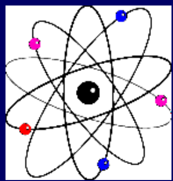


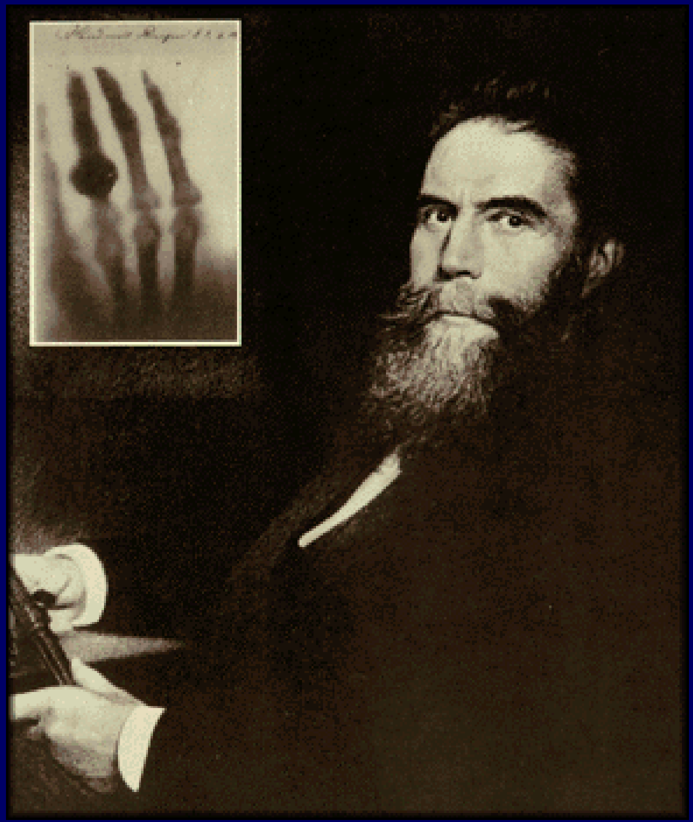
RADIOPHARMACEUTICALS

Samy Sadek, Ph.D.

Associate Professor, New York Medical College.

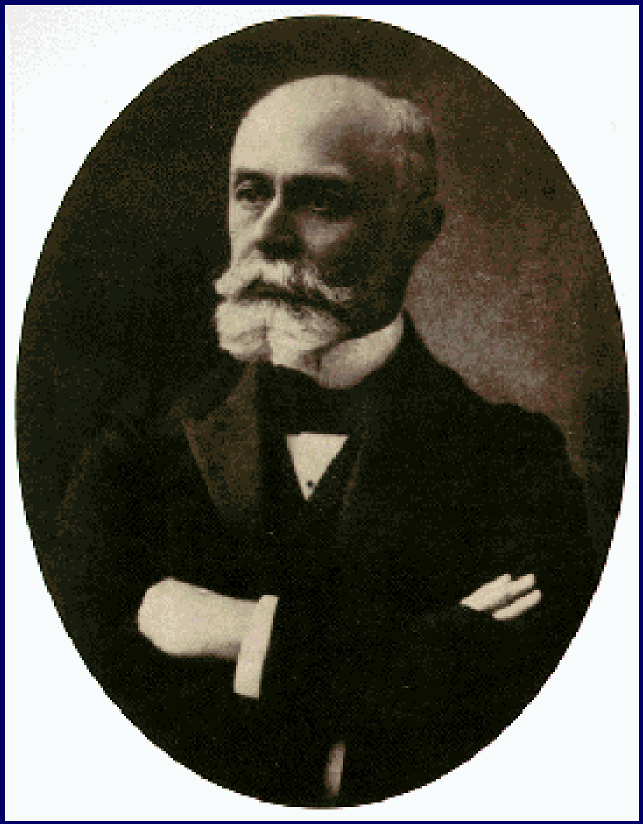
Radiopharmaceutical Chemist, St. Vincent's Hospital-Manhattan.

X-Ray Discovery: Roentgen



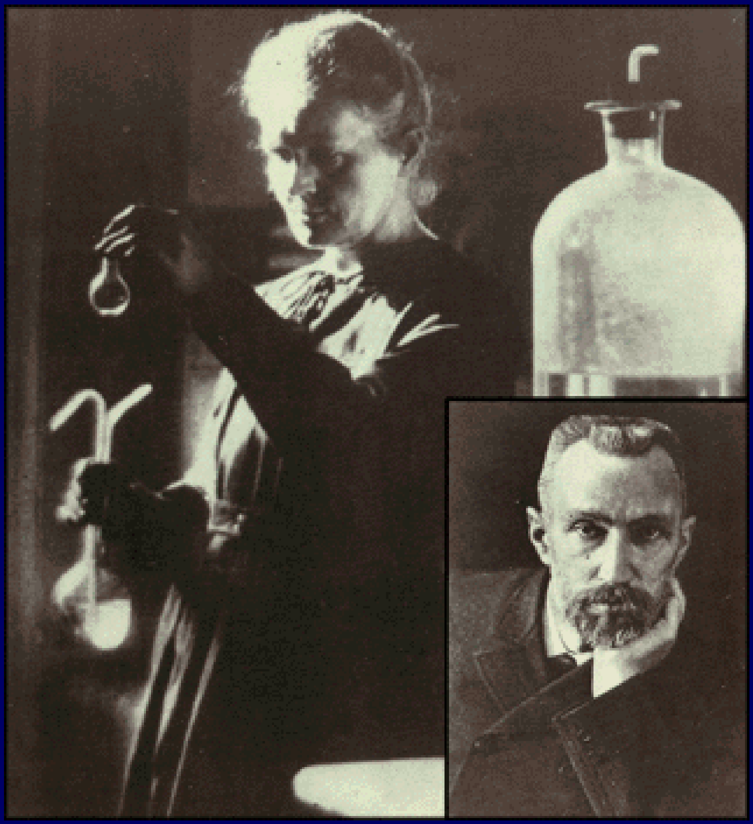
Wilhelm Roentgen ca. 1895. Inset photo: Radiograph of Frau Roentgen's hand.

Discovery of Radioactivity



Antoine Henri Becquerel (1852-1908)

