Inorganic Pharmaceutical Chemistry:

Non essential ions

Assistant Lecturer: Hasanain Salah

3rd Year Pharmacy

Faculty of Pharmacy/ Al-Muthanna University

2023/2024

Introduction

- The ions discussed in this chapter are currently considered nonessential, even though some of them have a beneficial pharmacological action in appropriate dosage.

- In the context of inorganic pharmaceutical chemistry, the term "non-essential ions" typically refers to ions that are not required for normal physiological functions or are not essential components of the human body.

Fluoride

- Fluorides are widely used today for their anticariogentic action (inhibition of dental cavity development).
- When fluoride is taken orally, approximately 95% is absorbed, and the balance is excreted in the feces. About 50% of the ingested fluoride is excreted in the urine.
- While some fluoride is excreted in perspiration, the balance is retained in the bone and is released very slowly to be excreted in the urine.
- There seems to be an excellent margin of safety between the effective dose of 2.2 mg sodium fluoride per day for the prevention of caries and the acute lethal dose of 4 g.
- Sodium fluoride, in toxic doses, is a general protoplasmic poison that inhibits enzyme activity. A double-blind study of human subjects ingesting a controlled daily dose of 5 mg fluoride ion (equivalent to an average daily intake of water fluoridated at 5 ppm) for three months showed a 20% reduction in alkaline phosphatase activity.

❑*Fluoride Mouth Rinse*

- The most common fluoride compound used in mouth rinse is sodium fluoride.
- Over-the-counter solutions of 0.05% sodium fluoride (230 ppm fluoride) for daily rinsing are available for use by persons older than 6 years of age.

➢Mechanisms of Action of Fluoride for Caries Control

- Fluoride works primarily via topical mechanisms which include (1) inhibition of demineralization at the crystal surfaces inside the tooth, (2) enhancement of remineralization at the crystal surfaces (the resulting remineralized layer is very resistant to acid attack), and (3) inhibition of bacterial enzymes.
- Sugars are the pivotal, negative factor, responsible for caries lesion progression.
- The acid pH produced from the fermentation of dietary sugars not only provokes dissolution of the underlying dental minerals but also selects the biofilm formed by the most cariogenic bacteria.
- Sucrose is the most cariogenic because besides being easily fermented into acids, it is the only carbohydrate that changes the matrix of the biofilm formed, making the biofilm more cariogenic.

- Every time sugar is ingested, biofilm bacteria produce acids and, consequently, the pH drops in the biofilm fluid. Thus, pH is the driving force governing the loss or gain of Ca and Pi from the mineral structure of the teeth. While pH remains below around 6.5 for dentin and 5.5 for enamel, the minerals of these tissues are dissolved (demineralization).
- Fluoride interferes with the caries process, reducing demineralization and enhancing remineralization of enamel and dentin.
- This physico-chemical mechanism occurs every time sugar is ingested and the pH falls in biofilm fluid; if fluoride is present, the amount of mineral dissolved is reduced because part of Ca and Pi is lost as hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ returns to the tooth as fluorapatite $Ca_{10}(PO_4)_6F_2$ (reduction of demineralization) (Fig. 2a).
- When the ingestion of sugar ceases and the pH rises again, fluoride present in the oral fluids enhances the natural phenomenon of remineralization (Fig. 2b).
- As a consequence, the progression of caries lesions is slowed down.

