Minerals

University Of Fallujah
College Of Medicine

Lecture : (5)

Stage : 2th Stage

Lecturer : Dr. Mohammed amer

Department: Chemistry and Biochemistry

Date:

MINEARALS

IRON

Learning Objectives

- **Define the normal distribution of iron in the body & food availability.**
- **Determine the Iron body requirements & identify the specific proteins (or factors) that are involved in its regulation.**
- **Illustrate the mechanism of Iron control.**
- **Group the functions of Iron.**

❑ IRON

- **Distribution of Iron**
  - Body iron content is 3-4 grams.
  - Iron (Fe^{2+}) is found mainly in:
    - Hemoglobin (Hb) in RBCs (2-2.2 grams).
    - Iron-containing proteins like myoglobin.
    - Enzymes (e.g., electron transport chain dehydrogenases, cytochromes a, b, & c, glutathione peroxidase).
    - Bound to the transporter protein Transferrin.
    - Bound to storage proteins (Ferritin, Haemosiderin).

❑ ABSORPTION, STORAGE, AND TRANSPORT:

- **Heme iron:** Very readily absorbed as haem via haem carrier protein 1 (HCP1) on the duodenal enterocyte.
- **Non-heme iron (Fe^{3+}):** Freed from food by HCl in the stomach. In the duodenum, ascorbic acid (Vitamin C) reduces Fe^{3+} to Fe^{2+}, enhancing absorption. Tannates inhibit absorption.
- Note:Vitamin C enhances absorption of nonheme Fe because it is the coenzyme for duodenal cytochrome b (Dcytb), a ferrireductase that reduces Fe3+ to Fe.+2
- Absorbed Fe2+ from heme and nonheme sources has two possible fates: It can be

1. Oxidized to Fe3+ and stored by the intracellular protein ferritin .
2. Iron is exported from enterocytes via the basolateral membrane transporter **ferroportin**, subsequently **oxidized to Fe^{3+} by the copper-dependent enzyme hephaestin**, and then **bound to plasma transferrin for systemic transport**.

