Lecture No. 23

Autoimmune hemolytic anemia (AIHA)

In this disease, red blood cells (RBC) survive for a shorter time than in normal (less than 120 days) due to immune mechanism destructions of these RBC. In all conditions, the immune destruction is mediated by autoantibodies against certain components of the RBCs. AIHA are classified according to the thermic activity of the autoantibodies:

1. **Warm antibody hemolytic anemias** bind more efficiently to RBC at 37 C.
2. **Cold antibody hemolytic anemias** bind more efficiently to RBC at 4 C.

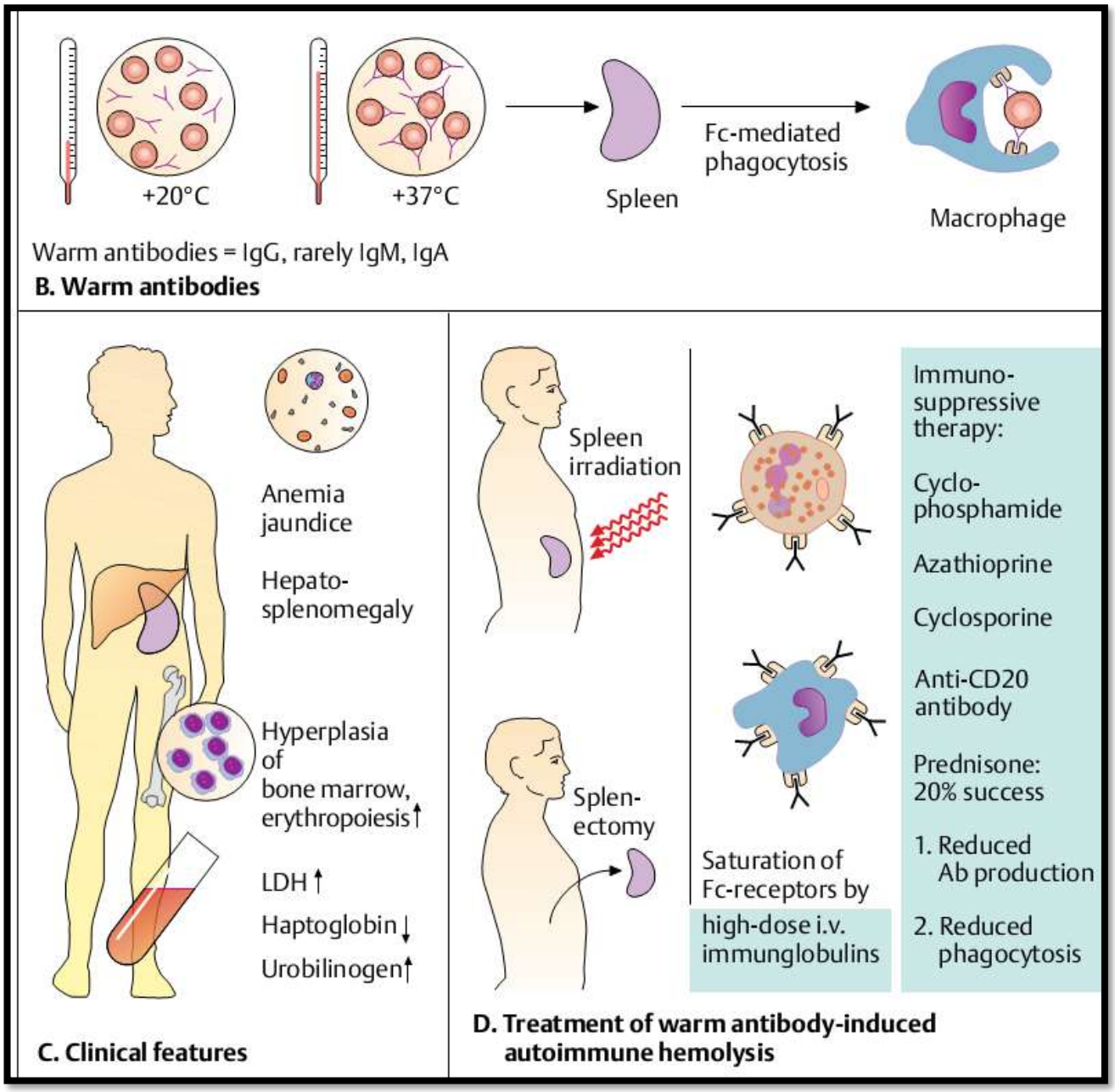
In all types of AIHA, there are autoantibody against certain components of the RBC surface which are attached to the patients RBC or free in the serum. In many occasion, complement may participate in the reaction to produce an Ab-Ag-complement complex. The screening test that used for the diagnosis of AIHA is called (Coombs test) which can demonstrate the presence of these autoantibody either attached to the patients RBC or free in serum. Coombs test could be direct or indirect.

