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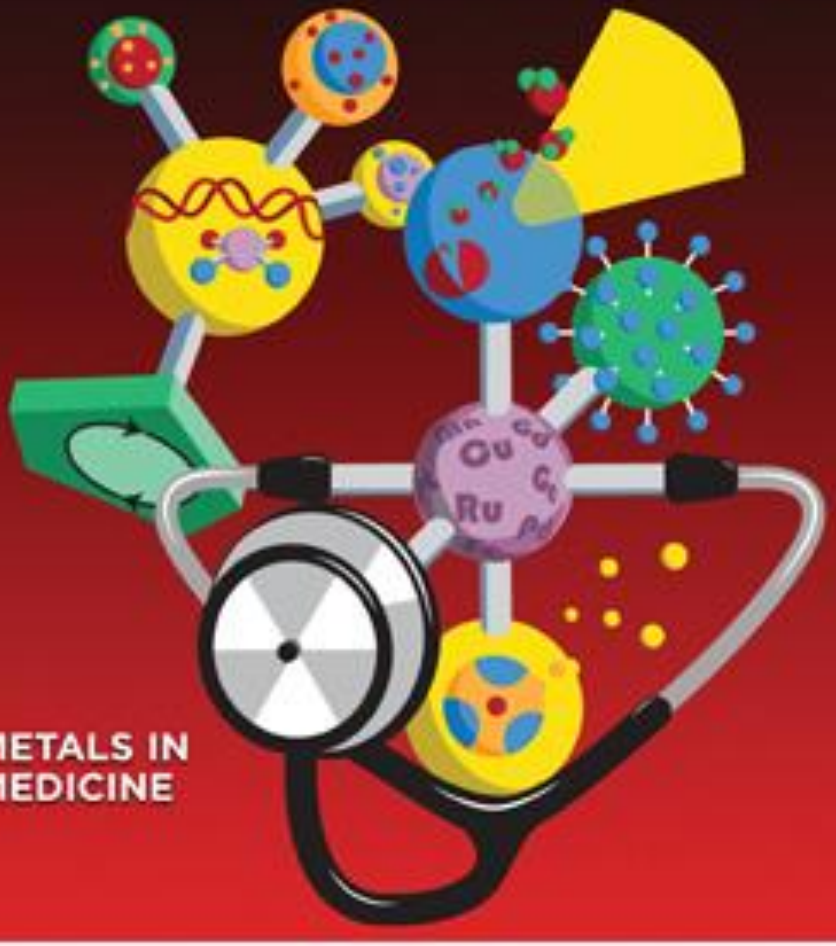
CHEMICAL REVIEWS



METALS IN MEDICINE

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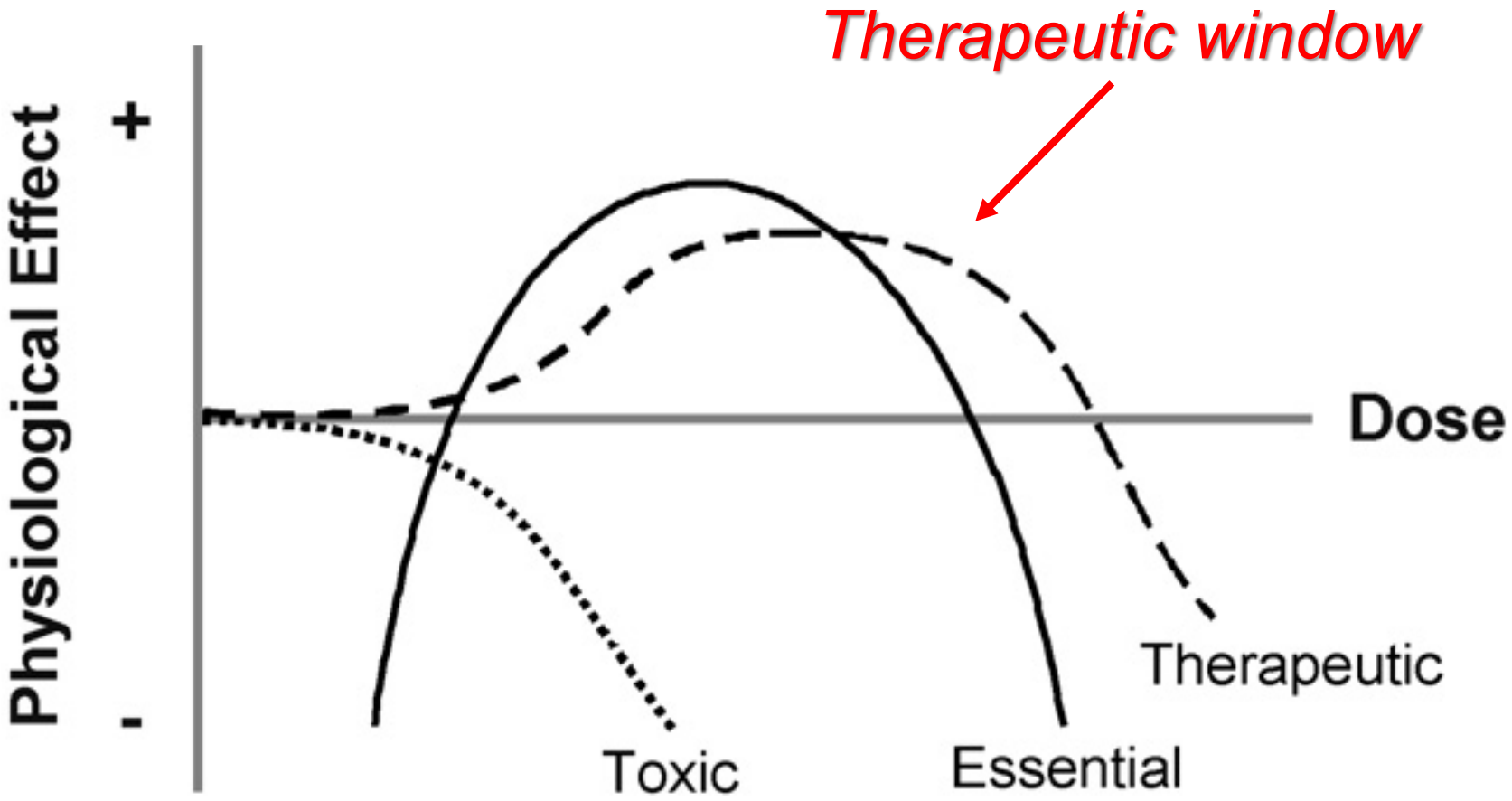
Edited by Enzo Alessio

