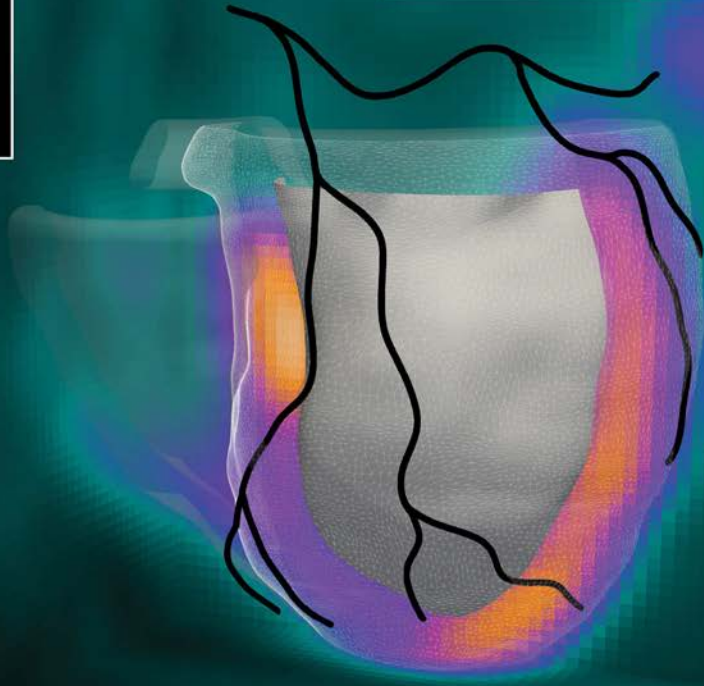
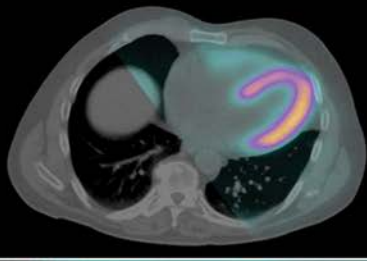


FOURTH EDITION



NUCLEAR CARDIOLOGY

PRACTICAL APPLICATIONS

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GARY V. HELLER
ROBERT C. HENDEL

Nuclear Cardiology

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Nuclear Cardiology

Practical Applications

Fourth Edition

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This edition is dedicated to the readers who will find this edition useful as this has been the goal of our efforts to complete this revision, especially an era of COVID where everything has been more difficult, but new important knowledge has been emerging and important. I primarily dedicate this to my co-editor, friend and colleague, Bob Hendel, who has had such an important role in all four editions bringing important comments, revisions, and humor to the process.

G.V.H.

For my colleagues-past, present, and future, who have provided me with inspiration throughout my career. Additionally, this book is also dedicated to those “behind the scenes,” such as our dedicated and passionate technologists, thoughtful administrators, and societal/regulatory personnel who help optimize the value of nuclear cardiology. And of course, to Gary Heller, the instigator and inspirator for Nuclear Cardiology: Practical Applications and kayaker extraordinaire.

R.C.H.

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PREFACE

We are pleased to present this fourth edition of *Nuclear Cardiology: Practical Applications*. We have undertaken substantial revisions, emphasizing recent changes in technology as well as the contemporary clinical applications of nuclear cardiology. We have provided insight as to future directions of the field, delineating where this important imaging modality is positioned in current-day clinical practice, especially in the setting of multi-modality imaging. We have greatly expanded information regarding positron emission tomography, including an entire chapter on the assessment of myocardial blood flow. Each chapter now features a table of key points and many of the tables and figures have been updated and expanded. We believe these help in the learning process as well as providing easy referencing key pieces of information. For your personal knowledge assessment, especially for preparation for credentialing examinations, we have provided a multitude of

questions with detailed answers related to each chapter, found at the end of the book.

This fourth edition is ideally suited for trainees and early-career professionals both radiologists and cardiologists. Additionally, this book should be very useful for technologists and healthcare professionals involved in decision-making for testing procedures.

