Chapter 14
Nuclear Medicine

Radiation Dosimetry I

Text: H.E Johns and J.R. Cunningham, The physics of radiology, 4th ed.

http://www.utoledo.edu/med/depts/radther

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Outline

- Introduction
- Radiopharmaceuticals
- Detectors for nuclear medicine
- Counting statistics
- Types of studies
- Absorbed dose from radionulides

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Introduction

- The field involving the clinical use of *non-sealed* radionuclides is referred to as nuclear medicine
- Most of the activities are related to
  - the imaging of internal organs
  - the evaluation of various physiological functions
  - to a lesser degree treatment of specific types of disease
- Typical procedures use a radioactive material (radiopharmaceutical or radiotracer), which is injected into the bloodstream, swallowed, or inhaled as a gas
- This radioactive material accumulates in the organ or area of the body being examined, where it gives off a small amount of energy in the form of gamma rays

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Radiopharmaceuticals

- Radiopharmaceuticals are medicinal formulations containing one or more radionuclides
- Once administered to the patient they can localize to specific organs or cellular receptors
- Properties of ideal radiopharmaceutical:
  - Low dose radiation => appropriate half-life
  - High target/non-target activity ratio
  - Low toxicity (including the carrier compound, shelf-life)
  - Cost-effectiveness (available from several manufacturers)

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Radiopharmaceuticals

- Shielded vial used to hold reconstituted radiopharmaceuticals
- Using long forceps to handle a vial containing radioactivity

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Mechanisms of localization

- Compartmental localization (leakage points to abnormality)
- Phagocytosis (normal vs cancer cells)
- Cell sequestration (spleen imaging)
- Passive diffusion (often through membranes, e.g., BBB)
- Active transport (membranes with pumps)
- Metabolism (glucose-like molecules, F-18 labelled FDG)
- Capillary blockade/Perfusion
- Receptor binding (e.g., antibody-antigen)
- Others

Comprehensive review at: http://pharmacyce.unm.edu/nuclear_program/freelessonfiles/Vol16Lesson4.pdf

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Radiopharmaceuticals production

Nuclide	Half-life	Preferentially imaged γ-energy (keV)	Intensity (%)	Decay mode	Source
^{67}Ca	78.28 h	93.3	38.81	EC	Cyclotron
		184.6	21.41		
		300.2	16.64		
^{81m}Kr	13.10 s	190.5	64.9	IT	Generator
^{99m}Tc	6.015 h	140.5	89.06	IT	Generator
^{111}In	67.31 h	171.3	90.7	EC	Cyclotron
		245.4	94.1		
^{123}I	13.22 h	159	83.3	EC	Cyclotron
^{131}I	8.025 days	364.5	81.5	β^-	Reactor
^{133}Xe	5.243 days	81.0	38.0	β^-	Reactor
^{201}Tl	73.01 h	167.4	10.0	EC	Cyclotron

^{99}Mo (produced in nuclear reactors) is a precursor of ^{99m}Tc

- Cyclotron
- Nuclear reactor (fission or neutron activation)
- Radionuclide generators

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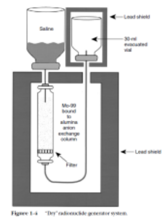
Radiopharmaceuticals production: Tc-99m generator

- Mo-99 (t_h=66h) is produced in the fission reaction, it is then chemically purified and shipped in Tc-99m (t_h=6h) generators



From: Ziessman, et al., Nuclear Medicine: the Requisites In Radiology, 3d ed., Elsevier, 2006

http://www.gedrytec.com/design/technical_features_annotations.php

- Molybdate, MoO_4^{2-} is passed on to an anion exchange column of alumina (Al_2O_3); acid pH promotes binding
- As Mo-99 decays it forms pertechnetate TcO_4^-; because of its single charge, it is less tightly bound to the alumina. Pouring normal saline solution through the column of immobilized ^{99}Mo elutes the soluble ^{99m}Tc

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Mo-99 production

- Tc-99m is used in more than 80% of all nuc. med. procedures
  - 50% of these procedures are conducted in US
- Production of Mo-99 precursor was limited to several locations outside US; involved fission of HEU (highly enriched U-235)
  - Canadian National Research Universal (NRU) reactor constructed in 1957 was the main source for US
  - Other sources: the HFR in the Netherlands (1961), the BR2 in Belgium (1961), SAFARI-1 in South Africa (1965), and OSIRIS in France (1966)
- After 2009-2010 crisis when several aging reactors were brought off line for extended time period plans were made for US production, which started in 2018
  - Companies in Australia, Canada, Europe, South Africa, and US currently participate in the global supply chain for Mo-99/(Tc-99m)

