Inorganic Pharmaceutical Chemistry

in Pharmaceutical Chemistry

Lec 3: Essential and Trace Ions

Iron

- **Importance**:
  - Iron is present in some form wherever respiration occurs in higher animals.
    1. It is essential to the elementary metabolic processes in the cell.
    2. In the respiratory chain, iron functions as an electron carrier. Iron is responsible for the transport of molecular oxygen in higher organisms.
  - Both of these functions depend on the ability of iron to exist in coordination compounds in different states of oxidation and bonding.

transferrin - measures levels of the iron protein carrier; total iron binding capacity (TIBC) - measures the **transferrin** capacity to bind iron; serum **ferritin** - measures the body's ability to store iron. **Hemosiderin**, a degradation product of **ferritin**

$$\underset{[\mathrm{Ar}]3d^6 4s^2}{\mathrm{Fe}} \rightarrow \underset{[\mathrm{Ar}]3d^6}{\mathrm{Fe}^{2+}} + 2\mathrm{e}^-$$

$$\underset{[\mathrm{Ar}]3d^6 4s^2}{\mathrm{Fe}} \rightarrow \underset{[\mathrm{Ar}]3d^5}{\mathrm{Fe}^{3+}} + 3\mathrm{e}^-$$

Body Components Containing Iron:

Occurrence	Iron Bound As	Mode of Linkage	Function	Iron Content	
				Total	% of Body Iron
Blood System	Haemoglobin	Heme	0_2 Transport	3 g	64.4
	Plasma	Transferrin	Fe Transport	4 mg	0.1
Tissues	Functional Iron (Myoglobin, Cell Hemes)	Heme	Cell Respiration	650 mg	14
	Storage Iron	Ferritin	Iron Pool	1 g	21.5
		Hemosiderin	Detoxication		

- The bioavailability of iron is highly dependent on the food source. Meat, poultry and fish are rich in easy-to-absorb iron. Absorption [usually occur in upper part of deudenum] can also decrease depending on other dietary components. **Some compounds, such as polyphenols (in vegetables) or tannins (in tea), can form chelates with iron.**

- Usually, iron is administered orally as Fe2+ or Fe3+ salts. Fe2+ compounds are more soluble at physiological pH. The advantage of Fe3+ salts is that they are not prone to oxidation in aqueous solutions. The most common medicinal preparations include FeCl3, FeSO4, Fe(II) fumarate, Fe(II) succinate and Fe(II) gluconate

- It is recommended continuing the treatment for **3** months once the normal range is reached.

- In general iron in **liver and muscle** is better absorbed than is the iron in eggs and leafy vegetables and , in particular, the iron in wheat, corn and black beans is relatively unavailable to the body.
- Iron transport in to intestinal mucosa is facilitate by **ascorbic acid**, HCl and fructose to hold iron in a **soluble ferrous state**.

Iron absorption

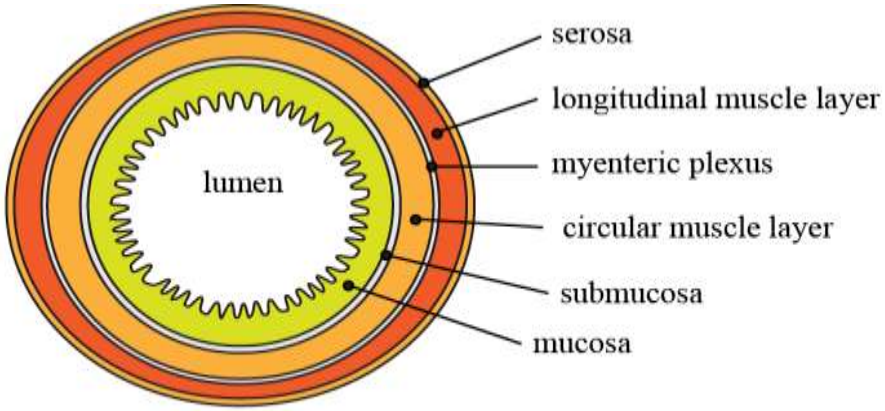
- There are three hypotheses of the control of intestinal iron absorption :

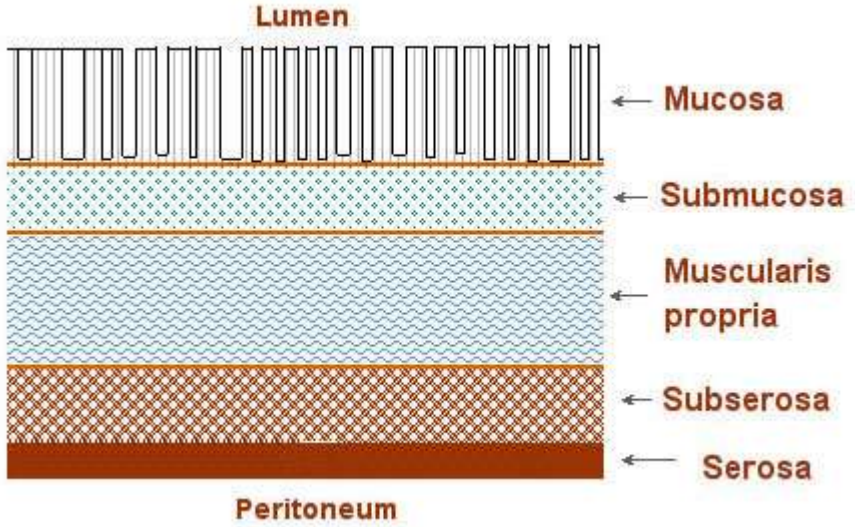
✓*Mucosal block hypothesis.*

✓*Active transport hypothesis.*

✓*Iron-chelate hypothesis.*

Mucosal block hypothesis.





