NUCLEAR MEDICINE

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MEDICAL NEWS TODAY

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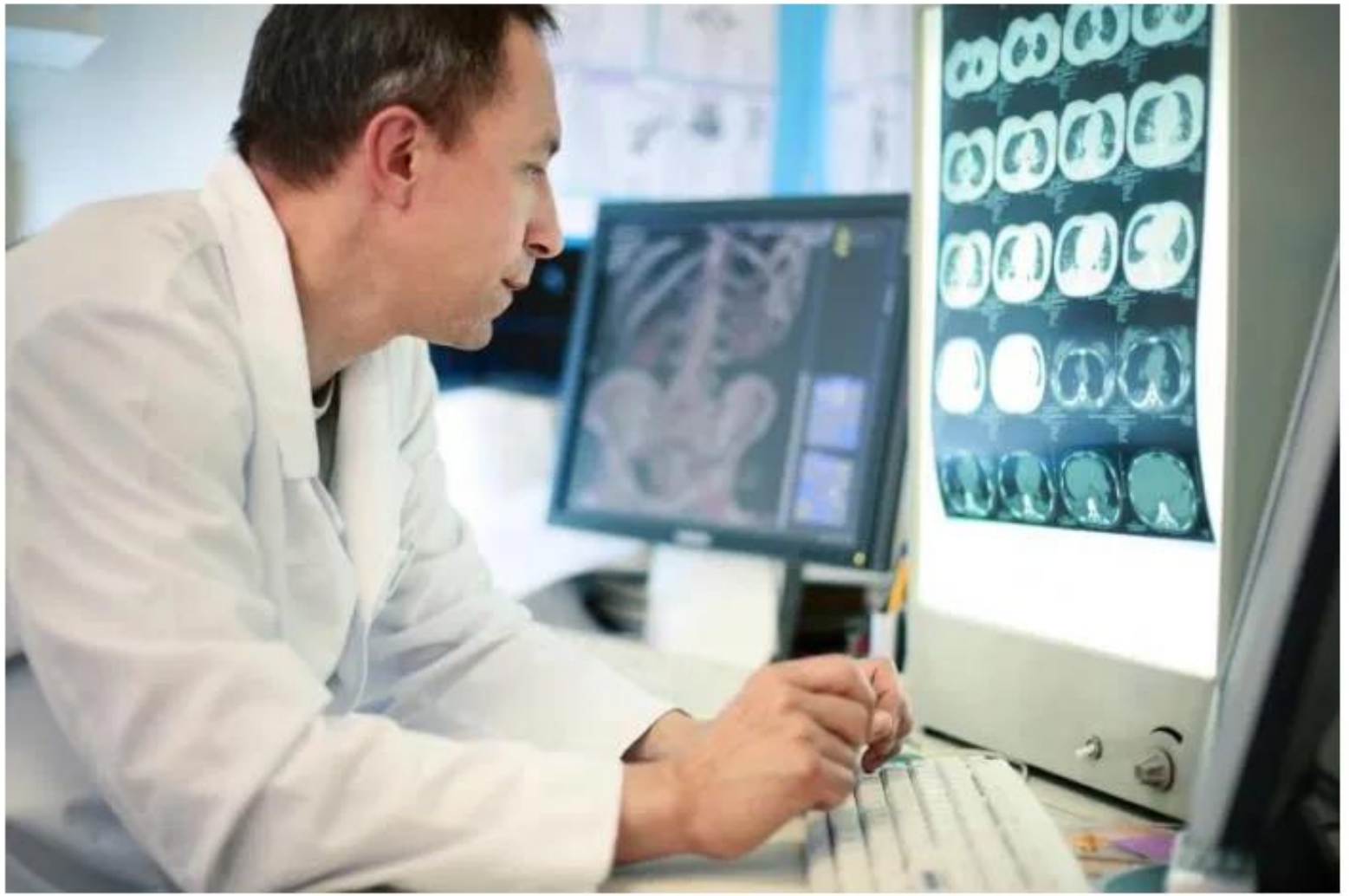
What is nuclear medicine?

In diagnosis | In treatment | What to expect | Safety

Radiation is used in nuclear medicine and radiology. In nuclear medicine, radioactive materials known as radioisotopes, or radiopharmaceuticals, are introduced into the body. In radiology, X-rays enter the body from outside.

According to the Center for Nuclear Science and Technology Information, about one-third of all procedures used in modern hospitals involve radiation or radioactivity. The procedures offered are effective, safe, and painless and they do not need anesthesia.

Nuclear medicine in diagnosis



Nuclear medicine is used to diagnose a wide range of conditions.

The patient will inhale, swallow, or be injected with a radiopharmaceutical. This is a radioactive material. After taking the substance, the patient will normally lie down on a table, while a camera takes pictures.

The camera will focus on the area where the radioactive material is concentrated, and this will show the doctor what kind of a problem there is, and where it is.

Types of imaging techniques include positon emission tomography (PET) and single-photon emission computed tomography (SPECT).

PET and SPECT scans can provide detailed information about how a body organ is functioning.

This type of imaging is particularly helpful for diagnosing thyroid disease, gall bladder disease, heart conditions, and cancer. It can also help diagnose Alzheimer's disease and other types of dementia and brain conditions.

In the past, diagnosing internal problems often needed surgery, but nuclear medicine makes this unnecessary.

After diagnosis, and when treatment starts, PET and SPECT can show how well the treatment is working.

PET and SPECT are also offering new insights into psychiatric conditions, neurological disorders, and addiction.

Other types of imaging involved in nuclear medicine include targeted molecular ultrasound, which is useful in detecting different kinds of cancer and highlighting blood flow; and magnetic resonance sonography, which has a role in diagnosing cancer and metabolic disorders.

Nuclear medicine in treatment

Radioactive agents may be swallowed in pills form, inhaled or injected as part of person's treatment

Radioactive techniques are also used in treatment. The same agents that are used in nuclear imaging can be used to deliver treatment. The radiopharmaceutical can be swallowed, injected, or inhaled.

One example is radioactive iodine (I-131). It has been used for over 50 years to treat thyroid cancer and hyperthyroidism, or an overactive thyroid. Now, it is also used to treat non-Hodgkin lymphoma and bone pain from some kinds of cancer.

Iodine-131 (I-131) targeted radionuclide therapy (TRT) introduces radioactive iodine into the body. As the thyroid cells or cancer cells absorb this substance, it kills them. I-131 can be given as capsules or in liquid form.

In the future, it may be possible to embed chemotherapy into medication imaging agents that will attach only to cancer cells. In this way, the chemotherapy would kill only the target cells and not the nearby healthy tissue. This would reduce some of the adverse effects of chemotherapy.

Radioimmunotherapy (RIT) combines nuclear medicine (radiation therapy) with immunotherapy. Immunotherapy is a treatment that mimics cellular activity in the body. Combining the two types of treatment means the nuclear medicine can be targeted more directly to the cells that need it.

Various radionuclides are used. The most common one is I-131, or radioactive iodine therapy (RAI). Other options include 90Y-ibritumomab tiuxetan, or Zevalin, which is used to treat different types of lymphoma. 131-I-tositumomab, or Bexxar, is used to treat lymphoma and multiple myeloma.

Experts in nanotechnology, advanced polymer chemistry, molecular biology, and biomedical engineering are investigating ways to deliver the drugs to the correct site without affecting surrounding tissues.

Theranostics is an approach that integrates nuclear medicine techniques for diagnosis and imaging with those for treatment. By combining molecular targeting vectors, such as peptides, with radionuclides, it can direct the radioactive substance to the target area to diagnose and deliver treatment at the same time.

What to expect

A person who is going for diagnosis or treatment with nuclear medicine should be sure to inform the health professional if they are pregnant or breastfeeding, or if they may be pregnant.

Nuclear imaging

The patient may have to wear a gown, or they may be able to wear their own clothes, but they will have to remove jewelry and other metal-base accessories.