We are grateful to the contributors who have done an outstanding job updating and expanding the book and its value. We hope that you find the fourth edition of *Nuclear Cardiology: Practical Applications* useful and that it will be a focal point for your nuclear cardiology education. To this end, it is our goal to assist in the improvement of nuclear cardiology practice and to benefit the patients for which we care.

Gary V. Heller
Robert C. Hendel

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SECTION

1

**FUNDAMENTALS OF
NUCLEAR CARDIOLOGY**

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Fundamentals of Nuclear Cardiology Physics

CHAPTER

1

C. David Cooke, James R. Galt and E. Lindsey Tauxe

KEY POINTS

- Elements are defined by the number of protons in the nucleus. Nuclides are defined by the number of protons and the number of neutrons.
- The ratio of protons to neutrons determines the stability of a nucleus.
- Unstable nuclei decay to a more stable state through several different mechanisms: α decay, β^- decay, β^+ (positron) decay, electron capture, and isomeric transition.
- The rate at which unstable nuclei decay can be described by the decay constant. It is often more convenient to describe the rate of decay by the half-life.
- The interaction of radiation with matter is dependent on the energy and type of the radiation, as well as the atomic number (Z number) of the matter.
- Attenuation is the loss of radiation as it passes through matter and is absorbed or deflected.

INTRODUCTION

A practical review of basic atomic and nuclear physics is essential to understand the origins of radiations, as well as their interactions with matter. The nature and type of emissions are determined by the

structural character of the atom and nucleus. The ways in which radiation interacts with matter have a direct relationship with imaging and radiation safety. The types of radiations and the ways in which they interact with matter are the foundation of radionuclide imaging and radiation safety. This chapter will focus on atomic and nuclear structure and the interaction of radiations with matter as they relate to radionuclide imaging.

ATOMIC AND NUCLEAR STRUCTURE

Matter is composed of atoms and the characteristics of a specific form of matter are determined by the number and type of atoms that make it up. How atoms combine is a function of their electron structure. The electron structure is determined by the nuclear architecture. As we have yet to image the atom, its structure is based on a “most-probable” model that fits physical behaviors we observe. The probabilistic approach is based on the model of the atom proposed by Niels Bohr in 1913. The Bohr atom proposed a positively charged nucleus, surrounded by negatively charged electrons. A neutral atom is one in which the positive and negative charges are matched. A mismatch in these charges determines the ionic character of the atom, which is the basis for its chemistry. The electron configuration is also a source for emissions used in radionuclide imaging.

These emissions, or *radiations*, will be in one of two forms: particulate or electromagnetic. The

origins of either type of radiation may be from the nucleus or the electron structure.

► Electron Configuration

Electrons are arranged around the nucleus in shells. The number of shells is determined by the number of electrons, which is, in turn, determined by the number of protons in the nucleus. The force exerted on these shells, called *binding energy*, is determined by the proximity of the shell to the nucleus. Higher binding energies are exerted on shells closest to the nucleus and conversely, lower binding energies for those more distant from the nucleus. The innermost shell is named the “K” shell and electrons in this shell are subject to the highest binding energy. The magnitude of that energy is dependent on the positive forces, which is determined by the number of protons in the nucleus. The shells more distant from the nucleus are named L, M, N, and so on. Each of these shells has lower binding energies as a result of their distance from the nucleus (Fig. 1-1).

The radii of each of these shells increase as a function of their distance from the nucleus. An expression of this is given by assigning an integer value (1, 2, 3, ...) to each shell. The lower values represent smaller radii. These integer values are called *quantum numbers*. Therefore, the K shell has a quantum number of 1, L = 2, M = 3, etc. This pattern continues until all available electrons are bound to a shell. The innermost shells are filled with electrons preferentially. The maximum number of electrons is specific to each shell and is calculated by $2n^2$, where

