

Basic Sciences of Nuclear Medicine

Magdy M. Khalil
Editor

Second Edition

 Springer

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(وَاللَّهُ أَخْرَجَكُمْ مِنْ بُطُونِ أُمَّهَاتِكُمْ لَا تَعْلَمُونَ شَيْئًا
وَجَعَلَ لَكُمُ السَّمْعَ وَالْأَبْصَارَ وَالْأَفْئِدَةَ لَعَلَّكُمْ تَشْكُرُونَ)

"النحل-78"

(Allah has extracted you from the wombs of your mothers
not knowing a thing, and He made for you hearing and vision
and intellect that perhaps you would be grateful)

"An-Nahl 78"

*I dedicate this book to my Parents,
My Family,
My Colleagues,
And my Students*

Preface

The parent book *Basic Sciences of Nuclear Medicine*, 2010, Springer, was initially designed to cover a wide spectrum of basic science disciplines as relevant and consistent with nuclear medicine and molecular imaging theory and practice. I believe the first edition was concomitant with a number of revolutions in nuclear medicine including wide spread of hybrid imaging, radionuclide therapy, new innovations in gamma camera and PET scanner technology, radiochemistry, radiation biology and dosimetry, computational algorithms and image reconstructions. The momentum of this second edition is also associated with new developments including extended axial of view PET scanners, radiomics and texture feature analysis, artificial intelligence including machine and deep learning and many others. This really reflects the dynamic nature of the field and how the scientific community rapidly cope with recent advances and their application for the benefit of patients. While the book deals with fundamental concepts and principles, there was a need to update some contents adding new ideas and approaches recently developed.

This second edition consists of six parts including physics and radiation protection, radiopharmacy and radiochemistry, internal dosimetry and radiobiology, SPECT and PET imaging instrumentation, image reconstruction and analysis as well as quantitative imaging analysis. A panel of expert scientists were carefully selected to document the theoretical and practical aspects of nuclear medicine and molecular imaging.

The day-to-day innovations observed in diagnostic imaging and particularly in nuclear medicine are due to better understanding and integration of key concepts and fundamental rules of physics, chemistry, biology, mathematics, engineering including computer science and electronics. This book was made to cover most of those disciplines and their direct applications in the field.

The audience of the book remain those who are interested in a one-stop-shop textbook that handles most of the important and relevant topics of nuclear medicine and molecular imaging. Potential targets are medical physicists, radiochemists, physicians, radiologists, medical students, clinical scientists and others. I wish the reader will find this new edition a valuable resource on their way towards deep understanding of the discipline and better practice for serving ill people.

Cairo, Egypt
21 August 2020

Magdy M. Khalil

Acknowledgements

I would like to express my gratitude to “Allah” for his support and assistance in bringing this book to light: without his help, nothing will exist. I would like also to send my great thanks to my parents and pray for them with mercy and forgiveness. Special thanks to my family who suffered from my absence during the whole journey of editing this book. This is also a unique opportunity to thank the contributing authors for their time, efforts and expertise that appeared very clearly in their writing and handling the scientific material in a very professional way. I am indebted to all of them and wish them all the best. The Springer team was also very supportive from the birth of this book in 2010 till this moment and would like to send them my appreciation and admiration. Last but not least, I am so thankful to my colleagues in the Department of Physics, Faculty of Science, Helwan University, Cairo, Egypt, for their continuous support, encouragement and love.

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Part I

Physics and Radiation Protection



Basic Radiation Physics as Relevant to Nuclear Medicine

1

Gauri Shankar Pant and Anil Kumar Pandey

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Most of the text has been reproduced from our contribution in the book 'Basic Physics and Radiation Safety in Nuclear Medicine' G.S. Pant (2nd Ed) Himalaya Publishing House, Mumbai, India, 2018.

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The peaceful applications of atomic radiations have been well established, in many areas particularly in the field of medicine for diagnosis and treatment. The basic understanding of atomic radiations and their characteristics is therefore important for those working in nuclear medicine and other allied disciplines. A brief description on basic physics as relevant to nuclear medicine is given here.

1.1 Atom

It is well known that matter is comprised of atoms, and atom is the smallest unit of a chemical element. An atom rarely exists alone and often combines with other atoms to form the molecule, the component of a chemical compound.

1.2 Modern Atomic Theory

1.2.1 Wave–Particle Duality

According to classical physics, the particles cannot be wave and vice versa. However, Einstein, while explaining the photoelectric effect, postulated that electromagnetic radiation has wave–particle nature. He used the term photon for the packet of electromagnetic radiation and proposed a simple formula to relate the energy of the photon E to its frequency ν or the wavelength.

$$E = h\nu = h \frac{c}{\lambda} \quad (1.1)$$

In this equation, h is the Planck's constant (6.634×10^{-34} J s) and c is the velocity of light in vacuum.

De Broglie generalized the idea and postulated that all sub-atomic particles have wave–particle nature. In some phenomena, the particle behaves as a particle, and in others, it behaves as a wave but in none as both (wave–particle duality). He suggested the following equation to relate the momentum of the particle P to its wavelengths λ :

$$\lambda = \frac{h}{p} \quad (1.2)$$

Only when the particles are with extremely small mass (subatomic particles), the associated wave is appreciable. Electron microscope is an instrument that proves the accuracy of the wave–particle duality. In macroscopic scale, De Broglie theory is not applicable. Erwin Schrodinger derived an equation in 1925, which describes not only the subatomic, atomic and molecular system but also the macroscopic systems. This discovery was a significant landmark in quantum mechanics for which he was awarded Nobel Prize in Physics in 1933. The detailed

discussion on Schrodinger equation is beyond the scope of this chapter.

1.2.2 Electron Configuration

Electrons around a nucleus can be described with wave functions. Wave functions determine the location, energy and momentum of the particle. The square of a wave function gives probability distribution of the particle. At a given time, electrons can be anywhere around the nucleus, but different locations have different probabilities. The space around the nucleus in which the probability is highest is called an orbital. In quantum mechanics, orbital is a mathematical concept that suggests the average location of an electron around the nucleus. If the energy of the electron changes, this average location also changes. For the single electron of hydrogen atom, an infinite number of wave functions and therefore infinite number of orbitals exist.

Orbital can completely be described using the corresponding wave function, but the process is tedious and difficult. In simple terms, an orbital can be described by four quantum numbers.

- The principal quantum number n characterizes the energy and shell size in an atom. It is an integer and can have value from 1 to ∞ , but practically n is always less than 8. Maximum number of electrons in the orbital n , is given as $2n^2$. The shells of electrons are labelled alphabetically as $K(n = 1)$, $L(n = 2)$, $M(n = 3)$, etc. based on the principal quantum number.
- The orbital quantum number l relates to the angular momentum of the electron; l can take integer values from 0 to $n - 1$. In a stable atom, its value does not go beyond 3. Orbital quantum number characterizes the configuration of the electron orbital. In the hydrogen atom, the value of l does not appreciably affect the total energy, but in atoms with more than one electron, the energy depends on both n and l . The sub-shells or orbitals of electrons are labelled as $s(l = 0)$, $p(l = 1)$, $d(l = 2)$ and $f(l = 3)$.
- The azimuthal or magnetic quantum number m_l relates to the direction of the electron's

angular momentum and takes on integer values from $-l$ to $+l$.

