

METALLI IN MEDICINA
A.A. 2016-2017

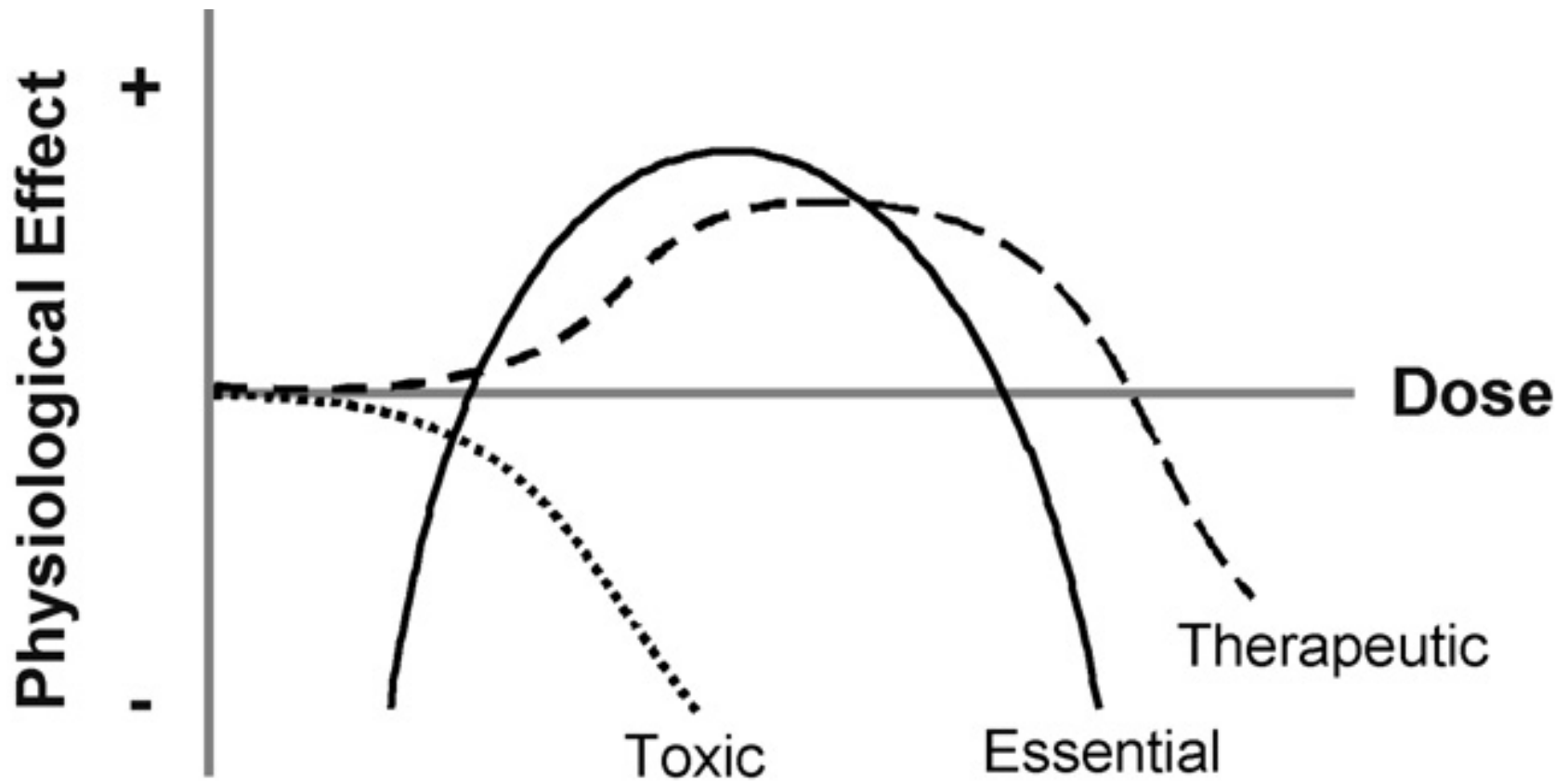
PARTE 1

Enzo Alessio

alessi@units.it



Diagramma di Bertrand





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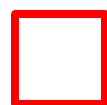
s-block elements

d-block elements

p-block elements

Group 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

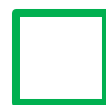
1 H																	2 He	
3 Li	4 Be												5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg												13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr	
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe	
55 Cs	56 Ba	57-71 La-Lu	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn	
87 Fr	88 Ra	89-103 Ac-Lr	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Uub							



Bulk Metals



Trace



Ultra-trace

f-block elements

Lanthanoids	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu
Actinoids	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr

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Metal	g/75 kg
Na	70 – 120
K	160 – 200
Ca	1100
Mg	25
Fe	4 – 5
Zn	2 – 3
Cu	$80 - 120 \times 10^{-3}$
V	15×10^{-3}
Mn	1×10^{-2}
Co	1.2×10^{-3}
Mo	10×10^{-3}
Ni	?

Average
intracellular
concentration

$$[\text{Fe}]_{\text{total}} = 0.5 \text{ mM}$$

$$[\text{Zn}]_{\text{total}} = 0.5 \text{ mM}$$

$$[\text{Cu}]_{\text{total}} = 50 \text{ } \mu\text{M}$$

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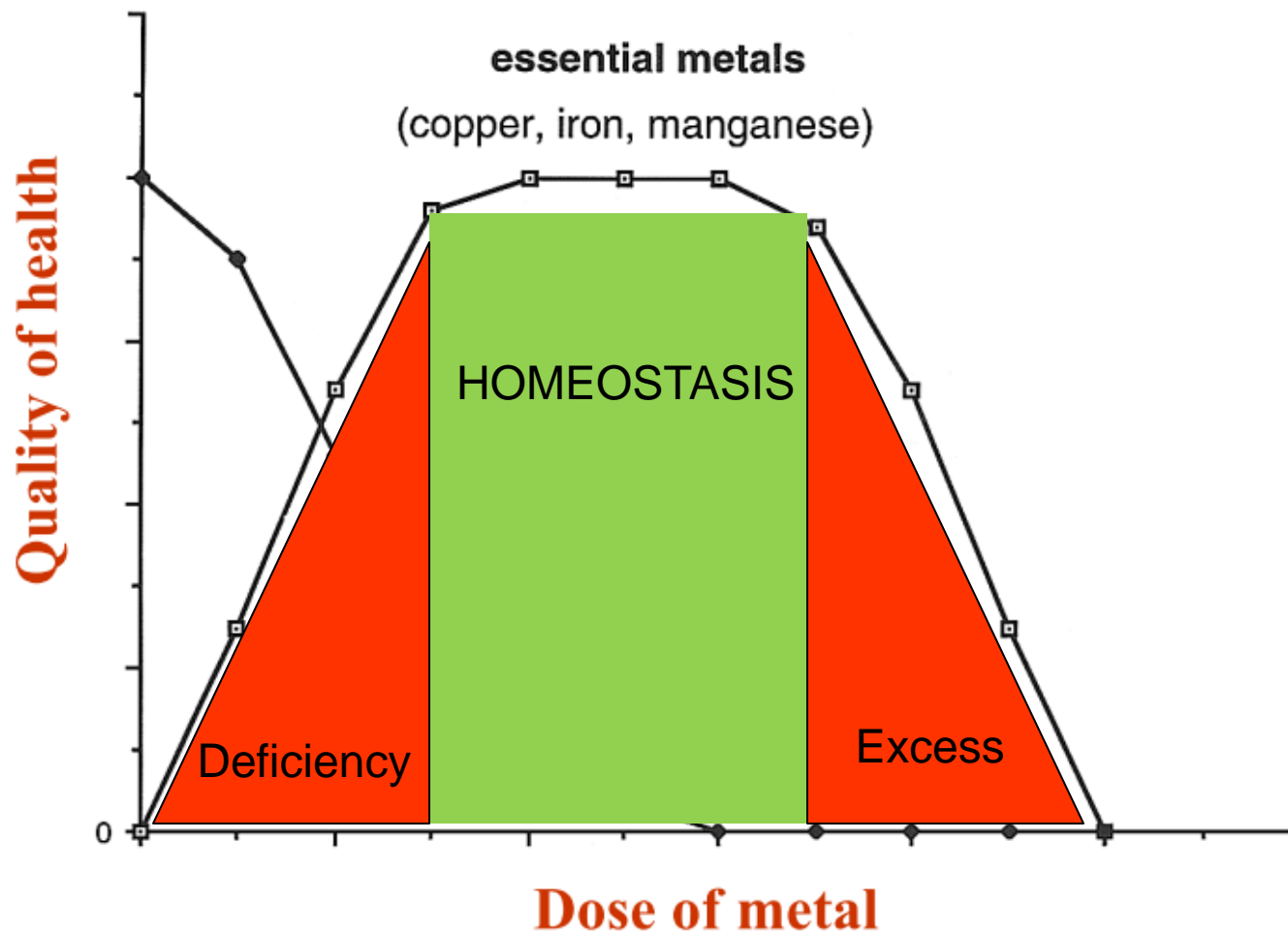
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Ion	Intracellular (mM)	Extracellular (mM)
Na ⁺	10	150
K ⁺	100	5
Mg ²⁺	2.5	1.5
Ca ²⁺	0.1 ^a	2.5
Cl ⁻	4	100