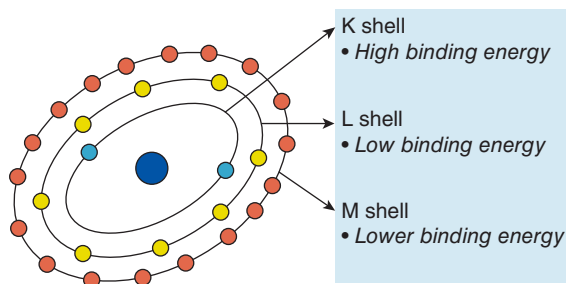


FIGURE 1-1 Atomic structure. The nucleus is surrounded by electron shells. The binding energy decreases as the distance from the nucleus increases ($K > L > M$).

n is the *quantum number*. Therefore, the maximum number of electrons for each shell is:

$$K = \text{quantum \#1} = 2(1)^2 = 2 \text{ electrons}$$

$$L = \text{quantum \#2} = 2(2)^2 = 8 \text{ electrons}$$

$$M = \text{quantum \#3} = 2(3)^2 = 18 \text{ electrons}$$

These shells are further subdivided into *substates*. The number of *substates* for each shell can be calculated by $2n - 1$; therefore:

$$K \text{ shell} = 2(1) - 1 = 1 \text{ substate}$$

$$L \text{ shell} = 2(2) - 1 = 3 \text{ substates}$$

$$M \text{ shell} = 2(3) - 1 = 5 \text{ substates}$$

Each substate for a given shell will have a unique binding energy. For instance, the L shell has three substates, L_I , L_{II} , and L_{III} .¹ Each of these has slightly different distances from the nucleus, and therefore slightly different binding energies (Fig. 1-2).²

Atomic Radiations

Electrons in inner shells being under high binding energy and thus tightly bound to the nucleus are in an inherently low-energy state. Outer shell and free electrons are in an inherently higher-energy state. Therefore, to move an inner shell electron to an outer shell *requires* energy. The amount of energy required is simply the difference between binding energies.

Example: Binding energy for a hypothetical “K” shell = 100 keV and “L” = 50 keV. $K_{100} - L_{50} = 50$ keV

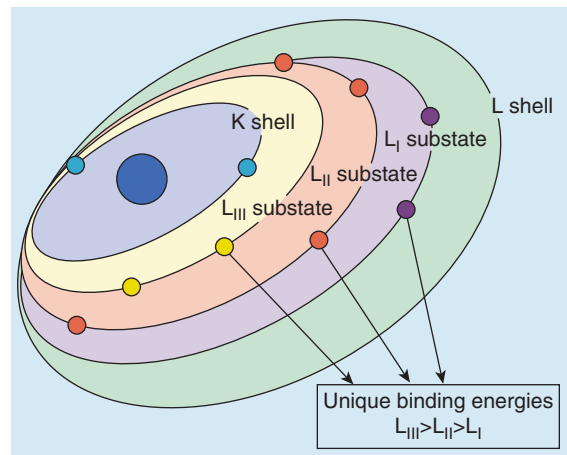


FIGURE 1-2 Electron configuration. Electrons are arranged in subshells, as illustrated for the L shell. Each subshell has a unique binding energy.

of energy *input* to move the electron from the “K” shell to the “L” shell.

Conversely, the movement of an electron from an outer shell to an inner shell, $L \rightarrow K$, yields energy. This energy yield results in the emission of radiation. The energy of the radiation is equal to the differences in binding energies of the shells. The radiation may take on two different forms: characteristic x-ray or Auger (oh-zhay) effect.

Example: Binding energy for a hypothetical “K” shell = 100 keV and “L” = 50 keV. $K_{100} - L_{50} = 50$ keV of energy *released* as the electron moves from the “L” shell to the “K” shell.

Characteristic x-rays are electromagnetic radiations (photons) that are created when an outer shell electron moves to fill an inner shell vacancy. This vacancy may occur for several reasons—to be discussed later. The energy of this photon is equal to the difference between binding energies. Since binding energies are determined by, or characteristic of, the number of protons in the nucleus, and it is the number of protons that determines an element’s identity, the characteristic x-ray energies are specific to each element and the electron shells from which they originate. X-radiation is defined as an electromagnetic radiation originating outside the nucleus, therefore the term characteristic x-ray.

