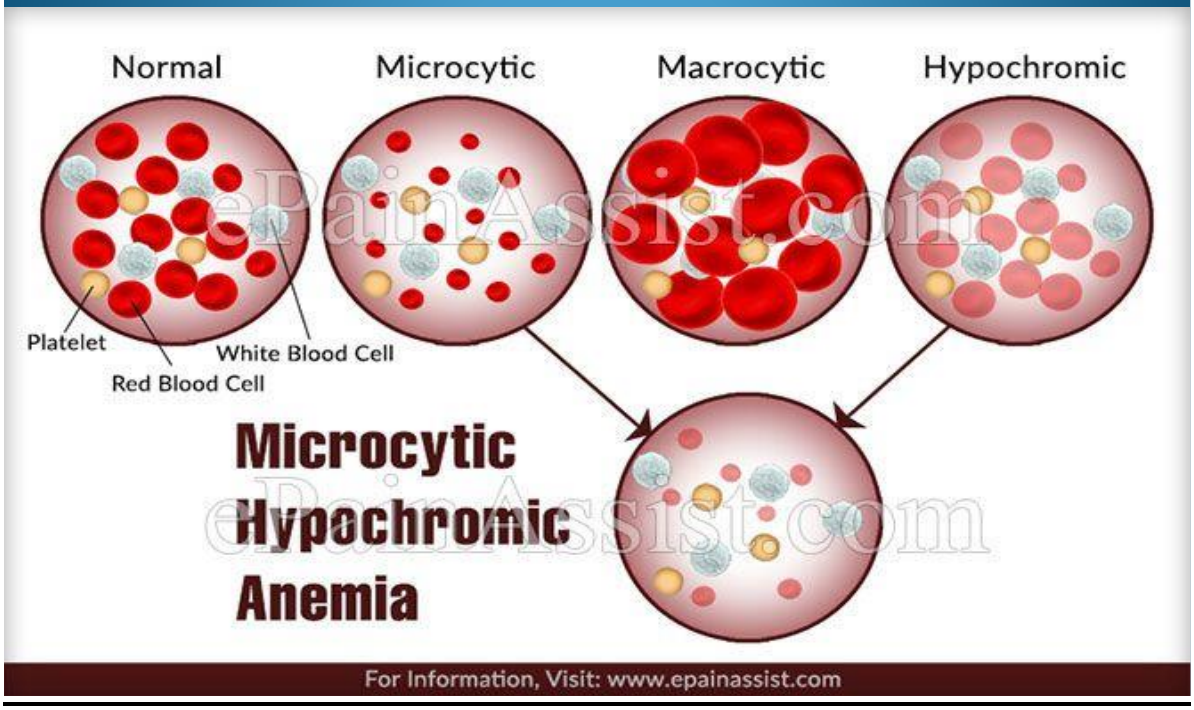
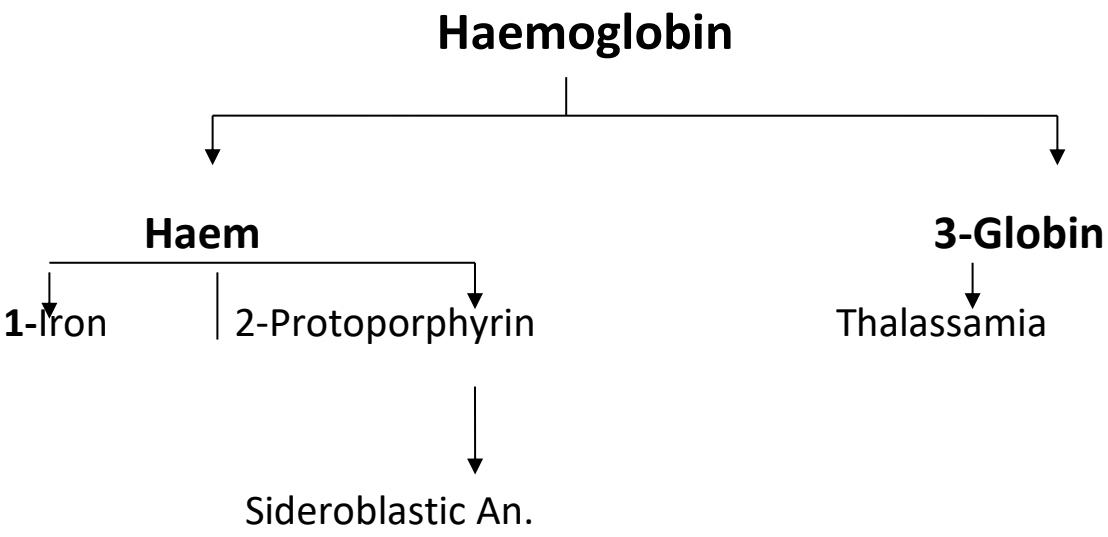
Microcytic Hypochromic Anemia



