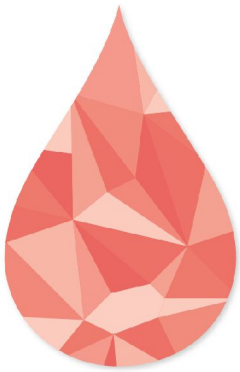


1- Anemia = Haematology 435 =

إن أحسنا فمن الله عزوجل, وإن أخطأنا فمن أنفسنا والشيطان.
نظراً لشمولية العمل لمحاضرات الطلاب والطالبات بإمكانكم اعتماده كمصدر للمذاكرة.

Objectives:

- Hemoglobin & Hb Structure.
- Hematopoiesis and Erythropoiesis.
- Normal ranges of blood contents.
- Anemia and its clinical features and classifications.
- Iron deficiency anemia and its causes, development, signs and symptoms, investigation, treatment and prevention.
- Iron absorption and studies.
- Anemia of chronic disease and its treatment, causes and management.

➢ Color Codes:

- Pink: Girls' notes. Blue: Boys' notes. Red: Important Notes. Gray: Extra notes.
- Purple: Lecture notes & Pathoma notes.

➢ **Done by:** Samar AlOtaibi.

➢ **Revised by:** Nouf AlRushaid & Rifan Hashim.

➢ References:

- Girls&Boys Doctors Slides and Notes.
- Lecture notes pathology (chapter 12)
- Pathoma (chapter 5)
- Team 434 & 433.

Revised by
خولة العماري & هشام الغفيلي

➢ **Correction file:** (HERE)

➢ **Check Your Understanding!** (HERE)

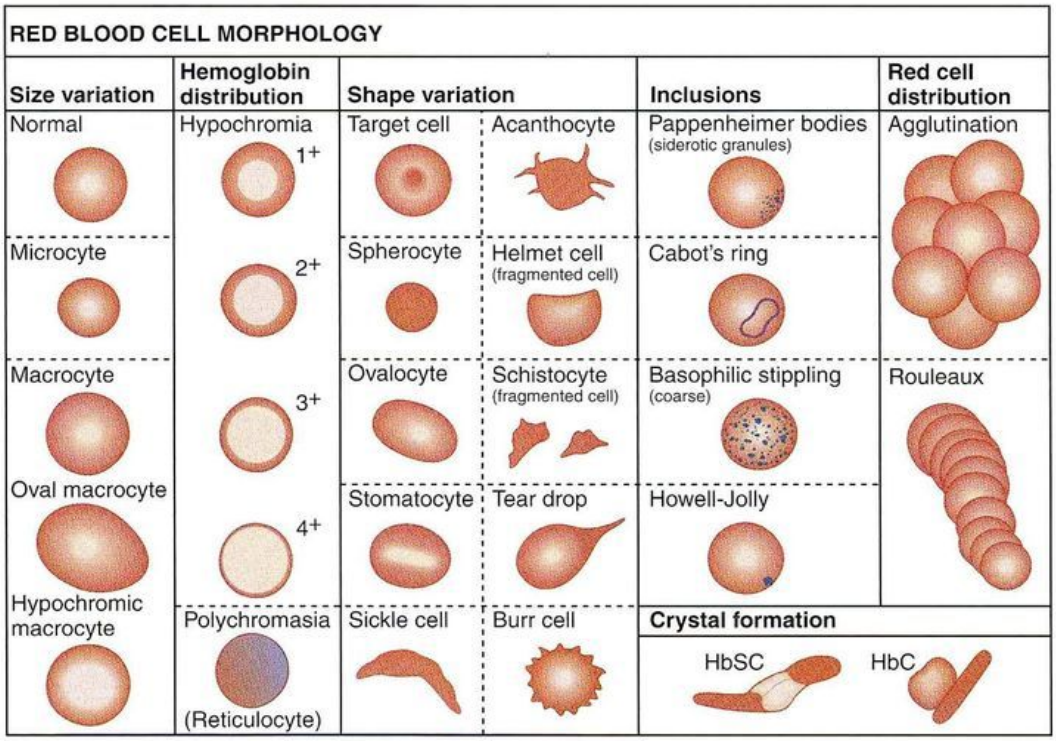
➢ (Lecture Notes. Extra)

