# Inorganic Pharmaceutical Chemistry

## Essential and Non-Essential Ions

## Lecture 9

# Essential and Trace Ions

The ions that :

1- have specialized biochemical functions

2- are not found in the general electrolyte replacement preparations

3- at least, two of them, Iron and Iodide, show a defined deficiency syndrome

# 1)Iron

- It is essential to the metabolic processes in the cell
- In the respiratory chain, Iron :

  a- functions as an electron carrier

  b- is responsible for the transport of molecular oxygen
- These functions depend on the ability of iron to exist in coordination compounds in different states of oxidation and bonding.

Most of the iron found in the body associated with two types of proteins:

**I- Hemoproteins:**

are iron containing proteins

**a- Cytochrome – c:**

- is a respiratory enzyme in which where iron is complexed in a porphyrin ring (heme) which is in turn covalently bound to the protein portion of the molecule.
- Iron act as electron carrier and can be present as ferrous ($Fe^{+2}$) or ferric ($Fe^{+3}$) as it picks up or donates an electron in the process of electron transfer.
- Cytochrome – c role is in oxidation – reduction process of iron.

**Catalase and peroxidase:**

Other oxidative enzymes containing iron

**b- Hemoglobin and Myoglobin:**

store and/or transport Oxygen

**Myoglobin:**

- is a single polypeptide with one oxygen binding site
- An oxygen carrying protein .
- Binds and releases oxygen depend at the changes in oxygen concentration.

**Hemoglobin:**

- Found in high concentration in the red blood cells.
- It binds to oxygen in lungs and transports it to body cells,
- It transports carbon dioxide from tissues to lungs.
- Hemoglobin has 4 protein chains, each of which contains a heme unit of porphyrin ring and ferrous iron .
- Iron complexes molecular oxygen by utilizing its vacant orbital which can be used by a pair of nonbonding electrons from oxygen.

- Uptake and release of molecular oxygen is influenced by :-
  - The oxygen tension.
  - pH
  - Presence of 2,3 diphosphoglycerate .
  - Carbon dioxide concentration.

**II- Iron storage and /or transport proteins:**

**a – The iron storage proteins:**

Found in liver, bone marrow and spleen.

**Ferritin:**

- A water soluble iron protein built up from apoferrtin and micelles of ferric hydroxide-phosphate complex.
- Apoferritin is a protein commonly present in the intestinal mucosa membrane. The important biological function of apoferritin is its ability to bind and store iron, by combining with a ferric hydroxide–phosphate compound to form ferritin.
- Iron is stored in ferritin as $Fe^{+3}$ form and released as $Fe^{+2}$

**Hemosiderin:**

A water **insoluble** protein considered to be a dehydrated form of ferritin.

## b – Iron transport proteins

### Transferrin:

- Major glycoprotein in blood plasma synthesized by the liver
- It binds two atoms of ferric iron per molecule, so tightly that is no free plasma iron.
- It releases **iron** to the red cell precursor by attaching to a receptor on the surface of the developing red blood cell.

- The body has a control mechanism for the absorption of iron across the intestinal wall.
- There are three postulates (hypothesises) put forth as explanations of the control of the intestinal iron absorption:

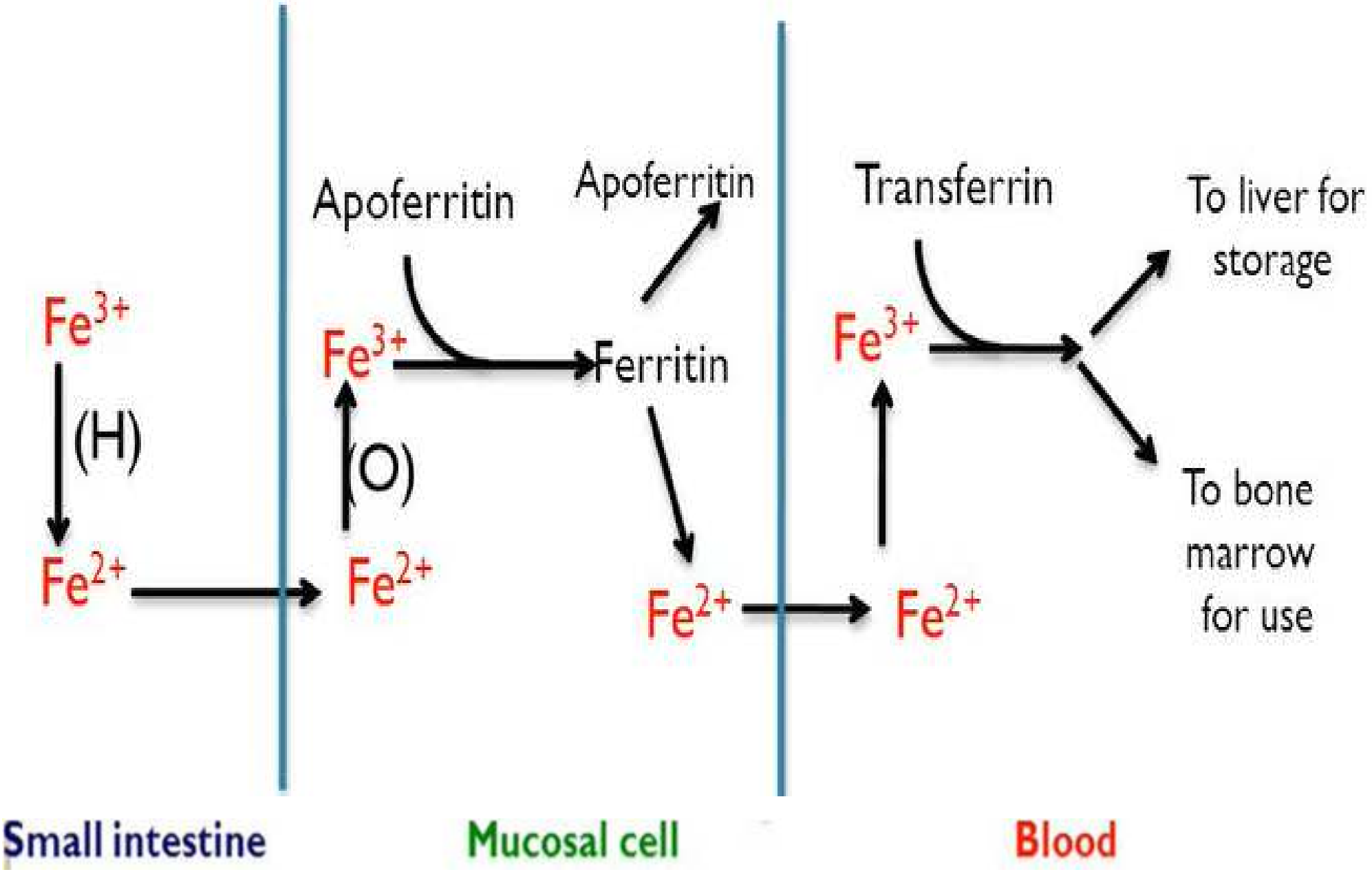
1. Mucosal block hypothesis
2. Active transport hypothesis
3. Iron-chelate hypothesis

**1- Mucosal block hypothesis:**

- Iron absorption is regulated and controlled by availability of apoferritin.
- The dietary or administered iron is reduced to ferrous form which diffuses into the mucosal cell where it is reoxidized to ferric form and then combined with apoferritin (which is being continually formed and destroyed) to form stable ferritin (the iron carrying protein).
- As ferritin crosses the cell and ferric iron is released to be reduced again to ferrous iron for diffusion across the serosal cell membrane (membrane covering the intestine) and eventual reoxidation to ferric iron and combination with the iron-transport protein (transferrin).

- In ferric iron form, it is transferred to the liver for storage or to the bone marrow for use in heme synthesis for erythrocyte production.
- The key of Mucosal block hypothesis is the assertion of that only small amounts of ferritin can be formed in each cell.