^a0.1 mM in the cytoplasm of resting cells

Dose-response curve



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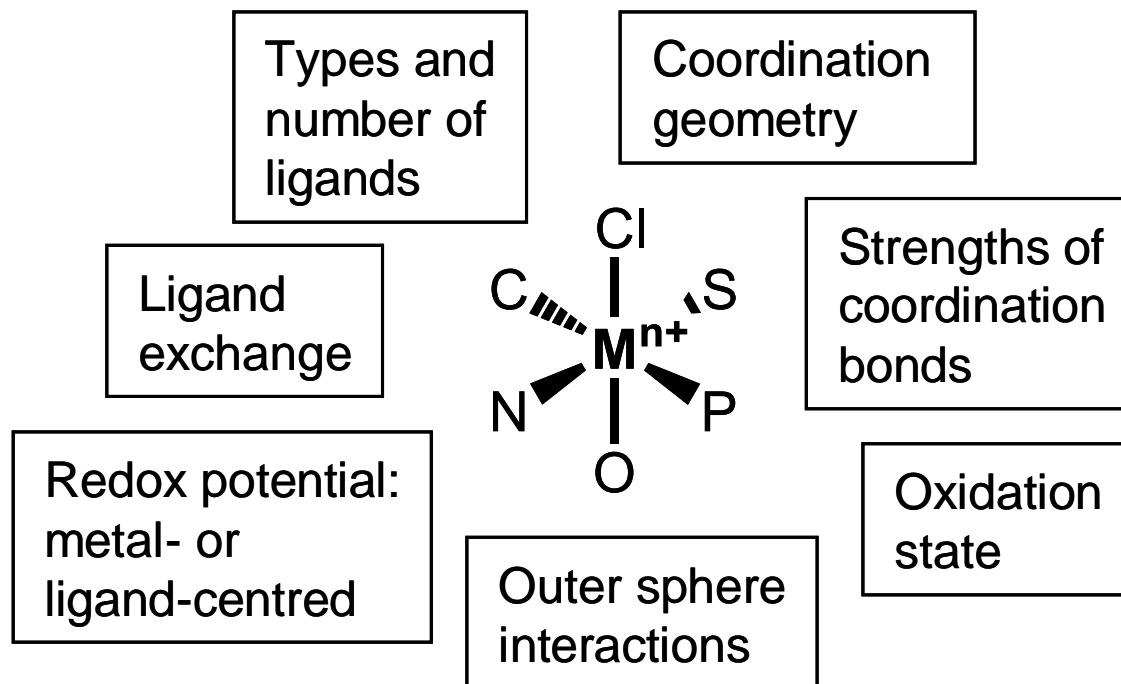


Elemento	Sintomi da deficienza	Sintomi da eccesso
Ca	Ritardo nella crescita dello scheletro	
Mg	Crampi muscolari, convulsioni	
Fe	Anemia , disordini nel sistema immunitario	Stress ossidativo
Zn	Danni alla pelle, ritardata maturazione sessuale	
Cu	Debolezza delle arterie, disordini del fegato, anemia secondaria, Sindrome di Menkes	Sindrome di Wilson
Mn	Infertilità, ridotta crescita dello scheletro	Disturbi psichiatrici
Mo	Ritardo nella crescita delle cellule, propensione alla carie	Anemia
Co	Anemia perniciosa	Disturbi cardiaci
Si	Disordini nella crescita dello scheletro	
F	Carie	
I	Gotta, disordini tiroidei, metabolismo ritardato	Gotta
Se	Debolezza muscolare, cardiomiopatia	
As	Crescita ritardata	

Genome
Proteome
Metallome

The entirety of metals contained in each type of cell of a species, each with its specific **amount, speciation and localization**

Speciation



Metal centres (Lewis acids)

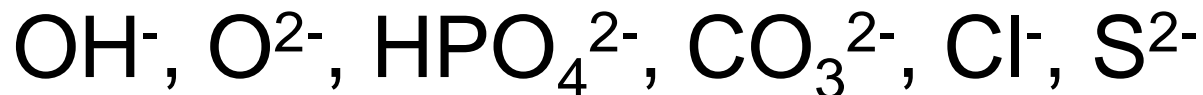
Hard; class (a)	Li^+ , Na^+ , K^+ , Rb^+ , Be^{2+} , Mg^{2+} , Ca^{2+} , Sr^{2+} , Sn^{2+} , Mn^{2+} , Zn^{2+} , Al^{3+} , Ga^{3+} , In^{3+} , Sc^{3+} , Cr^{3+} , Fe^{3+} , Co^{3+} , Y^{3+} , Th^{4+} , Pu^{4+} , Ti^{4+} , Zr^{4+} , $[\text{VO}]^{2+}$, $[\text{VO}_2]^+$
Soft; class (b)	Zero oxidation state metal centres, Tl^+ , Cu^+ , Ag^+ , Au^+ , $[\text{Hg}_2]^{2+}$, Hg^{2+} , Cd^{2+} , Pd^{2+} , Pt^{2+} , Tl^{3+}
Intermediate	Pb^{2+} , Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Os^{2+} , Ru^{3+} , Rh^{3+} , Ir^{3+}

Ligands (Lewis bases)

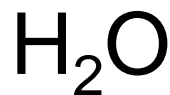
Hard; class (a)	F^- , Cl^- , H_2O , ROH , R_2O , $[OH]^-$, $[RO]^-$, $[RCO_2]^-$, $[CO_3]^{2-}$, $[NO_3]^-$, $[PO_4]^{3-}$, $[SO_4]^{2-}$, $[ClO_4]^-$, $[ox]^{2-}$, NH_3 , RNH_2
Soft; class (b)	I^- , H^- , R^- , $[CN]^-$ (<i>C</i> -bound), CO (<i>C</i> -bound), RNC , RSH , R_2S , $[RS]^-$, $[SCN]^-$ (<i>S</i> -bound), R_3P , R_3As , R_3Sb , alkenes, arenes
Intermediate	Br^- , $[N_3]^-$, py , $[SCN]^-$ (<i>N</i> -bound), $ArNH_2$, $[NO_2]^-$, $[SO_3]^{2-}$

Biological ligands

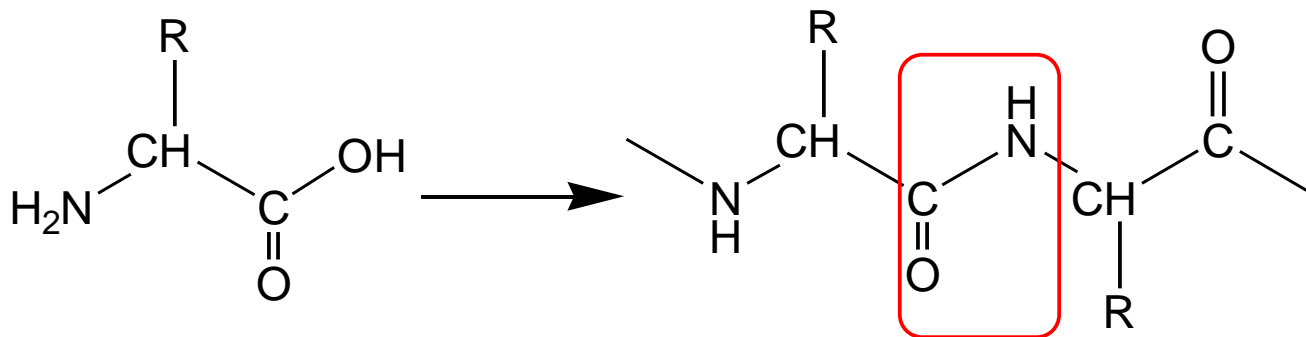
Anions



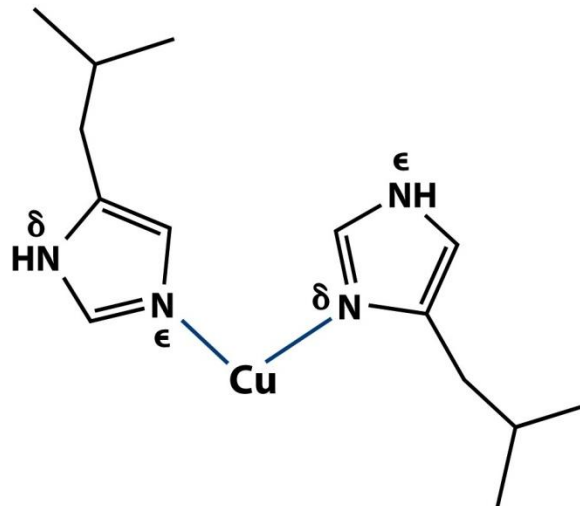
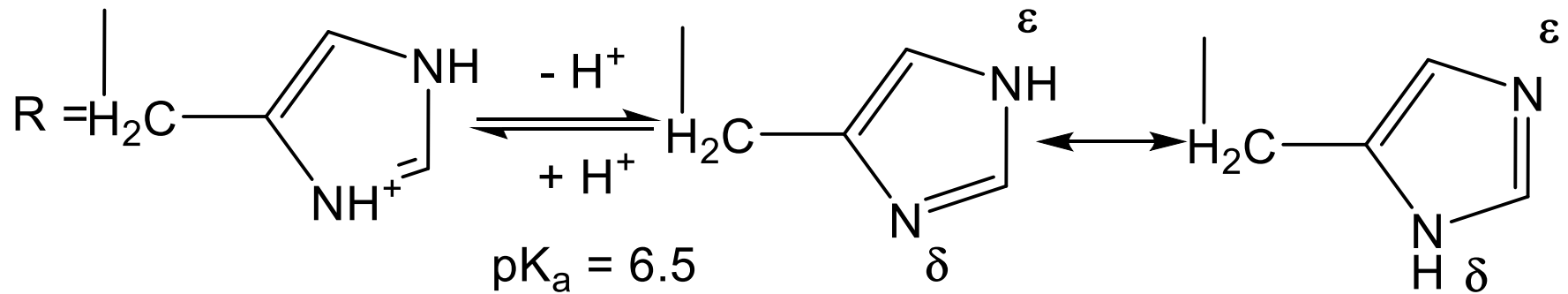
Water



