From Antimatter to Disease Detection: The Use of Radioisotopes in the Life Sciences

Part 1: Tc-99m

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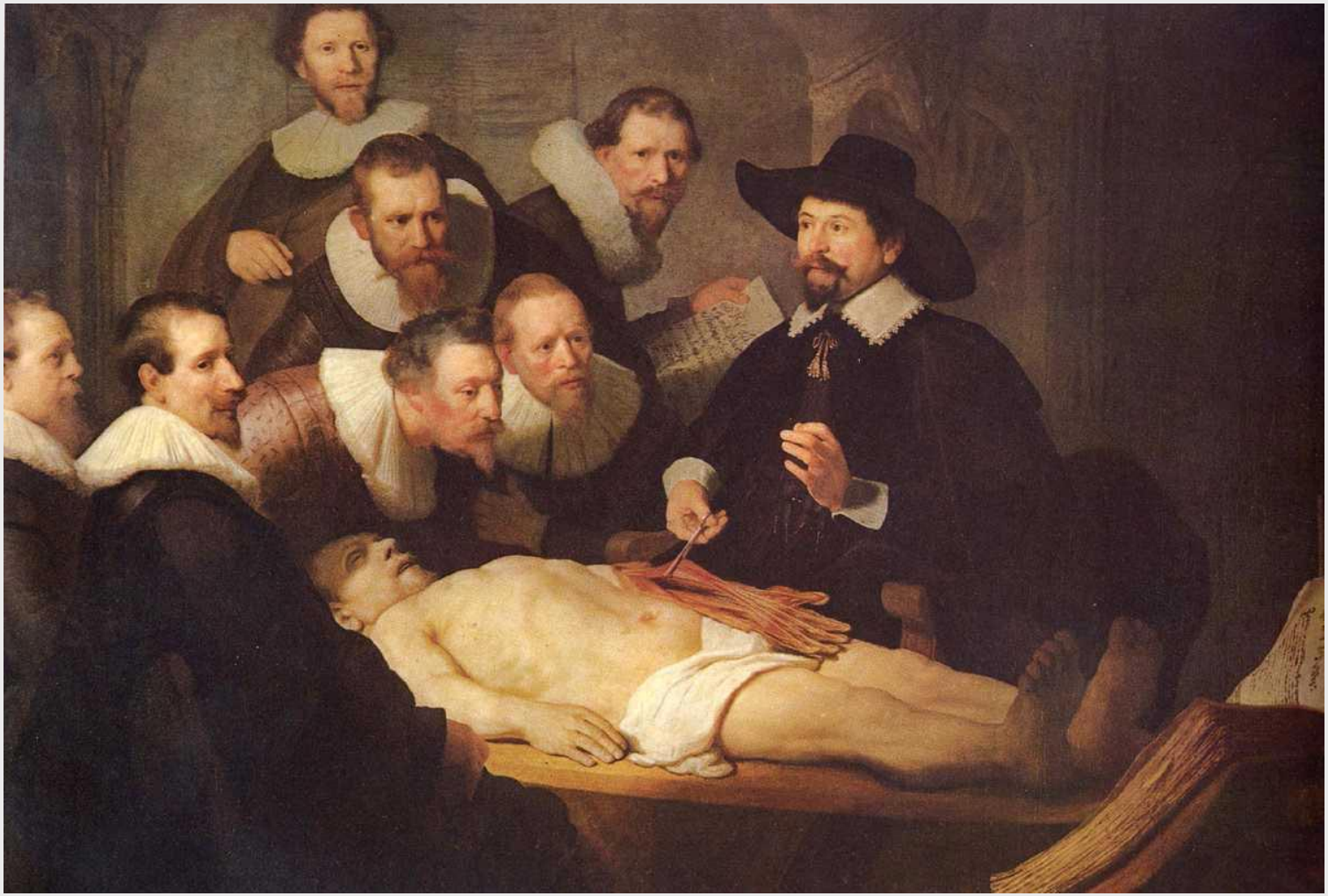
Types of Radioactive Decay

- α – emission of a He nucleus
- β^- – electron emission
- β^+ – positron emission
- γ – gamma emission

Therapy

Imaging

Diagnostic medicine:
Look into the body to see what is happening



Rembrandt - anatomy lesion

How can we probe the human body without a knife?