- Once the full complement of ferritin is obtain for a cell, it can no longer pick up iron.
- Further absorption occur only in cells that do not have their full amount of ferritin or if the ferritin unloads its iron thorough the serosal membrane to regenerate apoferritin.

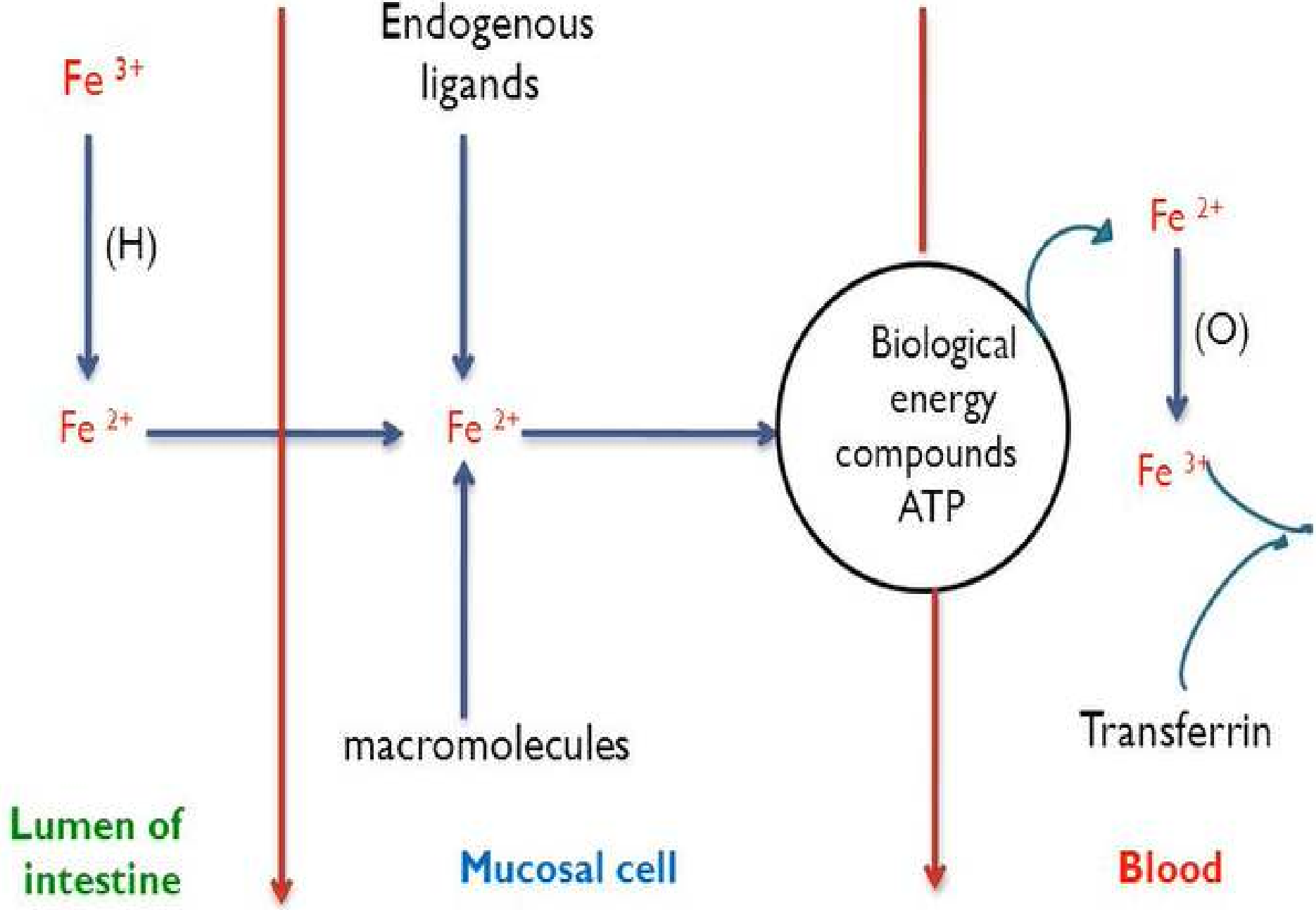

Apoferritin
Apoferritin
Transferrin
To liver for storage
$Fe^{3+}$
$Fe^{3+}$
Ferritin
$Fe^{3+}$
(H)
(O)
To bone marrow for use
$Fe^{2+}$
$Fe^{2+}$
$Fe^{2+}$
$Fe^{2+}$
Small intestine
Mucosal cell
Blood

- There are numerous arguments against this hypothesis, among which the facts that:

- no maximum limit of absorption has been demonstrated, that increased amount (although smaller percentage) of iron are absorbed from large doses
- unphysiologic amounts of iron are required to show the blocking effect
- nonferritin-bound iron is found in the intestinal mucosal cells

## 2. The active transport hypothesis:

- Regulation and control of iron absorption by regulating the amount of cellular energy available for active transport.
- Ferrous iron enters the mucosal cell by diffusion where it combines with endogenous low molecular weight ligands or it stored as ferritin.
- To cross the serosal membrane into the blood, a specific transport system intimately linked to adenosine triphosphate (ATP) has been suggested.
- The control of iron entry into the blood occurs by this active transport system.
- Once past the serosal membrane the events are the same as postulated by the mucosal block hypothesis.

