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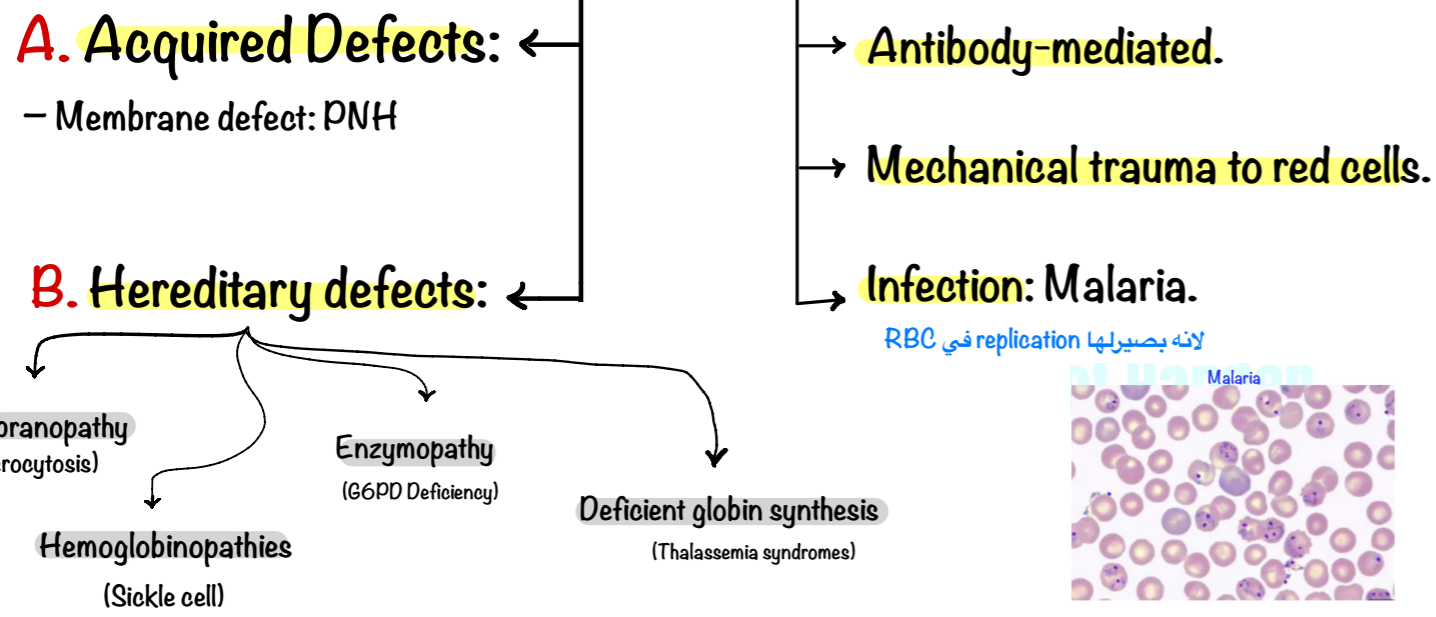
# Hemolytic anemia

caused by

- 1- accelerated destruction of RBCs
- 2- ↑ Hb catabolism (↑ hb breakdown → jaundice)
- 3- ↓ Hb
- 4- ↑ Efforts of BM to regenerate product  
رج يحاول يعمل compensation BM hyperplasia ←

Acute and chronic disease  
 Immune vs. non-immune mediated  
(Depending on mechanism)  
 Inherited or acquired  
(Cause)

## Intracorpuseular or extracorpuseular



## Intravascular or extravascular (Site of hemolysis)

- Cell destruction inside the B.V
- Hemoglobinemia.
- Hemoglobinuria.
- Hemosiderinuria.
- Marked decrease in Haptoglobin  
لأنه استهلكته حتى يمسيك free Hb  
 "almost absent"

- Destruction of red cells by phagocytes
- In reticuloendothelial system (spleen & liver)
- Splenomegaly
- Hyperbilirubinemia and jaundice.  
Occur in both IV. H and EV. H
- Mild decrease in Haptoglobin
- No (Hburia, Hbemia, Hemosiderinuria)

