Immune haemolytic anaemia

Dr Durga Moratuwagama

Haemolytic anaemias

- IVH&EVH
- Hereditary vs Acquired

Membrane
Enzyme def
Haemoglobin

Immune
Red cell fragmentation syndrome
March haemoglobinuria
Infections
Chemical &Physical agents
Secondary
PNH

IHA

- Autoimmune
- Alloimmune
- Drug induced

IHA,AIHA

At the end of this lecture student should be able to:

- Define Immune(IHA) and auto immune haemolytic anaemia(AIHA).
- List the causes of IHA.
- Describe the classification of AIHA.
- Describe how to investigate a patient with suspected IHA/AIHA.
- List the management options of AIHA

Autoimmune hemolytic anemia (AIHA)

- Autoimmune hemolytic anemia (AHA) is characterized by shortened red blood cell (RBC) survival and the presence of autoantibodies directed against autologous RBCs.

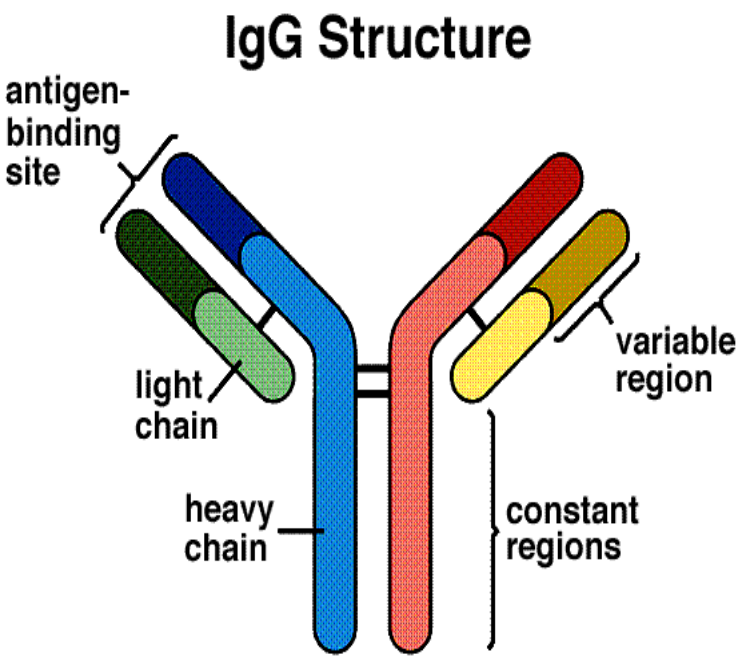
AIHA

Warm

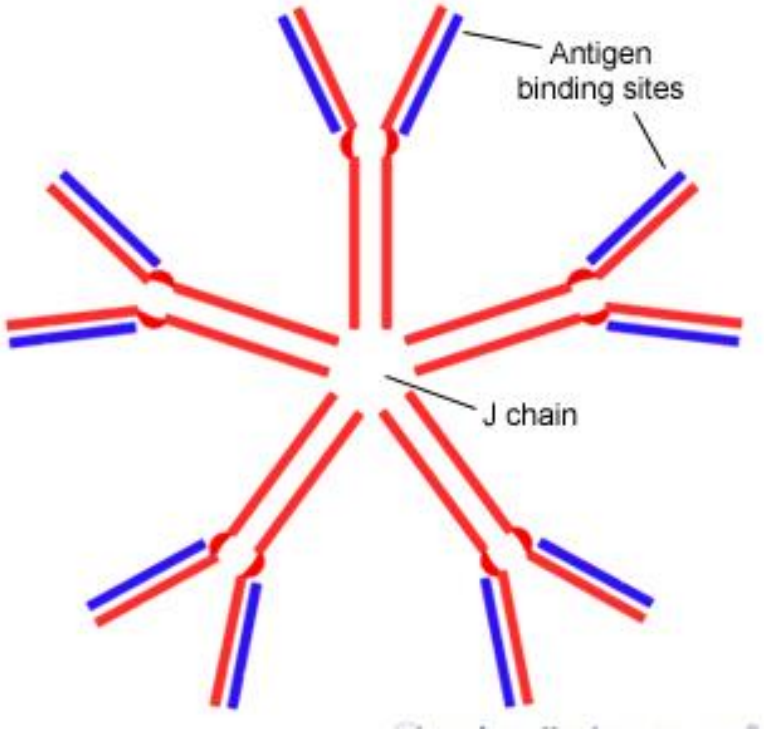
Cold

Auto antibodies

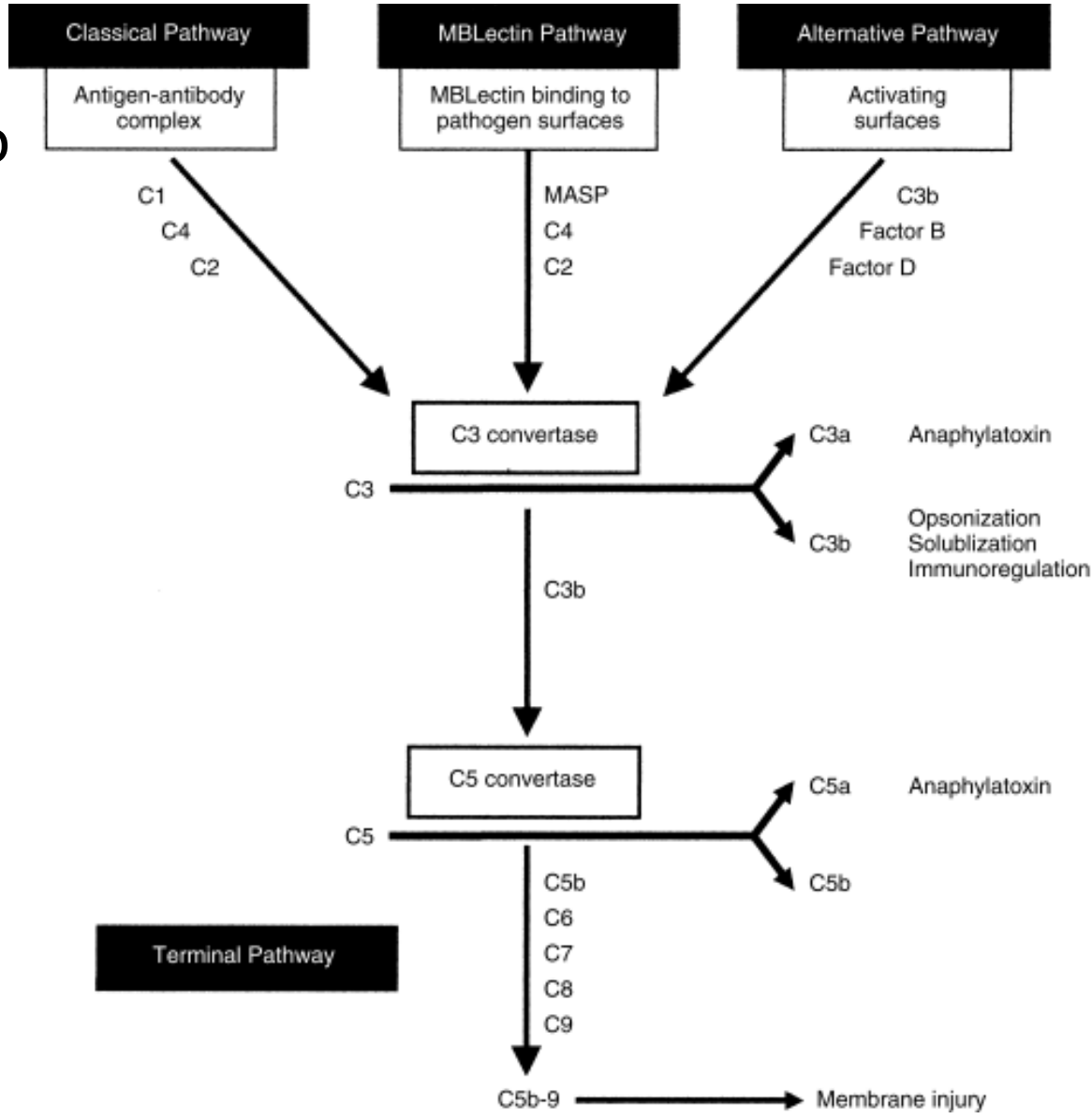
Ig G



Ig M

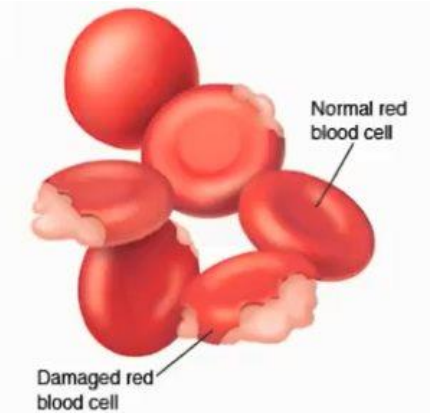


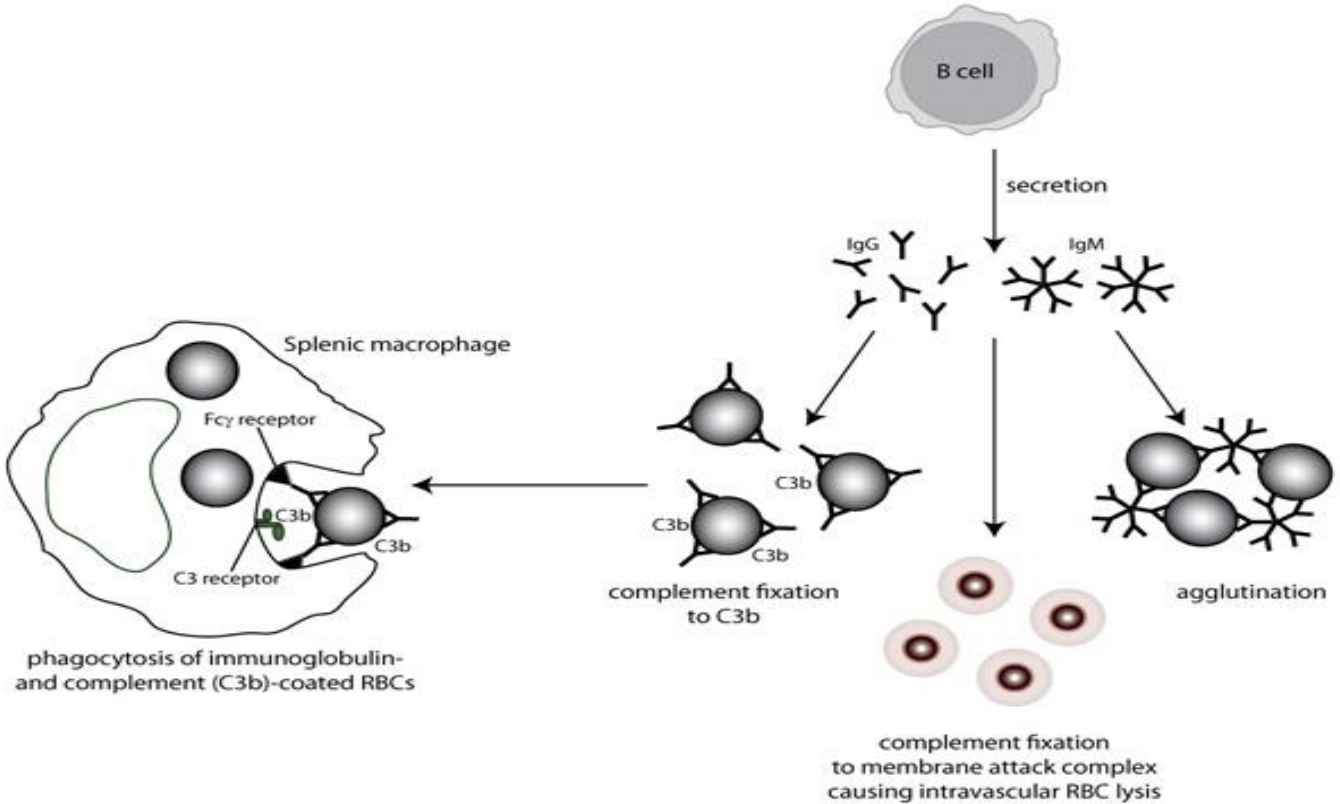
- Ag & Ab binding activate complement cascade
- Activation
  a. Partial –stop at C3
  b. Complete-progress to to MAC(C5b-9)