❖ Red Cell Shapes:

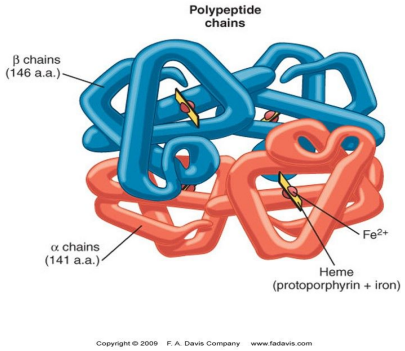
- Abnormal size is called : Anisocytosis. (aniso means unequal)
- Abnormal shape is called : Poikilocytosis. (poikilo means various)
- **Spherocytes:** result from **D**ecreased erythrocyte membrane, seen in Hereditary spherocytosis and in Autoimmune Hemolytic Anemia.
- **Target cells:** result from **I**ncreased erythrocyte membrane, seen in Hemoglobinopathies, Thalassemia and Liver disease.

❖ Red Cell Inclusions:

- **Basophilic stippling:** in reticulocytosis or lead poisoning.
- **Howell Jolly bodies:** in severe anemias or patients without spleen.
- **Pappenheimer bodies:** found in the peripheral blood following splenectomy.
- **Ring sideroblasts:** in Sideroblastic anemia.
- **Heinz bodies:** in Glucose-6-Phosphate Dehydrogenase Deficiency.



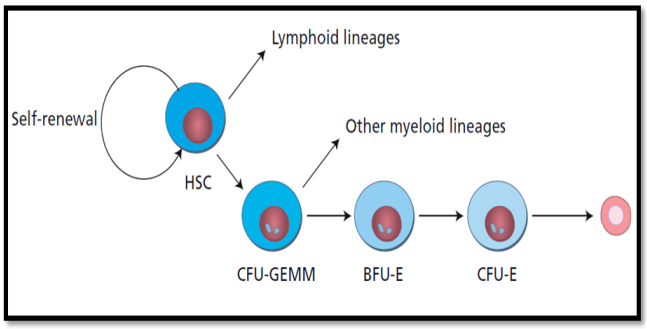
❖ Hemoglobin:



- Hemoglobin is the **protein molecule in RBC that carries O2** from the lungs to the body's tissues and returns carbon CO2 from the tissues back to the lungs.
- Hemoglobin **maintains the shape of RBC** also.
- Hemoglobin is composed of 4 heme groups (each heme has a protoporphyrin ring and iron fe+2)and 4 globin chains (these all must be normal in structure and function or else a disease will occur)

❖ Hematopoiesis: Formation of blood cells.

A. Hematopoiesis stem cells (HSC) characteristics:



- Self renewal. (In bone marrow)
- Cell differentiation.

If HSC go to the circulation that means there is a disorder. Malignancy of HSC ⇨ **Leukemia.**

B. Transcriptional factor:

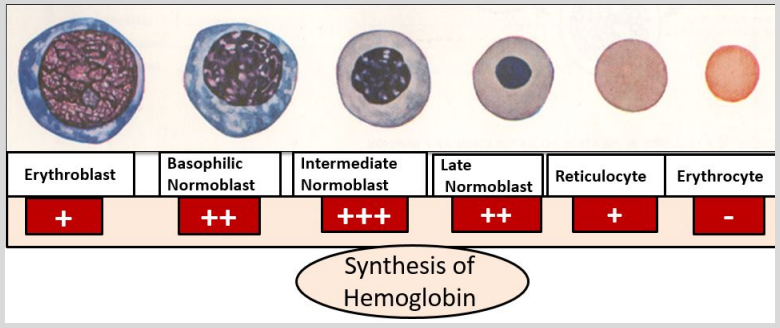
It's effects permit HSC proliferation and nuclear regulation. Like erythropoietin ⇨Erythrocyte. GATA1 is a gene required for the maturation of red blood cells.

Note that the formation of hematopoietic cells occurs mainly in the bone marrow in adults!

❖ Erythropoiesis: Formation of RBC's.

