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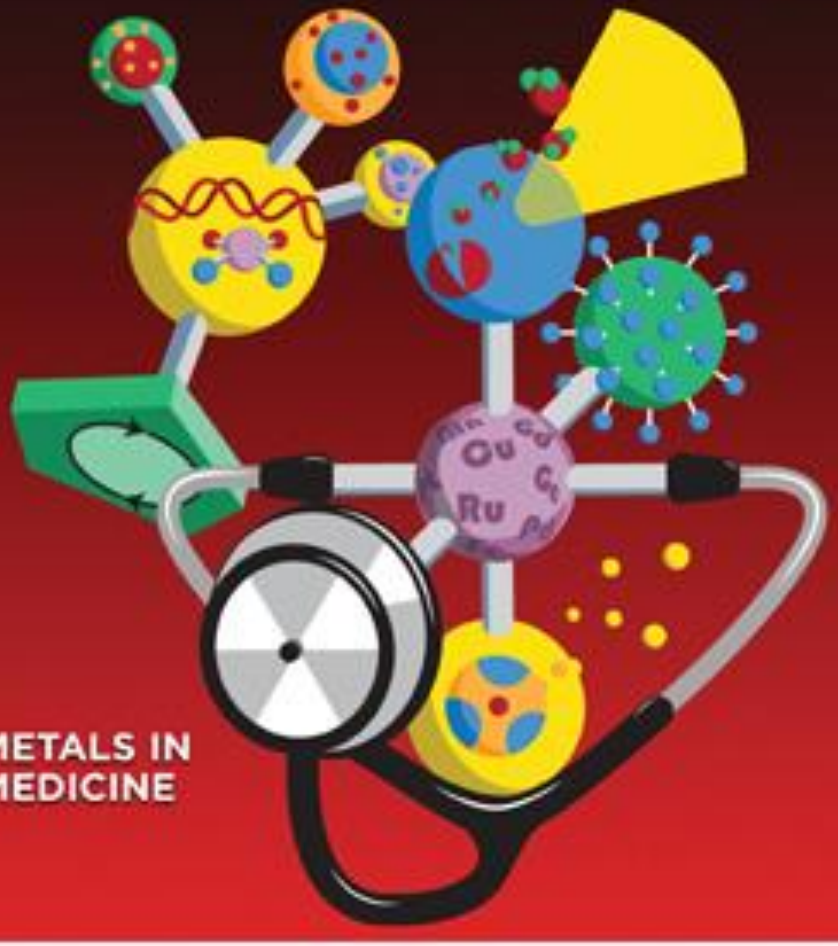
CHEMICAL REVIEWS



METALS IN MEDICINE

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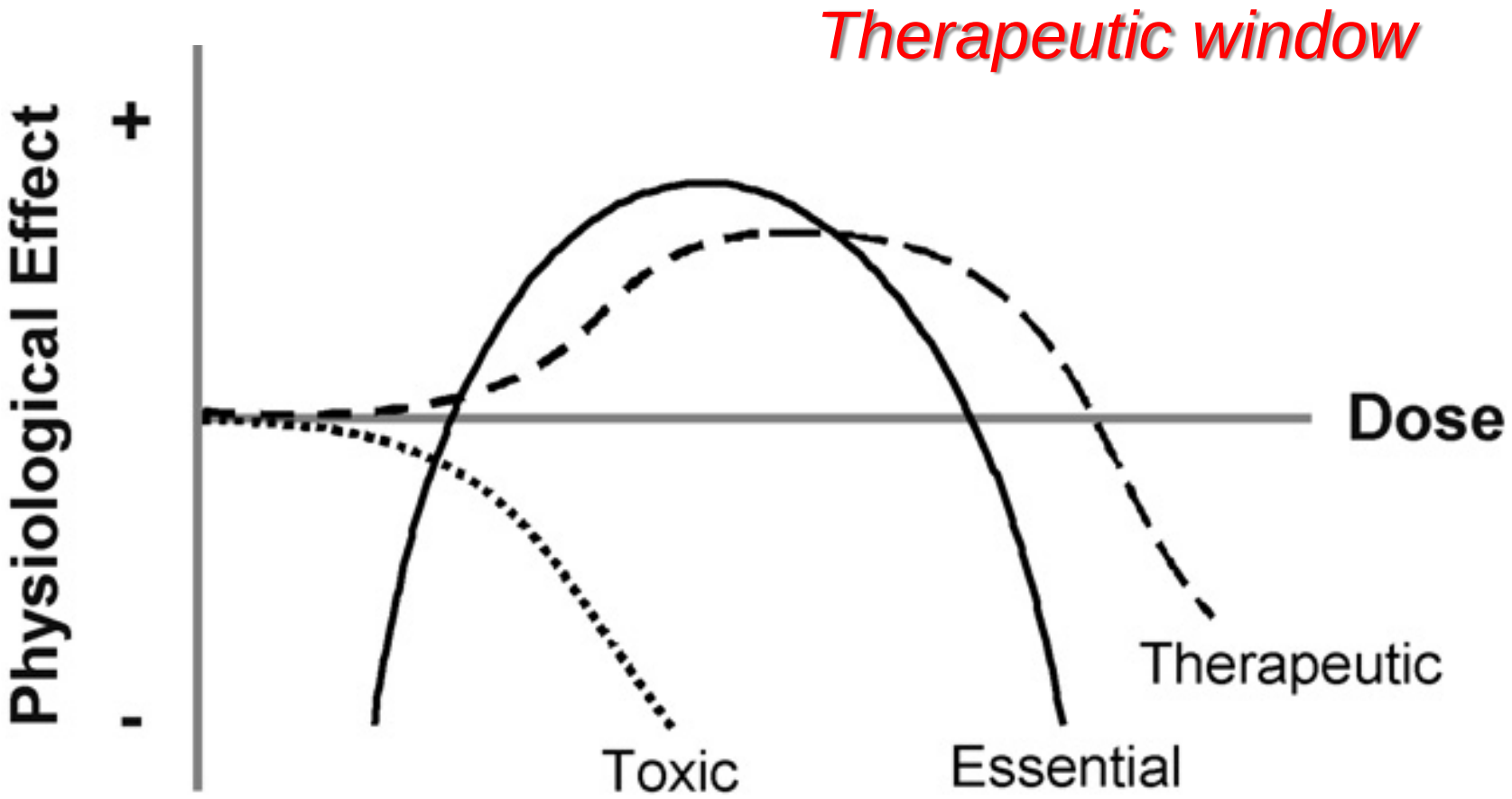
Diagramma di Bertrand

