Iron Metabolism

DR BELA GOYAL

Minerals

Trace elements: Required in amounts in mg/day

Ultratrace elements: Required in amounts less than 1mg/day or ug/day

*(**Trace** and **ultratrace** elements in health and disease FH Nielsen - Comprehensive therapy, 1991 - naldc.nal.usda.gov)*

Calcium (mg/d)	Chromium (µg/d)	Copper (µg/d)	Fluoride (mg/d)	Iodine (µg/d)	Iron (mg/d)	Magnesium (mg/d)	Manganese (mg/d)	Molybdenum (µg/d)	Phosphorus (mg/d)	Selenium (µg/d)	Zinc (mg/d)	Potassium (g/d)	Sodium (g/d)	Chloride (g/d)

Learning objectives(Iron)

Distribution and requirements of Iron

Metabolism of Iron

Molecular mechanisms of Regulation

Laboratory evaluation of Iron deficiency anemia

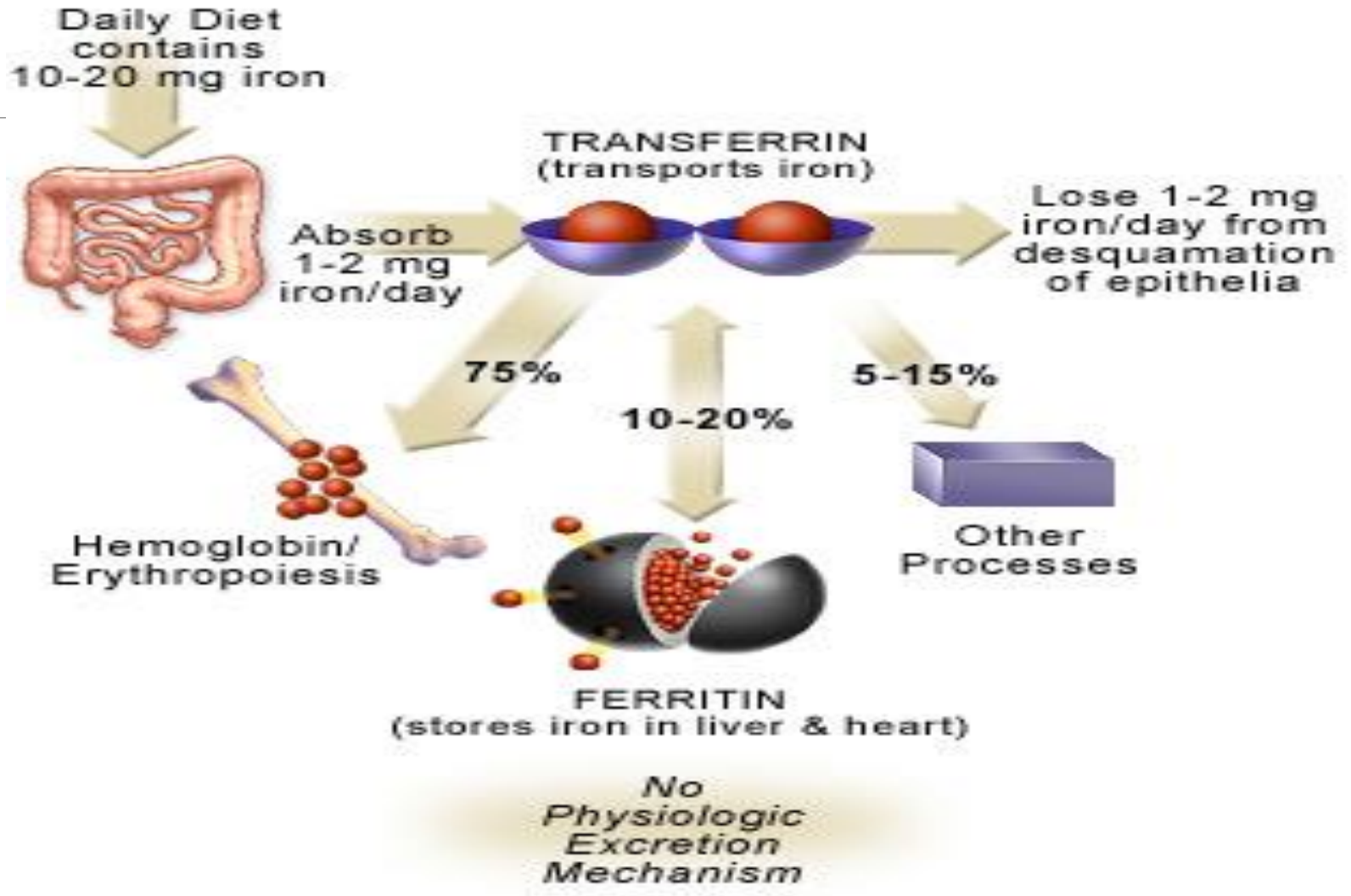
Iron overload disorders

Body Iron Distribution

TABLE 126-1 BODY IRON DISTRIBUTION

	Iron Content, mg	
	Adult Male, 80 kg	**Adult Female, 60 kg**
Hemoglobin	2500	1700
Myoglobin/enzymes	500	300
Transferrin iron	3	3
Iron stores	600–1000	0–300

Iron cycle


Daily Diet
contains
10-20 mg iron
TRANSFERRIN
(transports iron)
Absorb
1-2 mg
iron/day
Lose 1-2 mg
iron/day from
desquamation
of epithelia
75%
10-20%
5-15%
Hemoglobin/
Erythropoiesis
Other
Processes
FERRITIN
(stores iron in liver & heart)
No
Physiologic
Excretion
Mechanism