WILEY-VCH

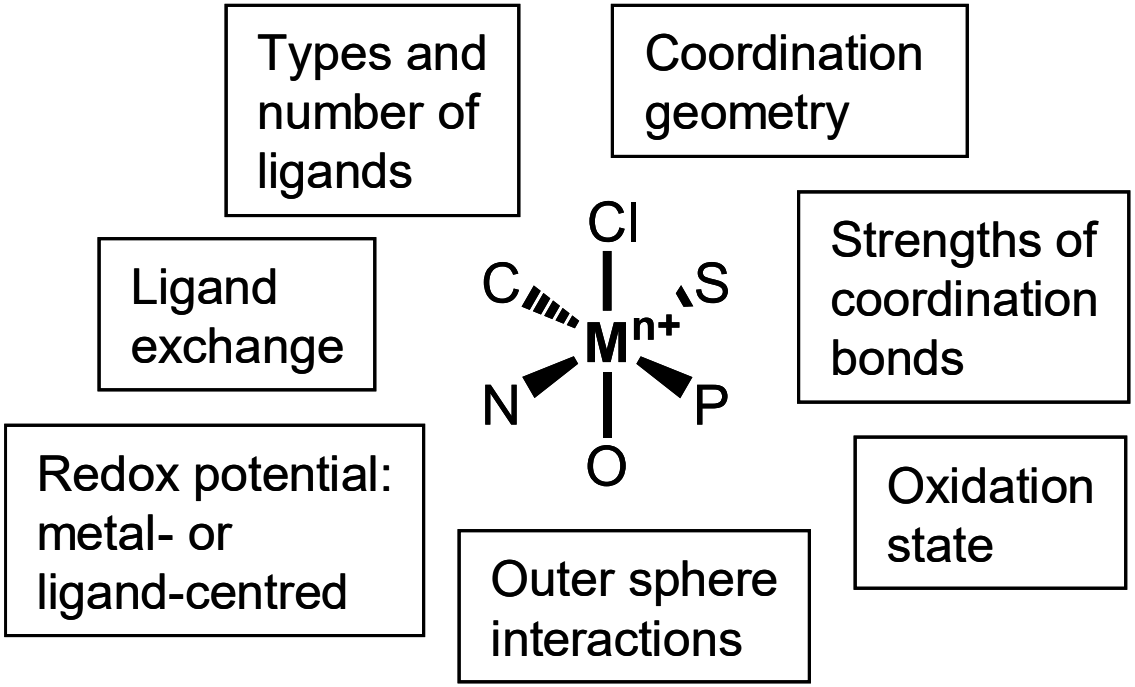
Bioinorganic Medicinal Chemistry

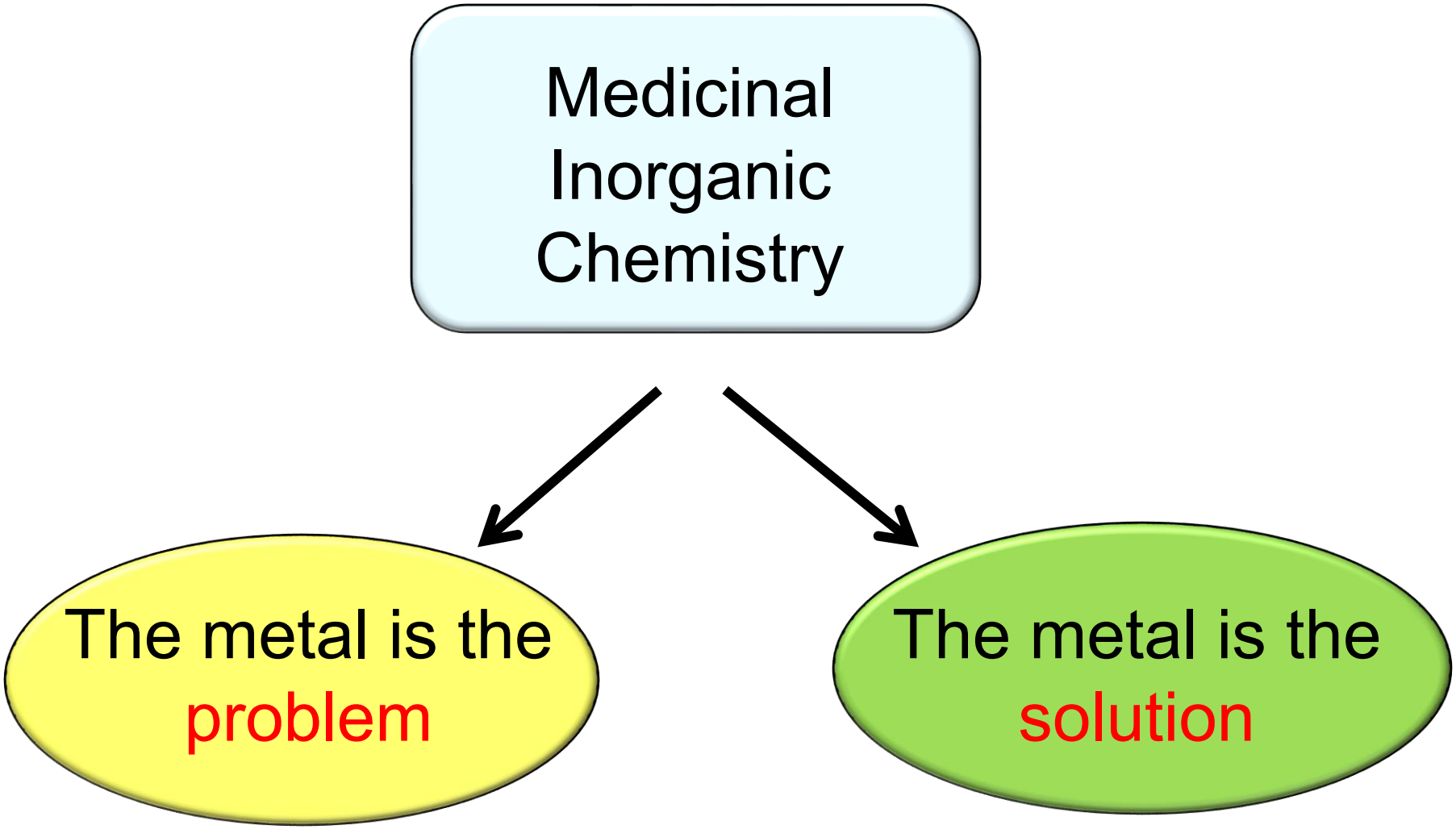
Bertrand's diagram

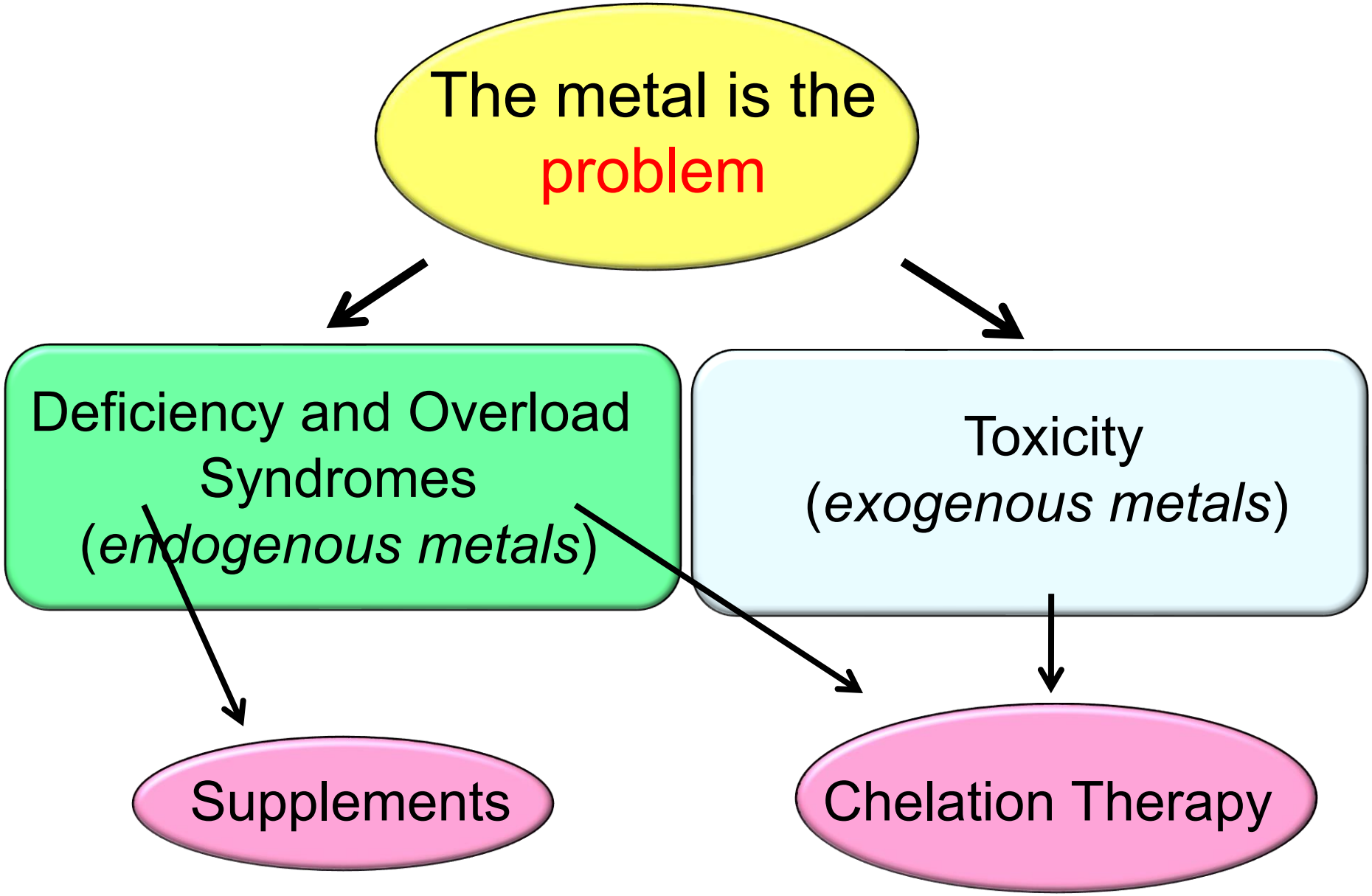


Therapeutic compounds have no deficiency syndrome

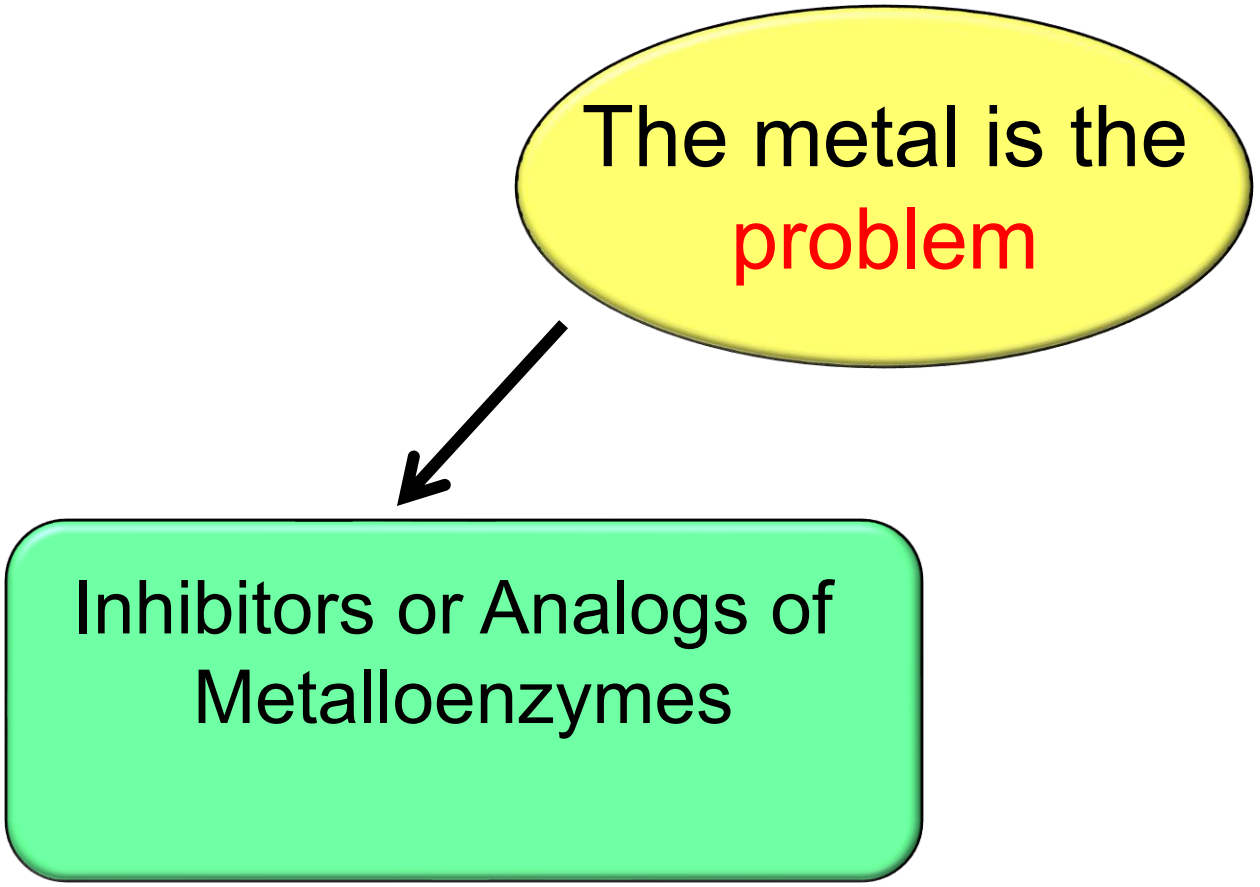