**التوضيح:**

RBC destruction → Release of hb (toxic) → يرتبط فيه haptoglobin  
 انه affinity معينة اذا وصلها رج يصير supersaturation وبالتالي عندي كمية من free hb تروح لل kidney ويصير له absorption من renal tubule ورج تفك iron عن heme  
 Shedding of renal tubule cells وتنزل مع urine ← hemosiderin (toxic) ←



## A simplified approach to diagnosis of haemolytic anaemias

(CBC → ↓ Hb)  
 مريض Anemia وعنده H.A sign  
 Next step  
 عمل peripheral blood smear

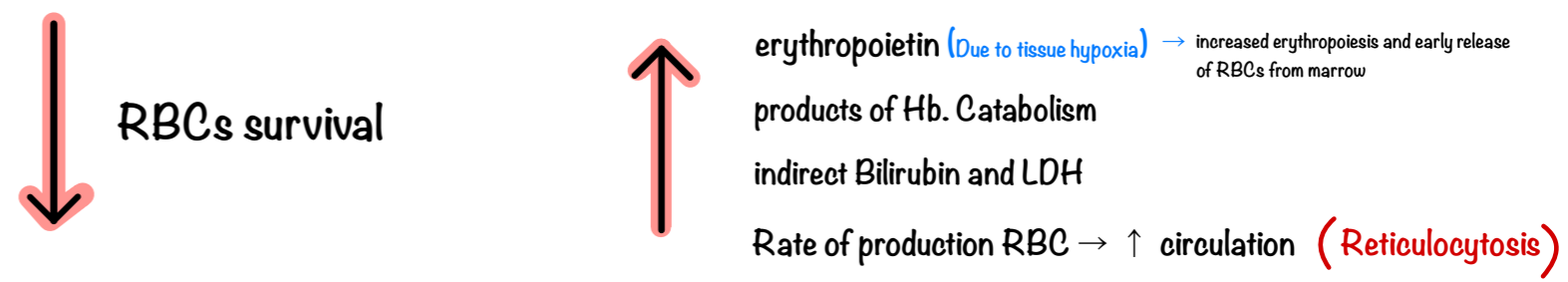
Laboratory features suggestive of haemolytic anaemia  
 (Low haemoglobin, raised indirect serum bilirubin, reticulocytosis)

Examination of blood smear

- Spherocytes**
  - DAT +ve → Autoimmune haemolytic anaemia
  - DAT -ve → Hereditary spherocytosis
- Schistocytes (fragmented RBCs)** → Microangiopathic haemolytic anaemia
  - Thrombotic thrombocytopenic purpura
  - Haemolytic uraemic syndrome
  - Disseminated intravascular coagulation
- Microcytic hypochromic cells** → Thalassaemia
- Sickle cells** → Sickle-cell disorders
- Bite cells** → G6PD deficiency
- Normal red cells** → PNH, G6PD deficiency, unstable haemoglobin disease
- Malaria parasite** (Dot inside RBCs)

Activation of complement in RBC membrane	Physical or Mechanical Trauma to the RBC	Toxic Microenvironment of the RBC
<ul style="list-style-type: none"> <li>- Paroxysmal nocturnal hemoglobinuria</li> <li>- Paroxysmal cold hemoglobinuria</li> <li>- Some transfusion reactions</li> <li>- Some autoimmune hemolytic anemias</li> </ul>	<ul style="list-style-type: none"> <li>- Microangiopathic hemolytic anemia</li> <li>- Abnormalities of heart vessels  <small>↑ risk ← Turbulent B.F ← Narrowing of BV</small></li> <li>- DIC</li> </ul>	<ul style="list-style-type: none"> <li>- Bacterial infections</li> <li>- Plasmodium falciparum infection (Malaria)</li> <li>- Venoms</li> <li>- Thermal injury</li> <li>- Acute drug reaction in G6PD deficiency</li> </ul>

## Features of Hemolytic Anemia :



# Hereditary Spherocytosis

- **Inherited (intrinsic) defects** in the red cell membrane / Run in families, AD, fx of splenectomy

