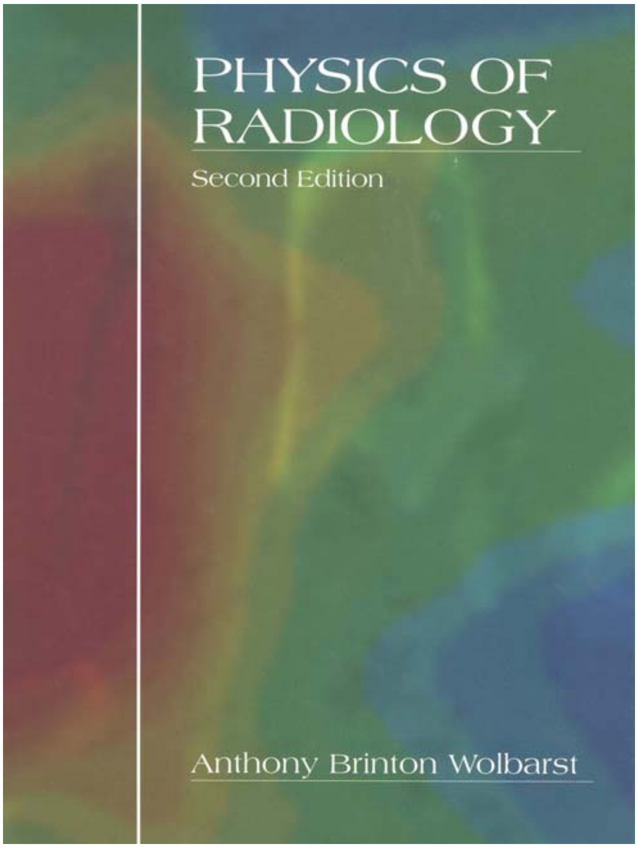
MEDICAL PHYSICS PUBLISHING


PHYSICS OF RADIOLOGY
Second Edition
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Here is a sample chapter from this book.

Chapter 13

Gamma Ray Imaging I: Harnessing Radioactive Decay

There are three essential ingredients to a nuclear medicine study: (1) a pharmacologic agent that is taken up preferentially by some organ or other biologic compartment of interest; (2) a radionuclide that can be attached to the agent and emits gamma rays of sufficient energy to escape the body; and (3) a device to detect or image these gamma rays. A nuclear medicine image is of relatively low spatial resolution, and reveals only the rough shape and size of the organ under consideration. But if a portion of the organ fails to take up the radiopharmaceutical, or is missing, or is obscured by overlying abnormal tissues, the corresponding region of the image appears dark. Likewise, any part of the organ that takes up more radiopharmaceutical than normal, or fails to wash it out properly, will glow especially brightly on the display. Thus a nuclear medicine image provides information on the physiologic status and pathologies of an organ, rather than on its anatomic details.

This chapter will provide an elementary introduction to radioactivity, and to the ways in which radionuclides can be put to work producing medical images. It will discuss the workings, in particular, of an early imaging device known as a rectilinear scanner. Chapters 41 through 44 will examine nuclear medicine in greater depth, considering the details of the ubiquitous gamma camera, along with its offshoots, SPECT and PET.

1. Henri Becquerel, Uranium, and Paris in the Springtime

Let us return, for a moment, to the months immediately following Roentgen's momentous discovery of 1895. No one had any idea what his strange x-rays really were—particles of some sort, perhaps, or an unusual form of ordinary light?—or how they came into being. Many of the world's leading scientists naturally turned their attention to this mystery. And in so doing, one of them, Henri Becquerel, stumbled onto an equally bizarre new phenomenon, radioactivity, which has had every bit as profound an impact on world affairs as have x-rays. He did so by coming from a good family and following a bad hunch.

Becquerel was the third in a direct line of four generations of outstanding physicists. Henri's grandfather, Antoine Cesar Becquerel, had graduated as an officer from the prestigious Ecole Polytechnique (France's equivalent of MIT and West Point rolled into one) in time to serve under Napoleon between 1810 and 1812. Severely wounded and told he had but a short while to live, Antoine Cesar resigned from the army, got a second opinion, and went on to a long and brilliant academic career in science. Among his primary interests was luminescence, and he was the first to publish the optical spectra of phosphorescent materials. For these and other efforts, a chair in physics was created for him at the Museum of Natural History in Paris. He published 529 research papers, was appointed Director of the Museum, and lived to see age 90.

Antoine Cesar's third son, Alexandre Edmond, assisted with his father's experiments as a youngster, also studied at the Ecole Polytechnique, became one of the world's leading authorities on luminescence, and succeeded his father as professor of physics at the museum. One of his findings, that some salts of uranium (an element discovered in 1789) are strongly phosphorescent, would later be of great importance to the work of his own second son, Henri.

Henri Becquerel (Figure 13–1), the central character of our little drama, followed in the family tradition and devoted much of his life to the study of luminescent materials. By the time of Roentgen's discovery, he had, at the age of 43, succeeded his father as professor of physics at the museum. (And Henri's

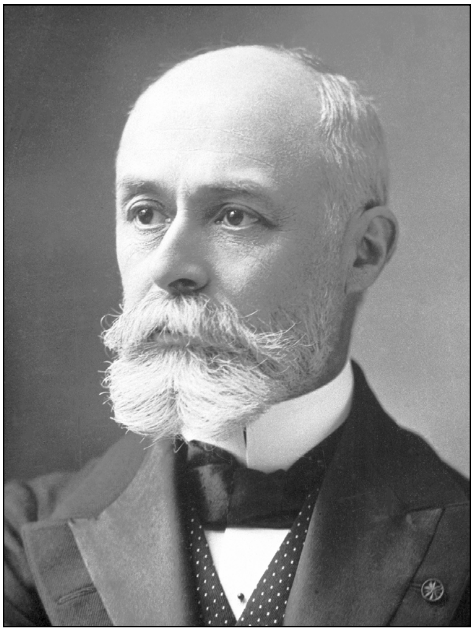

Figure 13–1. Henri Becquerel discovered radioactivity in 1896 while examining some of the findings on x-rays that Roentgen had published the previous year. [© *The Nobel Foundation.*]

only child, Jean, would eventually become the fourth in an unbroken chain of Becquerels holding that position for 110 years consecutively.)

Like everyone else at the time, Henri was intrigued by x-rays, and his fascination became all the more intense when he learned of one particular observation by Roentgen: x-rays appeared to emanate primarily from the glowing spot on the wall of the vacuum tube where cathode rays seemed to be striking, i.e., from a part of the glass that appeared to display fluorescence. Is it not possible, he reasoned, that anything that causes fluorescence in a material also produces Roentgen's rays at the same time? And they just had never been noticed before? Might it be that x-rays automatically accompany fluorescence?

To test this hypothesis, he wrapped a photographic plate in thick black paper impervious to light, put it in direct sunlight, and placed a piece of phosphorescent material on top. If he were correct, the sun should stimulate the phosphorescent material to emit both light and x-rays, and the plate would still be exposed and darkened, because the x-rays could get to it even through its wrapping.

His initial negative results did not deter him. He believed that all he needed was a luminescent material that emitted x-rays with sufficient intensity. ". . . I had great hopes," he later recalled, "for experimentation with the uranium salts, the fluorescence of which I had studied on an earlier occasion, following the work of my father . . ."[1] Putting a covered photographic plate in the sun and placing a sample of uranyl potassium sulfate on it, he found that the portion of the plate where the sample had been became darkened, exactly as expected. He conveyed this finding to the French Academy of Science on February 24, 1896.