Speciation

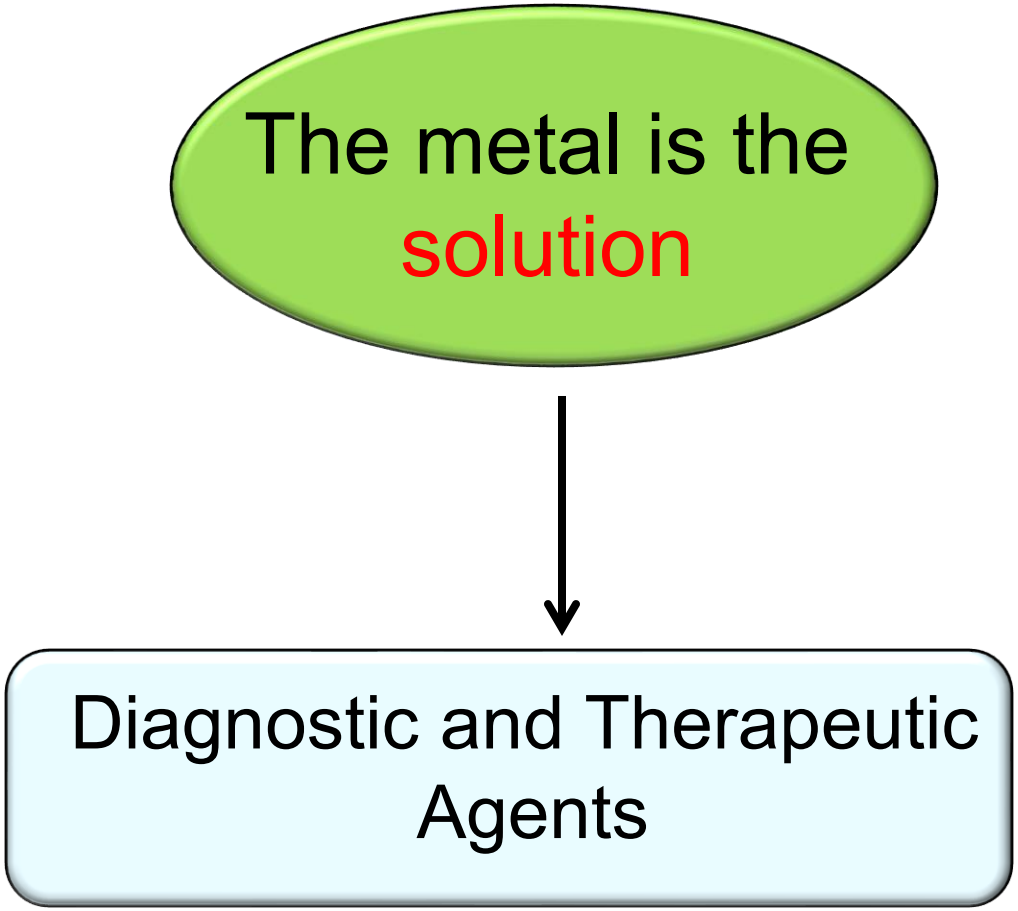

Types and number of ligands
Coordination geometry
Ligand exchange
Strengths of coordination bonds
Redox potential: metal- or ligand-centred
Outer sphere interactions
Oxidation state
Cl
C
S
M n+
N
P
O