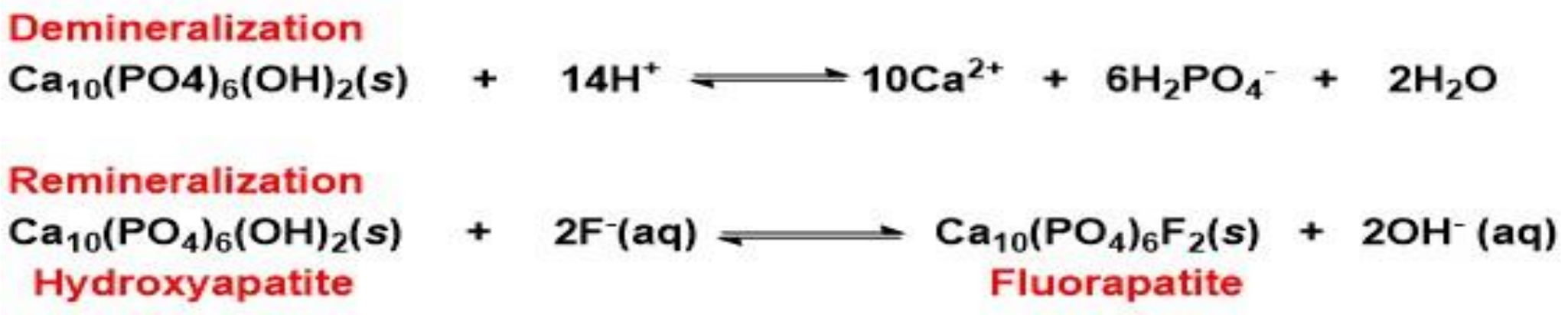


Fig. 1

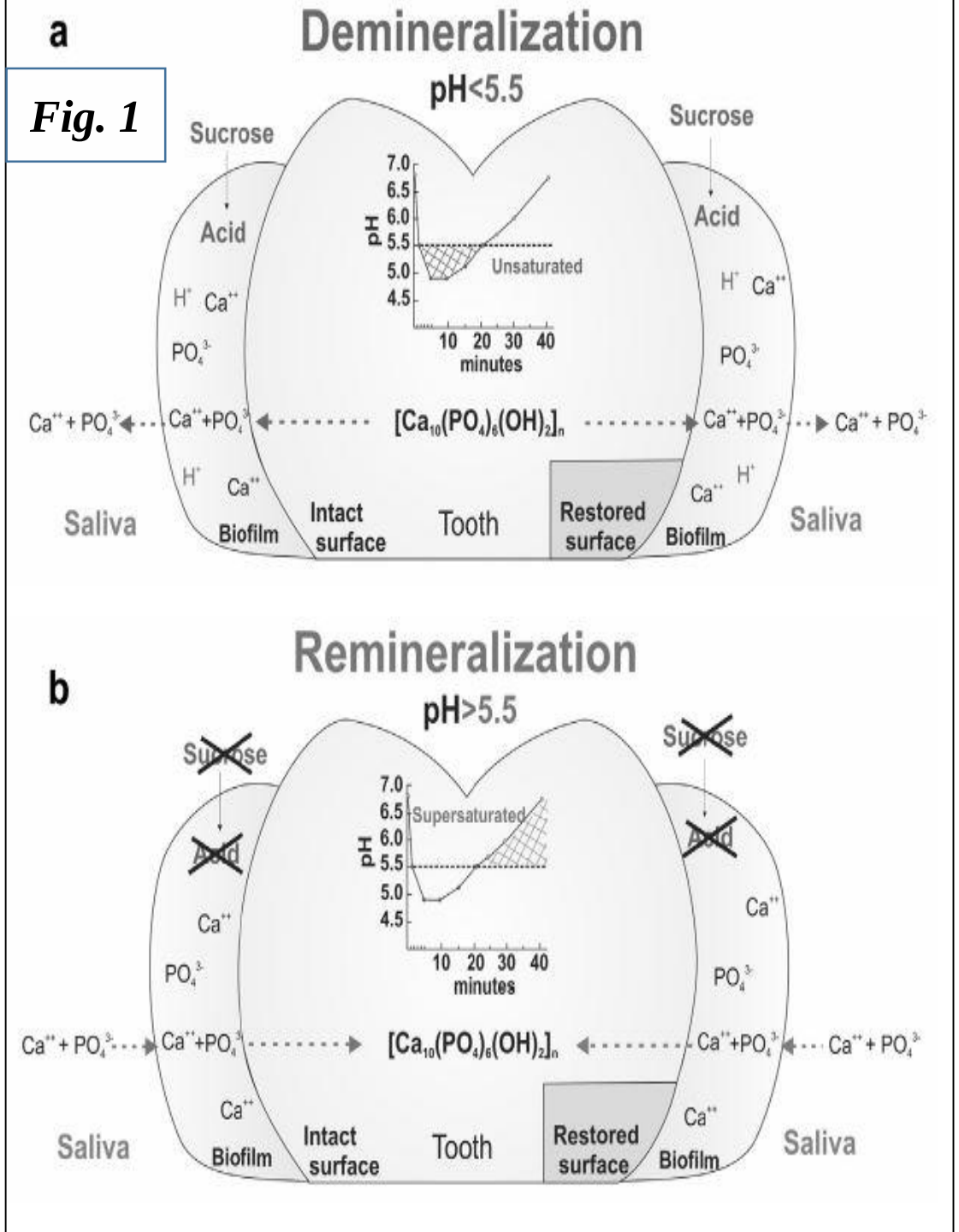
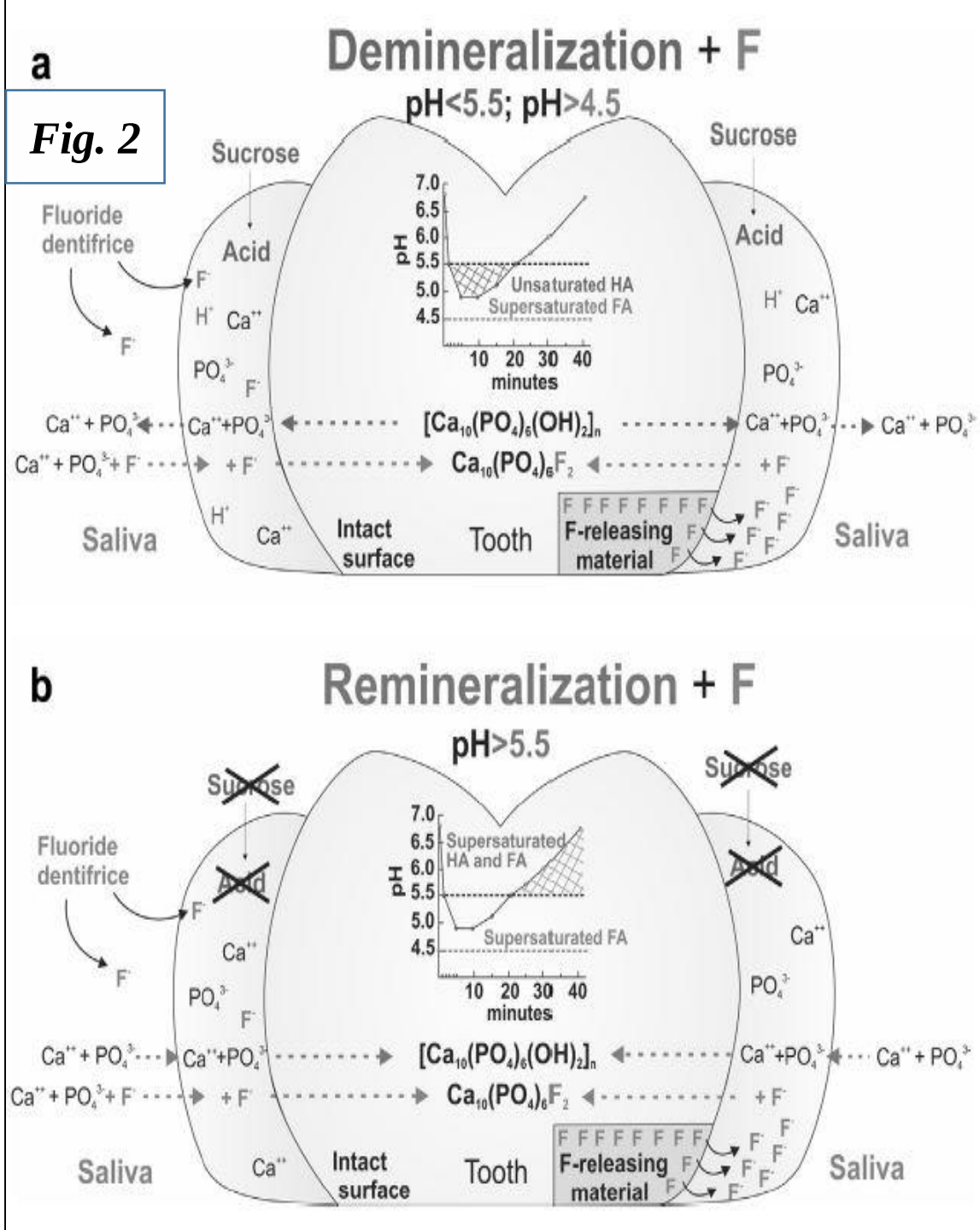

