Pharmaceutical Inorganic Chemistry-1

Unit-5 Notes

Rx Pharma Education

Introduction

❖Radiopharmaceuticals, as the name suggests, are pharmaceutical formulations consisting of radioactive substances (radioisotopes and molecules labelled with radioisotopes), which are intended for use either in **diagnosis or therapy.**

❖Radiopharmaceuticals are essential components of **nuclear medicine** practice, where radiopharmaceuticals are administered to patients for diagnosing, managing and treating number of diseases.

❖ **Nearly 95%** of radiopharmaceuticals are used for diagnostic purposes, while the rest is used for therapy.

Definitions and Terminology

- **A nuclide** (or nucleide, from **nucleus**, also known as nuclear species) is **an atomic species** characterized by the **specific constitution of its nucleus**, i.e., by its number of protons, Z, its number of neutrons, N, and its nuclear energy state.

- **A radionuclide** (radioactive nuclide, radioisotope or radioactive isotope) is ***an atom that has excess nuclear energy,*** making it **unstable**.

- This **excess energy** can be used in one of three ways: **emitted from the nucleus** as ***gamma radiation***; transferred to one of its electrons to release it as a conversion electron; or used to ***create and emit a new particle (alpha particle or beta particle) from the nucleus.***

Nuclides vs isotopes

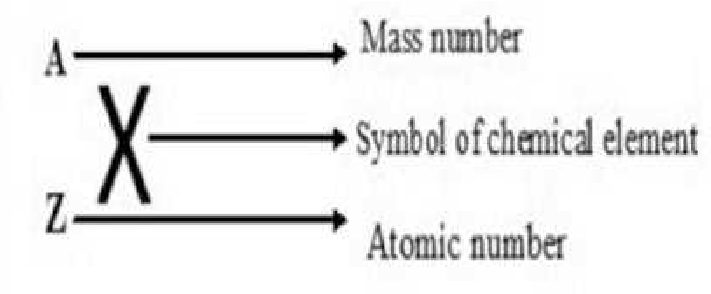
- **A nuclide** is a species of an atom with a specific number of protons and neutrons in the nucleus, for example carbon-13 with 6 protons and 7 neutrons.
- ***The nuclide concept (referring to individual nuclear species) emphasizes nuclear properties over chemical properties, while the isotope concept (grouping all atoms of each element) emphasizes chemical over nuclear***.
- The neutron number has large effects on nuclear properties, but its effect on chemical reactions is negligible for most elements.

Isotopes:

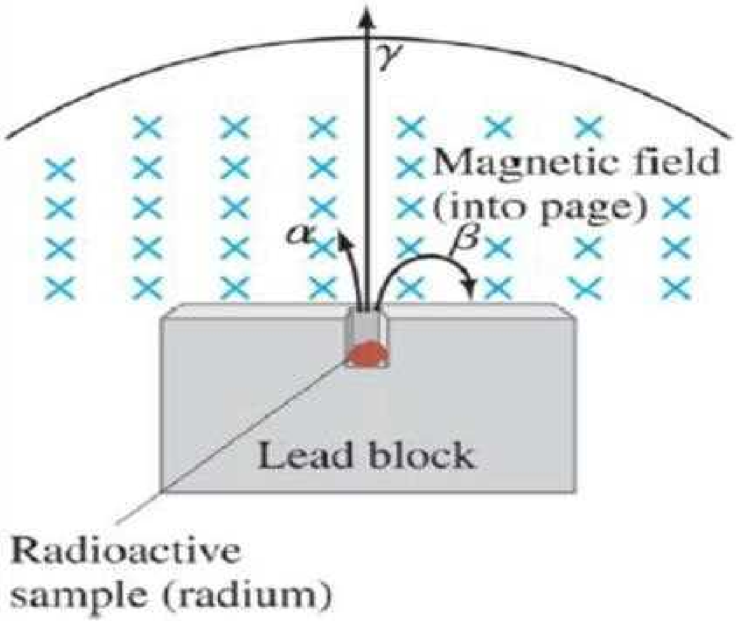
- Isotopes are variants of a particular chemical element ***which differ in neutron number,*** and consequently in ***nucleon number***.
- All isotopes of a given element have the same number of protons but different numbers of neutrons in each atom.
- ***Isotopes of an element are atoms of same element with the same atomic number 'Z' but different mass numbers 'A'.***
- ***They occupy the same place in the periodic table and have similar chemical properties***.

$${}^{12}_{6}C \quad \text{and} \quad {}^{13}_{6}C$$

Nucleon number: The number of nucleons (proton and Neutron both) in a nucleus defines an isotope's mass number (nucleon number).



Chemical element and its mass and atomic number



Radioactivity:

❖ Radioactive decay (also known as nuclear decay, radioactivity, radioactive disintegration or nuclear disintegration) is the process by which an unstable atomic nucleus loses energy by radiation.

❖***A material containing unstable nuclei is considered radioactive***. Three of the *most common types of decay* ***are alpha decay***, ***beta decay, and gamma decay***,

❖all of which involve emitting one or more particles.