Medicinal Inorganic Chemistry
The metal is the problem
The metal is the solution


The metal is the problem
Deficiency and Overload Syndromes (*endogenous metals*)
Toxicity (*exogenous metals*)
Supplements
Chelation Therapy

Malfunctioning of metallo-enzymes




The metal is the
solution
Diagnostic and Therapeutic
Agents

Toxicity of some exogenous elements

Pb

Cd

Tl

Hg

Be

Cr

Itai Itai Disease (Toyama, JP, 1950s, ca 100 death)

Martedì 17 Settembre 2019 (0) Facebook Twitt

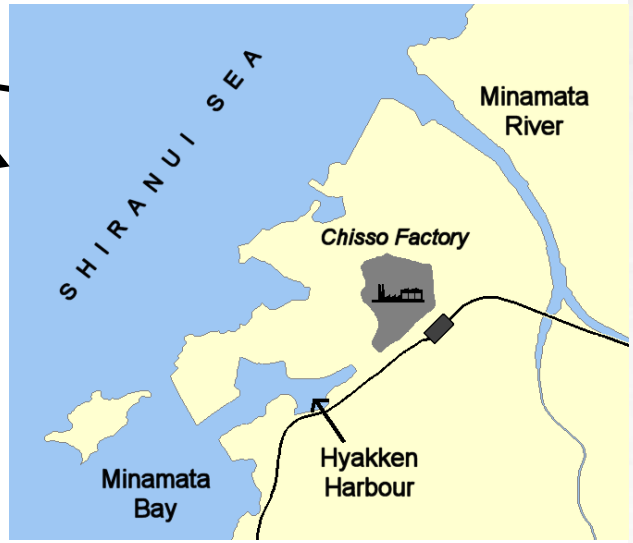
Processo d'appello per il killer del tallio: la procura chiede l'ergastolo

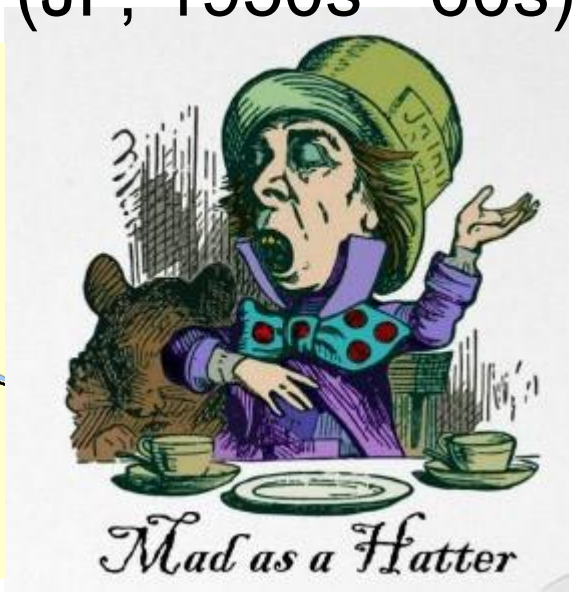
As

F

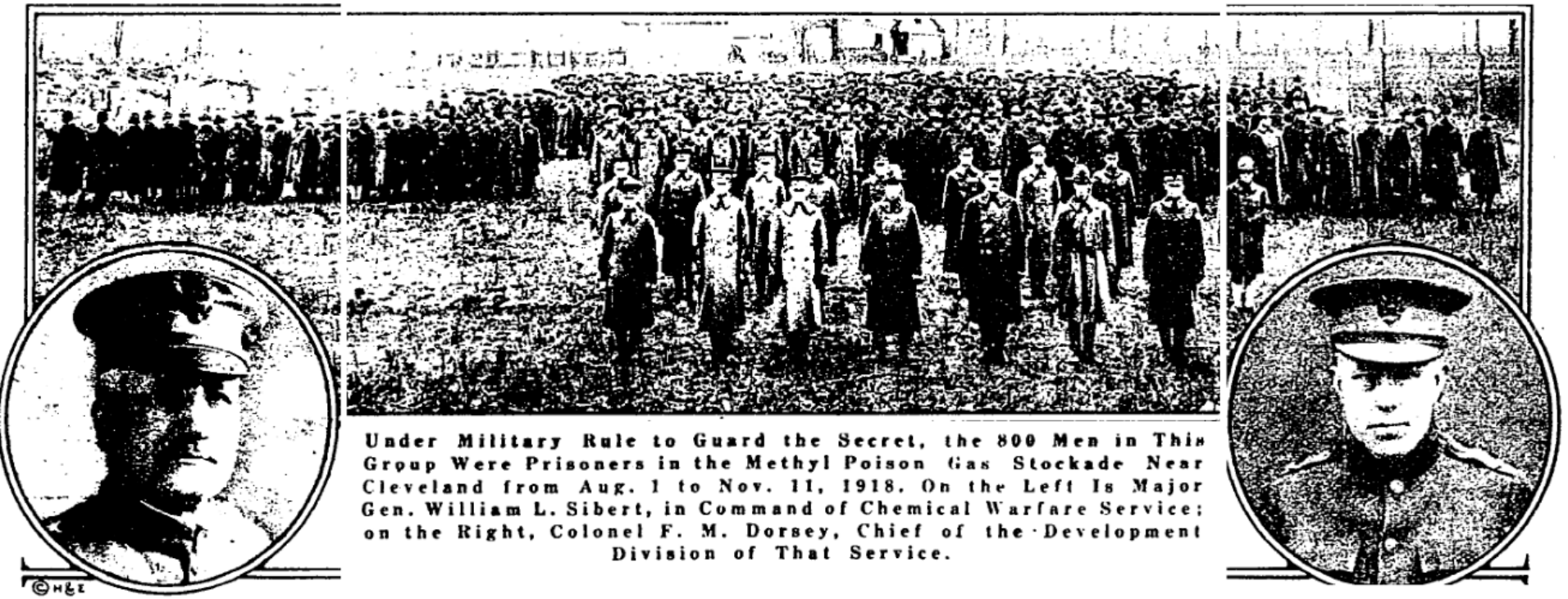
Minamata Disease (JP, 1950s - 60s)

Se





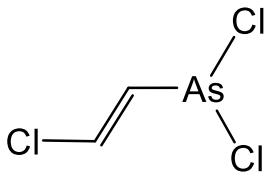
Lewisite: a gaseous As blister agent



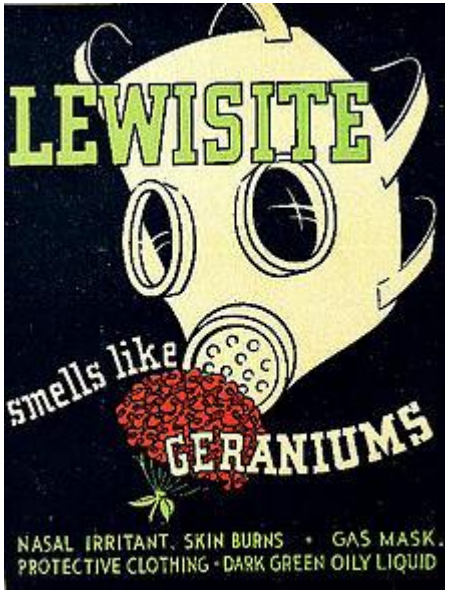
Under Military Rule to Guard the Secret, the 800 Men in This Group Were Prisoners in the Methyl Poison Gas Stockade Near Cleveland from Aug. 1 to Nov. 11, 1918. On the Left Is Major Gen. William L. Sibert, in Command of Chemical Warfare Service; on the Right, Colonel F. M. Dorsey, Chief of the Development Division of That Service.