The Auger effect occurs under the same conditions as characteristic x-ray, that is, an inner shell vacancy being filled by an outer shell electron. The difference is that the excess energy from the cascading electron is radiated to another electron. This ejects that electron from its shell. This free electron will have kinetic energy equal to the difference in the binding energies less the binding energy of the shell of the free electron. The Auger effect is more common in elements with lower numbers of protons (Z number).¹⁻³

► Nuclear Structure

The nucleus is composed mainly of neutrons and protons. Any particle contributing to the structure of the nucleus is called a *nucleon*. The conventional nomenclature to describe the nucleons is: A_ZX_N .

where:

X = Symbol of the chemical element

A (Atomic mass number) = Total number of nucleons = # Protons + # Neutrons

Z (Atomic number) = # Protons

N = # Neutrons

Since the number of neutrons (N) can be derived from the atomic mass number (A) and the number of protons (Z), it is usually omitted ($N = A - Z$). In addition, since the number of protons (Z) defines an element, as does its chemical symbol (X), only one is necessary; hence, Z is often omitted as well.

The total mass of an atom is essentially the combined masses of the nucleons. Electrons contribute less than 1% to the total mass.¹

Nuclides having the same number of protons (Z) are called *isotopes*. Isotopes are the same element, but have different atomic masses (A) and therefore have different numbers of neutrons (N); for example: ${}^{125}_{53}\text{I}_{72}$, ${}^{127}_{53}\text{I}_{74}$, and ${}^{131}_{53}\text{I}_{78}$. Nuclides with the same number of neutrons (N) are called *isotones* and will be different elements, since the number of protons (Z) will be different; for example: ${}^{131}_{53}\text{I}_{78}$, ${}^{132}_{54}\text{Xe}_{78}$, and ${}^{133}_{55}\text{Cs}_{78}$. Nuclides with the same atomic mass number (A) are called *isobars* and are different elements as well, since they will have different numbers of protons (Z) and neutrons (N); for example: ${}^{99}_{42}\text{Mo}_{57}$ and ${}^{99}_{43}\text{Tc}_{56}$. Finally, nuclides with the same number of protons (Z) and neutrons (N), but in different energy states are called *isomers*; for example: ${}^{99m}_{43}\text{Tc}$ and ${}^{99}_{43}\text{Tc}$. An easy mnemonic for remembering this is that **isotopes** (with a **p**) have the same number of **protons**, **isotones** (with an **n**) have the same number of **neutrons**, **isobars** (with an **a**) have the same **atomic** number, and **isomers** (with an **e**) are the same nuclide with different energies.

Isotopes having different N numbers are of particular interest to imagers because they have the same chemistry, since their Z numbers and, therefore, electron numbers are the same.¹⁻⁵ Some isotopes exhibit the emission of radiations, which is due to the differences in the number of neutrons. These isotopes are called *unstable*. If all the stable isotopes of all elements are plotted, comparing proton number to neutron number, a pattern emerges as illustrated in Figure 1-3.

Elements with low Z numbers have proton to neutron ratios that are 1:1. As Z numbers increase, this ratio increases to as high as 1.5. This distribution of stable elements is called the *line of stability*. By definition, an element with a proton to neutron ratio that falls to either the left or right of the *line of*

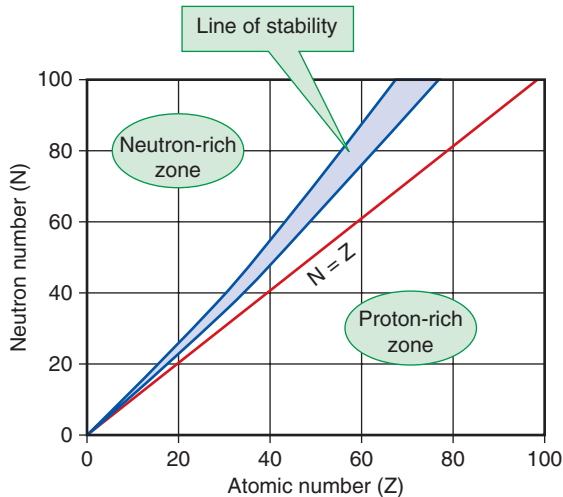


FIGURE 1-3 Line of stability. All naturally occurring stable nuclides fall along a distribution known as the line of stability (LOS). As illustrated, for light elements ($Z < 20$) $N \sim Z$ and for heavier elements $N \sim 1.5Z$. Unstable elements, lying to the left of the LOS, are neutron rich; those lying to the right of the LOS are proton rich.