a
Demineralization
pH<5.5
Sucrose
Acid
Unsaturated
pH
minutes
$[Ca_{10}(PO_4)_6(OH)_2]_n$
$Ca^{++} + PO_4^{3-}$
Saliva
Biofilm
Intact surface
Tooth
Restored surface
b
Remineralization
pH>5.5
Supersaturated

Fig. 2


a
Demineralization + F
pH<5.5; pH>4.5
Sucrose
Acid
Fluoride dentifrice
Unsaturated HA
Supersaturated FA
pH
minutes
$[Ca_{10}(PO_4)_6(OH)_2]_n$
$Ca_{10}(PO_4)_6F_2$
Saliva
Intact surface
Tooth
F-releasing material
b
Remineralization + F
pH>5.5
Supersaturated HA and FA
Supersaturated FA

Bromides

- Bromides have been a standard form of medication for epileptiform seizures. Their usefulness in epilepsy depends on their ability to depress the motor areas of the brain, an effect brought about by large doses.
- Administration of small doses (0.5 to 2 g) of a bromide (e.g., KBr) serves to cause a depression of the central nervous system.
- Larger doses (4 to 8 g) depress all reflexes and cause a narcotic type of effect.
- The use of repeated small doses for a sedative effect depends on the abovementioned depression of the central nervous system.
- Bromides are rapidly absorbed and are excreted principally in the urine.
- Repeated doses tend to cause accumulation with a consequent replacement of chloride ions by accumulated bromide ions.
- The administration of sodium chloride tends to hasten the elimination of bromide.
- The distribution of bromide ions in the body is virtually the same as that of chloride ions.

- The early signs of bromide intoxication include insomnia and restlessness as well as dizziness, weakness, and headache.

- A skin rash known as bromide acne often occurs with bromism. Bromide psychosis (mental disease) may also be induced by long-continued use of bromides. Death from bromides is rare, and the symptoms.

