NUCLEAR MEDICINE IN CLINICAL PRACTICE:

Selective Correlation with Ultrasound and Computerized Tomography

Edited by
Larry D. Greenfield
and
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PREFACE

Nuclear medicine is the application of radionuclides both by imaging and in vitro techniques for the evaluation of physiology and the detection, diagnosis and therapy of disease. Nuclear medicine has demonstrated many capabilities in these diagnostic and therapeutic areas during its development over the last 50 years. However, there still remains a need for continued review of the fundamentals and the applications of nuclear medicine on the part of practicing physicians and residents-in-training in radiology, radiation oncology, nuclear medicine and medical/surgical specialties such as orthopedics and internal medicine. The aim of this book is to explain the clinical applications and the clinically related technical aspects of nuclear medicine to these residents and practicing physicians.

The basic nature of nuclear medicine involves continuing evolution and development of procedures to better evaluate physiologic functions. This book provides the most up-to-date statement of this evolution and development at this point. The applications of nuclear medicine are frequently complementary to and at times competitive with other diagnostic and therapeutic modalities. This book attempts to give the reader a good understanding of the relationships between these complementary and competitive roles.

There are two important points for the reader to keep in mind regarding nuclear medicine. First of all there is an apparent widespread concern on the part of many people in the general population about "nuclear" activities, whatever these activities might be. This has been particularly so regarding the known problems concerning the use of nuclear power to generate electricity on a commercial basis. It is interesting to note that in spite of this anxiety and the fact that the term "nuclear medicine" does including the word "nuclear", most patients do not show apprehension regarding the performance of a radionuclide study when needed in the scope of their health care evaluation. This is certainly very appropriate because the medical use of radionuclides virtually never includes a significant radiation risk factor during the performance of the indicated diagnostic studies.

It is important also for the reader to keep in mind that the basic function of nuclear medicine is to evaluate physiologic function rather than anatomic detail in the human body. Nuclear medicine had its origin in the evaluation of physiologic function of the heart and the thyroid, and this basic functional testing aspect continues as the substance of virtually all nuclear medicine procedures to this date.

Larry D. Greenfield
J. Michael Uszler

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NUCLEAR MEDICINE PHYSICS AND INSTRUMENTATION

L. STEPHEN GRAHAM

F. EUGENE HOLLY

Introduction

In the last few years there have been significant advances in the field of nuclear medicine. Some of these advances have come through the use of radiopharmaceuticals labeled with radionuclides having more desirable physical and biologic characteristics. Others have come as a result of significant improvements in imaging instrumentation.

The purpose of this chapter is to briefly describe the basic principles of radioactive decay and radiation detection, primarily from the standpoint of how these characteristics relate to the selection of a radiopharmaceutical. In addition, the principles of operation of counting systems and imaging instruments are described.

Radioactivity

Whereas most atoms have stable nuclei, others have nuclei that are unstable, that is, radioactive. Atoms with unstable nuclei spontaneously transform themselves (decay) and release energy in the process. This energy may be in the form of kinetic energy of a particle as in the case of beta emission, or in the form of an electromagnetic wave, as in the case of x-ray or gamma emission. These emissions may be thought of as a result of a rearrangement of either the components or the structure of the atomic nucleus in order to achieve a more "stable" configuration. More often than not, a change from one element to another (transmutation) is the end result. Assuming a basic knowledge of atomic structure, very little further knowledge of physics is required for understanding the underlying principles of radioactivity. What extra is required can be couched in terms of analogies to simplify its understanding.

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Nuclear Structure and Stability

The nucleus involves an extremely small fraction of the atomic volume (nuclear diameter $\simeq$ 1/10,000 atomic diameter) and may be thought of as consisting of neutrons and protons in a specific ordered structure.[1] The properties of some elementary particles are shown in Table 1-1.

Table 1-1. Elementary particles and radiations

Particle	Symbol	Mass		Charge	Comment
		amu[a]	kgm		
Proton	p, p^+	1.007597	1.6724×10^{-27}	+1	Fundamental nuclear building block
Neutron	n, ${}^1_0n$	1.008986	1.6747×10^{-27}	0	Fundamental nuclear building block
Alpha	α, ${}^4_2He$	4.002603	6.6435×10^{-27}	+2	Particle emitted from nucleus during alpha decay; identical to helium nucleus[b]
Electron (negatron)	e, e^-, β^-	0.000548	9.1×10^{-31}	−1	Called a beta particle when it originates in the nucleus[b]
Position	e^+, β^+	0.000548	9.1×10^{-31}	+1	A form of antimatter; the counterpart of an electron
Photon[c]	γ, X	0	0	0	X-rays are produced when electrons change orbits; gamma rays originate within the nucleus
Neutrino and anti-neutrino	ν, $\tilde{\nu}$	Very small		0	Associated with β^-, β^+ decay, and electron capture

[a] On the atomic mass unit (amu) scale, ${}^{12}_6C$ is arbitrarily assigned a value of 12.000000000000000 and is the standard for comparison of atomic masses.