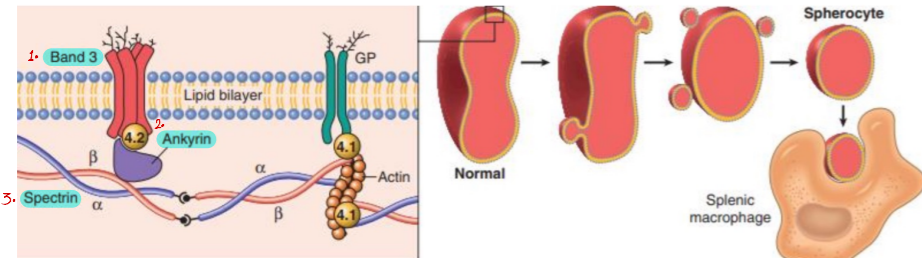
**lead to** → formation of spherocytes, **nondeformable cells** that are highly vulnerable to sequestration and destruction in the spleen. ↗ Rigid RBC

**Caused by** → inherited defects in the membrane skeleton, a network of proteins that stabilizes the lipid bilayer of the red cell.

(Loss of cell membrane in the form of blebs due to membrane instability  
Decrease cell membrane to cytoplasmic ration > spherical RBCs that are non-deformable)

\* mutations in (1+2+3)

رج اخسر lipid bilayer stability & biconcave shape



## Clinical

✓ **Anemia, splenomegaly and jaundice.**

✓ **Gallbladder stones.** bilirubin من مكونة من Bigmented stone نوع اذا المريض عنده (chronic hemolysis)

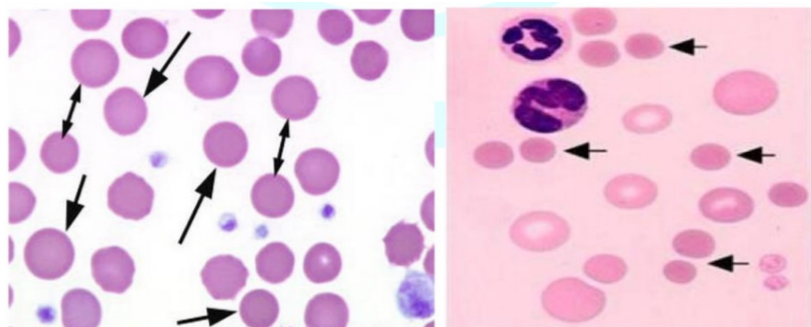
(Severity of anemia correlates with spectrin deficiency)

✓ **Aplastic crisis: 2ry to Parvovirus B19.**

BM suppression ←

يعمل infection لل erythroid precursor inside B.M

Sheddown of RBCs production ←



# G6PD Deficiency

- More common in males

- on chromosome X

- Anti-oxidant (disposal of H<sub>2</sub>O<sub>2</sub>)

- ↓ in GSH causes hemolysis in cells exposed to oxidant agent



Patients are asymptomatic until exposed to:

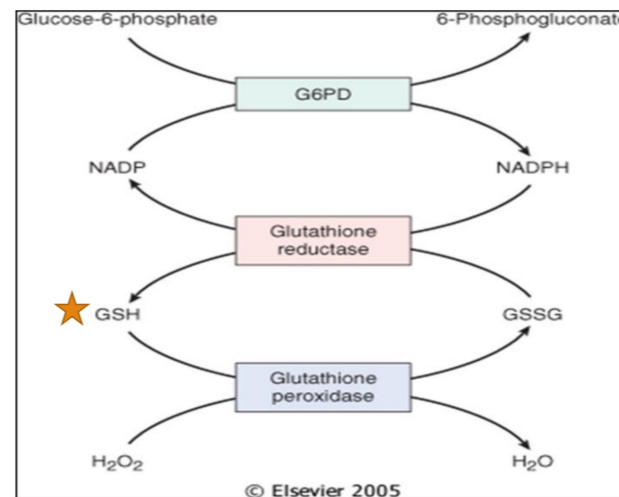
✓ **Drugs:** Antimalarial, sulfonamides.

✓ **Favism.**

✓ **Products of FR** in infections.



