- HLS MED pathololgy summary
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Anemia:

- is a reduction of oxygen carrying capacity of blood secondary to decrease in red cell mass
- Leads to tissue hypoxia
- Practically, measure by Hemoglobin concentration, and Hematocrit

- Anemia and erythropoietin:

- Anemia triggers production of erythropoietin
- Causes compensatory erythroid hyperplasia in bone marrow (BM)
- In **acute anemia**, production can increase by 5x or more in healthy people
- In severe cases, causes **extramedullary hematopoiesis** in secondary hematopoietic organs (spleen, liver and lymph nodes).
- Exceptions: anemia of *renal failure*, anemia of *chronic inflammation.*

Classification according to cause:

1) Blood loss
2) Diminished RBC production

• **Iron** deficiency anemia • Anemia of **chronic inflammation** • **Megaloblastic** anemia
• **Aplastic** anemia • Pure red cell **aplasia** • **Myelophthisic** anemia
• **Myelodysplastic** syndrome • Anemia of **renal failure** • Anemia of **hypothyroidism**

3) Increased destruction (hemolytic anemia)

- **Extrinsic** factors (infection, antibody, mechanical).
- **Intrinsic** RBC abnormalities:

1) Hereditary (membrane, enzyme, Hg abnormalities)
2) Acquired (**Paroxysmal nocturnal hematuria**).

Classification according to morphology:

- Size: normo, micro, macrocytic (MC**V**).
- Color: normo, hypochromic (MC**H**)
- Shape: anisopoikelocytosis (spherocytes, sickle, schistiocytes) (RBC distribution width)
- Hypochromic microcytic anemia usually reflects impaired Hg synthesis
- Macrocytic anemia reflects stem cell disease and maturation

- RBC indices:

- Can be directly measured, or automated.
- Slight variation is present between labs, geographic areas.
- Sex, age, race, mobility status have effect.
- **Reticulocyte count:** helps differentiate anemia of hemolytic anemia (high) from aregenerative anemia (low)

- Clinical features of anemia:

- Dizziness | Fatigue | Pallor | Headache.

- Adaptive changes:

- Tachycardia | Tachypnea | Increased red cell 2,3-diphosphoglycerate.

*If the patient has heart or lung diseases, symptoms will be worse.

- Clinical symptoms in special types of anemia:

- Chronic hemolytic anemia: jaundice, pigmented gall bladder stones, red urine.
- Extramedullary hematopoiesis: splenomegaly, hepatomegaly.
- Thalassemia major & sickle cell anemia: growth retardation, bone deformity, secondary hemochromatosis (damage to heart, endocrine glands).

- Anemia of acute blood loss:

- Symptoms are related to decreased intravascular volume.
- If loss is **>20%** of blood volume, patient might have hypovolemic shock & death.
- Body responds by **shifting fluid** from interstitial to intravascular space, causing **dilutional anemia & worse hypoxia** (stays 2-3 days).
- **Erythropoietin secretion** is stimulated, activating BM erythropoiesis (needs 5-7 days).
- In internal hemorrhage, iron is restored from extravasated RBCs & **used again** in erythropoiesis.
- In external & GIT hemorrhage, **iron is lost**, which complicates **anemia.**
- The anemia is **normochromic normocytic, with reticulocytosis.**

- Anemia of chronic blood loss:

- Occurs when the rate of RBC loss exceeds regeneration.
- Mostly occurs in **gastrointestinal diseases**, also in **excessive menstruation**.
- Results in iron deficiency, anemia appears hypochromic and microcytic, low reticulocytes.

- anemias of decreased production:

- General causes:
- Nutritional deficiency - Chronic inflammation - Bone marrow failure.