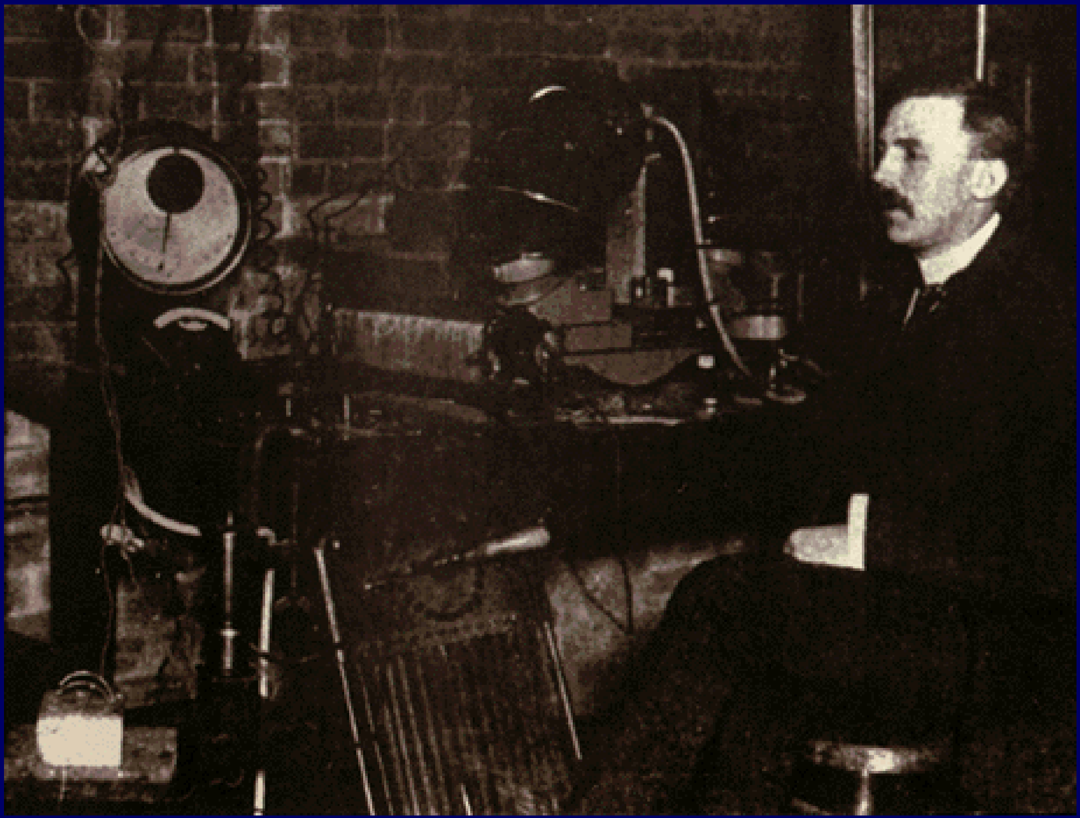
Discovery of Radium & Polonium



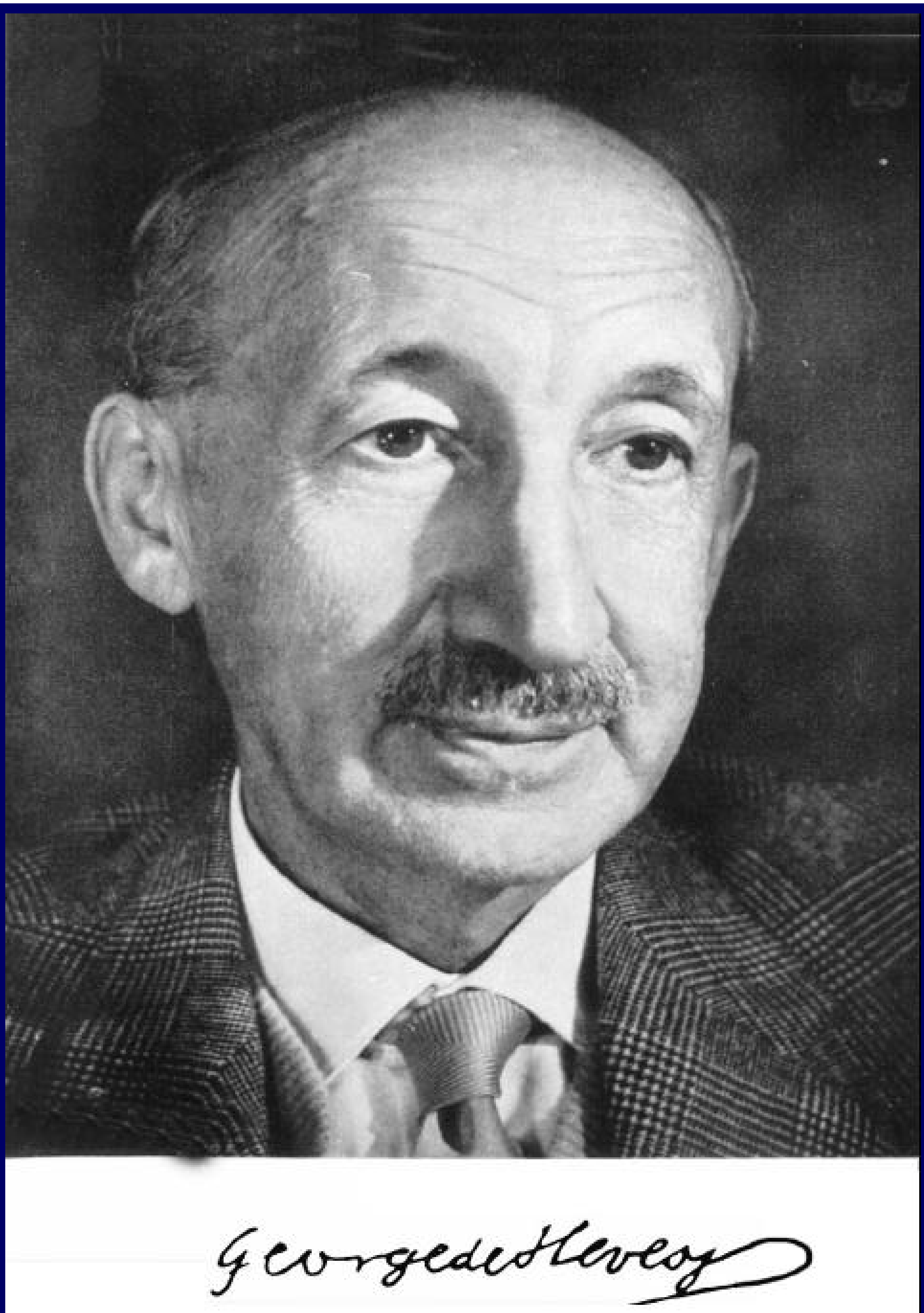
Marie Curie ca. 1920. Inset: Pierre Curie (Marie's favorite picture of her husband).

Pierre Curie (1859-1906)
Marie Curie (1867-1934)

The FATHER OF NUCLEAR PHYSICS: ERNEST RUTHERFORD



Ernest Rutherford in his Laboratory at McGill University ca. 1903.



The Father of Nuclear Medicine:

George de Hevesy

(1885 - 1966)

Received Nobel Prize in 1943 for his pioneering work with isotopes as tracers.

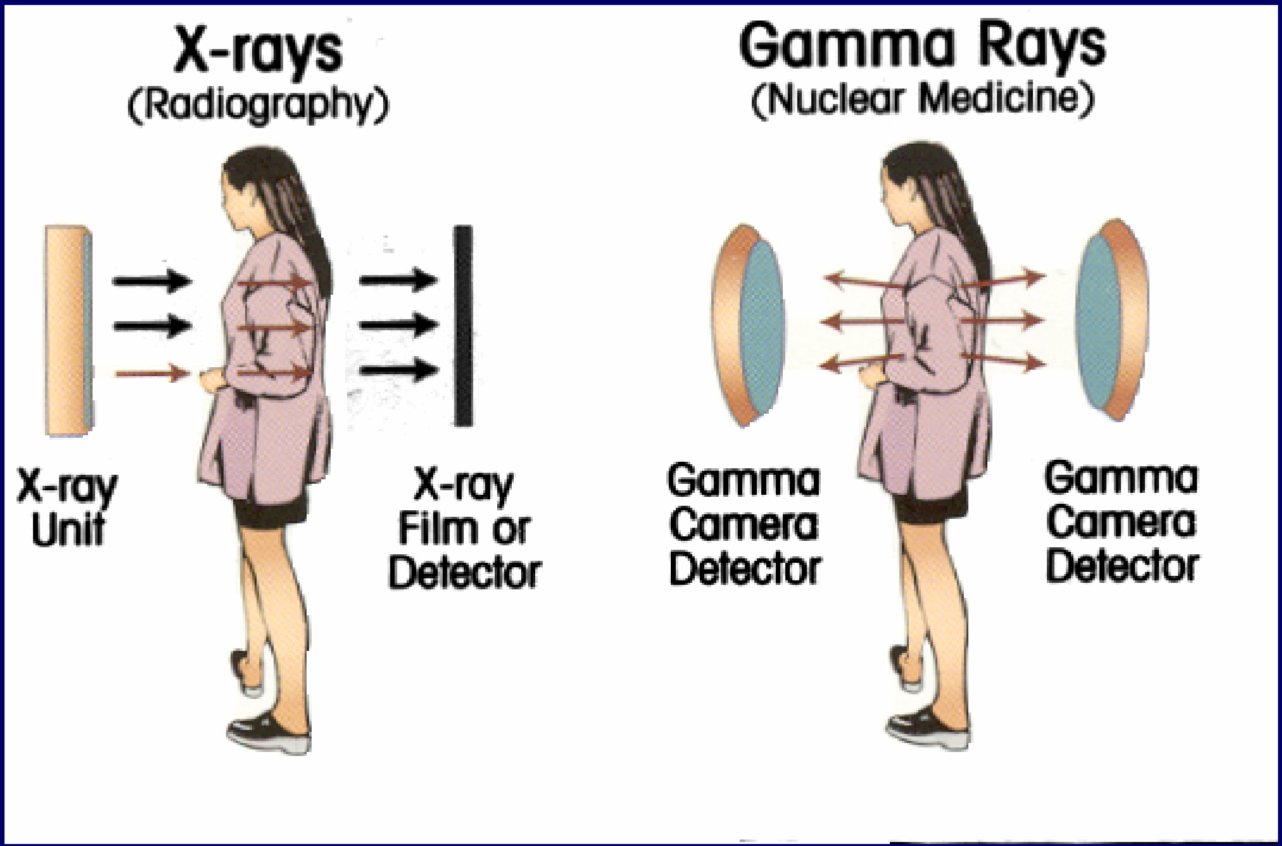
Winner of Atom for Peace Award 1959.

The First Practical Application of Radioisotopes

George de Hevesy & his landlady:

- **Using radioactive material he proved two things:**
  - The landlady was indeed "recycling" leftovers from their plates!
  - More importantly, that small amounts of radioactive materials could be used to "trace" the fate of a substance in a system.

