Hemolytic Anemias Part II

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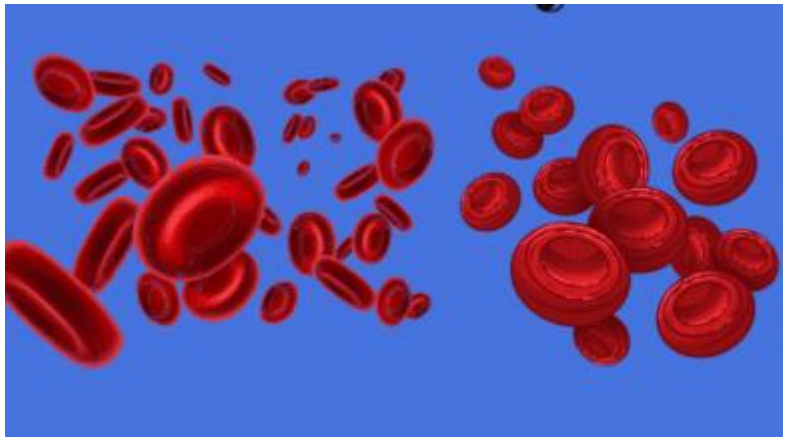


Hemolytic Anemia
Extrinsic RBC Defects

Nonimmune Causes

- Microangiopathic Hemolytic Anemia
- Macroangiopathic Hemolytic Anemia
- Infection
- Chemical/Drugs
- Venoms
- Other physical trauma

Immune Causes

- Autoimmune Hemolytic Anemia (AIHA)
- Alloimmune Hemolytic Anemia
- Drug-induced Hemolytic Anemia

Microangiopathic Hemolytic Anemia

- A group of potentially life-threatening conditions characterized by the presence of fragmentation and thrombocytopenia.
- Intravascular hemolysis
- Causes of fragmentation hemolysis include:
  - Thrombotic thrombocytopenic Purpura
  - Hemolytic uremic syndrome
  - Disseminated intravascular coagulation
  - HELLP(hemolysis, elevated liver enzymes, low platelet count syndrome)

Microangiopathic Hemolytic Anemia

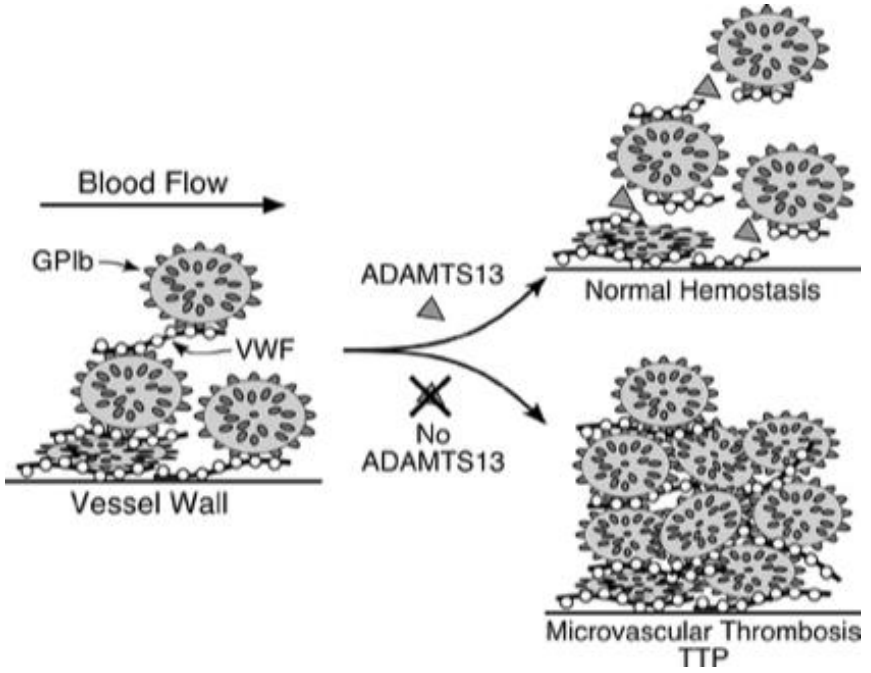
- Laboratory findings:
  - Low hemoglobin
  - Thrombocytopenia
  - RBC fragments and micro spherocytes
  - Increased reticulocytes
  - Increased unconjugated bilirubin
  - Increased serum LD
  - Increased urine urobilinogen
  - Hemoglobulinemia and hemoglobinuria
  - Low haptoglobin

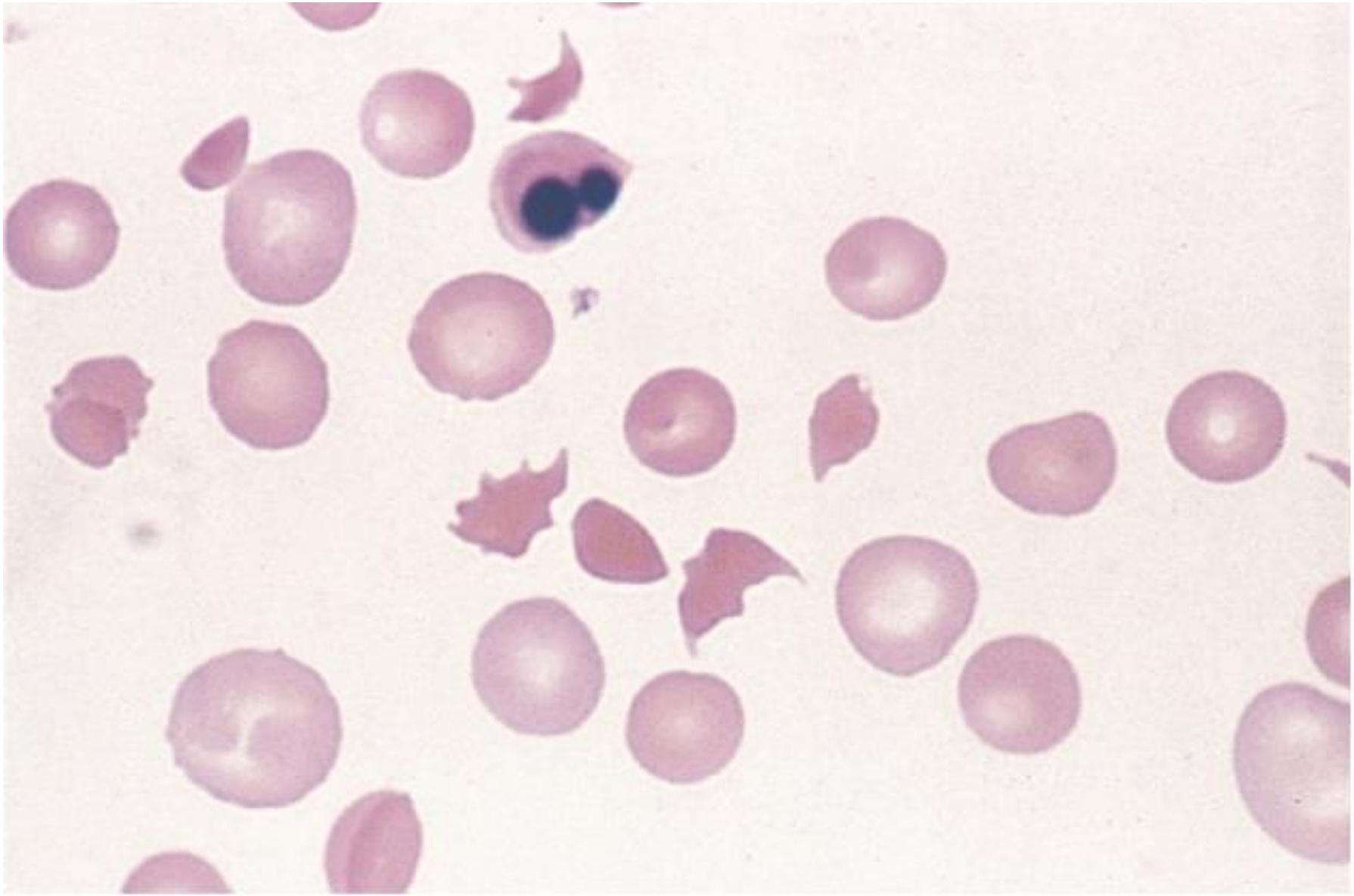
Thrombotic thrombocytopenic Purpura(TTP)