Myoglobin vs Hemoglobin

Myoglobin is an iron- and oxygen-binding protein found in the skeletal muscle tissue of vertebrates in general and in almost all mammals. Myoglobin is distantly related to hemoglobin, oxygen-binding protein in red blood cells. In humans, myoglobin is only found in the bloodstream after muscle injury

Hemoglobin or haemoglobin + -o- + globulin, abbreviated Hb or Hgb, is the iron-containing oxygen-transport metalloprotein in the red blood cells of almost all vertebrates as well as the tissues of some invertebrates. Hemoglobin in blood carries oxygen from the lungs or gills to the rest of the body

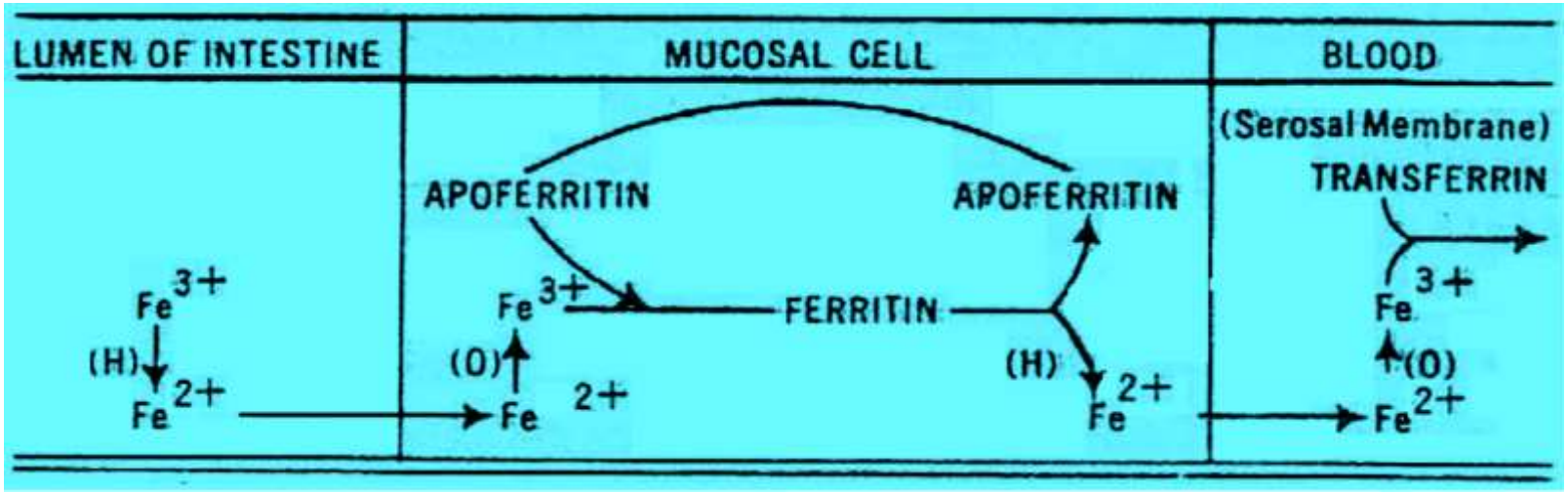
Mucosal block hypothesis

- Iron absorption regulated and controlled by the existence of **apoferritin [Apoferritin** is a protein commonly present in the intestinal mucosa membrane].
- The dietary or administered iron is **reduced** to ferrous form (Fe^{2+}) which diffuses into the mucosal cell where it is oxidized and then combined with apoferritin to ultimately form the stable iron carrying protein, **ferritin**.

- As ferritin iron crosses the cell and then released to be reduced again to ferrous iron which diffuses across the serosal cell (cover the intestine) and eventually oxidized to ferric iron (Fe3+) and combined with the iron-transport protein (transferrin).

Mucosal block hypothesis

- In this form it is transferred to the liver for storage [as ferritin and as hemosiderin] or to the bone marrow for use in heme synthesis for erythrocyte production.



- *This hypothesis does not stand against saturation* i.e. no maximum limit of absorption has been demonstrated with increased iron doses.

The active transport hypothesis:

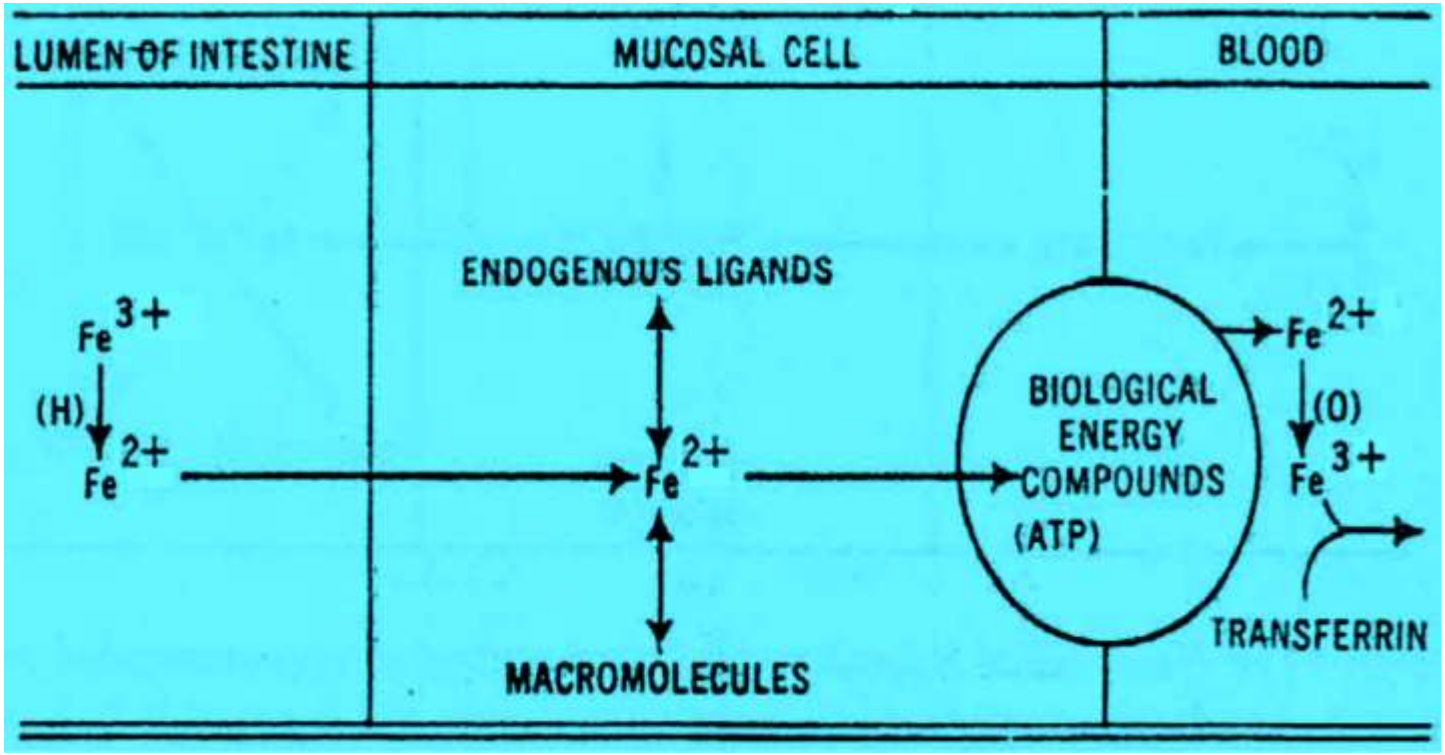
- Like in the mucosal block mechanism, Fe^{2+} enters the mucosal cell by **diffusion** where it combines with endogenous low Mwt ligands or it stored as ferritin.
- Iron absorption regulated and controlled by regulation the amount of cellular energy available for active transport (**ATP**).
- To cross the serosal membrane into the blood specific transport system linked to ATP.