Nuclear Medicine Vs Radiography



Nuclear Medicine = Function

- **Blood Flow:** Myocardial, Brain
- **Metabolic Marker:** ^{18}FDG, ^{123}I-Fatty Acids
- **Organ Function:** Phagocytosis/ Liver
- **Compartmental Localization:** Gated-Cardiac, ^{133}Xe, GI Bleeding.
- **Cell Sequestration:** Heat Denatured ^{99m}Tc-RBCs/Spleen
- **Receptors Density:** Dopamine
- **Targeted:** Antibodies
- **Gastric Emptying:** Real Meal Vs Barium Meal

Nomenclature

- **Nuclide**
  - It is identified by an exact nuclear composition including the mass # A and atomic # Z
- **Radionuclide**
  - Unstable or radioactive nuclide
- **Isotopes**
  - Nuclides with the same atomic # and exhibit the same chemical properties
- **Isomers**
  - Nuclides having the same number of protons and neutrons but differing in energy states

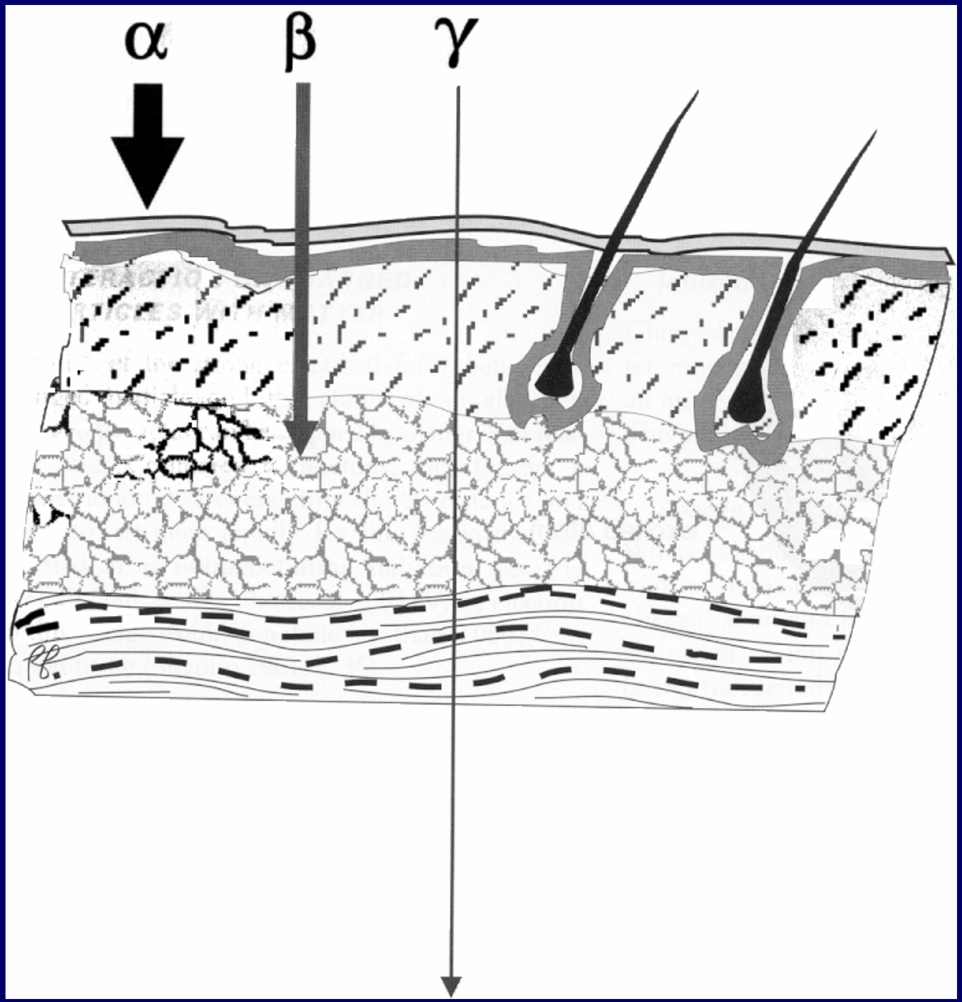
Radiopharmaceuticals

- ***Definition*:** **A Radiopharmaceutical is a Radioactive Drug used for Diagnosis or Therapy in a Tracer Quantities with no Pharmacological Effect.**
- **Composed of two parts**
  - **Radionuclide**
  - **Pharmaceutical**
- **They Should undergo all quality control measures required of a conventional drug.**
- **Radiopharmaceutical Vs Radiochemical**

Properties of an Ideal Diagnostic Radiopharmaceutical

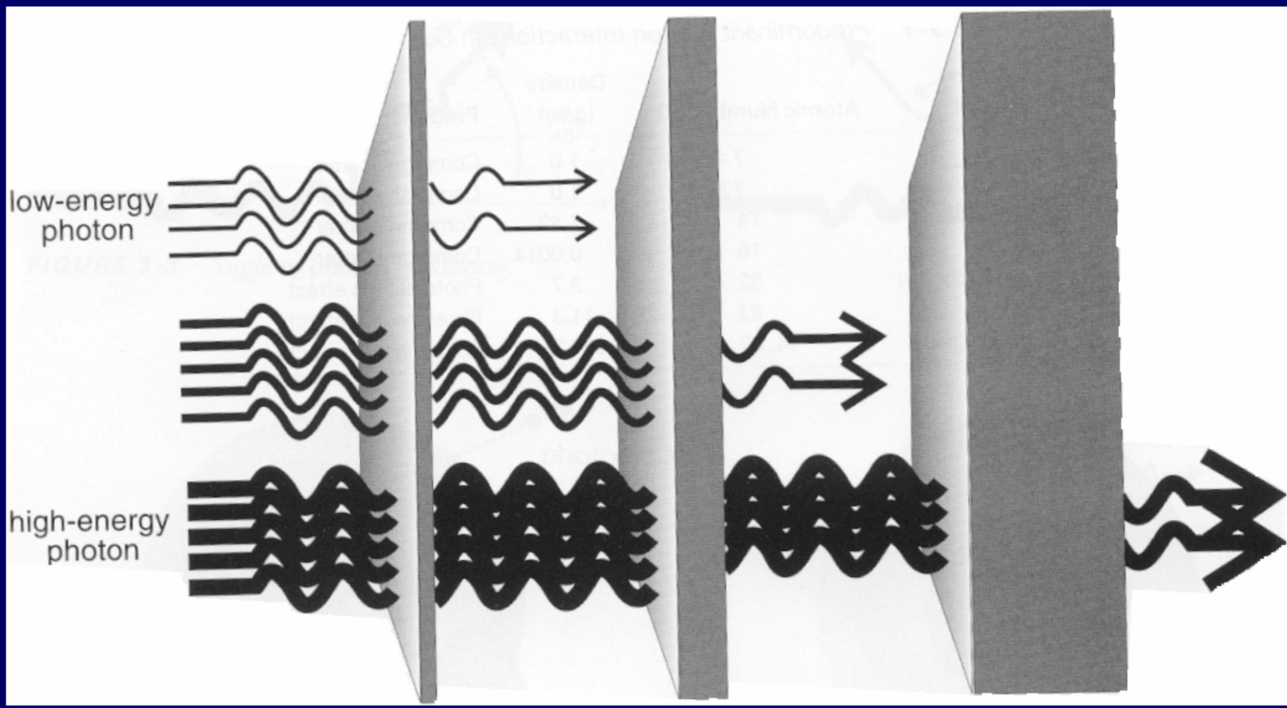
- **Types of Emission:**
  - **Pure Gamma Emitter: (Alpha & Beta Particles are Unimageable & Deliver High Radiation Dose.)**
- **Energy of Gamma Rays:**
  - **Ideal: 100-250 keV e.g. ^{99m}Tc, ^{123}I, ^{111}In**
  - **Suboptimal:<100 keV e.g. ^{201}Tl**

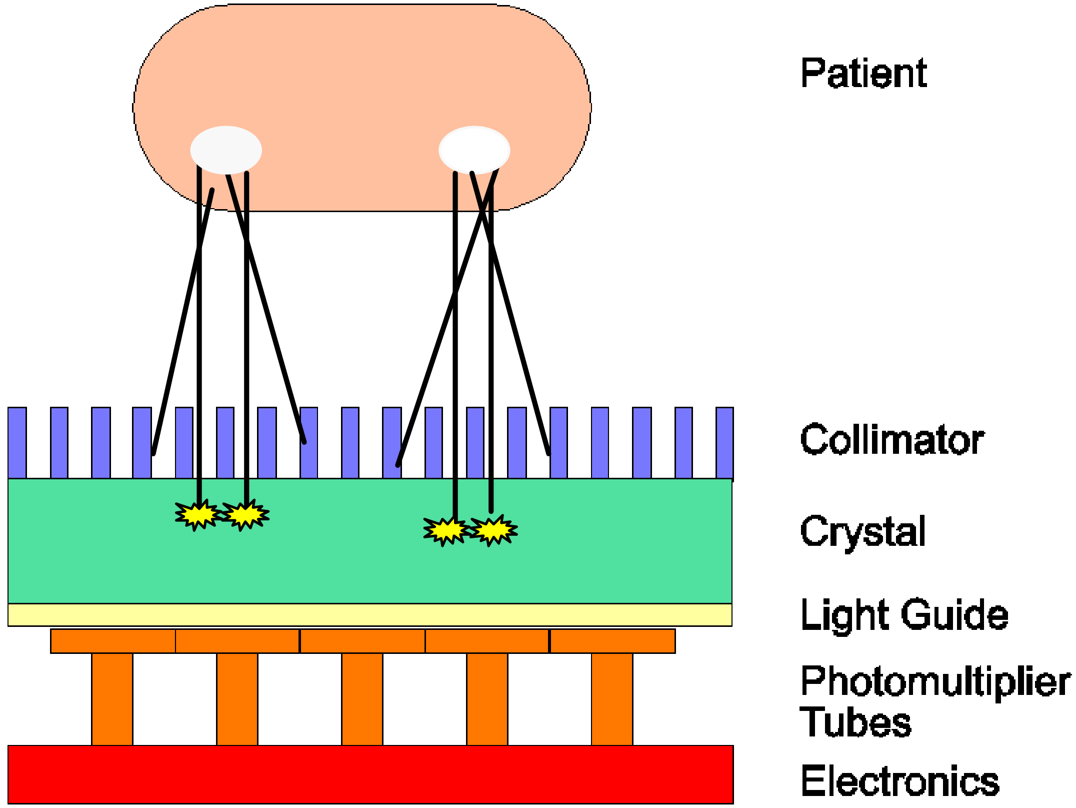
    >250 keV e.g. ^{67}Ga & ^{131}I
- **Photon Abundance.**
  - **Should be high to minimize imaging time**


