

Immune Haemolytic Anaemias

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- Haemolytic diseases are those conditions in which the red cells of the individual do not survive normally *in vivo*.
- Haemolysis lead to red cell destruction and may be associated with anaemia.
- If red cell destruction occur inside the blood vessels it is called **intravascular haemolysis**.
- Intravascular haemolysis is **mediated by compliment** activation and results in free Hb in circulation (not good for the kidney) and DIC.
- Red cell destruction in the RES (e.g. Liver and spleen) is known as **extravascular haemolysis** (e.g. aged red cells).
- Extravascular haemolysis is **macrophage mediated** red cell destruction.
- The liver is vital for the removal of toxic metabolites which are produced following red cell haemolysis.

Role of the liver in RBC haemolysis

1) Intravascular haemolysis:

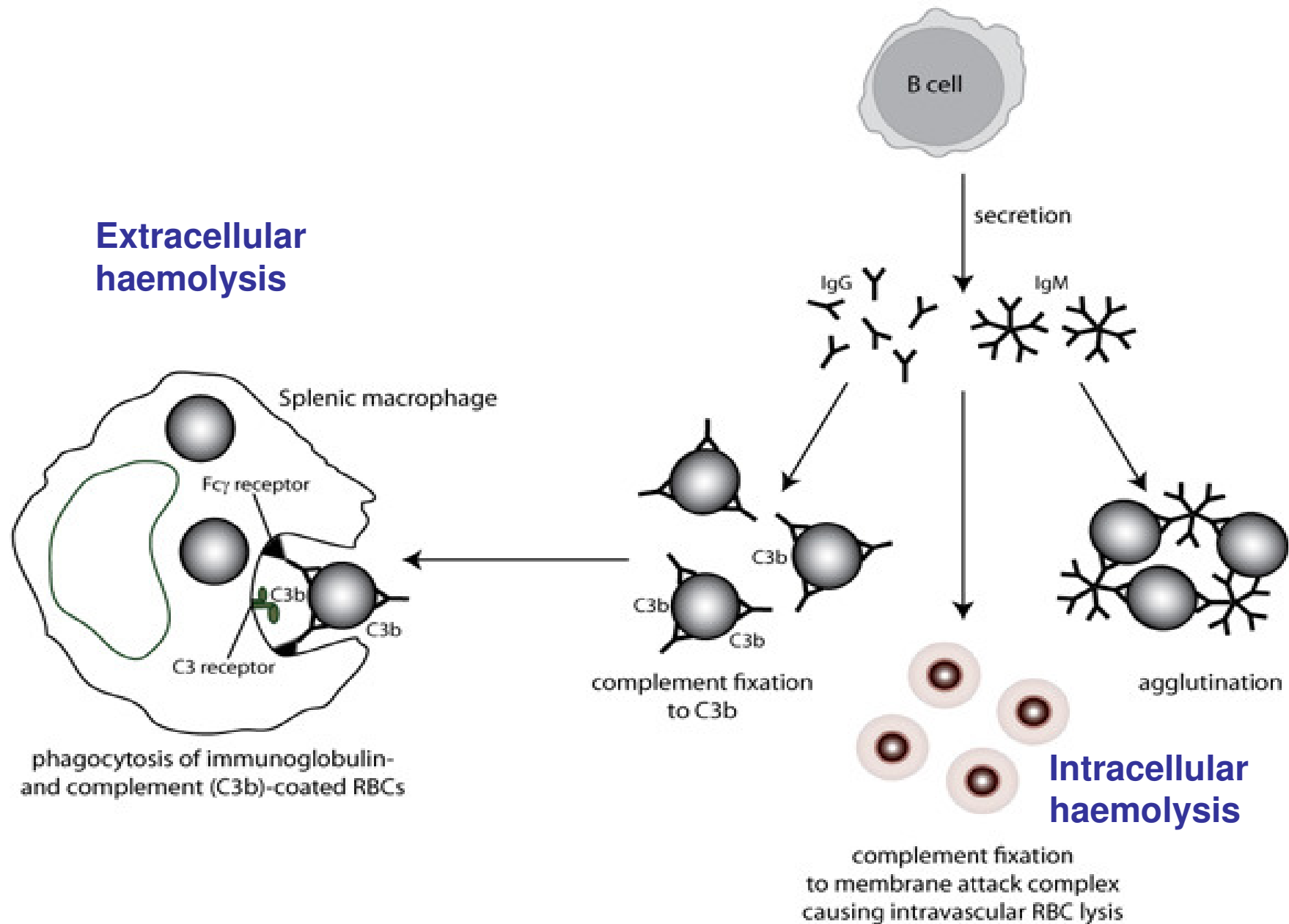
- Releases free hemoglobin in the circulation which is toxic to the kidney.
- Hb is immediately bound by haptoglobin in the plasma.
- Hb-haptoglobin complex is removed by hepatic RE cells.
- If the haemolysis is too much, haptoglobin get consumed and extra Hb set free in the circulation (**hemoglobinemia**).