- Iron deficiency anemia:

- **Most common** type of anemia
- Affects 10% of people in developed countries & 25-50% of people in developing countries.
- Iron storage pool: iron is stored in ferritin (soluble) & hemosiderin (insoluble) in bone marrow, liver & spleen, forming 15-20% of total iron.
- Hemosiderin consists of large iron particles, granular in shape, intracellular, visible by light microscope.
- Serum ferritin is derived from stored ferritin.
- Indicators of iron status:
- **Bone marrow aspirate:** earliest changes, invasive procedure, Perl's Prussian blue stain (↓ in IDA)
- Serum **ferritin** level (↓ in IDA)*
- Serum **iron** level (↓ in IDA)
- **transferrin** saturation (serum iron/ serum transferrin) (normally 30%, ↓ in IDA)
- Total **iron binding capacity** (↑ in IDA)
- Serum transferrin & transferrin receptors (↑ in IDA)
- Reticulocyte hemoglobin content (CHr): (↓ in IDA)
- Mean reticulocyte volume (MRV): (↓ in IDA)

* Affected by inflammation, fasting, vitamin C status and pregnancy

- Iron homeostasis:

- Normal loss of body iron: shedding skin and mucosal epithelium (no excretion)
- Dietary iron is either hem (red meat) or non-hem (inorganic, vegetarian)
- 20% of hem and 1% of non-hem iron are absorbed in duodenum

- **Hepcidin**: hormone secreted from liver, **inhibits iron absorption** (degrade ferroportin on enterocytes)
- Hepcidin increases in situations of **high serum iron & inflammation** (effect of IL-6)
- Low hepcidin: **iron deficiency**. Very low: **thalassemia major, primary hemaochromatosis**.
- **Causes of iron deficiency:**
- Chronic **blood loss**.
- **Dietary**: vegetarians, infants, teenagers.
- **Decreased absorption**: gastrectomy, hypochlorhydria, intestinal diseases, elderly.
- **Increased demands**: growing children, pregnancy, myeloproliferative neoplasms.
- **Hypotransferritinemia**: decreased synthesis of transferritin, secondary to liver disease, protein deficiency (diet, malabsorption) or loss in urine (**nephrotic syndrome**).
- **Enzymatic deficiency.**
- Morphology:
- RBCs appear small & empty (***hypochromic microcytic***).
- Different shapes of RBCs appear (***poikelocytosis***).
- Target cells.
- Low reticulocytes (***Erythropoietin is high, but ineffective***).
- Thrombocytosis is common (low iron medium in bone marrow).
(shifts progenitor cells to megakaryocytic lineage instead of erythroid).
- Symptoms:
- IDA is a **chronic anemia** - General symptoms of anemia | **Pica** | **Glossitis, stomatitis** | **Spooning of fingernails** | **Restless leg syndrome** | **Hair loss** | **Blue sclera** | **Weakened immunity** | **Cognitive impairment**.

- Anemia of chronic inflammation (anemia of chronic disease):

- Seen in chronic infections, cancer, chronic immune diseases.
- Common in inpatients.
- Chronic inflammation inhibits synthesis of erythropoietin from kidneys.
- **High IL-6** - **high hepcidin** - blocks iron transfer from macrophages to RBC precursors in bone marrow (**degrade ferroportin on macrophages**).
- Laboratory findings:
- **Similar to IDA**: serum iron is low, transferrin saturation ↓.
- RBCs: normal morphology, then ***hypochromic microcytic***.
- Reticulocytes ↓.
- In contrast:
Bone marrow iron stores ↑ Serum ferritin ↑ Serum transferrin ↓ Total iron binding capacity ↓
- Transferrin saturation: normal | Transferrin receptor: normal.

- Megaloblastic anemia:

- Caused by deficiency in **vitamin B12 or folate**.
- Both are required for synthesis of **thymidine**, thus **DNA replication is impaired**.
- Abnormalities occur in all rapidly dividing cells, but hematopoietic cells are most affected.
- **Maturation** of RBC progenitors **is deranged**, many undergo apoptosis inside bone marrow (ineffective erythropoiesis, mild hemolysis).
- Viable nucleated RBCs take a **longer time to mature**, resulting in typical morphology (megaloblastoid).

- Folate deficincy:

- Normally, minimal amount of folate is stored in human body
- Folate is vastly present in food (**green leaves**), but it is **destroyed by cooking.**
- Causes of deficiency:
- Decreased **dietary** intake.
- Increased **demands** (pregnancy, chronic hemolytic anemia).
- Intestinal **diseases**.
- **Beans, legume, alcohol, phenytoin** (inhibit absorption).
- **Methotrexate**: inhibits folate metabolism & cellular usage.