- TTP is found predominantly in adults and characterized by severe thrombocytopenia and acute microangiopathic hemolytic anemia.
- Markedly increased serum LD
- Fever
- Neurologic dysfunction
- Renal failure
- Often associated with preceding viral infection
- Some other causes:
  - stem cell transplantation, disseminated cancer, pregnancy, and certain drugs.

Thrombotic thrombocytopenic Purpura

- TTP is due to autoimmune antibodies to the vWF cleaving protease ADAMTS- 13 causing a severe functional deficiency.
- Lab findings:
  - Low hemoglobin, critically low platelets, and presence of NRBCs
  - RBC fragments on the blood smear, polychromasia,
  - BM erythroid hyperplasia.
  - Hemoglobinuria in extensive intravascular hemolysis.
  - Normal coagulation results






THIS EXPLAINS IT ALL!

Hemolytic-Uremic Syndrome (HUS)

- It is classically characterized by the triad of
  - thrombocytopenia
  - microangiopathic hemolytic anemia
  - acute kidney injury.
- Infection, typically with Shiga toxin–producing bacteria
  - Escherichia coli O157:H7 or viral or bacterial (Shigella) infection
- Often associated with children
- Evidence of hemolysis
- Normal ADAMTS13 activity

Disseminated intravascular coagulation(DIC)

- DIC is the systemic activation of the coagulation cascade and characterized by abnormal coagulation studies
  - Prolonged prothrombin time and partial thromboplastin time
  - Elevated D dimer
  - Decreased fibrinogen
  - Elevated fibrin degradation products
- Presence of schistocytes in 50% of DIC cases, and thrombocytopenia
- Patient with DIC usually has a very serious underlying illness like septic shock, trauma, malignancy etc.

HELLP Syndrome

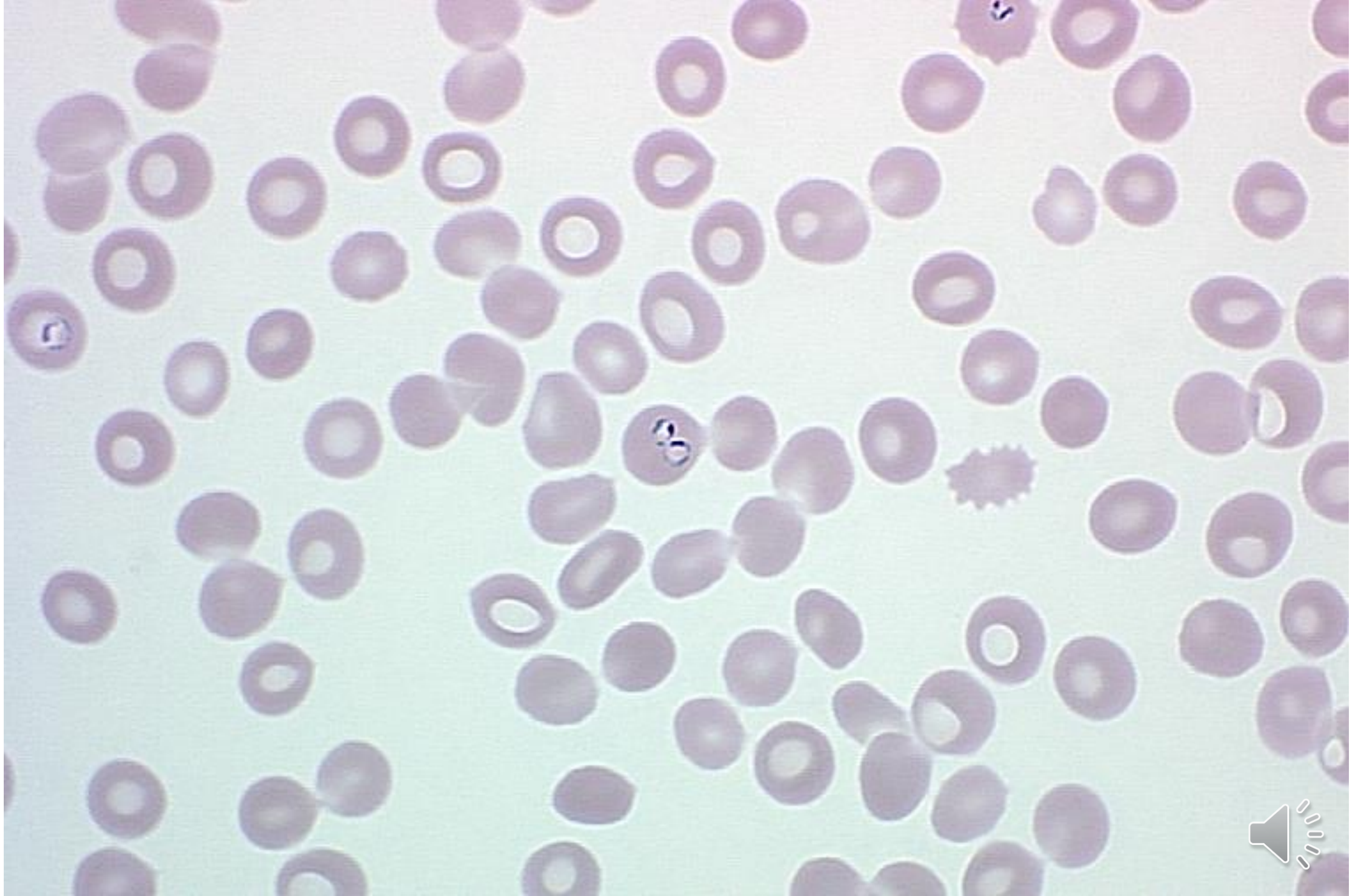
- It is characterized by hemolysis of red blood cells, elevated liver enzymes and low platelet count occurring in pregnancy and severe preeclampsia.