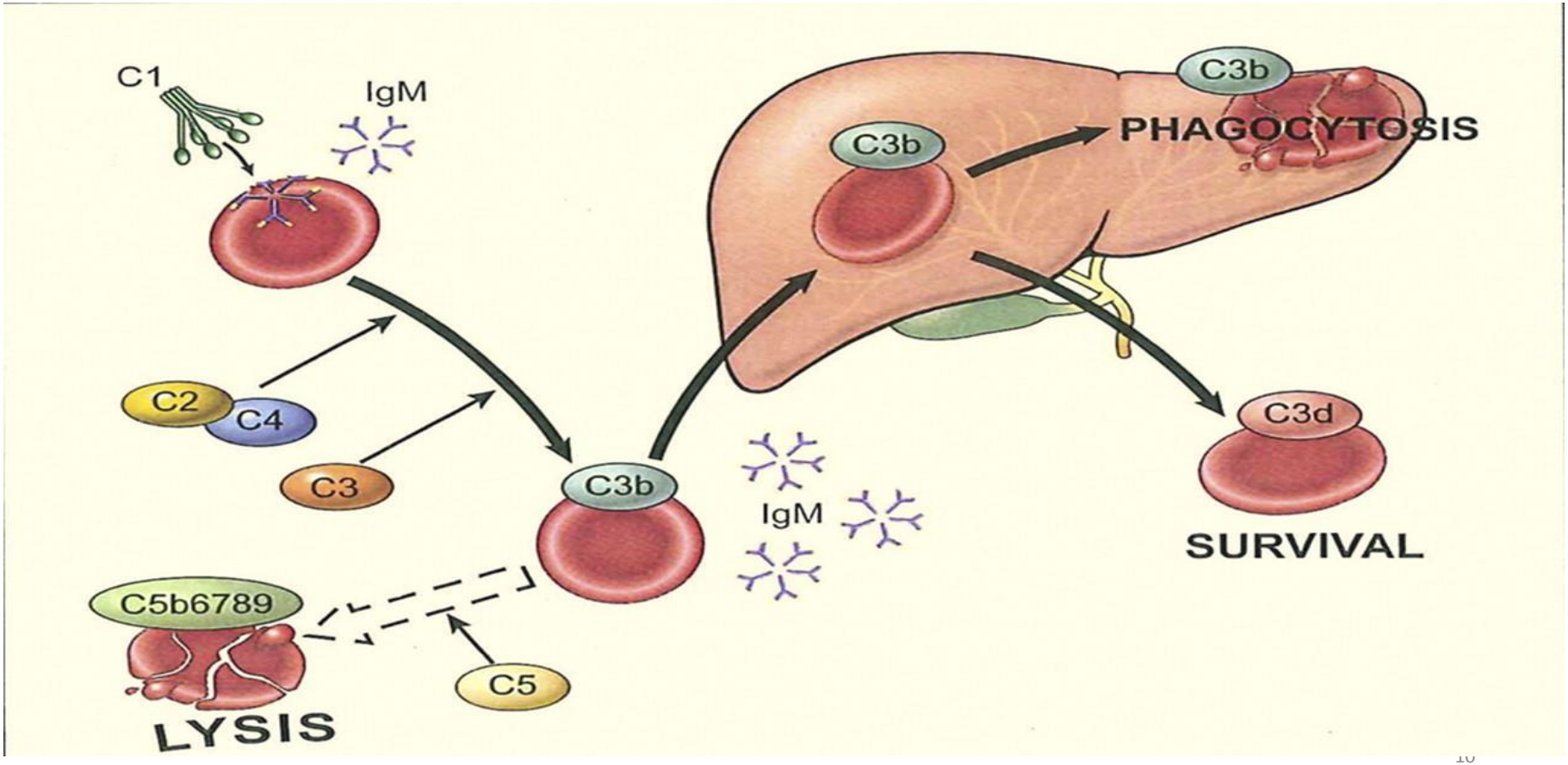
Pathophysiology

- Attachment of IgG or IgM causes fixation of complement (to C3b) on red cell membranes.
- Macrophages possess receptors for the Fc portion of IgG and IgM as well as for C3b, thus causing red cells with attached immunoglobulin or C3b to be phagocytized
- Partial phagocytosis of erythrocytes forms **spherocytes** which, in large numbers, are pathognomonic for IMHA





- Strong complement-fixing antibodies result in formation of the membrane attack complex, which punches holes in the red cell membrane causing them to rupture within the circulation (IVH). Ex:Ig M ab