Therapy

After having radioactive treatment, a person should avoid physical contact with other people as much as possible for 2-5 days, which may involve taking time off work.

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When a patient has treatment for the thyroid with I-131, no special equipment is used.

A single, prepared dose will be taken by mouth. This is a one-time treatment.

The patient should not eat or drink after midnight on the day of the treatment. If the treatment is for a thyroid problem, the doctor will normally advise them to stop taking their regular thyroid medication between 3 and 7 days before the treatment.

The patient may be able to return home after the dose, or they may have to stay overnight in the hospital.

However, because the body will not absorb all the radioactive iodine, it will continue to leave the body over the next 2 to 5 days.

The individual should avoid contact with other people as far as possible, and especially with infants and pregnant women.

This may mean taking time off work. They should also prepare their own food, avoid sleeping with another person, flush the lavatory twice after use, and wash their clothes and laundry separately.

Most of the iodine will leave the body through the urine, but it is also excreted through tears, sweat, saliva, vaginal discharge, and feces.

Women are advised to avoid becoming pregnant for 6 to 12 months following treatment.

Anyone who plans to travel immediately after treatment should get a letter from the doctor, as radioactivity may show up on scanning machines at airports.

INTRODUCTION

- Nuclear medicine is a medicinal specialty involving the application of radioactive substances in the diagnosis and treatment of disease.
- Nuclear medicine, in a sense is radiology done inside out or endoradiology because it records radiation emitting from within the body rather than radiation that is generated by external source like X-rays.
- Nuclear medicine scans differ from radiology as the emphasis is not on imaging anatomy but the physiological function of the system being investigated and for this reason, it is called a physiology imaging modality.
- Nuclear medicine procedures permit the determination of medical information that may otherwise be unavailable, require surgery, or necessitate more expensive and invasive diagnostic tests.

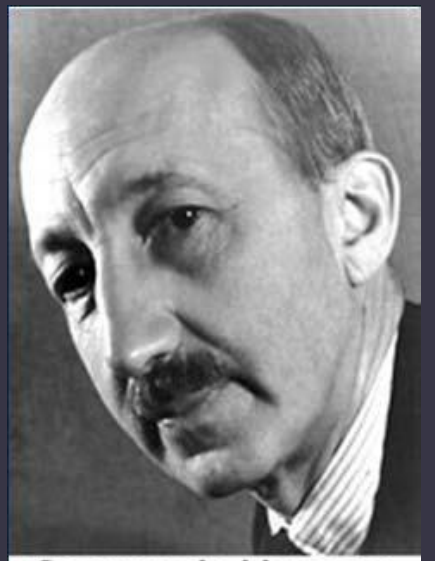
Why is it called nuclear medicine?

- Nuclear medicine refers to medicine(a pharmaceutical)that is attached to a small quantity of radioactive material (a radioisotope). This combination is called a radiopharmaceutical.

- There are many different radiopharmaceuticals available to study different parts of the body. Which radiopharmaceutical is used will depend upon the condition to be diagnosed or treated.

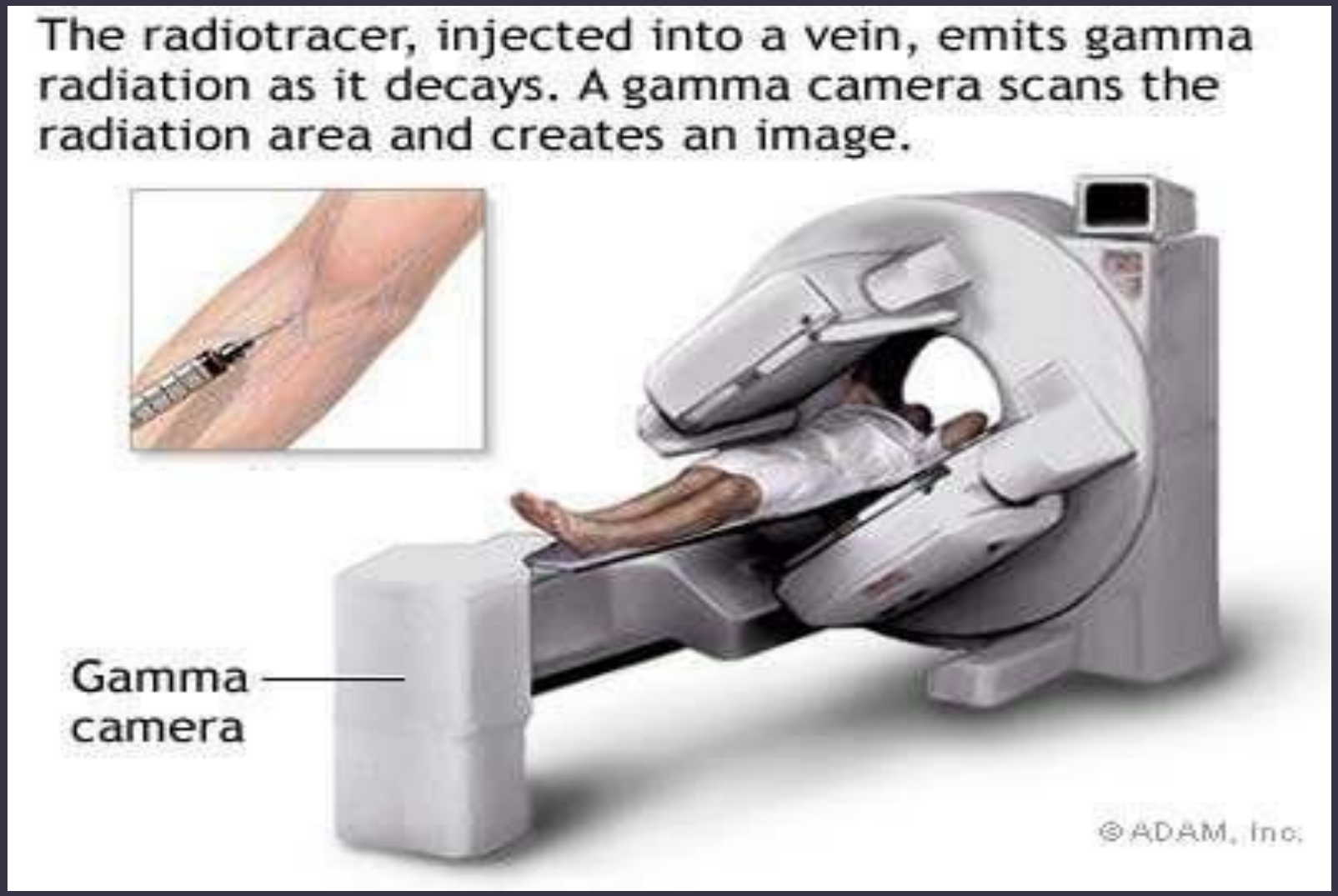
The Father of Nuclear Medicine

- George Charles de Hevesy.
- A Hungarian radiochemist, got Nobel Prize in 1943 in Chemistry.
- He has a vital role in the development of radioactive tracers to study chemical processes such as in the metabolism of animals.