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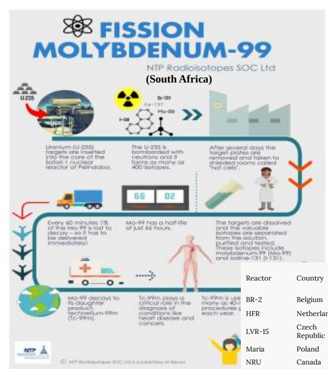

- Recent development: US-based North Star started production of Tc-99m generators, brand name RadioGenix System, in 2018 (Wisconsin)
- Uses neutron capture: Mo-98(n,γ)Mo-99, no Uranium involved

https://www.nap.edu/read/23563/chapter/6#55

TABLE 3.2 Reactors That Irradiate Targets for Global Mo-99 Suppliers as of June 2016

Reactor	Country	Power (MWt)	Fuel Type	Target Type	Start of Operation (year)
BR-2	Belgium	100	HEU	HEU	1961
HFR	Netherlands	45	LEU	HEU	1961
LVR-15	Czech Republic	10	LEU	HEU	1957
Maria	Poland	30	LEU	HEU	1974
NRU	Canada	135	LEU	HEU	1957
OPAL	Australia	20	LEU	LEU	2006
SAFARI-1	South Africa	20	LEU	HEU/LEU	1965

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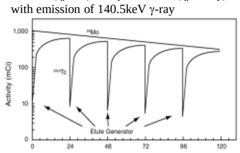
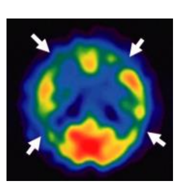
Radiopharmaceuticals production: Tc-99m generator

- A technetium generator can be eluted several times a day for ~1 week before it needs to be replaced with a fresh generator

Tc-99m (t_h~ 6h) decays to Tc-99 (t_h~ 10^5 y) with emission of 140.5keV γ-ray





Left. Plot of typical Mo-99 and Tc-99m activity **Right.** Image acquired from a Tc-99m cerebral blood flow brain scan of a person with Alzheimer's disease. The arrows indicate areas of diminished blood flow due to the disease.
From: Molybdenum-99/Technetium-99m Production and Use, NRC 2009 https://www.ncbi.nlm.nih.gov/books/NBK215133/

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Detectors in nuclear medicine

- The standard methods for the detection and measurement of radiation are not sensitive enough to detect the emission of a single particle arising from the disintegration of a nucleus
- Special gas-filled, scintillating, or semiconductor detectors are used almost exclusively
- For visualization of the distribution of activity use computer-aided signal processing (PET scanners, gamma cameras, etc.)

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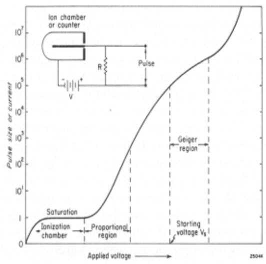
Geiger counter



- Counter filled with a special gas mixture, at p=10 cm of Hg
- Operated at high voltages, where the passage of each particle creates a controlled avalanche, resulting in a gain of ~10^5-10^6
- A single particle can produce a pulse of charge in the detectable range (10^{-10} C)

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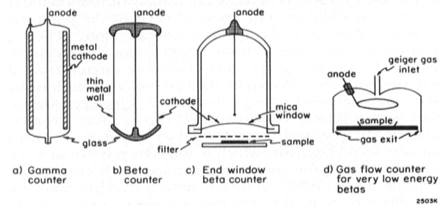
Geiger counters



- Efficiency of gamma counter is very low, ~5%
- Efficiency of beta counters is ~100%; their configuration depends on the energy of particles to be detected

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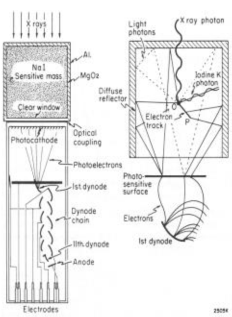
Scintillation detectors



