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قسم الصيدلانيات والتكنولوجيا الصيدلية

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السنة الرابعة

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Radiopharmaceutics

Nuclear medicine is a multidisciplinary specialty in which medicine, physics and pharmacy are involved. The **Radiopharmacy** is an integral part of a nuclear medicine department and its prime responsibility is the **preparation of high quality radiopharmaceuticals**, the base for a high quality nuclear medicine examination.

The majority of these **radiopharmaceuticals is mainly used for diagnostic imaging**, which is the main activity of nuclear medicine.

2

Definition of a Radiopharmaceutical

- A radiopharmaceutical is a radioactive compound used for the **diagnosis** and **therapeutic treatment** of human diseases.
- In nuclear medicine nearly **95% of the radiopharmaceuticals are used for diagnostic** purposes, while the rest are used for therapeutic treatment.
- Radiopharmaceuticals usually have minimal pharmacologic effect, because in most cases they **are used in tracer quantities**.
- Therapeutic radiopharmaceuticals can cause tissue damage by radiation.

3

Radiopharmacy

- Radiopharmacy encompasses studies related to the **pharmaceutical**, **chemical**, **physical**, **biochemical**, and **biological** aspects of radiopharmaceuticals.
- Radiopharmacy comprises a rational understanding of the **design**, **preparation** and **quality control** of radiopharmaceuticals, the relationship between the physiochemical and biological properties of radiopharmaceuticals and their clinical application, as well as radiopharmaceuticals chemistry and issues related to the management, selection, **storage, dispensing,** and **proper use of radiopharmaceuticals**.

4

History

•In 1896, ***Becquerel discovered the natural radioactivity in potassium uranyl sulfate.***

•Pierre and Marie Curie, E. Rutherford, and F. Soddy all made tremendous contributions to the discovery of many other radioactive elements. The work of all these scientists has shown that ***all elements found in nature with an atomic number greater than 83 (bismuth) are radioactive.***

• **Artificial radioactivity** was first reported by I. Curie and F. Joliot in 1934. These scientists irradiated boron and aluminum targets with a particles from polonium and observed **positrons** emitted from the target even after the removal of the α-particle source.

• Around the same time, the discovery of the **cyclotron**, neutron, and deuteron by various scientists facilitated the production of many more artificial radioactivities.

• At present, more than 2700 radionuclides have been produced artificially in the cyclotron, the reactor, and the linear accelerator.

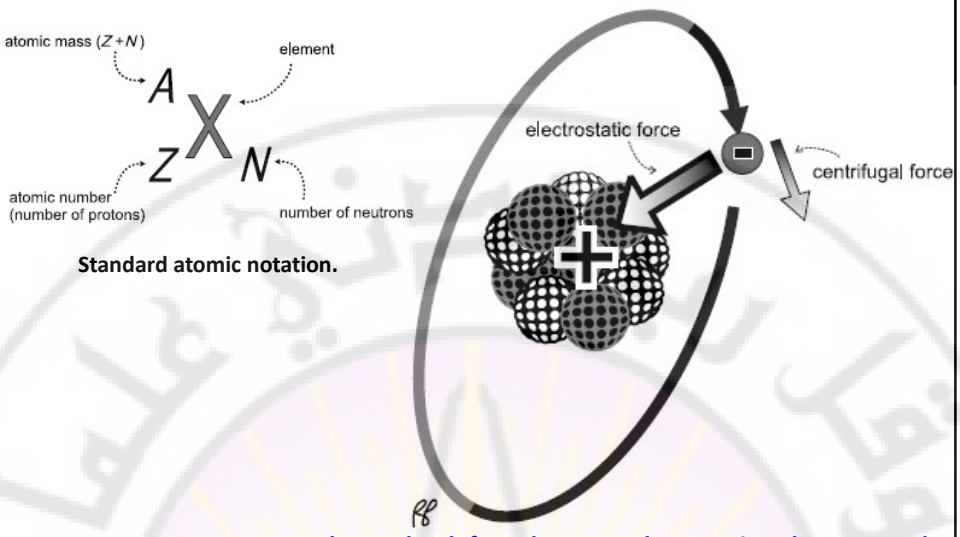
Radionuclides used in nuclear medicine are mostly artificial ones.

5

The Atom

According to Bohr's atomic theory, an atom is composed of a nucleus at the center and one or more electrons rotating around the nucleus along different energy orbits. The nucleus is primarily composed of **protons** and **neutrons**, collectively called **nucleons**. For an atom of a given element, the number of electrons moving around the nucleus equals the number of protons, balancing the electrical charge of the nucleus. **The size of an atom is of the order of 10^{-8} cm** (1 angstrom, Å) **and that of a nucleus is of the order of 10^{-13} cm (1 fermi, F).** ***The electron configuration of the atom determines the chemical properties of an element, whereas the nuclear structure characterizes the stability and radioactive decay of the nucleus of an atom.***

6



Standard atomic notation.

The Coulomb force between the negative electrons and the positive protons keeps the electron in orbit. Without this electric force the electron would fly off into space.

7

According to the quantum theory, each shell is designated by a *quantum number n*, called *the principal quantum number*, and denoted by integers, for example, 1 for the *K* shell, 2 for the *L* shell, 3 for the *M* shell, 4 for the *N* shell, and 5 for the O shell (*Table 1.1*). Each energy shell is subdivided into subshells or orbitals, which are designated as *s, p, d, f,* and so forth. For a principal quantum number n, there are n orbitals in the main shell. These orbitals are assigned *azimuthal quantum numbers l,* (or orbital angular momentum quantum number, second quantum number), which designate the electron's angular momentum and can assume numerical values of *l* = 0, 1, 2,..., n-1. Thus for the s orbital *l* = 0, the p orbital *l* = 1, the d orbital *l* = 2, and so forth.**

According to the above description, the *K* shell has one orbital, designated as 1s; the L shell has two orbitals, designated as 2s and 2p, and so forth.

8

TABLE 1.1. Electron configuration in different energy shells

Principal shell	Principal quantum number (n)	Orbital (l)	No. of electrons in each orbital $2(2l + 1)$	$2n^2$
K	1	$s(0)$	2	2
L	2	$s(0)$	2	
		$p(1)$	6	8
M	3	$s(0)$	2	
		$p(1)$	6	
		$d(2)$	10	18
N	4	$s(0)$	2	
		$p(1)$	6	
		$d(2)$	10	
		$f(3)$	14	32
O	5	$s(0)$	2	
		$p(1)$	6	
		$d(2)$	10	
		$f(3)$	14	
		$g(4)$	18	50

9

Another quantum number, the spin quantum number, s(s = -1/2 or +1/2), is assigned to each electron in order to specify its rotation about its own axis. Each orbital can accommodate a maximum of 2(2l + 1) electrons and the total number of electrons in a given shell is $2n^2$.

The electron configurations of some elements are given below:

$_{11}Na\ 1s^2 2s^2 2p^6 3s^1$

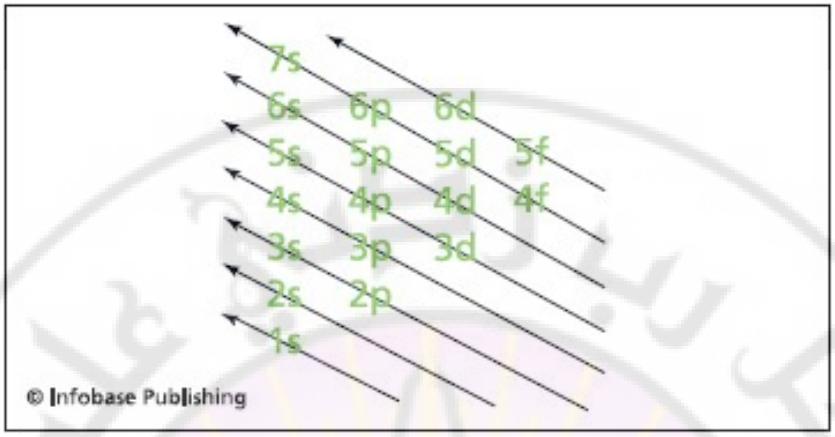
$_{18}Ar\ 1s^2 2s^2 2p^6 3s^2 3p^6$

$_{26}Fe\ 1s^2 2s^2 2p^6 3s^2 3p^6 3d^6 4s^2$

$_{43}Tc\ 1s^2 2s^2 2p^6 3s^2 3p^6 3d^{10} 4s^2 4p^6 4d^6 5s^1$

$_{49}In\ 1s^2 2s^2 2p^6 3s^2 3p^6 3d^{10} 4s^2 4p^6 4d^{10} 5s^2 5p^1$

10



The order of increasing sublevel energy can be determined by following the arrow's head to tail. Electrons fill the sublevels from low energy to high energy.

11

Structure of the Nucleus

The nucleus of an atom is composed of protons and neutrons, collectively called nucleons.

The number of *protons* in a nucleus is called the *atomic number* of the atom, denoted by *Z*. The number of *neutrons* is denoted by *N*. The total number of nucleons in a nucleus is referred to as the *mass number*, denoted by A. Thus, A is equal to Z + N.

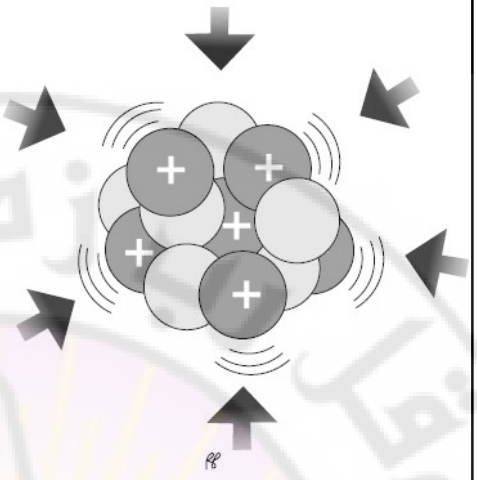
According to the **Bohr** liquid drop model, the **nucleus** is assumed to be spherical and composed of closely packed nucleons, and **particle emission by the nucleus resembles evaporation of molecules from a liquid drop.** This theory explains various phenomena, such as **nuclear density, binding energy, energetics of particle emission by radioactive nuclei, and fission of heavy nuclei.**

12

Table 1-3 The Subatomic Particles

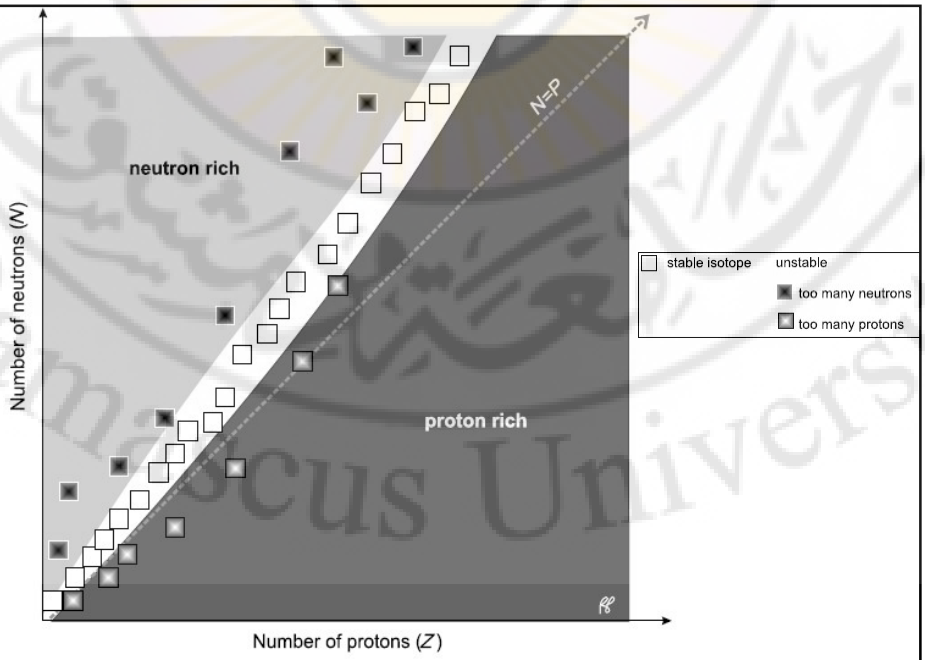
Name	Symbol	Location	Mass[a]	Charge
Neutron	N	Nucleus	1840	None
Proton	P	Nucleus	1836	Positive (+)
Electron	e^-	Shell	1	Negative (−)

[a] Relative to an electron.



Nuclear binding force is strong enough to overcome the electrical repulsion between the positively charged protons.

13



All combinations of neutrons and protons that can coexist in a stable nuclear configuration lie within the broad white band.

14

Binding Energy

The **binding energy** of an individual nucleon has a definite value depending on the shell it occupies; the average energy is approximately equal to the total binding energy divided by the number of nucleons. This energy is about 6–9 MeV and has to be supplied to remove a single nucleon from the nucleus.

Table 1.1 Mass and charge of a proton, neutron, and electron

Particle	Symbol	Charge[a]	Mass[b]	Mass (kg)	Energy (MeV)
Proton	p	+1	1.007276	1.6726×10^{-27}	938.272
Neutron	n	0	1.008665	1.6749×10^{-27}	939.573
Electron	e^-	1	0.000548	9.1093×10^{-31}	0.511

[a] Unit charge 1.6×10^{-19} coulombs
[b] Mass expressed in universal mass unit (mass of 1/12 of ^{12}C atom)
Data from Particles and Nuclei (1999)

An electron volt (eV) is the energy acquired by an electron accelerated through a potential difference of 1 V.
1 electron volt = $1{,}60217646 \times 10^{-19}$ joules

15

Nomenclature

Several nomenclatures are important and need to be mentioned here. An exact nuclear composition including the mass number A, atomic number Z, and arrangement of nucleons in the nucleus identifies a distinct species, called the nuclide نُوَيدات.
If a nuclide is unstable or radioactive, it decays (تَلاشٍ)by spontaneous fission (انْشِطار), or α-particle, β-particle, or γ-ray emission and the nuclide is termed a radionuclide. ***Nuclides of the same atomic number are called isotopes*** and exhibit the same chemical properties. Examples of oxygen isotopes are $^{15}_{8}O$, $^{16}_{8}O$, $^{17}_{8}O$, and $^{18}_{8}O$.

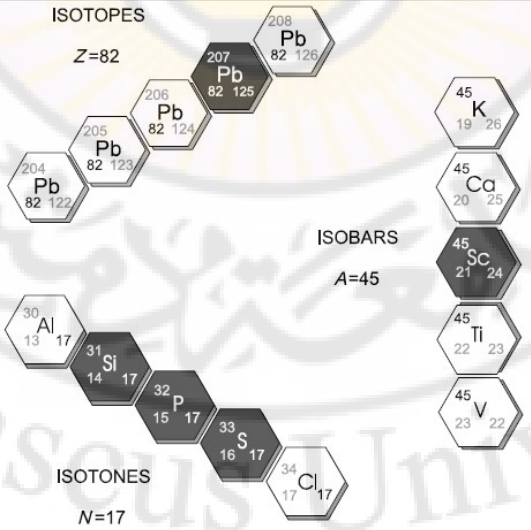
16

Nuclides having the same number of neutrons but different atomic numbers are called *isotones (مُتَسَاوِي النترونات)*. Examples are $^{59}{}_{26}Fe$, $^{60}{}_{27}Co$, $^{62}{}_{29}Cu$ each having 33 neutrons.

Isobars are nuclides with the same number of nucleons, that is, the same mass number, but a different number of protons and neutrons. For example, $^{67}{}_{29}Cu$, $^{67}{}_{30}Zn$, $^{67}{}_{31}Ga$, and $^{67}{}_{32}Ge$ are isobars having the same mass number 67.

Nuclides having the same number of protons and neutrons but *differing in energy states and spins are called isomers مُصاوِغات*. ^{99}Tc and ^{99m}Tc are isomers of the same nuclide. The lifetime of the isomeric states ranges from picoseconds to years and those *with long half-life are represented by "m"* as in ^{99m}Tc.

17

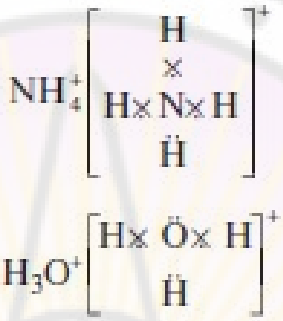


Nuclides of the same atomic number but different atomic mass are called isotopes, those of an equal number of neutrons are called isotones, and those of the same atomic mass but different atomic number are called isobars.

18

Coordinate Covalent Bond

In a coordinate covalent bond, the pair of electrons required for bond formation is donated by only one atom to another that can accommodate two electrons in octet formation. These bonds are also called semipolar bonds, because only a partial positive charge is generated on the donor atom and a partial negative charge on the acceptor atom. The following molecules are examples of coordinate covalent bonds:



19

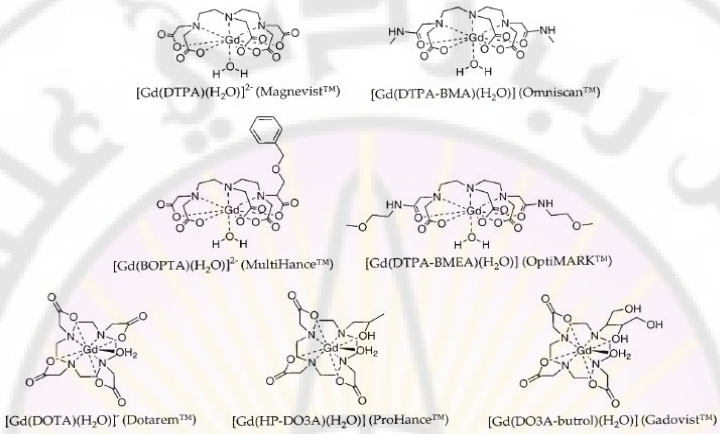
The chemical species such as NH3, –CN, –SH, –COO, –NH2, and CO are called :

Ligands (جزيء يلتحم بجزيء آخر) [لَجائِن], which may be neutral or ionic in structure. The common characteristic of the ligands is that they all possess an unshared pair of electrons that can be donated to a metal ion to form a complex. These ligands are firmly attached to the metal ion, and the number of ligands in a complex is called the coordination number of the complex. For example, Co in $[Co(NH^3)_6]^{3+}$ has the coordination number 6.