George de Hevesy
(1885 - 1966)

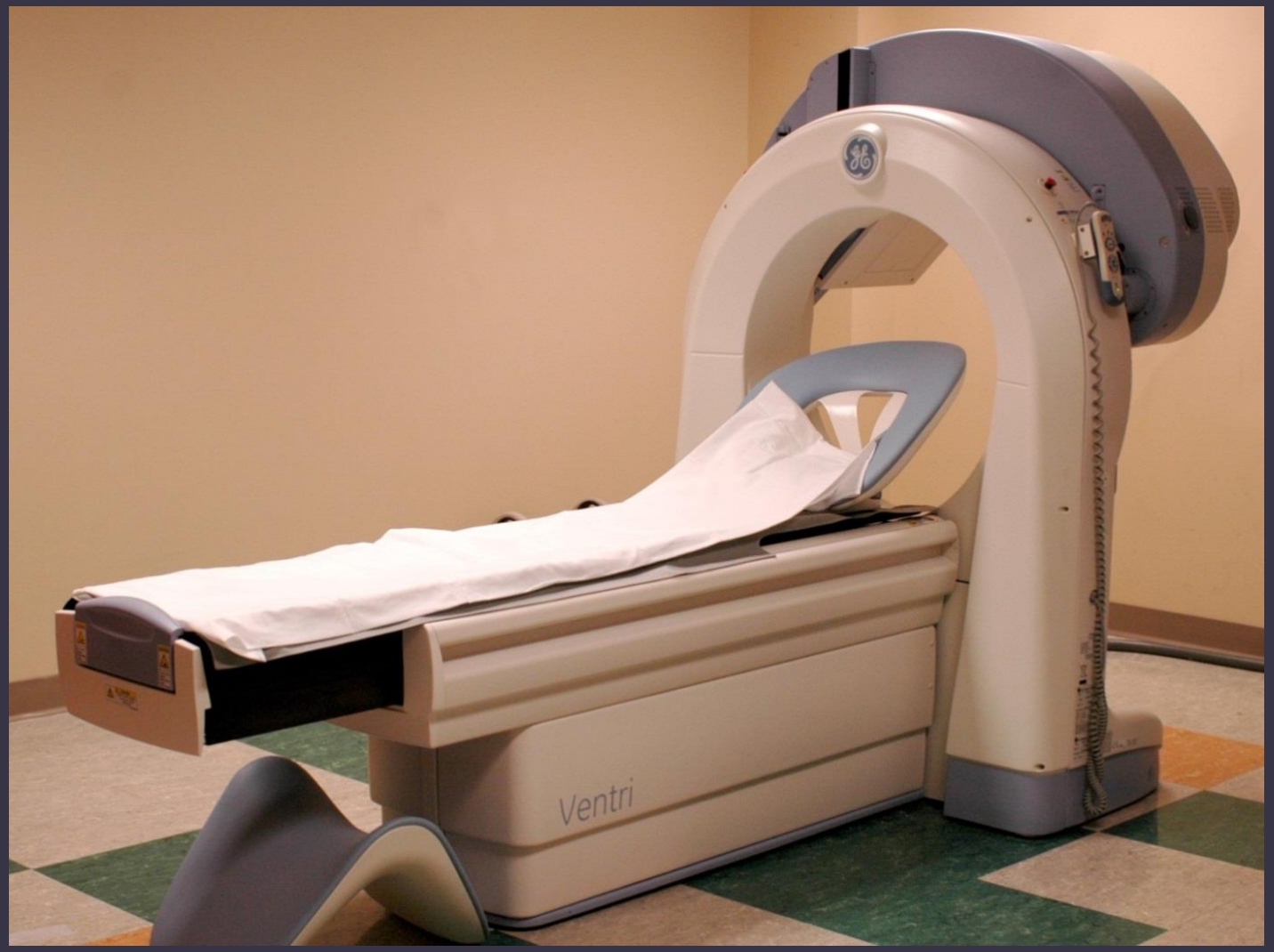
How do radiopharmaceuticals work?



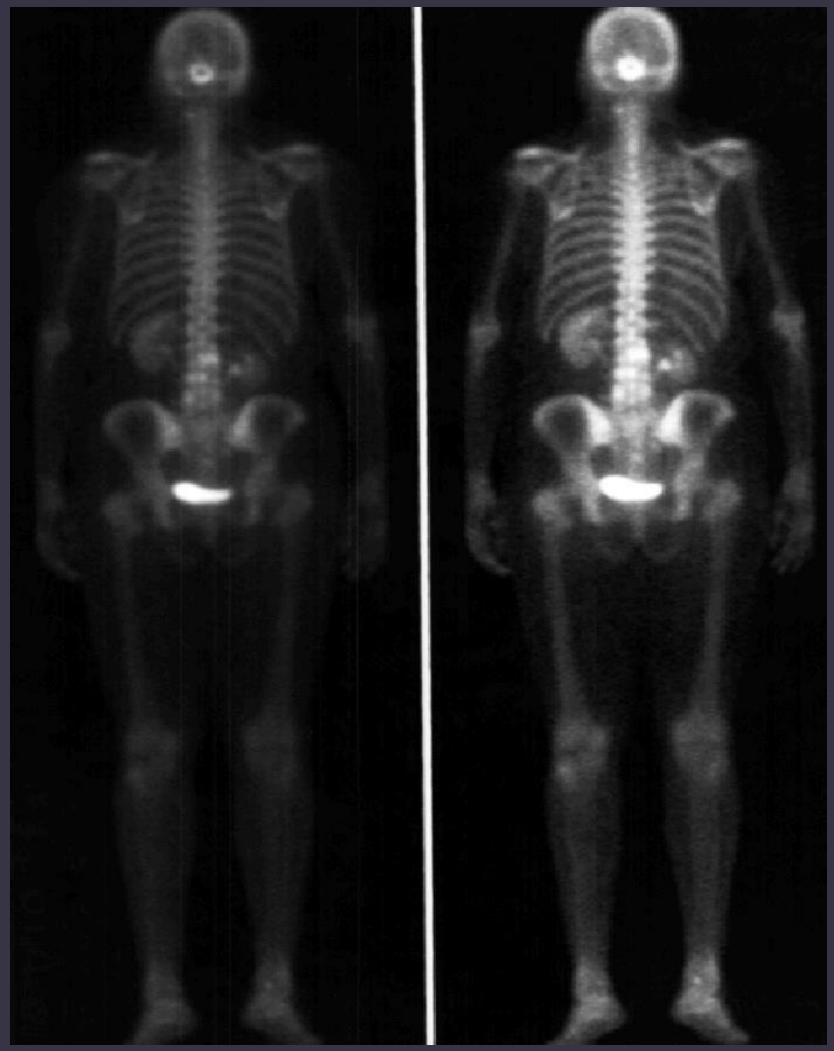
Diagnostic medical imaging

In nuclear medicine imaging, radiopharmaceuticals are taken internally, for example, intravenously or orally. Then, external detectors (gamma cameras) capture and form images from the radiation emitted by the radiopharmaceuticals. This process is unlike a diagnostic X-ray, where external radiation is passed through the body to form an image.

Gamma Camera



Bone Scan



Current Diagnostic Methods

- **Imaging (Planer/SPECT and PET Cameras)**
  Bone, Brain, Lungs , Thyroid, Kidneys, Liver/Spleen, Cardiovascular, Stomach/GI-tract, Tumours, Whole Body, Abscesses

- **Non-imaging (probes)**
  Thyroid uptake, Renography, Cardiac Output, Bile Acid resorption

- **Laboratory tests**
  Red Cell Volume/Survival, Absorption Studies (B12, iron, fat), Blood Volume, Exhangeable Electrolytes, Body Water, Bone Metabolism

- **Radioimmunoassays (RIA)**

- **Radionuclide guided Surgery**

Physiological Imaging

- Radioactive isotopes which emit gamma rays or other ionizing forms (half life for most is hours to days).
- Radionuclides are injected intravenously or inhaled where, depending on substance, they concentrate in organ of study.
- The emitted gamma rays are then picked up by gamma camera and displayed.

Physiological Imaging

- Conventional Nuclear Medicine
  - Emitted gamma rays create image

- SPECT (Single Photon Emission Computed Tomography)
  - Tomographic images of emitted gamma rays
  - Rotating gamma camera creates 3-D data set
  - Data set is then manipulated to create volume images (sum of all images in stack), multiplanar thin section images and 3-D volume data sets

Growth of Nuclear Medicine

- The growth of nuclear medicine depends on advances in:
    - Radiopharmaceutical development and discovery.
    - Improvements in instrumentation (such as imaging devices).
    - Positron Emission Tomography/Computed Tomography (PET/CT)

Nuclear Medicine Procedures

- Nuclear medicine procedures may be:
  - diagnostic studies, which are tests of body function
  - therapeutic procedures in which the radiation is used to treat disease.

