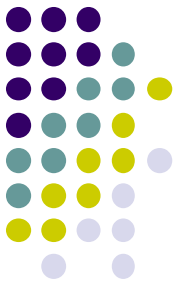
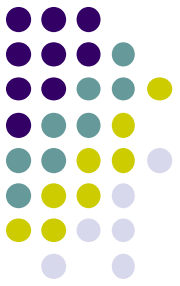


● IRON

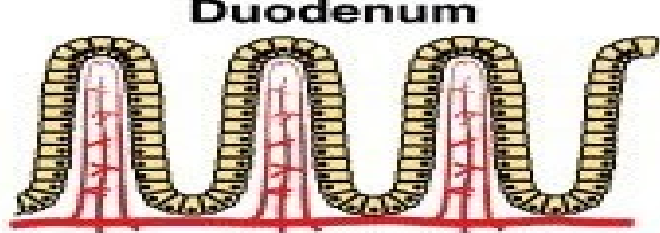


- **Total body iron content--- 3-5gm**

Distribution



- - 75% in Hb
- - 15% in ferritin
- - 5% in myoglobin & enzymes
- Transferrin – 3-4 mg
- Absorption – 1 mg/day
- Losses – 1 mg/day



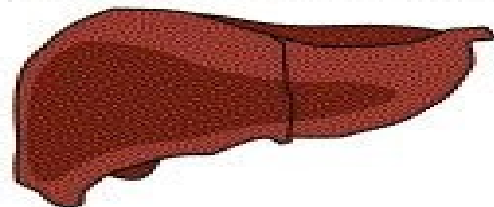
Dietary iron absorption

~1-2 mg/day

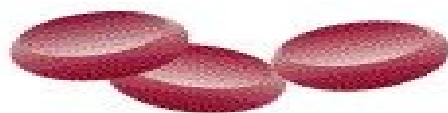
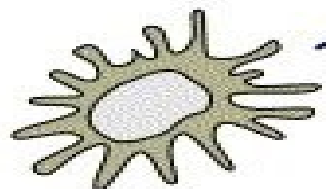
Muscle
~300 mg
(primarily in myoglobin)



Liver parenchyma
~1000 mg
(primarily stored in ferritin)



Macrophages
~600 mg



Erythrocytes
~1800 mg
(in hemoglobin)



Bone marrow
~300 mg
(primarily in hemoglobin)

Body iron loss

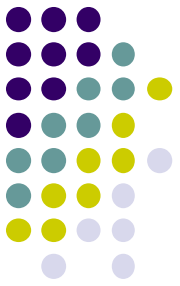
Sloughed mucosal cells
Desquamation

~1-2 mg/day

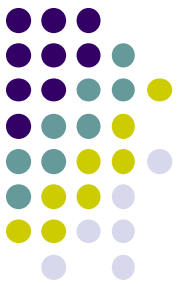
Menstruation
Other blood loss



Iron containing proteins



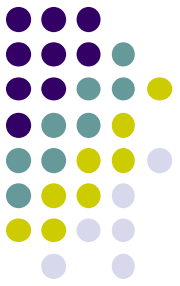
- **1. Heme containing proteins**
- **2. Non-heme iron containing proteins**
- **3. Iron requiring enzymes**



1. Heme containing proteins

- **Hemoglobin -----2500mg -----60-70%**
- **Myoglobin -----400mg -----5-10%**
- **Heme enzymes -2-3mg ----- 1%**
 - **Cytochromes**
 - **Peroxidase**
 - **Catalase**
 - **Tryptophan pyrrolase**

2. Non-heme iron containing proteins



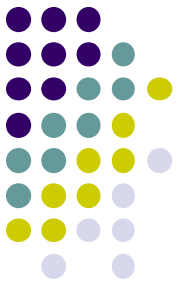
- **Iron storage proteins**

- **Ferritin** **300—400mg** **10—15%**
- **Hemosiderin**

- **Iron transport protein**

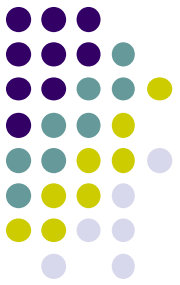
Transferrin **6-8mg** **1-2%**

3. Iron requiring enzymes



- **Xanthine oxidase**
- **Succinate dehydrogenase**

Sources of iron

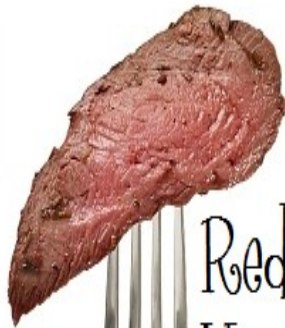


- **Animal sources**
 - **Meat, fish, liver**
 - **Milk----- very poor source**
- **Vegetable sources**
 - **Cereals, legumes, nuts, leafy vegetables, jaggery (good source), dates**

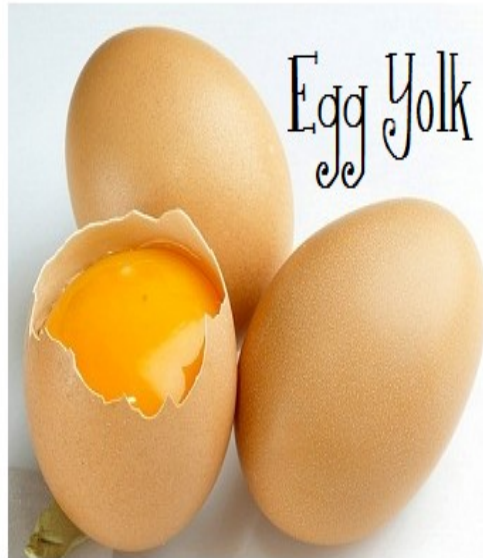
Iron-Rich Foods



Artichoke



Red Meat



Egg Yolk



Parsley



Spinach



Potato

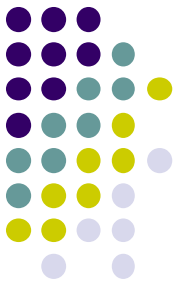


Beans



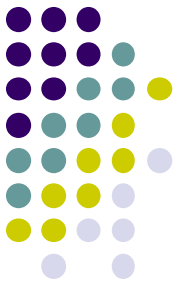
Broccoli



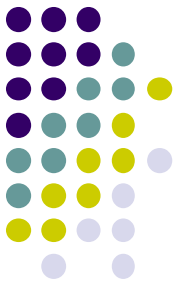


Daily requirement

- **Adult** ----- **20mg**
- **Children** ----- **20—30mg**
- **Pregnancy** ---- **40mg**