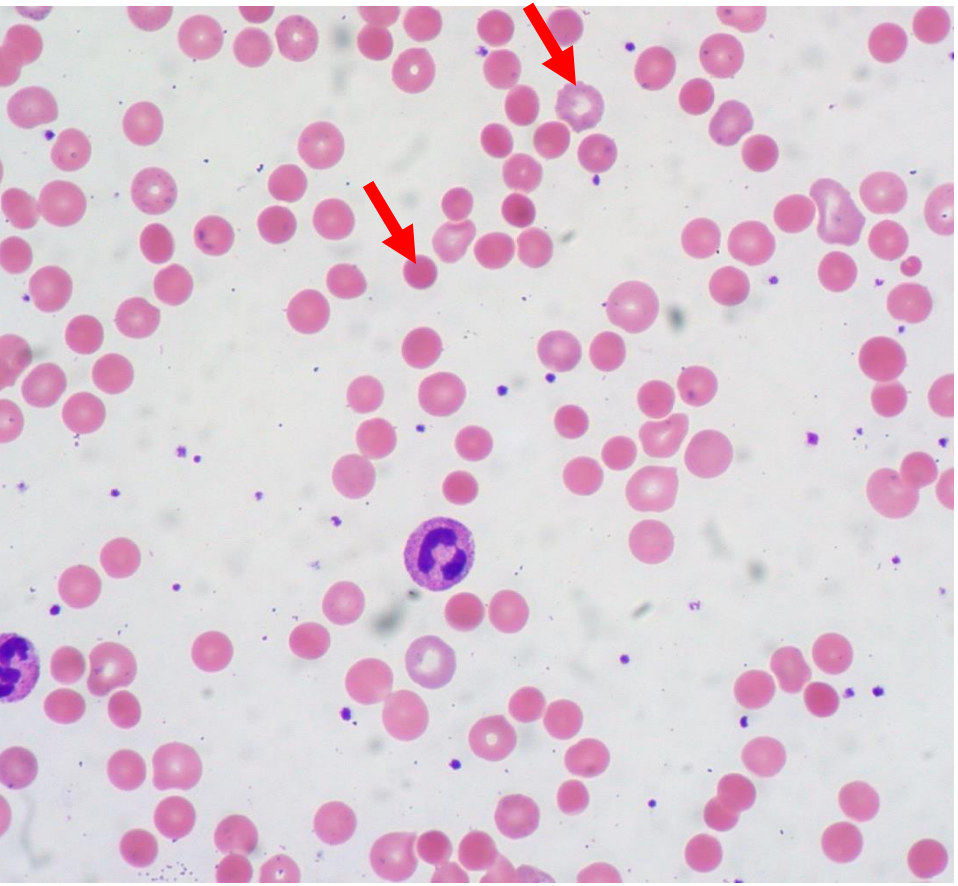


AIHA

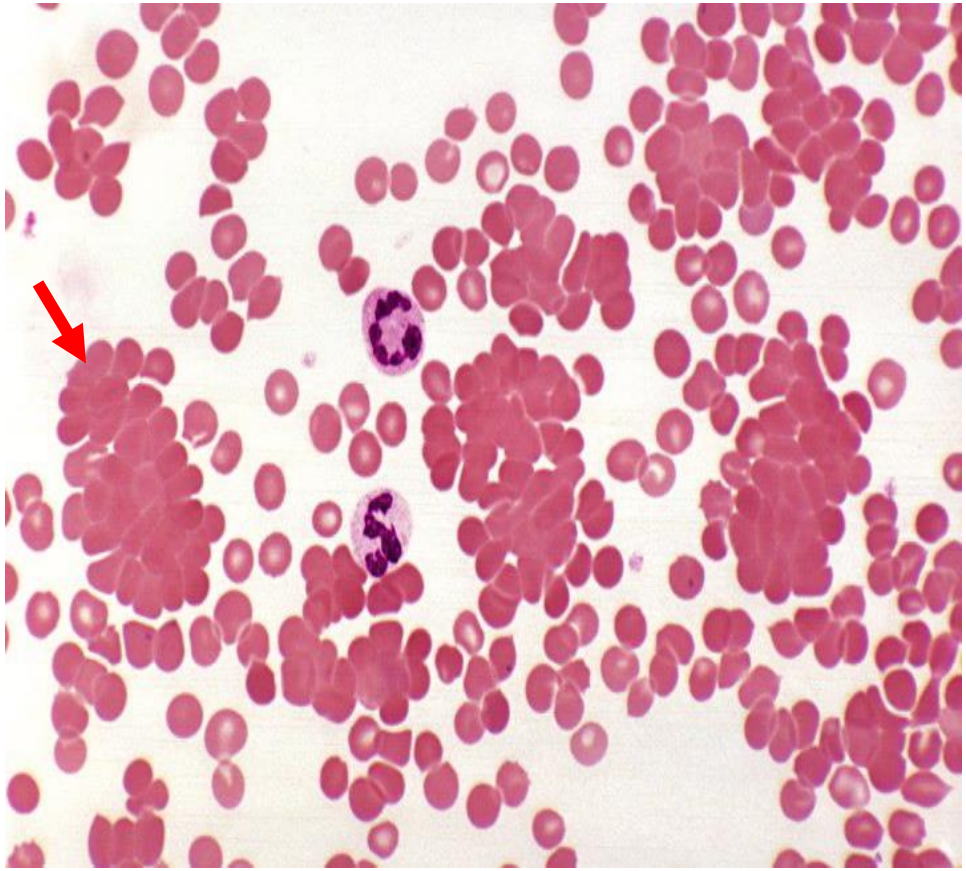
Diagnosis

- Anaemia — Low Hb
- Haemolysis
  - Increased retic count
  - Increased LDH
  - Indirect hyperbilirubinaemia
  - Increased urine urobilinogen
  - Low haptoglobin
- Auto immune — Direct Coombs positive