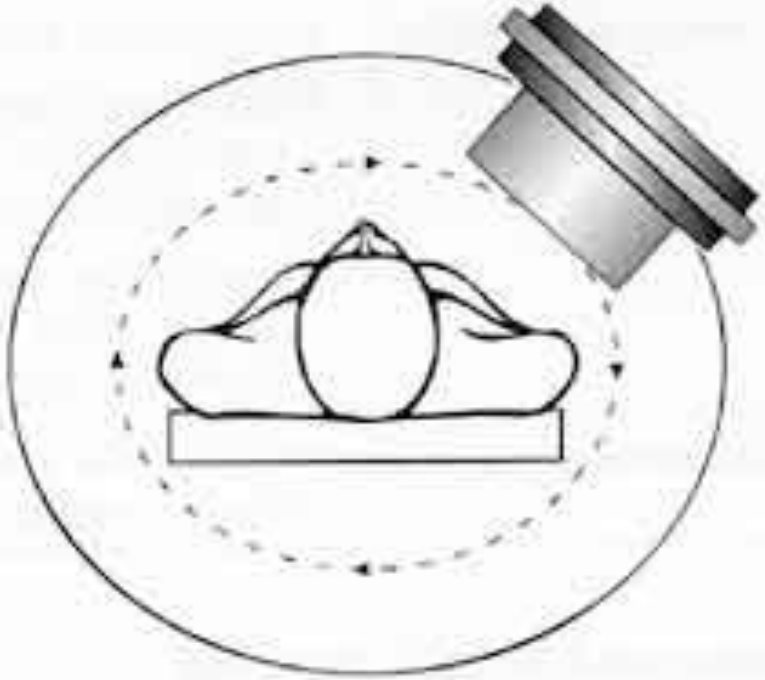
Nuclear Imaging

SPECT: Single Photon Emission Computed Tomography

PET: Positron Emission Tomography

Imaging with γ emitters

In planar imaging, the camera records an image from one perspective



In SPECT imaging, the camera rotates around the patient, recording multiple images that are then reconstructed into a three-dimensional data set by a computer

Tc - Background

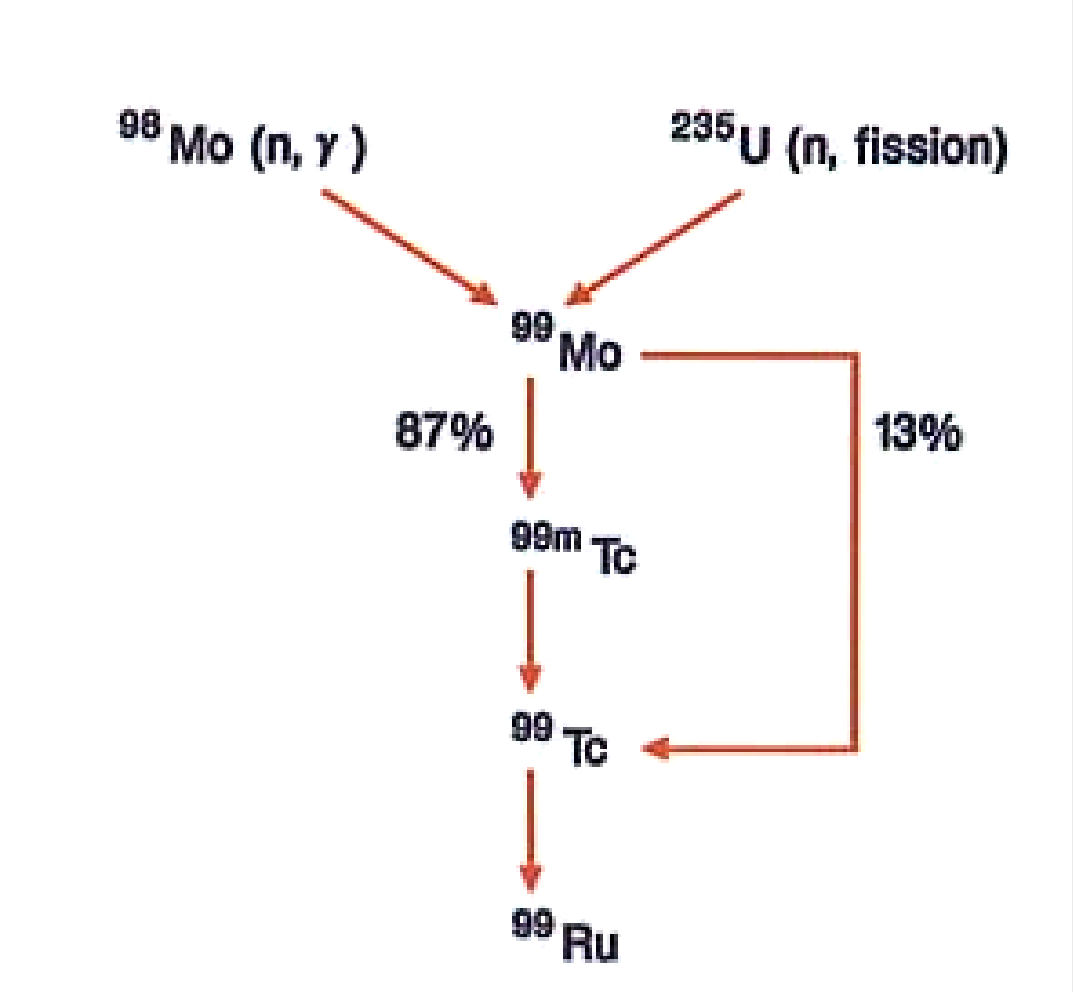
- Tc discovered in 1937 by Perrier and Segré, who separated it from a Mo deflector plate after years of deuteron irradiation in the Berkeley cyclotron
- 17 known isotopes of Tc - all radioactive
  - ^{99m}Tc ($T_{1/2}$ = 6.03 h) is most widely used in Nuclear Medicine - discovered in 1938 by Seaborg and Segré
  - ^{99}Tc ($T_{1/2}$ = 2.1 x 10^5 y) is produced by U fission; used to establish chemistry of the element under conventional chemical concentrations
  - ^{92}Tc, ^{93}Tc and ^{94m}Tc have shorter $T_{1/2}$'s (4-165 min), and have potential use as PET radionuclides