α
β
γ

POP QUIZ

- **Explain why gamma rays with energy lower than 100 keV and higher than 250 keV are not ideal for imaging?**


low-energy photon
high-energy photon


Patient
Collimator
Crystal
Light Guide
Photomultiplier Tubes
Electronics

Ideal Diagnostic Radiopharmaceutical (Cont..)

- **Target to Nontarget Ratio:**
  - **It should be high to maximize the efficacy of diagnosis and minimize the radiation dose to patient**
- **Easy Availability:**
  - **Readily Available, Easily Produced & Inexpensive:**
    - **^{11}C Vs ^{99m}Tc**

Ideal Diagnostic Radiopharmaceutical (Cont..)

- **Effective Half-life:**
  - It should be short enough to minimize the radiation dose to patients and long enough to perform the procedure. Ideally 1.5 times the duration of the diagnostic procedure.

$$1/T_E = 1/T_B + 1/T_P$$

$$T_E = T_B T_P / T_B + T_P$$

POP QUIZ

- **For a Bone Scan which is a 4-hr procedure, ^{99m}Tc-MDP with an effective half-life of 6 hrs is the ideal radiopharmaceutical:**
  - **True** **- False**
- **For a liver scan which is 1-hr procedure, ^{99m}Tc-sulfur colloid with an effective half-life of 6 hrs is the ideal agent:**
  - **True** **-False**

Ideal Diagnostic Radiopharmaceutical (Cont..)

- **Patient Safety**
  – Should exhibit no toxicity to the patient.
- **Preparation and Quality Control**
  – Should be simple with little manipulation.
  – No complicated equipment
  – No time consuming steps

POP QUIZ

- **Given the physical properties of commonly used radionuclides in the next two slides, mention which radionuclides are ideal for imaging. Explain why?**

Physical Constants of Commonly Used Radionuclides

Nuclide	T_{phys}	$E_{??}$(keV)	% abundance
Cr-51	28 d	320	9
Ga-67	79.2 h	94	40
		184	24
		296	22
I-123	13.3 h	159	83
I-125	60 d	35	140

Physical Constants of Commonly Used Radionuclides

Nuclide	T_{phys}	$E_{??}$(keV)	% abundance
^{131}I	8.08 d	364.5	82
^{111}In	67 h	173	89
		247	94
^{99m}Tc	6.02 h	140	90
^{201}Tl	73 h	135	2
		167	8
		71(Hg X-rays)	95

Properties of the Ideal Therapeutic Radiopharmaceutical

- **<u>Types of Emission:</u>**
  - **Pure ? -particles: It is more controllable and easier to detect if spilled compared to ? -particles.**
- **<u>Energy of ? -particles</u>:**
  - **Medium/high energy (>1 MeV): It causes adequate and regulated tissue damage.**

Properties of the Ideal Therapeutic Radiopharmaceutical

- **Effective half-life:**
  - Moderately long (5-20 days) to deliver enough dose to target tissues.
- **Target-to-Nontarget Ratio:**
  - High ratio results in damage to the target tissue with minimal dose to other tissues.
- **Easy Availability:**
  - Readily available, Easily produced & Inexpensive

Types of Radiopharmaceuticals

- **<u>Ready-to-use:</u>**
  - ^{123}I Capsules, ^{67}Ga Citrate, ^{201}Th Chloride, ^{133}Xe gas, ^{99m}Tc Pertechnetate
- **<u>Instant Tc-99m Kits</u>:**
  - MDP, DTPA, MAA, ….
- **<u>Tc-99m Requiring Heating</u>:**
  - MAG_3, Sestamibi, Sulfur Colloid
- **<u>Products Requiring Significant Manipulation</u>:**
  - ^{99m}Tc or ^{111}In-WBCs, ^{99m}Tc-RBCs, ^{51}Cr-RBCs.

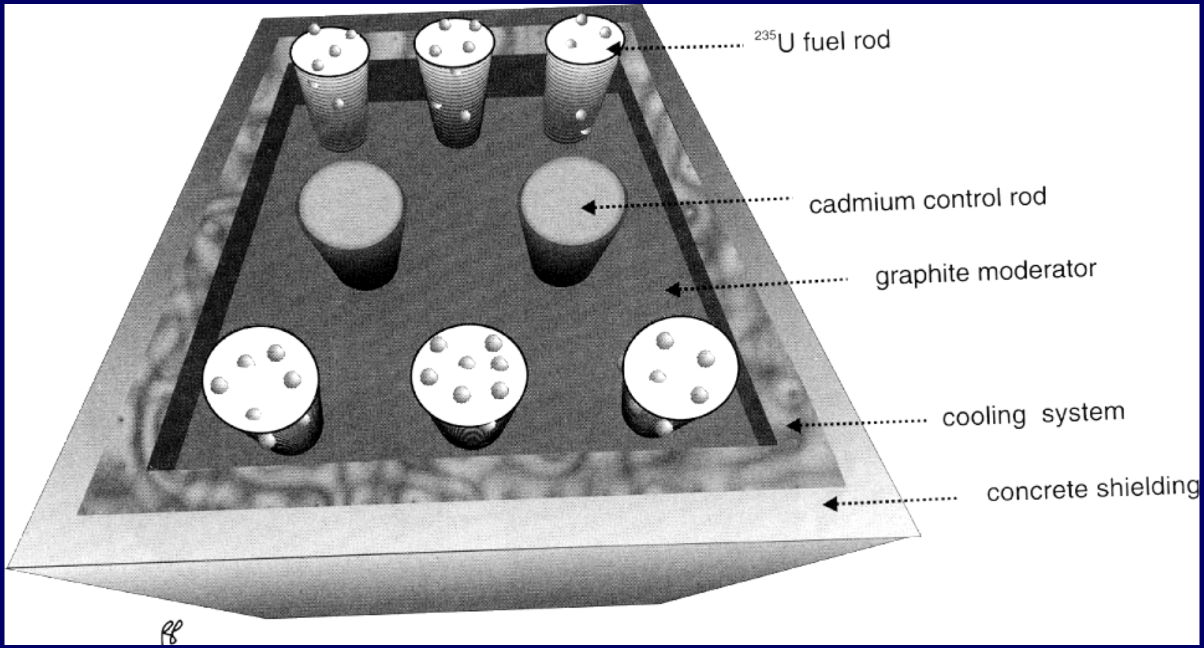
Preparation of Radiopharmaceuticals

- Production of Radionuclides.
- Synthesis of Non-Radioactive Carrier
- Reaction of the Radionuclide with the Non-Radioactive Carrier.