[b] Because of lack of proper information at the time of discovery, identical particles or photons may have different names which relate to their place of origin.

[c] A photon is a packet of energy, an electromagnetic disturbance propagating through space. It is a means of transferring energy through a medium without disrupting it.

An interesting feature of any atom is that its mass is less than the combined masses of its elemental components (protons, neutrons, and electrons). This "mass defect," or "mass decrement" as it is known, arises from the fact that a portion of the total mass is transformed into the energy required to bind the nuclear particles together. The "lost" mass prevents disassembly or "splitting" of the nucleus unless energy is supplied from an external source. The binding energy can be calculated from Einstein's mass–energy equivalence formula:

$$E = mc^2 \tag{1-1}$$

where E is the energy, m is the mass, and c is the velocity of light.

The nuclear shorthand notation for an isotope is ${}^A_Z X$ or Z-X-A (eg, ${}^{12}_6C$ or *6-C-12*), where X represents the chemical symbol of the element, Z the atomic number, and A the mass number. The atomic number of the element equals the number of protons contained in the nucleus. The mass number is equivalent to the number of nuclear protons and neutrons. The number of neutrons in the nucleus can be found by subtracting the atomic number from the mass number (ie, N = A − Z). It should be noted that in the electrically neutral atom the number of orbital electrons is the same as the atomic number. Atoms that have the same number of protons (Z) but different numbers of neutrons (A − Z) are chemically indistinguishable and known as isotopes or radioisotopes if they are radioactive. Radioisotopes (also known by the more modern term "radionuclides") are the basis of nuclear medicine, as

discussed in the section on radiopharmaceuticals. Isotones, isobars, and isomers are other terms used to describe specific relationships between nuclides: their properties are listed in Table 1-2.

Table 1-2. Terminology

	Atomic number (Z)	Neutron number (N)	Mass number (A)	Examples
Isoto*P*es	Same	Different	Different	43-Tc-98, 43-Tc-99, 43-Tc-100
Isoto*N*es	Different	Same	Different	4-Be-10, 5-B-11, 6-C-12
Isob*A*rs	Different	Different	Same	5-B-12, 6-C-12, 7-N-12
Iso*M*ers	Same	Same	Same[a]	43-Tc-99m, 43-Tc-99

[a]The use of a lower case "m" following the mass number indicates that the nucleus is in a metastable state. See the next section for an explanation of metastable.

A specific nucleus (nuclide) may be either stable or unstable (radionuclide) depending on the particular number of neutrons and protons it contains and how they are arranged.[2] Nuclei tend to be stable if there is a certain ratio of neutrons to protons; this ratio ranges from $\simeq$ 1:1 for light elements to $\simeq$ 1.6:1 for heavy elements, such as lead. Radionuclides have improper ratios and are known as "neutron rich" or "neutron poor" according to this criterion. Atoms select a mode of decay that will restore the proper balance, as shown in the first example of the next section. In general terms, the farther the ratio is from that needed for stability, the shorter the half-life. With the exception of Bismuth-209 (Bi-209), all nuclei with atomic numbers greater than 82 are unstable.

Nuclei that have odd numbers of protons and neutrons also tend to be unstable, whereas even numbers of protons and neutrons tend to create stability. For example, only about 6% of all known stable isotopes have odd–odd nuclear construction and about 59% have even–even construction. Furthermore, nuclei tend to be extraordinarily stable if they contain 2, 8, 20, 28, 50, 82, or 126 protons or neutrons. This appears to reflect full occupancy of nuclear energy levels similar to the full electron orbitals of the inert gases.

Modes of Decay

Negatron or Beta Emission

Negatron or beta emission sometimes is referred to as beta decay and occurs when a nucleus is neutron rich. In simple terms, the process can be considered as that of a neutron splitting into a proton and an electron (beta particle) with the beta particle being ejected from the nucleus. This picture is consistent with the data presented in Table 1-1, which show that a neutron is slightly heavier than a proton. The emission of a beta particle from the nucleus is also accompanied by the release of an antineutrino, a particle with no charge and essentially no mass. It was first postulated to explain the fact that beta particles are observed to have a spectrum of energies, yet the total amount of energy released by a specific radionuclide when it decays is constant. Since its existence was first proposed it has been observed experimentally.