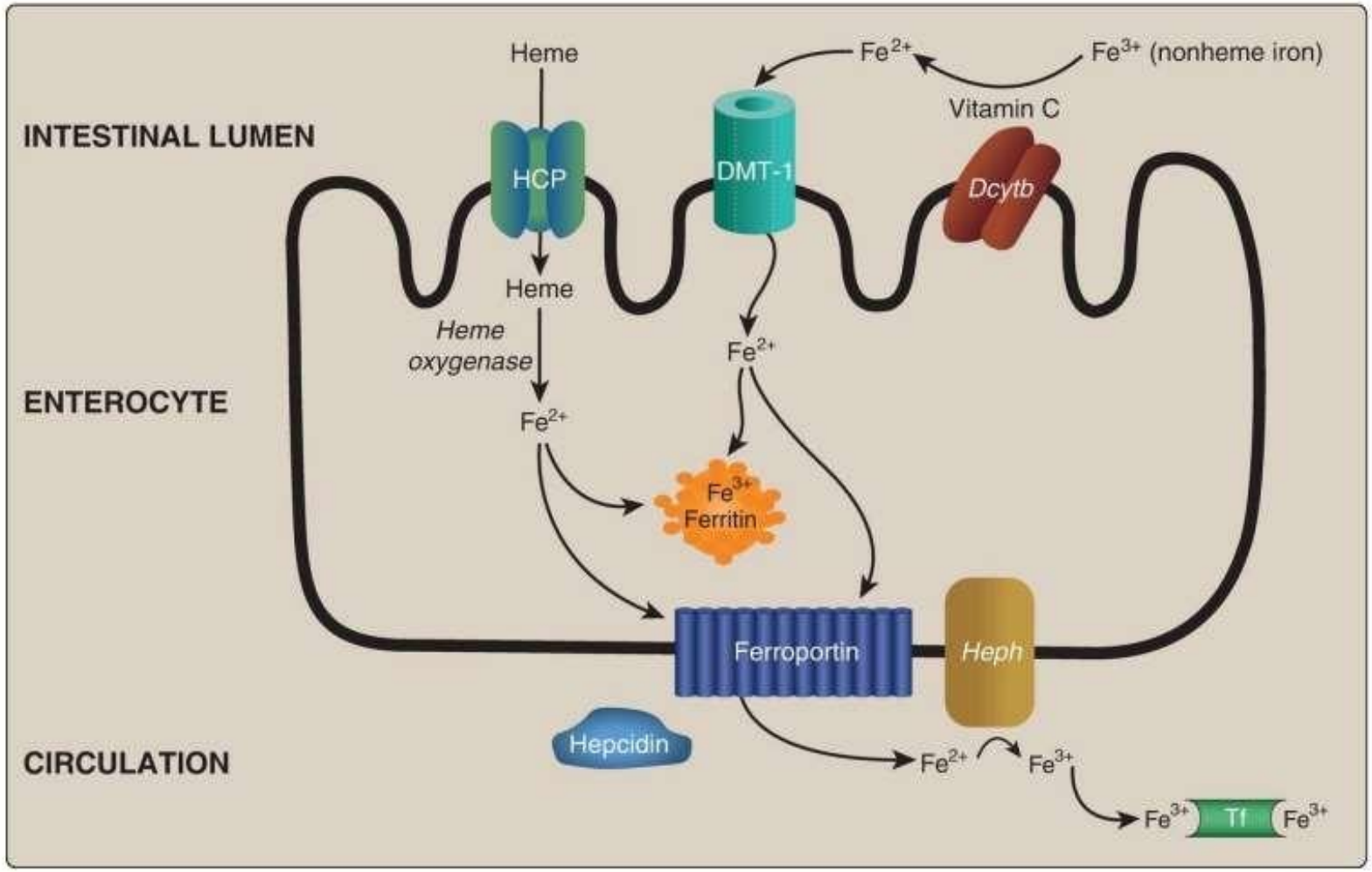
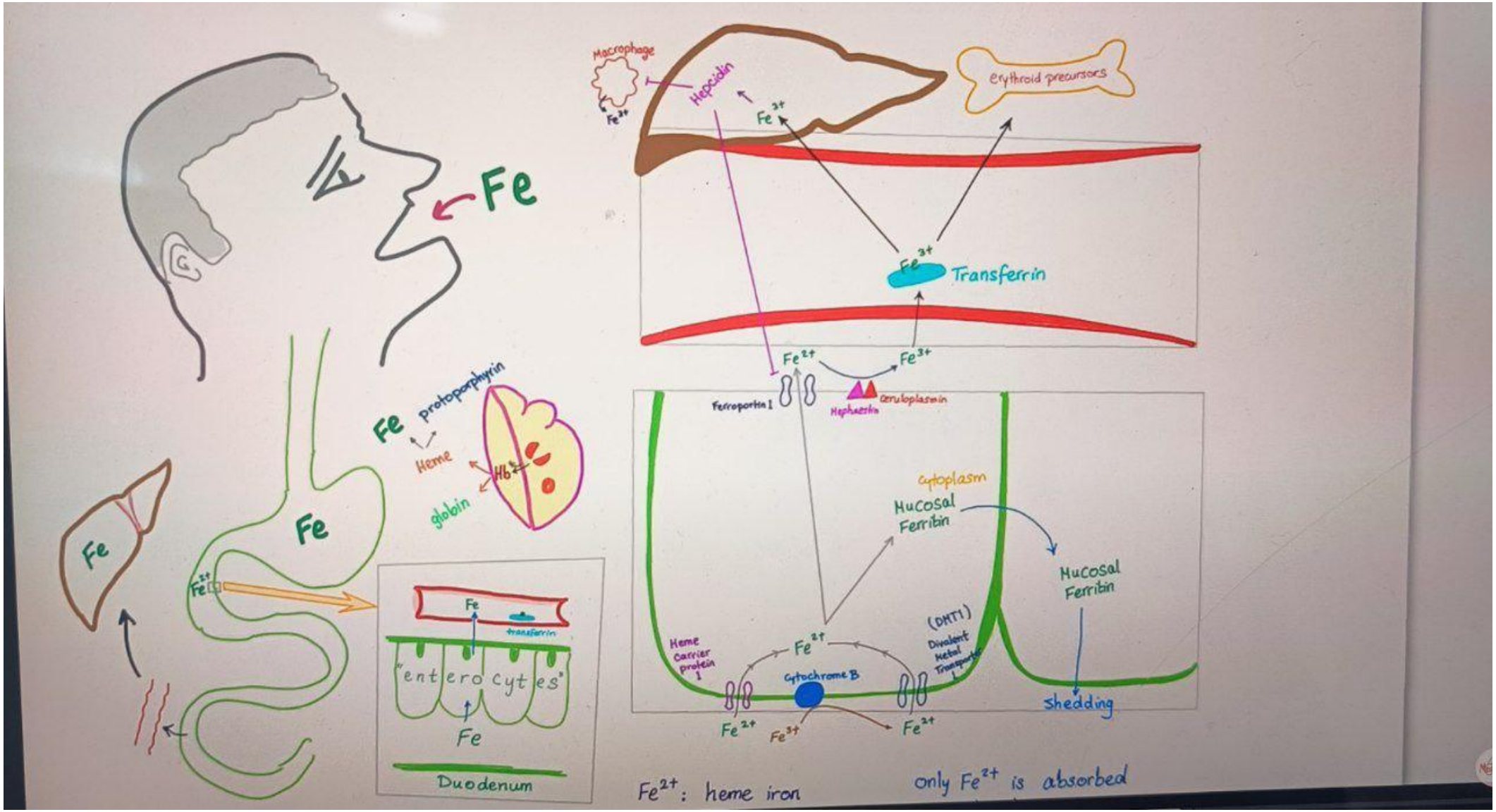