- The spin quantum number m_s relates to electron angular momentum and can have only two values $-1/2$ or $+1/2$.

In 1925 Wolfgang Pauli added a complementary rule for the arrangement of electrons around the nucleus. The postulation is now called **Pauli's exclusion principle** and states that no two electrons can have all quantum numbers same or exist in identical quantum states.

The filling of electrons in orbitals obeys the so-called Aufbau principle. The Aufbau principle assumes that electrons are added to an atom, one at a time, starting with the lowest energy orbital, until all of the electrons have been placed in an appropriate orbital. The sequence of energy states and electron filling in orbitals of a multi-electron atom can be represented as:

$$1s - 2s - 2p - 3s - 3p - 4s - 3d - 4p - 5s \\ - 4d - 5p - 6s - 4f - 5d - 6p - 7s - 5f - 6d - 7p$$

1.3 Electron Binding Energies

The bound electrons need some external energy to make them free from the nucleus. It can be assumed that electrons around a nucleus have negative potential energy. The absolute value of the potential energy is called binding energy and is the minimum energy that is required to make an electron free of the atom.

1.3.1 Atomic Emissions

For stability, electrons are required to be in the minimum possible energy level or in the innermost orbitals. However, there is no restriction for an electron to transfer into outer orbitals if it gains sufficient energy. If an electron absorbs external energy that is more than or equal to the binding energy of its orbital, the electron is freed from the atom. A pair of ion, the electron and the atom with positive charge, is created. This process is termed as *ionization*. If the external energy

is more than the binding energy of the electron, the excess energy is divided between the two in such a way that conservation of momentum is preserved. The energy level of a free electron is not necessarily discrete.

If an electron absorbs energy and is either elevated to outer orbits or becomes free to move out of the atom, the original orbital does not remain vacant. Soon the vacancy will be filled by electron from outer layers. This is a random process, and occupier may be any electron from outer orbital. However, closer electron has more chance to occupy the vacancy. In each individual filling-up process, a quantum of energy equal to the difference between the binding energies $E_2 - E_1$ of the two involved orbitals is released, usually in the form of single photon. The frequency ν and wavelength λ of the emitted photon (radiation) are as follows:

$$E_2 - E_1 = \Delta E = h\nu = h \frac{c}{\lambda} \quad (1.3)$$

When an atom has excess energy, it is in an unstable or *excited state*. The excess energy is released usually in the form of electromagnetic radiation until the atom is again in its natural *stable state*. The frequency spectrum of the radiation emitted from an excited atom can be used as the fingerprint of atom. Such radiation is called characteristic radiation.

1.3.2 Nucleus

In simple terms, the nucleus is made up of two fundamental particles, protons and neutrons. These particles together are called nucleons. The protons are positively charged, and neutrons are electrically neutral. Since electrons are light particles (with mass about 1/1840 times the mass of either neutron or protons), the entire mass of the atom is concentrated in the nucleus.

1.4 Nuclear Structure

There are several notations to summarize nuclear composition of an atom. The most commonly used is ${}^A_Z X_N$, where X represents the chemical

Table 1.1 Mass and charge of proton, neutron and electron

Particle	Symbol	Charge ^a	Mass ^b	Mass (kg)	Energy (MeV)	Relative mass
Proton	P	+1	1.007276	1.6726×10^{-27}	938.272	1836
Neutron	N	0	1.008665	1.6749×10^{-27}	939.573	1839
Electron	e^-	-1	0.000548	9.1093×10^{-31}	0.511	1

^aUnit charge = 1.6×10^{-11} coulombs

^bMass expressed in Universal mass unit (mass of 1/12 of ^{12}C atom)

(Data from "Particles and nuclei 1999)

symbol of the element. Chemical symbol and atomic number carry the same information, and neutron number is the difference between A and Z . Hence, for the sake of simplicity, the notation is briefed to AX that is quite comprehensible and popular now. For example, in ^{137}Cs , where 137 is the mass number ($A + Z$), and the symbol Cs represents the 55th element in the periodic table. The neutron number can easily be calculated ($A - Z = 82$). Table 1.1 shows the mass, charge and energy of proton, neutron and electron.

1.5 Nuclear Forces

Protons in a nucleus are fairly at close distance ($\approx 10^{-15}$ m). This closeness results in an enormously strong repulsive force between them. They still remain within the nucleus due to the existence of a very strong (short range) nuclear force between nucleons that dominate the repulsive force and make the atom stable. The force is effective in a very short range, and neutrons must have an essential role in creating such force. Without neutrons, protons cannot stay in close distances.

In 1935, Yukawa proposed that the short-range *strong force* came about from the exchange of particles that he called *mesons*. The strong nuclear force is one of the four fundamental forces in nature that is created between nucleons by the exchange of mesons. This exchange can be compared to constantly hitting a tennis ball back and forth between two people. As long as this meson exchange is happening, the strong force holds the nucleons together. Neutrons also participate in the meson exchange and are even a bigger source of strong force. Neutrons have no

charge so they approach other nuclei without adding extra repulsive force, and meanwhile, they increase the average distance between protons and help to reduce the repulsion between them within a nucleus.

1.5.1 Nuclear Binding Energy and Mass Defect

Nuclear strong force is the resultant of the phenomenon known as *mass defect*. Direct measurements show that the mass of a nucleus is always less than the sum of the individual masses of the constituent protons and neutrons. Using the Einstein relationship, the deficient mass Δm is exactly equal to the energy required to separate the nucleons or *binding energy* E_b of the nucleus.

$E_b = \Delta m c^2$, c is the speed of the light in vacuum.

The **nuclear mass defect** (Δm) is the nuclear binding energy holding the nucleons together. The **average binding energy** per nucleon is a measure of nuclear stability. The higher the average binding energy, the more stable is the nucleus.