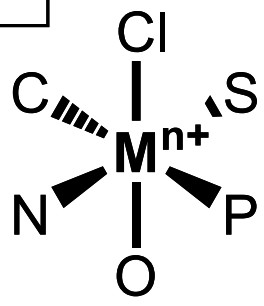


Speciation

Types and number of ligands

Coordination geometry

Ligand exchange



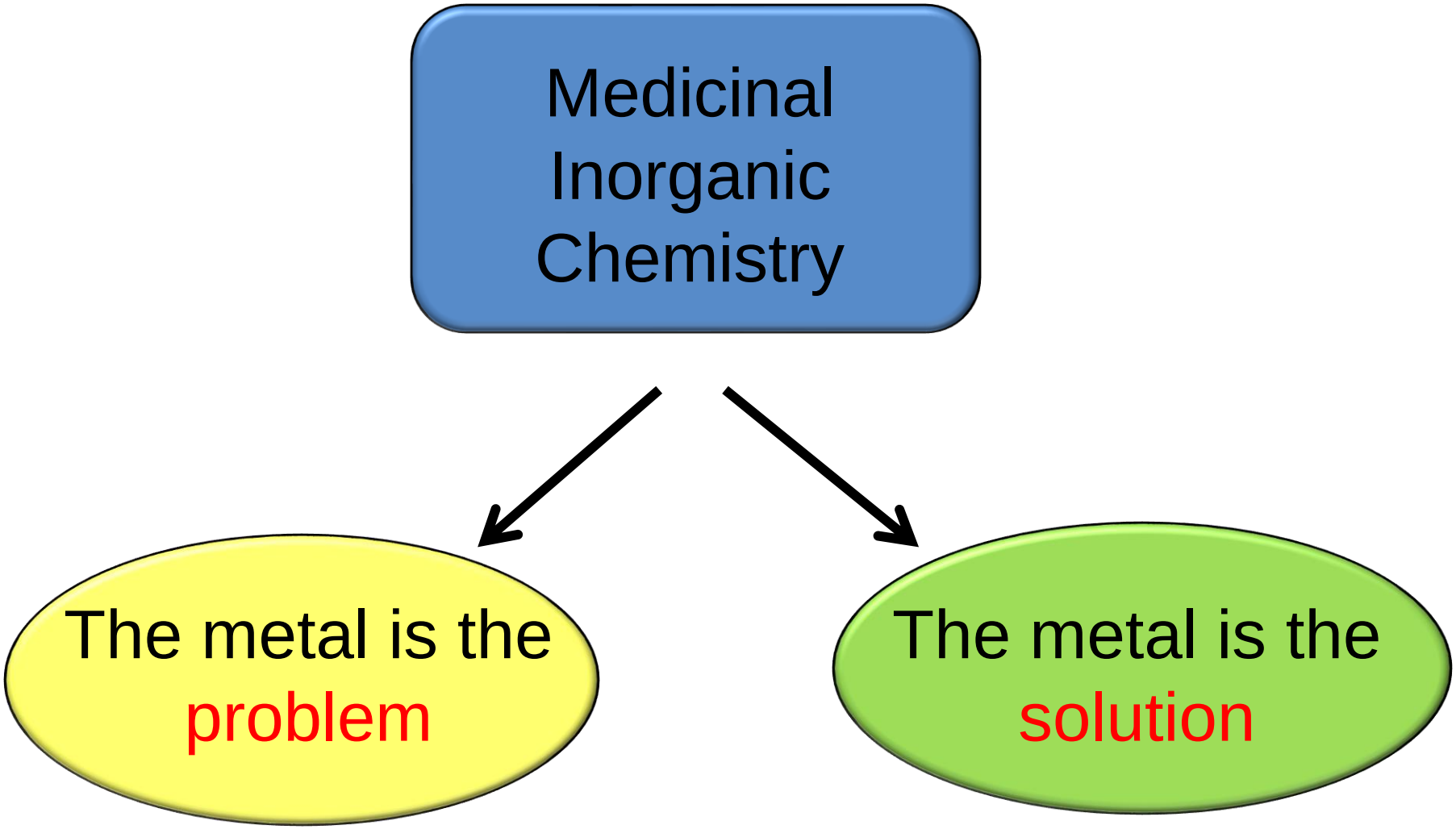
Strengths of coordination bonds

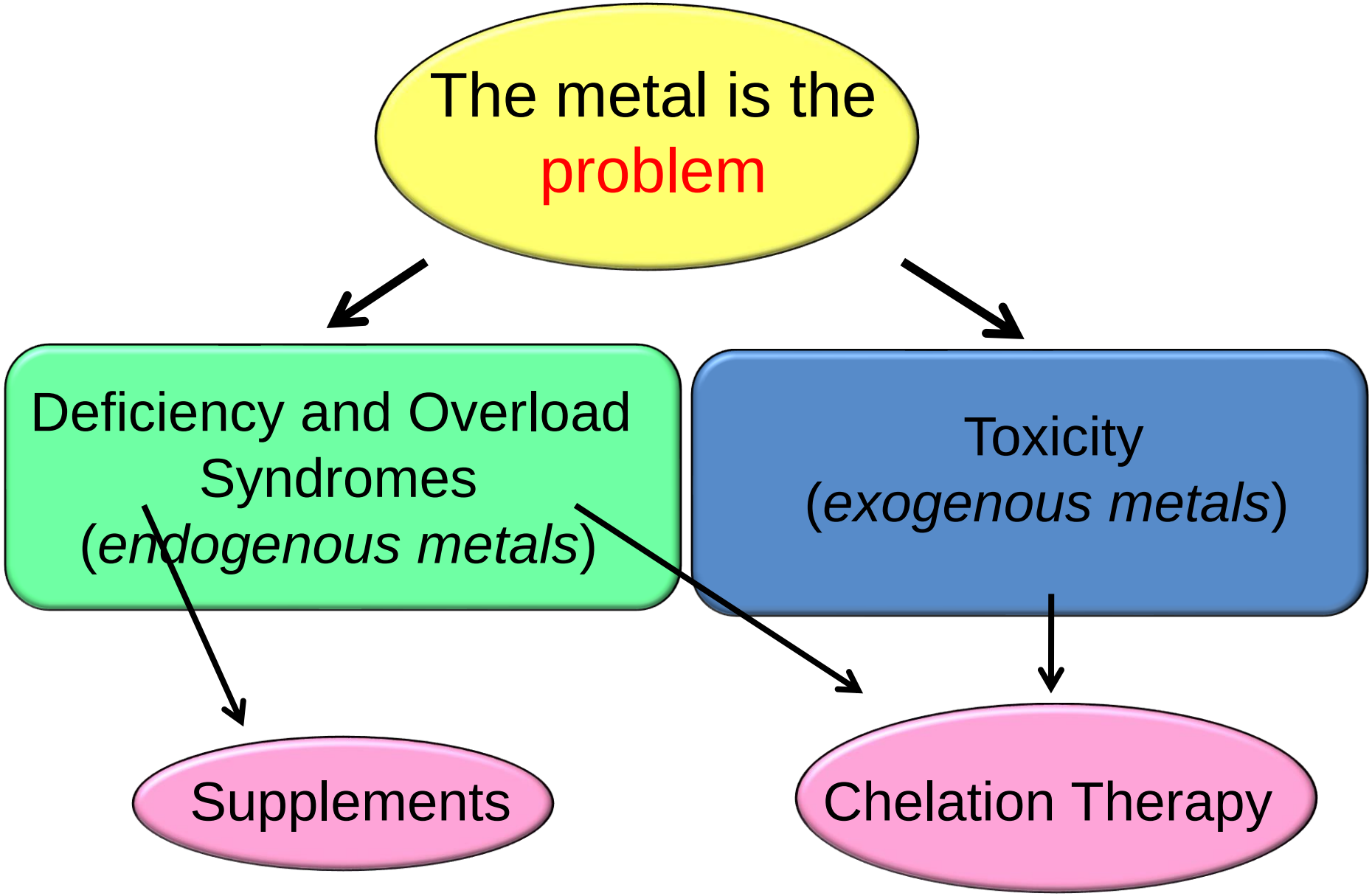
Redox potential: metal- or ligand-centred