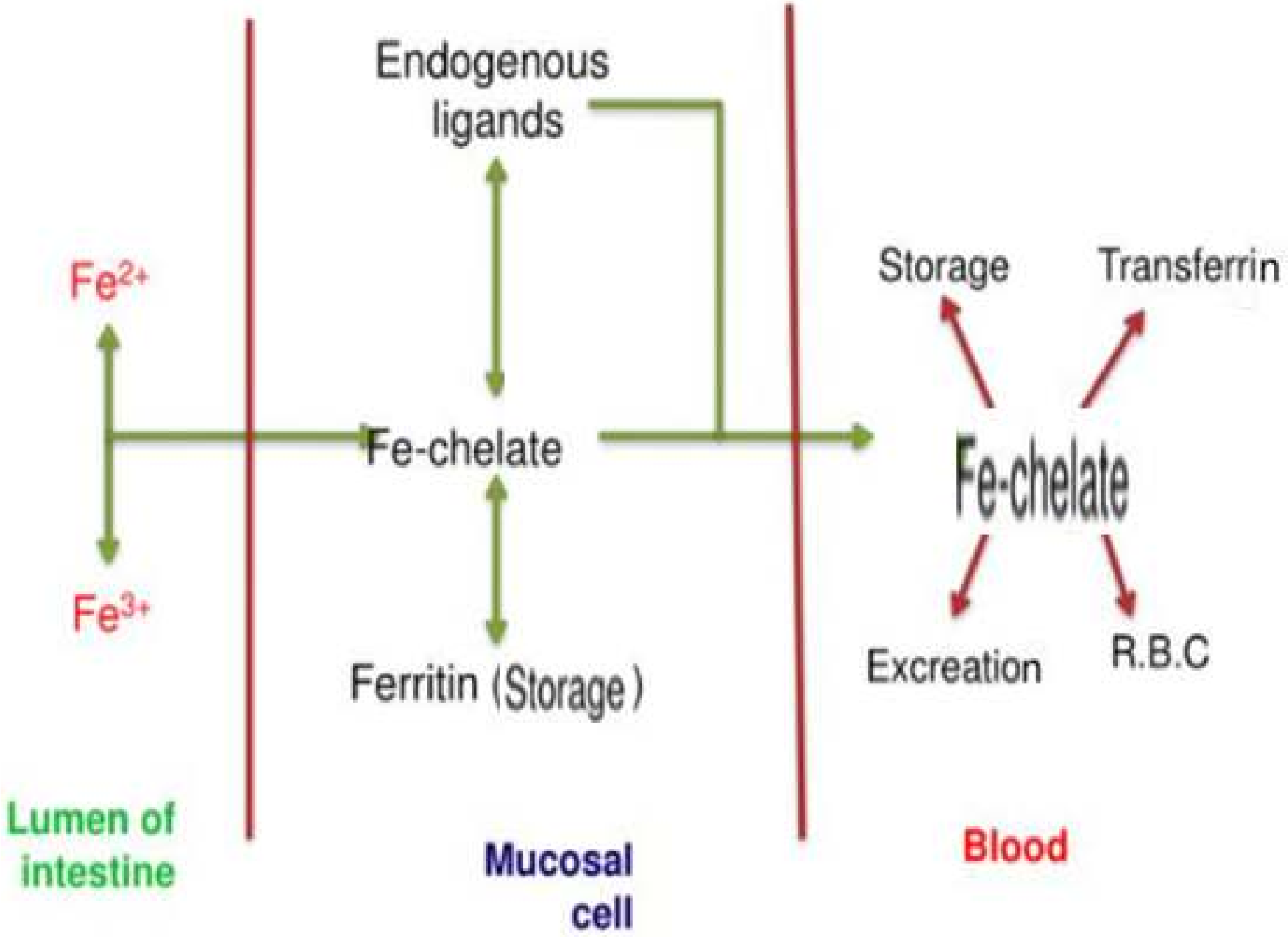

Endogenous
ligands
Fe 3+
(H)
Fe 2+
Fe 2+
Biological
energy
compounds
ATP
Fe 2+
(O)
Fe 3+
macromolecules
Transferrin
Lumen of
intestine
Mucosal cell
Blood

- One of the most telling points against this hypothesis is the fact that iron movement is not affected by an anaerobic condition, where as other known active transport processes (e.g.Na+) are vitally affected.
- This hypothesis fails in that there has been no demonstrations that iron movement across the serosal membrane is dependent upon metabolic energy.

## 3. The Iron Chelate Hypothesis:

- It proposed that primary control of iron absorption is exerted by endogenous or exogenous ligands or chelating agents which are able to bind either oxidation states of iron ($Fe^{+2}$ or $Fe^{+3}$) to form soluble low molecular weight complexes capable of passively diffusing through the mucosal cell membrane from intestine.
- No prior reduction to ferrous iron is postulated.
- Within the cell, the iron can be transferred to other endogenous ligands or stored as ferritin.

- Diffusion across the serosal membrane is occurred with either the original chelating material or with some endogenous ligand.
- Ones across the membrane , the iron is transported in the chelated form to depot cells where it is transferred to Transferrin.
- The sequence following this is the same as in the other hypotheses.
- The major attributes of this theory are that no redox reactions or metabolic energy requirements are directly involved.


Endogenous ligands
Fe2+
Fe3+
Fe-chelate
Ferritin (Storage)
Storage
Transferrin
Fe-chelate
Excreation
R.B.C
Lumen of intestine
Mucosal cell
Blood

- The arguments against this hypothesis include:

1. There is doubt that low molecular weight chelates are present in the gastrointestinal mucosal cells.
2. The suggestion that both $Fe^{+2}$ and $Fe^{+3}$ are equally complexed for diffusion into the mucosal cell could be difficult to rationalize because $Fe^{+2}$ absorption more than $Fe^{+3}$ (due to poorer solubility of $Fe^{+3}$ salts as compared to $Fe^{+2}$ salts).

**Iron-Deficiency Anemia (IDA):**

A person deficient in iron will become anemic, anemia is a general term for a condition which:

1. circulating red blood cells are deficient in number.
2. deficient in total hemoglobin content per unit of blood volume.

- The net result is lower oxygen carrying capacity by the blood
- (i.e) Patients with Iron-Deficiency Anemia have decreased capability for oxygen transport or decreased in hemoglobin synthesis .