## Pathogenesis:



Loss of G6PD enzyme → Inability to form NADPH

→ Inability to maintain GSH in reduced form → ↑ susceptibility to **FR**

regeneration of GSH is impaired

"attack" red cell components (globin chains)

### (intravascular hemolysis)

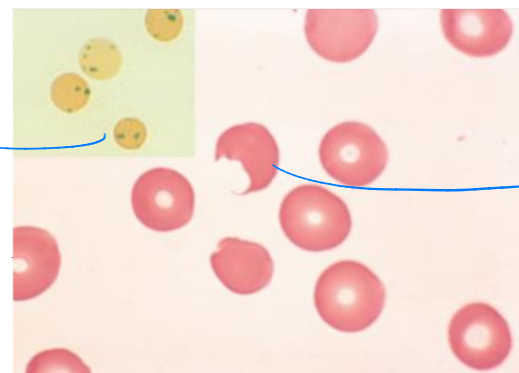
Oxidized hemoglobin denatures and precipitates, forming **Heinz bodies**, which can **damage the red cell membrane**

### (extravascular hemolysis)

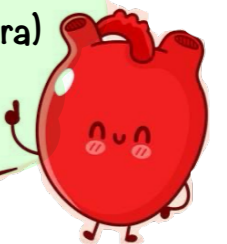
cells with **lesser damage** lose their deformability and suffer further injury when splenic phagocytes attempt to remove the **Heinz bodies** → creating **bite cells**

Heinz body

Bite cell



Type of hemolysis: Both (intro & extra)

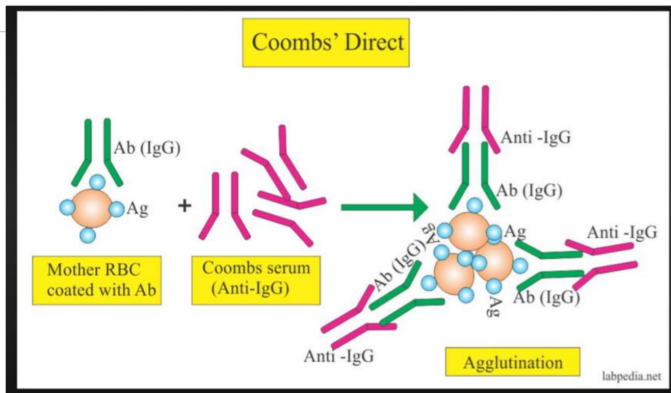


# Immune Hemolytic Anemia

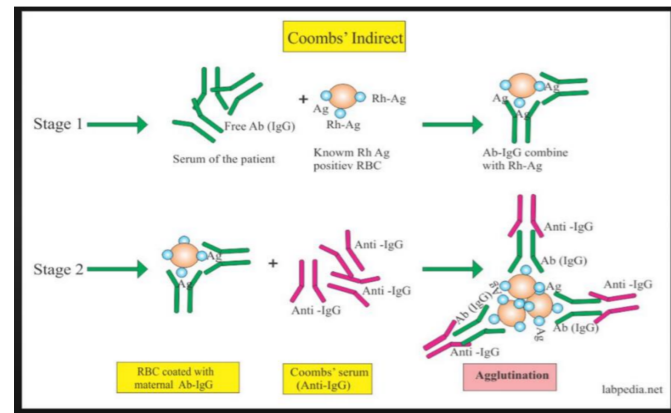
caused by → antibodies that bind to determinants on red cell membranes

↳ spontaneously  
↳ 2ry to exogenous agents

diagnosis → detection of antibodies and/or complement on red cells



You took Blood sample from the pt ( RBCs coated by Ab)  
You add coombs reagent ( anti IgG abx)  
If agglutination occur = autoimmune hemolytic anemia



You took serum sample from the pt ( Abs)  
Step 1 :You add synthetic RBCs  
Step 2 :You add coombs reagent ( anti IgG abx)  
If agglutination occur = autoimmune hemolytic anemia

# Hemolytic Anemia Due to Mechanical Trauma to RBC

## Etiology:

### Macro-angiopathic Hemolytic anemia

Artificial valves. (Aortic stenosis)

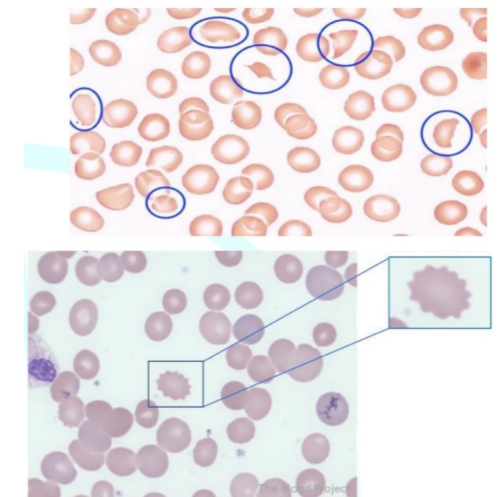
### Microangiopathic hemolytic anemia

- o DIC.
- o Malignant hypertension.
- o TTP.
- o Hemolytic uremic syndrome.