1.5.2 Radioactivity

Radioactivity is the spontaneous emission of particles and/or photons as a result of nuclear instability. The stability of a nucleus depends upon the arrangement of its nucleons particularly the ratio of the number of neutrons to the number of protons. Presence of adequate number of neutrons in relation to protons is essential for stability. Amongst the many possible combinations of protons and neutrons, only around 260 are stable, and

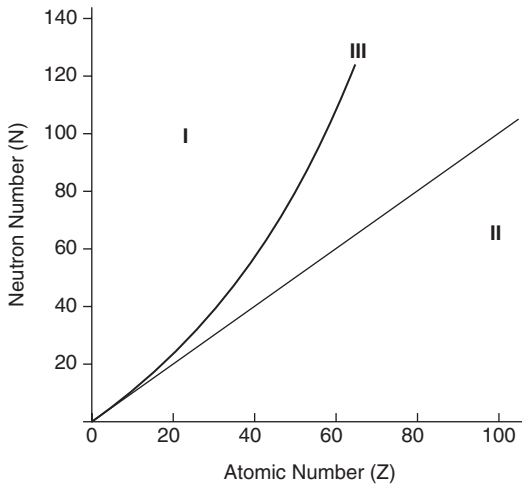


Fig. 1.1 The line of stability and different regions around it. (Reproduced from [2])

the rest all are unstable. It seems that there are favoured neutron-to-proton ratios amongst the stable nuclides. Figure 1.1 shows the function of the number of neutron (N) against the number of proton (Z) for all available nuclides. The stable nuclides gather around an imaginary line, called the line of stability. For light elements ($A < 50$), this line corresponds to $N = Z$, but with increasing atomic number, neutron-to-proton ratio increases up to 1.5 ($N = 1.5Z$). The line of stability ends at $A = 209$ (Bi), and all nuclides above that and those that are not close to this line are unstable. Nuclides that lie on the left of the line of stability (Area I) have excess of neutrons, those lying on the right of the line (Area II) are neutron deficient, and those above the line (Area III) are too heavy (excess of both neutrons and protons) to be stable.

An unstable nucleus sooner or later (nanoseconds to years) changes to a more stable proton–neutron combination by emitting particle(s) such as alpha, beta and gamma. As mentioned earlier, the phenomenon of spontaneous emission of such particles from the nucleus is called radioactivity, and nuclides involved in this phenomenon are called radionuclides. The change from the unstable nuclide (parent) to more stable nuclide (daughter) is called radioactive decay or disintegration. During disintegration, in addition to the emission of nuclear particle(s) energy is released. The process is spontaneous and remains unaf-

ected by external factors. It is also not possible to predict as to which radioactive atom will disintegrate first.

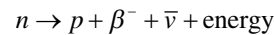
1.6 Modes of Decay

The radionuclide, which decays to another nuclide in order to attain stability, is called the ‘parent’ nuclide, and the nuclide so formed is called ‘daughter’. The unstable nuclide may undergo transformation by any one of the following modes:

1.6.1 Nuclides Having an Excess Number of Neutrons

1.6.1.1 Beta Emission

Nuclides having excess number of neutrons attempt to acquire a stable form by the emission of beta particle (also called negatron). In this process, a neutron converts to a proton. Along with an electron (negatron or beta minus), an antineutrino is also emitted. The nuclear equation may be given as follows:



Here n , p , β^{-} and $\bar{\nu}$ represent the neutron, the proton, the negatron (beta minus) and the antineutrino, respectively. The proton stays in the nucleus, but the beta minus and the antineutrino are ejected out carrying the released energy as their kinetic energy. In this mode of decay, atomic number of the daughter nuclide is one more than that of the parent, but the mass number remains the same. The daughter may or may not be stable. The mass of the neutron is very slightly more than the masses of the proton, the beta and the antineutrino combined (the daughter is lighter than her parent). This difference in mass is converted into energy and randomly shared between beta particle and antineutrino. Hence, the beta particle may have energy between zero to a certain maximum level. The antineutrino has no mass and charge.

Radionuclides in which the daughter attains a ground or stable state by just emitting beta parti-

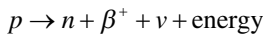
cles only are called pure beta emitters such as ${}^3\text{H}$, ${}^{14}\text{C}$, ${}^{32}\text{P}$ and ${}^{35}\text{S}$. Those that cannot attain a stable state after beta emission and that still remain in one of the excited states of the daughter emit gamma photon(s) either in a single transition or through cascades to attain the ground state. In the latter situations, we get more than one gamma photon per beta emission. For example, ${}^{131}\text{I}$, ${}^{132}\text{Xe}$ and ${}^{60}\text{Co}$ all of which emit beta particle followed by number of gamma emissions.

1.6.1.2 Nuclides Which Lack in Neutrons

In such cases, there are two alternatives for the nucleus to come to a stable state:

(a) Positron emission and subsequent emission of annihilation photons

In this mode of decay, a proton transforms to a neutron with the emission of a positron and a neutrino.

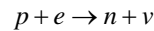


The neutron stays in the nucleus, but a positron and a neutrino are ejected out carrying the emitted energy as their kinetic energy. The positron is the antiparticle of the electron. They are very much alike but with opposite charge. In this mode of decay, the atomic number of the daughter is one less than that of the parent, but the mass number remains the same. The daughter may or may not be stable. The mass of the proton is slightly less than the combined mass of the neutron, the positron and the neutrino. Energy for the creation of this mass is supplied by the whole nucleus; hence, the difference between masses of parent and daughter elements must be sufficient to produce this energy ($E > 1.022 \text{ MeV}$). Therefore, for positron emission to take place, the energy of parent nuclide must exceed that of the daughter by at least 1.022 MeV. The excess energy, if any, is randomly shared by positron and neutrino. Energy spectrum of the positron is like that of the beta minus (from zero up to a certain maximum). Some of the positron emitting radionuclides are ${}^{11}\text{C}$, ${}^{13}\text{N}$, ${}^{15}\text{O}$ and ${}^{18}\text{F}$.

Just a few nanoseconds after its production, when its kinetic energy comes to zero, the positron combines with an electron at rest. Their masses are converted into energy in the form of two equal energy photons (0.511 MeV each) which leave the site of their creation in exactly opposite directions to conserve the momentum. This phenomenon is called annihilation reaction, and the photons so created are called annihilation photons.

(b) Electron captures

For a nucleus with excess protons has an alternative way to get a stable configuration by capturing one of its own orbital electrons (usually k electron). The electron combines with the proton producing a neutron and a neutrino in the process.



The electron capture is an important phenomenon because an electron from outer orbit fills the vacancy of the attracted electron. Photons (characteristic radiation) are emitted in the process, which may have a considerable amount of energy. These photons may knock out orbital electrons from outer orbits before leaving the atom creating the so-called Auger electrons. Auger electrons may be useful for therapeutic application (targeted therapy) due to their short range in the medium.

Electron capture is more likely to occur in heavy elements (electrons more close to the nucleus), whereas positron emission is more likely in lighter elements provided the energy of the parent exceeds that of the daughter by at least 1.022 MeV. Radionuclides such as ${}^{67}\text{Ga}$, ${}^{111}\text{In}$, ${}^{123}\text{I}$ and ${}^{125}\text{I}$ decay partially or fully by electron capture.

1.6.1.3 Nuclides Having an Excess of Protons and Neutrons

When the nuclides are too heavy (many nucleons) (region III in Fig. 1.1) and unstable, there are two ways for them to become stable, either by alpha emission or by fission process.