Radionuclide Generator

A device that separates a daughter radionuclide from a parent radionuclide

- **Typically a chromatographic separation based on the different chemical properties of the parent and daughter radionuclides**
- **The daughter radionuclide is the desired radionuclide used for nuclear medicine applications**

Decay of Mo-99



Decay Constants

$$\text{Parent} \xrightarrow{T_{1/2}} \text{Daughter} \xrightarrow{T_{1/2}}$$

$$\lambda_1 = \frac{0.693}{T_{1/2\,Parent}}$$

$$\lambda_2 = \frac{0.693}{T_{1/2\,Daughter}}$$

$$A_t = A_0 e^{-\lambda t}$$

A_t = activity at time t
A_0 = activity at time 0

Transient Equilibrium

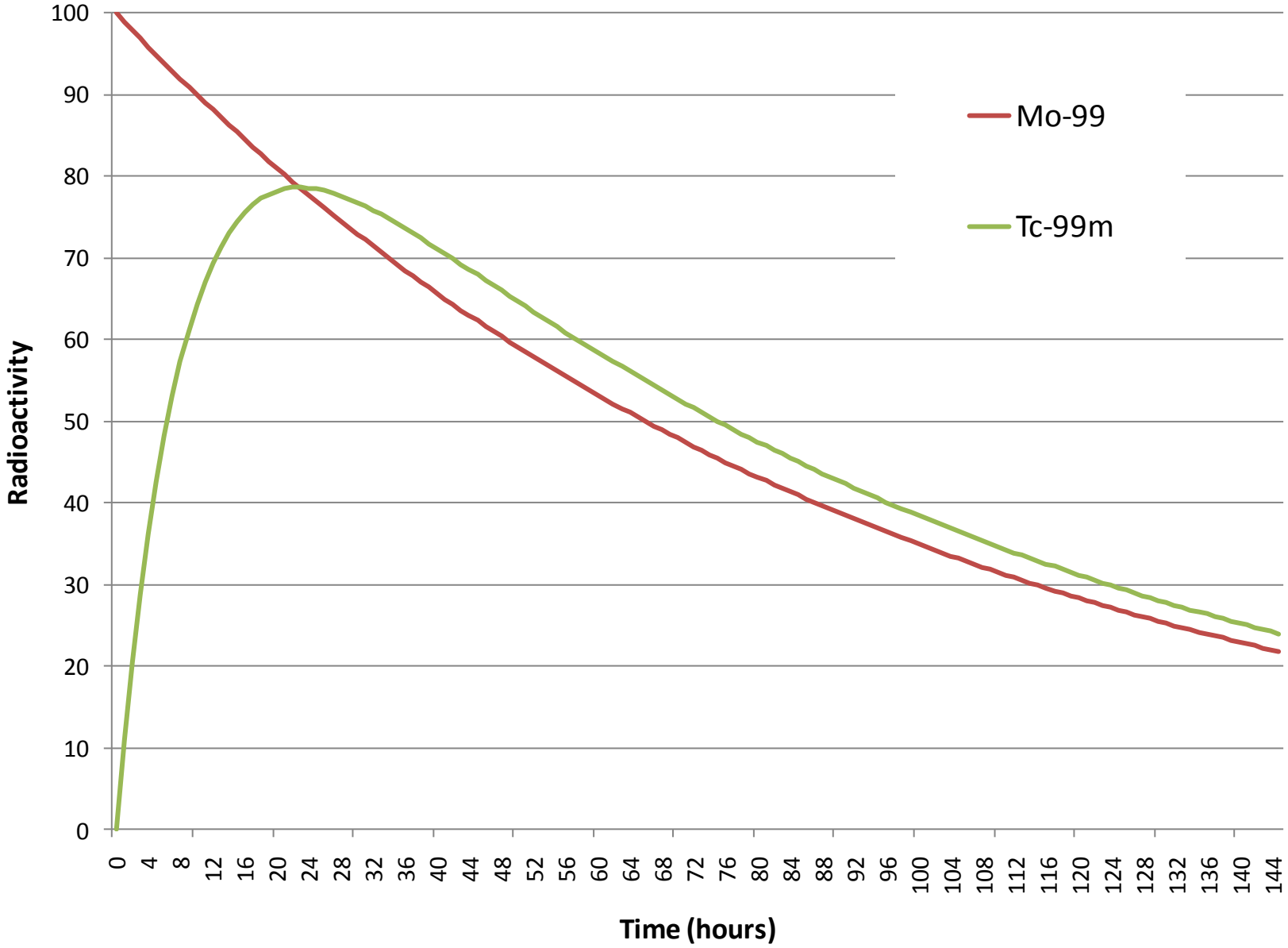
$$A_2 = \frac{\lambda_2}{\lambda_2 - \lambda_1} A^o_1 (e^{-\lambda_1 t} - e^{-\lambda_2 t}) + A^o_2 e^{-\lambda_2 t}$$