- It can be caused by:

1- excessive loss of blood, can be caused by:

a- bleeding ulcer

b- hemorrhaging

c- menstrual flow

2- blood destruction, can be caused by:

a- haemolytic agents (drug therapy, infections, toxins)

b- defective haemoglobins (sickle cell anaemia, thalassemia).

3- decreased blood formation, can be caused by:

a- deficiencies of key materials (cobalamine, folic acid, pyridoxine and iron ).

b- infections

c- renal insufficiency

d- malignancy

e- marrow failure

Treatment of IDA usually consists of:

1. dietary supplementation:

- Iron is poorly absorbed from vegetables, grain products, dairy products, and eggs; it is best absorbed from meat, fish, and poultry.
- Beverages have been shown to affect iron absorption.

  orange juice, and other ascorbic acid containing natural juices should be included with meals, whereas milk and tea should be consumed in moderation between meals.

2. Administration of therapeutic iron preparations:

- Oral administration of iron therapy with soluble ferrous iron salts is appropriate. Ferrous iron can used as sulfate, succinate, lactate, fumarate, glycine sulfate, glutamate, and gluconate, all these are absorbed similarly.
- Parenteral iron preparations are indicated only if there are problems interferes with oral administration or in sever cases.

- **Iron compound used for replacement therapy must meet two requirements:**

1. must be biologically available
2. must be not irritant .

- usually water soluble, ferrous sulphate is the standard to which other iron salts are compared.
- Sustained released iron formulation have been utilized to minimize the irritant property of iron.

- Parenteral iron preparations are indicated only in:

1. defect in iron absorption as in gastroctomy, steatorrhea .
2. iron salt may irritate GIT so not used as in ulcerative colitis, peptic ulcer.

- **Official Iron Products:**

1. Ferrous sulphate $FeSO_4.7H_2O$

- it oxidizes readily in moist air to form basic ferric sulphate
- Ferrous sulphate is the most widely used oral iron preparation and is considered as the drug of choice for treating uncomplicated iron deficiency anemia.
- It can be irritating to GIT mucosa due to the astringent action of soluble iron but iron salt equivalent doses are used.
- Found as ferrous sulphate tablets, ferrous sulphate syrup, dried ferrous sulphate.

2. Ferrous fumarate:

- It is resistant to oxidation on exposure to air so it may be superior to both ferrous sulphate and gluconate.
- Found as tablets

3.Ferrous gluconate.

- It has a good bioavailability
- Found as tablets

4- Iron Dextran:

Found as I.M. Injection

5- Iron Sorbitex Injection

Found as I.M. Injection

# Iron - Drug Interactions

| Drugs That Decrease Iron Absorption | Object Drugs Affected by Iron |
|---|---|
| Al-, Mg-, and $Ca^{+2}$-containing antacids | Levodopa ↓ (chelates with iron) |
| Tetracycline and doxycycline | Methyldopa ↓ (decreases efficacy of methyldopa) |
| $Histamine_2$ antagonists | Levothyroxine ↓ (decreased efficacy of levothyroxine) |
| Proton-pump inhibitors | Penicillamine ↓ (chelates with iron) |
| Cholestyramine | Fluoroquinolones ↓ (forms ferric ion quinolone complex) |
| | Tetracycline and doxycycline ↓ (when administered within 2 hours of iron salt) |
| | Mycophenolate ↓ (decreases absorption) |

**2) Copper :**

- It is required for many enzymes, for synthesis of hemoglobin and for normal bone formation.
- Unlike iron it is believed that most of the population obtain the sufficient amount of copper from diet.
- Copper supplements are probably not necessary.
- Copper is solubilized in stomach acid and absorbed from the stomach and upper small intestine,
- From intestine copper moves into the blood where it exists first as copper albumin complex, then goes to the liver where the copper become part of copper protein, ceruloplasmin .
- Copper is found in the brain in form of cerebrocuprein , in blood cells as erythrocuprein.