Blood picture

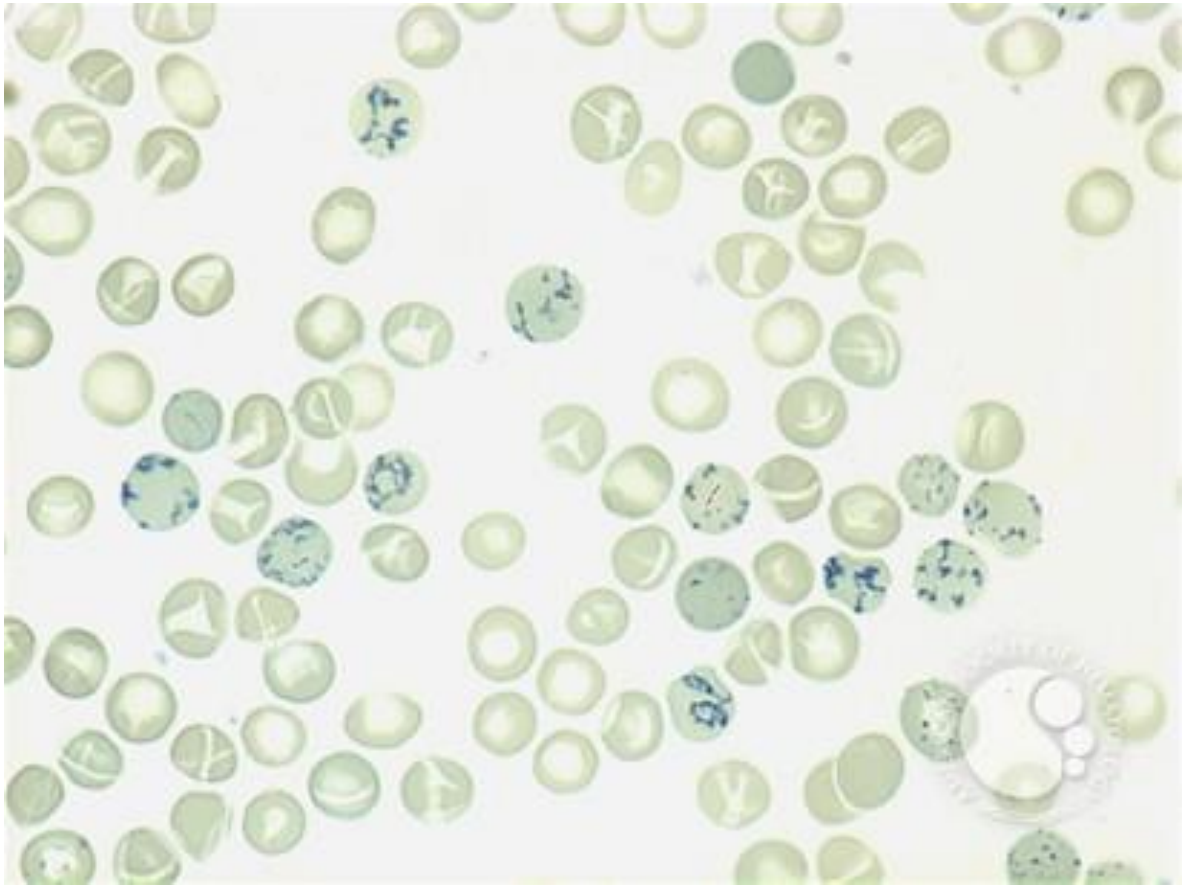


Warm



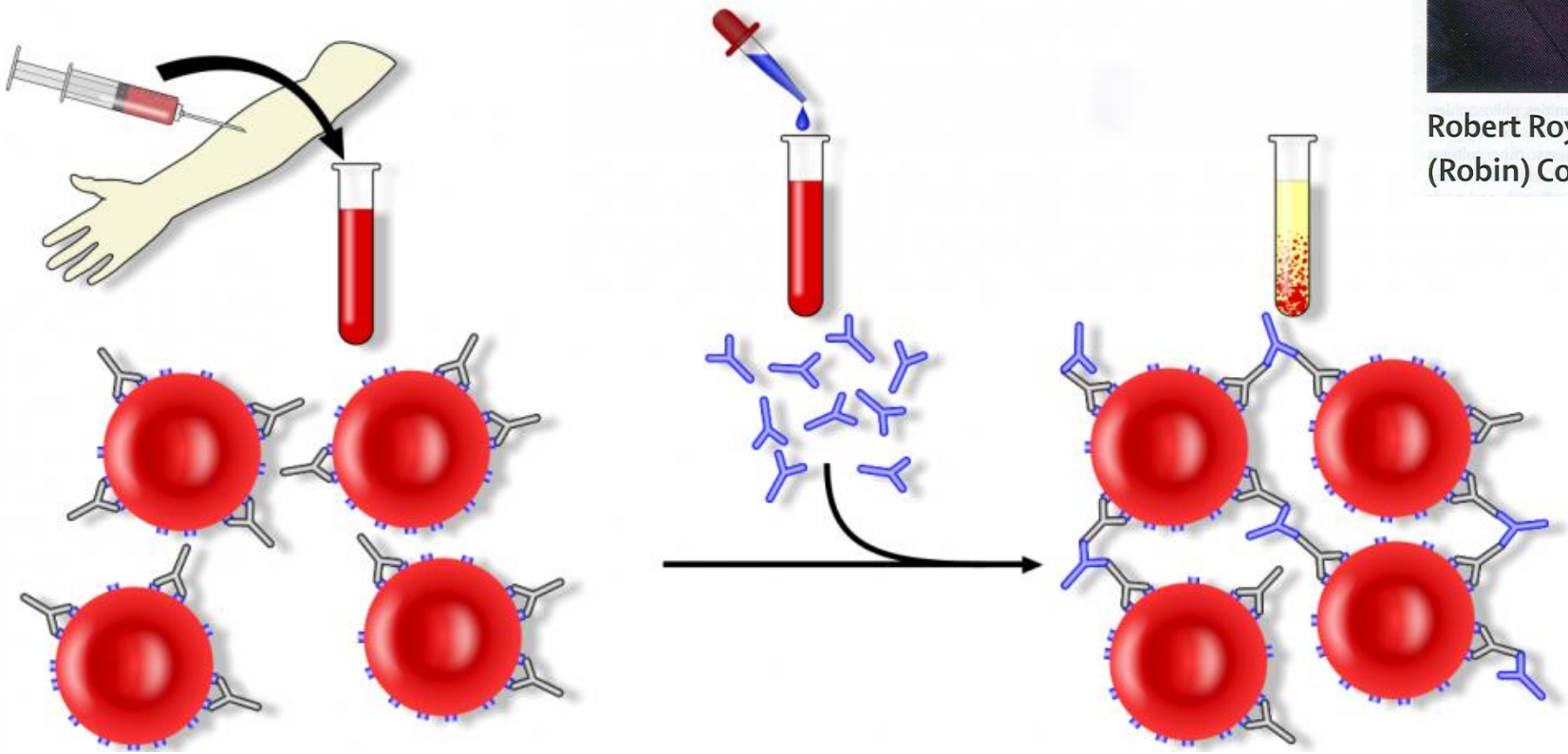
Cold

Reticulocyte preparation



Direct Coombs test

Robert Royston Amos (Robin) Coombs



Direct Coombs test

Warm

- Ig G/Ig G+C3d

Cold

- C3d

Table 5.5 Immune haemolytic anaemias: classification.

Warm type	Cold type
Autoimmune	
Idiopathic	*Idiopathic*
Secondary	*Secondary*
SLE, other 'autoimmune' diseases	Infections—*Mycoplasma* pneumonia, infectious mononucleosis
CLL, lymphomas	Lymphoma
Drugs (e.g. methyldopa)	Paroxysmal cold haemoglobinuria (rare, sometimes associated with infections, e.g. syphilis)
Alloimmune	
Induced by red cell antigens	
Haemolytic transfusion reactions	
Haemolytic disease of the newborn post stem cell grafts	
Drug induced	
Drug–red cell membrane complex	
Immune complex	

Other investigations

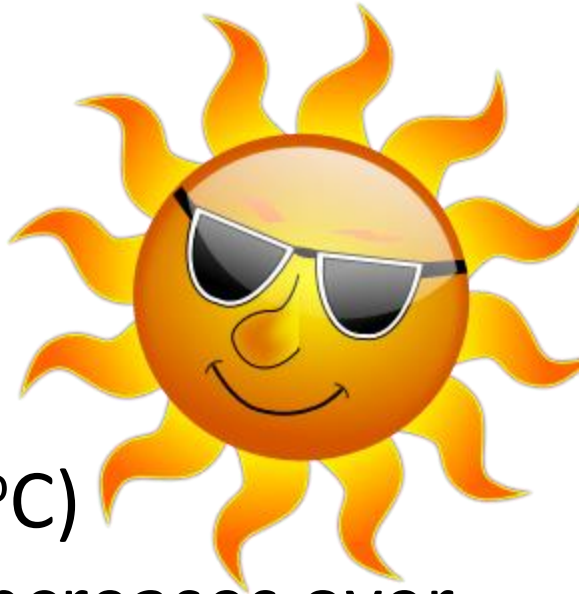
- Find the cause for AIHA

Ex: BM Biopsy

ANA

Mycoplasma serology

Warm AIHA (WAIHA)



- Most common form of AIHA ~70%
- Reacts best at body temperature (37^{o}C)
- Can occur at any age, but incidence increases over the age of 40
- Cases can be idiopathic or secondary to another disease
- IgG coats red cells with or without complement fixation
- Antibody usually directed against antigens of the Rh system

Clinical Features

- Pallor
- Jaundice
- Splenomegaly
- Features of underlying disease

  Ex: Lymphadenopathy, arthritis, vasculitis
- Purpra-Ass. with ITP---***EVANS SYNDROME***