- The suspected mechanism of action of bromide anticonvulsants is hyperpolarization of the neuron via the movement of the bromide ions intracellularly through chloride channels. Bromide is administered as a compounded KBr or NaBr product. Bromide is not metabolized and is excreted unchanged in the urine.

- Today there is no bromide salt or combination product that is official. The product on the market associated with bromide therapy, Bromo-Seltzer contains 162.5 mg potassium bromide per capful (maximum of 6 capfuls per day).

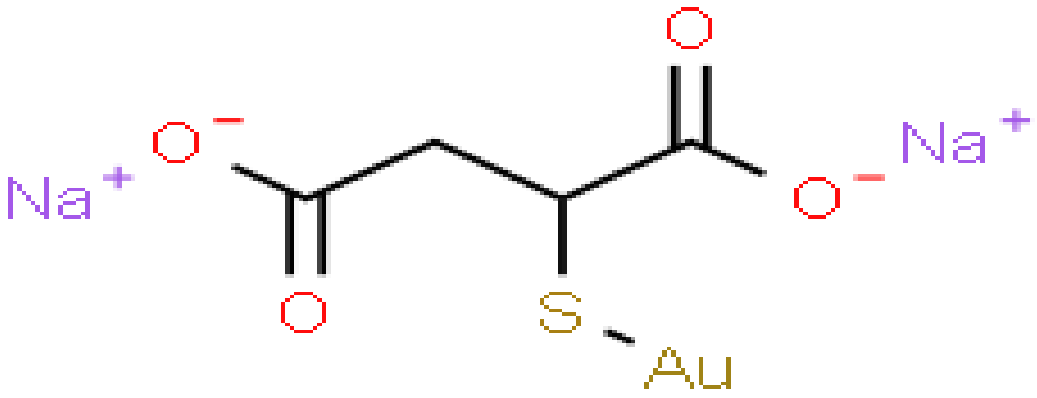
Gold

- The current use of gold (chrysotherapy) in rheumatoid arthritis is based on the early belief that this disease was an atypical form of tuberculosis.
- Therapeutic gold compounds are administered by **intramuscular injections**.
- The gold rapidly enters the plasma where it remains bound to albumin for several days.
- Orally administered gold is poorly and erratically absorbed.
- Gold is toxic. It is slowly excreted by the kidney and will accumulate in the body.
- Much of the time, cessation of gold administration and supportive treatment are adequate to remove the toxic effects.
- If gold toxicity is severe, **dimercaprol** can be used to remove the accumulated gold from the body.
- Gold should not be given to individuals with renal disease, a history of infectious hepatitis, skin or blood disorders, diabetes, pregnancy, hypertension, or congestive heart failure.
- Gold-based compounds typically accumulate in the kidneys, where they are nephrotoxic and cause a leakage of proteins at the glomerulus.

Gold Therapy

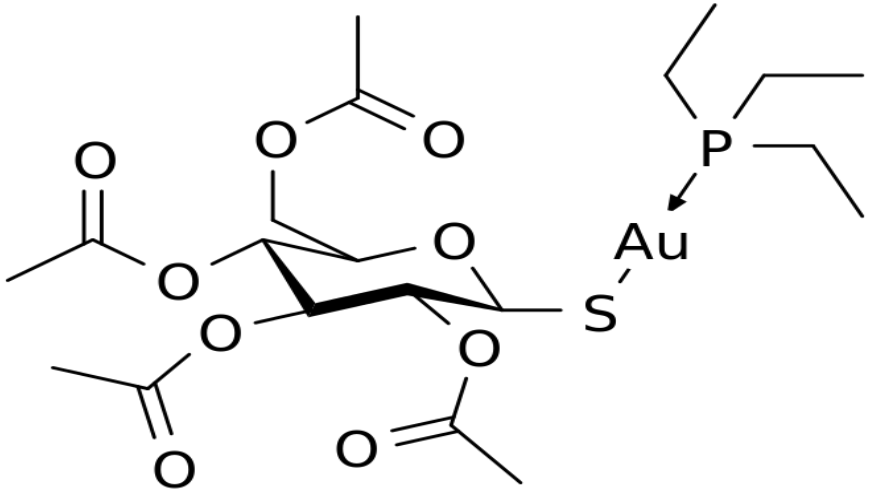
- Au(I)thiolates, such as aurothioglucose, disodium aurothiomalate, and trisodium bis(thiosulfate)gold, are the first-generation gold-based drugs and/or disease-modifying antirheumatic drugs (DMARDs).
- They feature linear, two-coordinated Au(I) thiolates and are polymeric with the exception of trisodium bis(thiosulfato)gold.
- The thiolate group stabilizes the oxidation state of +1 for the gold atom and therefore hinders disproportionation to Au^0 and Au(II).
- ***Sodium aurothiomalate*** is a commonly used gold-based DMARD and is indicated for active progressive RA. It is administered by deep intramuscular injection.
- Administration is started with a test dose of 10mg followed by weekly intervals of 50 mg doses.