Microcytic Hypochromic Anemia

Causes:



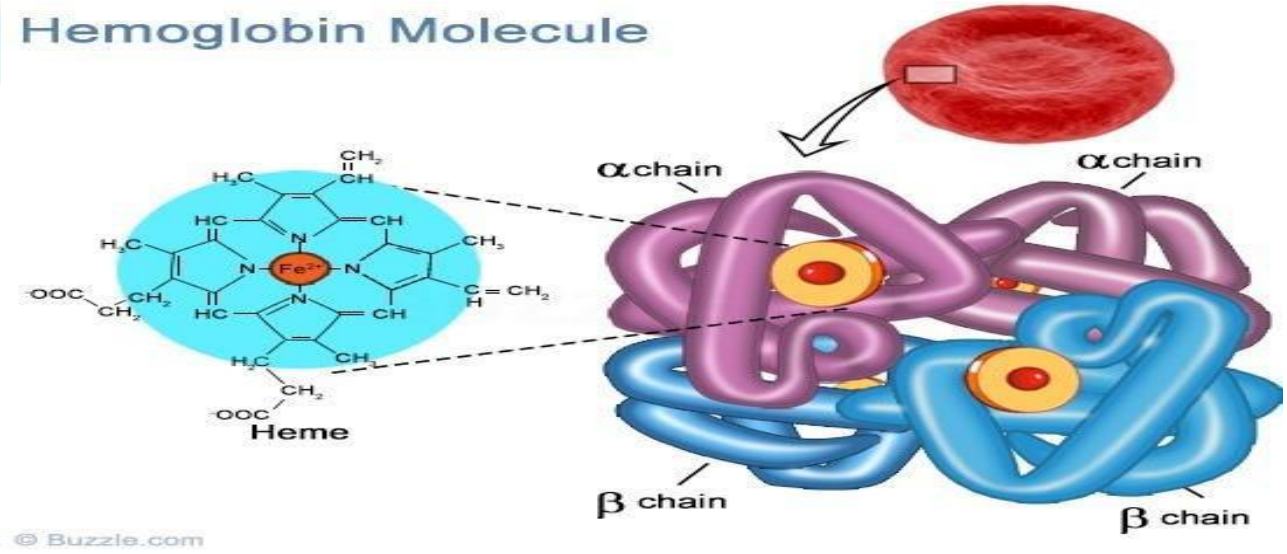
- ↓ Fe
- Iron Def Ana.
- ↓ Fe reutilization
- An. Of chronic disease

