Ministry of Higher Education and Scientific Research

Al-Muthanna University

Inorganic Pharmaceutical chemistry

For the 3rd year students of the «faculty of Pharmacy»

Lecture (5)

- **Geometry of complexes:**
- **Therapeutically used complexes**
- **Radiopharmaceuticals and their Applications**

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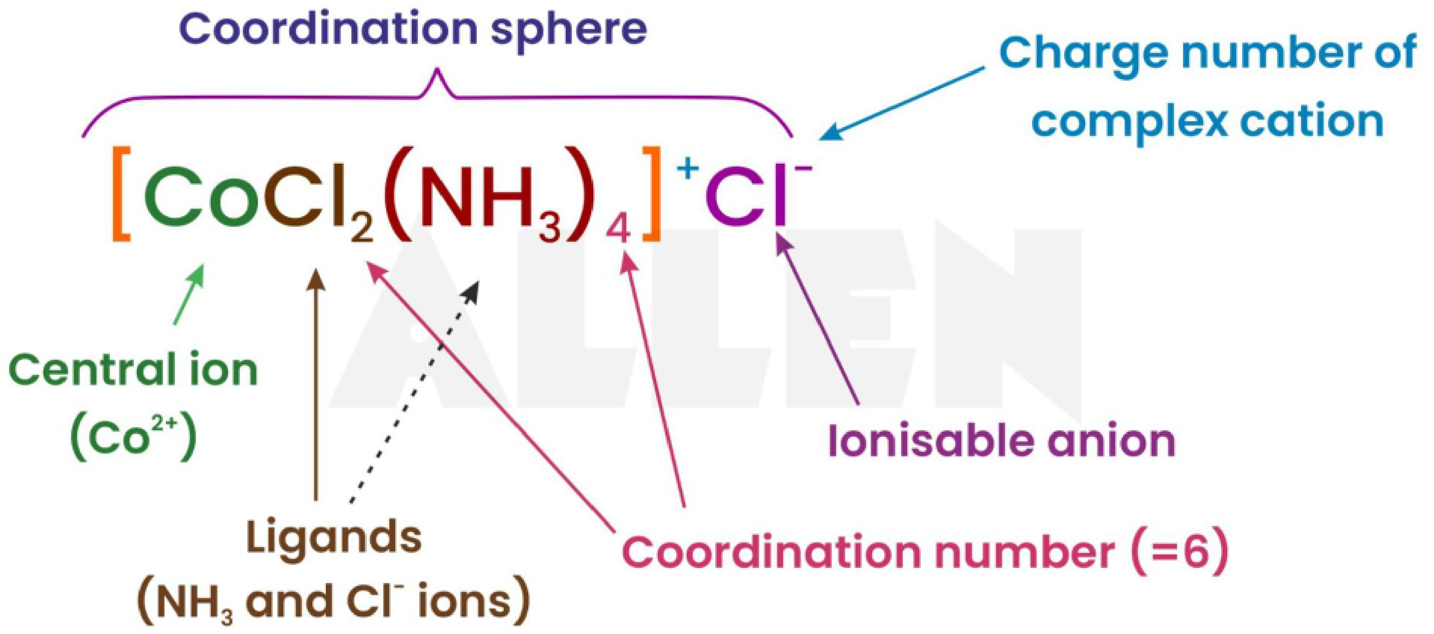
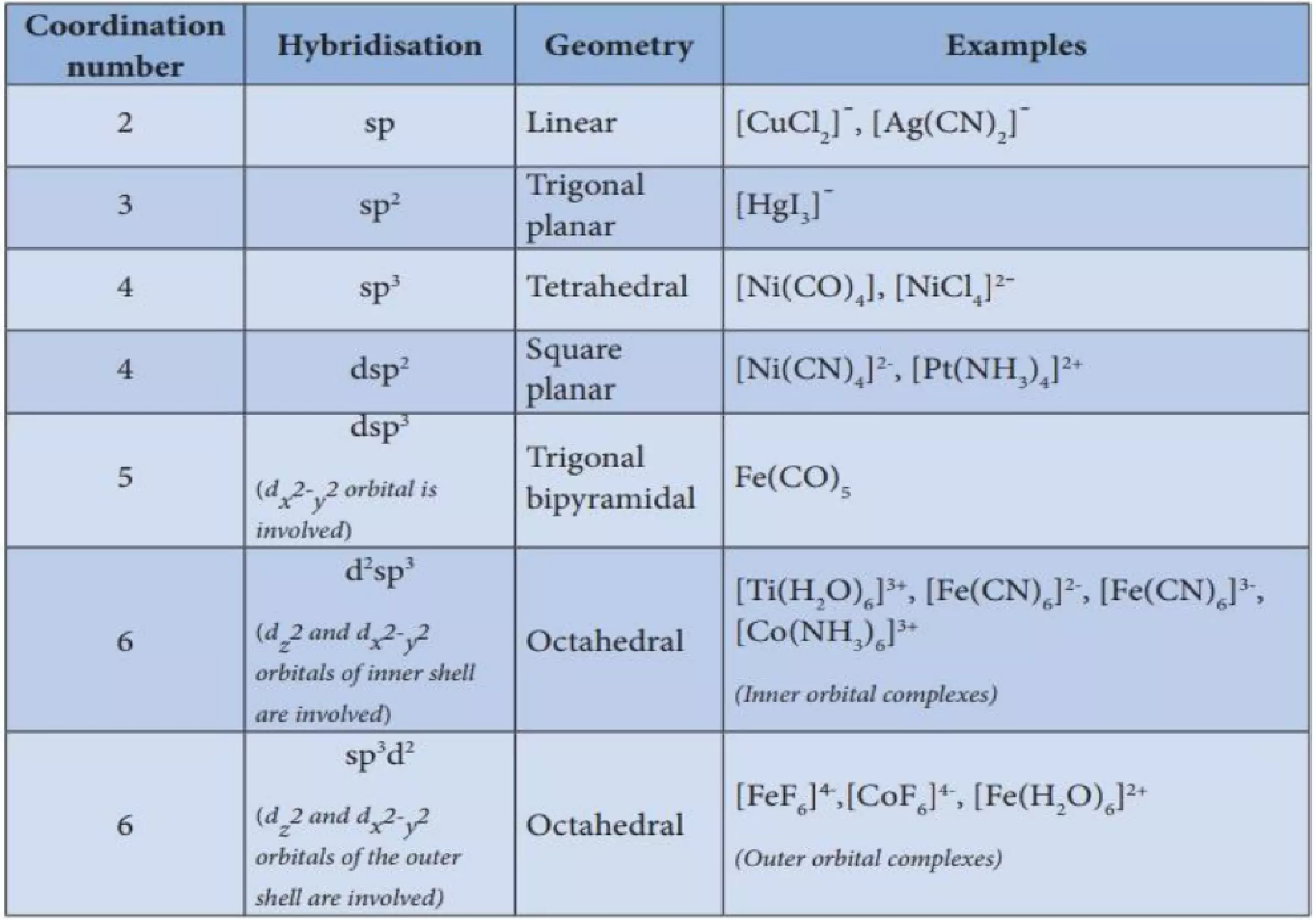
Component of coordination compounds