(a) **Alpha decay**

There are some nuclides, which have excess protons and neutrons and try to get rid of them by emitting an alpha particle (two neutrons and two protons). The atomic number of the daughter in such decay is reduced by 2, and the mass number is reduced by 4. The alpha particle emission may be sufficient to bring the daughter to the stable state or may follow with gamma emission. Naturally occurring radionuclides such as ^{238}U , ^{232}Th and ^{226}Ra not only decay by alpha emission but also form a chain of decay process as their daughter products are also radioactive.

(b) **Fission**

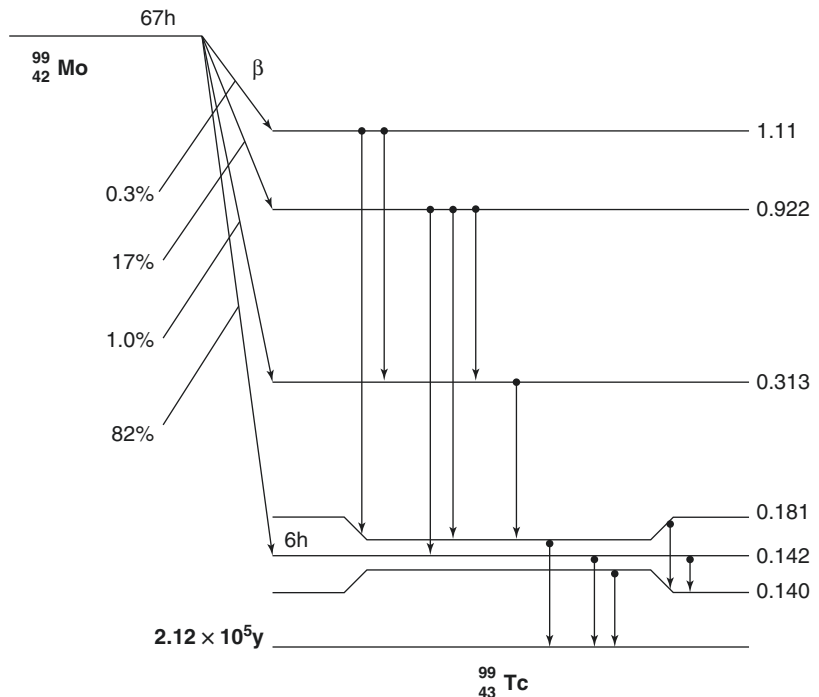
It is the spontaneous fragmentation of very heavy nuclei into two lighter nuclei usually with the emission of two to three neutrons. A large amount of energy (hundreds of MeVs) is also released in this process. Fissile nuclides themselves have no clinical application, but some of their fragments are found quite useful because of being carrier free. Thus, specific activity of fission-produced radionuclides is always higher than those produced by nuclear reactor.

1.7 Gamma Radiation and Internal Conversion

In some decay processes, the daughter nuclei are not in their ground state. This happens when all the energy associated with decay process is not carried away by the emitted particles. Such nuclei can be either in an excited state or in a metastable (isomeric) state. In both the situations, the excess energy is often released in the form of one or more gamma photons. Average life time of excited states is very short, and energy is released within a fraction of a nanosecond, but the average life time of metastable states is very much longer, and emission may vary from few milliseconds to few days or even more. During this period, the isomeric state behaves as an independent isotope that becomes a pure gamma emitter. Some of the metastable states have great clinical application in nuclear medicine. The decay scheme of ^{99}Mo – $^{99\text{m}}\text{Tc}$ is an example of isomeric transition and shown in Fig. 1.2.

There are situations when the excited nuclei instead of emitting a gamma photon utilise the energy in knocking out one of the orbital electrons from their own atom. This process is called

Fig. 1.2 Decay scheme of ^{99}Mo . (Reproduced from [2])



internal conversion, and the emitted electron is called a conversion electron. The probability of K conversion electron is more than L or M conversion electrons, and the phenomenon is more common in heavy atoms. The internal conversion is followed by emission of characteristic X-rays and Auger electrons as the outer shell electrons move in to fill the inner shell vacancies. It should be noted here that the X-ray emission is an atomic phenomenon even though there is no difference between an X-ray and a gamma photon of equal energy.

1.8 Laws of Radioactive Decay

There is no way to predict the time of disintegration of an atom nor should one be really interested about the fate of an individual atom. The number of atoms disintegrating within a given time interval can however be estimated which is of our interest. The radioactive decay has been found to be a spontaneous and random process independent of any environmental factor. In other words, nothing can influence the process of radioactive disintegration. Any random process just can be described in terms of probabilities and average constants.

In a sample containing a large number of identical radioactive atoms, during a short period of time (δt) the number of decayed atoms ($-\delta N$) is proportional to the total number of atoms (N) present at that time. Mathematically, it can be expressed as:

$$\begin{aligned} -\delta N &\propto N \delta t \\ -\delta N &= \lambda N \delta t \\ \text{or } \frac{\delta N}{N} &= -\lambda \delta t \end{aligned} \quad (1.4)$$

In this equation, the constant λ (known as decay constant) has a characteristic value for each radionuclide. Decay constant is the fraction of atoms undergoing decay per unit time in a very large number of atoms. Its unit is inverse of time.

In simple terms, the decay constant can be defined as the probability of disintegration of a nucleus per unit time. Thus $\lambda = 0.01$ per second means that the probability of disintegration of each atom is 1% per second. It is important to note that this probability does not change with time.

The exact number of parent radionuclides in a sample at any time can be calculated by integrating Eq. (1.4), which takes the following form:

$$N = N_0 * \exp(-\lambda t) \quad (1.5)$$

where N_0 is the initial number of atoms in the sample, and N is the number present at time t .

The term $\frac{\partial N}{\partial t}$ shows the number of disintegration per unit time and is known as activity. The SI unit of activity is Bq (one decay per second). The conventional unit of activity is Curie (Ci) which is equal to 3.7×10^{10} disintegrations per second (dps).

1.8.1 Half-Life

The time after which 50% of the atoms in a sample undergo disintegration is called the half-life. The half-life and decay constant are related to each other by the following equation:

$$T_{1/2} = 0.693/\lambda \quad \text{or} \quad \lambda = 0.693/T_{1/2} \quad (1.6)$$

1.8.2 Average Life

The actual lifetimes of individual atoms in a sample are quite different. Some have very short and some have very long lifetime. The average lifetime, characteristics of the atoms, is related to the half-life by:

$$T_{av} = 1.44 * T_{1/2} \quad (1.7)$$

The average life is a useful parameter for calculating the cumulated activity in source organ in internal dosimetry in nuclear medicine.

1.8.3 Radioactive Equilibrium

In many cases, the daughter element is also radioactive and immediately starts disintegrating after its formation. Although the daughter obeys the general rule of radioactive decay, its activity does not follow the exponential law of decay of its own while existing with the parent. The reason is that the daughter is produced (mono-exponentially) by disintegration of its parent, and at the same time, it disintegrates (mono-exponentially) as a radioactive element. So the activity of such elements changes bi-exponentially, first the activity increases, reaches a maximum value and then starts decreasing. The rate at which the activity changes in such a mixture of radionuclides depends on the decay constant of both the parent and the daughter.