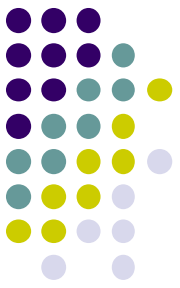


- Note: premature babies are at a risk of iron deficiency, since iron transfer from mother to fetus mainly occurs in last trimester of pregnancy



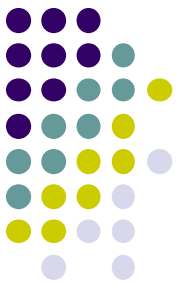
Iron absorption

- **Absorbed in duodenum**
- **Only Fe^{2+} (reduced) form is absorbed**



Factors increasing absorption

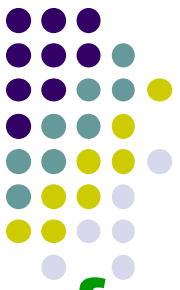
- **Gastric Hcl**
- **Ascorbic acid**
- **Cysteine & SH group of proteins**
(all these reduce ferric ions)



Factors decreasing absorption

- **Oxalates (leafy vegetables)**
- **Phytates (cereals)**
- **Tea/ coffee**
- **Ca, Cu, Zn, Pb, phosphates**
- **Alkaline PH**

Iron absorption

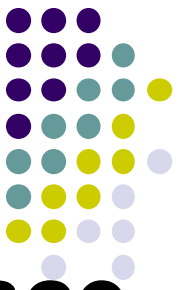


Mucosal block theory

Homeostasis by regulation at level of absorption, no physiologic pathway for excretion.

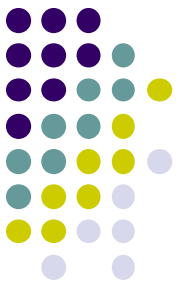
- When Iron stores in body is depleted, absorption \uparrow & vice versa. This is called **Mucosal block** of regulation
- Site of absorption - Duodenum
 - Only ferrous iron absorbed
 - ferric form reduced by **ferric reductase** present on enterocyte surface

Iron absorption



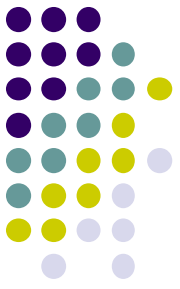
Mucosal block theory

- Ferrous iron on the luminal surface of enterocyte binds to a transporter protein-divalent metal transporter-1 (**DMT-1**) & transported into the cell
- Unabsorbed iron is excreted
- Heme iron uptake is by heme carrier protein (**HCP1**)
- Inside the enterocyte, **heme oxygenase** releases iron



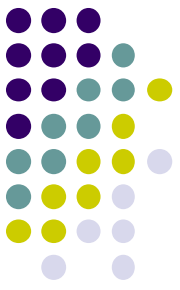
Iron absorption

- Once inside an enterocyte, iron can either be stored as ferritin or transferred across membrane into plasma
- For storage, iron oxidized to ferric, complexed with apoferritin to form Ferritin
- Retained temporarily in the mucosal cell
- Further absorption or retention is decided by the iron status