OUR SUPER-POISON GAS

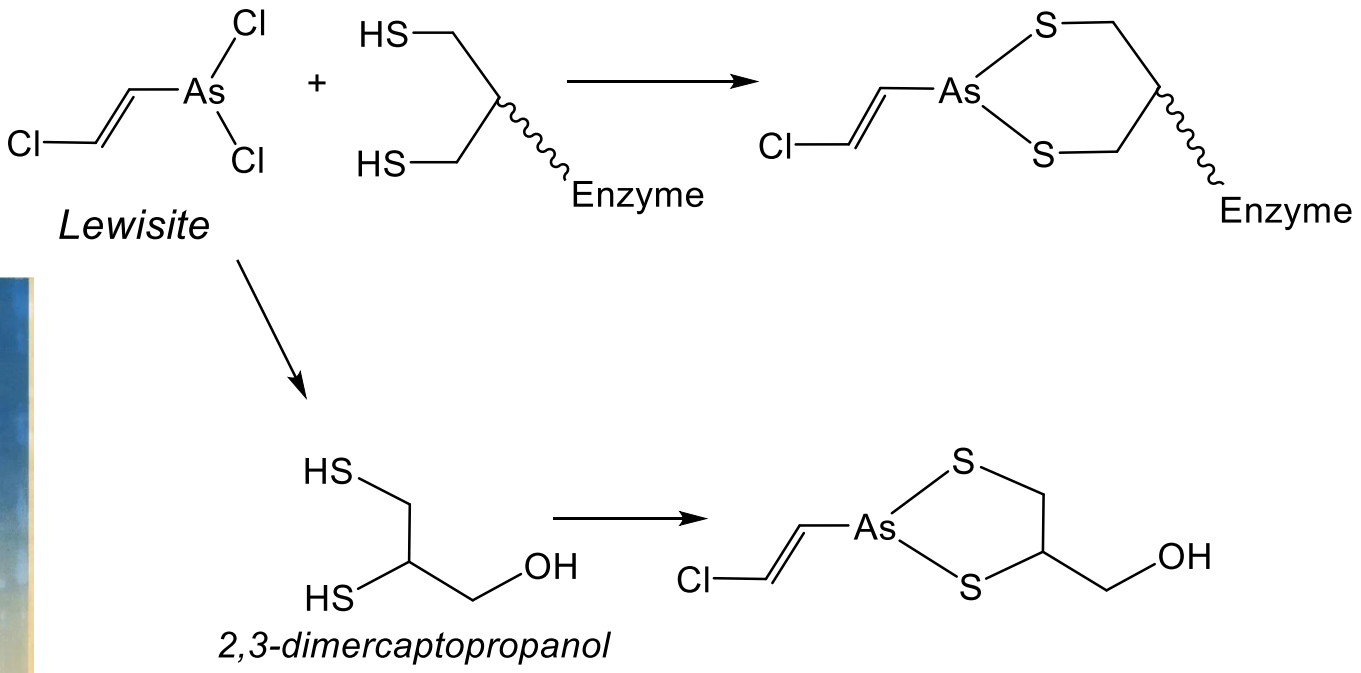
First Story of Compound 72 Times Deadlier Than "Mustard."

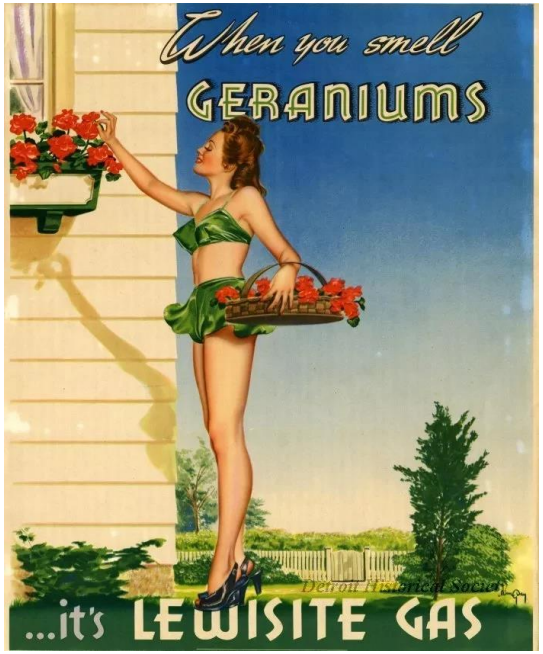


Lewisite



Chelation Therapy



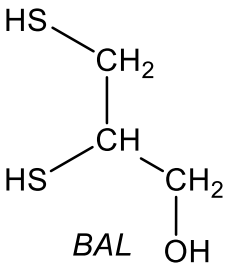


BAL = *British Anti-Lewisite*

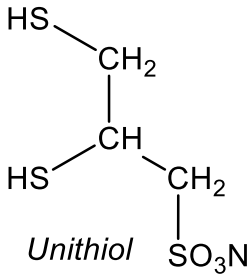
Chelation Therapy

Agent:

- Effective (i.e. match the binding preferences of the ion)
- Selective
- Non toxic
- Resistant to metabolism
- Unexpensive

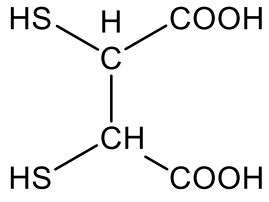


LD_{50} = 105 mg/kg



dimercaptoproane sulfonate

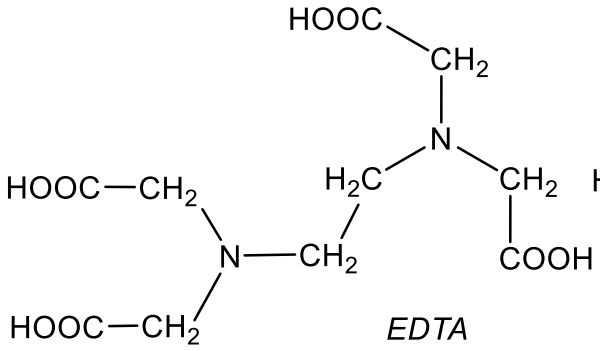
LD_{50} = 2000 mg/kg



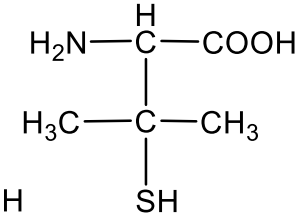
dimercaptosuccinic acid

Adducts:

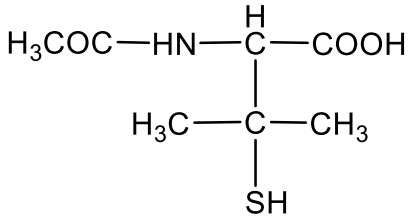
- Stable
- Non toxic
- Highly soluble in water (rapid clearance)
- Resistant to metabolism



$Na_2CaEDTA$



penicillamine



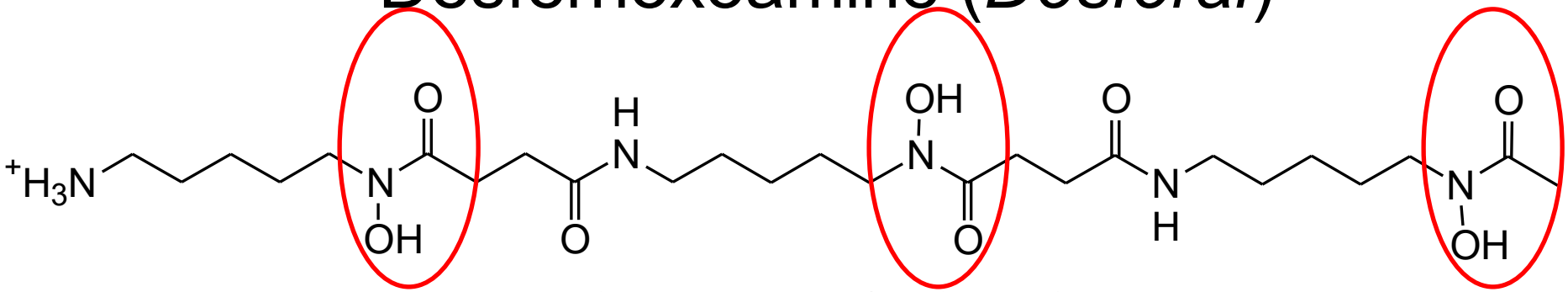
N-acetil-penicillamine

Iron chelation therapy

- Mammals are unable to regulate the export of Fe
- Patients affected by severe forms of anemia (e.g. thalassemia and sickle cell anemia) need frequent blood transfusions
- Transfusions lead to iron overload
- Iron overload, if untreated, leads to premature death
  Fenton chemistry: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^{-}$
- Chelation therapy is essential