Henri intended to repeat and expand on this experiment right away. He prepared and wrapped a fresh photographic plate but, when the weather in Paris took a turn for the worse, he stuck it in a dark drawer with, as it happened, a sample of the uranium salt resting on it. A few days later, for reasons that remain unclear, he removed the plate and developed it:

> Since the sun did not show itself again for several days, I developed the photographic plates on the 1st of March, expecting to find the images very feeble. On the contrary, the silhouettes appeared with great intensity. I thought at once that the action might be able to go on in the dark.[2]

Becquerel's discovery of radioactivity, and the subsequent isolation of the radioactive elements polonium and radium by Marie Curie and her co-workers, aroused little of the excitement that had surrounded the announcement of x-rays. Early applications were few and limited in scope. In medicine, radium-filled hollow needles could be inserted into certain inoperable tumors, with some degree of therapeutic success. And a mixture of fluorescent materials and radium would glow continuously, which made possible luminous meter dials that would remain visible in the dark. There were several other minor uses, but that was about it.

Then suddenly in the late 1930s, a discovery about certain radioactive materials riveted the attention of scientists everywhere: A uranium-235 nucleus could be made to undergo *fission*—to break into two pieces, two new atomic nuclei, each roughly half the size of the original—if struck by a neutron. In the process, moreover, a tremendous quantity of energy is released, along with about two (on average) additional neutrons. Each of those two neutrons, in turn, could cause another uranium nucleus to fission, in a large enough piece of uranium, and to liberate two more new neutrons, and so on and on and on. The numbers of free neutrons flying about, and of uranium nuclei undergoing fission and giving off energy, could increase explosively, within a fraction of a millisecond, in a fast *nuclear chain reaction*. The potential implications of this finding were both obvious and, with Europe and the Far East writhing in bloody turmoil, of immense importance.

Within a nuclear power reactor, alternatively, the rate at which energy is being produced is fully controlled. This situation can occur in a fission chain reaction if neutrons are removed from the process exactly as fast as they are being spawned, resulting in a stable condition and the steady creation of heat. This energy given off can be harnessed to boil water, and the resulting steam can drive turbines to generate electricity.

And, incidentally, among the fission and activation byproducts created in nuclear reactors are certain radioactive materials that make possible the practice of nuclear medical imaging.

2. Atomic Nuclei: Elements and Isotopes

Gravitational and electromagnetic interactions are responsible for the ordinary processes of everyday life. Virtually all the chemical and physical properties of an atom, or of a gas, liquid or solid made up of that kind of atom, are determined solely by the arrangement of its electrons, hence ultimately by

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[1] Pais A. *Inward Bound*. Oxford (1986), p. 44.

[2] Comptes-rendus 126, 1086 (1896).

the atomic number, Z. The properties of the nucleus itself—in particular whether or not it has a magnetic moment, or is stable or radioactive—are determined largely by the two other fundamental forces, the strong and weak nuclear forces, which have effect *only* within nuclei.

The nucleus is held together by the attractive **strong nuclear force** between nucleons: proton-to-proton, neutron-neutron, and proton-neutron. This force is extremely powerful, as its name implies, but it extends for just a very short distance, about the diameter of a proton or neutron—so at any instant it is pulling together only those nucleons that happen to be adjacent. Also present within the nucleus are the *electric forces* among the positively charged protons, which tend to shove one another (hence the entire nucleus) apart. In contrast to the strong nuclear force, the electric field of a proton falls off slowly over distance, with the familiar inverse-square form of Equation (5.1); indeed, the combined electric field of the Z protons extends way beyond the nucleus, and is what binds electrons to it. It is the balance between the attractive strong nuclear forces, on the one hand, and the electric repulsion among the protons, on the other, along with some input from the weak interaction, that determines whether a particular nuclide will be stable or radioactive.

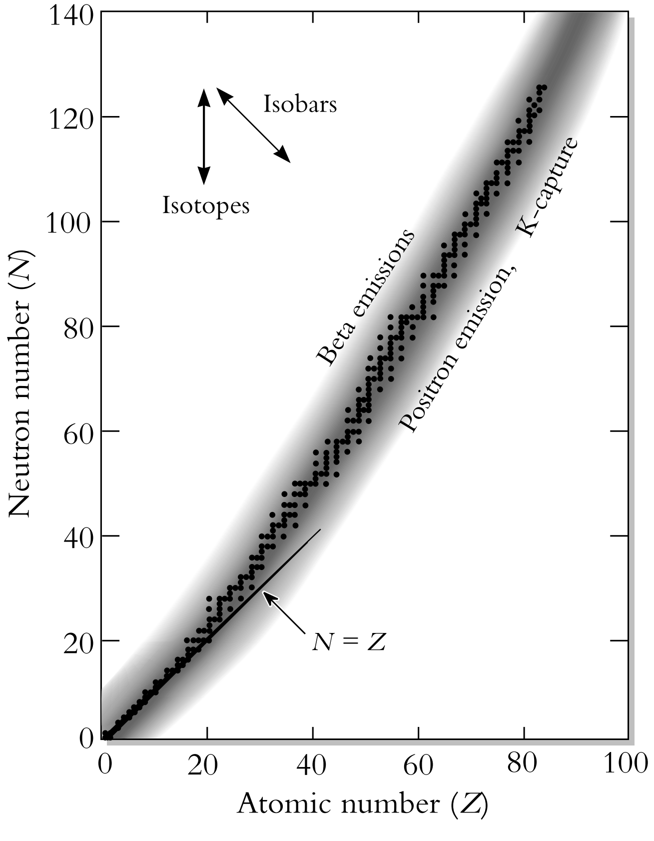

Figure 13–2. Of the 2800 known nuclear forms, 266 are stable, and these are indicated by the black dots. For the lightest elements, the number of neutrons tends to be about the same as the number of protons, $N = Z$. The N/Z ratio for high-Z elements increases to about 1.6. An unstable nucleus with too high or too low an N/Z ratio will try to move toward the line of stability through radioactive decay.

Of the 2800 or so different naturally occurring and man-made nuclides, or distinct combinations of protons and neutrons (with about 30 still being added every year), for only 266 of them, indicated by the **line of stability** in Figure 13–2, does the interplay of the strong, weak, and electromagnetic forces result in a stable nuclear balance. Fortunately, the common isotopes of hydrogen, carbon, nitrogen, oxygen, sulphur, phosphorus, silicon, iron, and the other elements that comprise us and our planet are stable.

The other 2500 nuclei come into being with an unsuitable N/Z ratio, with too much energy or other problems, rendering them *unstable,* or **radioactive**. A particular radioactive isotope of a specific element is called a **radioisotope** or a **radionuclide**.

3. Unstable Nuclei and Radioactive Decay

Every element, even hydrogen, has one or more radioactive isotopes, and for any element of atomic number 84 or above, every nuclide is radioactive. All radioactive nuclei emit *alpha* or *beta* particles and *gamma* rays. The gamma rays and positrons (positive beta particles) make standard nuclear medicine, SPECT, and PET possible. Alpha and negative beta particles take no part in imaging, but still can pose radiation hazards.

A glance at Figure 13–2 reveals that a nucleus with Z protons also contains typically between Z neutrons, for the lighter elements, and 1.6 × Z neutrons, for the heavy ones. (Ordinary hydrogen, with *no* neutrons, is the important exception to the rule.) The reason that the heavier elements tend to favor a higher neutron-to-proton ratio involves the balance we have just discussed. For a small nucleus, the short-range strong nuclear force among neighboring nucleons is sufficient to hold the nucleus intact. But as Z grows larger, and as the long-range electric forces become more pronounced, a few extra squirts of nuclear glue are required, along with a bit more separation between the protons, and these are provided by the neutrons, resulting in a higher N/Z ratio. It is also why some heavy radionuclides attempt to improve the situation by getting rid of some of their positive charge; three of the ways they can do that are through the nuclear transformations of alpha and positron emission and electron capture.

