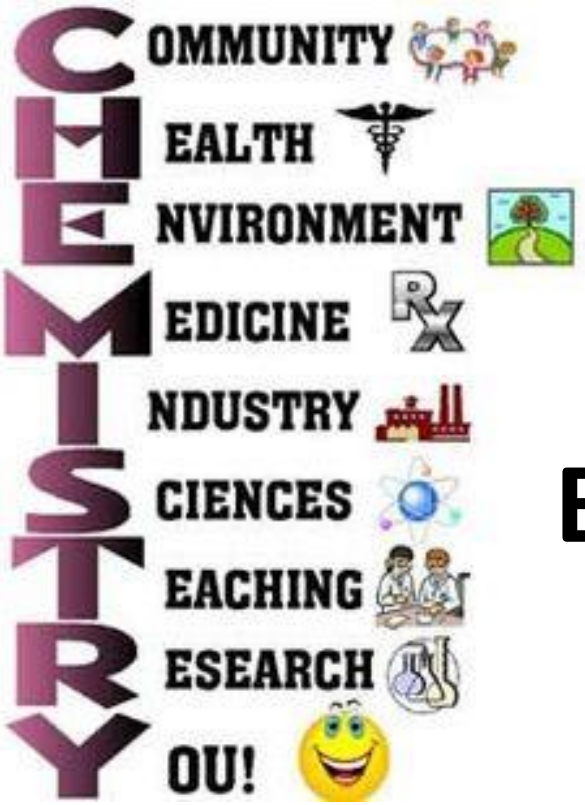



# 418 Chem.
# Bioinorganic Chemistry

## Part V: Metals in Medicine

# Outline- Part V

- Overview
- Metal deficiency, overload and disease.
- Toxic effects of metals.
- Diagnosis and metallotherapy

# Overview

- Metal ions are required for many critical functions in living organisms.

- Scarcity of some metal ions can lead to disease (e.g. anemia from iron deficiency, growth retardation from insufficient dietary zinc, heart disease in infants from copper deficiency).

# Overview

- Some metal ions are toxic for humans (e.g. mercury and lead).

- *Some essential metal ions can be toxic when in excess* (e.g iron is a common household poison in USA, usually by children, of the dietary supplement ferrous sulfate).

# Overview

- Metal ions are required in biology as pharmaceuticals:

➢ Supplementary ( e.g. vitamins and minerals)

➢ Treatment (e.g. Pt and Au drugs for cancer)

➢ Diagnosis (e.g. $^{99m}$Tc and Gd for imaging)


# Overview

## The medical periodic table

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | | | | | | | | | | | | | | | | | He |
| Li | Be | | | | | | | | | | | B | C | N | O | F | Ne |
| Na | Mg | | | | | | | | | | | Al | Si | P | S | Cl | Ar |
| K | Ca | Sc | Ti | V | Cr | Mn | Fe | Co | Ni | Cu | Zn | Ga | Ge | As | Se | Br | Kr |
| Rb | Sr | Y | Zr | Nb | Mo | Tc | Ru | Rh | Pd | Ag | Cd | In | Sn | Sb | Te | I | Xe |
| Cs | Ba | La | Hf | Ta | W | Re | Os | Ir | Pt | Au | Hg | Tl | Pb | Bi | Po | At | Rn |
| Fr | Ra | Ac | Rf | Db | Sg | Bh | Hs | Mt | | | | | | | | | |
| | | | Ce | Pr | Nd | Pm | Sm | Eu | Gd | Tb | Dy | Ho | Er | Tm | Yb | Lu | |
| | | | Th | Pa | U | Np | Pu | Am | Cm | Bk | Cf | Es | Fm | Md | No | Lr | |

# Outline- Part V

- Overview
- Metal deficiency, overload and disease.
- Toxic effects of metals.
- Diagnosis and metallotherapy

# Metal Deficiency, Overload and Diseases

## Essential metals

Generally:

- Four main group (Na, K, Mg, and Ca)
- and ten transition (V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Mo, and Cd) metals.

are known or thought to be required for normal biological functions in humans.

