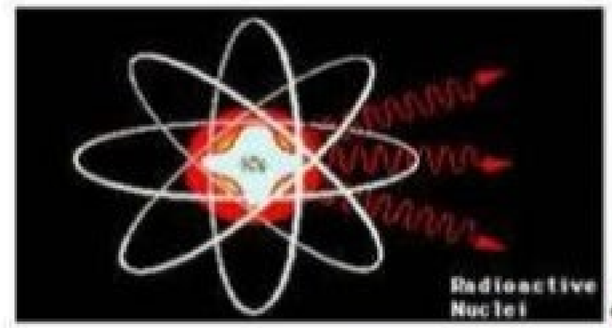
RADIO PHARMACEUTICALS

- Production control
- Safety precautions
- Applications
- Storage.




RADIOPHARMACEUTICALS



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DEFINITION:

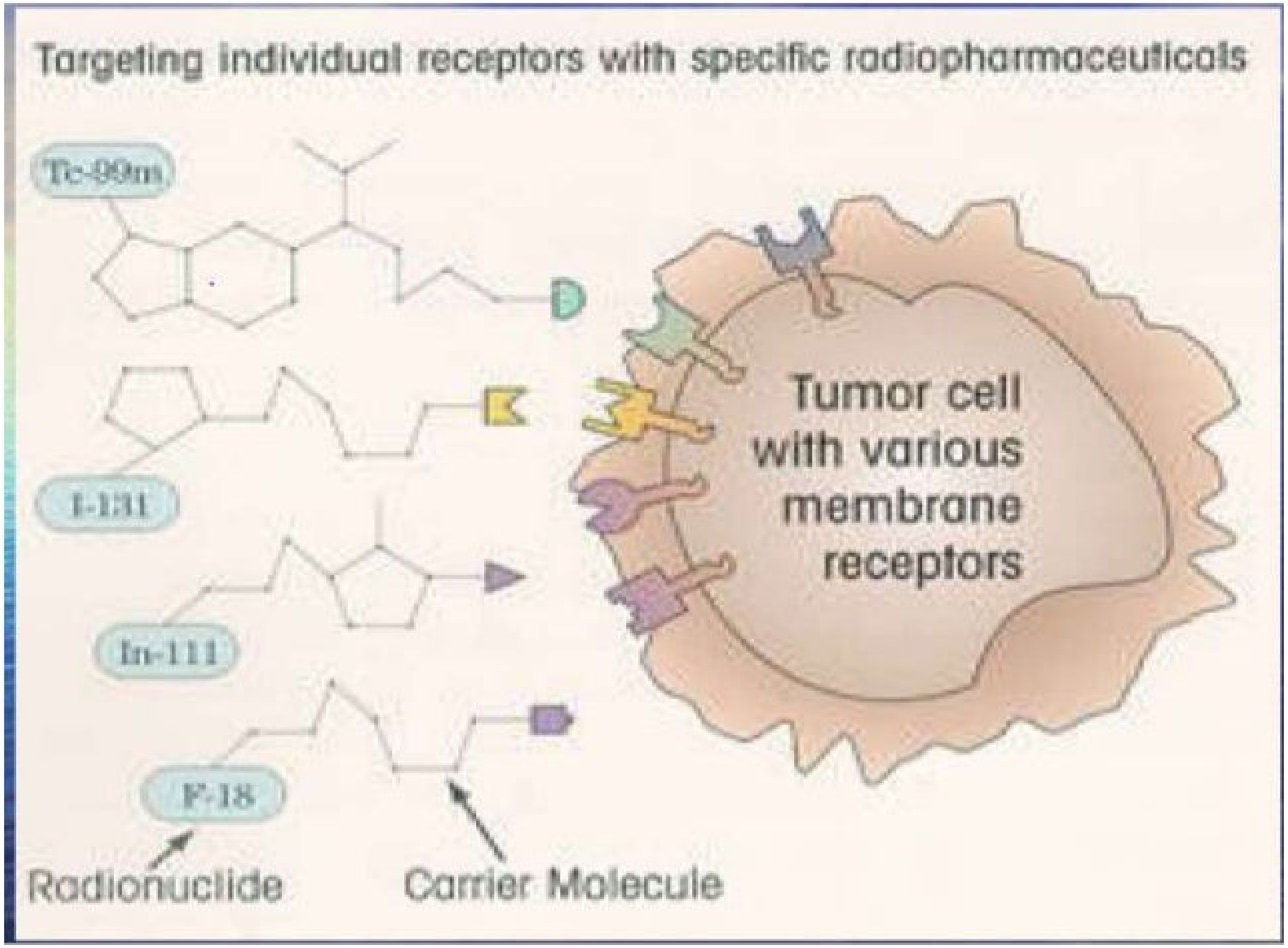
Radiopharmaceuticals are the radioactive substances or radioactive drugs for diagnostic or therapeutic interventions.