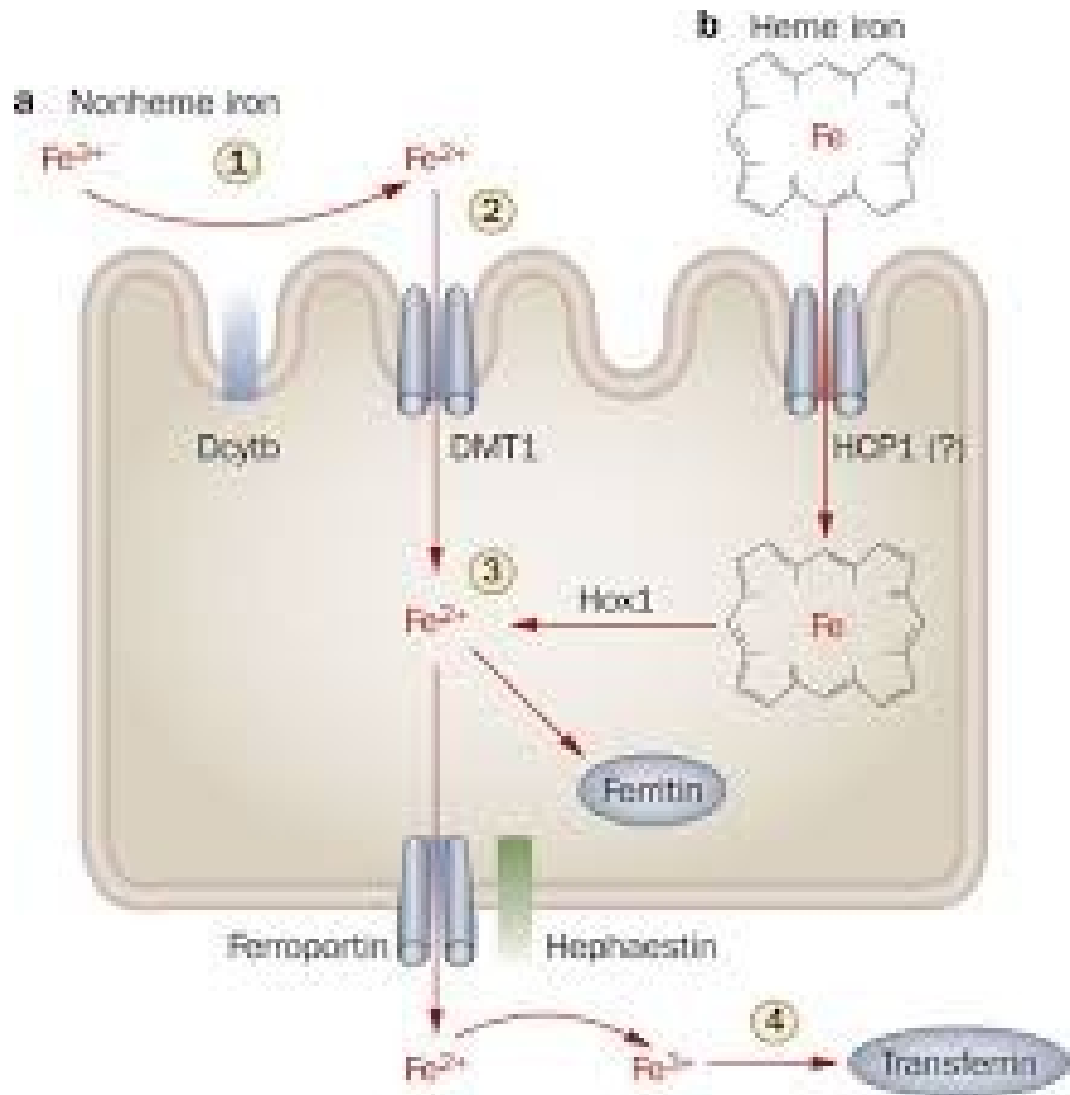


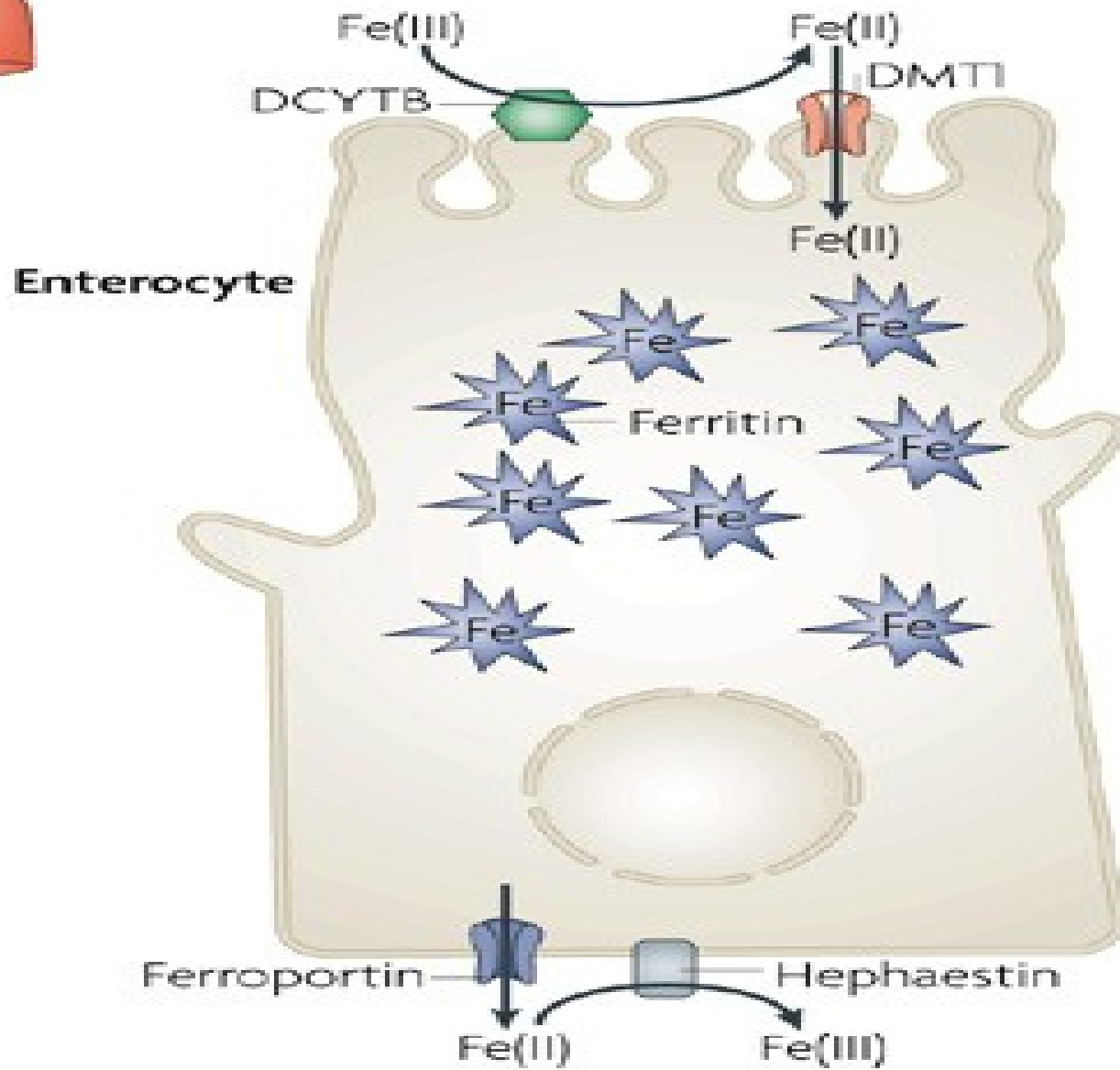
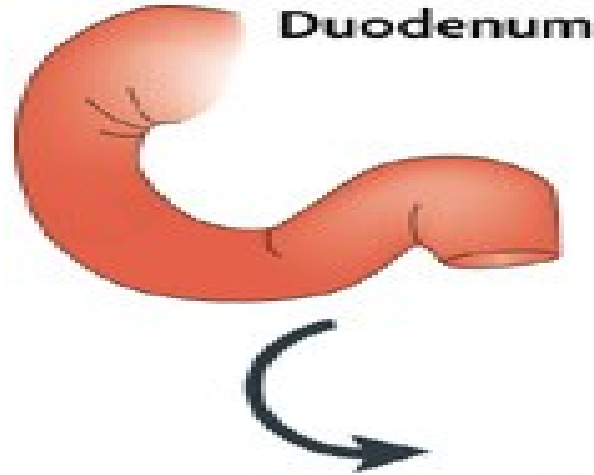
- If there is free transferrin in plasma, iron is absorbed into bloodstream
- If transferrin is saturated with iron, then this iron is lost when cell is desquamated

