IRON

Functions : O_2 and $\bar{e}$ carrier

Chemistry : Fe^{2+}, Fe^{3+}.

Compartments

Body Content 3.5 to 5 gr

Compartment	Iron content mg	% total body iron
Hb	2500	68
Storage iron (tissue) [Ferritin, Hemosiderin]	1000	27
Myoglobin	150	4
Other tissue iron [e.g. Enzymes]	20	0.6
Transport iron (Transferrin)	4	0.1

Nonheme-Proteins

- Transferrin
- Ferritin
- Hemosiderin
- Ferredoxins

Heme-Proteins : Hb, Mb,
Enzymes (Catalase, peroxidases, trp pyrrolase, PG synthase, Guanylate cyclase, NO synthase, Cytochromes

TRANSFERRIN –

Transports iron in serum

- β1 glycoprotein synthesis is in liver
- single polypeptide (78 KDa)
- two non-cooperative iron binding sites

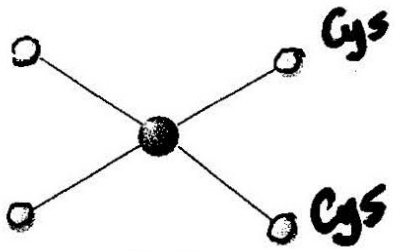
- Several metals can bind – but highest affinity for Fe^{3+} – ; Fe^{2+} is NOT BOUND
  Binding is dependent on coordinate binding of an anion
- $$\text{Transferrin} + Fe^{3+} + CO_3^{2-} \longrightarrow \text{Transferrin} . Fe^{3+} . CO_3^{2-}$$
  $$Fe^{3+} + CO_3^{2-} + \text{transferrin} . Fe^{3+} . CO_3^{2-} \longrightarrow \text{Transferrin} . 2[Fe^{3+} . CO_3^{2-}]$$
- Association constant 10^{19} to 10^{21} M^{-1} from different species
- 1/9 sites are saturated
  4/9 sites at one site
  4/9 sites are free
  20 – 50% are extent of saturation
- Unsaturated transferrin protects against infection
- Transferrin Receptor
  Transmembrane protein, heterodimer of subunits of 90 KDa – joined by disulfid bond, each subunit contain 670 ~~aa~~ residues as extra cellular segment bind transferrin of diferric form (iron + apotransferrin)
- Internalization of receptor – transferrin complex is dependent on receptor phosphorylation by Ca^{2+} – calmodulin – protein kinase C.

- Lactoferrin binds Iron in Milk
  - Resemble transferrin
  - Intestinal receptor
  - Antimicrobial effect

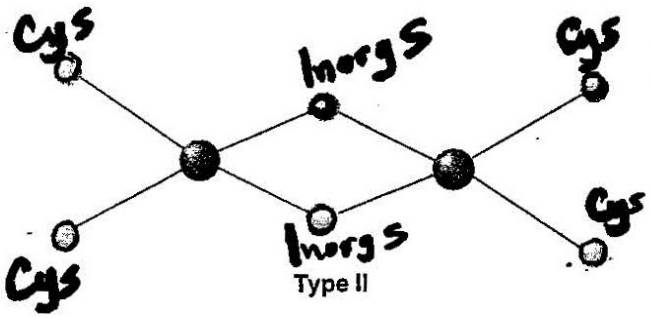
- Ferritin:
  - M. W. 460,000 of 24 subunits
    - H-subunit 21,000
    - L-subunit 19,000
  - 130 Å shell enclosing 4300 atom per molecule (ferric oxide hydroxyphosphate)
  - H-chain: ferroxidase activity.
  - plasma level of ferritin ($t_{\frac{1}{2}}$ = 50 hr)
  - Isoforms
  - Hemosiderin

- Ferredoxins :- Iron-sulfur proteins
  - Fe- Cysteine
  - Fe - Cysteine and disulfide anions