20

Chelating agents

Chelating agents are complexes, unlike simple ligands, e.g. ferrocyanide ($Fe(CN_6^{-4})$, which form complex salts by a single bond provided by a lone electron pair. **Chelating agents are capable of forming more than one bond**. For example, ethylene diamine is bidentate (two links), tripyridyl is tridentate (three) and ethylene diamine tetra-acetic acid (EDTA) is hexadentate (six), which makes it particularly effective as a pharmaceutical chelating agent.



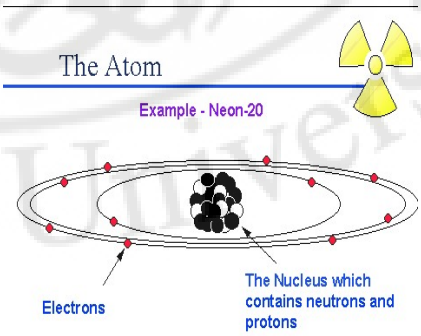
21

What is Radiation?

Invisible energy waves or particles

What is Radioactivity?

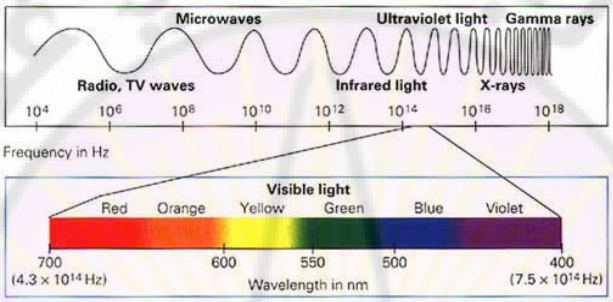
The radioactivity is the property of some atoms to spontaneously give off energy as particles or rays. The atoms that make up the radioactive materials are the source of radiation.



22

Ionizing and Non-ionizing radiation?

- **Radiation carries a range of energy forming an electromagnetic spectrum.**
- **Radiation that does not have enough energy to break chemical bonds but can vibrate atom is referred to as "Non-ionizing Radiations" e.g. radiowaves, microwaves, infrared, visible light etc.**
- **Radiation that has enough energy to break chemical bonds is referred to as 'ionizing radiation, e.g. alpha particles, beta particles, gamma rays etc.**



23

Electromagnetic waves

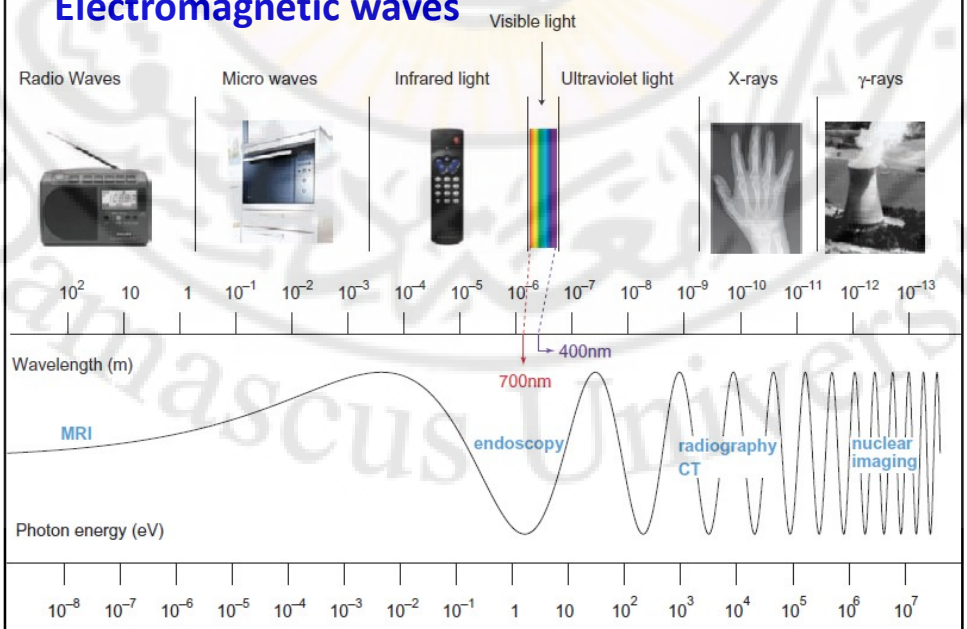


Figure 2.1 The electromagnetic spectrum.

Decay of Radionuclides

Unstable nuclei decay by spontaneous fission, α-particle, β-particle, or γ-ray emission, or electron capture (EC) in order to achieve stability. The stability of a nuclide is governed by the structural arrangement and binding energy of the nucleons in the nucleus.

Radioactive decay by particle emission or electron capture changes the atomic number of the radionuclide, whereas decay by γ-ray emission does not.

Radionuclides may decay by any one or a combination of six processes: spontaneous fission, α- decay, β decay, β + decay, electron capture, and isomeric transition (IT). In radioactive decay, particle emission or electron capture may be followed by isomeric transition. In all decay processes, the energy, mass, and charge of radionuclides must be conserved.

25

Spontaneous Fission

Fission is a process in which a heavy nucleus breaks down into two fragments typically in the ratio of 60:40. This process is accompanied by the emission of two or three neutrons with a mean energy of 1.5 MeV and a release of nearly 200 MeV energy, which appears mostly as heat.

Fission in heavy nuclei can occur spontaneously or by bombardment with energetic particles. The probability of spontaneous fission is low and increases with mass number of the heavy nuclei. The half-life for spontaneous fission is $2x10^{17}$ years for ^{235}U and only 55 days for ^{254}Cf. It should be noted that spontaneous fission is an alternative to α decay or γ emission.

26

Fission or (n, f) Reaction

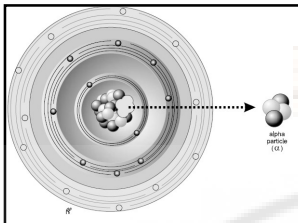
Fission is a breakup of a heavy nucleus into two fragments of approximately equal mass. When a target of heavy elements is inserted in the reactor core, heavy nuclei absorb thermal neutrons and undergo fission. Fissionable heavy elements are ^{235}U, ^{239}Pu, ^{237}Np, ^{233}U, ^{232}Th, and many others having atomic numbers greater than 90. Fission of heavy elements may also be induced in a cyclotron by irradiation with highenergy charged particles.

27

Fission or (n, f) Reaction

$$
\begin{aligned}
{}^{235}_{92}U + {}^{1}_{0}n \rightarrow {}^{236}_{92}U &\rightarrow {}^{131}_{53}I + {}^{102}_{39}Y + 3{}^{1}_{0}n \\
&\rightarrow {}^{99}_{42}Mo + {}^{135}_{50}Sn + 2{}^{1}_{0}n \\
&\rightarrow {}^{117}_{46}Pd + {}^{117}_{46}Pd + 2{}^{1}_{0}n \\
&\rightarrow {}^{133}_{54}Xe + {}^{101}_{38}Sr + 2{}^{1}_{0}n \\
&\rightarrow {}^{137}_{55}Cs + {}^{97}_{37}Rb + 2{}^{1}_{0}n \\
&\rightarrow {}^{155}_{62}Sm + {}^{78}_{30}Zn + 3{}^{1}_{0}n \\
&\rightarrow {}^{156}_{62}Sm + {}^{77}_{30}Zn + 3{}^{1}_{0}n
\end{aligned}
$$

28



$$^{235}_{92}U \rightarrow ^{231}_{90}Th + ^{4}_{2}\alpha^{2+}$$

Alpha (α) Decay

Usually heavy nuclei such as radon, uranium, neptunium, and so forth decay by α-particle emission. The α particle is a helium ion with two electrons stripped off the atom and contains two protons and two neutrons bound together in the nucleus. In a decay, the atomic number of the parent nuclide is therefore reduced by 2 and the mass number by 4. An example of a decay is $^{235}_{92}U \rightarrow ^{231}_{90}Th + ^{4}_{2}\alpha^{2+}$

An α transition may be followed by β emission or γ-ray emission or both.

The a particles are mono energetic, and their range in matter is very short (on the order of 10^{-6} cm) and is approximately 0.03 mm in body tissue.

29

A. Radioactive Decay

Types of Radioactive Decay

- Alpha-particle production
- Alpha particle – helium nucleus
  - Examples $^{235}_{92}U \rightarrow ^{231}_{90}Th + ^{4}_{2}\alpha^{2+}$

$$^{222}_{88}Ra \rightarrow ^{4}_{2}He + ^{218}_{86}Rn$$

$$^{230}_{90}Th \rightarrow ^{4}_{2}He + ^{226}_{88}Ra$$

- Net effect is loss of 4 in mass number and loss of 2 in atomic number.

30

Beta (β) Decay

When a nucleus is "neutron rich" (i.e., has a higher N/Z ratio compared to the stable nucleus), it decays by β particle emission along with an antineutrino. An *antineutrino* (ν) is an entity almost without mass and charge and is primarily needed to conserve energy in the decay. In **β decay, a neutron (n) essentially decays into a proton (p) and a β particle**; for example,

n → p + β+ ν

The β particle is emitted with variable energy from zero up to the decay energy. *The decay or transition energy is the difference in energy between the parent and daughter nuclides.* An antineutrino carries away the difference between the β particle energy and the decay energy. The β decay may be followed by γ-ray emission, if the daughter nuclide is in an excited state and the number of γ rays emitted depends on the excitation energy. After β decay, the atomic number of the daughter nuclide is one more than that of the parent nuclide; however, the mass number remains the same for both nuclides.

A. Radioactive Decay

Types of Radioactive Decay

- Beta-particle production

- Beta particle – electron
  - Examples

$$n \rightarrow p + \beta + \nu$$

$$^{131}_{53}I \rightarrow ^{131}_{54}Xe + \beta + \nu$$

$$^{59}_{26}Fe \rightarrow ^{59}_{27}Co + \beta + \nu$$

$$^{99}_{42}Mo \rightarrow ^{99m}_{43}Tc + \beta + \nu$$

$$^{60}_{27}Co \rightarrow ^{60}_{28}Ni + \beta + \nu$$

- Net effect is to change a neutron to a proton.

$$^{14}_{6}C \rightarrow ^{14}_{7}N + ^{0}_{-1}e$$

32

A. Radioactive Decay

Types of Radioactive Decay

- Gamma ray release
- Gamma ray – high energy photon
  - Examples

$$^{238}_{92}U \rightarrow {}^{4}_{2}He + {}^{234}_{90}Th + 2{}^{0}_{0}\gamma$$

- Net effect is no change in mass number or atomic number.

33

Positron or β+ Decay

Nuclei that are "neutron deficient" or "proton rich" (i.e., have an N/Z ratio less than that of the stable nuclei) can decay by β^+ particle emission accompanied by the emission of a neutrino (v), which is an opposite entity of the antineutrino.

$$^{64}_{29}Cu \rightarrow {}^{64}_{28}Ni + \beta^+ + \nu$$

$$^{18}_{9}F \rightarrow {}^{18}_{8}O + \beta^+ + \nu$$

$$^{15}_{8}O \rightarrow {}^{15}_{7}N + \beta^+ + \nu$$

$$^{52}_{26}Fe \rightarrow {}^{52}_{25}Mn + \beta^+ + \nu$$

34

Positron or β+ Decay

- After β+-particle emission, the daughter nuclide has an atomic number that is 1 less than that of the parent. The range of positrons is short in matter. At the end of the path of β+ particles, positrons combine with electrons and are thus **annihilated**, each event giving rise to **two photons of 511 keV that are emitted in opposite directions.** These photons are referred to as **annihilation radiations**.

35

Electron Capture

When a nucleus has a smaller N/Z ratio compared to the stable nucleus, as an alternative to β+ decay, it may also decay by the so-called electron capture process, in which an electron is captured from the extranuclear electron shells, thus transforming a proton into a neutron and emitting a neutrino.

$$^{67}_{31}\mathrm{Ga} + \mathrm{e} \rightarrow {}^{67}_{30}\mathrm{Zn} + \nu$$

$$^{111}_{49}\mathrm{In} + \mathrm{e} \rightarrow {}^{111}_{48}\mathrm{Cd} + \nu$$

$$^{57}_{27}\mathrm{Co} + \mathrm{e} \rightarrow {}^{57}_{26}\mathrm{Fe} + \nu$$

$$^{201}_{80}\mathrm{Hg} + {}^{0}_{-1}\mathrm{e} \rightarrow {}^{201}_{79}\mathrm{Au} + {}^{0}_{0}\gamma$$

↑
Inner-orbital electron

36

A. Radioactive Decay

Table 19.1

Various Types of Radioactive Processes

Process	Example
β-particle (electron) production	${}^{227}_{89}Ac \rightarrow {}^{227}_{90}Th + {}^{0}_{-1}e$
positron production	${}^{13}_{7}N \rightarrow {}^{13}_{6}C + {}^{0}_{1}e$
electron capture	${}^{73}_{33}As + {}^{0}_{-1}e \rightarrow {}^{73}_{32}Ge$
α-particle production	${}^{210}_{84}Po \rightarrow {}^{206}_{82}Pb + {}^{4}_{2}He$
γ-ray production	excited nucleus → ground-state nucleus + ${}^{0}_{0}\gamma$ (excess energy → lower energy)

37

Units of Radioactivity

Radioactivity is expressed in units called curies. Historically, it was initially defined as the disintegration rate of 1 g radium, which was considered to be 3.7 x 10^{10} disintegrations per second.

$$1 \text{ curie (Ci)} = 3.7 \times 10^{10} \text{ disintegrations per second (dps)}$$
$$= 2.22 \times 10^{12} \text{ disintegrations per minute (dpm)}$$

The System Internationale (SI) unit for radioactivity is becquerel (Bq), which is defined as one disintegration per second. Thus,

$$1 \text{ becquerel (Bq)} = 1 \text{ dps} = 2.7 \times 10^{-11} \text{ Ci}$$
$$1 \text{ kilobecquerel (kBq)} = 10^{3} \text{ dps} = 2.7 \times 10^{-8} \text{ Ci}$$
$$1 \text{ megabecquerel (MBq)} = 10^{6} \text{ dps} = 2.7 \times 10^{-5} \text{ Ci}$$
$$1 \text{ gigabecquerel (GBq)} = 10^{9} \text{ dps} = 2.7 \times 10^{-2} \text{ Ci}$$
$$1 \text{ terabecquerel (TBq)} = 10^{12} \text{ dps} = 27 \text{ Ci}$$

38

Radioactive decay:

- **Half life** — symbol $t_{1/2}$ — **The time in which a given quantity of a radionuclide decays to half its initial value is termed the half-life ($T_{1/2}$).**

- *The rate of decay can be described by:*

$$N = N_o e^{-\lambda t}$$

where N is the number of atoms at elapsed time t الوقتُ المُسْتَغْرَق, N_o is the number of atoms when t = 0, and λ is the disintegration constant characteristic of each individual radionuclide.

$$T_{1/2} = 0.693 / \lambda$$

The intensity of radiation can be described by:

$$I = I_0 e^{-0.693/T1/2}$$

39

Radiation Units

There are three basic units related to radiation: the **roentgen (R)** for exposure, the **rad (radiation absorbed dose)** for absorbed dose, and the **rem (roentgen equivalent man)** for dose equivalent.

- The roentgen is the amount of x or γ radiation that produces ionization of one electrostatic unit of either positive or negative charge per cubic centimeter of air at 0°C and 760 mmHg (STP).

$$1\,R = 2.58 \times 10^{-4}\,C/kg$$

C : coulomb

40

- the roentgen applies only to air and to x or γ radiations.
- the R unit is applicable only to photons of less than 3 MeV energy.
- The rad is a more universal unit. It is a measure of the energy deposited in unit mass of any material by any type of radiation.

41

$$1 \text{ rad} = 100 \text{ ergs/g absorber}$$

Since 1 joule (J) $= 10^7$ ergs,

$$1 \text{ rad} = 10^{-2} \text{ J/kg}$$

In SI units, the gray (Gy) is the unit of radiation absorbed dose

$$1 \text{ gray (Gy)} = 100 \text{ rad}$$
$$= 1 \text{ J/kg absorber}$$

It can be shown that the energy absorbed per kilogram of air due to an exposure

$$1 \text{ R} = 86.9 \times 10^{-4} \text{ J/kg in air}$$

Therefore, $1 \text{ R} = 0.869 \text{ rad in air}$

42

The dose equivalent unit, Hr, in rem, has been developed to account for the differences in effectiveness of different radiations in causing biological damage. In radiobiology, the dose equival $H_r\,(\text{rem}) = \text{rad} \times (\text{RBE})_r$ **radiation is defined as :**

where (RBE) is the relative biological effectiveness of the radiation.

In SI units, the dose equivalent Hr is expressed in sievert (Sv), which $1\ \text{sievert (Sv)} = 100\,\text{rem}$

43

Type of radiation	QF
X rays, γ rays, β particles	1.0
Neutrons and protons	10.0
α particles	20.0
Heavy ions	20.0

relative biological effectiveness of the radiation = **Quality factors for different radiations.**

44

Radioactive decay:

- **Half life** — symbol $t_{1/2}$ — **The time in which a given quantity of a radionuclide decays to half its initial value is termed the half-life ($T_{1/2}$).**

- *The rate of decay can be described by:*

$$N = N_o e^{-\lambda t}$$

where N is the number of atoms at elapsed time t الوقتُ المُسْتَغْرَق, N_o is the number of atoms when t = 0, and λ is the disintegration constant characteristic of each individual radionuclide.

$$T_{1/2} = 0.693 / \lambda$$

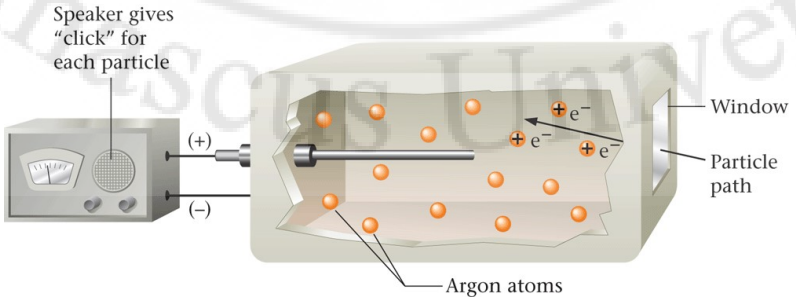
The intensity of radiation can be described by:

$$I = I_0 e^{-0.693/T1/2}$$

45

Detection of Radioactivity and the Concept of Half-life

- Geiger-Muller counter – instrument which measures radioactive decay by registering the ions and electrons produced as a radioactive particle passes through a gas-filled chamber



46

Detection of Radioactivity and the Concept of Half-life

- Scintillation counter – instrument which measures the rate of radioactive decay by sensing flashes of light that the radiation produces in the detector

47

Type of radiation	QF
X rays, γ rays, β particles	1.0
Neutrons and protons	10.0
α particles	20.0
Heavy ions	20.0

Quality factors for different radiations.