The active transport hypothesis:

- Once past the serosal membrane the rest steps are the same as explained by the mucosal block hypothesis.

- *One of the most points against this hypothesis* is the fact that iron movement (absorption) is not affected by an anaerobic condition, where as other known active transport processes (e.g. Na^{+}) are vitally affected.

The active transport hypothesis:



The iron chelate hypothesis:

- This hypothesis indicates that iron absorption depends on the availability of endogenous or exogenous chelating agents which are able to bind either Fe^{2+} or Fe^{3+} to form soluble low Mwt complexes.
- Within the cell the iron can be transferred to other endogenous ligands or stored as ferritin.
- The major attributes of this theory are that no redox reactions or metabolic energy requirements are directly involved.

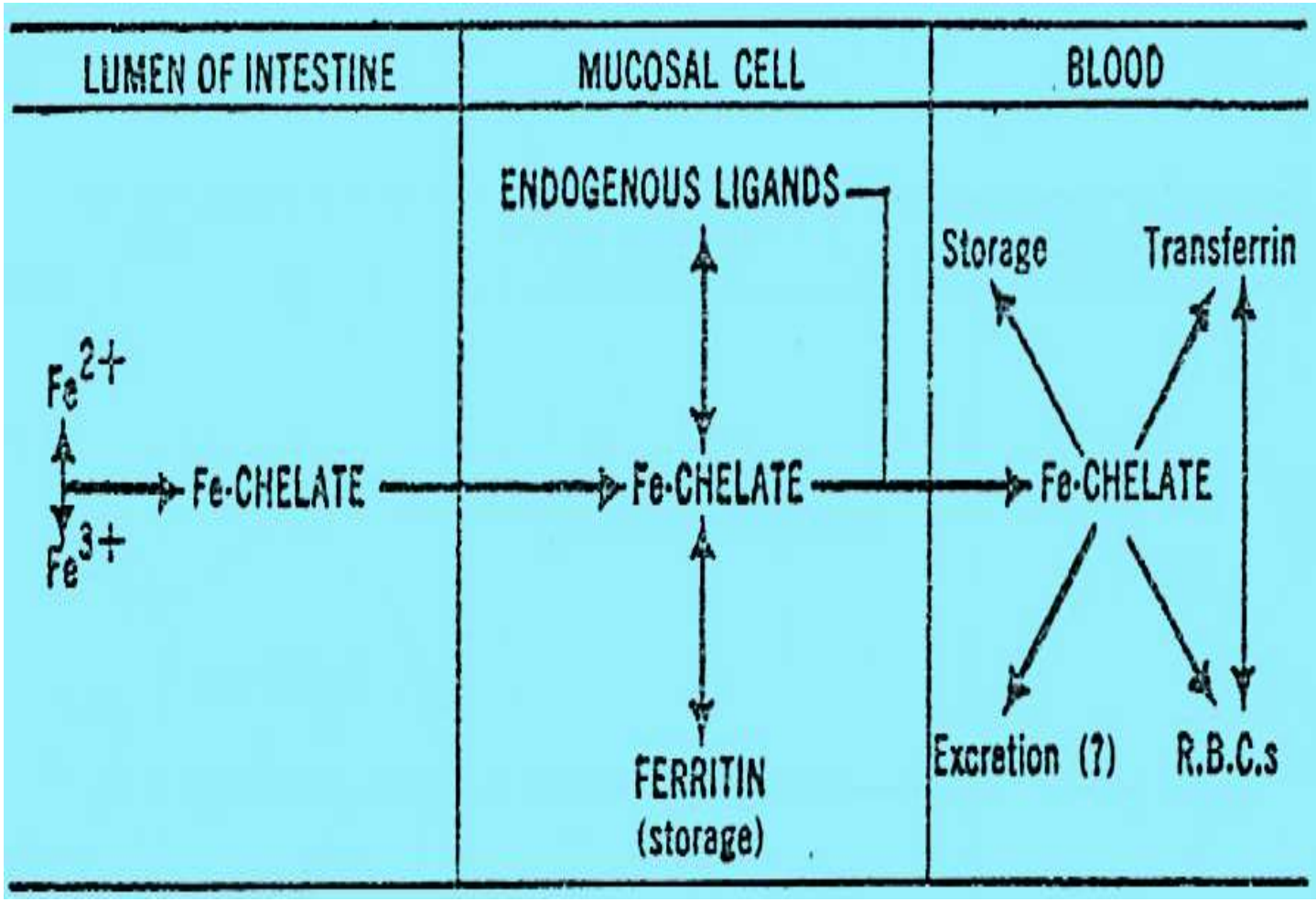
The iron chelate hypothesis:

- *Points against this hypothesis:*

  a) It is not really clear that low Mwt chelates are present in the GIT cells.

  b) The assumption that both Fe^{2+} and Fe^{3+} are equally complexed for diffusion into the mucosal cell is not easy to understand especially when the Fe^{2+} absorption is more than Fe^{3+}. *(Due to poor solubility of Fe^{3+} salts as compared to Fe^{2+} salts).*

The iron chelate hypothesis:



Iron requirements:

Standard formula:

Total milligrams of iron needed =

Patient's wt. (kg) × [normal Hb value (g%) – Patient's Hb value (g%)] × 2.5

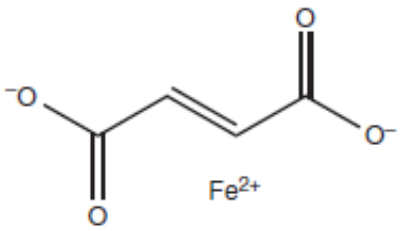
IRON BALANCE

	Iron Requirements mg	*Dietary Iron mg*	*Required Absorption %*
Men	0.9 (0.6–1.2)	15	6 (4–8)
Menstruating Women	1.3 (0.7–2.5)	10	13 (7–25)
Pregnant Women	2.5 (2.0–5.0)	10	25 (20–50)

70 * [0.13- 0.09] * 2.5= 7 mg of iron needed

Official Iron Products:

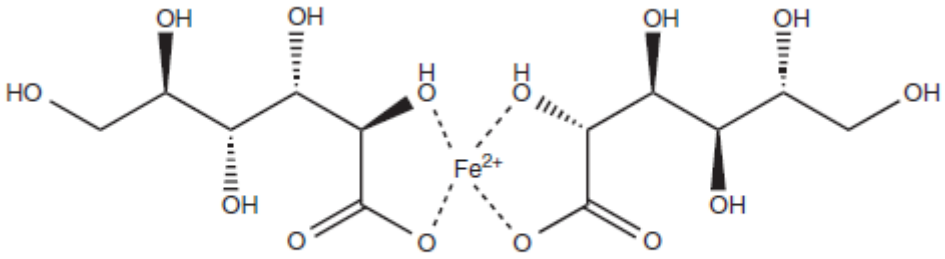
- **Ferrous Fumarate** U.S.P. (Mol. Wt. 169.9, Fe = 55.8 a.m.u)
- Iron content: (32.8% elemental iron)
- It has been assumed that Ferrous Fumarate is less irritating than ferrous sulfate if one administers equivalent doses of iron.
- One of the useful attributes of this salt is its resistance to oxidation on exposure to air.
- In this respect it may be superior to both ferrous sulfate and ferrous gluconate.
- Usual Dose: 200 mg (the equivalent of 65 mg of elemental iron) two or three times a day.



Ferrous fumerate

Official Iron Products:

- **Ferrous Gluconate,** N.F. (Mol. Wt. 482.18, Fe = 55.8 a.m.u)
- Iron content: (11.6% elemental iron)
- Ferrous gluconate was a great improvement as it has good bioavailability.
- It is doubtful if it is any less irritating than ferrous fumarate or sulfate when equivalent doses of iron are administered.
- Usual Dose: 300 mg
- Elemental iron= 36 mg



Ferrous gluconate

Official Iron Products:

- **Ferrous Sulfate**, U.S.P. ($FeSO_4.7H_20$; Mol. Wt. 278.02, Fe = 55.8 a.m.u) (20% iron)

- Ferrous Sulfate oxidizes readily in moist air to form brownish yellow basic ferric sulfate [approximate formula $Fe_4(0H)_2(SO_4)_5$).

- For this reason the U.S.P. carries the italicized warning: Note-*Do not use Ferrous Sulfate that is coated with brownish yellow basic ferric sulfate*.
- Ferrous sulfate is the most widely used oral iron preparation and is considered as the drug of choice for treating uncomplicated iron-deficiency anaemia.
- It can be irritating to the gastrointestinal mucosa due to the astringent action of soluble iron, but it is probably not more irritating than any other iron salt when equivalent doses are used.

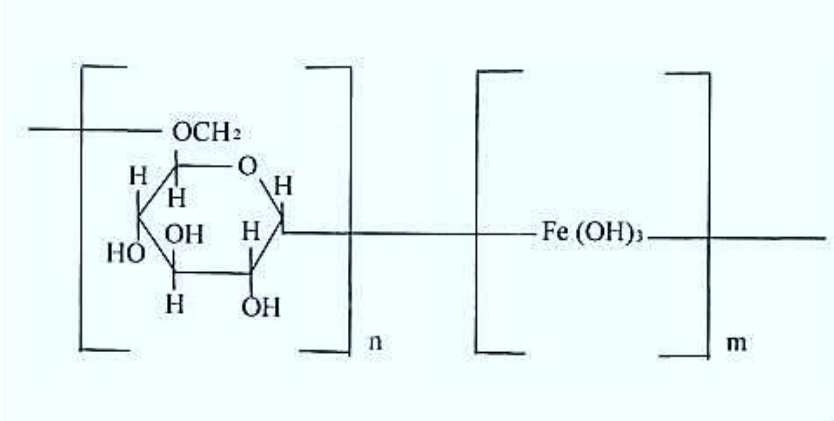
- Although there are a large number of ferrous sulfate tablets on the market, they can vary as to the potential bioavailability of the iron. Usual Dose: 300 mg, this equivalent to 60 mg of elemental iron.