# Metal Deficiency, Overload and Diseases

## 1. Fe deficiency

- Anemia results from insufficient oxygen supply, often because of a decrease in hemoglobin (Hb) blood levels.

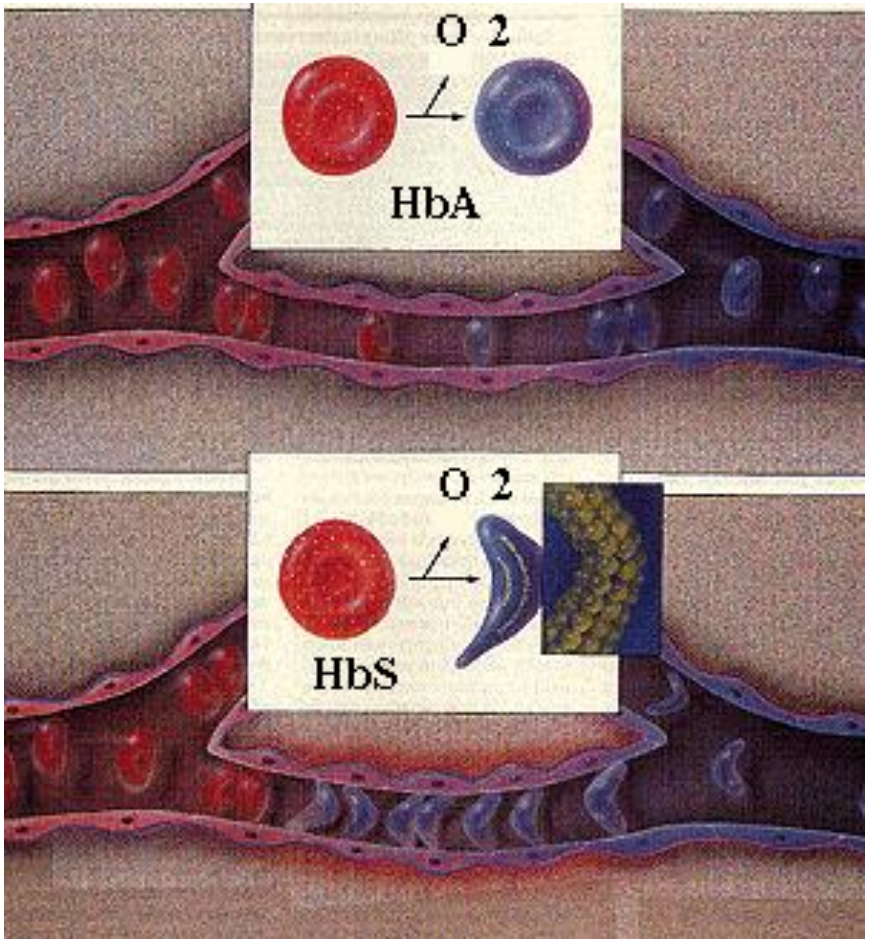
- New structures formed that would lowers the ability of blood to carry oxygen effectively to the tissues.

# What is sickle cell anemia?

- blood disorder that affects red blood cells

- Red blood cells are normally round and flexible.

-In people with sickle cell anemia, red blood cells become stiff and shaped like a crescent moon



# Metal Deficiency, Overload and Diseases

## 1. Fe overload

- Chelation therapy is used to treat iron overload (from ingestion of tablets or using iron pots in cooking) resulting in corrosion of the gastrointestinal tract.

- The chelating agent for iron toxicity is the siderophore desferrioxamine (a polypeptide having a very high affinity for Fe(III) but not for other metals).

# Metal Deficiency, Overload and Diseases

## 2. Zn Deficiency

- The average adult requires a daily intake of 15 to 20 mg Zn, only half of which is absorbed, to maintain the normal level of ~ 2g.

- Zinc deficiency produces:
- Growth retardation
- Skin Lesions,
- Poor Appetite
- Loss Of Body Hair

- The three most affected enzymes by Zn deficiency are alkaline phosphatase and carboxypeptidase

# Metal Deficiency, Overload and Diseases

## 2. Zn Deficiency

- About 30 % of Zn in adults occurs in skin and bones, which are also likely to be affected by an insufficient supply of the element.