- An improvement is expected to be seen once 500 –300mg is administered.
- Treatment should be discontinued if there is no improvement after administering 1 g or 2 months. Intervals of administration should be gradually increased to 4 weeks in patients in an effect can be seen.
- If any blood disorders or other side effects such as GI bleeding or proteinuria are observed, sodium aurothiomalate should be discontinued.



❑*Metabolism of gold drugs*

- The precise mechanism of action is not known, but most probably it involves a thiol exchange.
- This means that the thiolate ligand will be replaced by a biological thiol such as albumin, which is a major protein in the serum and is sulfur-rich.
- Cysteine-34, one of the cysteine residues in albumin, is likely to be deprotonated at physiological pH and is a likely target for the gold compounds.
- In the case of **Auranofin**, the triethylphosphine (Et_3P) is oxidized, whilst the disulfide link in the albumin is reduced, and the harmless oxidized species $Et_3P{=}O$ is excreted via the kidneys.



Lithium

- Lithium is a chemical element with the symbol Li and atomic number 3 with an oxidation state is +1.
- The lithium-ion is a depressant to the central nervous system and to circulation. The ion also has a diuretic action.
- Its toxic nature led to the discontinuance of lithium chloride as a component of salt substitutes used by patients on salt-free diets.
- Lithium is readily absorbed from the intestine and accumulates in the body. The extent of lithium accumulation is dependent upon the sodium intake. A decreased intake of sodium accelerates lithium accumulation and accentuates its toxic effects.
- Conversely, lithium intoxication is treated by withholding the lithium salt and providing an adequate sodium intake.
- The supposed advantage of administering lithium bromide was that there was more bromide available per unit weight of lithium bromide since lithium (At. Wt. 7) is so much lighter than sodium (At. Wt. 23), ammonium (Mol. Wt. 18), or potassium (At. Wt. 39).

Lithium Carbonate

- Lithium carbonate (Li_2CO_3; Eskalith, Lithonate, Lithane) is administered orally in doses of 300 to 600 mg three times a day to manic patients.
- The lower dose range is used for elderly patients in whom renal clearance is likely to be reduced.
- A phenothiazine tranquilizer usually is administered for the first few days since it takes three to ten days for lithium to become effective.
- Lithium carbonate should be discontinued if a satisfactory response is not obtained in 14 days.

✓Since lithium is toxic, serum lithium levels should be monitored.

✓A satisfactory range is 0.5 to 1.5 mEq Li/l with the upper level for the acute manic phase and about 1 mEq/l for maintenance.

✓Due to its toxic effects, and because it is excreted by the kidneys, if blood levels of lithium are elevated lithium carbonate is contraindicated in patients with impaired renal function.

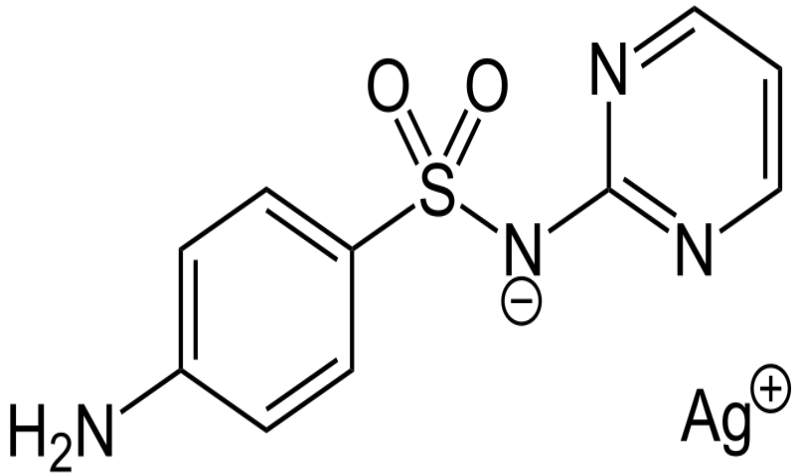
Silver

- Silver is a chemical element with the symbol Ag and atomic number 47.
- Silver has no known active biological role in the human body, and the levels of Ag(I) within the body are below detection limits.
- Silver ion, in common with other heavy metals is a protein precipitant.
- The action of silver ions on tissue ranges from antiseptic, astringent, and irritant to corrosive, as the concentration of free silver ions increases.
- Silver ion in sufficient concentration is corrosive to the mucosa of the digestive tract.
- The toxic dose of silver nitrate has been stated to be about 10 g, although survival has been noted with larger doses.
- Whenever silver preparations are used for long periods of time they can cause discoloration of the skin called **argyria**.
- Since this reduction is facilitated by light (as in photographic emulsion), those portions of skin exposed to light are more likely to become discolored.

- It has been proposed that silver ions irreversibly damage key enzymes in the cell membrane of bacteria. This would lead to an inactivation of the pathogen.
- Silver reacts, as many other transition metals, preferentially with the thiol groups and also amino, carboxyl, phosphate and imidazole groups.