Official Iron Products:

- **Iron Dextran Injection**, U.S.P. (Imferon®)
- Iron Dextran Injection U.S.P. is a sterile, colloidal solution of ferric hydroxide [$Fe(OH)_3$] complexed with partially hydrolysed dextran (glucose polymer) of low molecular weight, in Water for Injection.
- It is used only in confirmed cases of severe iron-deficiency anaemia where oral therapy is contraindicated or ineffective, or if the patient cannot be relied upon to take oral medication.
- It should not be used in a prophylactic manner.

Official Iron Products:

- **Iron Dextran Injection**, U.S.P. (Imferon®)
- Anaphylactic (severe allergic response) reactions, including three deaths, have been reported.
- A recent study indicates that iron dextran is effective in iron deficiency anaemia only when the bone marrow iron stores are depleted.
- In iron-deficiency anaemia Usual Dose: Intramuscular, the equivalent of 100 mg of iron once a day.



- **Venofer**
- 20 mg/ml (iron-lll-hydroxide sucrose complex) (iron sucrose injection, USP),
- Iron replacement product, is a brown, sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use.
- Each mL contains 20 mg elemental iron
- as iron sucrose in water for injection.
- Venofer is available in 10 Ml single-dose
- vials (200 mg elemental iron per 10 mL)

Copper:

- It is required for many **enzymes**, for synthesis of haemoglobin and for normal bone formation.
- **Unlike iron** it is believed that most of the population obtain the sufficient amount of copper from food, water, and cooking utensils. Thus 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 is either stored, incorporated into ceruloplasmin [**Ceruloplasmin** is the major copper-carrying protein in the blood], or excreted in the bile.
- Copper is found in the brain in form of **cerebrocuprein** , in blood cells as **erythrocuprein**.

Copper

Several roles in metabolism have been attributed to copper :

- ✓ Copper is utilized in haemoglobin formation.
- ✓ Copper is required to prevent anaemic conditions through:
  1. *facilitates iron absorption.*
  2. *Stimulates enzymes involve heme and globin biosynthesis.*
  3. *Could involve in metabolism of stored iron.*
- ✓ Copper is important in oxidative phosphorylation (ATP production) .
- ✓ Copper is associated with the formation of aortic elastin.
- ✓ Copper is a component of tyrosinase, an enzyme responsible for conversion of tyrosine to the black pigment, melanin.

Wilson's disease:

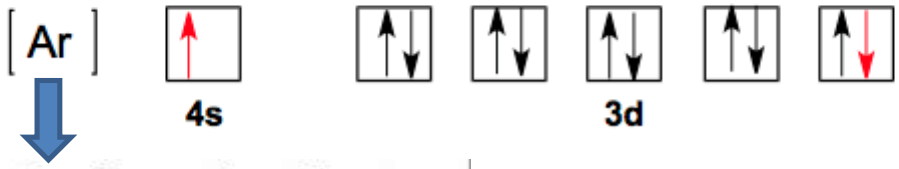
- More common, although still rare (4 or 5 per million).
- **A condition of excess copper storage**.
- Wilson's disease is of genetic origin, being transmitted by an autosomal recessive gene. (both parents are carriers for a defect gene)
- Patients have increased copper levels in liver, brain, kidney, and cornea.
- The symptoms are hepatic cirrhosis, brain damage and demyelination, and kidney defects.
- Treatment is usually done by diet and by use of the chelating agent penicillamine.

Electron Config

for

Cu Cu^{+} Cu^{2+}

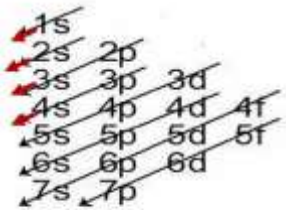
Cu (29 Electrons) $[Ar]\ 4s^2 3d^9 \longrightarrow [Ar]\ 4s^1 3d^{10}$