- Scintillating material coupled with a photomultiplier (PM)
- X-rays → electrons within the scintillator → optical photons within the scintillator → photoelectrons from the photocathode of the PM → secondary electrons from each dynode → collected at the final anode of PM
- PM multiplication factors ~10^6
- Pulse size is proportional to the *energy* of the initial x-ray

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Scintillation detectors

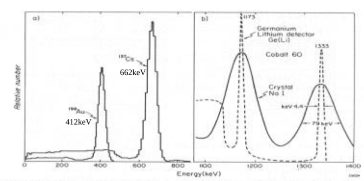

Figure 14-5. (a) Pulse height distribution for Cs-137 and Au-198 obtained on a 100-channel pulse-height analyzer using a 6 × 6 cm sodium iodide crystal. (b) Comparison of γ ray spectrum of Co-60 observed with a 3.5 mm-deep germanium lithium detector and with a 7.5 × 7.5 cm sodium iodide scintillation spectrometer.

- Pulse height distributions always have Gaussian shaped peaks and low-energy tails

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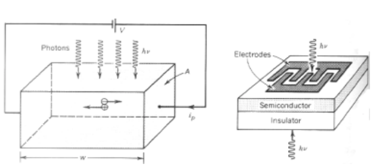
Semiconductor detectors



- Ionization produced within the sensitive volume of semiconductor detector is converted directly into a measurable electric pulse
- Fewer losses result in much sharper pulse height spectra
- Sensitivity is typically lower compared to scintillators

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Stochastic quantities

- Radiation is random in nature, associated physical quantities are described by probability distributions
- For a "constant" radiation field a number of x-rays observed at a point per unit area and time interval follows Poisson distribution
- For large number of events it may be approximated by normal (Gaussian) distribution, characterized by standard deviation for a single measurement

$$\sigma = \sqrt{N_e} \cong \sqrt{N}$$

$$\%\sigma = \frac{100\sigma}{N_e} = \frac{100}{\sqrt{N_e}} \cong \frac{100}{\sqrt{N}}$$

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Statistics of isotope counting

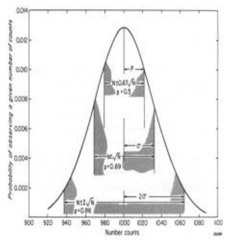

Figure 14-7. Probability of observing a given number of counts N when, on the average, 1000 counts are observed.

- The probability of observing the value N when the expected value is a:

$$P_N = \frac{a^N e^{-a}}{N!}$$

- For each measurement there is always an error due to statistical fluctuations:
  - Standard deviation
    $\sigma = \sqrt{N}$
  - Probable error
    $p = 0.67\sqrt{N}$

The PE defines the middle 50% of the normal distribution

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Statistics of isotope counting

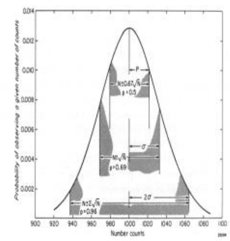

Figure 14-7. Probability of observing a given number of counts N when, on the average, 1000 counts are observed.

- In a normal distribution 68.3% of all measured values fall within 1σ interval on either side of the mean a, 95.5% to be within 2σ, and 99.7% to be within interval 3σ
- These are not device-related fluctuations

The probable error p defines the middle 50% of the normal distribution

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Standard deviation

- Standard deviation can be estimated from a sample mean value a determined from a series of measurements, $\sigma = \sqrt{a}$
- The sample standard deviation can be constructed from a series of N measurements of a variable x

$$\sigma_s = \sqrt{\frac{\sum_{i=1}^{N}(x_i - a)^2}{N-1}}$$

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Example 1

- Concerning the Poisson distribution, which one of the following statements is false?

A. It is an approximation to the binomial distribution for small sample sizes
B. It describes rare and random events
C. Radioactive decay as a function of time fits the Poisson distribution
D. The standard deviation σ is approximaly equal to the square root of the number of counts for large numbers
E. The percent standard deviation decreases as the number of counts increases

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Example 2

- If the average number of counts in a region of a planar gamma camera image is 25 counts per pixel, what is the percent standard deviation per pixel, assuming Poisson statistics?