48

Ideal characteristics of a radiopharmaceutical

- Half-life should be similar to the length of the test
- The radionuclide should emit gamma rays and there should be no charged particle emissions
- The energy of the gamma rays should be between 50 and 300 keV
- The radionuclide should be chemically suitable for incorporating into a pharmaceutical without altering its biological behavior
- The radionuclide should be readily available at the hospital site
- The pharmaceutical should localize only in the area of interest
- The pharmaceutical should be eliminated from the body with a half-life similar to the duration of the examination
- The radiopharmaceutical should be simple to prepare

49

The practical ways of producing radionuclides for use in, or as radiopharmaceutical preparations are:

— neutron bombardment of target materials (generally in nuclear reactors),

— charged particles bombardment of target materials (in accelerators such as cyclotrons),

— nuclear fission of heavy nuclides of target materials (generally after neutron or particle bombardment),

— from a radionuclide generator.

50

Production of radionuclides:

1- Charged particle bombardment

Radionuclides may be produced by bombarding target materials with charged particles in ***particle accelarators such as cyclotrons.***

- A cyclotron consists of :

Two flat hollow objects called dees.

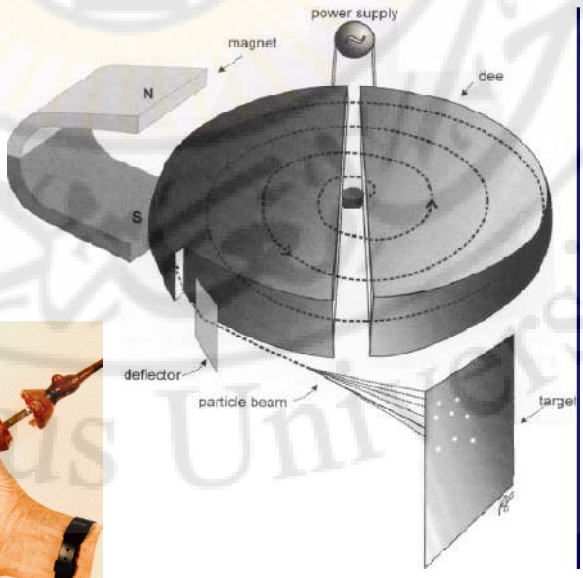
The dees are part of an electrical circuit.

On the other side of the dees are large magnets that (drive) steer the injected charged particles (protons, deutrons, alpha and helium) in a circular path

The charged particle follows a circular path until the particle has sufficient energy that it passes out of the field and interact with the target nucleus.

51

Cyclotron



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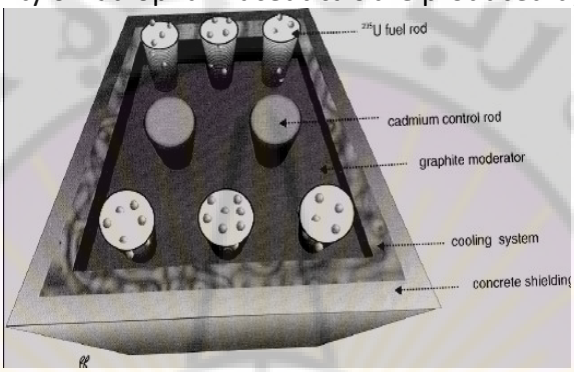
Production of radionuclides:

2- Neutron bombardment

Radionuclides may be produced by bombarding target materials with neutrons in nuclear reactors

- The majority of radiopharmaceuticals are produced by this process



53

Production of radionuclides: :

3- Radionuclide generator systems

- *Principle:*

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.

Example:

- technetium-99m, obtained from a generator constructed of molybdenum-99 absorbed to an alumina column.

Eluted from the column with normal saline

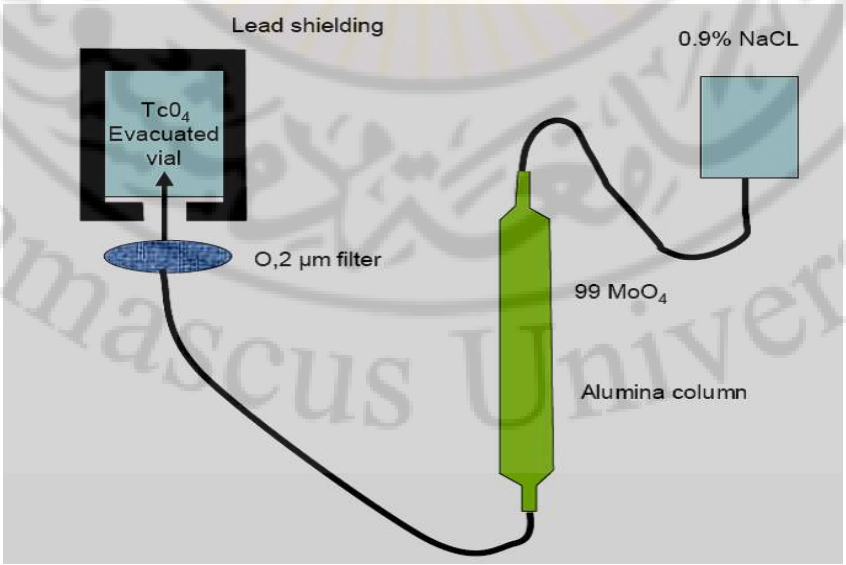
54

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

- *Parent*: ^{99}Mo as molybdate $^{99}MoO_4^{-2}$.
- *Half-life*: 67 hr.
- *Decays by* β^- - emission, gamma: 740, 780 keV.
- High affinity to alumina compared to ^{99m}Tc .
- *Daughter:* ^{99m}Tc as pertechnetate ($^{99m}Tc\ O_4^{-1}$).
- Adsorbent Material: Alumina (aluminum oxide, Al_2O_3)
- *Eluent*: saline (0.9% NaCl)
- *Eluate:* ($^{99m}Tc\ O_4^{-1}$).

55

99Mo/99mTc Generator



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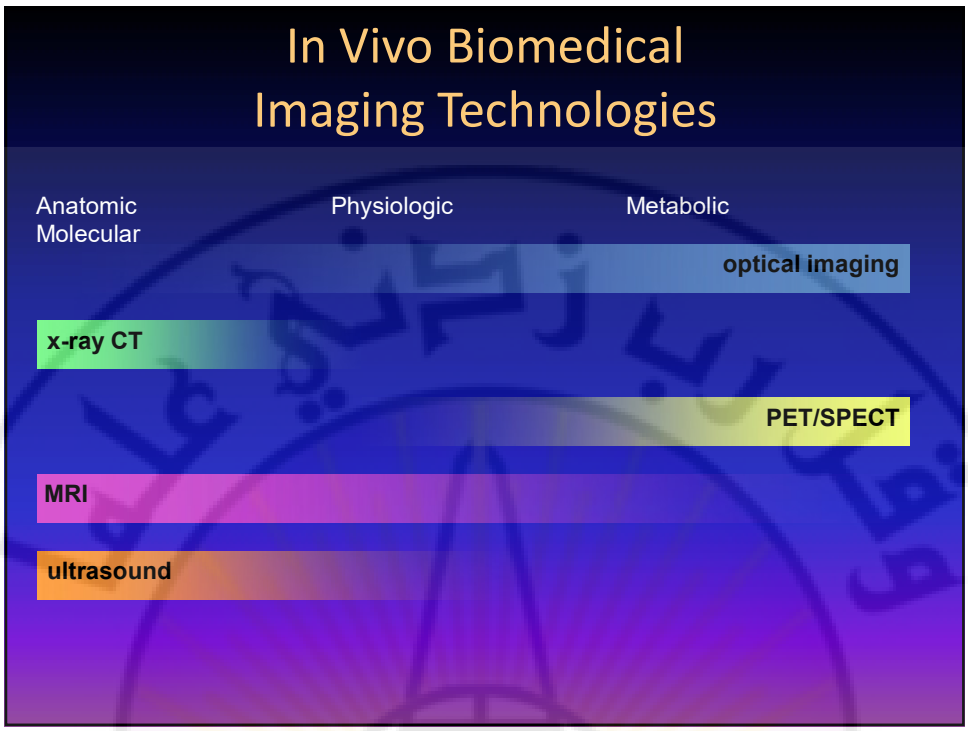


IMAGING MODALITIES

Biomedical imaging measures the interactions of electromagnetic waves with the body or the emission of electromagnetic waves from the body. These imaging modalities utilize the physical characteristics of the waves across the electromagnetic spectrum. Covering the range from low-frequency to high-frequency electromagnetic waves, ultrasound imaging, MRI, optical imaging, X-ray radiography and X-ray CT, γ-scintigraphy, SPECT, and PET are routinely used for preclinical and clinical studies

58

IMAGING MODALITIES

Table 1 Imaging Modalities Available for Preclinical and Clinical Studies

Modality	Energy level	Image generation	Application
Ultrasound	1–10 MHz	Sound echo	Anatomic, functional, and molecular imaging
MRI	42.6/T MHz	Proton relaxation	Anatomic, functional, and molecular imaging
Optical imaging	3.5–4.5 × 10^8 MHz	Fluorescence luminescence	Anatomic, functional, and molecular imaging
X-ray CT	3 × 10^{11} MHz	X-ray attenuation	Anatomic and functional imaging
SPECT	100–200 keV	γ-Ray emission	Functional and molecular imaging
PET	511 keV	Positron annihilation	Functional and molecular imaging

Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography; SPECT, single-photon emission computed tomography; PET, positron-emission tomography.

59

Electromagnetic waves

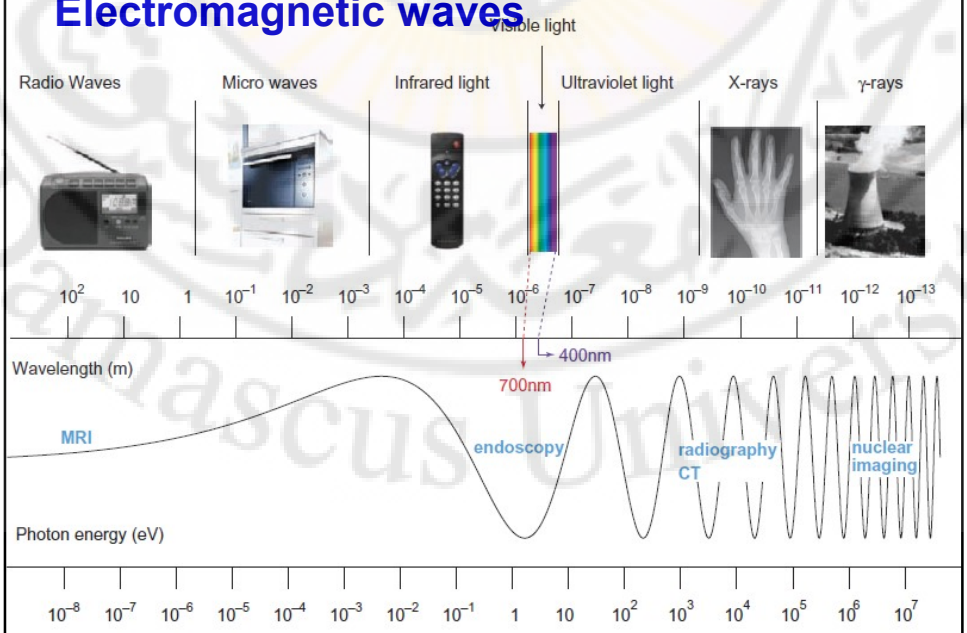


Figure 2.1 The electromagnetic spectrum.

Ultrasound Imaging

Ultrasound imaging or sonography measures the interaction of high-frequency sound waves (1–10 MHz) with the body. Sound waves travel fast in solids and liquids, are slow in gas, and have no progression in vacuum. When sound waves are applied to a living subject through a transducer, they are reflected at the interface of tissues or organs of different densities and recorded in the transducer تَرْجام. Stronger signals are generated in the tissues with greater density differences. Images are constructed on the basis of echoes, attenuation of the sound, and sound speed.

61

Ultrasound Imaging

Advanced ultrasound imaging technologies, for example, Doppler imaging technology, can provide real-time two-dimensional and three-dimensional images. The real-time blood flow can also be visualized with ultrasound in high resolution.

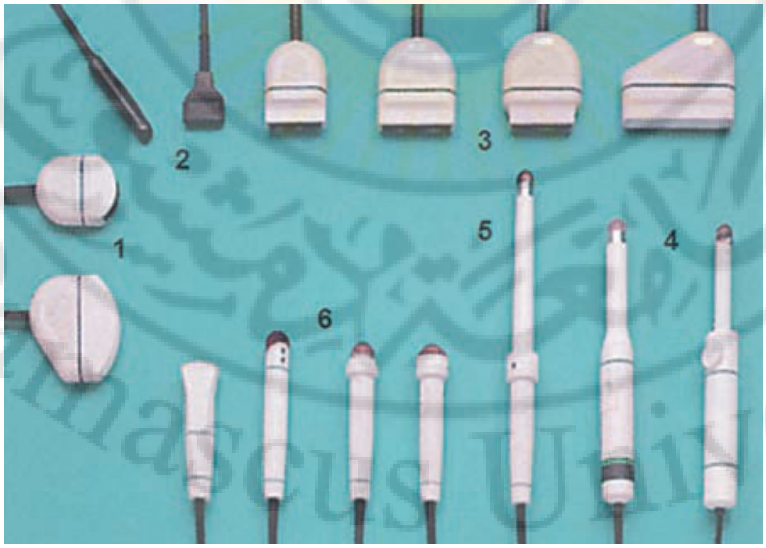
Microbubbles, microspheres filled with gas or low-density liquid, are used as contrast agents for ultrasound imaging to enhance echo differences between tissue types for more accurate diagnostic imaging, These contrast agents are based on the fact that gas is resistant to sound propagation, resulting in strong echoes.

62

Substance	c (m/s)	$Z = \rho c$ (10^6 kg/m^2 s)
Air (25° C)	346	0.000410
Fat	1450	1.38
Water (25° C)	1493	1.48
Soft tissue	1540	1.63
Liver	1550	1.64
Blood (37° C)	1570	1.67
Bone	4000	3.8 to 7.4
Aluminum	6320	17.0

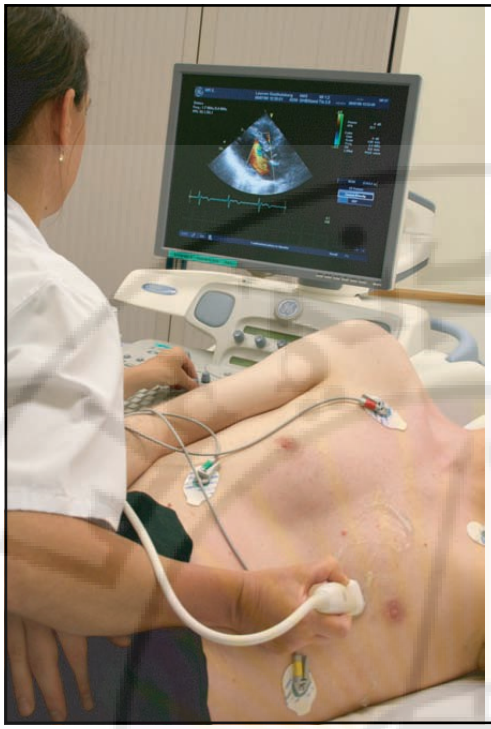
Values of the acoustic wave velocity *c and* acoustic impedance *Z of some substances*

63



The shape of the transducer is adapted to the application: (1) abdominal transducers – general purpose; (2) intraoperative transducers; (3) small parts transducers (muscles, tendons, skin, thyroid, breast, scrotum); (4) intrarectal transducer (rectal wall, prostate); (5) intravaginal transducer (uterus, ovaries, pregnancy); (6) infants (abdominal, brain).

64



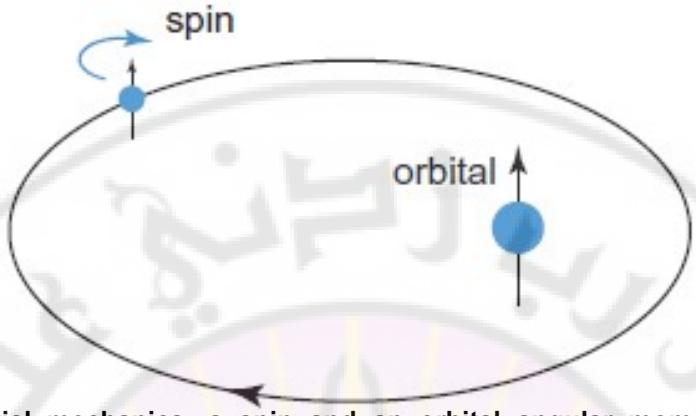
Example of a commercial echocaradiographic scanner.

65

Magnetic Resonance Imaging

MRI uses a powerful magnet and radio waves to produce detailed images of the body's organs and structures. MRI measures the longitudinal (T1) and transverse (T2) relaxation rates of protons (mainly water protons) in the body. Water forms more than 60% of the body weight of a normal human adult. Water protons have magnetic moments with random orientations. When placed in a strong magnetic field, the proton magnetic moments align either along or against the static magnetic field (B_0) and create a net magnetization pointing in the direction of the

Magnetic resonance imaging



In celestial mechanics, a spin and an orbital angular momentum are associated with the Earth's motion about the Sun. In the classical theory, electron and nucleus replace Earth and Sun, respectively. Because the electron is a charged particle, it also has a magnetic moment. Unfortunately, the classical model is incorrect: spin of elementary particles has no classical analog.