- Vitamin B12:

- Mainly present in **animal products**.
- **Resistant to cooking**.
- Synthesized by **bacteria** in **bowel**.
- Enormous stores in the **liver**.
- Dietary deficiency occurs most commonly in **vegetarians**.
- More commonly: deficiency results from **defective absorption**.

- Pernicious anemia: فقر الدم الخبيث

- Autoimmune gastritis.
- Autoreactive T-lymphocytes, causing **injury to parietal cells**.
- Activates B-lymphocytes & plasma cells to synthesize & secrete auto antibodies that further damage parietal cells, & blocks binding of vitamin B12 to intrinsic factors.
- Other causes of vitamin B12 deficiency:
- **Gastrectomy**.
- Small bowel diseases (**malabsorption**).
- **Elderly people** are susceptible (decreased gastric acids & pepsin, thus decreased release of vitamin B12 from food).
- **Metformin** (inhibits absorption)
- Other function of vitamin B12:
- **Recycling** or tetrahydrofolate | **Synthesis** of myelin sheath | **Synthesis** of neurotransmitters (dopamine, serotonin) | **Metabolism** of homocysteine (toxic to neurons).

- Degree of neuronal damage does not correlate with the degree of anemia.

- Symptoms:
- Chronic, **general symptoms** of anemia | **Glossitis (beefy tongue)** | **Mild jaundice.**
- In severe cases: **pancytopenia** قلّة الكريات الشاملة.
- In vitamin B12 deficiency:
- Posterior & lateral columns degeneration of spinal cord (paresthesiaتنميل, loss of proprioception) | Peripheral neuropathy | Neuropsychotic symptoms.

- Aplastic anemia: فقر الدم اللاتنسجي / فشل نخاع العظم

- Damage to **multipotent myeloid stem cell** in bone marrow so it becomes depleted of hematopoietic cells.
- **Peripheral blood pancytopenia**.
- **Low reticulocytes**.
- Pathogenesis:

a. Acquired aplastic anemia (due to Extrinsic factors) (drug, virus, environmental factor).

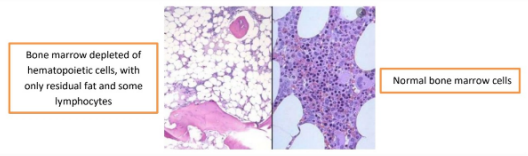
- Mechanism: a process called **Antigen cross-reactivity** (antibodies raised against the extrinsic factor can also react with stem cells in the bone marrow). Activated T-lymphocytes destroys stem cells.
- Evidence: **immunesuppressive drug restores bone marrow in 70% of cases**.
- Most cases are **idiopathic (60-70%)**.
- Associated factors (30%): chloramphenicol, gold injections (used in rheumatoid arthritis), NSAID, pregnancy, some hepatitis viruses.

b. Inherited aplastic anemia (due to Intrinsic factors):

- 10% of aplastic anemia patients have inherited defects in telomerase (that gives chromosomes stability) so stem cells die early.
- These genetically altered stem cells might express abnormal antigen **attracting T-cells**.
- Laboratory findings:
- In peripheral blood: **pancytopenia**, anemia is **normochromic or macrocytic**.

●● Problems with stem cells usually give macrocytic anemia ●●

- In bone marrow: **decreased hematopoietic cells**.
- Patients of aplastic anemia might develop severe infections or major bleeding (due to leukopenia & thrombocytopenia, respectively.). That's why aplastic anemia is an emergency.



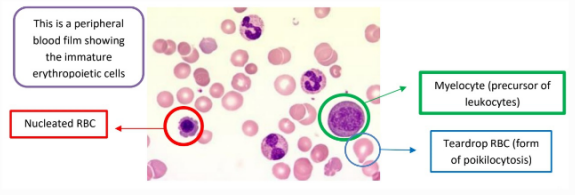
- **Fanconi anemia**: rare, inherited form of AA (aplastic anemia), defect in DNA repair proteins, patients develop AA & acute leukemia in early life because of accumulated mutations.