Macroangiopathic Hemolytic Anemia

- Prosthetic cardiac valves
  - Hemolysis occur as red cell pass through and around implanted devices
  - Peripheral blood smear shows fragments, normal platelet count
  - Hemolysis occurs is often compensated by the bone marrow
- Exercise- Induced
  - Caused by traumatic destruction of the red cells in strenuous and sustained physical activity such as marching or running

Hemolytic Anemia
Extrinsic Defects- Infectious Agents

- Parasites: Intracellular infections
- Malaria
  - Carried by mosquito
  - Release of the parasite from the cell causes cell lysis
  - Species of malaria include:
    - Plasmodium vivax
    - P. falciparum
    - P. malariae
    - P. ovale
  - Peripheral blood smear will reveal intracellular parasites
    - Morphology depends on the species



Hemolytic Anemia
Extrinsic Defects- Infectious Agents

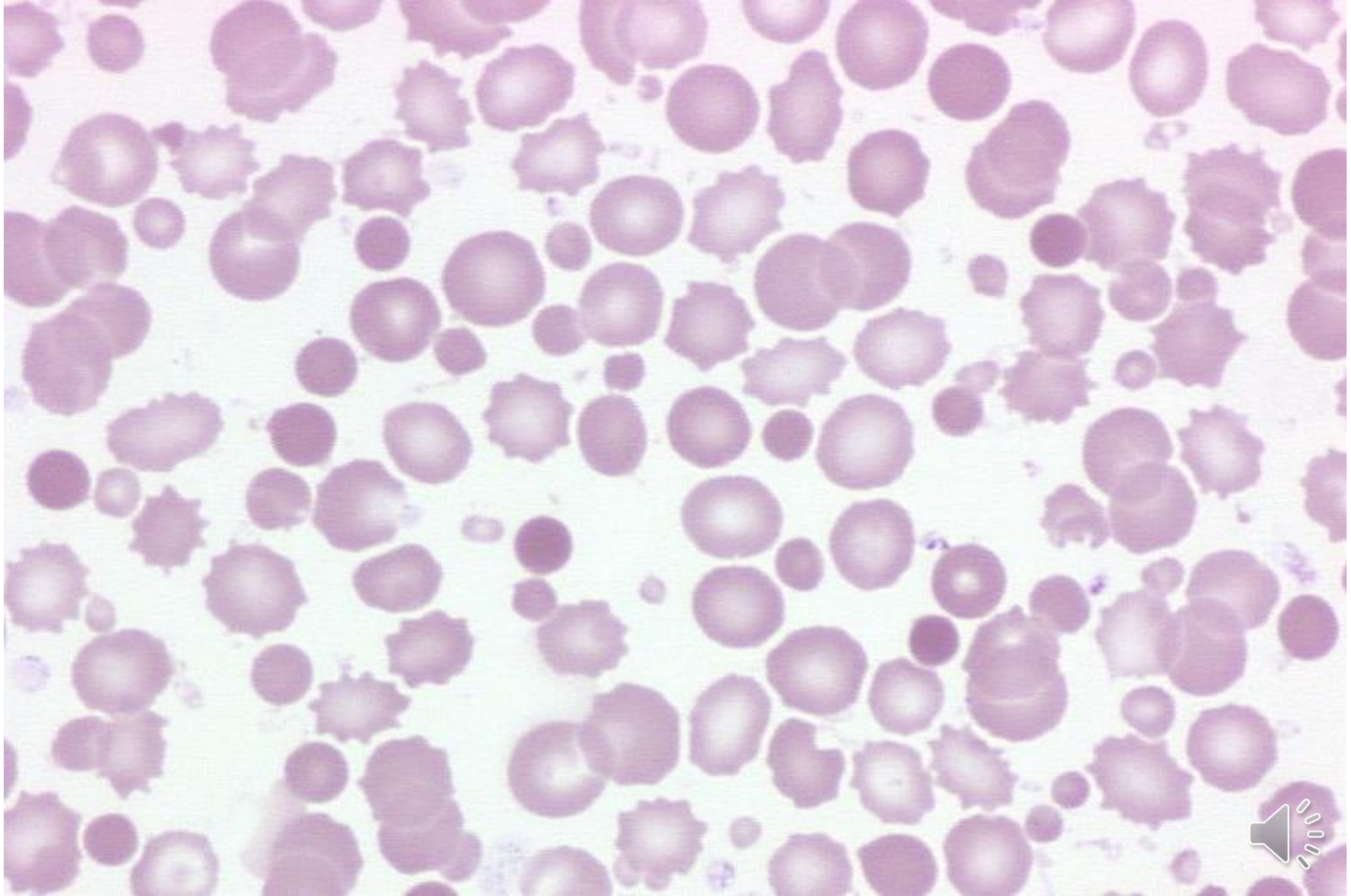
- Babesiosis
  - Tick-borne
  - Peripheral blood smear will reveal intracellular parasites
- Bartonellosis - transmitted by sand fly
- Clostridium perfringens
  - Exotoxin production affects integrity of host cell membrane

Hemolytic Anemia
Extrinsic Defects- Red Blood Cell Injury

- Drugs: dose-dependent. Hemoglobin denaturation and Heinz body formation
- Arsine gas inhalation
- Acute lead poisoning
- Bee, wasp, spider, scorpion venoms

Hemolytic Anemia
Extrinsic Defects- Thermal Injury

- Microspherocytes prominent
- Abnormal RBC rapidly cleared
- Usually present with extensive skin burns.
- Degree of hemolysis depends on extent of burn.