Body I

Utilizat

Muscl
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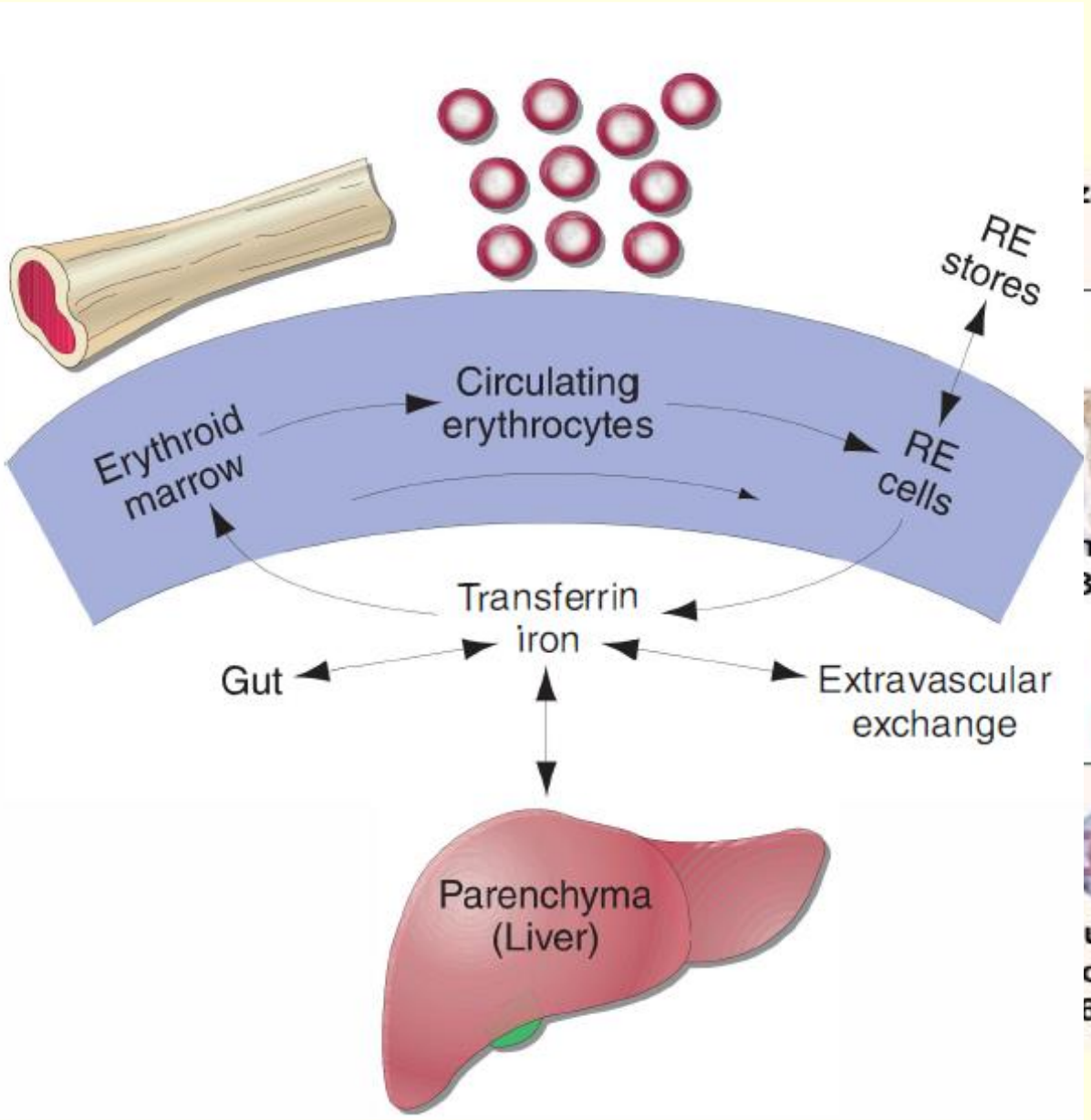
(300 mg

Liver
(1,000 r



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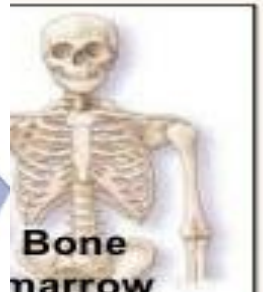


Bone
narrow
300 mg)

uloendothelial
crophages
600 mg)

Daily requirement(RDA)

Male: 8-10mg

Female: 10-15mg

Preg. & lactation: 20-40mg

Children: 10-15mg

liver, meat, fish, spleen, leafy veg., legumes, pulses,cereals, <u>JAGGERY, DATES</u>
Cooking in iron utensils

Types of iron

Heme Proteins: Hb, myoglobin, Cytochromes (cytb,c,c1,p450), cyt oxidase, catalase, peroxidase, tryptophan pyrrolase, nitric oxide synthase

Iron-sulphur complexes : ETC, NADH dehydrogenase, succinate dehydrogenase, xanthine oxidase

Non-heme iron containing proteins :Aconitase, Transferrin , Ferritin, Hemosiderin