❑*Silver(I) Sulfadiazine*

- Silver sulfadiazine is indicated for the prophylaxis and treatment of infections in burn wounds.
- Silver sulfadiazine is highly insoluble in water, and as a result, it does not cause hypochloraemia in burns in contrast to silver nitrate.
- The active ingredient silver sulfadiazine is a sulfur-derived topical antibacterial used primarily on second and third-degree burns.

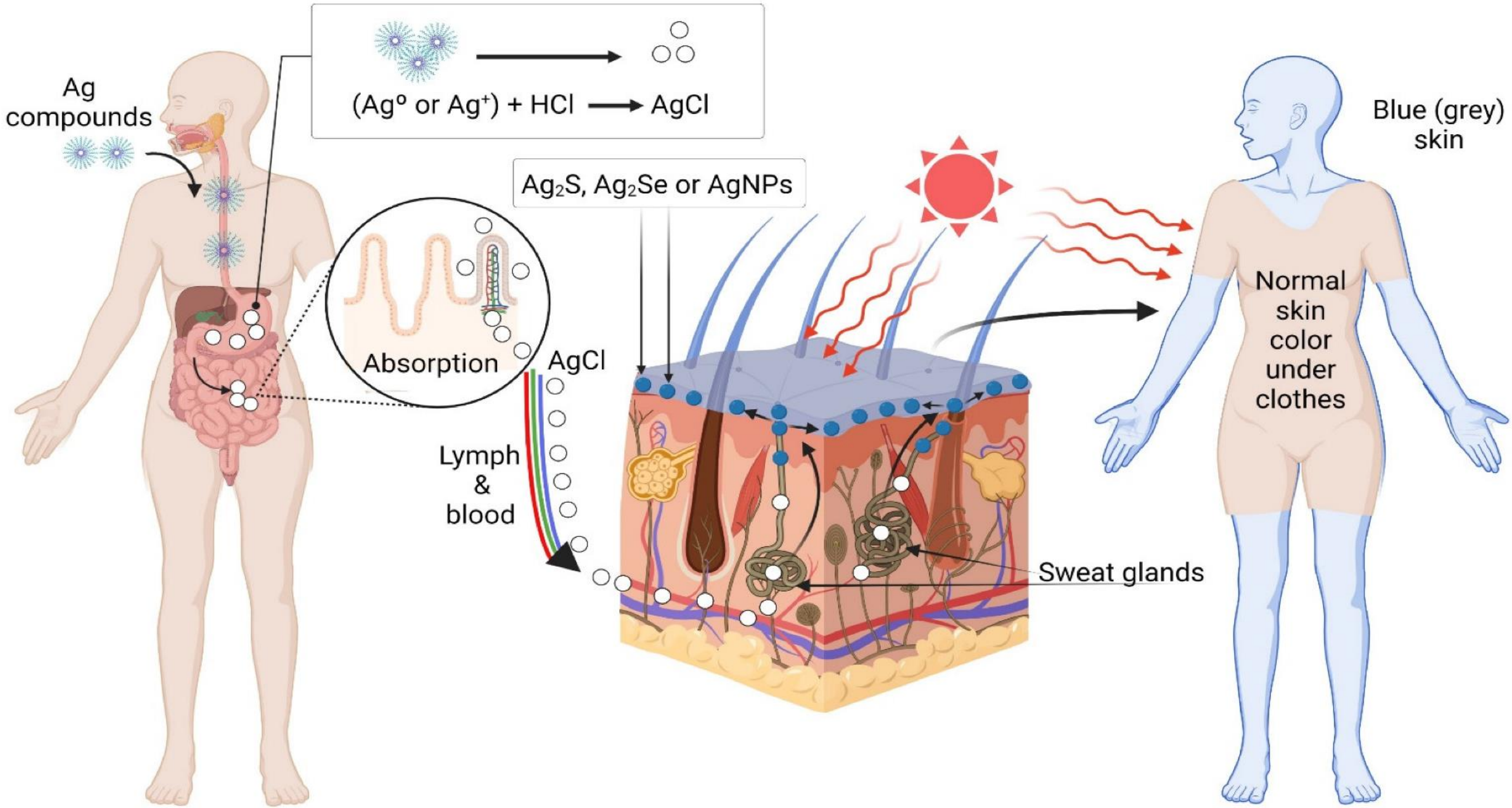


Argyria

- Argyria is an acquired skin condition that appears after the exposure or consumption of silver, leading to blue or grey coloration of the skin and mucosa.
- For many of metals, sweating is an important mechanism for removing them from the body.
- When silver compounds enter the body, it is logical to assume that silver, like other metals, represents part of sweat, presumably in the form of a complex of silver chloride with sweat components and/or in the form of a sol.
- The uniqueness of silver in comparison with other metals lies in the high photosensitivity of its compounds.
- When a silver complex in sweat enters the near-surface layers of the skin, under the influence of sunlight, the ionic silver is reduced, forming the nuclei of metallic silver particles.
- With the further supply of ionic silver, these particles gradually grow and are visualized, and the skin acquires the corresponding color.