Hemolytic Anemia
Extrinsic RBC Defects-Immune Causes

- Classification
  - Autoimmune Hemolytic Anemia (AIHA)
  - Alloimmune Hemolytic Anemia
  - Drug-induced Hemolytic Anemia

Autoimmune Hemolytic Anemia (AIHA)

- It is defined as a group of hemolytic anemias that results from the development of autoantibodies
- They are directed against the antigen on the surface of the patient's own cell
- Can affect both children and adults
- The anemia can be mild or severe and the onset can be acute or gradual
- Characterized by a positive direct antiglobulin test (DAT)
- Distinguishing AIHAs (cold, warm, drug etc.) is of utmost important

AIHA- Subtypes

1. Warm Autoimmune Hemolytic Anemia
2. Cold Autoimmune Hemolytic Anemia
3. Paroxysmal Cold Hemoglobinuria (PCH)
4. Mixed –type Autoimmune Hemolytic Anemia

Warm Autoimmune Hemolytic Anemia

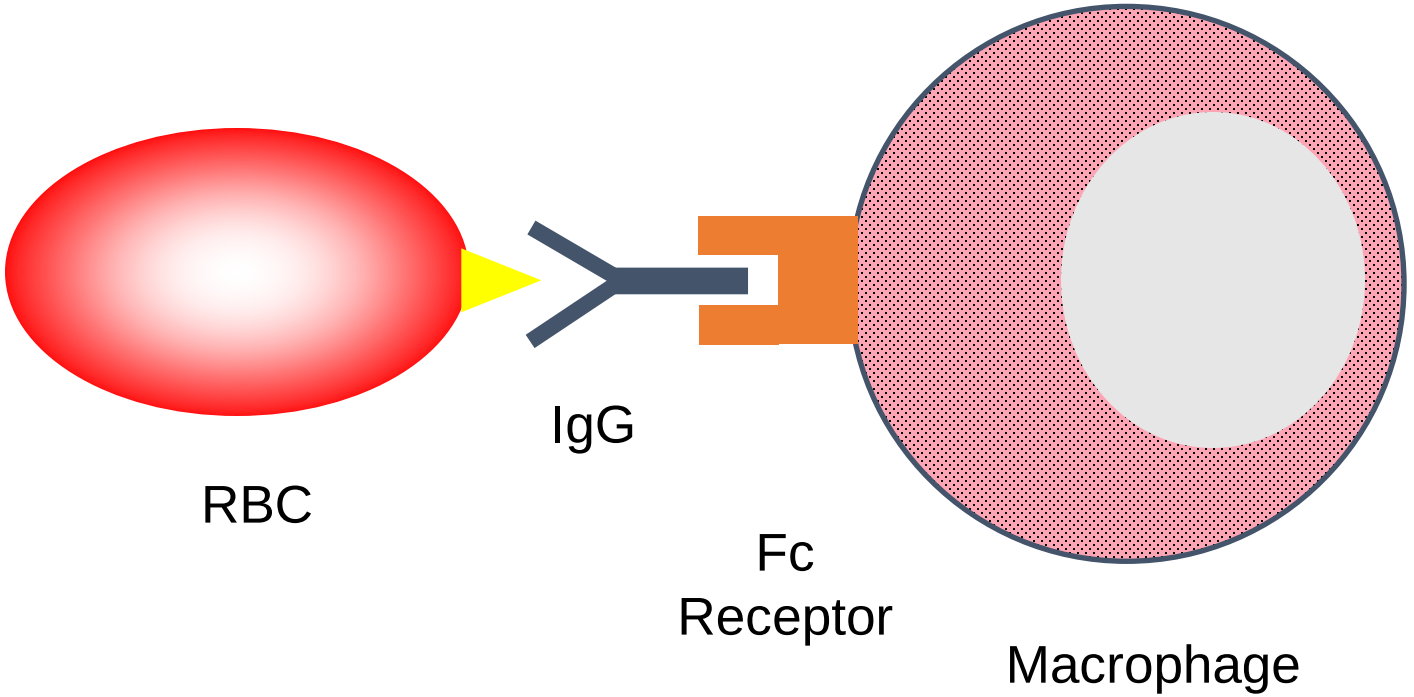
- Most common autoimmune hemolytic anemia
  - Account for 70% cases
- Can occur at all age groups
- IgG autoantibody, binds to membrane of erythrocyte at ~37°C
- Causes primarily extravascular hemolysis
- Mild to severe anemia
- Splenomegaly

Warm Autoimmune Hemolytic Anemia

- Causes:
- Primary (idiopathic)
- Secondary causes (70 % cases):
    - Lymphoid neoplasm: CLL, Lymphoma, Myeloma
    - Solid tumors: Lung, Kidney, Thymoma
    - SLE (Systemic lupus erythematosus)
    - Drugs: Penicillin, Quinine , Chloroquine