- Free hemoglobin reaches the kidney and if hemolysis is beyond the reabsorptive capacity of the renal tubules, hemoglobin will appear in the urine (**hemoglobinuria**).

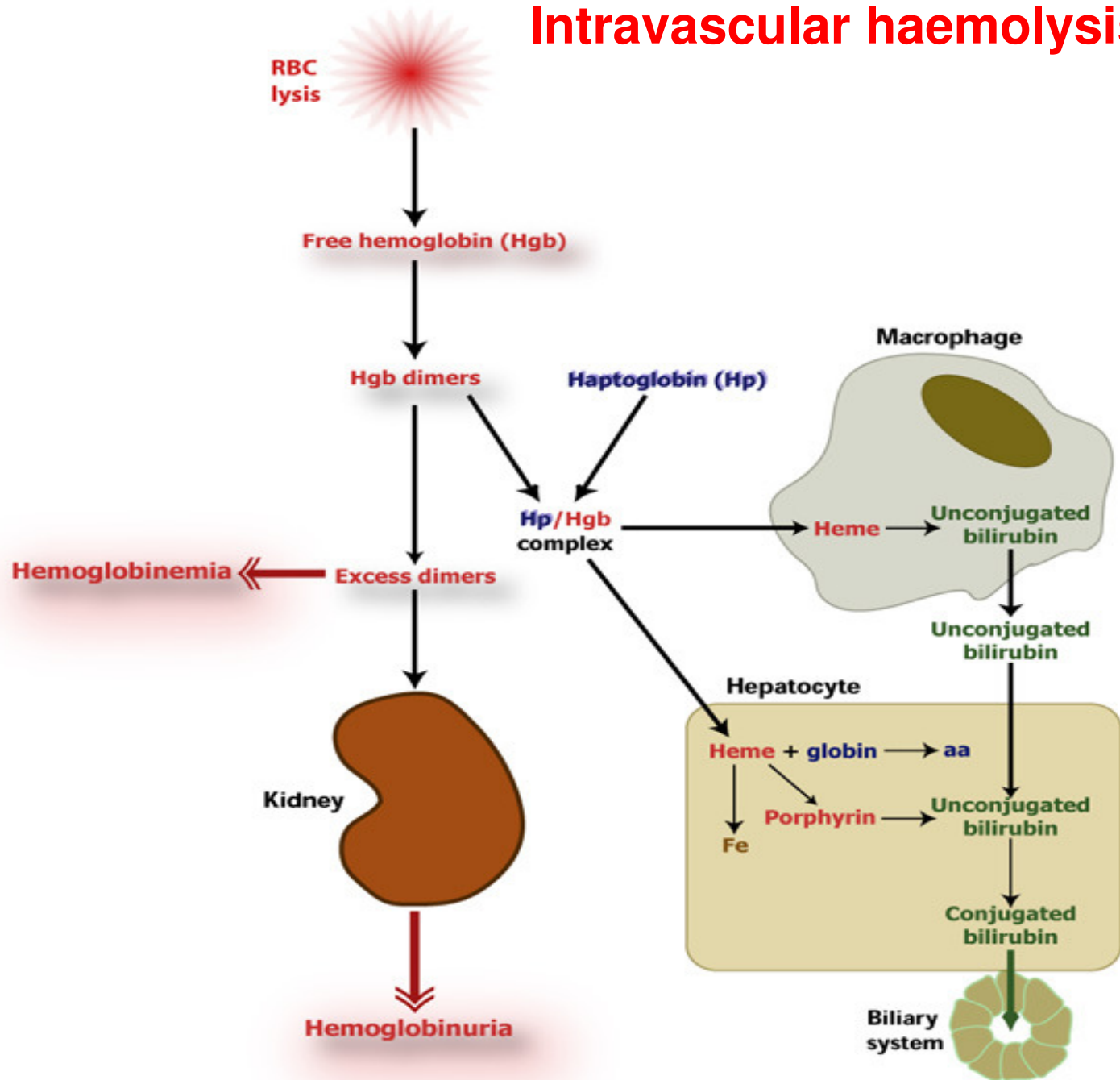
Role of the liver in RBC haemolysis

- **2) Extravascular haemolysis:**
- Free Hb → haem molecules → bilirubin.