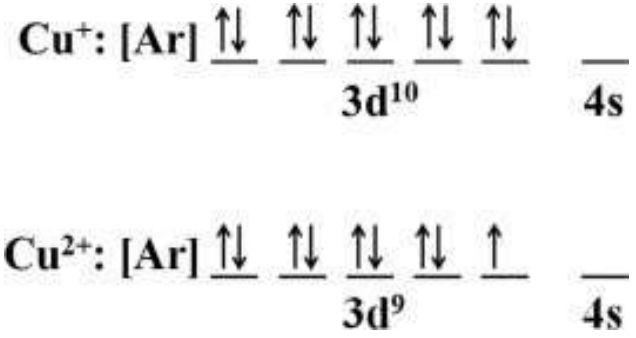
Electron Configuration Chart

s holds up to 2 p holds up to 6 d holds up to 10

18
Ar
Argon
39.95

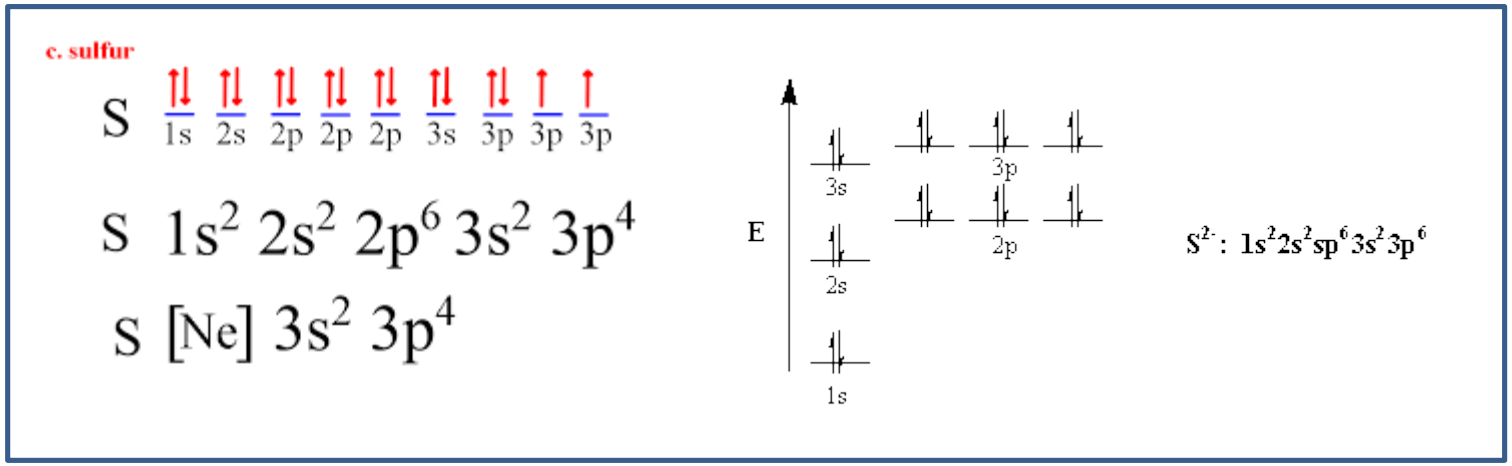


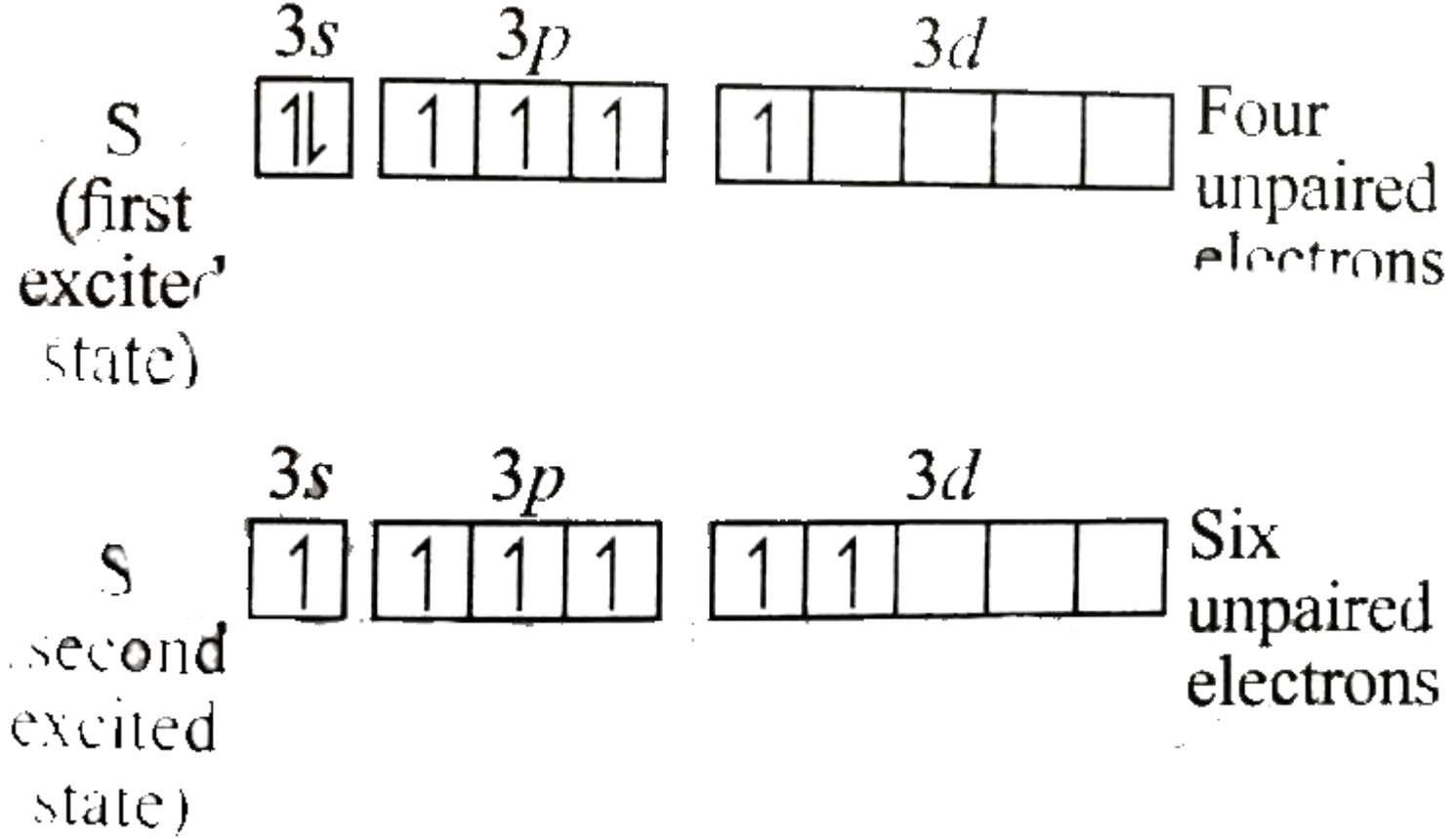
$1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6$



Sulfur

- Sulfur is widely distributed throughout the body as sulfhydryl groups of cysteine, disulfide linkages in protein from cystine and sulfate salts and esters found in mucopolysaccharides and sulfolipids, Dietary sulfur comes from these same groupings found in plant and animal foodstuffs.
- The minimum daily requirements are 2-3 g.
- Currently there seems to be no need for dietary supplements of sulfur.



