Biophysical & Biochemical Techniques

Radio-isotopic techniques

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Keywords
Isotopes, radioisotopes, Bohr’s model of atom, radioactivity, half-life, particulate emission, gamma rays, isomeric transition, particle accelerators, cyclotrons, positron emission, radioactive detectors, Liquid scintillation detector, radioimmunoassay, gamma camera, PET/CT scanners
I. Introduction
Myriads of complex biological processes go on simultaneously in the human body. The disease is the ultimate manifestation of abnormal sub-cellular/cellular/organ functions leading to physical signs and symptoms. It is logical to think that the disease process could be detected much before they clinically manifest by screening a biochemical marker or serial study of abnormal organ function. How convenient it would be, if there was a way of putting something in the blood flowing through the vessels so that it could with impunity traverse the entire circulatory system and relay all the information it obtains during its travel or, in other words, perform the functions of a detective sent through enemy territory to relay all possible information. This can be done with the help of radiopharmaceuticals or radiotracers. The radioactive tracers are in a way biological detective. They are substances, which behave like natural biological substances, and tracing their course in the body provides useful information for diagnosis and understanding of diseases. For this purpose either an radioisotope of most commonly used elements such as carbon, nitrogen, oxygen, fluorine, iodine, iron, phosphorus, sulphur, etc is used directly or is tagged with some other chemical agent, which is used by the body in a known and predictable way. An isotope is defined as an element, having the same atomic number but different atomic mass number. The chemical behavior of an element is dictated by its atomic number and therefore, all isotopes of the same element have identical behavior. Biological systems, by and large, fail to recognize the differences between atomic weights and treat all isotopes in the similar fashion. Radioactive isotopes are those isotopes, which emit radiation in the form of particulate or photons or combination of both. An element can have several isotopes, for example carbon has $^{11}$C, $^{12}$C, $^{13}$C and $^{14}$C isotopes. The $^{11}$C and $^{14}$C are radioactive and $^{12}$C and $^{13}$C are non-radioactive stable isotopes. The radioisotopes or radiotracers can be detected in vitro or in vivo with ease, because it is possible to detect radioactivity with a great deal of sensitivity and precision by means of modern electronic equipments.

The following can be considered as basic requirements for any radioisotope before using it as a tracer:
(i) It should have a biological behavior identical to that of its stable counterpart, which is a normal component of a biological system.
(ii) If it is tagged with some pharmaceuticals, it should be reasonably stable and should not change its identity during the course of a biological process.
(iii) Introduction of a radioactive tracer in a system should not disturb the normal physiological equilibrium.
(iv) The radioactivity associated with a tracer should not be hazardous to the subject under study.

A. The History of Nuclear Medicine
Nuclear medicine has a complex and multifaceted heritage. Its origin stems from the scientific discovery of $\gamma$-rays in 1896 by French physicist Henri Bequerel and the discovery of "artificial radioactivity" in 1934 by a couple, Frederick Joliet and Irene Curie. The first clinical use of "artificial radioactivity" was carried out in 1937 for the treatment of a patient with leukemia at the University of California at Berkeley and subsequently, use of radioiodine in the treatment of Graves’ disease in 1942 at Boston, opened up a new era in Nuclear Medicine. A further landmark event for nuclear medicine occurred in 1946 when a thyroid cancer patient's treatment with radioactive iodine caused complete disappearance of the spread of the patient's cancer. This
has been considered by some as the true beginning of nuclear medicine. Widespread clinical use of nuclear medicine, however, did not start until the early 1950s, because of Second World War.

The value of radioactive iodine became apparent as its use increased to measure the function of the thyroid gland and to diagnose thyroid diseases. Simultaneously, more and more physicians begin to use "radioiodine" for the treatment of patients with hyperthyroidism. The concept of nuclear medicine was a dramatic breakthrough for diagnostic medicine. Moreover, the ability to treat a disease with radiopharmaceuticals and to record and make a "picture" of the form and structure of an organ was invaluable at that time.

In 1951, Dr. Benedict Cassen of UCLA developed the first nuclear scanner. This device was used to produce planar images from $^{131}$I. In 1958, Dr. Hal Anger unveiled the scintillation camera. The camera became commercially available in 1962. In 1966, he showed that two static scintillation cameras could detect positron decay and produce images. In the mid-sixties and the years that followed, the growth of nuclear medicine as a specialty discipline was phenomenal. The advances in nuclear medicine technology and instrumentation were critical to this development.

The 1970s brought the visualization of most other organs of the body with nuclear medicine, including liver and spleen scanning, brain tumor localization, and studies of the gastrointestinal track. In 1973, the first prototype PET scanner was built by Phelps, Hoffman, and Ter-Pogossian.

The 1980s provided the use of radiopharmaceuticals for such critical diagnoses as heart disease and the development of cutting-edge nuclear medicine cameras and computers. Today, there are nearly 100 different nuclear medicine procedures that uniquely provide information about virtually every major organ system within the body. Nuclear medicine is an integral part of patient care, and an important diagnostic and therapeutic specialty in the armamentarium of modern medical science.

**B. Benefits of Nuclear Medicine**

Nuclear medicine is a medical subspeciality that uses safe, painless, and cost-effective techniques both to image the body and treat diseases with the help of radioisotopes / radiopharmaceuticals. Nuclear medicine imaging is unique in that it documents organ function and structure, in contrast to diagnostic radiology, which is based upon anatomy. It is a way to gather medical information that may otherwise be unavailable, require surgery, or necessitate more expensive diagnostic tests. As an integral part of patient care, nuclear medicine is used in the diagnosis, treatment, and prevention of serious diseases. Nuclear medicine imaging procedures often identify abnormalities very early in the progression of a disease -long before some medical problems are apparent with other diagnostic tests. This early detection allows a disease to be treated early in its course when there may be a more successful prognosis. Nuclear medicine uses very small amounts of radioactive materials or radiopharmaceuticals to diagnose and treat disease. Radiopharmaceuticals are substances that are attracted to specific organs, bones, or tissues. The radiopharmaceuticals used in nuclear medicine emit gamma rays that can be detected externally by special types of instruments: gamma or PET cameras. These cameras work in conjunction with computers used to form images that provide data and information about the area of body being imaged.
Today, nuclear medicine offers procedures that are helpful to a broad span of medical specialties, from pediatrics to cardiology to psychiatry. There are nearly one hundred different nuclear medicine imaging procedures available, and not single major organ system which is not imaged by nuclear medicine. Although, nuclear medicine is commonly used for diagnostic purposes, it also has valuable therapeutic applications such as treatment of hyperthyroidism, thyroid cancer, liver cancer, joint pains, blood imbalances, and pain relief from certain types of bone metastases.

Nuclear medicine procedures are among the safest diagnostic imaging modalities available. A patient only receives an extremely small amount of a radiopharmaceutical, just enough to provide sufficient diagnostic information. In fact, the amount of radiation from a nuclear medicine procedure is comparable to, or often significantly less than, that of a diagnostic X-ray. Although we don't think much about it, everyone is continually exposed to radiation from natural and man-made sources. For most people, natural background radiation from space, rocks, soil, and even carbon and potassium atoms in his or her own body, accounts for 85 percent of their annual exposure. Additional exposure is received from consumer products such as household smoke detectors, colour television sets, and luminous dial clocks. The remainder is from X-rays and radioactive materials used for medical diagnosis and therapy. With most nuclear medicine procedures, the patient receives about the same amount of radiation as that acquired in a few months of normal living.

C. Nuclear physics

A typical model of the atom is called the Bohr Model, in honour of Nobel Laureate Niels Bohr who proposed the structure in 1913. The Bohr atom consists of a central nucleus composed of neutrons and protons, which is surrounded by electrons which "orbit" around the nucleus. (Figure-1) Protons carry a positive charge of one and have a mass of about 1 atomic mass unit or amu (1 amu =1.7x10^{-27} kg, a very small number). Neutrons are electrically neutral and also have a mass of about 1 amu. In contrast, electrons carry a negative charge and have mass of only 0.00055 amu.

The number of protons in a nucleus determines the type of element. For example, the number of protons in uranium is 92 and the number in neon is 10. The proton number is often referred to, as
Z. Almost the entire mass of an atom is concentrated in the nucleus. However, the diameter of the nucleus is very small as compared to that of the atom (10^{-15} \text{cm} \text{ versus} \text{ 10^{-10} cm}) . The number of electrons is always the same as the number of protons inside the nucleus and, as both of them carry opposite charges. The parity between the protons and electrons make an atom electrically neutral.

One would wonder how such a simple arrangement of elementary particles would release energy in the form of radioactivity or would cause havoc by a tremendous release of energy as in atomic fission. The normal structure of a stable atom is intricately balanced, the number of neutrons counterbalancing the number of protons, and the amount of electric charge inside the nucleus balanced by that outside the nucleus. If this normal arrangement is disturbed, the atom becomes unstable and gets rid of some of its particles by releasing energy. For instance, normal hydrogen atom has 1 proton inside the nucleus. An isotope of hydrogen called deuterium has 1 proton and 1 neutron. This arrangement is still acceptable and deuterium is a stable isotope of hydrogen. Tritium, another isotope of hydrogen, has one proton and two neutrons and this arrangement makes the atom unstable. To achieve stability the atom rearranges its nuclear configuration by breaking up one extra neutron into a proton and a negative particle called $\beta$ (beta), which finally escapes from the nucleus. As the atomic number defines the chemical nature of an element, with increase of proton in the nucleus, hydrogen has transmuted itself to another element having two protons and one neutron, namely Helium shown as:

$$^{3}_1\text{H} \rightarrow ^3_2\text{H} + \beta^-$$

(Transmutation of element occurs by release of charged particles).