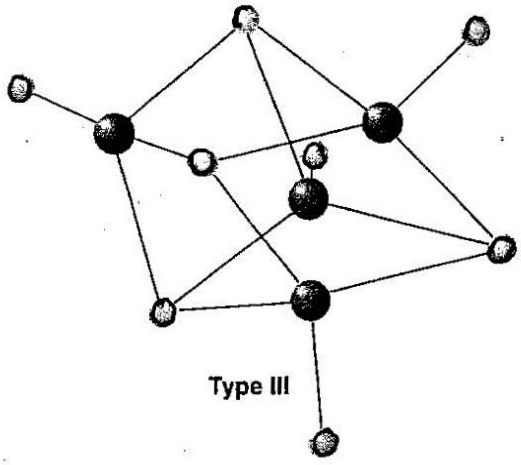
Ferrodoxins



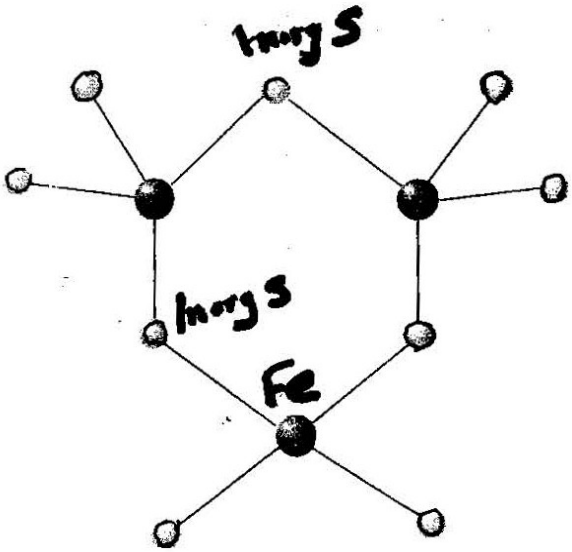
Type I



Type II



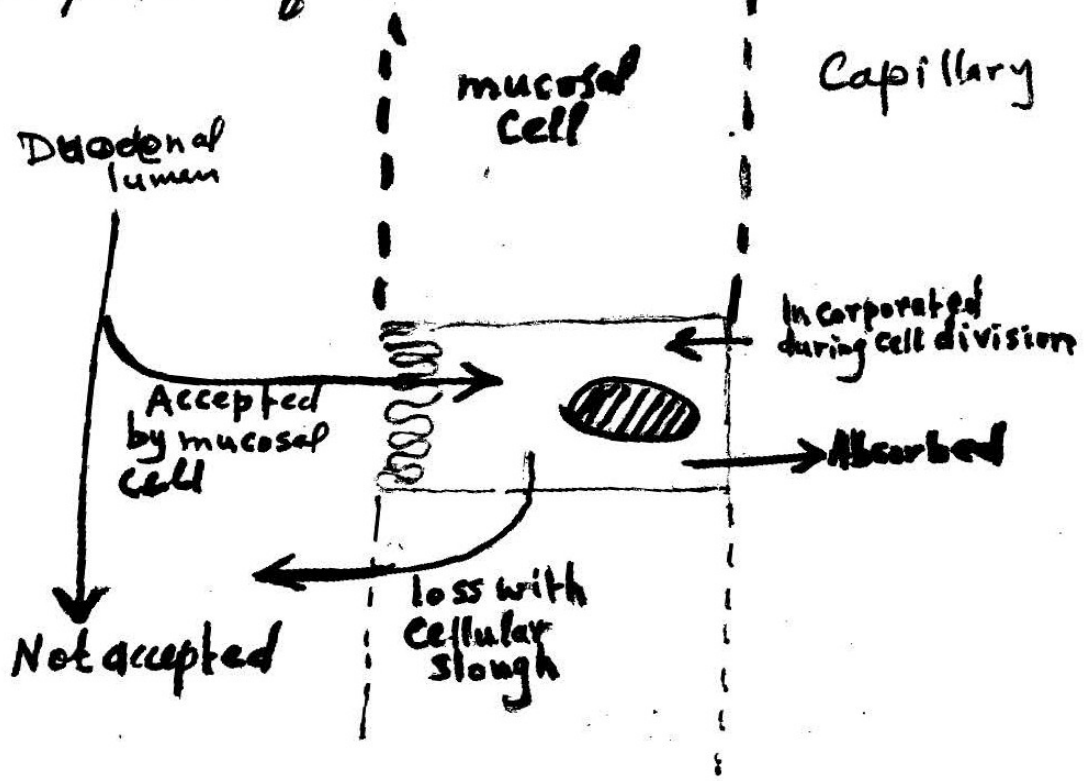
Type III



Type IV

Intestinal Absorption of Iron

- Deudonum is the major site of absorption
- Fe^{2+} is only absorbed by mucosal cells.
- Majority of dietary iron is Fe^{3+} in complex with org. compounds.
- Spinach is a poor source of available iron
  Fe – phytate (inositol hexa phosphate)
  absorption is also reduced by tannin., oxalate, large quantit of inorg. phosphate + antiacids.
- Cooking of food + low pH of stomach + Ascorbic acid ⟶ dissociation + reduction of Fe.
- Heme can be absorbed
- Absorption is regulated at the level of mucosal-capillary interface.
- Large portion of iron is not absorbed.