If we start with a pure sample of a parent with a half-life of T_1 and decay constant λ_1 and contains $(N_1)_0$ atoms initially, the decay of this parent can be expressed by:

$$N_1 = (N_1)_0 e^{-\lambda_1 t} \quad (1.8)$$

The rate of decay of the parent is the rate of formation of the daughter. Let the daughter decays at the rate $\lambda_2 N_2$, where λ_2 is the decay constant of the daughter and N_2 is the number of atoms of the daughter present. The net rate of formation of the daughter can be given by:

$$\frac{\partial N_2}{\partial t} = \lambda_1 N_1 - \lambda_2 N_2 \quad (1.9)$$

The solution of this equation in terms of activity can be given as:

$$A_2 = A_1 \frac{T_1}{T_1 - T_2} \left(1 - e^{-0.693 \left(\frac{T_1 - T_2}{T_1 T_2} \right) t} \right) \quad (1.10)$$

where A_1 and A_2 are the activity of the parent and the daughter, respectively, T_1 and T_2 are their physical half-lives and t is the elapsed time. This equation is for a simple parent–daughter mixture. In general, three different situations arise from Eq. (1.10).

(a) Secular equilibrium

When the half-life of the parent (T_1) is too long in comparison to that of the daughter (T_2), Eq. (1.10) may be expressed as:

$$A_2 = A_1 \left(1 - e^{-\frac{0.693t}{T_2}} \right) \quad (1.11)$$

After one half-life of the daughter ($t = T_2$; A_2) will become nearly $A_1/2$; after two half-lives, the daughter may grow up to $3/4$ of the parent, and after four half-lives (of the daughter), it rises to about 94% of the parent activity. Thus, activity of the daughter gradually increases, and after few half-lives, the activity of the parent and the daughter become almost equal (Fig. 1.3). The parent and the daughter are said to be in secular equilibrium.

(b) Transient equilibrium

Half-life of the parent is few times (>10 times) longer than that of the daughter but not as much long as in secular equilibrium. In this case, the activity of daughter increases, eventually exceeds the activity of parent, reaches a maximum and then decays with the half-life of the parent, but the activity of the

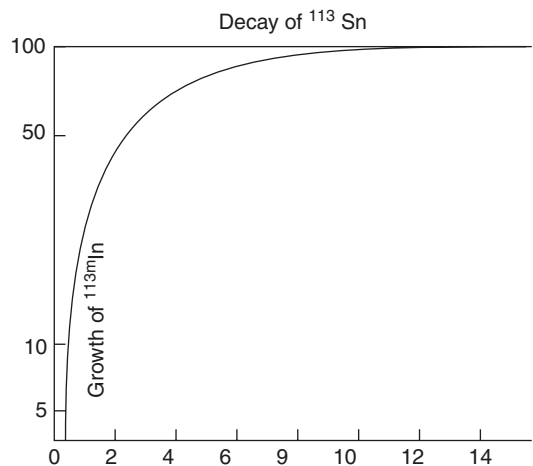


Fig. 1.3 Secular equilibrium

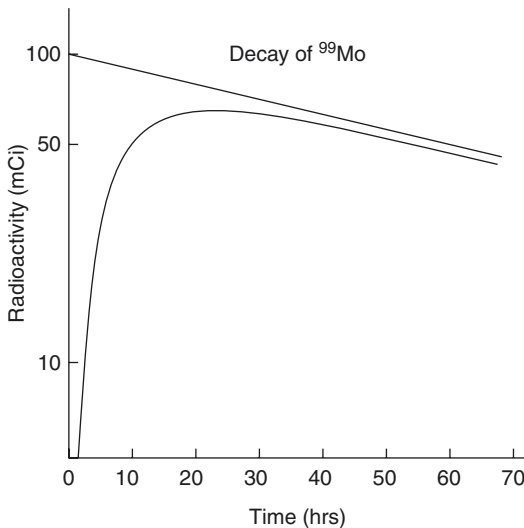


Fig. 1.4 Transient equilibrium. In case of 100% abundance of the daughter product and 100% extraction efficiency in elution, the growth curve of ^{99m}Tc will first cross over the decay curve of ^{99}Mo slightly then will decay in parallel to the parent. However, ^{99m}Tc has an abundance of 89% and extraction during elution is also less than 100%; therefore, the actual curve of transient equilibrium will look as given above

daughter slightly exceeds the parent activity after its maximum growth but practically the activity of daughter remains less than the parent because the extraction efficiency is normally less than 1 or 100%, as can be seen in Fig. 1.4a, b. Equation (1.10) in such a case can be written as:

$$A_2 = A_1 \frac{T_1}{T_1 - T_2} \quad \text{for } t \gg T_2 \quad (1.12)$$

The growth of the daughter for multiples of T_2 ($T_2, 2T_2, 3T_2, 4T_2$, etc.) will be nearly 50%, 75%, 87.5% and 94%, respectively, of the activity of the parent. It is therefore advisable to elute the activity from technetium generator after every 24 h (Mo-99 with 67 h half-life and Tc-99m with 6 h half-life).

1.8.4 No Equilibrium

When the half-life of the daughter is longer than the half-life of the parent, there would be no equilibrium between them.

1.9 Interaction of Radiation with Matter

Ionizing radiations transfer their energy in full or part to the medium through which they pass by way of interactions. The significant types of interactions are excitation and ionization of atoms or molecules of the matter by both the charged particles and electromagnetic radiation (X- or gamma rays).

1.9.1 Interaction of Charged Particles with Matter

The charge particles lose some of their energy by way of the following interactions:

- Ejection of electrons from the target atoms (ionization)
- Excitation of electrons from lower to higher energy state
- Molecular vibrations along the path (elastic collision) and conversion of energy into heat
- Emission of electromagnetic radiation

For the charged particles in the energy range of 10 keV to 10 MeV, ionization predominates over excitation. The probability of absorption of charged particles is so high that even a small thickness of the material can stop them completely.

The nature of interaction of all charged particles in the energy range mentioned above is similar to each other. Light particles such as electrons deflect at larger angles than heavier particles, and there is a wide variation in their tortuous path. The path of a heavier particle is more or less a straight line. When electrons are deflected at large angles, they transfer more energy to the target atom and eject electrons from it. These electrons while passing through the medium produce secondary electrons along their track (delta rays). The charged particles undergo a large number of interactions before they come to rest. In each interaction, they lose a small amount of energy. These losses are called collision losses.

Energetic electrons can approach the nucleus where they get decelerated and produce brems-

strahlung radiation (X-rays). The chance of such an interaction increases with increase in electron energy and atomic number of the target material. Loss of electron energy by this mode is termed as radiative loss. The energy lost per unit path length along the track is known as the linear energy transfer (LET) and is generally expressed in keV/ μm .