67

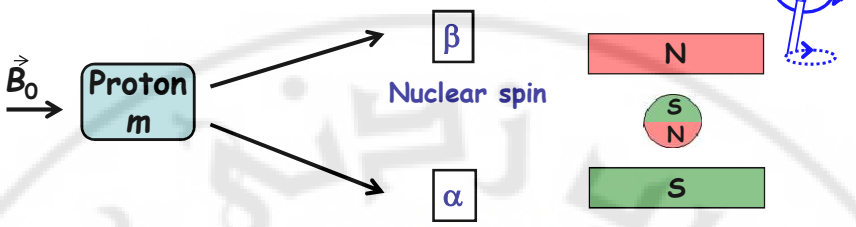
Spin values of several nuclei of biomedical interest.

A given nucleus is characterized by a unique spin value. Note that the biomedically important nuclei ^{12}C and ^{16}O have no spin and thus no NMR sensitivity.

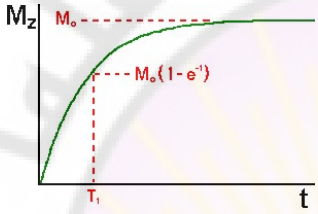
Nucleus	Spin	$\frac{\gamma}{2\pi}$ (MHz/T)
$^{1}_{1}H$	$\frac{1}{2}$	42.57
$^{2}_{1}H$	1	6.54
$^{12}_{6}C$	0	
$^{13}_{6}C$	$\frac{1}{2}$	10.71
$^{14}_{7}N$	1	3.08
$^{15}_{7}N$	$\frac{1}{2}$	−4.31
$^{16}_{8}O$	0	
$^{17}_{8}O$	$\frac{5}{2}$	−5.77
$^{31}_{15}P$	$\frac{1}{2}$	17.23
$^{33}_{16}S$	$\frac{3}{2}$	3.27
$^{43}_{21}Ca$	$\frac{7}{2}$	−2.86

68

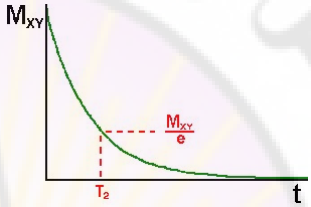
Magnetic Resonance Imaging



Relaxation → return of the excited nucleus to their ground states



Longitudinale Relaxation (spin-lattice, T_1)
(↑ of the signal)



Transvers Relaxation (spin-spin, T_2)
(↓ of the signal)

http://www.cis.rit.edu/htbooks/mri/inside.htm

69

Magnetic Resonance Imaging

The magnetization magnitude is proportional to the external magnetic field strength. When a radiofrequency (RF) pulse is applied to create an oscillating electromagnetic field (B1) perpendicular to the main field, the protons absorb energy and the net magnetization is tipped away from the static magnetic field. The second magnetic field oscillates at the Larmor frequency, that is, the proton resonance frequency (42.58 MHz/T). Immediately after the RF pulse, the magnetization returns to its equilibrium state, or ground state, due to longitudinal (T1) and transverse (T2) relaxation processes.

70

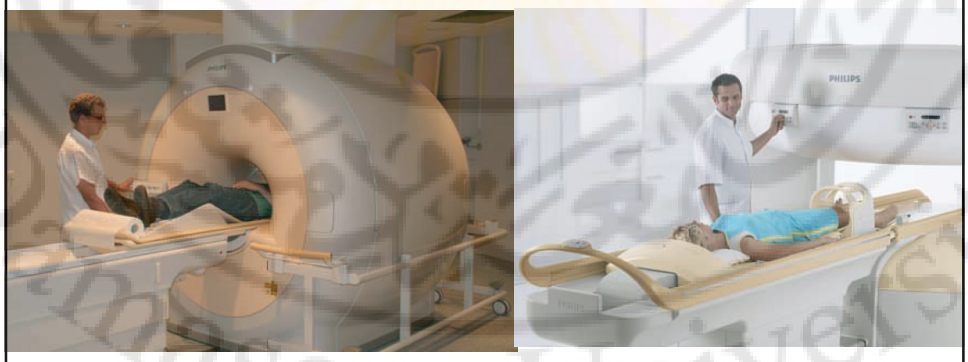
Magnetic Resonance Imaging

The longitudinal relaxation, or **spin-lattice** relaxation, involves the return of protons from the high-energy state to the equilibrium state by dissipating their excess energy to their surroundings. The transverse relaxation, or spin-spin relaxation, involves energy transfer from proton to proton. The decaying magnetization induces a voltage in a tuned detector coil to generate nuclear magnetic resonance (NMR) signal. Three-dimensional images are constructed from the signals of the proton relaxation in different tissues. Image contrast between tissues is the result of differences of proton density, relaxation rates, and flow and diffusion properties.

Paramagnetic materials, including paramagnetic metal ion chelates and nanoparticles, have been developed as contrast agents for MRI to enhance the image contrast in the tissue

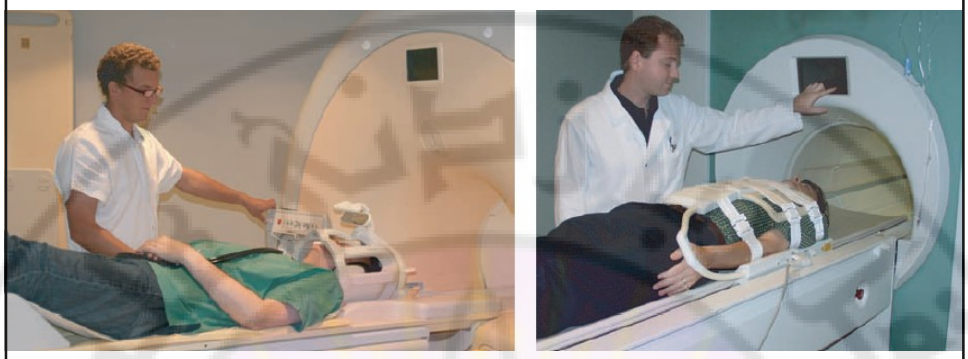
71

MRI



(a) Whole-body 3 T scanner, (b) C-shaped 1.5 T open MR system with vertical magnetic field.

72



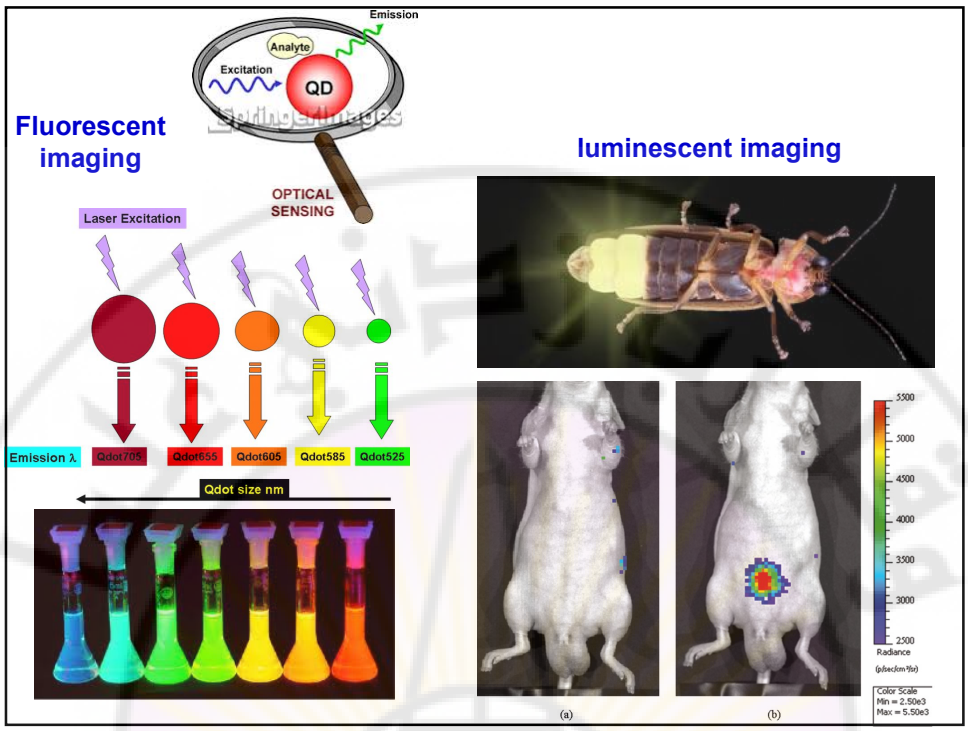
(a) Head coil and (b) body coil, used to detect optimally the RF signals received from the surrounded body part.

73

Optical Imaging

Optical microscopy has been broadly used for in vitro study of tissue samples and cells with high spatial resolution. Optical imaging for in vivo studies largely depends on the depth of light penetration into tissues, which is inversely proportional to the light wavelengths. Visible and infrared light can be absorbed by water, proteins, and lipids in the tissues, which limits imaging of deep tissues. Fluorescent and luminescent imaging techniques are the popular optical imaging methods for in vivo imaging. Fluorescent imaging requires excitation of a fluorochrome with an external light source to emit fluorescence of a longer wavelength. Luminescence imaging measures light emission from a chemical or biochemical reaction without excitation from an external source. Near-infrared (NIR) light (650–900 nm) has relatively low tissue absorption and is commonly used for in vivo imaging. Tissue penetration of NIR can be as deep as a few centimeters. Recently, a new optical imaging technique, fluorescence resonance energy transfer (FRET), using activatable imaging probes has also been developed for in vivo imaging

74



X-Ray Radiography and Computed Tomography

X rays are a form of electromagnetic radiation of higher energy (λ≈ 0.01 nm), which pass through the body and can be recorded in the opposite side of the body. X-ray images are constructed as two-dimensional projection from differential attenuation of X rays by the body tissues through which they pass. Attenuation is a process by which X rays are removed from the beam through absorption and scattering. *X-ray attenuation is efficient in dense tissue (such as bone) and less in soft tissues.* As a result, bone appears white, air black, and other tissues gray, depending on tissue density in the body. X-ray radiography is commonly used in the imaging of chest, dental structure, bone, neck, skull, abdomen, spine, etc.

76

X-Ray Radiography and Computed Tomography

X-ray CT provides three-dimensional images of the body with high spatial resolution. In CT imaging, X-ray sources and detectors rotate together around the body, and projections are collected from different angles. The computer processes the data to create two-dimensional and three-dimensional images. X-ray CT gives high resolution anatomical images of air, soft tissues, and bones in the body but has a low sensitivity for molecular imaging. A major disadvantage of X-ray imaging and CT is the ionization of X rays. It has been reported that exposure to high-dose X rays increases the risk of cancer.

Biologically inert substances containing elements of high atomic weights are effective to attenuate X rays and are used as contrast agents for CT. The electrons of these elements have a high probability to interact with incident photons, resulting in substantial attenuation and bright image contrast enhancement. Water-soluble iodinated benzene derivatives are commonly used as CT contrast agents. High doses of these contrast agents are often required to produce good contrast enhancement.

77

Figure 1. An engraving of Wilhelm Conrad Roentgen, published in 1896, less than a year after his discovery. From E. Trevert, *Something about X-Rays for Everyone* (1896; reprint, Madison, Wis.: Medical Physics Publishing Company, 1988). Shortly after this engraving was published, one visitor described Roentgen as "a very tall man, with a scholarly stoop, his face somewhat pockmarked, stern but kindly, and very modest in his remarks upon his achievements." Quoted in R. E. Mould, *A Century of X-Rays and Radioactivity in Medicine* (London: Institute of Physics Publishing, 1993), 2.

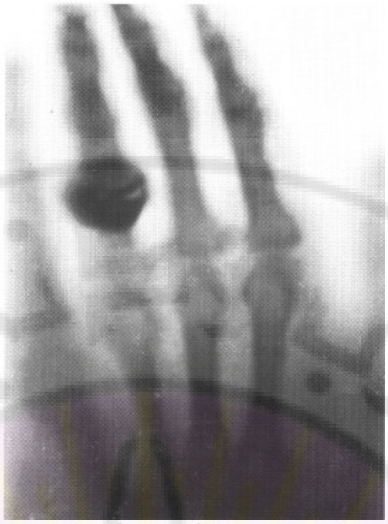
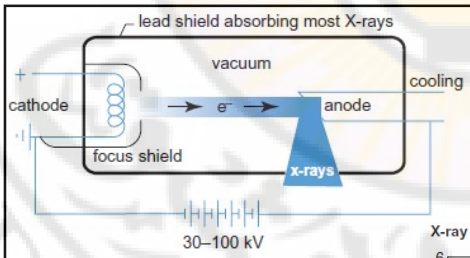
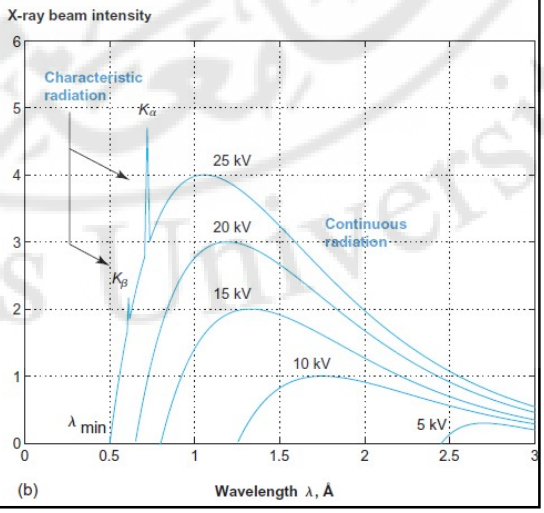


Figure 2. The earliest extant X-ray record, taken by Roentgen on December 22, 1895, of his wife's hand and signet ring. Courtesy of the Deutsches Roentgen-Museum, Remscheid-Lennep, Germany.

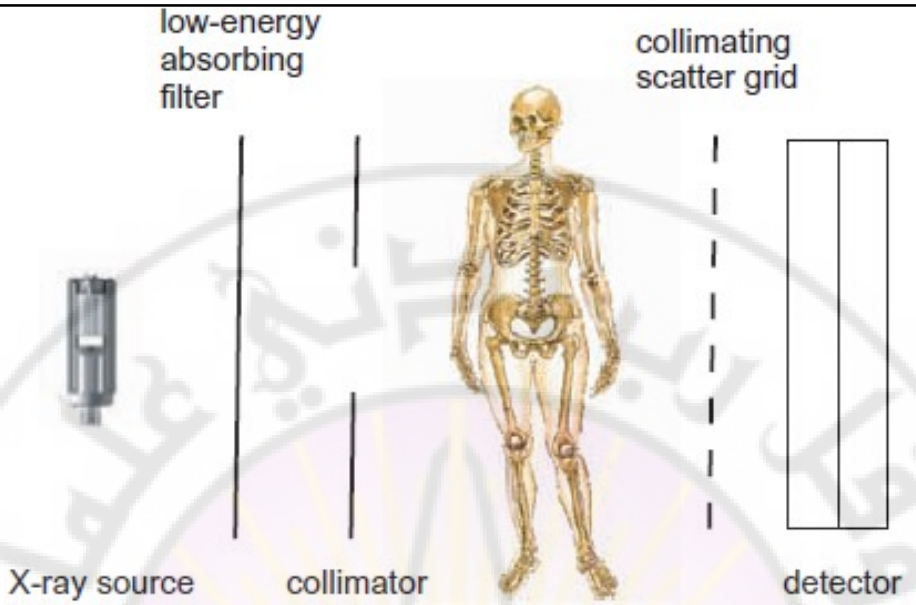


Scheme of an X-ray tube.



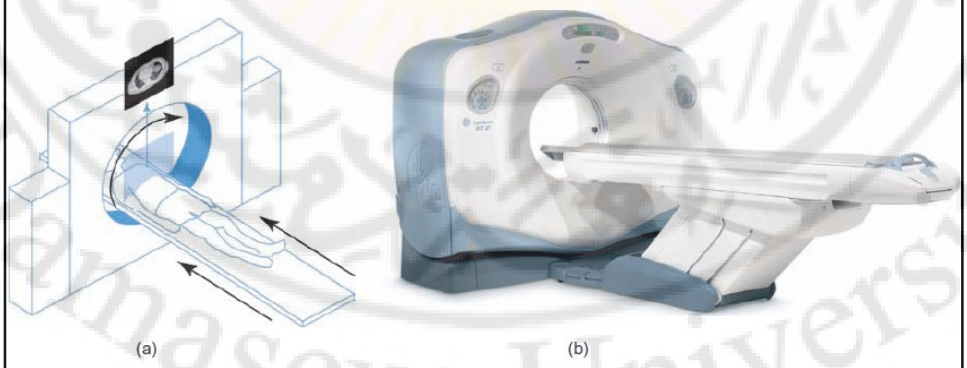
(b) Intensity distribution in the Röntgen spectrum of molybdenum for different voltages. The excitation potential of the K-series is 20.1 kV. This series appears as characteristic peaks in the 25 kV curve. The peaks *Kα and Kβ are due to* L-shell and M-shell drops respectively.

80



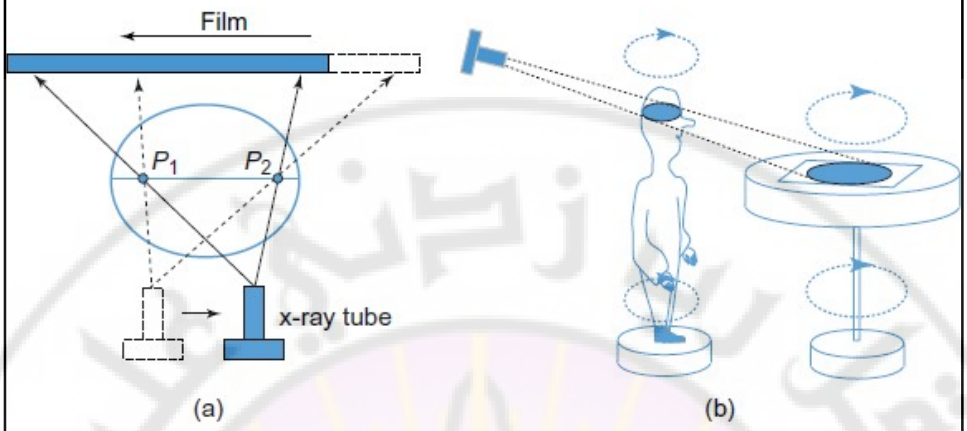
Schematic representation of the radiographic imaging chain.