Figure ;Absorption, Storage, And Transport Of Dietary Iron (Fe). Hcp = Heme Carrier Protein; Dmt = Divalent Metal Ion Transporter; Dcytb = Duodenal Cytochrome B (A Ferrireductase); Heph = Hephaestin ;tf = Transferrin .


Fe
Fe
Fe
Fe
Fe
Protoporphyrin
Heme
Hb
globin
Fe
transferrin
"enterocytes"
Fe
Duodenum
Macrophage
Hepcidin
Fe3+
Fe2+
erythroid precursors
Fe3+
Transferrin
Fe2+
Fe3+
Ferroportin I
Hephaestin
ceruloplasmin
cytoplasm
Mucosal Ferritin
Mucosal Ferritin
Heme Carrier protein 1
Fe2+
(DMT1) Divalent Metal Transporter 1
Cytochrome B
shedding
Fe2+
Fe3+
Fe2+
Fe2+: heme iron
only Fe2+ is absorbed

❑ Iron Requirements

- The average diet contains 10-15 mg of iron, but only 5-10% (0.5-1.0 mg) is normally absorbed, compensating for daily losses.
- Absorption can increase to 20-30% during pregnancy and iron deficiency.

❑ Daily Requirements:

- Adult males/postmenopausal females: 0.5-1.0 mg/d
- Pregnant woman: 1-2 mg/d
- Menstruating female: 1-2 mg/d
- Female (12-15 y): 1.6-2.6 mg/d
- Children: 1.1 mg/d

❑ Specific Proteins (Factors) and Iron Control

1. Transferrin (Tf)

Fe^{3+} - apotransferrin complex.

- Transporter of iron in blood and intracellularly.
- 1/3 is occupied by iron; the remainder 2/3 is unoccupied and is the **Total Iron Binding Capacity (TIBC)**.
- Half-life: 8 days.
- Synthesized in the liver.