In the above illustration, the release of energy from the nucleus was in the form of a $\beta^-$ particle, which, in all respects, is like an electron having the same charge and mass but nuclear in origin instead of being extra nuclear like an electron.

D. Physical characteristics of radioisotopes

Every radioisotope is an unstable element and to reach a stable state, it undergoes a process of disintegration whereby energy is released either in the form of particles or as electromagnetic waves. According to Einstein, energy can exist in various forms, particulate or electromagnetic and is interconvertible from one form to the other with a definite quantitative relationship between energy and mass. ($E=mc^2$).

The amount and type of energy released is constant for each radioisotope, e.g., radioactive tritium ($^3\text{H}$) emits $\beta$ particles of maximum energy 18 KeV.

Radionuclide tries to attain stability through following three processes

1. Alpha ($\alpha$) decay

Alpha decay is a radioactive process in which a particle with two neutrons and two protons is ejected from the nucleus of a radioactive atom. The particle is identical to the nucleus of a helium atom and is called alpha particle. (Figure-2).
Alpha decay occurs only in very heavy elements (when mass number (A) is greater than 150) such as uranium, thorium and radium. The nuclei of these atoms are very "neutron rich" which makes emission of the alpha particle possible. Kinetic energy of emitted α-particle is fixed and discrete for a given decay. After an atom ejects an alpha particle, a new parent atom is formed which has two less neutrons and two less protons. Thus, when Uranium-238 (which has a Z of 92) decays by alpha emission, Thorium-234 is created (which has a Z of 90). Because alpha particles contain two protons, they have a positive charge of two. Further, alpha particles are very heavy and very energetic compared to other common types of radiation. These characteristics allow alpha particles to interact readily with materials they encounter, including air, causing much ionization in a very short distance. Typical alpha particles will travel no more than a few centimeters in air and are stopped by a sheet of paper. Alpha particles are only considered hazardous to a person's health if an alpha emitting material is ingested or inhaled.

2. Beta (β) decay

In this process, a neutron or proton inside the nucleus is converted into a proton or neutron and
excessive energy is lost. (Figure-3).

Beta decay is isobaric transition because only atomic number \( (Z) \) changes, mass number \( (A) \) remains same. Since atomic number is changed, a new element is formed. In beta decay an electron or positron (electron with positive charge) is emitted from the nucleus of a radioactive atom, along with an unusual particle called an antineutrino or neutrino. Because this electron is from the nucleus of the atom it is called beta particle to distinguish it from the electrons, which orbits the nucleus. A neutrino or antineutrino has no rest mass and no electric charge \( (Z=0) \) but it carries away some of the energy from the decay process. It rarely interacts with matter and therefore is of no biological significance. Its existence was postulated so that law of energy conservation would not be violated. However, its existence has now been proven. Like alpha decay, beta decay usually occurs in isotopes which are "neutron rich" (i.e. have a lot more neutrons in their nucleus than they do protons). Atoms, which undergo beta decay, are located below the line of stable elements on the chart of the nuclides, and are typically produced in nuclear reactors and cyclotrons.

Beta decay occurs through one of the following processes: \( \beta^- \) emission or electron emission, \( \beta^+ \) emission or positron emission, or electron capture.

\( a) \) \( \beta^- \) Emission

In this process one of the neutrons in the nucleus is transformed into a proton and the excess energy is released as a pair of particles, an electron and an antineutrino (\( \nu \)). As such there are no electrons or antineutrino inside the nucleus. These are created from excess of energy at the time of radioactive decay. Beta particles have a single negative charge and weigh only a small fraction of a neutron or proton. As a result, beta particles interact less readily with material than alpha particles. Depending on the beta particles energy (which depends on the radioactive atom and how much energy the antineutrino carries away), beta particles will travel up to several meters in air, and are stopped by thin layers of metal or plastic. Beta particle is considered hazardous if a beta emitter is ingested or inhaled. \( \beta^- \) Decay can be expressed as:

\[
^{A}_{Z}X =^{A}_{Z-1}Y + e^- + \nu
\]

Some well-known examples of radionuclide, which decay through \( \beta^- \) emission, are:

\( ^{1}\text{H}, ^{14}\text{C}, ^{32}\text{P} \)

\( b) \) \( \beta^+ \) Emission

In this process, a proton inside the nucleus is converted into a neutron and the excess energy is emitted as a pair of particles, in this case a positron and a neutrino (\( \nu \)). A positron is an electron with unit positive charge. It has the same mass as an electron and interacts with matter in a manner similar to that of an electron. Positron decay can be expressed as:

\[
^{A}_{Z}X =^{A}_{Z+1}Y + e^+ + \nu
\]

Some examples of radionuclide, which decay through positron emission, are:

\( ^{11}\text{C}, ^{13}\text{N}, ^{15}\text{O}, ^{18}\text{F} \)
c) Electron capture

In this process, a proton inside the nucleus is converted into a neutron by capturing an electron from one of the atomic shells (e.g. K, L, or M). No electron or positron but only a neutrino is emitted. Once an electron is captured from the K, L, or M shell, a vacancy is created in the inner shell of the atom. This vacancy is filled by electrons from higher shells with simultaneous emission of a characteristic X-ray or Auger electron. Electron capture can be expressed as:

\[ ^{\text{A}}_{\text{Z}} \text{X} + e^{-} \text{(orbital)} = ^{\text{A}}_{\text{Z-1}} \text{Y} + \nu \]

Common examples of radionuclide, which try to attain stability through electron capture, are: \( ^{51}_{24} \text{Cr}, ^{125}_{53} \text{I} \)

3) Gamma (\( \gamma \)) decay or Isomeric Transition

After a decay reaction, the nucleus is often in an “excited” state. This means that the decay has resulted in producing a nucleus, which still has excess energy to get rid of. Rather than emitting another beta or alpha particle, this energy is lost through two processes: an emission of high-energy photon, or internal conversion. Decay through these processes is called gamma decay or isomeric transition. (Figure-4)

\[ \text{Parent Nucleus} \rightarrow \text{Daughter Nucleus} \]

\[ \text{Cobalt-60} \rightarrow \text{Ni-60} \]

\[ \text{Gamma Rays} \]

\[ \text{\( \gamma \)-ray) } \]

In this process, the excess energy is released in the form of a high-energy photon or a pulse of electromagnetic radiation known as a gamma ray. The gamma ray is identical in nature to light or microwaves, but of very high energy (>100eV). A gamma ray and an X-ray of the same energy cannot be distinguished from each other because both interact with matter in exactly the same manner. The only difference between the two is that of origin. Gamma ray originating from the nucleus and X-ray from the outer shells. Like all forms of electromagnetic radiation, the gamma ray has no mass and no charge. Gamma rays interact with material by colliding with the electrons in the shells of atoms. They lose their energy slowly in material, being able to travel significant distances before stopping. Depending on their initial energy, gamma rays can travel from one to hundreds of meters in air and can easily go right through people.
It is important to note that most alpha and beta emitters also emit gamma rays as part of their decay process. However, there is no such thing as a “pure” gamma emitter. Important gamma emitters includes Technetium-99m, which is, used in nuclear medicine and Cesium-137 which is used for calibration of nuclear instruments.

**b) Internal conversion**

Sometimes a nuclide in an excited state, instead of emitting a γ-ray, transfers its excess energy directly to an orbital electron and this electron will be knocked out of the shell. This process is called internal conversion. A single nucleus will emit either a γ-ray or an electron. However, in a collection of nuclei, some will emit γ-ray and some conversion electrons. The ratio of the number of electrons to the number of γ-rays emitted by a collection of excited nuclei is called the coefficient of internal conversion (ic) for that excited state.

![Penetrating Distances](image)

**Radiation Measurement (unit of radioactivity)**

When given a certain amount of radioactive material, it is customary to refer to the quantity based on its activity rather than its mass. The activity is simply the number of disintegrations or transformations the quantity of material undergoes in a given period of time. The two most common units of activity are the Curie and the Becquerel. One Curie is equal to $3.7 \times 10^{10}$ disintegration per second. The SI unit of activity is the Becquerel named for Henri Becquerel who is credited with the discovery of radioactivity. One Becquerel is equal to one disintegration per second ($1\text{Ci} = 3.7 \times 10^{10} \text{Bq}$ or $37 \text{GBq}$). It is obvious that the Curie is a very large amount of activity and the Becquerel is a very small amount. To make discussion of common amounts of radioactivity more convenient, we often talk in terms of milli- and microCuries or kilo- and MegaBecquerels.

- $1/1000$ of a curie = millicurie (mCi) = $37 \text{ MBq}$
- $1/1000$ of a millicurie = microcurie (µCi)
**Half life**

The rate of disintegration of a radioactive atom or reduction in its radioactivity is exponential, i.e., in a fixed period of time, it becomes half of what it was to start with. This is called half-life of that particular element. Each radioisotope has its own invariable, immutable half-life, which may be expressed in terms of seconds, days or years.