Types of decay (Alpha, Beta and Gamma Radiations)

Radioactive rays were observed to be of three types:

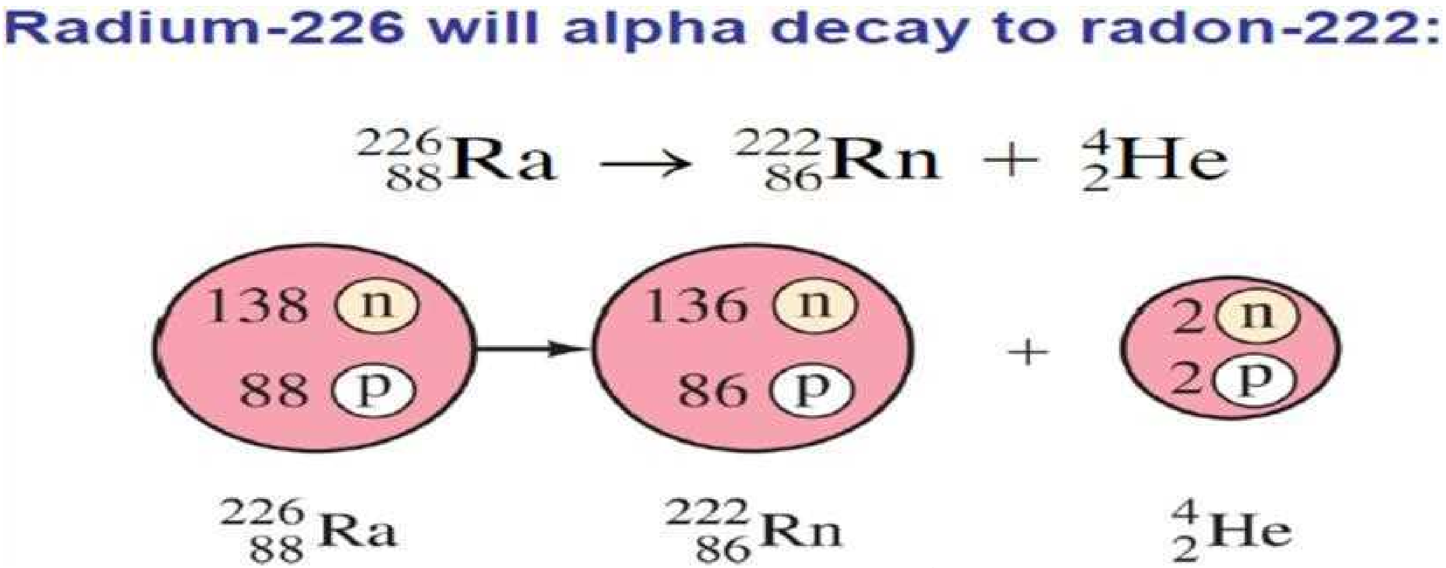
1. **Alpha rays**, which could barely penetrate a piece of paper
2. **Beta rays**, which could penetrate 3 mm of aluminium
3. **Gamma rays**, which could penetrate several centimetres of lead

We now know that alpha rays are helium nuclei, beta rays are electrons, and gamma rays are electromagnetic radiation.

Alpha Decay

$${}^{A}_{Z}\mathrm{N} \rightarrow {}^{A-4}_{Z-2}\mathrm{N}' + {}^{4}_{2}\mathrm{He}$$

- Strong nuclear force cannot hold a large nucleus together
- Mass of the parent nucleus is greater than the sum of the masses of the daughter nucleus and the alpha particle
- This difference is called the disintegration energy.
- When a nucleus decays through alpha emission, energy



Radium-226 will alpha decay to radon-222:

$${}^{226}_{88}\mathrm{Ra} \rightarrow {}^{222}_{86}\mathrm{Rn} + {}^{4}_{2}\mathrm{He}$$

Beta Decay

β^- & β^+

$$^{14}_{6}\mathrm{C} \rightarrow {}^{14}_{7}\mathrm{N} + e^- + \text{neutrino}$$

$$n \rightarrow p + e^- + \text{neutrino}$$

$$^{1}_{1}p \longrightarrow {}^{1}_{0}n + {}^{0}_{+1}e + {}^{0}_{0}\upsilon_e$$

$$^{19}_{10}\mathrm{Ne} \rightarrow {}^{19}_{9}\mathrm{F} + e^+ + \nu. \qquad \beta+$$

And a nucleus can capture one of its inner electrons:

$$^{7}_{4}\mathrm{Be} + e^- \rightarrow {}^{7}_{3}\mathrm{Li} + \nu. \qquad \text{EC}$$

