Bioinorganic Chemistry:

Metal ions present in biological systems, classification of elements according to their action in biological system. Geochemical effect on the distribution of metals. Sodium / K-pump, carbonic anhydrase and carboxypeptidase. Excess and deficiency of some trace metals. Toxicity of metal ions (Hg, Pb, Cd and As), reasons for toxicity, Use of chelating agents in medicine.

Iron and its application in bio-systems, Haemoglobin; Storage and transfer of iron.

Carbonic Anhydrase

❖The **carbonic anhydrases** (or **carbonate dehydratases**) form a family of enzymes that catalyze the interconversion between carbon dioxide and water and the dissociated ions of carbonic acid (i.e. bicarbonate and hydrogen ions). The active site of most carbonic anhydrases contains a zinc ion. They are therefore classified as metalloenzymes. The enzyme maintains acid-base balance and helps transport carbon dioxide.

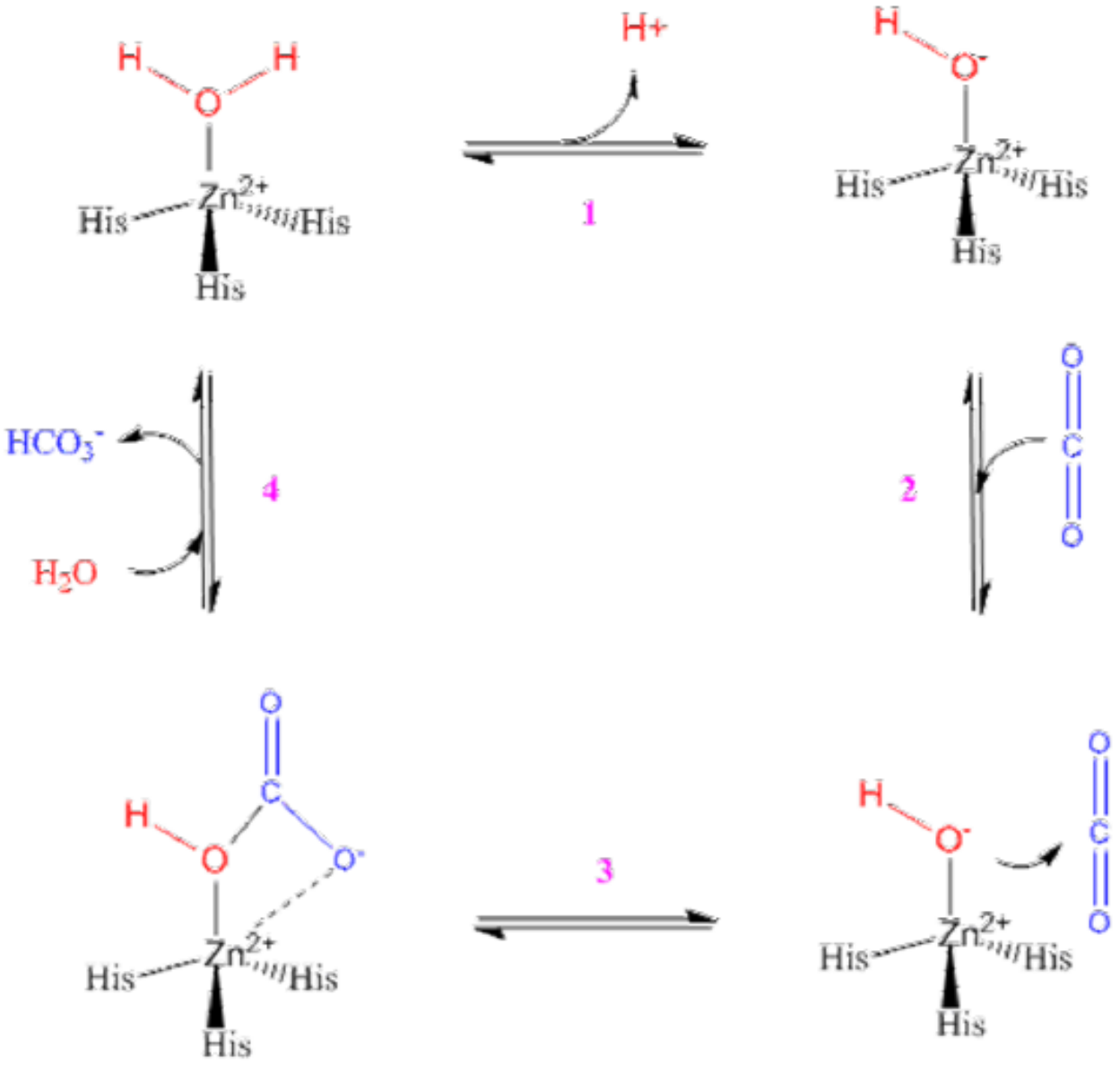
❖Carbonic Anhydraseis an enzyme that is located in red blood cells.

❖It contains about .31 to .34% zinc.

❖This is important because it's the first known direct physiological function of zinc.

$$H_2O + CO_2 \rightleftharpoons H^+ + HCO_3^-$$

Carbonic Anhydrase Mechanism

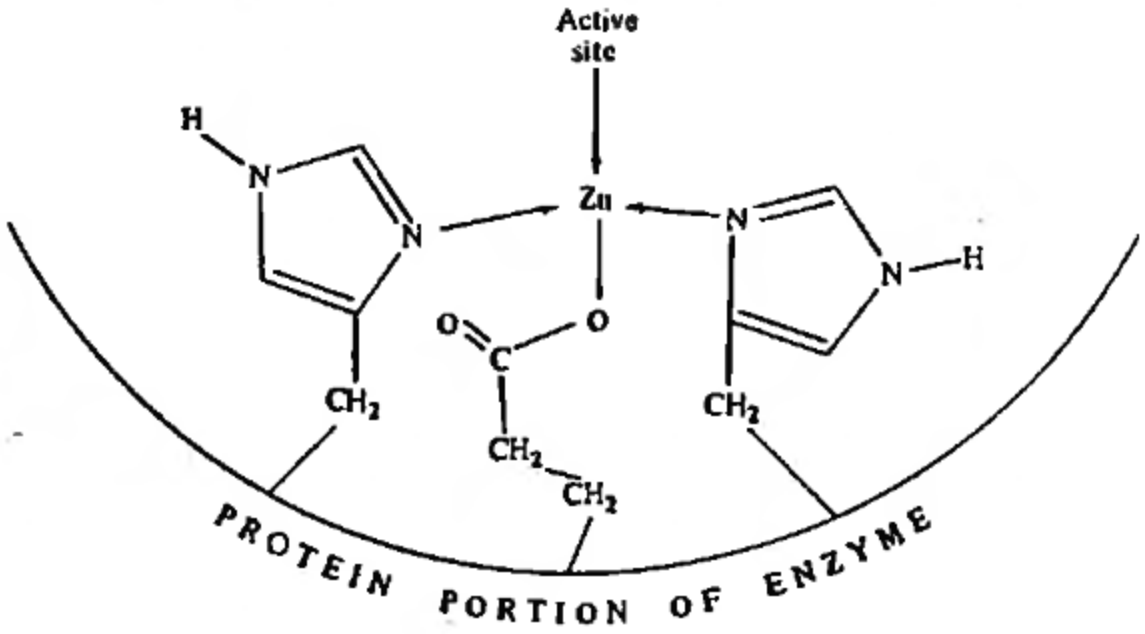


Carboxypeptidase

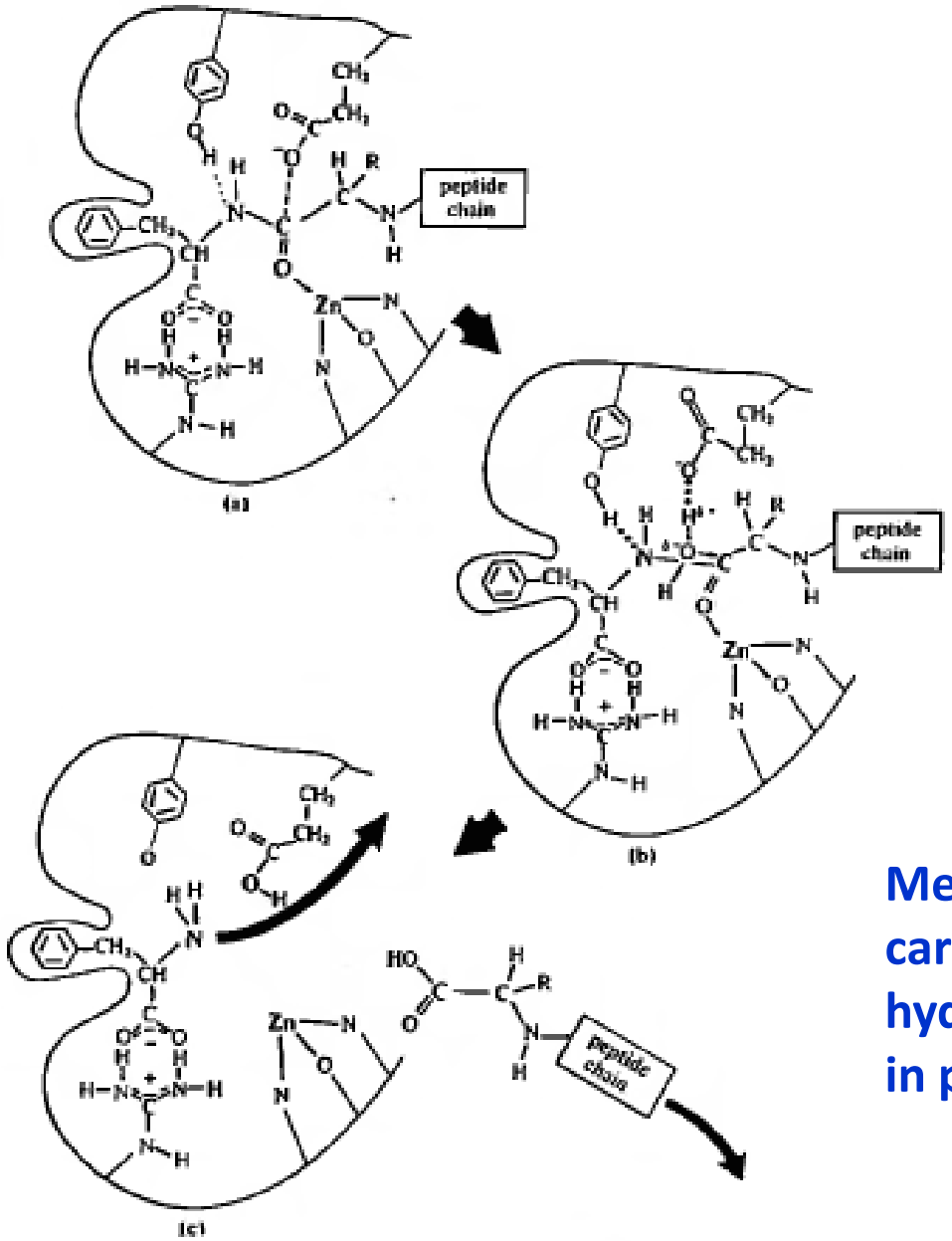
❖A carboxypeptidase is a protease enzyme that hydrolyzes (cleaves) a peptide bond at the carboxy-terminal (C-terminal) end of a protein or peptide. Humans, animals, bacteria and plants contain several types of carboxypeptidases that have diverse functions ranging from catabolism to protein maturation.

❖**Structure: Carboxypeptidase A** (CPA) contains a zinc (Zn^{2+}) metal center in a tetrahedral geometry with amino acid residues in close proximity around zinc to facilitate catalysis and binding. Out of the 307 amino acids bonded in a peptide chain, the following amino acid residues are important for catalysis and binding; Glu-270, Arg-71, Arg-127, Asn-144, Arg-145, and Tyr-248. The zinc metal is a strong electrophilic Lewis acid catalyst which stabilizes a coordinated water molecule as well as stabilizes the negative intermediates that occur throughout the hydrolytic reaction. Stabilization of both the coordinated water molecule and negative intermediates are assisted by polar residues in the active site which are in close proximity to facilitate hydrogen bonding. An active site of Carboxypeptidase A is shown in the figure.

Carboxypeptidase



Carboxypeptidase



Mechanism of action of carboxypeptidase A in the hydrolysis of an amide linkage in polypeptide.

Use of Chelating Agents in Medicine

Chelating agents are chemical compounds that react with metal ions to form a stable, water-soluble complex. They are also known as chelants, chelators, or sequestering agents. Chelating agents have a ring-like center which forms at least two bonds with the metal ion allowing it to be excreted. Chelating agents are usually organic compounds (a compound that contains carbon). Specific chelating agents bind iron, lead, or copper in the blood and can be used to treat excessively high levels of these metals. Chelating agents may also be used in the treatment of heavy metal poisoning.

Chelation therapy is a medical procedure that involves the administration of chelating agents to remove heavy metals from the body. Chelation therapy has a long history of use in clinical toxicology and remains in use for some very specific medical treatments, although it is administered under very careful medical supervision due to various inherent risks.

Use of Chelating Agents in Medicine

Chelation therapy Administration of chelating agents to remove heavy metal ions from body

Injecting Chelating agents (in liquid form) into body..

That form bonds with specific toxic metals like As, Hg, Pb

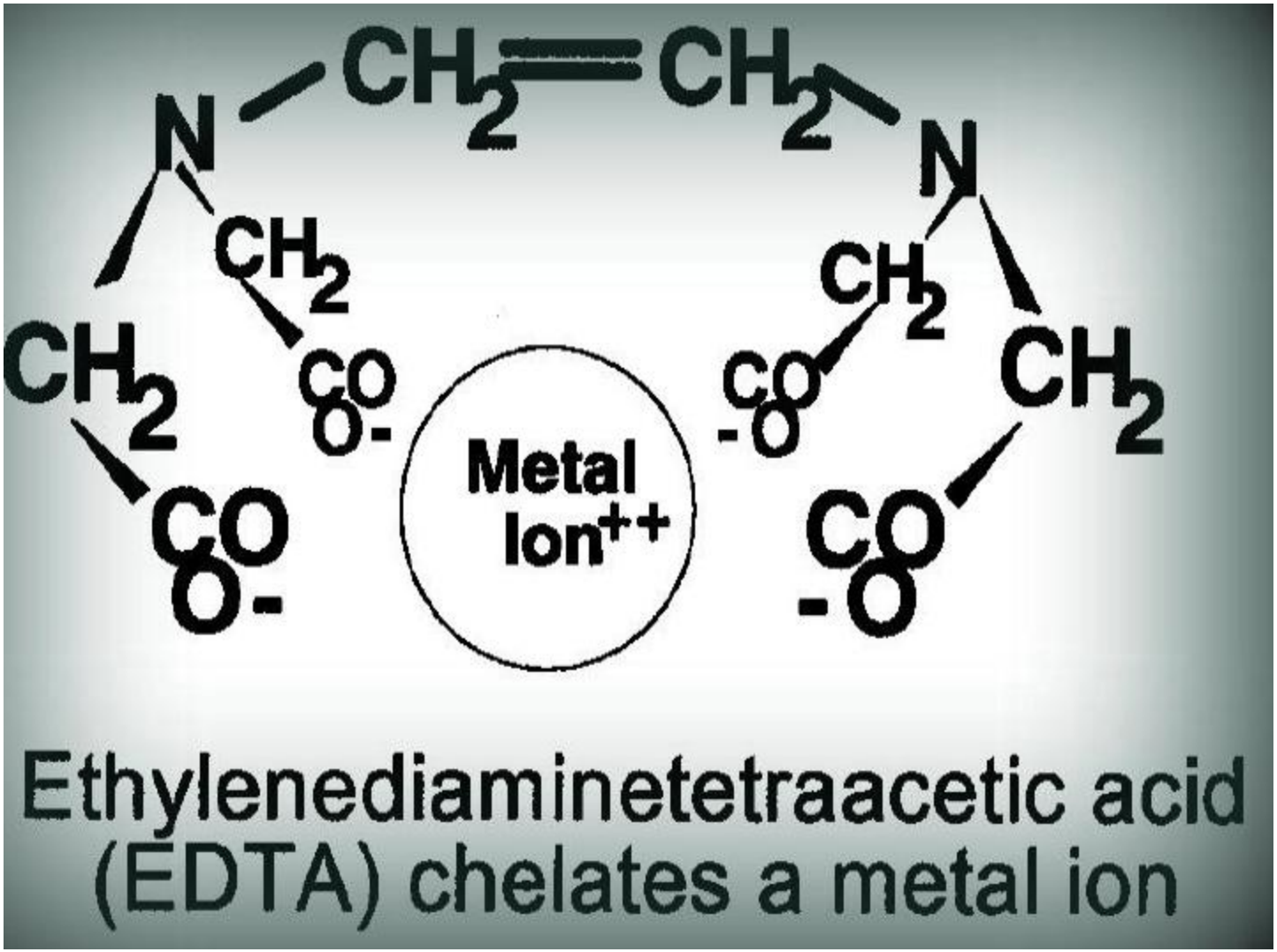
The toxic metals then extracted from that tissue or organ of the body