- **4- Multi factorial:**

  Lead poisoning

- **5- Other causes:**

- Hereditary: A trans ferrinaemia
- Idiopathic: Pulmonary Haemosiderosis



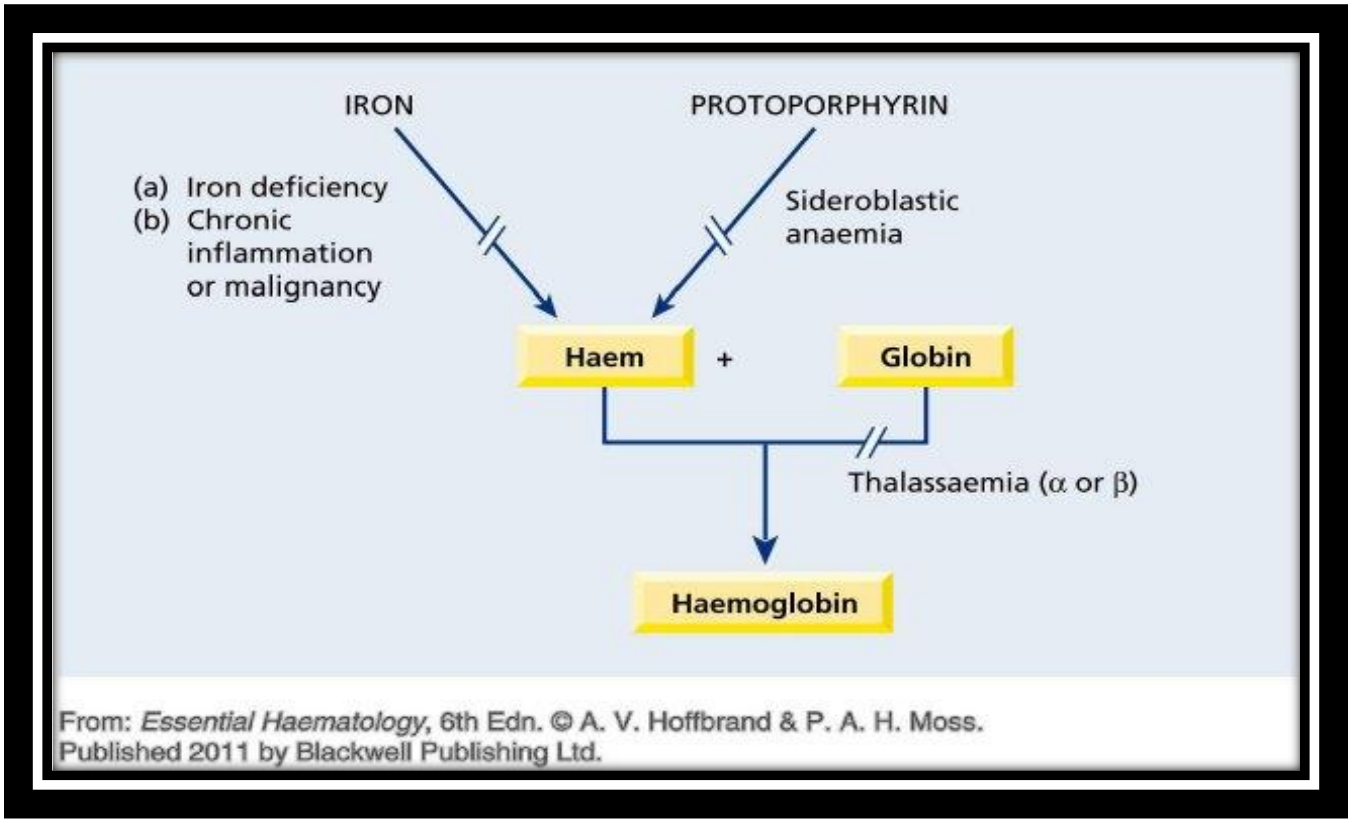


Figure 3.1 The causes of a hypochromic microcytic anaemia. These include lack of iron (iron deficiency) or of iron release from macrophages to serum (anaemia of chronic inflammation or malignancy), failure of protoporphyrin synthesis (sideroblastic anaemia) or of globin synthesis (α- or β-thalassaemia). Lead also inhibits haem and globin synthesis.

- **Mechanism of microcytosis:**
- Hb synthesis → ↓ MCHC & ↓ MCH, division of erythroid series → till a certain level of MCHC, this repeated division ↓ MCV → Microcytosis.
- (**1st hypochromia then microcytosis)**

Iron Deficiency Anaemia

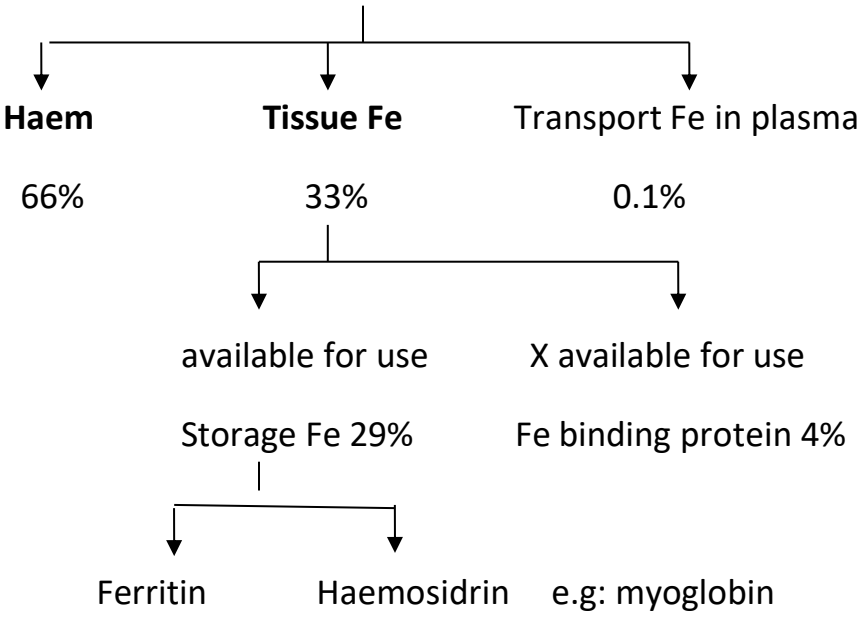
Iron Metabolism

- **Fe intake:**

1 mg /day (continuously reutilized)

Intake= loss (small)

- **Fe distribution:**
  - Total body Fe = 3-5 gm



Nutritional requirements:

- Diet: 15-20 mg/day : a- Haem : meat, fish, liver

  b- ferritin : vegetables e.g Spanish

  5-10 % is absorbed → Abs. 1 mg/day

- **Exceptions:**
  - **Extra-needs:** abs. up to 3-4 mg/d (max)
  - **Increased demands:** preg, menses, growing 1 mg/d

Factors affecting requirements: ↑ Req.