- Radionuclide therapy is used in the treatment of both benign disease (eg. hyperthyroidism and arthritis) and malignant disease (eg. thyroid cancer and hepatocellular carcinoma)

Iodine-131 Nuclear Medicine

Iodine-131 (^{131}I), is an important radioisotope of iodine discovered by Glenn Seaborg and John Livingood in 1938 at the University of California, Berkeley. It has a radioactive decay half-life of about eight days. It is associated with nuclear energy, medical diagnostic and treatment procedures, and natural gas production. It also plays a major role as a radioactive isotope present in nuclear fission products, and was a significant contributor to the health hazards from open-air atomic bomb testing in the 1950s, and from the Chernobyl disaster, as well as being a large fraction of the contamination hazard in the first weeks in the Fukushima nuclear crisis. This is because I-131 is a major uranium, plutonium fission product, comprising nearly 3% of the total products of fission (by weight).

Due to its mode of beta decay, iodine-131 is notable for causing mutation and death in cells that it penetrates, and other cells up to several millimeters away. For this reason, high doses of the isotope are sometimes less dangerous than low doses, since they tend to kill thyroid tissues that would otherwise become cancerous as a result of the radiation. For example, children treated with moderate dose of I-131 for thyroid adenomas had a detectable increase in thyroid cancer, but children treated with a much higher dose did not. Likewise, most studies of very-high-dose I-131 for treatment of Graves disease have failed to find any increase in thyroid cancer, even though there is linear increase in thyroid cancer risk with I-131 absorption at moderate doses. Thus, iodine-131 is increasingly less employed in small doses in medical use (especially in children), but increasingly is used only in large and maximal treatment doses, as a way of killing targeted tissues. This is known as "therapeutic use".

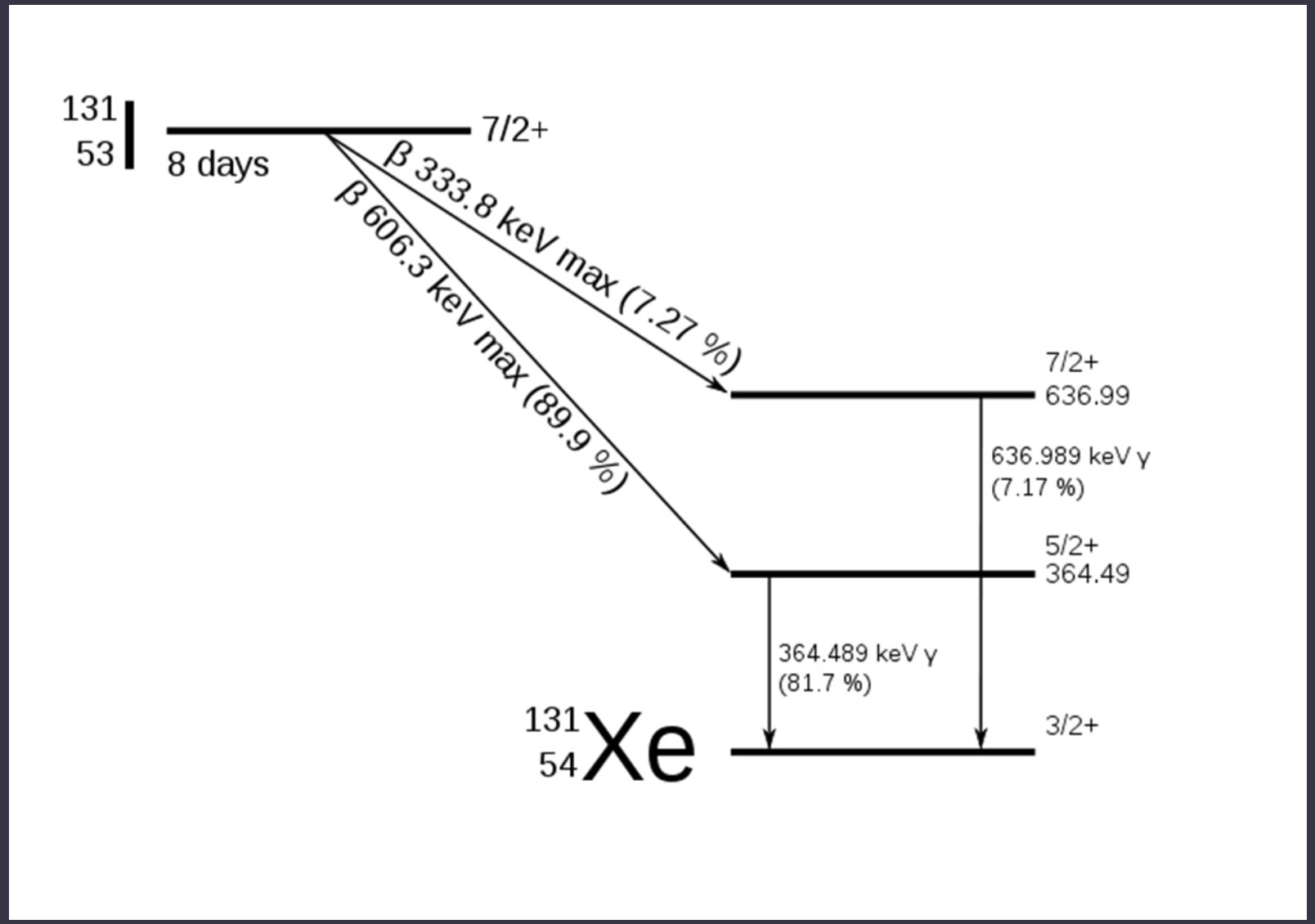
Radioactive decay of I-131

- I-131 decays with a half-life of 8.02 days with beta minus and gamma emissions. This nuclide of iodine has 78 neutrons in its nucleus, while the only stable nuclide, 127I, has 74. On decaying, 131I most often (89% of the time) expends its 971 keV of decay energy by transforming into the stable 131Xe (Xenon) in two steps, with gamma decay following rapidly after beta decay:

$$^{131}_{53}\mathrm{I} \rightarrow \beta + \bar{\nu}_e + {}^{131}_{54}\mathrm{Xe}^*$$

$$^{131}_{54}\mathrm{Xe}^* \rightarrow {}^{131}_{54}\mathrm{Xe} + \gamma$$

- The primary emissions of 131I decay are thus electrons with a maximal energy of 606 keV (89% abundance, others 248–807 keV) and 364 keV gamma rays (81% abundance, others 723 keV). Beta decay also produces an antineutrino, which carries off variable amounts of the beta decay energy. The electrons, due to their high mean energy (190 keV, with typical beta-decay spectra present) have a tissue penetration of 0.6 to 2 mm.



Iodine-131 decay scheme

Radioactive Iodine (I-131) Therapy

1. Benign Conditions

- Hyperthyroidism: 137I may be indicated for the treatment of Graves' disease, toxic multinodular goiter, or toxic autonomously functioning thyroid nodule(s).
- Nontoxic multinodular goiter: 137I therapy has been used successfully to diminish the size of nontoxic multinodular goiter.

2. Thyroid Cancer

- ^{131}I therapy has been used for postoperative ablation of thyroid remnants after thyroidectomy.
- ^{131}I therapy has been used to treat residual thyroid cancer and metastatic disease after partial or complete thyroidectomy

Technetium nuclear medicine

Nuclear medicine tests differ from most other imaging modalities, in that diagnostic tests primarily show the physiological function of the system being investigated as opposed to traditional anatomical imaging such as CT or MRI.