or

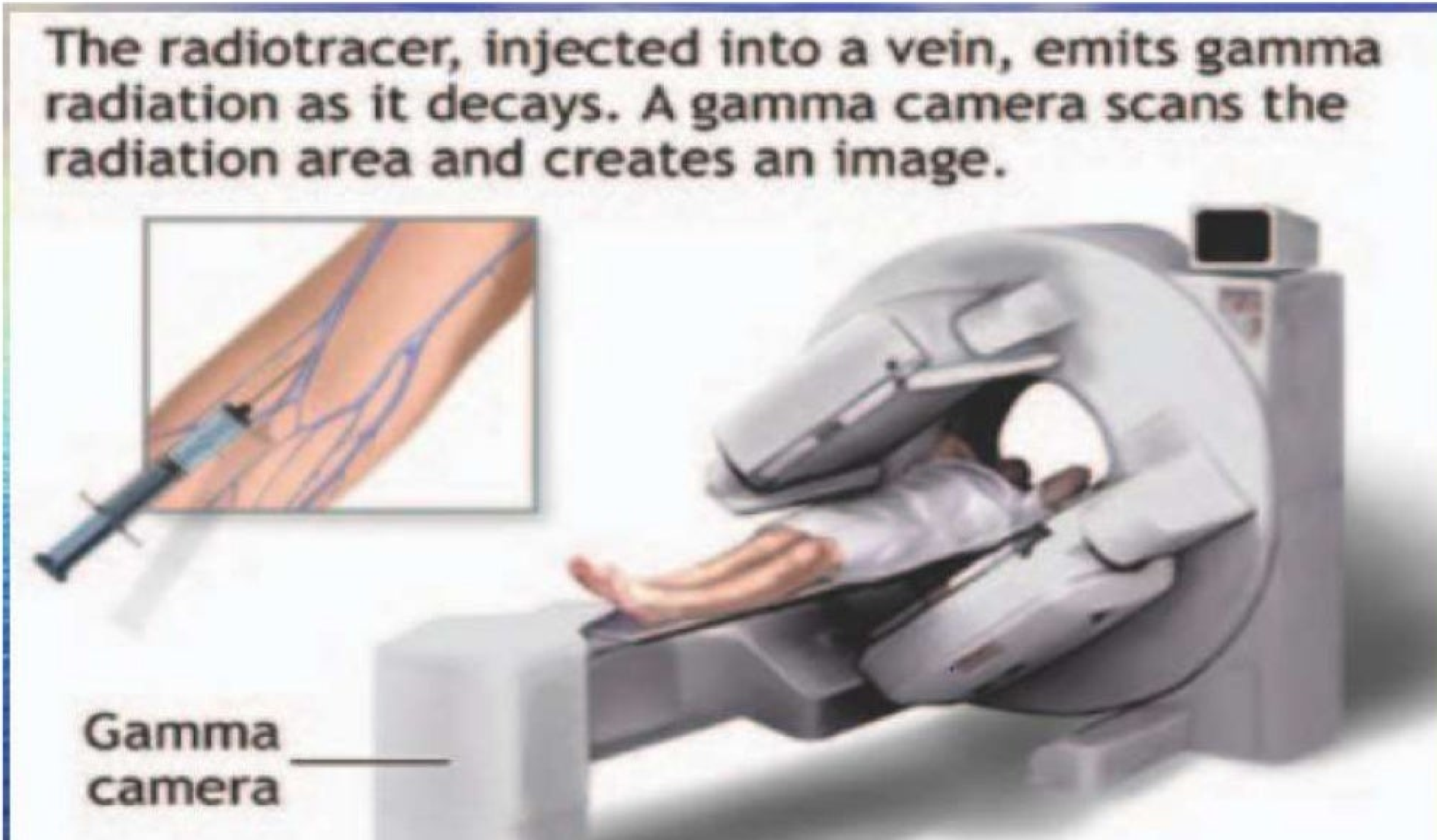
Radiopharmaceuticals are medicinal formulations containing radioisotopes which are safe for administration in humans for diagnosis or for therapy.