- Menstruation: 0.7 mg Fe lost / d
- Growth: infancy > childhood > adolescence
- Pregnancy :
  - Expansion of mother blood
  - Formation of placenta & cord
  - Fetal requirements
  - Loss during delivery

N.B: One pregnancy without Fe supplement leads to depletion of Fe stores.

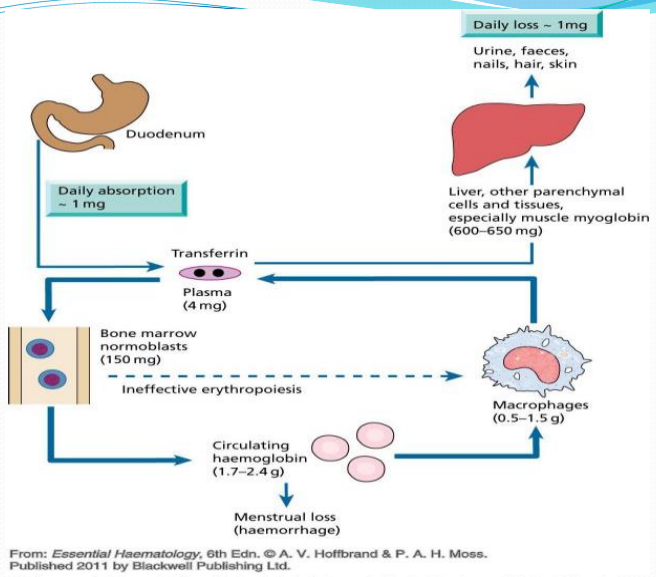


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Figure 3.2 Daily iron cycle. Most of the iron in the body is contained in circulating haemoglobin (see Table 3.1) and is reutilized for haemoglobin synthesis after the red cells die. Iron is transferred from macrophages to plasma transferrin and so to bone marrow erythroblasts. Iron absorption is normally just sufficient to make up for iron loss. The dashed line indicates ineffective erythropoiesis.

Iron Absorption:

Luminal Stage	**Mucosal Stage**	**Blood vessel**
Ferric complexes	Ferritin (store)	Transferrin
Hcl, ptn,enzy	Apoferritin	Apotransferrin
	Fe+++	
	Oxidation	Fe+++
Fe+++ Ascorbate succinate (Reduction)	Fe++ ceruloplasmin xanthine oxidase	

N.B: **Fe + ptn must be in Fe+++**

Sites:

duodenum & upper jejunum

Amount :

1 mg/ day

Forms: - animal diet (haem Fe), meat, fish, liver

- vegetable diet (ferric complex) , spanish

Mechanisms:

Non Haem Fe (veg.)	**Haem Fe (animal)**
Luminal stage	**X luminal processes**
Mucosal stage: Enters by : Receptor mediated, passive diffusion, + surface mucin	Mucosal stage: Enters + mucosal R Fe present in haem ring→ Porphyrin ring broke → Fe release
Blood	Blood

Factors affecting Fe absorption:

1-Amount of Fe in diet : absorption is α $\frac{1}{\text{amount}}$

2-**Forms of Fe in diet**:

Haem is easier than non haem Fe

3-Other substance in diet: Ascorbic acid →↑ absorption

Phytates, phosphates, tea →↓ absorption

4-Pancreatic secretions:

→↓ absorption

So in pancreatic diseases (e.g. pancearititis) ↓ secretions →↑ absorption → Haemochromatosis

5-Gastoferrin:

Present in gastric juice , bind to Fe (unavailable for abs.) →↓ absorption

- **Gastroferrin ↓↓ :**

-In Fe def an. 2ry to it (protective mechanism to prevent further ↓ from abs.)

In hemochromatosis : as a cause of it

(↓ Gast. ↑ abs. → Haemochromatosis)

6- Hcl: ↑ abs.

Liberate Fe+++ from its complexes

Facilitates ↑ abs. of Fe++

Imp. For chelation

Regulation of Fe absorption:

- Stage of Mucosal uptake:

  no. of R.