- Pure red cell aplasia:

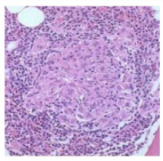
only erythroid cells are absent in bone marrow, can be congenital (**Diamond-Blackfan anemia**) or acquired (with **autoimmune disease** or **Parvovirus B19 infection**).

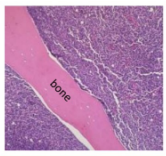
- Myelophthisic anemia:

- Infiltration of bone marrow causing **physical** damage to hematopoietic cells.
- These infiltrations can be:
- **Cancer**: most commonly in acute leukemia, advanced lymphoma, metastatic cancer.
- **Granulomatous disease**: TB.
- **Storage diseases**: **Gaucher disease** (buildup of fat).
- Mechanism: The bone marrow will be crowded with these infiltrations forcing the hematopoietic cells to be pushed out of the bone marrow, so **immature granulocytic & erythroid precursors commonly appear in peripheral blood.**
- Peripheral blood: **leucoerythroblastic anemia** (shift to left + nucleated RBCs)

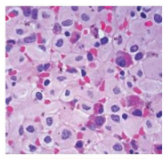


- Symptoms:
- Insidious (gradual) but accelerated symptoms of anemia.
- **Thrombocytopenia** manifests as **skin bleeding**.
- **Neutropenia** may results in serious **infections** & death.


Granuloma infiltration of the bone

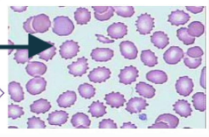


Hypercellular bone marrow (but NOT erythropoietic cells)


Bone marrow full of infiltrative cells

- Anemia of renal disease:

- Mainly results from **decreased erythropoietin production from kidneys.**
- **No correlation between kidney function & the severity of anemia**, so, if we measure **serum creatinine** it does not give an indication about the degree of anemia.
- Decreased RBC production (low reticulocyte count).
- Patients with **uremia** develop abnormal platelets function (**bleeding**), & **echinocytes** (**Burr cells**).


RBCs appear with many projections on the cell membrane

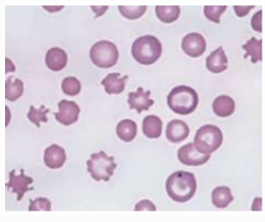
In chronic renal failure (advanced stages), kidneys are not able to excrete urea, so it accumulates in blood; a condition called uremia

- Anemia of liver disease:

- Multiple factors-causing anemia:

1- Decreased synthesis of clotting factors (**bleeding**).
2- Bleeding from **varices**.
3- Decreased synthesis of **transferrin**.

- **Acanthocyte** (**spur cell**) appears (longer & larger than burr cells).



- Anemia of hypothyroidism:

- Thyroid hormones stimulate erythropoiesis & erythropoietin production.
- Anemia is most commonly **normocytic**, but can be **marcocytic**.

- Myelodysplastic syndrome: (a neoplastic disease)

- Acquired, relatively common disease of old age.
- Mutations in **BM stem cell**, results in prolonged survival but defective maturation (the bone marrow will be full of cells but they are unfunctional).
- Most patients have **anemia**, refractory to treatment (doesn't respond to treatment).
- RBCs are **macrocytes.**

- Hemolytic anemia:

- RBC life span <120 days, but in hemolytic anemia it is much less (Hemolytic anemia = acceleration in RBCs destruction (hemolysis)).
- Characteristics:
- **Erythroid hyperplasia** in bone marrow (coz hypoxia triggers release of erythropoietin).
- **Reticulocytosis** in peripheral blood.
- **Extramedullary hematopoiesis** & **hepatosplenomegaly** in severe cases.
- **Jaundice** (Hb is released from the damaged RBCs).
- **Decreased serum haptoglobin** (binds free Hg).