COMPOSITION:

- A radioactive isotope that can be injected safely into the body, and
- A carrier molecule which delivers the isotope to the area to be treated or examined.



USAGE/WORKING:



BASICS

Nuclide:

This is a particular nuclear species characterized by its atomic number (No. of protons) and mass number (No. of protons + neutrons). $_{6}C^{12}$, $_{11}Na^{23}$

Isotopes:

These are nuclides with same atomic number and **different mass number.**

Hydrogen has 3 isotopes --- $_{1}H^{1}$, $_{1}H^{2}$, $_{1}H^{3}$.

Carbon has 5 isotopes ------$_{6}C^{10}$, $_{6}C^{11}$, $_{6}C^{12}$, $_{6}C^{13}$, $_{6}C^{14}$.

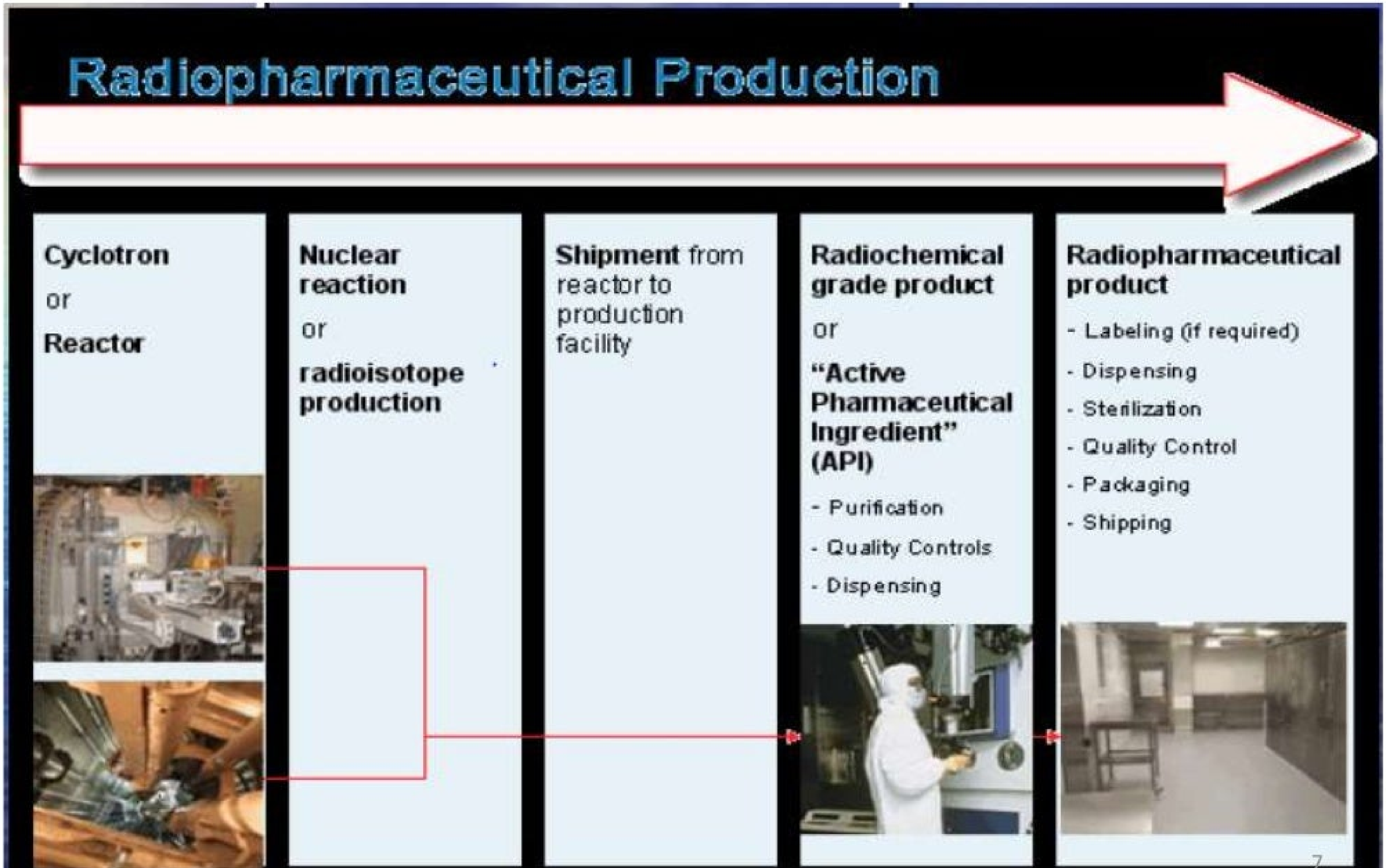
- ISOTOPES MAY BE STABLE OR UNSTABLE.
- The nucleus is unstable if the number of neutrons is less or greater than the number of protons.
- If they are unstable, they under go radioactive decay or disintegration and are known as radioactive isotopes/ radioactive nuclides.