The Bone Marrow is the major site with the need of:

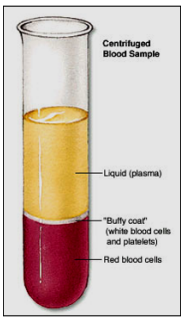
- Folic acid (DNA synthesis)
- Iron Ferrous (haem synthesis)
- Vit B12 (DNA synthesis)
- Erythropoietin (growth factor) (hormone secreted by kidney binds onto membrane receptors of cells that will become Erythrocyte (RBCs).
- Amino acids (globin chain)
- Minerals and other regulatory factors.



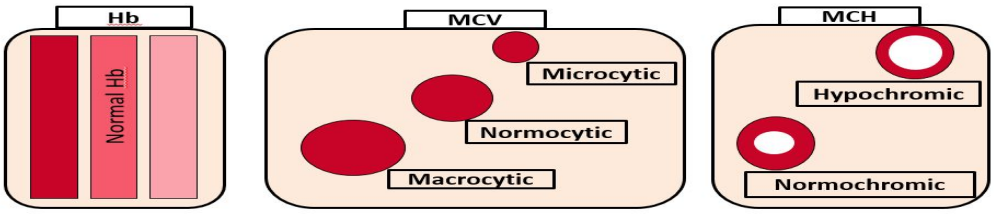
- Hb synthesis begin at erythroblast and stop at reticulocyte, but it is highly active at normoblasts (especially intermediate normoblast).
- Erythroblast is the early recognizable erythroid precursor.
- **Reticulocyte : found in the circulation only in severe anemia or increase demand on RBC (bone marrow is under stress)**
- **Erythrocyte = mature RBC , will be found in the circulation.**
- **The Rest found in circulation only in abnormality like malignancy.**
- Intermediate normoblast (+++) ⇨ Has the biggest Hb synthesis.
- Erythrocyte (-) ⇨ No Hb synthesis.(so HB synthesis occurs in all stages of RBC synthesis except in mature erythrocytes!!

❖ Normal Ranges: (depend upon age and sex)

Indices	Male	Female
Hemoglobin(g/dL)	13.5-17.5	11.5-15.5
Hematocrit (PCV) (%)	40-52	36-48
Red Cell Count ($\times 10^{12}$)	4.5-6.5	3.9-5.6
Mean Cell Volume (MCV) (fL)	80-95	
Mean Cell Hemoglobin (MCH) (pg)	30-35	



- Note that the mhc may either be : hypochromic(color is less than two thirds) Or normochromic color in two thirds of cell.



- PCV = the ratio of RBCs to the blood.
- MCV = the size of RBC.
- MCH = The average mass of Hb, normally Hb stain will be ⅔ peripherally stained and ⅓ pale center.

❖ Anemia:

An (without) -aemia (blood)

- Reduction of Hb concentration below the normal range based on age and gender.
- Leading to decreased O2 carrying capacity of blood and thus O2 availability to tissues (hypoxia).

❖ Clinical features of Anemia:

Presence or absence of clinical feature depends on:

1- Speed of onset:

Rapidly progressive anemia causes more symptoms than slow onset anemia due to lack of compensatory mechanisms: (cardiovascular system, BM &O2 dissociation curve)

2-Severity: classified as mild-moderate-severe

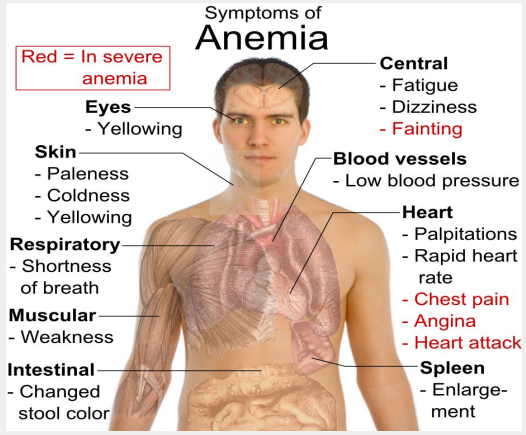
• Mild anemia :no symptoms usually (it will be border line or little lower than borderline)

• Symptoms appear if Hb less than 9g/dL (very severe type)

3- Age:

•Elderly tolerate anemia less than young patient-can't compensate.