Warm Autoimmune Hemolytic Anemia

Pathophysiology

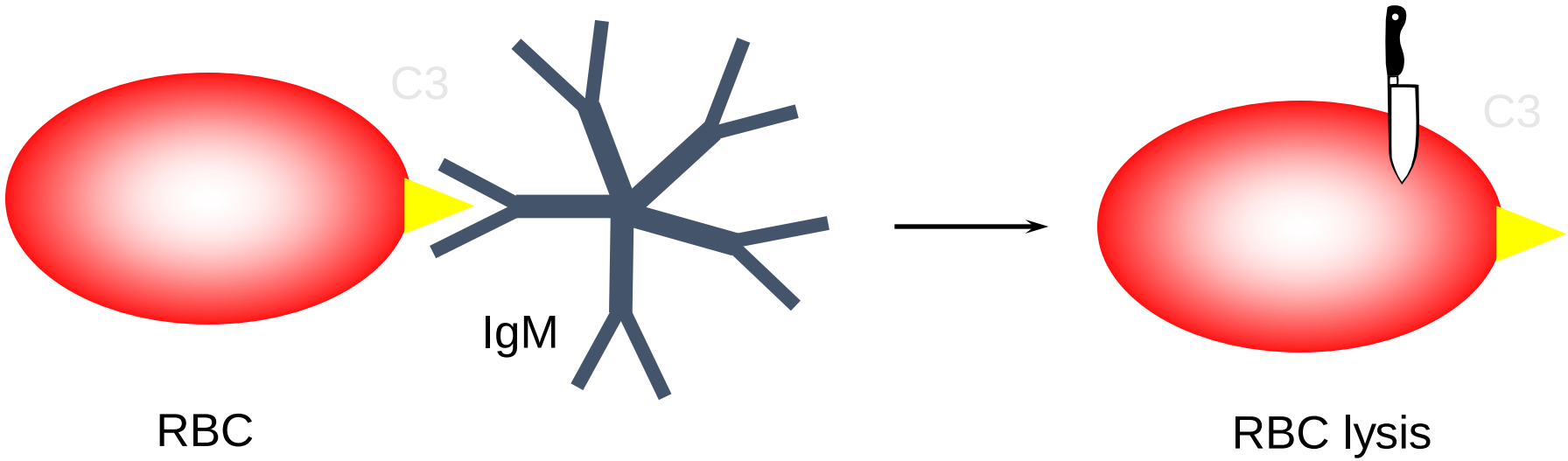


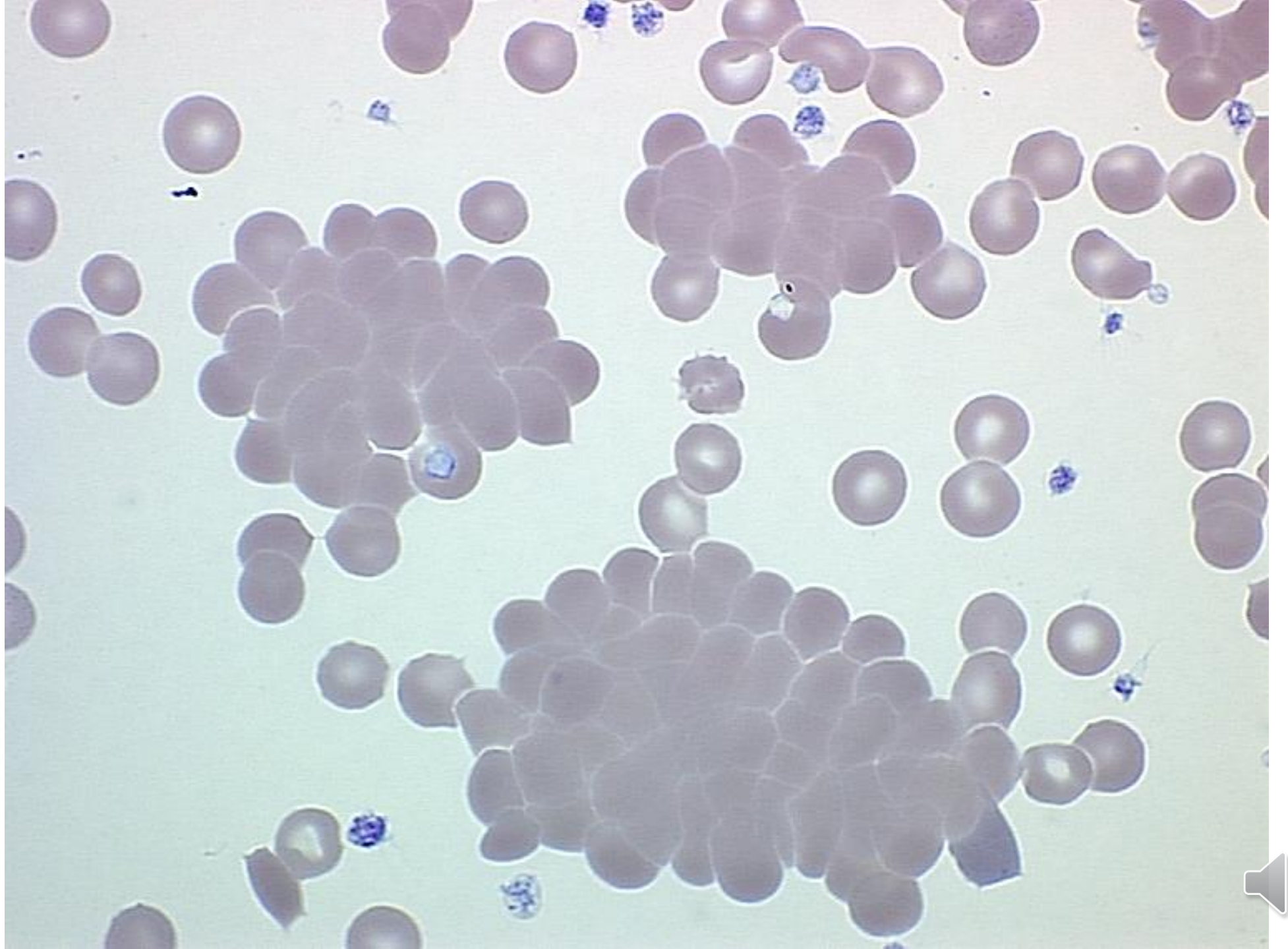
Cold Autoimmune Hemolytic Anemia

- IgM autoantibody that binds preferentially to erythrocyte membranes at 4°C
- Causes complement activation and intravascular hemolysis
- Antigen specificity: often I or i
- Causes:
  - Idiopathic (elderly)
  - Infectious
    - Mycoplasma pneumonia
    - Mononucelosis