stability is unstable. The unstable isotopes, *radioisotopes*, are unstable because their nuclear configurations are either proton rich or neutron rich relative to stable configurations. These radioactive elements seek stability by undergoing transformations in their nuclear configurations to a more stable $P \leftrightarrow N$ ratio. The type of transformation will be a result of the $P \leftrightarrow N$ ratio, that is, proton rich versus neutron rich. This type of transition is called the mode of decay.¹⁻⁴

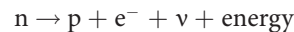
Modes of Decay

The goal of nuclear decay is to equate the balance of forces in the nucleus. The repelling forces originating from the positive charge (*coulombic forces*) of the protons, when matched by the attractive forces from within the nucleus (*exchange forces*), define **stability**. When these forces are mismatched, nuclear transformations (*radioactive decay*) result. The mode of decay will produce unique emissions and lead to a more stable nuclear configuration. In radionuclide imaging, the ideal mode of decay would result in a high yield of photons, at an energy that is efficiently detected by our imaging instrumentation. Photon emission is also desirable from the radiation safety

and dosimetry perspectives, due to their lower probability of creating potentially damaging interactions as compared to particles. With these considerations, it is important to understand the modes of decay of ^{99m}Tc , ^{201}Tl , and ^{82}Rb —the most commonly used radionuclides in nuclear cardiology.^{1,2}

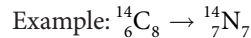
β^- Decay

In an unstable nuclear configuration where the nucleus is neutron rich, β^- decay occurs. To decrease the neutron–proton ratio, a neutron is converted to a proton and an energized electron is emitted. The expression of this nuclear transition is:



where n is the neutron, p the proton, e^- the electron, and ν is the neutrino.

The neutrino (ν) behaves like a particle with no mass and is not critical to imaging considerations. The primary emission is the energized electron (e^-). The nuclear configuration that results from β^- decay is a *daughter* with a stable or more stable energy state and an additional proton in its nucleus.

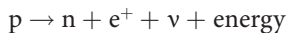


Since the number of protons is changed, the elemental identity changes. This is called a transmutation. The daughter atomic mass (A) remains the same as the parent nucleus, and the energy carried off by the ejected electron is called transition energy. This leads to a more balanced relationship of coulombic force (repelling forces due to the protons) and exchange force (attractive nuclear forces). The resulting emission of the energized electron, a β^- particle, is of no use in imaging and contributes to an increase in radiation dose in a biologic system. This decay process may lead to a daughter that is not fully stable, but more stable than the parent.^{1,2} The change in nuclear configuration is an increase in Z and a decrease in N .

β^+ Decay

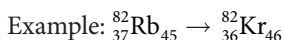
In nuclear configurations where the *parent* is proton rich, β^+ decay may occur. In this mode of decay, a proton is converted to a neutron and the emission of

an energized, positively charged electron (β^+) results. The nuclear equation is:



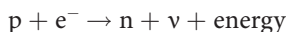
The energy of the β^+ particle contributes to resolving the *transition energy* between the unstable parent and more stable daughter, as in β^- decay.

An important secondary emission will result from the formation of the β^+ particle. Since there is an abundance of negatively charged electrons in nature, the resulting positively charged electron (β^+) will be attracted to, and collide with, a free negatively charged electron. This collision results in the *annihilation* of both particles. The annihilation leads to the conversion of the mass of these particles to their equivalent energy state. This is expressed by Einstein's equation $E = mc^2$, where E is energy, m the mass, and c is the speed of light. This essentially states that energy and mass are simply two physical forms of the same thing. Therefore, two photons (E) are emitted, each with the energy equivalent to the mass (m) of an electron, which is 511 keV. Unique to this annihilation is that these photons are emitted in a 180-degree trajectory from each other. It is these photons that are detected and registered into an image in positron imaging, such as with ^{82}Rb . The change in nuclear configuration is a decrease in Z and an increase in N .