After beta decay occurs, the nucleus has one less neutron and one more proton, thus making it less neutron rich and therefore more likely to be stable. Often beta emission is also accompanied by the release of one or more gamma rays.

Electron (or K) Capture and Positron Emission

Electron capture and positron emission are two competing modes of decay for neutron-poor nuclei. In the first, the nucleus captures an electron from one of the inner orbits and uses it to convert a proton into a neutron. Use of the term "K capture" comes from the fact that K-orbit electrons have the highest probability of being captured. Accompanying this reaction is the emission of characteristic x-rays when the vacancy left by the electron is filled.

Positron emission involves the conversion of a proton into a neutron by the emission of a positively charged electron (positron). After the positron loses virtually all of its kinetic energy it combines with a free electron and both are annihilated. Annihilation is the conversion of their mass into energy and results in the emission of two photons which leave the site of annihilation in opposite directions.

Both of these reactions are accompanied by the emission of a neutrino and possibly a gamma ray. The end result is a nucleus with an atomic number that is one unit less than that of the parent; the mass number does not change. Because these modes of decay are competitive, the selection is based on the energy available in the transition. If the daughter nucleus is at least two electron masses (1.02 MeV) less than that of the parent, either positron decay or electron capture can occur. If the energy is less than 1.02 MeV, only electron capture can occur.

Alpha Decay

Alpha decay occurs only in elements that have an atomic number greather than 80 and reduces the atomic number by two and the mass number by four units. Alpha particles that are ejected from the nucleus during this mode of decay are indistinguishable from helium nuclei and are composed of two protons and two neutrons. Alpha-emitting radionuclides are not used for diagnostic purposes in nuclear medicine because of the high radiation dose to the patient.

Isomeric Transition

Isomeric transition occurs when a nucleus is in an excited metastable state (exists longer than a microsecond) and deexcites by emitting a gamma ray. The decay of technetium-99-m (Tc-99m) to technetium-99 (Tc-99) is the best known example of such a transition. It should be noted that, unlike all other modes of decay, no transmutation occurs and the resulting nucleus is chemically the same element.

The Radioactive Decay Law

Given a large population of radioactive atoms, the probability that a given atom will decay in a certain time interval is the same as that for any other atom in the population.[3] The decay is strictly a statistical process similar in some respects to the popping of a pan of popcorn. The fraction of the available atoms that will decay in a given time interval is called the disintegration or transformation constant and is signified by the Greek letter lambda, λ. The number of atoms (N) of a given original population (N_0) which will remain after a given time interval (t) can be calculated by the equation:

$$N = N_0 e^{-\lambda t} \tag{1-2}$$

This is the basic exponential equation for radioactive decay. If desired, the equation also can be written in terms of activity (A).

$$A = A_0 e^{-\lambda t} \tag{1-3}$$

Activity is the number of atoms decaying per unit time. Very often the activity is expressed in terms of a curie (Ci) or one of its subunits, ie, millicurie or microcurie, where 1 Ci is 3.7×10^{10} disintegrations per second. Recently a new unit of activity has been proposed named the becquerel (Bq). One becquerel equals one disintegration per second. This unit eventually will replace the curie as the unit of measurement of radioactivity.

An interesting result of the exponential decay law expressed in equations 1-2 and 1-3 is that given equal times, equal fractions of the original population of atoms will decay. Most often, this is expressed in terms of the physical half-life of a radionuclide, that is, the time it takes for one half of the original number of atoms to decay. For example, after one half-life only one half of the original atoms will remain; after a second half-life, only one fourth; after three half-lives, one eighth; etc. Another term that is often used is the average or mean life. It is the length of time it would take for all the atoms of a group to disintegrate if they were to disintegrate at a constant rate equal to the initial rate. The average life is numerically equal to 1.443 times the half-life.

Interactions of Radiation

When x- or gamma rays strike tissue, they generally interact by either photoelectric or Compton events.[4] A photoelectric event occurs when an x- or gamma ray transfers all of its energy to an inner-orbital electron. The resultant "photoelectron" is knocked out of the atom and deposits its energy in the immediately surrounding tissue. Interactions of x- or gamma rays with outer-orbital electrons cause Compton events. As a result of the collision a Compton electron and scattered photon are generated. Because energy must be conserved, the scattered photon has less energy than the incident electromagnetic wave.