Both chelating agent and toxic metal are simply excreted from kidneys

Use of Chelating Agents in Medicine

Chelator	Used in
Dimercaprol (British anti-Lewisite; BAL)	• acute arsenic poisoning • acute mercury poisoning • Lead poisoning (in addition to EDTA) • Lewisite poisoning (for which it was developed as an antidote)
Dimercaptosuccinic acid(DMSA)	• Lead poisoning • arsenic poisoning • mercury poisoning
Dimercapto -propane sulfonate (DMPS)	• severe acute arsenic poisoning • severe acute mercury poisoning
Penicillamine	• *Mainly in:* copper toxicity *Occasionally adjunctive therapy in:* • gold toxicity • arsenic poisoning • Lead poisoning • rheumatoid arthritis
Ethylenediamine tetraacetic acid (calcium disodium versante) ($CaNa_2$-EDTA)	• Lead poisoning
Deferoxamine and Deferasirox	• acute iron poisoning • Iron overload

Use of Chelating Agents in Medicine



Use of Chelating Agents in Medicine

✓ EDTA Chelation therapy is a treatment that involves repeated intravenous administration of a chemical solution of ethylenediaminetetraacetic acid.

✓ Injected intravenously and once in the bloodstream, EDTA traps lead and other metals, forming a compound that the body can get rid of in the urine. The process generally takes 1-3 hours.

✓ Is regarded by the body as a foreign substance, so the body eliminates the entire particle - the heavy particle coated with EDTA.

✓ Has been used extensively in mainstream medical settings to remove the toxic metal lead from the human body.

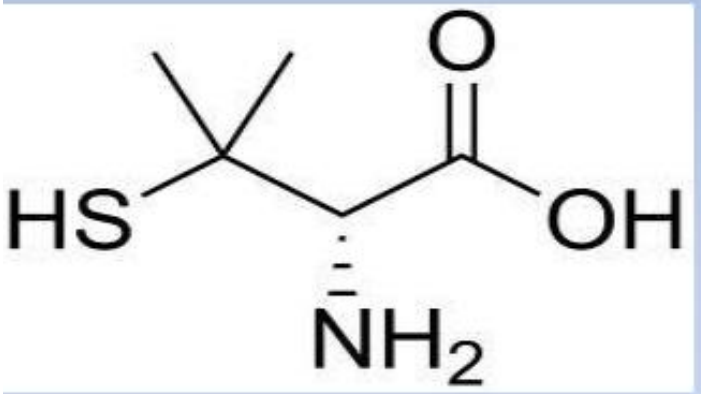
✓ Acts as a powerful antioxidant to protect blood vessels from free radical damage.

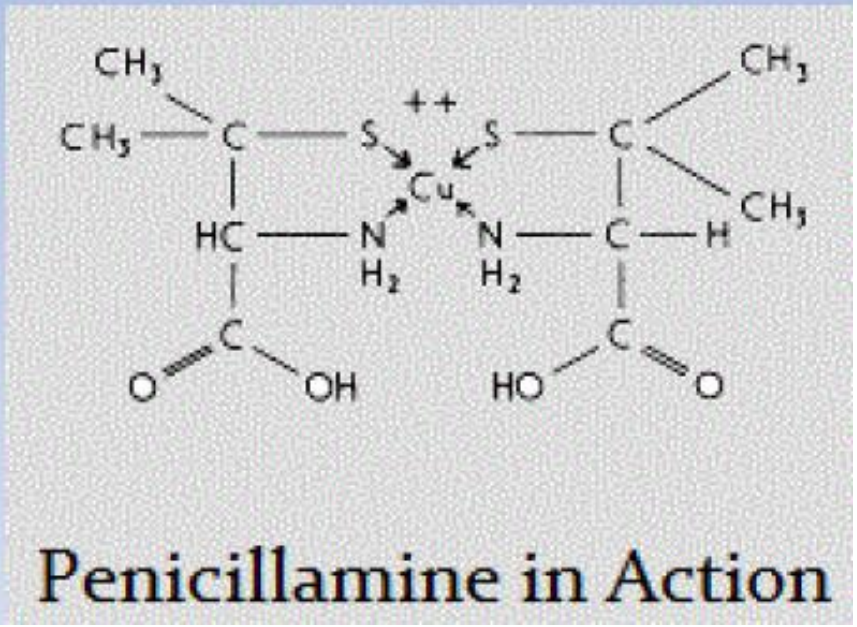
✓ EDTA chelation therapy is approved by the U.S. Food and Drug Administration (FDA) as a treatment for lead and heavy metal poisoning. It is used to treat acute and chronic lead poisoning by pulling toxins (including heavy metals such as lead, cadmium, and mercury) from the bloodstream.

