chapter 5

Radionuclide and Radiopharmaceutical Production

Most of the naturally occurring radionuclides are very long-lived (e.g., ^{40}K, $T_{1/2} \sim 10^9$ years), represent very heavy elements (e.g., uranium and radium) that are unimportant in metabolic or physiologic processes, or both. Some of the first applications of radioactivity for medical tracer studies in the 1920s and 1930s made use of natural radionuclides; however, because of their generally unfavorable characteristics indicated here, they have found virtually no use in medical diagnosis since that time. The radionuclides used in modern nuclear medicine all are of the manufactured or "artificial" variety. They are made by bombarding nuclei of stable atoms with subnuclear particles (such as neutrons and protons) so as to cause nuclear reactions that convert a stable nucleus into an unstable (radioactive) one. This chapter describes the methods used to produce radionuclides for nuclear medicine as well as some considerations in the labeling of biologically relevant compounds to form radiopharmaceuticals.

A. REACTOR-PRODUCED RADIONUCLIDES

1. Reactor Principles

Nuclear reactors have for many years provided large quantities of radionuclides for nuclear medicine. Because of their long and continuing importance for this application, a brief description of their basic principles is presented.

The "core" of a nuclear reactor contains a quantity of fissionable material, typically natural uranium (^{235}U and ^{238}U) enriched in ^{235}U content. Uranium-235 undergoes spontaneous nuclear fission ($T_{1/2} \sim 7 \times 10^8$ years), splitting into two lighter *nuclear fragments* and emitting two or three *fission neutrons* in the process (see Chapter 3, Section I). Spontaneous fission of ^{235}U is not a significant source of neutrons or energy in of itself; however, the fission neutrons emitted stimulate additional fission events when they bombard ^{235}U and ^{238}U nuclei. The most important reaction is

$$^{235}U + n \rightarrow {}^{236}U^* \qquad (5\text{-}1)$$

The $^{236}U^*$ nucleus is highly unstable and promptly undergoes nuclear fission, releasing additional fission neutrons. In the nuclear reactor, the objective is to have the fission neutrons emitted in each spontaneous or stimulated fission event stimulate, on the average, one additional fission event. This establishes a controlled, self-sustaining *nuclear chain reaction.*

Figure 5-1 is a schematic representation of a nuclear reactor core. "Fuel cells" containing fissionable material (e.g., uranium) are surrounded by a *moderator* material. The purpose of the moderator is to slow down the rather energetic fission neutrons. Slow neutrons (also called *thermal neutrons*) are more efficient initiators of additional fission events. Commonly used moderators are "heavy water" [containing deuterium (D_2O)] and graphite. *Control rods* are positioned to either expose or shield the fuel cells from one another. The control rods contain materials that are strong neutron absorbers but that do not themselves undergo nuclear fission (e.g., cadmium or boron). The fuel cells and control rods are positioned carefully so as to establish the critical conditions for a controlled chain reaction. If the control rods were removed (or