Radioactivity:

The property of unstable nuclides of emitting radiation by spontaneous transformation of nuclei into other nuclides is called radioactivity.

- Radioactive isotopes emit radiations or rays like **α, β, γ rays.**

PRODUCTION CONTROL



PRODUCTION OF RADIONUCLIDES

Most, if not all, radionuclides used in medicine and pharmacy are produced artificially. Table 29-3 is a compilation of medical radionuclides along with their physical properties. These radionuclides are produced by three general methods: (1) in a nuclear reactor as a fission by-product, (2) as the product of a neutron reaction—either by activation or transmutation, and (3) by use of a particle accelerator such as a cyclotron.

FISSION BY-PRODUCTS

Fission is a radioactive process in which a relatively heavy nucleus is divided into two new nuclei of nearly equal size with the simultaneous emission of two or three neutrons. Fission may be spontaneous, but normally the reaction is induced by bombardment of the parent nucleus with a neutron:

$$^{235}_{92}\mathrm{U} + ^{1}_{0}\mathrm{n} \rightarrow X + Y + 2.5\ \mathrm{n}$$

where X and Y are fission products (new nuclei) with a Z value of between 30 and 65 and a sum of 92. Fission reactions may be self-sustaining. For each neutron consumed, an average of 2.5 new neutrons are produced that may initiate the fission of other nuclei. Such a reaction is called a *chain reaction*. If at least one

The following illustrates one of many combinations of fission reactions that are possible:

$$^{238}_{92}\mathrm{U} + {}^{1}_{0}\mathrm{n} \rightarrow {}^{131}_{50}\mathrm{Sn} + {}^{106}_{42}\mathrm{Mo} + {}^{1}_{0}\mathrm{n} + {}^{1}_{0}\mathrm{n}$$

The ^{131}Sn and the ^{106}Mo are very radioactive and have very short half-lives. They immediately decay by a series of beta decay processes:

$$^{131}_{50}\mathrm{Sn} \rightarrow {}^{131}_{51}\mathrm{Sb} \rightarrow {}^{131}_{52}\mathrm{Te} \rightarrow {}^{131}_{53}\mathrm{I}$$

$$^{106}_{46}\mathrm{Mo} \rightarrow {}^{106}_{43}\mathrm{Tc} \rightarrow {}^{106}_{44}\mathrm{Ru} \rightarrow {}^{106}_{45}\mathrm{Rh}$$

Both ^{131}I and ^{106}Ru are available commercially as fission-produced radionuclides, although ^{106}Ru is not routinely used for medical applications.