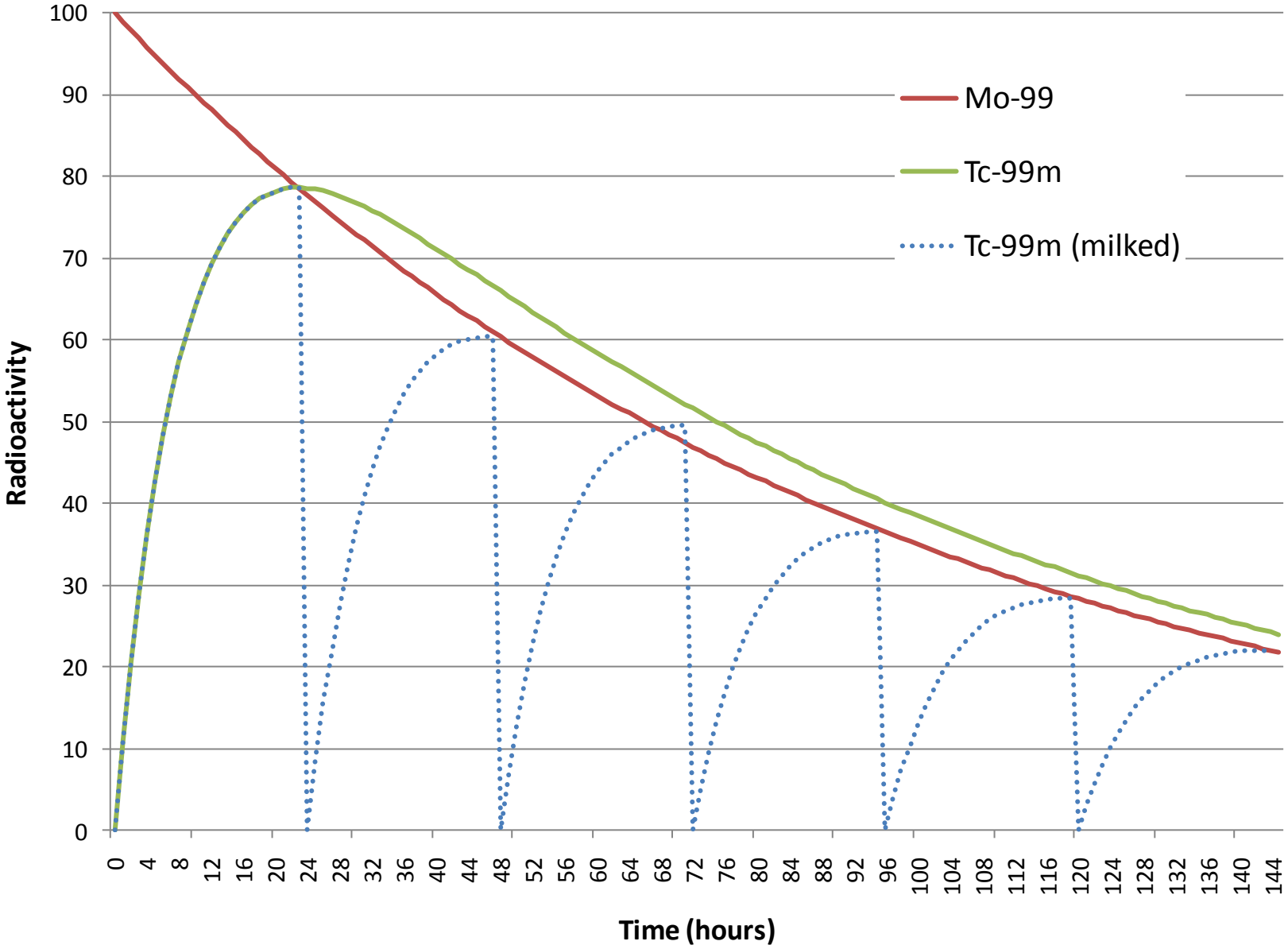
A_1 = activity of parent
A_2 = activity of daughter

As e^{-l2t} becomes negligible and $l_2 > l_1$ ($T_{1/2}(2) < T_{1/2}(1)$), Transient equilibrium is simplified to:

$$A_2 = \frac{\lambda_2}{\lambda_2 - \lambda_1} \bullet A_1$$

$$(A_1 = A_o e^{-\lambda_1 t})$$


Mo-99
Tc-99m
Radioactivity
Time (hours)
0
10
20
30
40
50
60
70
80
90
100
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100 104 108 112 116 120 124 128 132 136 140 144


Mo-99
Tc-99m
Tc-99m (milked)
Radioactivity
Time (hours)
0
10
20
30
40
50
60
70
80
90
100
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100 104 108 112 116 120 124 128 132 136 140 144