Iron absorption into blood stream

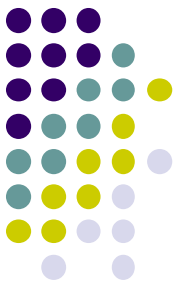


- If free transferrin is available, then Iron is released from ferritin, crosses basolateral membrane of enterocyte in ferrous form , using a transport protein called **Ferroportin**, reoxidized to ferric by **hephaestin** & transported by transferrin



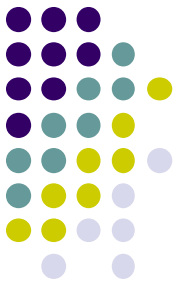


Mechanism of Regulation of Iron absorption



A. Mucosal regulation:

- 📖 Iron absorption needs 2 proteins – **DMT-1** & **Ferroportin**
- 📖 Synthesis of both is downregulated by a peptide – **Hepcidin**
- 📖 (hepcidin is a peptide secreted by liver in conditions of adequate iron reserve)
- 📖 In anemia, hepcidin is reduced, so absorption ↑



B. Stores regulation:



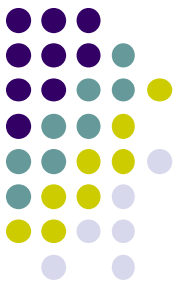
When body stores fall, Iron absorption \uparrow