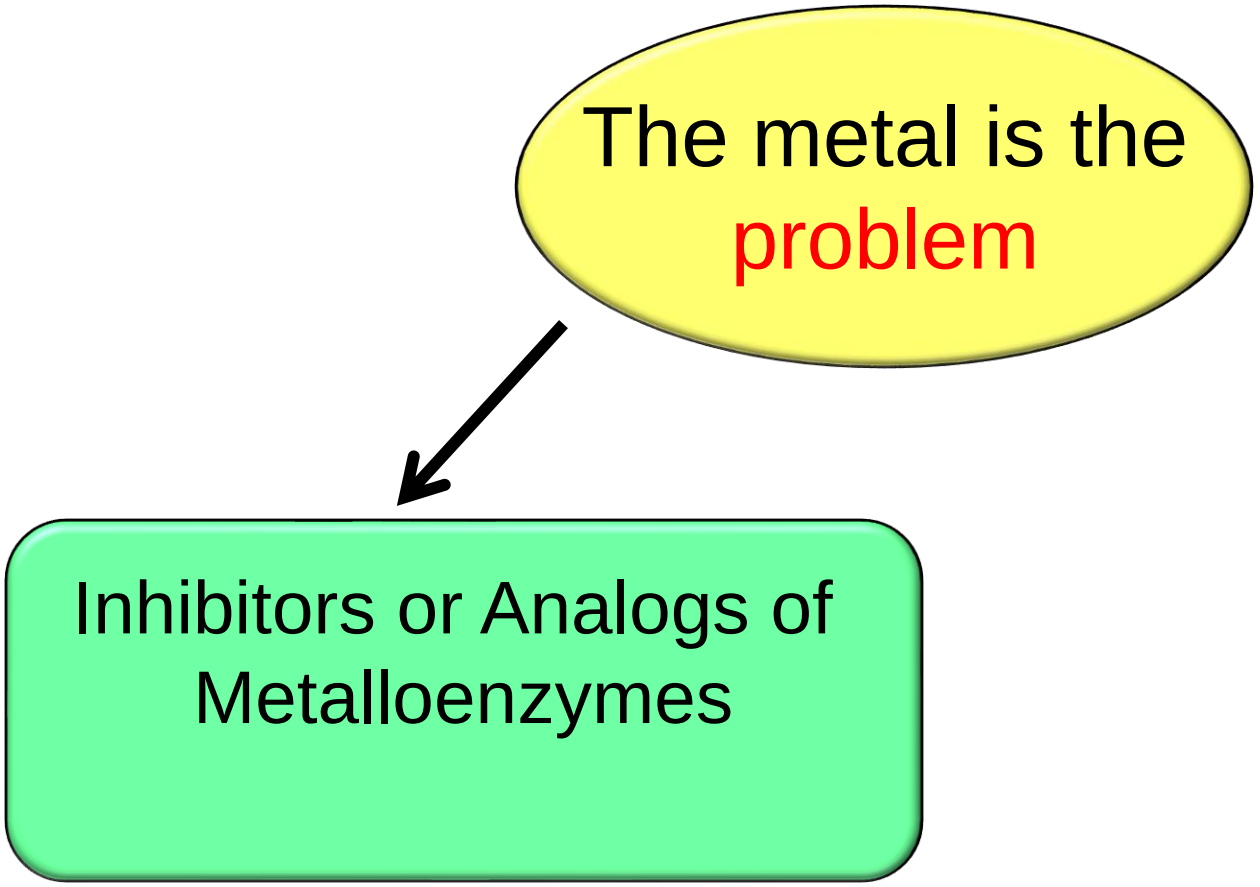
Outer sphere interactions

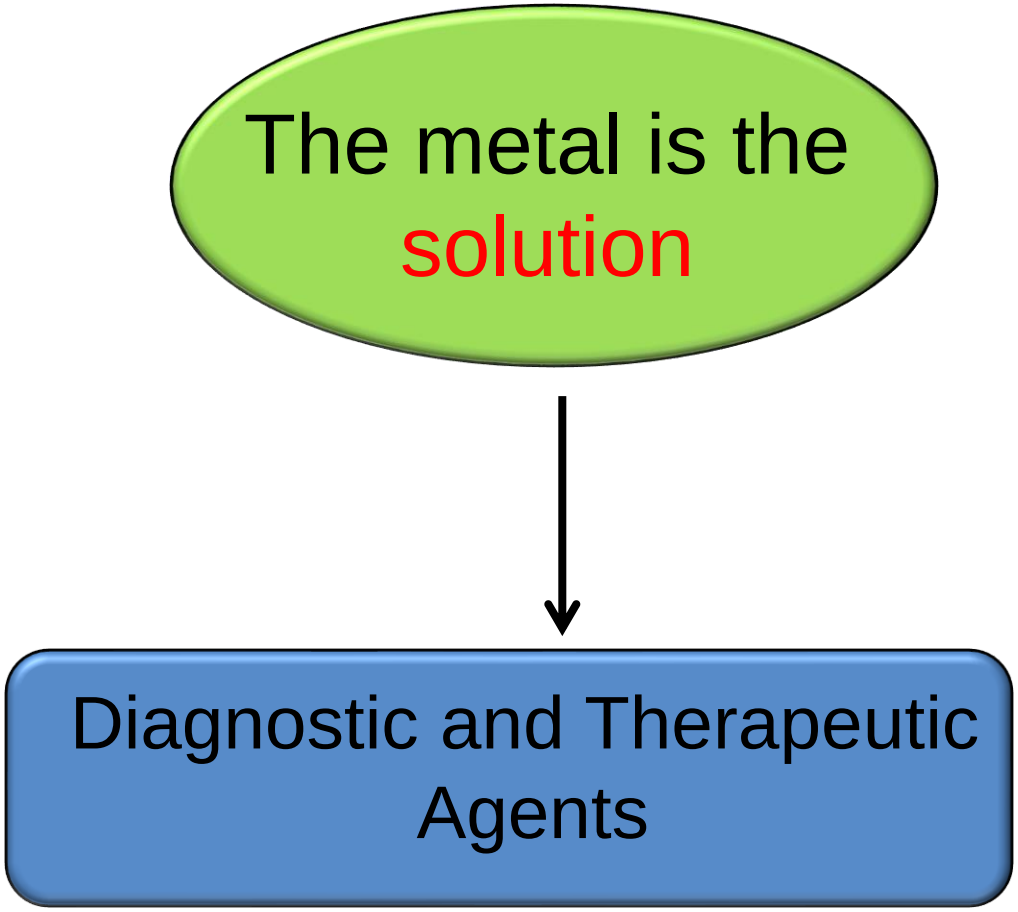
Oxidation state

Proprietà	**Commenti (esempi)**
Numero di Coordinazione	Intero intervallo: 2 – 10; tipicamente da 4 a 6 per i metalli di transizione, può essere più variabile per i metalli dei gruppi principali (*e.g.* Bi) e più grande per i lantanidi (*e.g.* 9)
Geometria	Esempi: lineare (Au^{I}), planare-quadrata (Pt^{II}), tetraedrica (*e.g.* complessi 'piano-stool' Ru^{II}), bipiramidale trigonale, ottaedrica (Ti^{IV}, Ru^{III}, Pt^{IV}), possibile chiralità centrata sul metallo (Co^{III}, Rh^{III})
Stato di Ossidazione	Ampio intervallo (tipicamente 0 – 7 in ambiente biologico); i diversi stati di ossidazione favoriscono diversi numeri di coordinazione e velocità di scambio dei leganti (*e.g.* Pt^{IV} *vs* Pt^{II})
Tipo di Legante	Ampio numero di atomi donatori *e.g.* C, N, O, alogenuri, P, S, Se. Leganti chelanti; denticità *e.g.* (κ^2) 1,2-diamminoetano, (κ^6) EDTA; apticità *e.g.* legami di tipo η^6 e η^4 per il benzene
Stabilità Termodinamica	Ampio intervallo di forza del legame M–L (tipicamente 50-150 $kJ \cdot mol^{-1}$), molto più debole rispetto al tipico legame covalente, *e.g.* legame singolo C–C (250 – 500 $kJ \cdot mol^{-1}$)