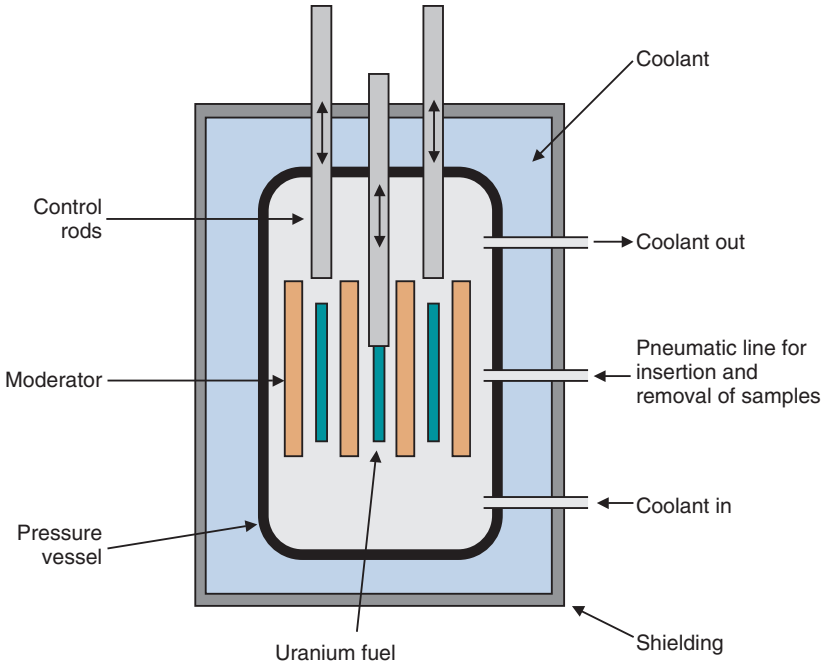

FIGURE 5-1 Schematic representation of a nuclear reactor.

incorrectly positioned), conditions would exist wherein each fission event would stimulate more than one additional nuclear fission. This could lead to a runaway reaction and to a possible "meltdown" of the reactor core. (This sequence occurs in a very rapid time scale in nuclear explosives. Fortunately, the critical conditions of a nuclear explosion cannot be achieved in a nuclear reactor.) Insertion of additional control rods results in excess absorption of neutrons and terminates the chain reaction. This procedure is used to shut down the reactor.

Each nuclear fission event results in the release of a substantial amount of energy (200-300 MeV per fission fragment), most of which is dissipated ultimately as thermal energy. This energy can be used as a thermal power source in reactors. Some radionuclides are produced directly in the fission process and can be subsequently extracted by chemical separation from the fission fragments.

A second method for producing radionuclides uses the large neutron flux in the reactor to activate samples situated around the reactor core. Pneumatic lines are used for the insertion and removal of samples. The method of choice largely depends on yield of the desired radionuclide, whether suitable sample materials are available for neutron activation, the desired specific activity, and cost considerations.

2. Fission Fragments

The fission process that takes place in a reactor can lead to useful quantities of medically important radionuclides such as ^{99}Mo, the parent material in the ^{99m}Tc generator (see Section C). As described earlier, $^{236}U^{*}$ promptly decays by splitting into two fragments. A typical fission reaction (Fig. 5-2A) is

$$^{235}_{92}\mathrm{U} + \mathrm{n} \rightarrow {}^{236}_{92}\mathrm{U}^{*} \rightarrow {}^{144}_{56}\mathrm{Ba} + {}^{89}_{36}\mathrm{Kr} + 3\mathrm{n} \qquad (5\text{-}2)$$

More than 100 nuclides representing 20 different elements are found among the fission products of $^{236}U^{*}$. The mass distribution of the fission fragments is shown in Figure 5-2B. It can be seen that fission of $^{236}U^{*}$ generally leads to one fragment with a mass number in the range of 85 to 105 and the other fragment with a mass number in the range of 130 to 150. It also is apparent that fission rarely results in fragments with nearly equal masses.

The fission products always have an excess of neutrons and hence undergo further radioactive decay by β^{-} emission, until a stable nuclide is reached. If one of the radioactive intermediates has a sufficiently long half-life, it can be extracted from the fission products and used as a medical radionuclide. For example,

$$^{99}_{39}\mathrm{Y} \xrightarrow{\beta^{-}(1.5\,\mathrm{s})} {}^{99}_{40}\mathrm{Zr} \xrightarrow{\beta^{-}(21\,\mathrm{s})} {}^{99}_{41}\mathrm{Nb} \xrightarrow{\beta^{-}(15\,\mathrm{s})} {}^{99}_{42}\mathrm{Mo} \qquad (5\text{-}3)$$