- Transfer stage:

  Controlled by state of stores

Transfer stage: (Controlled **by state of stores)**

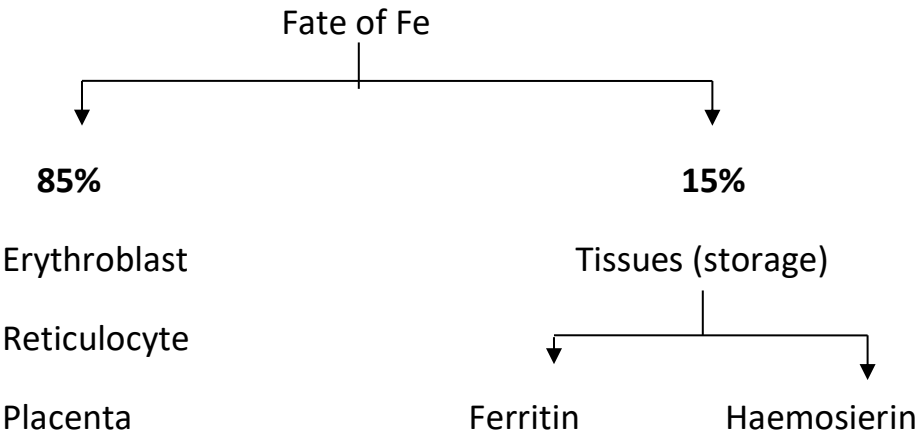
- Tissues: gut , liver , MQ → Fe to plasma transferrin

  → Erythropoiesis

- **Amount abs. depends on that given by tissues**
- ↓amount ↓ Fe , ↓stores, ↑abs. e.g. Fe def. anamia
- ↑Erythropoiesis ↑amount given by tissues stores (overloaded) ↓ absorption
- **This is known as <u>Mucosal Block Theory</u>**

- **<u>Except in :</u>**
- **Haemochromatosis:**↑ stores ↑ absorption
- **Ineffective Erythropoiesis** : e.g. Thalasamia, sideroblastic an.

<u>Iron Transport :</u>



Transferrin

- β glycoprotein
- Synthesized in liver α 1 stores
- Half life 8 days
- MW 80,000
- Carry 4mg Fe (but > 30mg pass through it every day (absorption, RBCs destruction)
- Level 180-260 mg/dl
- 2 Fe+++ atoms binds to its N & c terminals & needs 2 HCO3 for their bindings (but 1 site is better than other) .
- N Transferrin is 1/3 saturated with Fe (Saturated Capacity)
- **TIBC** = 300-400 ug/dl (amount of Fe that can bind to transferrin) ↓ Fe sat! ↑ TIBC
- Serum Fe = 100-150 ug/dl
- **Transferrin Receptors:**
- Protein coded by a gene on chromosome 3 & bind transferrin
- Specific R. on various tissues:

1- cells: erythroblast, reticulocyte, placenta & small % on non erythroid tiss. e.g liver, heart

2- plasma: (soluble form):

- Detected by CD 71/Abs

- Level in plasma α $\frac{1}{\text{Fe supply}}$ ↓ Fe↑ R
- Can be used instead of ferrokinetices
- Once transferrin gives up Fe → apotransferrin

  → circulation → reutilized
- With normal life span (120 days) 1% of RBCs destroyed 20-25 mg Fe till taken by transferrin → reutilized RBCs

Lactoferrin:

- It's a glycoprotein that can bind to 2 atoms of Fe.
- But this Fe cannot be reutilized.
- MW 77,000.
- Found in milk, other secretions,2ry granules of neutrophils.
- Has R. on MQ.
- It has bacteriostatic action by depriving microorganisms of Fe needed for growth.

During inflammation, lactoferrin is excreted from neutrophils → plasma → bind to R on MQ & compete with transferrin for Fe. (This is the pathogenesis of anaemia of chronic disease).

Table 1: Iron Absorption:

Factors favoring absorption	Factors reducing absorption
Haem iron Ferrous form (Fe2+) Acids (HCl, vitamin C) Solubilizing agents (e.g. sugars, amino acids) iron deficiency Ineffective erythropoiesis Pregnancy Hereditary haemochromatosis	Inorganic iron Ferric form (Fe3+) Alkalis – antacids, pancreatic secretions Precipitating agents phytates, phosphates, tea iron excess Decreased erythropoiesis Inflammation

Storage of Iron:

Ferritin	Haemosiderin
• 2/3 of storage Fe • H2o soluble. • Protein Fe complex. • Contains 20% of its wt. Fe. • Small in size → x visible by light microscope. • Considered as 1ry Fe stores. • Gives Fe rapidly to tissues. • Present in plasma. • Present in tissues	• 1/3 • H2o insoluble. • Protein Fe complex. • Contains 37% of its wt. Fe. • Larger in size → visible by L.M. by Perl's stain. • Considered as 2ry Fe stores. • Gives Fe less easily to tissues. • X present in plasma. • Present in tissues (RBCs, BM, spleen, ms.).