- Free unconjugated bilirubin is transported to the liver where it is conjugated to glucuronic acid and eventually removed (90 % in faeces).

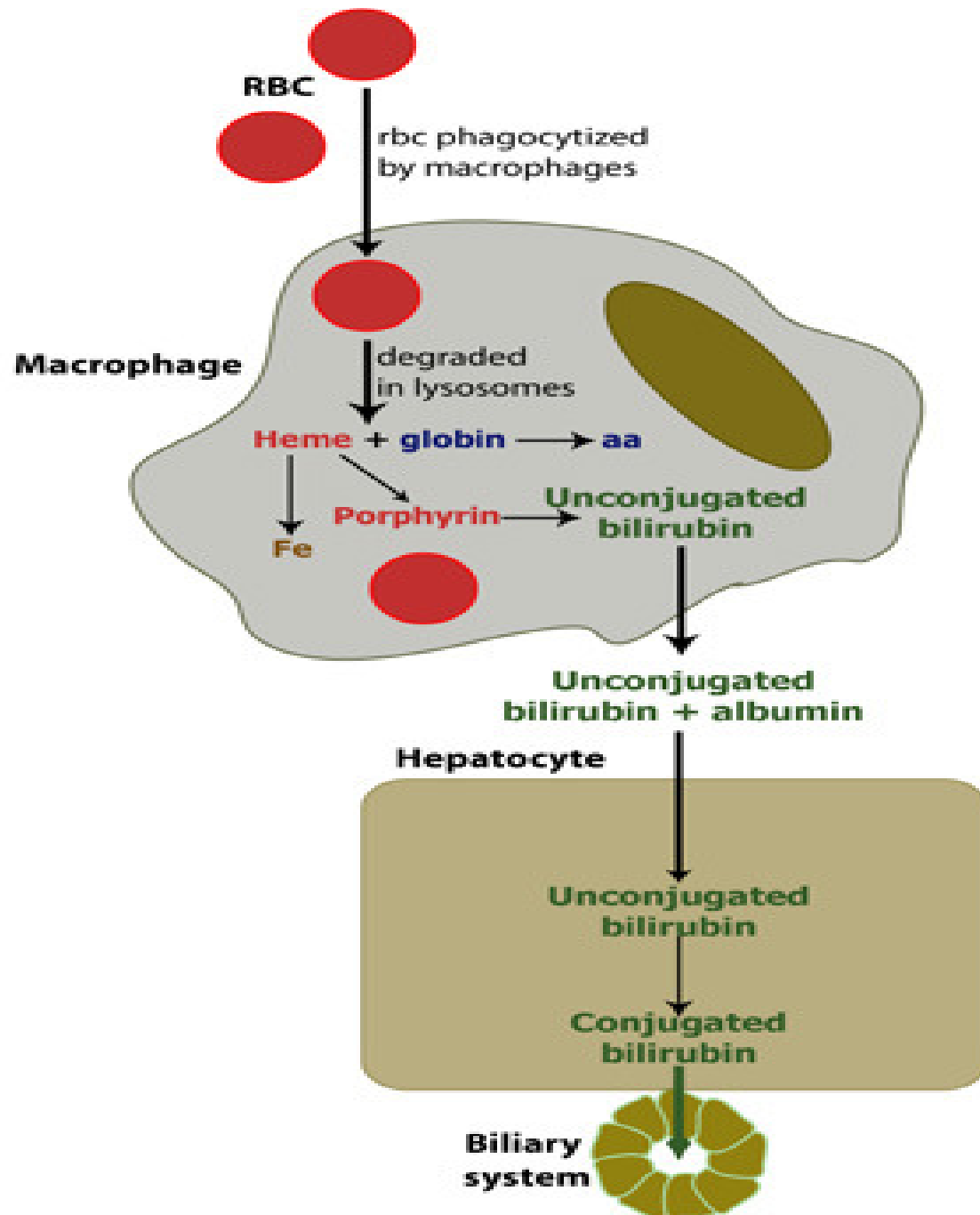
Intravascular and extravascular haemolysis



Intravascular haemolysis



Extravascular haemolysis



Classification of immune haemolytic anaemia

Table 5.5 Immune haemolytic anaemias: classification.