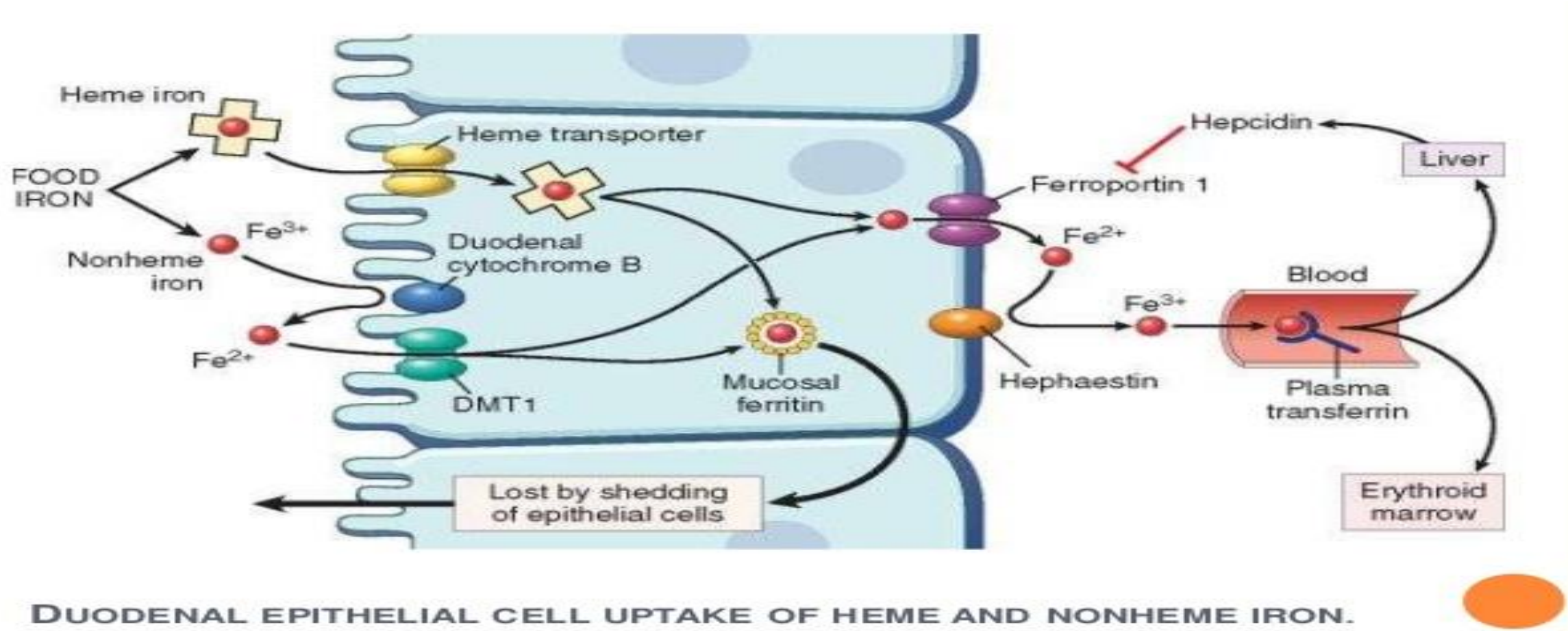
Absorption

10% of dietary iron is absorbed

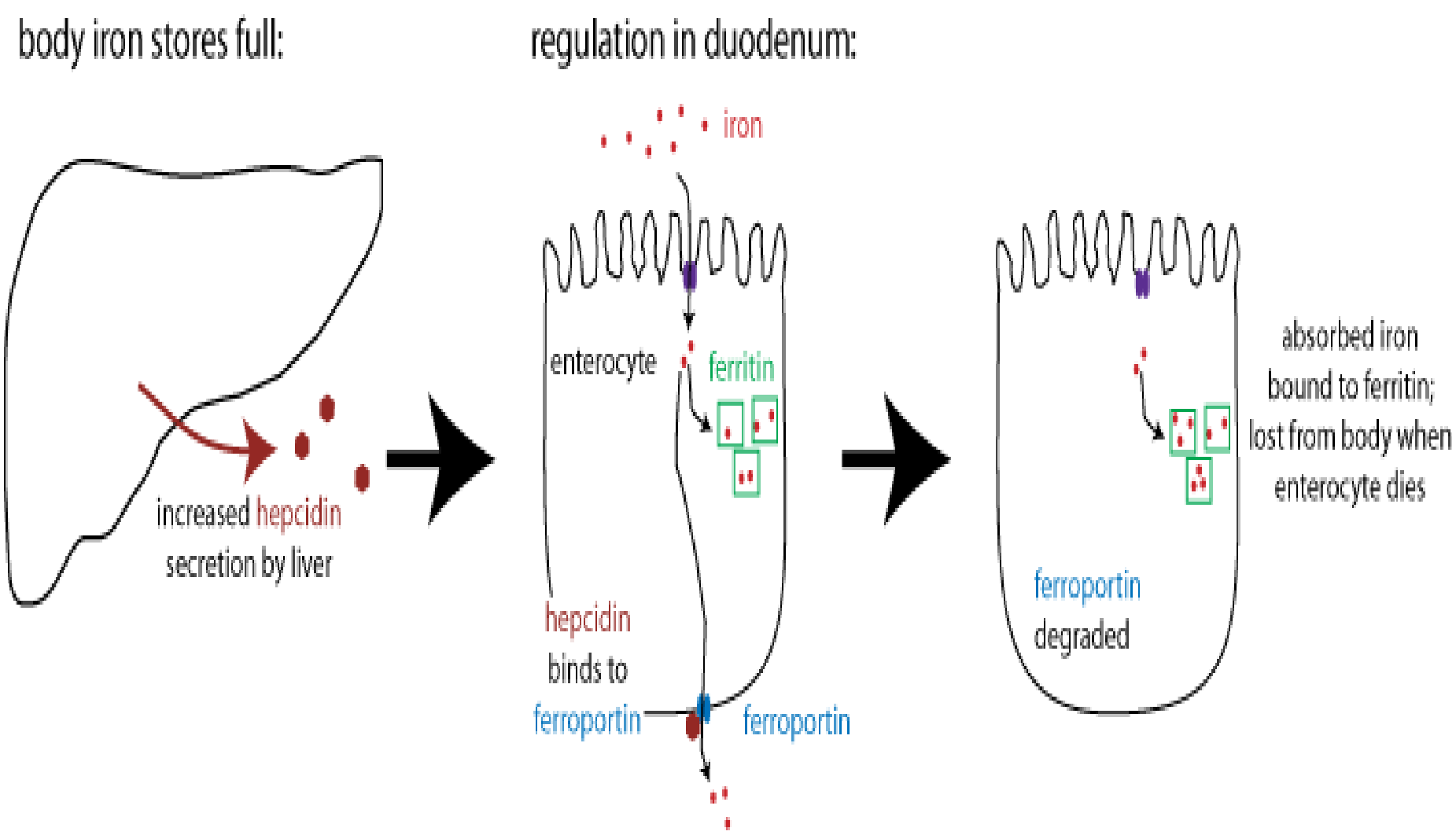
In duodenum & jejunum

Gastric juice HCl liberates free ferric ions from proteins

Iron absorption



DUODENAL EPITHELIAL CELL UPTAKE OF HEME AND NONHEME IRON.


body iron stores full:
regulation in duodenum:
increased hepcidin
secretion by liver
iron
enterocyte
ferritin
hepcidin
binds to
ferroportin
ferroportin
ferroportin
degraded
absorbed iron
bound to ferritin;
lost from body when
enterocyte dies

Factors affecting absorption

Heme iron more efficiently absorbed.

Ferrous form is absorbed

Increased by: Vit.C , cysteine , glutathione , acidic pH & iron deficient state

Decreased by: alkaline medium , tea , coffee, phytates , oxalates, Ca, gastrectomy

Transport

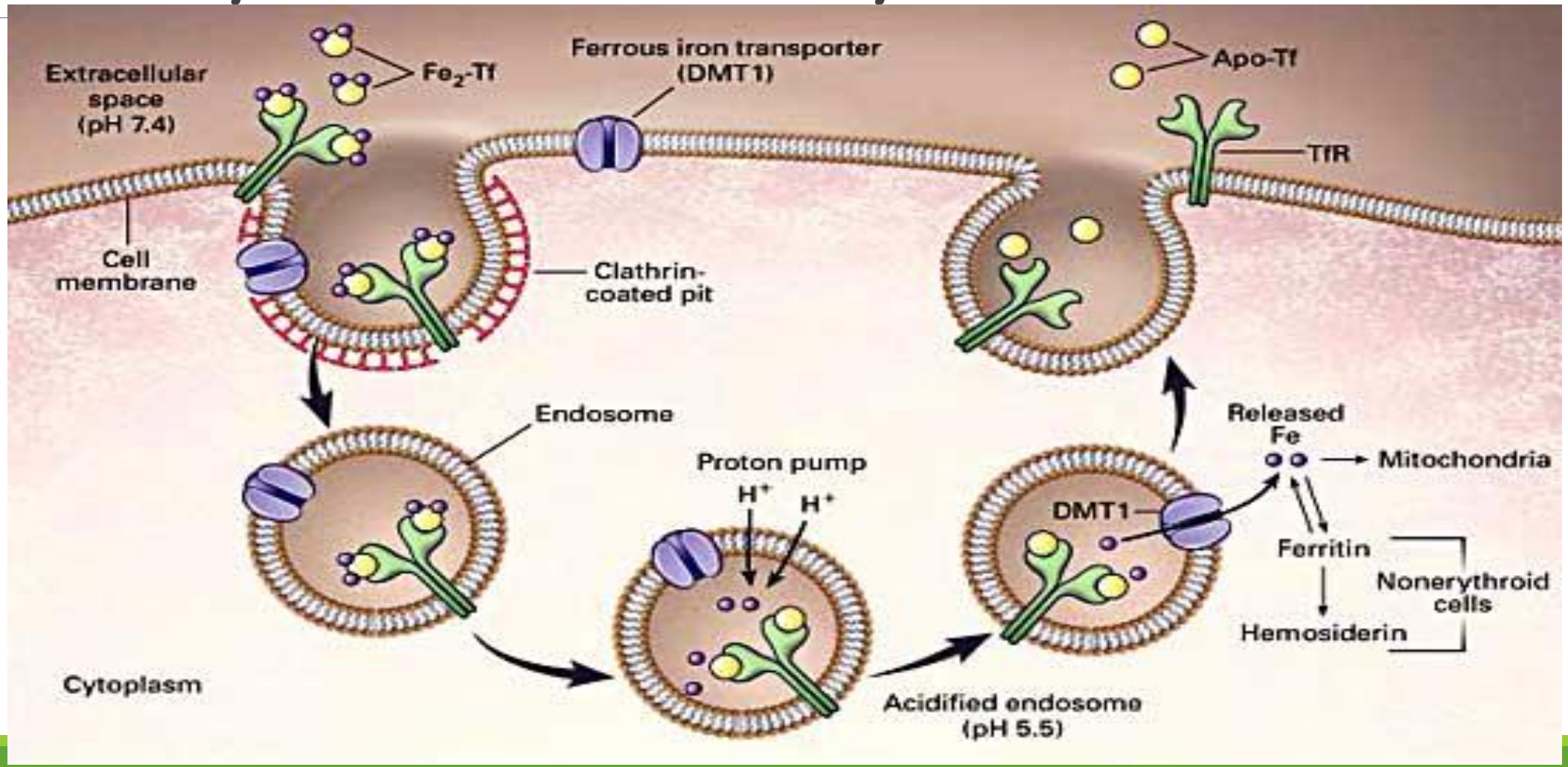
Transferrin: non–heme iron binding glycoprotein

