diagnosis depends on the detection of antibodies and/or complement on red cells → the *direct Coombs test*


Direct antiglobulin test (DAT) (Coombs test)
Patient's RBCs with antibodies bound to RBC membrane
Indirect (Coombs) antiglobulin test-IAT
Patient's serum with free antibodies
Patient's serum with free antibodies
'O' +ve red cells
'O' +ve red cells with Ag-Ab complex on the red cell surface
Coombs serum (antibodies to human globulin)
Red cell agglutination


Blood from patient with immune mediated hemolytic anemia
Anti-human antibody (Coombs reagent)
Positive test result: Hemagglutination
Blood cell surface antigen
Human anti-RBC antibody
Patient washed RBCs are incubated with anti-human Ab
Anti-human antibody form links between RBCs
©2023 Cleveland Clinic


Recipient
Donor
Anti-human antibody (Coombs reagent)
Positive test result: Hemagglutination
Recipient's serum (containing antibodies) is collected
Donor blood added to recipient serum
Recipient serum anti-RBC antibodies target donor blood cells
Coombs reagent is added to RBC antibody/antigen complexes
Anti-human antibody form links between RBCs
©2023 Cleveland Clinic

Immunohemolytic Anemia

Warm Antibody Type

Primary (idiopathic)

Secondary: B cell neoplasms (e.g., chronic lymphocytic leukemia), autoimmune disorders (e.g., systemic lupus erythematosus), drugs (e.g., α-methyldopa, penicillin, quinidine)

Cold Antibody Type

Acute: Mycoplasma infection, infectious mononucleosis

Chronic: idiopathic, B cell lymphoid neoplasms (e.g., lymphoplasmacytic lymphoma)

Warm Antibody Immunohemolytic Anemia

- **Binding of high-affinity autoantibodies to red cells → removed from the circulation by phagocytes in the spleen and elsewhere.**
- **PB:** Erythrophagocytosis, spherocytes *(*incomplete consumption (nibbling) of antibody-coated RBCs by macrophages)
- Caused by immunoglobulin G (IgG) or (rarely)IgA →active at 37°C.

  - 60% idiopathic (primary)
  - 25% secondary to an immunologic disorder (e.g., systemic lupus erythematosus), B cells neoplasms, or drugs.
- Patients have chronic mild anemia and moderate splenomegaly and require no treatment.

Cold Antibody Immunohemolytic Anemia

- **Binding by low-affinity IgM antibodies to red cell membranes only at temperatures below 30°C.**
- **Occur in distal parts of the body (e.g., ears, hands, and toes) in cold weather.**
- IgM fixes complement → latter steps of the complement cascade occur

inefficiently due to lower temp. (< 37°C) → most cells are not lysed intravascularly.

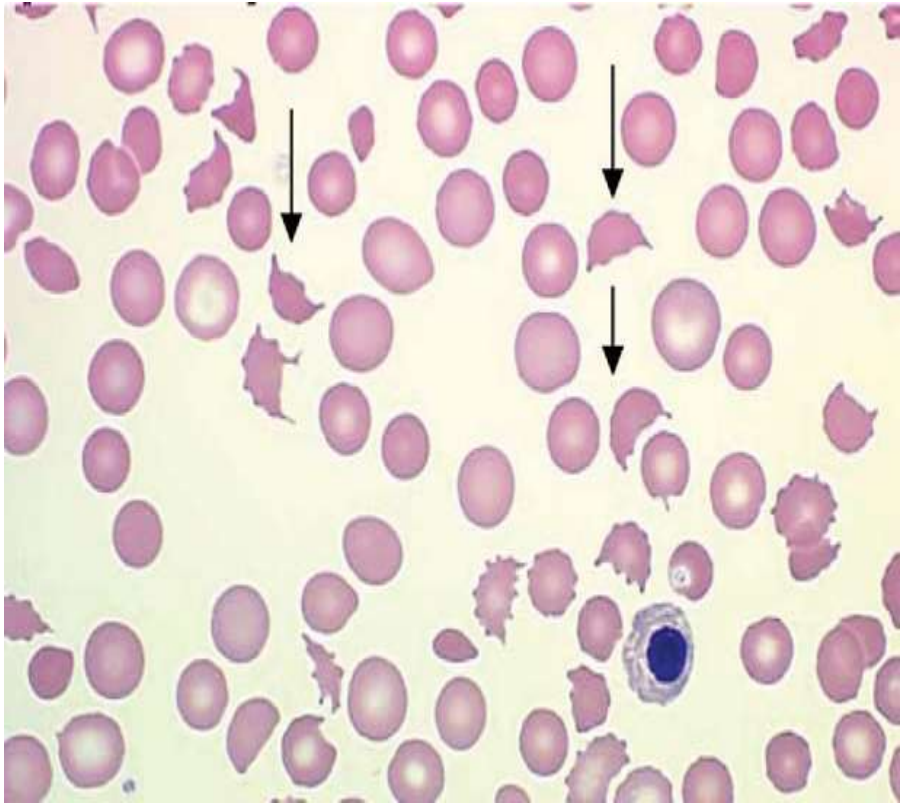
- But cells are phagocytosed by macrophages mainly in the spleen and liver→ extravascular.
- IgM also crosslinks red cells and causes them to clump (*agglutinate*)→ Sludging of blood in capillaries because of agglutination → *Raynaud phenomenon* in the extremities of affected individuals.

Hemolytic Anemia Resulting From Mechanical Trauma to Red Cells

- Hemolysis of red cells due to their exposure to abnormal mechanical forces.
  1. Traumatic hemolysis: defective cardiac valve prostheses→ create sufficiently turbulent blood flow to shear red cells.
  2. Microangiopathic hemolytic anemia: a pathologic states in which small vessels become partially obstructed (narrowed) by lesions → mechanical damage RBC, e.g.: disseminated intravascular coagulation (DIC), malignant hypertension, systemic lupuserythematosus, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated cancer.
- PB: Mechanical fragmentation of red cells (schistocytosis). Wide variation in shape (poikilocytosis).

Microangiopathic hemolytic anemia

Schistocytosis: leads to the appearance of characteristic “burr cells,” “helmet cells,” and “triangle cells” in peripheral blood smears.



Thanks!