Radionuclide Production

As indicated in the previous section, radionuclides are characterized by having too many (neutron rich) or too few (neutron poor) neutrons in the nucleus, relative to the number needed for stability. This fact immediately suggests a method for producing radioactive materials from stable nuclides; namely, either add neutrons to or remove neutrons from the nucleus.

Use of a nuclear reactor to produce radionuclides is based on its ability to produce neutron-rich nuclei.[5] This is actually accomplished in two different ways. Some radionuclides are produced by placing stable isotopes near or "in" the core of a nuclear reactor. This is called "activation." Because the fission (splitting) of heavy nuclei such as uranium-235 (U-235) releases enormous numbers of neutrons, there is a high probability that some of these will be absorbed by the nuclei, thereby making them neutron rich. Molybdenum-99 (Mo-99) can be produced in this way. The actual amount of activity that is produced depends on the number of available atoms, the flux of neutrons, the probability of absorbing neutrons, and the time of irradiation.

Reactors can also be used to produce radioactive materials in a different way. When U-235 fissions, or splits into two parts, the fragments have higher neutron/proton ratios than they should have to be stable. Therefore, they are neutron rich. These "fission fragments" can be obtained by chemically processing and removing the desired radionuclides from old fuel elements. Iodine-131 (I-131) can be obtained in this way; Mo-99 also can be obtained in this manner. Molybdenum-99 obtained as a fission fragment has the advantage of containing more activity per gram of molybdenum, thereby giving more concentrated solutions.

To produce neutron-poor radionuclides, a different technique is required. Charged particles such as protons, deuterons, and alpha particles are accelerated and used to bombard stable isotopes. Various kinds of reactions may occur, but the end result is production of proton-rich radionuclides that decay by electron capture or positron emission. Examples of radionuclides made in this way are thallium-201 (Tl-201), gallium-67 (Ga-67), iodine-123 (I-123), carbon-11 (C-11), nitrogen-13 (N-13), and fluorine-18 (F-18). The most commonly used accelerator for this purpose is the cyclotron. Compact biomedical cyclotrons can be found at some large medical centers and are primarily used for producing short-lived positron-emitting radionuclides such as C-11, N-13, and O-15. As with the nuclear reactors, the activity that is produced is a function of the particle flux, the number of atoms present, the probability that a particle will be absorbed, and the time of irradiation.

The availability of radionuclides for studies in nuclear medicine has been enhanced considerably by the use of generators.[5] The Mo-99/Tc-99m generator consists of an alumina column on which Mo-99 has been adsorbed. Each day the column is eluted, that is, washed with a saline solution. The Tc-99m that has been formed by the decay of Mo-99 is soluble in saline and is washed off the column into a collection vial. A special ionization chamber (dose calibrator) is used to measure the total amount of radioactivity that is present. The resultant chemical, pertechnetate, (TcO_4^-), then can be used to form various radiopharmaceuticals. The only real problem with the Mo–Tc generator is the relatively short half-life of the parent Mo-99 ($T_{1/2}$ = 67 hours); thus, a new generator must be purchased each week.

Fundamentals of Scintillation Detector Counting Systems

For a number of years it has been known that certain crystalline materials have an unusual property called luminescence. When these materials are exposed to ionizing radiation they scintillate, that is, they produce light, some of which is in the visible portion of the spectrum. Although a number of materials have this property the one most commonly used as a detector in nuclear medicine instrumentation is sodium iodide containing a small amount of thallium, NaI (Tl).

The property that makes luminescent substances of particular interest as detectors is the direct proportional relationship between the energy deposited in the crystal and the amount of light released. Because of this valuable property it is possible to differentiate those photons which have lost significant amounts of energy through scattering from those which have not. When scattered photons are used in the image formation process a loss of detail will occur. Thus, each photon that interacts with the detector generates a signal that can be analyzed to determine whether or not it represents an "acceptable" event. The following

paragraphs briefly describe the major components of a scintillation detector system used either for counting or for imaging.[5]

NaI (Tl) crystals are made in a variety of shapes as determined by the application of the detector. Because NaI (Tl) is hygroscopic the crystals are housed in aluminum containers or "cans." To quantitate the amount of light produced in the crystal by the interaction of a photon, an electronic device called a photomultiplier tube (PMT) is interfaced to one end of the crystal. The purpose of this component is to generate a voltage pulse with an amplitude that is proportional to the amount of light produced inside the crystal. Operation of the PMT requires a very stable high-voltage power supply. Even small fluctuations produce large changes in the amplitude of the signals, and, therefore, the apparent energy of the interacting gamma or x-ray. For this reason it is generally advisable to leave the high voltage on at all times unless an instrument is not being used for a considerable length of time.