Warm type	@ 37 C°	Cold type	@ 0-20 C°
Autoimmune			
<i>Idiopathic</i>		<i>Idiopathic</i>	
<i>Secondary</i>		<i>Secondary</i>	
SLE, other 'autoimmune' diseases		Infections— <i>Mycoplasma pneumoniae</i> , infectious mononucleosis	
CLL, lymphomas		Lymphoma	
Drugs (e.g. methyldopa)		Paroxysmal cold haemoglobinuria (rare, sometimes associated with infections, e.g. syphilis)	
Alloimmune			
<i>Induced by red cell antigens</i>			
Haemolytic transfusion reactions			
Haemolytic disease of the newborn post stem cell grafts			
<i>Drug induced</i>			
Drug-red cell membrane complex			
Immune complex			

Alloimmune hemolysis

- **Hemolytic disease of the newborn** (also known as HDN or erythroblastosis fetalis)
 - Rh D hemolytic disease of the newborn (also known as Rh disease)
 - ABO hemolytic disease of the newborn (the indirect Coombs test may only be weakly positive)
 - Anti-Kell hemolytic disease of the newborn
 - Rh c hemolytic disease of the newborn
 - Rh E hemolytic disease of the newborn
 - Other blood group incompatibility (RhC, Rhe, Kidd, Duffy, MN, P and others)
- **Alloimmune hemolytic transfusion reactions**
 - Acute or delayed transfusion reaction.
 - Could be intra or extravascular.
 - Mechanism is required (see chapter 8, transfusion science).

Autoimmune hemolytic anaemia

- **Warm antibody autoimmune hemolytic anemia**
 - Idiopathic (48%)
 - Drug induced (8%)
 - Systemic lupus erythematosus, lymphoma, rheumatoid arthritis.
 - Evans' syndrome (antiplatelet antibodies and hemolytic antibodies)
- **Cold antibody autoimmune hemolytic anemia**
 - Idiopathic
 - Chronic cold hemagglutinin syndrome
 - **Infections:** Infectious mononucleosis and *mycoplasma pneumoniae*.
 - Paroxysmal cold hemoglobinuria

Cold haemolytic anaemia

1) Chronic cold hemagglutinin syndrome

- 45% of cold AIHA
- Auto antibodies against I Ag on RBC (IgM)
- Antibody binding to RBC occurs when skin temperature $< 30\text{ C}^\circ$
- Complement fixation \rightarrow intravascular haemolysis \rightarrow Hb-uria,..etc

2) Infection induced cold haemolytic anaemia

- *M. Pneumoniae* cause acute haemolytic anaemia due to anti-I Ab.
- Infectious mononucleosis: only rarely the patient produce high titers of anti-i auto Abs
- Cold haemolytic anaemia due to Infectious mononucleosis does not affect adults. Why?????????

Cold haemolytic anaemia

3) Paroxysmal cold haemoglobinuria (PCH)

- Rare disease in which the antibody reacts @ 15 C°
- Antibody type: anti-P (IgG)
- Biphasic: Ag-Ab binding @ cold, haemolysis @ Normal temp.
- If occurs: complement activation and subsequent I.V.haemolysis → haemoglobinuria.