The following table expresses the half-lives of some of the commoner radioisotopes:

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tritium ($^3$H)</td>
<td>12 years</td>
</tr>
<tr>
<td>Carbon ($^{14}$C)</td>
<td>5730 years</td>
</tr>
<tr>
<td>($^{11}$C)</td>
<td>20 min</td>
</tr>
<tr>
<td>Nitrogen ($^{13}$N)</td>
<td>10 min</td>
</tr>
<tr>
<td>Oxygen ($^{15}$O)</td>
<td>2 min</td>
</tr>
<tr>
<td>Fluorine ($^{18}$F)</td>
<td>110 min</td>
</tr>
<tr>
<td>Phosphorus ($^{32}$P)</td>
<td>14 days</td>
</tr>
<tr>
<td>Chromium ($^{51}$Cr)</td>
<td>28 days</td>
</tr>
<tr>
<td>Cobalt ($^{57}$Co)</td>
<td>9 months</td>
</tr>
<tr>
<td>Gallium ($^{67}$Ga)</td>
<td>78 hours</td>
</tr>
<tr>
<td>($^{68}$Ga)</td>
<td>68 min</td>
</tr>
<tr>
<td>Strontium ($^{89}$Sr)</td>
<td>52 days</td>
</tr>
<tr>
<td>Yttrium ($^{90}$Y)</td>
<td>2.8 days</td>
</tr>
<tr>
<td>Technetium ($^{99m}$Tc)</td>
<td>6 hours</td>
</tr>
<tr>
<td>Indium ($^{111}$I)</td>
<td>2.8 days</td>
</tr>
<tr>
<td>Iodine ($^{131}$I)</td>
<td>8 days</td>
</tr>
<tr>
<td>($^{125}$I)</td>
<td>60 days</td>
</tr>
<tr>
<td>($^{123}$I)</td>
<td>13 hours</td>
</tr>
<tr>
<td>Xenon ($^{133}$Xe)</td>
<td>5.3 days</td>
</tr>
<tr>
<td>Cesium ($^{137}$Cs)</td>
<td>30 years</td>
</tr>
<tr>
<td>Samarium ($^{153}$Sm)</td>
<td>1.9 days</td>
</tr>
<tr>
<td>Rhenium ($^{188}$Re)</td>
<td>17 hours</td>
</tr>
<tr>
<td>Thallium ($^{201}$Tl)</td>
<td>73 hours</td>
</tr>
</tbody>
</table>

The half-life of a radioisotope is an important consideration in biological experiments: it indicates the duration of time during which it will be, possible to detect a tracer because of its radioactivity and during which it would continue to affect the biological systems by its radiation.

Many biological processes in the body follow, the exponential rate, for instance, metabolic rates, excretion, clearance, etc. Half-life in terms of radioactivity is physical half-life, while half-life in terms of presence in the biological systems is called biological half-life. For a radioisotope injected in a patient, both physical and biological half-lives can be ascertained and usually the resultant of both is called effective half-life of a radioisotope. Relationship between them can be expressed as:

\[
\frac{1}{T_{\text{effective}}} = \frac{1}{T_{\text{biol}}} + \frac{1}{T_{\text{physical}}}
\]
It tells us how long a radioisotope will be effective in the body as a result of its continuous physical and biological decay.

**E. Basis of application of radioactive tracers in medical sciences**

Radioisotopes are employed usually to answer following questions.

1. How much of an administered radioactive tracer is detected at a particular site at the end of a specific reaction? Examples: Thyroid uptake measurement, where amount of orally administered radioactive iodine trapped by the thyroid gland at different time periods is determined. In vitamin B\textsubscript{12} absorption study, the orally administered radioactive vitamin B\textsubscript{12} absorbed from the gut is measured.

2. Where does the administered tracer localize? The renal cells concentrate 99m-DMSA and imaging of kidney can show the distribution of the tracer in this organ. A colloidal solution of 99m-sulphur colloid is trapped in reticuloendothelial system while large aggregates or particulate material are trapped in the capillary circulation of lungs after an intravenous injection. Sometimes inquiry into where and how much can be combined into a single investigation.

3. At what rate are events happening in the body? In a renogram, e.g., radiation detectors placed externally over both the kidneys record the rate at which the injected radioactive hippuran is passing through each kidney. In metabolic studies with radioactive albumin, the rate of synthesis and catabolism of this protein can be determined.

4. How does the biochemical processes progress? The study of intermediate metabolism of various substrates falls in this category. If carbon position 1 of the glucose molecule were labeled, detection of this radioactivity would allow us to find steps in which this particular carbon moiety is handled.

**II. Detection Of Radiation**

Radioactive tracers emit radiation or, in other words energy in one form or other. Being energy, it can be transferred in various interactions to living or non-living matter. Such an energy transfer in proper detector medium makes it possible to detect radiation.

Alpha particles have very poor penetration, not beyond a few millimeters, in matter. Although, they can transfer a lot of energy in their interactions, the poor penetrability makes them unsuitable for external detection and, therefore, there are hardly any alpha emitting radioisotopes used in medical diagnosis. Beta particles can traverse up to a few centimeters in matter and are easy to detect \textit{in vitro} in biological samples. Gamma rays have a greater range of penetrability and are the easiest to detect if emitted from a source inside the body.

The basic process of transfer of energy in tissues or in detector is ionization, where the passage of energetic charged particles or a gamma ray induces stripping of an electron from an atom. The normal stable atom, which is electrically neutral, is broken up into two ion pairs, a negatively charged electron and a positively charged remainder of the atom. These charged ion pairs are highly reactive and can lead to a series of physico-chemical events. An original particulate or electromagnetic radiation can produce a large number of such ion pairs in its pathway leading to a disturbance in the total electrical field, which can be detected by a sensitive instrument. Since
we cannot see, smell or taste radiation, we are dependent on instruments to indicate the presence of ionizing radiation.

The most common type of instrument is a gas filled radiation detector. This instrument works on the principle that as radiation passes through air or a specific gas, ionization of the molecules in the air occurs. When a high voltage is placed between two areas of the gas filled space, the positive ions will be attracted to the negative side of the detector (the cathode) and the free electrons will travel to the positive side (the anode). The anode and cathode collect these charges, which then form a very small current in the wires going to the detector. By placing a very sensitive current measuring device between the wires from the cathode and anode, the small current measured and displayed as a signal. The more radiation which enters the chamber, the more current displayed by the instrument. Many types of gas-filled detectors exist, but the two most common are the ion chamber used for measuring large amounts of radiation and the Geiger-Muller or GM detector used to measure very small amounts of radiation (Figure-6).

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**Radiation Detection**
**Gas Filled Detectors**

**Fig. 6**

The second most common type of radiation detecting instrument is the scintillation detector. The basic principle behind this instrument is the use of a special material, which glows or “scintillates” when radiation interacts with it. The most common type of material is sodium-iodide doped with very small amount of thallium. The light produced from the scintillation process is reflected through a clear window where it interacts with device called a photomultiplier tube. The first part of the photomultiplier tube is made of another special material called a photocathode. The photocathode has the unique characteristic of producing electrons when light strikes its surface. These electrons are then pulled towards a series of plates called dynodes through the application of a positive high voltage. When electrons from the photocathode hit the first dynode, several electrons are produced for each initial electron hitting its surface. This “bunch” of electrons is then pulled towards the next dynode, where more electron “multiplication” occurs. The sequence continues until the last dynode is reached, where the electron pulse is now millions of times larger than it was at the beginning of the tube. At this point the electrons are collected by an anode at the end of the tube forming an electronic pulse. The pulse is then detected and displayed by a special instrument. Scintillation detectors are very
sensitive radiation instruments and are used for special environmental surveys and as laboratory instruments (Figure-7).

Detection of radiation, therefore, basically depends on interposing a suitable interacting medium in the path of radiation and then detecting the change produced by interaction of radiation with matter by sensitive electronic instruments attached to the detector. In Geiger-Muller tubes and ionization chambers, the interaction of radiation is with the gas filled in glass tubes or other similar containers. In scintillation counter, the interaction is with a solid crystal, which has the property of emitting a flash of light whenever energy from impinging radiation is absorbed in it. In liquid scintillation counting, the interacting medium is intimately mixed with the radioactive substance.

The following general rules can serve as a guide in the maze of electronic instruments available for radiation detection:

(i) If the tracer investigation requires detection of radioactivity at a distance from the source of emission, gamma, or hard beta-emitting, radioisotopes are required. Solid crystal scintillation detectors can best detect them.

(ii) Very weak β radiation as emanating from $^{14}\text{C}$ and $^3\text{H}$, two of the common radioisotopes employed in biochemistry, can best be detected by a liquid scintillation counting system.

(iii) Beta particles with intermediate types of energy and gamma radiation can be detected by Geiger-Muller tubes, although somewhat ineffectively.

(iv) Ionization chambers are usually useful for measuring therapeutic doses and for monitoring contamination.

(v) A spectrometer is useful, primarily, when more than one radioisotope is used in a study so that the energy of one radioisotope can be discerned from that of the other.
III. Radiopharmaceuticals

Nuclear medicine images give pictorial representation of distribution of the administered radiopharmaceuticals. This in turn depends on specific mechanisms by which radiotracers accumulate in different organ systems. There are many factors influencing the biodistribution of radiopharmaceuticals such as:

1. Physico-chemical properties of radiopharmaceuticals
2. Stability of the label
3. Purity of the radiopharmaceutical preparation
4. Pathophysiological state of the patient
5. Drugs interactions

It can be seen that a full understanding of properties, quality control and mechanism of localization of radiopharmaceuticals is extremely important in identifying the source of abnormal biodistribution and in differentiating abnormality due to disease process from radiopharmaceutical and drug induced artifacts.