Geometry of complexes



Coordination number	Hybridisation	Geometry	Examples
2	sp	Linear	$[CuCl_2]^-$, $[Ag(CN)_2]^-$
3	sp^2	Trigonal planar	$[HgI_3]^-$
4	sp^3	Tetrahedral	$[Ni(CO)_4]$, $[NiCl_4]^{2-}$
4	dsp^2	Square planar	$[Ni(CN)_4]^{2-}$, $[Pt(NH_3)_4]^{2+}$
5	dsp^3 *($d_{x^2-y^2}$ orbital is involved)*	Trigonal bipyramidal	$Fe(CO)_5$
6	d^2sp^3 *(d_{z^2} and $d_{x^2-y^2}$ orbitals of inner shell are involved)*	Octahedral	$[Ti(H_2O)_6]^{3+}$, $[Fe(CN)_6]^{2-}$, $[Fe(CN)_6]^{3-}$, $[Co(NH_3)_6]^{3+}$ *(Inner orbital complexes)*
6	sp^3d^2 *(d_{z^2} and $d_{x^2-y^2}$ orbitals of the outer shell are involved)*	Octahedral	$[FeF_6]^{4-}$, $[CoF_6]^{4-}$, $[Fe(H_2O)_6]^{2+}$ *(Outer orbital complexes)*

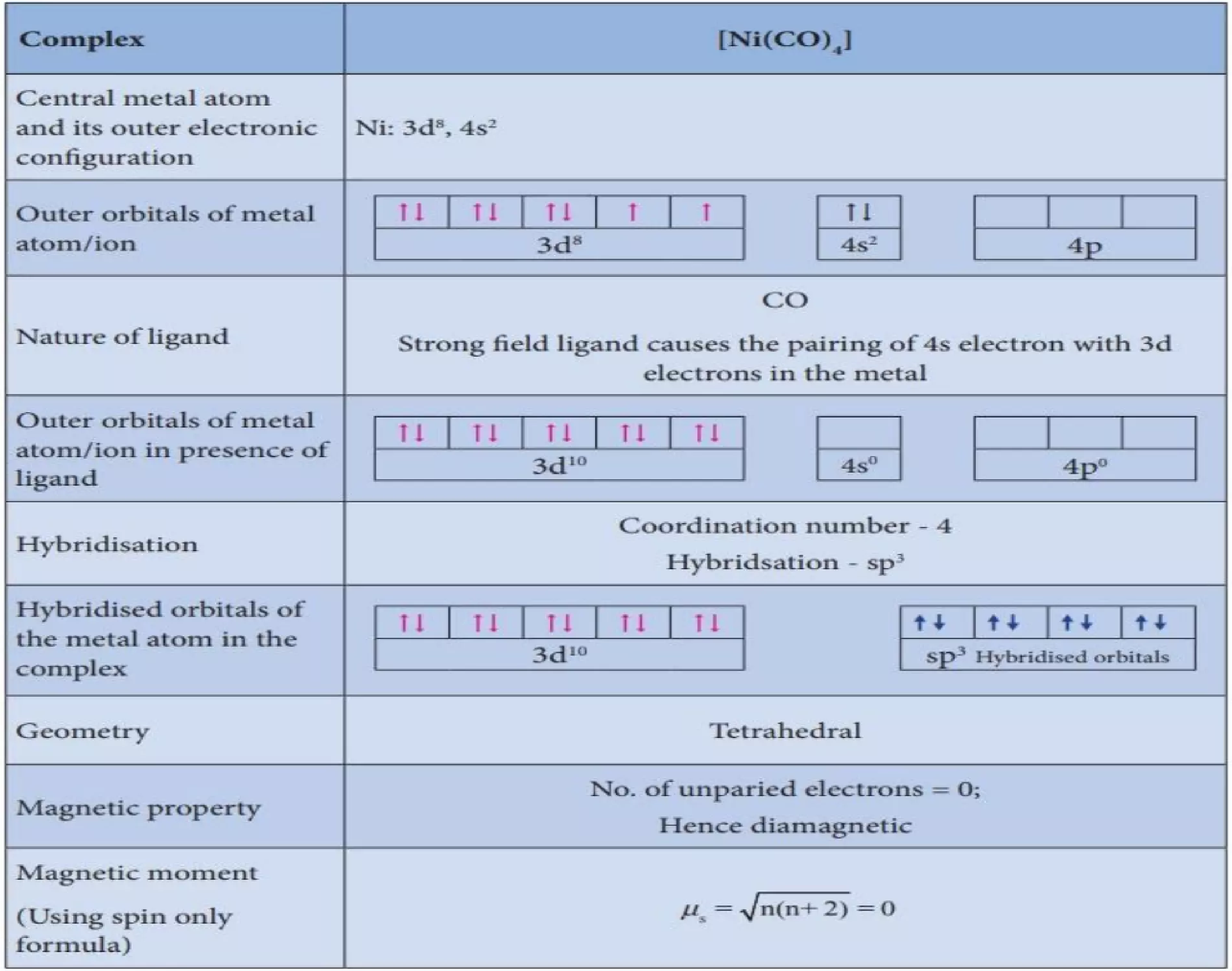
$$I^- < Br^- < SCN^- < Cl^- < S^{-2} < N_3^- < F^- < ONO^- < OH^- < SO_4^{-2} < NO_4^-$$