Production of Radionuclides

- **Primary Source:**
  *** Reactor** *** Cyclotron**
- **Secondary Source:**
  Generators: *A -------> *B --------> C

Nuclear Reactor



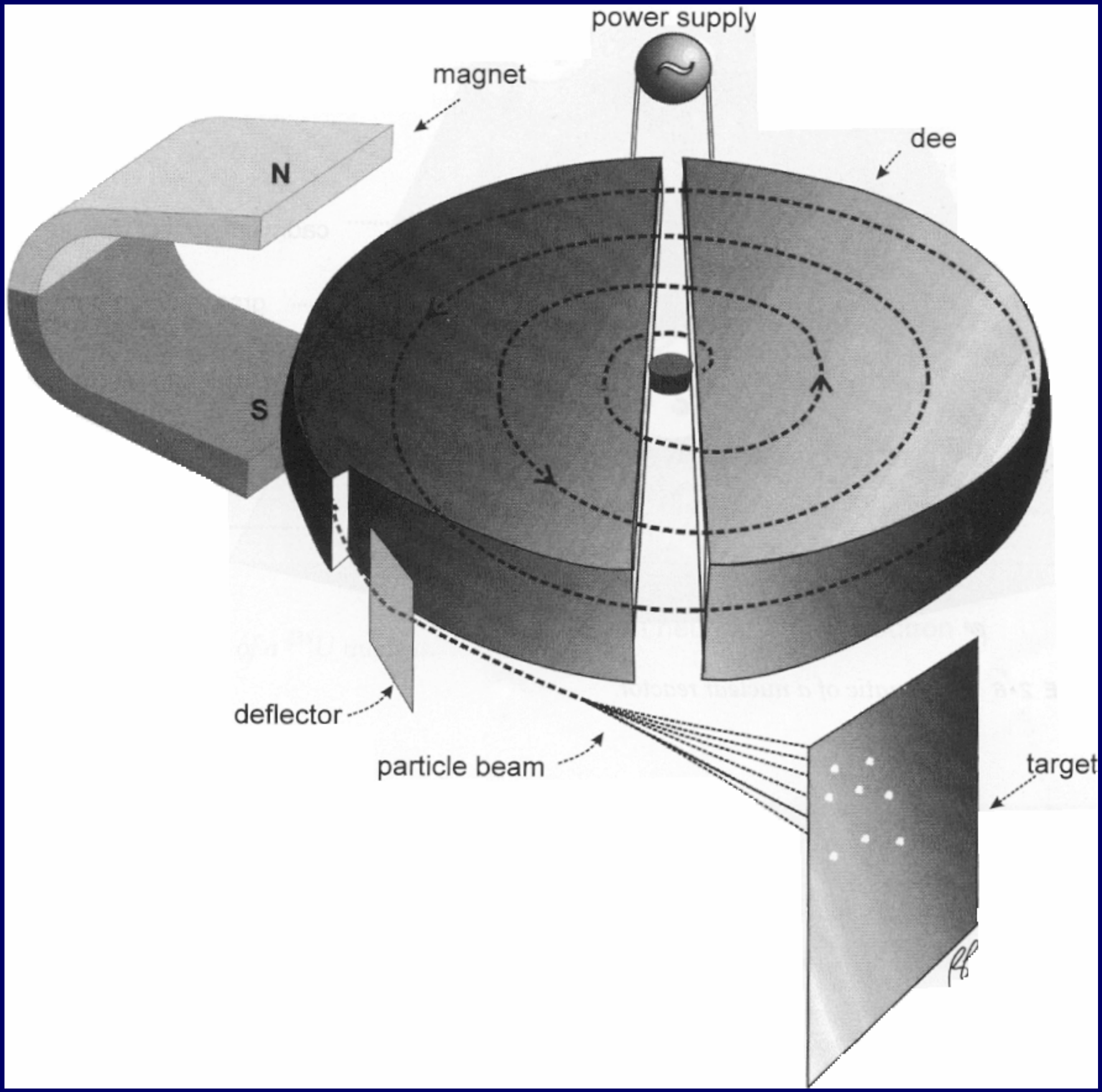
Nuclear Reactors

- ^{A}X (n, ?) ^{A+1}X
- ^{98}Mo (n, ?) ^{99}Mo------> ^{99m}Tc
- Starting Material and Products have the Same Chemical Identity.
- Low Specific Activity Radionuclides

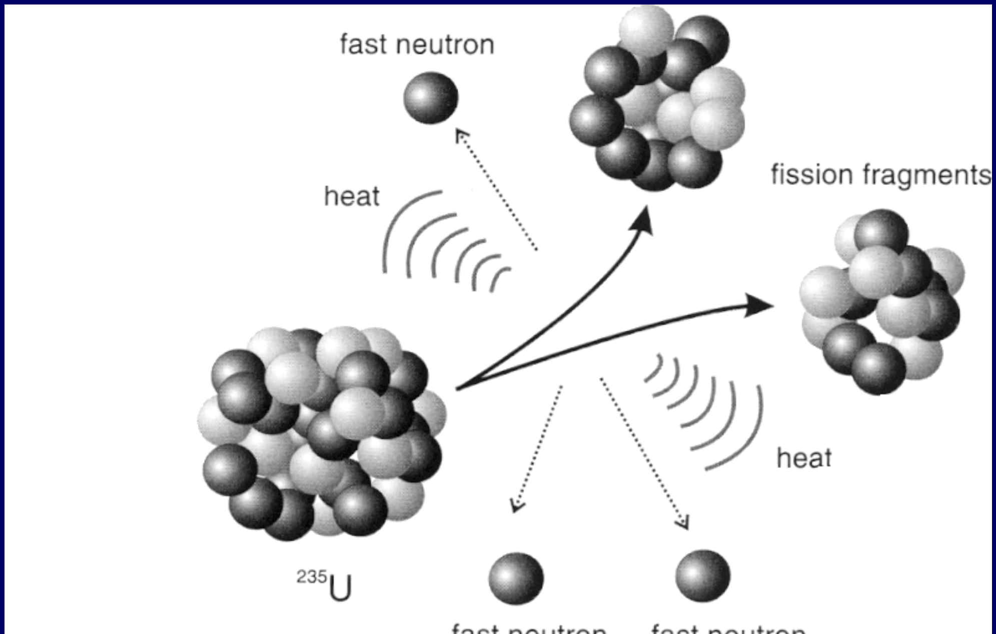
Cyclotrons

- **Example :** $^{68}Zn\ (p,2n)\ ^{67}Ga$
- **Starting Material & Product Have Different Chemical Identity**
- **Radionuclides with High Specific Activity**
- **Expensive**
- **Radionuclides Decay by** ?$^{+}$ **or EC**

Cyclotron



Fission Reaction



Fission of a ^{235}U nucleus

Byproducts of Fission Reactions

- (n,f) : $^{235}U(n)$ $^{236}U(f)$ -------> ^{99}Mo, ^{131}I, ^{133}Xe, ….etc
  - Starting Material and Products are Different
  - High Specific Activity Radionuclides.

Radionuclide Generators: Principles

- **A long-lived parent radionuclide is allowed to decay to its short-lived daughter radionuclide and the latter is chemically separated in a physiological solution.**

Successive Decay and Parent/Daughter Equilibrium

A------> B -------> C

- If $t_{1/2}$ of B < $t_{1/2}$ of A (10 t0 50 times)
  - Transient equilibrium. : Activity of Daughter becomes higher than that of the parent and decay with the same rate.
  - If $t_{1/2}$ of B << $t_{1/2}$ of A (100-1000 times)
  - Secular equilibrium: Activity and decay rate of daughter and parent are the same.

