IRON

History

- The ancient Greeks administered iron to their injured soldiers to improve muscle weakness
- 1825 - hemoglobin iron content was determined to be 0.35%.
- 1832 – 1843 - Chlorosis was defined by low level of iron in the blood and reduced number of red cells
- 1872 – Bossingault first described the nutritional essentiality of iron

History

- 1892 - Bungee describes special vulnerability of infants to iron deficiency and notes that milk is a particularly poor source of iron
- 1928 - Mackay shows that infantile anemia can be avoided by use of iron fortified formula
- By 1960's - Physiology and clinical nutrition largely completed
- 1990's- - molecular details of how iron metabolism is regulated

SOURCES of IRON

- Rich sources--------- includes organ meat(liver, heart, kidney)

- Good sources-------- includes leafy

vegetables ,pulse, fruits, dried fruits, fish.

- Poor sources -------- milk,wheat, polished rice.

IRON ABSORPTION

- Iron is mainly absorbed in the stomach and duodenum.
- in normal people about 10% of dietry iron is usually absorbed.
- Iron is mostly find in foods in ferric form (Fe^{3+}) bound to proteins or organic acids. In acid medium provided by gastric HCL, the Fe^{3+} is released from foods.
- Reducing substances such as Ascobic acid and cysteine convert ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}),iron in ferrous form is soluble and readily absorbed.

The only mechanism by which total body stores of iron is regulated is at the level of absorption. ***Garnick* proposed a *"mucosal block theory"* for iron absorption.**

Mucosal Block Theory

1. Soluble inorganic salts of iron are easily absorbed from the small intestine. HCl present in gastric juice liberates free Fe3+ from non-haem proteins. VitaminC and glutathione in diet reduce Fe3+ to Fe2+, which is less polymerisable and more soluble form of iron. Vitamin C and amino acids can form iron-ascorbate and iron-amino acid chelates which are readily absorbed. Haem is absorbed as such.

2. *Gastroferrin,* a glycoprotein in gastric juice is believed to bind iron and facilitate its uptake in duodenum and jejunum.