Destructed RBCs release hemoglobin which is toxic for tissues, so another molecule called haptoglobin - from the liver- binds this free hemoglobin. Therefore, free haptoglobin decreases in serum.(useful for diagnosis of hemolytic anemia)

- General classification of hemolytic anemia:

*According to main site of hemolysis:

1) **Extravascular**: occurs primarily in **spleen** (RBCs have abnormal shape or coated with antibodies, removed by macrophages, patients have **jaundice**, **pigmented gall bladder stones**, & **splenomegaly**).
2) **Intravascular**: inside blood stream (sudden release of Hg, patients have **hemoglobinemia**, **hemoglobinurea**, **hemosiderinurea**, **iron deficiency**)

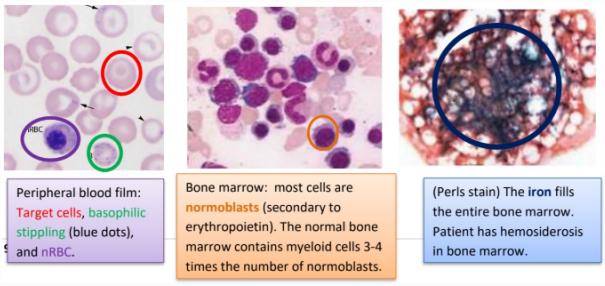
Hemoglobinemia: increased Hb in plasma
Hemoglobinuria: presence of Hb in urine, which gives it a red color.
Hemosiderinuria: presence of hemosiderin -iron storage complex- in

*According to cause of hemolysis: Extracorpuscular vs intracorpuscular.

a. **Extracorpuscular:** the cause is from outside the RBC e.g. antibodies or microorganisms like malaria.
b. **Intracorpuscular:** the cause is from within the RBC e.g. enzymatic deficiencies, thalassemia.

- Thalassemia:

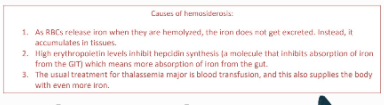
- Group of inherited disorders that result in decrease production of either α/β chains.
- Amount of synthesized Hg is below normal.
- The deficiency in one of globin chains results in relative increase in the other one, excessive unpaired chains will cause instability & hemolysis.
- Mode of inheritance: **autosomal recessive**.
- Common in Middle East, Africa & South East Asia.
- **Resistant to malaria falciparum infection**.
- Normal Hg types in adults: HgA, HgA2, HgF.



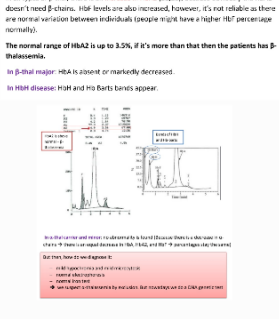
- Genetics:
- α-chain is encoded by 2 genes on chromosome 16.
- Most mutations in α-thalassemia are **deletions.**
- Deletion in 1,2 gene(s) results in a **silent carrier.**
- Deletion of 4 genes results in **hydrops fetalis.**
- Deletion of 3 genes results in **Hemoglobin H disease** (extra β- chains binds each other to a tetramer called **Hg-H**, extra γ- chains form **Hg-Barts**). Both have high affinity to oxygen.
- B-chain is encoded by a single gene of chromosome 11.
- Most mutations in β-thal are **point mutations**.

● β°: no production of β-chain ● β+: decreased production of β-chain
● β/β+:silent carrier or mild anemia (thal-minor) ● β+/β+: thalassemia intermedia
● β°/β° or β°/β+: thalassemia major (**Cooley anemia**).

- Extra α-chains remain uncoupled, causing hemolysis of RBCs & precursors (ineffective erythropoiesis).
- Morphology:
- **Hypochromic microcytic** anemia | **Target cells** (because of abnormal hemoglobinization) | **Basophilic stippling** (small blue dots -remnants of ribosomes) | **Reticulocytosis.**
- In thalassemia major:



- Peripheral blood: + **poikelocytosis**, **nucleated RBCs**.
- Bone marrow: ↑ ↑ **normoblasts**, filling BM spaces & expanding into bone, **hemosiderosis**.
- Clinical symptoms:
- Thalassemia traits are **asymptomatic**, normal life span, premarital test is important.
- Thalassemia major: symptoms begin after age of **6 months**, persistent **symptoms of anemia, growth retardation, skeletal abnormalities**, both are ameliorated by regular blood transfusion.
- **Systemic hemochromatosis & related organ damage** occurs in 2nd or 3rd decade of life
- **Thalassemia intermedia & HgH disease have moderate anemia, do not require regular blood transfusion**.
- Diagnosis:
- Hemoglobin **electrophoresis** test.
- In all types of β-thal, there is an **increase in HgA2 (2α,2δ) & HgF percentages.**
- In β-thal major, **HgA is absent** or markedly decreased.
- In HgH disease, **HgH & Hg Barts bands appear**.
- In α-thal carrier & minor, no abnormality is found. Genetic testing is available.



- Sickle cell anemia:

- Most common **familial hemolytic anemia** worldwide.
- Common in Africa, Middle East, Saudi Arabia, African Americans.
- **Resistant to malaria falciparum infection** (like thalassemia).
- Autosomal recessive.
- Caused by single amino acid **substitution** (glutamic acid ➡️ valine) in **β-chain**.
- In sickle cell disease (homozygous), Hg electrophoresis shows HgS & absent HgA.
- In sickle cell carrier (heterozygous), Hg electrophoresis shows both HgA & HgS bands.
- Pathogenesis:
- In deoxygentated case, HgS tends to polymerize in a longitudinal pattern, distorting cell shape & creating sickle shape.
- The change is **reversible** by re-oxygenation, but with repeated sicklings, cell membrane is damaged & hemolysis occurs.
- Presence of **normal HgA** (carrier) & **increased HgF** (newborn) **inhibits HgS polymerization**.
- Increased HgS concentration inside RBC promotes sickling (dehydration, acidosis), while the **presence of additional α-thal decreases sickling**.
- Sickle-shaped RBCs take a longer time to pass through capillaries.
- Removed by **macrophages in spleen** (extravascular hemolysis).
- Also adhere to endothelial cells, may create a **thrombus**.
- Clinical symptoms of SSA:

1- **Chronic moderate-severe hemolytic anemia**, manifesting after the age of 6-months (dependent on fraction of sickled cells). The chronic course is interrupted by repeated sudden attacks of worsening anemia.

2- **Vaso-occlusive crisis:** sickled cells can form **thrombus** without the need of platelets. It is independent on fraction of sickled cells: occurs in any patient with SSA even if the number of sickled cells in blood stream is low, results in organ infarction. Commonly associated with systemic infection, inflammation, dehydration, & acidosis.

3- **Aplastic-crisis**: patients with SSA can develop **pure red aplasia** secondary to infection of B19, usually it worsens the anemia but it's mild and self-limited. It occurs secondary to **Parvovirus B19** infection or secondary to infarction by vaso crisis so bone marrow stops producing any cell lineages.

4- **Hand-foot syndrome**: severe pain in digits because of ischemia & repeated infarction in bones & soft tissue of digits + abnormal growth of the fingers & toes.

5- **stroke**: If it affects the **cerebral circulation.**

6- **myocardial infarction** (heart attack): so patients with SSA usually have shorter life expectancy than normal adults.

7- **acute chest syndrome**: If it affects the **lungs** & the **ribcage**.

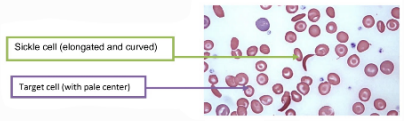
8- **Retinopathy:** retina blood vessels can directly cause **thrombosis**; ischemia & hypoxia promote other blood vessels to grow in order to compensate for the loss in retina.
-The new blood vessels will block the movement of the light, so it worsens the symptoms.

9- **Autosplenectomy**: spleen enlargment because of hemolytic anemia. With repeated infarction, the spleen becomes fibrotic & it **disappears** (Self removal without surgery).

10- **Susceptibility for encapsulated bacteria** (pneumococcus, salmonella), coz no spleen.