synthesized by liver cells

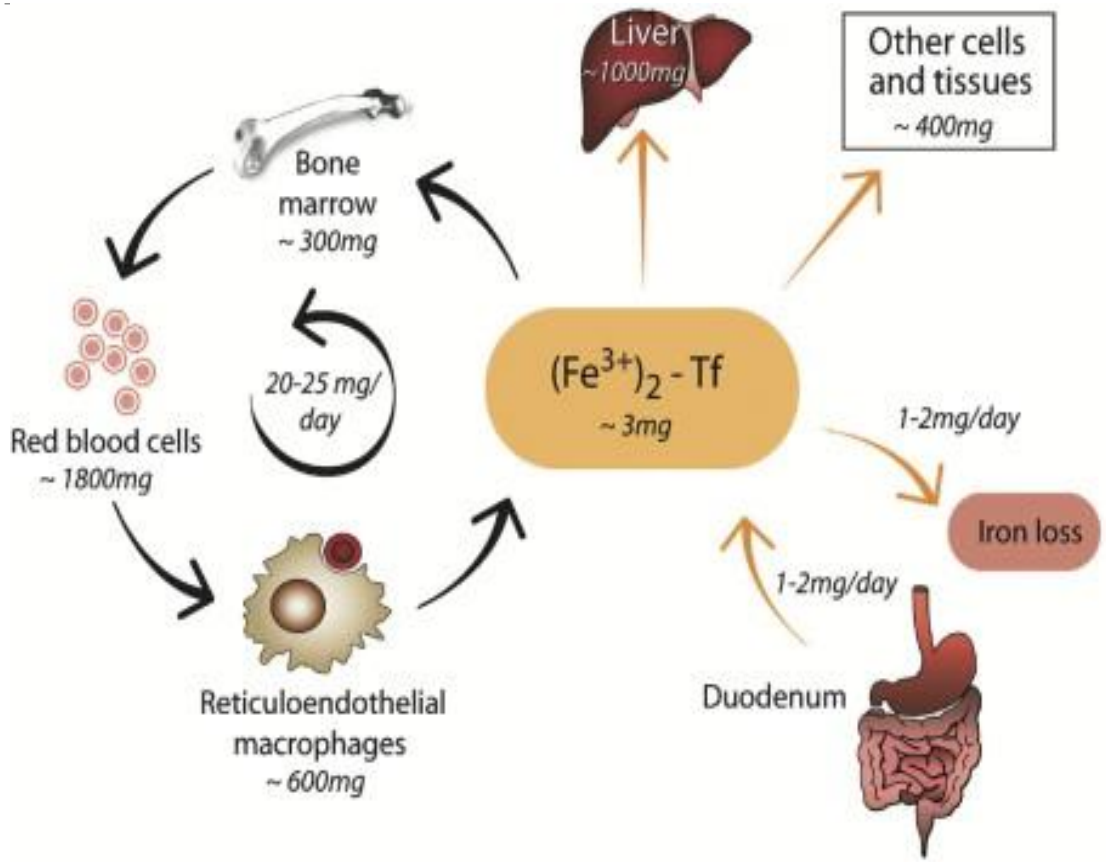
apotransferrin is apoprotein binds two atoms of iron

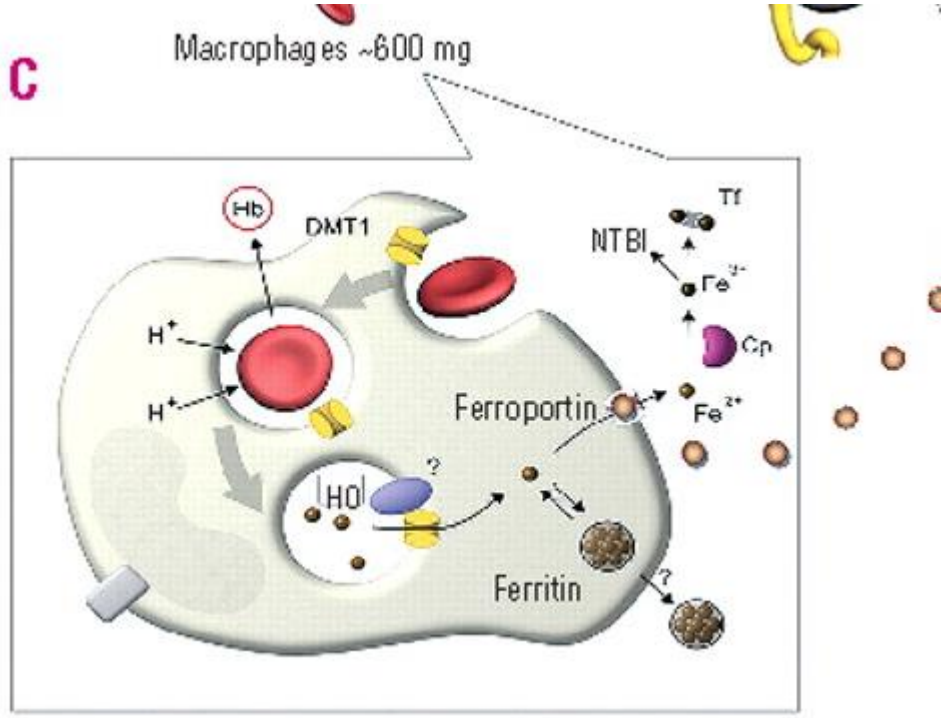
Iron transported to RE cells, bone marrow (immature RBCs)