C. Erythropoietic regulation:

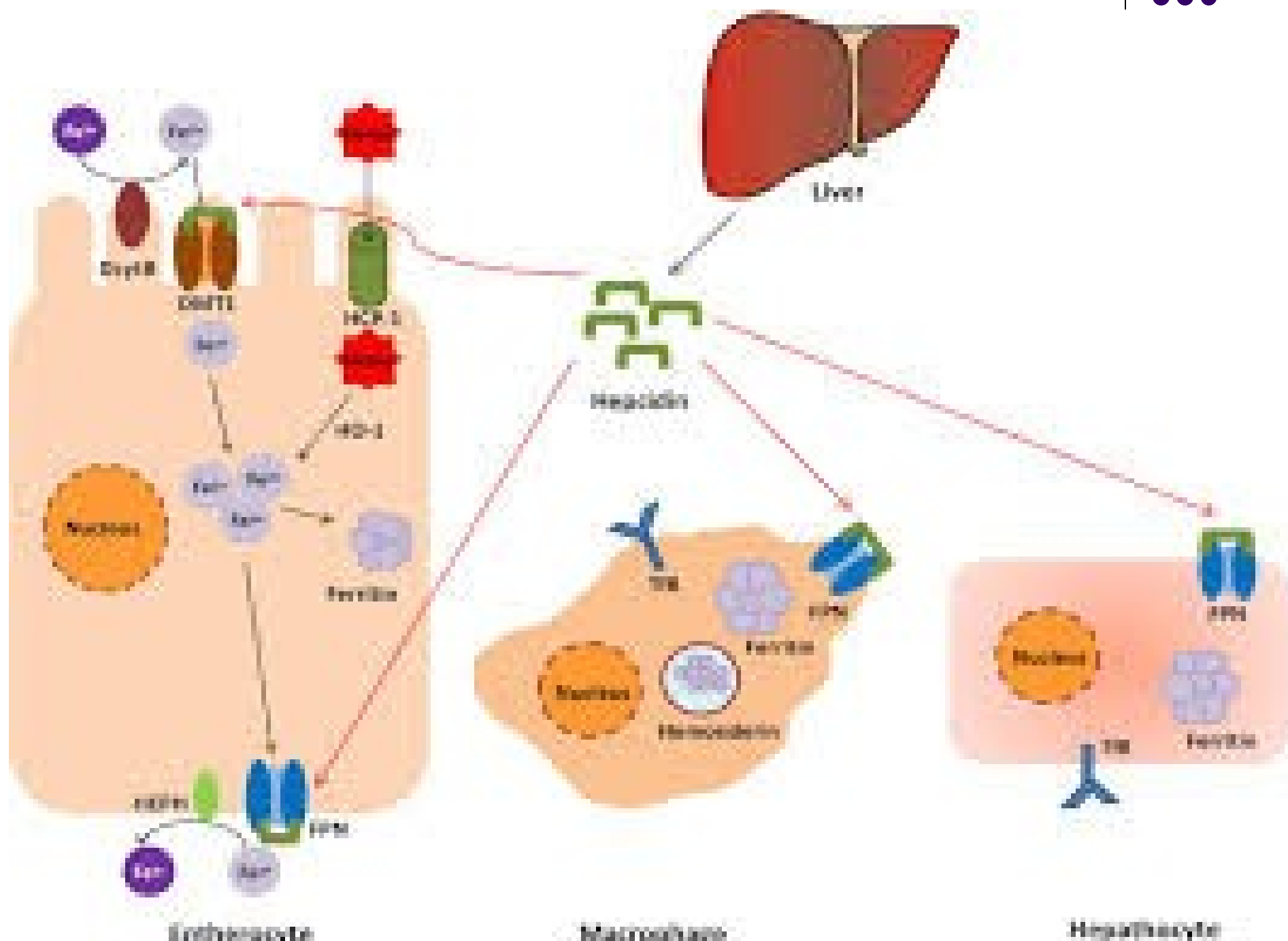


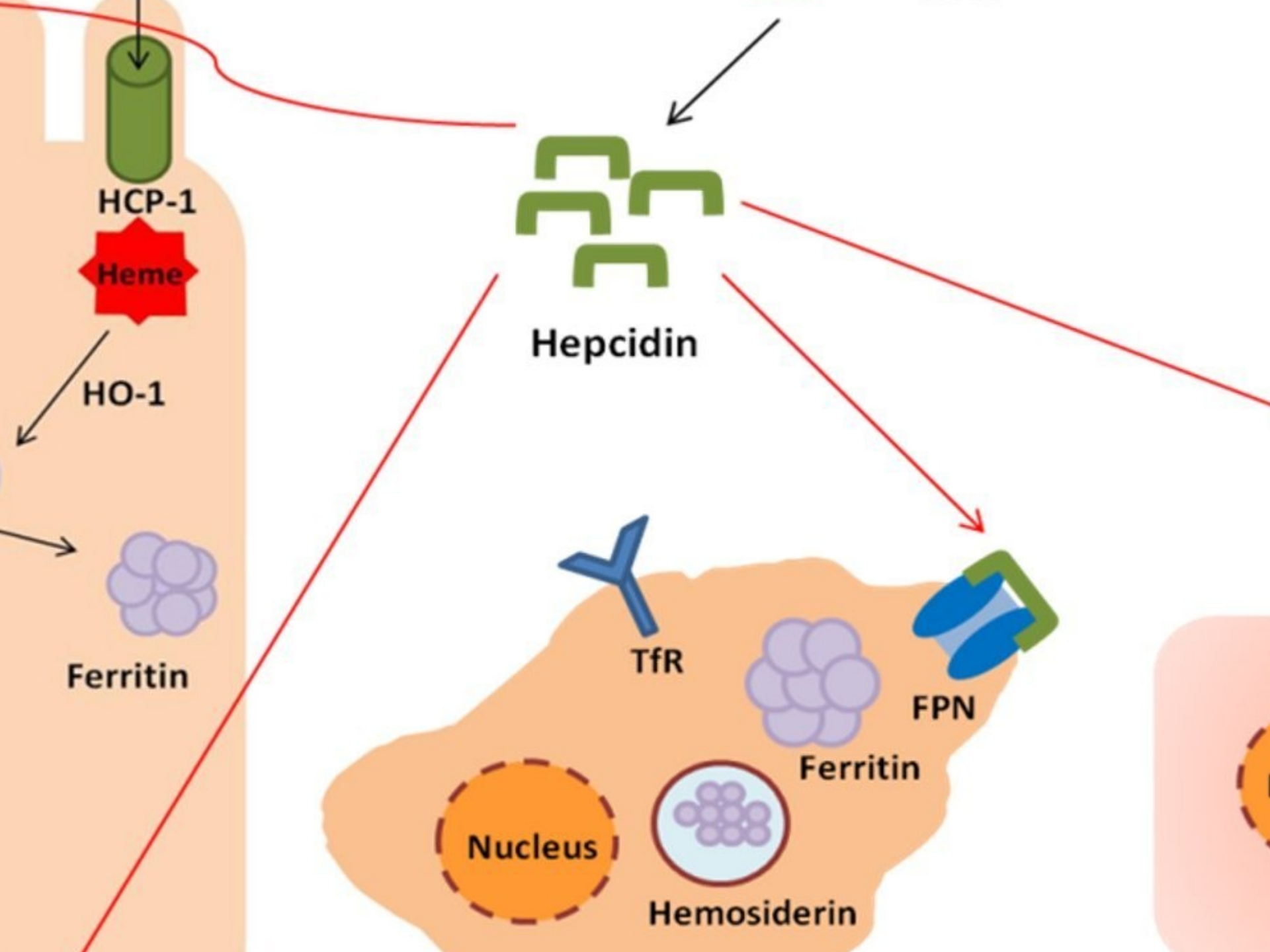
In anemia, erythroid cells signal mucosa to \uparrow absorption

D. Synthesis of ferritin & transferrin receptor (TfR)



- 📖 Reciprocal relationship bt the 2
- 📖 In high Fe levels,
- 📖 mRNA for ferritin is translated so ferritin synthesis increased (to store Fe) &
- 📖 mRNA for TfR is degraded so TfR synthesis blocked (Fe uptake not required)
- 📖 (example of regulation of gene expression at translation level)





Iron transport in blood

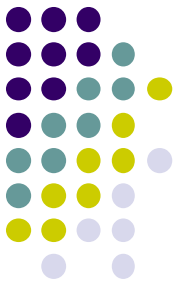


- By transferrin
- β -1 globulin, synthesized in liver
- One molecule binds to 2 Fe^{3+} atoms

Ferroxidase

- Apotransferrin + 2 Fe^{2+} \longrightarrow
Transferrin – 2 Fe^{3+}
- In blood **Ceruloplasmin** is the ferroxidase, which maintains the ferric form

Iron transport in blood - Transferrin



- **Usually 30-33% saturated**
- **Normal level in plasma- 300mg/100ml**
- **↑ in iron deficiency**
- **Useful index of nutritional status**

Total iron binding Capacity(TIBC)



- **Provided by transferrin**
- **Usually 30-33% saturated (120mg/dl)**
- **In iron deficiency anemia, Transferrin level \uparrow , TIBC \uparrow , serum iron level \downarrow**

Daily Diet
contains
10-20 mg iron



Absorb
1-2 mg
iron/day

TRANSFERRIN
(transports iron)



Lose 1-2 mg
iron/day from
desquamation
of epithelia

75%



Hemoglobin/
Erythropoiesis

10-20%



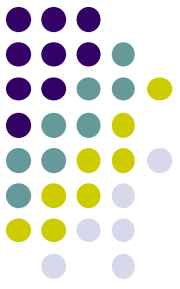
FERRITIN
(stores iron in liver & heart)

5-15%



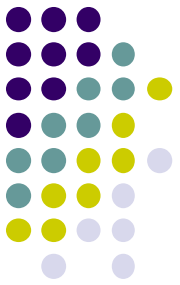
Other
Processes

No
Physiologic
Excretion
Mechanism



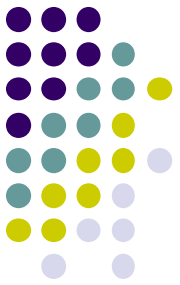
Uptake of iron by cells

- **TfR – Transferrin receptors present on most cells- liver, spleen etc.**
- **Receptor binds 2 molecules of transferrin**
- **Iron-Tf- TfR internalized**
- **Lysosomal acid pH dissociates iron from apo-Tf - TfR**



- Apo- Tf – TfR returns to plasma membrane
- Apo –Tf dissociates from its receptor, reenters the plasma, picks up more iron & delivers to needy cells.