A. 0%
B. 10%
C. 20%
D. 50%

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Resolving time and loss of counts

- Most of detectors become unresponsive for a short time after receiving each pulse
  - For Geiger counters resolving time τ ~100 μs
  - Scintillators τ <10 μs
- At high counting rates some pulses can be missed
- For observed number of counts per second N_0, the corrected number of counts

$$N_c = \frac{N_0}{1 - N_0\tau}$$

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Resolving time and loss of counts

- To determine the resolving experimentally, can use two sources of similar activities
- For measured number of counts per second N_A, N_B, N_{AB}, the corrected number of counts

$$\frac{N_A}{1-N_A\tau}+\frac{N_B}{1-N_B\tau}=\frac{N_{AB}}{1-N_{AB}\tau}$$

- The resolving time:

$$\tau=\frac{N_A+N_B-N_{AB}}{2N_AN_B}$$

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Uptake and volume studies

- Activity of a sample (P) is compared with a standard source (S) measured in the same geometry
- Thyroid uptake of I-131 taken orally

$$\%\text{Uptake}=\frac{\text{P - P}_{\text{bkg}}}{\text{S - S}_{\text{bkg}}}\times 100$$

- Plasma volume determination by injection of RISA (radioactive iodine-tagged, I-125, serum albumin)

$$\text{Vol}=\text{Vol}_{dilution}\frac{\text{S - S}_{\text{bkg}}}{\text{P - P}_{\text{bkg}}}$$

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Example 3

- A radioactive sample is counted for 1 minute and produces 900 counts. The background is counted for 10 minutes and produces 100 counts. The net count rate and net standard deviation are about __ ,__ counts.

A. 800, 28
B. 800, 30
C. 890, 28
D. 890, 30
E. 899, 30

$$N_{corr}=900/1-100/10=890$$

$$\sigma=\sqrt{\sigma_c^2+\sigma_{bkg}^2}=\sqrt{\frac{N_c}{t_c}+\frac{N_{bkg}}{t_{bkg}}}=$$

$$\sqrt{\frac{900}{1}+\frac{100}{10}}=30$$

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Example 4

- A wipe test over a countertop yields a count rate of 1000 counts per minute in a nuclear medicine clinic that uses ^{99m}Tc only. If the background is 40 counts per minute and the detector efficiency is 0.8, the activity of the ^{99m}Tc source corresponding to this surface is ___Bq.

A. 5
B. 10
C. 20
D. 40
E. 100

$$N_{corr}=(N-N_{bkg})/\eta=(1000-40)/0.8=$$

$$1200\,\text{dpm}=1200/60\,\text{dps}=20\,\text{Bq}$$

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Imaging using radioactive materials: Rectilinear scanner

Electronics
PMT
Scintillator
Collimator

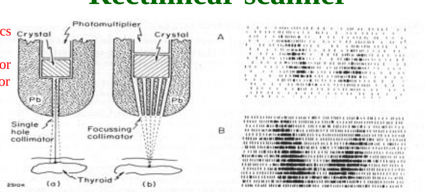
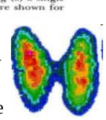


Figure 14-9. Diagram showing 2 methods of obtaining a thyroid scan using (a) a single hole collimator, and (b) a focusing collimator. Scans of normal thyroids are shown for the two types of collimators in A and B.

- Computerized Rectilinear Thyroid (CRT) scanner utilizes computer to improve the clarity of thyroid scans and enhance thyroid nodules
- Measures both thyroid function and thyroid size



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Imaging using radioactive materials: Gamma camera

Electronics
PMT
Scintillator
Collimator

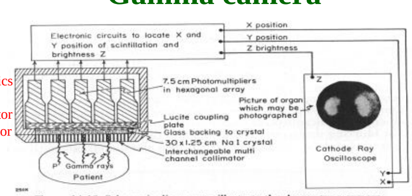

Figure 14-10. Schematic diagram to illustrate the Anger type camera.

- 2-D array of PMT's allows obtaining 3D images
- Used to observe physiological function of different organs

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Gamma camera

Image from: https://usa.healthcare.siemens.com/

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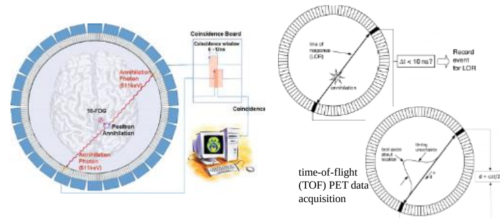
Imaging using radioactive materials: Positron emission tomography



- Requires positron-emitting isotopes, produced in cyclotrons, have short half-life. Fluorine-18 is the most common (t_h~110 min)
- Positron annihilation results in two γ-rays emitted at 180º to one another; detectors are arranged to record **coincidences**

Images from: The Physics of PET/CT scanners, R.E. Schmitz et al., Dept. of Radiology, Univ. of Washington; Cho, Zang et al. (2011). Fusion of PET and MRI for Hybrid Imaging. 10.1007/978-3-642-15816-2_2.