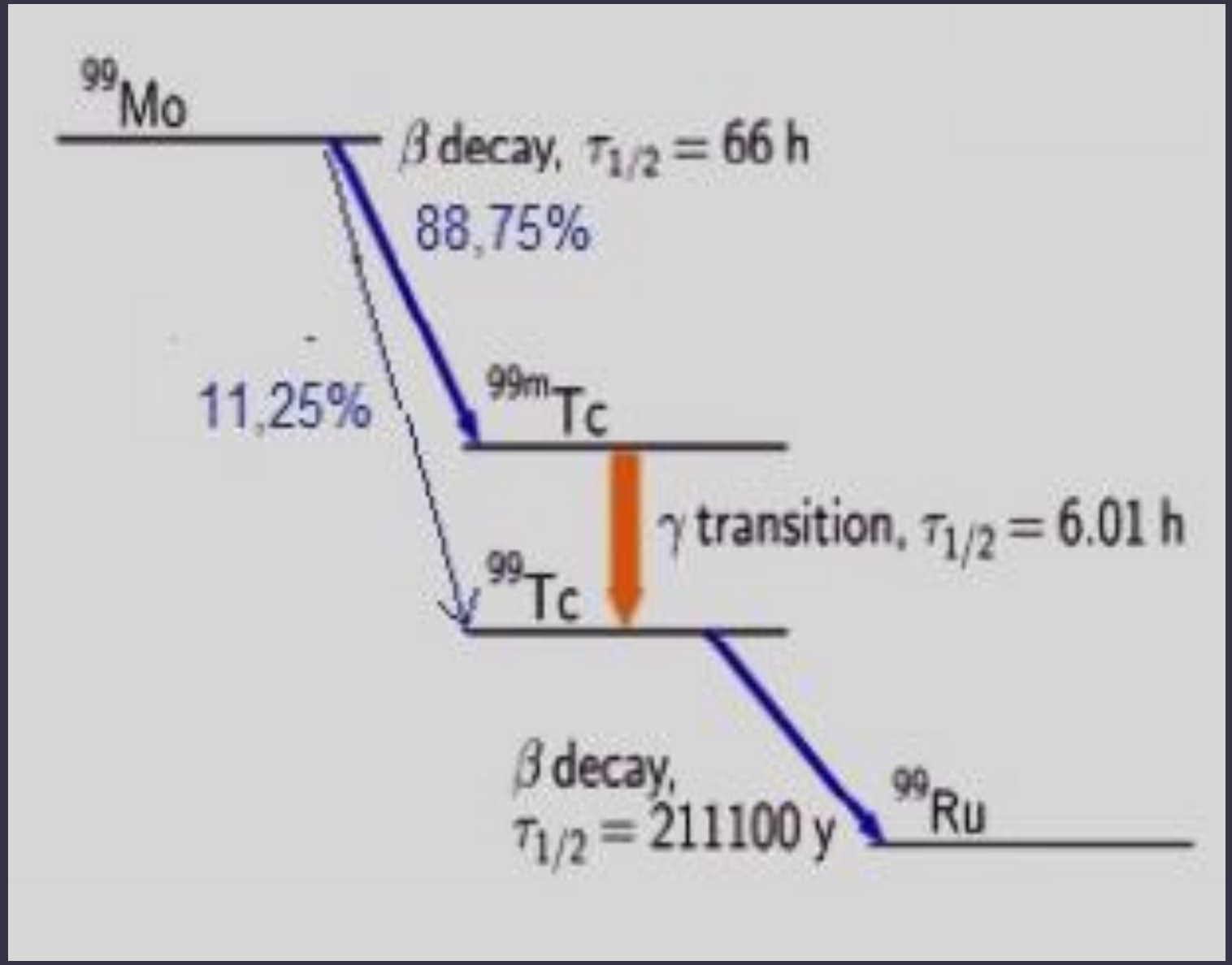
- The most intensively used radioisotope is Technetium-99m
- Among many radionuclides that were considered for medical-use, none were as important as the Technetium-99m.

- Discovered in 1937 by C.Perrier and E.Segre as an artificial element, it filled an empty space number 43 in the Periodic Table.
- The development of a Mo-99-Tc-99m generator system in the 1960s became a practical method for medical use.
- Today, Technetium-99m is the most utilized element in nuclear medicine and is employed in a wide variety of nuclear medicine imaging studies.
- The reason: its ideal nuclear and chemical properties

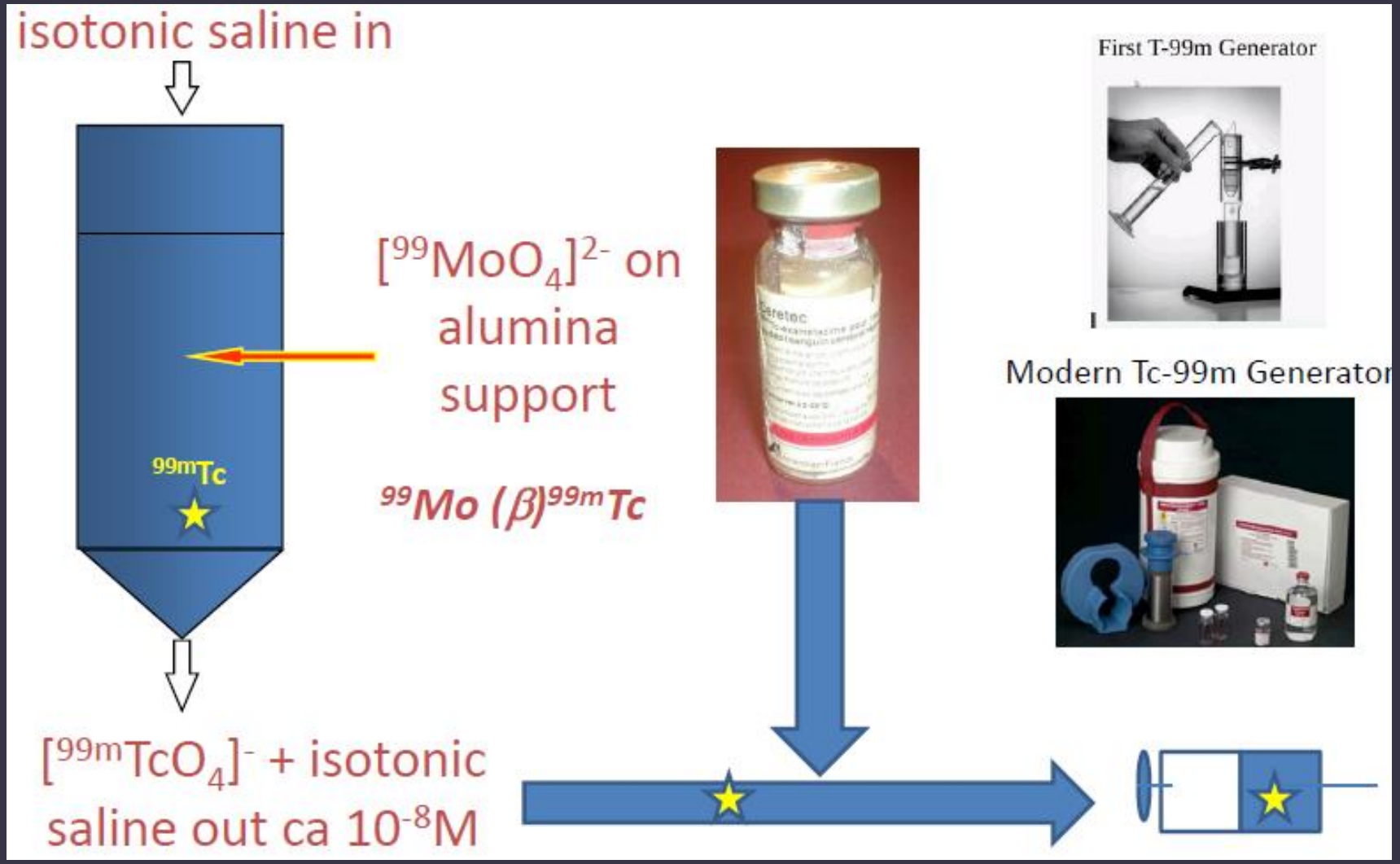
Tc-99m Radionuclide properties in Nuclear Medicine

- Nuclear diagnostics SPECT (single photon emission computer tomography) requirements: gamma emitters 100-200 keV, $T_{½}$= hours-days

- Tc^{99m} nuclear isotope is used for medical imaging in 90% of cases all over the world due to its near ideal nuclear characteristics of a 6h half life and γ-ray emission energy of 142 keV.