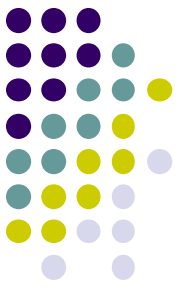
Storage of iron



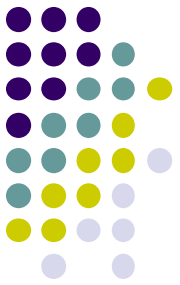
- **Ferritin** – iron Storage protein
- Found in liver, bone marrow, spleen & intestinal mucosal cells
- Apoferritin –24 subunits, can take up 4,000 iron atoms/ molecule



Iron
Mineral
Core



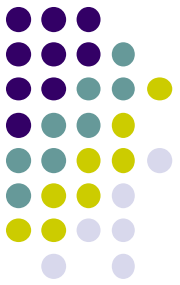
- Normally very little seen in plasma
- Estimation of ferritin – index of body iron stores
- **Increased** ---- iron overload
- **Decreased** ---- iron deficiency anemia
- Estimation is of significance in CKD to assess extent of anemia
- **Ferritin is an Acute phase protein high in inflammatory diseases.**



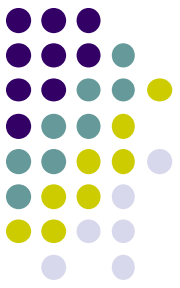
Hemosiderin

- **Derived from ferritin by partial deproteinization**
- **Hemosiderin contains a large fraction of its mass as iron than ferritin.**
- **Usually seen in iron overload.**

Excretion



- ***Iron homeostasis at absorption level only***
(about 1-2mg out of 20mg)
 - Feces contain unabsorbed & iron trapped in intestinal cells.**
 - Desquamation of skin.**
 - Any bleeding(menstruation in females)**
No iron excretion through urine



Normal Amount
of Red Blood
Cells

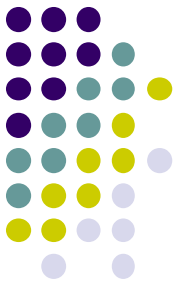


Anemic Amount
of Red Blood
Cells

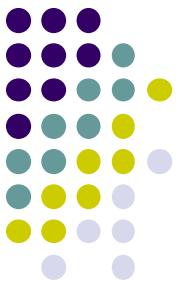


Iron Deficiency Anemia

Iron deficiency - causes

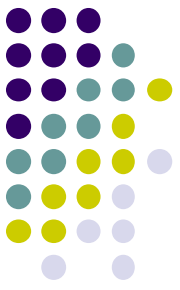


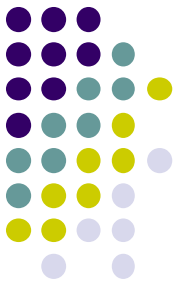
- **Nutritional**
- **Hook worm infection**
- **Repeated pregnancies**
- **Nephrosis**
- **Subtotal gastrectomy & achlorhydria**
- **Blood loss – hemorrhoids, menorrhagia**
- **Lead poisoning – 2 enzymes in heme synthesis inhibited and also interferes with absorption**



Clinical manifestations

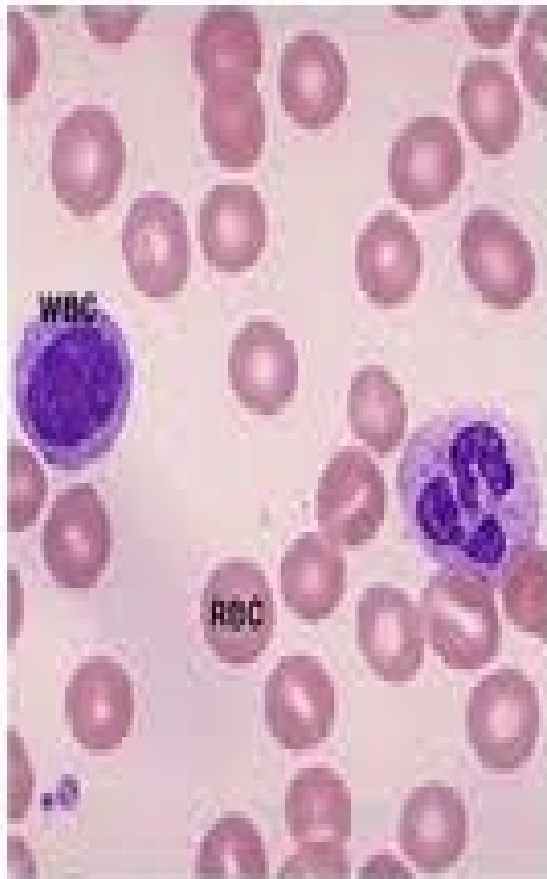
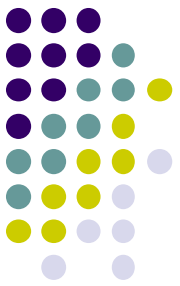
- **Anemia**
- **Apathy (lack of oxygen in cells – uninterested in surroundings)**
- **Fatigue -**
- **Derangement in cellular respiration**
- **Sluggish metabolism**
- **Atrophy of gastric epithelium –achlorhydria**
- **Atrophy of epithelium in oral cavity & esophagus causes dysphagia – Plummer – Wilson syndrome**
- **Impaired attention, irritability**
- **Poor memory & scholastic performance**