3. The absorption of iron from intestinal lumen into mucosal cells takes place as Fe2+.

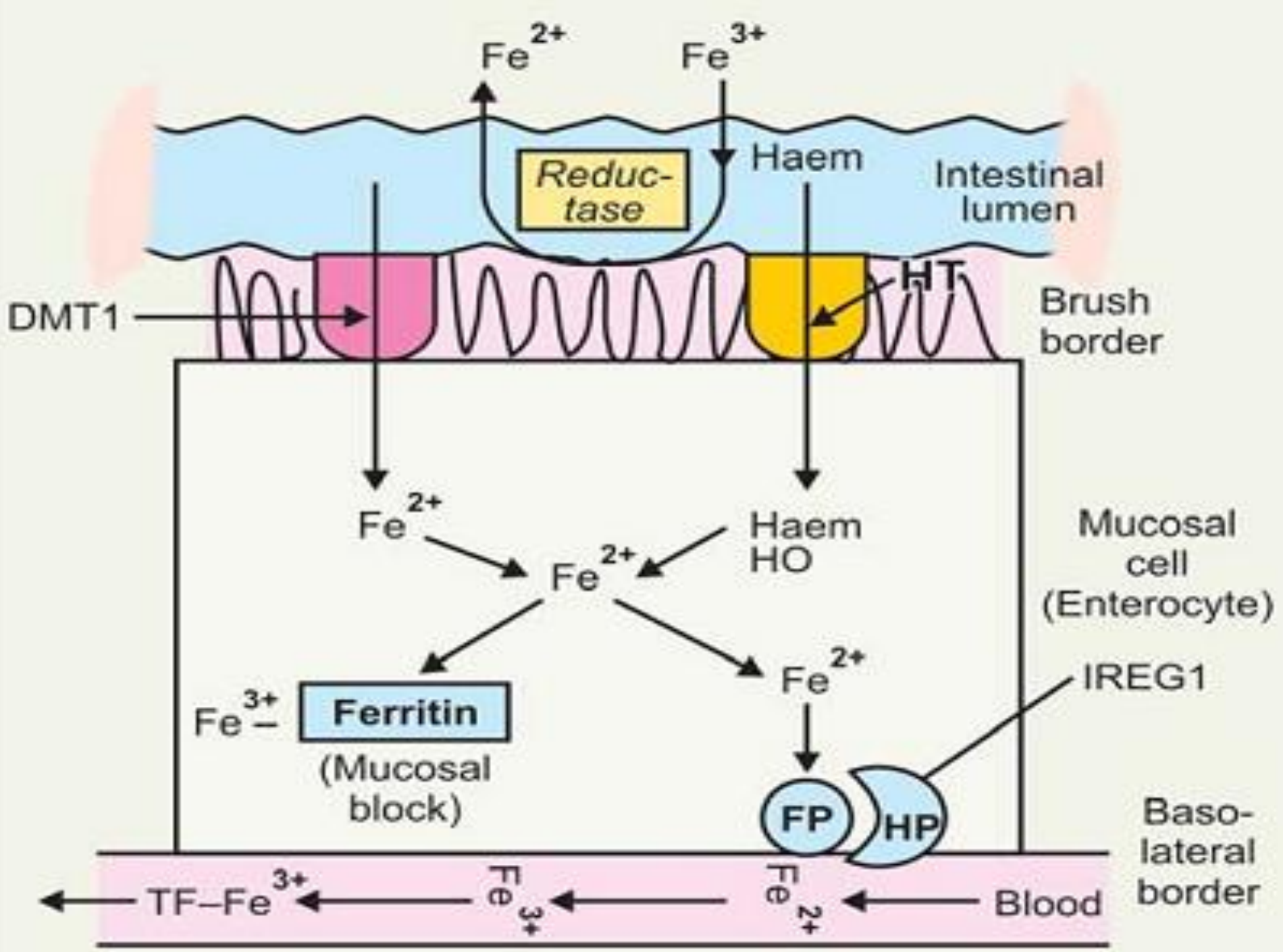
- **4. *Events in intestinal mucosal cells (Enterocyte):***
  • Enterocytes in the *proximal duodenum are responsible for absorption of iron*.

- **• Incoming iron in the Fe3+ state is reduced to Fe2+ by an enzyme *"Ferrireductase"* present on the surface of enterocytes, it is helped by vitamin C present in the foods.**

- **• The transfer of iron (Fe2+) from the apical surfaces of enterocytes into their interiors is performed by a proton-coupled divalent metal transporter (DMT1). This protein is not specific for iron as it can transport a wide variety of divalent cations.**

- Once it is inside, it can either be **stored as "ferritin"** or it can be transferred across the basolateral membrane into the plasma where it is carried bound to **transferrin**.
  • Passage of Fe2+ across the basolateral membrane is carried out by another protein called **iron regulatory protein 1 (IREG 1)**.
  • Most of Fe2+ required to be absorbed is transferred to plasma by a **Fe2+ transporter (FP).**
  • Fe2+ in the enterocytes also come from **"haem"** by the action of ***"haem oxidase"* enzyme on haem.**

- • IREG1 may interact with the copper containing protein called “hephaestin”, a protein similar to caeruloplasmin. Hephaestin is thought to have a ‘ferroxidase’ activity which is important in the release of iron from cells *as Fe3+, the form in which it is transported in the plasma by transferrin.*
  Overall regulation of iron absorption is complex and not well understood mechanistically. It is exerted at the level of the enterocyte where further absorption of iron is blocked if sufficient amount taken up, for body need—so called dietary regulation exerted by “mucosal block” (Garnick’s hypothesis