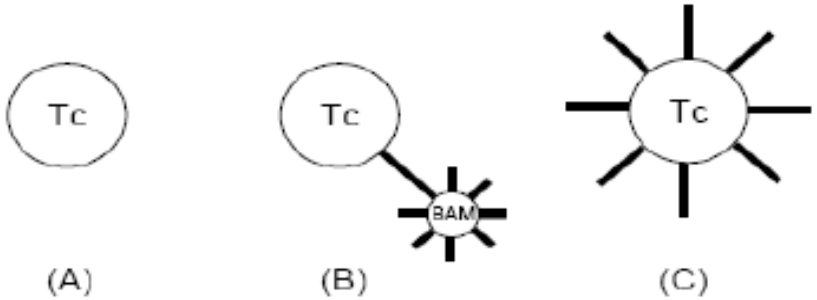

^{99}Mo
β decay, $\tau_{1/2}$ = 66 h
88,75%
11,25%
^{99m}Tc
γ transition, $\tau_{1/2}$ = 6.01 h
^{99}Tc
β decay,
$\tau_{1/2}$ = 211100 y
^{99}Ru

Tc generator and kit



Types of technetium imaging agents

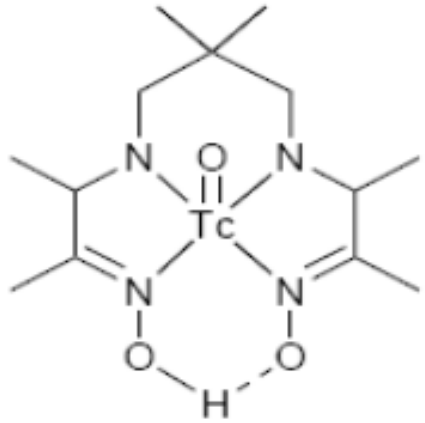
- Tc-99m application for imaging in 1961 involved the use of $[^{99m}TcO_4]^-$ for diagnosis of thyroid disease based on the principle that it behave similarly to ***iodide***, known to be taken up by the ***thyroid***.
- The biodistribution and targeting ability thus depended solely on the size, and charge of $[^{99m}TcO_4]^-$.



- 'Tc essential' or 1st generation agents (A) have been deployed with great success to image organs such as the heart, the brain, the kidney and the liver.
- 2nd generation agents (B) - the targeting capability resides in a biologically active molecule (BAM) covalently linked to an appropriate Tc complex (typically – peptide).
- 3rd generation agents (C) are under way

1st Generation Tc imaging agents

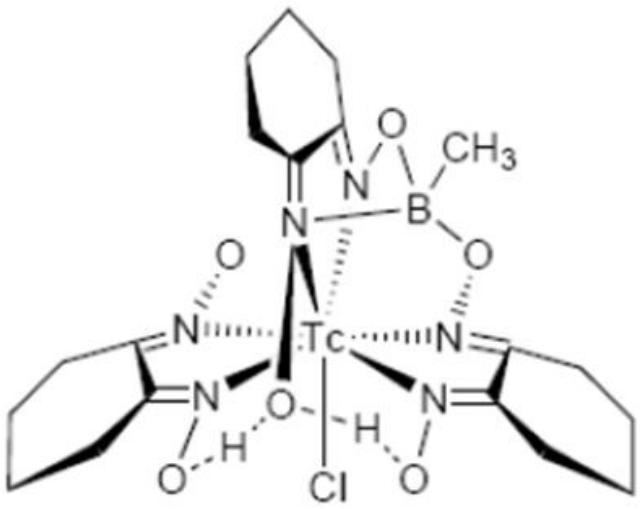
- ***Brain imaging***
- The principle demand to the agent that is to be accumulated in the brain is that it should be capable for traversing the blood–brain barrier (BBB).
- The complexe should be moderately lipophilic and not charged. In 1980s a series of neutral Tc-amine–oxime complexes we proposed to be prepared by reduction of [TcO4]- with SnCl2 in excess of the ligand.
- Amersham Intl. commercialized ***Ceretec*** agent utilising the HMPAO hexametazime which forms a neutral, square pyramidal TcV mono-oxo complex



(A)

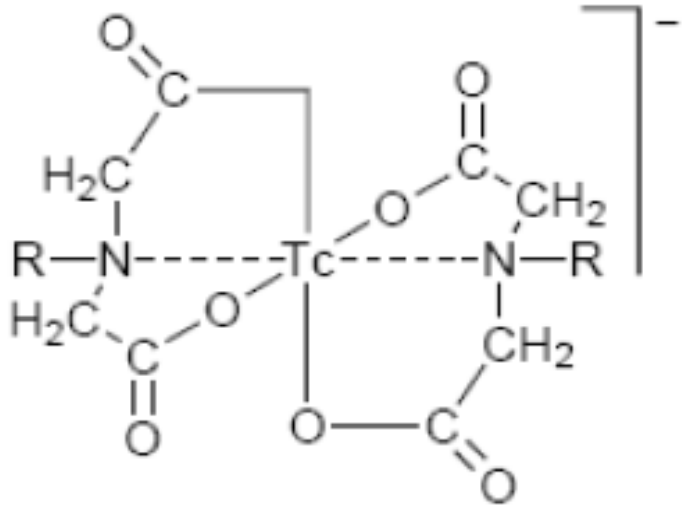
The Ceretec agent has limited stability and of Co2+ is now added to increase its lifetime.

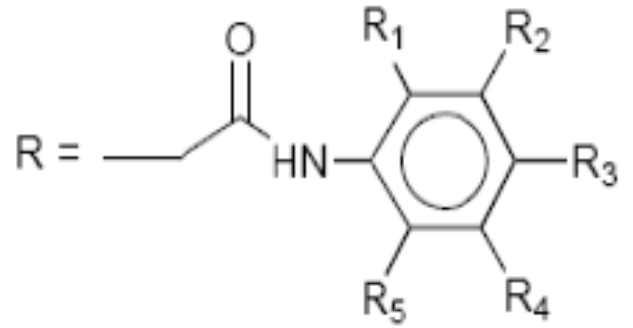
- ***Heart imaging***
- The first approved neutral myocardial perfusion agent is ^{99m}Tc-teboroxime (**Cardiotec**), which is a member of the BATO class of complexes, (BATO—boronic acid adducts of Tc dioximes).
- The complex has the formula [TcCl(CDO)(CDOH)2BMe], where CDOH2 = cyclohexane dione dioxime and is prepared by the reaction of $^{99m}TcO_4^-$ with a mixture of cyclohexane-1,2-dione dioxime and methyl boronic acid with SnCl2 as a reducing agent.
- 5 Min after injection 2.2% of the injected dose of this TcIII complex is found to accumulate in the heart *via a mechanism which is unknown* at this time,
- The complex exhibits rapid myocardial clearance in normal myocardium.



It is postulated that the neutral complexes may be washed out of the heart and it is the cationic complex which is subsequently retained.

- ***Liver imaging***
- Technetium(III) complexes of HIDA [2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid] derivatives have been shown to be suitable for imaging the *hepatobiliary system (liver)*.
- Three ^{99m}Tc-HIDA analogues have been approved:
- ^{99m}Tc-Lidofenin **(TechneScan HIDA)**
- ^{99m}Tc-Mebrofenin **(Choletec)** and
- ^{99m}Tc-Disofenin **(Hepatolite)**.





Lidoferin $R_1 = CH_3$
Disoferin R_1 = isopropyl
Mebroferin $R_1 = R_3 = CH_3$, R_2 = Br

- Tc-sulfur colloid is also used for liver imaging and is believed to be made up of $^{99m}Tc_2S_7$ and colloidal sulfur.
- The Tc-sulfur colloid is produced by the sodium dithionite reduction of TcO^{4-} in an acidic solution.
- 80–85% of the colloid is accumulated in the liver via uptake in Kupffer cells by phagocytosis.