Stabilità Cinetica	Il tempo di vita dei legami M–L copre un intervallo molto ampio (ns – anni). Dipende molto dallo stato di ossidazione del metallo e dagli altri leganti; può essere stereospecifico, *e.g.* effetto *trans* nel Pt^{II}.
Proprietà dei Leganti	Interazioni relative alla sfera esterna dei leganti, *e.g.* legame a idrogeno, interazioni idrofobiche (< 50 $kJ \cdot mol^{-1}$), possono servire al riconoscimento recettoriale (chiralità inclusa); possono subire trasformazioni *in vivo e.g.* di tipo redox, idrolisi, reazioni enzimatiche (*e.g.* ad opera del P450 nel fegato).
Stabilità Nucleare	Nuclei radioattivi possono essere usati per seguire il metabolismo dei composti *e.g.* ^{195m}Pt ($t_{½}$ = 4 d) e ^{99m}Tc ($t_{½}$ = 6 h). A seconda del nuclide variano il tipo di decadimento (α, β, γ) e il tempo di semi-vita.


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


The metal is the problem
Inhibitors or Analogs of Metalloenzymes


The metal is the
solution
Diagnostic and Therapeutic
Agents

Tossicità di metalli esogeni e altri elementi

Pb

Cd

Tl

Hg

Be

Cr

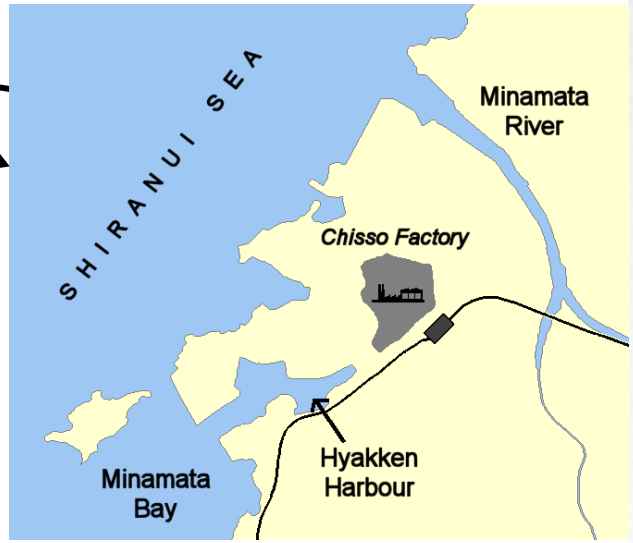
Itai Itai Disease (Toyama, JP)

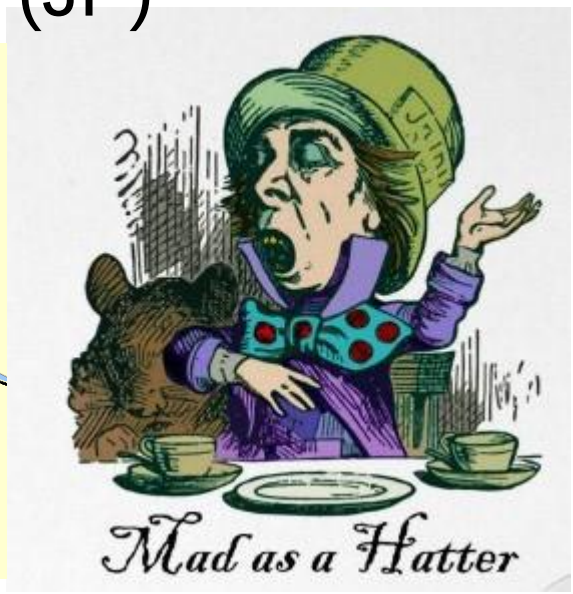
Martedì 17 Settembre 2019 (0)

Facebook Twitt

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

Minamata Disease (JP)