Warm antibody hemolytic anemias

Affects all ages and mostly over 30 years of age and could be transient or persistent. About the half of the cases are idiopathic and the other half are due to secondary causes (lymphoproliferation, autoimmune disease as SLE, drugs and infections).the commonest pathogenesis of hemolytic anemia is the destruction of the opsonized RBC (with IgG and/or C3) by splenic macrophages and liver kupffers cells.

With warm antibodies, erythrocyte lysis takes place mainly in the RE system; the serum concentration of the hemoglobin-binding protein haptoglobin decreases only if there is severe hemolysis. Hepatosplenomegaly occurs due to the increased rate of hemolysis in the spleen and liver. Intracellular enzymes, such as lactate dehydrogenase (LDH), are released. Erythropoiesis is stimulated in the bone marrow, and reticulocytes are increased. The freed hemoglobin is reduced to bilirubin, which binds to glucuronate in the liver and is excreted in the bile. Hyperbilirubinemia, which leads to yellowish discoloration of the sclera and skin (jaundice), is frequently seen. Urobilinogen, another degradation product, cause dark discoloration of the urine.

Most cases are positive for direct Coombs test (50% are positive for both IgGand C3, 40% are positive for only IgG, 10% are positive for only C3). About 35% are positive for free autoantibody (indirect Coombs test).