81



(a) Schematic representation, and (b) photograph of a CT scanner.

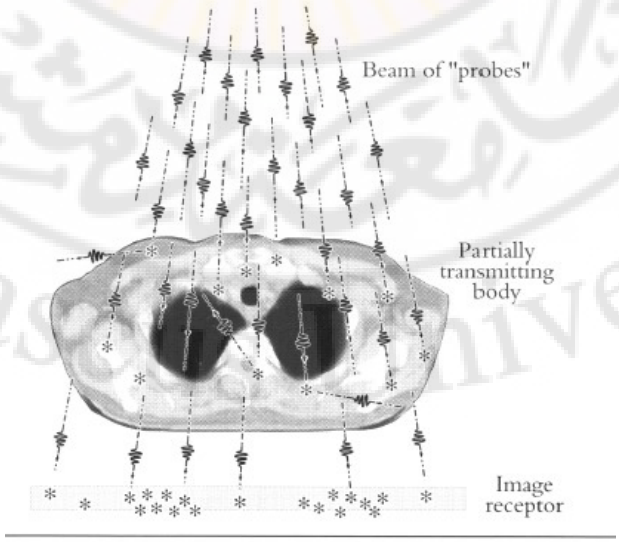
82



(a) Linear tomography. The X-ray source and film move at constant speed in opposite directions. (b) Axial transverse tomography. The film is positioned horizontally in front of the patient and slightly below the focal plane. Both the patient and the film rotate at the same fixed speed around a vertical axis while the X-ray source remains stationary.

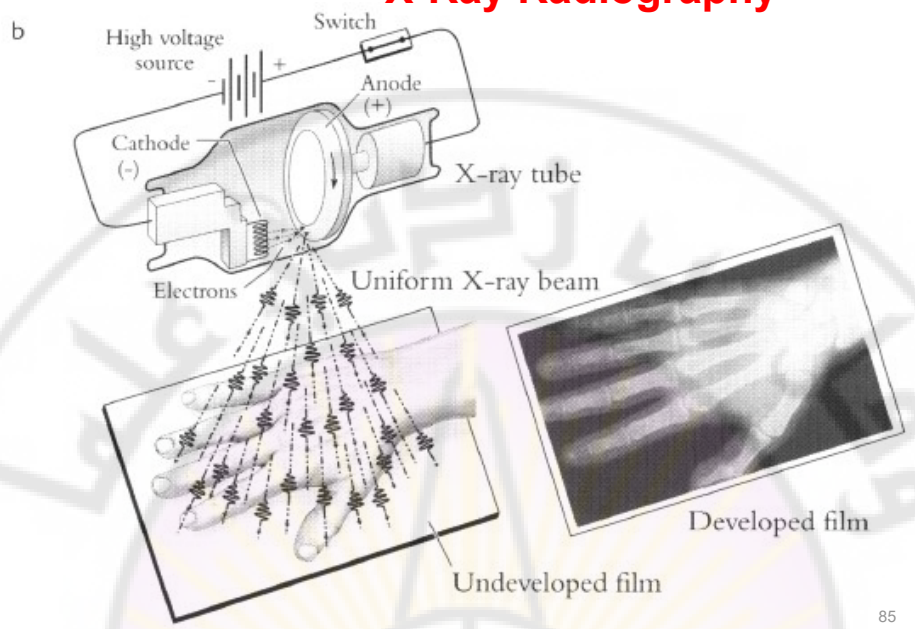
83

X-Ray Radiography



84

X-Ray Radiography



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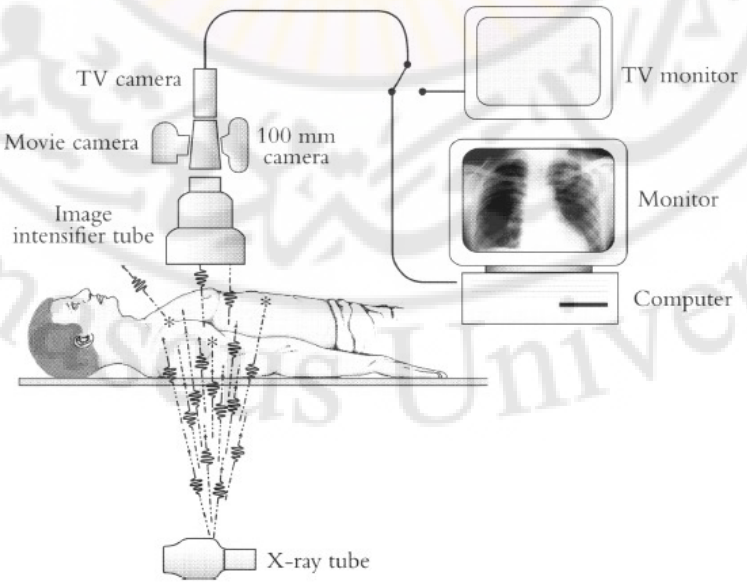
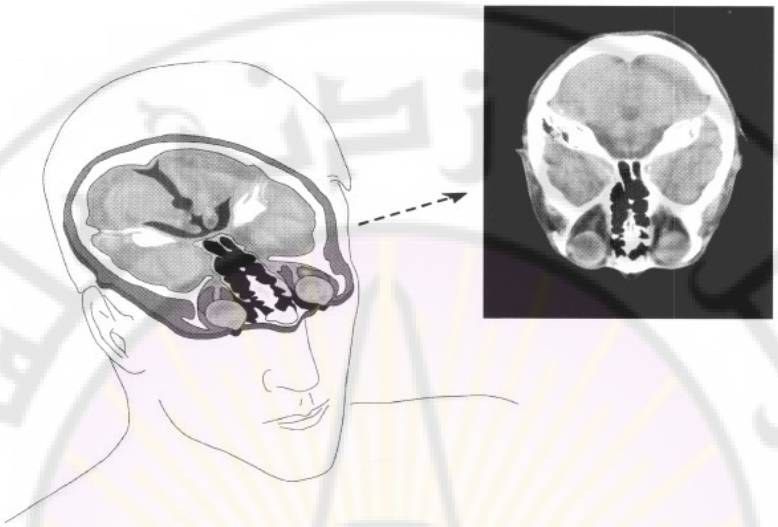
X-Ray Radiography



86

Computed Tomography



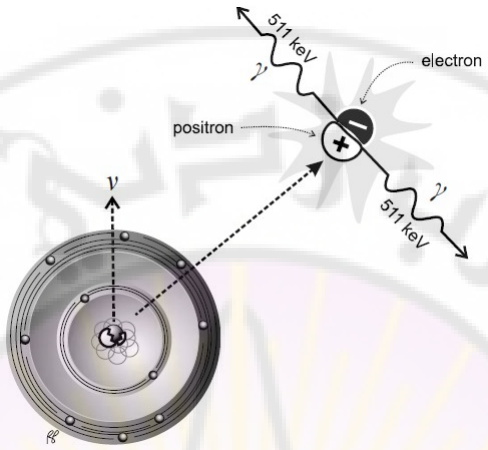
87

Positron-Emission Tomography

PET also detects γ -rays from the body after administration of radiopharmaceuticals containing radionuclides that emit positrons. The difference between PET and SPECT is that two γ-rays are detected in PET after one decay, compared with one in SPECT. Positrons emitted by PET probes annihilate with electrons in the tissue to give a pair of γ-rays with energy of 511 keV. The γ-rays are emitted at almost 180° and are recorded by detectors after escaping from the body. Like SPECT, PET is used for functional imaging and molecular imaging, rather than anatomical imaging. PET provides a much higher signal to noise ratio and spatial resolution than does SPECT.

C-11, N-13, O-15, and F-18 are the commonly used isotopes for PET imaging.

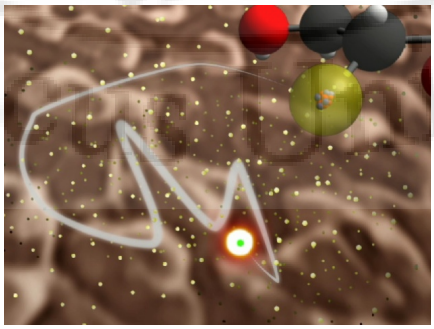
88



Annihilation reaction.

89

Positron Emission Tomography



Positron-Emission Tomography

The major advantage of using these isotopes, means C^{-11}, N^{-13}, O^{-15}, and F^{-18}, is that one or more atoms in a biologically active molecule, e.g., a drug compound, can be replaced by a radioactive isotope without changing its chemical structure. This is particularly attractive for in vivo imaging of biological and pharmaceutical properties of a drug or drug candidate. One limitation of using these isotopes is that they have very short half-lives. The half-lives of C^{-11},N^{-13}, O^{-15}, and F^{-18} are 20.4, 9.96, 2.07, and 109.7 minutes. Because of the short half-life of the emitters, an on-site cyclotron is required for the production of positron emitters before imaging.

These imaging modalities can be used for noninvasive in vivo evaluation of dosage forms in preclinical and clinical studies.

91

PET Radionuclides and Labeled Probes

Small molecules
- enzyme substrates, ligands, drugs…

Peptides
- receptor targeted…

Antibodies
- fragments, minibodies, diabodies

Reporter Genes
- enzyme-based, receptor-based

Cells
- T-cells, stem cells…

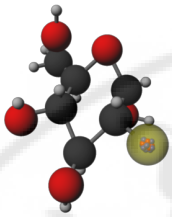
Particles
- Liposomes, lipospheres, nanoparticles…

PET Radionuclides

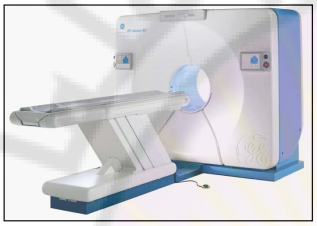
	$T_{1/2}$
^{11}C	20.4 mins
^{18}F	110 mins
^{64}Cu	12.6 hrs
^{68}Ga	68 mins
^{89}Zr	3.3 days
^{124}I	4.2 days

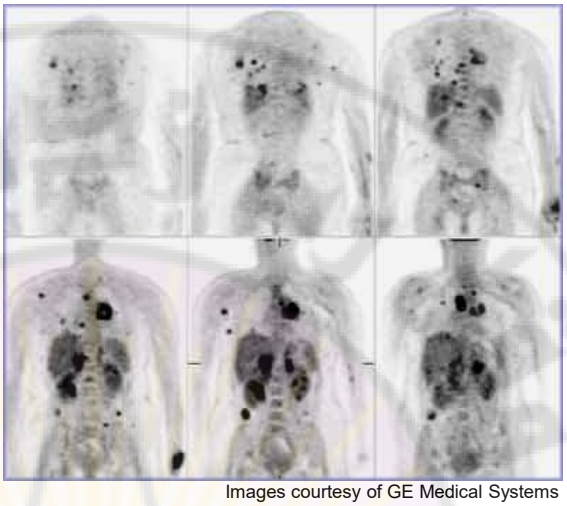
PET Imaging in Cancer

^{18}F-Fluorodeoxyglucose



[^{18}F]-fluoro-2-deoxy-D-glucose



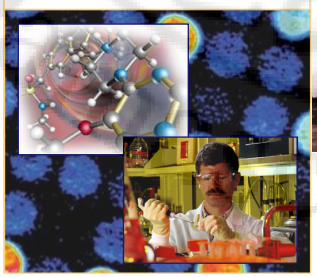


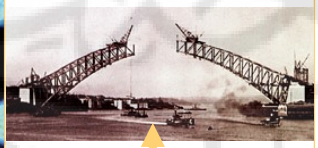
Images courtesy of GE Medical Systems

Preclinical *In Vivo* Imaging
Bridging the Divide

IN VITRO, EX VIVO

GENOMICS/PROTEOMICS
COMBINATORIAL CHEM

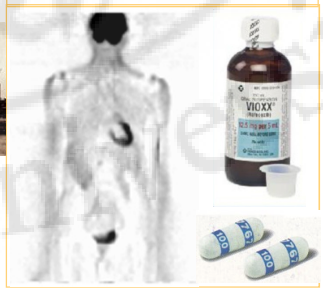




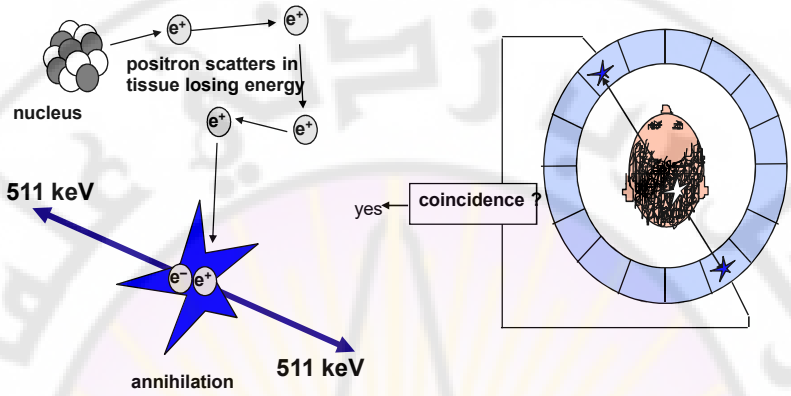
In Vivo Imaging

IN VIVO

MEDICAL DIAGNOSTICS
AND THERAPEUTICS



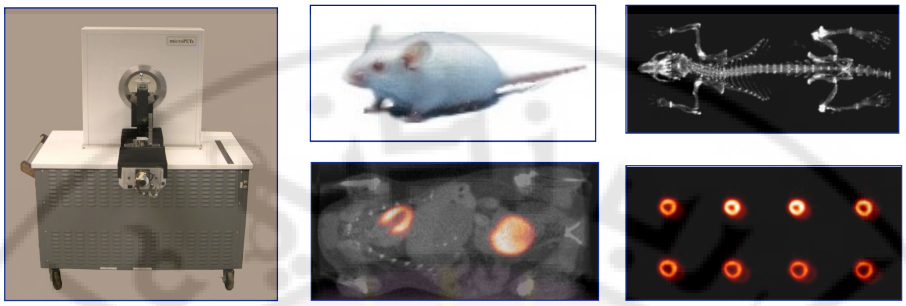
Positron Emission Tomography



Positron-Emitting Radionuclides

Isotope	Halflife	β^+ fraction	Max. Energy	range(mm)	productior
C–11	20.4 mins	0.99	0.96 MeV	0.4 mm	cyclotron
N–13	9.96 mins	1.00	1.20 MeV	0.7 mm	cyclotron
O–15	123 secs	1.00	1.74 MeV	1.1 mm	cyclotron
F–18	110 mins	0.97	0.63 MeV	0.3 mm	cyclotron
Cu–62	9.74 mins	0.98	2.93 MeV	2.7 mm	generator
Cu-64	12.7 hours	0.19	0.65 MeV	0.3 mm	cyclotron
Ga–68	68.3 mins	0.88	1.83 MeV	1.2 mm	generator
Br-76	16.1 hours	1.00	1.90 MeV	1.2 mm	cyclotron
Rb–82	78 secs	0.96	3.15 MeV	2.8 mm	generator
I–124	4.18 days	0.22	1.50 MeV	0.9 mm	cyclotron

Small Animal Imaging

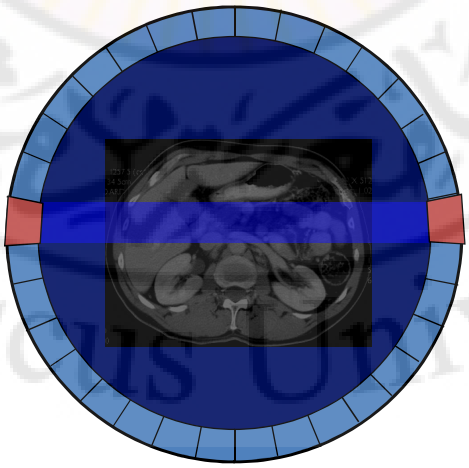


Requires both:
High spatial resolution
- mouse organs ~1000-fold smaller volume than human

High sensitivity
- number of targets also smaller, radiation dosimetry can be limiting

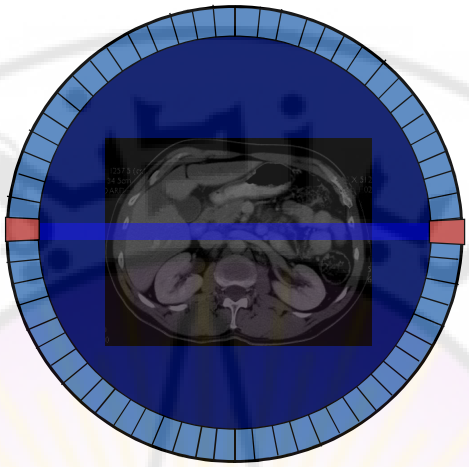
Spatial Resolution and Sensitivity

spatial resolution determined by detector width



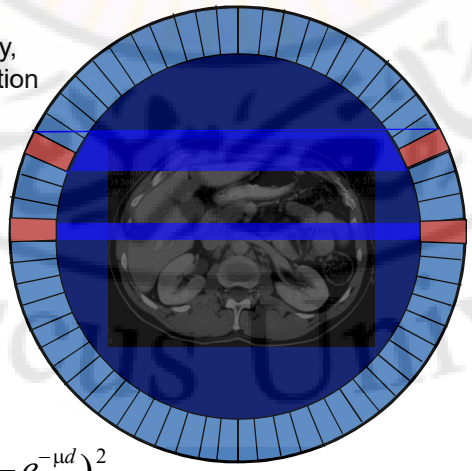
Spatial Resolution and Sensitivity

smaller detectors yield better resolution and better sampling



Spatial Resolution and Sensitivity

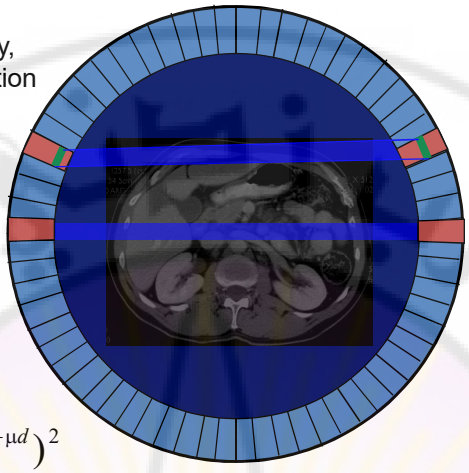
Thicker detectors improve sensitivity, but spatial resolution degrades due to parallax effects



$$sensitivity \propto (1 - e^{-\mu d})^2$$

Spatial Resolution and Sensitivity

Thicker detectors improve sensitivity, but spatial resolution degrades due to parallax effects



$$sensitivity \propto (e^{-\mu d})^2$$

Requirements

- High Sensitivity
  - High efficiency (thick) detectors
  - High solid angle coverage
    - Small Detector Ring Diameter
    - Long axial extent
- High Spatial Resolution
  - Very small cross-section detector elements
  - Depth-Encoding Detectors