1.9.2 Range of a Charged Particle

After travelling through a distance in the medium, the charged particle loses all its kinetic energy and comes to rest. The average distance travelled in a given direction by a charged particle is known as its 'range' in that medium and is influenced by the following factors:

- Energy: Higher the energy of the particle more is the range
- Mass: Higher the mass of the charged particle smaller is the range
- Charge: The range is inversely proportional to square of the charge
- Density of the medium: Higher the density of the medium shorter is the range of charged particle

1.9.3 Interaction of Electromagnetic Radiation with Matter

When a beam of X- or gamma rays passes through an absorbing medium, some of the photons are completely absorbed, some are scattered, and the rest pass through the medium almost unchanged in energy and direction. The transferred energy results in excitation and ionization of atoms or molecules of the medium and also in the production of heat. The attenuation of the beam through a given medium may be summarized as follows:

- Greater the thickness of the absorbing material more is the attenuation.
- Greater the atomic number of the material more is the attenuation.

- Higher the photon energy lesser is the attenuation produced by a given thickness of material.

1.9.4 Linear Attenuation Coefficient

The linear attenuation coefficient (μ) is defined as the fractional reduction in the beam per unit thickness as determined by a thin layer of the material.

$$\mu = \frac{\text{Fractional reduction in a thin layer}}{\text{Thickness of the layers(cm)}}$$

The unit of μ is cm^{-1} .

1.9.4.1 Exponential Attenuation

Exponential law can explain the attenuation of radiation beam intensity. The mathematical derivation is given below.

Let N_0 be the initial number of photons in the beam, and N is the number recorded by the detector placed behind the absorber (Fig. 1.5).

The number δN , which gets attenuated, will be proportional to the thickness (δx) of the absorber and to the number of photons N present in the beam.

Mathematically:

$$\begin{aligned} \delta N &\propto N \cdot \delta x \\ \text{or } \delta N &= -\mu \cdot N \cdot \delta x \end{aligned} \quad (1.13)$$

where μ is a constant called linear attenuation coefficient for the radiation. The negative sign indicates that as δx increases, the number of photons in the beam decreases. Equation 1.13 can be rearranged as:

$$\mu = -\frac{\delta N}{N \cdot \delta x} \quad (1.14)$$

The formal definition of attenuation coefficient is derived from Eq. 1.14, integration of which gives the following relationship:

$$N = N_0 \cdot e^{-\mu x} \quad (1.15)$$

Fig. 1.5 Attenuation of a radiation beam by an absorber. The transmitted beam is measured by the detector 'P'. (Reproduced from [3])

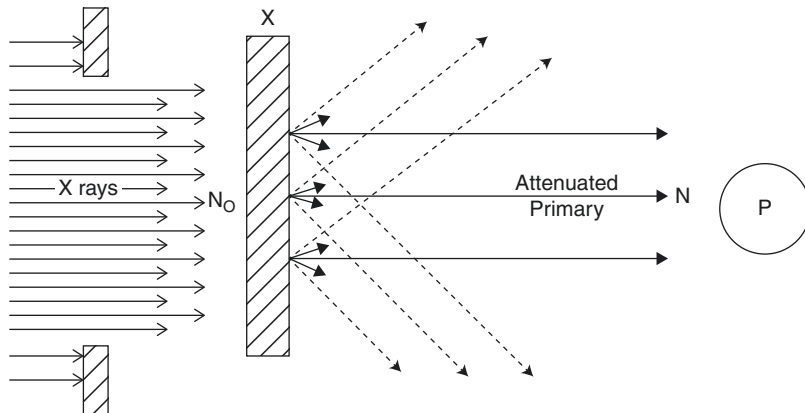


Table 1.2 Attenuation coefficients (cm^{-1}), mass attenuation coefficients (cm^2/g) and HVL (cm) in lead and concrete for 140 and 511 keV photons

Radiation type	HVL in cm lead (Pb 11.35 g/cm ³)	HVL in cm concrete (2.35 g/cm ³)	Attenuation coefficient ($\mu \text{ cm}^{-1}$) in lead (11.35 g/cm ³)	Attenuation coefficient ($\mu \text{ cm}^{-1}$) in concrete)	Mass attenuation coefficient (cm^2/g) in lead	Mass attenuation coefficient (cm^2/g) in concrete
Tc-99m 140 keV	0.027	1.99	25.67	0.348	2.26	0.148
PET annihilation photons 511 keV	0.4	3.4	1.7325	0.206	0.1526	0.0877

Equation 1.15 can also be expressed in terms of beam intensity as:

$$I = I_0 \cdot e^{-\mu x} \tag{1.16}$$

I and I_0 are the intensities of the beam as recorded by the detector with and without absorbing material, respectively. The attenuation coefficient may vary for a given material due to non-uniformity in its thickness. This is particularly so if the absorbing material is malleable. It is therefore better to express the **mass absorption coefficient**, which is independent of the thickness of the absorbing material. Mass absorption coefficient is obtained by dividing the linear attenuation coefficient with the density of the material. The unit of mass attenuation coefficient is cm^2/gm . Table 1.2 gives the values of attenuation coefficient, mass attenuation coefficient and HVL in lead and concrete for 140 keV photons and 511 keV photons. The electronic and atomic attenuation coefficients are also defined accordingly. The electronic attenuation coefficient is the

fractional reduction in X- or gamma ray intensity produced by a layer of thickness of 1 electron per cm^2 , whereas the atomic attenuation coefficient is the fractional reduction by a layer of thickness of 1 atom per cm^2 . Thus, the atomic attenuation coefficient will be Z times the electronic one.

1.9.5 Half-Value Layer (HVL)

From Eq. 1.16, it can be seen that for a certain thickness ($d_{1/2}$) of the absorbing material the intensity becomes half of its original value, i.e., $I = I_0/2$. Substituting these values, Eq. 1.4 can be rearranged as:

$$d_{1/2} (\text{HVL}) = \frac{0.693}{\mu} \tag{1.17}$$

Half-value layer (thickness) can be defined as the thickness of an absorbing material, which reduces the beam intensity to half of its

original value. Depending upon the energy of radiation, various materials are used for the measurement of HVL such as aluminium, copper, lead, brick and concrete. Similarly tenth-value layer (TVL) can also be defined that reduces the intensity of the beam to 1/10th of its initial value.

1.9.6 Mechanism of Attenuation

There are many types of interactions between a photon and the matter, but only few are important for us as described below.

1.9.6.1 Photon Scattering

The scattering may or may not result in transfer of energy during interaction of photon with atom of the medium.

1.9.6.2 Elastic Scattering

In elastic scattering or unmodified scattering, the photons are scattered in different directions without any loss of energy. The process, thus, attenuates the beam without absorption. In this process, the photon interacts with a tightly bound electron in an atom. The electron later releases the photon in any direction without absorbing energy from it. The contribution of this mode of interaction is relatively insignificant in medical applications of radiation. However, it has tremendous application in X-ray crystallography.