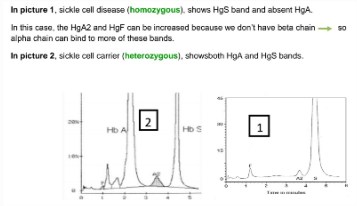
- Sickle cell carriers are **asymptomatic**.

- Diagnosis:



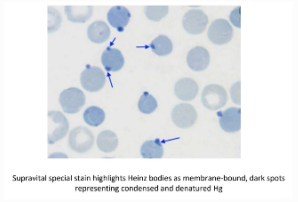
- Routine **blood smear**: presence of sickle cells, **target cells** (abnormal hemoglobinization).

●●● Recall: target cell is also formed in IDA & thalassemia ●●●

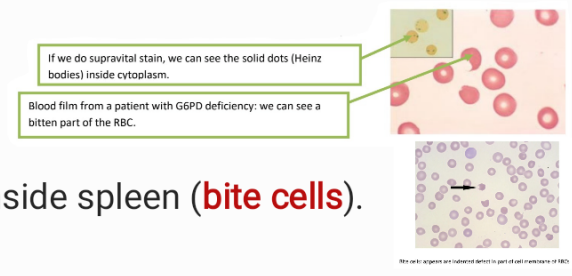


- **Sickling test**: adding hypoxic agent to RBCs to promote sickling.
- Hemoglobin **electrophoresis**.
- **DNA testing**.

- G6PD deficiency: Glucose 6-phosphate dehydrogenase deficiency.

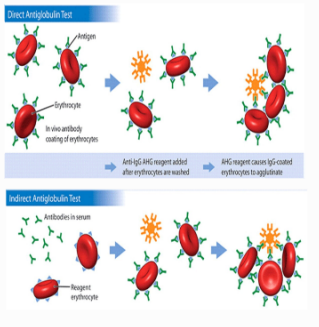


- This enzyme is important for the reduction of NADP+ to NADPH which is important for glutathione production that protects cells from free radicals.
- **X-linked** inheritance.
- Causes recurrent, transient episodes of **intravascular hemolysis**.
- Triggers of hemolysis:
- **Infection** | **Drugs**: sulfonamides, nitrofurantoin, large dose of aspirin, vitamin K, primaquine (a malaria drug) | **Fava beans** (antioxidant agents) we call this disease **Favism** (patients become sick after eating fava beans) | **aniline dye** (food coloring agent) | **Naphthalene**.
- In all, large amount of oxidants are generated, G6PD cannot neutralize them, causing <u>hemoglobin denaturation & precipitate</u> (**Heinz bodies**), damaging cell membrane & massive hemolysis of RBCs, 2-3 days after trigger.



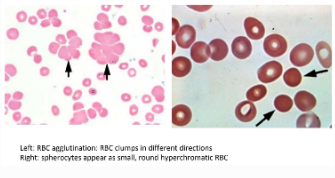
- Other cells lose demorfmability & partially phagocytosed inside spleen (**bite cells**).
- Clinical symptoms:
- Symptoms of intravascular hemolysis.
- **G6PD-A type**: decreased G6PD <u>amount</u>, bone marrow compensate by producing new RBCs.
- **G6PD-Mediterranian**: <u>qualitative</u> defect of enzyme (low function), more severe symptoms.
- Females: can have symptoms if random inactivation affects the normal X-chromosome. (Females can develop this disease (Remember that sometimes one X chromosome is randomly <u>inactivated</u> in females. So, if the normal X chromosome is inactivated & she left with the mutated one, symptoms will present).

- Immune hemolytic anemia (IHA):



- The presence of <u>auto-antibody</u> against RBC membrane protein.
- These antibodies are detected by Coombs test.
- **Direct Coombs test**: <u>RBCs</u> of patient are incubated with antibodies that target normal human antibodies (RBCs will agglutinate).
- **Indirect Coombs test**: patients <u>serum</u> is added to **"test RBCs"** which are manufactured RBCs that have certain surface proteins (antigens), these antigens are previously known to be commonly targeted by auto-antibodiesin IHA.