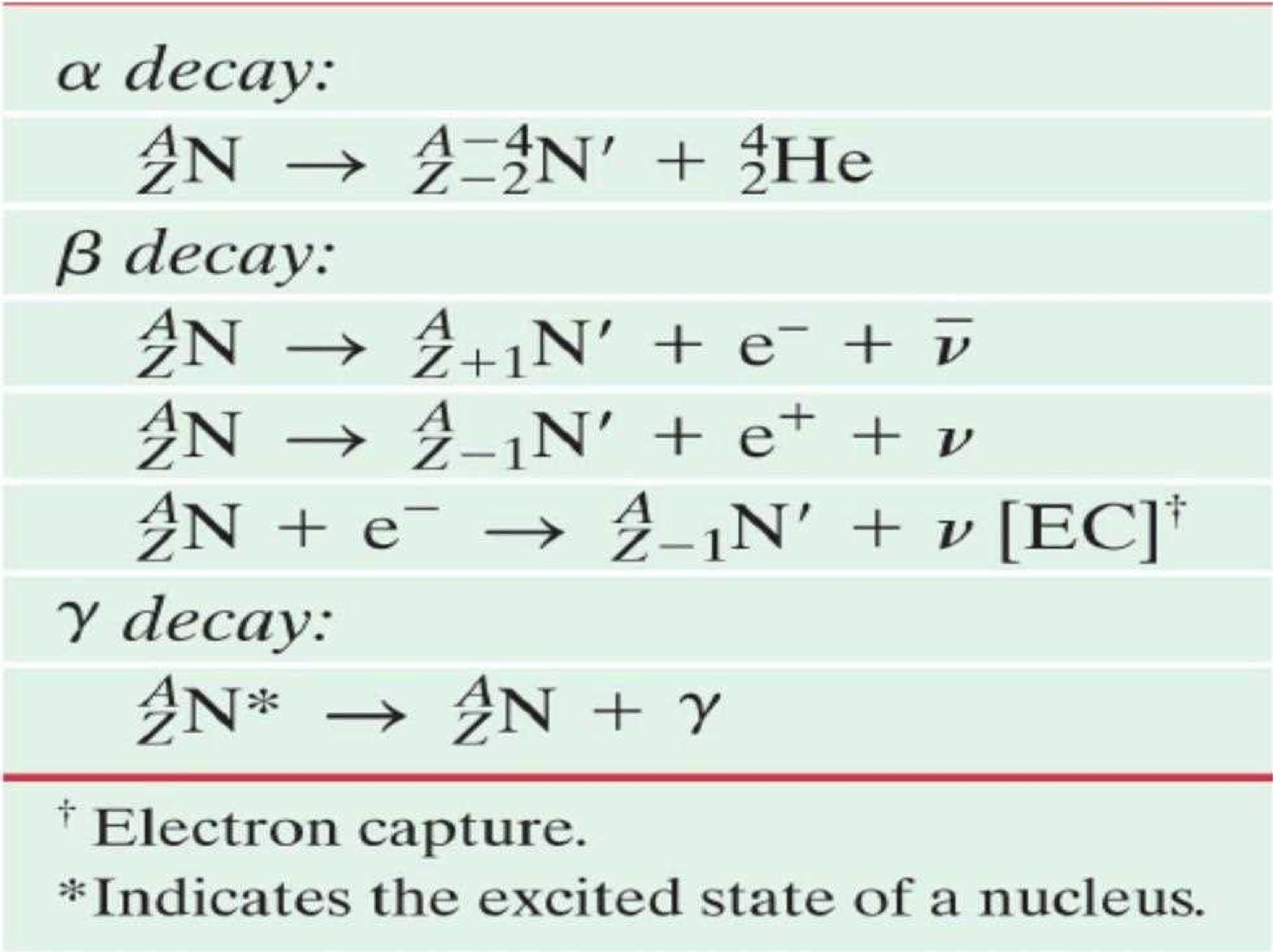
$${}^{A}_{Z}\mathrm{N} \rightarrow {}^{A}_{Z+1}\mathrm{N}' + \mathrm{e}^{-} + \bar{\nu} \qquad [\beta^{-}\ \mathrm{decay}],$$

$${}^{A}_{Z}\mathrm{N} \rightarrow {}^{A}_{Z-1}\mathrm{N}' + \mathrm{e}^{+} + \nu \qquad [\beta^{+}\ \mathrm{decay}].$$

$${}^{A}_{Z}\mathrm{N} + \mathrm{e}^{-} \longrightarrow {}^{A}_{Z-1}\mathrm{N}' + \nu$$

Gamma Decay

Gamma rays are very high-energy photons. They are emitted when a nucleus decays from an excited state to a lower state, just as photons are emitted by electrons returning to a lower state.



α decay:

$$^{A}_{Z}\mathrm{N} \rightarrow {}^{A-4}_{Z-2}\mathrm{N}' + {}^{4}_{2}\mathrm{He}$$

β decay:

$$^{A}_{Z}\mathrm{N} \rightarrow {}^{A}_{Z+1}\mathrm{N}' + \mathrm{e}^{-} + \bar{\nu}$$

$$^{A}_{Z}\mathrm{N} \rightarrow {}^{A}_{Z-1}\mathrm{N}' + \mathrm{e}^{+} + \nu$$

$$^{A}_{Z}\mathrm{N} + \mathrm{e}^{-} \rightarrow {}^{A}_{Z-1}\mathrm{N}' + \nu\ [\mathrm{EC}]^{\dagger}$$

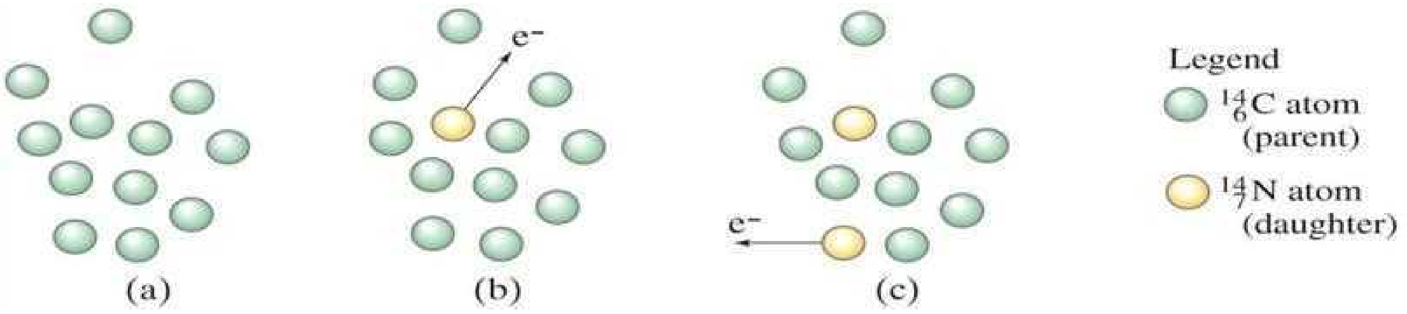
γ decay:

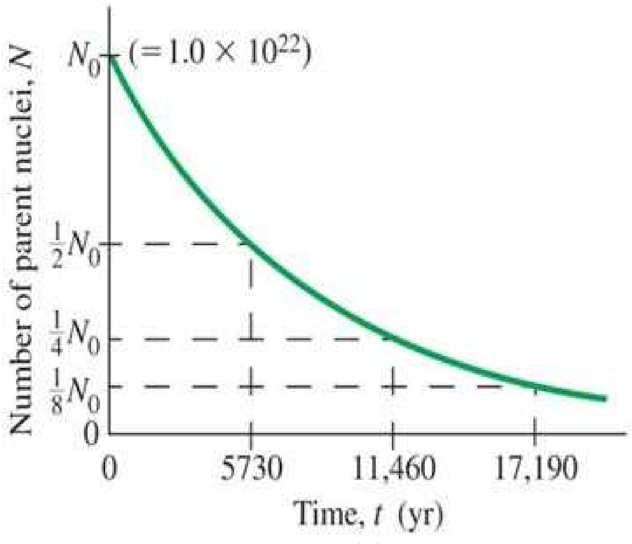
$$^{A}_{Z}\mathrm{N}^{*} \rightarrow {}^{A}_{Z}\mathrm{N} + \gamma$$

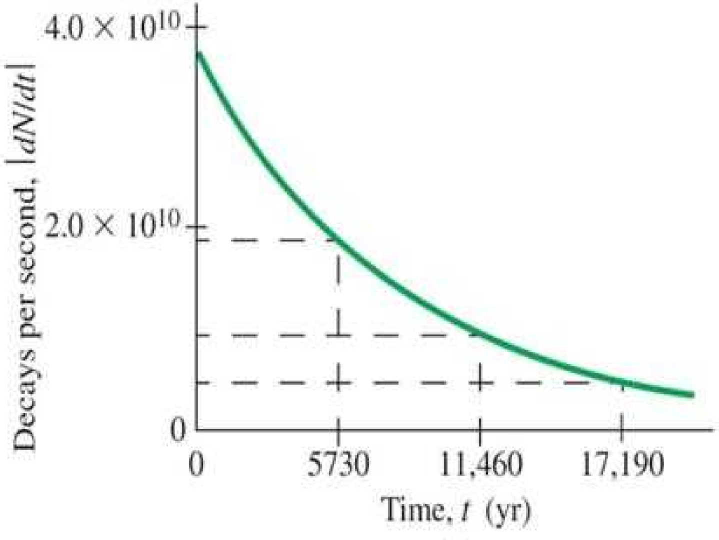
† Electron capture.

*Indicates the excited state of a nucleus.

Half-Life and Rate of Decay







The half-life is the time it takes for half the nuclei in a given sample to decay.

$$T_{\frac{1}{2}} = \frac{\ln 2}{\lambda} = \frac{0.693}{\lambda}.$$

It is related to the decay constant:

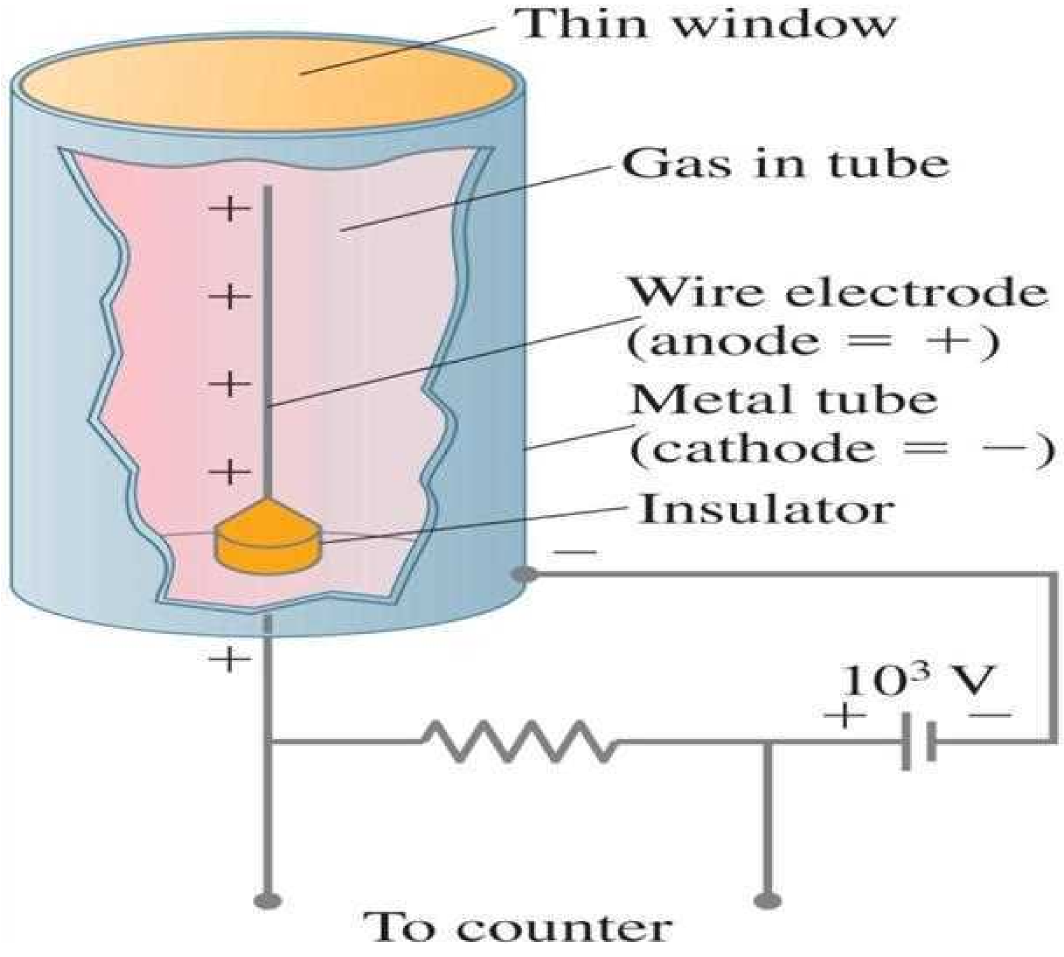
Units of Radioactivity

❖In the International System (SI), the unit of radioactivity is one nuclear transmutation per second and is expressed in Becquerel (Bq), named after the scientist Henri Becquerel.

❖The old unit of radioactivity was Curie (Ci), named after the scientists Madame Marie Curie and Pierre Curie, the pioneers who studied the phenomenon of radioactivity.

❖One Ci is the number of disintegrations emanating from 1 g of Radium-226, and is equal to 3.7×10^{10} Bq.

The Geiger counter is a gas-filled tube with a wire in the centre. The wire is at high voltage; the case is grounded. When a charged particle passes through, it ionizes the gas. The ions cascade onto the wire, producing a pulse.



The Geiger counter

Principle and working:

❖As ionizing radiation coming from the surrounding medium passes through the mica window and enters the **Geiger-Muller tube**, it ionizes the gas inside, transforming it into positively charged ions and electrons.

❖The electrons eventually migrate towards the anode of the tube detector, while the positively **charged ions accelerate towards the cathode.**

- As the positive ions move towards the cathode, they collide with the remaining inert gas thus producing more ions through an **avalanche effect. When this happens an electrical current is established between the two electrodes.**

Quenching

It is the process to prevent the continuous discharge. Self-quenching is done by vapours of ethyl alcohol because its ionization energy is less than the ionization energy of Argon atom.

Counting rate

The GM Counter can count about **5000 particles / sec.** The counting rate depends upon the death and recovery time of G M Counter.

Death time

In the counter, the slowly moving positive argon ion **takes 200 sec** to reach the cathode. If the second radiation enters the tube during this time, it will not be registered this time is called death time of the counter

Recovery time

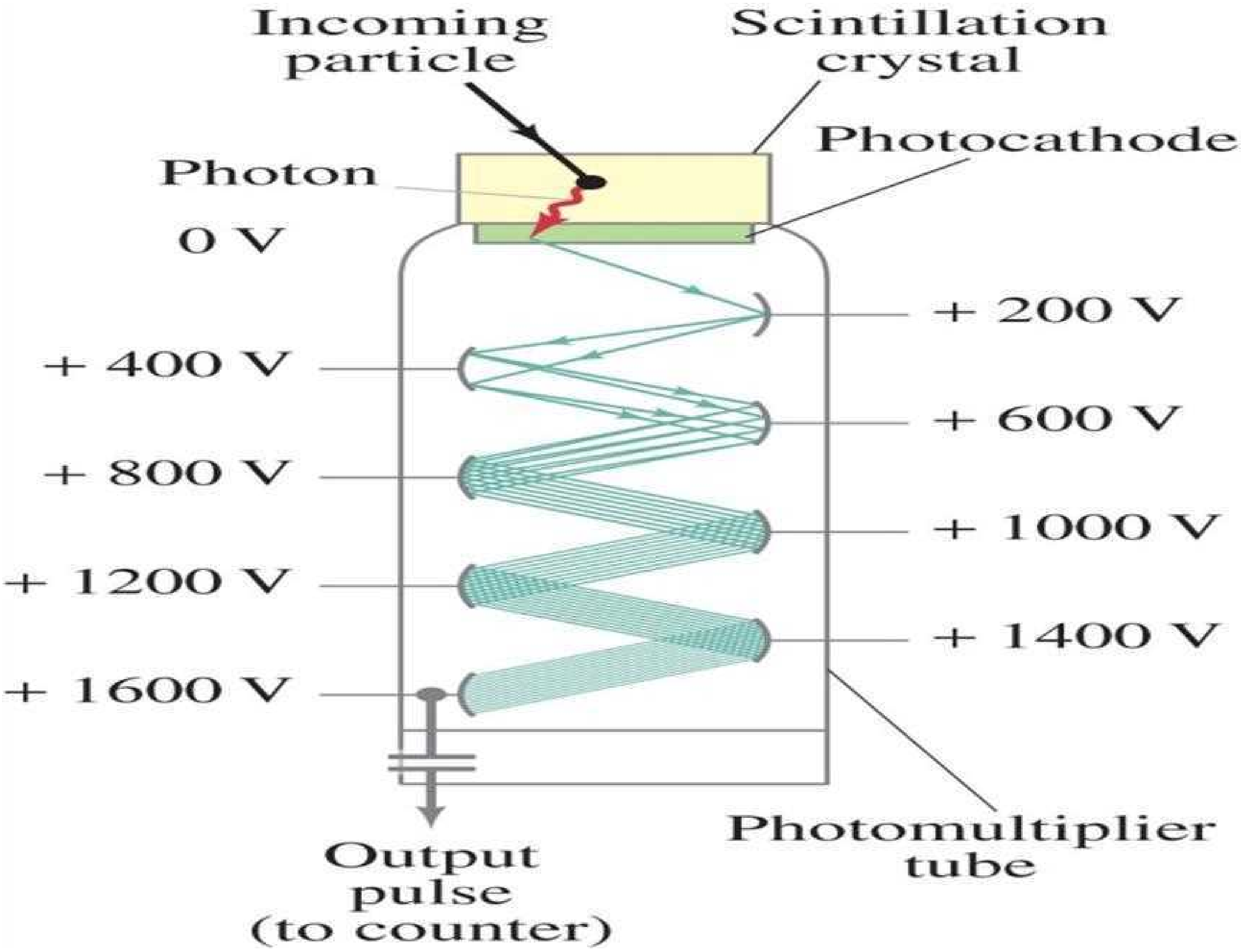
After death time the tube takes another **200 sec** to regain the original working condition. This time is called recovery time of the counter.