$$< C_2O_4^{-2} < O^{-2} < H_2O \sim NCS^- < EDTA^{-4} < NH_3 \sim Py < en < bpy \sim phen$$

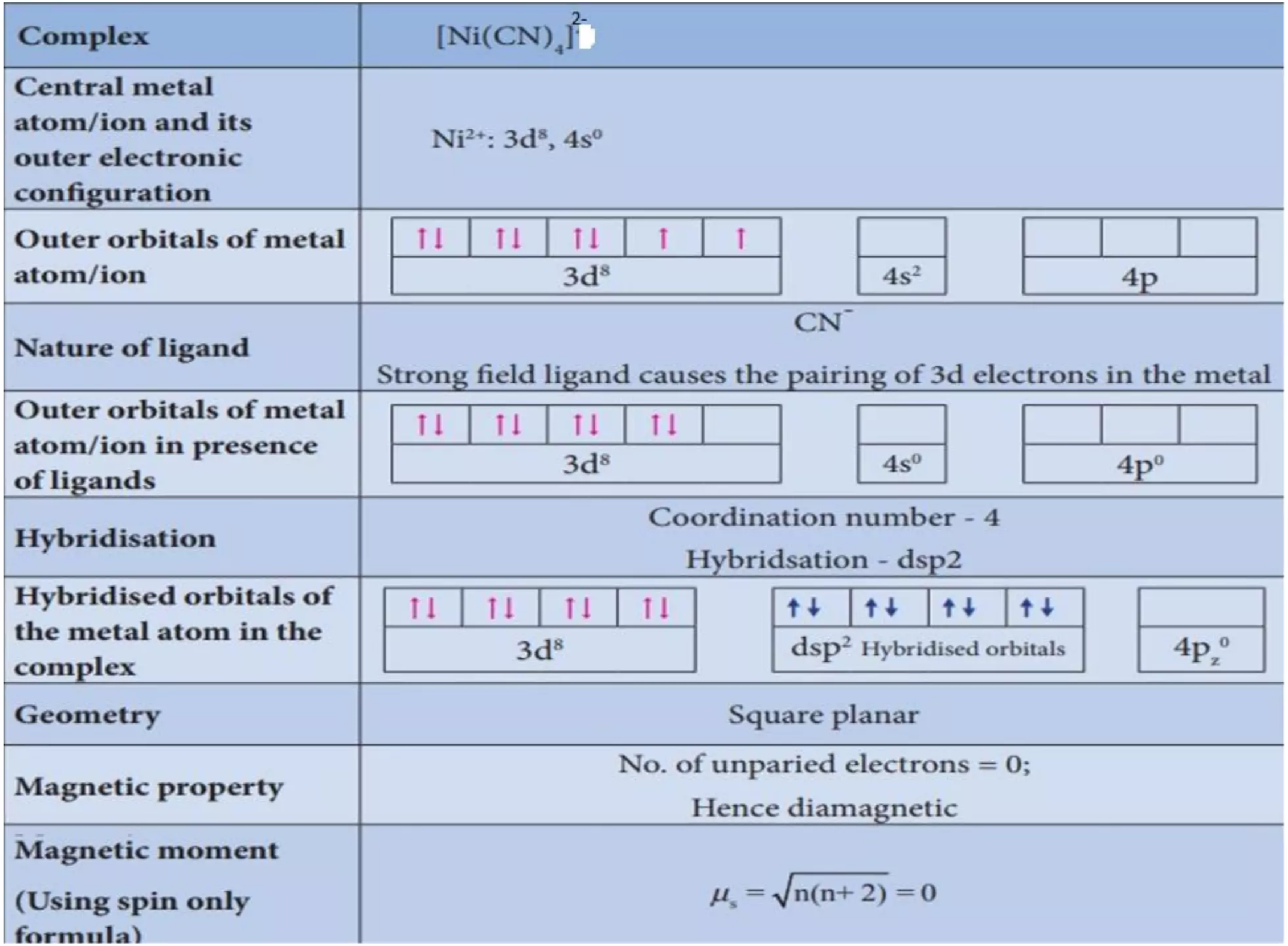
$$< NO_2^- < PR_3 < CH_3 < CN^- \sim CO$$