- Mechanism of Skin Argyria
- First, silver compounds are orally consumed by an individual.
- In the stomach, these compounds (silver salts or nanoparticles [NPs]) interact with HCl and are converted into **AgCl** and pass into the intestine, where they are absorbed into the blood and lymphatic fluid as Ag-proteinates and AgCl.
- Blood and lymphatic fluid deliver these silver compounds into sweat glands.
- From sweat glands, they move through sweat pores with sweat fluid to the skin surface, converting into grey and blue compounds (Ag_2S, Ag_2Se, and AgNPs) under light irradiation.

- Argyria is irreversible, although it is said that injection of 6% sodium thiosulfate and 1% potassium ferricyanide subcutaneously will remove the color.
- This treatment requires numerous small injections in the affected area.
- Chelating agents are not effective since argyria involves free rather than ionized silver.

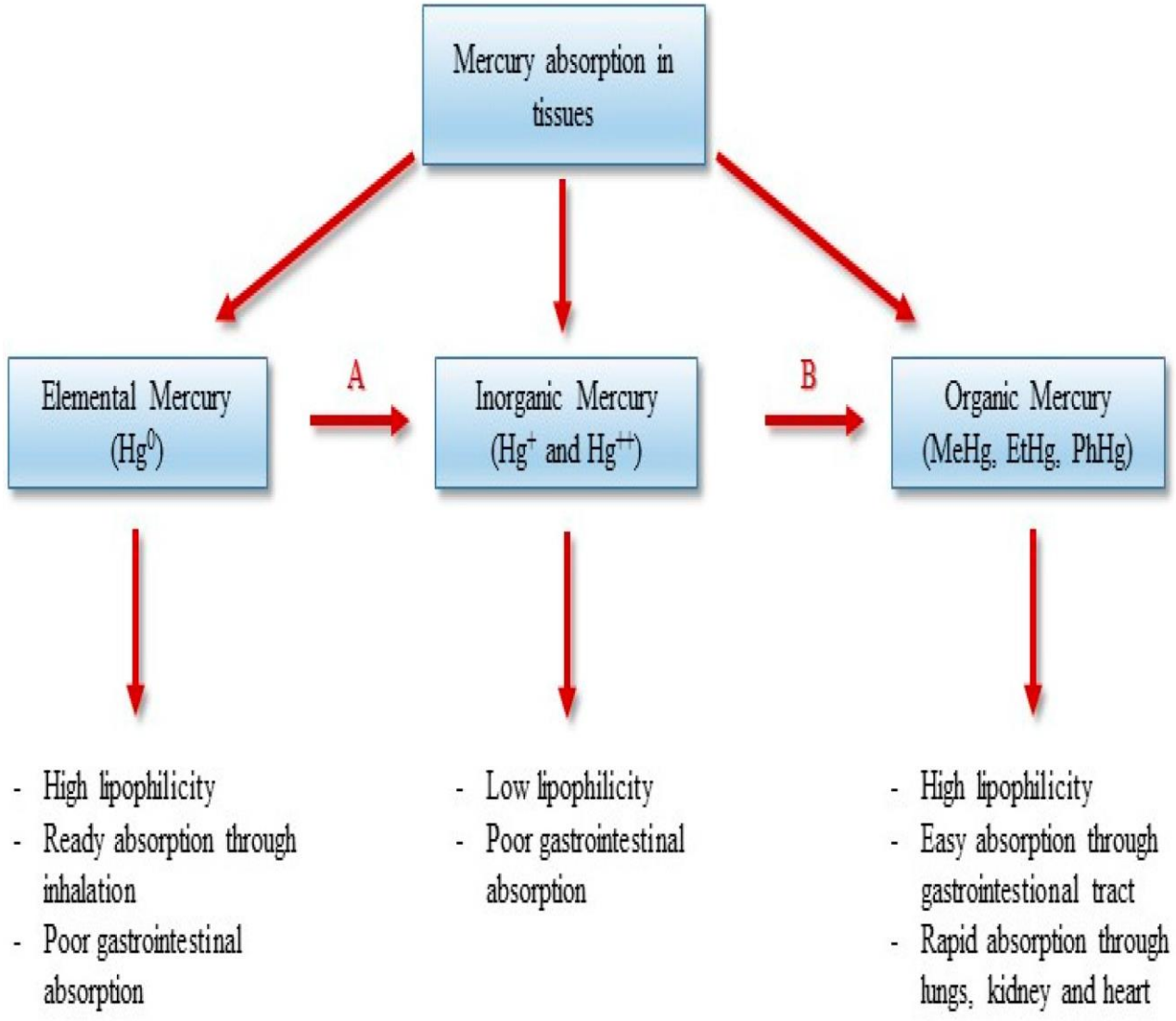

Ag compounds
(Ag⁰ or Ag⁺) + HCl → AgCl
Ag2S, Ag2Se or AgNPs
Absorption
AgCl
Lymph & blood
Sweat glands
Blue (grey) skin
Normal skin color under clothes