Cold Autoimmune Hemolytic Anemia

Pathophysiology

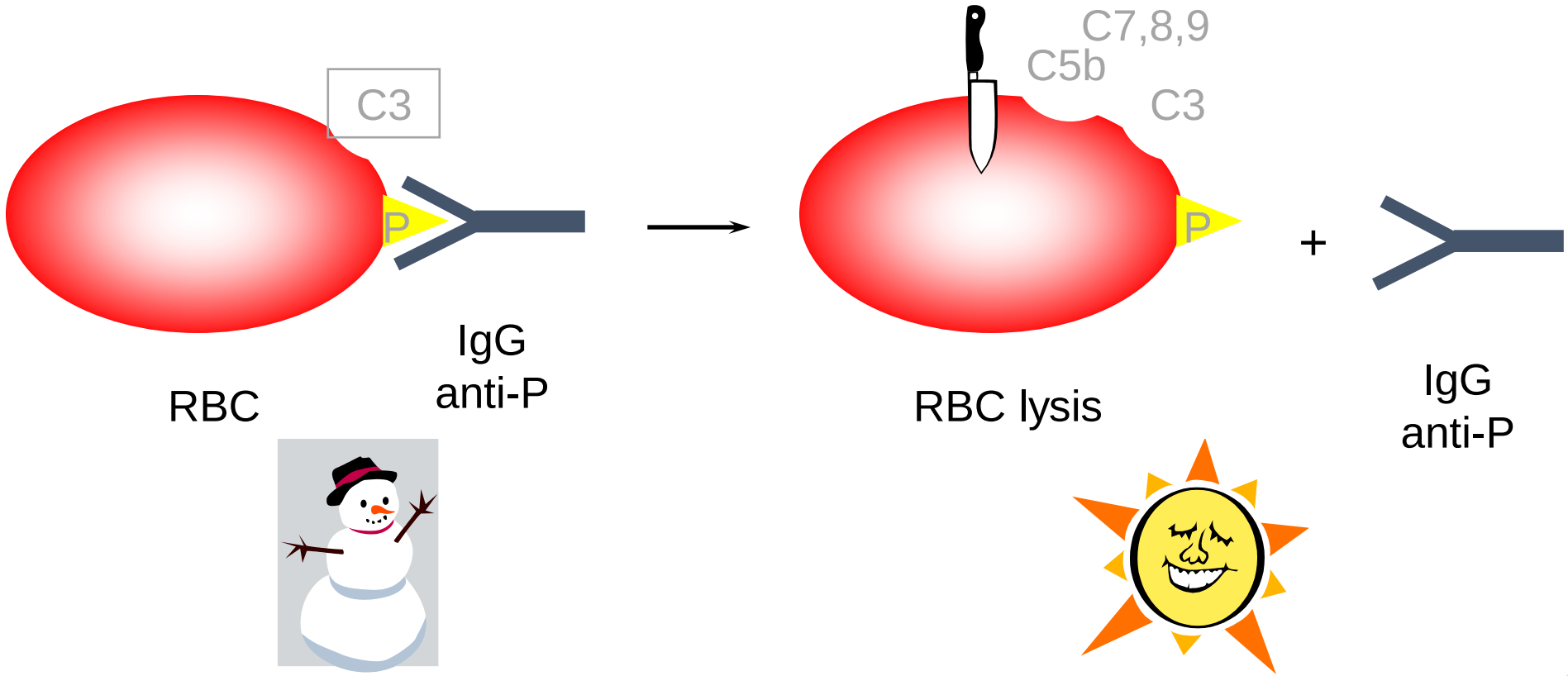




Paroxysmal Cold Hemoglobinuria (PCH)

- anti-P autoantibody, also known as *Donath-Landsteiner antibody*
- Very rare AIHA
  - More common in children
- When cold, binding of autoantibodies to RBC membranes and fixes complement
- When warmed, causes intravascular hemolysis
- Causes:
  - Viral infections
    - Upper respiratory tract infection
  - Syphilis

Paroxysmal Cold Hemoglobinuria
Pathophysiology



AIHA: Clinical and Lab Findings

- Hemolysis
  - Increased bilirubin
  - Decreased free haptoglobin
  - Increased LDH
- Normocytic anemia
  - Pallor, fatigue, dyspnea
- Jaundice
  - Due to increased bilirubin
- Splenomegaly

AIHA: Clinical and Lab Findings

- Reticulocytosis
- Paroxysmal Cold Hemoglobinuria
  - Constitutional symptoms (fever,/chills, aches ,headaches)
  - Hemoglobinuria
  - Raynaud’s phenomenon
- Direct Antiglobulin Test
  - DAT positive
- Warm AIHA
  - IgG coated RBCs
  - Spherocytes , Polychromasia

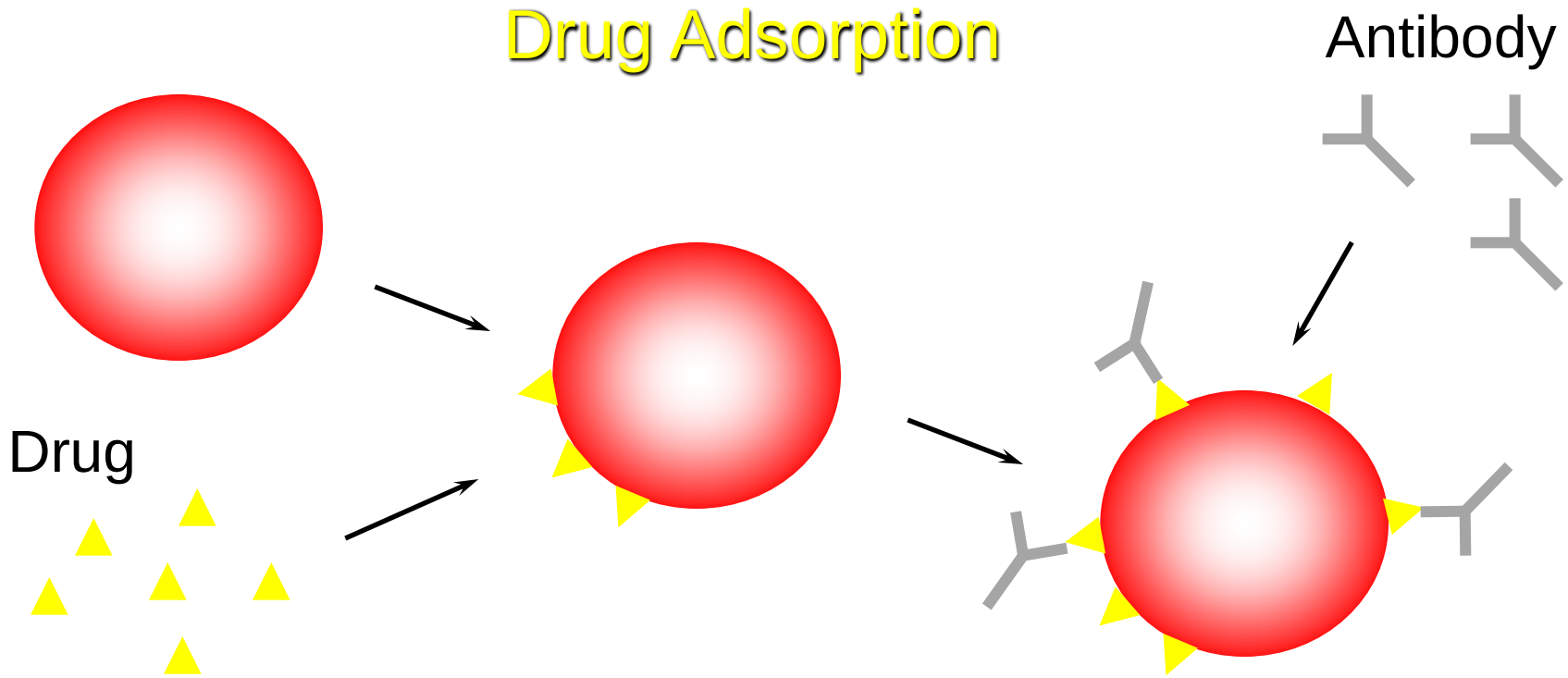
AIHA: Clinical and Lab Findings

- Cold AIHA
  - Complement coated RBCs
  - Hemoglobinuria accompanies acute attacks
  - Interfere with CBC count on analyzer due to RBC agglutination
  - Increased MCV
  - Increased MCHC
  - Polychromasia , NRBCs
  - Thermal amplitude and titer

Drug-Induced Immune Hemolytic Anemia

- Estimated incidence about 1 per million of population
- Condition is suspected when sudden decrease in Hgb after drug is administered and biochemical evidence of hemolysis and positive DAT
- Antibodies directed against or one of its metabolites
- Drug induces immune destruction of RBC
- The drug itself does not cause RBC injury