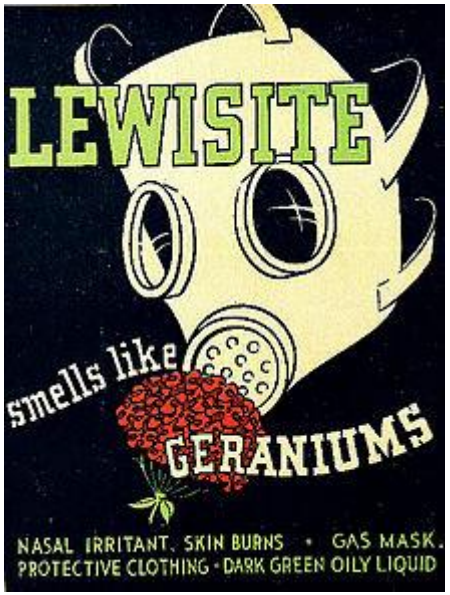


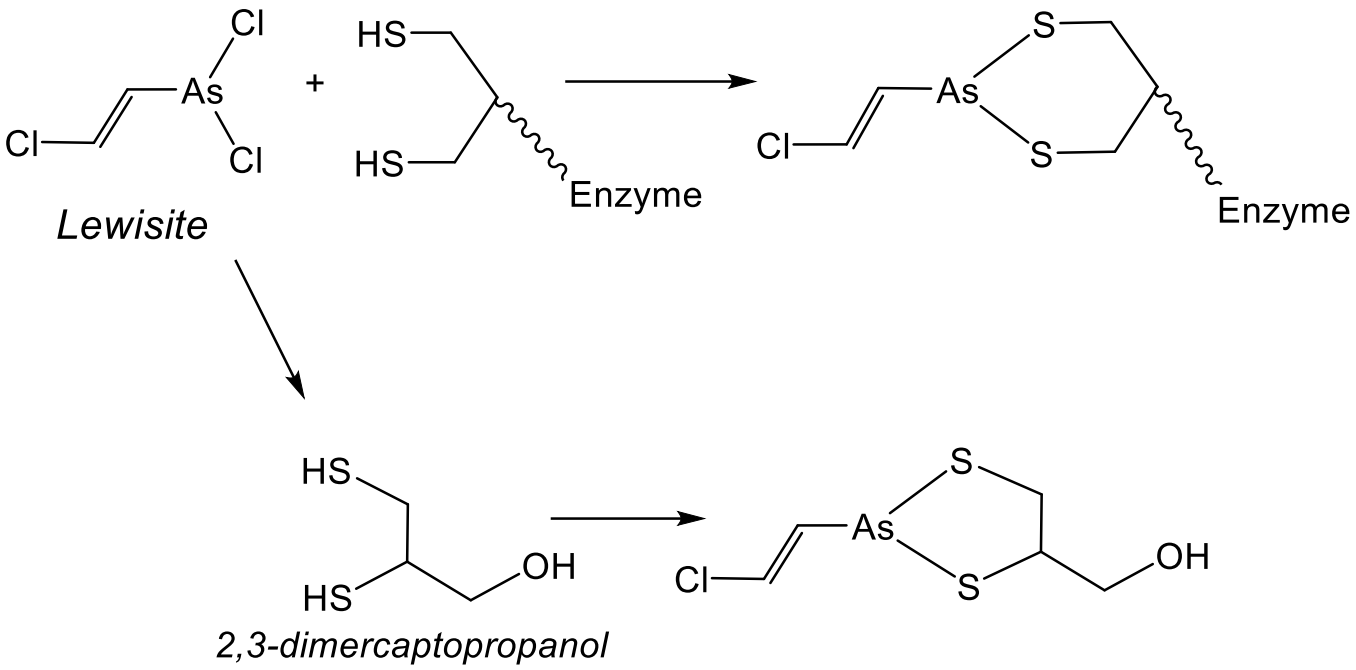
As

F

Se

Chelation Therapy



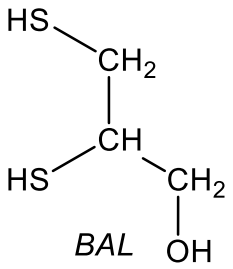


BAL = *British Anti-Lewisite*

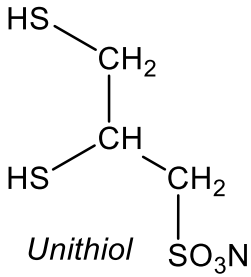
Chelation Therapy

Agent:

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

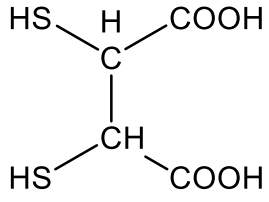


LD_{50} = 105 mg/kg



dimercaptoproane sulfonate

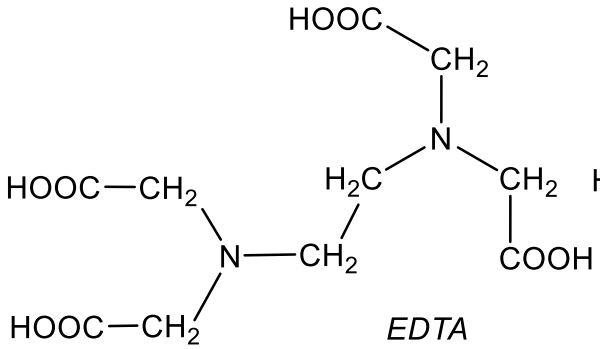
LD_{50} = 2000 mg/kg



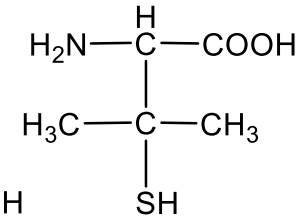
dimercaptosuccinic acid

Adducts:

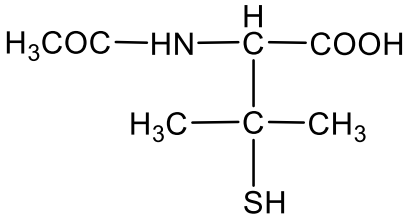
- Stable
- Non toxic
- Highly soluble in water (rapid clearance)
- Resistant to metabolism



EDTA



penicillamine



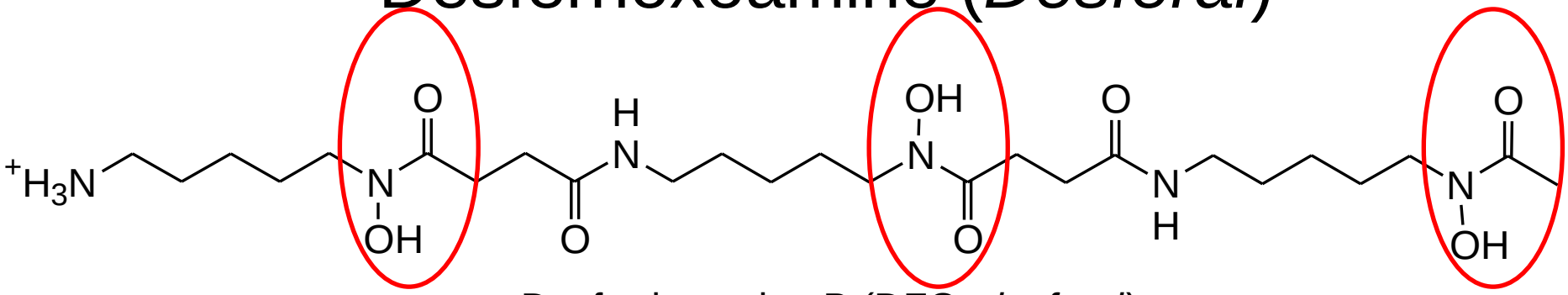
N-acetil-penicillamine

Iron chelation therapy

- Mammals are unable to regulate the export of Fe
- Patients affected by severe forms of anemia (e.g. thalassemia) 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. Efficacia del chelante
2. Tossicità
3. Costo
4. Modo di somministrazione (*compliance*)

Desferrioxoamine (*Desferal*)