General features of anemia	Specific features of anemia -IMPORTANT-
• Related to anemia: -Weakness -Headache (if headache is Continuous and not gone by paracetamol,this may be a sign of anemia so CBC is indicated in this case) -Pallor -Lethargy(lack of energy and enthusiasm) -Dizziness • Related to compensatory mechanism: -Palpitation (tachycardia) -Angina in very severe less than 3-4g\dl -Cardiac failure in very severe less than 3-4g\dl	• Specific signs are associated with particular types of anemia: -Spoon nail with **iron deficiency.** -Leg ulcers with **sickle cell anemia.** -Jaundice with **hemolytic anemia.** **Due to release of bilirubin from damaged rbc** **First differential of jaundice is hemolytic anemia.** -bone deformities in **thalassemia major.**



❖ Classification of Anemia:

Presentation:	Site:	Structure Affected:
Hypochromic microcytic anemia	**Hb**	• Prophyrin ⇨ Sideroblastic anemia[1]. • Iron ⇨ Iron deficiency anemia. • Globin chain ⇨ Thalassemia.
Macrocytic anemia	**DNA**	• DNA synthesis ⇨ Megaloblastic anemia: -Vit. B12 deficiency. -Folate deficiency. • DNA synthesis ⇨ MDS[2] (Myelodysplastic syndromes)
Normocytic normochromic anemia	**RBC count**	• Blood loss ⇨ Acute bleeding. • Hemolysis ⇨ (Autoimmune, Enzymopathy, Membranopathy, Mechanical, Sickle cell anemia[3]) • RBC production ⇨ BM failure: -Chemotherapy -Aplastic anemia[4] -Malignancy -Anemia of chronic disease.

	Hypochromic microcytic anemia	Macrocytic anemia	Normocytic normochromic anemia
MCV	Low	High	Normal
MCH	Low	-	Normal
HB	Low	High	Low
Red Cell count	-	-	Low

1-Is a disorder in which the body has adequate iron stores, but is unable to incorporate the iron into hemoglobin.
2-are a group of cancers in which immature blood cells in the bone marrow do not mature or become healthy blood cells.
3- is an inherited disorder leading to the formation of Hb-s and ↑ propensity for the affected RBC to become sickle-shaped.
4-is a rare disease in which the bone marrow and the hematopoietic stem cells that reside there are damaged.

❖ Iron Deficiency Anemia (IDA):

- Dietary deficiency of iron is seen in elderly populations and in children and the poor.
- Increase demand for iron is seen in children and pregnant women.
- Iron is among the abundant minerals on earth (6%).
- Iron deficiency is the most common disorder(24%).
- Limited absorption ability :

  1-Only 5-10% of taken iron will be absorbed

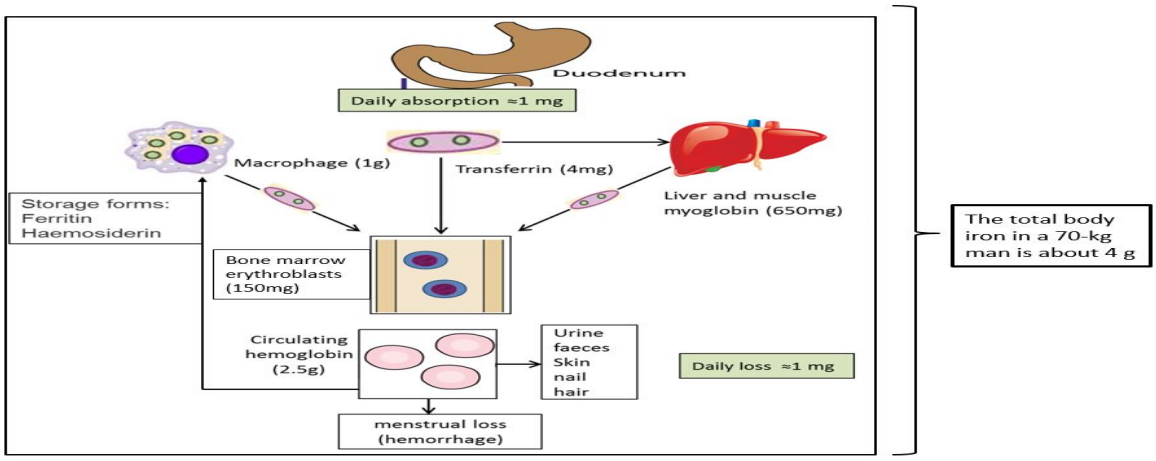
  2- Inorganic iron can not be absorbed easily.
- Excess loss due to hemorrhage. (increased iron demand for hematopoiesis ,which will lead to depletion of iron stores.
- IDA affect mental activity in children .