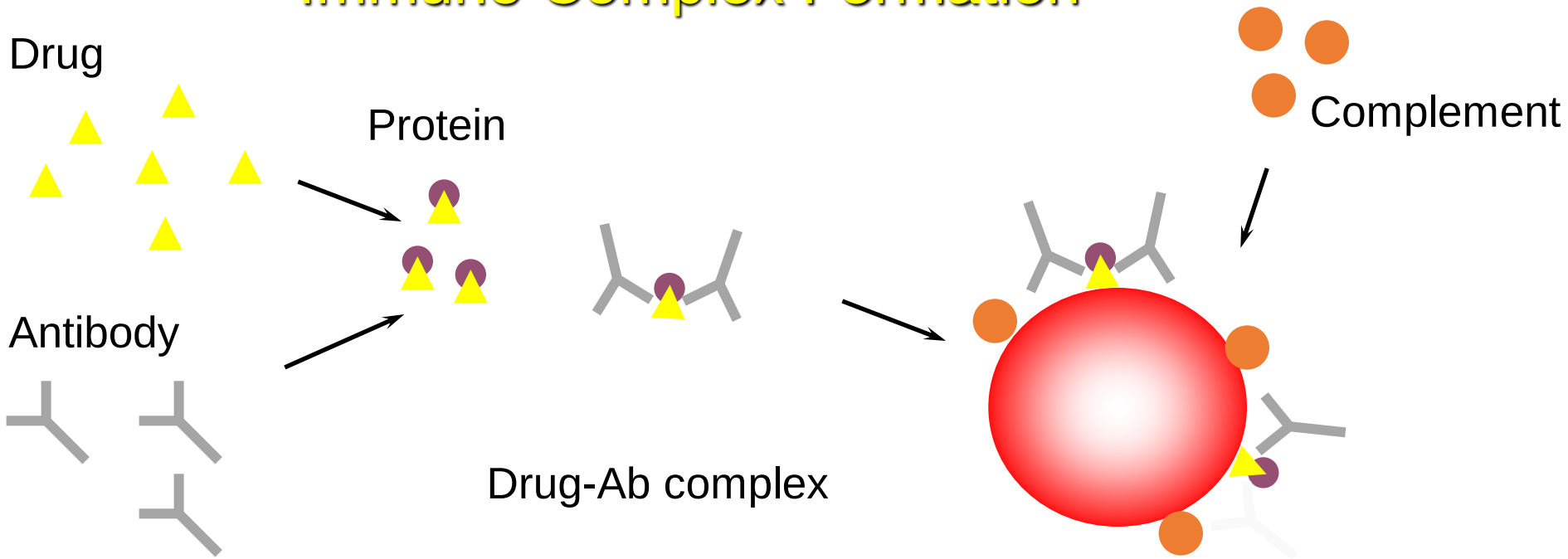
Drug-Related Hemolytic Anemia
Pathophysiology



Drug binds to proteins on RBC to form immunogenic complex.

Drug-Related Hemolytic Anemia
Pathophysiology

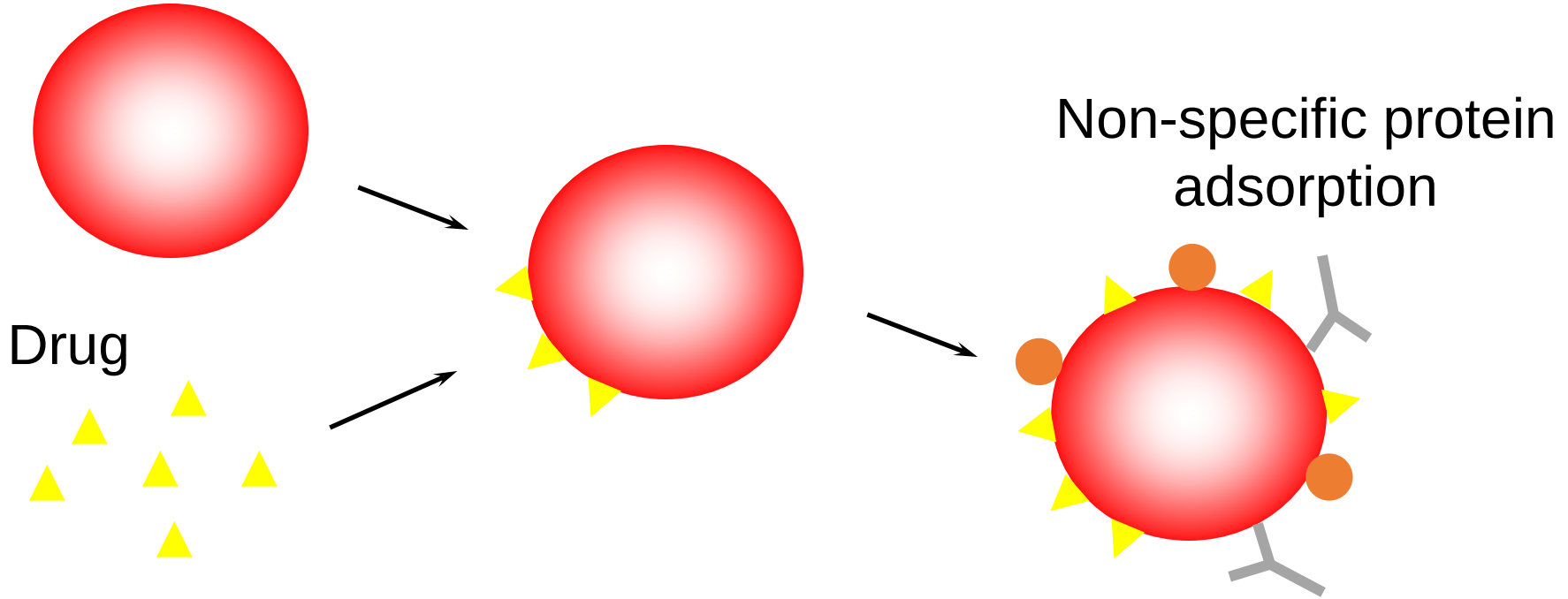
Immune Complex Formation



Drug combines with plasma protein to form new antigenic complex (neoantigen).