Delivery of Iron to cells by transferrin



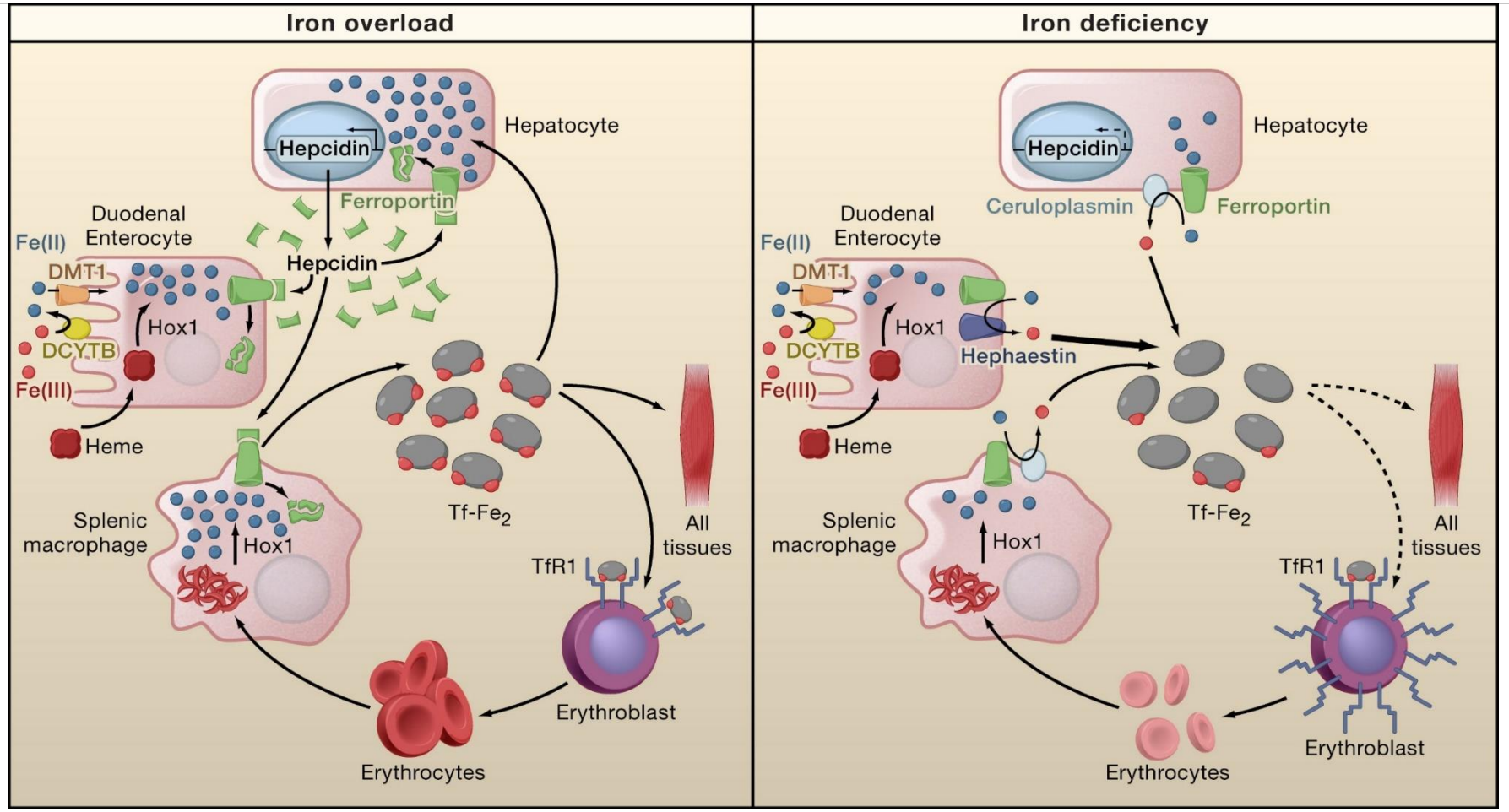
Iron Recycling





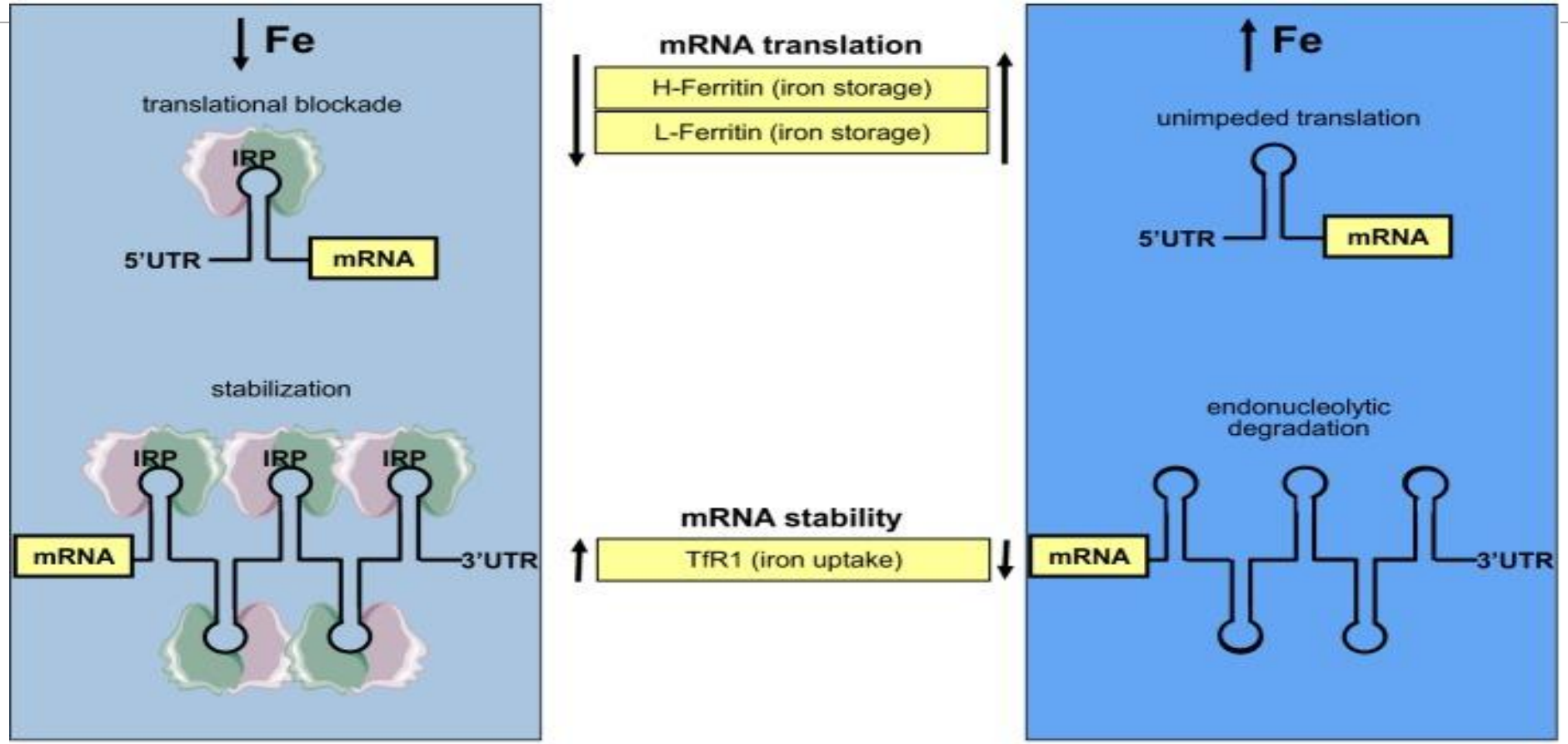
Cell. 2004 Apr 30;117(3):285-97.
Balancing acts: molecular control of mammalian iron metabolism.

Regulation of systemic Iron homeostasis



Cell. 2010 Jul 9;142(1):24-38. doi: 10.1016/j.cell.2010.06.028.

Regulation of Cellular Iron Metabolism



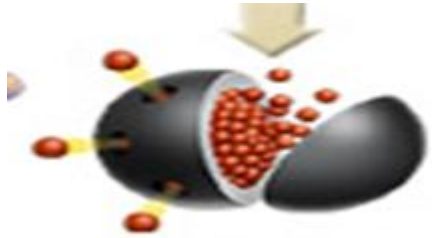
Cell. 2010 Jul 9;142(1):24-38. doi: 10.1016/j.cell.2010.06.028.

Hepcidin based Therapy

Hepcidin agonist?

Antibodies/siRNA for hepcidin?