2. Transferrin Receptor (TfR1)

- Homodimeric transmembrane protein.
- Found on the cell membrane of most cells, most dense on erythroid precursors, hepatocytes, and placental cells.
- Both Tf and TfR are encoded on chromosome 3.
- The Tf/TfR complex is internalized to release iron into cells.

3. Storage Iron

- Stored as **Ferritin** and **Hemosiderin**.
- **Ferritin:** Apoferritin-Fe^{3+} complex. Water-soluble, MW 465 KD, can contain up to 20% of its weight as iron (up to 4000-5000 atoms per molecule).
- Found in nearly all cells, especially hepatocytes and macrophages. Provides a readily available iron reserve.
- **Hemosiderin:** An insoluble protein-iron complex, containing ~37% iron by weight.

4. DMT-1 (Divalent Metal Transporter 1)

- Iron transporter (also transports Pb, Zn, Cu).
- Widely expressed, especially in the proximal duodenum.
- Transfers iron as Fe^{2+} from the gut lumen into the enterocyte.
- High body iron stores down regulate DMT-1, reducing absorption.

5. Ferrireductase

- Found on the luminal surface of enterocytes.
- Converts Fe^{3+} to Fe^{2+} for absorption via DMT-1.

- **6. Duodenal Iron Exporters**
- Transport iron from the basolateral membrane of enterocytes and macrophages into the circulation.
- **Ferroportin-1:** A transmembrane iron transport protein found on the basolateral surface of duodenal enterocytes, placenta, macrophages, and hepatocytes. It controls the exit of iron into the portal plasma. It acts as the receptor for hepcidin.
- **Hephaestin:** A membrane-bound ferroxidase enzyme that contains copper. It converts Fe^{2+} to Fe^{3+} at the basal surface prior to binding to apotransferrin.
- **7. Ceruloplasmin**
- A circulated ferroxidase (copper-containing protein).
- Its deficiency leads to iron deficiency.
- Links iron and copper deficiency; copper administration facilitates iron egress from tissues into circulation.

❑ 8. Hepcidin

- A 25-amino acid peptide hormone (Chromosome 19).

Synthesized by hepatocytes.

- The master regulator of iron body status.
- **Mechanism:** Binds to ferroportin, causing the complex to be internalized and degraded. This blocks iron transport from the intestine and release from macrophages into the circulation.
- **Negative Feedback:**

  Iron excess: High hepcidin decreases iron release.

  Iron deficiency: Low hepcidin allows increased ferroportin activity and more iron entry into plasma.

  Fe-Tf increases hepcidin production (dose-dependent).

❑ Iron Recycling and Cellular Uptake Mechanisms

- Recycling: Macrophages phagocytose old and/or damaged red blood cells (RBC), freeing heme Fe that is sent out of the cells via ferroportin, oxidized by ceruloplasmin, and transported by Tf as described above.
- This recycled Fe meets ~90% of our daily need, which is predominantly for erythropoiesis.
- Transferrin-bound Fe^{3+}, originating from enterocytes and macrophages, binds to transferrin receptors (TfR) on erythroblasts and other iron-requiring cells.
- The complex is internalized through receptor-mediated endocytosis, and Fe^{3+} is then released from transferrin for cellular utilization or stored in ferritin.