From I^- To H_2O are weak field ligands

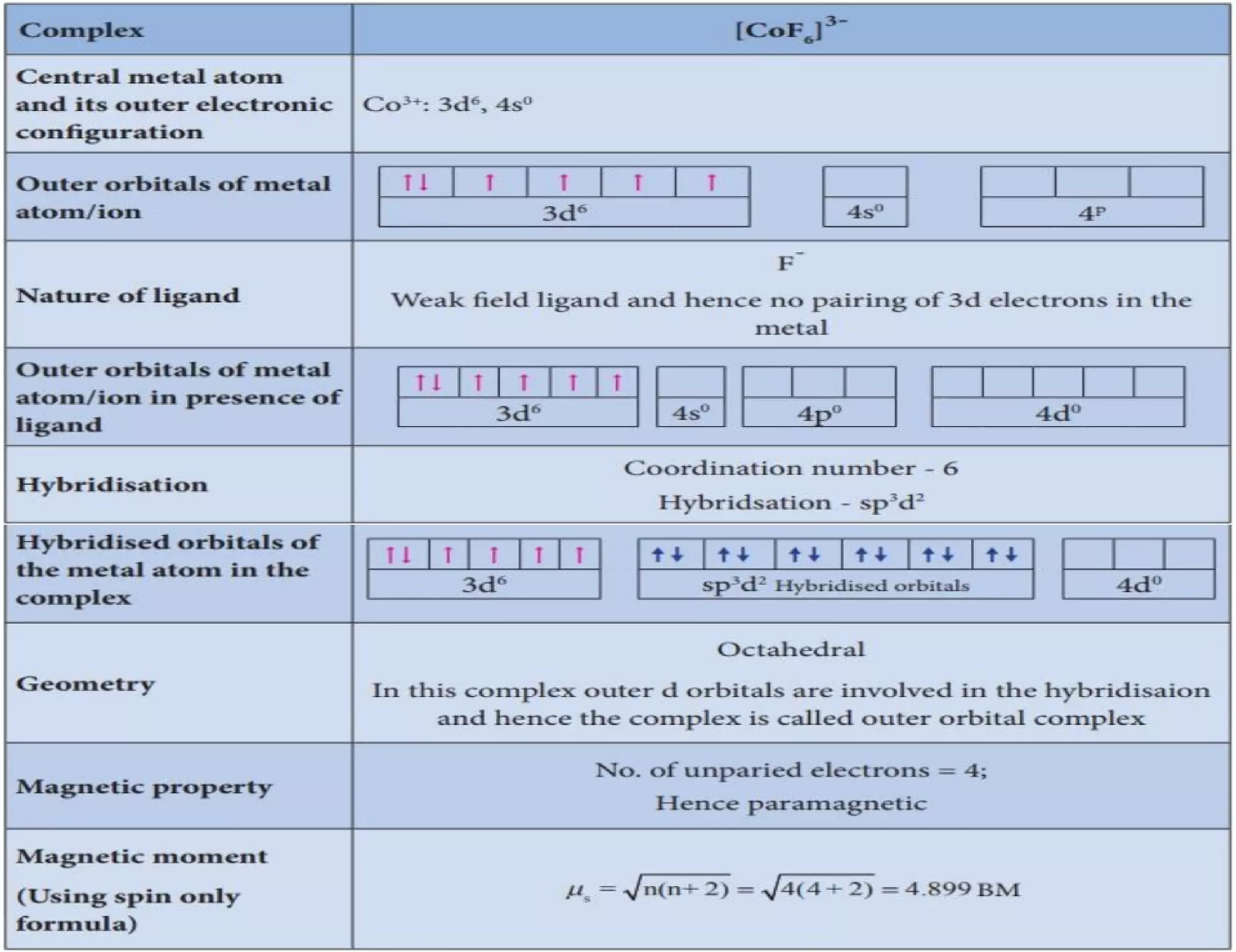
From NCS^- To CO are strong field ligands



Complex	$[Ni(CO)_4]$
Central metal atom and its outer electronic configuration	Ni: $3d^8$, $4s^2$
Outer orbitals of metal atom/ion	↑↓ ↑↓ ↑↓ ↑ ↑ $3d^8$ ↑↓ $4s^2$ 4p
Nature of ligand	CO Strong field ligand causes the pairing of 4s electron with 3d electrons in the metal
Outer orbitals of metal atom/ion in presence of ligand	↑↓ ↑↓ ↑↓ ↑↓ ↑↓ $3d^{10}$ $4s^0$ $4p^0$
Hybridisation	Coordination number - 4 Hybridsation - sp^3
Hybridised orbitals of the metal atom in the complex	↑↓ ↑↓ ↑↓ ↑↓ ↑↓ $3d^{10}$ ↑↓ ↑↓ ↑↓ ↑↓ sp^3 Hybridised orbitals
Geometry	Tetrahedral
Magnetic property	No. of unparied electrons = 0; Hence diamagnetic
Magnetic moment (Using spin only formula)	$\mu_s = \sqrt{n(n+2)} = 0$