Ferritin

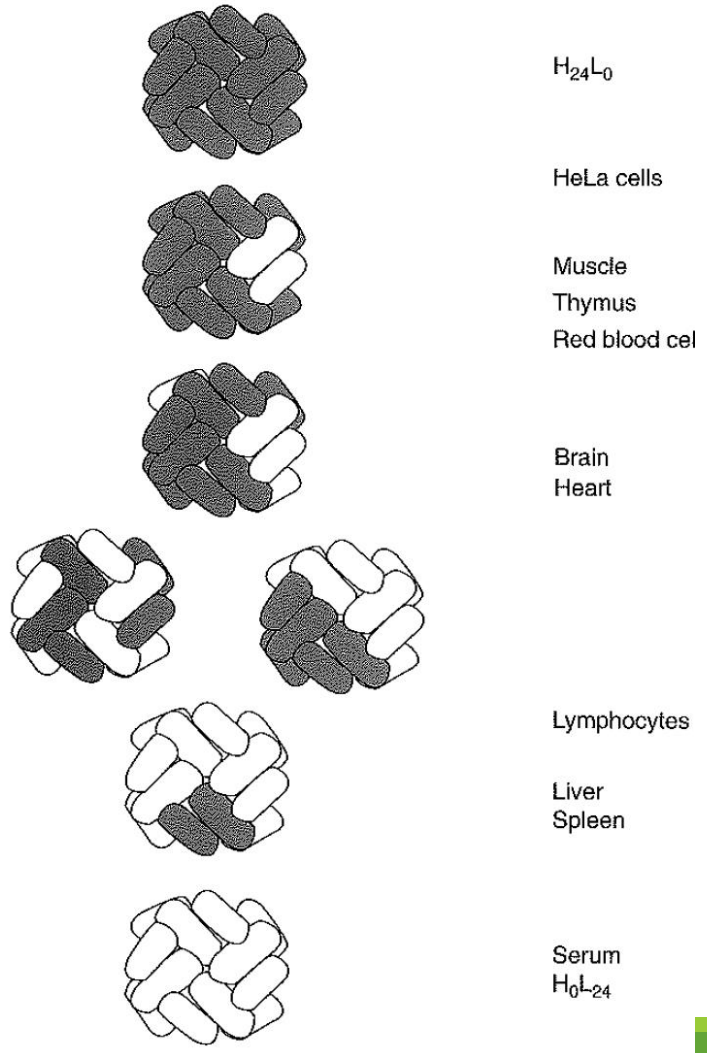


Iron is stored in liver, spleen, bone marrow & intestinal mucosal cells

Apoferritin – apoprotein(500 Kda), 24 subunits

4000 iron atoms stored in a ferritin molecule

Ferritin an index of total body iron stores



Hemosiderin

Derived from ferritin

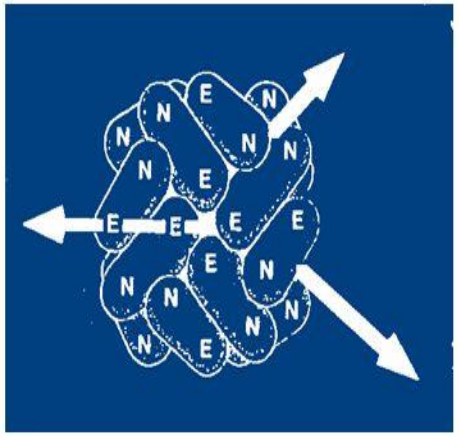
(sec. lysosomes)

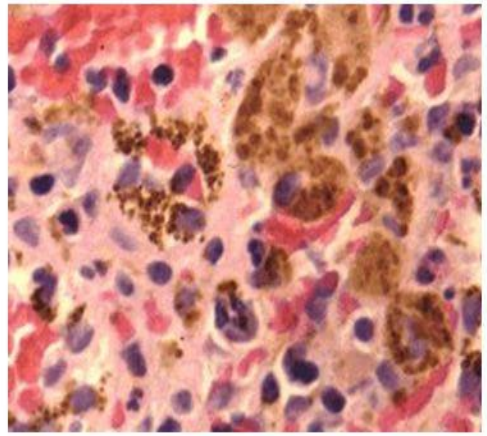
Seen in iron overload

Mobilisation of iron slower

Iron Storage

- Ferritin
  - multi-subunit protein
  - primarily intracellular
  - some in plasma
- Hemosiderin
  - insoluble form of ferritin
  - visible microscopically





Excretion

excreted (1-2mg/d)

Haptoglobin binds Hb to prevent its loss in urine

Hemopexin binds heme

Faeces contain unabsorbed iron & iron inside the **desquamated intestinal cells**

In **females**, more excreted during mensturation

Laboratory evaluation of Iron Metabolism

Packed cell volume

Hemoglobin

Red cell count and indices

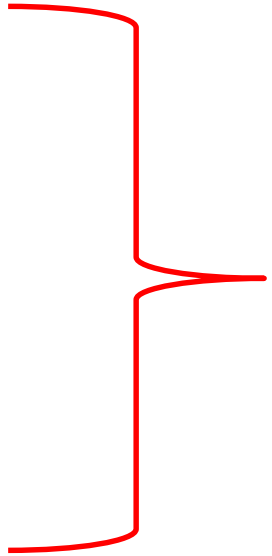
Total iron

TIBC

Percent saturation

Transferrin

Ferritin



Total Iron Content (Serum Iron)

Fe^3 bound to transferrin (50-170µg/dL)

Specimen of choice: serum or plasma with heparin. (Oxalate, citrate, or EDTA binds Fe ions)

Steps:

Fe^3 is released from binding proteins by acidification,

reduced to Fe^2 by ascorbate

complexed with a color reagent such as ferrozine, ferene, or bathophenanthroline.

Spectrophotometric determination

Total Iron Content (Serum Iron)

Decreased

Hemorrhage

Iron Deficiency anemia

Increased

Iron loading disorders

Iron poisoning

Total Iron-Binding Capacity (TIBC)

The amount of iron that could be bound by saturating transferrin and other minor iron-binding proteins present in the serum or plasma sample.

one-third of the iron binding sites on transferrin are saturated

Total Iron-Binding Capacity

Determined by

Adding **sufficient Fe3** to saturate the binding sites on transferrin,

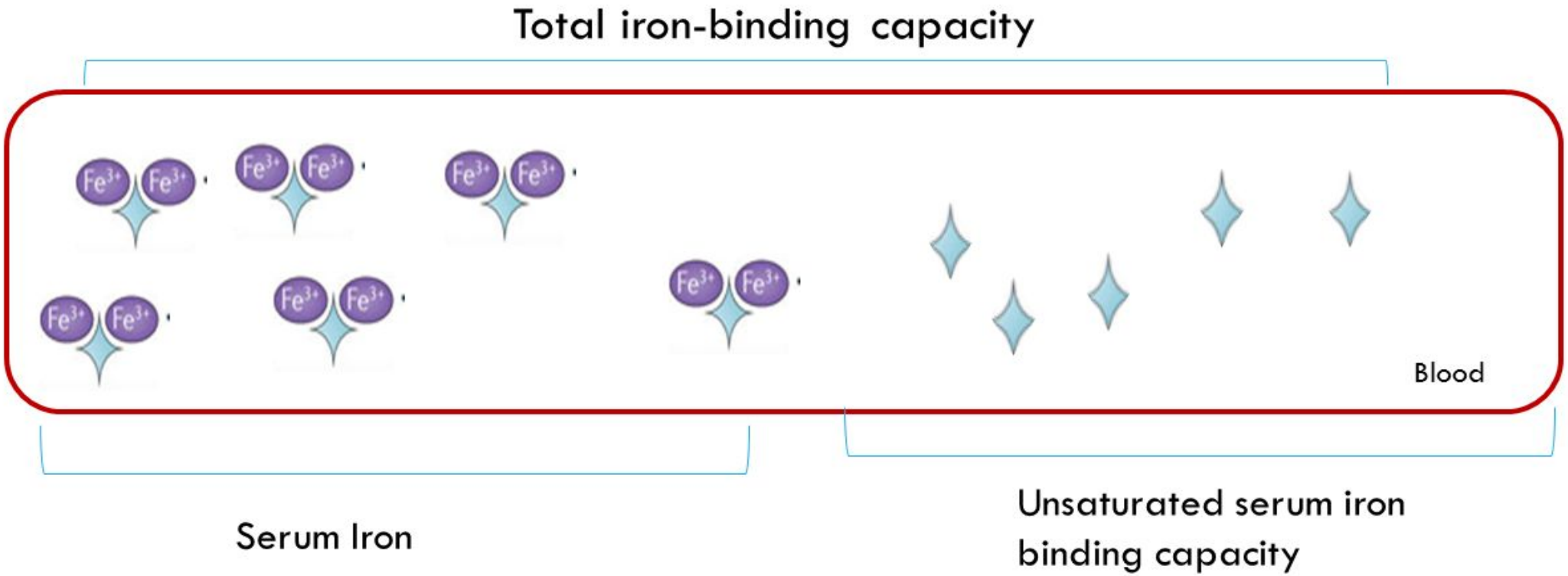
Excess iron removed by addition of **MgCO3** to precipitate any Fe3 remaining in solution.

