Hemolytic Anemia (HA)

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ANEMIAS … GENERAL

SUMMARY

PATHOLOGY OF ANEMIA

Causes

- Blood loss (hemorrhage)
- Increased red cell destruction (hemolysis)
- Decreased red cell production

Morphology

- Microcytic (iron deficiency, thalassemia)
- Macrocytic (folate or vitamin B_{12} deficiency)
- Normocytic but with abnormal shapes (hereditary spherocytosis, sickle cell disease)

Clinical Manifestations

- **Acute:** shortness of breath, organ failure, shock
- **Chronic**
  - Pallor, fatigue, lassitude
  - With hemolysis: jaundice and gallstones
  - With ineffective erythropoiesis: iron overload, heart and endocrine failure
  - If severe and congenital: growth retardation, bone deformities due to reactive marrow hyperplasia

Start up basic test

Table 12.2 Adult Reference Ranges for Red Blood Cells[a]

	Units	Men	Women
Hemoglobin (Hb)	g/dL	13.2–16.7	11.9–15.0
Hematocrit (Hct)	%	38–48	35–44
Red cell count	$\times 10^6/\mu L$	4.2–5.6	3.8–5.0
Reticulocyte count	%	0.5–1.5	0.5–1.5
Mean cell volume (MCV)	fL	81–97	81–97
Mean cell Hb (MCH)	pg	28–34	28–34
Mean cell Hb concentration (MCHC)	g/dL	33–35	33–35
Red cell distribution width (RDW)		11.5–14.8	

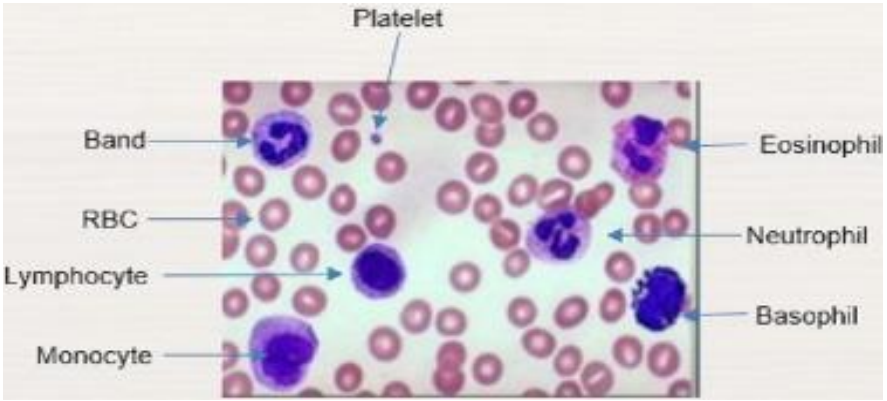
[a]Reference ranges vary among laboratories. The reference ranges for the laboratory providing the result should always be used in interpreting a laboratory test.

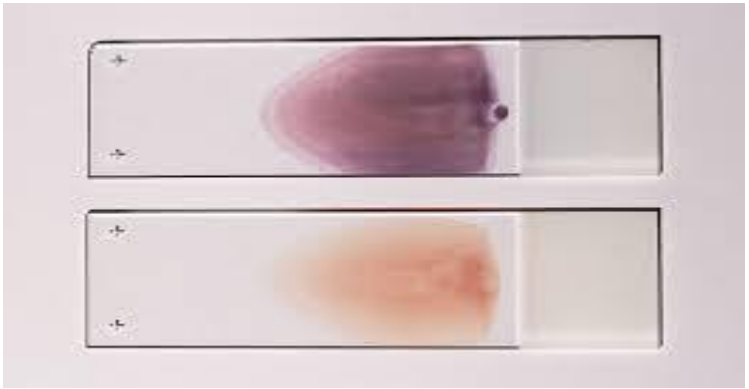
Additional tests

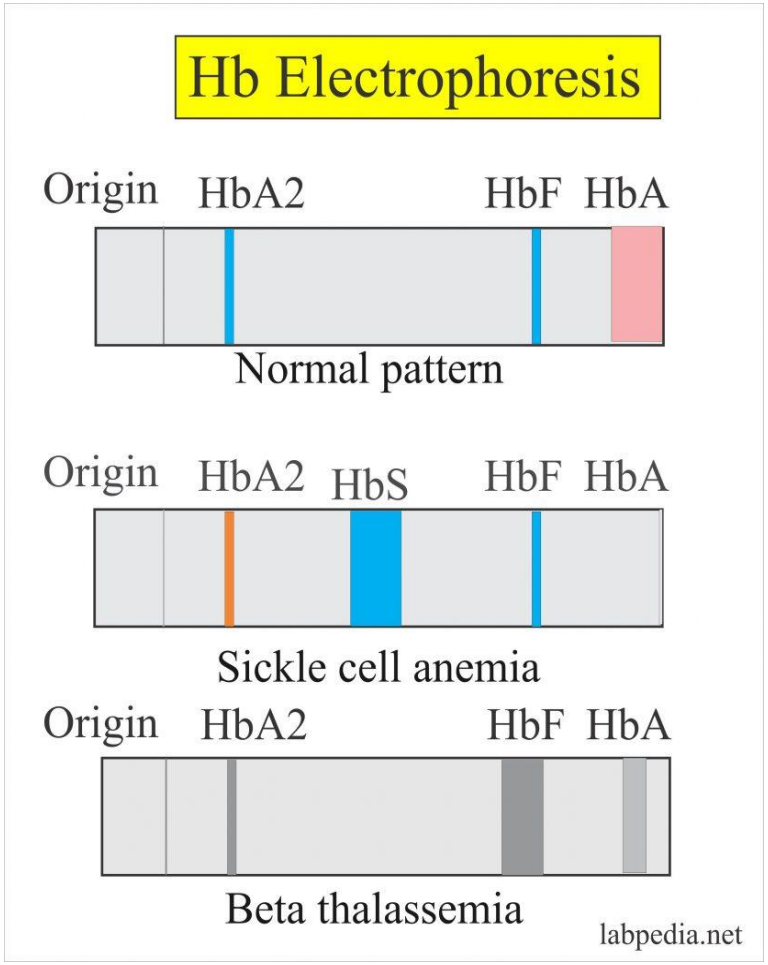
- Serum iron indices (iron levels, iron-binding capacity, transferrin saturation, and ferritin concentrations)
- plasma unconjugated bilirubin, haptoglobin, and lactate dehydrogenase levels, which are abnormal in hemolytic anemia;
- serum and red cell folate and vitamin B12 concentrations, which are low in megaloblastic anemia;
- hemoglobin electrophoresis, which is used to detect abnormal hemoglobin;
- Coombs test, which is used to detect antibodies or complements
- Peripheral blood smear (film)