Complex	$[Ni(CN)_4]^{2-}$
Central metal atom/ion and its outer electronic configuration	Ni^{2+}: $3d^8$, $4s^0$
Outer orbitals of metal atom/ion	↑↓ ↑↓ ↑↓ ↑ ↑ $3d^8$ ☐ $4s^2$ ☐ ☐ ☐ 4p
Nature of ligand	CN^- Strong field ligand causes the pairing of 3d electrons in the metal
Outer orbitals of metal atom/ion in presence of ligands	↑↓ ↑↓ ↑↓ ↑↓ ☐ $3d^8$ ☐ $4s^0$ ☐ ☐ ☐ $4p^0$
Hybridisation	Coordination number - 4 Hybridsation - dsp2
Hybridised orbitals of the metal atom in the complex	↑↓ ↑↓ ↑↓ ↑↓ $3d^8$ ↑↓ ↑↓ ↑↓ ↑↓ dsp^2 Hybridised orbitals ☐ $4p_z^0$
Geometry	Square planar
Magnetic property	No. of unparied electrons = 0; Hence diamagnetic
Magnetic moment (Using spin only formula)	$\mu_s = \sqrt{n(n+2)} = 0$



Complex	$[CoF_6]^{3-}$
Central metal atom and its outer electronic configuration	Co^{3+}: $3d^6$, $4s^0$
Outer orbitals of metal atom/ion	[↑↓][↑][↑][↑][↑] $3d^6$ [ ] $4s^0$ [ ][ ][ ] 4^p
Nature of ligand	F^- Weak field ligand and hence no pairing of 3d electrons in the metal
Outer orbitals of metal atom/ion in presence of ligand	[↑↓][↑][↑][↑][↑] $3d^6$ [ ] $4s^0$ [ ][ ][ ] $4p^0$ [ ][ ][ ][ ][ ] $4d^0$
Hybridisation	Coordination number - 6 Hybridsation - sp^3d^2
Hybridised orbitals of the metal atom in the complex	[↑↓][↑][↑][↑][↑] $3d^6$ [↑↓][↑↓][↑↓][↑↓][↑↓][↑↓] sp^3d^2 Hybridised orbitals [ ][ ][ ] $4d^0$
Geometry	Octahedral In this complex outer d orbitals are involved in the hybridisaion and hence the complex is called outer orbital complex
Magnetic property	No. of unparied electrons = 4; Hence paramagnetic
Magnetic moment (Using spin only formula)	$\mu_s = \sqrt{n(n+2)} = \sqrt{4(4+2)} = 4.899$ BM

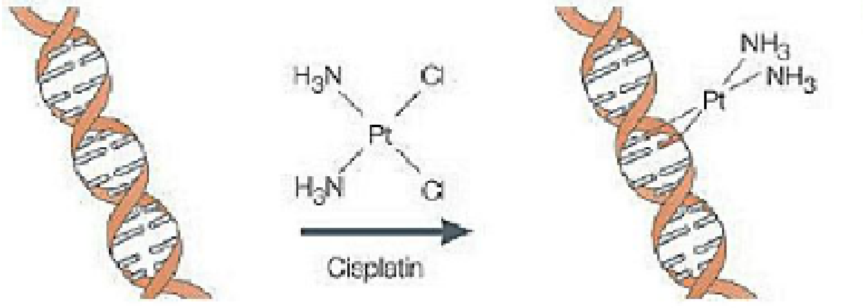
Complexes and complexing agents are important aspects of pharmacy:

- Used to treat certain metabolic disorder where metals such as iron & copper are accumulated in abnormal amounts in various tissues.

- Therapeutic uses of complexes: anticancer, antimicrobial and antiarthritics.

Therapeutically used complexes

1 -Anticancer agents: ex. Cisplatin and Carboplatin that coordinate to DNA resulting in a distinct bend in DNA, which leads to suppression of replication of cancer cell.



2- Antiarthritics: copper complexes as cupralene due to their antiinflammatory action, gold complexes as Auranofin.

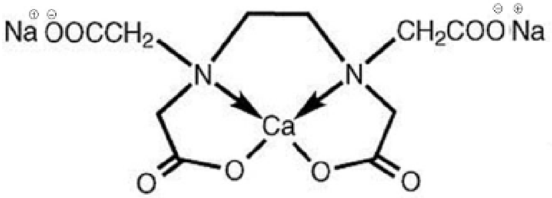
3-Antimicrobial: Silver sulfadiazine as antifungal and antibacterial.

Chelation Therapy

- Chelation therapy is one treatment option for most heavy-metal poisoning. The mode of action is based on the ability of the chelating agent to bind to the metal in the body’s tissues and form a chelate. This complex is then released from the tissue and travels in the bloodstream. Finally, the complex is filtered by the kidneys and excreted in the urine. Unfortunately, this process requires admission to the hospital because it may be painful and it is important to stabilize the vital functions of the patient. The patient additionally may require treatment for complications associated with heavy-metal poisoning, including anaemia and kidney failure or shock reactions.

1-Calcium Disodium Edetate:

- Calcium disodium ethylinediaminetetraacetate (calcium disodium versenate).