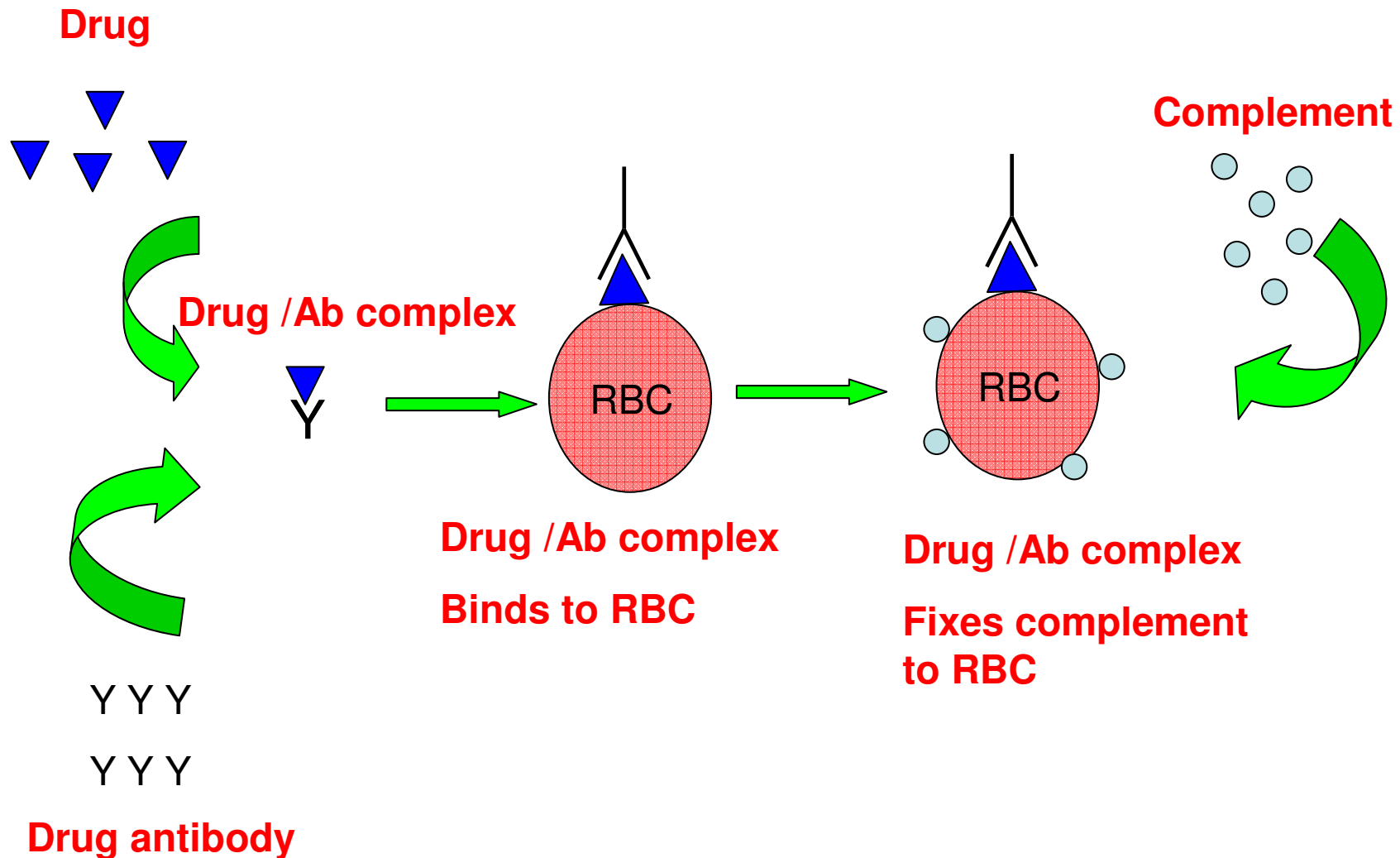
Drug-induced immune-mediated hemolysis

- Methyldopa (IgG mediated type II hypersensitivity)
- Penicillin (high dose)
- Quinidine (IgM mediated activation of classical complement pathway and Membrane attack complex, MAC)