Nuclear medicine relies on tracer principles in diagnosis and evaluation of medical disorders. For a substance to qualify as a tracer its chemical nature should be identical to the systemic substance being traced. An ideal radiotracer is one in which a stable atom of the systemic substance is replaced by a radioactive atom. Hence radiopharmaceutical, tracing the systemic process, should contain radioisotopes of C, N, O, H atoms (since these are constituent atoms of biomolecules). Unfortunately, these radioisotopes are predominantly positron emitters, which have a disadvantage of short half-life. No single radionuclide can be proclaimed to be ideal for all diagnostic purposes. This is evident from the fact that a variety of radionuclides indeed are being used for diagnosis. Despite this, many of the properties of $^{99m}$Tc make it the most desired radionuclide for diagnostic purposes in conventional nuclear medicine.

A. The properties of an ideal diagnostic radiopharmaceutical

1. Pure gamma emitter
   For diagnostic purposes, external detection of radiation with minimal absorbed radiation dose is necessary. Hence pure gamma ray emitters with high penetrating power are preferred. Radiation dose to the patient is increased in the presence of alpha and beta particles.

2. Energy range
   Since photoelectric absorption is inversely proportional to cube of energy ($E^3$), low energy radionuclides will be the ones for gamma camera imaging. With the commercially available NaI crystals (with 3/8” or 5/8” thickness) energy range of 80-240 keV gives the highest photofraction and is optimal for imaging. From radiation safety point of view, Technetium-99m, Indium-111 and Iodine-123 fall in this range.

3. Effective half-life
   The desired half-life of radionuclide is a tradeoff between adequate counting statistics and minimal radiation dose. For practical purposes, a half-life of 1.5 times the duration of diagnostic procedure is most desirable.
4. Target to non-target ratio
This does not depend on the specific radionuclide but on the physico-chemical characteristics of specific radiopharmaceutical. A high target to non-target ratio (minimum of 5:1 for planar and 2:1 for SPECT) is necessary to interpret the images. A systematic analysis of structure-distribution relationship (study of effect of variation in molecular structure on biodistribution of radiopharmaceutical) can lead to the development of radiopharmaceuticals with high target to non-target ratio. For example, Tc-99m-mebrofenin and I-131 MIBG are developed based on the analysis of structure-distribution relationship.

5. Chemistry of radionuclide
For conventional nuclear medicine, ability of the radionuclide to form a wide variety of compounds is essential. This is because biodistribution of the radiopharmaceuticals depends predominantly on the physico-chemical characteristics of the chelate (pharmaceutical component) rather than on the radionuclide. Tc-99m, being a transition metal with multiple oxidation levels, has the ability to bind to a large number of compounds under physiologic conditions making it one of the most desired radiopharmaceutical. However it is known that some compounds can be labeled only with specific radionuclide. Hence there is always a need to use multiple radionuclides.

6. Radionuclides should be cheap and readily available.

7. It should have long shelf-life.

8. It should be cost effective.

B. Properties of an ideal therapeutic radiopharmaceutical
The aim of radionuclide therapy is complete ablation of the target with minimal radiation exposure to surrounding structure. Important considerations to achieve high target to non-target ratio are:

a) Type of emission: Pure beta emitting radionuclides are the most suitable for radioablation. Because of high LET (linear energy transfer) and short range (in mm to cm), delivery of energy to target tissue will be high. Despite this, radionuclides with beta and gamma radiation can be used if high target to non-target ratio can be achieved. Radioiodine which is used for thyrotoxicosis and thyroid cancer emits both beta and gamma rays; 90% of damage is caused by beta particles of $^{131}$I. Gamma allows to image the distribution of $^{131}$I and helps in further planning.

b) Energy: Radionuclides emitting high energy $\beta$ - particles are preferred since delivery of more energy to target tissue leads to better ablation. There is no strict cut-off energy level, but radionuclides with $\beta$ - particle energy of more than 1MeV are desirable.

c) Effective half-life: Radionuclides with effective half-life in the order of days are preferred. As the half-life of the radionuclide increases cumulative radiation dose to the target tissue increases thus leading to better ablation. However, it also increases the radiation dose to adjacent organs. Thus a balance between efficacy and safety needs to be maintained in selecting the radionuclide.

d) Target to non-target ratio: This is the single most important parameter in the selection of radiopharmaceuticals for therapy. While high target to non-target ratio is desirable for
diagnosis, it is mandatory for therapeutic purposes to minimize radiation exposure to non-target organs. A figure of merit is used to express target to non-target ratio. $T/\sqrt{N}$ represents the figure of merit, where $T$ is the dose to the target and $N$ is the dose to the non-target organ. Attainment of high target to non-target ratio depends on physical and chemical properties of radiopharmaceutical.

e) Others: The radiopharmaceutical should be cheap and readily available. Radiation exposure to the occupational workers and the patient should be kept to the minimum level possible.

**C. Mechanism of localization of radiopharmaceuticals**

The clinical utility of a radiopharmaceutical depends on its ability to concentrate in target tissue and in target lesion. In order for the radiopharmaceutical to be useful for evaluation of function, concentration in target tissue is sufficient. If one wants to use it in differential diagnosis, it has to accumulate only in the target lesion and not in the other lesions of the same organ. $^{67}$Ga accumulates in a variety of lesions (inflammatory, malignant and others) making it less useful in differential diagnosis. $^{99m}$Tc-HMPAO-labelled WBC studies, on the other hand, reliably differentiates inflammatory from non-inflammatory lesions and is definitely an improvement over $^{67}$Ga citrate. Still there is scope for further improvement because the cause of inflammation cannot be established by $^{99m}$Tc-HMPAO WBC studies. Agents like $^{99m}$Tc-labelled ciprofloxacin claiming to be useful in differentiating infection from sterile inflammation are clearly needed to improve the specificity of diagnosis.

A useful classification of radiopharmaceuticals based on the mechanism of localization is given here (modified from the original proposal of Eckelman and Reba (1978).

**Classification of radiopharmaceuticals**

**Substrate non-specific**
1. Simple diffusion
2. Exchange diffusion
3. Active transport
4. Phagocytosis
5. Compartmental localization
6. Capillary blockade
7. Cell sequestration
8. Chemisorptions

**Substrate specific**
1. Isotopically substituted biochemical
2. Metabolic trapping
3. Enzyme substrate
4. Receptor binding
5. Antigen-antibody reaction

**Substrate non-specific**
1. **Simple diffusion**

This refers to the transport of radiopharmaceutical along the concentration gradient due to increased permeability to a particular region. This mechanism does not require energy. Example
of this type of mechanism is the uptake of $^{99m}$TcO$_4$ (pertechnetate) in the brain due to defect in the blood brain barrier.

2. **Exchange diffusion**
This involves the principles of ion exchange. $^{18}$F (fluorine) exchange with hydroxyl group of amorphous portion of hydroxyapatite is an example of this mechanism. The exchange process leads to the formation of $^{18}$Flouroapatite, which can be imaged by PET (positron emission tomography).

3. **Active transport**
It refers to the transport of radiopharmaceutical against an electrochemical gradient. The mechanism requires the presence of naturally occurring transporter protein and energy utilization. Radiopharmaceuticals, which are structurally analogous to the natural substance undergoing transport, are also handled in a similar manner. $^{99m}$Tc-MAG$_3$ (mercaptoacetyl triglycine) and $^{131}$I-OIH (orthoiodo hippurate) localise with this mechanism. Some compounds like $^{201}$Tl (Thallium) being structural analogue of K$^+$ (potassium) localise by active transport as well as diffusion.

4. **Phagocytosis**
Physical entrapment of colloidal particles by macrophages, distributed throughout the reticulo-endothelial system, is called phagocytosis. The mechanism critically depends on the size of the particles. Different organs require optimum particle size for their visualization. For lymphoscintigraphy particles with 1-10 nm size are optimum. Under normal circumstances, $^{99m}$Tc phytate uptake in spleen is minimal and most of the tracer goes to liver. However, in liver disfunction (chronic liver disease) there is ‘colloid shift’ with significant uptake in spleen and bone marrow.

5. **Compartmental localization**
A compartment refers to a single homogeneous well-mixed distinct component of a biological system. Here it represents a distinct physical fluid space. The tracer is introduced into the space and maintained for some time for imaging purpose. Introduction of $^{111}$In labeled DTPA into the subarachnoid space by lumbar puncture and imaging CSF kinetics is one example of this mechanism.

6. **Cell Sequestration**
This mechanism utilizes the normal function of the spleen, which recognizes and traps damaged erythrocytes. The method involves heat denaturing of a small volume of erythrocytes and radiolabeling them for imaging. In splenectomised patients, detection of accessory spleen is best accomplished by this method.

7. **Capillary blockade**
It is deliberate microembolisation of capillaries with radiolabeled particles. The amount of microembolisation is proportional to arterial blood flow to that region. In lung perfusion imaging $^{99m}$Tc-MAA is used. An average of 350,000 particles (range 200,000 to 700,000) with 90% of them with 10-90 µm size is injected intravenously. Approximately 600 million pulmonary arterioles are estimated to be small enough to trap these particles. Thus the physiological effect
of the microembolisation is insignificant. However, in patients with pulmonary hypertension, number of particles in adults is reduced to 150,000.

8. Chemisorptions or physico-chemical adsorption
This is avid and irreversible binding of specific chemical structure onto a surface. For example, $^{99m}$Tc-diphosphonate complexes adsorb onto bone surface. The structural configuration of the molecule is more important than the presence of specific atom in the molecule e.g. both diphosphonate (P-C-P) adsorb on the bone surface to the same extent.