## Morphology:

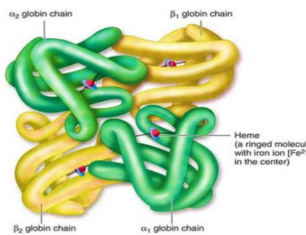
↳ Variation in RBCs shape  
poikilocytosis with & helmet cells/schistocytes, burr cells, and triangle cells

↳ Spike RBC



# Hemoglobinopathies

\* are a group of hereditary disorders caused by inherited mutations that lead to structural abnormalities in Hb.



\* Normal Human Hbs :

Hb A ( $\alpha_2\beta_2$ ):  
95% of adult Hb

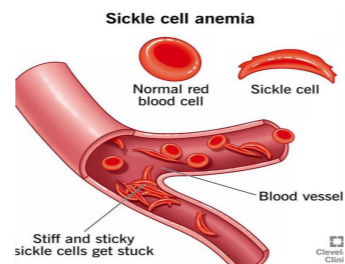
Hb A2 ( $\alpha_2\delta_2$ ):  
3% of adult Hb

Hb F ( $\alpha_2\gamma_2$ ):  
✓ 75% at birth.  
✓ < 5% at 6 months.  
✓ < 1% in adults.

# Sickle Cell Disease

\* the prototypic hemoglobinopathy and the most common

RBC life span ↓ from a normal 120 days to 10-12 days

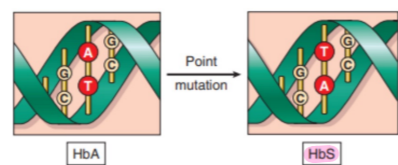


mutation : in β-globin

Substitution mutation at position 6 in B globin gene  
Lead to change in the 6th a.a from glutamic acid  
( water soluble ) to valine ( water insoluble )

change in Hb structure from globular to sickled shape  
once deoxygenated or got dehydrated  
→ change in RBC shape to sickle shape

NORMAL β-GLOBIN			
DNA.....	TGA	GGA	CTC
mRNA.....	ACU	CCU	GAG
Amino acid.....	thr	pro	glu
MUTANT β-GLOBIN			
DNA.....	TGA	GGA	CAC
mRNA.....	ACU	CCU	GUG
Amino acid.....	thr	pro	val



Sickling can be reversible initially, then be irreversible

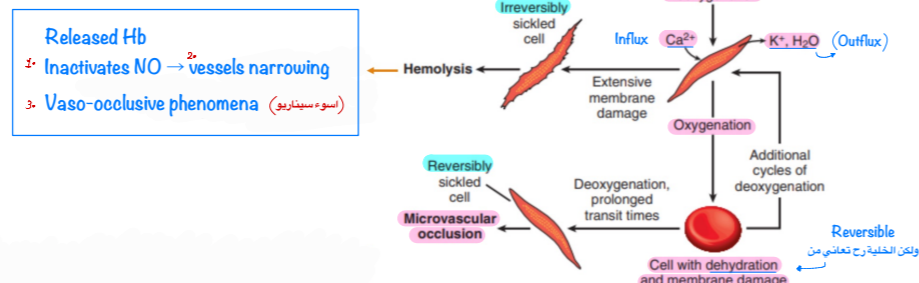
sickled RBC tend to aggregate inside Small BV lead to :

1-vaso-occlusive crisis

2-Intra-vascular Hemolysis

permanently sickled RBCs will be sequestered and remove

inside spleen : Extravascular hemolysis



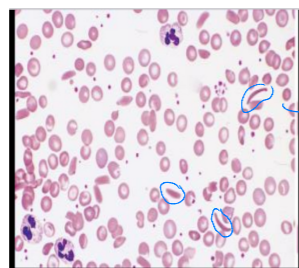
Clinical presentation :

- Asymptomatic till 6 months of age. (Due to presence of HbF)
- Moderate to severe anemia (6-8 g/dl).
- Unrelenting course complicated by sudden crises.