Fe2+
Fe3+
Reduc-tase
Haem
Intestinal lumen
HT
DMT1
Brush border
Fe2+
Haem HO
Fe2+
Mucosal cell (Enterocyte)
Fe2+
IREG1
Fe3+
Ferritin
(Mucosal block)
FP
HP
Baso-lateral border
TF–Fe3+
Fe3+
Fe2+
Blood

IRON ABSORPTION

- Foods contain two types of iron – heme and nonheme
- Heme iron is supplied by animal foods which also contain non-heme iron (~40% heme, 60% non-heme)
- Plant based foods contain only non-heme iron.
- Heme iron is 2 to 3 times more absorbable than non-heme iron
- People with severe iron deficiency absorb both heme and non-heme iron more efficiently.

Absorption

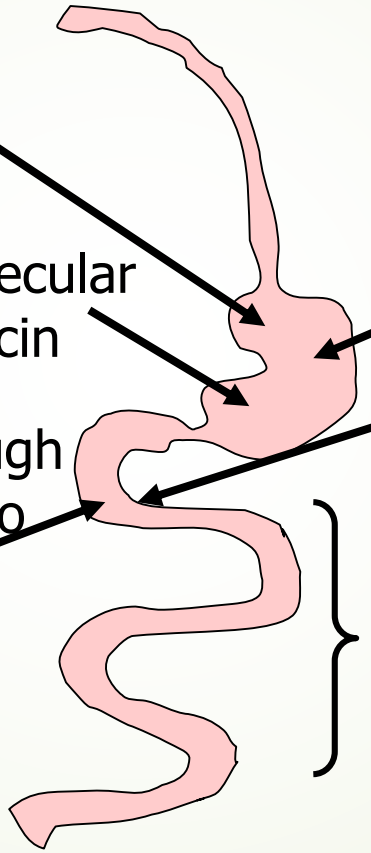
Nonheme

1. Iron solublized and ionized by stomach acid

2. Chelation with small molecular weight compounds and mucin

3. Iron chelates pass through unstirred water layer bind to surface proteins and are internalized

4. Absorption all along the small intestine, but highest in duodenum



Heme

1. Protein digestion of hemoglobin and myoglobin releases heme

2. Heme transported as such into the cell

Absorption

- Duodenal lumen to Duodenal mucosa

- Promotors
  - Amino Acids
  - Animal Proteins(for heme)
  - Ascorbic Acid
  - Hydrochloric Acid
  - Organic Acids
  - Sugars
  - Mucin
- Inhibitors
  - Carbonates
  - Calcium (for heme)
  - Egg yolk
  - Fiber
  - Oxalates
  - Phosphates
  - Phytates
  - Plant polyphenols
  - Soy proteins

IRON IN THE BODY

- More than 80% of the body's functional iron is found in the RBCs, and the rest is in myoglobin and enzymes
- The body regulates its iron status by balancing absorption, transport, storage, and losses'

Transferrin

- The iron liberated form the ferritin of mucosal cells enters the plasma in ferrous state. Here, it is oxidized to ferric form by a copper-containing protein, ceruloplasmin which possesses ferroxidase activity. Another cuproprotein ferroxidase II also helps for the coversion of Fe^{2+} to Fe^{3+} .