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A white crystalline powder. It is odorless, hygroscopic, has a faint saline taste. Its stable in air, freely soluble in water, pH =6.5-8.

- The compound is the calcium complex of the disodium salt of ethylenediaminetetraaceticacid (EDTA).

- Used in the treatment of heavy metal poisoning like lead (plumbism). This chelating agent remove lead from the tissue by forming highly inactive soluble complex which can be removed from the circulation by the kidneys and excreted in the urine.

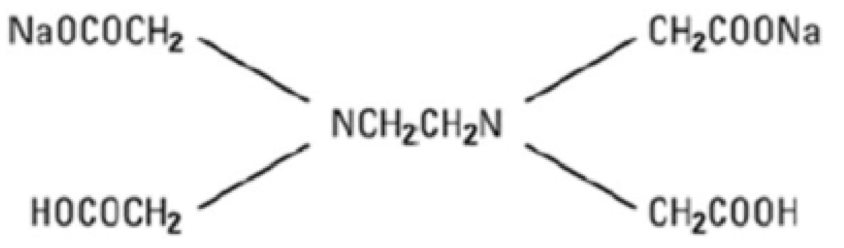
- May also be employed in poisoning due to Copper, Nickel, Cadmium, Zinc, Chromium and Manganese, but no value in the treatment of toxicities produced by Mercury, Arsenic and Gold.

- Usual route of administration is IV injection, because it is poorly absorbed from the GIT and may even aid in the absorption of lead which may be in the gut, thereby producing toxic reactions or aggravating established toxicity.

- EDTA in and its salts can act as an anticoagulant for blood samples and is therefore often found as additives in blood sampling tubes.

2- Disodium Edetate:

- Disodium ethylenediaminetetra acetate
- White crystalline powder which is soluble in water providing an aqueous solution of pH = 4-6.
- Chelate metals as disodium calcium form, in addition the chance of hypocalcemia during therapy exists, limit its usefulness.
- Used in condition with hypercalcemic state, The compound may be useful in treating occlusive vascular disease, cardiac arrhythmia when associated with high blood Ca level.
- No value in aiding dissolution of urinary calculi " Ca containing stones " in the urinary tract.
- The usual rout of administration is I.V. injection.



3-D- Penicillamine:

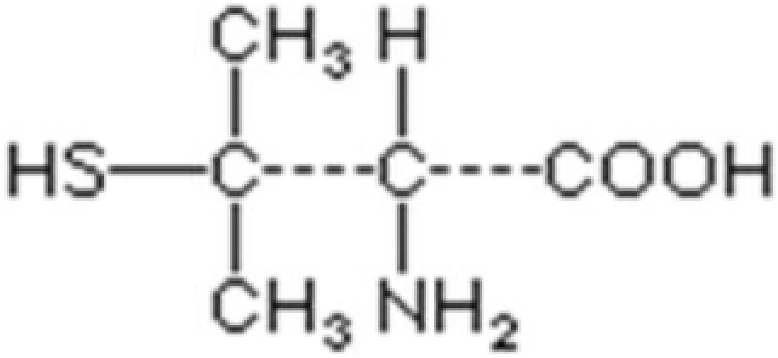
- This compound is a white crystalline powder, having a slight characteristic odor. Its freely soluble in water and slightly soluble in alcohol. The pH of the aqueous solution is between 4.5-5.5.
- Improvement of copper excretion in patient with hepato lenticular degeneration " Wilson's disease "[degenerative changes in the brain associated with increased level of copper deposited in the eye, liver, brain and kidney] and promoting urinary excretion of excess copper in the chelated form.
- The effectiveness of Penicillamine is related to:

1- its resistance to metabolism by amino acid oxidase ,since it lack Hydrogen on β-

carbon atom .

2- The ability of its –SH group to reduce the copper (II) in the tissue into copper (I).

- It's also used with iron, mercury, lead, gold toxicity.
- Unlike the other chelating agents discussed before, the route of administration is orally as capsules. Another use : 1-The treatment of gold dermatitis in patient on chronic gold therapy. 2-In cystinuria " presence of crystals of amino acid cystine in urine " which is not related to its chelating ability.



Radiopharmaceuticals

- Every atom of an element is composed of a nucleus, containing protons and neutrons, surrounded by electrons. In the electrically neutral atom, the number of electrons is equal to the number of protons in the nucleus. Furthermore, the number of protons in the nucleus is equal to the atomic number of the atom. The atomic mass is the number of protons + neutrons in its nucleus.

- Isotopes of a particular element have the same atomic number (same number of protons) but different mass numbers (differing numbers of neutrons). The isotopes of a particular element have the same chemical properties. The only variation that is usually found is in the kinetics or rates of chemical reactions, since the mass is a very important aspect of reaction rates.

- Two major types of isotopes are found in nature:

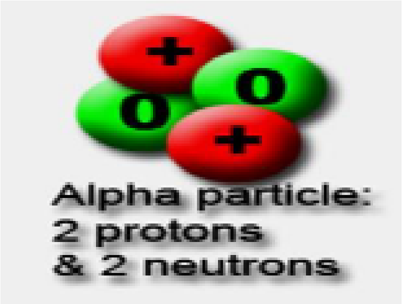
- Stable isotopes maintain their elemental decompose to other isotopic or elemental forms.
- Unstable isotopes (Radioisotopes) which are decompose or decay, by emission of nuclear particles, into other isotopes of the same or different elements, the decay is characteristic for a particular isotope, and continues until a stable isotopic level is achieved.