- 1- hemolytic crisis ( hemolysis ) due to excessive sickling  
Drop in Hb from baseline + high Retic count
- 2- aplastic crisis ( parvo b19 infection )  
Drop in Hb from baseline+ low retic count
- 3- vaso-occlusive crisis : pain

Laboratory investigation:

- \* CBC and blood smear( Sickled RBCs)
- \* Hemoglobin electrophoresis. ( ↑ Hbs )



Sickled RBC

Treatment:

- Adequate hydration.
- Pain relief.
- Antibiotic therapy.
- Exchange transfusion to ↓ theHbS.

# Thalassemia (Quantitative disorder)

\* mutations in globin genes that decrease the synthesis of α- or β-globin



deficiency of Hb and red cell damage

Features :

\* hypochromic microcytic anemia

\* Imbalance of globin chains → Reduced Hb synthesis and anemia

\* Precipitation of abnormal Hb → hemolysis and ineffective erythropoiesis.

Presentation depend on the severity of the mutation

- if globin is present but in decreased amount : IDA like presentation : hypo-chromic microcytic anemia
- If certain globin is completely absent > the other globin will compensate > forming tetramers > tetramers precipitate inside RBCs lead to hemolysis ( sever anemia )

1- severely defected RBCs ( with tetramers ) fail to leave BM : ineffective erythropoiesis and got hemolyzed there

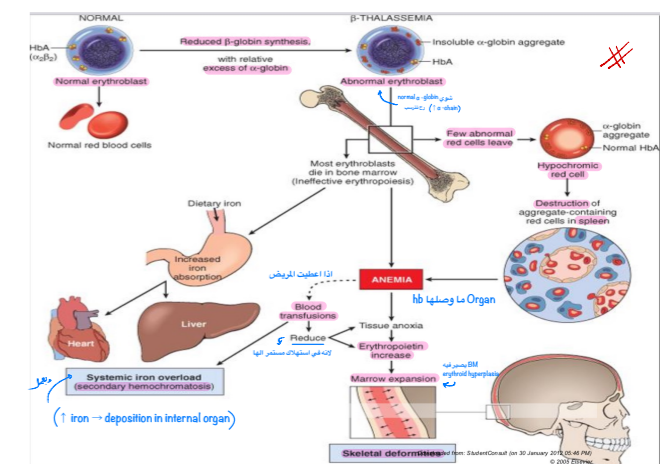
2- moderately defected RBCs :leave the BM but got hemolyzed at spleen due to hb defect

3- mildly defected RBCs : decrease Hb synthesis > decrease amount of hb inside each RBC : microcytic hypochromic anemia



common in malaria is endemic.

mutations associated with thalassemia protect against falciparum malaria  
Malaria infected RBCs died before the bacteria had time to replicate due to short RBC life span



β-Thalassemia

Defect in β-globin (Mutation) leading to aberrant RNA splicing (M.C cause)

- 1. β0: No β-globin chains are produced.
- 2. β+: Reduced (but detectable) β-globin synthesis.

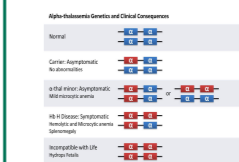
β-Thalassemia Major	β-Thalassemia Minor
* β0/β0, β+/β+, β0/β+	* Heterozygous for β0 or β+ gene.
* Hb. Level: 3-6 gm/dl (if un-transfused).	* ↑ HbA2 (> 3.5%) and/or HbF (1- 5%).
* ↑ HbF / ↑ or normal (HbA2) / absent or ↓ (HbA)	* Mild microcytic anemia (Hb 9-11 g/dL).
( Age :6-9 months )	* Differential Dx: IDA
* Treatment →transfusion dependent.	

α-Thalassemia

Defect in α-globin (deletion)

Severity of the disease is proportional to the number of α-globin genes that are missing →

- α/α: silent carrier state: asymptomatic.
- /αα, -α/-α: α thalassemia minor: asymptomatic.
- /-α: Excess beta: Beta 4: HbH disease.
- /--: Excess Gamma: Hb Barts, Death in utero (Hydrops fetalis).



Peripheral smear:

