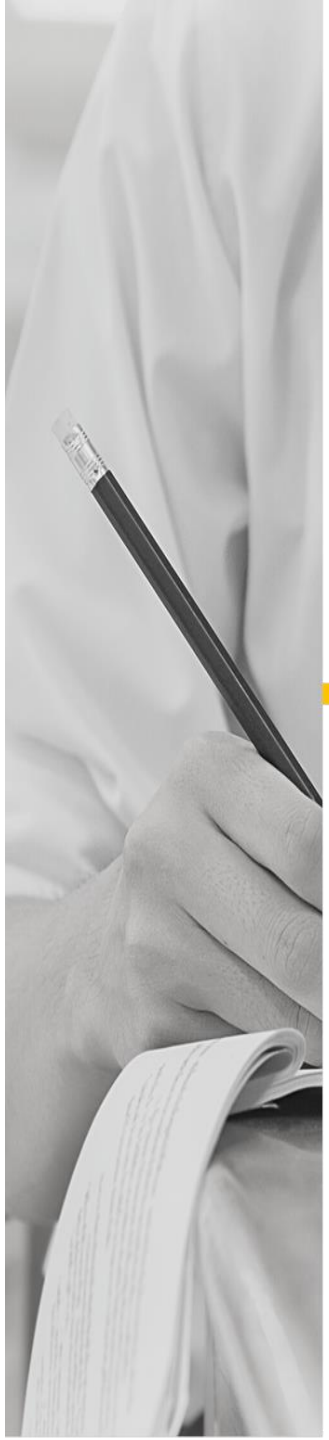

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Subject year: MSc - PHARMA

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PHAMACOLOGY MASTER – DRUG EVALUATION

HEAVY-METAL ANTAGONISTS

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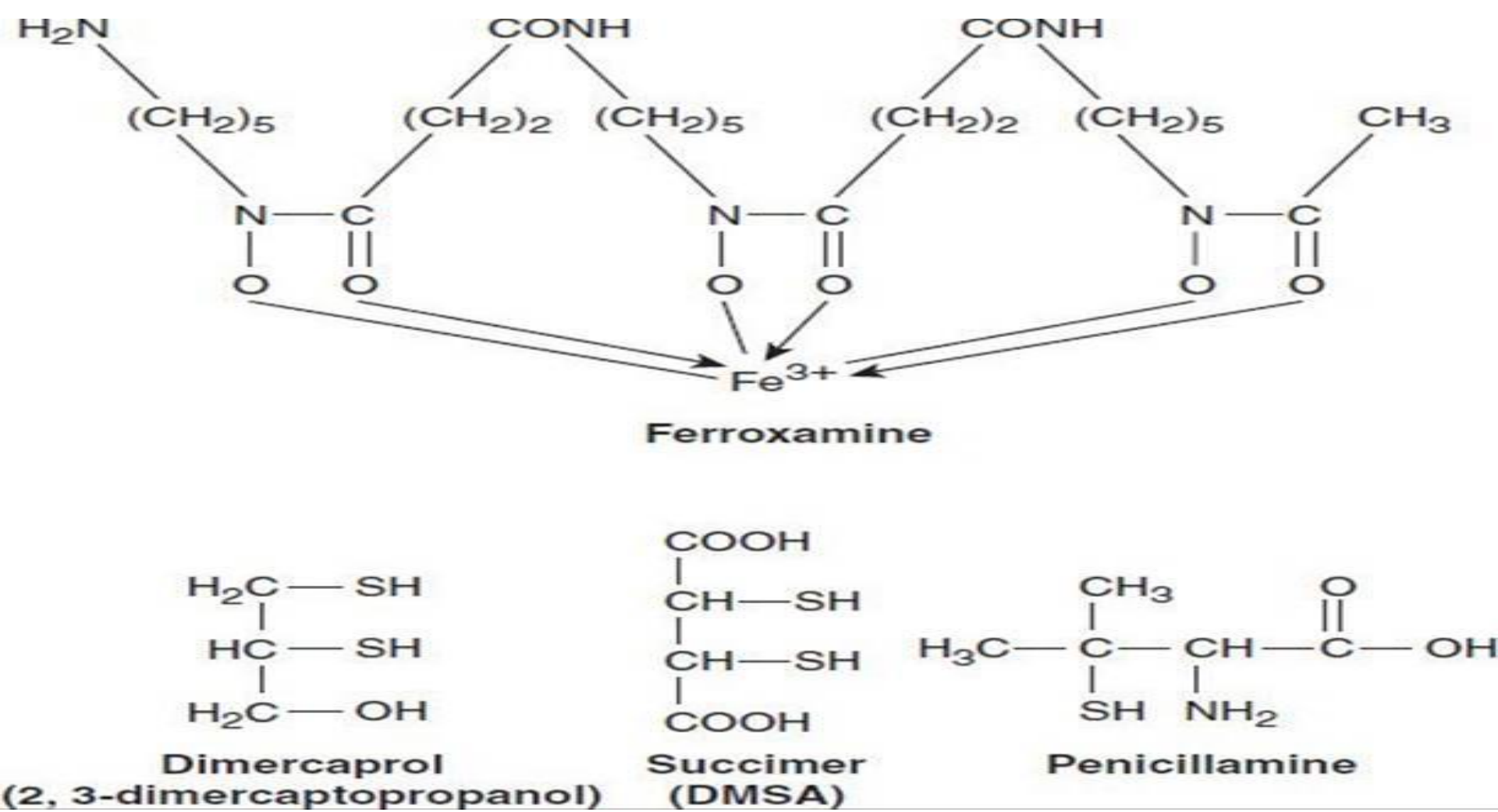
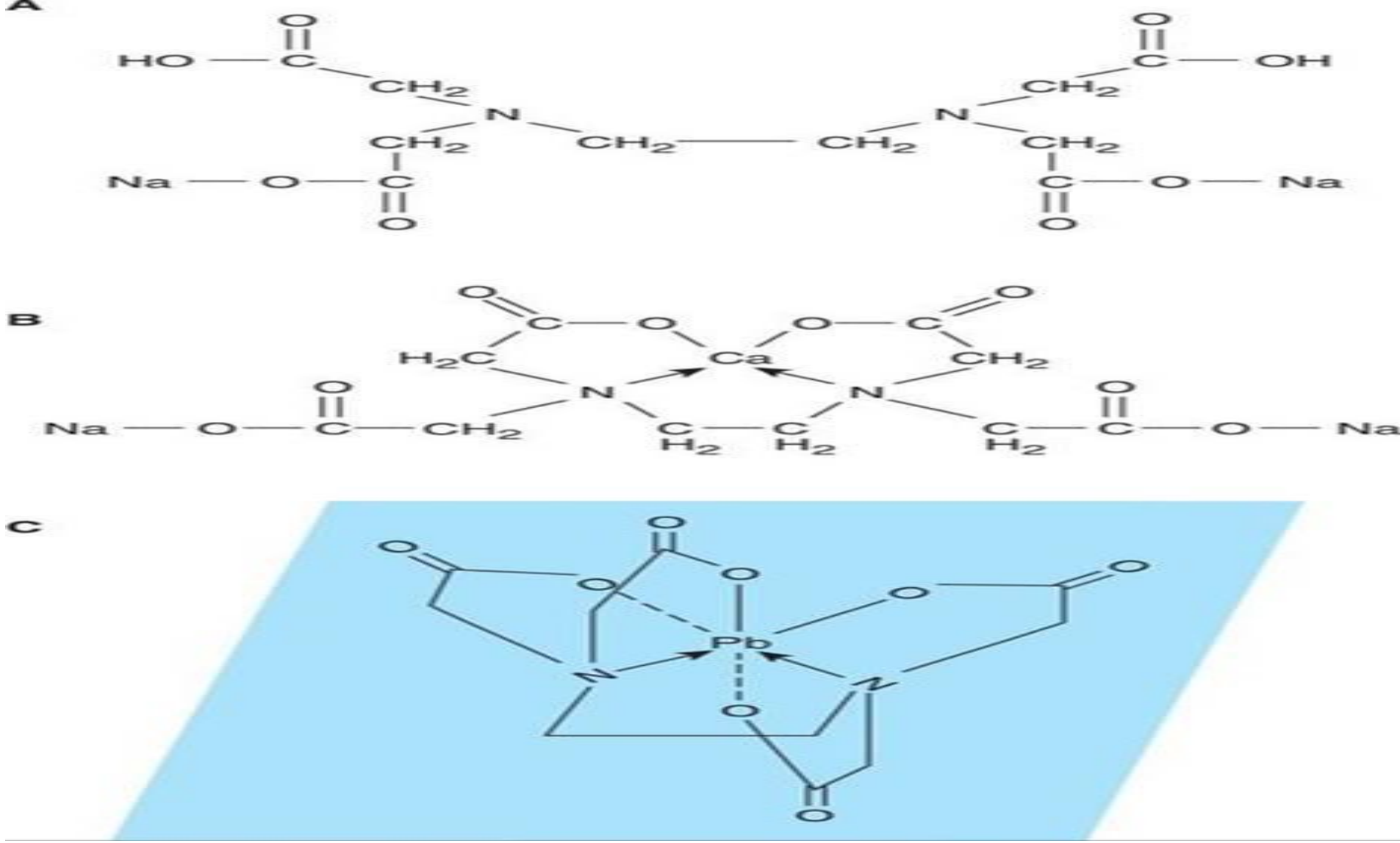
Heavy metals exert their toxic effects **by combining with one or more reactive groups (ligands) essential for normal physiological functions.**

Heavy-metal antagonists (chelating agents) are designed specifically to **compete with these groups for the metals and thereby prevent or reverse toxic effects and enhance the excretion of metals.**



Chemical structures of several chelators. Ferroxamine (ferrioxamine) without the chelated iron is deferoxamine. It is represented here to show the functional groups; **the iron is actually held in a caged system.**



Salt and chelate formation with edetate (ethylenediaminetetraacetate, EDTA). A: In a solution of calcium disodium salt of EDTA, the sodium and hydrogen ions are chemically and biologically available. B: In solutions of calcium disodium edetate, **calcium is bound by coordinate-covalent bonds with nitrogens as well as by the usual ionic bonds**. C: In the lead–edetate chelate, lead is incorporated into five heterocyclic rings.

A chelate is a complex formed between a metal and a compound that contains two or more potential ligands. The product of such a reaction is a heterocyclic ring.

The stability of chelates varies with the metal and the ligand atoms. For example, **lead and mercury have greater affinities for sulfur and nitrogen than for oxygen ligands; calcium, however, has a greater affinity for oxygen than for sulfur and nitrogen.**

These differences in affinity serve as the basis for selectivity of action of a chelating agent in the body

The effectiveness of a chelating agent for the treatment of poisoning by a heavy metal depends on numerous factors:

the relative affinity of the chelator for the heavy metal as compared with essential body metals,

the distribution of the chelator in the body as compared with the distribution of the metal,

and **the capacity of the chelator to remove the metal from the body once chelated.**

Consider the properties of an ideal chelating agent:

high solubility in water,

resistance to biotransformation,

ability to reach sites of metal storage,

capacity to form nontoxic complexes with toxic metals,

ability to retain chelating activity at the pH of body fluids,

and ready excretion of the chelate.

Edetate Calcium Disodium Ethylenediamine tetraacetic acid (EDTA) is a polycarboxylic acid chelator; its sodium salt (edetate disodium, Na2 EDTA), and a number of closely related compounds chelate many divalent and trivalent metals.