- Deficiency is readily reversed by dietary supplements such as $ZnSO_4$

- Nausea and vomiting are commonly reported side effects of zinc toxicity.

# Metal Deficiency, Overload and Diseases

## 3. Cu deficiency and overload

- Cu is found mostly in the brain and heart (also stored in liver).

- The high metabolic rate of the heart and brain requires relatively large amounts of copper metalloenzymes (e.g. tyrosinase, cytochrome oxidase).

- Cu deficiency leads to brain disease in infants, anemia (since cytochrome oxidase is required for blood formation), and heart disease.

# Metal Deficiency, Overload and Diseases

## 3. Cu overload

- Wilson's disease results from a genetically inherited metabolic defect in which Cu can no longer be tolerated at normal levels (overload).

- Ligands with sulfhydryl groups are used to remove copper as Cu(I) thiolate complexes.

# Why are ligands with sulfhydryl groups used to treat copper overload?

# Metal Deficiency, Overload and Diseases

## 4. Ca deficiency and overload

- Calcium levels in the body are controlled by vitamin D.

- Failure to regulate $Ca^{2+}$ leads to:
- calcification of tissue
- formation of stones
- cataracts.

- Metal poisoning has been treated by chelating agents ($CaNa_2(EDTA)$).

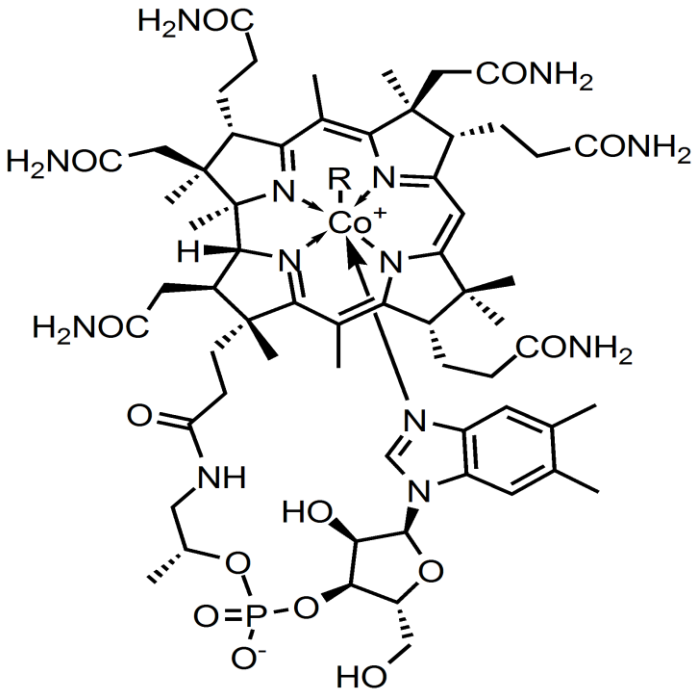
# Metal Deficiency, Overload and Diseases

## 5. Vitamin $B_{12}$ (Cobalamin)

- Is the only metal-containing vitamin.

- Water-soluble, stored in liver, must come from diet.

- Cobalamin= nucleotide attached to a corrin ring (four pyrrole groups and an atom of Co in center.




R = 5'-deoxyadenosyl, Me, OH, CN

# Metal Deficiency, Overload and Diseases

## 5. Vitamin $B_{12}$ (Cobalamin)

- Cobalamine is involved in the metabolism of every cell of the body, especially affecting DNA synthesis and regulation, and in fatty acid synthesis and energy production.

- The unique ability of Co atom in the cobalamins to shuttle between three oxidation states, Co(I), Co(II) and Co(III), is the enabling factor for all of the activities of Vitamin $B_{12}$.