Drug-Related Hemolytic Anemia
Pathophysiology

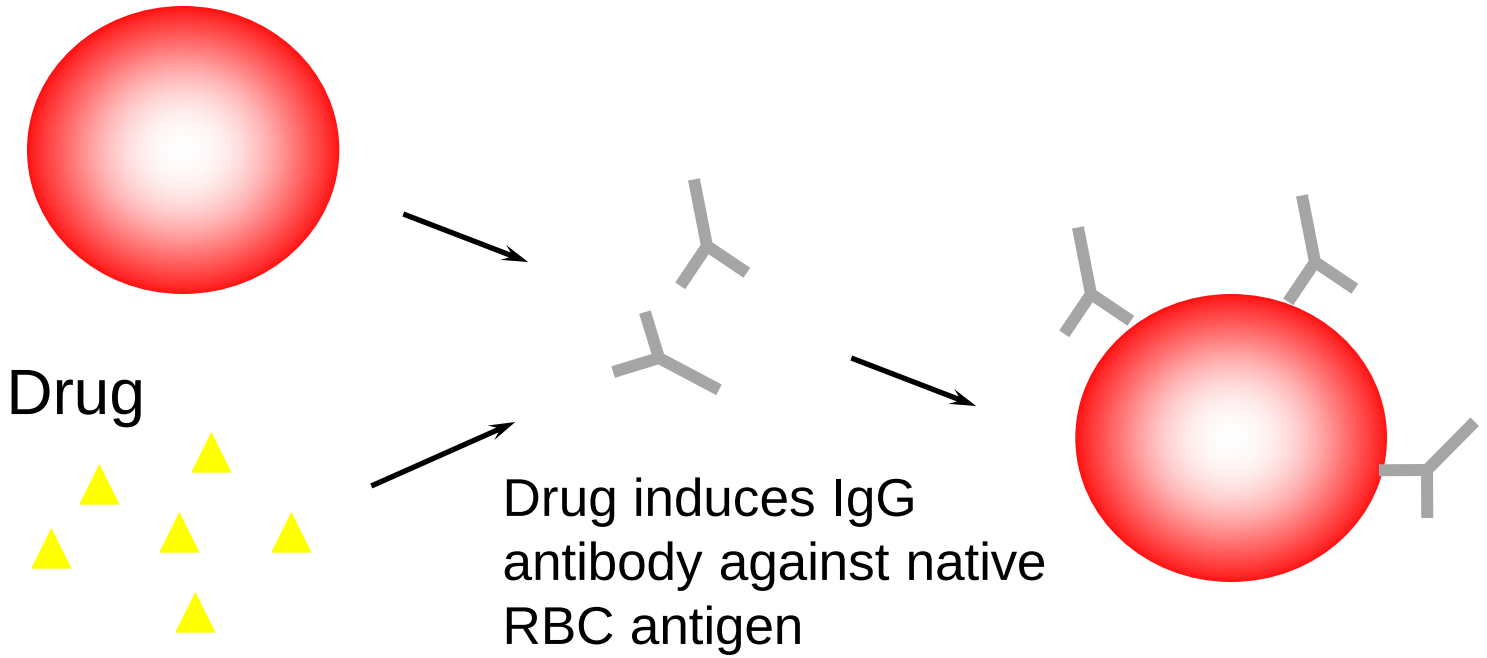
Membrane Modification



Drug modifies RBC membrane so that normal IgG and C3 can bind to membrane nonspecifically.

Drug-Related Hemolytic Anemia
Pathophysiology

Autoantibody Induction



Drug induces formation of IgG antibody against native RBC antigens

DIHA-Clinical Findings

- Extravascular hemolysis most common; occasional intravascular hemolysis if C3 present
- Positive DAT for IgG and/or C3
- DAT may remain positive depending on mechanism

Alloimmune Hemolytic Anemia

Acute Hemolytic transfusion Reaction

- Most severe and potentially life-threatening complication of blood transfusion
- IgM binds to RBC and activates C3
- Release of RBC content may activate coagulation (DIC)
- Immediate intravascular hemolysis
- Occur within minutes to hours of the initiation of transfusion
- Anti-A, Anti-B, Anti-I, Anti-P1, etc.

Alloimmune Hemolytic Anemia

Delayed Hemolytic transfusion Reaction

- Occur in days to weeks after transfusion as the titer of alloantibodies increases.
- Mediated by IgG antibody
  - Patient previously exposed to RBC antigen and has low antibody titer until exposed again
  - Cannot be detected at initial cross match testing
- Rh, Kidd , Duffy and Kell
- The patient antibody binds to transfuse RBC resulting extravascular hemolysis with or without complement activation.

Alloimmune hemolytic Anemia Clinical Findings

Acute

- Immediate reaction
- Fever, back pain , nausea
- Hypotension and shock
- Brown urine
- Anuria
- DIC
- Severity is variable and proportional to transfused volume

Delayed

- Unexplained anemia 2-14 days after transfusion
- Inadequate post transfusion Hgb increase
- Jaundice

Alloimmune hemolytic Anemia Laboratory Findings

Acute

- Hemoglobinemia
- Hemoglobinuria
- Positive DAT
- Decreased haptoglobin
- Increased bilirubin

Delayed

- Increased bilirubin
- Decreased haptoglobin
- Positive DAT

Alloimmune Hemolytic Anemia

Hemolytic Disease of the Fetus and Newborn Pathophysiology

- Due to incompatibility between mother negative for an antigen and fetus/father positive for that antigen.
- Rh incompatibility or ABO incompatibility most common causes.
- Required maternal IgG antibodies vs. RBC antigens in fetus
- Mother produce IgG antibody against RBC antigen
- Antibody enters fetal circulation via placenta

Hemolytic Disease of the fetus and Newborn Pathophysiology

- Sensitization occurs during the first pregnancy
  - In Rh- HDFN, D-negative mother may first encounter the D antigen while being pregnant with an Rh D-positive child and mother has preformed anti D antibody from the exposure of D antigen.
  - Receiving a blood transfusion of Rh D-positive blood.
- HDN occurs in subsequent pregnancies
  - A repeat encounter with the Rh D antigen stimulates the rapid production of type IgG anti-D, which can be transported across the placenta and enter the fetal circulation.
- Less common causes of HDN: anti-K

Hemolytic Disease of the fetus and Newborn Pathophysiology

What happens to fetus?

- Fetal RBC coated with maternal antibody are cleared in fetal spleen and liver.
- Fetus develops progressive anemia and attempts to increase RBC production
- Organomely: extramedullary hematopoiesis
- Increased indirect bilirubin cleared via maternal circulation

Hemolytic Disease of the Newborn Pathophysiology

What are complications of HDN?

- Fetal cardiac failure due to progressive anemia.
- Increased indirect bilirubin: initially cleared via maternal circulation
- Kernicterus: bilirubin toxicity in CNS
- Death in utero (hydrops fetalis)

Hemolytic Disease of the Newborn

- Preventing HDFN:
  - injection of anti-D Ig(RhoGam) at about 28 weeks gestation
  - Another dose at about 34 weeks,
- Lab findings:
  - Blood smear – Macrocytosis, Polychromasia , NRBCs, & reticulocytosis
  - Increased serum bilirubin
  - Positive DAT
  - Elute for antibody specificity

References

- Rodak’s Hematology, Clinical Principles and Applications 6th Edition
- Additional material courtesy of Dr. Karl Theil