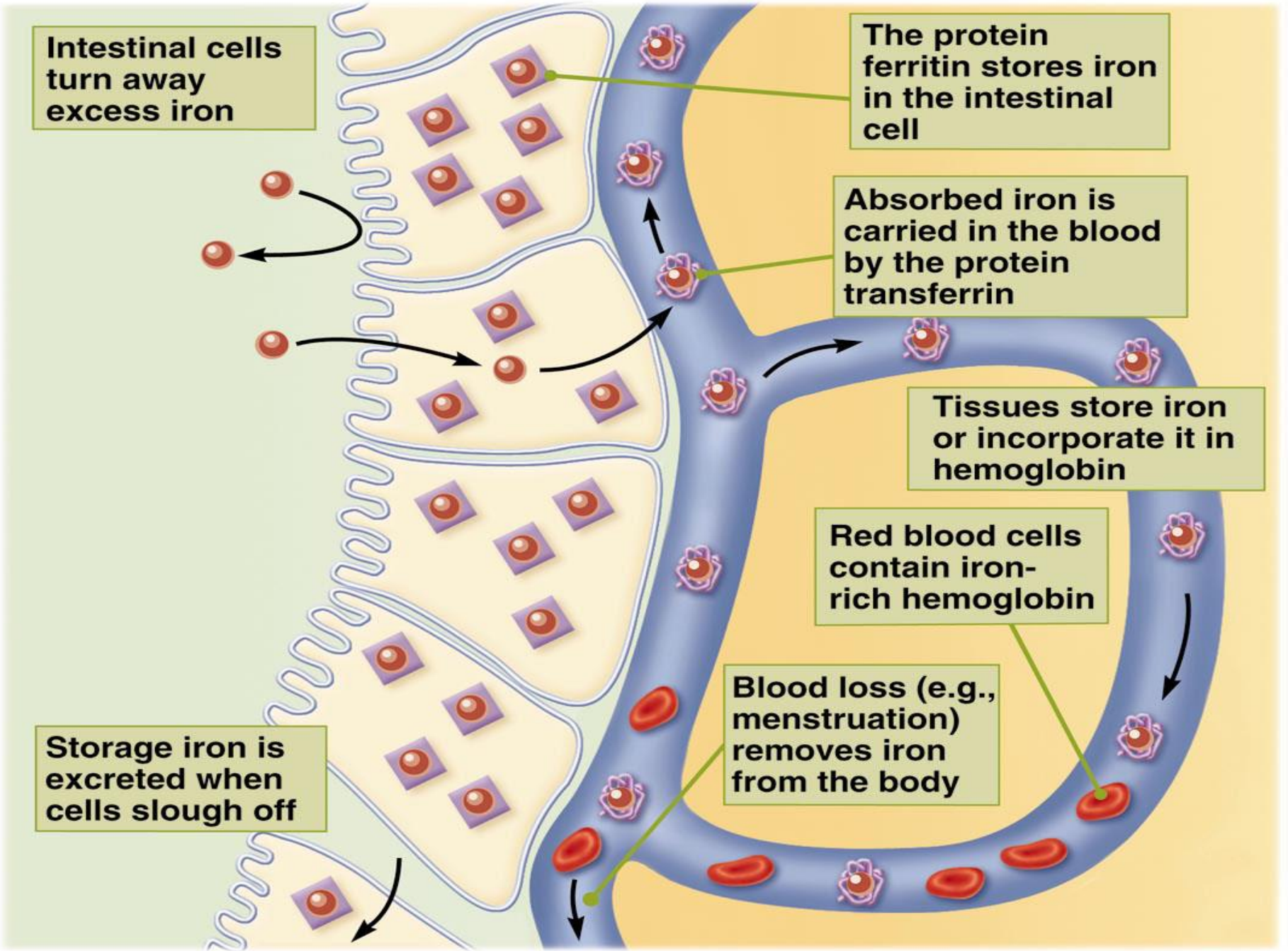
- Ferric iron then binds with a specific iron binding protein, namely transferrin or siderophilin (a glycoprotein with mol. Wt. 90,000) . Each transferrin molecule can bind with two atoms of ferric iron (Fe^{3+}). The plasma transferrin (concentration 250 mg/dl) can bind with 400 mg of iron/dl plasma. This is known as total iron binding capacity (TIBC) of plasma.

Storage of iron

- Iron is stored in liver, spleen and bone marrow in the form of ferritin. In the mucosal cells, ferritin is the temporary storage form of iron. The maximum iron content of ferritin on weight basis is around 25%.

Hemosiderin

- Is another is another storage protein which can hold about 35% of iron by weight .
- Hemosiderin accumulates in the body (spleen, liver) when the supply of iron is in excess of body demands.