After **centrifugation** to remove the precipitated Fe3,

The **supernatant** solution containing the soluble iron bound to proteins is analyzed for total iron content.

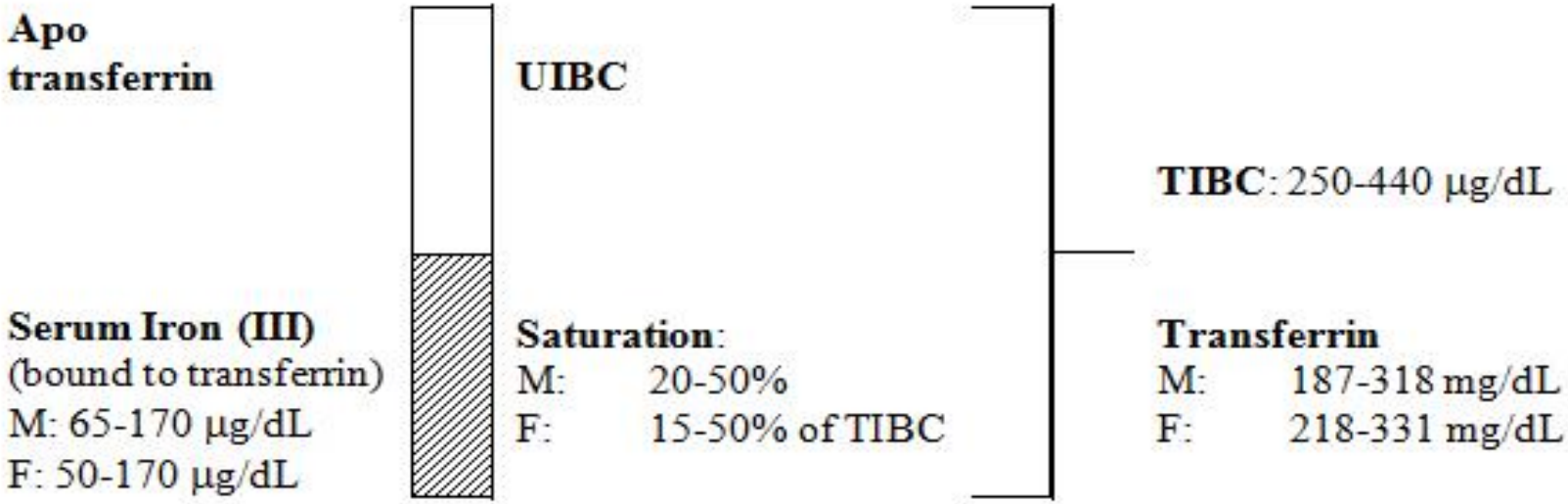
This is the TIBC, which ranges from around **250 to 425 µg/dL.**

SERUM IRON, TIBC, UIBC



Percent Saturation

$$\text{Transferrin saturation (\%)} = \frac{100 \times \text{serum iron}}{\text{TIBC}}$$



UIBC = Unsaturated Iron Binding Capacity
TIBC = Total Iron Binding Capacity

Transferrin

measured by immunochemical methods

Increased

Iron deficiency

Decreased

iron overload

Chronic infections and malignancies

primarily monitored as an indicator of nutritional status.

Ferritin

Measured by immunochemical methods like ELISA and chemiluminescent techniques.

Reflects Iron store

Earliest marker to decline

Ferritin

Decreased

iron-deficiency anemia(most sensitive and earliest)

Increased

Iron overload (used to gauge effectiveness of phlebotomy therapy).

Chronic infections, malignancy

Viral hepatitis release of ferritin from diseased liver cells

Clinical Significance

Iron Deficiency anemia

Iron overload disorders

Iron deficiency anemia

Globally 50% anemia

Approx 841,000 deaths

TABLE 126-2 CAUSES OF IRON DEFICIENCY
Increased Demand for Iron
Rapid growth in infancy or adolescence
Pregnancy
Erythropoietin therapy
Increased Iron Loss
Chronic blood loss
Menses
Acute blood loss
Blood donation
Phlebotomy as treatment for polycythemia vera
Decreased Iron Intake or Absorption
Inadequate diet
Malabsorption from disease (sprue, Crohn's disease)
Malabsorption from surgery (gastrectomy and some forms of bariatric surgery)
Acute or chronic inflammation

Clinical presentation of IDA

Muscle abnormalities

Koilonychia

Pica

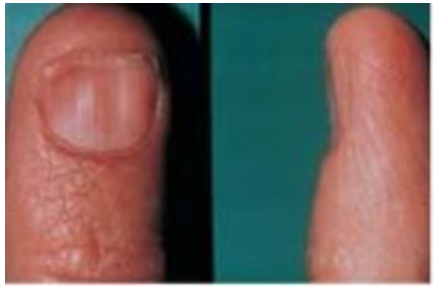
Anemia

Reduced work performance

Impaired cognitive development

Premature labour

Increased Perinatal deaths



Diagnosis

Microscopic examination of a blood smear : microcytic hypochromic RBCs

Bone marrow aspiration: no storage iron

serum ferritin: virtually zero

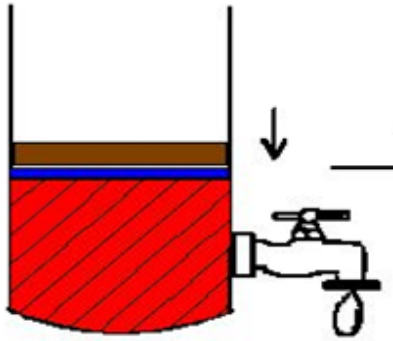
serum TIBC: elevated

serum iron saturation: less than 16%.