- Plasma ferritin:

  - M: 40-340 ug/L

  - F: 14-150 ug/L

- 24 subunits of 2 Ig types:

➢ H subunit (heart, RBCs).

➢ L subunit (liver, spleen, placenta).

Both ferritin & haemosiderin act as stores for unneeded Fe & a source of Fe when required.

Functional Fe containing proteins:

1- Hemoglobin :

- MW 64,000.
- Contains 66% of the Fe.
- Formed of 4 haem & 4 globin.
- Can bind to 4 mol. Of o2.

2- Myoglobin:

- MW 17,000.
- Contains 4-5% of Fe.
- Has 1 haem gp.
- Has higher affinity for o2 (act as o2 reservoir in ms.).

3- Haem & non haem Fe proteins of mitochondria:

- Cytochrome a, b, c.
- Succinate dehydrogenase.
- Cytochrome oxidase.
- Catalase & lactoperoxidase.

For oxidation of Intra-cellular substrates & ATP formation

4- Fe Sulphur protein:

- Xanthine oxidase, reduced NAD.

5- Ferritin & haemosidrin

6- Lactoferrin

Iron Deficiency Anaemia

- **Def.:**

It is the most advanced state of Fe deficiency ch. By:

- ↓ or absent Fe stores.
- ↓ serum Fe conc.
- ↓ Transferrin sat.
- ↓ Hb conc., Hct level

Aeitology:

Causes of iron deficiency:

- ***Chronic blood loss: Bleeding: ↑ loss***

Uterine

Gastrointestinal, e.g. peptic ulcer, oesophageal varices, piles, etc.

Rarely, **haematuria**, haemoglobinuria, pulmonary haemosiderosis, self-inflicted blood loss

- ***Increased demands: ↑ demands:***

Prematurity

Growth

Pregnancy

Erythropoietin therapy

- ***Malabsorption: ↓ absorption:***

Gastrectomy,

Autoimmune gastritis

- ***Decrease intake: Poor diet: ↓ intake:***

A major factor in many developing countries but rarely the sole cause in developed countries.

Stages of Fe deficiency:

1- Iron depletion : (earliest stage)

- Only Fe stores ↓ (N s. Fe, Hb, Hct).

2- Iron deficient erythropoiesis: (Fe def. e out anaemia)

- ↓ stores
- ↓ serum Fe But N Hb, Hct
- ↓ transferrin sat.

3- Iron deficiency anaemia:

- ↓ stores
- ↓ serum Fe
- ↓ Transferrin sat.
- ↓ Hb, Hct
- If anaemia is present MHA

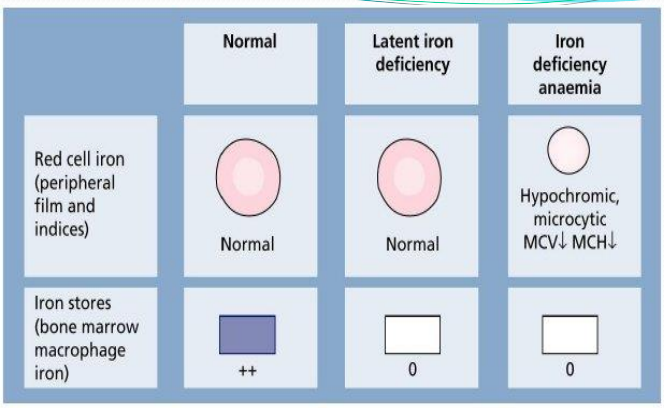


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Figure 3.6 The development of iron deficiency anaemia. Reticuloendothelial (macrophage) stores are lost completely before anaemia develops. MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume.

Diagnosis:

- **Clinical picture:**

1- General symptoms:

- symptoms of the cause
- symptoms of anaemia
- Specific symptoms of Fe def. an. E.g. pica.

2- Epithelial changes: (2ry to↓ intracellular enzy. Fe ptn)

- Angular stomatitis & glossitis (atrophic changes in epith. of tongue & mouth).
- Post cricoid oesophageal web: Atrophy & keritinization of oesophageal epith.→ dysphagia → **Plummer-Vinson Syndrome** (it may turn malignant esp. in males).
- Achlorhydria

- 2ry to def.: Fe def → atrophic gastritis
- cause: mucosal atrophy 1st →↓ Fe absorption (HCL imp. in abs.)
- Koilonychia: flatening of nail concavity (return to N after ttt).