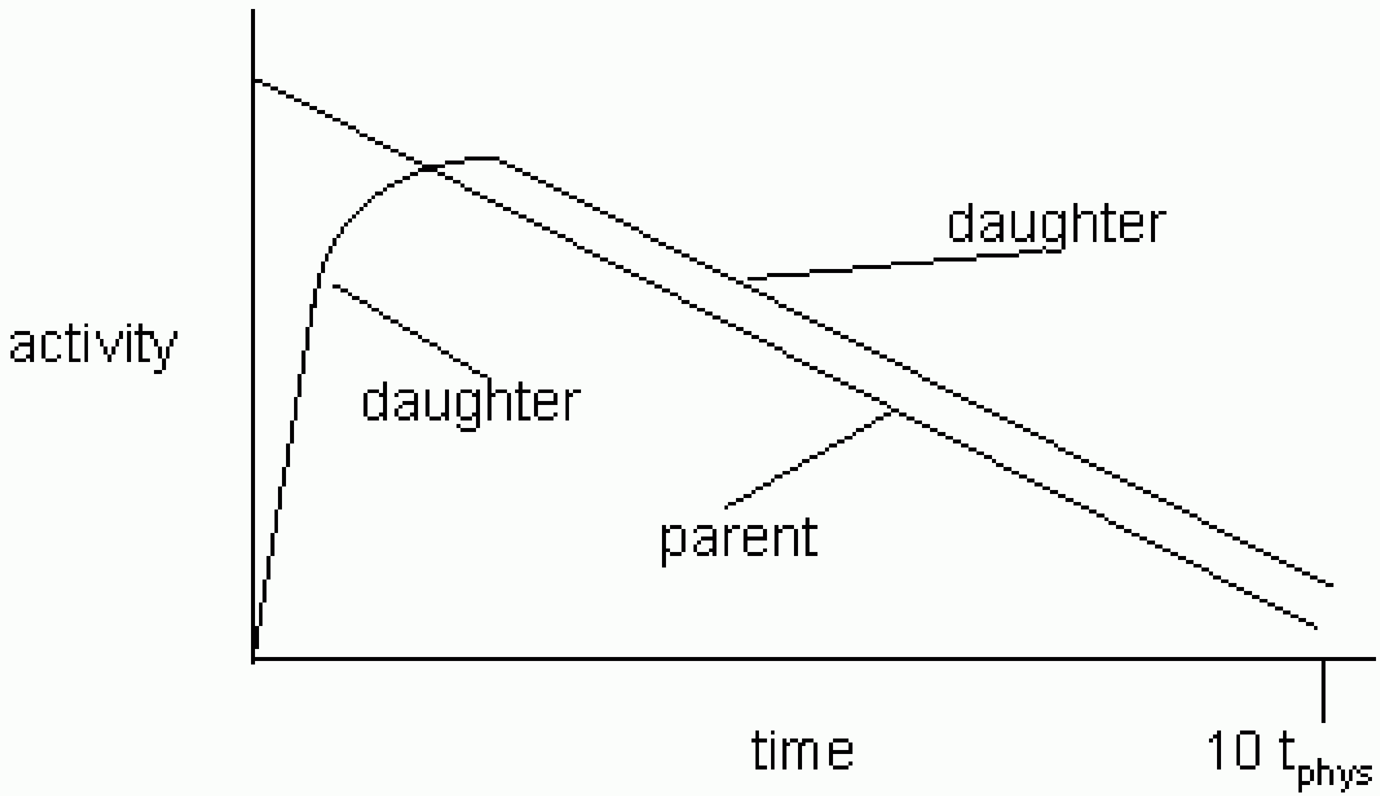
GENERATORS

- Types of Equilibrium
- Characteristics of Ideal Generators System
- Principles of Operation of a $^{99}Mo/^{99m}Tc$ Generator
- Quality Control of $^{99}Mo/^{99m}Tc$ Generator

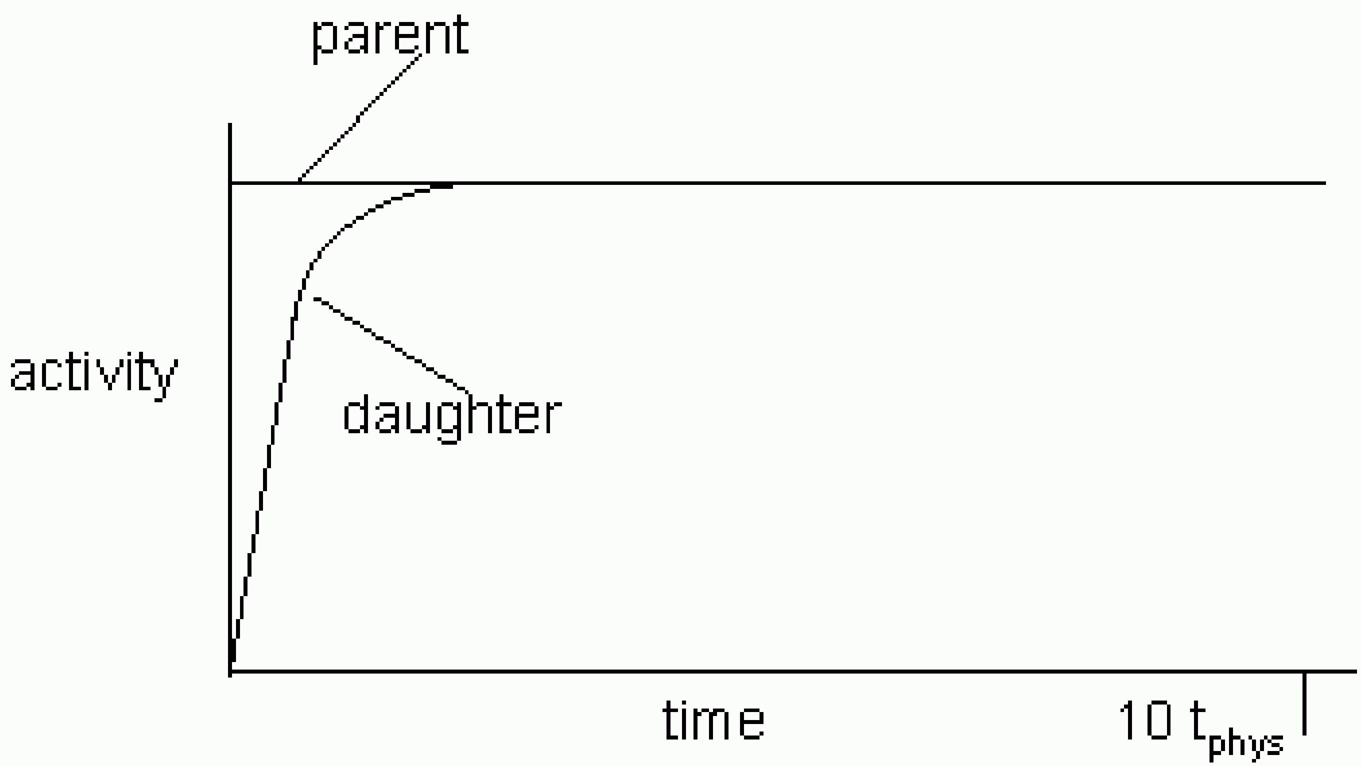
PARENT-DAUGHTER EQUILIBRIA

- Transient Equilibrium
- Secular Equilibrium

Transient Equilibrium



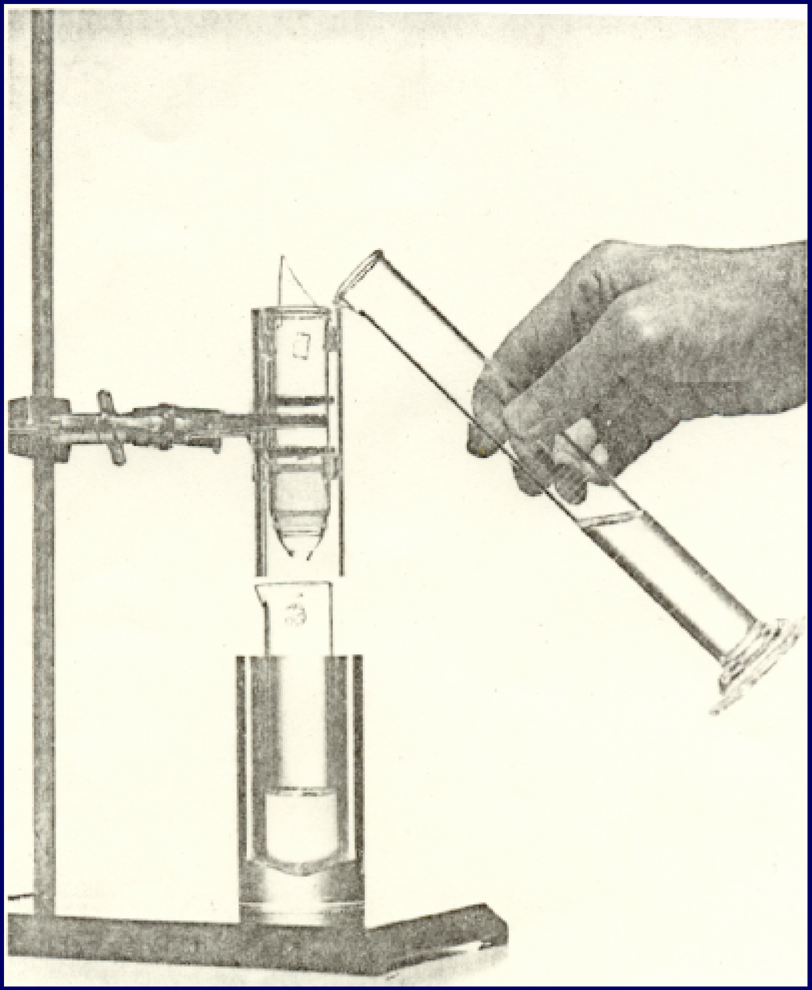
Secular Equilibrium



Ideal Generators: Characteristics

- Easily Transportable
- Easy Separation of Daughter From Parent in Sterile, Pyrogen-Free Form.
- High Yield of Separation.
- No Radionuclidic Impurities.
- Parent with Reasonable Half Life.
- Daughter with Ideal Half life and Gamma Energy.
- Chemistry of the Daughter Allows Hospital Preparation