Treatment:

- Careful examination for the **cause** and supplementation with iron (**oral** ferrous sulfate tablets)
- **intravenous** iron therapy
- **transfusion** with packed red blood cells

Stages of iron deficiency

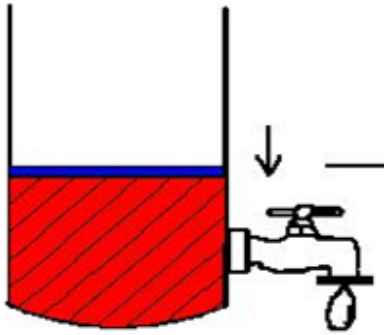


Depletion of storage iron in liver, bone marrow, muscle

prelatent iron deficiency

serum ferritin ↓

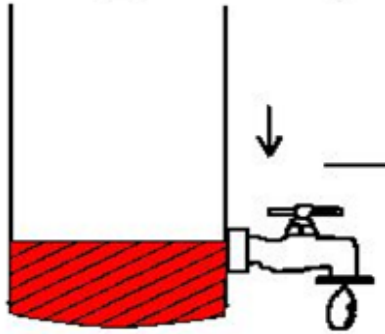
partially depl. : <30ug/l
fully depleted: < 12 ug/l



depletion of the transport iron pool in blood plasma

latent iron deficiency

serum iron ↓
TIBC = transferrin ↑



loss of haemoglobin iron

manifest iron deficiency

hemoglobin ↓

	SERUM IRON	SERUM FERRITIN	TRANSFERRIN AND TIBC	PERCENT TRANSFERRIN SATURATION
IRON DEFICIENCY ANEMIA	Decreased	**Decreased**	**Increased** (Liver produces more transferrin, to maximize use of the little iron that is available)	Decreased (insufficient iron)
ANEMIA OF CHRONIC DISEASE	Decreased	**Increased**	**Decreased** (The body produces less transferrin but more ferritin, to keep iron away from pathogens that require it for their metabolism. This is mainly regulated by increased hepcidin)	Normal

Iron overload

Hemosiderosis

Hemochromatosis

Hemosiderosis

Causes: Repeated blood transfusions (Thalassemia, Hemophilia)

Hemosiderin pigments- golden brown granules in liver, spleen

No associated tissue injury

Hereditary Hemochromatosis(HHC)

Primary (Bronze Diabetes)

autosomal recessive

abnormal gene on chromosome 6

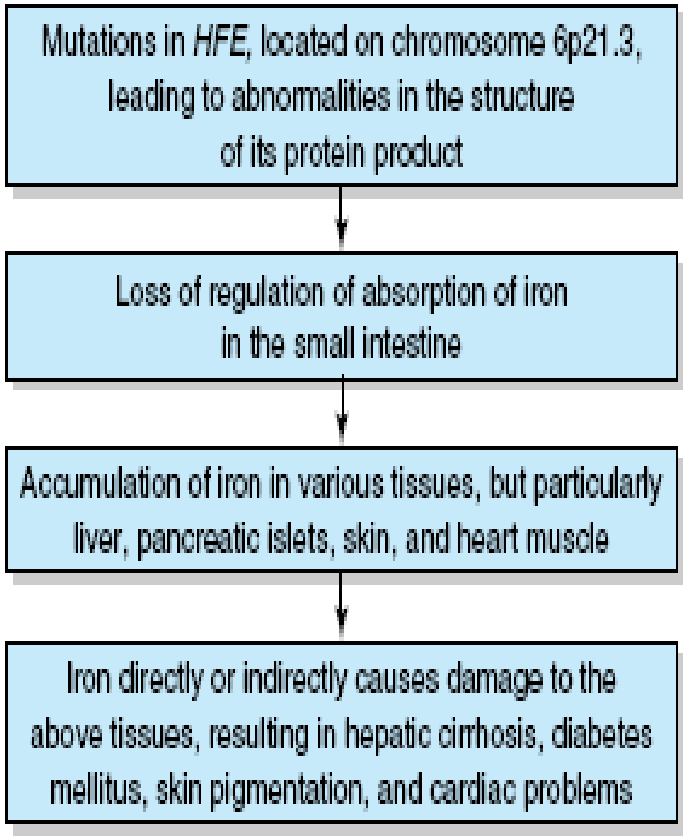
↑ iron absorption

Triad of Bronzing of skin, cirrhosis and diabetes

The liver is the first organ to be affected (hepatomegaly)

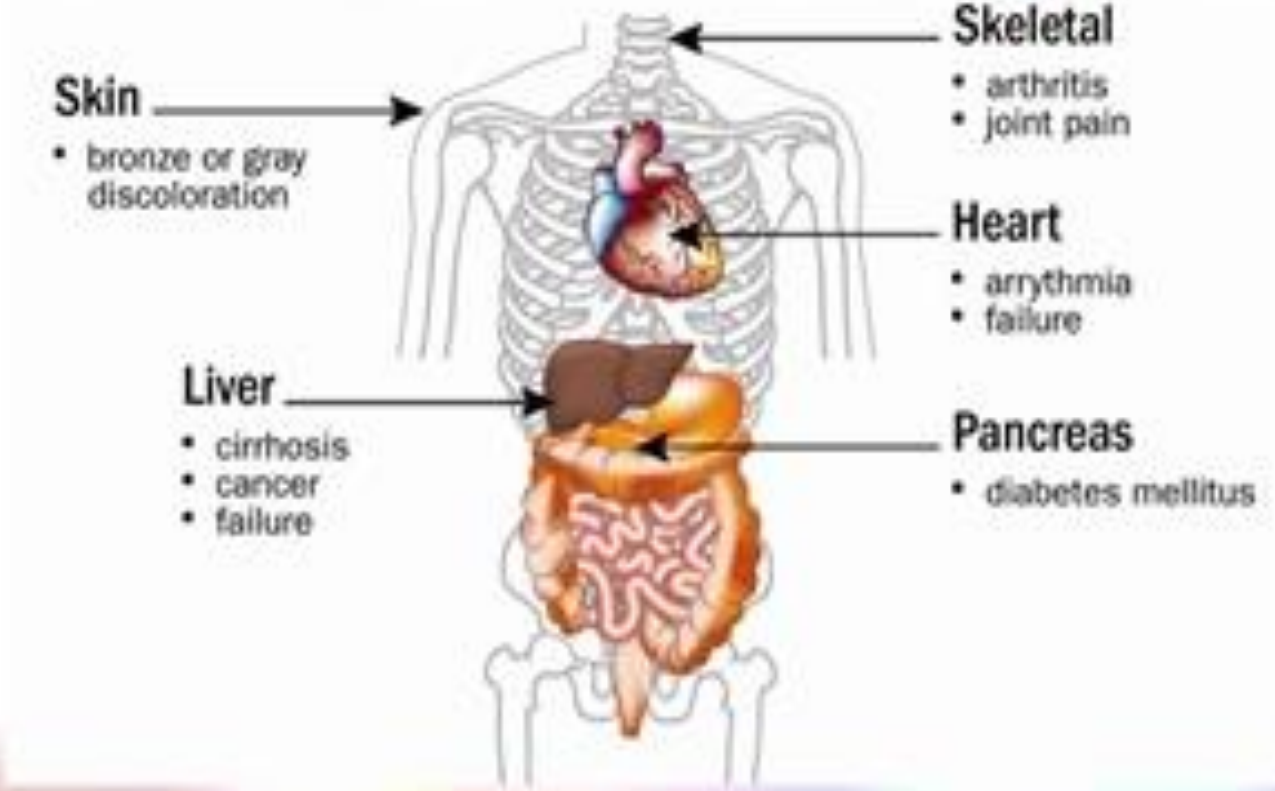
Primary hepatocellular carcinoma is 200 times more

Common



MAYO CLINIC
Mayo Medical Laboratories

Hemochromatosis – Clinical Syndrome



Skin
- bronze or gray discoloration

Skeletal
- arthritis
- joint pain

Heart
- arrythmia
- failure

Liver
- cirrhosis
- cancer
- failure

Pancreas
- diabetes mellitus

Hereditary Hemochromatosis

Hemochromatosis

Juvenile : ? Mutation in hepcidin

Variant: Mutation in ferroportin

Secondary : BT in Thal major, myelodysplastic syndromes

Diagnosis: Transferrin saturation and Ferritin

Treatment:

Phlebotomy

Iron chelating therapies


Thank
you