γ-Scintigraphy and Single-Photon Emission Computed Tomography (SPECT)

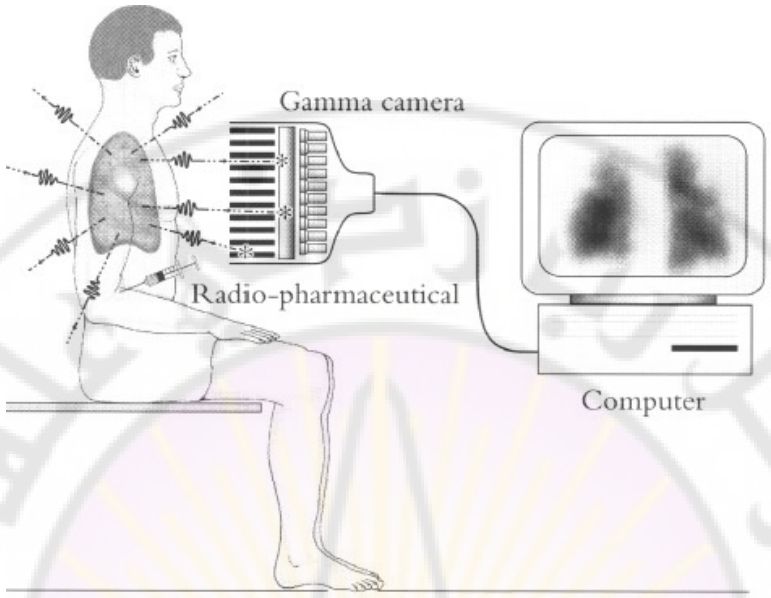
γ -Scintigraphy تَصْوِيرٌ وَمَضانِيّ detects the γ -rays emitted by the administered radiopharmaceuticals in the body, the derivatives of γ -ray-emitting isotopes. The radioactive emission is detected by a γ -camera and processed by a computer to generate an image. γ –Scintigraphy gives two-dimensional images of signal intensity distribution. *When a rotating camera is used with the same principle of tomography as in X-ray CT, three-dimensional images are produced in a technique called SPECT*. Compared with contrast-enhanced MRI and CT, SPECT has a high sensitivity for measuring radiopharmaceuticals in molecular imaging and gives qualitative and quantitative information about the distribution of a γ -emitter in the body. However, it does not provide high-resolution anatomical images of the body.

103

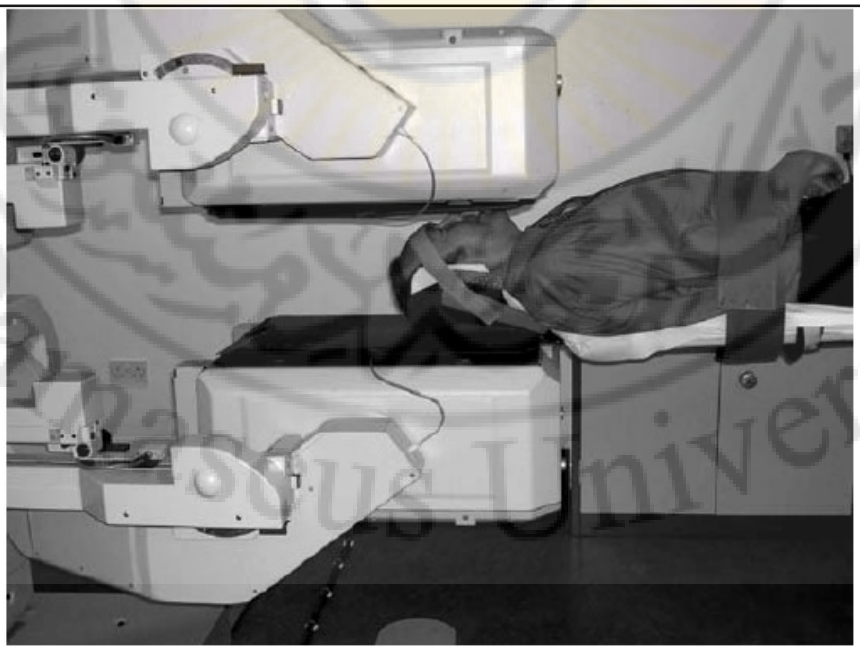
γ-Scintigraphy and Single-Photon Emission Computed Tomography (SPECT)

Radiopharmaceuticals or radiotracers used for γ -scintigraphy and SPECT are composed of the radionuclides decaying by γ -ray emission and with relatively short halflives. The preferable γ -rays are those with energies greater than 30 keV, because γ -rays below 30 keV are not detectable due to the absorption by the body. The commonly used SPECT tracers are the complexes of radioactive transition metal ions (e.g., In^{111} and Tc^{99m}) with short half-lives. Specificity and biodistribution of the tracers can be manipulated by altering the chemical structures of chelating ligands or incorporating tissue-specific agents. Unlike CT and MRI, only picomolar level radiotracer is needed for effective imaging in SPECT.

104

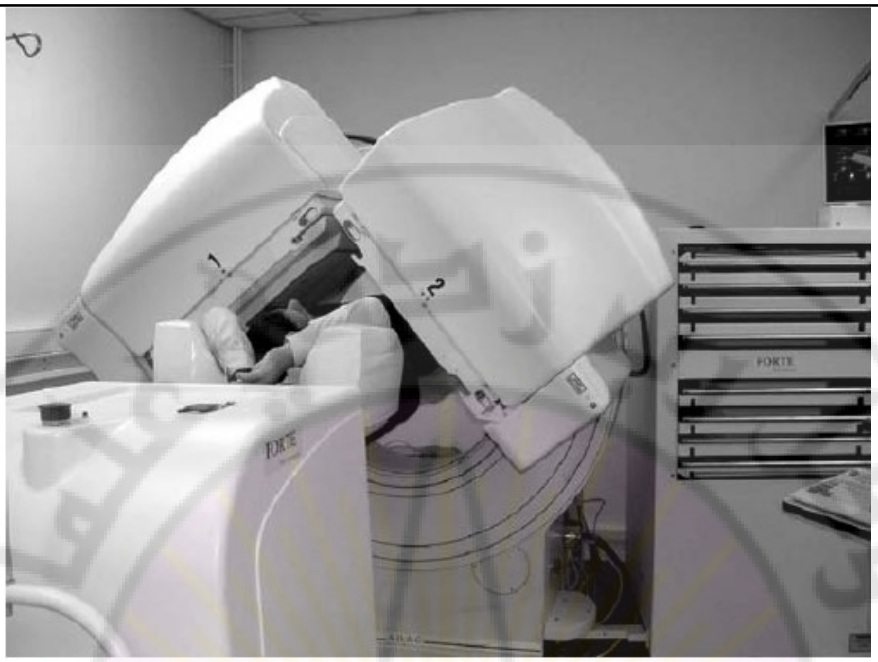


105



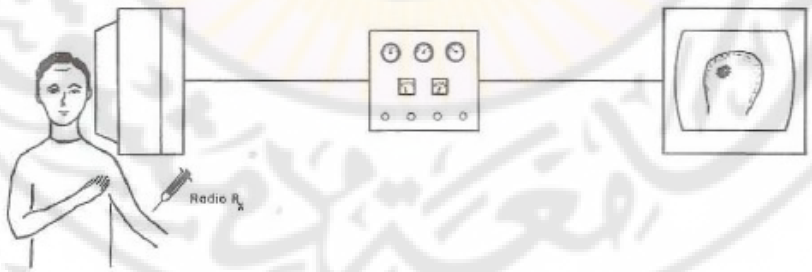
Dual-headed gamma cameras with the heads at **180◦ for brain imaging**

106



Dual-headed gamma cameras with the heads **90◦ for myocardial perfusion imaging.**

107



Gamma Camera Detection

Information Processing

Image Display

Schematic of a scintillation gamma camera system demonstrating radiopharmaceutical
injection, detection of radioactivity, electronic processing, and image display.

108

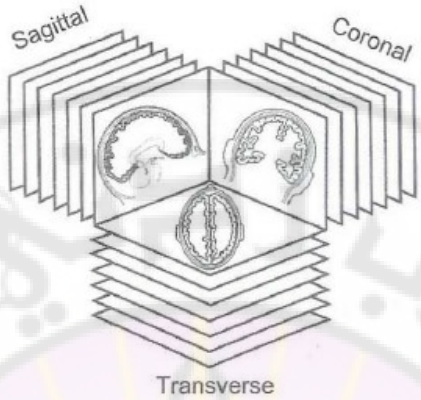
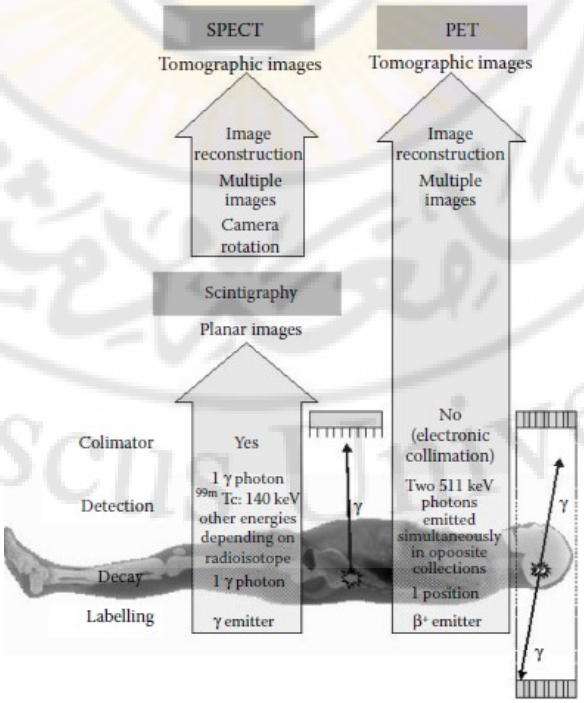
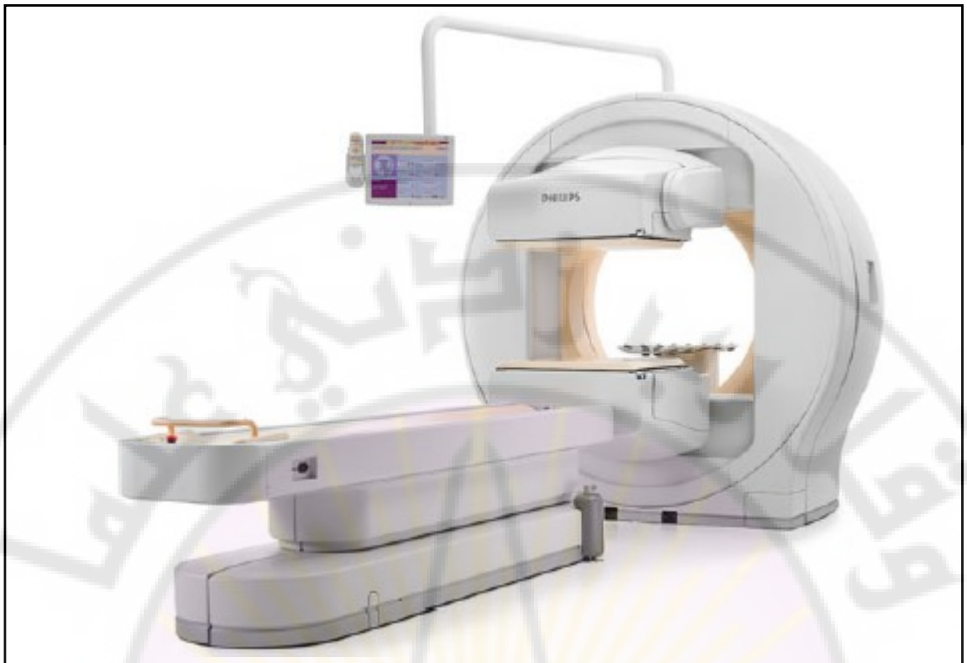


Diagram of three-dimensional, computer-generated slice images obtained with a gamma camera, showing organ in transverse مُسْتَعْرِض, sagittal سَهْمِيّ, and coronal جَبْهِيّ planes.

109



110



A SPECT scintillation camera, Philips BrightView X.

111

Optical imaging, SPECT, and PET have high sensitivity for functional and molecular imaging. CT and MRI produce high-resolution anatomical images for soft tissues. Ultrasound imaging is the least expensive imaging modality with high sensitivity to microbubbles. Each imaging modality has its own distinct advantages and characteristics. They are complementary to each other and can be used together to obtain more complete in vivo information of dosage forms. Combined imaging modalities, such as PET-CT, SPECT-CT, and PET-MRI, have been developed for preclinical and clinical applications

112

Current imaging modalities of interest in drug research and discovery

Technique	Spatial resolution and time scale	Clinical imaging	Application	Main characteristics
Ultrasound	50 μm; min	Yes	Anatomical, functional	Difficult to image through bone or lungs; microbubbles used for contrast enhancement
CT	50–100 μm; min	Yes	Anatomical, functional	Poor soft tissue contrast
MRI	80–100 μm; s to h	Yes	Anatomical, functional, molecular	High spatial resolution and soft tissue contrast
SPECT (low-energy γ-rays)	1–2 mm; min	Yes	Functional	Radioisotopes have longer half-lives than those used in PET; sensitivity 10 to 100 times smaller than PET
PET (high-energy γ-rays)	1–2 mm; min	Yes	Metabolic, functional, molecular	High sensitivity (picomolar concentrations); cyclotron needed
Bioluminescence	1–10 mm; s to min	No	Molecular	High sensitivity; transgene-based approach; light emission prone to attenuation with increased tissue depth
NIRF	1–3 mm; s to min	No	Molecular	Excitation and emission light prone to attenuation with increased tissue depth

Beckmann et al. NMR Biomed 2007: 154-185 113

- the photon abundance should be high so that imaging time can be minimized due to the high photon flux.
- Biomedical imaging measures the interactions of electromagnetic waves with the body or the emission of electromagnetic waves from the body.
- A radiopharmaceutical has two components: a radionuclide and a pharmaceutical.

114

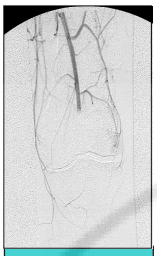
Development of Biomarkers and Imaging Agents

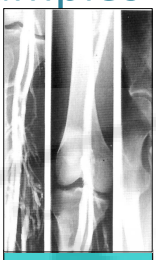
115

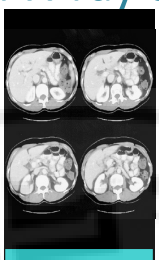
Formulation in Imaging

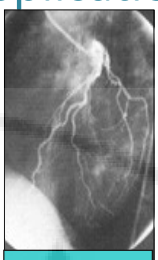
- Five modalities
  - X-ray
    (X- ray computed tomography) التَصْوير المَقْطَعِيٌّ المُحَوسَب بأشعة X
  - Magnetic resonance Imaging (MRI (التصوير بالرنين المغناطيسي) - Molecular
  - Ultrasound الإيكوغرافي
  - Nuclear Medicine
    التصوير المقطعي بالإصدار وحيد الفوتون
    - (Single Photon Emission Tomography (SPECT) - Molecular
    التصوير المقطعي بإصدار البوزيترون
    - Positron Emission tomography (PET) - Molecular
  - Optical - Molecular
- Mainly i.v.