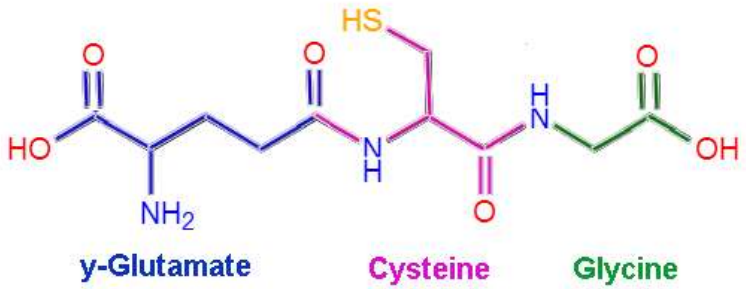

3s
3p
3d
S
(first
excited
state)
Four
unpaired
electrons
3s
3p
3d
S
(second
excited
state)
Six
unpaired
electrons

Synthesis of Glutathione (GSH)

- Glutathione is a **tripeptide**.
- Widely distributed in tissues.
- Present in **oxidized** and **reduced** state.

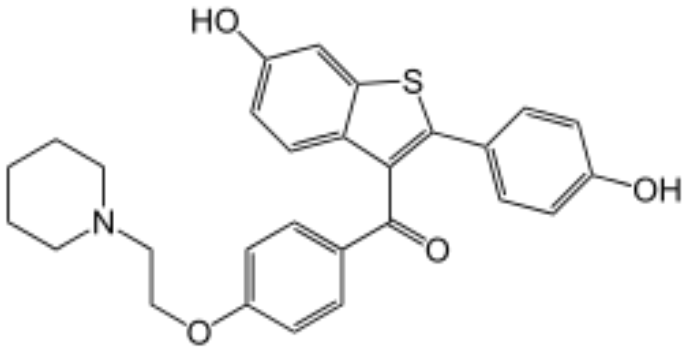
Functions of Glutathione

- Component of an antioxidant enzyme **Glutathione peroxidase** which is required for free radical scavenging.
- Maintains integrity of RBC membrane.
- Protect Hb from oxidation by H_2O_2
- Transport of amino acids (Meister cycle)
- Detoxification
- Formation and stabilization of disulphide linkage in proteins.
- Acts as cofactor for some enzymes.

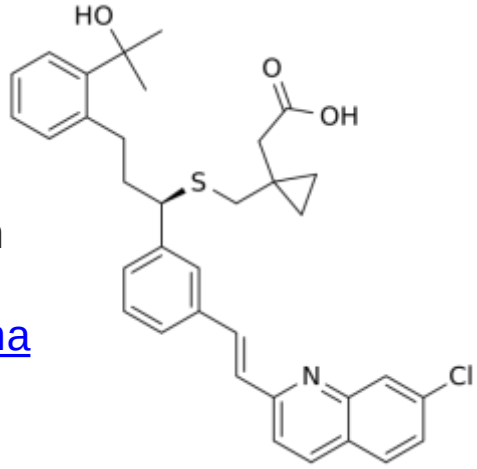


Sulfur

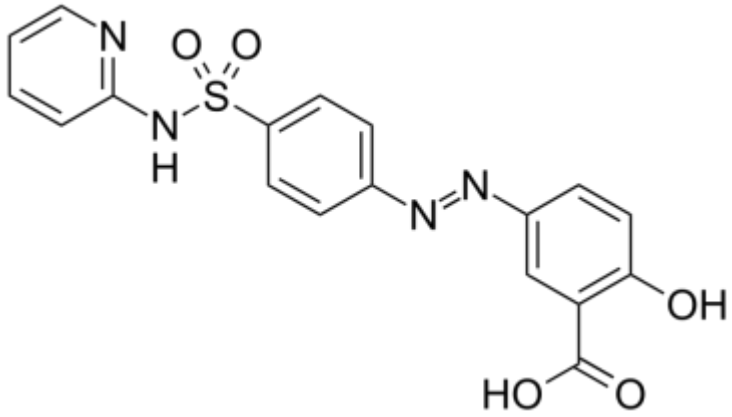
- Sulfur has been used therapeutically since antiquity and, during that time, certain well defined uses emerged.
- These are:
  1. Cathartic action.
  2. Parasiticide in scabies.
  3. Stimulant in alopecia.
  4. Fumigation. is a method of **pest control** that completely fills an area with gaseous pesticides
  5. Miscellaneous skin diseases.
  6. Sulfides have been used for many years as depilatories.



Raloxifene, is a medication used to prevent and treat osteoporosis in postmenopausal women. It is also used to reduce the risk of breast cancer in those at high risk.



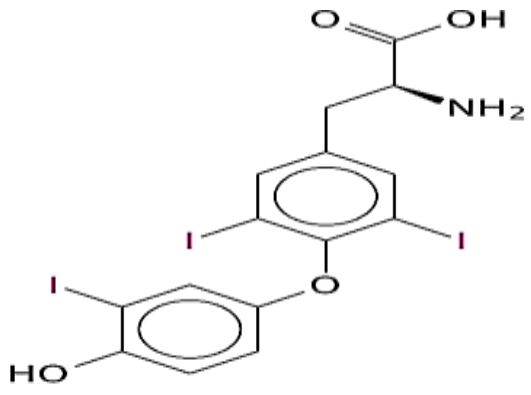
Montelukast is a medication used in the maintenance treatment of asthma



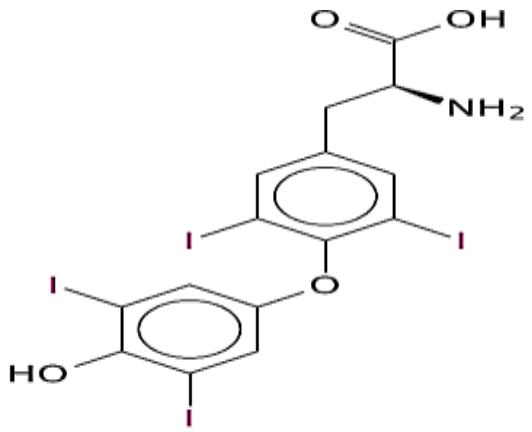
- **Sulfasalazine** is used to treat ulcerative colitis (UC) and rheumatoid arthritis

Iodine (Iodide)

- Iodide is an essential ion necessary for the synthesis of the two hormones produced by the thyroid gland, triiodothyronine (T_3) and thyroxin (T_4).