❑ .Factors Influencing Iron Absorption

Most absorption occurs in the duodenum.The rate of absorption is controlled by physiological and dietary factors:

- •State of iron stores in the body:Absorption is increased in iron deficiency and decreased when there is iron overload.The mechanism is unclear.
- •Rate of erythropoiesis:When this rate is increased, absorption may be increased even though the iron stores are adequate or overloaded.
- •Contents of diet: Substances that form soluble complexes with iron (e.g. ascorbic acid) facilitate absorption. Substances that form insoluble complexes (e.g. phytate) inhibit absorption.
- •The chemical state of the iron: Iron in the diet does not usually become available for absorption unless released during digestion.This depends, at least partly, on gastric acid production; Fe^{2+} is more readily absorbed than Fe^{3+}, and the presence of H^+ helps to keep iron in the Fe^{2+} form. Iron in haem (in meat products) can be absorbed while still contained in the haem molecule

❑DEFICIENCY:

- Iron deficiency leads to a **microcytic, hypochromic anemia**, which is the most common form of anemia in the world .
- It results from impaired hemoglobin synthesis, causing a reduction in red blood cell size.
- **Treatment involves iron supplementation** to restore normal levels.

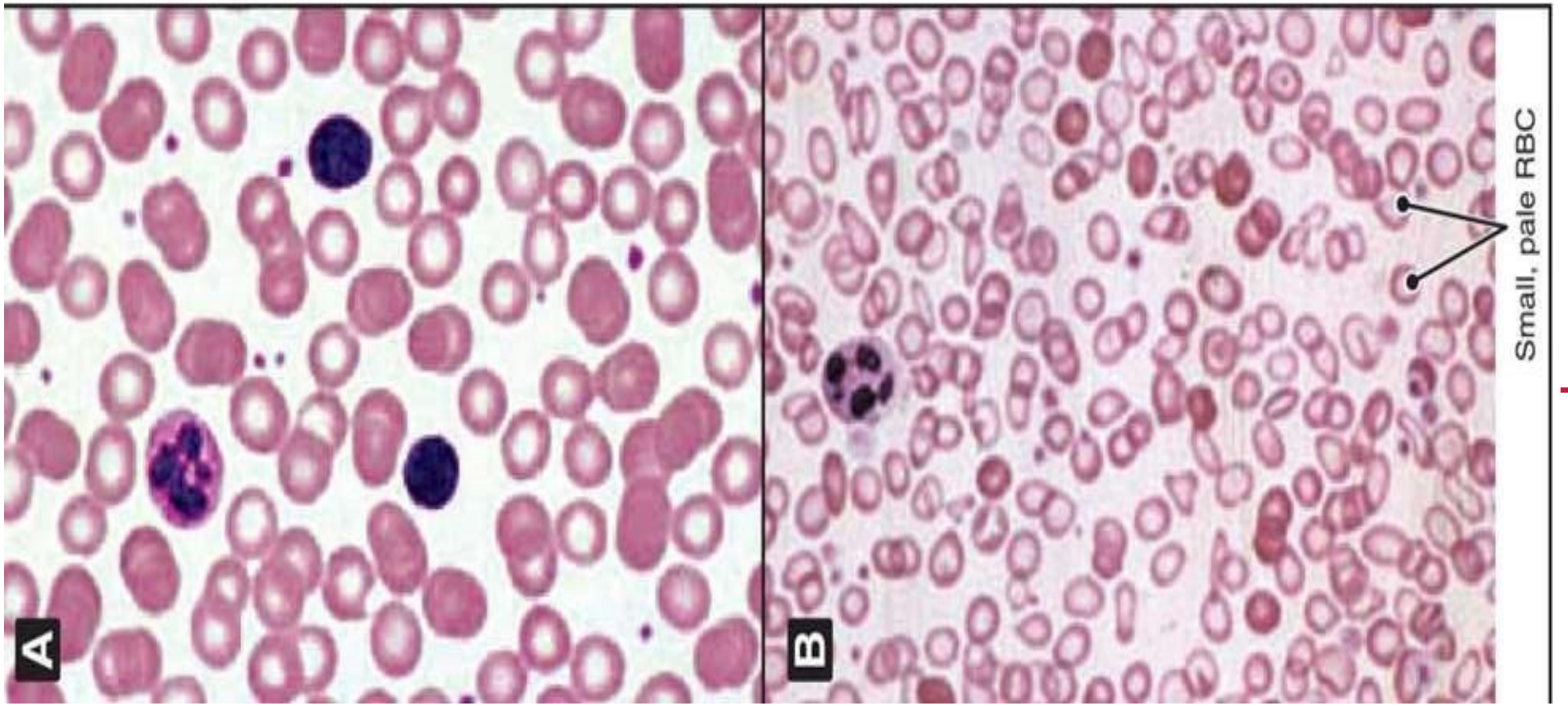
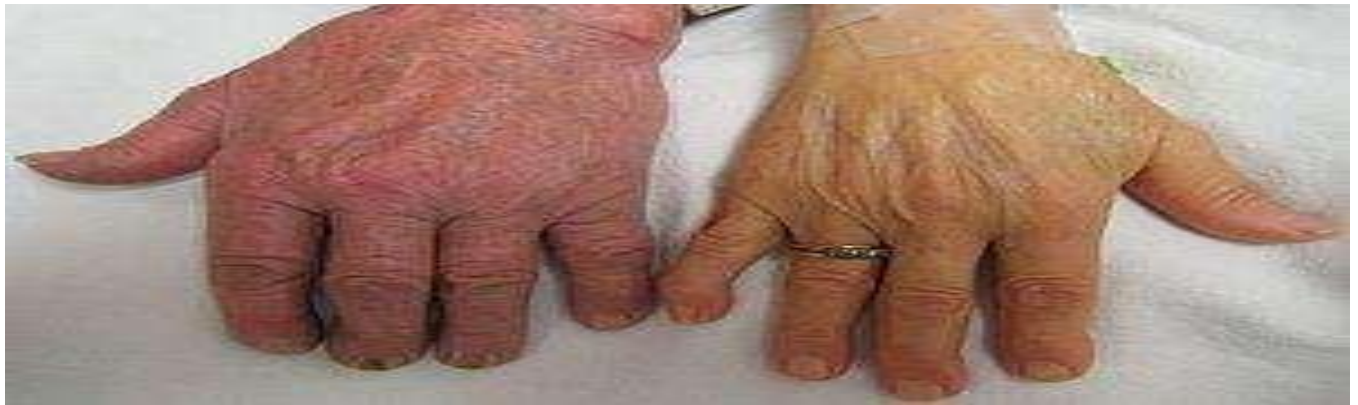