The Original $^{99m}Tc/^{99}Mo$ Generator Without Shielding



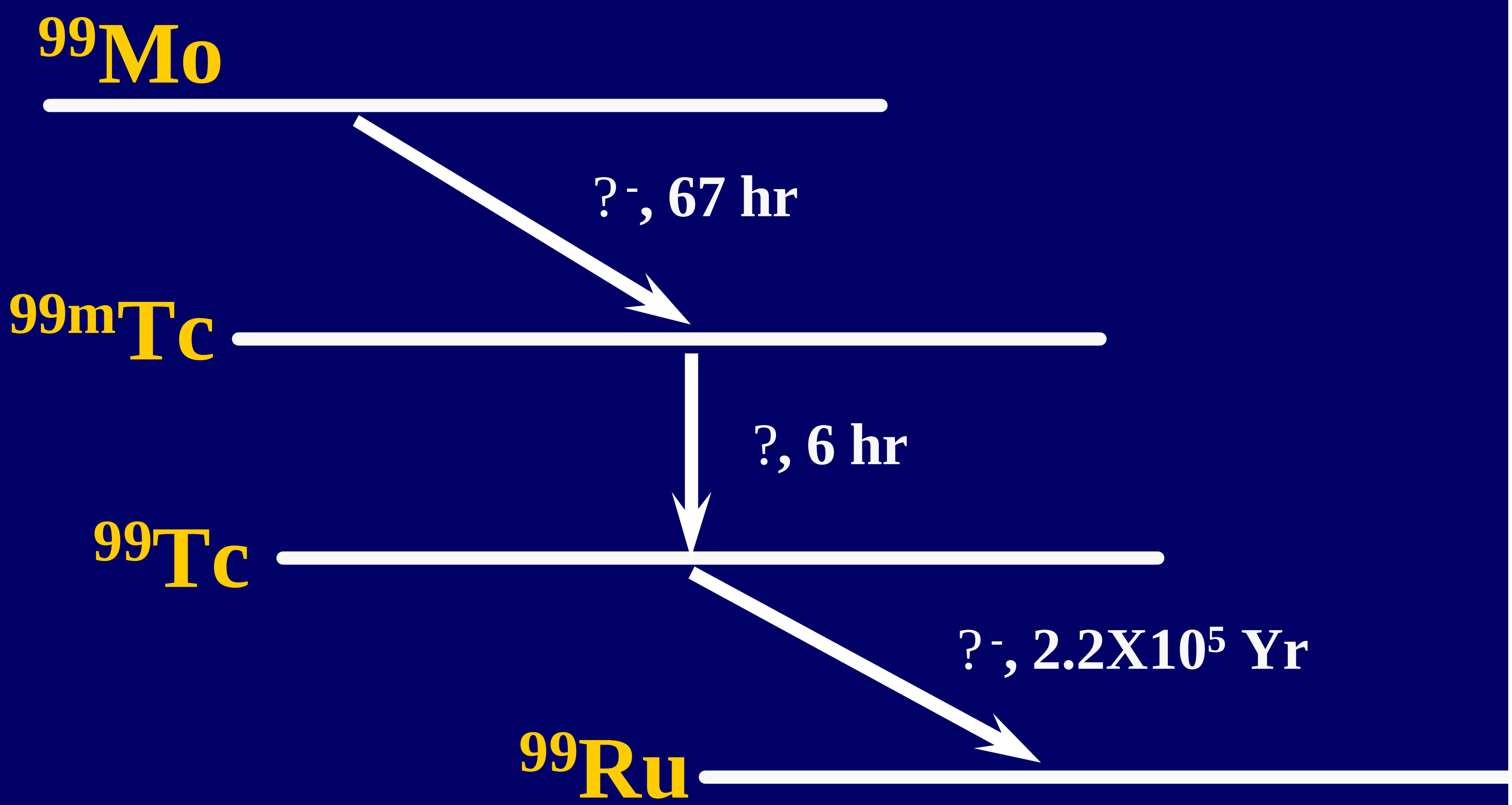
$^{99}Mo/^{99m}Tc$ Generator

- Parent: ^{99}Mo as molybdate ($^{99}MO_4^{-2}$)
- Daughter: ^{99m}Tc as pertechnetate($^{99m}TcO_4^{-1}$)
- Adsorbent Material: Alumina (aluminum oxide, Al_2O_3)
- Eluent: saline (0.9% NaCl)
- Eluate: $^{99m}TcO_4^-$

^{99}Mo

- Half-life: 66 hr.
- Decays by ? $^-$ emission, gamma: 740, 780 keV.
- High affinity to alumina compared to ^{99m}Tc.

