Classifying hemolytic anemia	
Mode of acquisition	
Inherited	**Acquired**
• *Defect in the membrane:* Spherocytosis • *Defect in enzymes:* G6PD deficiency Pyruvate kinase deficiency • *Defect in hemoglobin:* Sickle cell disease (HbS) Thalassemia	• *Immune mediated:* Warm reactive & cold reactive • *Traumatic* • *PNH*
Location of the abnormality	
Intrinsic	**Extrinsic**
Destruction of RBCs due to defects in RBCs themselves (they have shorter lifespan).	Healthy RBCs destroyed by external agents and these include: - Infections. - Drugs: penicillin, anti-malarial & sulfa medications. - Autoimmune disorders: SLE - Leukemias & lymphomas.
Site of RBCs destruction	
Intravascular	**Extravascular**

- **Hereditary spherocytosis:**
  - ✓ It is an autosomal dominant disease resulting from defects in red blood cells membrane proteins (mostly spectrins and ankyrin).
  - ✓ If one of the parents is affected, there is 50% chance of passing the defect to their children.
  - ✓ It is more common in northern Europe & Japan.
  - ✓ RBCs are spherical in shape instead of being biconcave. They have a smaller diameter and the surface are to volume ratio is decreased.
  - ✓ The membrane is fragile and can be easily ruptured.
- **Human hemoglobin:**
  - ✓ Hemoglobin is a tetramer (quaternary) molecule consisting of heme (which is a prosthetic group) & globin.
  - ✓ α-globin gene family is present on chromosome 16 and includes: 2 copies of the α-globin gene (α1 & α2) + ζ
  - ✓ β-globin gene family is present on chromosome 11 and includes: β + δ + A_γ & G_γ + ε

HbA	2α2β
HbA_{1c}	2α2β (glycosylated)
HbA_2	2α2δ
HbF	2α2γ
HbH	4β

Note: HbF will be replaced by normal adult hemoglobin HbA after 3-6 months of birth when the production of γ-chains is replaced by β-chains.

- **Sickle cell disease (SCD):**
  - ✓ It is an autosomal recessive disease which results from point mutation at the 6th amino acid position of the β-chain (valine instead of glutamate) ---> HbS.
  - ✓ **Genotypes**: $S\beta^+$, $S\beta^0$, SC (doubly heterozygous).
  - ✓ ↑Hbf ---> protects red blood cells from the severity of sickling that's why patients with sickle cell disease will be given hydroxyuria (which increases HbF).
  - ✓ **Pathogenesis**: When there is decreased oxygen tension, HbS polymerizes into long, rope-like fibers. These intracellular fibers of the HbS will distort the erythrocytes resulting in rigid erythrocytes that will occlude blood flow in the capillaries. Therefore, microinfarcts will produce tissue anoxia resulting in severe pain.

- ✓ **Clinical presentation**: pain crises – chronic hemolytic anemia with associated hyperbilirubinemia – increased susceptibility to infections – acute chest pain – stroke – splenic & renal dysfunction & hyperproliferative bone marrow.
- ✓ **Haplotypes**: they influence the clinical severity of SCD.
  Bantu/CAR: they have low HbF & high risk of sudden death (severe) – Senegal: has high HbF level & less severe SCD (moderate) – Indian-Arab: has highest HbF level & ↑incidence of thalassemia.

- **Thalassemia:**
  - ✓ A recessive trait RBC inherited disease.
  - ✓ ↓ normal globin chain synthesis (α or β).
  - ✓ **α-thalassemia:**
    * The defect involves α1 & α2 genes located on chromosome 16 (4 copies).
    * If the defect is in 4 loci: this will result in hydrops fetalis (4γ) and it is incompatible with life.
    * In 3 loci: HbH (4β).
    * in 2 loci: α-thalassemia trait type 1 (cis: on the same chromosome or trans: one on each copy of chromosome 16).
    * 1 loci: α-thalassemia trait type 2.
  - ✓ **β-thalassemia:**
    * ↓ β-globin chain production.
    * β^0: no production of beta chain at all.
    * β^+: there is some production of beta chain.

β-thalassemia major	β-thalassemia minor
Homozygous (β^0)	Heterozygous (β^+)
Transfusion-dependent	Transfusion usually not needed
↑HbF (>80%) & variable HbA_2 (levels)	↑HbA_2 (4-8%)
Characterized by: thalassemia facies, hair-on-end appearance on skull x-ray, hepatosplenomegaly & increased susceptibility to infections.