Tests

Peripheral blood smear





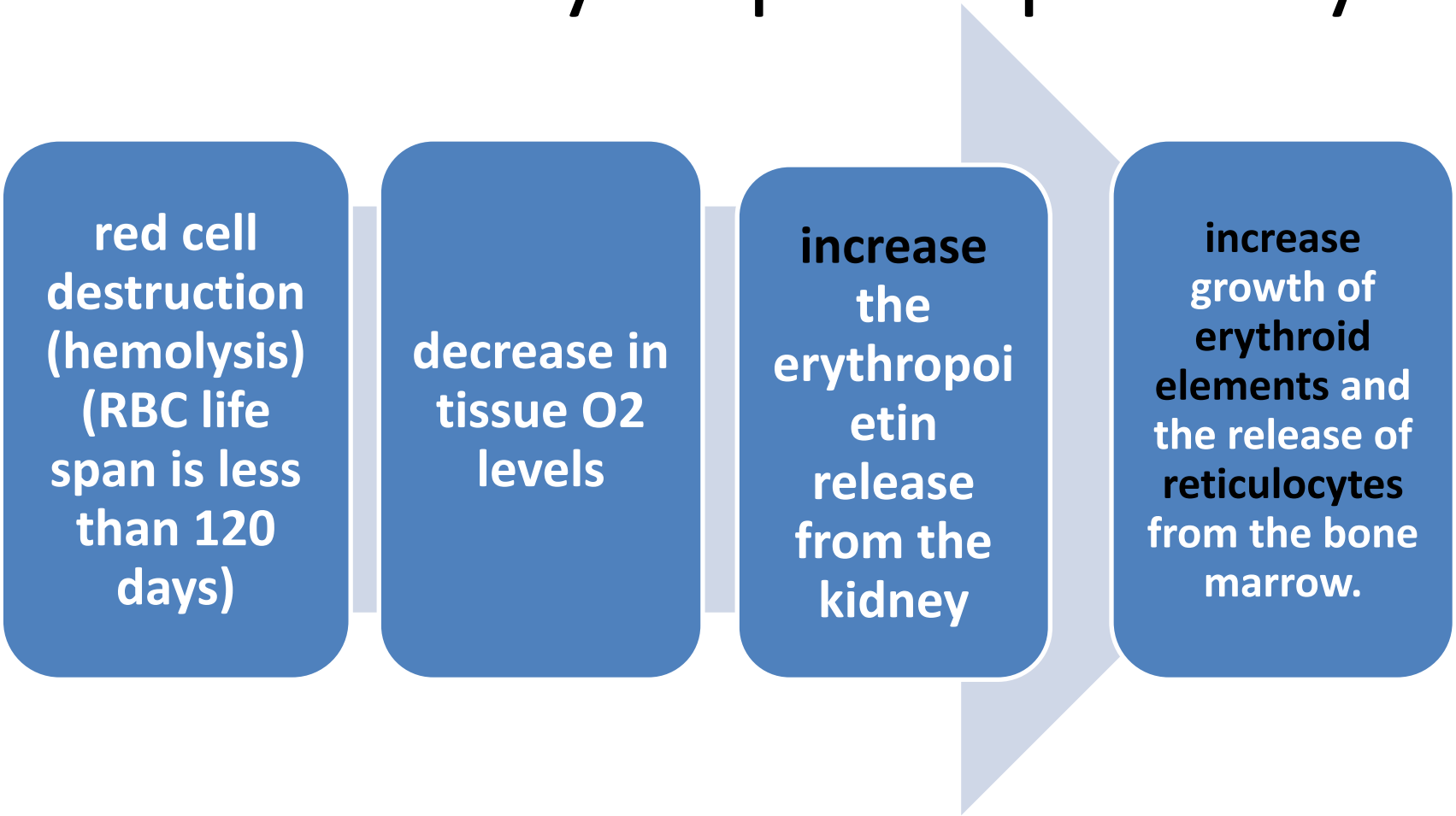


HEMOLYTIC ANEMIA

- Hemolytic anemias are a diverse group of disorders that have as a common feature **accelerated red cell destruction (hemolysis) and so decrease in RBC life span**.

- *Normal RBC life span is 120 days.*

Normal body response pathway

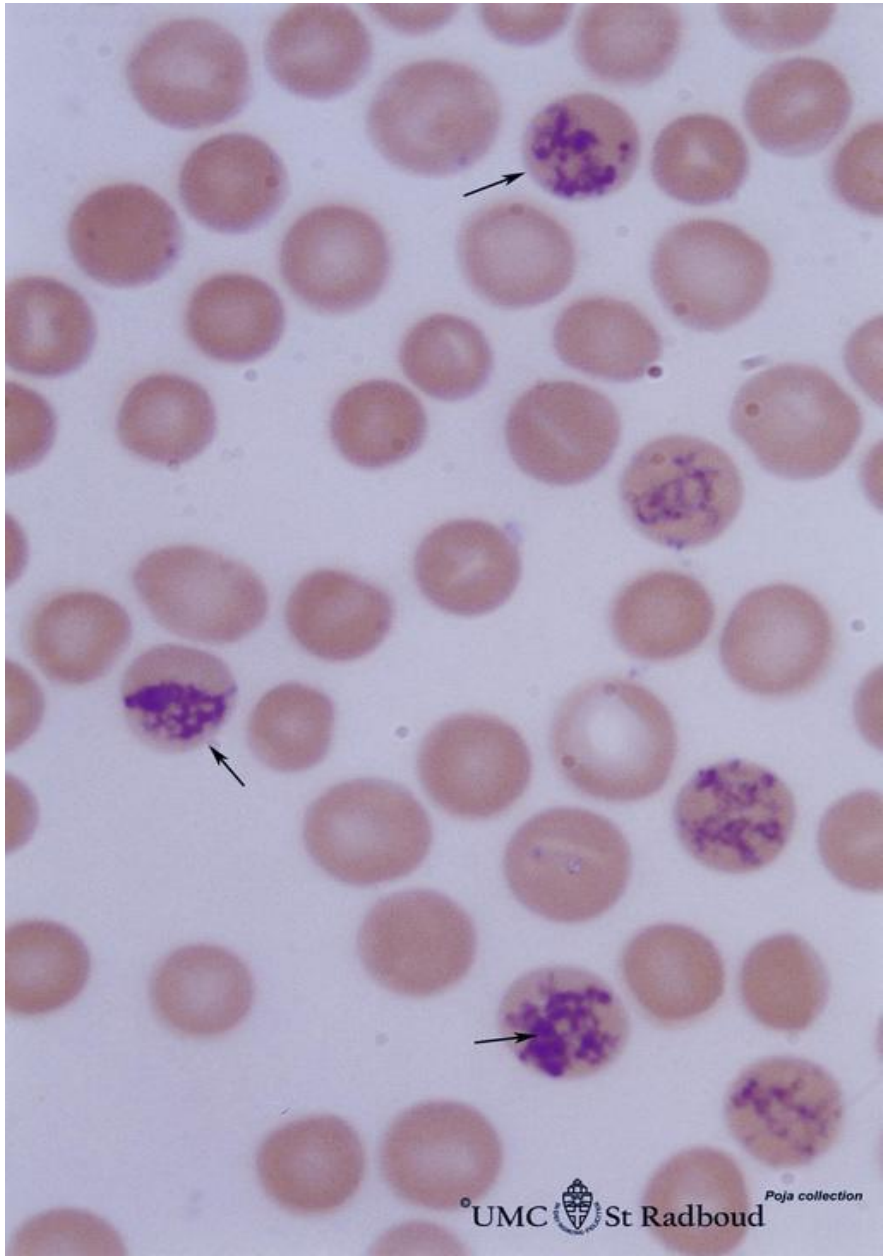


erythroid hyperplasia and reticulocytosis....

Hallmarks of hemolytic anemias

Reticulocytes:

- **Immature (RBCs).**
- Normally getting mature within bone marrow.
- may be seen in peripheral blood normally in range of 0.5% to 2.5% in adults and 2% to 6% in infants.
- Reticulocytes **do not have a cell nucleus** . But have reticular (mesh-like) network of **ribosomal RNA.**
- **Increase in count in hemolysis.**



- In **severe** hemolytic anemias there may be ***extramedullary hematopoiesis*** *in the liver, spleen, and lymph* nodes (not only in bone marrow).

Pathological classification of HA

Increased Destruction (Hemolytic Anemias)

Intrinsic (Intracorpuscular) Abnormalities

Hereditary

Membrane abnormalities
- Membrane skeleton proteins: spherocytosis, elliptocytosis
- Membrane lipids: abetalipoproteinemia

Enzyme deficiencies
- Enzymes of hexose monophosphate shunt: glucose-6-phosphate dehydrogenase, glutathione synthetase
- Glycolytic enzymes: pyruvate kinase, hexokinase

Disorders of hemoglobin synthesis
- Structurally abnormal globin synthesis (hemoglobinopathies): sickle cell anemia, unstable hemoglobins
- Deficient globin synthesis: thalassemia syndromes

Acquired

Membrane defect: paroxysmal nocturnal hemoglobinuria

Extrinsic (Extracorpuscular) Abnormalities

Antibody-mediated
- Isohemagglutinins: transfusion reactions, immune hydrops (Rh disease of the newborn)
- Autoantibodies: idiopathic (primary), drug-associated, systemic lupus erythematosus

Mechanical trauma to red cells
- Microangiopathic hemolytic anemias: thrombotic thrombocytopenic purpura, disseminated intravascular coagulation
- Defective cardiac valves

Infections: malaria

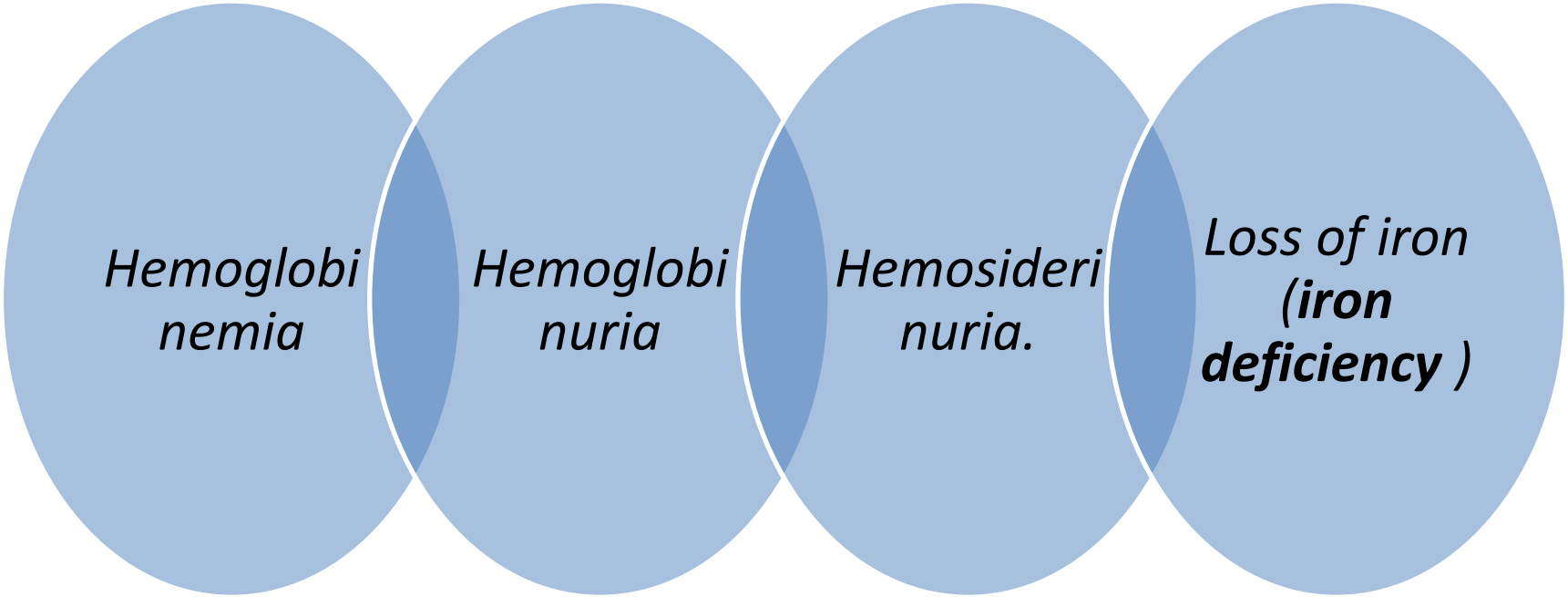
Clinical classification of HA

- ***Intravascular hemolysis***
- ***Extravascular hemolysis***

Intravascular hemolysis

- ***Intravascular hemolysis is characterized* by injuries so severe that red cells literally burst within the circulation.**
- **Causes;**
  - mechanical forces (e.g., defective heart valve)
  - biochemical factors (e.g fixation of complement, clostridial toxins)
  - physical agents (e.g heat).

hemolysis Findings that distinguish intravascular :from extravascular hemolysis include

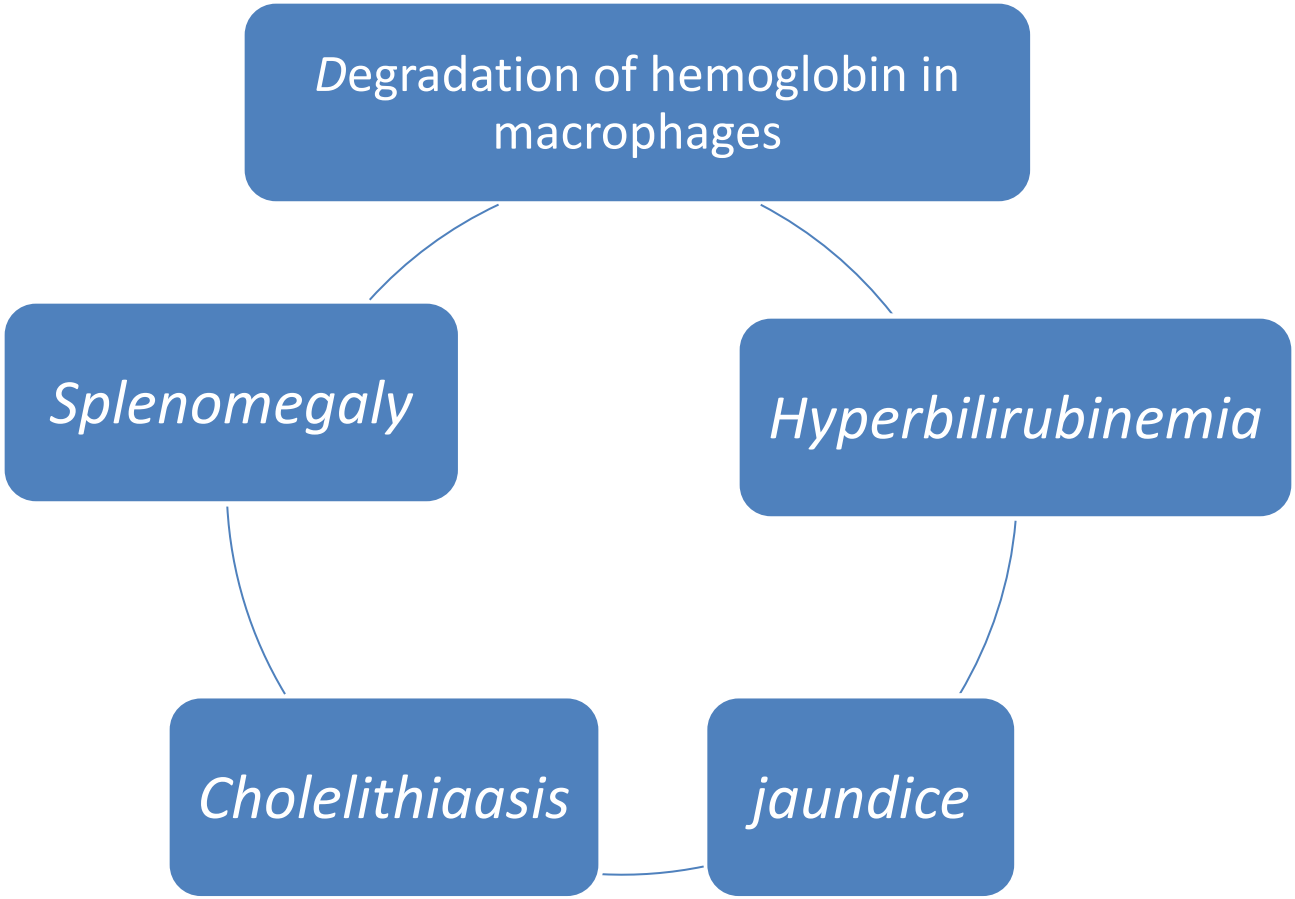


***Haptoglobin (*plasma protein) that binds free hemoglobin…. So low haptoglobin level in blood**

Extravascular hemolysis

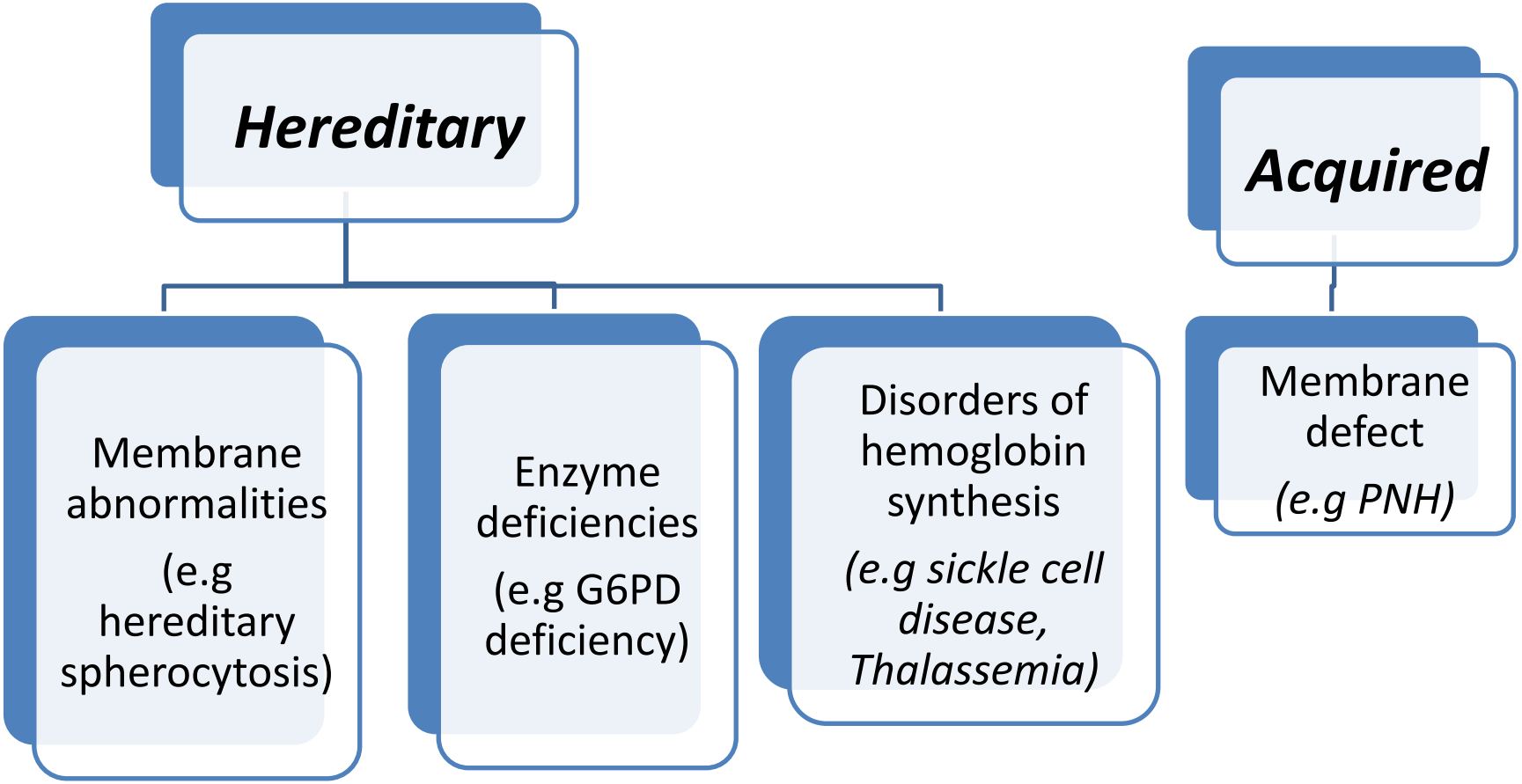
- ***Extravascular hemolysis is caused by defects that* increase the destruction of red cells by phagocytes, particularly in the spleen.**
- Abnormal RBC (for any reason) will lead to **diminished deformability** … so cannot pass through the splenic sinusoides…. Stuck there… then phagocytosed by resident splenic macrophages.

Findings that are relatively specific for extravascular hemolysis



macrophages“regurgitate” hemoglobin… So low haptoglobin level

intrinsic (intracorpuscular)



Hereditary Spherocytosis (HS)

- **inherited (intrinsic) defects in the red cell membrane that lead to the formation of spherocytes, nondeformable cells that are highly vulnerable to sequestration and destruction in the spleen**
- autosomal dominant(AD), mainly
- autosomal recessive (AR), in a minority, more sever

HS.. Pathogenesis

- **Hereditary spherocytosis is caused by inherited defects in the membrane skeleton, a network of proteins that stabilizes the lipid bilayer of the red cell.**
- **Mainly : ankyrin, band 3, spectrin.**

HS.. Pathogenesis.. Cont'd

Weakening of vertical interactions between the membrane skeleton and intrinsic red cell membrane proteins.

↓

Destabilizes the lipid bilayer

↓

shed membrane vesicles as they age.

↓

Little cytoplasm is lost in this process

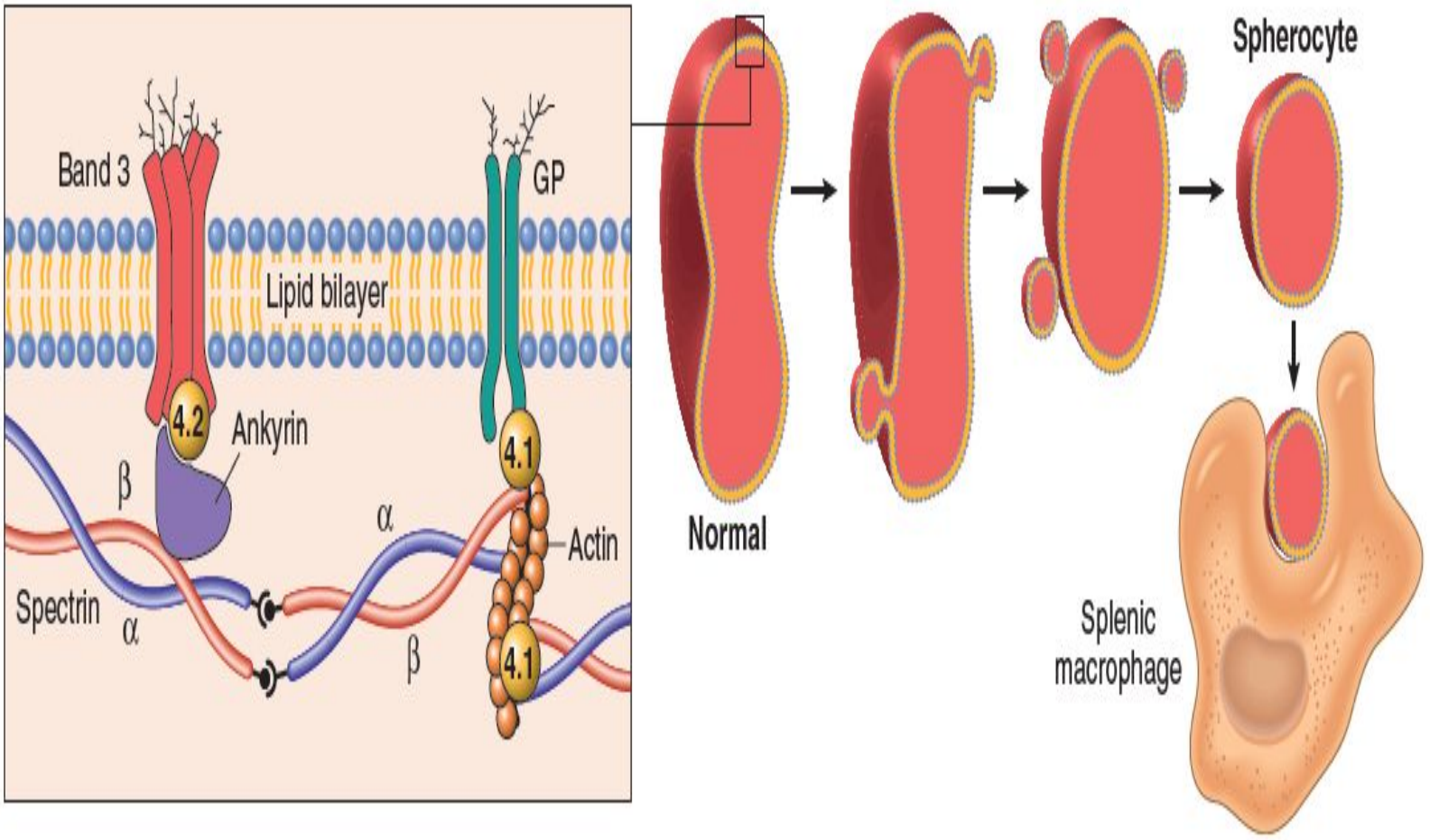
↓

decreases surface area-to volume ratio

↓

become spherical red cell shape

HS.. Pathogenesis.. Cont'd



HS.. Pathogenesis.. Cont'd

Spherocytes have limited deformability

↓

Sequestered in the splenic cords

↓

Destroyed by the resident macrophages

↓

Cause anemia

↓

Compensatory hyperplasia of red cell progenitors in the marrow

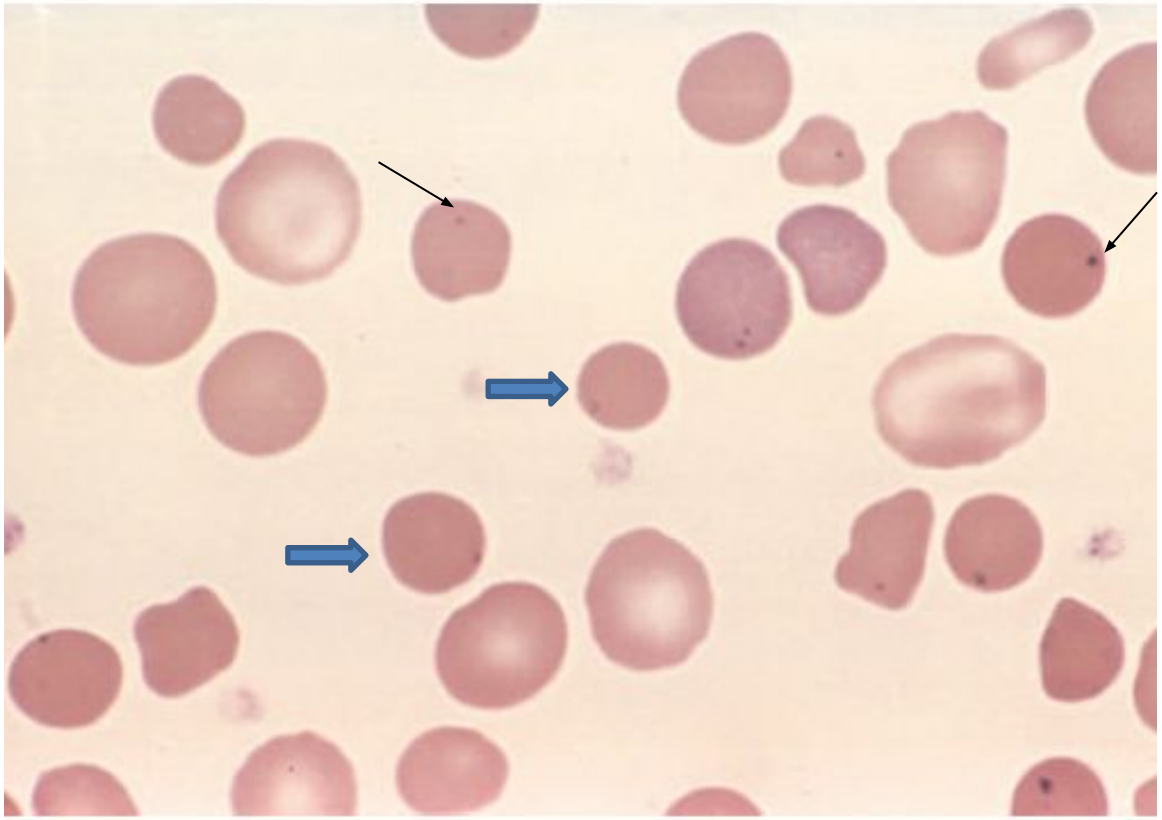
↓

Increase in red cell production

↓

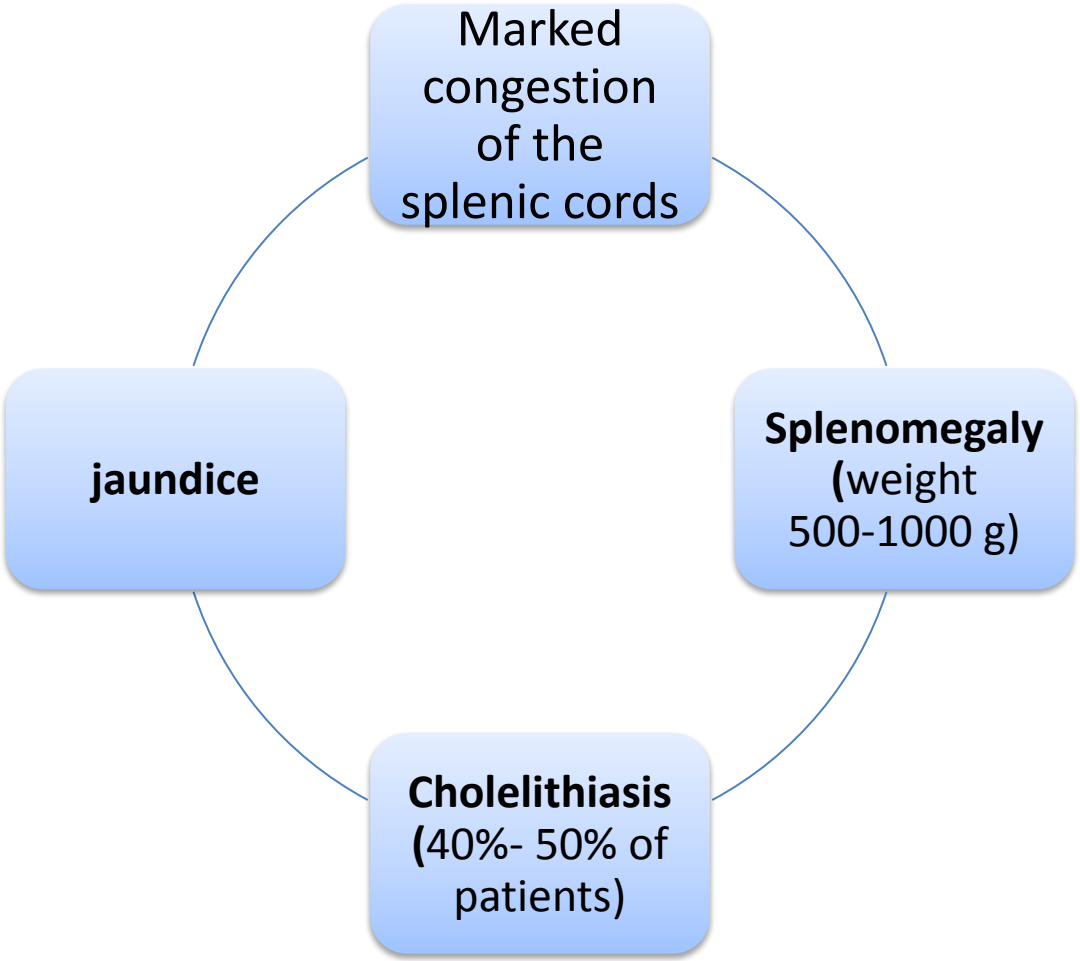
Reticulocytosis

On peripheral blood smear:



- **Spherocytes (⟶) RBC are dark red and lack central pallor**
- **Howell-Jolly bodies (⟶) : small nuclear remnants in RBC (normally removed in spleen .. But it will be seen if asplenic / splenectomy done)**

Clinical Features



Clinical Features

- anemia, splenomegaly, and jaundice, Variable (mild .. moderate … sever)
- **Increased *osmotic fragility*** *(decreased capacity of spherocytes to expand when placed in hypotonic salt solutions)*
- *The clinical course is generally stable .. Unless* ***parvovirus B19 infection*** → *attack mainly the* ***erytheroblsts*** → *delayed RBC production cause* ***aplastic crises*** *+short spherocytes life span* → *worsening of anemia … need* Blood transfusions until the infection cleared (10-14 days)

Treatment

- There is no specific treatment.
- **Splenectomy** improves the anemia by removing the major site of red cell destruction.
- in **children** increased risk of serious bacterial infections, (less in adults), so, **Partial** splenectomy is **favored**
- **BUT…** the partially resected spleen eventually regains its size…. May need a second resection…

Glucose-6-Phosphate Dehydrogenase (**G6PD**)

- Glucose-6-phosphate dehydrogenase (**G6PD**) and other **enzymes** are needed to produce **Glutathiaon (GSH).**
- The G6PD gene is on the **X chromosome**.
- Endogenous and exogenous **oxidants** are normally inactivated by reduced glutathione (GSH)… by formation of an oxidized GSH… so no RBC injury occur.

Glucose-6-Phosphate Dehydrogenase (**G6PD**) Deficiency

- The G6PD deficiency disease is an **X- linked disease**.
- More than 400 G6PD variants
- Also Known as **Favism** (Fava beans)
- **G6PD A– variant (10% of black males in the USA).**
- G6PD A– has a normal enzymatic activity but a decreased half-life.
- older G6PD A– red cells become progressively deficient in enzyme activity and GSH.
- So older red cells more sensitive to oxidant damage.
- **G6PD Mediterranean variant**, found mainly in the Middle East, the enzyme deficiency and the hemolysis that occur on exposure to oxidants are **more severe.**

Pathogenesis

- G6PD deficiency is associated with **transient episodes of intravascular hemolysis** caused by exposure to an **environmental factors** (usually infectious agents or drugs) that produces **oxidant** stress.
- **Foods**: fava beans, falafel…..
- **Drugs**: antimalarials (e.g., primaquine), sulfonamides, nitrofurantoin, phenacetin, aspirin (in large doses), and vitamin K derivatives.
- **Infections**: More common.