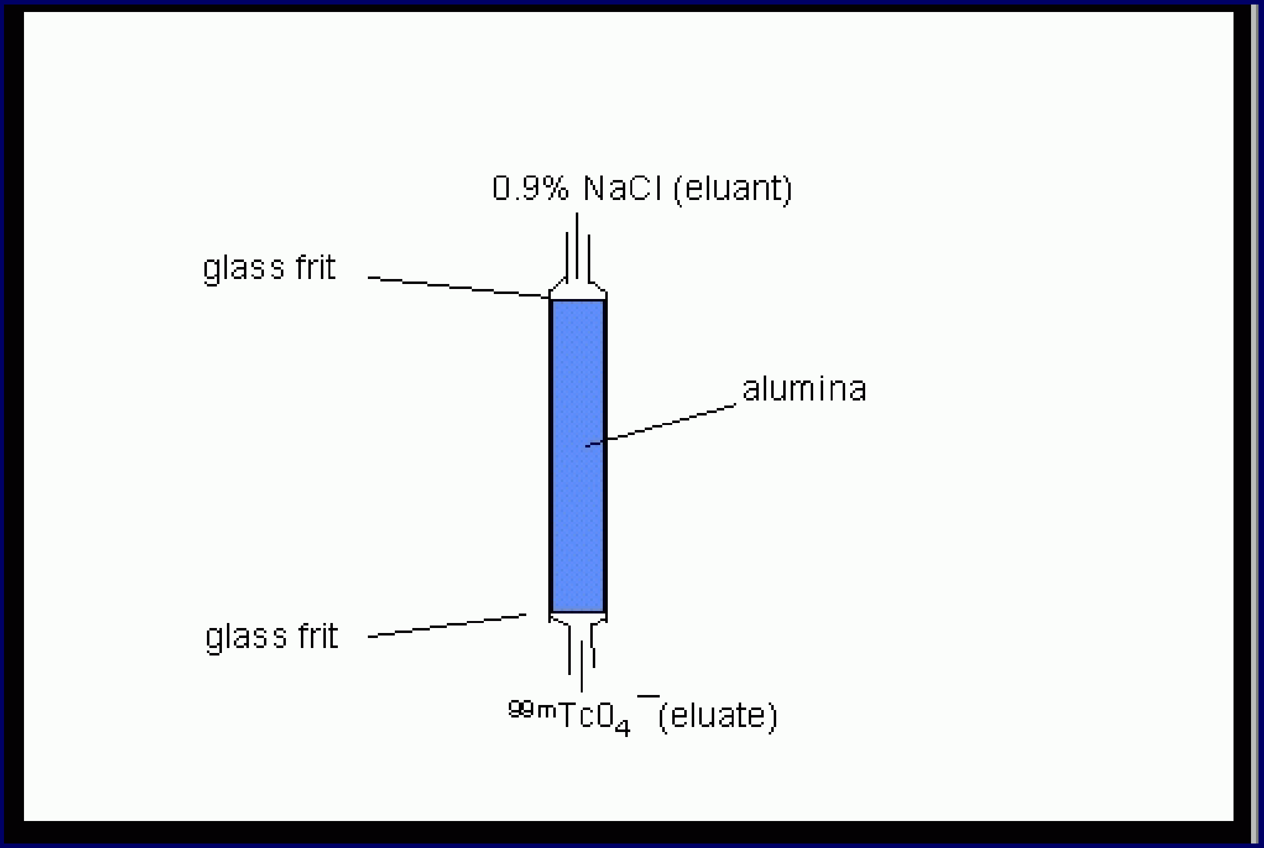
Decay Scheme of ^{99}Mo

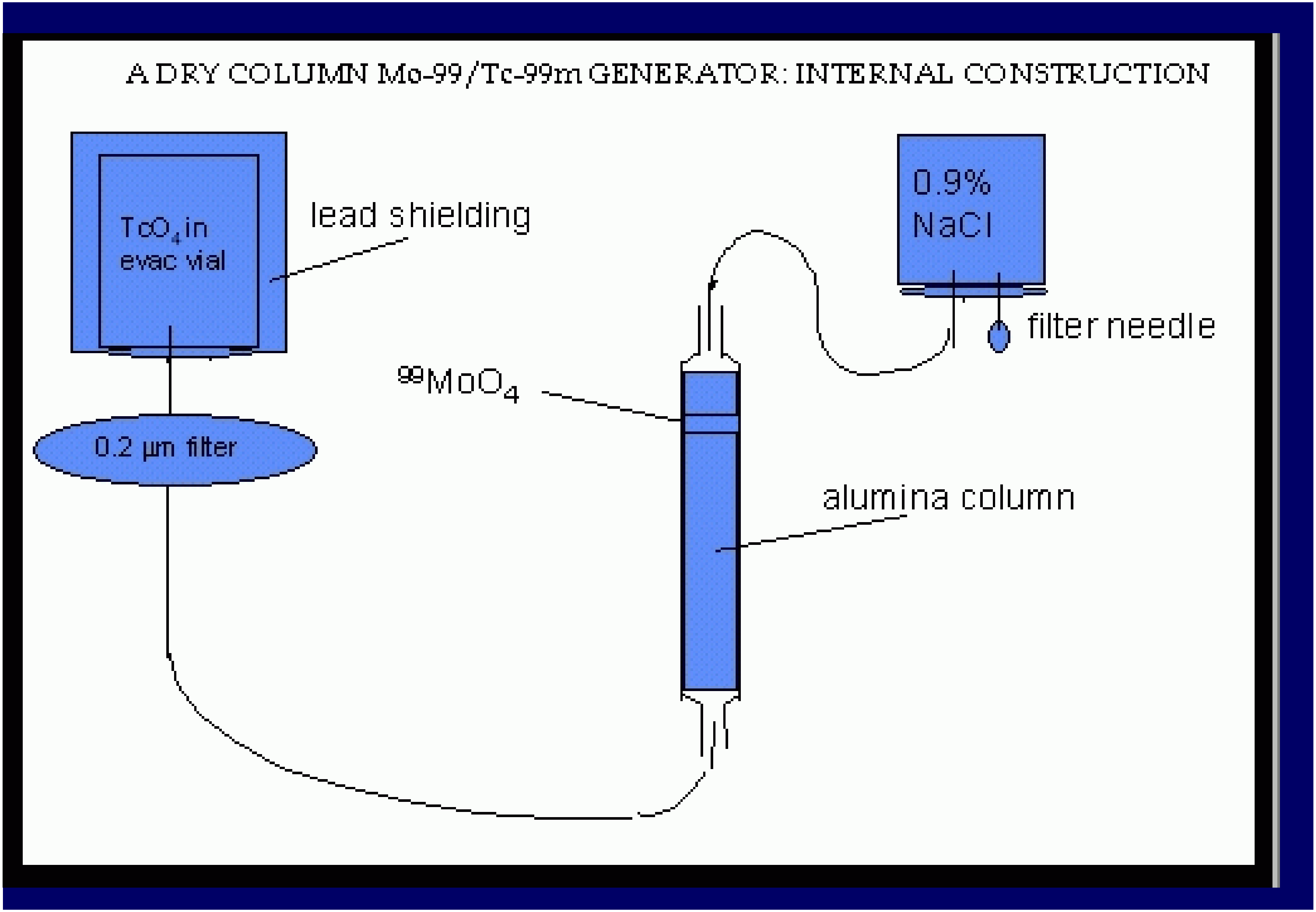


Technetium-99m

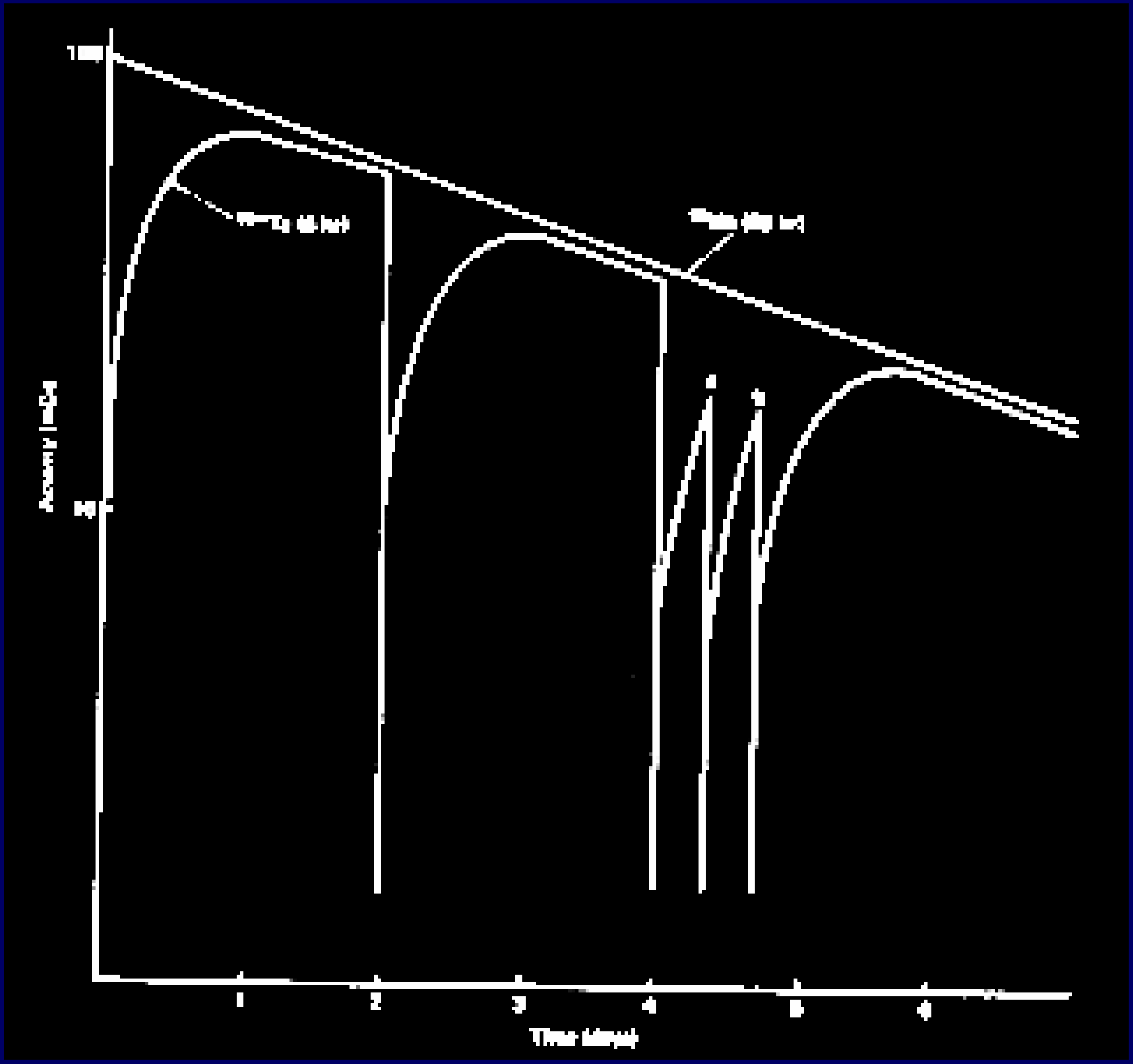
- **<u>Desirable Characteristics</u>:**
  - **Available in a generator form**
  - **Emits monoenergetic gamma rays of 140 keV**
  - **ideal physical half life: 6 hours**
  - **Lack of beta emissions**
  - **Its daughter (^{99}Tc) has a half-life of 2.12X10 ^{5} Years ---> no extra radiation dose to the patient**
  - **Suitable for in-house preparation of many radiopharmaceuticals.**

$^{99}Mo/^{99m}Tc$ Generator: Principles of Operation




A DRY COLUMN Mo-99/Tc-99m GENERATOR: INTERNAL CONSTRUCTION
TcO4 in
evac vial
lead shielding
0.9%
NaCl
filter needle
99MoO4
0.2 µm filter
alumina column

Typical Decay-Growth Relationship of ^{99}Mo & ^{99m}Tc in a Generator



Other Radionuclide Generators

Daughter	^{113m}In	^{81m}Kr	^{82}Rb	^{68}Ga
$T_{1/2}$(min)	100	0.22	1.33	68
$E_?$ (keV)	393	193	511,777	511
Parent	Sn-113	Rb-81	Sr-82	Ge-68
$T_{1/2}$(day)	118	0.2	25	275

GENERATOR QUALITY CONTROL

- Types of Impurities
  - Radionuclide Impurity: ^{99}Mo
  - Chemical Impurity: Al^{+3}
- Required QC Testing
  - Moly Breakthrough
  - Al^{+3} Breakthrough

^{99}Mo Breakthrough

- **<u>Limit (USP & NRC)</u>: 0.15 ? Ci ^{99}Mo/mCi ^{99m}Tc at the time of administration. As a rule of thumb:0.038? Ci ^{99}Mo/mCi of ^{99m}Tc at elution time is good for 12 hr.**
- **<u>Detection Method</u>: the eluate vial is shielded in a lead pot (6mm) to stop all 140-keV photons of ^{99m}Tc and count 740-780 keV of ^{99}Mo. The shielded vial is assayed in a dose calibrator using ^{99}Mo setting.**
- **<u>Frequency</u>: Every elution**

Aluminum Breakthrough

- **<u>Effect</u>: interferes with labeling:**
  - **Sulfur colloid: precipitate**
  - **labeling of RBCs: agglutination**
- **<u>Limit (USP):</u> 10?g Al/ml ^{99m}Tc or 10 ppm.**
- **<u>Method of Detection</u>: one drop each of the eluate and the standard solution are spotted on a special strip and the intensities of the colors are compared. If the eluate spot is more red then Al is excessive.**
- **<u>Frequency</u>: every elution**