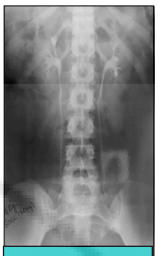
Examples of X-ray applications

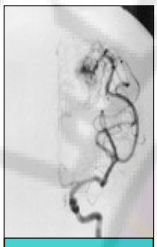

Peripheral angiography

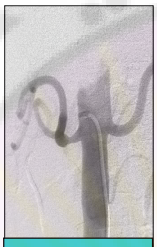

Phlebography

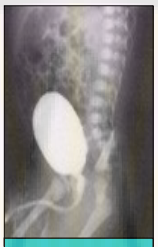

CT enhancement


Cardioangio-graphy

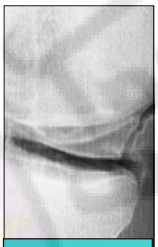

Urography


Cerebral angiography


DSA


Paediatric radiology

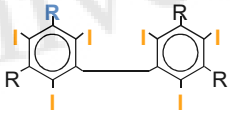

Myelography

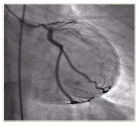

Body cavities

117

X-ray formulation challenges

- Agents with high atomic weight to increase signal intensity between tissues
- High concentration, low-osmolar, non-ionic dimers
- Up to 800 mg CM/ml
- 50-150 ml injected volume
- Solubility
- Viscosity
- Heat treatment - sterilization
- Stability

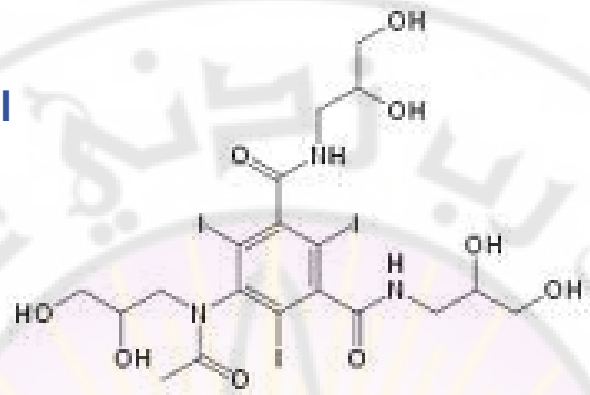




118

X-ray contrast agent

Iohexol



119

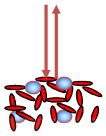
Quantitative composition

OMNIPAQUE®	140 mg I/ml	180 mg I/ml	200 mg I/ml	240 mg I/ml	300 mg I/ml	350 mg I/ml
Ingredients	per ml	per ml	per ml	per ml	per ml	per ml
Iohexol	302 mg	388 mg	431 mg	518 mg	647 mg	755 mg
Trometamol	1.21 mg	1.21 mg	1.21 mg	1.21 mg	1.21 mg	1.21 mg
NaCaEDTA	0.10 mg	0.10 mg	0.10 mg	0.10 mg	0.10 mg	0.10 mg
5M HCL acid to pH 6.8-7.6	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water for injection	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml

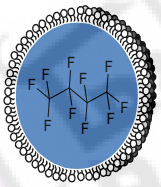
Trometamol = tris buffer

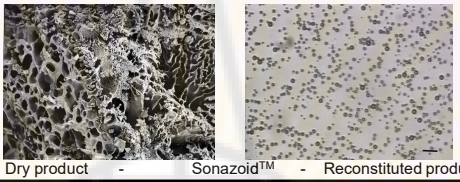
120

Ultrasound formulation challenges



- Contrast agents normally gas filled particles
- Critical formulation parameters ***(in vivo):***
  - Efficacy: Density, size, compressibility
  - Safety: Particle size & distribution, impurities
  - Stability: Destruction by i.e. phagocytosis, pressure etc.
- Perfluoro compounds: High MW => Slower diffusion, Higher compressibility => positive for resonance
- Flexible shell by phospholipids
- Freeze dried product - long shelf life

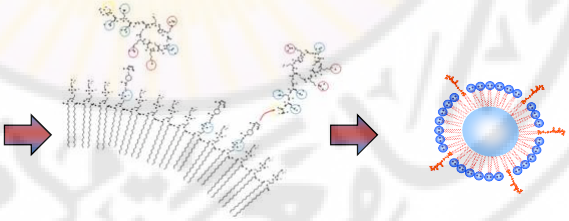




Dry product - Sonazoid™ - Reconstituted product

121

TUSCA principle

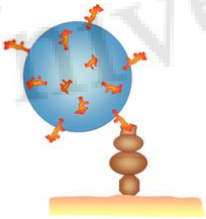


Peptide-binders with affinity for a disease specific target

chemically coupled to phospholipid microbubbles

- to generate the Targeted UltraSound Contrast Agent.

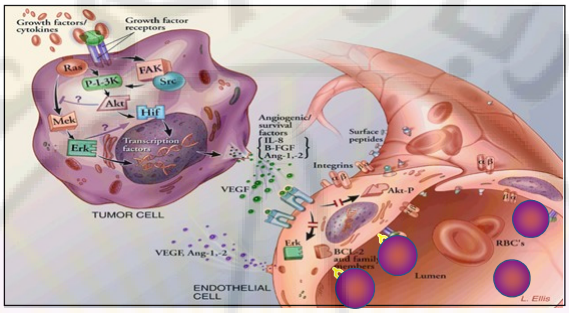
The targeted agent should bind to the disease specific target expressed on cells



TUSCA = **Targeted ultrasound contrast agent**

TUSCA - Product Characteristics

Mechanism of action: After intravenous injection, the microbubbles will bind to VEGF-receptor 2 (KDR) expressed on the luminal side of tumour endothelium. The gas microbubbles will increase the backscattered ultrasound signal from the region of interest. The contrast effect depends on the ratio of targeted bubbles over circulating or unspecifically bound bubbles.



TUSCA = **Targeted ultrasound contrast agent**

123

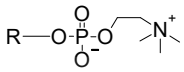
Therapy with TUSCA

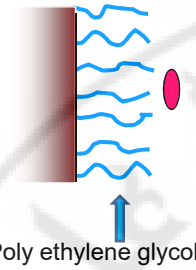
- Active principle incorporated in the microbubbles
- Possible to release the drug by destruction of microbubbles by high intensity US.
- Active principle must be highly potent because few bubbles will bind to the relevant site.
  - Gene therapy
  - VEGF (increase angiogenesis in damaged tissue)
  - Cytostaticum

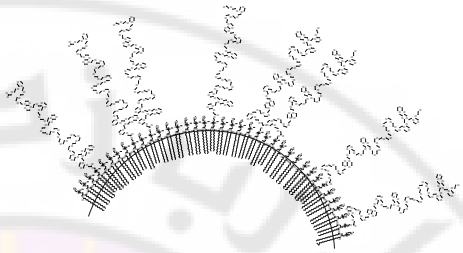
vascular endothelial growth factor (VEGF)

124

Challenges







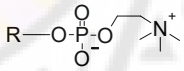
Poly ethylene glycol chains (PEG)

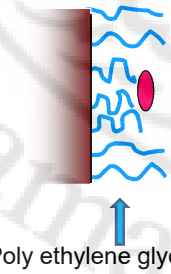
- Adsorption of serum components
- Sufficient circulation time in the blood system (avoid RES)
- Stability of the microbubbles in the US beam.

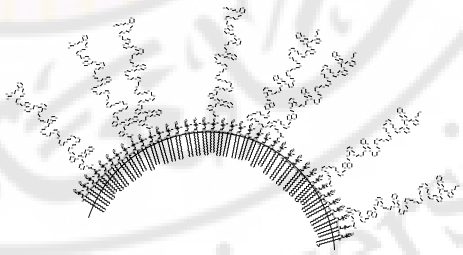
US = Ultra Sound
RES = Reticulo Endothelial System

125

Challenges







Poly ethylene glycol chains (PEG)

- Adsorption of serum components
- Sufficient circulation time in the blood system (avoid RES)
- Stability of the microbubbles in the US beam.

126

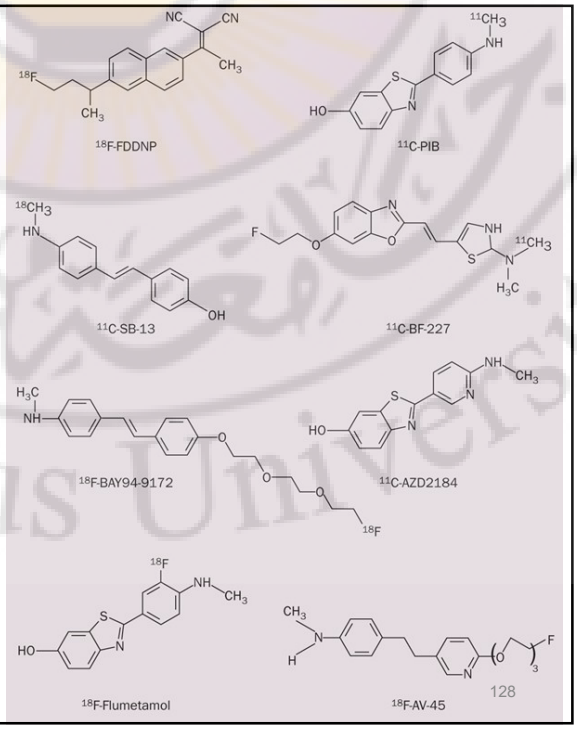
Molecular Imaging by Targeting

- Targeting specific structures:
  - Circulating
  - Cell surface
  - Intracellular
- Biomarkers for disease
  - ^{18}F-FDG (fluorodeoxyglucose) widely used in PET
  - beta-amyloid plaque in Alzheimer's Disease, ^{11}C-PIB, ^{18}F-PIB
  - ^{11}C-choline, prostate tumor models
  - ^{11}C-DTBZ, biomarker for the VMAT2-transporter
  - and others commercially available

11C-PIB: ((11)C-6-OH-BTA-1) (where BTA is benzothiazole)

127

Chemical structures of amyloid PET tracers.



Nordberg, A. *et al.* (2010) The use of PET in Alzheimer disease *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2009.217

128

Biomarkers

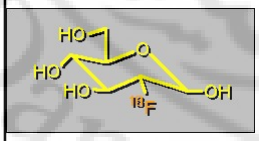
- Biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
  - Body temperature - Fever
  - Blood pressure - risk of stroke
  - Pharmacologic agent

*NIH & FDA, 1999

129

Molecular Imaging by Targeting

- Biomarker examples cont'd



^{18}F-FDG (fluorodeoxyglucose) widely used to study glucose metabolism

- beta-amyloid plaque in Alzheimer's Disease, ^{11}C-PIB widely studied, ^{18}F-PIB in progress for automated platforms
- ^{11}C-choline, prostate tumor models. Made from ^{11}C-CO_2, via ^{11}C-methyl triflate+2-dimethylaminoethanol

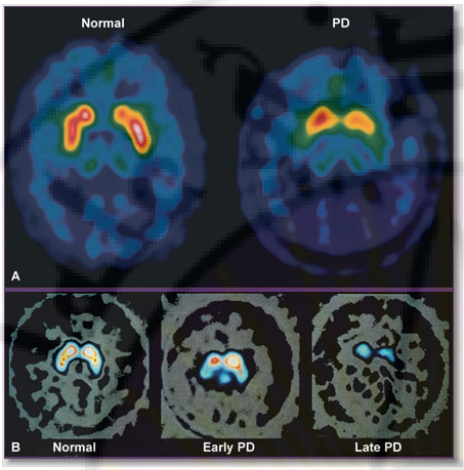
  Zheng et al, Bioorg & Medicinal Chem, 12, 2004
- ^{11}C-DTBZ (dihydrobenazine), biomarker for the VMAT2-transporter in obesity, type 1+2 diabetes Freeby et al, Diabet, Obesity & Metabol, 10, 2008

The vesicular monoamine transporter 2 (*VMAT2*)

130

Parkinson's Disease biomarkers

PET and SPECT images



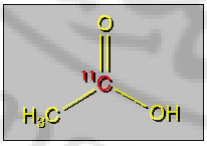
[^{18}F]-Dopa PET uptake in the putamen is reduced in patients with PD compared with normal controls (A).

Reduction in ^{123}I-CIT SPECT uptake in the putamen correlates with the severity of PD (B).

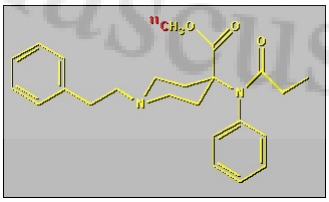
Olanow et al, Neurology 2001, 56, S1-S88

131

^{11}C, $t_{1/2}$ = 20.4 min



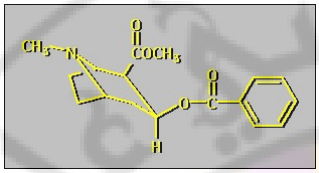
Acetate - **Oxidative metabolism**



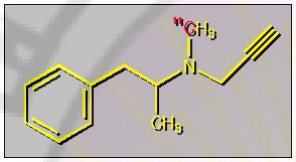
Carfentanil - **μ-opiate receptor agonist**
opiate receptors of the brain

132

^{11}C, $t_{1/2}$ = 20.4 min



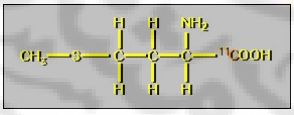
Cocaine - ID and characterisation of drug binding sites



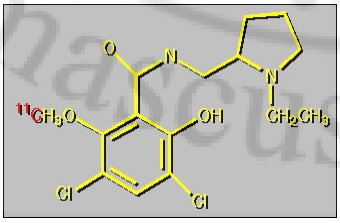
Deprenyl - MAO-B (dopamine catabolic تَقْوِيضِيّ enzyme) inhibitor Parkinson's

133

^{11}C, $t_{1/2}$ = 20.4 min



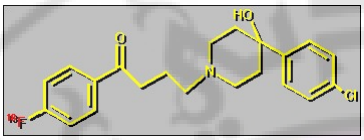
Methionine - (and leucine) AA uptake tumor viability



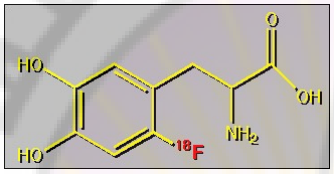
Raclopride - D2 inhibitor

134

^{18}F, $t_{1/2}$ = 110 min



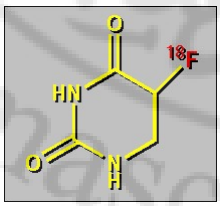
Haloperidol - **Dopamine receptor antagonist**



Fluorodopa - **Presynaptic distribution of dopamine Parkinson's disease**

135

^{18}F, $t_{1/2}$ = 110 min



Fluorouracil - **Measure delivery of chemotherapeutic agents**

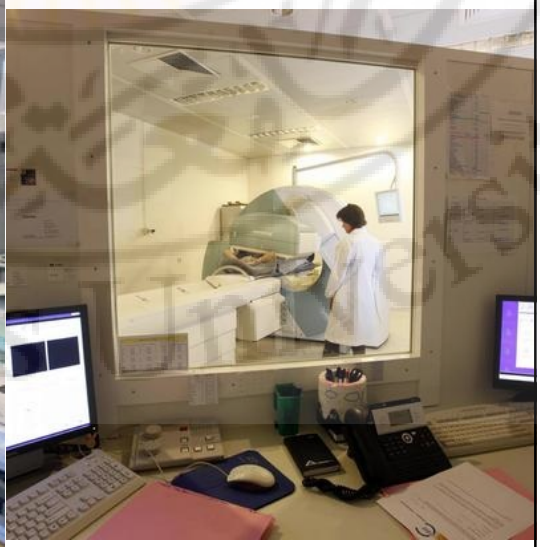
136

Clinical Applications of PET

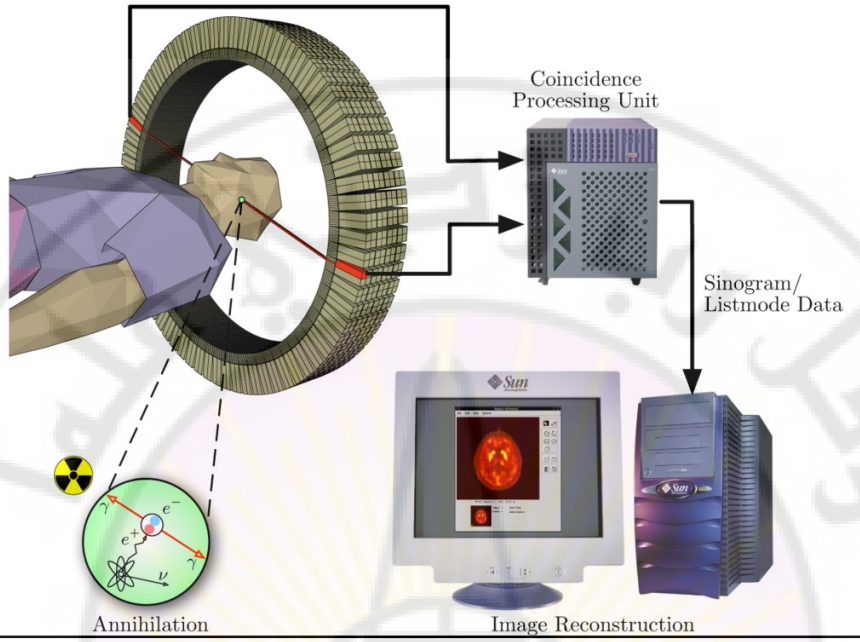
- Cancer:
  - Lung Cancer
  - Colorectal Cancer
  - Breast Cancer
  - Prostate Cancer
- Heart Disease:
  - Coronary Artery Disease
- Brain Disorders:
  - Alzheimer's
  - Parkinson's

137

PET scanning machines



PET scanning machines

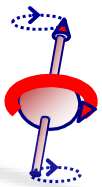


Cancer

- The most dangerous aspect of cancer is how it spreads throughout the organ systems of the body.
- PET is medical imaging modality that inspects all organ systems of the body to search for cancer in a single examination.
- PET can tell where is the tumor, if it is benign or malignant and if the chemotherapy treatment is working.