MECHANISM OF ACTION **The pharmacological effects of CaNa2 EDTA result from formation of chelates with divalent and trivalent metals in the body.**

Accessible metal ions (both exogenous and endogenous) with an affinity for CaNa2 EDTA that is higher than that of Ca2+ will be chelated, mobilized, and usually excreted.

Because EDTA is charged at physiological pH, it does not significantly penetrate cells; its volume of distribution approximates extracellular fluid space.

The main therapeutic use of CaNa2 EDTA is in the treatment of metal intoxications, especially lead intoxication

Indications: Lead Poisoning

The successful use of CaNa2 EDTA in the treatment of lead poisoning is due, in part, to the capacity of lead to displace calcium from the chelate.

Enhanced mobilization and excretion of lead indicate that the metal is accessible to EDTA.

Bone provides the primary source of lead that is chelated by CaNa2 EDTA. After such chelation, lead is redistributed from soft tissues to the skeleton.

Mercury poisoning, by contrast, does not respond to the drug despite the fact that mercury displaces calcium from CaNa2 EDTA in vitro. Mercury is unavailable to the chelate, perhaps because it is too tightly bound by –SH groups or sequestered in body compartments that are not penetrated by CaNa2 EDTA.

Dimercaprol Dimercaprol (2,3-dimercaptopropanol) was developed during World War II as an antidote to lewisite, a vesicant arsenical war gas, hence its alternative name, British antilewisite (BAL).

MECHANISM OF ACTION **The pharmacological actions of dimercaprol result from formation of chelation complexes between its -SH groups and metals.** The molecular properties of the dimercaprol–metal chelate have considerable practical significance. With metals such as mercury, gold, and arsenic, the strategy is to attain a stable complex to promote elimination of the metal.

Penicillamine:

The D-isomer of penicillamine, D-b,b-dimethylcysteine, is used clinically, although the L-isomer also forms chelation complexes. **Penicillamine is an effective chelator of copper, mercury, zinc, and lead and promotes the excretion of these metals in the urine.**

THERAPEUTIC USES

Penicillamine (CUPRIMINE, DEPEN) is available for oral administration.

The drug should be given on an empty stomach to avoid interference by metals in food. In addition to its use as a chelating agent for the treatment of copper, mercury, and lead poisoning, penicillamine is used in Wilson's disease (hepatolenticular degeneration owing to an excess of copper).

Deferoxamine:

has the desirable properties of a remarkably high affinity for ferric iron coupled with a very low affinity for calcium .

Studies in vitro have shown that **it removes iron from hemosiderin and ferritin and, to a lesser extent, from transferrin. Iron in hemoglobin or cytochromes is not removed by deferoxamine.**

Deferoxamine (deferoxamine mesylate, DESFERAL MESYLATE) is **poorly absorbed after oral administration, and parenteral administration is required in most cases.**

For chronic iron intoxication (e.g., thalassemia), an intramuscular dose of 0.5–1.0 g/day is recommended, although continuous subcutaneous administration (1–2 g/day) is almost as effective as intravenous administration.