1. Efficacy of the chelating agent
2. Toxicity
3. Cost
4. Administration modality (*compliance*)

Desferrioxoamine (*Desferal*)



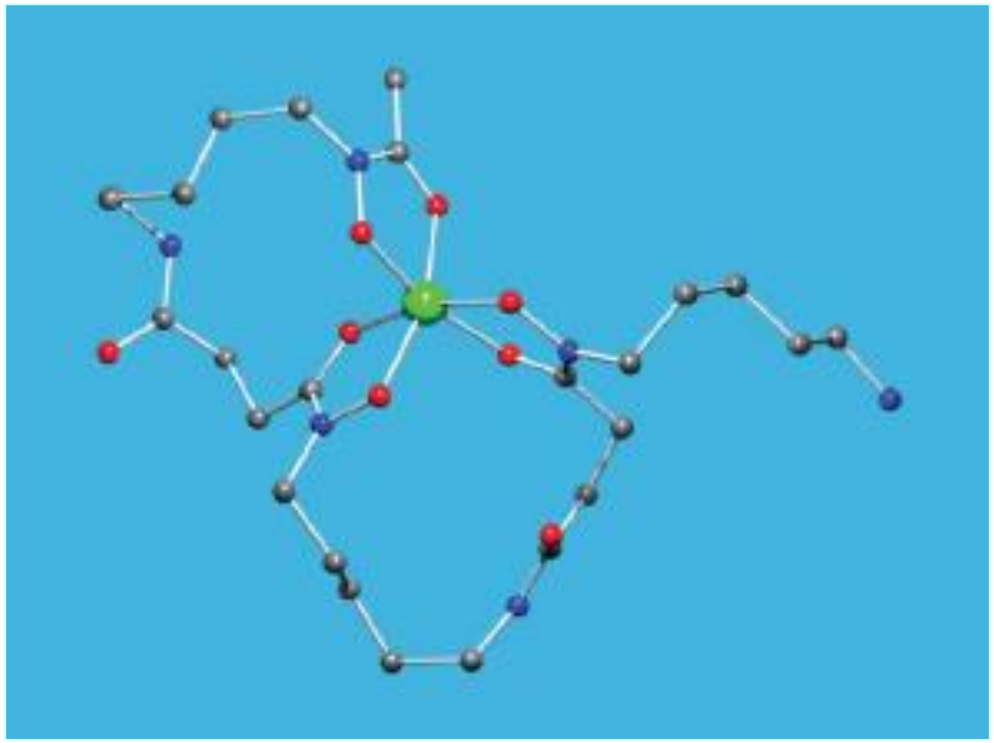
Desferrioxamine B (DFO, *desferal)*

Natural siderophore from *Streptomyces pilosus*

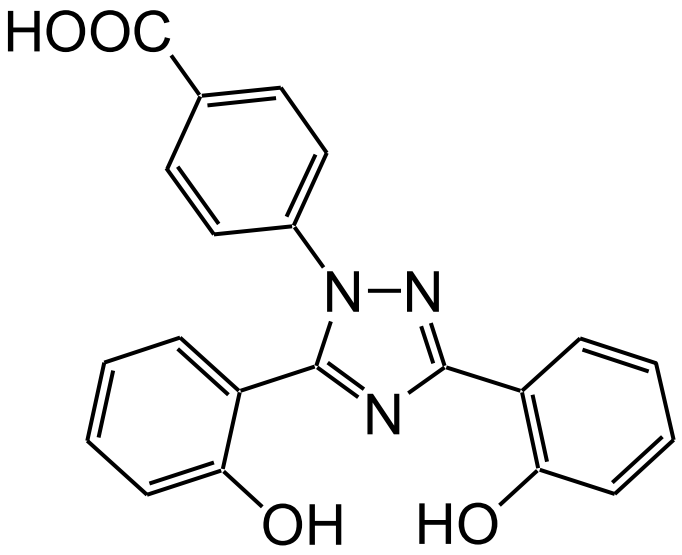
FDA approval: 1968

pFe = 26.6
pFe = -log[Fe^{n+}]

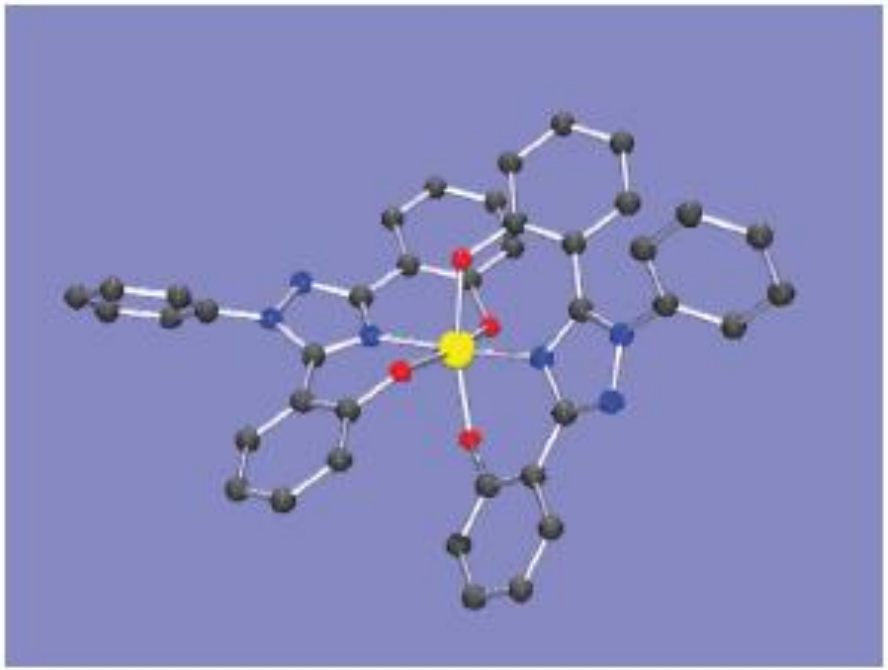
Drawback: very long infusion time: 8 – 12 h