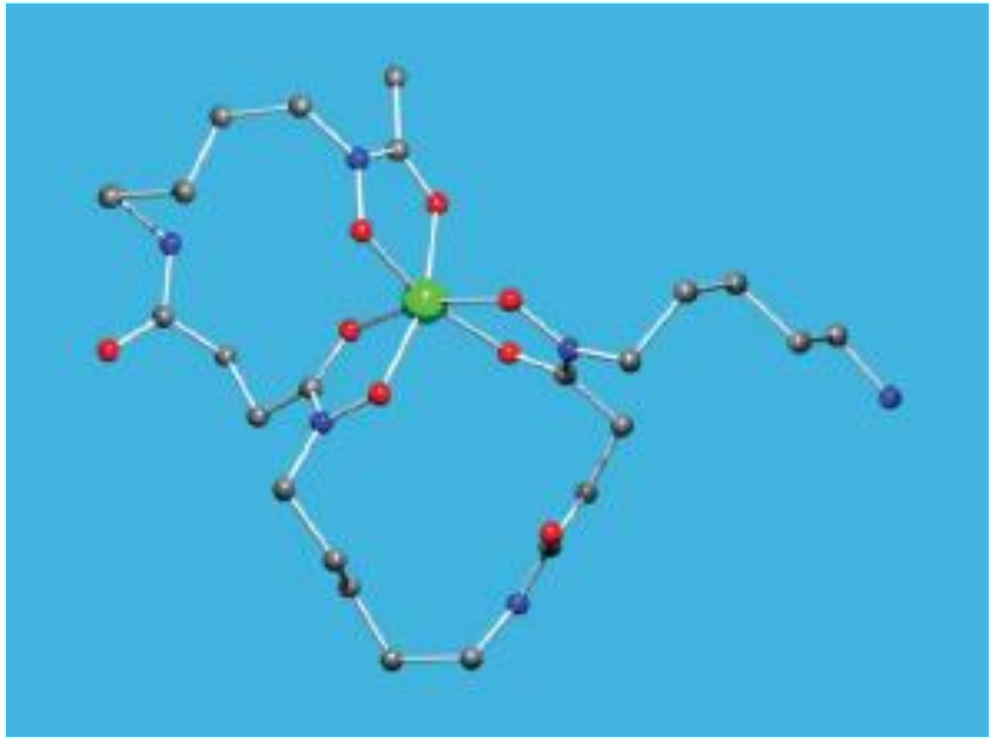
Desferrioxamine B (DFO, *desferal)*

Natural siderophore from *Streptomyces pilosus*

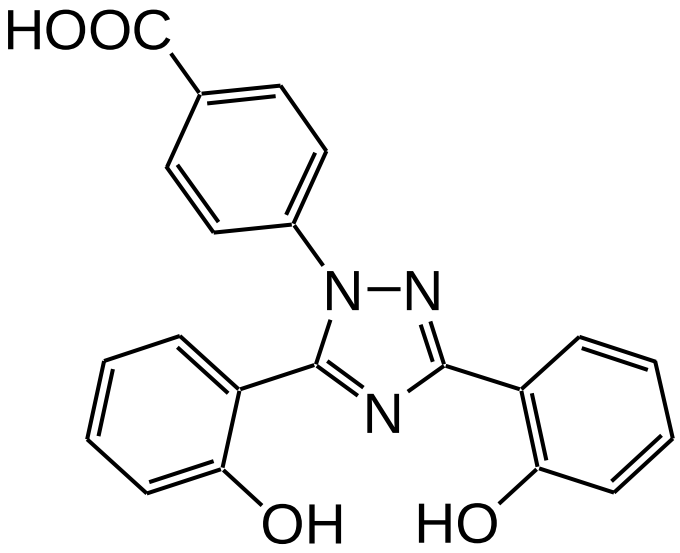
FDA approval: 1968

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

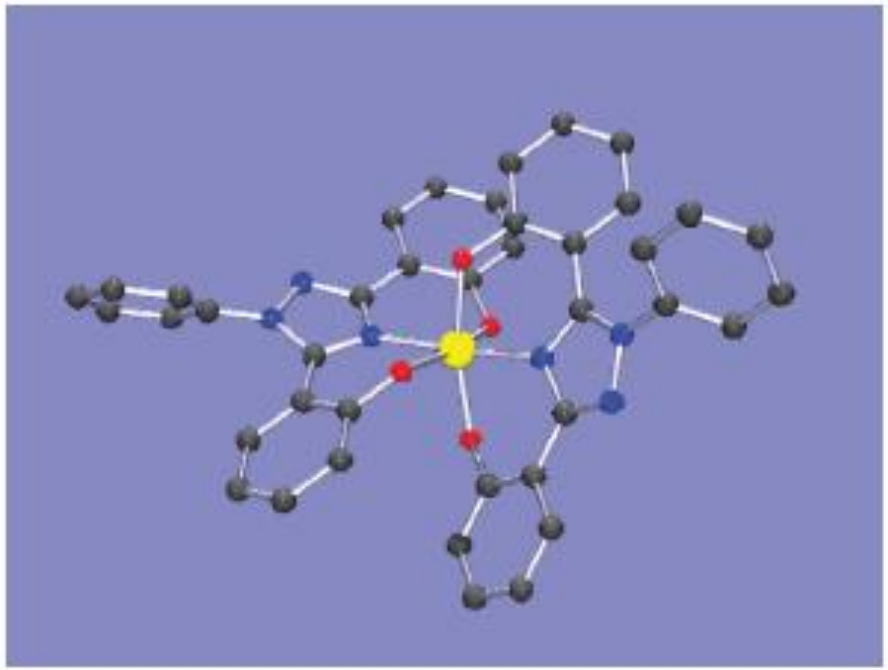
Drawback: very long infusion time: 8 – 12 h