Absorption, Storage and Utilization of Food Iron

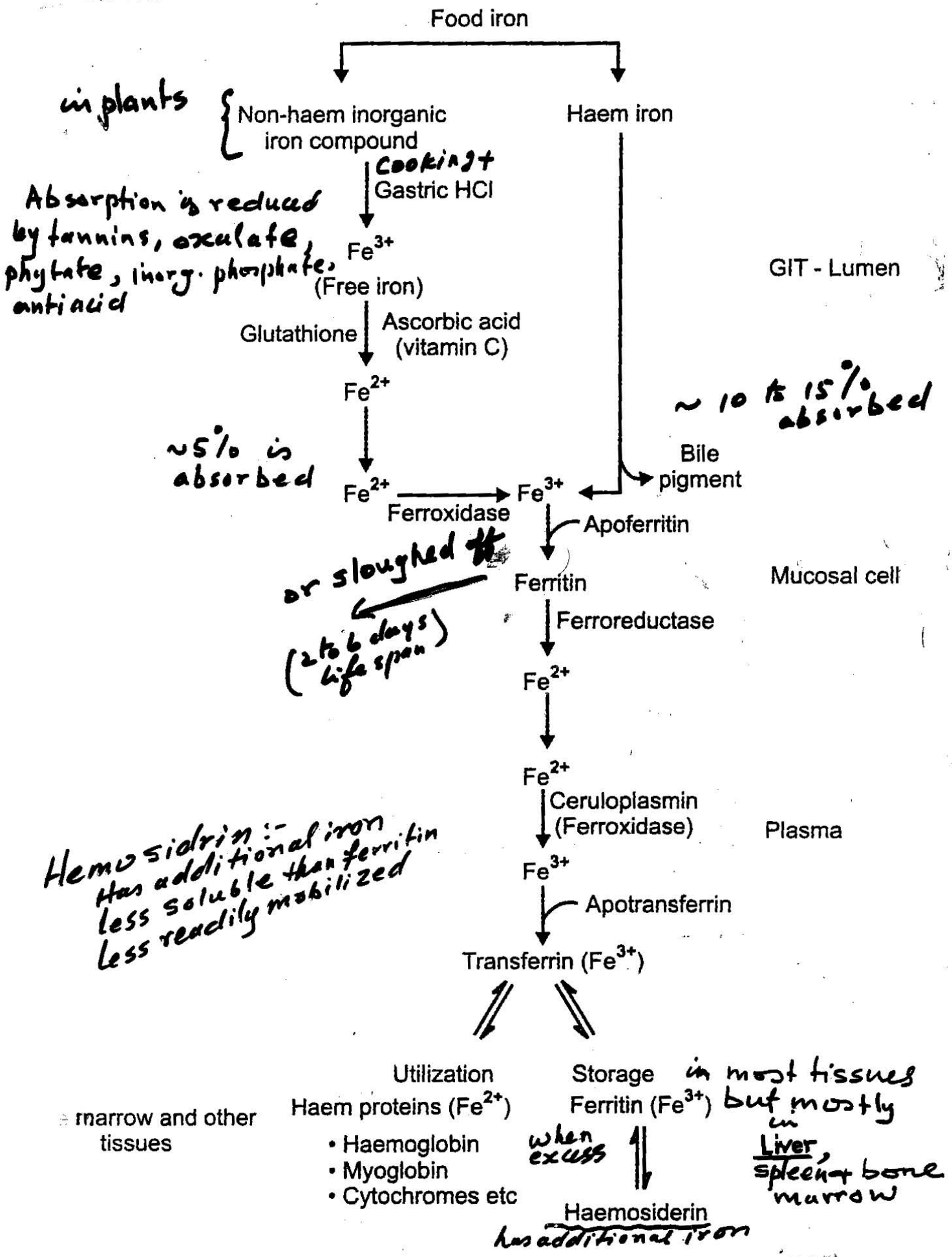
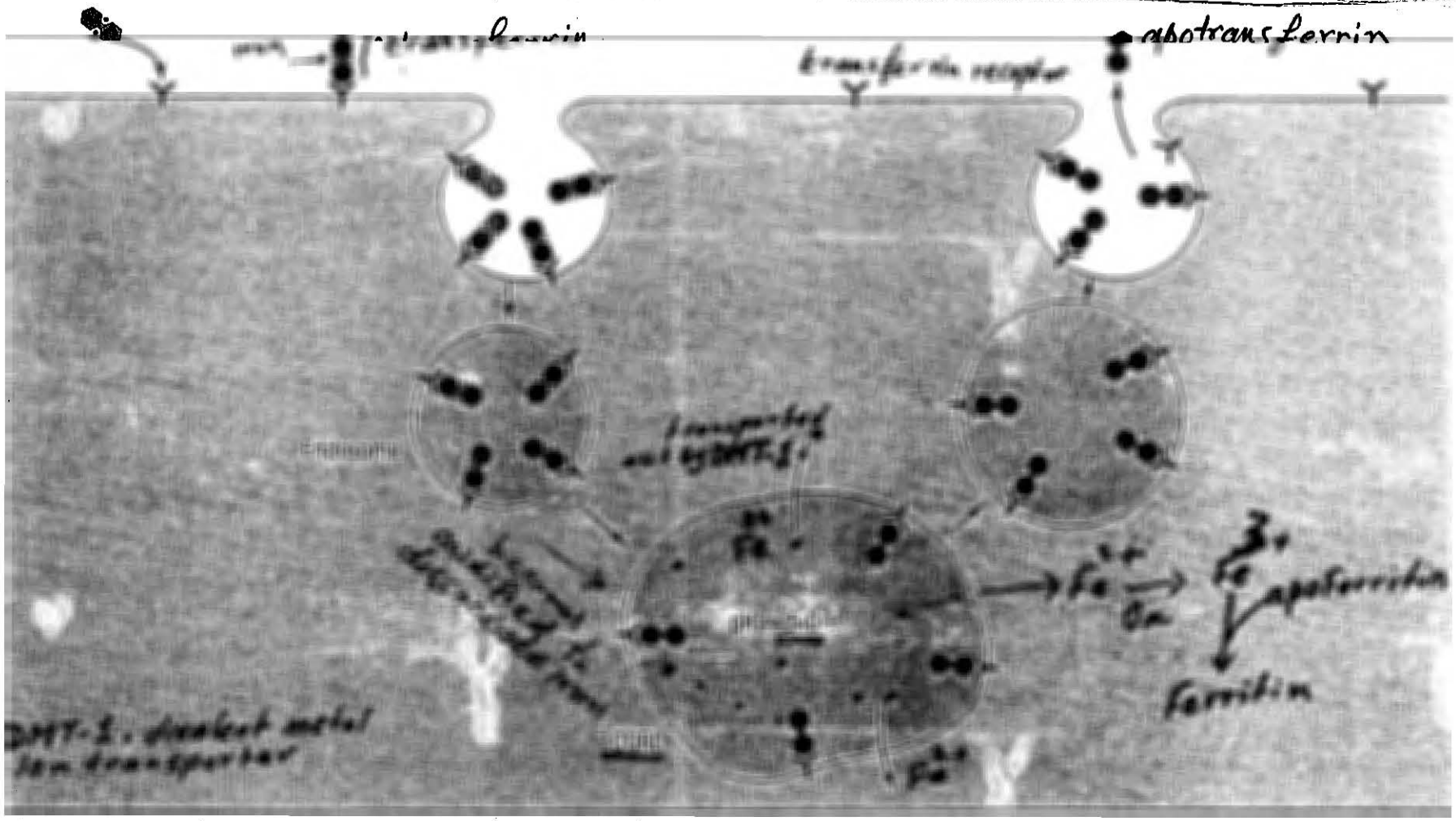