صار عندنا هيمورج وش بيصير ؟ بيزيد الديماند على الايرون ستور عشان يطلع ايرون كثير ويصنع لي بلود ، كانه يحاول يعوض عشان كذا الايرون ستور رح يتأثر ويقل بزيادة.

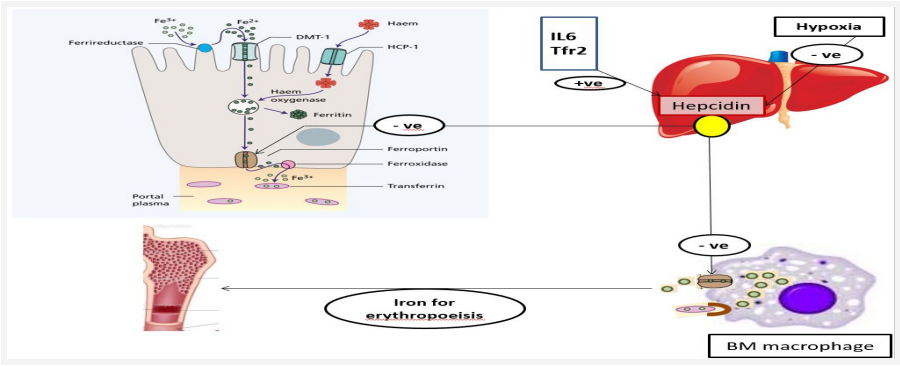
❖ Causes of Iron Deficiency Anemia (IDA):

Chronic blood loss	Increased demands	Malabsorption	Poor diet
•GIT Bleeding: peptic ulcer, esophageal varices, hookworm & cancer (In US think carcinoma, in the rest of the world think Hookworm"parasite") •Uterine bleeding (Due to Gynecologic = Menstrual bleeding) •Hematuria the presence of blood in urine	•Immaturity We need to give them milk with iron form 6m old. •Growth •Pregnancy •EPO (erythropoietin) therapy	• Enteropathy • Gastrectomy (Due to ⇩ acid, which is needed for ferrous absorption)	Rare as the only cause (rule out other causes)

❖ **Iron Absorption:** "Iron Physiology"



- First part of Duodenum is the site of absorption.
- **Transferrin:** carrier of 2 molecule of iron. (so iron is taken by transferrin to bone marry for hematopoiesis ,it is also taken to the liver and muscle to be stored in myoglobin)
- Iron can also be found in macrophages
- **Myoglobin:** is an iron-and oxygen-binding protein found in liver and muscles. "Storage form"
- **Ferritin&Haemosiderin:** Are storage forms in Bone marrow.
- **Daily Absorption=Daily loss =1mg**
- **Excretion occurs mostly through urine and feces,and menstrual loss.**



- Dietary iron **(ferric fe3+)** converted to ferrous (fe2+) before its absorption, and its entry controlled by **DMT-1.**
- dietary haem source : liver and red meat, its absorption controlled by **HCP-1**
- **Hepcidin** produced in liver and it's the major hormonal regulator of iron, it interfere with ferroportin either in intestine or macrophages so it inhibits iron absorption and release.
- Hepcidin is stimulated by IL6& Tfr2 and inhibited by hypoxia-says to it stop i need the iron-

- Hypoxia has a negative feedback on hepcidin(why?)because in hypoxia we want to increase the number of RBCs ,hence we want to increase erythropoiesis ,in order to do so we must increase iron absorption (how?)by decrease in hepcidin!
- Abnormality in hepcidin → Iron will enter without control → iron overload !
- **ferroportin** is a protein responsible for the exit of iron (the only exit pathway).