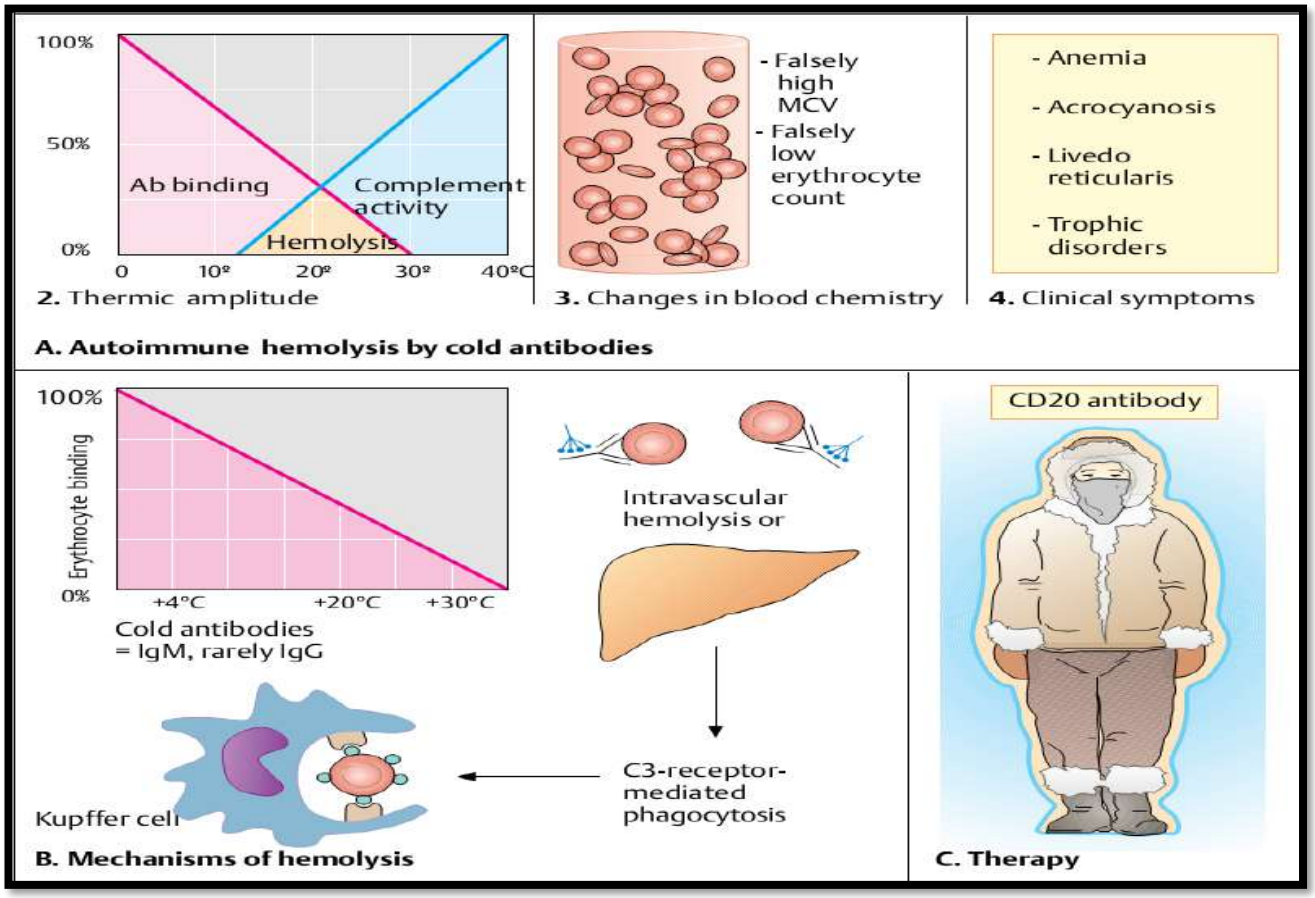
Cold antibody hemolytic anemias

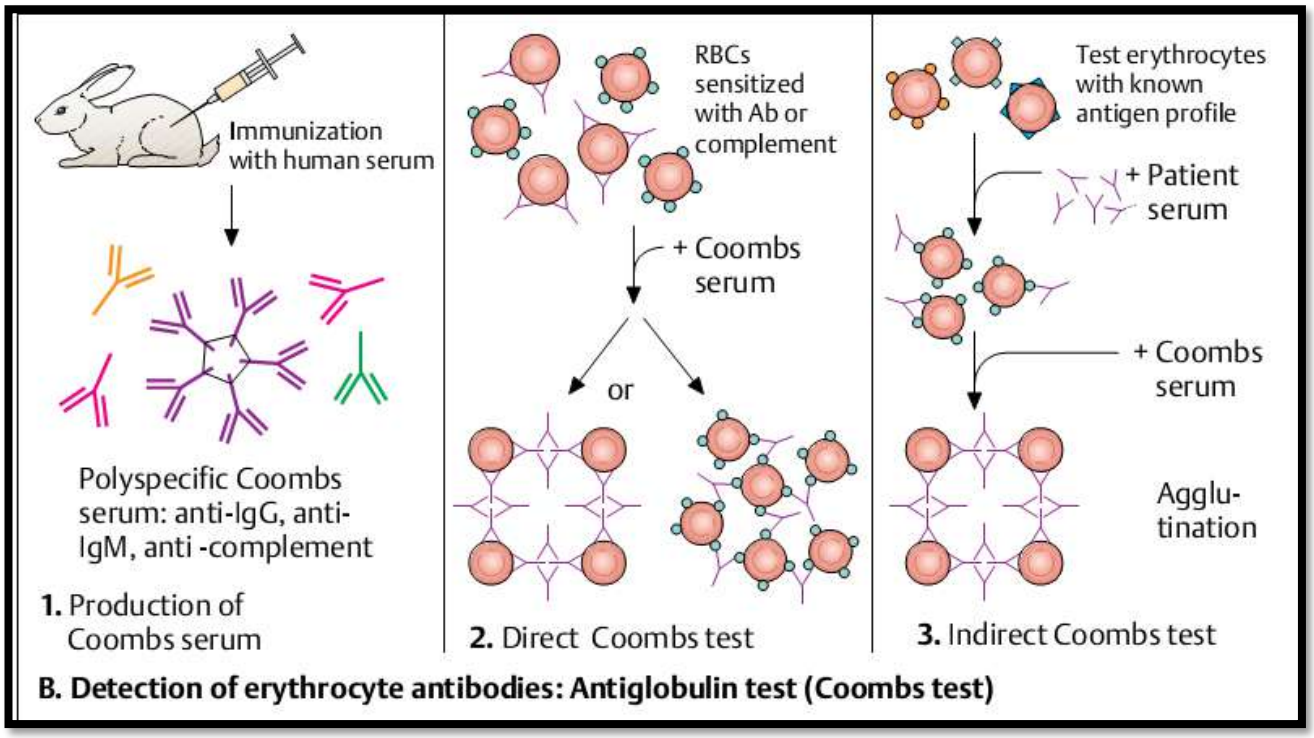
Cold antibodies are usually IgM and only occasionally IgG. Accordingly, they can cause agglutination of erythrocytes and are therefore called agglutinins.It is a disease of elderly people (over60years) mainly due to primary (idiopathic causes) and rarely due to secondary cause (infections, lymphoproliferation). They are most commonly observed following infections, especially by Mycoplasma, Epstein-Barr virus, or cytomegalovirus, and rarely after bacterial diseases. These infections usually lead to the formation of polyclonal cold reactive antibodies that bind to erythrocytes most efficiently at low temperature. In most cases, cold antibodies are directed against I antigen, which is mainly expressed on mature RBCs, but also on some pathogens. Some malignant lymphatic diseases may lead to