Figure 17.3: Absorption, storage and utilization of food iron

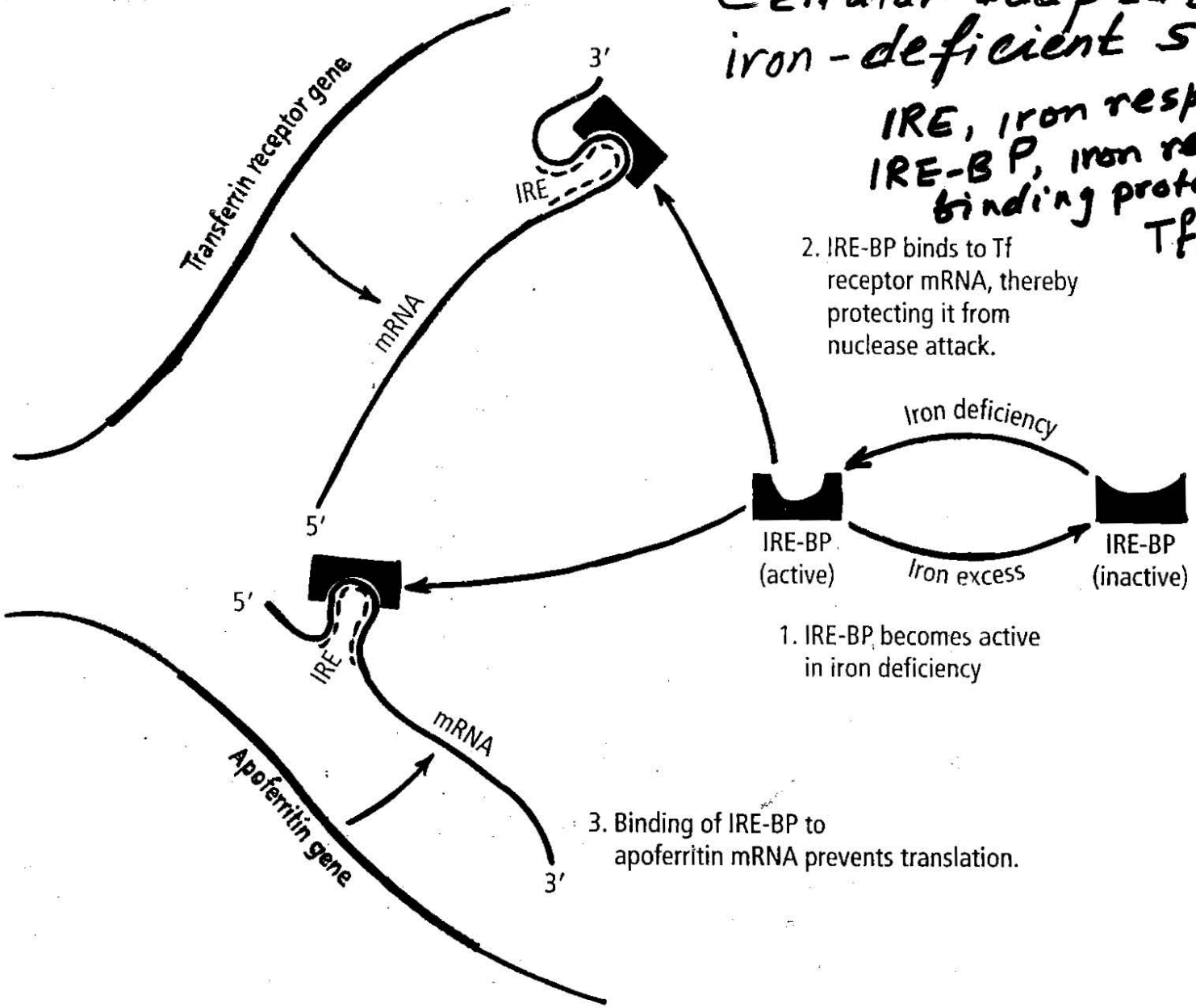
Utilization of transferrin-bound iron by receptor mediated endocytosis



CURL: compartment of uncoupling of receptor and ligand.

Cellular adaptations in the iron-deficient state

IRE, iron response element
IRE-BP, iron response element binding protein.
Tf, transferrin



Iron deficiency is the most common nutritional deficiency worldwide

There is no excretory mechanism for iron, which slowly accumulates in the body throughout life – absorbed in small quantity from diet. It is called a ONE WAY SUBSTANCE

Only ~ 1.0 mg of iron is absorbed per day in man – about the same ammount is lost by desquamated cells of the skin and intestinal mucosa, bile, urine and sweat.