❖ Factor affecting iron absorption:

Factors Reducing absorption	Factors Favoring (Increasing) absorption
Inorganic iron (any other iron than red meat)	Haem iron (Called:Red iron from red meat)
Ferric iron Fe3+	Ferrous Iron Fe2+
Alkalines	Acid
Iron overload	Iron deficiency
Tea (Don't eat meat then drink green tea)	Pregnancy
Increase Hepcidin iron تتاسب عكسي بينه و بين ال	Hemochromatosis (inherited disorder)
Precipitating agent (Phenol)	Solubilizing agent (Sugar)

❖ Factor affecting iron absorption (Same as the table):-

1- **Iron body status:**
- Increased demands (iron def., pregnancy) →low iron stores (increase release)→**high** absorption.
- Iron overload →full iron stores→**low** absorption.

2- **Content and form of dietary iron:**
- More iron, Haem iron and Ferrous iron → **More** absorption.

3- **GIT mucosa:**
- Disruption of GIT mucosa → **cannot** absorb iron.

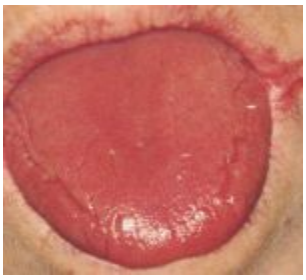
4- **Balance between dietary enhancers and Inhibitory factors:**
- **Enhancers:** Meat (haem iron), fruit (Vit-C), sugar (solubilizing agent),and acids.
- You can combine orange juice with meat to enhance iron absorption.
- **Inhibitory:** Dairy foods (calcium), high fiber foods (phytate), coffee and tea (polyphenoles), and anti-acids (Alkalines).

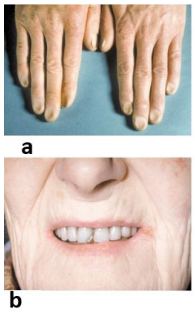
❖ Development of IDA:

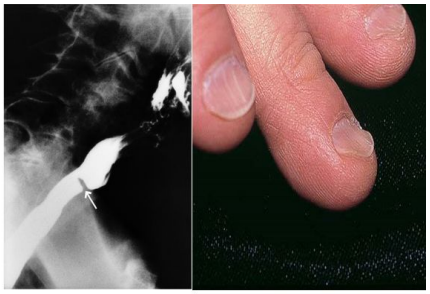
	1 Normal	2 Pre-latent	3 Latent	4 Iron def. anemia
Stores	Normal	Low	Low	Low
MCV/MCH	Normal	Normal	Low	Low
Hemoglobin	Normal	Normal	Normal	Low

❖ Signs and symptoms of IDA:

Beside symptoms and signs of anaemia +/- bleeding patients present with:
Iron maintain epithelial cells , so these symptoms appear .
(a): Koilonychia (spoon-shaped nails)(Concave nails)
(b): Angular stomatitis and/or glossitis (fissures and inflammation at the edges of the mouth)
(c): Dysphagia due to pharyngeal web (Plummer-Vinson syndrome) (is iron deficiency anemia with esophageal web and atrophic glossitis; presents with anemia, dysphagia, and beefy-red tongue)



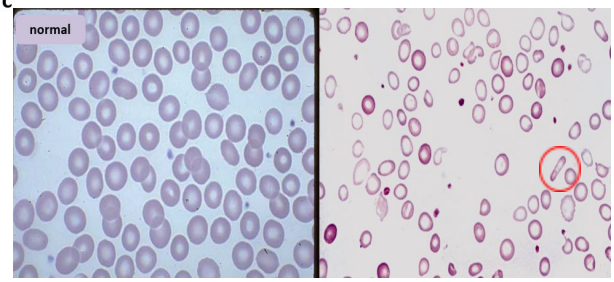




❖ Investigation pd IDA:

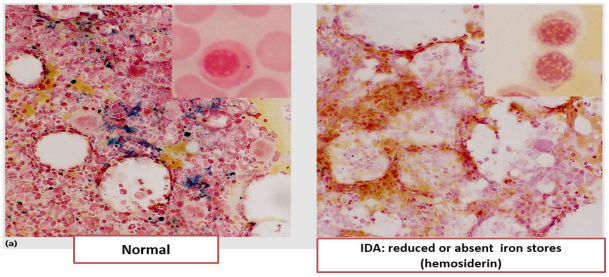
1- **Microcytic hypochromic anemia with:**

- Anisocytosis (variation in size)
- Poikilocytosis (variation in shape)
- Pencil-shaped cells (the circled one)
- Target cells.