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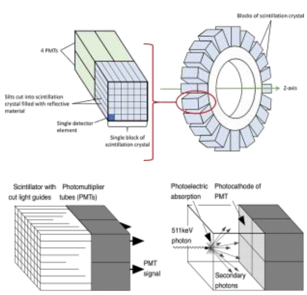
Imaging using radioactive materials: Positron emission tomography



- The incident annihilation photon (511 keV energy) interacts within scintillator producing tens of thousands visible wavelength photons (~1eV)
- Example of scintillators: of BGO = bismuth germinate, NaI(Tl) = thalium-doped sodium iodide, LSO = lutetium oxyorthosilicate, LYSO = lutetium yttrium orthosilicate, GSO = gadolinium orthosilicate

Images from: https://www.radiologycafe.com/radiology-trainees/frcr-physics-notes/pet-imaging; The Physics of PET/CT scanners, R.E. Schmitz et al., Dept. of Radiology, Univ. of Washington

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Imaging using radioactive materials: Positron emission tomography

- Regions of high metabolic activity appear dark through radioactive labeling
- In raw images lungs and skin show higher tracer uptake than muscle
- Images require attenuation correction based on patient anatomy (use CT image acquired with PET)

Images from: The Physics of PET/CT scanners, R.E. Schmitz et al., Dept. of Radiology, Univ. of Washington

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Radioactive tracers

TABLE 14-1
Important Isotopes Used in Nuclear Medicine

Z	Nuclide	Half-Life	Principle Photon Energy (MeV)
6	carbon 14	5760 y	beta emitter
15	phosphorus 32	14.3 d	beta emitter
24	chromium 51	27.7 d	0.320
27	cobalt 57	270 d	0.014, 0.122, 0.136
27	cobalt 58	70.7 d	0.811, 0.864, 1.675 plus annihilation gammas
31	gallium 67	3.24 d	0.092, 0.184, 0.299, 0.393
43	technetium 99m	6.0 h	0.141
53	iodine 123	13.0 h	0.159
53	iodine 131	8.04 d	0.284, 0.364, 0.637, 0.723
50	xenon 133	5.2 d	0.081
79	gold 198	65.0 h	0.412, 0.676, 1.088
81	thallium 201	73.0 h	0.135, 0.166

- Radioactive tags are incorporated in a variety of molecules
- Availability of short half-life isotopes (Tc-99m) allow for shorter image acquisition times, higher resolution

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Radioactive tracers

- The amount of the radioactive isotope decreases with time by two processes: biological elimination and physical decay
- The effective fraction of the isotope that disappears per unit time

$$\lambda_{eff} = \lambda_b + \lambda_p$$

- The effective half-life is

$$\frac{1}{T_{eff}} = \frac{1}{T_b} + \frac{1}{T_p} \quad \Rightarrow \quad T_{eff} = \frac{T_p \cdot T_b}{T_p + T_b}$$

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Absorbed dose from radionuclides

TABLE 14-3
Input Data for Tc-99m, Half-Life 6.03h*

(1) Transition	(2) Mean No. per Disintegration	(3) Transition Energy (MeV)	(4) Other Nuclear Data
gamma 1	.9860	.0021	E3
gamma 2	.9860	.1405	M1, $a_K = .104$, K/L conv. ratio = 7.7
gamma 3	.0140	.1426	M4, $\alpha_K = 23.0$, $\alpha_L = 9.21$

energy emitted per dis. = (.9860) (.0021) + (.9860) (.1405) + (.0140) (.1426) = .1426 MeV
= (.1426) (1.602×10^{-13} J) = $.2284 \times 10^{-13}$ J

- A committee of the Society of Nuclear Medicine called MIRD (Medical Internal Radiation Dose) has produced extensive tables for dose calculations for all the commonly used radionuclides

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Absorbed dose from radionuclides