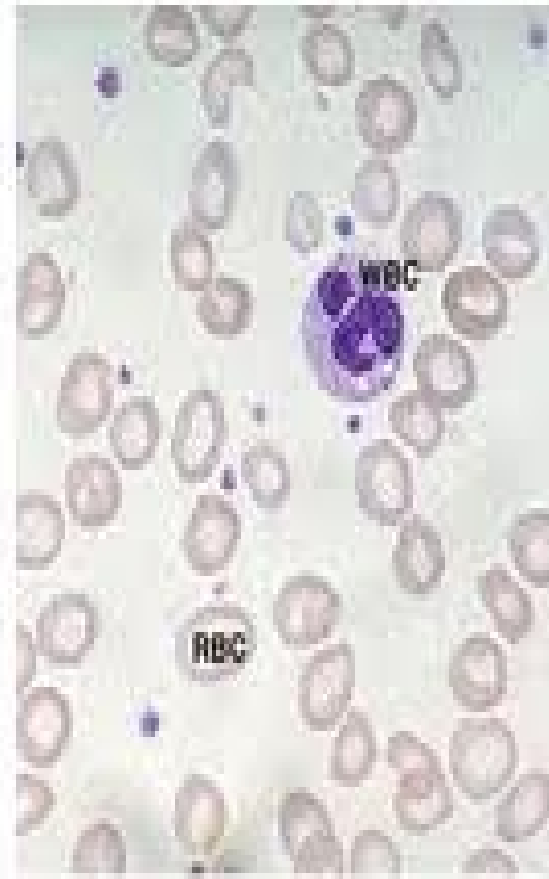


Lab findings

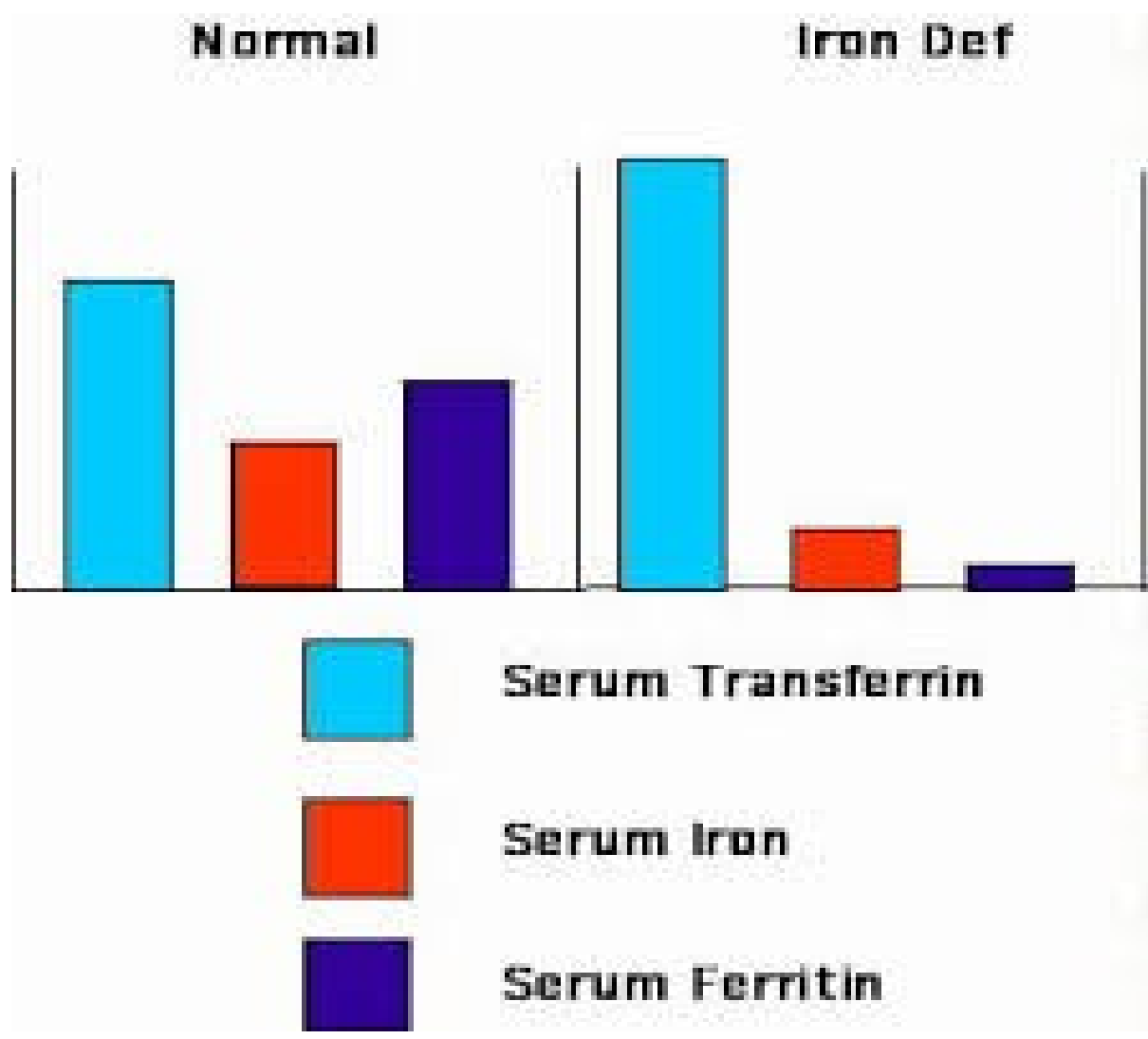
- Peripheral smear will show
Microcytic hypochromic anemia
- Serum Fe ↓
- TIBC ↑
- TfR ↑
- Serum Ferritin ↓

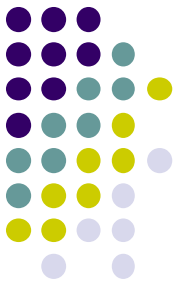


Normal Blood Smear



Iron Deficiency Anemia

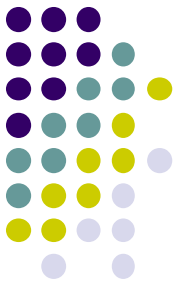




Treatment

- Oral iron supplementation
 1. Pregnant women – 100mg Fe + 500 μ g FA
 2. Children – 20mg Fe + 100 μ g FA
- Along with iron tablets
- 📖 Vit C (for easy absorption)
 - 📖 Vit E (to prevent free radical formation)
- is given