# What is unique about Co in vitamin B12?

# Outline- Part V

- Overview
- Metal deficiency, overload and disease.
- Toxic effects of metals.
- Diagnosis and metallotherapy

# Toxic Effects of Metals

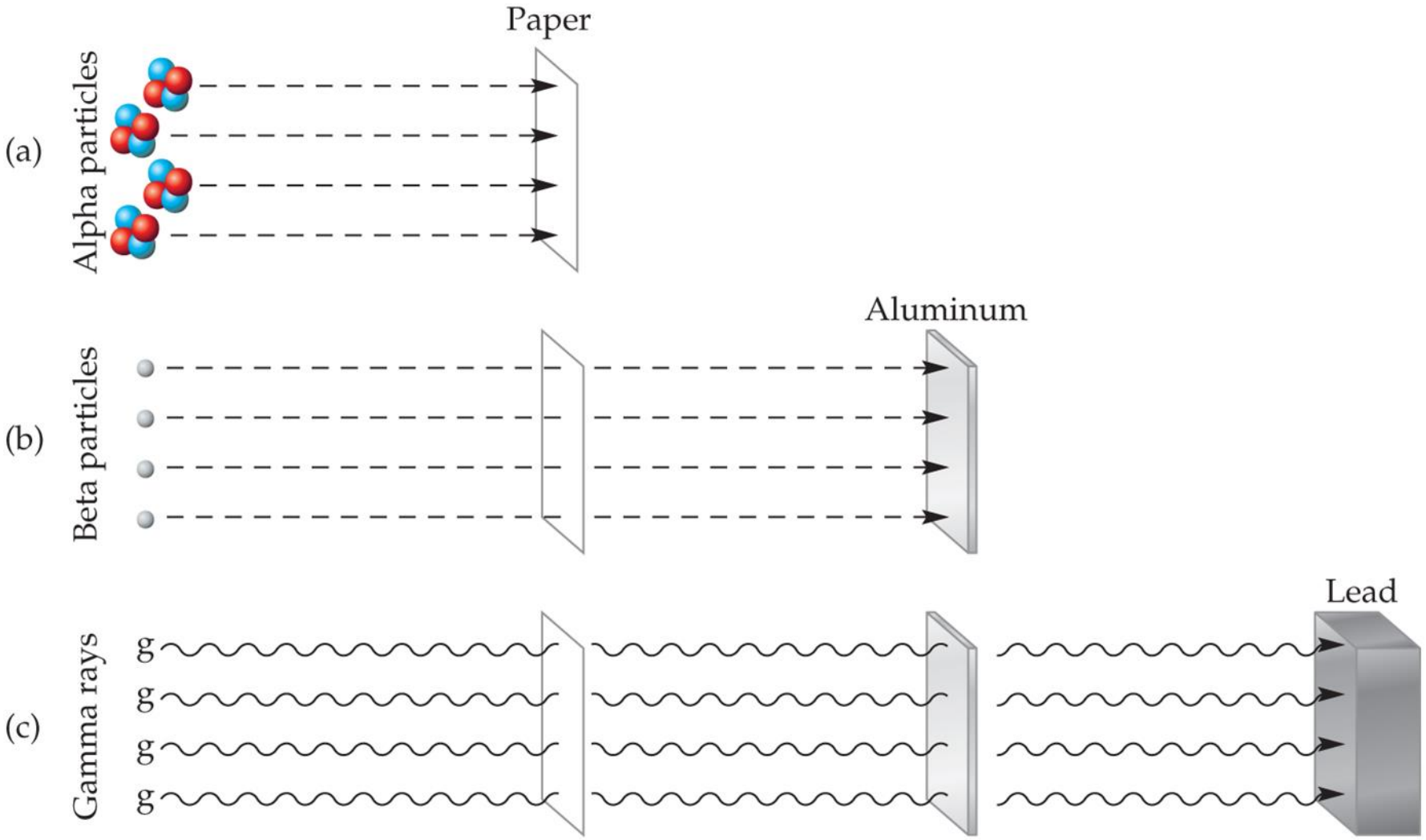
Two classes of toxic metal compounds:

- As in the previous section, the presence of excess quantities of an essential metal can be toxic.

- Nonessential metals: enter to cells through food, skin absorption, or ingestion.