Paralysis time

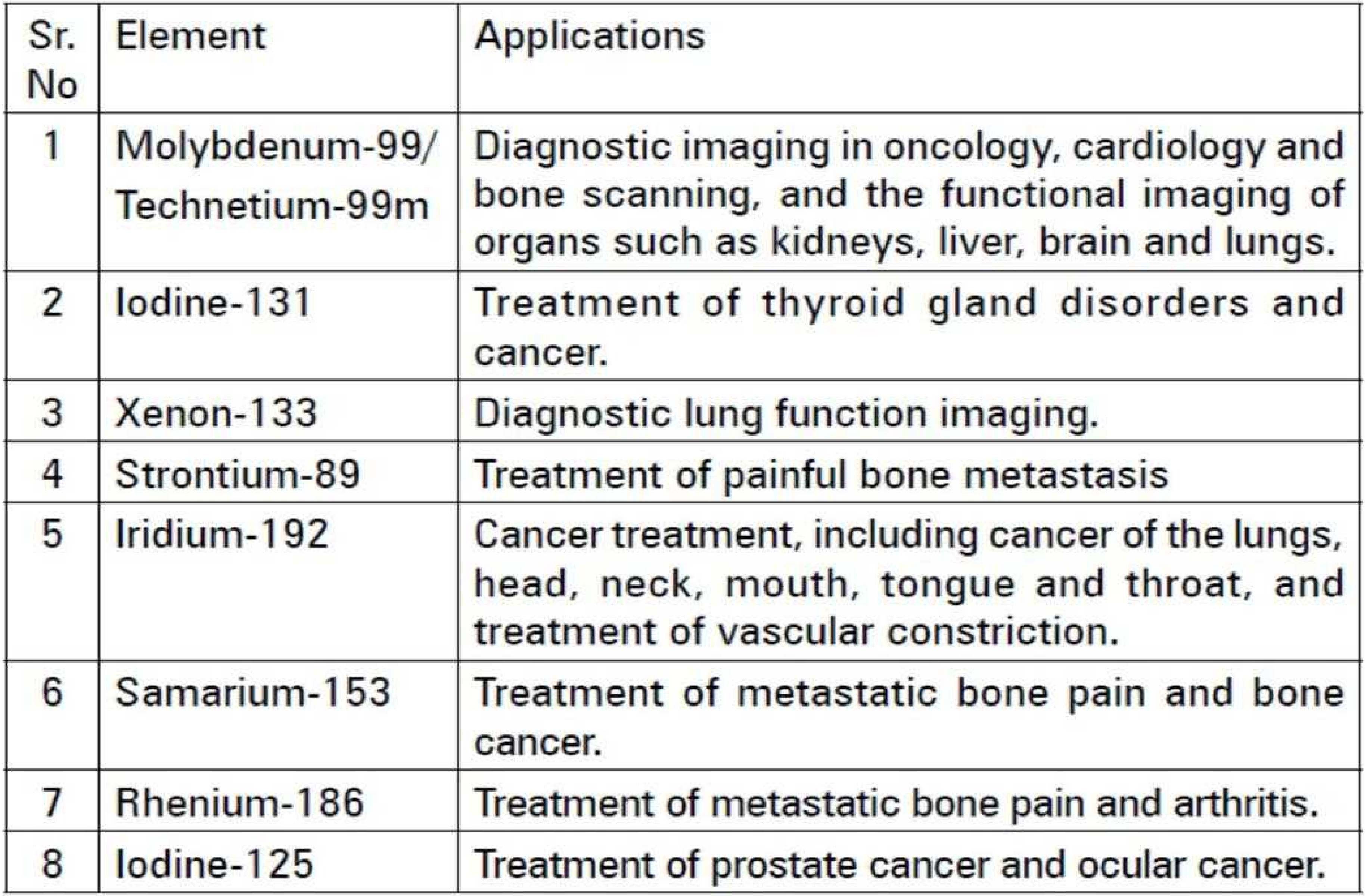
The sum of death and recovery time is known as paralysis time, which is 400 sec. The tube can respond to the second radiation after **400 sec**

A scintillation counter

- This uses a scintillator – a material that emits light when a charged particle goes through it.
- The scintillator is made light-tight, and the light flashes are viewed with a photomultiplier tube,
- A photocathode that emits an electron when struck by a photon and then a series of amplifiers.