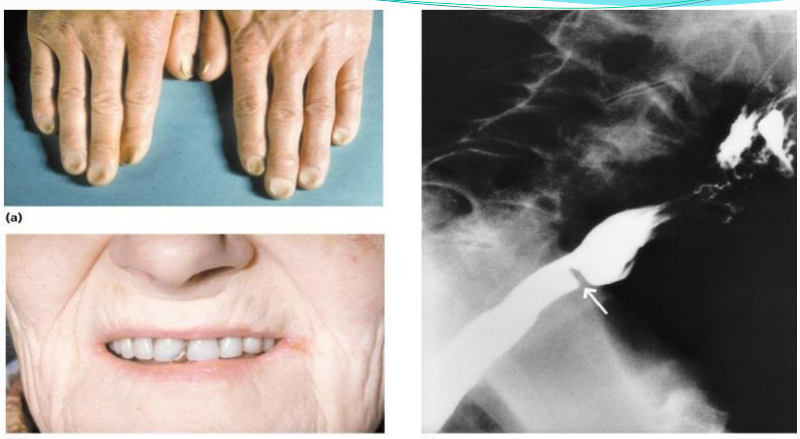

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Figure 3.7 Iron deficiency anaemia. **(a)** Koilonychia: typical 'spoon' nails. **(b)** Angular cheilosis: fissuring and ulceration of the corner of the mouth. **(c)** Paterson–Kelly (Plummer–Vinson) syndrome: barium swallow X-ray showing a filling defect (arrow) caused by a post-cricoid web.

Lab Findings:

1-CBC:

- **RBCs**

➢ ↓ Hb , ↓ MCHC↓ MCV ↓Hct

➢ Microcytic hypochromic anaemia

➢ Occasional target cells, pencil shaped cells.

➢ Poikilocytosis in severe cases.

➢ Retics are low or N.

➢ It may show Dimorphic picture → microcytes

→ macrocytes

due to:

combined B12, folate def.

recent ttt.

recent transfusion.

- **WBCs:** N
- **Platelets:** may be ↑↑ (↓ Fe →↑ megakaryopoiesis).

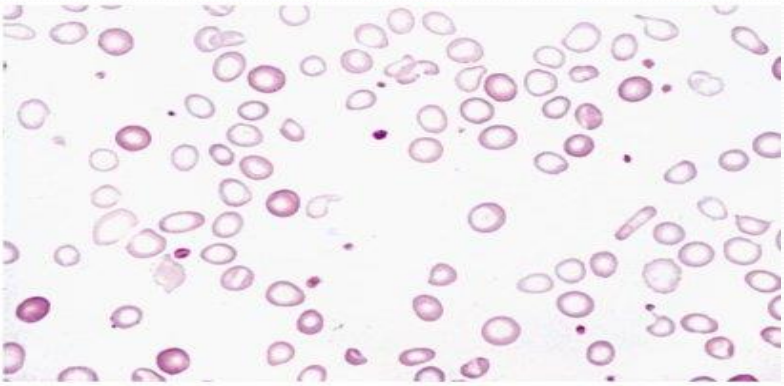


Figure 3.8 The peripheral blood film in severe iron deficiency anaemia. The cells are microcytic and hypochromic with occasional target cells.

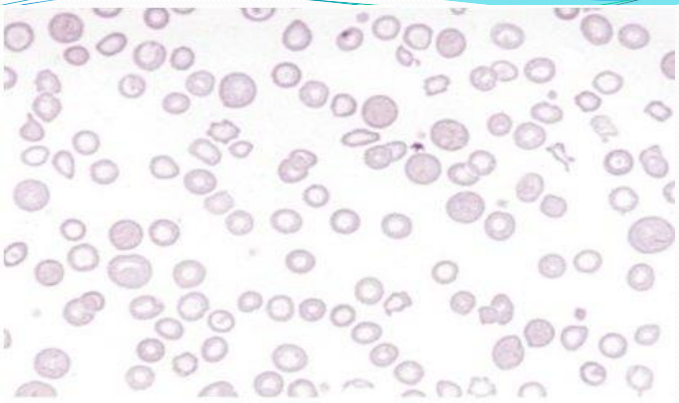


Figure 3.9 Dimorphic blood film in iron deficiency anaemia responding to iron therapy. Two populations of red cells are present: one microcytic and hypochromic, the other normocytic and well haemoglobinized.

2-B.M:

- Erythroid Hyperplasia with under haemoglobinisation (ragged normoblasts).
- By Iron stains:

  - absence of Fe stores in MQ.

  - absence of sideroblasts with small ragged cytoplasm.
- Occasionally megaloblastic changes (if combined def.)