Intestinal cells turn away excess iron
The protein ferritin stores iron in the intestinal cell
Absorbed iron is carried in the blood by the protein transferrin
Tissues store iron or incorporate it in hemoglobin
Red blood cells contain iron-rich hemoglobin
Blood loss (e.g., menstruation) removes iron from the body
Storage iron is excreted when cells slough off

IRON DEFICIENCY

- Stages of Iron Deficiency: depletion of iron stores – depletion of functional iron – iron deficiency anemia
- Iron-deficiency anemia is characterized by microcytic, hypochromic RBC

CAUSES OF IRON DEFICIENCY

- Increased physiologic demand eg. pregnancy, lactation, rapid growth
- Blood loss from GI tract, uterus, haemoglobinuria
- Malabsorption
- Diet

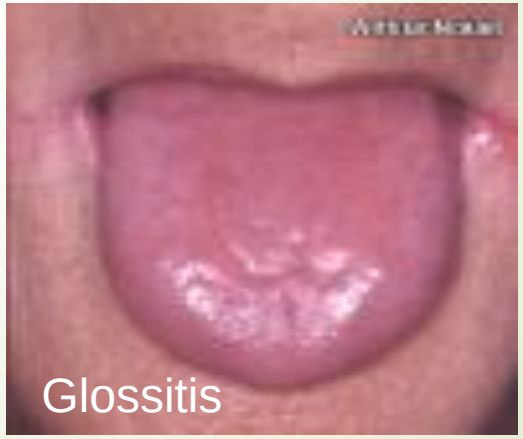
IRON DEFICIENCY

- Commonest cause of anaemia worldwide
- Cause of chronic ill health
- May indicate the presence of important underlying disease eg. blood loss from tumour

2. CLINICAL FEATURE of IRON DEFICIENCY

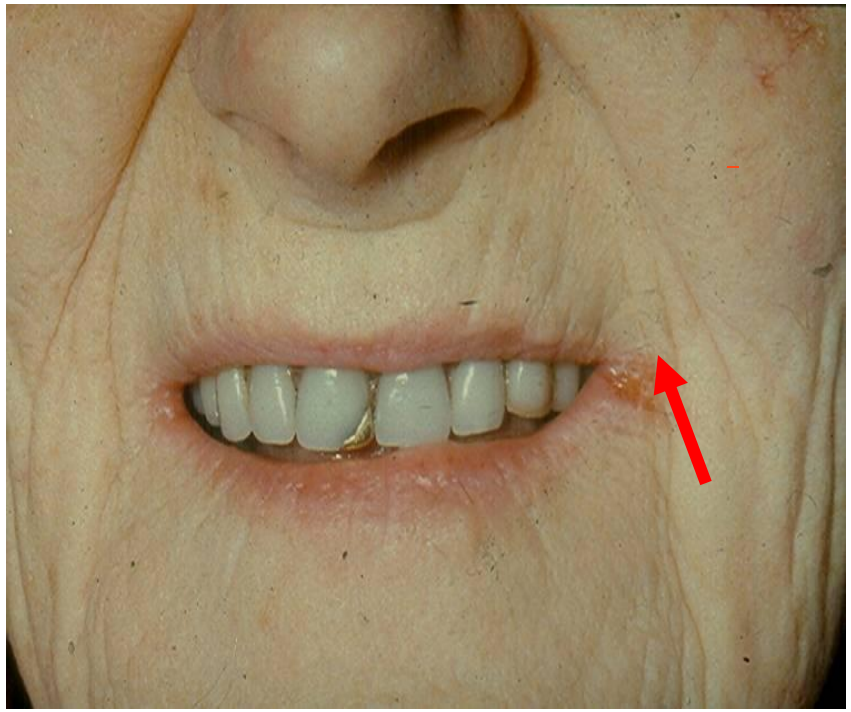
- Symptoms eg. fatigue, dizziness, headache
- Signs eg. pallor, glossitis, angular cheilosis, koilonychia, Plummer Vinson syndrome