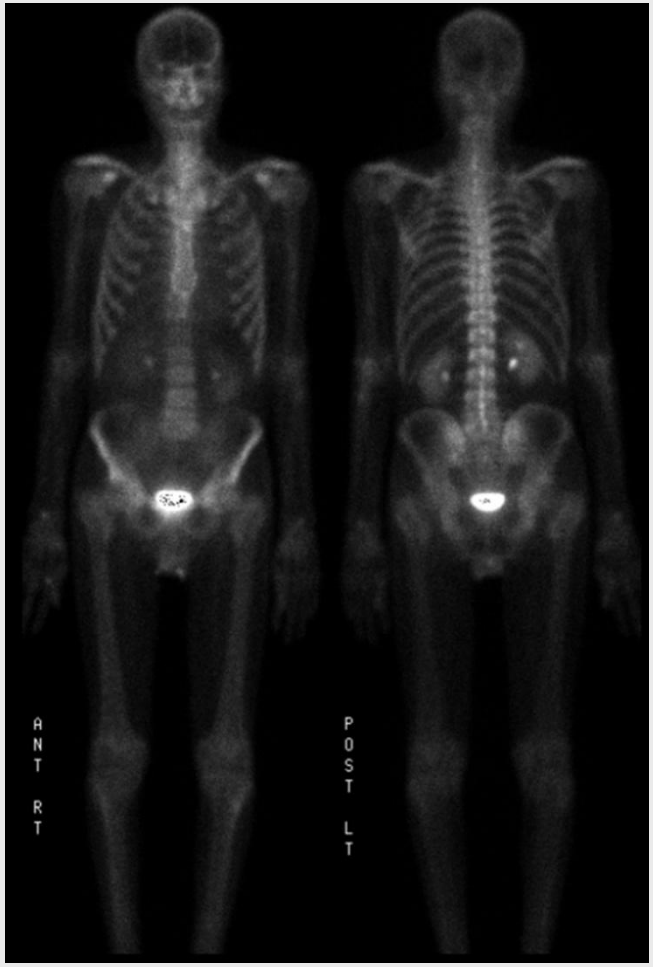
Background, II

- Comments on patent application of Green, Richards and Tucker in 1958 for $^{99}Mo/^{99m}Tc$ generator:
  - "While this method is probably novel, it appears the product will probably be used mostly for experimental purposes in the laboratory. On this basis no further patent action is believed warranted…" Atomic Energy Commission
  - "We are not aware of a potential market for ^{99m}Tc… We would recommend against filing…" Research Corporation for Associated Universities, Inc.
- First injection of $^{99m}TcO_4^-$ into a human was made in 1961, following development of the BNL generator
- By 1970, it was estimated that more than 2000 daily diagnostic procedures were carried out in the U.S.
- By 1985 market for ^{99m}Tc was >$30 million
- Diagnostic radiopharmaceutical market was $1.69 billion in 2005 ($259 million for FDG)

Skeletal imaging

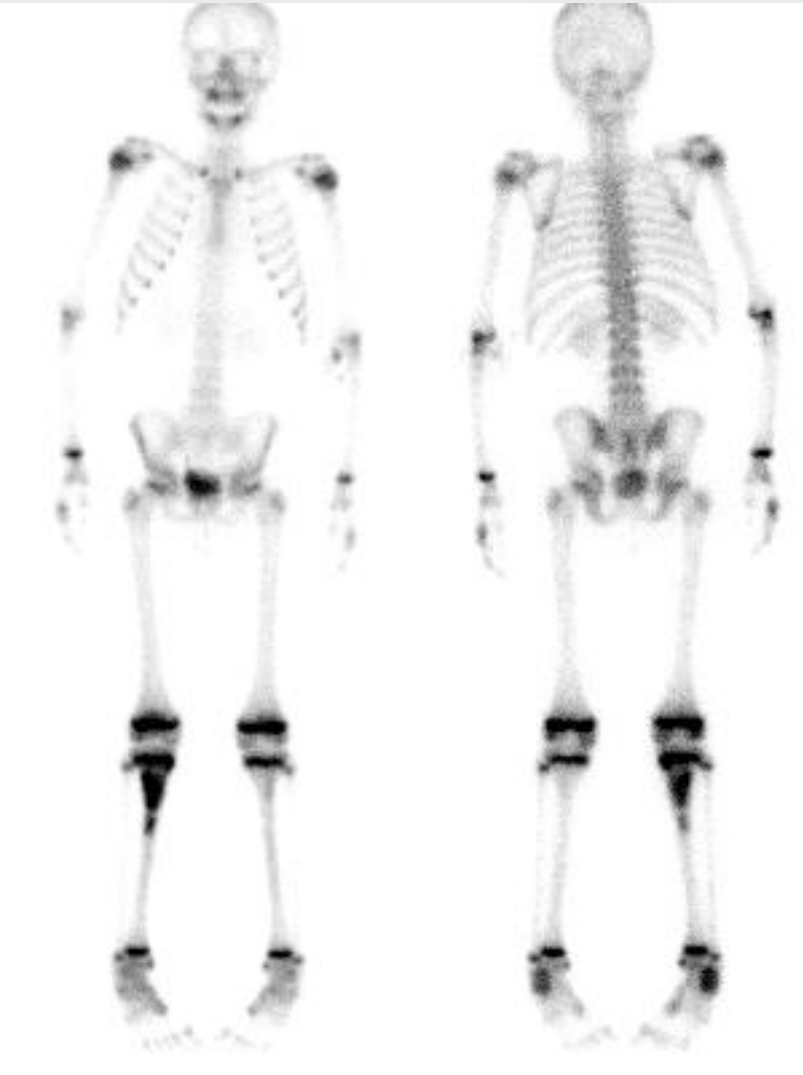
- Used to detect osseous metastases, fractures and infection
- Often called a bone scan
- Common radiopharmaceuticals:
  - ^{99m}Tc-MDP binds to calcium matrix
  - ^{18}F-fluoride can be used for PET skeletal imaging
- Non-specific marker of increased bone matrix turnover