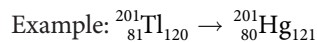
Electron Capture

An alternative to β^+ decay in proton-rich nuclear configuration is *electron capture*. This mode of decay is defined as the capture of a K-shell electron by the nucleus, the subsequent combination with a proton, and creation of a neutron. The nuclear expression is therefore:



The vacancy left by the captured electron would then be filled by an outer shell electron. A cascade of an electron, filling subsequent vacancies, creates secondary emissions called *characteristic x-rays* and *Auger electrons*. The energies of these emissions will be characteristic of the binding energy of the

daughter, since the nuclear transition occurred prior to the production of the x-rays and Auger electrons. It is the *characteristic x-rays* that are imaged in ^{201}Tl myocardial perfusion imaging. The energy of the x-rays is determined by the binding energy of ^{201}Hg , the daughter of the decay of ^{201}Tl . Electron capture decreases the proton–neutron ratio.¹



Isomeric Transitions and Internal Conversions

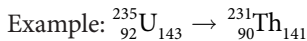
The daughter of the decay of a radioactive parent will ideally be in its most stable energy configuration or *ground state*. This does not always occur, leading to either of the two unstable states: *excited state* or *metastable state*. Excited states are very unstable and exist for very short time periods, usually less than 10^{-12} seconds. Metastable states, however, may exist for several hours. These metastable states lead to the release of energy in the form of electromagnetic emissions, without changing the proton–neutron ratios. The daughter nucleus has the same nuclear structure as the parent has, but in a more stable energy configuration. This form of decay is called an *isomeric transition* and results in electromagnetic emissions called γ -rays. These emissions are the same as x-rays, differing only by their location of origin, that is, the nucleus. As noted with the production of characteristic x-rays, there is a competing process, resulting in a particulate radiation. This process is called *internal conversion*. For any given metastable state, there is a specific ratio of *isomeric transitions* to *internal conversions*. In imaging, the higher percentage of isomeric transitions compared to internal conversions is preferred due to the resulting higher yield of photons. The decay of $^{99\text{m}}\text{Tc}$ to ^{99}Tc is an example of an isomeric transition of the metastable state ($^{99\text{m}}\text{Tc}$). The percent occurrence of isomeric transitions of a population of $^{99\text{m}}\text{Tc}$ nuclei is approximately 87%. For example, for every 100 decays of $^{99\text{m}}\text{Tc}$ nuclei, there is a yield of 87 γ -photons and 13 internal conversion electrons.

For any given mode of decay, should the daughter be metastable, there will be the emission of γ -photons and internal conversion electrons as secondary emissions. This will be indicated as $[\text{B}^-, \gamma]$, $[\text{B}^+, \gamma]$, $[\text{EC}, \gamma]$, and so forth. The internal conversion electron

yield, in ratio to γ -photon yield, is specific to a given radionuclide.^{1,2,5}

Alpha (α) Decay

In unstable nuclei with very high atomic masses, the most probable mode of decay is α decay. An alpha particle consists of two protons and two neutrons, which is essentially a helium nucleus. Alpha decay results in a daughter with a Z number of 2 less than the parent and an atomic mass less by 4 relative to the parent.



Due to its high charges and heavy mass, the alpha particle has a very short travel distance in matter and deposits its energy very quickly. It has no application in diagnostic imaging and induces significant potential for biologic damage.^{1,3}

Decay Schemes

The modes of decay may be expressed graphically, called *decay schemes*. Decay schemes graphically illustrate all possible nuclear transitions that unstable nuclei undergo. They are often accompanied by tables with detailed information about the transitions, such as the percentage occurrence, isomeric transitions, internal conversions, characteristic x-rays, Auger electrons, and biologic dose information.

In decay schemes, the nuclear energy levels are expressed as horizontal lines. The space between these lines represents the *transition energy* (Q).