3-Plasma studies:

- ↓ serum Fe
- ↓ serum ferritin
- ↑ TIBC
- ↓transferrin saturation

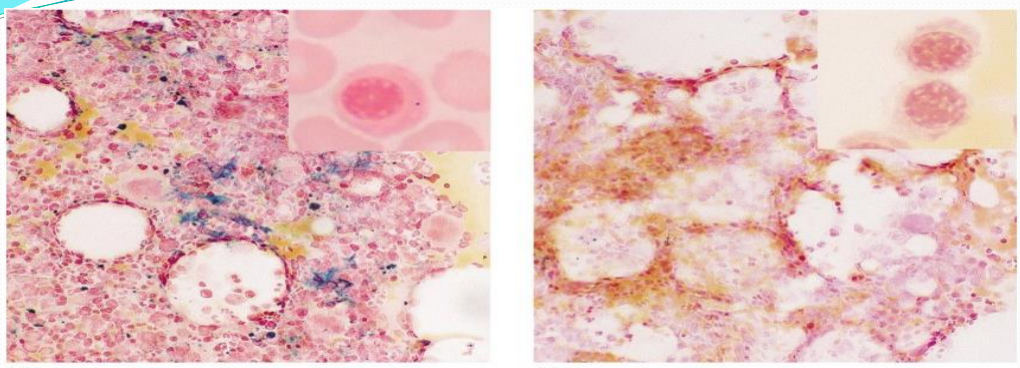
4-Flowcytometry:

↑ Transferrin Receptors (CD 71+ve)

5-↑ protoporphyrin in erythrocyte

<u>Differential Diagnosis :</u>

All other causes of MHA (see table)



(a) (b)

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Figure 3.10 Bone marrow iron assessed by Perls' stain. **(a)** Normal iron stores indicated by blue staining in the macrophages. Inset: normal siderotic granule in erythroblast. **(b)** Absence of blue staining (absence of haemosiderin) in iron deficiency. Inset: absence of siderotic granules in erythroblasts.

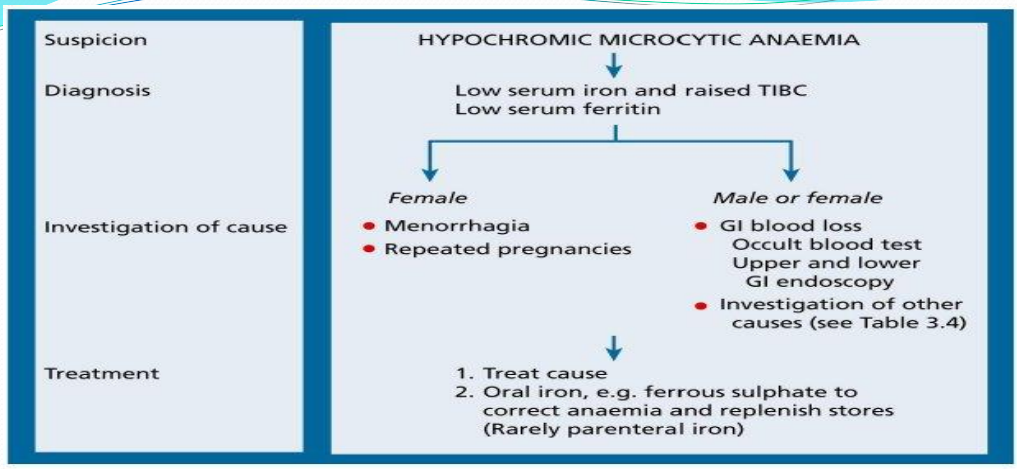

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Figure 3.12 Investigation and management of iron deficiency anaemia. GI, gastrointestinal; TIBC, total iron-binding capacity.

Treatment: → underlying cause
→ correction of Fe def.

Oral Iron	**Parental Iron** (in emergency only)
Ferrous sulphate Ferrous gluconate	Fe dextran Fe sorbitol
➢ 100-200 mg/d ➢ 3 tabletes/d ➢ for 3-6 ms (to correct stores) ➢ **Side effects**: GIT disturbance, nausea, vomiting	➢ x tolerate oral Fe ➢ Rapid correction of stores is needed ➢ Late pregnancy ➢ Before operations with severe Fe def. ➢ **Side effects:** headache, vomiting anaphylactic shock → death

Evaluation for ttt for Fe def. Anaemia:

- Within 3-4 days ↑ Retics
- Within 3-7 days ↑ serum Fe
- Every 3 weeks ↑ Hb 2 g/dl
- After 1 month ↑ serum ferritin

Table 2: Failure of response to oral iron.

- Continuing haemorrhage
- Failure to take tablets
- Wrong diagnosis – especially thalassaemia trait,
- sideroblastic anaemia
- Mixed deficiency – associated folate or vitamin B12 deficiency
- Another cause for anaemia (e.g. malignancy, inflammation)
- Malabsorption – coeliac disease, atrophic gastritis, *Helicobacter* infection.