Substrate specific
1. Isotopically substituted bio-chemicals
This mechanism depends on the substitution of radioactive atoms in place of a stable atom of biochemical substances. The Radionuclides will be isotopes of carbon, nitrogen, oxygen and hydrogen. All of the currently used radionuclides for this purpose are positron emitters. This is one of the reasons why PET is widely recognized as the best imaging modality for functional imaging.

2. Metabolic trapping
$^{18}$FDG (2-fluoro-2-deoxy-glucose) is an example of metabolic trapping. While $^{18}$FDG goes to almost all organs immediately after intravenous injection, it is retained for a long time only in brain and heart. Unlike glucose, it does not undergo renal tubular reabsorption leading to rapid renal excretion. This leads to rapidly decreasing plasma $^{18}$FDG levels. Because of their high glucose-6-phosphatase levels tissues other than brain and heart respond by releasing $^{18}$FDG which in turn is excreted in urine. The net effect is selective trapping of $^{18}$FDG in brain and heart.

3. Enzyme substrate
Radiopharmaceuticals acting as substrate for specific enzyme catalyzed reaction can be used to study the reaction. Here the substrate needs to be specific for the enzyme and should have high specific activity. It should not produce any physiologic or pharmacologic response. Radiolabeled fatty acids to study myocardial fatty acid metabolism is an example of this mechanism. Potentially, radiopharmaceuticals acting as substrate for microbial enzymes can be developed offering an opportunity to be etiology specific.

4. Receptor binding
Receptors are protein molecules located at cell membrane or cytosol in very low concentration, which initiate highly specific changes when activated by specific ligands or their structural analogues. Changes in receptor concentration are known in many diseases like Parkinson’s disease, Schizophrenia, Huntington’s chorea etc. By knowing the map of receptor density, diagnosis and response to treatment of many diseases can be obtained.

There are some requirements for a radiopharmaceutical to be useful as a receptor-imaging agent:
1. High specific activity
2. High binding affinity to the receptor
3. Low binding affinity to non-receptor binding sites
Potentially radiopharmaceuticals can be designed for the receptors of microbial agents. If this can be realized, it can lead to a whole new class of radiopharmaceuticals capable of identifying etiologic agents in many disease processes. $^{123}$I-MIBG acting as a ligands for the adrenergic receptors of myocardium is an example of this mechanism.

5. Antigen-antibody reaction
Radiolabeled monoclonal antibodies act by their immunologic specificity against a specific target antigen. In-111 Oncoscent (Anti-CEA antibody) is useful in the detection of recurrence of colorectal cancers. In the presence of rising CEA levels after surgery with normal CT/MR studies, the study is useful in identifying the source of rise in CEA. Antigenic diversity of the tumors, inadequate dose delivered to the target region are some of the limiting factors in the widespread usage of monoclonal antibodies.

IV. Production of radionuclides
The radionuclides most commonly used in nuclear medicine are artificial, produced by following methods:

A. Reactor produced radionuclides
A nuclear reactor is a source of a large number of thermal neutrons. Thermal neutrons are those neutrons whose energy is very small (~0.025 eV). At these energies, neutrons can be easily captured by stable nucleus, and nucleus can become unstable. In a nuclear reactor the stable nucleus of various chemical compounds are bombarded with low energy thermal neutrons. The nucleus of the bombarded atom is rearranged and this becomes radioactive or unstable.

In nuclear reactor radionuclide can be produced either by fusion or fission.

Fusion
When bombarded, one neutron fuses with the given stable nuclide. Resultant nuclide (if radioactive) quite often decays through $\beta^-$ emission.

\[
\begin{align*}
^{98}\text{Mo} + \text{n} & \rightarrow ^{99}\text{Mo} \rightarrow ^{99m}\text{Tc} \\
^{130}\text{Te} + \text{n} & \rightarrow ^{131}\text{Te} \rightarrow \beta^- \rightarrow ^{131}\text{I} \\
^{124}\text{Xe} + \text{n} & \rightarrow ^{125}\text{Xe} \rightarrow \beta^- \rightarrow ^{125}\text{I}
\end{align*}
\]

Fission
Many heavy nuclei (A~200) after capturing a neutron, instead of producing a heavier radionuclide, gets splitted into smaller nuclei. This is called fission.

\[
^{235}\text{U} + \text{n} = ^{236}\text{U}(f) \rightarrow ^{99}\text{Mo} + ^{135}\text{Sn} + 2\text{n} \text{ or } ^{131}\text{I} + ^{102}\text{Y} + 3\text{n} \text{ or } ^{137}\text{Cs} + ^{97}\text{Rb} + 2\text{n}
\]

B. Accelerator produced radionuclides
In accelerators, stable non-radioactive nucleus is bombarded with high-speed charged particles like electrons, protons, deuteron and alpha particles to make them radioactive. There are two types of accelerators: (a) Linear and (b) Cyclical accelerator or Cyclotron.

In Linear accelerators bombarding particles are accelerated along a linear path using an electric current and voltage for control while in cyclotron the bombarding particles are accelerated along
a circular path using electric field and magnetic field for control. Usually these radionuclides decay through positron emission or electron capture.

\[
\begin{align*}
^{203}\text{Tl} + p & \rightarrow ^{201}\text{Pb} + 3n \rightarrow \beta^+ \text{ or } \text{EC} \rightarrow ^{201}\text{Tl} \\
^{122}\text{Te} + \alpha & \rightarrow ^{123}\text{Xe} + 3n \rightarrow \beta^+ \text{ or } \text{EC} \rightarrow ^{123}\text{I}
\end{align*}
\]

### C. Radionuclide generators

A radionuclide generator is a two or three step radioactive series in which a long-lived radionuclide (also called parent) decays into a short-lived radionuclide (also known as daughter) of interest. A stable element is made radioactive by neutron bombardment of its atoms in a reactor. The radioactive element resulting from the unstable state of the nucleus starts disintegrating to a daughter product, which is also, radioactive and, in turn, disintegrates to another element, which is stable. Parent nuclide is kept in a suitable container, known as generator, and can be transported to distant location. Daughter nuclide can be easily separated from its parent at hospitals and central Radiopharmacies locally and used for various imaging purposes. Most commonly used generators are Molybdenum-Technetium generator.

Radioactive molybdenum \((^{99}\text{mo})\) \(\rightarrow\) Radioactive technetium \(\rightarrow (^{99m}\text{Tc})\) technetium

- 2.7 days half-life
- 6 hours half-life

In the above example, the parent has a long life from which a daughter of shorter half-life can be separated periodically. The shorter half-life permits administration of a larger dose to the patient without unduly increasing his radiation exposure and making it easier to detect this radioactivity in the body. Apart from that, the greatest advantage of these compounds lies in their constant availability in the laboratory.

### V. In Vitro Assays

This is a unique kind of radioisotopic investigation where no radioisotope is administered to the patient. The basic principle of these assays is worth elucidating. *In vitro* test, also known as saturation analysis, three factors are essential: (1) a specific binding agent with only a limited capacity for binding the substance of interest, (2) a radioactive form of the substance which can be added in amounts that are normally just sufficient to saturate the binding sites, and (3) a method for separating the bound and the unbound fractions of the substance of interest.

In radioimmunoassay of various hormones, antibodies to a hormone are used as a binding agent, a high specific activity labeled hormone sufficient to saturate the amount of antibody is added extrinsically and various techniques like chromatography, electrophoresis, etc., are employed to separate the bound and unbound fractions of hormones. The ratio of these fractions in a particular serum sample depends upon the amount of hormone originally present in the serum. The basis of the radioimmunoassay methods, the most commonly followed *in vitro* assays, is the competitive inhibition by unlabeled hormone to its specific antibody.

In this system, the specific antibody serves as the binding agent. High specific activity labeled hormone is prepared by iodinating with 125-I, the hormone of interest. When the concentration of unlabeled hormone in the unknown serum sample is high, the antibody available for binding
of labeled hormone is insufficient and a large fraction of the labeled hormone added to the serum remains unbound to the antibody. The assay system needs separation of unbound from free fractions by use of various biochemical techniques like chromatography, electrophoresis, etc. The concentration of hormone in unknown plasma is determined from the degree of binding of labeled hormone in the sample by comparison with the binding observed with standard solutions containing known amounts of hormone. The basic principle of radioimmunoassay is also called competitive inhibition where the true competition is between immunoreactivity of the hormone in the standard and in the unknown serum for the antibody added for the reaction.

Substances that can be estimated by radioimmunoassays are innumerable, e.g., a variety of peptide hormones, drugs, nutrients, steroids, infective agents. Growth hormone, TSH, thyroxine, insulin, FSH and LH can be assayed easily by these techniques and interesting new physiological data has emerged from widespread application of these assays.

Dr. Yalow and Dr. Berson first enunciated the basic principle of radioimmunoassay. Their discovery was awarded the Nobel Prize in Medicine for 1977.

VI. Study of intermediary metabolism
Many organic compounds of biochemical interest are available in radioactive labeled form, labeled either by radioactive carbon ($^{14}$C) or hydrogen ($^{3}$H). By introducing them in a biochemical reaction in vitro or in vivo, their fate can be followed, e.g., $^{14}$C labeled acetate gets incorporated into fatty acids, cholesterol, etc. The fatty acids are catabolized by the removal of two carbon fragments. The $^{14}$C-cholesterol is used for steroid formation. All these processes can be traced because of the initial introduction of $^{14}$C acetate as a tracer. Similarly in the study of carbohydrate metabolism, $^{14}$C-glucose can be employed. If C in 1 position is labeled, the C is metabolized through HMP shunt pathway, while if the C in 6 position is in the labeled form its final metabolism can take place through the Embden-Meyerhof pathway. With the labeled amino acids, information on the synthesis and turnover of various body proteins can be obtained. Similarly, by using simple $^{14}$C labeled precursors the synthesis of nucleic acids can be followed.