Pathogenesis.. Cont'd

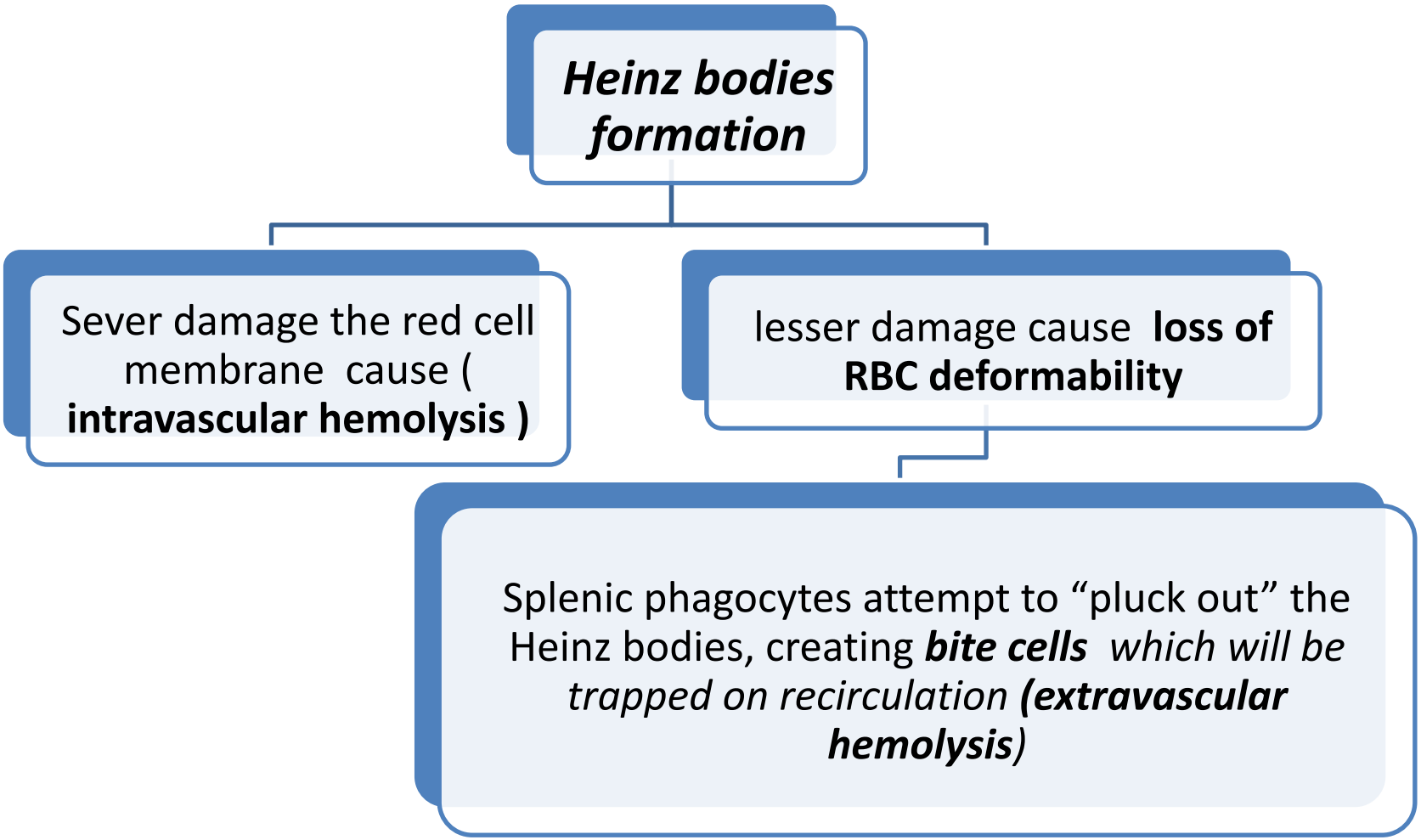
Infections

induce phagocytes to generate oxidants (e.g hydrogen peroxide).

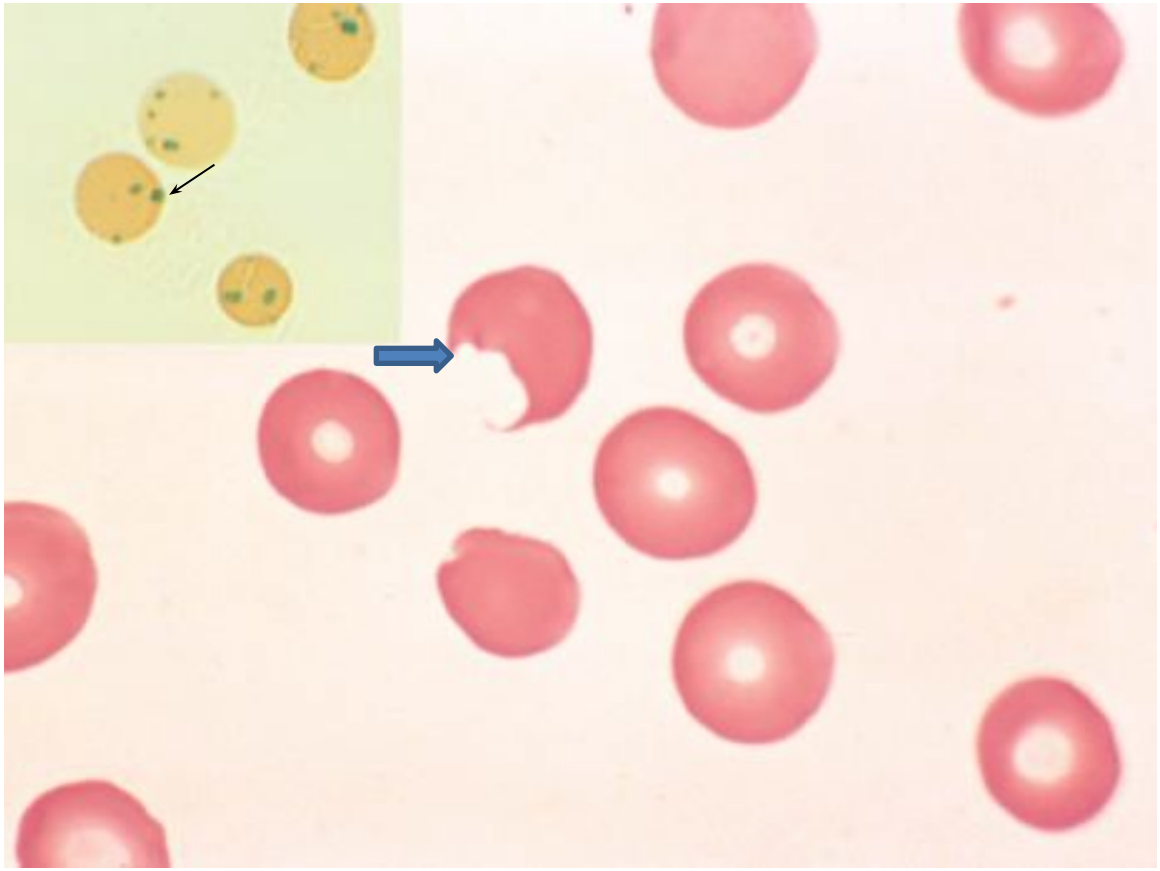
"attack" other red cell components including globin chains.

Oxidized hemoglobin denatures and precipitates, **forming intracellular inclusions** called ***Heinz bodies***

Morphology


Heinz bodies formation
Sever damage the red cell membrane cause (**intravascular hemolysis)**
lesser damage cause **loss of RBC deformability**
Splenic phagocytes attempt to “pluck out” the Heinz bodies, creating ***bite cells*** *which will be trapped on recirculation* ***(extravascular hemolysis)***

Peripheral blood smear



Heinz bodies and bite cells

Clinical Features

- Hemolysis typically develops 2 or 3 days after drug/food exposure and is of variable severity.
- G6PD is X-linked, the red cells of affected **males** are **uniformly** deficient and vulnerable to oxidant injury.
- Random inactivation of one X chromosome in heterozygous **females** cause a **carrier** females.. have two RBC population… So usually **unaffected** …
  - Unless (*unfavorable lyonization)*

Paroxysmal Nocturnal Hemoglobinuria (PNH)

- An example of **intracorpuscular** (intrinsic) **acquired** anemia with **membrane** defect.
- Acquired mutations in ***PIGA.***
- *PIGA: an* ***X-linked*** gene required for the **synthesis** of phosphatidylinositol glycan (**PIG**), which serves as a membrane anchor for many proteins.