- Warm type IHA:

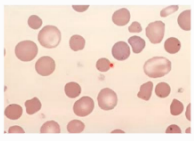


- **High affinity** auto-antibody (mostly **<u>IgG</u>** type).
- Binding occurs in <u>core circulation</u> (37oC).
- Removed by macrophages in spleen.
- **Spherocytes** develop, then destroyed by spleen (extravascular hemolysis).
- Causes: 60% are **idiopathic**, 25% associated with **systemic lupus erythematosus**, 15% by **drugs** (α-methyldopa, penicillin).

- Severity of anemia is variable, most patients have mild chronic anemia & splenomegaly.

- Cold type IHA:

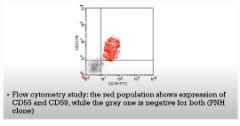
- Low-affinity autoantibody (IgM).
- Binding occurs in peripheral areas of body (<30oC).
- After IgM binding, few **C3b** molecules bind RBCs.
- When RBCs return to core circulation, IgM dissociates, but **C3b stays**, identified by splenic macrophages & removed.
- **IgM binds 5 RBCs, thus creating in vivo agglutination** that might block small capillaries in fingers and toes causing **Raynaud phenomenon**.
- Transient forms of cold-IHA occur in recovery of infections by **mycoplasma pneumonia** & **infectious mononucleosis**.



- (mild, self-limited).
- Chronic persistent form occur in **B-cell lymphoma** or **idiopathic**.

- Paroxysmal nocturnal hemoglobinuria: paroxysmal = sudden nocturnal = at night

- Rare, **acquired** disease.
- Mutation in **PIGA gene**, results in deficiency in phosphatidylinositol glycan **(PIG)**, a **structural protein on cell membrane that anchors many other proteins**.



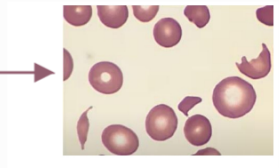
- Mutation occurs in **bone marrow stem cell** (leukocytes, RBCs & platelets are all affected).
- Pathogenesis:
- Normally, blood cells protect themselves by membrane proteins **CD55 & CD59**, that are normally attached to PIG, these proteins protect cells against the complement system.

No PIG protein ➡ No CD55 & CD59 proteins ➡ cells are destroyed (lysed)

- Mostly RBCs, & to a lesser degree WBCs & platelets, are spontaneously lysed inside blood.
- Nocturnal = During sleep: ↑ CO2, ↓ blood PH, ↑ active complement system, ↑ **hemolysis**.
- **Thrombosis** is common (when platelets are lysed & release their content).

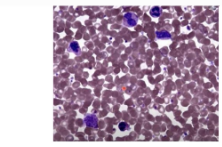
- Traumatic hemolysis:

- Direct **physical** force, or turbulence causing lysis of RBCs.
- Prosthetic **heart valves** | Repetitive **physical pounding** (marathon, boxing, marching) | Disseminated **thrombi** (microangiopathic hemolytic anemia).
- Hallmark of traumatic hemolysis: **schistocytes**. ⟶


Schistocytes: torn and distorted RBCs

- Polycythemia:

- **Increase in total RBC mass**.
- Erythrocytosis: increased RBCs number.
- **Relative polycythemia**: secondary to **decreased plasma volume** (in water deprivation, severe diarrhea, diuretics). **plasma lost ➡ RBCs become concentrated ➡ polycythemia**.
- **Absolute polycythemia**: true increase in RBC mass, **secondary to increased BM production** as in chronic **hypoxia**, it can be primary or secondary:
- **Primary**: **polycythemia vera** due to a **neoplasm** in bone marrow which produces large amount of RBCs. **⬇ erythropoietin (negative feedback), ⬆ RBCs count ➡ splenomegaly.**
- **Secondary**: causes: **adaptive** (in **high altitudes or cyanotic heart disease**), **paraneoplastc syndrome** (in renal cancer patients), **surreptitious** -hidden- cases (in endurance athletes), alcoholism.
- Erythropoietin in high, no splenomegaly.


Polycythemia: packed RBCs in peripheral blood

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