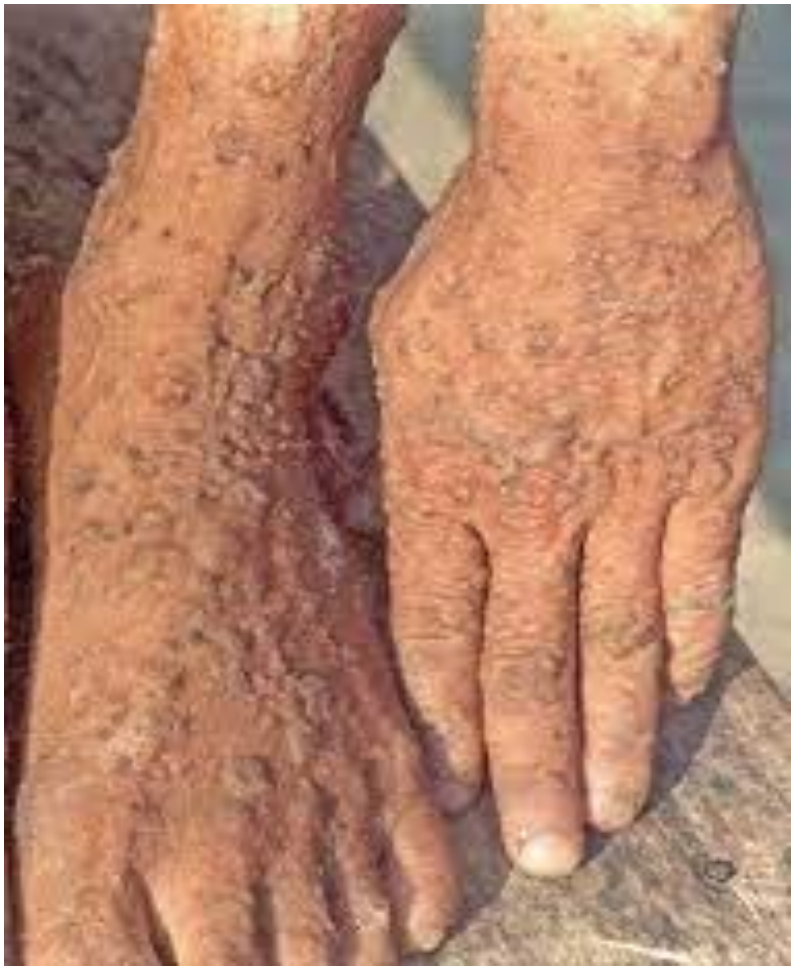
When blood is being transfused to patients with thalassemia, 2 g deferoxamine (per unit of blood) should be given by slow intravenous infusion (rate not to exceed 15 mg/kg/h) during the transfusion but not by the same intravenous line.

Deferoxamine also has been used for the chelation of aluminum in dialysis patients.

Deferoxamine causes a number of allergic reactions, including pruritus, wheals, rash, and anaphylaxis. Other adverse effects include dysuria, abdominal discomfort, diarrhea, fever, leg cramps, and tachycardia.

Occasional cases of cataract formation have been reported. Deferoxamine may cause neurotoxicity during long-term, high-dose therapy for transfusion-dependent thalassemia major; both visual and auditory changes have been described.

Contraindications to the use of deferoxamine include renal insufficiency and anuria; during pregnancy, the drug should be used only if clearly indicated.



- Dermatologic lesions associated with chronic ingestion of arsenic in drinking water.

CASE STUDY

A 48-year-old painter is referred for evaluation of recent onset of severe abdominal pains, headaches, and myalgias.

For the last week, he has been removing old paint from an iron bridge using grinding tools and a blow torch.

His employer states that all the bridge workers are provided with the equivalent of “hazmat” (hazardous materials) suits.

What tests should be carried out?

Assuming positive test results, what therapy would be appropriate?

CASE STUDY ANSWER

This scenario is highly suspicious for acute lead intoxication.

Lead-based paints have been commonly used as anticorrosion coatings on iron and steel structures, and grinding and torch cutting can result in high-dose exposure to inhaled lead dust and fumes.

Measurement of a whole blood lead concentration would be a key diagnostic test. If an elevated blood lead concentration is confirmed, the primary therapeutic intervention will be removal of the individual from further work exposure until blood lead concentration has declined and symptoms resolved.

If the blood lead concentration is in excess of 80 mcg/dL (~ 4 µmol/L), treatment with a chelating agent, such as oral succimer or parenteral edetate calcium disodium, should be strongly considered.

Upon return to work, use of proper respiratory protection and adherence to protective work practices are essential.