An unstable nucleus will continually vibrate, contort, and generally churn away in attempts to rectify its nuclear discomfort, and sooner or later, it will undergo spontaneous **radioactive decay**. (Nothing is "decaying" in the ordinary sense of the word—the term refers loosely to the decline over time in the number of radioactive nuclei in a sample that still have not yet undergone such a transformation.) A decay transition most commonly begins with the emission of an alpha or a beta particle (Table 13–1). Either of these is usually followed immediately by the release of any excess energy in the form of a gamma ray.

A short while later, as the electron cloud settles down around its new nucleus (which contains more or fewer protons and neutrons than before), it is likely also to emit *x-rays.* This is a purely atomic phenomenon, however, rather than a nuclear one.

Alpha particle emission

Although not used in clinical imaging, alpha particles play important roles in research, particularly in radiobiology. An

Table 13–1. Processes involved in common nuclear transformations.

Transition	Nuclear process	*Z, N, A* changes		
		ΔZ	ΔN	ΔA
alpha emission: α, α^{++}	emission of He-4 nucleus, usually followed by gamma	*–2*	*–2*	*–4*
beta emission: β^-, e^-	emission of electron, usually followed by gamma	+1	–1	--
positron emission: β^+, e^+	emission of positron, usually followed by gamma	–1	+1	--
electron capture	nuclear capture of K-electron, usually followed by gamma	–1	+1	--
gamma emission: γ	drop to lower energy level	--	--	--
neutron emission: ${}^{1}_{0}n$	rare; emission of neutron, usually followed by gamma	--	–1	–1
neutron activation	capture of neutron	--	+1	+1
nuclear fission, after neutron activation	nucleus splits into fragments, releasing neutrons, energy	√	√	√

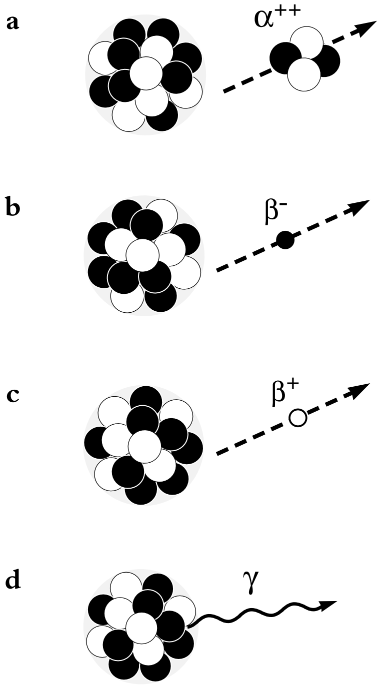

Figure 13–3. Common modes of nuclear decay. **(a)** Some heavy nuclei emit alpha particles, which are identical to ${}^{4}_{2}$He (ordinary helium) nuclei. **(b)** With the emission of a beta particle (an electron, but of nuclear origin), the atomic number increases by one, and the number of neutrons decreases by one. **(c)** A nucleus can reduce its atomic number (and net positive charge) by one by emitting a positron, which is a positively charged electron. **(d)** An excited nucleus may give up excess energy by emitting a gamma ray photon. Gamma emission commonly occurs subsequent to alpha, beta, and positron events.

alpha particle, indicated as α or α^{++}, is a tightly bound, stable cluster of two protons and two neutrons; once free of the nucleus, an alpha particle is indistinguishable from a standard ionized helium nucleus, ${}^{4}_{2}\mathrm{He}^{++}$ (Figure 13–3a). The resulting **daughter** radionuclide will contain two fewer protons and two fewer neutrons—that is, it will be of a new element type. Shades of the Philosopher's Stone!

Alphas are emitted predominantly by heavier elements, with $Z > 82$, such as radium, uranium, and plutonium, and they generally come out with a considerable amount of kinetic energy—in the 4 MeV to 9 MeV range. (By contrast, even the most energetic transitions involving atomic orbital electrons rarely exceed the exchange of a hundred keV.)

Beta particle emission

Beta particles tend to be ejected by radionuclides of lower mass number, and they come in two flavors. In the vast majority of cases they are, once out of the nucleus, just standard, garden-variety electrons (Figure 13–3b), and designated either β^- or e^-. The term "beta particle" is sometimes used to refer specifically to these emissions.

For a few radionuclides, however, the emitted entity is a **positron**—the so-called *anti-particle* to the electron (Figure 13–3c). It carries a positive charge, and is commonly written e^+ or β^+. When a positron and an electron come into contact, they annihilate one another, and their mass-energy is transformed into a pair of 0.511 MeV photons.

Gamma ray emission

Like the electron cloud of an atom, a nucleus can exist in a number of quantized energy states. The lowest of these is called the *ground state,* and the ones lying above it are *excited* states. And like an excited atomic electron cloud, an excited nucleus can often get rid of excess energy directly and easily by emitting a high-energy photon, a **gamma ray**, γ.

Alpha or beta emission brings about a change in the numbers of protons and neutrons present, hence a new overall charge in the resulting daughter nucleus. The new nucleus that an alpha or beta decay leaves behind, moreover, is almost always in an energetically excited state. This daughter nucleus can usually drop immediately into a state of lower energy, however, through the emission of a gamma ray photon (Figure 13–3d). Indeed, alpha and beta events are usually followed almost instantaneously (typically in less than a millionth of a second) by the emission of a gamma ray. That is, unlike alpha or beta events, a gamma emission does not just occur out of the blue; it follows some other nuclear transformation, rather, that happens to leave the resulting nucleus in an excited state.

A gamma ray photon differs from an x-ray photon only in that it originates from a nuclear transition, rather than from an atomic orbital electron transition (producing a characteristic x-ray) or a bremsstrahlung collision. Gamma rays from radionuclides generally tend to have more energy than diagnostic x-ray photons, but they are actually much less energetic than some of the x-ray photons produced by radiotherapy linear accelerators. In any case, it is where they come from, not their energy, that distinguishes gamma rays from x-rays. Once away from their respective sources, x-ray and gamma ray photons of the same energy are exactly the same stuff, and completely indistinguishable.

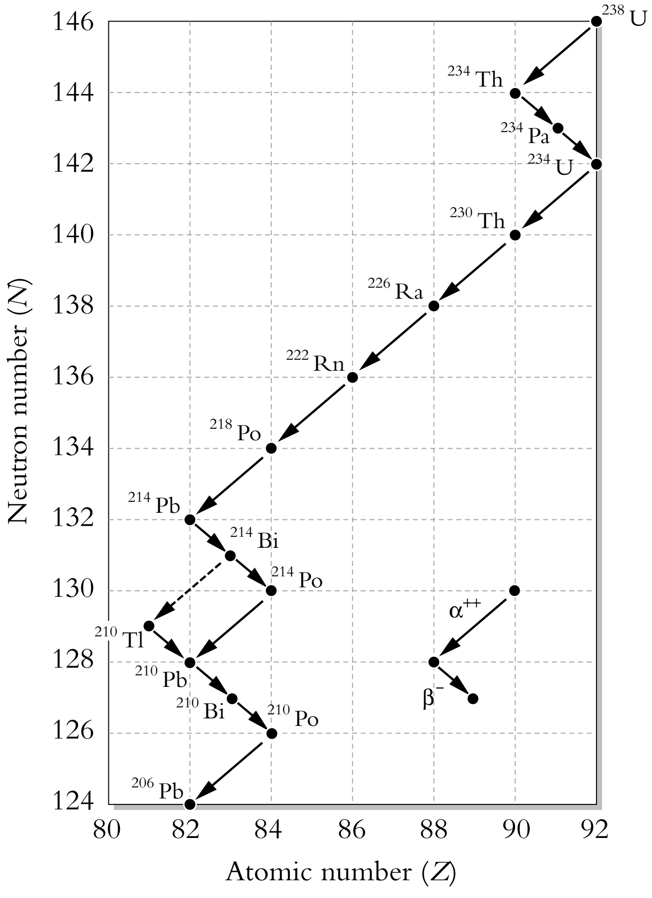

Figure 13–4. Decay chain. One particular radioactive series begins with the naturally occurring, long-lived (6.5×10^9 year half-life) radionuclide uranium-238, and ends up at the stable isotope lead-206. In the first step, uranium-238 emits an alpha particle; the daughter thorium-234 has four fewer nucleons. With the second step, thorium-234 emits a beta particle to become protactinium-234; the atomic number increases by one, but the total number of nucleons does not change. There are two other such major, naturally occurring series, beginning with uranium-235 (half-life of 1.0×10^9 years) and with thorium-232 (2×10^{10} years), respectively, and a fourth chain that is man-made.