- **Wilson's Disease :**

- It is a rare inherited disorder that causes copper to accumulate in the liver, brain and other vital organs. It is a condition of excess copper storage.
- Pencillamine is the drug of choice which is a chelating agent , in addition to diet restriction

- **Uses of Copper Preparations:**

1. Topically as fungicide and astringents.
2. Antidote for phosphorous poisoning.
3. Essential component of Fehling and benedict solutions which are used for determination of glucose.

   a positive test is the production of cuprous oxide.

**3) Zinc:**

- Zinc ion is widely distributed in the body.
- It has important roles in :

❖ Biochemically is associated with certain metalloenzymes include alcohol dehydrogenase, aldolase, carbonic anhydrase, alkaline phosphatase, glutamic dehydrogenase and others.

❖ Zinc bound to RNA stabilizing the secondary and tertiary structures.

❖ For normal growth and reproduction.

❖ It has a beneficial effect on tissue repair and wound healing.

❖ Zinc complexes with insulin present in B cells of pancreas.

❖ Necessary for vitamin A mobilization from liver and vitamin A metabolism affected by zinc deficiency.

- Food sources of zinc include seafood, nuts, meat, eggs, and milk.
- A person on vegetable diet may not receive a sufficient amount of Zinc because phytic acid which found in vegetables such as soya bean combine with zinc and lower its absorption.
- Zinc deficiency is associated with impaired growth , parakeratosis (a thickened , scaly , inflamed skin), retarded sexual maturation and affect immunity and enzymes functions.

**4) Sulphur:**

- Sulphur is widely distributed throughout the body as:

a. sulfhydryl groups of cysteine

b. Bisulfide linkages in protein from cysteine

c. sulphate salts and esters of mucopolysaccharides and sulfolipids.

- **Sulphur has been used therapeutically as:**

1. Cathartic action.
2. Parasiticide in scabies.
3. Stimulant in alopecia
4. Some skin diseases.

## 5) Iodine (Iodide):

- Iodide is an essential ion necessary for the synthesis of two hormones produced by thyroid gland , T3 (Triiodothyronine) and T4 (Thyroxin).
- Internally iodine or iodide can be administered, since iodine is reduced to iodide in the intestinal tract but more common iodide salts are administer because of solubility reasons.

- Lack of sufficient iodine in diet result in an enlargement of thyroid gland, known as simple or colloid goiter, characterized by a swelling at the neck.

- When iodine is administered its uptake is governed by three principle factors:

1. The character of local thyroid tissue because abnormal thyroid tissue (tumorous) has a slower uptake of iodide and a lower content of iodine than normal tissue.
2. Blood level of inorganic iodide, because a high level keeps the iodine at high level in the colloids thus using up only a small part of the administered iodide.

# Non Essential Ions

## 1)Fluoride

Fluorides are widely used today:

- For their anticariogenic action (inhibition of dental cavity development).
- Required for bones.
- About 95% of orally taken fluoride is absorbed.
- Sodium fluoride has awide range of therapeutic index.

- Many reports indicated that fluoride reduces the prevalence of osteoporosis (loss of bone Calcium).
- Visible calcification (in men) were actually higher in low fluoride area because fluoride facilitate calcium deposition in hard tissues (teeth & bones) and not in the soft tissues

## 2)Bromide

- Bromides were introduced into medicine in 1853 for their antiepileptic effect.
- Administration of small doses (0.5-2gm) of bromide serve to cause depression to CNS, while large doses(4 - 8 gm) may depress all reflexes and cause narcotic type effect.
- Bromides usefulness in epilepsy depend on their ability to depress the motor areas of the brain ,an effect brought about by large doses.

- Bromides are rapidly absorbed and are excreted mainly in urine, and repeated doses tend to cause accumulation with a consequent replacement of chloride ion.

- The use of bromide is stopped because of the possibility of bromism (bromide poisoning).

- The early sign of bromide intoxication include insomnia, restlessness, dizziness, weakness and headache.

- Treatment of bromism by administration of sodium chloride (6 gm daily in divided doses) or ammonium chloride  is used (if sodium intake is restricted).