Before use, the desired nuclide must be chemically separated from a large number of other fission-produced radionuclides. For many of the radionuclides produced by fission, separation of the desired nuclide from the mixture of fission products is too difficult or costly.

NEUTRON REACTIONS

Many radioactive nuclides used in radiopharmaceuticals are prepared by neutron activation (n, γ) or transmutation (n, p) reactions by placing a suitable target material in a nuclear reactor where it is bombarded by neutrons. By means of (n, γ) and (n, p) reactions, reactors produce radionuclides having a high neutron-to-proton ratio that typically decay by emission of a negatron. For example, radioactive phosphorus (^{32}P) can be prepared from stable phosphorus (^{31}P) by *neutron capture:*

$$^{31}_{15}P + ^{1}_{0}n \rightarrow ^{32}_{15}P + \gamma$$

The disadvantage of this method is that the radioactive phosphorus (^{32}P) is highly diluted with stable ^{31}P. Phosphorus-32 of

Radioactive phosphorus can be made by transmutation if high specific activities are required:

$$^{32}_{16}S + ^{1}_{0}n \rightarrow ^{32}_{15}P + ^{1}_{1}p$$

In this case, the radioactive phosphorus can be separated from the unreacted sulfur by chemical procedures. Where ^{32}P is made from ^{31}P, such chemical separations are not practical.

Transmutation is useful for the preparation of many radioactive nuclides, especially those of low atomic number. As the atomic number increases, (n, γ) reactions are favored over (n, p) reactions. For example, cobalt-60 is produced by the reaction $^{59}Co(n, \gamma)^{60}Co$ because the reaction $^{60}Ni(n, p)^{60}Co$ does not occur with sufficient frequency to make the process commercially feasible.

CYCLOTRON-PRODUCED RADIONUCLIDES

Certain radionuclides are cyclotron-produced. The cyclotron and similar *particle accelerators* can be used only with charged particles such as electrons, protons, alpha particles, or deuterons because the operation of such machines depends upon the interaction of magnetic and/or electrostatic fields with the charge (either + or −) of the particle undergoing acceleration. When the particles have been accelerated to a high velocity, even approaching the velocity of light and representing enormous energies, they are caused to strike a target containing the atoms to be bombarded. Sodium-22 is prepared in this way, by the interaction of high-velocity deuterons with magnesium. The nuclear equation is:

$$^{24}Mg(d, \alpha)^{22}Na$$

Cyclotrons produce neutron-deficient isotopes; that is, the neutron-to-proton ratio is low. These nuclides usually decay by positron emission or electron capture. Cyclotron-produced radionuclides are generally carrier-free because they are normally produced by transmutation.

Usually a nuclide can be made by more than one reaction. For example, ^{123}I can be prepared either directly or indirectly. Di-

Direct	Indirect
$^{123}Te(p, n)^{123}I$	$^{122}Te(^{4}He, 3n)^{123}Xe \rightarrow {}^{123}I$
$^{121}Sb(^{4}He, 2n)^{123}I$	$^{122}Te(^{3}He, 2n)^{123}Xe \rightarrow {}^{123}I$
$^{122}Te(d, n)^{123}I$	$^{123}Te(^{3}He, 3n)^{123}Xe \rightarrow {}^{123}I$
$^{124}Te(p, 2n)^{123}I$	$^{127}I(p, 5n)^{123}Xe \rightarrow {}^{123}I$
	$^{124}Xe(p, 2n)^{123}Cs \rightarrow {}^{123}Xe \rightarrow {}^{123}I$

Radiopharmaceuticals production occurs in **machines** like

1. **Cyclotron (low energy, high energy)**
2. **Nuclear reactors**
3. **Hot cells.**
4. **Radionuclide generator**

1. CYCLOTRON:

- Used for acceleration of particles to produce radioisotopes.
- The early use of cyclotron in radiopharmaceuticals field was for the production of long lived radioisotopes that can be used to prepare tracers for diagnostic imaging.
- For this, medium to high energy (20-70 MeV) cyclotrons with high beam currents were needed.
- Isotopes such as thallium-201, iodine-123 and indium-111 were prepared for use with single photon emission computed tomography (SPECT).