Deferasirox: Orally active



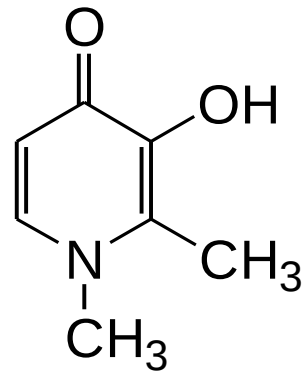
bis-hydroxyphenyl-triazole
deferasirox



pFe = 20

FDA approval: 2005

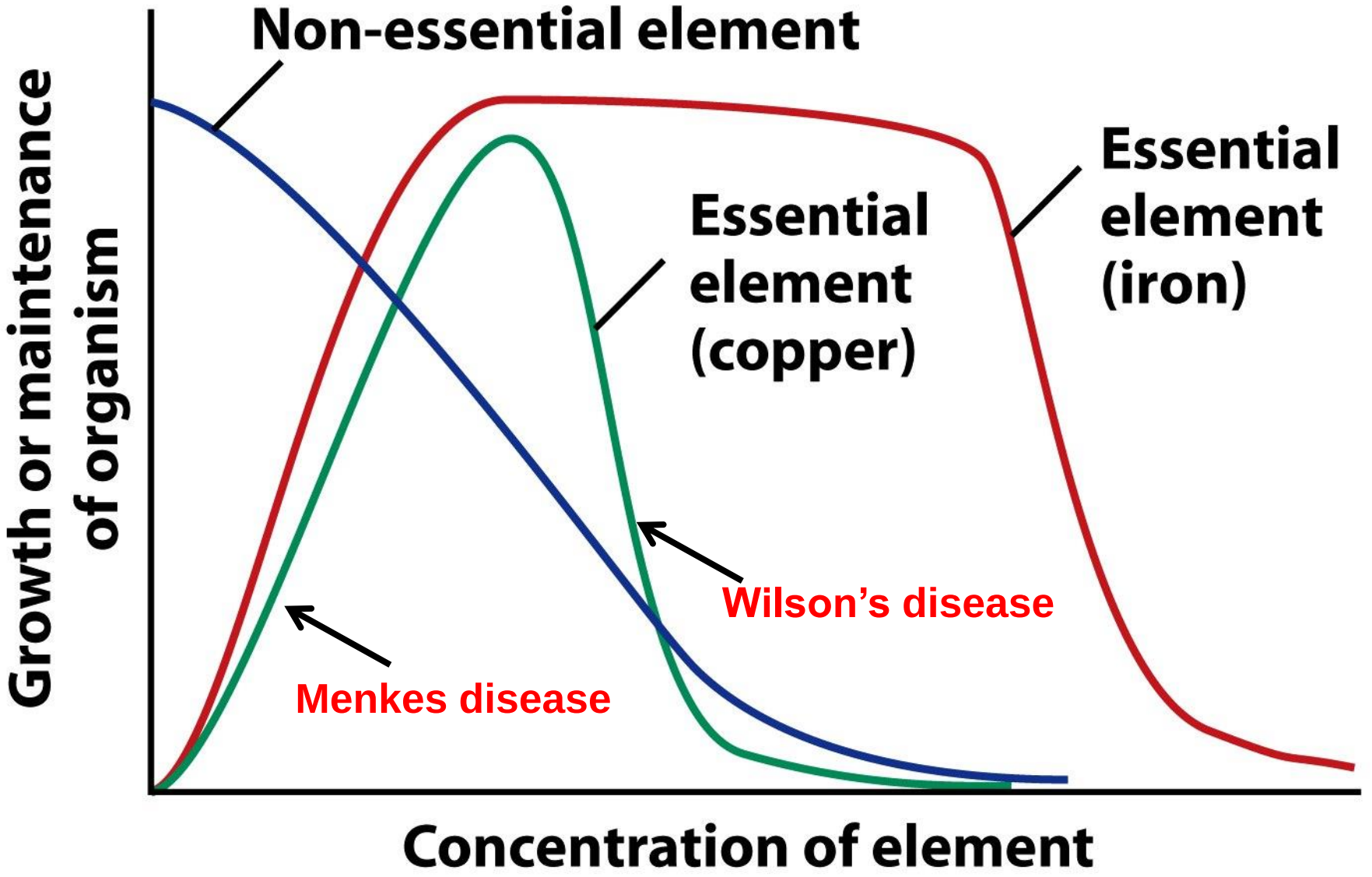
Deferiprone: Orally active



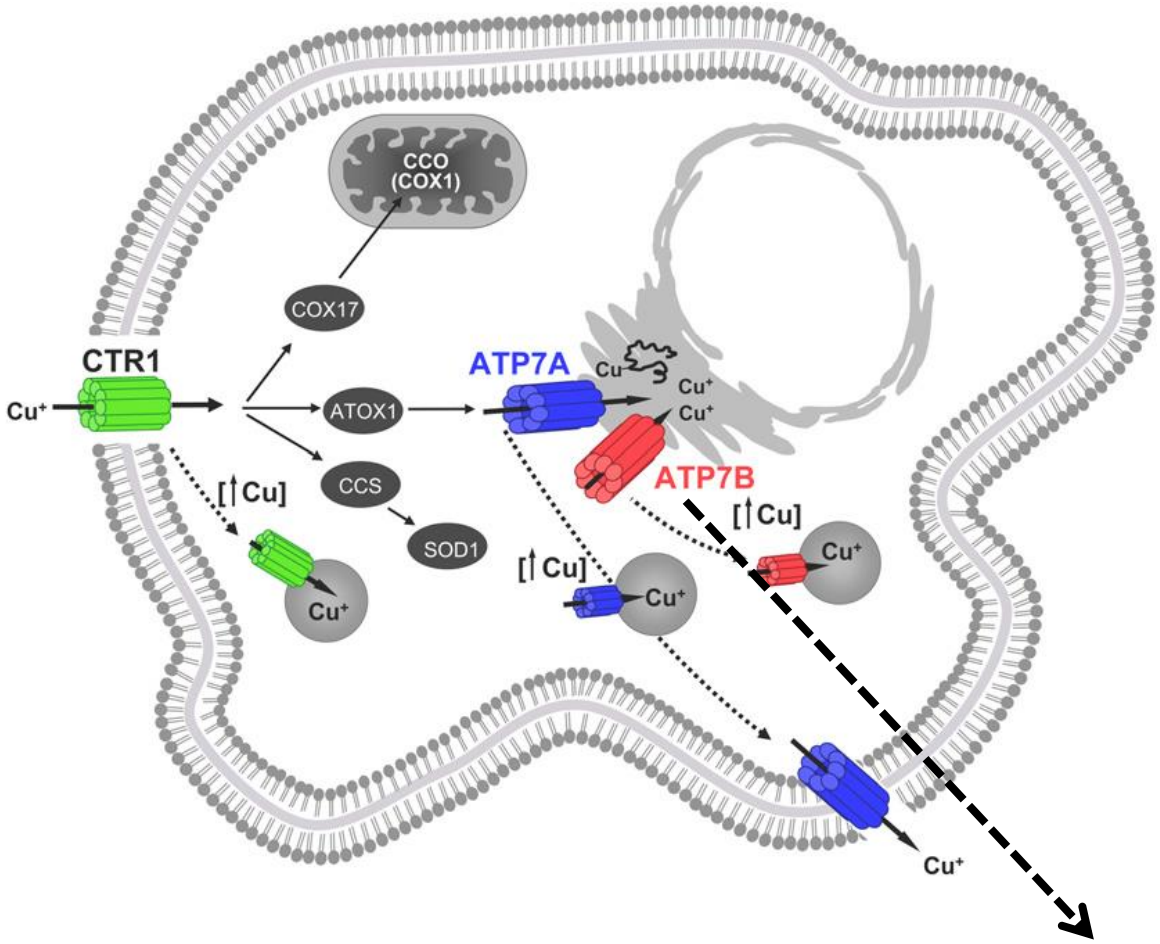
3,4-dihydroxypyridinone
deferiprone

pFe = 20

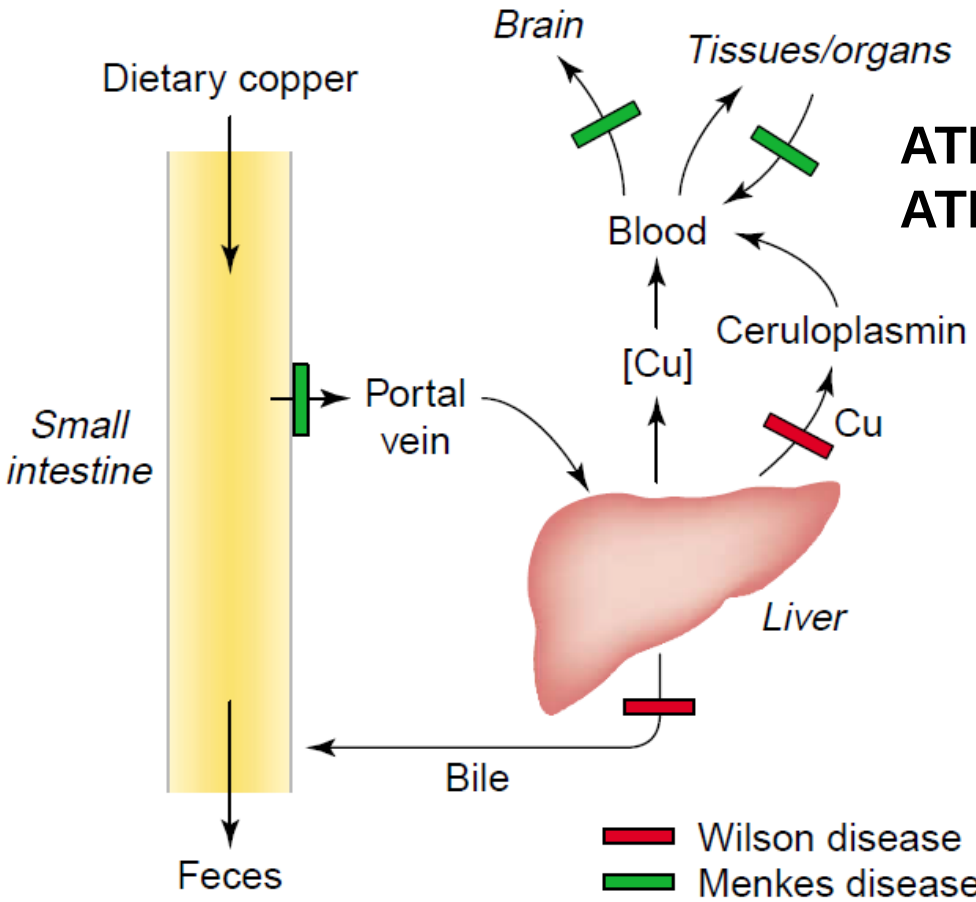
2011 FDA approval as <u>second-line</u> oral drug


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

Copper homeostasis



ATP7A: ubiquitous
ATP7B: liver, kidneys, brain

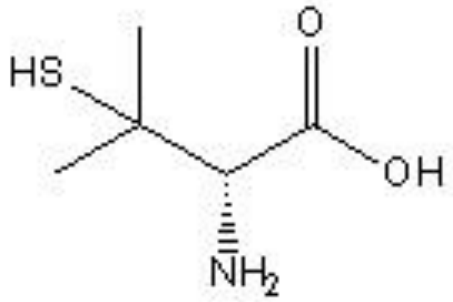


ATP7A: Menkes disease, Cu deficency
ATP7B: Wilson's disease, Cu overload

→ $Cu(II)(His)_2$

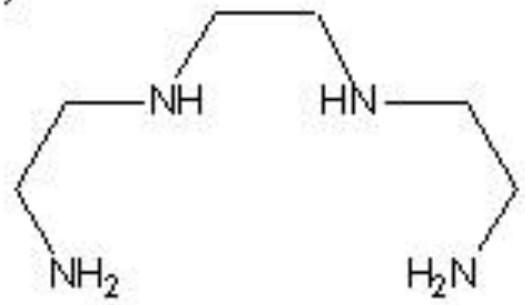