Aminoacid side-chains



Histidine

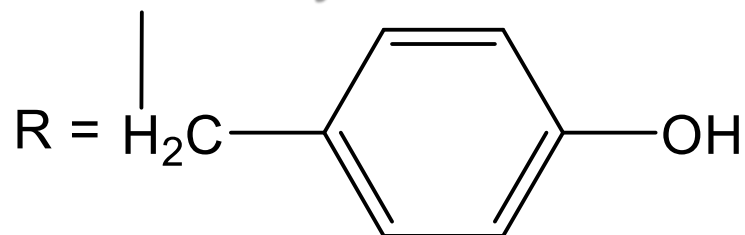


Cysteine and Methionine



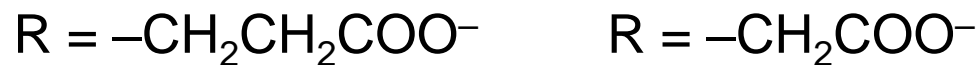
$\text{pK}_a = 8.5$

Tyrosine



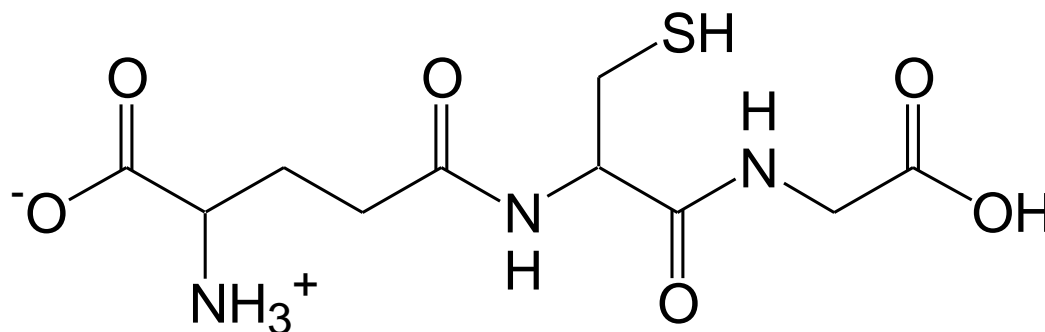
$\text{pK}_a = 10$

Glutammate and Aspartate



$\text{pK}_a = 4.5$

GLUTATHIONE

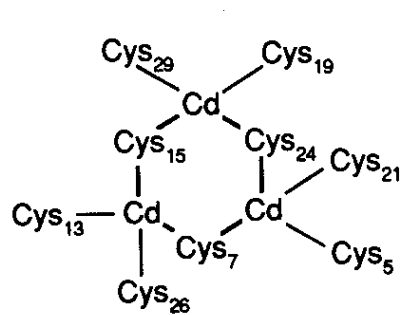
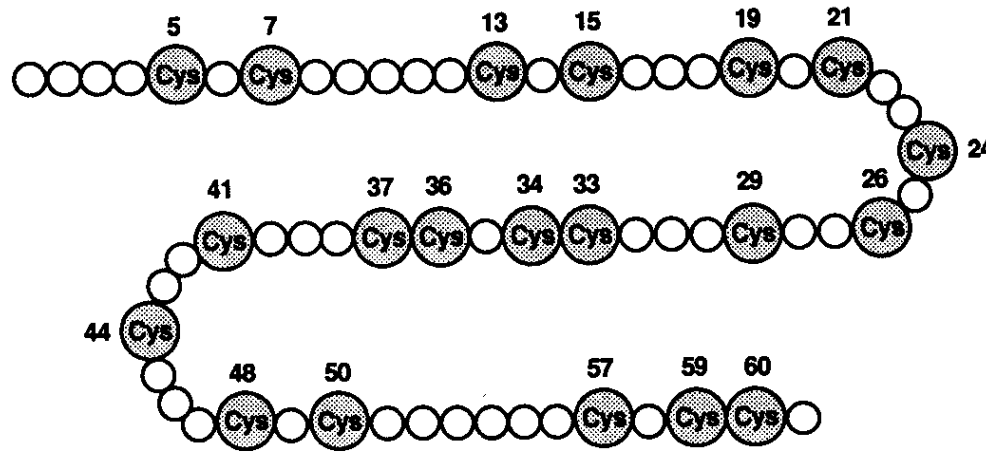


GSH

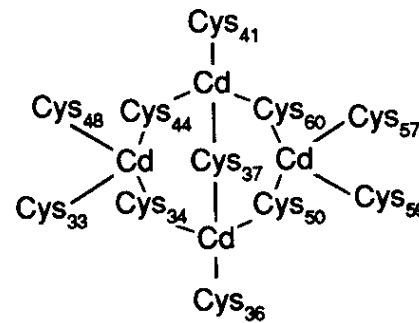
Glu-Cys-Gly

0.5 – 10 mM intracellular

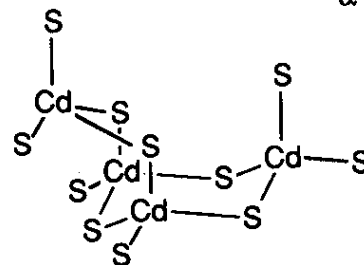
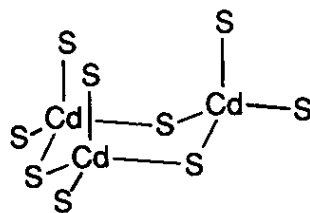
Metallothioneins



β

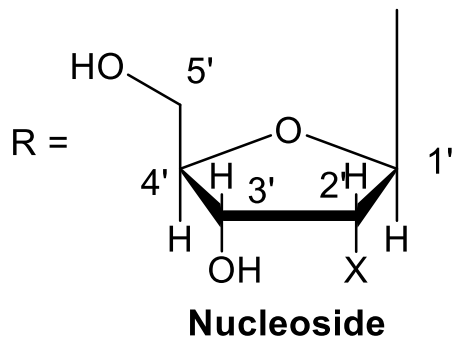
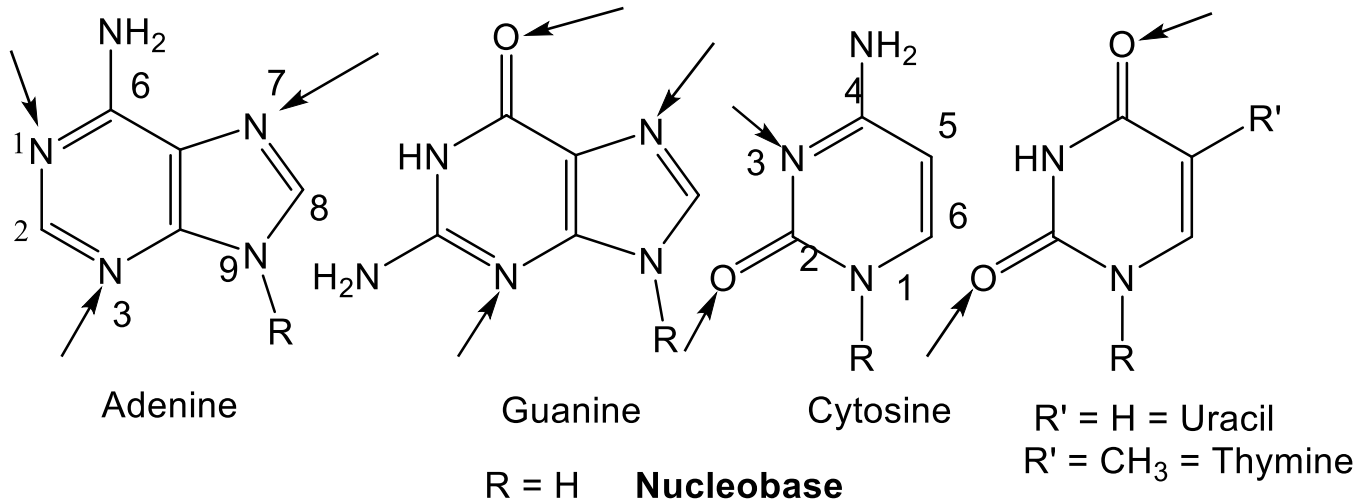