Decay chains

Depending on its own nuclear makeup, a newly minted daughter nucleus may, even after emission of a gamma ray, itself be radioactive. If it is, *its* daughter may be, too. Indeed, there are several naturally occurring radioisotopes (in particular, uranium-238, thorium-232, and uranium-235) that initiate long chains of sequential decays—as many as a dozen or so generations of radioactive progeny—before coming to rest with a stable final member (Figure 13–4).

The nuclear transformations sketched above are discussed in more detail in the appendix to chapter 41.

4. The Activity of a Sample of Radioactive Material Is the Rate at which Nuclear Transformations Are Occurring in It over Time

Since the atoms in any radioactive sample are undergoing nuclear transformations over time, the number of those that have not yet done so, of those remaining still intact, must be declining. A special terminology has evolved for keeping count of them.

Amounts of most substances are measured in units of weight or volume, but a radioactive material is quantified in terms of activity. The **activity** of a sample of radioactive material at time t, commonly represented as $A(t)$, is defined as the number of decay events occurring in it per unit time. If you put the sample into an ideal radiation detector, then $A(t)$ is the number of counts that would register per second.

The SI unit of activity is the **becquerel** (**Bq**), in which one nuclear transformation occurs per second:

$$1\ \mathrm{Bq} = 1\ \mathrm{s}^{-1}\ . \tag{13.1a}$$

More familiar in the United States is the curie (Ci), where 1 Ci of radioactive material refers to 3.7×10^{10} nuclear transformations per second, so that

$$1\ \mathrm{Ci} = 3.7 \times 10^{10}\ \mathrm{Bq}\,. \tag{13.1b}$$

This rather curious number stems from the original definition of 1 Ci of activity as the emission rate from one gram of pure radium (Figure 13–5). It may be convenient to remember that 1 mCi is exactly 37 megabecquerels (MBq):

$$1\ \mathrm{mCi} = 37\ \mathrm{MBq}$$

and (13.1c)

$$1\ \mathrm{MBq} = 1/37\ \mathrm{mCi}\,,$$

where $1\ \mathrm{MBq} = 10^6\ \mathrm{Bq}$. In nuclear medicine imaging, with some important exceptions, a few millicuries of radiopharmaceutical are administered to the patient, something like 100 MBq.

The true activity of a sample is not necessarily the same as the count rate obtained with a detector. If every nuclear decay resulted in the emission of exactly one ionizing particle, and if the detector were capable of sensing and registering each of them, then the number of counts per second would be the sample's activity. But some nuclear emissions are absorbed by the sample material itself, or followed by delayed gamma rays or characteristic x-rays. Also, the detector itself is not 100% efficient. Detector readings must be adjusted accordingly.

EXERCISE 13–1.

An imaging study makes use of 100 MBq of technetium-99m. What is that in curies?

EXERCISE 13–2.

A renogram (kidney uptake and clearance of fluid) study requires the use of 50 to 300 microcurie (μCi) of iodine-131 (depending on the age and medical status of the patient) attached to a suitable agent such as orthoiodohippurate. What is the activity range in SI units?

In view of the variety of nuclear decay mechanisms possible, it may be surprising that the activity of a pure sample of any radionuclide decreases in exactly the same manner: Whether it be an alpha, beta, positron, or gamma emitter, it decays *exponentially* with time.

5. Exponential Decay

The activity of a radionuclide sample at any time depends on two, and only, two things: what radionuclide is present, and how much there was of it originally.

Suppose $n(t)$ represents the number of nuclei in a pure radioactive sample at time t. The function $n(t)$ is exponential in shape, and we shall demonstrate this making use of the notion of half-life. The **half-life, $t_{½}$**, of a radionuclide is *unique*, applicable only to that specific nuclide. It is the time required for the number of remaining radioactive nuclei in a sample, hence its activity, to fall to half its original amount,

$$n(t_{½})/n(0) = ½ \,,$$

and

$$A(t_{½})/A(0) = ½ \,. \qquad (13.2a)$$

After one half-life, only half the original nuclei in a sample are still intact—the other half will have experienced alpha, beta, or gamma transitions. After two, three, four, or N half-lives, the fraction nuclei of the remaining will have fallen by a factor of ¼, ⅛, 1⁄16, and

$$A(N \times t_{½})/A(0) = (½)^N = 2^{-N} \,. \qquad (13.2b)$$

The half-life of technetium-99m, the workhorse of any nuclear medicine department, is 6 hours. If a patient receives a 4-mCi injection of Tc-99m at 6 a.m., then 2 mCi will remain in the body at noon, 1 mCi at 6 p.m., 0.5 mCi at midnight, and so on, as long as little is lost in urine, feces, vomit, perspiration, or by other means.

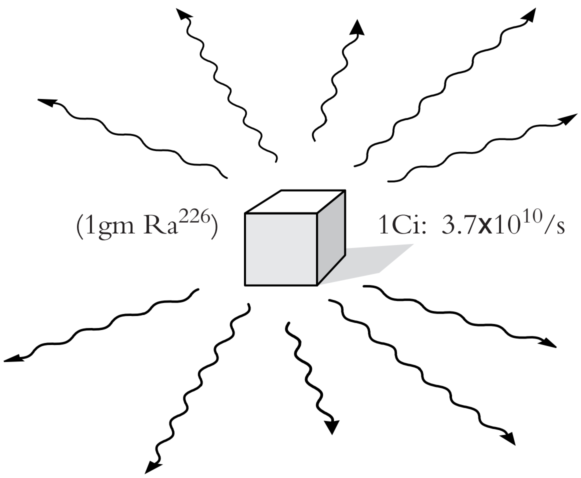

Figure 13–5. The term "activity" refers to an important characteristic of any sample of radioactive material—the rate at which nuclear transformations are occurring within it. The activity of a sample depends on the particular radionuclide in it, and also on its size: The more radioactive nuclei in the sample, the greater the activity. For historical reasons, the standard unit of activity, the curie (Ci), was defined as that of a gram of natural radium, or 3.7×10^{10} events per second. The SI unit is the becquerel (Bq), which is 1 disintegration per second.

EXERCISE 13–3.

One millicurie of technetium-99m is injected into a patient Monday at noon. What is the residual activity within the body at 12:01 a.m. Thursday?

EXERCISE 13–4.

The half-life of fluorine-18 is 110 minutes. Today's only PET patient will be scanned 5½ hours after delivery of the radionuclide to the clinic. How much more of it must be shipped than will actually be administered?

EXERCISE 13–5.

How much of a radioactive sample is left after 10 half-lives?