1.9.6.3 Inelastic (Compton) Scattering

Compton elucidated the mechanism of this type of scattering. In this process, photon interacts with loosely bound (free) electrons. Part of the energy of the photon is used in ejecting out the electron and rest is scattered in different direction (Fig. 1.6).

In a so-called head on collision, the photon turns back along its original track (scattered through 180°), and energy is transferred to the recoil electron. The change in wavelength $\delta\lambda$ of the photon is given by:

$$\delta\lambda = 0.024(1 - \cos\phi)A^0 \quad (1.18)$$

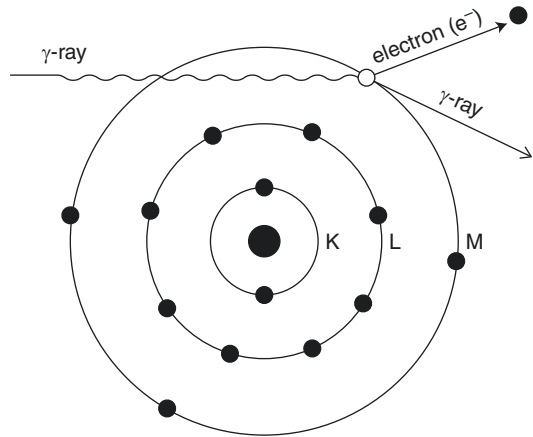


Fig. 1.6 Process of compton scattering. The incoming photon ejects the electron from outer orbit and gets scattered with reduced energy in a different direction. (Reproduced from [3])

where ϕ is the angle of scattering of gamma photon, and A^0 is angstrom unit for wave length. The energy of scattered photon is expressed as:

$$E_1 = E_0 / \left[1 + \left(E_0 / m_e c^2 \right) \{ 1 - \cos\phi \} \right] \quad (1.19)$$

where E_0 is the energy of incident photon and E_1 is that of the scattered photon, m_e is the mass of the electron, and c is the velocity of light in vacuum/space. Scattered photons at all angles therefore need appropriate shielding all around in X-ray rooms. The Compton scattering involves interaction between photons and electrons. The probability therefore depends upon the number of electrons present (electron density). With the exception of hydrogen, all elements contain nearly same number of electrons per gram (practically the same electron density). The Compton scattering thus depends upon the electron density and is the choice of interaction required in conventional radiation therapy, where the delivered dose is aimed to be homogeneous in spite of the tissue inhomogeneity within the body. The electron densities of some of the important elements are listed below:

Elements	Electron density
O ₂	3.01×10^{23}
Ca	3.00×10^{23}
Pb	2.38×10^{23}
H ₂	5.997×10^{23}

The total probability (σ) for Compton process is given by:

$$\sigma = \sigma_s + \sigma_a$$

where σ_s and σ_a are the probabilities for scattering and absorption, respectively.

1.9.7 Summary of Compton Scattering

- Involves interaction between a photon and a free electron.
- Is independent of Z (depends on electron density).
- Probability of occurrence decreases with increase in radiation energy.
- More the incident photon energy, more is the energy transferred as kinetic energy to the electron.
- Most common type of interaction in soft tissue in the energy ranges from 100 keV to 10 MeV.

1.9.8 Photoelectric Effect (PEE)

In this process, the photon disappears when it interacts with the bound electron. The photon energy has to be higher than the binding energy of the electron for this type of interaction to take place.

$$h\nu = \text{BE} + \text{Kinetic energy}$$

where $h\nu$ is the energy of the photon, and BE is the binding energy of the electron in the shell (Fig. 1.7). If the photon energy is slightly higher than the binding energy (BE), then the chance of PEE is more. For example, a photon of energy 100 keV has high probability of undergoing PEE when it interacts with Pb atom for which the K shell binding energy is 88 keV. Rest of the (100–88) 12 keV energy will be carried away by the

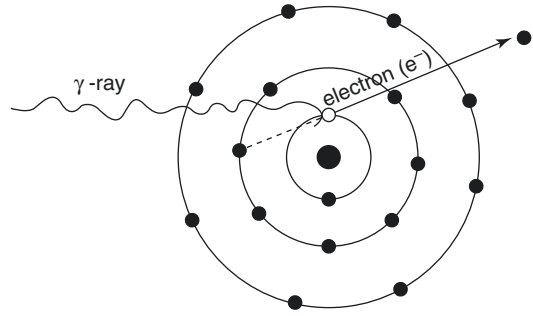


Fig. 1.7 Process of photoelectric absorption. The incoming photon disappears (absorbed) and orbital electron is knocked out. Electron from the outer shell falls (dotted line) into the inner shell to fill up the vacancy. (Reproduced from [3])

ejected electron as its kinetic energy. The ejection of electron creates a hole in the inner shell, which is filled by an electron from any one of the outer shells. Since the electron in outer shells possess higher energy than those in the inner shells, the difference in their energy is released as X-ray photon. Such photons are characteristic to the atom from which they are emitted. The K , L , M , etc. shells of a given atom have fixed energy so is the difference in their energies is also fixed. The radiation emitted are therefore termed as characteristic X-rays.

Three types of possibilities exist during photoelectric effect:

(i) Radiative transitions

As has been explained above, during the electron transition from the outer orbit to the inner one, a photon is emitted with energy equal to the difference of the binding energies of the orbits involved. The vacancy moves to a higher shell and consequently a characteristic photon of lower energy follows. The probability of emission of a photon is expressed as the fluorescent yield.

$$\text{Fluorescent yield} = \frac{\text{Number of X-ray photons emitted}}{\text{Number of orbital vacancies created}}$$

Mostly it is the K shell that is responsible for the fluorescent yield:

$$K \text{ shell fluorescent yield}(\omega_k) = \frac{\text{Number of } K \text{ X-ray photons emitted}}{\text{Number of } K \text{ shell vacancies}}$$

The yield increases with increase in the atomic number.

(ii) Auger electrons

The characteristic X-ray photon, instead of being emitted out, has a probability to eject another orbital electron from the atom. These electrons are called Auger electrons (Fig. 1.8). The energy of Auger electron is equal to the difference of the characteristic X-ray photon energy and the binding energy of the shell involved in the process. The Auger yield is expressed as the ratio of electrons emitted due to vacancies in subshell i and the total number of atoms with a vacancy in subshell i .

1.9.9 Coster–Kronig Electrons

The process is exactly like Auger transition except that the electron filling the vacancy comes from the subshell of the same principal shell in which the vacancy lies. The kinetic energy of the emitted electrons can be calculated exactly as for Auger electrons. The energy of Coster–Kronig electrons is so small that they are quickly absorbed in the medium.

1.9.10 Summary of the Photo Electric Effect

- The probability is very high when the photon has just enough energy to eject out electron from the shell.
- The process involves bound electrons.
- Effect is proportional to cube of the atomic number (Z^3) and is inversely proportional to the cube of the photon energy ($1/E^3$).
- Even though the PEE decreases with energy but suddenly increases near the K shell binding energy of the absorber. It is because of knocking out of K shell electron and emission of characteristic X-rays. The K edge depends upon the type of the absorber. In case of lead, the K edge is seen at 88 keV energy.