VII. Autoradiography
This technique makes it possible to detect the labeled biological compound at the cellular and sub-cellular level. Radiations from isotopes sensitize photographic emulsion. In fact, Roentgen first discovered radioactivity by an accidental exposure of a photographic plate by a radioactive source. If the radiation is the non-penetrating type of beta radiation (e.g., tritium) with only a limited range in matter (e.g., $^{3}$H), fine resolution is obtained.

The cell or tissue, which has the incorporated radioactivity, is processed and then the histological slide is left in close contact with a thin strip of photographic film or covered with a photographic emulsion. After a suitable time of exposure, the film is developed and examined under the microscope. The cells containing the radioactivity show it by the presence of dark grains of exposed silver halide.
VIII. Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is a medical imaging technology, which has an unparalleled capability to generate images of body function and metabolism. It combines a proper image reconstruction algorithm, annihilation coincidence detection, linear and angular sampling, and attenuation correction. It is mostly used to create functional images of the brain and heart and to evaluate cancer. In PET, positron-emitting radionuclides are used. Many PET tracers are physiologically identical to natural biological substrates. As a result, a PET tracer in the body will follow the same physiological pathways as the non-radioactive natural substrate that it mimics. Quite often, internal chemical or physiological changes related to metabolism predate or exceed changes in the structural appearance of tissue or organ. PET uses internal tracers to measure the rate of internal processes and can often distinguish between normal and abnormal physiology in cases where no anatomical change has occurred. Most commonly used PET tracers are $^{18}$F, $^{11}$C, $^{15}$O, and $^{13}$N. $^{18}$F is incorporated in glucose, and as, glucose is widely used as substrate for getting energy, and metabolism of various organs can be assessed by imaging that organ (Figure 8A & 8B).

IX. Scintigraphy and Imaging of Organs

How radiopharmaceuticals are useful in imaging of various organs was described briefly in the above section. The imaging of an organ is done by different kinds of instruments: (i) a rectilinear scanner, it is now obsolete and is of historical interest only, (ii) a gamma camera where the detector is so large that it views the entire organ at the same time and then electronically discerns the amount of radioactivity arising from each point. The process is quick and permits visualization of the dynamic function of an organ, for instance, sequential imaging of kidneys to visualize...
the passage of radioactive DTPA through it. Dynamic functional studies of an organ by a gamma camera provide a non-invasive way of investigating the regional biochemistry or physiology of an organ quantitatively in vivo by using a suitable radioactive tracer. (iii) PET scanner is used for imaging with high-energy positron emitting radionuclides.
Scintigraphy affords the best means to detect focal defects in an organ. A recent advance with the gamma camera type devices is the development of tomographic systems, which produces images of radioactivity in planes at different depths within the subject. If the radiopharmaceutical used is such that it localizes in the normally functioning cells of an organ, such a defect would be seen as a void, conventionally described as a 'cold area'. If the radiopharmaceutical localizes only in the pathological lesion, the image shows the lesion as a positive or a 'hot area'. This latter type affords a pathological diagnosis in addition to an anatomical diagnosis, if the concentration of a radiopharmaceutical is specific to a particular pathology. Some common scintigraphic procedures are described here:

**A. Thyroid**

Radioiodine ($^{131}$I, $^{123}$I) or radioactive pertechnetate ($^{99m}$TcO$_4$) which, biologically, behaves as iodine, are used for thyroid scanning. The image shows the degree of function of different parts of the gland. A nodule which concentrates radioiodine is less likely to be malignant than a cold nodule. Concentration of radioiodine at an abnormal extrathyroidal site is suggestive of thyroid cancer metastases (Figure-9: normal $^{99m}$Tc thyroid scan).

![Figure-9](image)

**B. Pancreas**

The largest amount of proteins is synthesized per unit time in this organ because of a number of digestive enzymes synthesized there and hence the turnover of amino acids is high. Radioactive selenium labeled methionine is, therefore, used for imaging the pancreas. Inflammation and tumors of the pancreas can be diagnosed by their specific images.

**C. Liver and Gall Bladder**

Colloidal preparations of $^{99m}$Tc, such as sulfur-colloid or phytate localize in the RES cells of liver. A pathological lesion like a malignancy or an abscess shows as a cold area in the liver. $^{99m}$Tc labeled iminodiacetic acid (lidocaine derivative) group of chemicals pass through the liver parenchymal cells into the biliary canaliculi to concentrate finally in the gall bladder which can be stimulated to evacuate by a fatty meal or an injection of cholecystokinin. This kind of studies gives useful information about the formation and kinetics of the bile flow. By this one can assess
the function and structure of liver, biliary tree and gall bladder (Figure-10: normal hepatobiliary scintigraphy).

**D. Spleen**
Red blood cells labeled with radioactive chromium ($^{51}$Cr) or $^{99m}$Tc and then denatured by heating tend to localize in the spleen. Scans taken after the injection of these agents can provide vital information about splenic infarcts, and ectopic or accessory spleen (Figure-11: Denatured RBC scan showing multiple accessory spleens in the left subcostal and hypogastric region).

**E. Kidney**
$^{99m}$Tc labeled DTPA, DMSA, GHA or radioiodine labeled hippuran localize in kidneys and are useful for imaging of the kidneys. Apart from showing space occupying lesions, kidney scans are useful in showing the relative function of the two kidneys and obstruction to the out flow tract. $^{99m}$Tc-DMSA renal scan is the method of choice to evaluate renal parenchyma (cortex). OIH can be used to measure effective renal plasma flow (Figure-12: normal $^{99m}$Tc-DTPA renal scan).
**F. Lung**

Macroaggregated-albumins are large particles and are held up, in the lung capillaries after an intravenous injection. This procedure is mostly useful for demonstrating a block in the vascular perfusion of lungs, such as acute pulmonary embolism, which is often fatal, if undetected and untreated. In a similar way, inhalation of a radioactive gas (such as Xenon) or radiolabeled aerosols can show the patency of the bronchial tree (Figure-13: normal lung scan).
G. Brain
There are radiopharmaceuticals which do not localize, to a significant extent, in the normal brain but only localize nonspecifically at the site of a pathological lesion, be it cancerous, vascular, or any other, causing break in the blood-brain barrier. Prominent amongst these radiopharmaceuticals is 201Tl, 99mTc-GHA (glucoheptonate), 99mTc-MIBI, and 99mTc-TF (tetrophosmine) etc. They help in localizing and identifying various tumors. Few radiopharmaceuticals such as 99mTc labeled HMPAO (hexamethylene propylamine oxime) and 99mTc–ECD (ethylene cysteine dimmer) are used for brain perfusion studies and are useful in seizure focus localization. 11C or 18F labeled glucose or amines, radioiodine labeled amphetamine and quite a few other chemicals cross the blood brain barrier to localise in the brain substance. The tomographic display of their distribution and variations in their distribution at different times provide a most dramatic in vivo method for the study of cerebral metabolism (Figure-14: normal 99mTc-HMPAO brain SPECT).

Figure-14

Vol Rendered
Ant. Right Left
Post.

Feet to Head

Transversal
Slice thickness 4.42 mm

Right to Left

Sagittal
Slice thickness 4.42 mm

Anterior to Posterior

Coronal
Slice thickness 4.42 mm
**H. Bone**
Bone scans, using $^{99m}$Tc-diphosphonate, show pathological lesions in bones as areas of positive or negative concentration. Inflammatory and malignant lesions show similar appearances but different patterns. This is one of the quickest and the most non-invasive method for the search of a metastatic spread in the skeleton of a primary cancer in a patient. Bone scan can be most conveniently used for serial follow-up for bony metastasis (Figure-15: normal bone scan in a child).

![Anterior and Posterior Bone Scan](image)

**I. Heart**
The recent interest in coronary heart disease has spurred Nuclear Medicine in developing several very useful investigations of the myocardial function. One group of studies concerns with the localization of a suitable radiopharmaceutical in the normal myocardium, e.g. 201-Thallium or the localization of a radioactive chemical in the infarcted myocardium. The former would show on imaging areas of Ischemia as areas of reduced uptake of the radiopharmaceutical while the latter would show an infarct as an area of increased uptake (hot area) of the radiopharmaceutical (Figure-16: normal cardiac SPECT in rest and stress).
X. Dynamic Function Studies
The imaging of organs by scintigraphy shows anatomical location and functional impairment in various local defects in an organ.

A. Dilutional studies
To take an example, if 1 ml containing 100 units of radioactive tracer is introduced into a beaker having 100 ml of water and if 1 ml sample of water is withdrawn from this beaker after thorough mixing, only 1 unit of radioactivity would be found in 1 ml of diluted sample. In other words, to state a general law, the degree of dilution of the tracer depends on the volume diluting the tracer. If the degree of dilution of a tracer that occurs after mixing can be determined, the total volume causing dilution can be computed. This basic principle is employed successfully in the following measurements:

1. **RBC volume.** A known amount of radioactive labeled RBCs is introduced in the blood. A sample of blood is withdrawn after few minutes to allow for uniform mixing of labeled RBCs in the blood. The degree of dilution of this sample, in terms of radioactivity, allows computation of total RBC volume.
2. **Plasma volume.** Radioiodine labeled albumin remains in the plasma compartment of the blood and the degree of its dilution allows determination of plasma volume.
3. **Total exchangeable sodium and potassium.** This is determined by using radioactive sodium and potassium as tracers:
4. **Total body water.** Administration of radioactive water permits the estimation of total body water.
B. Thyroid function studies
Radioactive iodine is the most commonly used tracer in medicine. It traces iodine metabolism in the body and while doing so provides useful information about the function of the thyroid gland. The percentage of the administered dose accumulating in the gland at various times can be determined. Increased trapping signifies hyperactivity while decreased trapping suggests hypoactivity of the gland (normal values in India for % uptakes at various times: 2 hr: 5-15%, 24 hr: 15-35%). The percentage of the administered dose excreted in urine is inversely related to the amount picked up by the thyroid gland and can also serve as an indirect index of thyroid function.