*Gastrointestinal, neurological, and kidney toxicity are among the symptoms experienced by acute or chronic exposure to these heavy metals.*

# Penetrating Power of Radiation



# Toxic Effects of Metals

## 1. $^{239}Pu$

- $^{239}Pu$ emits high energy $\alpha$-particles, leading to malignancies of bone, liver, lung and lymph nodes.
- Maximum tolerated dose 1.5 $\mu g$
- Pu is among the most toxic metals known.
- Some of the chelating agents developed to treat iron toxicity are used for plutonium poisoning (e.g. diethylenetriaminepentaacetic acid (DTPA) salts, siderophores).

# Toxic Effects of Metals

## 2. Hg

- Hg is released into the environment as Hg(II) ions through weathering of its most common ore, HgS ( red cinnabar).
- Hg(0) is nontoxic, but its conversion to RHg compounds by anaerobic microorganisms could make a serious health hazard.

- Hg binds to sulfhydryl groups in proteins, which can lead to neurological disease and kidney failure.

- Because of Hg high affinity for S-donor ligands, Hg poisoning is treated by ligands containing this functional group.

# Toxic Effects of Metals

## 3. Cd and Pb

- Pb in leaded gasoline and paint
- Cd sources include alkaline batteries, pigments.
- Cd can be carcinogenic.
- Both divalent metal ions bind sulfhydryl groups in thionein.

- Lead poisoning can be treated by chelation therapy using $CaNa_2(EDTA)$ (acute) or penicillamine (chronic).

# Toxic Effects of Metals

## 4. Ni and Cr

*Most effective cancer-causing metals*

- Nickel sulfide ($Ni_2S_3$) found in many Ni- ores. Ni altered bacterial DNA repair.

- Cr is most carcinogenic as ($CrO_4^{2-}$), which enters cells by the sulfate uptake pathway and is ultimately reduced to Cr(III) via a Cr(V).

# Outline- Part V

- Overview
- Metal deficiency, overload and disease.
- Toxic effects of metals.
- Diagnosis and metallotherapy

# Diagnosis and Metallotherapy

- Many metals (radioactive and non-radioactive) are used for therapeutic and diagnostic purposes.
- Radioisotopes used for diagnostic purposes must emit low-energy $\gamma$ photons and no $\alpha$ or $\beta$ particles.

# Diagnosis and Metallotherapy

**TABLE : PHYSICAL HALF-LIFE ($T_{P1/2}$) AND DECAY CONSTANT ($\lambda$) FOR RADIONUCLIDES USED IN NUCLEAR MEDICINE**

| Radionuclide | $T_{p1/2}$ | $\lambda$ |
|---|---|---|
| Fluorine 18 ($^{18}F$) | 110 min | 0.0063 m |
| Technetium 99m ($^{99m}Tc$) | 6.02 hr | 0.1151 $hr^{-1}$ |
| Iodine 123 ($^{123}I$) | 13.27 hr | 0.0522 $hr^{-1}$ |
| Samarium 153 ($^{153}Sm$) | 1.93 d | 0.3591 $d^{-1}$ |
| Molybdenum 99 ($^{99}Mo$) | 2.75 d | 0.2522 $d^{-1}$ |
| Indium 111 ($^{111}In$) | 2.81 d | 0.2466 $d^{-1}$ |
| Thallium 201 ($^{201}Tl$) | 3.04 d | 0.2281 $d^{-1}$ |
| Gallium 67 ($^{67}Ga$) | 3.26 d | 0.2126 $d^{-1}$ |
| Xenon 133 ($^{133}Xe$) | 5.24 d | 0.1323 $d^{-1}$ |
| Iodine 131 ($^{131}I$) | 8.02 d | 0.0864 $d^{-1}$ |
| Phosphorus 32 ($^{32}P$) | 14.26 d | 0.0486 $d^{-1}$ |
| Chromium 51 ($^{51}Cr$) | 27.70 d | 0.0250 $d^{-1}$ |
| Strontium 89 ($^{89}Sr$) | 50.53 d | 0.0137 $d^{-1}$ |
| Iodine 125 ($^{125}I$) | 59.41 d | 0.0117 $d^{-1}$ |
| Cobalt 57 ($^{57}Co$) | 271.79 d | 0.0025 $d^{-1}$ |

Radioactive metals used in diagnosis should have short half-lives and emit gamma radiation not alpha or beta. Explain.