Mechanism for drug induced HA

(1) Immune complex mechanism

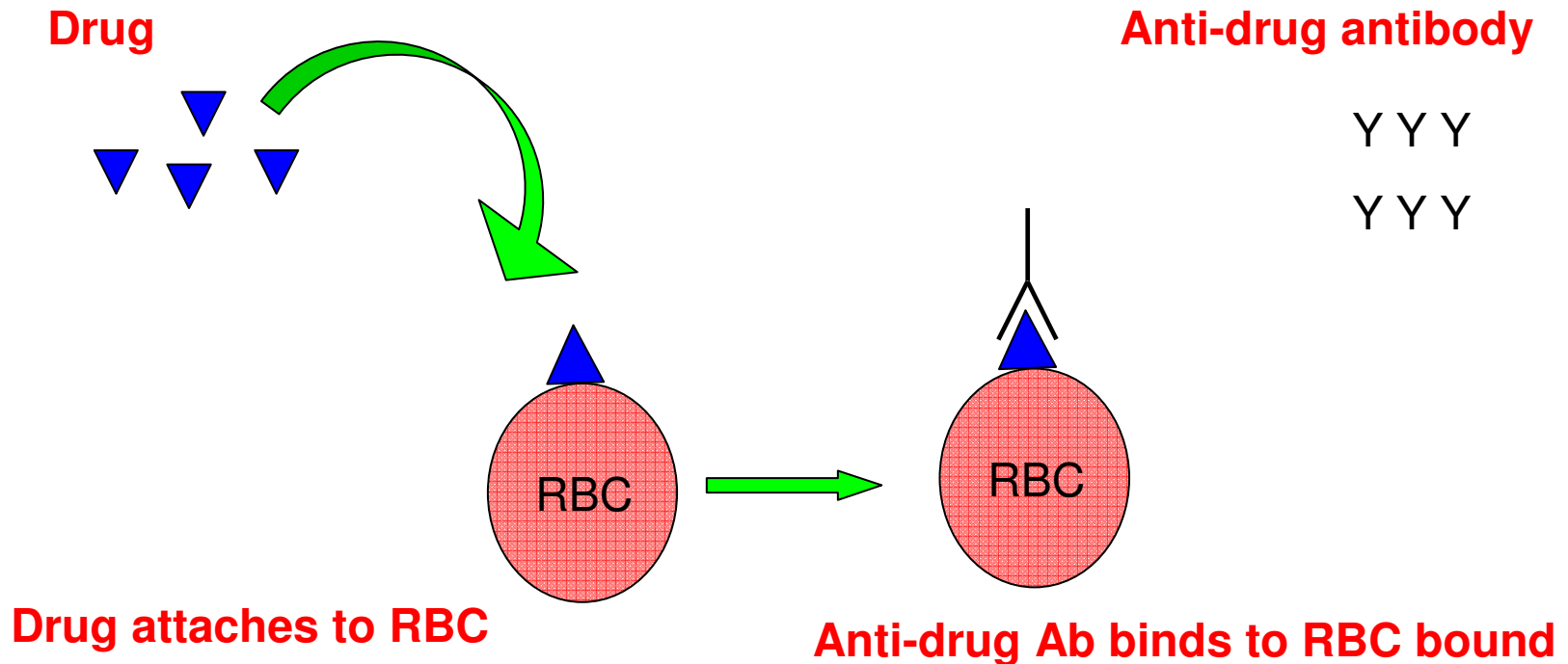
eg, Quinidine



Mechanism for drug induced HA

(2) Drug adsorption mechanism

eg, Penicillin



Antibody involved is usually IgG and complement is not involved

Drug-induced immune-mediated hemolysis

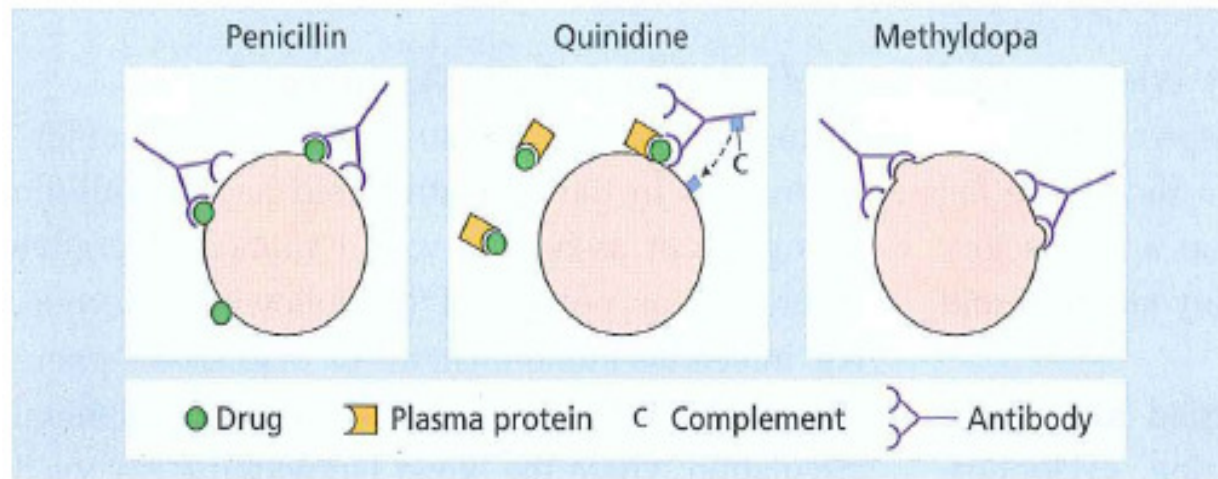


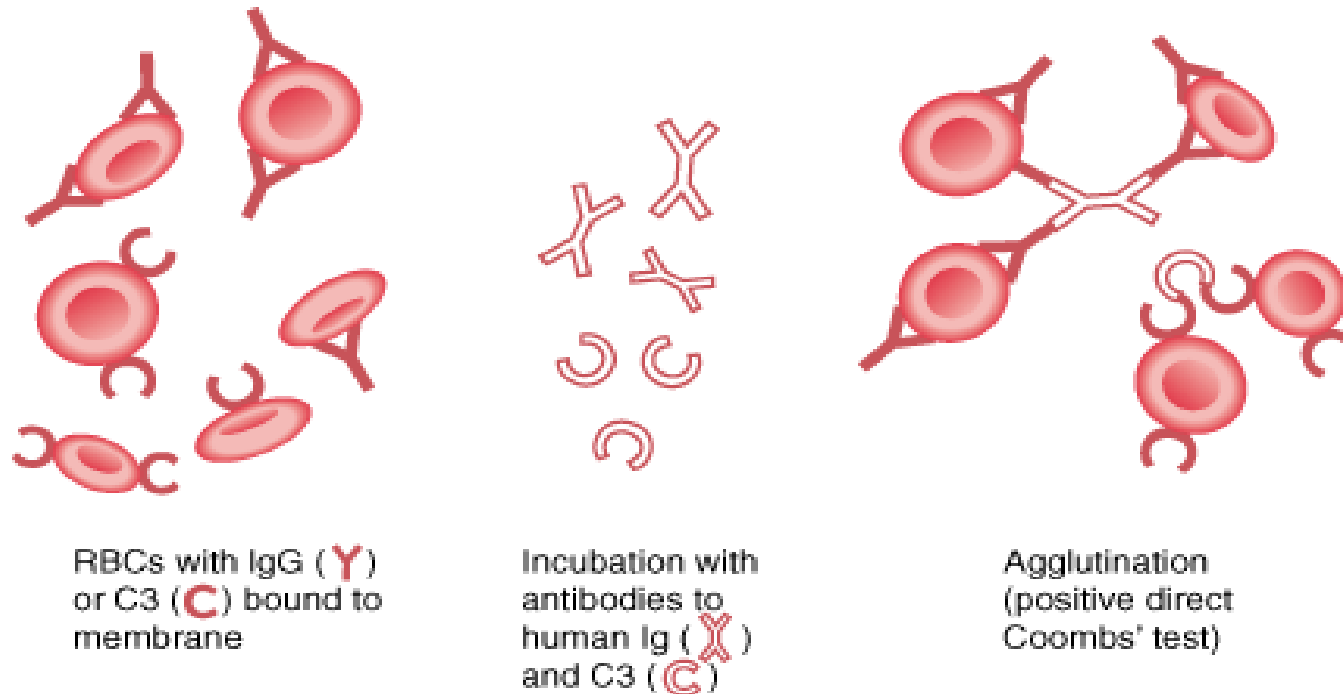
Fig. 5.10 Three different mechanisms of drug-induced immune haemolytic anaemia. In each case the coated (opsonized) cells are destroyed in the reticuloendothelial system.

- (**Methyldopa**) induces a warm AIHA, possibly by drug induced inhibition of T-suppressor allowing uninhibited autoantibody production by B cells (the auto antibody is either anti-c or anti-e IgG Ab).
- Despite drug withdrawal, antibodies may remain for months.

Diagnosis of autoimmune haemolytic anaemia

- Assays for hemolytic anemia (eg, peripheral smear, reticulocyte count; sometimes urinary hemosiderin, serum haptoglobin)
- Direct antiglobulin test

Direct antiglobulin test (Coombs test)



Remember that certain drugs may cause non-specific positive DAT due to modification of RBC membrane and subsequent adsorption of various plasma proteins.