Laboratory findings

Features of EVH-

Anaemia

raised reticulocyte count

urine urobilinogen

LDH

unconjugated hyperbilirubinaemia

low haptoglobulin

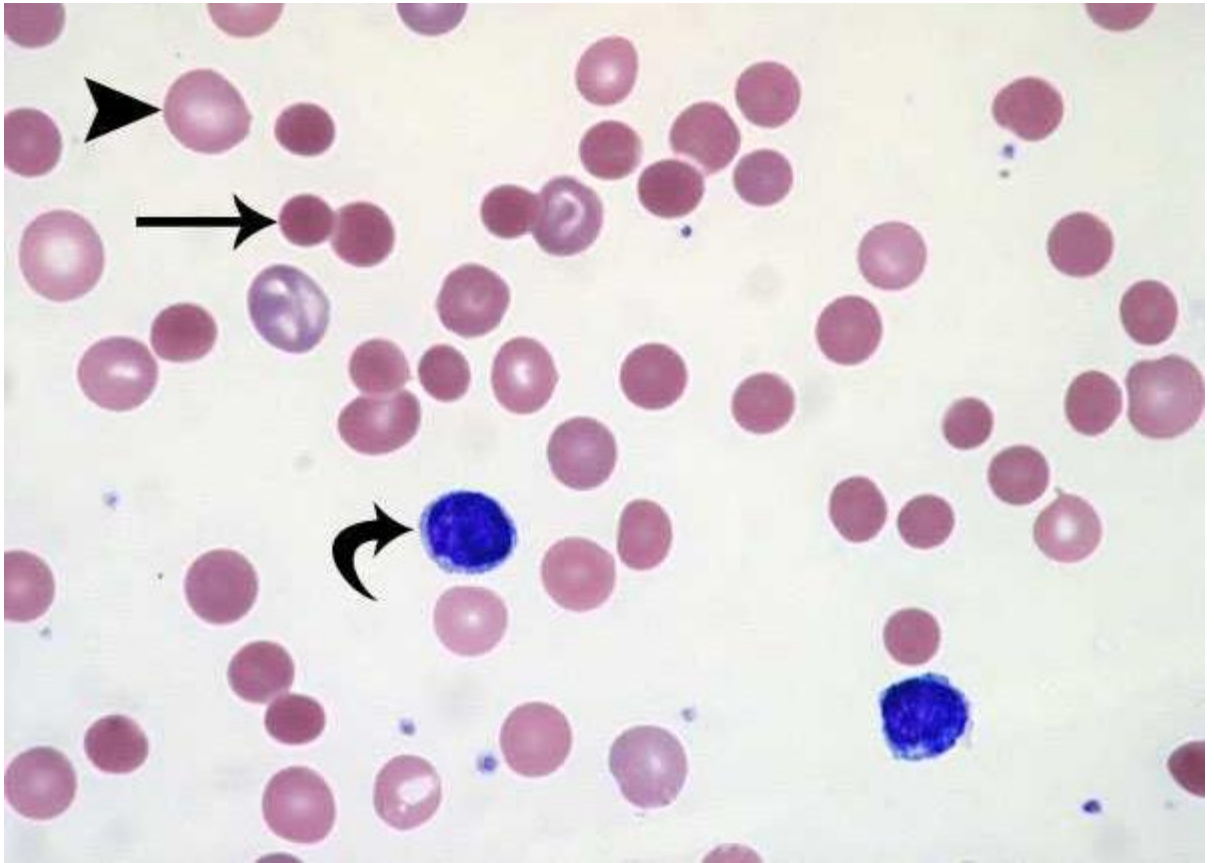
Blood picture- **Spherocytes**

Direct Coombs test- positive with Ig G+/-C3d

Autoantibody-often pan-reacting but specificity in 10–15%(Rh, mainly anti-e, anti-D or anti-c).

Laboratory findings

- Exclude underlying lymphoma (BM, blood and marrow cell markers).
- Autoimmune profile—to exclude SLE or other connective tissue disorder.



Treatment

- Remove the underlying cause

  ex: drugs
- Corticosteroids
- Splenectomy
- Immunosuppression- Rituximab,Azathioprine,Cyclosporin,Cyclophosphammide,MFM
- May need to treat underlying condition
- Folic acid

Treatment cont.

- Blood transfusion

  if symptomatic only
- Least incompatible blood
- Can make alloantibodies

AUTOIMMUNE HEMOLYSIS-*Cold Type*

- Most commonly IgM mediated
- Antibodies bind best at 4^0C(30º or lower)
- Fix entire complement cascade
- Leads to formation of membrane attack complex, which leads to RBC lysis in vasculature
- Both IVH& EVH
- Most common are designated anti-I antibodies, which react best with untreated adult RBCs.
- Anti-i antibodies react best with fetal or cord RBCs.
- Anti i seen in IMN

Clinical features

- Anaemia, jaundice-exacerbated by cold
- Acrocyanosis
- Features of underlying disease ex:LN,