Triiodothyronine (T_3)



Thyroxine (T_4)

Iodine (Iodide)

- Internally iodine or iodide can be administered , since iodine is reduced to iodide in the intestinal tract but more common iodide salts are administered because of solubility reasons.
- Iodine have :

1. biochemical role in thyroid hormone formation.
2. **Pharmacological action as:**
   a) *Fibrinolytic agent.*
   b) *Expectorant .*
   c) *Bactericidal agent.*

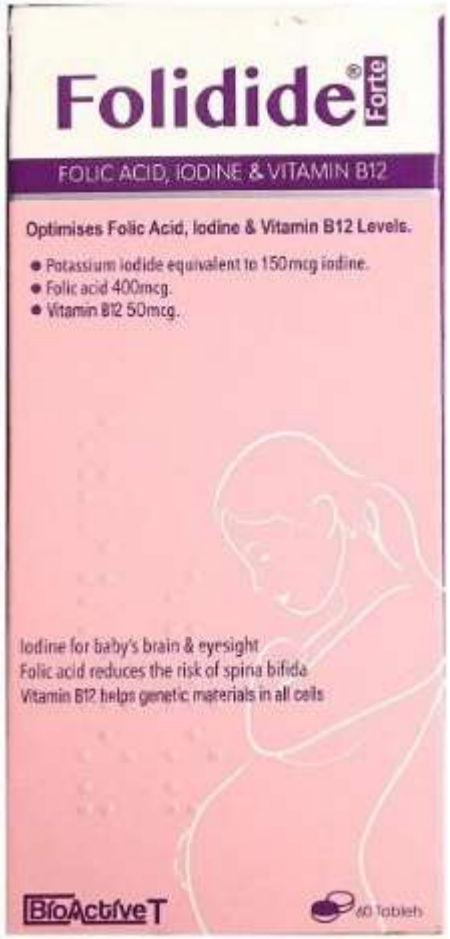
- The usual daily iodine requirement for an average male is 140 micrograms and female about 100 micrograms.
- Lack of sufficient iodine in diet result in an enlargement of thyroid gland.

Iodine (Iodide)

- When iodine is administered its uptake by the thyroid gland is governed by three principle factors:
  A. 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.
  B. Blood level of inorganic iodide because of high level keeps the iodine at high level in the colloids thus using up only a small part of the administered iodide.
  C. The level of TSH in blood which is a hormone secreted by pituitary gland which stimulates uptake of iodide by the gland, incorporate iodine into thyroxin, and stimulates the release of thyroid hormones from the gland.
- Excess of iodide inhibit release of TSH and decrease production of thyroid hormones.

Official Iodine Products

- Strong Iodine Solution, U.S.P. (Lugol's Solution)
  - Contains 5 g of iodine and 10 g of potassium iodide per 100 ml total volume.
  - It is a transparent liquid having a deep brown colour and odour of iodine.
  - Category: Source of iodine.
  - Usual Dose: 0.1 to 0.3 ml three times a day.
  - Usual Dose Range: 0.1 to 3 ml daily.



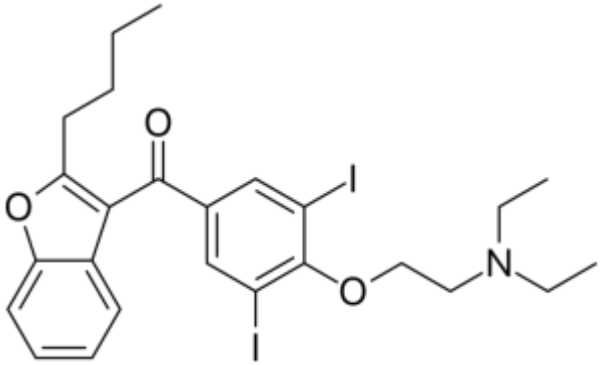
- iodine for Baby brain and eye sight

Amiodarone

- **Amiodarone** is an antiarrhythmic medication used to treat and prevent a number of types of cardiac dysrhythmias.

- Amiodarone is structurally similar to thyroxine and also contains iodine. Both of these contribute to the effects of amiodarone on thyroid function.

- Amiodarone also causes an anti-thyroid action, via Wolff–Chaikoff effect, due its large amount of iodine in its molecule, which causes bradycardia and arrhythmia.



QUIZ

Q1/ Identify the subshell in which electrons with the following quantum numbers are found:

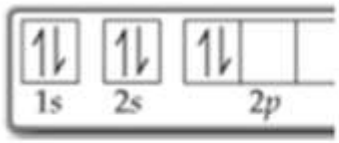
- **n = 2, l = 2**
- **n = 1, l = 0**
- **n = 5, l = 3**
- **n = 5, l = 0**

Q2/ Which guideline, Hund's rule or the Pauli exclusion principle, is violated in the following orbital diagrams

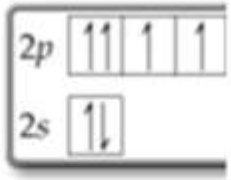
8. For the following five diagrams, list which one(s) violate the Aufbau Principle, Hund's Rule or the Pauli Exclusion Principle.

Violates Aufbau: Violates Hund's Rule: Violates Pauli Exclusion:

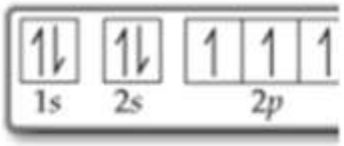
A



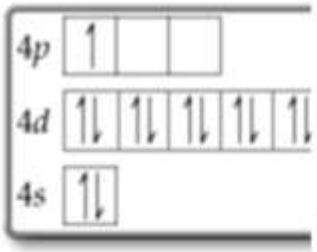
B



C



D



E