Iron Toxicity



- Hemosiderin pigments (golden brown) seen in various tissues
- Pigments give +ve reaction to prussian blue

Hemochromatosis



- Condition of iron toxicity
- Total body iron > 25-30gm
- Can be primary or secondary
- Primary hemochromatosis -
- genetic defect in HFE gene
- iron absorption & storage increased



Hemochromatosis



Secondary –

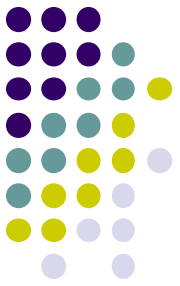


repeated blood transfusions.
Regulation at intestinal level
bypassed eg. Hemophilic
children (common cause)

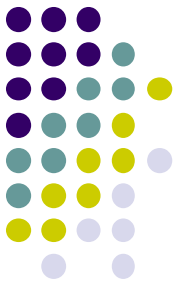


Among Bantu tribe in Africa –
cook in iron vessels

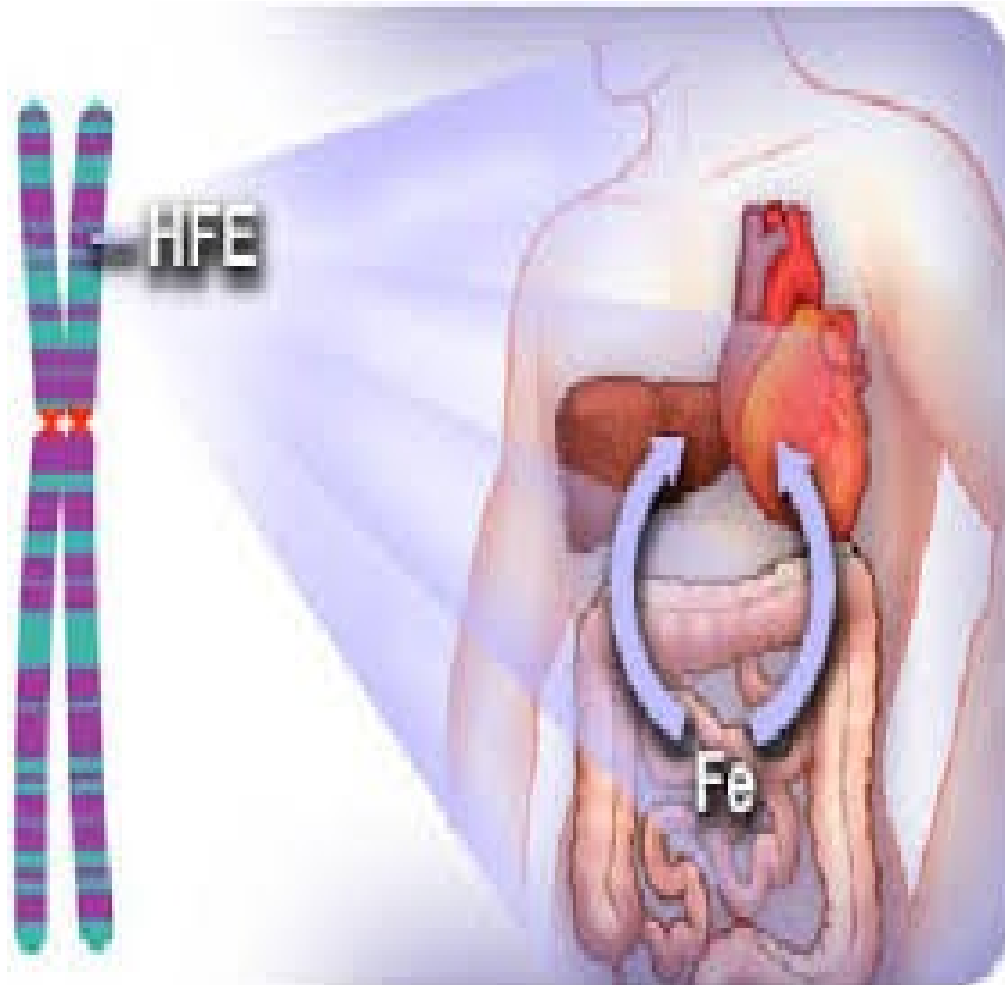
Hemochromatosis

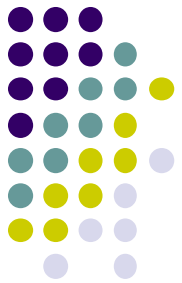


- In hemochromatosis –
Hemosiderin deposits
- 📁 in **liver** cause cell death &
cirrhosis
- 📁 **Pancreatic** cell death & **diabetes**
- 📁 Under **skin** yellow-brown
discoloration



- **Clinical triad for diagnosis**
- *Cirrhosis*
- *Diabetes mellitus*
- *Skin pigmentation*
- *Is called* **BRONZE DIABETES**





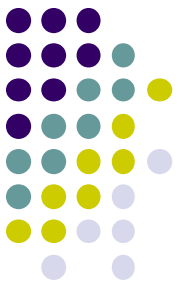
Hemochromatosis – Clinical Syndrome



Hereditary Hemochromatosis

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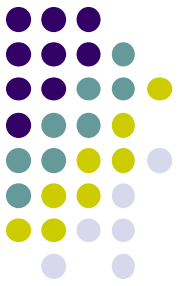




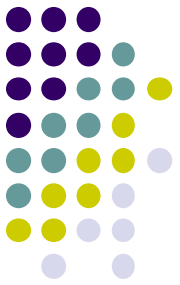
- **Treatment**

- **repeated phlebotomy till total serum iron & ferritin reach normal level**
- **chelating agents-**
Desferroxamine – chelate iron & excrete in urine

Iron conservation in the body



1. On RBC lysis, Hb released - taken up by **Haptoglobin**
 - Hb-Hp complex taken up by liver kupffer cells
 - Thus urinary loss of Hb prevented
2. When globin removed from Hb, Heme is bound by **Hemopexin**, complex taken up by hepatocytes
 - Urinary loss of Heme prevented



3. When porphyrin removed from Heme, iron released is bound by **Transferrin**

Loss of iron prevented