Laboratory findings

- Similar to warm type

Exceptions: less spherocytes

RBC agglutination at low temperature

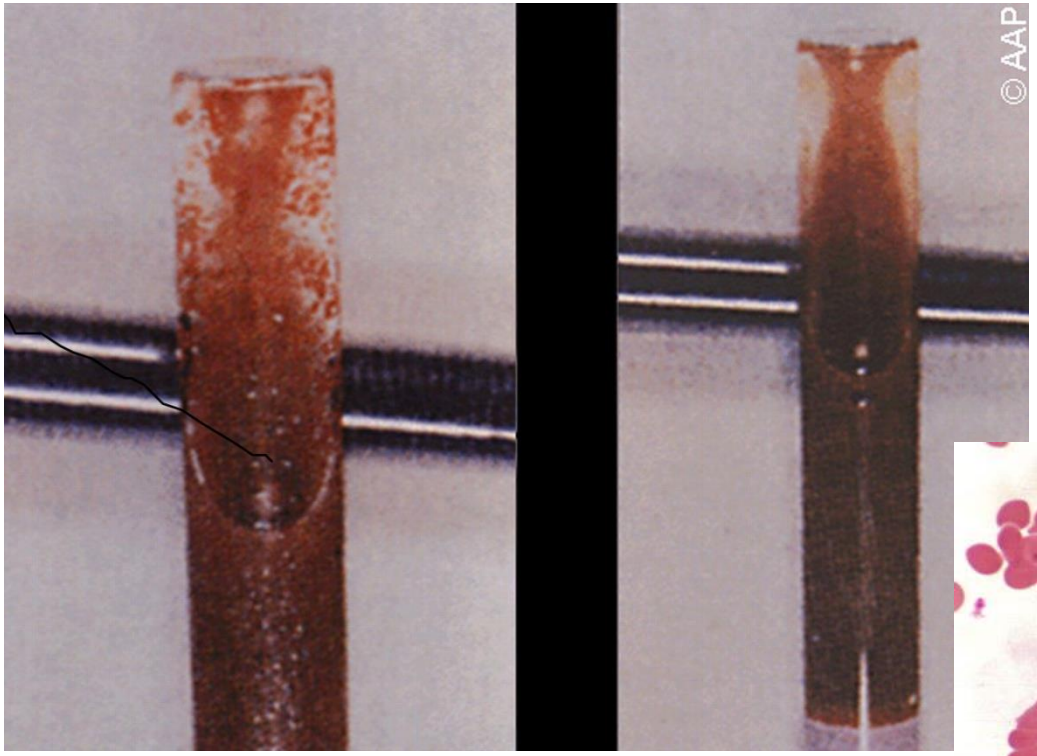
DAT-Positive with C3d only

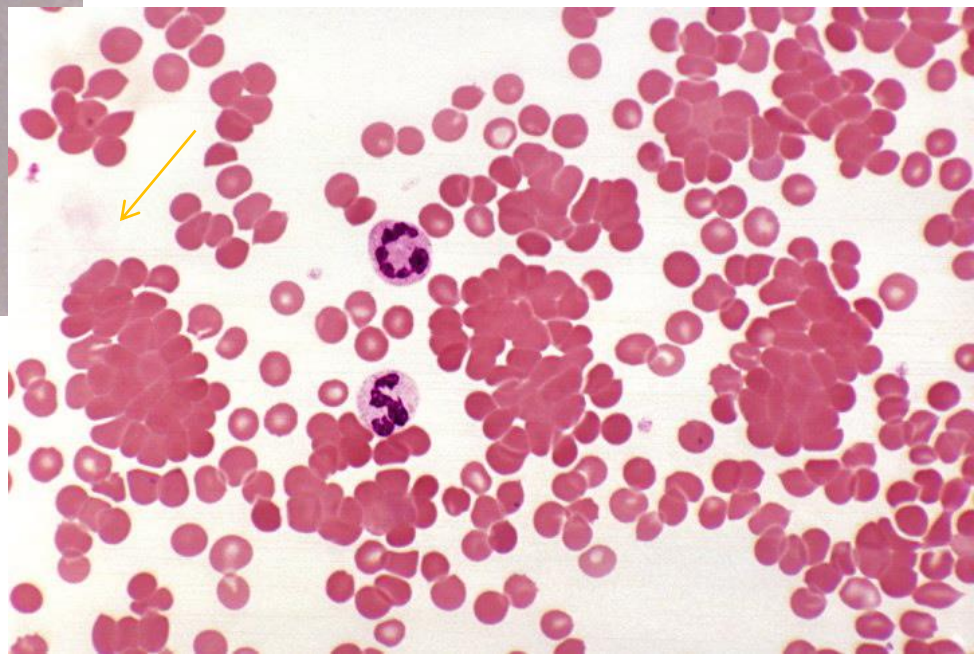
Ab elutes in the warmer parts of the body

Other tests- Ab titer, thermal range & specificity

tests for secondary cause

- Multivalent antibodies, such as IgM, can crosslink adjacent red blood cells, resulting in agglutination





Treatment

- Keep the patient warm
- Treat the underlying cause
- Monoclonal ab- Rituximab
- Alkylating agents- Chlorambucil
- Purine nucleoside analogues- Fludarabine
- **Steroids/Splenectomy-not useful**

Treatment cont.

- Blood transfusion- only for symptomatic patients
- Blood warmers

PRECAUTIONS

- Avoid cold exposure

PCH*(Paroxysmal cold haemoglobinuria)*

- Rare
- Biphasic Ig G Ab
- BG Ag P
- Binds to RBC Ag at cold; lysis with compliments in warm conditions
- **IVH** in cold
- Viral inf, Syphillis
- Donath- Landsteiner test

IMMUNE HEMOLYSIS

- 3 MECHANISMS

1.IC-Ab directed against drug RBC complex: Penicillin, Ampicillin

2.Hapten induced

Quinidine, rifampicin

3.True AIHA

EX: Methyl dopa

Drug should be discontinued

ALLOIMUNE HEMOLYSIS

Hemolytic Transfusion Reaction

- Caused by recognition of foreign antigens on transfused blood cells

Hemolytic Disease of the Newborn

- Due to incompatibility between mother negative for an antigen & fetus/father positive for that antigen.

Rh incompatibility, ABO incompatibility

Requires maternal IgG antibodies *vs.* RBC antigens in fetus

Other acquired haemolytic anaemia

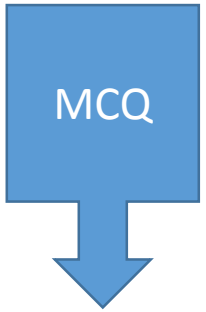
Acquired HA

- Immune
- ***Red cell fragmentation syndrome***
- March haemoglobinuria
- Infections
- Chemical and physical agents
- ***PNH***