α

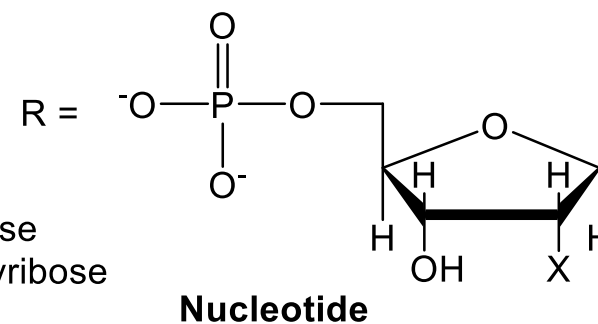


6 kDa,
ca. 60 a.a.
fino 30% cys

Nucleobases

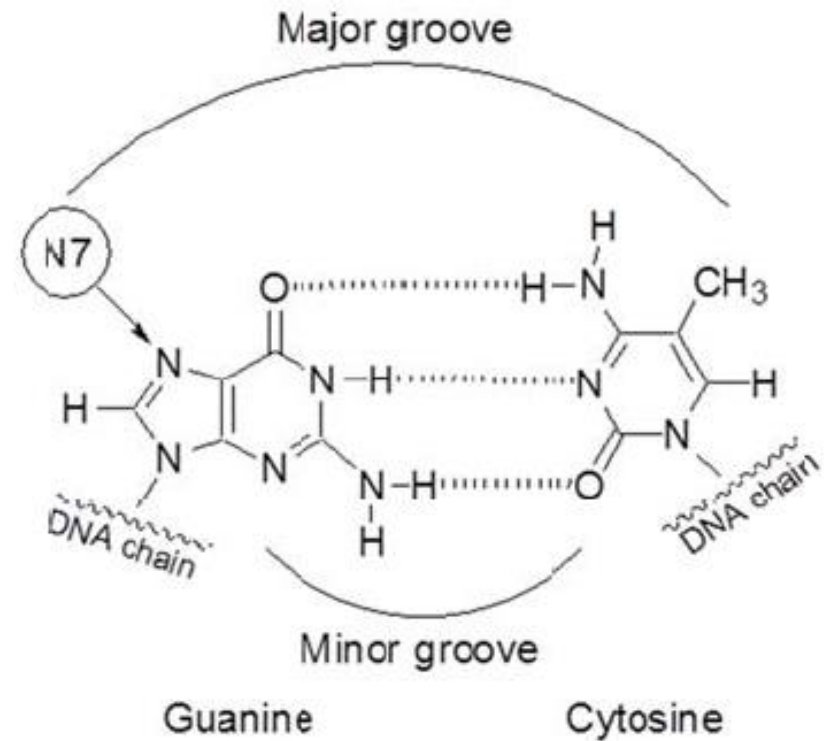
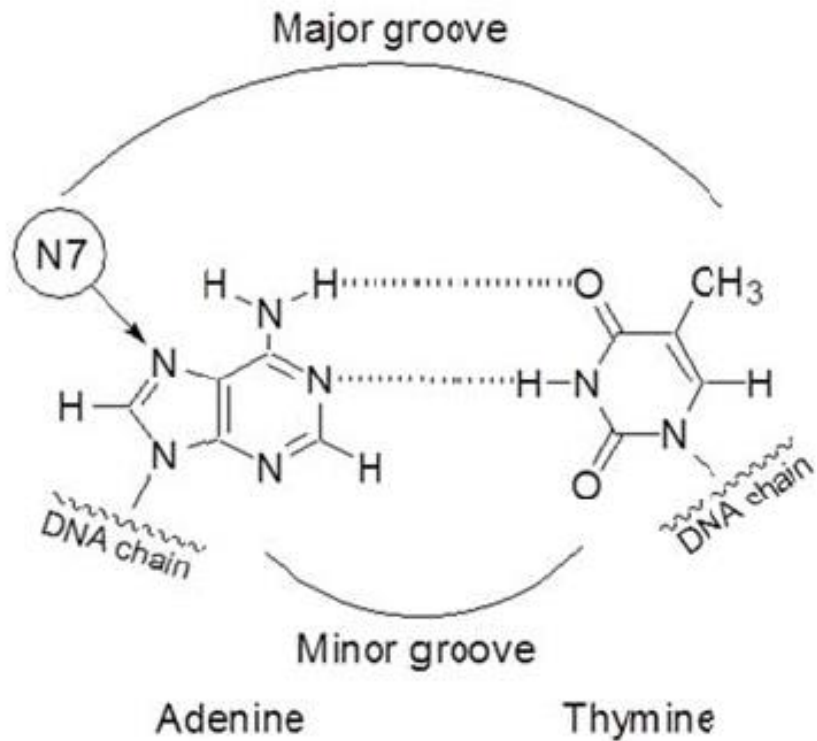


X = OH ribose
X = H deoxyribose



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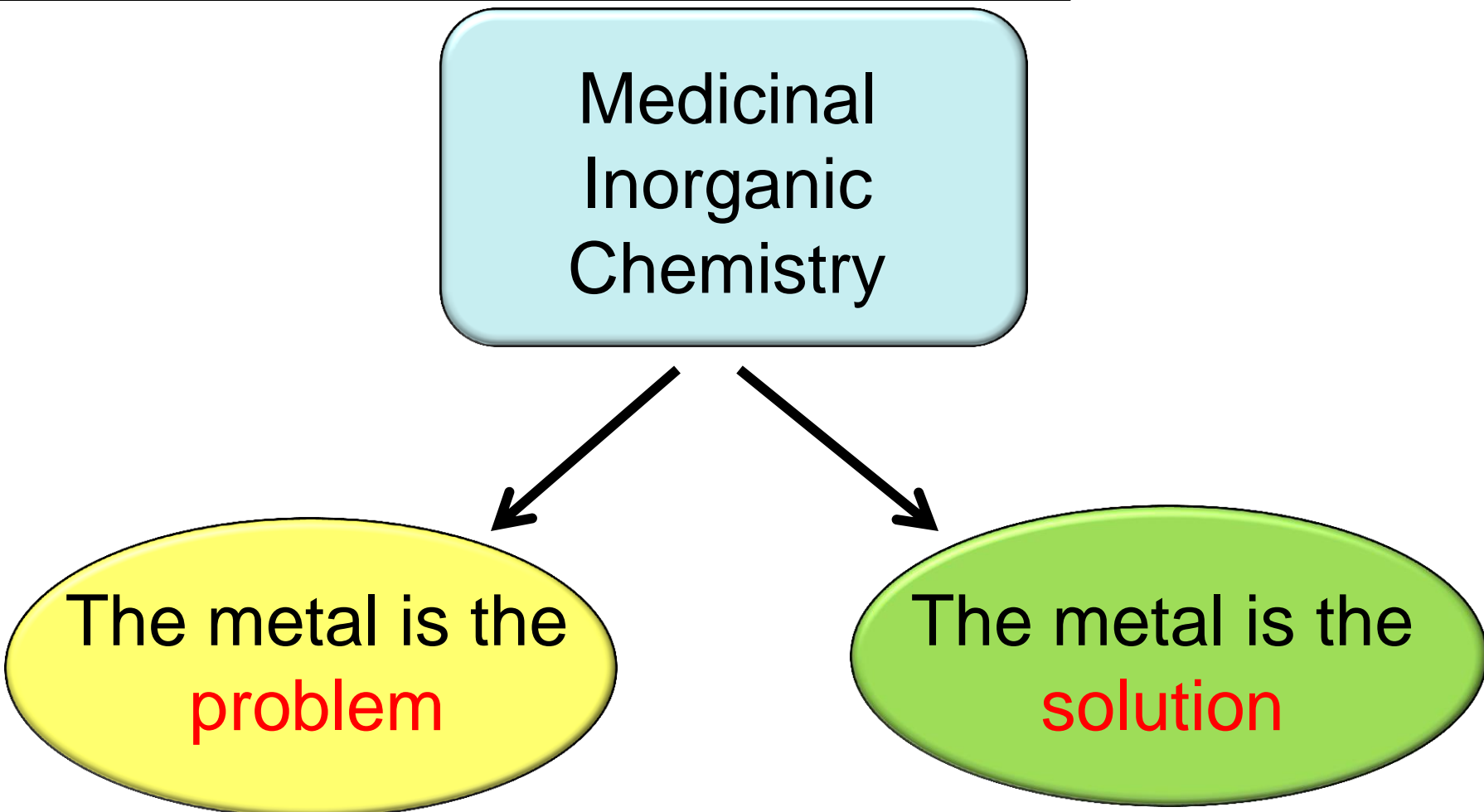
Endogenous reducing agents