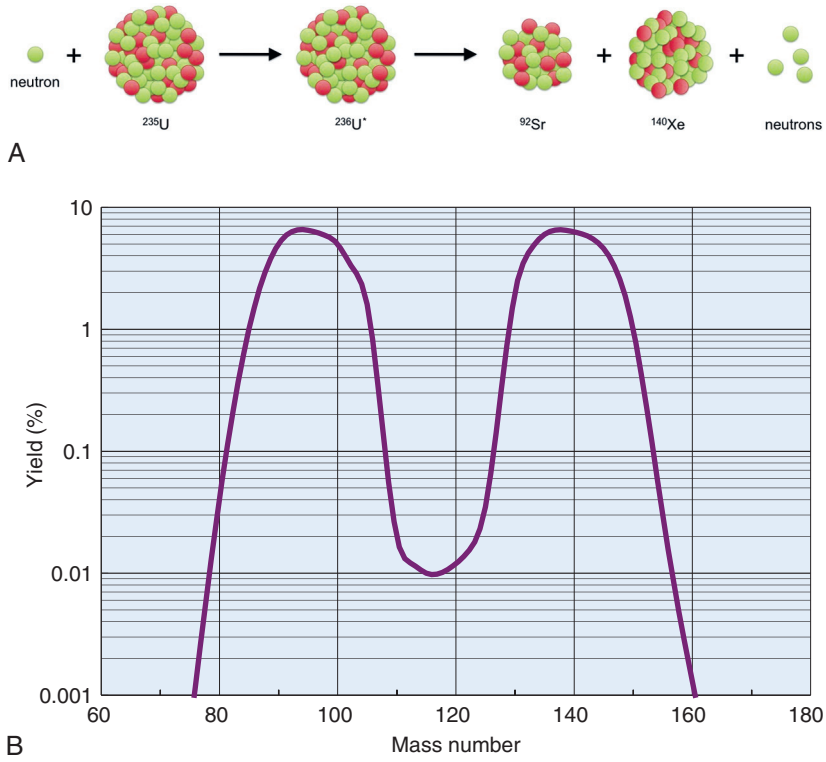

FIGURE 5-2 *A,* Example of production of fission fragments produced when neutrons interact with $^{236}U^{*}$. *B,* Mass distribution of fragments following fission of $^{236}U^{*}$.

The half-life of ^{99}Mo is 65.9 hours, which is sufficiently long to allow it to be chemically separated from other fission fragments. Molybdenum-99 plays an important role in nuclear medicine as the parent radionuclide in the ^{99}Mo-^{99m}Tc generator (see Section C). Technetium-99m is the most common radionuclide used in clinical nuclear medicine procedures today. Fission has also been used to produce ^{131}I and ^{133}Xe for nuclear medicine studies.

Radionuclides produced by the fission process have the following general characteristics:

1. Fission products always have an excess of neutrons, because N/Z is substantially higher for ^{235}U than it is for nuclei falling in the mass range of the fission fragments, even after the fission products have expelled a few neutrons (see Fig. 2-9). These radionuclides therefore tend to decay by β^- emission.
2. Fission products may be carrier free (no stable isotope of the element of interest is produced), and therefore radionuclides can be produced with high specific activity by chemical separation. (Sometimes other isotopes of the element of interest are also produced in the fission fragments. For example, high-specific-activity ^{131}I cannot be produced through fission because of significant contamination from ^{127}I and ^{129}I.)
3. The lack of specificity of the fission process is a drawback that results in a relatively low yield of the radionuclide of interest among a large amount of other radionuclides.

3. Neutron Activation

Neutrons carry no net electrical charge. Thus they are neither attracted nor repelled by atomic nuclei. When neutrons (e.g., from a nuclear reactor core) strike a target, some of the neutrons are "captured" by nuclei of the target atoms. A target nucleus may be converted into a radioactive product nucleus as a result. Such an event is called *neutron activation.* Two types of reactions commonly occur.