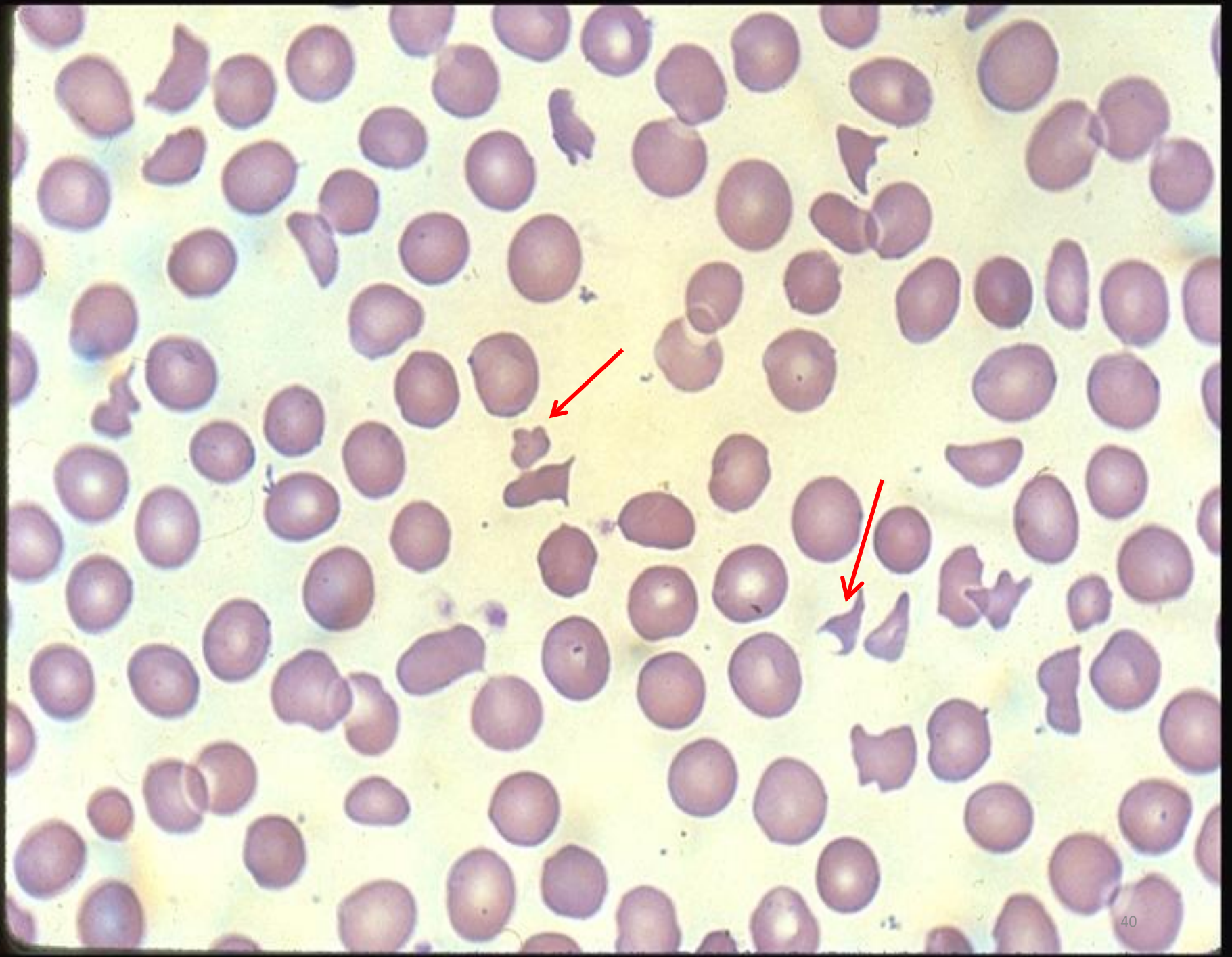
Red cell fragmentation syndrome

- Cardiac
- Arteriovenous malformations
- Microangiopathic

Microangiopathic haemolysis

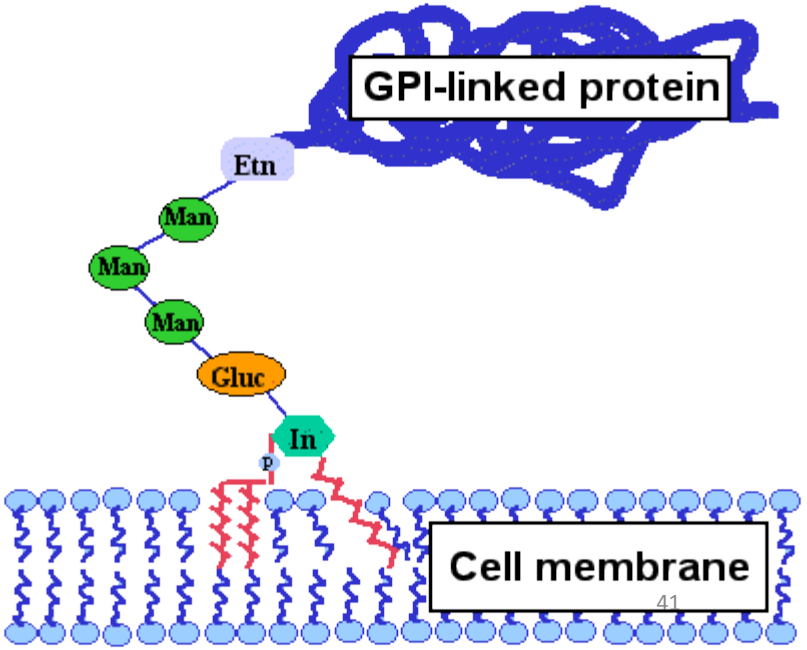


- TTP/HUS
- DIC
- Disseminated malignancy
- Severe vasculitis
- Malignant HPT
- Pre eclampsia/HELP
- Renal vascular disorders
- Ciclosporin



PNH

- Rare
- Acquired clonal disorder
- Deficient GPI(Glycosylphosphatidylinositol) anchor synthesis
- GPI attaches certain proteins to cell surface
- Mutation in the PIG A gene
- Can progress to AA/AML

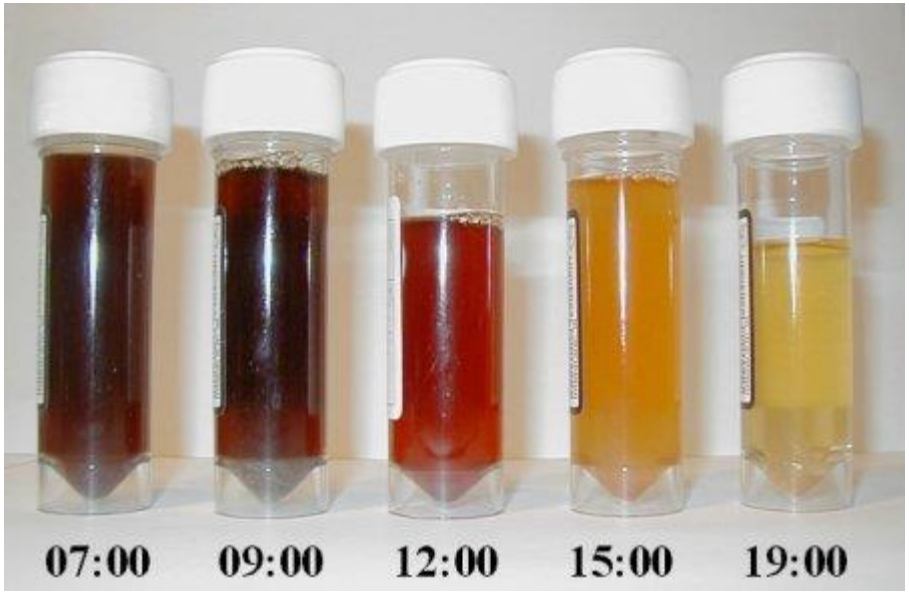


- GPI linked proteins:CD55 & 59
- CD 55-DAF
- CD 59-MIRL

} protect RBC from compliment lysis

Clinical features

- Ongoing Intra- & extra vascular haemolysis; classically at night-dark urine in the morning



- Symptoms related to cytopenias
- Recurrent thrombosis
- Thrombosis at unusual sites-Budd chiari xn

Investigations

- FBC+BP-Cytopenias, fe def features , Polychromasia
- Retic count
- Urine-haemosidderin
- Ham test-not confirmatory
- Flow cytometry- look for CD 55/59 def cells

Management

- Supportive-Blood Transfusion, iron therapy
- Eculizumab- ab against C5
- Long term anticoagulation in selected pts
- Allogenic BM transplantation –definitive treatment

- Immune haemolysis is an important cause of acquired haemolytic anaemia
- Two types of autoimmune haemolysis-Warm and cold
- Characterised by DAT positivity
- Secondary causes should be excluded
- Management depends on the type