Incoming particle
Scintillation crystal
Photocathode
Photon
0 V
+ 200 V
+ 400 V
+ 600 V
+ 800 V
+ 1000 V
+ 1200 V
+ 1400 V
+ 1600 V
Output pulse (to counter)
Photomultiplier tube

Applications of radiopharmaceuticals in healthcare system



Sr. No	Element	Applications
1	Molybdenum-99/ Technetium-99m	Diagnostic imaging in oncology, cardiology and bone scanning, and the functional imaging of organs such as kidneys, liver, brain and lungs.
2	Iodine-131	Treatment of thyroid gland disorders and cancer.
3	Xenon-133	Diagnostic lung function imaging.
4	Strontium-89	Treatment of painful bone metastasis
5	Iridium-192	Cancer treatment, including cancer of the lungs, head, neck, mouth, tongue and throat, and treatment of vascular constriction.
6	Samarium-153	Treatment of metastatic bone pain and bone cancer.
7	Rhenium-186	Treatment of metastatic bone pain and arthritis.
8	Iodine-125	Treatment of prostate cancer and ocular cancer.

Pharmaceutical Application of Radioactive Substances

Treatment of Cancers and Tumours

- Americium 241 used as antineoplastic.
- Californium 252 used as antineoplastic."
- Cobalt 60 used as antineoplastic.
- Gold 94 used as antineoplastic.
- Holmium 66 (26 h) being developed for diagnosis and treatment of liver tumours.
- Iodine-125 (60 d) used in cancer brachytherapy (prostate and brain).

Treatment of Thyroid Disease with Iodine 131

- Iodine-131 is therapeutically used for to treat thyroid cancer, hyperthyroidism (including Graves’ disease, toxic multinodular goitre, and toxic autonomously functioning thyroid nodules), and **Nontoxic multinodular goitre.**

Palliative Treatment of Bone Metastasis

- Various radioisotopes and pharmaceuticals are used to deliver palliative treatment of bone metastases, **including samarium-153 (Sm-153), strontium-89 (Sr-89) chloride, and phosphorus-32 (P-32) sodium phosphate.**

- The two most common side effects occurring from radiopharmaceutical therapy for metastatic bone disease are initial increased bone pain (flare) and a decrease in **WBC and platelet counts.**

Treatment of Arthritis

- Erbium-169: Use for relieving arthritis pain in synovial joints

Diagnostic Radiopharmaceuticals

- Ammonia N 13 Injection used for diagnostic coronary artery disease.
- Chromium 51 used for diagnosis of pernicious anaemia.
- Holmium 166 used for diagnosis and treatment of liver tumours.
- Iodine 125 used diagnostically to evaluate the filtration rate of kidneys.

Storage of Radioactive Substances

- Radiopharmaceuticals should be kept in **well-closed containers** and stored in an area assigned for the purpose.
- The storage conditions should be such that the **maximum radiation dose rate** to which persons may be exposed is reduced to an acceptable level.
- Care should be taken to comply with national regulations for protection against **ionizing radiation.**
- Radiopharmaceutical preparations that are intended for parenteral use should be kept in a glass vial, ampoule or syringe that is sufficiently transparent to permit the visual inspection of the contents.
- Glass containers may darken under the **effect of radiation.**

Precautions to be taken in Handling of Radiopharmaceuticals

Great care has to be taken in handling storage of radioactive material for protecting people and personnel who handle it:

- The working areas should not get contaminated with radioactive material.
- If the radioactive liquid has to be handled, it must be carried in trays having absorbent tissue paper so that any spillage will get absorbed by paper.
- Rubber gloves have to be used when working with radioactive liquids.

- Pipettes operated by mouth should never be employed. Before making use of glass apparatus, it must be ensured that they have been inactive. The waste radioactive materials have to be stored till the activity becomes low before its disposal.
- **Smoking, eating, drinking** activities are prohibited in the area of radioactive work.
- The radioactive emitter should be handled with forceps and never by hand.
- Sufficient shielding device should be used.
- Radioactive materials have to be stored in suitable labelled containers**, shielding by bricks** and preferably in a remote corner.
- Great care has to be applied for disposal of radioactive materials.
- A regular monitoring of radioactivity is to be done in area where radioactive material is stored.

Radio opaque Contrast Media

- Contrast materials, also called contrast agents or contrast media, are used to improve pictures of the inside of the body produced by **x-rays, computed tomography (CT), magnetic resonance (MR) imaging, and ultrasound**.

- Often, contrast materials allow the radiologist to distinguish normal from abnormal conditions.
- **They are substances that temporarily change the way x-rays or other imaging tools interact with the body.**

- When introduced into the body prior to an imaging exam, contrast materials make certain structures or tissues in the body appear different on the images than they would if no contrast material had been administered.

Contrast materials help distinguish or "contrast" selected areas of the body from surrounding tissue.

By improving the visibility of specific organs, blood vessels or tissues, contrast materials help physicians diagnose medical conditions.

Contrast materials enter the body in one of three ways. They can be:

- swallowed (taken by mouth or orally)
- administered by enema (given rectally)
- injected into a blood vessel (vein or artery; also called given intravenously or intra-arterially)

Following an imaging exam with contrast material, the material is absorbed by the body or eliminated through urine or bowel movements.

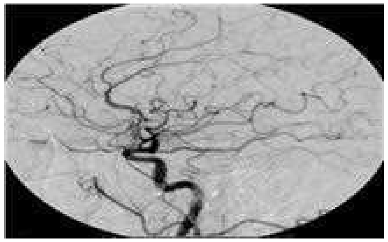
There are several types of contrast materials:

(1)Iodine-based
(2) (2) Barium-sulphate

These two compounds are used in x-ray and computed tomography (CT) imaging exams.