In an (n,γ) *reaction* a target nucleus, ${}^{A}_{Z}X$, captures a neutron and is converted into a product nucleus, ${}^{A+1}_{Z}X^{*}$, which is formed in an excited state. The product nucleus immediately undergoes de-excitation to its ground

state by emitting a *prompt* γ *ray*. The reaction is represented schematically as

$$ {}^{A}_{Z}X(n, \gamma)^{A+1}_{Z}X \qquad (5\text{-}4) $$

The target and product nuclei of this reaction represent different isotopes of the same chemical element.

A second type of reaction is the (*n,p*) *reaction*. In this case, the target nucleus captures a neutron and promptly ejects a proton. This reaction is represented as

$$ {}^{A}_{Z}X(n, p)_{Z-1}{}^{A}Y \qquad (5\text{-}5) $$

Note that the target and product nuclei for an (n,p) reaction do not represent the same chemical element.

In these examples, the products ($^{A+1}_{Z}X$ or $_{Z-1}{}^{A}Y$) usually are radioactive species. The quantity of radioactivity that is produced by neutron activation depends on a number of factors, including the intensity of the neutron flux and the neutron energies. This is discussed in detail in Section D. Production methods for biomedically important radionuclides produced by neutron activation are summarized in Table 5-1.

Radionuclides produced by neutron activation have the following general characteristics:

1. Because neutrons are added to the nucleus, the products of neutron activation generally lie above the line of stability (see Fig. 2-9). Therefore they tend to decay by β^- emission.
2. The most common production mode is by the (n,γ) reaction, and the products of this reaction are not carrier free because they are the same chemical element as the bombarded target material. It is possible to produce carrier-free products in a reactor by using the (n,p) reaction (e.g., ^{32}P from ^{32}S) or by activating a short-lived intermediate product, such as ^{131}I from ^{131}Te using the reaction

$$ {}^{130}Te(n, \gamma)^{131}Te \xrightarrow{\beta^-} {}^{131}I \qquad (5\text{-}6) $$

3. Even in intense neutron fluxes, only a very small fraction of the target nuclei actually are activated, typically $1:10^6$ to 10^9 (see Section D). Thus an (n,γ) product may have very low specific activity because of the overwhelming presence of a large amount of unactivated stable carrier (target material).

There are a few examples of the production of electron capture (EC) decay or β^+-emitting radionuclides with a nuclear reactor, for example, ^{51}Cr by (n,γ) activation of ^{50}Cr. They may also be produced by using more complicated production techniques. An example is the production of ^{18}F (β^+, $T_{1/2}$ = 110 min). The target material is lithium carbonate (Li_2CO_3). The first step is the reaction

TABLE 5-1
NEUTRON-ACTIVATED RADIONUCLIDES OF IMPORTANCE IN BIOLOGY AND MEDICINE

Radionuclide	Decay Mode	Production Reaction	Natural Abundance of Target Isotope (%)*	σ_c(b)†
^{14}C	β^-	$^{14}N(n,p)^{14}C$	99.6	1.81
^{24}Na	(β^-,γ)	$^{23}Na(n,\gamma)^{24}Na$	100	0.53
^{32}P	β^-	$^{31}P(n,\gamma)^{32}P$ $^{32}S(n,p)^{32}P$	100 95.0	0.19 0.1
^{35}S	β^-	$^{35}Cl(n,p)^{35}S$	75.8	0.4
^{42}K	(β^-,γ)	$^{41}K(n,\gamma)^{42}K$	6.7	1.2
^{51}Cr	(EC,γ)	$^{50}Cr(n,\gamma)^{51}Cr$	4.3	17
^{59}Fe	(β^-,γ)	$^{58}Fe(n,\gamma)^{59}Fe$	0.3	1.1
^{75}Se	(EC,γ)	$^{74}Se(n,\gamma)^{75}Se$	0.9	30
^{125}I	(EC,γ)	$^{124}Xe(n,\gamma)^{125}Xe \xrightarrow{EC} {}^{125}I$	0.1	110
^{131}I	(β^-,γ)	$^{130}Te(n,\gamma)^{131}Te \xrightarrow{\beta^-} {}^{131}I$	33.8	0.24