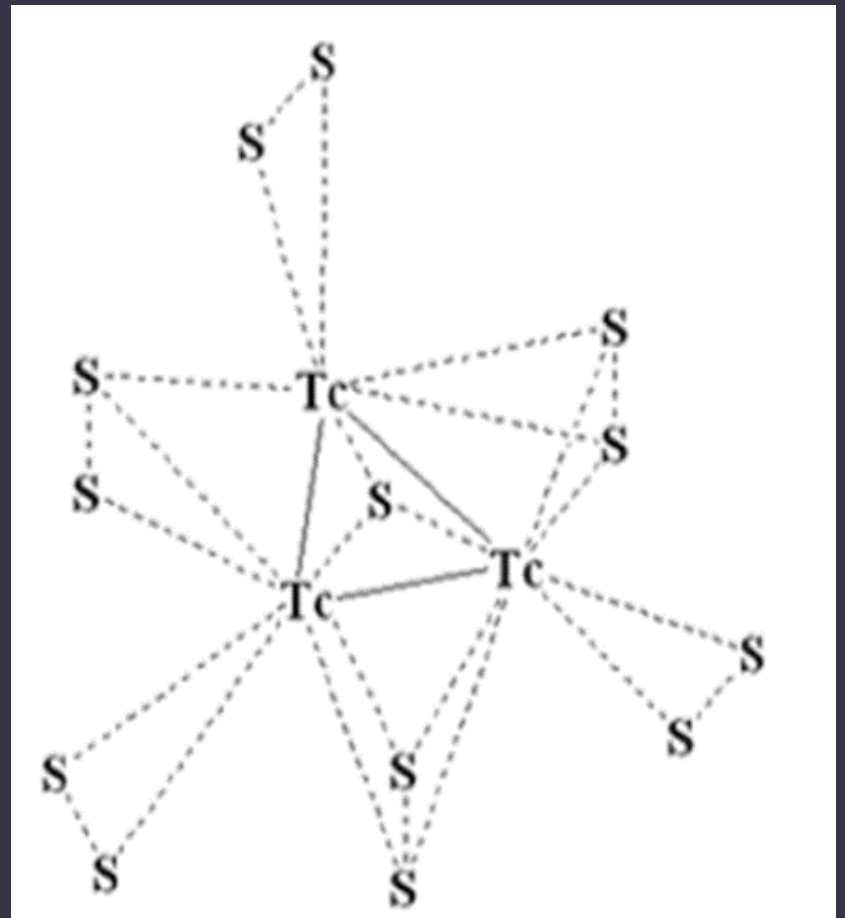
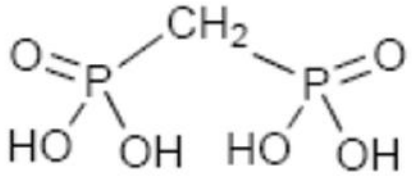


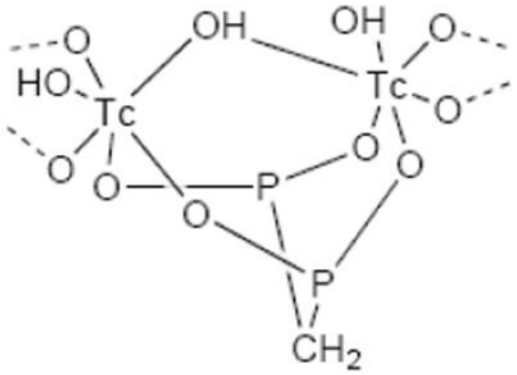
Fig: Structure unit fragment Tc_3S_{13} for technetium sulfide

1st generation Tc imaging agents
Bone imaging

- Tc-99-Diphosphonates such as methylenediphosphonate [MDP, show high performance as bone-imaging agents.
- The agent is prepared by reaction of the $[^{99m}TcO_4]^-$ generator eluate with MDP in the presence of $SnCl_2 \cdot 2H_2O$ as reductant



- At the ^{99}Tc level, reaction of $[^{99}TcBr_6]_2$- with H_4MDP led to the isolation and structural characterisation of a polymeric complex, so *no direct evidence for the RadPhPrep structure exists*

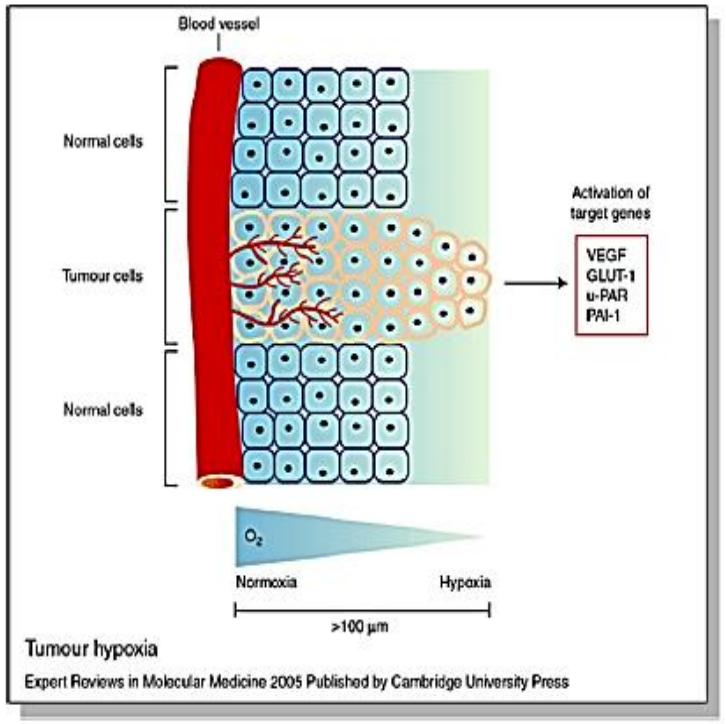


Advantages of Variability

- Widely variable oxidation state (0 to +7) with simple redox interconversion
- Accessible from $[TcO_4]^-$ in aqueous media
- Ready formation of multiple bonds to O and N which are stable in aqueous/saline media

Thiosemicarbazone ligands and targeting hypoxia

Why are tumours hypoxic?



The hypoxic areas do not respond to radiotherapy. Essential to know extent of hypoxic zone for appropriate treatment regime

Second generation Tc^{99m} radiopharmaceuticals

- The ability to determine the exact molecular structure of the coordination compounds using powerful modern analytical tools helped researchers to understand the structure–activity relationships underlying the biological behaviour of the Tc^{99m} agents.
- As a consequence, careful design of new ligands and their Tc^{99m} complexes led to the discovery of imaging agents for perfusion in the myocardium and brain.
- The widely used cardiac imaging agents Tc^99m-MIBI (sestamibi, Cardiolite®) and ^{99m}Tc-tetrofosmin (Myoview®), and the brain imaging agents ^{99m}Tc-HMPAO (exametazime, Ceretec®) and Tc^{99m} (bicisate, Neurolite®) are the result of the above strategy in the development of Tc^99m complexes.
- The in vivo behaviour of these radiopharmaceuticals is driven by their molecular properties, such as size, charge and lipophilicity.
- These products, including the novel renal agent Tc^{99m} (Mertiatide) and hepatobiliary agents such as Tc^{99m} -mebrofenin, are generally referred to as second generation Tc^{99m} radiopharmaceuticals.

Third generation Tc^{99m} radiopharmaceuticals

- Current designs of imaging agents are based on the careful selection of suitable biomolecules to function as effective vectors for in vivo delivery of Tc to more specific biological targets such as receptors and transporters.

- This strategy implies that the labeling approach employed for introducing a radionuclide into a biomolecule should not lead to any distortion of that part of the molecule responsible for its biological activity. Thus, these agents have required the development of sophisticated labeling approaches that go beyond the technologies previously used.

- The introduction of the bifunctional chelating agent (BFCA) concept and new chemistries such as the Tc-tricarbonyl, Tc-nitrido, Tc-HYNIC and mixed ligand complexes have helped to achieve that objective.