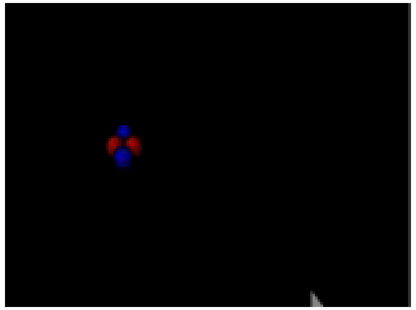
- Not all unstable isotopes are found naturally, a large number is produced artificially by bombardment of the nucleus with subatomic particles.

- Radioactivity: the process in which an unstable isotope undergoes changes until a stable state is reached and in the transformation emits energy in the form of radiation (**alpha particles, beta particles and gamma rays**).

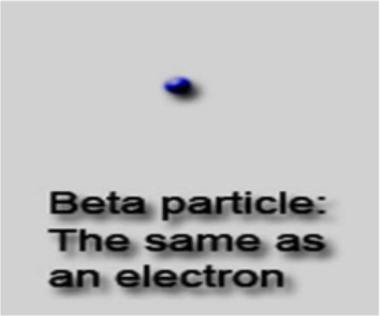
- **Half-life ($t_{1/2}$)** is defined as the time it takes for the activity (or the amount of radioactivity) to reduce by 50%. The shorter the half-life, the faster the isotope decays and the more unstable it is. The half-life is unique for any given radioisotope. It can vary from several years to less than a second.

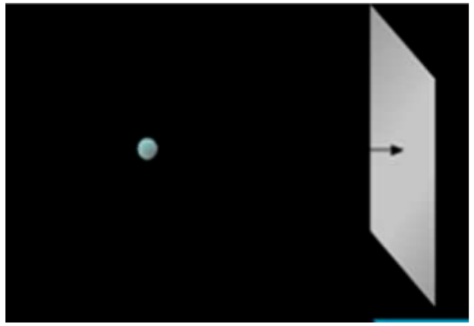
- **1-Alpha particles $^{4}_{2}\alpha$**: are made of 2 protons and 2 neutrons. This means that when a nucleus emits an alpha particle, its atomic number decreases by 2 and its atomic mass decreases by 4. Alpha particles are relatively slow and heavy. They have a low penetrating power - you can stop them with just a sheet of paper, clothing or a few centimeters of air.





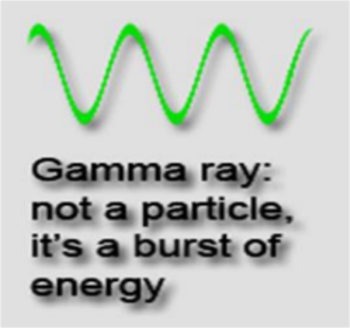
- **2-Beta particles β**: have a charge of minus 1. This means that beta particles are the same as an electron. This means that when a nucleus emits a β particle, the atomic mass is unchanged. They are fast, and light. β particles have a medium penetrating power - they are stopped by a sheet of aluminum.

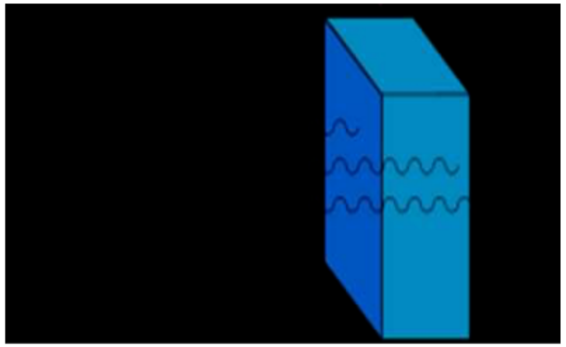




3-Gamma rays γ: gamma rays are waves, not particles. This means that they have no mass and no charge and high energy.

- Gamma rays have a high penetrating power - it takes a thick sheet of metal such as lead to stop them.





Biological Effects of Radiation

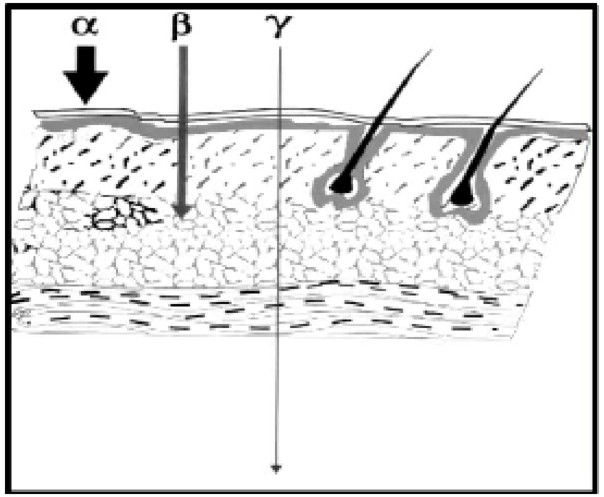
- The effect of radioactive particles impinging upon biological tissue depends upon a number of factors:

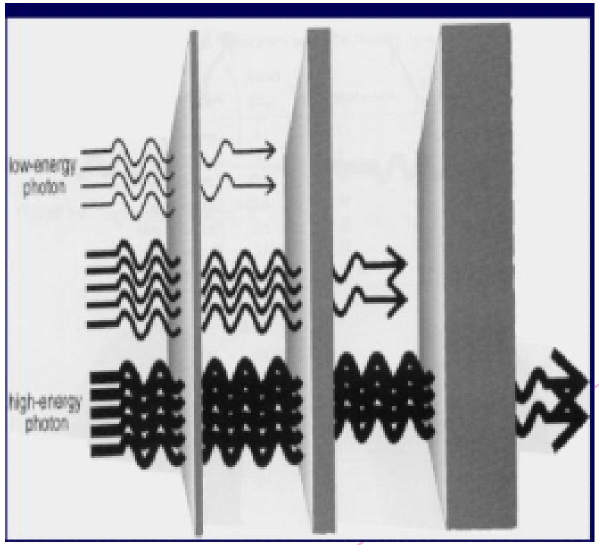
1- The ability of the radiation to penetrate tissue.

2- The energy of the radiation.

3- The particular tissue and surface area exposed.

4- The dose rate of the radiation.





Radiation Safety

Radiation can cause harmful effects in humans, which include nausea, skin burns, cancer, sterility, hair loss and even death.

There are three ways to keep exposure to radiation to a minimum:

1- Maintain as much distance as possible from the source.

2- Use adequate shielding.

3- Minimize the time of exposure.

Radiopharmaceuticals

- There are a number of preparations containing radioisotopes which are used internally for therapeutic and diagnostic purposes. These preparations are referred to collectively as radiopharmaceuticals .

- Isotopes employed in diagnostic procedures must be of sufficient energy to allow measurement of radioactivity outside the body. Radioisotopes emitting penetrating gamma rays are used for diagnostic (imaging) where the radiation has to escape the body before being detected by a specific device (gamma, SPECT/PET cameras). Typically,
- the radiation emitted by isotope used for imaging vanishes completely after 1 day through radioactive decay and normal body excretion.

Therapeutic isotopes

- Therapeutic isotopes are utilized for their destructive effects on tissue, its necessary that they have sufficient energy to penetrate through the tissue being treated, but radioactivity spreading to surrounding tissue is undesirable and difficult to control. Radioisotopes emitting short range particles (alpha or beta) are used for therapy due to their power to lose all their energy over a very short distance, therefore causing a lot of local damage (such as cell destruction). This property is used for therapeutic purposes: cancer cells destruction, pain treatment in palliative care for bone cancer or arthritis. Such isotopes stay longer in the body than imaging ones; this is intentional in order to increase treatment efficiency, but this remains limited to several days.
- Sometimes the isotope must be incorporated into or "tagged" onto a molecule which aids in directing it into a particular tissue with some degree of specificity.
- The isotopes should be eliminated from the body easily and, a side

Application of radiopharmaceuticals:

- **1-Treatment of disease (therapeutic radiopharmaceuticals)**
- They are radiolabeled molecules designed to deliver therapeutic doses of ionizing radiation to specific diseased sites.
- **Gold-198(Gold 198 Au Injection) :**
- Is a sterile, red colloidal solution of radioactive gold It is most frequently used therapeutically.
- The solution is administered by intracavitary injection into the pleural and peritoneal cavities as an aid in the management of pleural effusion and ascites, (fluid accumulations secondary to neoplastic disease in the area), can be inhibited by the effect of beta radiation on the cancerous tissue cells.

- **I 131 (capsules and solution):**
- Is employed therapeutically to destroy cancer cells in thyroid tissue. The activity is dependent on the ability of the thyroid to concentrate the iodine. The tissue effect is primarily due to the beta radiation. It's used for the treatment of thyrotoxicosis and thyroid cancer.

- **Sodium phosphate P32 (solution)**: for oral and intravenous administration for red and white blood cells diseases (polycythemia vera and leukemia).

- **Chromic phosphate P32** for lung, ovarian, uterine, and prostate cancers.

2- As an aid in the diagnosis of disease (diagnostic radiopharmaceuticals)

- Technetium-99m (^{99m} Tc): IV Administration, for imaging and functional studies of the brain, myocardium, thyroid, lungs, liver, gallbladder, kidneys, skeleton, blood, and tumors. Depending on the procedure, the 99mTc is bound to a pharmaceutical that transports it to its required location.
- chromium-51(sodium chromate Cr 51 injection(It is used diagnostically to determine red blood cell mass, volume, and survival time, and for scanning the spleen. Chromium is readily taken up by erythrocytes and becomes fixed to the globin portion of hemoglobin as chromium(III).
- Cobalt -57 and 60 (Cyanocobalamin Co 60 Capsules and Solution)
- They are used in diagnostic procedures for pernicious anemia, the basis of the test suppose that if vitamin B 12 is absorbed from the GIT, it will be excreted in the urine.Therefore, the radio activity from an oral dose of 60 Co-labeled vitamin B 12 should be detectable in the

- **Iron-59 (Ferrous Citrate Fe 59)** in diagnostic procedures relating to iron metabolism and red blood cell formation. The preparation can be administered orally to study the absorption of iron from the GIT, and injected intravenously for determinations of plasma iron clearance, turnover, and the incorporation of iron into erythrocytes.

- **Sodium iodide ^{131} I** is the most common isotope and chemical form in use as a diagnostic aid in the study of the functioning of the thyroid gland and in scanning the thyroid to determine size, position, and possible tumor .

Best Regards!

Thank you!