Iron deficiency is rarely caused by dietary deficiency alone.
The typical situations are:

1. Acute massive hemorrhage

500 to 550 mg of iron / 1 litre blood loss
if enough storage is mobilized → hematocrit returns to normal within few weeks

2. Chronic hemorrhage

. Young women lose 20 to 40 ml per each menstrual period → 11 to 22 mg iron
. occult blood loss from chronic bleeding of G.I.T, hemorrhoids or tumors.

3. Growth

4. Pregnancy + lactation

← 250 to 300 mg → fetus during pregnancy
Max. loss during 3rd trimester
80 to 400 mg → placenta, cord blood + blood loss during birth
180 mg lost during lactation

IRON Deficiency Anemia →
Microcytic Hypochromic Anemia

- Most impt differential diagnosis to exclude thalassemia before initiation of iron therapy

- Treated with ferrous sulphate + ascorbic acid

- most prevalent in
  - growing children
  - → menstruating females
  - → Pregnant women

- Prevelance
  - most prevalent nutritional deficiency
  - 2 – 10% in developed countries
  - 10 — 50% in developing "

- Common Causes
  Excessive menstrual flow, multiple birth + G.I. bleeding

Normal levels

3 – 4 gr in 70 Kg man
2.5 gr in Hb
0.1% (3.5 mg) in plasma
50 – 160 μg/dL in plasma
% transferrin saturation ~ 33%
Ferritin:
male 5 – 30 μg/dl
female 1.2 – 10 μg/dl

Initial stage of Iron deficiency

- depletion of store
- ↓ ferritin in plasma
- level and percent of saturation of plasma transferrin is ~ normal

Second Stage:

- Hb level begins to fall
- morphological changes
- fall in serum iron
- Rise in transferrin level
- decrease in transferrin Sat. (<16%)

3rd stage

- depletion of iron containing enzymes with pronounced metabolic defects

Hemochromatosis

- Iron overload as high as 100 gr (>20gr)
- no effective mechanism for iron excretion → one way
- Initial accumelation → Ferritin → hemosiderin (hemosiderosis)
  - Initially asymptomatic
  - Excessive accumelation → dangerous → destructive free radicals
  - Longer life-span of females

Hemochromatosis :- iron overload syndrome → progressive hemosiderosis and organ damage

Primary- or genetic
- more common among men
- most common inherited metabolic disorder in the white population
  1 of every 400 is homozygous
  10% are heterozygous } absorbs ~ 4mg iron daily
- Accumelation in heart, liver, pancreas and joints

Secondary or Acquired
- Can develope from iron-rich diet in absence of predisposing gene
- life-long consumption of iron-rich food + Alcohol
- treatment - periodic blood withdrawal
- secondary hemochromatosis in patients with hemolytic anemia or thalassemia - treated with iron chelators

Minimal Daily Iron Requirements

	Amounts must be Absorbed, mg	Minimal am must be mg
Infants	1	10
Children	0.5	5
Young, nonpregnant women	2	15-20
Pregnant women	3	30
Men and Postmenopausal women	1	10

500-550 mg iron / 1 l blood
20-40 ml blood loss / each menstrual period
" → loss of 11 to 22 mg iron
→ 0.35 to 0.9 mg loss / day

250-300 mg → fetus during pregnancy
80-400 mg → placenta and cord, blood loss during birth

100-180 mg lost during lactation

Iron loss is maximal during the third trimester of pregnancy
~ 5 mg / day

TABLE 24.2

Biochemical indices of iron deficiency and iron overload

Index	*Normal*	*Changes in:* *Iron deficiency*	*Iron overload*
Hematocrit			
Male	43%-49%	Decreased	Normal
Female	41%-46%		
Blood hemoglobin			
Male	14%-18%	Decreased	Normal
Female	12%-16%		
Total plasma iron	50-160 μg/dL	Decreased	Increased
Total iron binding capacity	250-400 μg/dL	Increased	Increased
% Transferrin saturation	20%-55%	Decreased	Increased
Serum ferritin			
Male	5-30 μg/dL	Decreased	Increased
Female	1.2-10 μg/dL		