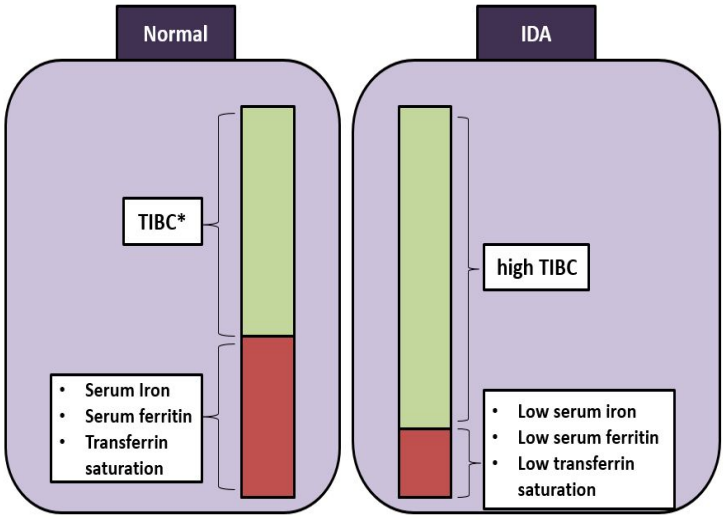


Notice in Normal pic : 1-same size 2- circular in shape 3- normal staining 4- smaller area between cells.
You can see RBC precursors and violet stain
Abnormal : 1-smaller in size 2-variation in shape 3- more pale center 4- wider area 5- cells less in number.
Absence of violet color ,syderetic granules are absent

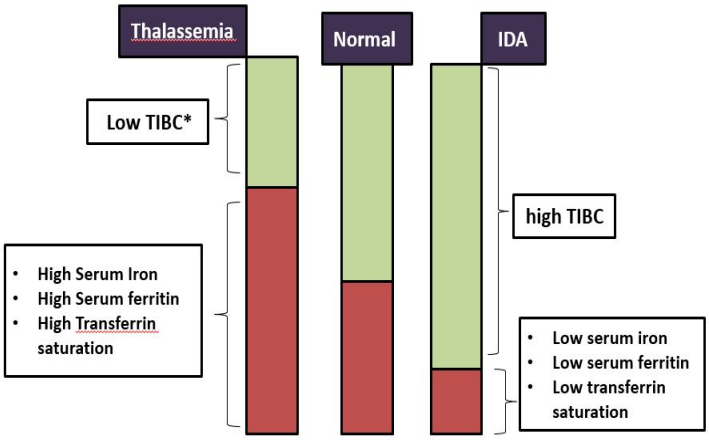
2- **Bone Marrow** Iron stain (Perl's stain):
The gold standard but invasive procedure. Rarely done because it's an invasive procedure but 100% result.



❖ Iron Studies:



TIBC : total iron binding capacity of transferrin



Very important to note the difference between thalassemia and IDA Cause both of them are microcytic hypochromic anemia.

❖ Treatment of IDH:

- Treat the underlying cause. So investing the reason is the first step.
- **Iron replacement therapy:**

- **Oral:** (Ferrous Sulphate OD for 6 months) The best.
- **Intravenous:** (Ferric sucrose OD for 6 months). (in severe symptoms or In case of malabsorption)

(Hb should rise 2g/dL every 3 weeks)

❖ Prevention of IDH:

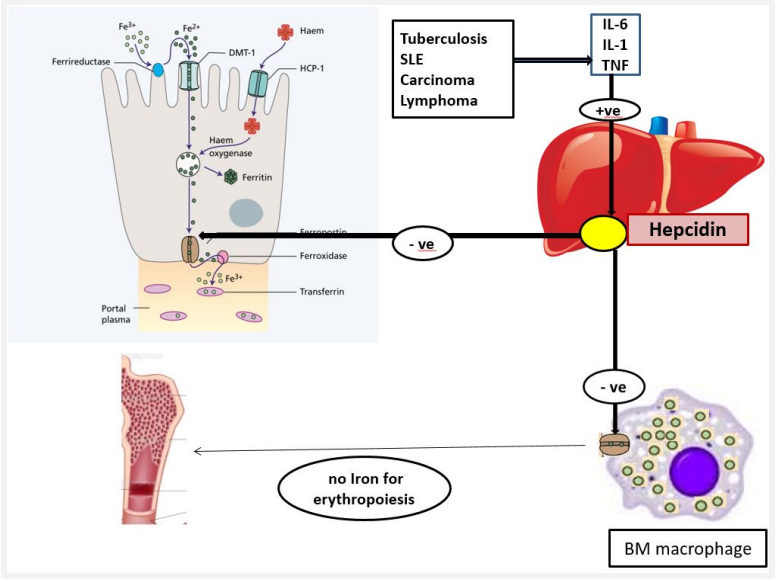
- **Dietary modification:**
  Meat is better source than vegetables.
- **Food fortification** (with ferrous sulphate) :
  GIT disturbances (Constipation),staining of teeth & metallic taste.
- **Iron supplementation:**
  For high risk groups.

Such as in patients who did a gastrectomy or in premature infants (prophylaxis is needed)

❖ Anemia of chronic disease (AOCD):

Normochromic normocytic (usually) anemia caused by decreased release of iron from iron stores (Bone marrow macrophages) and reduction of iron absorption due to raised serum **Hepcidin.**

Patient has iron but can not use it.



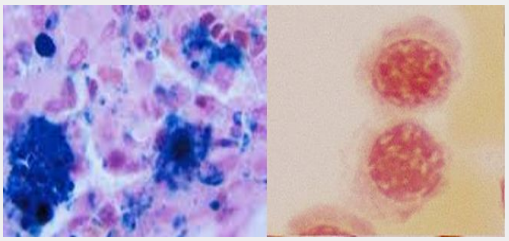
"LectureNotes P100" **Laboratory studies** shows increased serum ferritin with decreased total iron binding capacity.
Chronic inflammatory disorders may be associated with increased IL-1,IL-6, TNF, and hepcidin, produced by the liver, prevents the release of iron stores, trapping it in bone marrow macrophages, leading to the anemia of chronic disease.

Associated with:

- Chronic infection including HIV, malaria.
- Chronic inflammations.
- Tissue necrosis.
- Malignancy.

❖ Work-up and Treatment of (AOCD):

- Normocytic normochromic or mildly microcytic anaemia.



Finding:

- Low serum iron and TIBC (total iron binding capacity of transferrin = empty)
- Normal or high serum ferritin (acute phase reactant).
- High haemosiderin in macrophages but low in normoblasts.

Management:

- Treat the underlying cause: Iron replacement +/- EPO

(Pathoma Bridge)EXTRA!

❖ Anemia "Basic principles" :

- Reduction in the total circulating red blood cell mass.
- Present with Signs & symptoms of hypoxia : weakness, fatigue, dyspnea, pale conjunctiva, pale skin and nails, headache, lightheadedness, angina.

❖ (IDH):

- Most common type of anemia.
- Iron consumed in HEME (meat-derived) more absorbed & NON-HEME (vegetable-derived).
- Stages of iron deficiency:

1. Storage iron is depleted: ↓ ferritin, ↑ TIBC
2. Serum iron is depleted: ↓ serum iron, ↓ %saturation
3. Normocytic anemia: Bone marrow makes fewer, but normal-sized RBCs.
4. Microcytic, hypochromic anemia: Bone marrow makes smaller and fewer RBCs.

❖ (AOCD):

Anemia associated with chronic inflammation (e.g., endocarditis or autoimmune conditions) or cancer; most common type of anemia in hospitalized patients B.

- **Chronic disease** results in production of acute phase reactants from the liver, including hepcidin.

1- Hepcidin sequesters iron in storage sites by:

(1) limiting iron transfer from macrophages to erythroid precursors.

(2) suppressing erythropoietin (EPO) production; aim is to prevent bacteria from accessing iron, which is necessary for their survival.

2. ↓ Available iron → ↓ Heme → ↓ Hemoglobin → Microcytic anemia.

- **Laboratory findings include:**

I. ↑ Ferritin, ↓ TlBC, ↓ serum iron, and ↓ % saturation

2. ↑ Free erythrocyte protoporphyrin (FEP)