- The radiopharmaceuticals Tc^{99m}-HYNICEDDA-TOC are the best examples of third generation Tc^{99m} radiopharmaceuticals. It is the first, and to date the only, Tc^99m compound for receptor studies in the brain.

Sn(II) content assay

- Most kits for Tc-99m radiopharmaceuticals employ Sn(II) ions to reduce it from +7 to the desired oxidation state.

- The amount of Sn(II) is variable. It is important to maintain at least minimum Sn(II) level, when parallel reduction reactions could occur as very low amounts of Sn(II) will result in incomplete reduction of technetium. High amounts could damage the compound formed.

- One such example is the kit for ^{99m}Tc-HMPAO:
  - It is often necessary to measure the Sn(II) content in the kit vial. Estimation of the Sn(II) content could be carried out by simple methods such as titration with iodine or N-bromosuccinimide. However, interference owing to the presence of other reducing agents is possible, and it is necessary to ensure that such interference does not occur. Radiochemical purity test is imperative.

PREPARATION OF KIT FOR ^{99m}Tc-MDP

Reagents

- Methylene diphosphonic acid (MDP)
- Ascorbic acid
- Stannous chloride dihydrate: $SnCl_2.2H_2O$
- Hydrochloric acid: HCl (concentrated, 1N, 0.2N)
- Sodium hydroxide: NaOH (1N)
- Water for injection; Nitrogen gas.

Preparation of kit solution for a final volume of 500 mL

Use water for injection bubbled with nitrogen gas. Solution A: Dissolve 500 mg of stannous chloride dihydrate using 50 mL of 0.2N HCl (or 0.4 mL of concentrated HCl, adjusting the volume to 50 mL) just before it is added to the final solution. Dissolve 5 g of MDP in approximately 400 mL of water for injection. Add 1 g of ascorbic acid; the pH will be in the range of 3.5–4.0 after the addition. Slowly add solution A to the MDP solution, with continuous N_2 bubbling and stirring. Adjust the pH to between 4 and 5 using 1N NaOH or 1N HCl. Adjust the final pH to 5.8–6.0 using a pH meter. Adjust the final volume to 500 mL. Filter the solution through a sterile 0.22 µm filter. Dispense 1 mL per vial.

Freeze-dry using the following conditions:

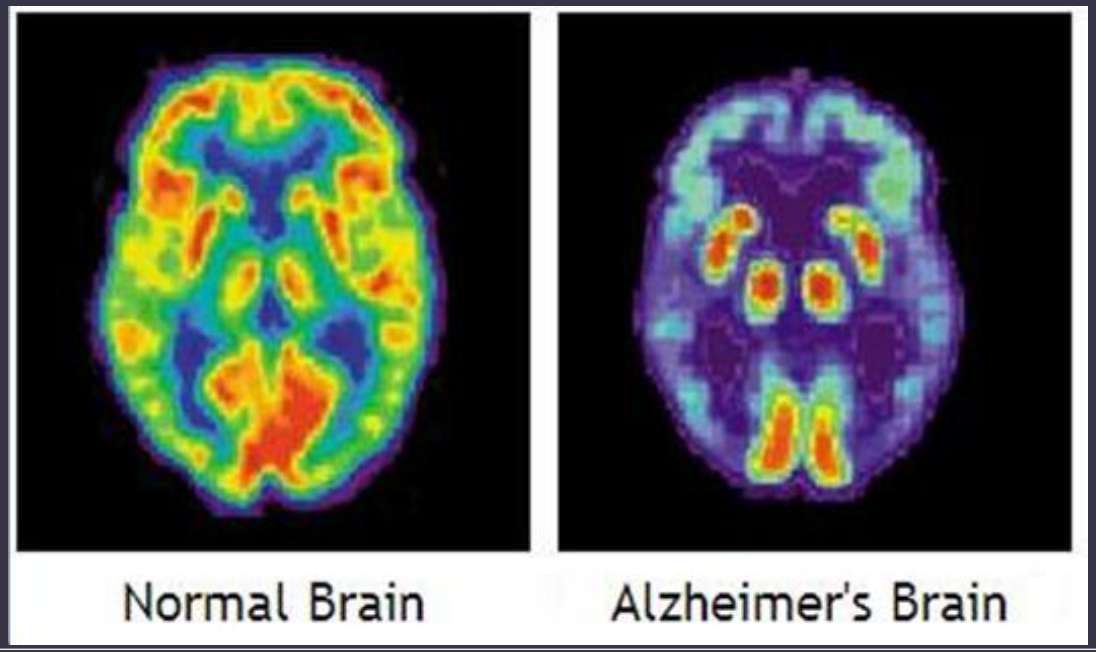
Store refrigerated at 2–8°C.

Freeze temperature	Dried temperature	Time
–30°C	24°C	24–48 h

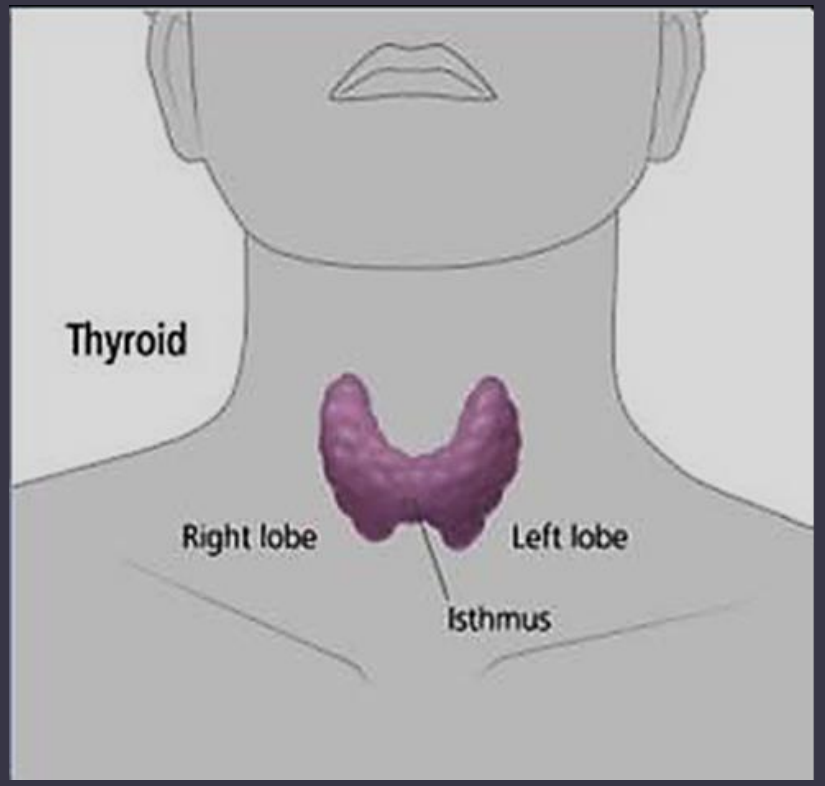
Advancement of Nuclear medicine

Current clinical applications of nuclear medicine include the ability to:

- Diagnose diseases such as cancer, neurological disorders (e.g., Alzheimer's and Parkinson's diseases), and cardiovascular disease in their initial stages.



- Provide molecularly targeted treatment of cancer and certain endocrine disorders (e.g., thyroid disease and neuroendocrine tumors).



Future applications in nuclear medicine include the ability to:

- Understand the relationship between brain chemistry and behavior (e.g., addictive behavior, eating disorders, depression).
- Understand the metabolism and pharmacology of new drugs; and assess the efficacy of new drugs and other forms of treatments, speeding their introduction into clinical practice.
- Develop higher resolution, more sensitive imaging instruments to detect and quantify disease faster and more accurately.

Challenges to advancing nuclear medicine:

- Loss of federal commitment
- Shortage of trained nuclear medicine scientists
- Inadequate supply of medical radionuclides for research
- Need for technology development and transfer