Suppose the half-life of some radionuclide is $t_{½}$, and you need to know the fraction of it that remains after time t. The number of half-lives is just $N = t/t_{½}$, so from Equation (13.2b), the activity and the number of nuclei present will decrease as

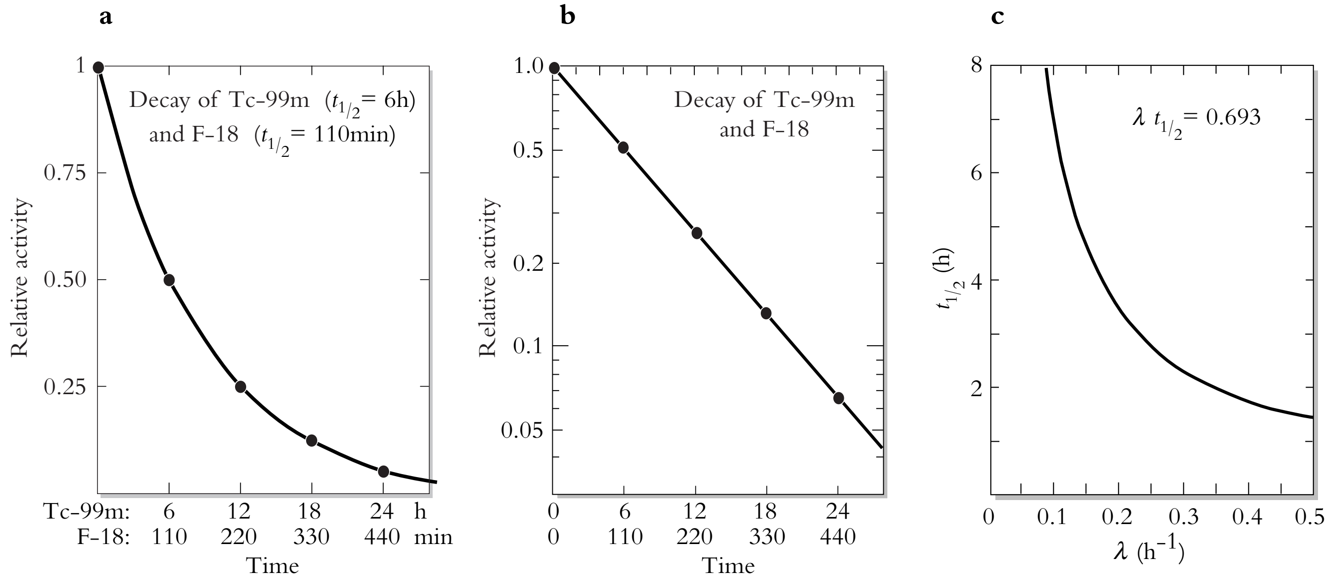

Figure 13–6. Exponential decay. **(a)** Both the activity and the number of nuclei of a radioisotope in a sample will decline exponentially with time at a rate characteristic of the isotope, λ, called the transformation, or decay, constant: $n(t)/n(0) = e^{-\lambda t}$. The transformation coefficients for technetium-99m and fluorine-18 are 0.115 hours^{-1} and 0.0063 min^{-1}, respectively. The half-life for Tc-99m is 6 hours, and that for F-18 is 110 minutes. **(b)** The same information, graphed on semi-logarithmic paper, upon which an exponential function plots out as a straight line. **(c)** The half-life, $t_{1/2}$, carries essentially the same information as the decay constant, and is related to it through $t_{1/2}\,\lambda = 0.693$.

$$A(t)/A(0) = 2^{-t/t_{1/2}},$$

and (13.2c)

$$n(t)/n(0) = 2^{-t/t_{1/2}}.$$

A function of this form is an exponential, and the material is said to undergo **exponential decay**. A sample of technetium-99m, for example, decays exponentially with a half-life of 6 hours (Figure 13–6a).

Exactly the same functional (exponential) form can be expressed with the special number e = 2.71828183. . . . as the base, rather than 2; indeed, exponential processes are almost always described with the base **e** (e plays a special role in calculus, just as π does in trigonometry). Radioactive decay, for example, is usually formulated as

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

and (13.3)

$$n(t) = n(0)\, e^{-\lambda t}.$$

The half-life has been replaced here with the radionuclide-specific **decay constant** or **transformation coefficient**, represented by the Greek letter *lambda*, λ. It conveys the same kind of information as does the nuclide's half-life, just as Equations (13.2c) and (13.3) are equivalent.

The decays of technetium-99m (λ = 0.115 hour^{-1} and $t_{1/2}$ = 6 h) and of fluorine-18 (λ = 0.0063 min^{-1} and $t_{1/2}$ = 110 minutes) are plotted out in Figure 13–6a on regular, linear graph paper. The diagram makes it clear that the larger the value of the transformation parameter, the more rapidly the sample will decay away.

The same two curves are displayed on **semi-logarithmic graph paper** in Figure 13–6b. Semi-log paper is designed so that any purely exponential function, of the form of Equations (13.2c) or (13.3), will plot out as a straight line, with slope λ. Before there were computers, its use greatly facilitated the precise determination of the value of the parameter in the exponent. It is easy to see whether a line is truly straight or not and, if it is, to find its slope.

EXERCISE 13–6.

Show that the transformation constant of technetium-99m is 0.115 hr^{-1} two different ways: from Figures 13–6, and from knowledge of the 6-hour half-life.

All this depends on the existence of a well-defined half-life for a radioisotope, the length of which *does not change over time*. Equivalently, the transformation coefficient, λ, must be a *constant*, the same tomorrow as it was yesterday. Otherwise, the decay of radionuclides would not be described by Equations (13.2). But it is not obvious that things will, or even should, have fixed half-lives. Imagine, for example, a bunch of identical batteries in identical clocks; for a long while they work fine, and then they all fail more or less at the same time—quite unlike items with a constant half-life. Likewise, patterns of mortality in groups of people do not display half-lives. So why do radionuclei? We'll return to this interesting question in chapter 17.

Relationship between the decay constant, λ, and the half-life, $t_{1/2}$

Equations (13.2c) and (13.3) are essentially equivalent and, not surprisingly, there is a simple relationship between the decay constant and the half-life. This pops out in comparing the two equations:

$$A(t)/A(0) = e^{-\lambda t} = 2^{-t/t_{1/2}}.$$

Taking the base-e logarithm all the way through leads to

$$\ln e^{-\lambda t} = -\lambda t = \ln 2^{-t/t_{1/2}} = -(t/t_{1/2})(\ln 2).$$

The second and fourth terms in this yield

$$\lambda = 0.693/t_{1/2},$$

or (13.4)

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

(Figure 13–6c). So λ is just the inverse of the half-life, apart from a factor of about ⅔. And that's a perfectly fine way to think of it. A large λ, indicating rapid decay, simply means a short $t_{1/2}$, and vice versa. Since the half-lives of the various radionuclides range from a small fraction of a microsecond up to billions of years (the primordial ones, like uranium-238, still exist in nature precisely because they decay so slowly), values of λ have a correspondingly broad spread.

This is reminiscent of the MRI situation discussed in the final section of the previous chapter. There, it was argued that T1 (corresponding to half-life) is inversely proportional to the rate (transformation coefficient) at which spin relaxation occurs.

The activity is proportional to the number of radionuclei present

The activity of a sample depends not only on the what radionuclide is present (hence its half-life or decay constant), but also on how much of it is there. Double the amount of material, hence the number of radionuclei, and you double the activity. It is easy to put this proportionality on more solid ground, and find a useful relationship between the activity at any time, $A(t)$, and the number of remaining, undecayed nuclei, $n(t)$, but we have to be careful with definitions.

Activity refers to the number of decays that occur per unit time. You might suppose that it is none other than the time derivative of the number of radionuclei left, dn/dt, and you would be almost right. There is, however, a slight but important twist: Although the number of nuclei in the sample, n, is a positive number, it is decreasing because of decay, so that the very small change, dn, in the value of n that occurs over a very short period, dt, must be a negative number. So, then, must dn/dt, as well. The activity, A, is inherently positive, so everything works out nicely if, and only if, we (perhaps somewhat counterintuitively) set

$$A = -\,dn/dt\,. \tag{13.5a}$$

Making $A = +dn/dt$, instead, would suggest that $A(t)$ and dn/dt are both getting larger over time, which is not the case.