FIGURE A. NORMAL RED BLOOD CELLS (RBC). B. SMALL (MICROCYTIC), PALE (HYPOCHROMIC) RBC IN MICROCYTIC ANEMIA.

Insufficient Dietary Iron Can Result In Iron Deficiency

- fatigue
- lethargy
- more frequent infections
- reduced resistance to cold
- impaired learning
- Hypoferrimia



❑ Excess: Fe Overload

- **Iron Overload Disorders:**
  Iron overload may also occur due to genetic defects. A major example is **hereditary hemochromatosis (HH)**, an autosomal recessive disorder primarily affecting individuals of Northern European descent.
- It is most commonly caused by mutations in the **HFE (high iron)** gene. The condition is characterized by **hyperpigmentation, hyperglycemia ("bronze diabetes")**, and **organ damage**, particularly to the **liver**, **pancreas**, and **heart**—all major iron storage sites.
- In HH, **serum iron and transferrin saturation are elevated**. Treatment involves **regular phlebotomy** or the use of **iron chelators**.

Note: Iron overload can also result from mutations in proteins regulating iron metabolism that cause **inappropriately low levels of hepcidin**, leading to **hemosiderosis** (the deposition of hemosiderin, an insoluble intracellular form of stored iron).

❑ Hemosiderosis

- Hemosiderosis:is a form of Iron overload disorder resulting in the accumulation of hemosiderin in the lung, liver, pancreas, skin and kidney.
- **Features of Hemosiderosis:**

1. Cirrhosis of liver and liver failure.
2. Diabetes mellitus.
3. Yellow color of skin and hyperpigmentation.
4. Hemosiderin deposition in the brain.

Thank you