Use of Chelating Agents in Medicine

D-Penicillamine/ Cuprimine/ Depen

(2*S*)-2-amino-3-methyl-3-sulfanyl-butanoic acid

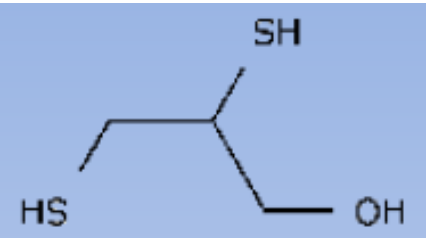




Penicillamine in Action

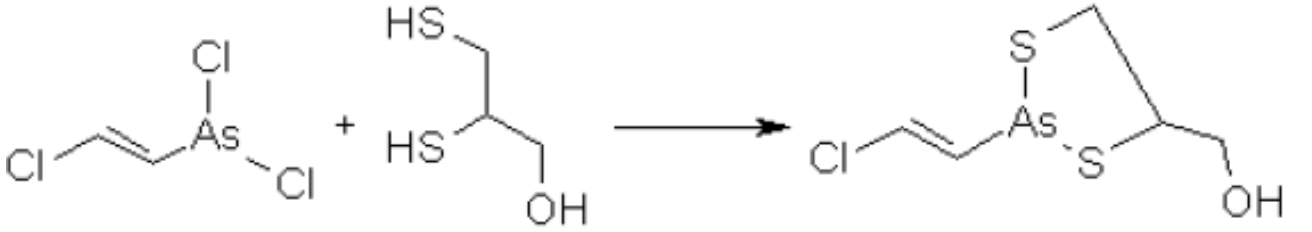
Use of Chelating Agents in Medicine

BAL/ British anti-Lewisite (Dimercaprol)



2,3-dimercaptopropanol

Lewisite Gas: $CH_2=CHAsCl_2$



USES:

In poisoning due to

1. Arsenic(10 days), gold(3 months), bismuth, antimony, thallium, mercury (until recovery); Pb, Hg

2. Oily solution of Dimercaprol instilled in to conjunctival sac in arsenic (vesicant) contamination of eye (within 5 min).

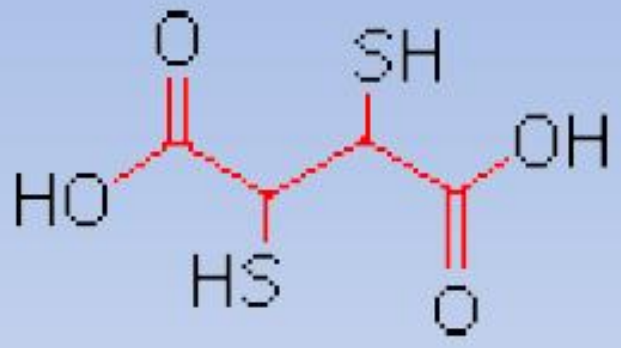
3. Wilson's disease – allergic to penicillamine; increases excretion of copper in urine.

Later on BAL was modified into DMSA

Use of Chelating Agents in Medicine

DMSA/ DIMERCAPTOSUCCINIC ACID

meso-2,3-dimercaptosuccinic acid (1995)

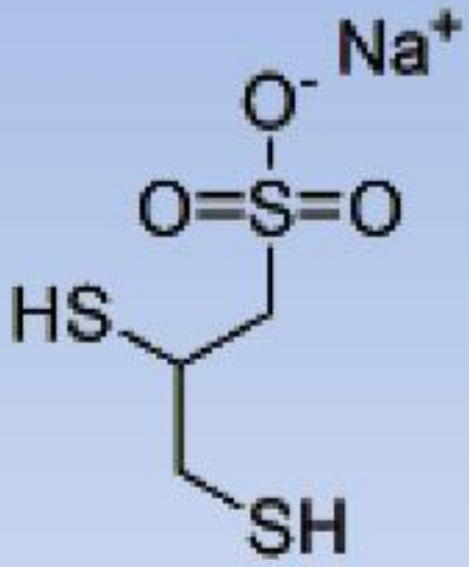


Hg, Pb

It can cross the blood brain barrier and is used for extracting heavy metal ions from brain.

Use of Chelating Agents in Medicine

DMPS/ Dimercapto -propane sulfonate Therapy
2,3,-dimercaptopropane-1-sulfonate (1956)



Used in heavy metal poisining of Po_{210}