Let us explicitly take the derivative of the function $n(t)/n(t)$ of Equation (13.3). Equation (A13.6b) in the appendix shows how to do this, and the result is

$$dn/dt = n(0)\, d[e^{-\lambda t}]/dt = (-\lambda)\, n(0)\, e^{-\lambda t} = -\lambda n(t)\,. \tag{13.5b}$$

When combined with the definition of activity in Equation (13.5a), this becomes

$$A(t) = \lambda n(t)\,. \tag{13.5c}$$

EXERCISE 13–7.

In a certain nuclear medicine study, 0.4-MBq of iodine-125, with a half-life of 60 days, is injected into a patient. Show that the mass of the iodine is a factor of 10^{-13} less than that of the 3000-gram blood pool in which it dilutes. Compare this with the amount of (nonradioactive) iodine contrast agent used in a typical CT study.

EXERCISE 13–8.

Why are $n(t)$ and $A(t)$ smoothly and continuously decreasing functions of t?

6. Organ Specificity of a Radiopharmaceutical

Now that you have reviewed some of what you knew about radioactive materials and how they behave, we can begin to discuss their application in diagnostic medicine.

Nuclear medicine makes use of **radiopharmaceuticals**, special radioactive materials that display two key features: An injected or inhaled sample of such a material tends to be taken up preferentially by, and concentrates in, a biologic compartment, such as a specific organ or tissue. From there, it emits gamma rays that can escape the body and be detected from outside it, thereby contributing to the creation of an image. Irregularities in the spatial uptake or eventual deposition of the radiopharmaceutical within the compartment, as revealed by a gamma camera, may thus provide information on patient physiology and pathology.

A typical radiopharmaceutical consists of molecules or microscopic particles each of which is made up of two components, an *agent* and a *gamma-emitting radionuclide* atom.

The essential characteristic of a good **agent** is that it be organ- or compartment-specific, preferably with a differential uptake between normal and pathologic tissues. There are a number of processes by which agents distinguish among and concentrate in organs.

Reticuloendothelial cells recognize minute (0.1 μm), radiolabeled sulfur colloid particles as being foreign objects, and remove them from the blood stream through *phagocytosis.* This allows imaging of the liver, spleen, and bone marrow.

Examination of the blood vessels of the lungs is made possible through a temporary *capillary blockade* of a small fraction (about 0.1%) of the fine pulmonary vessels by radioactively tagged macroaggregated albumin (MAA). These microscopic lumps of protein, slightly larger than erythrocytes, break down soon thereafter, and are flushed out of the lung.

Pulmonary ventilation can be examined through *compartment filling* of the lungs with, say, xenon-133 gas, or an aqueous mist of pertechnetate.

In studies of the thyroid, radioactive iodine is brought into cells of the gland through *active transport* by biochemical pumps in the cell walls.

And so on. Lately there has been much interest in certain *monoclonal antibodies*, mass-produced proteins designed to bind to specific antigens of certain normal or diseased cells. For some agents of nuclear medicine, concentration in a tissue is determined by the tissue's overall physiologic status, by the general level of functioning of its parenchymal cells. Monoclonal antibodies, by contrast, can be disease-specific, and can provide more precise information on the nature of a disorder, as well as on its location.

While a half dozen **gamma-emitting radionuclides** find routine use in a nuclear medicine department, the most common one, by far, is technetium-99m. Tc-99m has physical characteristics that make it nearly ideal for imaging (Table 13–2). It produces only gamma rays, no useless (but nonetheless dose-imparting) alphas or betas. (The "m" in Tc-99m stands for **metastable** which, for our purposes, means that it emits only gamma rays when in the patient.) Its complete decay scheme is complex, but only the 140-keV gamma ray is of significance, and one may think of the entire process that occurs within the patient as

$$\text{Tc-99m} \rightarrow \text{Tc-99} + \gamma \quad (140\ \text{keV})\,. \tag{13.6}$$

The energy of its gamma ray photons is such that they will likely escape the body, but then be detected by the dense and thick sodium iodide scintillation crystal of the gamma camera. Tc-99m can be delivered every day to the clinic by a commercial vendor, or it can be obtained by flushing sterile salt water through a technetium generator supplied weekly. Its 6-hour half-life provides sufficient time for preparation of radiopharmaceuticals in the clinic, and it can easily and rapidly be attached to a variety of agents that come in *kits*. But the half life is short enough to avoid long-term irradiation of the patient or others.

Technetium, incidentally, with atomic number 43, is one of the three elements lighter than uranium that do not occur naturally in significant amounts on Earth (the others are promethium and astatine), and the first to have been created artificially, in 1937.

Table 13–2. Technetium-99m as the nearly ideal radiopharmaceutical.

Radionuclide properties	
Gamma ray emission	140 keV
Particulates (beta, alpha)	None
Half-life	6 hours
Toxicity	Nontoxic
Radionuclide production	
Onsite source	Mo-99 generator
Source replacement	Weekly
Cost	Low
Preparation	Elution, in minutes
Purity	<0.1% Mo, etc.
Agents	
Availability	In kits
Specificity	Organ-specific
Preparation	In minutes
Binding to technetium	Stable
Quality assurance	ITLC, etc.

7. The Rectilinear Scanner

Rectilinear scanners are no longer around, but it can be instructive to spend a little time with them. They are conceptually simpler in operation than gamma cameras, and they allow us to explore more easily one of the basic trade-offs of nuclear medicine instrumentation.

Nuclear medicine involves the sensing of trace amounts of radioactive material that tend to accumulate in specific organs or biological compartments. A simple device that can accomplish this task is the **scintillation detector**, a crystal of fluorescent material (such as sodium iodide, NaI) optically coupled to a **photomultiplier tube** (**PMT**). When excited by a gamma ray photon, the crystal produces a burst of light. The photomultiplier generates a jolt of electricity whenever it registers

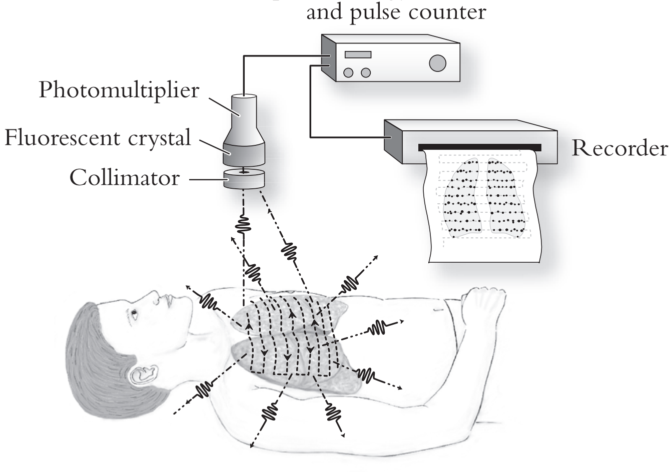

Figure 13–7. Mapping the spatial distribution within the body of a gamma-emitting radionuclide with a rectilinear scanner. The two-dimensional scanning motions of the scintillation detector are mimicked by those of the recorder pen, and the density of points laid down is proportional to the count rate sensed by the detector.

such a scintillation—and the brighter the flash, the greater the voltage of the pulse.

Before the advent of the gamma camera, spatial maps of differential radioisotope uptake were produced with the *rectilinear scanner* (Figure 13–7). A scanner consists of a scintillation detector with a **collimator** (a thick block of lead, through which one or several narrow, straight channels are drilled) on its front end. Only those few gamma rays that happened to be heading exactly along a channel of the collimator can reach an otherwise shielded sodium iodide crystal and PMT. The collimator/detector assembly is swept in a raster pattern, back and forth across while slowly down, the patient. A pen held over a sheet of paper is linked mechanically or electrically to the collimator/detector, and mimics its path—and every time a gamma ray registers, the pen taps the paper. Thus the density of ink dots anywhere on the paper indicates the rate at which gamma rays are emerging from the corresponding part of the body, hence of the concentration of radiopharmaceutical below the surface there.