Mercury

- Mercury is a chemical element with the symbol Hg and atomic number 80.
- The mercury salts used topically are, for the most part, water-insoluble and can be considered nontoxic for short-term use on intact skin.
- Metallic mercury is relatively nontoxic. The mercurous (Hg^{+}) and mercuric (Hg^{2+}) cations that are toxic
- Mercury vapor, however, is toxic. It is believed that mercury as a finely divided vapor is more readily oxidized and is absorbed through bronchi.
- The toxic effects of mercury, like those of lead and arsenic, are due to its combining with protein sulfhydryl groups. Indeed, the other common name for sulfhydryl groups, mercaptans, is based on the ability of sulfur atoms to bind or capture mercury. Once absorbed, the mercuric cation concentrates mostly in the kidney with a lower concentration in the liver, blood, bone marrow, and other tissues.
- Treatment includes gastric lavage, the use of a reducing agent such as sodium formaldehyde sulfoxylate ($Na[HOCH_2SO_2]$) to reduce the mercuric cation forming less soluble mercurous salts, and the use of chelating agents such as dimercaprol or penicillamine.

- Mercury and its salts have enjoyed several uses in therapeutics. Almost all therapeutic applications may be looked upon as modifications of the principal action of the mercuric ion: combining with the sulfhydryl groups of proteins.
- Currently, mercurials are used as diuretics, antiseptics, parasiticides, and fungicides.

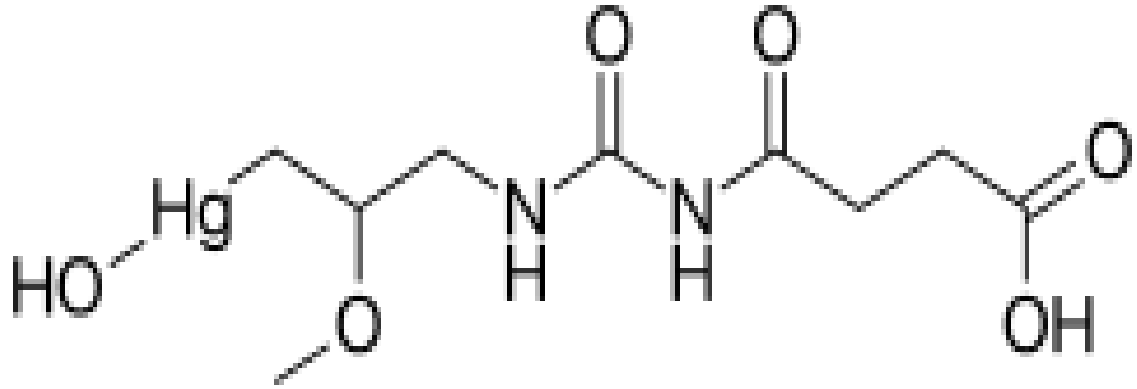
- The diuretic action of mercury salts, inorganic and organic, is due to a direct renal effect by mercuric ions. It is postulated that mercurial diuretics, by reacting with protein sulfhydryl groups, inactivate specific enzymes of the renal tubules, thus preventing sodium ion reabsorption in the proximal tubule and thereby bringing about a sodium and water diuresis.
- Acid-forming salts such as ammonium chloride potentiate the diuretic action of mercurials and the alkalizing salt sodium bicarbonate inhibits the diuretic action.



Official Mercury Products

❑***Meralluride Injection,*** U.S.P. XVIII ($C_{16}H_{22}HgN_6O_7$; Mol. W.t 610.98; Mercuhydrin)

- Meralluride U.S.P. occurs as a white to slightly yellow powder which is slowly affected by light. Its saturated solution is acid to litmus. Meralluride is slightly soluble in water, and soluble in hot water and in glacial acetic acid.
- Usual Dose: Parenteral,1 ml of the injection equivalent to 39 mg of mercury and 43.6 mg of anhydrous theophylline (48 mg of hydrous theophylline) one or two times a week.
- The usual Dose Range: is 1 to 2 ml.



❑***Sodium Mercaptomerin***, U.S.P. XVIII ($C_{16}H_{25}HgNNa_2O_6$; Mol. W.t 606.01; Thiomerin Sodium)

- Sodium Mercaptomerin, U.S.P occurs as a white hygroscopic powder or amorphous solid having a characteristic honeycomb structure. It is freely soluble in water, soluble in alcohol, and slightly soluble in chloroform and in ether. Its solution must be protected from light.
- Usual Dose: Parenteral, 125 mg once a day
- Usual Dose Rang: 25 to 250 mg daily to weekly.
- Occurrence
- Sodium Mercaptomerin Injection, U.S.P. XVIII
- Sterile Sodium Mercaptomerin, U.S.P. XVIII