Deferasirox: Orally active



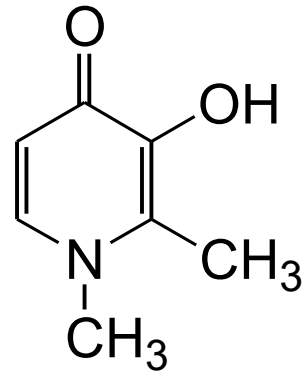
bis-hydroxyphenyl-triazole
deferasirox



pFe = 20

FDA approval: 2005

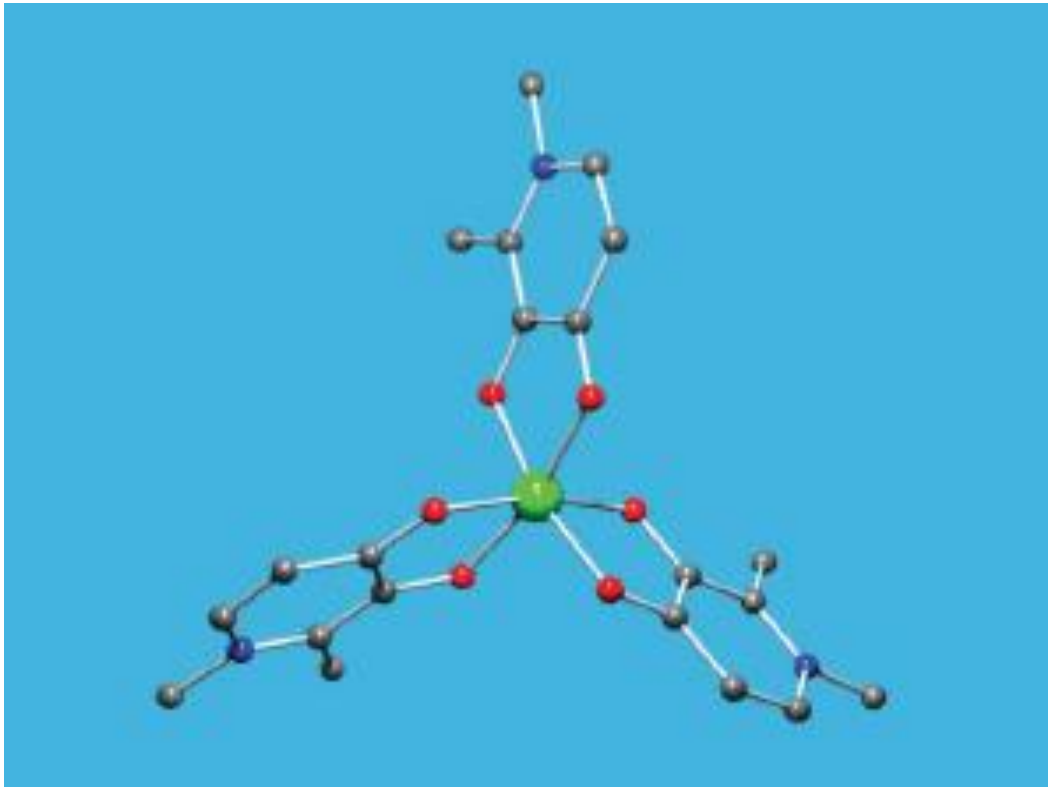
Deferiprone: Orally active

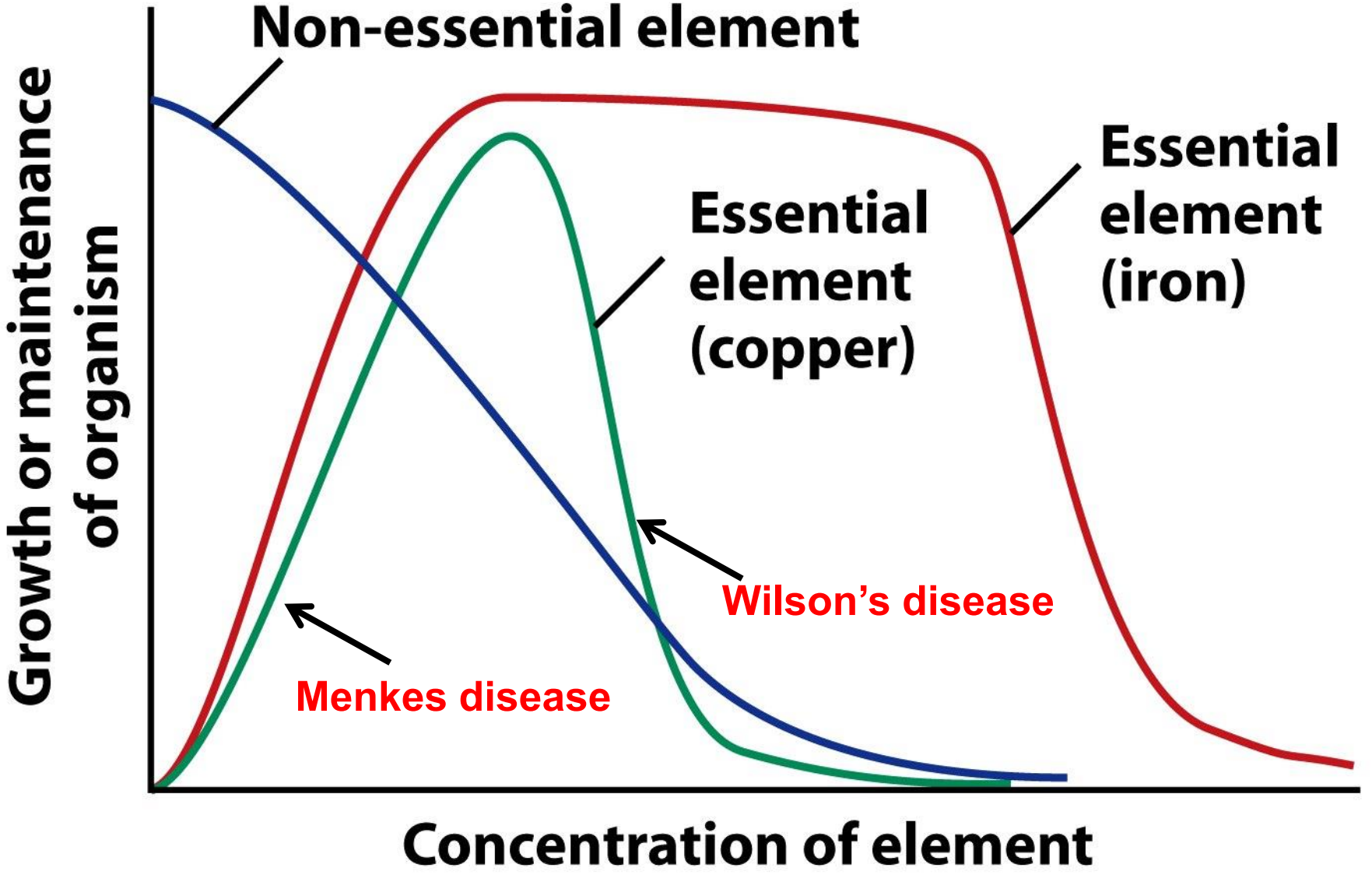


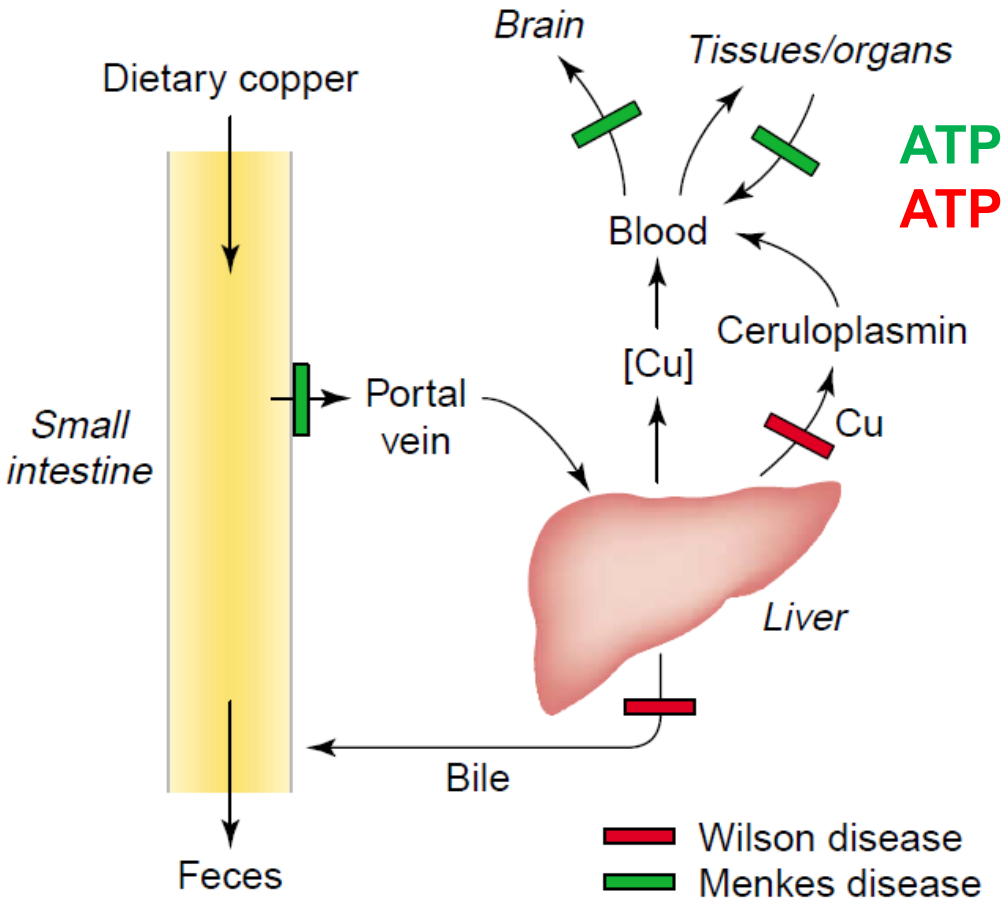
3,4-dihydroxypyridinone
deferiprone

pFe = 20

2011 FDA approval as
second-line oral drug




Non-essential element
Essential element (iron)
Essential element (copper)
Wilson's disease
Menkes disease
Growth or maintenance of organism
Concentration of element



ATP7A: Menkes disease, Cu deficency
ATP7B: Wilson's disease, Cu overload

ATP7A is expressed in most tissues/organs, with the exception of the liver.
ATP7B is found to be predominantly expressed in the liver

→ $Cu(II)(His)_2$

FDA NEWS RELEASE

FDA Approves First Treatment for Children With Menkes Disease

For Immediate Release: January 12, 2026

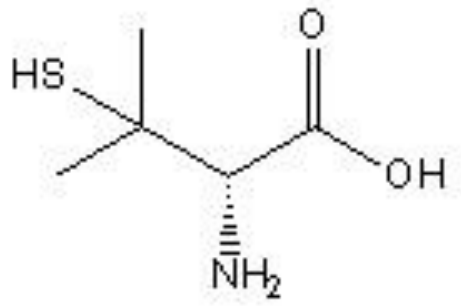
The U.S. Food and Drug Administration today approved the Zycubo (copper histidinate) injection as the first treatment for Menkes disease in pediatric patients.

“With today’s action, children with this devastating, degenerative disease will have an FDA-approved treatment option and the potential to live longer,” **said Christine Nguyen, M.D., Deputy Director of the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine in the FDA’s Center for Drug Evaluation and Research**. “The FDA will continue to work with the rare disease community to advance drug development for patients with Menkes disease and other rare conditions.”