Figure 13–8 suggests a fundamental and important image quality trade-off found with the rectilinear scanner, and with gamma cameras as well. A larger-diameter collimator channel will allow more gamma rays through, but will provide less information about the precise location of their source. Thus an improvement in detector sensitivity is paid for in loss of spatial resolution. There are many such trade-offs in every imaging modality, and an important job of equipment developers, and of medical staffs, is to strike the best possible balances among them.

The gamma rays detected by the scanner in Figure 13–7 could originate from radionuclei at any depth in the patient's body. But the image manifests a quasi depth-dependence: The shallower the point of origin of the gamma ray within the patient, the lower the probability that it will be absorbed or scattered by overlying tissue, and the more likely it is to reach the detector. A *focusing* multi-hole collimator (Figure 13–9), on the other hand, allows a scanner to focus attention separately on tissues lying at a particular depth beneath the surface. The collimator channels all converge to a focal point, and gamma rays coming from the vicinity of the focal point can reach the detector through all the channels; fewer avenues are available to those emitted above or below it. Thus, somewhat like an optical lens system, scanning with a focusing collimator selects a single plane of tissue, several centimeters thick, for special consideration. The relative response of the system as a function of the distance of radionuclide above or below the focal plane may be seen from a set of iso-response curves.

There are problems with the rectilinear scanner. Its head must move slowly enough for a statistically adequate reading of activity to be made at each position. But although increasing the amount of radionuclide (hence radiation dose) given to the patient can offset the problem of slow data acquisition, there is no way the system can be used to simultaneously follow rapid changes in different parts of an image over time. Both efficient data acquisition and the performance of dynamic studies call for the services of a gamma, or Anger, camera, as will be discussed in chapter 42.

Appendix: Derivatives of Functions

For those who have been thinking about other things since throwing out their introductory calculus books, here is a brief review of some simple, but nonetheless useful, ideas about derivatives.

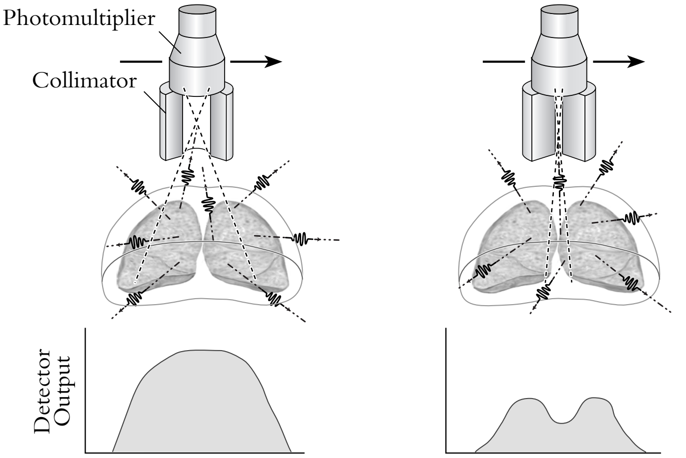

Figure 13–8. A basic trade-off in radionuclide imaging: The wider the collimator channel(s), the greater the sensitivity of the instrument, but the lower its resolving capability.

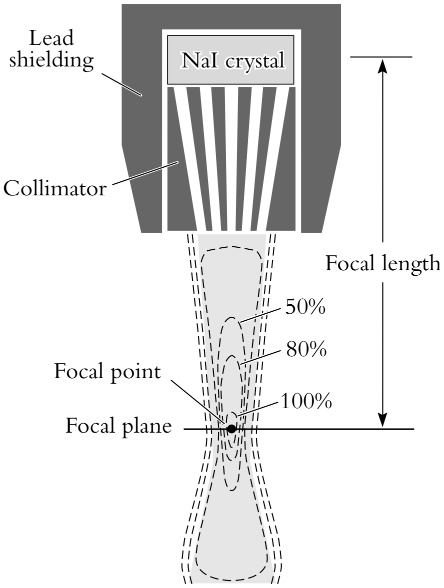

Figure 13–9. With a focusing collimator, the detector is most sensitive to radionuclide concentrated near the focal plane, in this case several centimeters beneath the skin surface. Percentages refer to detector sensitivity within the body relative to that at the focal point.

It is often important to know not only how things are, but also how and how rapidly they are changing. Calculus is an extension of algebra that allows us to ask questions such as "If you pour water at a constant rate into a bucket with a hole in it, how fast will the level rise?" (Can you think of any medical analogies?) Or "If x-ray photons are absorbed and scattered in a medium at a certain spatial rate, how much of a beam will make it through x centimeters of it?" Or "What fraction of a population of cells in a petri dish will survive after a D-gray irradiation with protons?" All these processes involve *changes*, and calculus is the appropriate language for exploring situations where change occurs. This appendix will provide a very elementary reminder of what you learned in high school about that language.

The central concept of calculus is that of the *derivative*, or *rate of change*, of a function, and its graphical equivalent, the *slope* of the corresponding curve.

Figure A13–1 reveals the number, $n(t)$, of radioactive technetium–99m atoms remaining at time t in a vial, after $n(0)$ were placed there at $t = 0$. The graph itself shows the numbers, $n(t_1)$ and $n(t_2)$ still there t_1 and t_2 hours later, respectively, relative to $n(0)$.

That's fine, but what you're really interested in, and can measure, is the activity $A(t)$ (the number of disintegrations per second), which also happens to be the rate at which $n(t)$ is changing over time. The simplest and most obvious way of thinking about this happens to be the correct one: If $n(t)$ changes by the amount $[n(t_2) - n(t_1)]$ over the time interval $[t_2 - t_1]$, then the average rate of change of $n(t)$ over this time, the average activity, is simply

$$[n(t_2) - n(t_1)]/[t_2 - t_1]\,, \qquad \text{(A13.1a)}$$

represented by the heavy dashed straight line.

But $[t_2 - t_1]$ is a broad enough span that $A(t)$ itself changes somewhat during it, so we choose to improve the precision by narrowing down its width. We move t_1 and t_2 closer and closer together until their separation is just Δt, where the symbol "Δ" can be translated into English as "a small increment in. . . ," or "a small change in. . . ." Thus, Δt is taken to mean "a small interval of time," running from t_1 to $t_1 + \Delta t$, say. Then $[t_2 - t_1]$ can be expressed as $[(t_1 + \Delta t) - t_1]$, which reduces simply to Δt. Likewise, Δn refers to the small change in the number of radionuclei that occurred over Δt, and we can rewrite Equation (A13.1a) as

$$\Delta n/\Delta t = [n(t + \Delta t) - n(t)]/\Delta t\,. \qquad \text{(A13.1b)}$$

Now imagine that Δt becomes not only small, but actually infinitesimally tiny, and Δn therefore does so, as well. It helps to distinguish this limiting case, in which Δt and Δn each separately approaches 0, by renaming them dt and dn. The critical point is this: Even though dt and dn are becoming infinitesimally small, their *ratio* remains finite and meaningful. The ratio dn/dt at some time t is known as the *derivative* of $n(t)$ at that time. Since dn/dt is most likely not a constant, but rather is itself a function of the independent variable, we can write it more generally as $dn/dt(t)$:

$$dn/dt(t) = [n(t + dt) - n(\mathrm{t})]/dt\,. \qquad \text{(A13.1c)}$$

As dn, and simultaneously dt, shrink to the infinitesimally small, this becomes this definition of the **derivative** of the function $n(t)$, the central expression of differential calculus.