1.9.11 Pair Production

When a photon with energy in excess of 1.022 MeV passes close to the nucleus of an atom, it may disappear and in its place two anti-particles (negatron and positron) may be produced as shown in Fig. 1.9. In this process, energy is converted into mass in accordance with

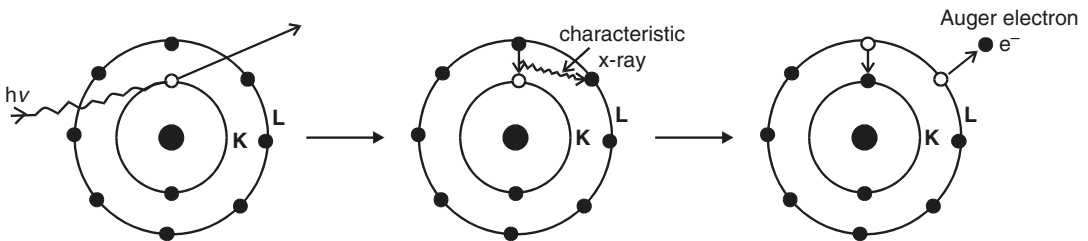


Fig. 1.8 Mechanism of Auger electron emission. (Reproduced from [3])

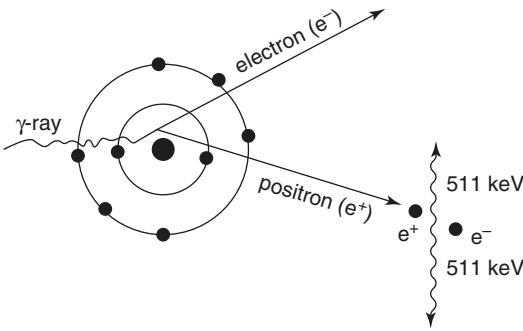


Fig. 1.9 Schematic representation of pair production. (Reproduced from [3])

Einstein mass energy equation ($E = mc^2$). After traversing some distance through the medium, the positron loses its energy and combines with an electron at rest and annihilates. During this process, both the antiparticles disappear (annihilate), and two photons of 0.511 MeV are emitted in opposite direction to obey the law of conservation of momentum.

1.9.12 Summary of Pair Production

- This involves interaction between photon and nucleus.
- Threshold energy for this process is 1.022 MeV, and the interaction is proportional to the energy in excess of 1.022 MeV.
- The probability of this type of interaction is proportional to the atomic number (Z) and density of the material.
- Two annihilated photons each of 0.511 MeV are produced per interaction and emitted from the site of interaction in the opposite directions.

1.9.13 Photo Nuclear Reaction

When photon energy is too high, either a neutron or proton may be knocked out (more likely the neutron) from the nucleus. For majority of atoms, the threshold energy for this effect is around 10 MeV, and the probability increases with increasing energy till a maximum is reached above which the probability falls rapidly.

1.10 Statistics in Radiation Measurements (Counting Statistics)

The purpose of counting statistics in nuclear medicine is to check the variability in the acquired data and to test the significance of observed variations. Let us first mention the types of error in the acquired data in nuclear medicine. There are three types of errors that are normally encountered:

1. Random error
2. Systematic error
3. Outliers or blunders

The random error is due to the random nature of physical processes involved in acquiring the data in nuclear medicine, such as radioactive disintegration, interaction of radiation with the detector material, etc. The nuclear medicine data usually suffers from random variation, resulting in imprecise results. Two measurements are from the same radiation source and, for exactly the same time period, are not identical. The data may however be accurate but not precise. The random nature of nuclear disintegration can be expressed in terms of Poisson statistics.

In systematic error, the result of several measurements may be same but not accurate. This error is mostly related to the instruments and may primarily be due to improper calibration of instruments or manufacturing defect.

The third type of error, not very common, is outlier or blunder, which results in grossly inaccurate results. Examples of blunders in radiation counting measurements result from:

- Incorrect energy window setting
- Counting heavily contaminated samples
- Using contaminated detectors
- High activities leading to excessive dead time effects
- Selecting wrong patient orientation during imaging

Blunders or outliers can be easily detected by experienced staff.

The measurement may be precise but inaccurate, or vice versa. Results of a radiation counting measurements may be imprecise (because of the random nature of emission) but still their (average) value may be accurate. Randomness is always present in counting measurements and during interactions of radiation with the scintillation detector. It is therefore necessary to know the statistical methods to analyse the data if so required. The statistical parameters and their application have been concisely described in the following text.

1.10.1 Measures of Central Tendency

It is convenient to summarize the results of a set of measurement with a single value in the form of **mean** or average value.

1.10.1.1 Mean

The mean of individual data points is simple to calculate. However, in grouped data, the central value of a group represents the class and the sum of their product with the respective frequency divided by the sum of frequencies results in the mean of the data.

Mathematically,

$$\text{Mean} = \sum X_i / N$$

where X_i is the i th data, and N is the total number of data points.

Simple mean cannot describe the data; therefore, two more terms, mode and median, are also defined.

1.10.1.2 Mode

Mode represents the most frequent value in the data distribution.

1.10.1.3 Median

Median divides the data into two equal parts. Each part can further be divided into two more parts. Thus, there are three data points which divide the distribution into four parts. The first data point is called first quartile or 25th(P25) percentile, the second is median or 50th percentile,

and the third is 3rd quartile or 75th(P75) percentile. Twenty five percent values lie below P25 (first quartile).

1.10.1.4 Skewness

When distribution curve is exactly symmetrical, then mean, mode and median are equal. The same is not true, when there is asymmetry in the distribution curve (skewness) as shown in Fig. 1.10. For positive skewness in the distribution curve, the mode is greater than median, and the median is greater than mean. In case of negative skewness, the mean is greater than median, and the median is greater than mode. Skewness is defined in terms of its first and second coefficients.

- The first coefficient of skewness = (mean – mode)/standard deviation
- The second coefficient = 3(mean – median)/standard deviation

1.10.1.5 Standard Deviation

One of the important statistical parameters which describes the variability in a set of data is the standard deviation. The standard deviation for a series of measurements determines the precision or reproducibility of the measured data. When data follows Poisson probability distribution, such as nuclear counting data, the standard deviation equals the square root of the mean. In some situations, where a single measurement is acquired as in digital imaging, the total pixel counts in the image is taken as mean for all practical purposes. This helps in estimating the noise in the image. For sample data, the standard deviation can be given by following equation:

$$\text{s.d.} = \sqrt{\left(\sum (x_i - \bar{x})^2 / (N - 1)\right)} \quad (1.20)$$

where x_i is the i th data, \bar{x} is the mean, and N is the total number of data points in the distribution.

Example The observed counts against each serial number and intermediate steps for the calculation of mean, standard deviation and coefficient of variation in a tabulated form is given below.