- With the advent of positron emission tomography (PET), there has been a surge in the production of low energy cyclotrons (9-19 MeV) exclusively for the production of short lived PET radionuclides.

Ex: fluorine-18, carbon-11, nitrogen-13 and oxygen-15.

- The majority of the cyclotrons (~350) worldwide are now used for the preparation of fluorine-18 for making radiolabelled glucose for medical imaging.

13 MeV cyclotron in operation in Chosun University, Republic of Korea.

2. Nuclear reactors:

These have ability to prepare larger quantities of radioisotopes.

3. Hot cells:

These used for radioisotopes/radiopharmaceuticals production.

They should be compatible with the requirements for both radiological and pharmaceutical safety.

FUTURE:

The need for rapid, remote and reliable synthesis of PET radiopharmaceuticals has led to the introduction of microprocessor controlled automated synthesis modules.

RADIONUCLIDE GENERATORS

When clinical procedures require that a radionuclide be administered internally, it is advantageous to use a nuclide with a short half-life to minimize the radiation dose received by the patient. It is evident, however, that the shorter the half-life, the greater the problem of supply. One answer to this problem is the radionuclide generator, which uses the phenomenon of *sequential decay*. A radionuclide generator provides a mechanism for separating a clinically useful, short half-life daughter nuclide from a long-lived parent nuclide. Radioactive decay of the long-lived parent results in the production of a short-lived radioactive daughter nuclide that is *eluted* or *milked* from the generator by means of an appropriate eluant. Characteristics of

The molybdenum-99/technetium-99m generator (Fig 29-10) consists of an alumina (Al_2O_3) column on which molybdenum-99 is adsorbed as ammonium molybdate. Radioactive decay of ^{99}Mo produces ^{99m}Tc, which is eluted from the column with0.9% sodium chloride, USP. Upon elution, the ^{99m}Tc is in the form of sodium pertechnetate ($Na^{99m}TcO_4$). Elution repeated every 24 hours provides a satisfactory balance between concentration and quantity of eluted ^{99m}Tc. If a high activity of ^{99m}Tc is not required, the generator can be eluted more frequently. A typical

- Radiopharmaceuticals **production involves** handling of large quantities of radioactive substances and chemical processing.
- **Aspects** which need to be addressed in production of radiopharmaceuticals, are

1. Management of radioisotope production,
2. Import,
3. Operation and maintenance of processing facilities,
4. Complying with the codes of cGMP,
5. Ensuring effective QA & QC systems,
6. Registration of the products with national/regional health authorities and
7. Radioactive material transport etc.

Radiopharmaceuticals production is still on a relatively small scale and implementing the CGMP guidelines and it involves taking care of several aspects

1. Proper selection and in service training of qualified personnel.
2. Drawing out of in house specifications for raw materials.
3. Generating test and storage standards.
4. Drawing out a manual of standardized procedures of safe handling and step by step processing ,testing and waste disposal.
5. Availability of qualified equipment.
6. Assignment of responsibilities in writing.
7. Applying validated processes and analytical methods.
8. Facilities for minimizing of surface and airborne contamination.
9. Periodic inspection of protective devices for wear and tear and performance.
10. Establishment of well understood emergency procedures.
11. Proper documentation system is required by law.

Production of radio pharmaceuticals is therefore a bit more complex than normal pharmaceuticals. **Good Radiation Practices (GRPs)** and Good Manufacturing Practices (GMPs) should be strictly followed during manufacturing and dispensing operations.

1. Strict personnel hygiene.
2. Avoidance of risk methodology.
3. Operations only in the recommended zones of hot Lab.
4. Proper techniques of distance and shielding.
5. Isolated storage , refrigeration of radionuclides and labelled compounds.
6. Trial run using dummy or inactive source.
7. Adequate washing facilities including showers.
8. Proper in service training of qualified personnel.