Koilonychia

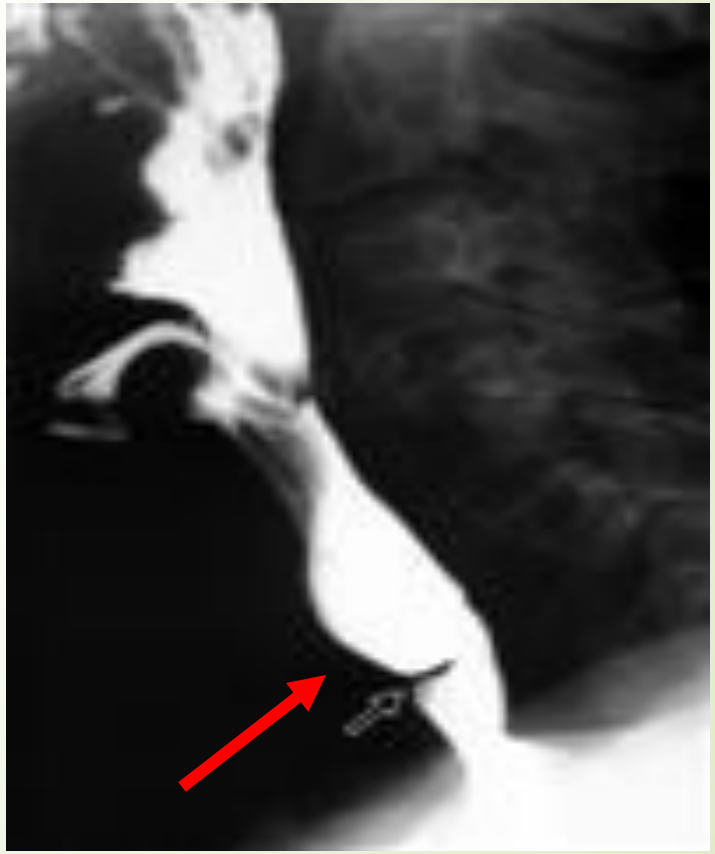

Glossitis

CLINICAL FEATURES OF IRON DEFICIENCY

Angular Cheilosis or Stomatitis



Plummer Vinson Syndrome : Oesophageal Web



PRINCIPLES OF TREATMENT

- Use oral iron.

- Replace iron deficit in total :
  - Restore haemoglobin .
  - Replenish iron stores.

- Establish and treat the cause

LABORATORY DIAGNOSIS: IRON DEFICIENCY

- Microcytic hypochromic anaemia
- Decreased serum ferritin
- Decreased serum iron
- Absent bone marrow haemosiderin : (rarely required for diagnosis)

Treatment

Iron deficiency is treated by Supplementation of iron along with folic acid and vit C.

- Iron intake is improved through ***"Dietary Diversification"*** including:

- Iron-rich foods
- Enhancement of iron absorption
- Food fortification and
- Iron supplementation

PREVENTION STRATEGIES

- WHO has developed a comprehensive package of public health measures addressing all aspects of iron deficiency and anaemia.

- It include:

- Increase iron intake
- Control infection.
- Improve nutritional status

CAUSES OF IRON OVERLOAD

- Hereditary haemochromatosis
- Multiple transfusions
- Liver disease
- Prolonged use medicinal iron

Hemosiderosis

This is less common disorder and its due to excessive iron in the body. It is commonly observed in subjects receiving repeated blood transfusions over the years, e.g. patients of hemolytic anemia, hemophilia.

Hemochromatosis

This is rare disease in which iron is directly deposited in the tissues (liver, spleen, pancreas, and skin). Hemosiderosis is sometime accompained by hemochromatosis bronzed-pigmentation of the skin, cirrhosis of liver, pancreatic fibrosis are the manifestation of this disorder.

TREATMENT AND PREVENTION

- Phlebotomy until ferritin <50µg/ml
- Maintenance venesection
- Screen family members