Normal ^{99m}Tc-MDP bone scan



Images acquired about 3 hours after injection

Abnormal ^{99m}Tc Bone Scan

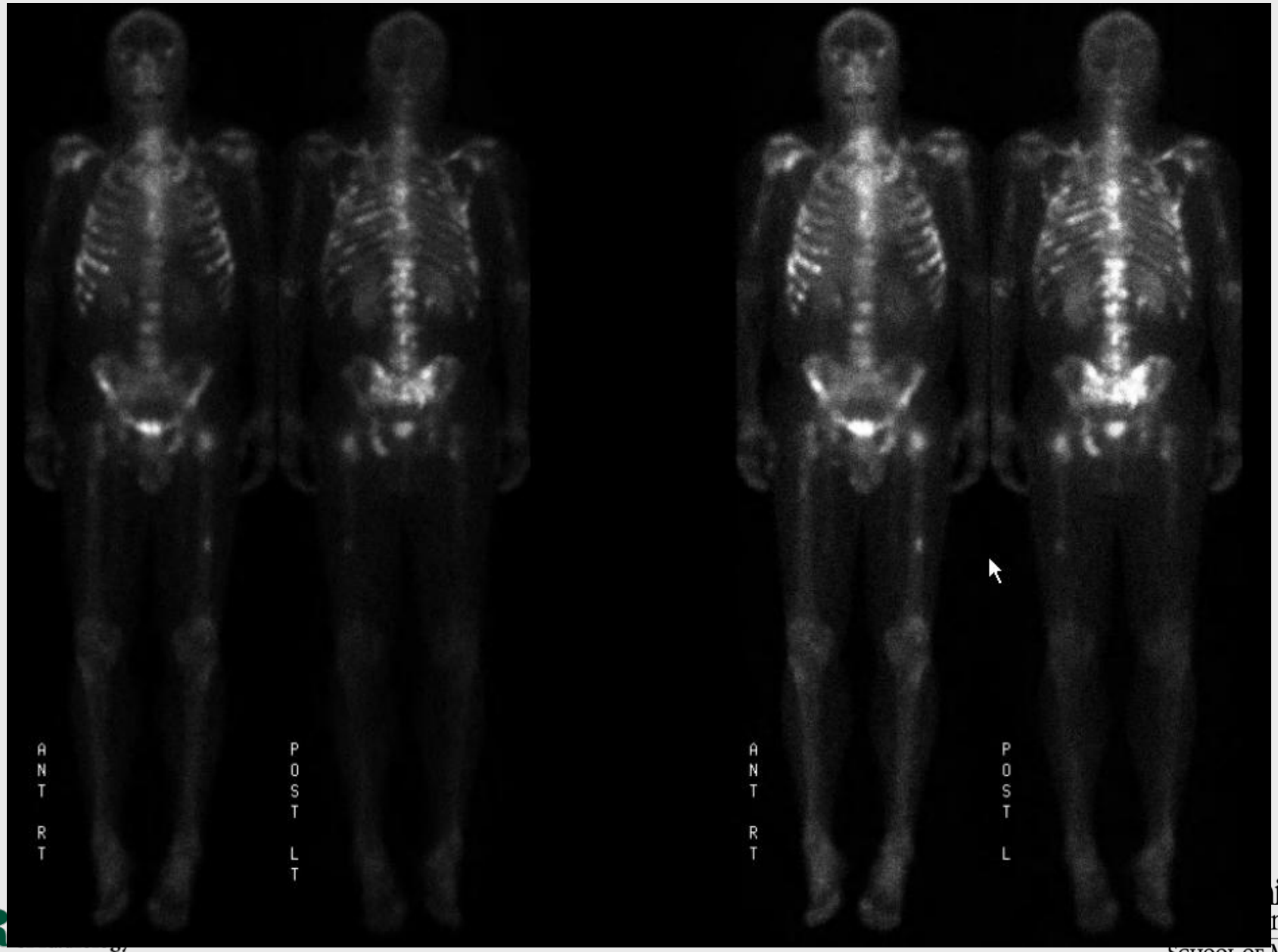


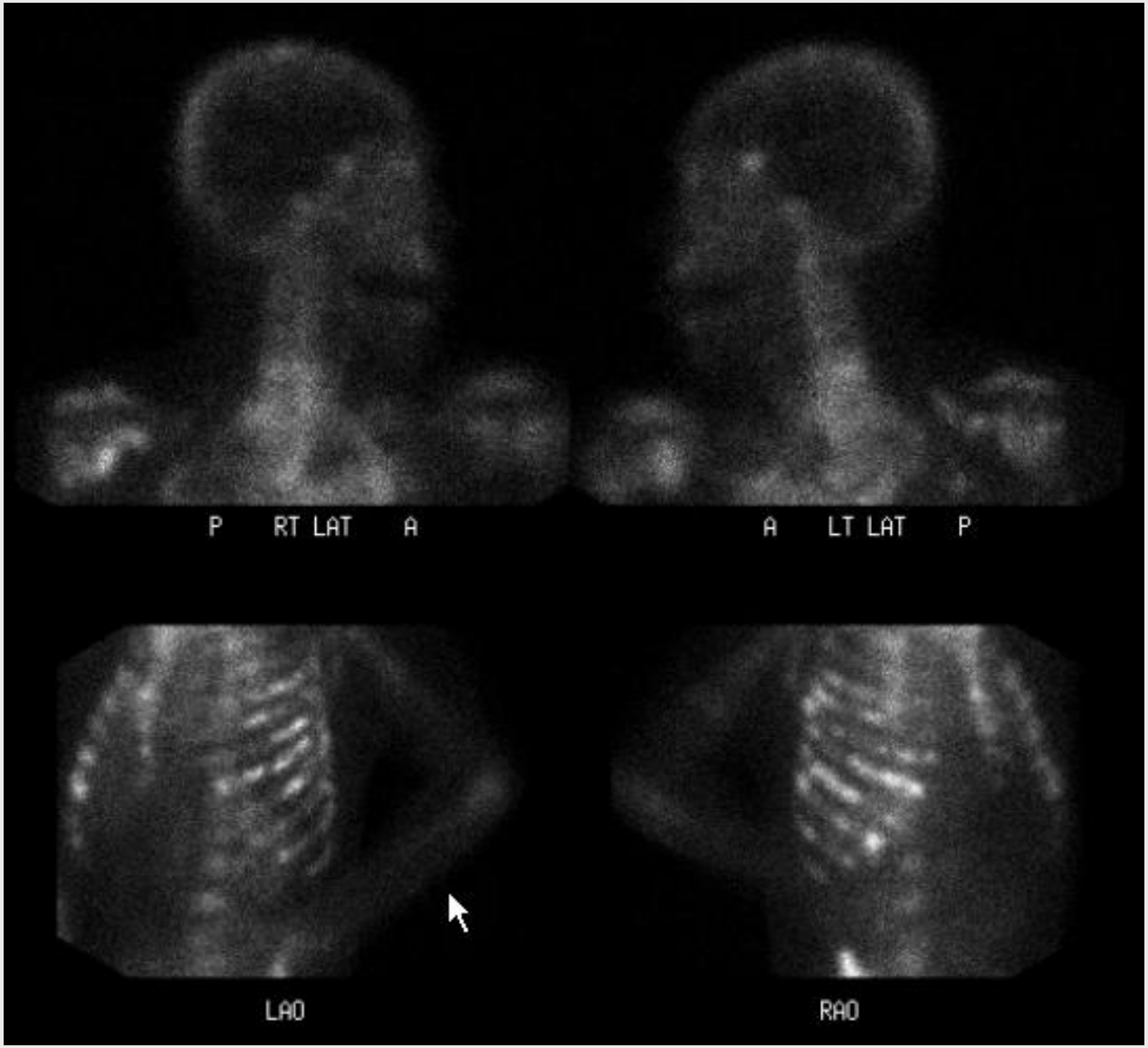
11-year old boy with a one month history of right knee pain