The types of emissions are depicted by a unique direction of a line (Fig. 1-4).

Note that the arrows may be angled to either the right or left. In neutron-rich parents, the mode of decay “shifts” the daughter to the right, corresponding to the shift on to the line of stability graph. Conversely, a mode of decay for a proton-rich parent moves to the left, toward the line of stability.

The tables that accompany decay schemes provide additional detail including the secondary emissions, as mentioned earlier. Since many of the secondary emissions are particulate, that is, electrons, these data are of particular interest in radiation dosimetry. In the decay scheme for ${}^{201}\text{Tl}$, the data regarding the characteristic x-rays of ${}^{201}\text{Hg}$ are in these tables.

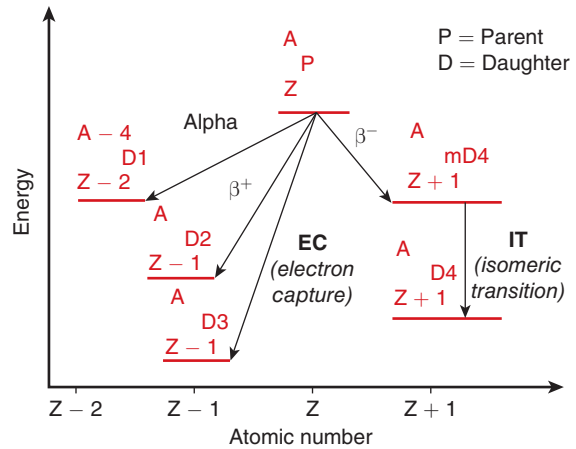


FIGURE 1-4 Decay schemes. This figure illustrates the configurations of decay schemes for the different modes of decay. The schemes move to the left for proton-rich radionuclides and to the right for neutron-rich radionuclides.

Parent–Daughter Equilibrium

Not all nuclear transitions lead to a stable daughter. The β^- decay of ${}^{99\text{m}}\text{Mo}$ yields ${}^{99\text{m}}\text{Tc}$, which then decays to ${}^{99}\text{Tc}$ by *isomeric transitions* and *internal conversions*. ${}^{99\text{m}}\text{Tc}$ decays to ${}^{99}\text{Tc}$ with an 87% frequency through isomeric transitions. Therefore, for every 100 decays of ${}^{99\text{m}}\text{Tc}$, we observe 87 γ -rays and 13 internal conversion electrons, as stated earlier. This higher yield of photons makes ${}^{99\text{m}}\text{Tc}$ a very desirable radionuclide for imaging. A sample of ${}^{99}\text{Mo}$ would always contain some proportion of ${}^{99\text{m}}\text{Tc}$ and ${}^{99}\text{Tc}$. Since both parent and daughter are decaying, the relative activities would reach equilibrium, based on their half-lives. These states of equilibrium are employed when using both technetium and rubidium generators. When the parent half-life is marginally longer than that of the daughter, the amount of the daughter in the mixture will reach a maximum over a period of time. That elapsed time will be a multiple of half-lives of the daughter. If the daughter radionuclide is removed from the mixture, the same multiple of half-lives will have to occur, before the maximum amount of the daughter is subsequently reached. This equilibrium state is called *transient equilibrium*.^{2,4} It is this transient state that is the basis of ${}^{99\text{m}}\text{Tc}$ production from ${}^{99}\text{Mo}$ – ${}^{99\text{m}}\text{Tc}$ generators (Fig. 1-5).