Menkes disease is a neurodegenerative disorder caused by a genetic defect that impairs a child’s ability to absorb copper. The disease is characterized by seizures, failure to gain weight and grow, developmental delays, and intellectual disability. It leads to abnormalities of the vascular system, bladder, bowel, bones, muscles, and nervous system. Children with classical Menkes (90% of those with the disease) begin to develop symptoms in infancy and typically do not live past three years. It affects approximately one in every 100,000-250,000 live births worldwide and is more common in boys.

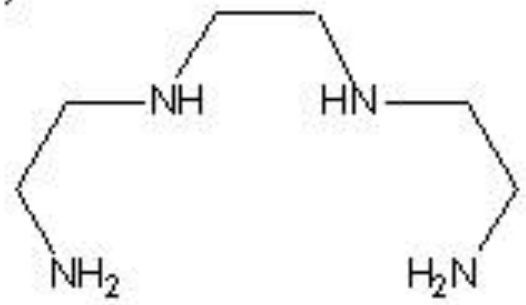
Chelating agents for Wilson syndrome (Cu removal)

a)



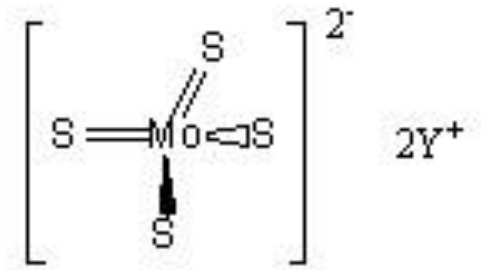
D-penicillamine

b)



Trien *(Trientine)*
(triethylenetetramine)

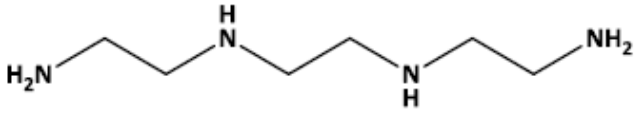
c)



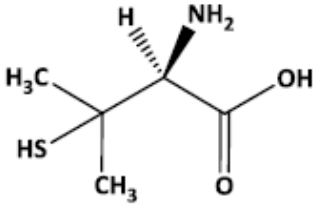
$Y = [NH_4]^+$ or

$Y = [(CH_3)_3NCH_2CH_2OH]^+$

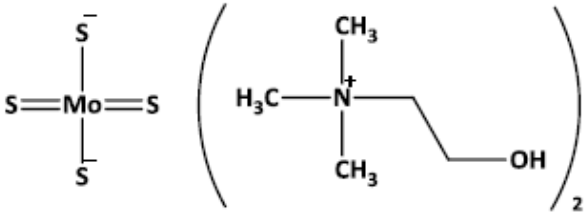
Tetrathiomolybdate


H
N
H2N
NH2
N
H

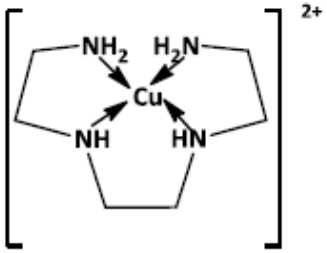
a

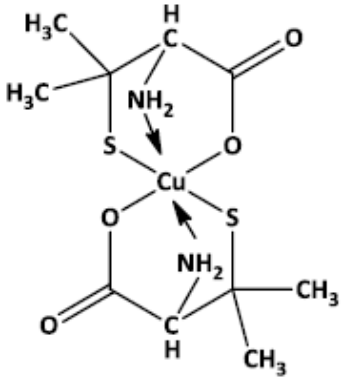

H
NH2
H3C
OH
HS
CH3
O

b


S
S
Mo
S
S
CH3
H3C
N
CH3
OH
2

c


NH2
H2N
Cu
NH
HN
2+


H3C
H
C
O
H3C
NH2
S
O
Cu
O
S
NH2
CH3
O
C
H
CH3

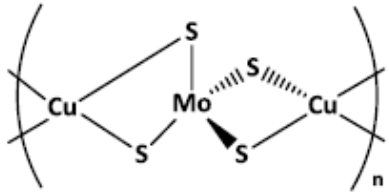

S
Cu
Mo
S
Cu
S
S
n

Table 2. Agents for the Treatment of Wilson Disease

agent	mechanism of action	daily adult dosage
D-penicillamine[a]	reduction and chelation of copper; urinary excretion of copper by mobilizing copper from organs	1−2 g orally in divided doses
triethylenetetramine (Trien)	copper chelator and urinary excretion	0.75−1.5 g orally in divided doses
zinc salts	inhibits intestinal absorption of copper by induction of intestinal cell metallothionein; may also induce hepatic metallothionein	150−200 mg orally in divided doses
british anti-Lewisite (BAL)	copper chelator	3 mL of 10% BAL in peanut oil im
tetrathiomolybdate[b]	blocking the intestinal absorption of copper and a copper chelator	Up to 2 mg/kg orally in divided doses

[a] Administered with supplementation of 25 mg of pyridoxine orally daily. [b] Experimental.