**3)Lithium:**

- It is readily absorbed from the intestine and accumulates in the body.
- The extent of its accumulation depend on sodium intake (decrease sodium intake accelerate lithium accumulation and potentiate its toxicity).

- Lithium intoxication is treated by withholding lithium salts and provide sodium intake.

- Lithium is a depressant to the CNS and has a diuretic action

- Lithium carbonate is administered orally in manic depressive disorder.

- Lithium carbonate can affect thyroid function causing myxedema (deficient thyroid function) decreased protein-bound iodine levels and increased iodine uptake.

- Lithium can cause diabetes insipidus (increase urination without glucosuria).

## 4) Gold:

- It is used in the rheumatoid arthritis, and therapeutic gold compounds are administered I.M.

- Orally is poorly absorbed and irritant.

- The gold is rapidly enters the plasma where it remains bound to albumin for several days so it is usually administered weekly

- Gold toxicity involves the skin, mucous membrane, joints, blood, kidney, liver and nervous tissue.

- Treatment of toxicity involves:

1. Stop gold administration.
2. Giving supportive treatment.
3. Dimercaprol can be used if toxicity sever, it is used to remove accumulated gold.

**5) Silver:**

- In common with heavy metal is a protein precipitant.

- Action range from antiseptic, astringent, and irritant to corrosive, as the concentration of silver increases.

- When ever silver preparation are used for long periods of time they can cause discoloration of skin, called argyria.

- The colour range from gray to one suggesting marked cyanosis.
- Part of the pigment may be silver sulfide ($Ag_2S$), but it is also partly metallic sulfur resulting from the reduction of silver in the tissues.
- Reduction is facilitated by light.
- It is irreversible.
- Chelating agents are not effective since argyria involves free rather than ionized silver

## 6) Lead:

- Its salts were used topically as astringent.

- Oral lead generally absorbed slowly and excreted reasonably well.

- Inorganic lead can not pass through intact skin but it will be absorbed through a braded skin, thus lead solution used as astringent could not be absorbed systemically while organic lead such as tetraethyllead can penetrate skin rapidly

- Once absorbed , lead can be found initially in the erythrocyte and soft tissue, in the latter the kidneys contain the most lead with the liver, then overtime redistribution occur to be found in bone, teeth and hair.

- Lead poisoning:

➢ While lead may be considered a protein precipitant by combining with the cysteine sulfhydryl groups of protein, chronic lead poisoning manifests itself by inhibition of heme synthesis.

## Treatment of chronic lead poisoning

- Treatment is based on the use of chelating agents to remove the accumulated lead from the erythrocyte and soft tissue.
- Dimercaprol and calcium disodium edetate are used initially followed by Pencillamine for follow up treatment.

**Treatment of  acute lead poisoning ,**which result from oral ingestion, :

- Administering sodium or magnesium sulfate to precipitate the lead.
- Followed by gastric lavage

## 7) Mercury:

- Metallic mercury is relatively nontoxic as such since it is the mercurous $Hg^{+}$ and the mercuric $Hg^{+2}$ cations that are toxic, in addition to that mercury vapour is also toxic.

- Poisoning by soluble inorganic mercury salts can be avoided while organic mercurials (alkylated mercurials) compounds are very toxic and are the cause of most modern reports of mercury poisoning.

- Toxic effects of mercury is similar to those of lead and arsenic, are due to its combining with protein sulfhydryl groups.

- Once absorbed, the mercuric cation concentrates mostly in the kidney, with less concentration in the liver, blood, bone marrow, and other tissues.

**Treatment of acute poisoning:**

- Gastric lavage.
- Using of reducing agent such as sodium formaldehyde sulfoxylate to reduce the mercuric cation forming less soluble mercurous salts.
- Using of chelating agents such as dimercaprol or pencillamine.

**Mercurial salts are used as:**

- Diuretics.
- Antiseptics.
- Parasiticides.
- Fungicides.