C. Renal function studies
Radioiodine labeled hippuran is rapidly excreted through the kidneys after an intravenous injection and its passage can be, monitored by a gamma camera. This is the simplest method of simultaneous assessment of functions of both the kidneys. The diuretic renogram is usually performed to differentiate obstructive from non-obstructive hydronephrosis. Angiotensin converting enzyme inhibitor (ACEI) renography is also a popular method to diagnose hemodynamically significant renal artery stenosis from anatomic narrowing of renal artery. The quantitative assessment of renal function namely ERPF (effective renal plasma flow) can be calculated by drawing blood samples at various time intervals. Similarly, GFR (glomerular filtration rate) can be calculated by gamma camera technique or by taking few blood samples at predetermined time interval, after injecting 99m-Tc DTPA.

D. Liver function studies
As explained earlier, it is possible to visualize the passage of a suitable radiopharmaceutical through the biliary tree by sequential imaging on a gamma camera. By these techniques, gall bladder function and the way it responds to normal physiological stimuli can be studied quantitatively.

E. Haematology
Fate of a radioactive tracer after its introduction in the body can be followed to obtain useful physiological information. Such studies are called kinetic studies because the movement of a tracer through various parts of the body is traced. The rate of plasma disappearance of radioactive iron indicates how avidly the iron stores and the bone marrow pick up the intravenously injected radioactive iron (59Fe). In anemia due to iron deficiency the iron would disappear rapidly from the plasma to bone marrow. External detectors placed over liver, spleen and sacrum, monitor the rate and the degree of accumulation of iron at the storage sites and the bone marrow. Later on, how much and the rate at which the same tracer reappears in the RBCs can be determined. If the same study is continued further the fate of these endogenously labeled RBCs can be observed. How long do they survive in circulation? Where are they destroyed? Does the iron from the RBCs get reutilized?

Iron as described in the above experiments is a physiological substance used in its radioactive form as a tracer. Chromium (51Cr) as a radioisotope is also taken up by the RBCs and bound to haemoglobin. If the fate of chromium labeled RBCs is followed, it can also provide somewhat similar information about the life span of RBCs and the sites of its destruction. Such kinetic studies can be done with many tracers, for instance, labeled albumin, calcium, vitamin B12, etc.
**F. Blood flow**
In the above type of studies, one is concerned with the fate of a radioactive tracer. If the tracer is such that it confines itself to the vascular compartment and remains in circulation, it can then provide information about the rate of flow of blood through several organs. Such tracers are labeled albumin, indium bound transferrin, etc. The flow studies include peripheral blood flow in a limb, cerebral blood flow, cardiac output, etc. The cardiac output study consists of the introduction of a radioactive bolus and detecting its passage by an external detector over the precordium. It can be done by two methods: first-pass method and ejection fraction method.

(a) The passage of a radioactive bolus is studied through various chambers of the heart by using a gamma camera attached to a digital computer. This can show shunts by abnormal patterns of time activity histograms for passage through each of the chambers of heart. This kind of single pass study can also estimate the left ventricular ejection fraction by measuring the variation in radioactivity over the left ventricle between systole and diastole.

(b) A radiopharmaceutical which remains circulating for several hours would show heart as a blood pool at equilibrium. The images of the heart can be collected at specific times during the cardiac cycle by triggering the gamma camera through an electronic signal from E.C.G. Estimation of change in the left ventricular volume during systole and diastole allows the measurement of left ventricular ejection fraction.

**XI. Absorption Studies**
How much of an orally administered radioisotope is absorbed in the body can be determined in various ways:

1. By collecting faeces for several days and finding out the total amount of unabsorbed radioisotope excreted in it.
2. By taking blood samples at appropriate times and determining the amount of radioactivity appearing in it as a result of absorption of the oral dose.
3. By collecting the urine and determining the amount of radioactivity in it, if the absorbed radioisotope is finally excreted through the urine.
4. By counting the entire human body in a whole body counter to find out how much of the absorbed radioisotope is retained in the body.

Such absorption studies can be done with various radioactive nutrients available: radioactive cobalt labeled vitamin B12, radioactive iron, calcium, folic acid, fat, etc. Most important amongst these is vitamin B12 absorption. In pernicious anemia, in the absence of intrinsic factor, the oral vitamin B12 is not absorbed, but returns to normal if vitamin B12 is administered with the intrinsic factor. In tropical sprue, it is not absorbed because of the defect in the mucous membrane of ileum where its absorption occurs normally. Usually, at least 30% of the orally administered vitamin B12 is absorbed.

**XII. Therapeutic Applications of Radioisotopes**
We have mentioned that radiation interacts with matter by transfer of energy. If excessive, this transfer can destroy the cell. In tracer investigations, the amount of radioactivity used is very small and the energy transfer is so minimal that only a sensitive electronic instrument can pick it up. However, as the difference between the destruction and the detection is only in the amount of dose, it is vitally important that the physician is intimately aware of the hazards involved in use
of radiation. This is especially so when radioisotopes are employed for therapeutic purposes where the margin between safety and hazard is narrow.

The following considerations apply to the use of radioisotopes for therapeutic purposes:
(1) A radioisotope should be capable of delivering a maximum dose to the pathological site while exposing the rest of the body to a minimum possible dose.
(2) Cautious use in children and young adults.
(3) It should not be administered to pregnant women.

Radioisotope therapy
During the last decade, major progress has been made in the treatment of disease with radioisotopes. Treatments involving the use of medical isotopes are gaining momentum in the race against many types of cancer. In contrast to external beam radiotherapy, radiotherapy delivered via internal administration of radionuclides targeted via a tumor-seeking carrier has the allure of the “magic bullet”. Some researchers predict that over 80% of cancer types should be treatable with radioisotopes.

Certain experimental treatments have had such remarkable success that current cancer sufferers should be made aware of their potential. Lives have been saved in numerous cases and in several clinical trials testing experimental treatments, very positive results were achieved on patients who had exhausted all other treatment options with no success.

Central to the progress of new radioisotope treatments has been the invention of unique and effective "delivery systems" which enable physicians to point the selected isotope directly at the diseased tissue. One of the most promising is called radioimmunotherapy (RIT). In this technique, radioisotopes are attached to antibodies with a specific affinity for certain cells in the body. The antibodies guide the isotope to the cancer cells where the radioisotope then destroys them. RIT provides an opportunity to deliver more specific radiation to tumor cells while sparing normal tissue. This new medical technology capitalizes on the knowledge accumulated by microbiologists about cell-level interactions inside our bodies. The power of radiation to kill cancer cells has been known for years, but the precise science of targeting cancer cells with specific proteins and packaging the radiation for direct delivery has taken time to create. The potential for treating cancer and other diseases with RIT technology is immense. While the process itself is still in its infancy, some very promising results have been achieved. This discovery uses millions of cancer seeking antibodies to guide radiation to the cancer. The radiation rides along like a backpack as the antibodies flow through the bloodstream. When the antibodies arrive at the cancer site, they attach and remain there, giving their radioactive "backpack" plenty of opportunity to destroy the cancer cells.

Clinical trials have shown RIT to be successful in treating leukemia and lymphoma, and animal studies have opened the way for testing these methods on a wide number of different cancers found in humans. More recently, the finding of receptors on breast tumors, neuroendocrine tumors, and melanoma has suggested delivery of radiotherapy via radiolabeled peptide ligands. Molecular targeting raises the possibility of treating metastases that are too small to be detected by standard diagnostic imaging. Such small lesions play an important role in relapse and
mortality from metastatic cancer. The ability of these molecular targeting methods to localize to the small lesions offers the opportunity to treat metastatic disease effectively.

Popular names for radioimmunotherapy include "smart bullets", "magic bullets", "guided missiles", and "smart bombs". These are great descriptors for a life-saving technology that pre-engineers biological molecules and their isotope backpacks to literally "seek and destroy" cancer cells.

Currently the most common therapeutic uses of medical isotopes are for treatment of thyroid and prostate cancer, hyperthyroidism, cancer bone pain, polycythemia and arthritis.

1. Thyrotoxicosis
A large amount of radioiodine specifically concentrates in the thyroid and hence it is possible to deliver a large, ablative dose to the thyroid without affecting other parts of the body. The purpose of this therapy is to destroy hyperfunctioning thyroid tissue to an extent that the patient becomes euthyroid. Calculation of the dose required to achieve this is complicated and difficult as it has to take into account several imponderables like the size of the thyroid gland, biological half-time of radioiodine in the thyroid, uptake of radioiodine by the thyroid gland, etc.

2. Thyroid cancer
Differentiated thyroid cancer retains the property of concentrating radioiodine. The metastases of thyroid cancer also have the same property. In a case where multiple metastases are present at various sites, radioiodine is the best means of producing their destruction. The mortality and morbidity in thyroid cancer is considerably lower than in much other kind of cancers because of this mode of therapy.