The signals generated by the PMT are generally small and must be amplified before they can be analyzed. The controls of the amplifier are in the form of a coarse and fine gain adjustment.

After amplification the signals are presented to the pulse height analyzer (sometimes called a single-channel analyzer). Most analyzers are capable of operating in several modes and contain two level-sensing devices called discriminators. All signals above a certain level (integral mode) or only those falling within a specific energy range (window mode) can be selected. Regardless of the mode that is used, the output of the pulse height analyzer (PHA) is the same, namely a logic signal indicating an "acceptable" event has occurred.

The final electronic component is a scaler (counts accepted pulses), a rate meter (indicates the number of acceptable pulses per unit time), or an image display (indicates the spatial location of acceptable events). Combinations of these components also may be present. A schematic diagram of a scintillation detector system is presented in Figure 1-1.

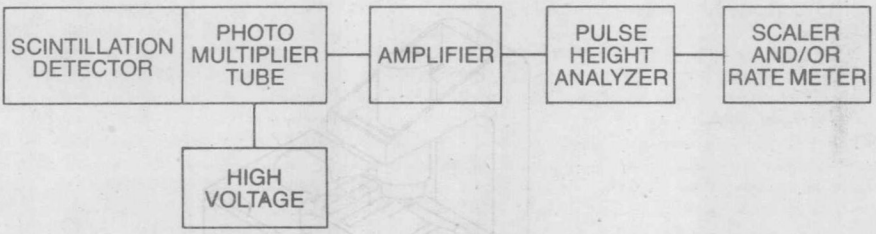

Figure 1-1. Block diagram of a scintillation detector system.

For certain applications such as radioimmunoassay (RIA), a variation of the system described above is used (see also Chapter 18). Because low-energy alpha and beta particles cannot penetrate the aluminum cover of the NaI (Tl) crystal, liquid scintillation solutions have been developed. A number of chemicals have been found that will scintillate when the energy of an alpha or beta particle is deposited in them. Thus the radionuclide to be counted is intimately mixed with the scintillation "cocktail." Although there are some differences between liquid scintillation counters and the NaI (Tl) system just described, the general principles of operation are the same.

Rectilinear Scanners

In 1950 the first system for automatically producing an image of the distribution of radioactivity within a patient was developed. As the detector moved back and forth over the patient, a typing element moved back and forth over a paper in synchrony. When photons were detected that information was transferred to the paper in the form of small lines or dots. A schematic representation of a rectilinear scanner is presented in Figure 1-2.

Since 1950 there has been a number of improvements in rectilinear scanners, although the general principle of operation is still the same. One of the first major improvements was that of photomodulation, the use of x-ray film instead of paper as the display medium. The image formation element consists of a light source that exposes the film. The result of this modification is a marked improvement in contrast. A second major improvement was the introduction of special electronics for modifying or subtracting unwanted background counts and altering the contrast in the image. A third modification was the incorporation of electronic circuitry that made it possible to obtain minified images — whole-body scans can be placed on a single 14 × 17 in. film.

Spatial resolution refers to the ability to see detail in a spatial distribution of radioactivity.[6] The spatial resolution that is obtainable with a rectilinear scanner is primarily determined by two factors: (1) the width and location of the analyzer window and (2) the type of collimator used. If the analyzer window is very narrow, all photons except those scattered through small angles, or not scattered at all, will be accepted. Although this potentially produces a scan with very good detail, it is generally found to be impractical in most scanning situations because excessively long scan times are required. On the other hand, if very wide windows are used to reduce scan time spatial resolution is very poor, because photons that have been scattered through very large angles are accepted.

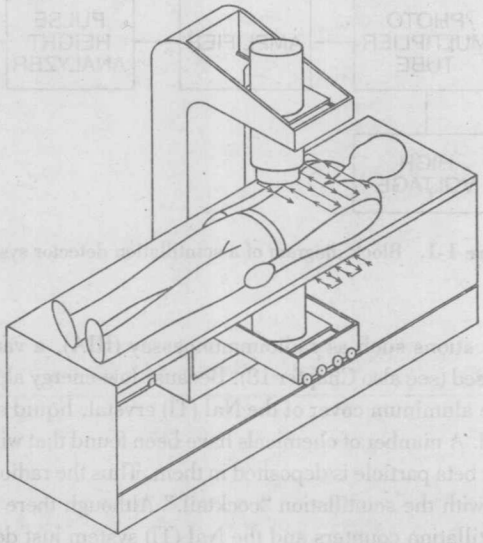

Figure 1-2. Schematic diagram of a rectilinear scanner.