Electron transfer enzymes

Ascorbic acid: 11–79 μM in the blood

Glutathione: 0.5 – 10 mM intracellular

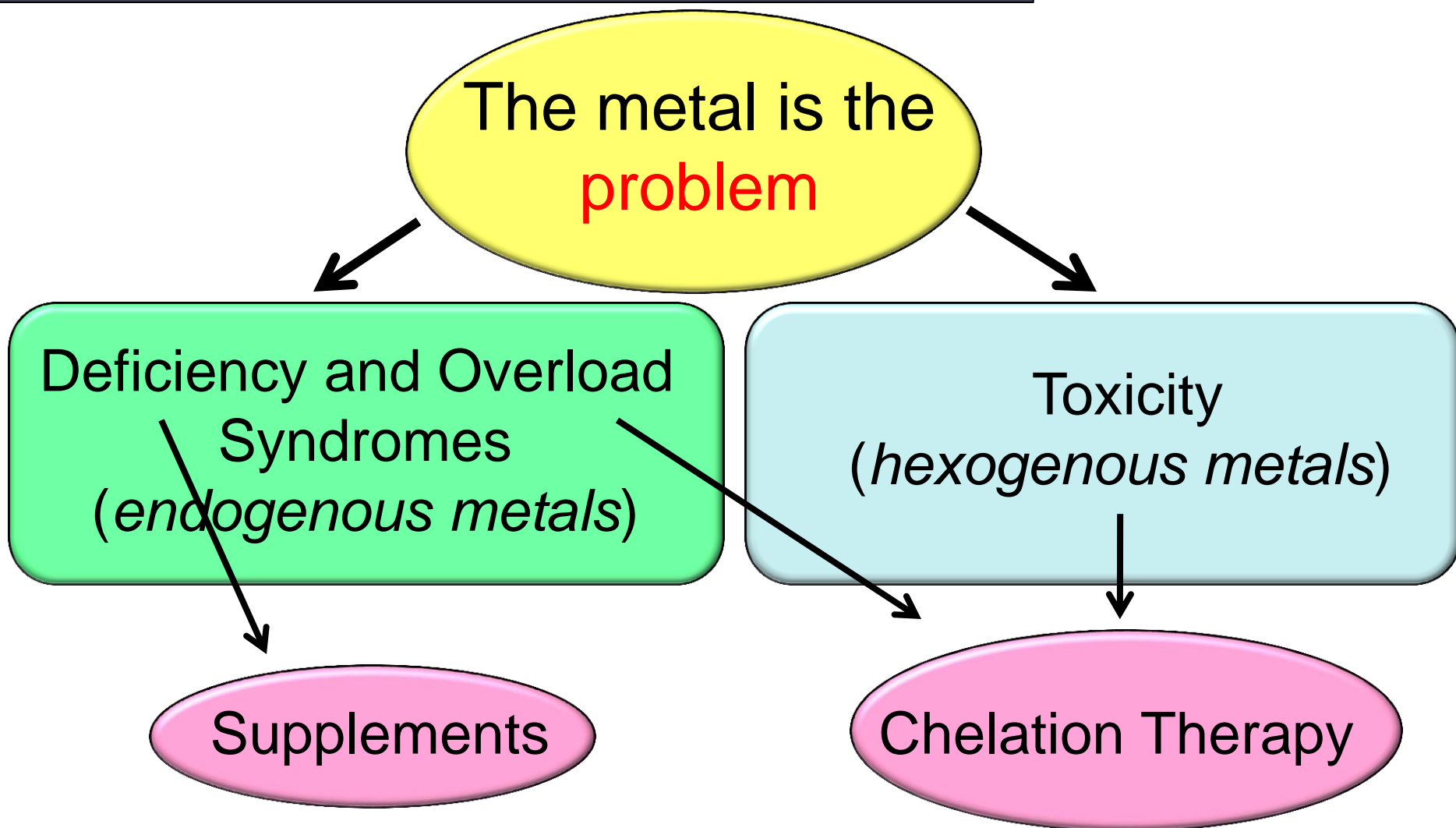
Medicinal
Inorganic
Chemistry



```
graph TD; A[Medicinal Inorganic Chemistry] --> B([The metal is the problem]); A --> C([The metal is the solution]);
```

The metal is the
problem

The metal is the
solution



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The metal is the
problem

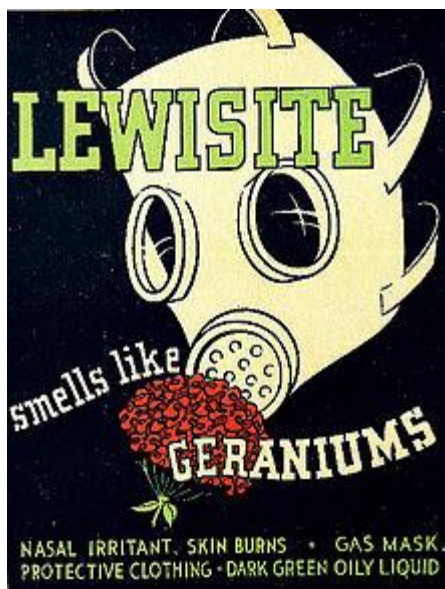


Inhibitors or Analogs of
Metalloenzymes

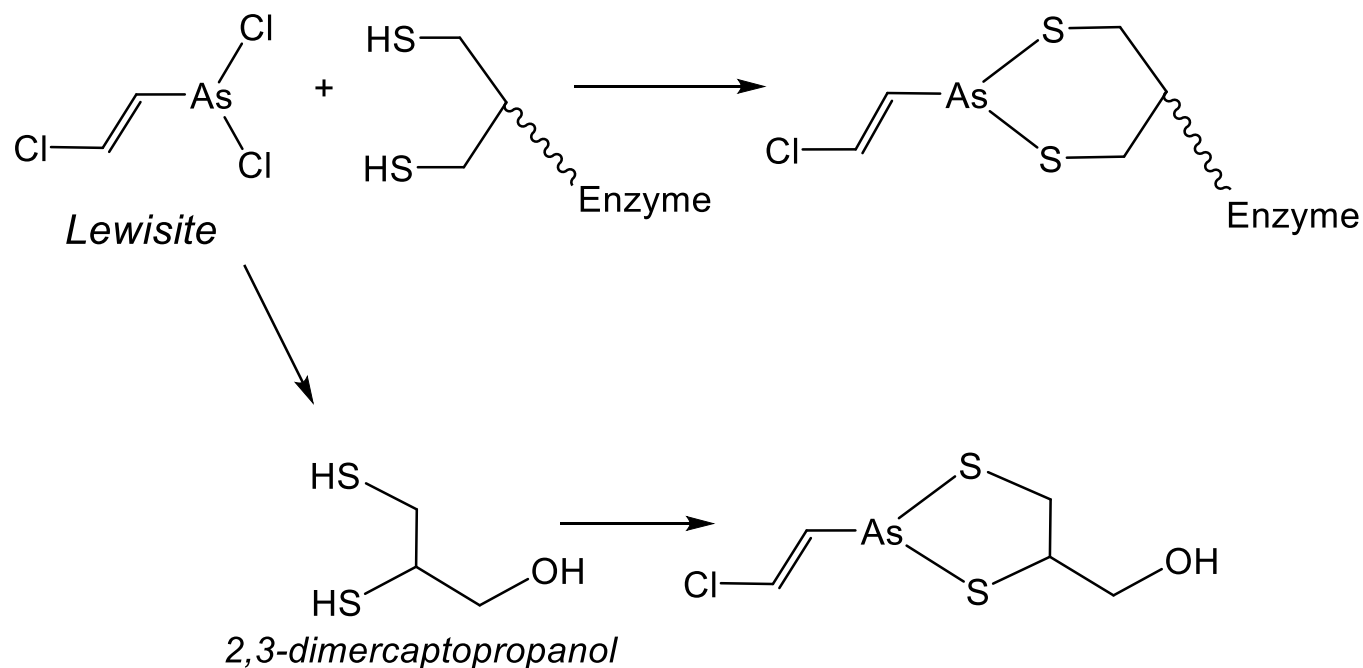
The metal is the
solution



Diagnostic and Therapeutic
Agents



Chelation Therapy



BAL = *British Anti-Lewisite*

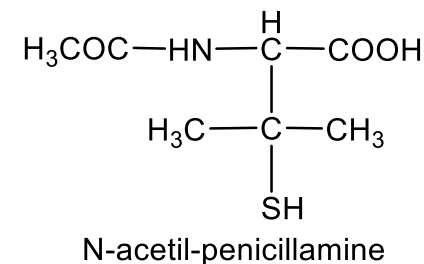
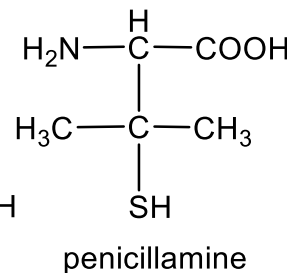
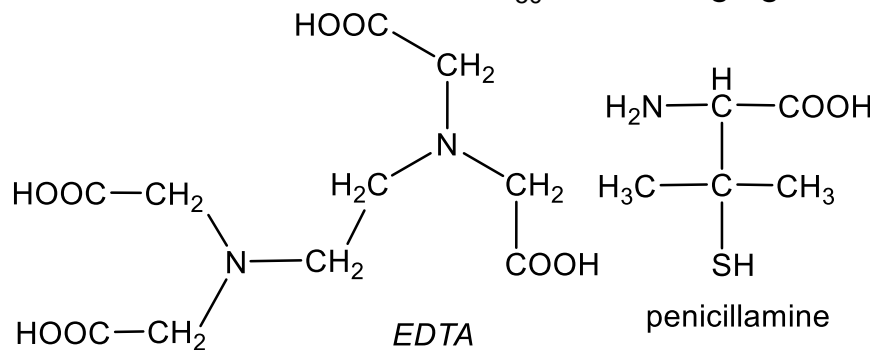
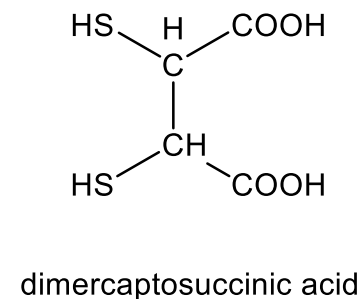
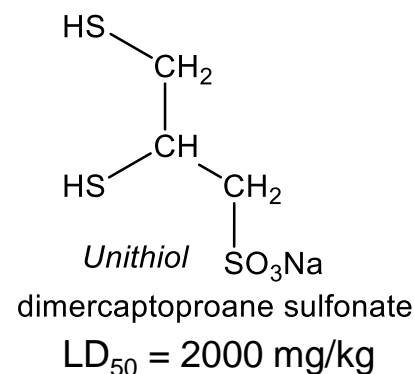
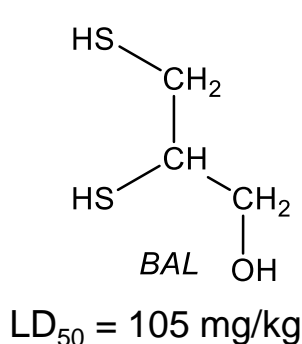
Agent:

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

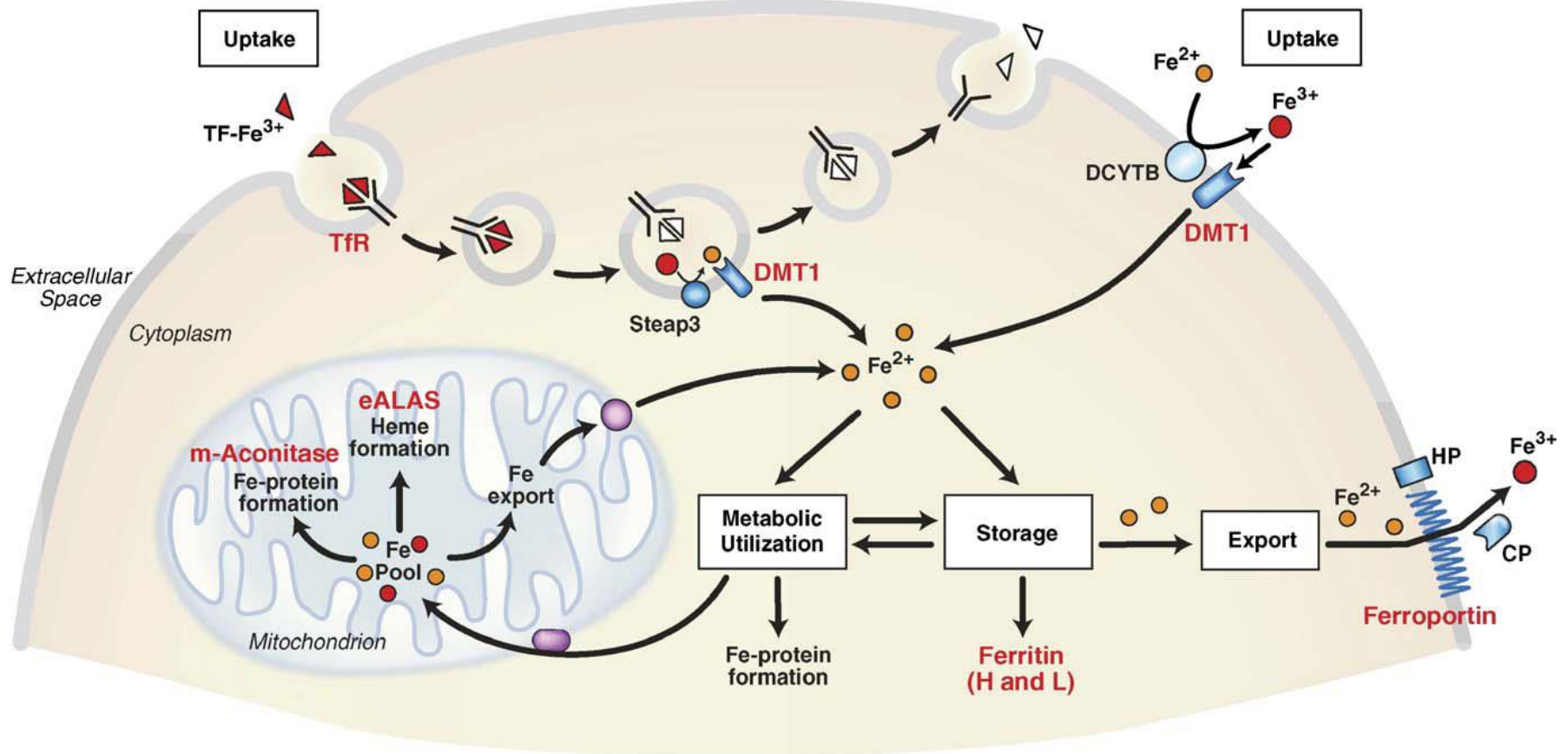
Adducts:

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

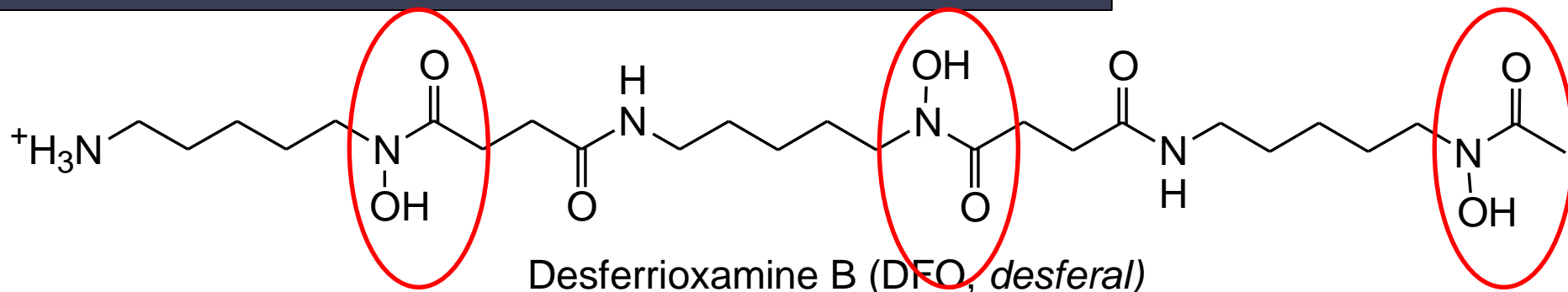
Chelation Therapy



Iron homeostasis



- 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: $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}\cdot + \text{OH}^-$
- Chelation therapy is essential



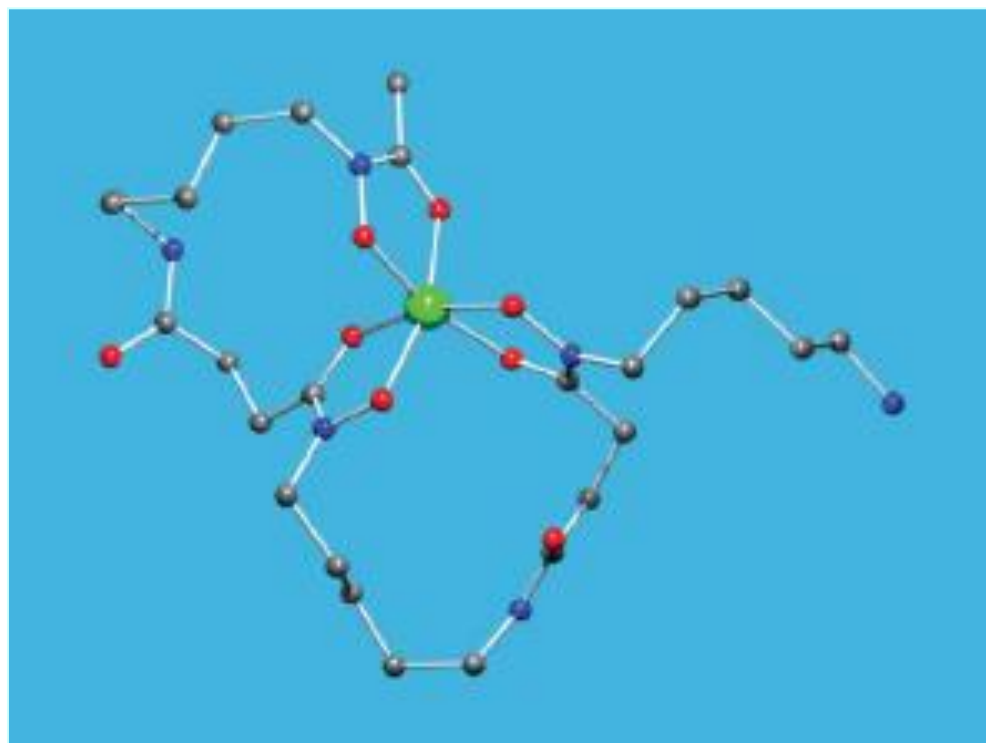
Natural Siderophore from *Streptomyces pilosus*