The function $dn/dt(t)$ is valid and significant for any t; to indicate its value for the *particular* time $t = t'$, it is written $dn/dt(t')$. Equation (A13.1c) becomes

$$dn/dt(t') = [n(t' + dt) - n(t')]/dt\,. \qquad \text{(A13.1d)}$$

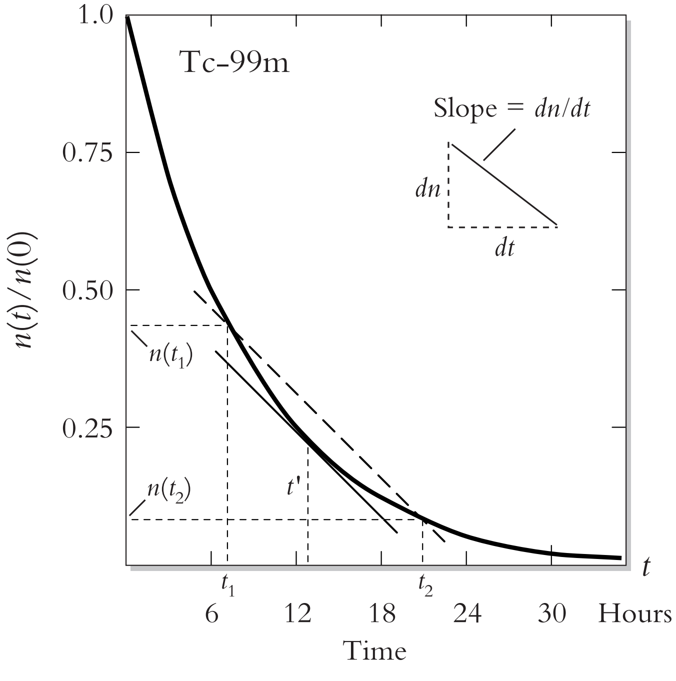

Figure A13–1. Equations (A13.1) and the decay of Tc-99m illustrate the basic idea of differential calculus.

On a graph, $dn/dt(t')$ refers to the slope of $n(t)$ at the specific time t'. This is seen in Figure A13–1, for example, as the solid tangent line.

If the function of interest is some $y(x)$, rather than $n(t)$, then the derivative is of exactly the same form:

$$dy/dx = dy/dx(x) = [y(x + dx) - y(x)]/dx \,. \qquad \text{(A13.2)}$$

Linear function: $y(x) = m\,x + b$

If $y(x)$ happens to be simply *proportional* to x, and plotting it on regular graph paper yields a straight line, then $y(x)$ is said to be a **linear** function of x. Linear functions are seen everywhere in descriptions of physical reality, and they can be expressed in the familiar form

$$y(x) = m\,x + b \,. \qquad \text{(A13.3a)}$$

The independent variable, x, is raised to the first power, but the superscript "1" is almost never shown explicitly. Equation (A13.3a) plots out as a straight line with slope m, and it intersects the y-axis at $y = b$.

Suppose that some physically meaningful process can be captured by the linear equation

$$y(x) = 3x + 5 \,. \qquad \text{(A13.3b)}$$

The slope is constant, and has a numerical value of 3. But let's arrive at this trivial result by way of Equation (A13.2), as a practice run. Replacing the $y(x)$ of Equation (A13.2) with that of Equation (A13.3b) gives

$$\begin{aligned} dy/dx &= [y(x + dx) - y(x)]/dx \\ &= [\{3(x + dx) + 5\} - \{3x + 5\}]/dx = 3\,dx/dx = 3. \end{aligned} \qquad \text{(A13.3c)}$$

Voila! We actually *calculated* the slope this time around, using the central expression of differential calculus, and it turned out to be exactly what we had anticipated.

Quadratic function: $y(x) = ax^2 + bx + c$

The appendix to chapter 2 examined an expression that described the vertical position, $y(t)$, of a physics book in free fall over time, t, as

$$y(t) = -\tfrac{1}{2}\,gt^2 \,, \qquad \text{(A13.4a)}$$

apart from a constant, $y(0)$, that we can ignore here. Because the independent variable is raised to the second power, this is called a *quadratic* or second-order function.

We want to know how fast the book is falling at any time—and the instantaneous speed is given simply by the slope, dy/dt, of $y(t)$ at that instant. Again, Equation (A13.2) does it all. When $y(t)$ from Equation (A13.4a) is inserted into it, Equation (A13.2) becomes

$$\begin{aligned} dy/dt &= [(-\tfrac{1}{2}\,g)(t + dt)^2 - (-\tfrac{1}{2}\,g)\,t^2\,]/dt \\ &= -\tfrac{1}{2}\,g\,[2t\,dt + dt^2]/dt = -\tfrac{1}{2}\,g\,(t + dt) \,. \end{aligned} \qquad \text{(A13.4b)}$$

The dt in Equation (A13.2) grows vanishingly small, by our own design, but the gt does not, so we are left with

$$dy/dt = -\,gt. \qquad \text{(A13.4c)}$$

Equation (A13.4c) says that the book is moving downward, and picking up speed linearly with time. The distance above ground is a quadratic function of time, Equation (A13.4a).

In general, the derivative of the power function $y(x) = c\,x^p$, where c and p are constants, is given by

$$d\,[c\,x^p]/dx = p\,c\,x^{p-1} = p\,y(x)/x \,. \qquad \text{(A13.5)}$$

EXERCISE A13–1.

Plot out Equation (A13.4a). Use Equation (A13.2) to obtain the slope at $x = 3$. Compare with the results of Equation (A13.5).

EXERCISE A13–2.

Find the first derivative of $y(x) = x^3$ two ways: with Equation (A13.2), and with Equation (A13.5).

Exponential function: $y(x) = ae^{bx}$

The exponential function plays many roles in radiology, and it will be helpful to find its derivative. We'll sketch the simplest scenario here, and leave the more general case for you to play with.

The derivative of $y(x) = e^x$ is given by

$$d[e^x]\,/dx = e^x \,. \qquad \text{(A13.6a)}$$

That is, the derivative of e^x is just e^x itself! This follows from Equation (A13.2):

$$\begin{aligned} dy/dx &= d\,[e^x]/dx = [e^{\,x+dx} - e^{\,x}]/dx \\ &= e^x\,[e^{\,dx} - 1] = e^x\,[1 + dx + \tfrac{1}{2}\,dx^2 + \ldots - 1]/dx \\ &= e^x\,[1 + \tfrac{1}{2}\,dx + \ldots\,] = e^x \quad , \end{aligned}$$

where, again, the dx becomes vanishingly small. The second line of this makes use of the Taylor series expansion.

$$e^z = 1 + z + \tfrac{1}{2}\,z^2 + \ldots \,,$$

which is valid if, but only if, z is small.

More generally, and perhaps more familiarly: if $y(x) = c\,e^{-\mu x}$, with constant c, then the derivative is

$$d\,[c\,e^{-\mu x}]/dx = -\,\mu\,c\,e^{-\mu x}. \qquad \text{(A13.6b)}$$

Differential equation: $dy/dx = -\,\mu\,y(x)$

Equation (A13.6b) becomes much more interesting if we replace the $c\,e^{-\mu x}$, both on the left and on the right-hand sides, with its generic name, $y(x)$. This gives the very simple **differential equation**

$$dy/dx = -\mu\, y(x). \tag{A13.6c}$$

A differential equation is one in which the rate of change of $y(x)$, namely dy/dx, is related to the value of $y(x)$ itself—regardless of whatever y and x happen to represent. Much of physics involves the study of how things change, and it would probably not be too much of an overstatement to say that the discipline is largely one of crafting the differential equations that describe the behavior of natural systems, and then finding their solutions.

The *solution* to a differential equation is a function that, when plugged into it, "satisfies" it, which is to say, leads to an identity. A solution to Equation (A13.6c), in particular, is of the form

$$y(x) = y(0)\, e^{-\mu x}\,. \tag{A13.6d}$$

The parameter μ is not only mathematically important, of course, but also physically meaningful. That, in fact, is where all the physics resides, as we shall see.

The above simple differential equation happens to pop up in a number of areas of radiology, in slightly different guises, and our being able to find its solution will prove to be most useful.

EXERCISE A13–3.

Prove Equation (A13.6b).

EXERCISE A13–4.

Equation (A13.4c) is a differential equation. Demonstrate that Equation (A13.4a) is a solution to it.