- Gamma radiation can penetrate the body and be detected by imaging devices.
- Gamma radiation has enough energy to travel through the body and be detected by imaging devices, such as a gamma camera.
- Alpha and beta radiation are stopped by the skin, so they cannot be used for imaging.
- Alpha and beta radiation are more damaging to cells than gamma radiation.

# Nuclear Medicine

## Diagnostic Uses of Radiation:

**Table 11.6** Some Radioisotopes and Their Medical Applications

| Isotope | Name | Half-Life[a] | Use |
|---|---|---|---|
| $^{11}C$ | Carbon-11 | 20.39 min | Brain scans |
| $^{51}Cr$ | Chromium-51 | 27.8 d | Blood volume determination |
| $^{57}Co$ | Cobalt-57 | 270 d | Measuring vitamin $B_{12}$ uptake |
| $^{60}Co$ | Cobalt-60 | 5.271 y | Radiation cancer therapy |
| $^{153}Gd$ | Gadolinium-153 | 242 d | Determining bone density |
| $^{67}Ga$ | Gallium-67 | 78.1 h | Scan for lung tumors |
| $^{131}I$ | Iodine-131 | 8.040 d | Thyroid diagnoses and therapy |
| $^{192}Ir$ | Iridium-192 | 74 d | Breast cancer therapy |
| $^{59}Fe$ | Iron-59 | 44.496 d | Detection of anemia |
| $^{32}P$ | Phosphorus-32 | 14.3 d | Detection of skin cancer or eye tumors |
| $^{238}Pu$ | Plutonium-238 | 86 y | Provision of power in pacemakers |
| $^{226}Ra$ | Radium-226 | 1600 y | Radiation therapy for cancer |
| $^{75}Se$ | Selenium-75 | 120 d | Pancreas scans |
| $^{24}Na$ | Sodium-24 | 14.659 h | Locating obstructions in blood flow |
| $^{99m}Tc$ | Technetium-99m | 6.0 h | Imaging of brain, liver, bone marrow, kidney, lung, or heart |
| $^{201}Tl$ | Thallium-201 | 73 h | Detecting heart problems during treadmill stress test |
| $^{3}H$ | Tritium | 12.26 y | Determining total body water |
| $^{133}Xe$ | Xenon-133 | 5.27 d | Lung imaging |

[a]Abbreviations: y, years; d, days; h, hours; min, minutes.

# Diagnosis

- Nuclear magnetic resonance (NMR) spectroscopy and Magnetic Resonance Imaging (MRI)

Can be used to image specific tissues of biological specimens because of differences in the relaxation times of water proton resonances, usually brought about by paramagnetic metal ions ( e.g. Mn(II) and Gd(III)

# Diagnosis

## Radiodiagnostic agents

### Example:

- ($^{99m}Tc$) is the most desirable (it gives off a 140-keV $\gamma$-ray that is detected easily and produces clear images).

- Gd

Used to target organs and tissues according to the ligands that are present, e.g. complexes of Gd (III) ($f^7$) are used as contrast agents in MRI for diagnosis.

# Metallotherapy

- Both acute and chronic exposure to toxic metals can be treated by chelation therapy (= *treat overloads of metals in biosystems using special ligands)*

- Hard-soft acid-base relationships are useful in the choice of chelating agent.

# Metallotherapy

## 1. Cancer treatment

Some drugs destroy malignant cells selectively, e.g. *cis*-$[PtCl_2(NH_3)_2]$ results in the inhibition of DNA replication and prevention of cell division (due to the stable cisplatin-DNA complex).

## 2. Anti-Arthritis drugs

Complexes of Au are effective against rheumatoid arthritis caused by hydrolytic enzymes.

## 3. Anti-depression drugs

Li (carbonate or citrate) has been used for treatment of depression since more than 100 years.