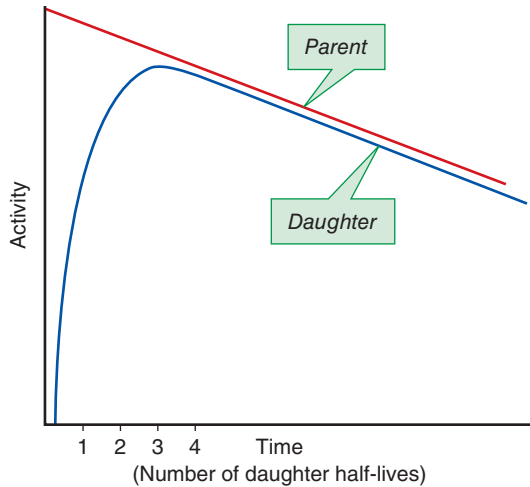


FIGURE 1-5 Transient equilibrium. When the parent half-life is marginally longer than that of the daughter, the amount of daughter activity will reach a maximum after relatively few daughter half-lives have passed. $^{99\text{m}}\text{Tc}$ and $^{99\text{m}}\text{Mo}$ typically reach transient equilibrium after approximately four $^{99\text{m}}\text{Tc}$ half-lives.

In parent–daughter mixtures where the half-life of the parent is markedly longer than that of the daughter, *secular equilibrium* is reached. In this state of equilibrium, the concentration of the parent is decreasing so slowly relative to the daughter that the mixture appears to have the half-life of the parent. It is this equilibrium that is the basis for the ^{82}Sr – ^{82}Rb generators used in ^{82}Rb positron emission tomography (PET) imaging (Fig. 1-6).¹

RADIOACTIVITY

The specific time that an unstable nucleus will undergo a transition cannot be determined, only *predicted*. Nuclear transitions are spontaneous and random, so the mathematics of radioactive decay is based on probabilities and rates, not specific nuclear events. If a population of radioactive atoms, N , is considered, the rate of nuclear transitions would be expressed as $\Delta N/\Delta t$. The rate implies that a constant would express the average number of transitions that occur per unit time. This constant is called the *decay constant*; which is specific to a given radionuclide and is expressed as λ . The mathematical relationship is: $\Delta N/\Delta t = -\lambda N$, where N is the total number of

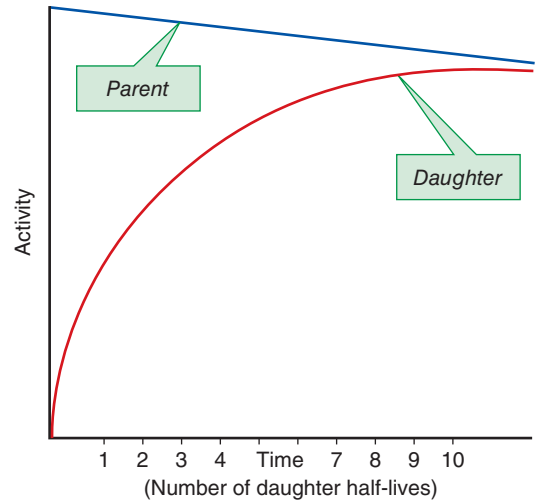


FIGURE 1-6 Secular equilibrium. When the parent half-life is considerably longer than that of the daughter, the amount of parent activity will decrease very little over time. Therefore, many more daughter half-lives must pass before the equilibrium is reached. An example is ^{82}Sr with a half-life of 25 days and ^{82}Rb with a 1.2-minute half-life.

radioactive nuclei and λ the decay constant. Since the total N decreases with time (t), the decay constant (λ) is a negative value.^{1,2,4} The number of transitions per unit time ($\Delta N/\Delta t$) is called *activity*. Activity is measured in curies (Ci), which is defined as 3.7×10^{10} disintegrations per second (dps). The International System of Units (SI) unit equivalent is the becquerel (Bq), which is defined as $1 \text{ Bq} = 1 \text{ dps}$. So $1 \text{ Ci} = 3.7 \times 10^{10} \text{ Bq}$. The most commonly used units are in the mCi (MBq) range for nuclear cardiology procedures.

In nuclear decay, the number of radioactive nuclei (N) is always decreasing as time passes at an average rate defined by the decay constant (λ). Decay is expressed, therefore, as an exponential function; that is, the number of radioactive nuclei available is affected by both the number of unstable nuclei and its average rate of decay. To calculate the specific number of decays for a given time, we have the following expression:

$$N_{(t)} = N_{(0)} e^{-\lambda t}$$

where $N_{(t)}$ is the number of unstable nuclei remaining after the elapsed time (t) has passed. The expression