3. Liver Cancer
Patients with inoperable and large HCC can be offered internal radionuclide therapy to prolong their survival and improve the quality of life. The aim of internal radionuclide therapy is to deliver the radionuclide to the hepatic tumor, where it must reside for a period sufficient to deliver the scheduled dose of radiation. At the same time the amount delivered to the healthy liver parenchyma and other organs should be as low as possible. A variety of radionuclides, such as $^{131}$I, $^{188}$Re, $^{90}$Y can be used for this purpose and targeting of the therapeutic agent to the tumor can be achieved by either direct intratumoral implantation of radionuclides or by injecting radionuclide through hepatic artery directly into the tumor (transarterial radionuclide therapy or TART) or through parenteral injection of radiolabeled antibodies specific to HCC antigens. The treatment, particularly TART, appears to be safe and effective.

4. Polycythemia Vera Rubra
Radioactive phosphorus ($^{32}$P) localizes in the marrow and erythroid precursors and inhibits its proliferation. The therapy requires to be repeated often but definitely cuts down the frequency of bloodletting required in this disease. Long term survival of these patients after $^{32}$P therapy is also very good.
5. Cancer bone pain

$^{32}$P, $^{153}$Sm and $^{89}$Sr can be effectively used for pain palliation in metastatic bone disease. Although they don’t affect the course of the disease, pain is significantly reduced and patients become mobile.

6. Arthritis

In various arthritis, involving synovium, $^{90}$Y, $^{188}$Re and other radioisotopes are now more and more frequently used with good outcome.

XIII. Biological Hazards Of Radiation

Interaction of radiation with biological systems results in a variety of biological changes that can be either deleterious or benign. These changes may become evident immediately or may take years or generations before being manifested. In general, the probability of occurrence and the type and severity of these changes depend on many factors, some related to radiation and its characteristics and others to biological characteristics of the system.

**Mechanism of biological damage**

Manifestation of bio-injury due to radiation is always preceded by a complex series of physio-chemical events. The first step in this series of events is the deposition of energy by radiation in the form of ionization and excitation of some atoms or molecules of the biological system. This generally lasts about $10^{-12}$ seconds or less.

The second step, which may last from $10^{-12}$ to $10^{-3}$ seconds, is the transfer of energy either to neighboring molecules (intermolecular) or, quite often, within the molecule itself (intra molecular) to form various short-lived and chemically active species known as free radicals (atomic or molecular entities with an unpaired electron and shown by a dot to the right side of the chemical symbol). Because water (H$_2$O) constitutes 75-85% of the mass of a living system, most ionization is produced in water, and the two most common radicals formed are H• and OH•.

In the next stage, which may last from milliseconds to several seconds, the free radicals react either among themselves or, more significantly, with other important biomolecules (e.g., DNA, RNA) to produce alterations in them. Reactions of H• and OH• radicals with important biological molecules cause most radiation damage observed in living systems.

The final step (i.e., the expression of the biological alteration produced in the previous stage) is the biological damage that is tied to the fate of these altered biomolecules. Eventual biological damage may be manifested within a short time or may be delayed up to several generations, depending on the type and function of these altered molecules and on the repair capacity of the irradiated biological system.

**Factors affecting biological damage**

Biological damage (or effect) of a system caused by radiation depends on the following factors.
i) Radiation Dose
Any biological effect of radiation, whether deleterious or benign, strongly depends on the radiation dose. Generally, more effects, and more serious effects are produced by high than low doses. Depending on the dose-effect relationship, radiation effects are termed as stochastic or deterministic. In stochastic effects, the probability of occurrence and not the severity of the effect depend on the radiation dose. Two important examples are induction of cancer and genetic damage, where the probabilities of induction are a function of radiation dose but their severity is not. Stochastic effects do not have a threshold, a dose level below which the probability of occurrence is zero.

In deterministic effects, on the other hand, the severity of effect depends on the radiation dose and has a threshold, a dose below which no effect is observed. Two examples of deterministic effects of radiation are production of cataracts and erythema.

ii) Dose Rate
High dose rates are more damaging than low dose rates. If the same dose is delivered to two identical biological systems, one with a short duration (high dose rate) and the other over a longer period of time (low dose rate), the high dose rate will have more effect.

iii) Type of Radiation
Per unit of absorbed dose radiations with higher linear energy transfer (LET) (such as α particles and protons) produce greater damage in a biological system than radiations with lower LET (electrons and γ and X-rays).

iv) Type of Tissue
Biological response of a system varies widely depending on the type of tissue (e.g., liver, bone marrow, or nerve tissue) involved. Given the same radiation dose and dose rate, bone marrow is much more sensitive than nerve tissue -to certain types of radiation damage.

v) Amount of Tissue
Injury to a biological system also depends on the amount of tissue irradiated. For example a mammal can tolerate a much higher dose to a part of the body than irradiation of the total body.

vi) Rate of Cell Turnover
For tissues with a rapid cell turnover (bone marrow), damage appears earlier than for a slow cell turnover (liver).

vii) Biological Variation
The response of a biological system, even with all other factors constant, may vary enormously even among closely related individuals.

Radiation effects on human
Radiation effects in human may be acute (mainly deterministic) or late (mainly stochastic)
a) Acute Effects
Acute effects are manifested within a short period after irradiation and range from transient nausea and vomiting to death. These are generally produced when the radiation dose is high and delivered to a large part of the body in a short duration. Five clinically distinct stages can be identified as the radiation dose is progressively increased: no effect, mild damage to bone marrow, severe damage to bone marrow and mild damage to the gastrointestinal tract, severe damage to the gastrointestinal tract, and damage to the central nervous system.

b) Late Effects
Late effects may occur in cases where the radiation dose to the total body is low or only part of the body is involved in the irradiation. In diagnostic uses of radiation, whether in radiology or nuclear medicine, the range of radiation doses generally delivered to a patient falls in this category. Regrettably, precise information about the risks involving low radiation doses is difficult to obtain for the following reasons. First, the probability of occurrence of any late effect after low doses is small. Therefore, to perform statistically valid studies, large populations have to be considered. In practice, this is difficult to implement. Second, the occurrence of a latent period in the expression of late effects requires a long follow-up (10 years or more). Finally, late effects of radiation also occur naturally and more frequently than those caused by low doses of radiation. Because accurate information is lacking on the natural frequency of these effects, it is difficult to estimate the influence (increase or decrease) of low radiation doses. In addition, the frequency of natural occurrence is influenced by many complex factors such as age, sex, genetic history, geography, and various environmental and socioeconomic factors. However, with experience and accumulated evidence it appears that nuclear medicine procedures are quite safe.

XIV. Safety Measures in Handling Radioisotopes
Any use of radionuclides is fraught with the danger of inadvertently exposing an individual to radiation and therefore to its attendant hazards. The danger can be of two types: a) hazard from external radiation sources and, b) hazard from internal contamination (such as inhalation or ingestion). This is especially true in the nuclear medicine laboratory where large amounts of unsealed radioactive sources are routinely handled and there is the possibility of exposure and contamination to the user (technician, scientists, physicist, or physician) and to the environment.

Reducing exposure from external sources
Hazard from external radiation sources is measured in terms of exposure. Exposure is a measure of the ability of radiation to produce ionization in air. The unit of exposure is roentgen (R), that level of radiation which produces ionization in air in the amount of $2.58 \times 10^{-4}$ coulomb/kg of air. If the exposure is known at a given point, one can calculate the absorbed dose to a person at that point by multiplying the exposure by a term known as ‘f’ factor. For muscles and soft tissue, f factor is close to unity. Therefore, for purposes in nuclear medicine, we may assume that exposure is more or less equivalent to the absorbed dose.

The principle of reducing exposure from external radiation sources (X- and γ-ray emitting radionuclides only) can be summed up in three words: time, distance and shielding. Less time should be spent while keeping as much distance as possible and using an appropriate shielding from the radiation source.
Avoiding internal contamination
Internal contamination by a radionuclide is possible by three routes: penetration through skin, ingestion and inhalation. To avoid ingestion or penetration through the skin, the following steps should be taken:
1. Wear overalls or a laboratory coat and disposable gloves each time handling a radioactive material. It should be remembered that the gloves once used to handle radioactive material, become contaminated.
2. Do not eat, drink, or smoke in the radionuclide laboratory or pipette radioactive solutions by mouth.
3. Keep the area neat in which radionuclides are handled. Use a tray with absorbent liners on the bench to limit the spread of radioactive material in case of an accident while working with unsealed radioactive sources.
4. Contamination by inhalation does not pose a great problem in nuclear medicine except in a few cases where radioactive gases are used or large amounts of radioiodine are handled. Inhalation of radioactive fume is possible during iodination of proteins and peptides. So use designated fume hood with laminar flow chambers.
5. Because the bed sheet, pillows, and stretchers used when scanning patients may be contaminated as a result of a patient's saliva, blood, or urine, one should be beware of this route of personal contamination.

XV. Conclusion
The use of radioisotopes in medicine is relatively recent. The rate of progress of science is rapid. Between the stethoscope and the cardiogram probably centuries elapsed, while between the development of rockets and the moon landing only decades have intervened. Within a few decades radioactive isotopes have been found to be extremely useful as diagnostic and therapeutic agents in clinical medicine and as important tools for exploration of the basic biological processes. Further growth is dependent on the imagination and resourcefulness of the present-day medical students.

Suggested Readings
3. Ramesh Chandra, Ed. (1998), Nuclear Medicine Physics, Williams & Wilkins.