Increase activity in the right tibia

Diagnosis: Osteosarcoma

58 year old man with prostate cancer




P RT LAT A
A LT LAT P
LAO
RAO

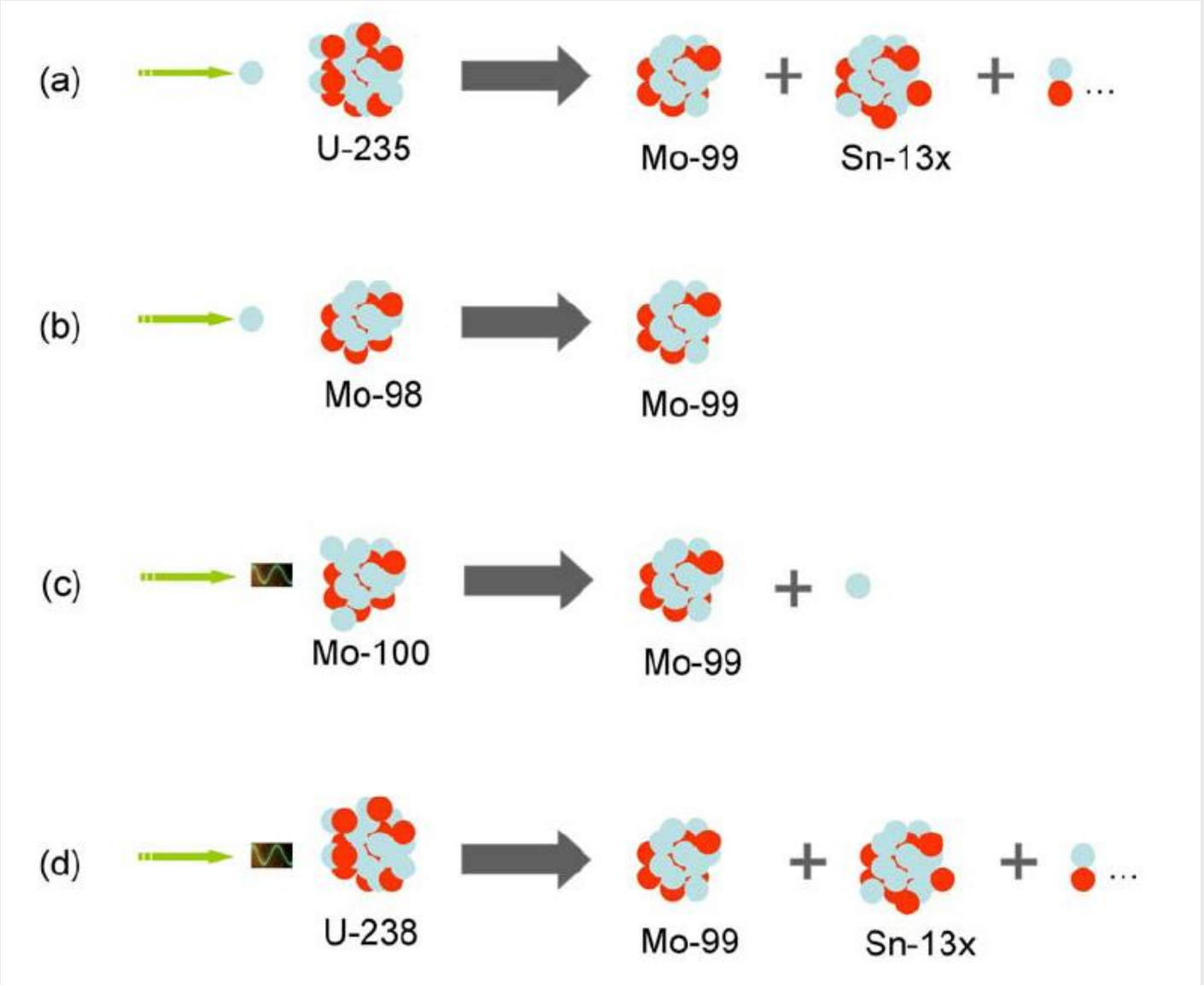
^{99m}Tc Availability Issues: "The Isotope Crisis"

- Tc-99m is most widely used radionuclide for nuclear medicine procedures in the world and accounts for >80% of all procedures
- Major efforts in connecting to biological molecules to assess
  - Cardiac function
  - Blood flow
  - Bone metastases
- Half life & chemical properties of Mo-99 and Tc-99m are exploited to separate them in generator
  - Mo-99/Tc-99m generator invented at Brookhaven National Laboratory
  - Mo-99 half life is 66 hours, Tc-99m has a half life of 6 hours
- Generators sent around the world

The simplicity of the $^{99}Mo/^{99m}Tc$ generator

Developed at BNL in 1958 it was never patented.

Production routes to ^{99}Mo



Major isotope-producing reactors

Reactor	*In-service date*	*Target uranium enrichment type*
NRU (Canada)	**1957**	**HEU**
BR2 (Belgium)	**1961**	**HEU**
HFR (Netherlands)	**1963**	**HEU**
SAFARI (South Africa)	**1965**	**HEU**

Notes:

- Other smaller suppliers: RA-3 (Argentina) is a domestic supplier and OSIRIS (France) provides some back-up to BR2 and HFR.
- OPAL (Australia): commissioned in 2008, in early stages of operation.

Issues

- Currently AECL/MDS Nordion supply 40% of world's demand and able to handle 80%

- AECL runs the (130 MW) NRU reactor with LEU fuel and HEU targets (HEU is highly enriched uranium & is weapons grade uranium)
  - Substantial radioactive waste is generated in processing
  - HEU (> 19.7% U-235) comes from the US and waste is also HEU
  - Fission of U-235 induced by thermal neutrons
  - Natural uranium is 99.284% U-238 and 0.711% U-235

Issues continued

- Chemistry is performed on targets by AECL resulting in a Mo-99 solution
- Solution shipped to MDS Nordion for purification and placement into column
- Mo-99 is eluted (extracted with a solvent) from the column
- Produced eluate is conditioned and ^{99}Mo re-extracted
- Meeting US demand requires about 34,000–46,000 Curies/week at the reactor

Other Issues

- US production was halted in 1989
  - Foreign subsidies were claimed to be the cause for lower costs abroad
  - Deemed “not worth it” to continue in US
- Low market price, risk of reactor business, and high cost of production facilities
- US demand shared by Canada + The Netherlands
- HEU has significant security issues; future will likely require use of something else

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