FDA approval: 1968

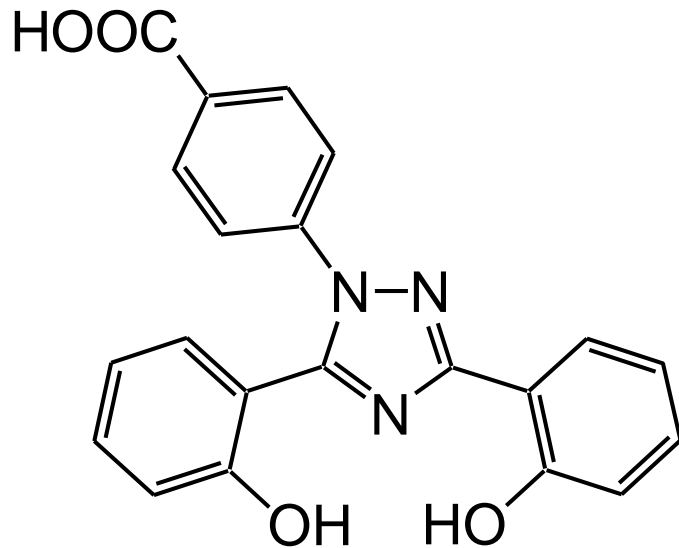
$pFe = 26.6$

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

Drawback: very long
infusion time: 8 – 12 h



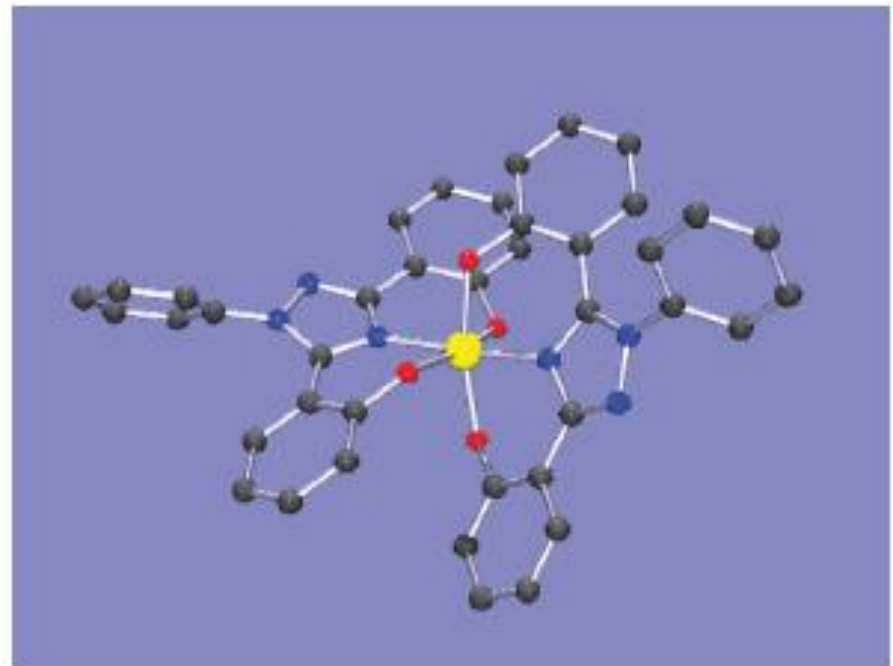
Orally active



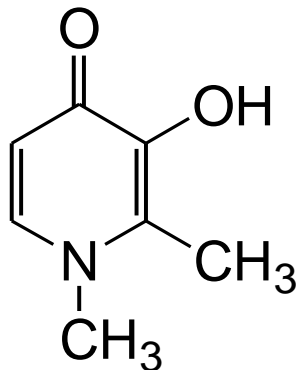
bis-hydroxyphenyl-triazole
deferasirox

pFe = 20

FDA approval: 2005



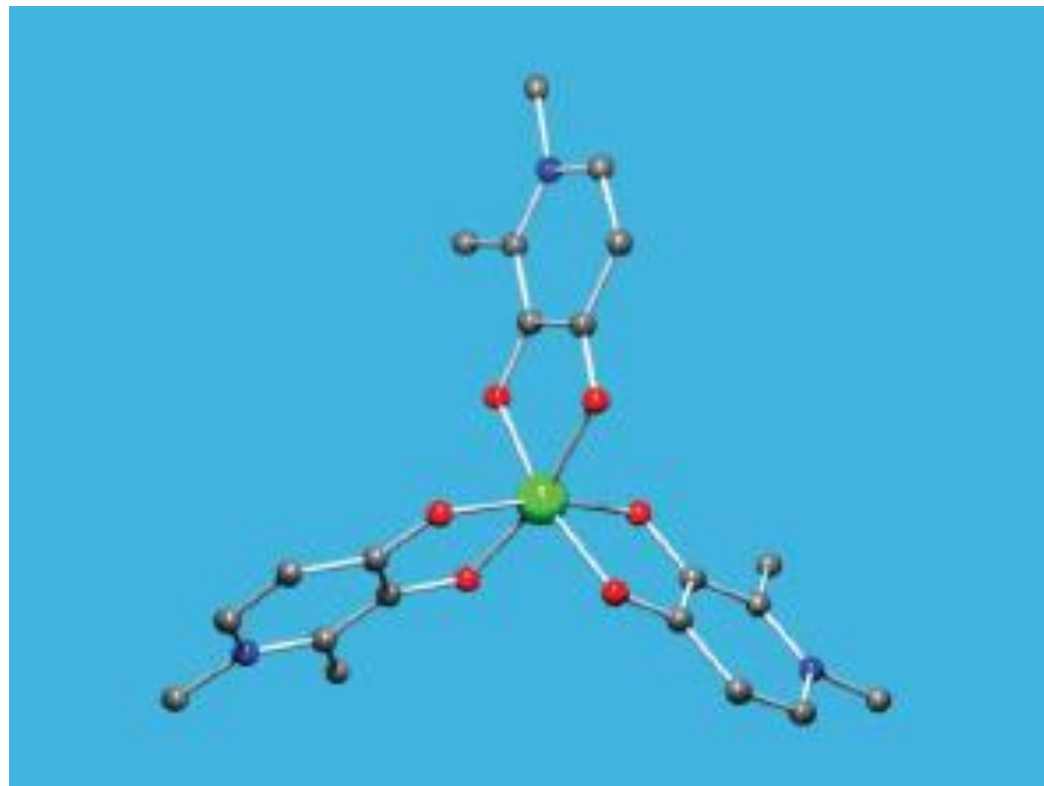
Orally active

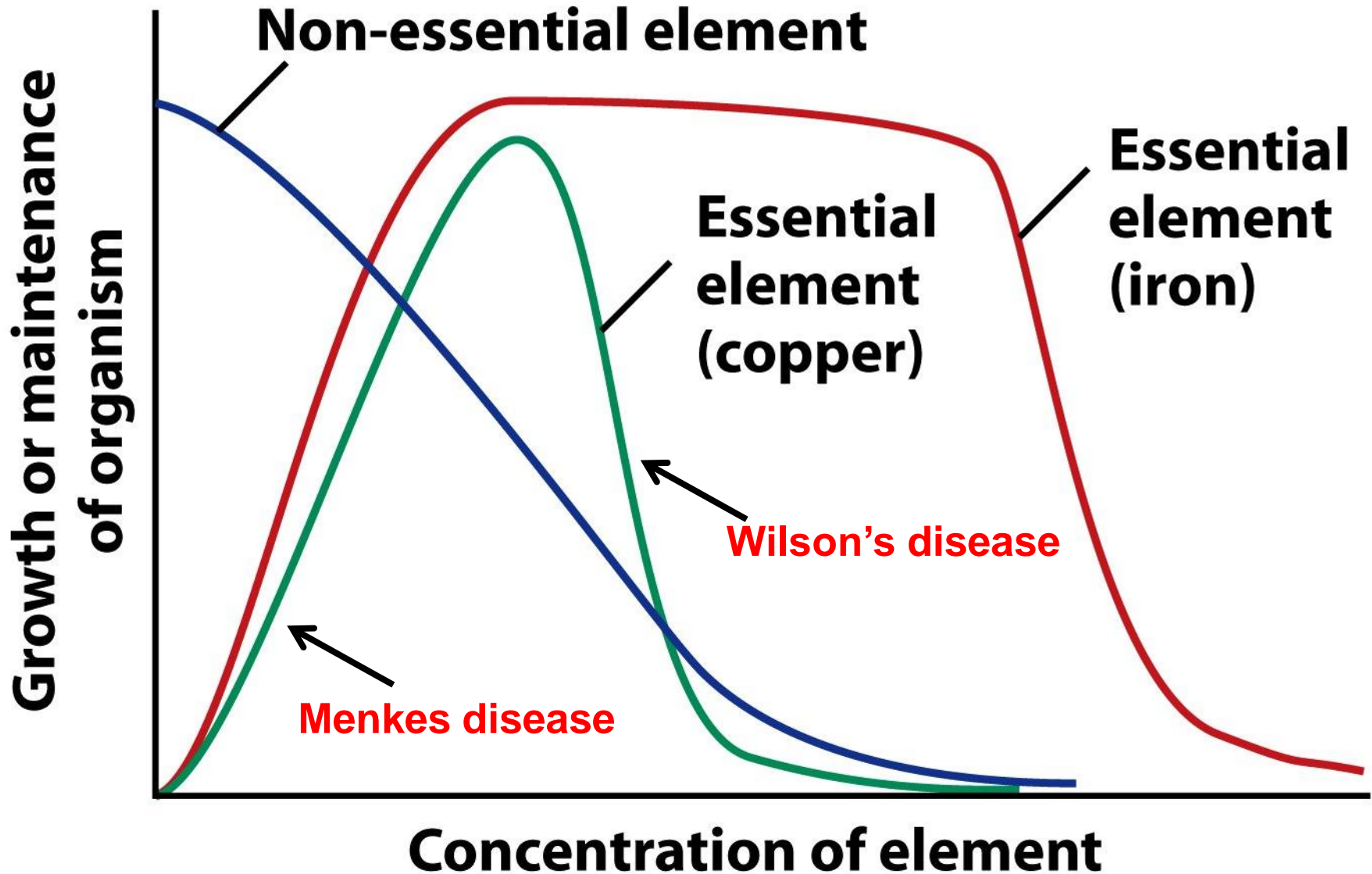


3,4-dihydroxypyridinone
deferiprone

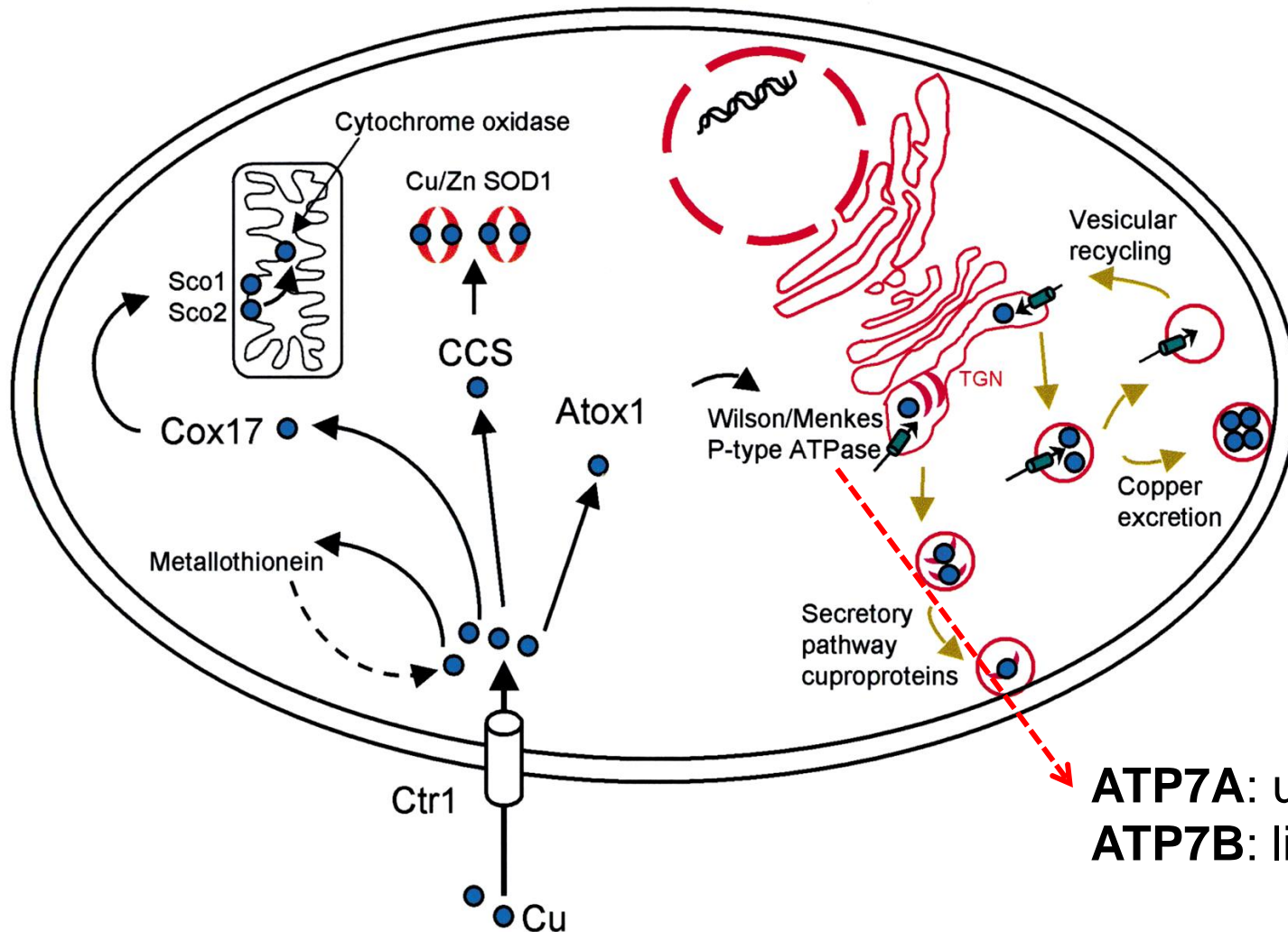
pFe = 20

2011 FDA approval as
second-line oral drug



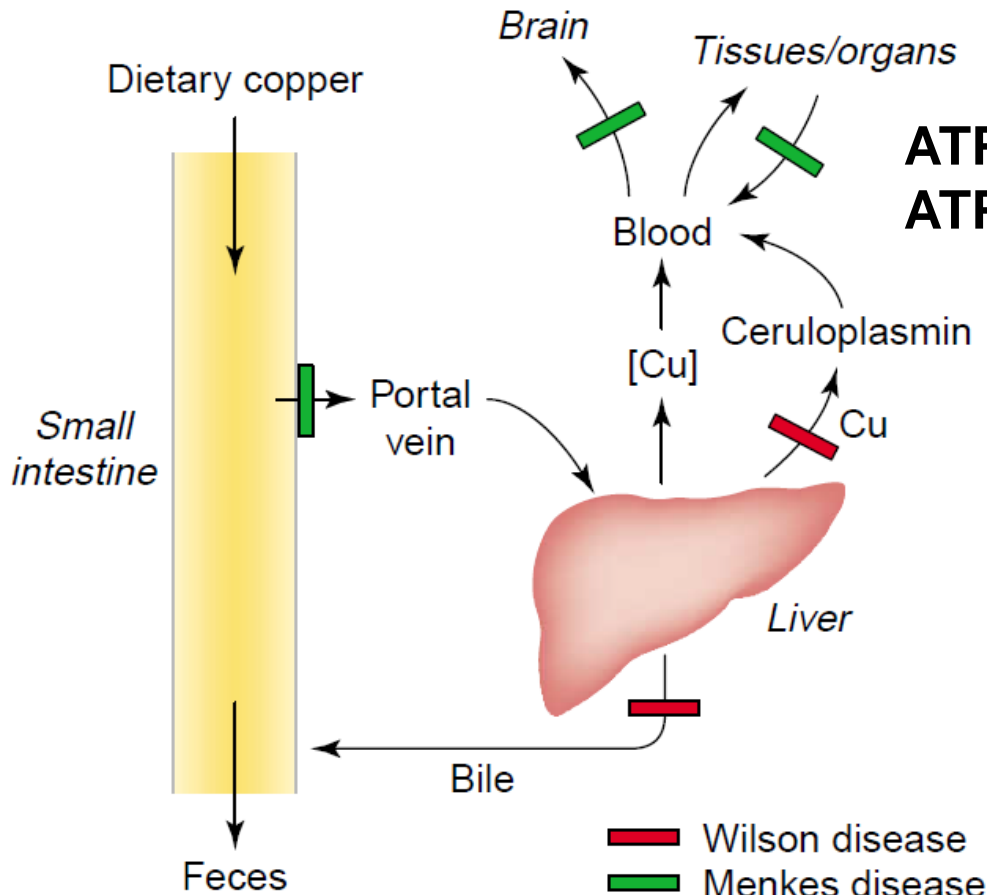


Copper homeostasis

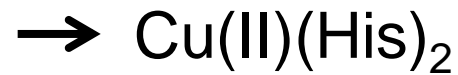


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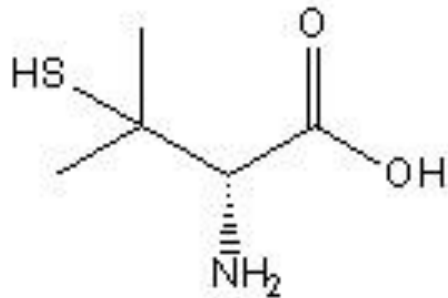