Radio contrast agents used in X-ray examinations can be grouped in ***positive*** (iodinated agents, barium sulphate), and ***negative agents*** (air, carbon dioxide, methylcellulose).

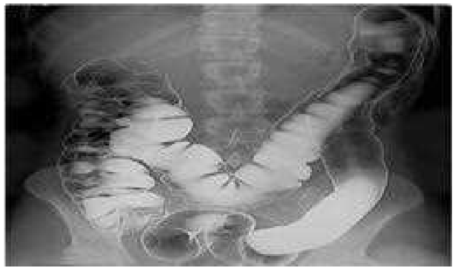
1. **Iodine (circulatory system):** Iodinated contrast contains iodine. It is the main type of radio contrast used for intravenous administration. Its uses include



- Contrast CTs
- Angiography (arterial investigations)
- Venography (venous investigations)

2.Barium sulphate is mainly used in the imaging of the digestive system. The substance exists as a water-insoluble white powder that is made into slurry with water and administered directly into the gastrointestinal tract.

- Barium enema (large bowel investigation) and DCBE (double contrast barium enema)
- Barium swallow (oesophageal investigation)
- Barium meal (stomach investigation) and double contrast barium meal
- Barium follow through (stomach and small bowel investigation)
- CT pneumocolon / virtual colonoscopy



Biological Effects of Radiations

Although we tend to think of biological effects in terms of the effect of radiation on living cells, in actuality, ionizing radiation, by definition, interacts only with atoms by a process called **ionization.**

Thus, ***all biological damage effects begin with the consequence of radiation interactions with the atoms forming the cells.***

As a result, radiation effects on humans proceed from the lowest to the highest levels as noted in the above list.

Cell Damage

❖There are two mechanisms by which radiation ultimately affects cells. These two mechanisms are commonly called ***direct and indirect effects***.

❖**Direct Effect:**

If radiation interacts with the atoms of the DNA molecule, or some other cellular component critical to the survival of the cell, it is referred to as a direct effect.

❖Such an interaction may affect the ability of the cell to reproduce and, thus, survive.

❖If enough atoms are affected such that the chromosomes do not replicate properly, or if there is significant alteration in the information carried by the DNA molecule.

❖Then the cell may be destroyed by “direct” interference with its life-sustaining system.

Indirect Effect:

- ❖Each cell, just as is the case for the human body, is mostly water.
- ❖Therefore, there is a much higher probability of radiation interacting with the water that makes up most of the cell's volume.
- ❖ ***When radiation interacts with water, it may break the bonds that hold the water molecule together, producing fragments such as hydrogen (H) and hydroxyls (OH).***
- ❖ These fragments may recombine or may interact with other fragments or ions to form compounds, such as water, which would not harm the cell.
- ❖However, ***they could combine to form toxic substances, such as hydrogen peroxide (H_2O_2), which can contribute to the destruction of the cell.***

Cellular Sensitivity to Radiation

Not all living cells are equally sensitive to radiation.

❖ ***Those cells which are actively reproducing are more sensitive than those which are not.***

❖***This is because dividing cells require correct DNA information in order for the cell's offspring to survive.***

❖ ***A direct interaction of radiation with an active cell could result in the death or mutation of the cell,*** whereas a direct interaction with the DNA of a dormant cell would have less of an effect.

As a result, living cells can be classified according to their rate of reproduction, which also indicates their relative sensitivity to radiation. This means that different cell systems have different sensitivities. ***Lymphocytes (white blood cells) and cells which produce blood are constantly regenerating, and are, therefore, the most sensitive***.

Rapid cell division: Tumor and Pregnancy

As the tumor is exposed to radiation, the outer layer of rapidly dividing cells is destroyed, causing it to "shrink" in size.

- ❖If the tumor is given a massive dose to destroy it completely, the patient might die as well. Instead, the tumor is given a small dose each day, which gives the healthy tissue a chance to recover from any damage while gradually shrinking the highly sensitive tumor.

- ❖Another cell system that is composed of rapidly dividing cells with a good blood supply and lots of oxygen is the developing embryo.

Therefore, the ***sensitivity of the developing embryo to radiation exposure is similar to that of the tumor; however, the consequences are dramatically different.***

Radiation Effects

High Doses (Acute):

High doses tend to kill cells, while low doses tend to damage or change them.

High doses can kill so many cells that tissues and organs are damaged. This in turn may cause a rapid**Acute Radiation Syndrome (ARS).** whole body response often called the

Low Doses (Chronic): Low doses spread out over long periods of time don’t cause an immediate problem to any body organ. The effects of low doses of radiation occur at the level of the cell, and the results may not be observed for many years.

High Dose Effects

Blood count changes

Vomiting (threshold) Death

(threshold)

Low Doses Effect

There are three general categories of effects resulting from exposure to low doses of radiation. These are:

Genetic - The effect is Mutation of the reproductive cells passed on to the offspring of the individual exposed.

Somatic - The effect is primarily suffered by the individual exposed. ***Since cancer is the primary result, it is sometimes called the Carcinogenic Effect.***

In-Utero - Some mistakenly consider this to be a genetic consequence of radiation exposure, because the effect, suffered by a developing embryo/foetus, is seen after birth. However, this is actually a special case of the somatic effect, since the embryo/foetus is the one exposed to the radiation.

Conclusion

General consensus among experts is that some *radiation risks* are related to radiation dose by a linear, no-threshold model.

LINEAR - An increase in dose results in a proportional increase in risk

NO-THRESHOLD - Any dose, no matter how small, produces some risk

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