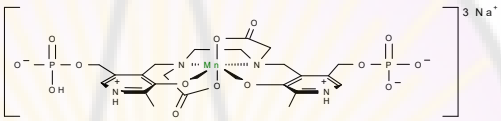
140

MRI formulation



- Contrast determined by;
  - Proton density of tissue
  - Relaxation properties of tissues
  - Signal acquisition technique
- Paramagnetic (Gd^{3+} , Mn^{2+} , Fe^{2+} ,Fe^{3+} ,Dy^{3+})
- 10-50 ml injection volumes
- Formulation of chelates

INGREDIENTS	AMOUNTS (mg/ml)	Rationale
Mangafodipir trisodium	7.57 mg (-> 0.01 mmol)	
Ascorbic acid	1.0 mg	Antioxidant Mn(II)DPDP to Mn(III)DPDP
Sodium chloride	7.5 mg	Tonicity
NaOH/HCl to pH 7.0 - 8.0	q.s.	Avoid hydrolytic dephosphorylation or oxidation
Water for injection	ad 1.0 ml	
Nitrogen	q.s.	Produced under N_2 flow



141

SPECT formulation example

Formulation of a kit for labelling of DNA-fragments

142

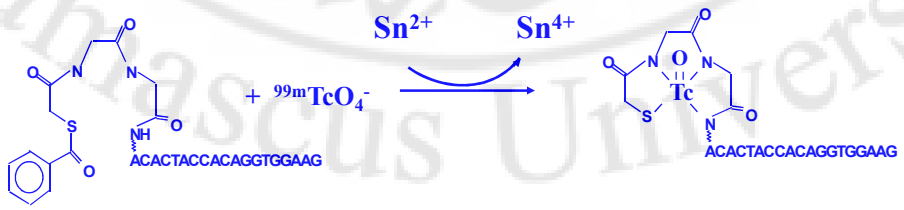
A one-step kit for ^{99m}Tc-labelling of DNA probes

LYOPHILISED KIT CONTENTS

S-Bz-MAG2-oligodeoxynucleotide	2 ug
$SnCl_2.2H_2O$	100 ug
KNa tartrate	5 mg
Carbonate buffer, 1 M pH 9.3	100 ul

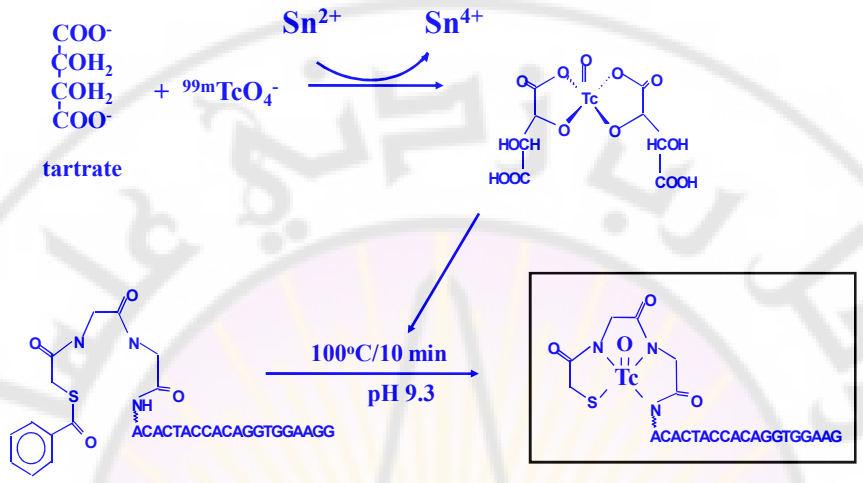
143

LABELLING WITH TECHNETIUM



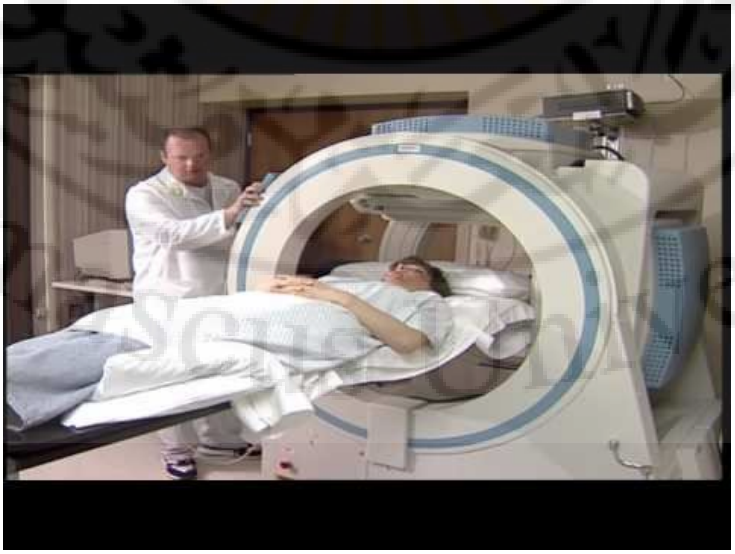
144

A one-step kit for ^{99m}Tc-labelling of DNA probes



145

SPECT Machine



146

Formulation development in ^{18}F PET - for human use

147

Steps in ^{18}F process/formulation development

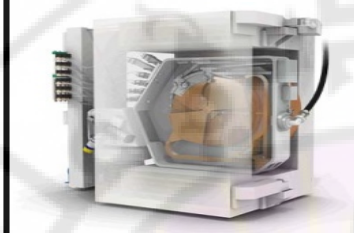
1. Radiochemistry process
2. Purification
3. Formulation
4. Dispensing

148

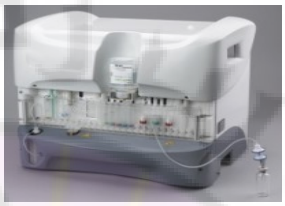
Formulation for PET center process

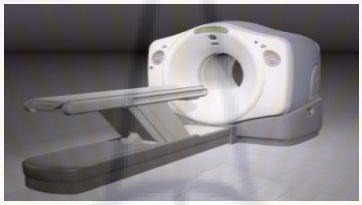
PET center

Cyclotron



Drug Synthesis





Patient Scanner

149

Why formulate?

- Stability
  - » Chemical
  - » Radiochemical
- Solubilize
  - » Limit adsorption
- Human compatibility
  - » pH
  - » Isotonicity
  - » Solvent dilution
- Safety
  - » Sterility
  - » Endotoxins

150

Radiochemical stability
For how long - at which purity?

- Radiolysis at elevated activity levels
- Add radioscavenger كاسِح, commonly used:
  - » Ethanol
  - » Buffer (phosphate, citrate)
  - » Ascorbic acid
  - » Gentisic acid
  - » .....
- – OBS: Chemical, safety or efficacy interactions

151

Solubilizer

- Poorly soluble molecules
- Avoid adsoption to surfaces, esp. filters
- Solvents: Ethanol up to 8%
- Surfactants
- Cyclodextrins

152

Human compatibility

- Volumes are normally small, i.e. <10 ml
- Isotonic/isoosmolar solutions at neutral pH normally preferred
- Buffers or acids/bases
- Not too good buffer capacity
- Ethanol dilution to <8%

153

Choice of materials

- Excipients: use pharmacopoeia materials
- Primary packaging (vials, stoppers, tubing):
  - Beware adsorption, leachables/extractables, ion exchange

154

Quality requirements

- Only FDG is commercial product yet.
- Others generally ex-temporaneous preparations, i.e. for the individual patient
- Sterilization 0.22 um filter (or autoclave)
- Quality Control
- Quality Assurance
- Guidelines

FDG (fluorodeoxyglucose)

155

Guidelines

- USA
  - USP823 - for academic tracers
  - USP797 - for dispensing
  - 21CFR212 - for commercial production
- EU
  - Annex 3 as for standard pharmaceuticals
  - Auditor differences and local exemptions

156

Dispensing

- Any step after sterilization is critical
- Dose, QC sample withdrawal, sterility testing
- Aseptic handling
- Automated dispensing
- Dispensing environment important

157

Conclusions

- Imaging agents require multi-disciplinary skills for rapid process and formulation development
- Biomarkers are useful for lead selection as well as clinical trials outcomes
- Novel biomarkers and molecular imaging agents are necessary for efficient drug development

158

Specific Activity

Specific activity is defined as the radioactivity per unit mass of a radionuclide or a labeled compound. For example, suppose that 100 mg ^{131}I-labeled albumin contains 150 mCi (5.55 GBq) ^{131}I radioactivity. Its specific activity would be 150/100, that is, 1.5 mCi/mg or 55.5 MBq/mg.

159

Commonly used radiopharmaceuticals involve one or more of the following mechanisms of localization in a given organ:

1. **Passive diffusion**: ^{99m}Tc-DTPA in brain imaging, ^{99m}Tc-DTPA aerosol and ^{133}Xe in ventilation imaging, ^{111}In-DTPA in cisternography تَصْويرُ الصَّهاريج.
2. **Ion exchange**: uptake of ^{99m}Tc-phosphonate complexes in bone.
3. **Capillary blockage**: ^{99m}Tc-macroaggregated albumin (MAA) particles trapped in the lung capillaries.
4. **Phagocytosis**: removal of ^{99m}Tc-sulfur colloid particles by the reticuloendothelial cells in the liver, spleen, and bone marrow.
5. **Active transport**: ^{131}I uptake in the thyroid, ^{201}Tl uptake in the myocardium.
6. **Cell sequestration** : sequestration of heat-damaged ^{99m}Tc-labeled red blood cells by the spleen.
7. **Metabolism:** ^{18}F-FDG uptake in myocardial and brain tissues.
8. **Receptor binding**: ^{11}C-dopamine binding to the dopamine receptors in the brain.
9. **Compartmental localization**: ^{99m}Tc-labeled red blood cells used in the gated blood pool study.
10. **Antigen–antibody complex formation**: ^{131}I-, ^{111}In-, and ^{99m}Tc-labeled antibody to localize tumors.
11. **Chemotaxis**: ^{111}In-labeled leukocytes to localize infections.

160

Mechanisms of Localization and Examples	
Capillary blockade	Macroaggregated albumin in lung
Diffusion	Filtration of DTPA by kidney
Sequestration	Leukocytes for abscess scanning
	Labeled platelets (damaged endothelium)
	Heat-damaged red blood cells for splenic scanning
Phagocytosis	Colloid scanning for liver and spleen, bone marrow, and lymph nodes
Receptor binding	Neuroreceptor imaging
Active transport	Iodocholesterol in adrenal scanning
	Iodine or pertechnetate (accumulation by choroid plexus, Meckel's diverticulum, salivary gland, stomach, and thyroid)
	Technetium-99m IDA analogs in liver/biliary tract
	Orthoiodohippurate in renal tubules
	Thallous ions in myocardium
Metabolism	Fluorodeoxyglucose imaging of brain, tumor, and myocardium
Compartmental containment	Labeled red blood cells for gated blood pool studies
Compartmental leakage	Labeled red blood cells for detection of gastrointestinal bleeding
Physicochemical adsorption	Phosphate bone-scanning agents
Antibody-antigen reactions	Tumor imaging, monoclonal antibodies

161

Methods of Radiolabeling

Isotope exchange	^{125}I labeled T3 and T4 ^{14}C , ^{35}S and ^{3}H labeled compounds
Introduction of a foreign label	All ^{99m}Tc radiopharmaceuticals ^{125}I labeled proteins ^{125}I labeled hormones ^{111}In labeled cells ^{18}F fluorodeoxyglucose
Labeling with bifunctional chelating agent	^{111}In DTPA albumin ^{99m}Tc DTPA antibody
Biosynthesis	^{75}Se selenomethionine ^{57}Co cyanocobalamin ^{14}C labeled compounds
Recoil labeling	^{3}H labeled compounds Iodinated compounds
Excitation labeling	^{123}I labeled compounds (from ^{123}Xe decay) ^{77}Br labeled compounds (from ^{77}Kr decay)

General methods of radiolabeling recoil ارْتداد 162

Radiation Therapy

- Radiation is used to deal with cancer and also for diagnostics (imaging)
- Rapidly growing cells hurt more by radiation (same as chemotherapy exploits)
  - Cells that divide quickly are:
    - Cancerous cells
    - Hair follicles (loss of hair)
    - Digestive tract epithelial cells (nausea)
- Try to localize radiation to the tumor

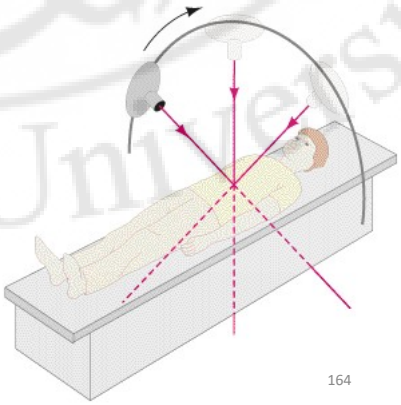
163

Radiation Therapy Methods

The goal is to minimize damage to surrounding tissue by limiting exposure.

Can achieve the same goal by implanting "seeds" directly into tumors.

Used for prostate cancers. Use body's natural processes for other cancers. Iodine concentrates in thyroid, so inject hot "iodine."



164

REPRESENTATIVE RADIOPHARMACEUTICAL DRUGS AND PRIMARY USES

DRUG	TRADE NAME	PRIMARY USES
^{111}In oxyquinoline	Indium-111 Oxine	Radiolabel autologous leukocytes and platelets
^{111}In capromab pendetide	ProstaScint	Monoclonal antibody for imaging prostate cancer
^{111}In pentetreotide	OctreoScan	Imaging of neuroendocrine tumors
^{123}I, sodium iodide	—	Thyroid imaging and uptake
^{131}I, sodium iodide	—	Thyroid imaging, uptake, therapy
^{131}I tositumomab	Bexxar	Treatment of non-Hodgkin lymphoma
^{131}I-*m*IBG	—	Treatment of neuroendocrine tumors
^{99m}Tc exametazime	Ceretec	Cerebral perfusion, radiolabeling autologous leukocytes
^{99m}Tc macroaggregated	Pulmonite	Pulmonary perfusion albumin
^{99m}Tc mebrofenin	Choletec	Hepatobiliary imaging
^{99m}Tc medronate (MDP)	—	Bone imaging
^{99m}Tc mertiatide	Technescan MAG3	Renal imaging
^{99m}Tc oxidronate (HDP)	OctreoScan HDP	Bone imaging
^{99m}Tc pentetate (DTPA)	Techneplex, Technescan DTPA	Renal imaging and function studies; radioaerosol ventilation imaging

165

REPRESENTATIVE RADIOPHARMACEUTICAL DRUGS AND PRIMARY USES

DRUG	TRADE NAME	PRIMARY USES
^{99m}Tc pertechnetate	—	Imaging of thyroid, salivary glands, ectopic gastric mucosa, parathyroid glands, dacryocystography, cystography
^{99m}Tc red blood cells	Ultratag	Imaging of gastrointestinal bleeding, cardiac chambers, cardiac first-pass, gated equilibrium imaging
^{99m}Tc sestamibi	Cardiolite, Miraluma	Imaging of myocardial perfusion, breast tumor
^{99m}Tc sulfur colloid		Imaging of reticuloendothelial system, bone marrow, gastric emptying, gastrointestinal bleeding, lymphoscintigraphy, arthrograms
^{99m}Tc tetrofosmin	Myoview	Myocardial perfusion imaging
^{201}Tl	—	Myocardial perfusion imaging; parathyroid and tumor imaging
^{133}Xe	Dupont Xenon, Mallinckrodt Xenon, GE Healthcare Xenon	Pulmonary ventilation imaging
^{90}Y microspheres	TheraSphere	Therapy for biopsy-proven, unresectable hepatocellular carcinoma
^{90}Y ibitumomab tiuxetan	Zevalin	Non-Hodgkin lymphoma
^{153}Sm-lexidronam (EDTMP)	Quadramet	Palliation of bone pain of skeletal metastases
^{166}Ho-DOTMP	—	Bone cancer therapy
^{186}Re-HEDP	—	Bone cancer therapy

166

^{90}Y-SIR-Spheres (SIR-TeX)

^{90}Y-SIR-Spheres are used to treat **unresectable metastatic hepatic tumor from primary colorectal cancer** with adjuvant intra-hepatic chemotherapy of Floxuridine.

The distribution of the spheres in the liver is non-uniform with more tumor uptake than normal liver uptake.

SIR-Spheres are neither metabolized nor excreted and are permanently lodged in the tumor cells. The **β radiation** from ^{90}Y effectively **destroys the tumor cells**.

Treatment of Non Hodgkin's Lymphoma

^{90}Y-Ibritumomab Tiuxetan (Zevalin)

Yttrium-90 decays by **β emission** (100%) with a ***half-life of 64 h***. It has high-energy β rays with an *effective path length of 5.3 mm*, meaning that 90% of β energy is absorbed in a sphere of 5.3-mm radius. ^{90}Y-ibritumomab tiuxetan (**Zevalin**) **is an anti-CD$_{20}$ antibody used for the treatment of non-Hodgkin's lymphoma** (NHL).

167

^{131}I-Tositumomab (Bexxar)

The ^{131}I-Bexxar treatment **is indicated for CD$_{20}$ antigen-expressing refractory, low grade, follicular** NHL and used as a single course of regimen. it is contraindicated in pregnant women.

Polycythemia Vera and Leukemia

- Polycythemia vera كَثْرَةُ الحُمْرِ الحَقِيقِيَّة is a disease characterized by an increased red blood cell mass, frequently associated with bone marrow hyperactivity.
- ^{32}P-sodium orthophosphate is used for the treatment of polycythemia vera.
- Therapy results from radiation injury to the cell precursors and the bone marrow due to bone accumulation of ^{32}P.

168

Table 1. Radionuclides with Established or Potential Therapeutic Applications

Radionuclide		*Particle*	*Half-Life*	*Max particle energy (MeV)*	*Max Range in tissue*
Yttrium-90	(^{90}Y)	(beta)	2.67 d	2.28	12.0 mm
Rhenium-188	(^{188}Re)	(beta)	17.00 h	2.11	10.8 mm
Phosphorus-32	(^{32}P)	(beta)	14.30 d	1.71	8.7 mm
Strontium-89	(^{89}Sr)	(beta)	50.50 d	1.49	8.0 mm
Dysprosium-165	(^{165}Dy)	(beta)	2.33 h	1.29	6.4 mm
Rhenium-186	(^{186}Re)	(beta)	3.77 d	1.08	5.0 mm
Gold-198	(^{198}Au)	(beta)	2.70 d	0.96	4.4 mm
Samarium-153	(^{153}Sm)	(beta)	1.95 d	0.81	3.0 mm
Iodine-131	(^{131}I)	(beta)	8.04 d	0.61	2.4 mm
Terbium-161	(^{161}Tb)	(beta)	6.90 d	0.59	2.2 mm
Lutetium-177	(^{177}Lu)	(beta)	6.70 d	0.50	1.8 mm
Erbium-169	(^{169}Er)	(beta)	9.40 d	0.34	1.0 mm
Indium-111	(^{111}In)	(c.e.*)	2.83 d	0.25	0.6 mm
Tin-117m	(^{117m}Sn)	(c.e.*)	13.60 d	0.16	0.3 mm
Iodine-125	(^{125}I)	(Auger)	60.30 d	30.0 (keV)**	17.0 μm
Bismuth-212	(^{212}Bi)	(alpha)	1.00 h	8.8	87.0 μm
Astatine-211	(^{211}At)	(alpha)	7.20 h	6.8	65.0 μm
Terbium-149	(^{149}Tb)	(alpha)	4.00 h	4.0	28.0 μm

d = days
h = hours
*internal conversion electrons
**the most abundant Auger electrons have energies less than 1 keV