Chelanti per la Sindrome di Wilson (rimozione Cu)

a)



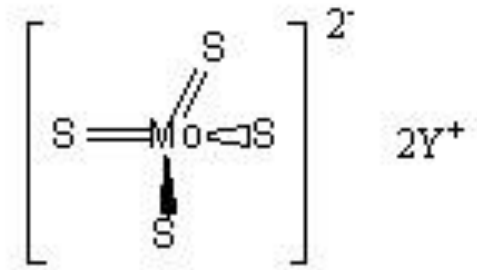
D-penicillamina

b)



Trien *(*o *Trientina*)
(tris-etilenetetrammina)

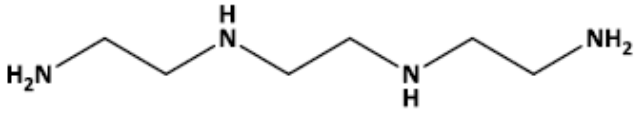
c)



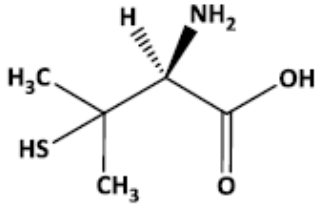
$Y = [NH_4]^+$ or

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

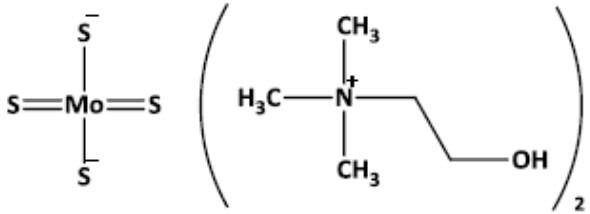
Tetratiomolibdato


H
N
H2N
NH2
N
H

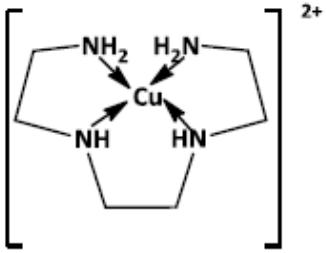
a

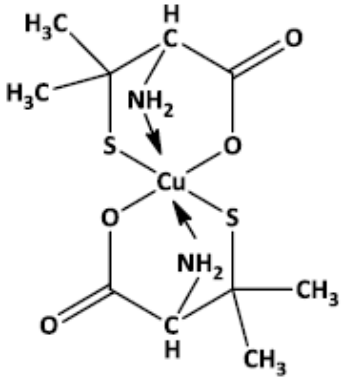

H
NH2
H3C
OH
HS
CH3
O

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

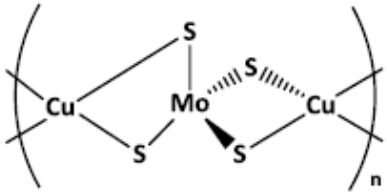

S
Cu
Mo
S
Cu
S
S
n

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.