9. Drawing out a manual of standardized procedures of safe handling and step by step processing , testing and waste disposal of radio active compounds.
10. Facilities of minimizing radiation levels , removal of surface and air borne contaminants.
11. Calibration and maintenance of instruments for radioactivity measurements.
12. Provision of appropriate personnel monitoring and protective devices.
13. Periodic inspection of protective devices for wear and tear and performance.
14. Establishment of well understood emergency procedures.
15. Proper documentation system is required by law.

SAFETY PRECAUTIONS

- Radiation Safety is a term applied to concepts requirements, technologies and operations related to protection of people against the harmful effects of ionizing radiation.

Safe Handling of Radio Isotopes :

1. GRP needs to be strictly followed for operations with unrelated sources to reduce the chances of getting unwanted and avoidable radiation exposure.
2. It is necessary to mark the area in which the radio active work is carried out and it should be monitored regularly at periodic intervals.

3. Unnecessary movements of persons or materials should be avoided in the hot laboratory or radiopharmacy.
4. All the radiation workers must wear suitable protective clothing and radiation monitoring devices, Surgical gloves is necessary.
5. When not in use, the radionuclides must be kept in sealed containers.
6. The area should be surveyed regularly for both contamination and exposure hazards.
7. Work areas should be covered with a plastic, glass or stainless.
8. Tray with absorbent paper should be use to catch any spills and to prevent the spread of contamination.

9. Do not pipette by mouth.
10. Wash hands thoroughly.
11. Radioactive materials should never be touched with hand but handled with forceps or suitable instrument.
12. Do not eat, drink and smoke in areas where unsealed radionuclides are stored.
13. The radiation survey meter should be used to ensure safety of worker and public.
14. Survey an wipe test suggested action levels are
    For **unrestricted area** 0.25 mR/hr. (milli Roentgens)
    For **restricted area** 20 mR/hr.

Are radiopharmaceuticals safe?

- **Absolutely.** Like any medicine.
- The quantity of the pharmaceutical part of the radiopharmaceutical is very small, generally 1/10th of a millionth of an ounce.
- The risk of a reaction is 2-3 incidents per 1,00,000 injections, over 50% of which are rashes.
- Tell your doctor, if you have ever had any unusual or allergic reaction to radiopharmaceutical products.
- These are not recommended for use during pregnancy to avoid exposing the fetus to radiation.
- It may be necessary for you to stop breast-feeding for some time after receiving it.
- Very low amount is used for children in diagnosis.

STORAGE

1. Because of the short life of the radiopharmaceuticals the nuclear pharmacist will order the drug directly from manufacturer usually through over night delivery.
2. In addition knowledge of shipping time / delivery schedules and radio active decay associated loss should be calculated while ordering radio pharmaceuticals.
3. Isotope storage areas should be as per the rules, there should be separate labs for the manipulation and preparation of radio pharmaceutical dosage and another for calibration of doses, treatment room must also be different

4. Store in an airtight, suitable labeled containers shielded by lead bricks to protect personnel from exposure to primary or secondary emissions and that complies with national and international regulations concerning the storage of radioactive substances.
5. During storage, containers may darken due to irradiation. Such darkening does not necessarily involve deterioration of the preparations.
6. Radiopharmaceuticals intended for parental use should be stored in such a manner so that pharmaceutical purity of the product is maintained.

APPLICATIONS

Radioisotopes and radiopharmaceuticals are widely used in many branches of medicine and surgery.

1. **Diagnostic applications**
2. **Radiotherapy**
3. **Sterilization techniques.**
4. **Research applications**

Radioiodine (iodine-131) was first introduced in 1946 for the treatment of thyroid cancer & hyperthyroidism

1. Diagnostic applications:

Radiation for diagnostic purpose must have sufficient energy to pass through tissues from inside the body to detecting device.

Phosphorous – 32 ($_{15}P^{32}$):

This is used as sodium phosphate for diagnosis of malignant neoplasamas affecting eye, brain & skin.

Chrominium – 51 ($_{24}Cr^{51}$):

Chrominium – 51 as sodium chromate sterile solution is used to label RBC to measure their survival, volume & gastrointestinal blood losses.