ATP7A: Menkes disease, Cu deficiency
ATP7B: Wilson's disease, Cu overload



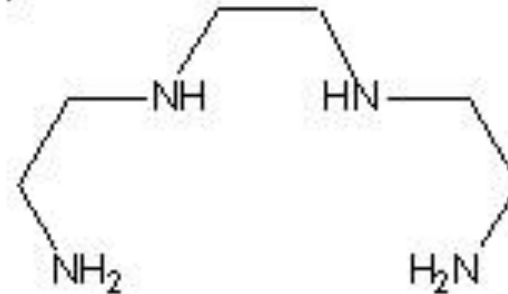
Chelanti per la Sindrome di Wilson (rimozione Cu)

a)



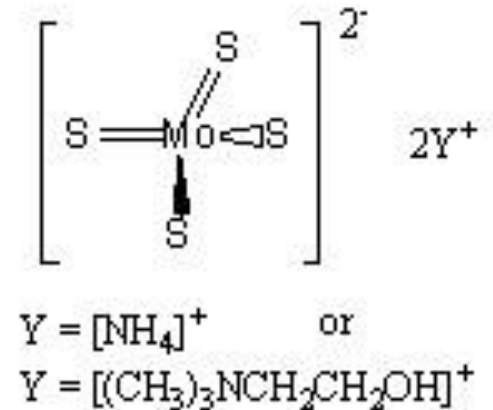
D-penicillamina

b)



Trientina

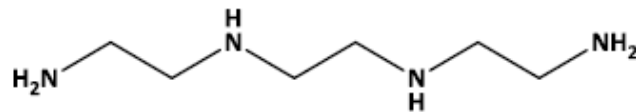
c)



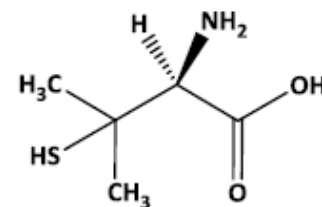
Tetratiomolibdato

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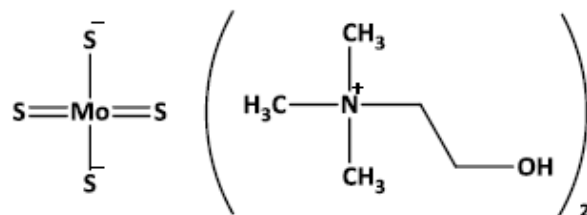
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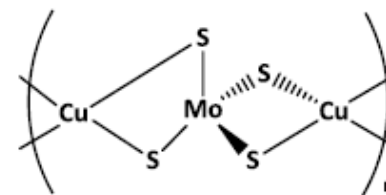
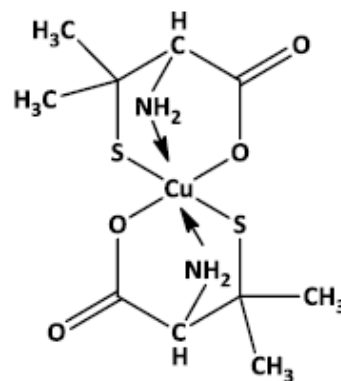
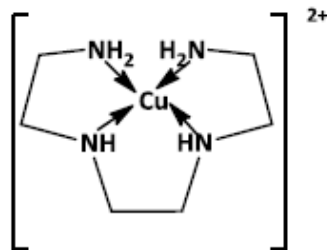
a



b



c



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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.