PNH… Cont'd

- Mutations in PNH occur in an **early hematopoietic progenitor** that will give rise to red cells, leukocytes, and platelets
- lack the ability to make "PIG-tailed" proteins .. So no control on complement activity… so lysis by the complement C5b-C9 membrane attack complex… mainly at **night** (**nocturnal**.. Low PH, activate complement fixation)
- (**RBC is more sensitive than WBC**)

Clinical features

- Intravascular hemolysis
- anemia and iron deficiency
- The most feared complication of PNH is **thrombosis**, which often occurs within abdominal vessels such as the portal vein and the hepatic vein.

extrinsic (extracorpuscular)

Antibody-mediated	• Isohemagglutinins: transfusion reactions, immune hydrops (Rh disease of the newborn) • **Autoantibodies**: idiopathic (primary), drug-associated, systemic lupus erythematosus
Mechanical trauma to red cells	• **Microangiopathic hemolytic anemias**: thrombotic thrombocytopenic purpura, disseminated intravascular coagulation • **Defective cardiac valves**
Infections	• malaria

Immunohemolytic Anemia

- **Caused by antibodies that bind to red cell membrane.**
- Diagnosis depends on the detection of antibodies and/or complement on red cells using Coombs test:
  - Direct Coombs test (patient RBC) to identify the type of antibody response
  - Indirect Coombs test (patient serum) to identify the target on RBC

Immunohemolytic Anemia.. Cont'd

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

- Results from the binding of high-affinity **autoantibodies** to red cells, which are then removed from the circulation by phagocytes in the spleen… so develop anemia and splenomegaly.
- caused by immunoglobulin G (**IgG**) or (rarely) IgA antibodies that are active at **37°C**.
- Causes**:**
  - **idiopathic** (**primary**) in more than **60**%
  - secondary to an underlying , B-cell neoplasm, immunologic disorder (e.g. systemic lupus erythematosus) or are induced by drugs in 25%.

Cold Antibody Immunohemolytic Anemia

- Caused by low-affinity **IgM** antibodies that bind to red cell membranes only at temperatures below **30°C**, such as occur in **distal parts** of the body (e.g., ears, hands, and toes) in **cold weather**.
- Causes:
  - *Acute: Mycoplasma infection, infectious mononucleosis*
  - *Chronic: idiopathic, B cell lymphoid neoplasms (e.g., lymphoplasmacytic* lymphoma)

Cold Antibody Immunohemolytic ..Anemia.. Cont'd

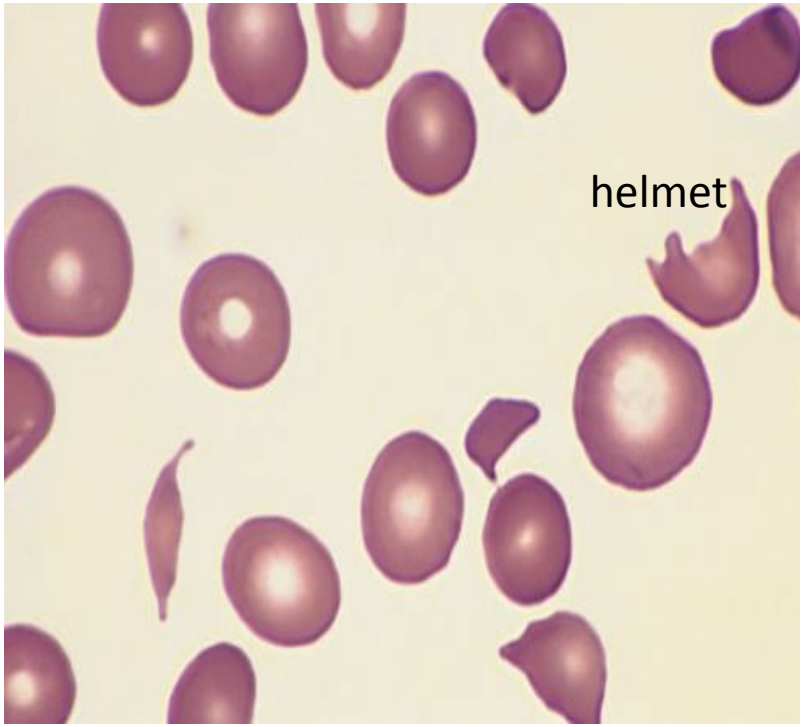
- The RBC will be coated with **C3b** complement and will be **phagocytosed** by macrophages, mainly in the spleen and liver… anemia and splenomegaly
- IgM also **cross links** red cells and causes them to clump (***agglutinate****)… lead to* ***Sludging*** *of blood in capillaries… cause* ***Raynaud phenomenon*** *in* the extremities of affected individuals.

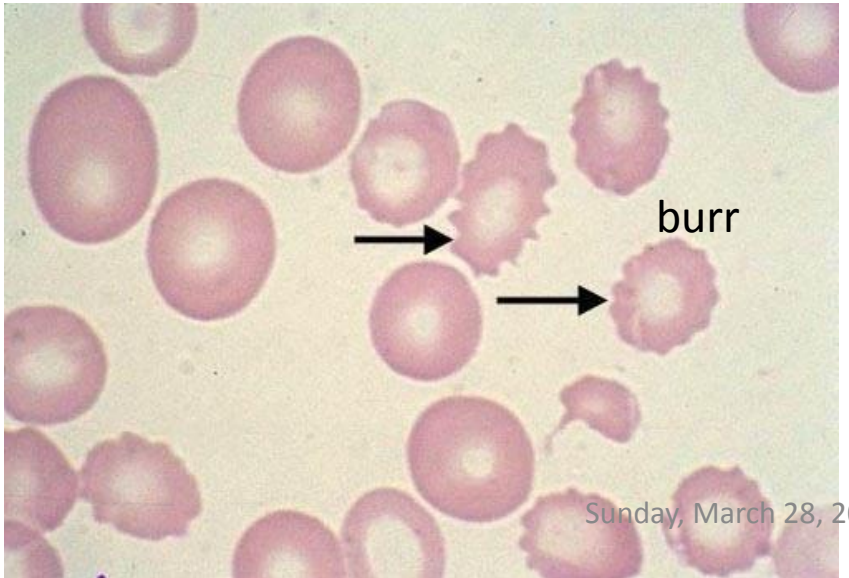
Hemolytic Anemia Resulting From Mechanical Trauma to Red Cells

Microangiopathic hemolytic anemias:	• Thrombotic thrombocytopenic purpura • Disseminated intravascular coagulation • Hemolytic uremic syndrome (HUS) • others
Defective cardiac valves	
Repeated physical pounding	• marathon racing, karate chopping, bongo drumming

Schistocytosis

Mechanical **fragmentation** of **red cells** (***schistocytosis***) *leads* to the appearance of characteristic “burr cells,” “helmet cells,” and “triangle cells” in peripheral blood smears.





THANKS