Cobalt – 57 ($_{27}Co^{57}$) & Cobalt – 58 ($_{27}Co^{58}$):

These are labeled with Cynacobalamine (Vit- B12) preparations for measurement of absorption, diagnosis of pernicious anemia and other malabsorption syndromes.

Technetium-99m:

1. Technetium-99m is the most widely used radioisotope in diagnostic nuclear medicine, over **80%** of the nearly 25 million diagnostic studies carried out annually.
2. Technetium-99m has a **half-life of 6 hours** and it is daughter product of the long lived molybdenum-99 (a half-life of 66 hours).
3. Technetium 99m has short half life of 6 hours , which allows administration of higher amounts for **faster and clearer images** while exposing the patient to a low radiation dose. it offers an abundance of gamma photons for imaging.
4. Technetium- 99m complexes, are used for imaging the thyroid, liver, bone, kidneys etc.

New Technetium-99m complexes , are used as agents for imaging the blood flow (perfusion) in the muscular tissue of the heart (myocardium) and the brain.

Technetium-99m complexes	USES
99mTc-Exametazime	Cerebral perfusion radio labeling
99mTc-Macro aggregated albumin	Pulmonary perfusion
99mTc-Methylene diphophonate	Detect bone metastasis associated with cancer.
99mTc-Medronate	Bone imaging
99mTc-Per technetate	Imaging of thyroid salivary glands
99mTc-Sulfur colloid	Imaging of reticuloendothelial cells

2. Radio Therapy:

Radio isotopes are used for therapeutic action.

The **Principle** of radiotherapy is to destroy diseased tissues with out destroying healthy tissues.

β- radiations have sufficient penetration so used to treat surface lesions on eyes.

γ- radiations have high penetrating power, used to treat deep seated tumors.

Iodine-131 ($_{53}I^{131}$) & Iodine-123 ($_{53}I^{123}$):

These are used in study of thyroid function, in treatment of thyrotoxicosis & thyroid carcinoma.

Yttrium – 90 ($_{39}Y^{90}$):

This is used as colloid al suspension of Yttrium silicate in treatment of arthritic conditions of joints.

Phosphorus – 32 ($_{15}P^{32}$):

Sodium phosphate is used in treatment of polycythaemia by I.V injection.

Radiopharmaceuticals for bone pain palliation:

- Persons suffering from breast, lung and prostate cancer develop metastasis in bones in the advanced stage of their diseases.
- Therapeutic radiopharmaceuticals containing radionuclides such as **strontium-89, samarium-153 and rhenium-186/188** are used for effective palliation of pain from skeletal metastases.
- The IAEA has initiated a programme for the development and clinical application of **lutetium-177** based radiopharmaceuticals for bone pain palliation.

Radiopharmaceuticals for primary cancer treatment:

- **Radiolabelled peptides** as molecular vectors are being developed for targeted therapy.
- Peptide molecules when labelled with therapeutic radionuclides, have the potential to destroy receptor-expressing tumours, an approach referred to as **Peptide Receptor Radionuclide Therapy** (PRRT).
- **Yttrium-90 and lutetium-177** are frequently used.

Radiopharmaceuticals for radiosynoviorthesis:

- Radiosynoviorthesis or radiosynovectomy is a technique wherein a radiopharmaceutical is delivered into the affected **synovial compartment** (the interior of joints that is lubricated by fluid) of patients suffering from **joint pain**, as in the case of rheumatoid arthritis.
- **Phosphorus-32, yttrium-90, samarium-153, holmium-166, erbium-169, lutetium-177, rhenium-186**, etc. and some of them used in treatment of joint pain, are registered for human use.

3. Sterilization techniques:

Radio isotopes are employed in radiation sterilization of heat liable drugs like hormones, vitamins, antibiotics and surgical dressings, disposable syringes etc.,

Cobalt – 60 ($_{27}Co^{60}$):

This is used as radiation source for sterilization by γ- irradiation of disposable syringes, catheters and surgical dressings.

4. Research applications:

Radioisotopes are used in biochemical research for determination of mechanism of reaction, locus of action.

Iodine – 131:

Sodium iodohippuric is used in determination of effective renal plasma flow.

THANK YOU……..