TABLE 14-4
Output Data for Technetium 99m

(1)	(2) Mean # per Dis.	(3) Mean Energy of Particle (MeV)	Equilibrium dose constant, Δ — Total (4) g rads/μCi.h	Total (5) J/dis × 10^{-13}	Local (6) J/dis × 10^{-13}	Remote (7) J/dis × 10^{-13}
(1) Gamma 1	.0000	.0021	.0000	.0000	.0000	.0000
(1a) Int. Conv. el-M	.9860	.0016	.0035	.0026	.0026	
(2) Gamma 2	.8787	.1405	.2630	.1980		.1980
(2a) Int. Conv. el-K	.0913	.1194	.0232	.0174	.0174	
(2b) Int. Conv. el-L	.0118	.1377	.0034	.0026	.0026	
(2c) Int. Conv. el-M	.0039	.1400	.0011	.0008	.0008	
(3) Gamma 3	.0003	.1426	.0001	.0001		.0001
(3a) Int. Conv. el-K	.0088	.1215	.0022	.0016	.0016	
(3b) Int. Conv. el-L	.0035	.1398	.0010	.0007	.0007	
(3c) Int. Conv. el-M	.0011	.1422	.0003	.0002	.0002	
(3d) Fluorescent $K_{\alpha 1}$	.0441	.0183	.0017	.0013	.0013	
(3e) Fluorescent $K_{\alpha 2}$	.0221	.0182	.0008	.0006	.0006	
(3f) Fluorescent $K_{\beta 1}$	.0105	.0206	.0004	.0003	.0003	
(3g) Auger el KLL	.0152	.0154	.0005	.0004	.0004	
(3h) Auger el KLX*	.0055	.0178	.0002	.0002	.0002	
(3i) Auger el LMM	.1093	.0019	.0004	.0003	.0003	
(3j) Auger el MXY†	1.2359	.0004	.0011	.0008	.0008	
			.3029	.2279	.0298	.1981
(1)	(2)	(3)	(4)	(5)	(6)	(7)

*KLX = an Auger electron emitted from the X shell in which X stands for any shell higher than the L shell as a result of the transition of an L shell electron to a vacancy in the K shell.
†MXY = X and Y each stand for any shell higher than the M shell.

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Absorbed dose from radionuclides

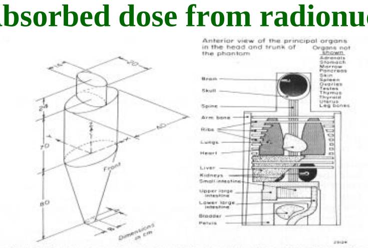

Figure 14-13. "Standard man" with internal organs developed by the MIRD committee #5 to make possible dose calculations for any organ due to the presence of radioactive material in any other organ. (Adapted from Snyder et al., S22.)

- The dose calculation involves the detailed physical information about radionuclide, biological information such as the biological half-life, as well as anatomical information concerning the shapes and sizes of different organs, and their locations

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Absorbed dose from radionuclides

TABLE 14-5
Absorbed Dose per Unit Accumulated Activity*

Isotope	Half-Life	Source	Target	rad/μCi h	Gy/Bq s
Tc-99m	6.03 h	liver	liver	4.6×10^{-5}	3.45×10^{-15}
			ovaries	4.5×10^{-7}	3.38×10^{-17}
			testes	6.2×10^{-8}	4.66×10^{-18}
			red marrow	1.6×10^{-6}	1.20×10^{-16}
		thyroid	thyroid	2.3×10^{-3}	1.73×10^{-13}
		bladder	thyroid	2.1×10^{-9}	1.58×10^{-19}
I-131	193 h	thyroid	thyroid	2.2×10^{-2}	1.65×10^{-12}

$$1\ \mathrm{g}\ \frac{\mathrm{rad}}{\mu\mathrm{Ci\ h}} = .751 \times 10^{-13}\ \frac{\mathrm{J}}{\mathrm{Bq\ s}}$$

$$1\ \frac{\mathrm{rad}}{\mu\mathrm{Ci\ h}} = .751 \times 10^{-10}\ \frac{\mathrm{Gy}}{\mathrm{Bq\ s}}$$

*Data taken from MIRD #11 (S22)

- Calculations for the "standard man" performed by Monte Carlo serve for estimates of absorbed dose

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Summary

- Radiopharmaceuticals
  - Mechanisms of localization
- Detectors for nuclear medicine
- Counting statistics
- Types of studies
- Absorbed dose from radionulides

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