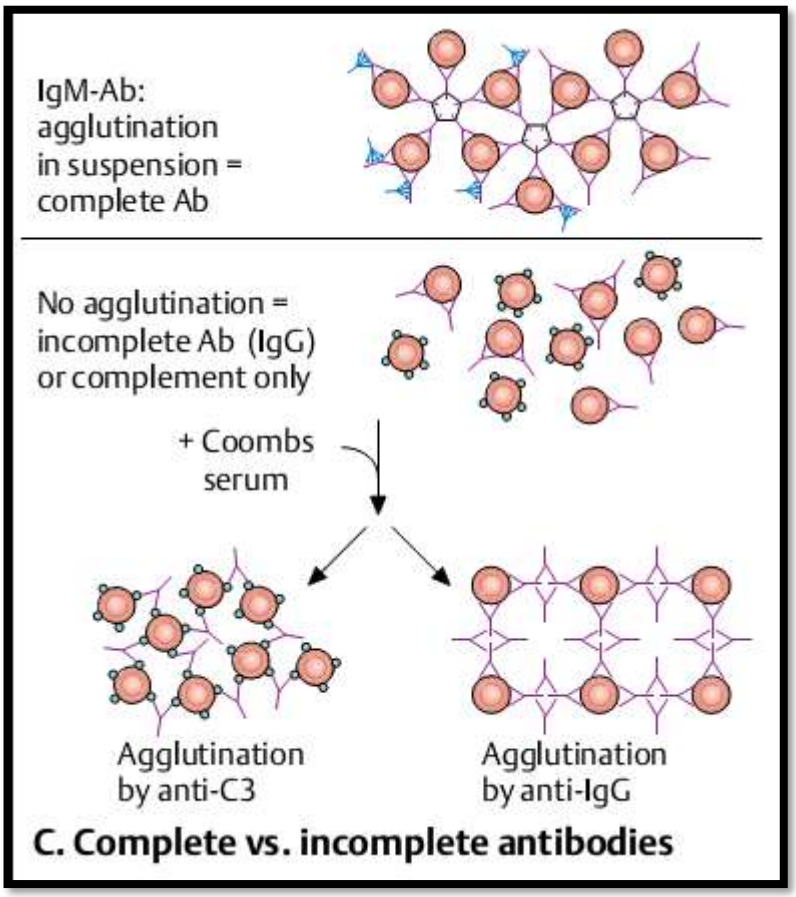
secretion of monoclonal agglutinins. Monoclonal agglutinins may be directed against both I and i antigen (immature fetal erythrocytes).

All patients have IgM coated RBC at 4c, but on warming the blood these Abs detached from RBC, however, fixed C3d can still be detected by direct Coombs test. The commonest pathogenesis of hemolysis is complement mediated mechanism. Free cold auto-Ab (cold agglutinins) are also found in the patients serum.

Since the temperature in the capillaries of the skin can drop below 30 C, the cold agglutinins cause the erythrocytes to clump together. This intravascular agglutination process leads to capillary obstruction, which manifests as acrocyanosis (bluish discoloration of the fingers, ears, and tip of the nose) or livedo reticularis (reddish/bluish reticular pattern of the skin). Trophic lesions (ulcer, necrosis) may occur in sever forms.




Immunization with human serum
Polyspecific Coombs serum: anti-IgG, anti-IgM, anti -complement
1. Production of Coombs serum
RBCs sensitized with Ab or complement
+ Coombs serum
or
2. Direct Coombs test
Test erythrocytes with known antigen profile
+ Patient serum
+ Coombs serum
Agglu-tination
3. Indirect Coombs test
B. Detection of erythrocyte antibodies: Antiglobulin test (Coombs test)


IgM-Ab: agglutination in suspension = complete Ab
No agglutination = incomplete Ab (IgG) or complement only
+ Coombs serum
Agglutination by anti-C3
Agglutination by anti-IgG
C. Complete vs. incomplete antibodies