*Values from Browne E, Firestone RB: Table of Radioactive Isotopes. New York, 1986, John Wiley.[1]

†Thermal neutron capture cross-section, in barns (b) (see "Activation Cross-Sections"). Values from Wang Y: Handbook of Radioactive Nuclides, Cleveland, Chemical Rubber Company, 1969.[2]

EC, Electron capture.

$$^{6}\mathrm{Li}\,(n,\gamma)^{7}\mathrm{Li} \qquad (5\text{-}7)$$

Lithium-7 is very unstable and promptly disintegrates:

$$^{7}_{3}\mathrm{Li} \rightarrow {}^{4}_{2}\mathrm{He} + {}^{3}_{1}\mathrm{H} + \text{energy} \qquad (5\text{-}8)$$

Some of the energetic recoiling tritium nuclei ($^{3}_{1}$H) bombard stable ^{16}O nuclei, causing the reaction

$$^{16}_{8}\mathrm{O}\left(^{3}_{1}\mathrm{H}, n\right)^{18}_{9}\mathrm{F} \qquad (5\text{-}9)$$

Useful quantities of ^{18}F can be produced in this way. One problem is removal from the product (by chemical means) of the rather substantial quantity of radioactive tritium that is formed in the reaction. More satisfactory methods for producing ^{18}F involve the use of charged particle accelerators, as discussed in Section B.

B. ACCELERATOR-PRODUCED RADIONUCLIDES

1. Charged-Particle Accelerators

Charged-particle accelerators are used to accelerate electrically charged particles, such as protons, deuterons ($^{2}_{1}$H nuclei), and α particles ($^{4}_{2}$He nuclei), to very high energies. When directed onto a target material, these particles may cause nuclear reactions that result in the formation of radionuclides in a manner similar to neutron activation in a reactor. A major difference is that the particles must have very high energies, typically 10-20 MeV, to penetrate the repulsive coulomb forces surrounding the nucleus.

Two types of nuclear reactions are commonly used to produce radionuclides using a charged-particle accelerator. In a *(p,n) reaction*, the target nucleus captures a proton and promptly releases a neutron. This reaction is represented as

$$^{A}_{Z}\mathrm{X}(p, n)_{Z+1}{}^{A}\mathrm{Y} \qquad (5\text{-}10)$$

This reaction can be considered the inverse of the (n,p) reaction that uses neutrons as the bombarding particle and was discussed in Section A.3.

A second common reaction is the *(d,n) reaction* in which the accelerated particle is a deuteron (d). The target nucleus captures a deuteron from the beam and immediately releases a neutron. This reaction is represented as

$$^{A}_{Z}\mathrm{X}(d, n)^{A+1}_{Z+1}\mathrm{Y} \qquad (5\text{-}11)$$

and results in a change of both the element (atomic number) and the mass number. In some cases, more than one neutron may be promptly released from the target nucleus after the bombarding particle has been captured. For example, a (p,2n) reaction involves the release of two neutrons following proton capture and a (d,3n) reaction involves the release of three neutrons following deuteron capture. Some accelerators also use alpha-particles to bombard a target and produce radionuclides. Indium-111 can be produced in this way using the reaction ^{109}Ag(α,2n)^{111}In.

Van de Graaff accelerators, linear accelerators, cyclotrons, and variations of cyclotrons have been used to accelerate charged particles. The cyclotron is the most widely used form of particle accelerator for production of medically important radionuclides.[3] Many larger institutions have their own compact *biomedical cyclotrons* for onsite production of the shorter-lived, positron-emitting radionuclides. The principles and design of cyclotrons dedicated to production of radionuclides for nuclear medicine are described briefly.

2. Cyclotron Principles

A cyclotron consists of a pair of hollow, semicircular metal electrodes (called *dees* because of their shape), positioned between the poles of a large electromagnet (Fig. 5-3). The dees are separated from one another by a narrow gap. Near the center of the dees is an ion source, S, (typically an electrical arc device in a gas) that is used to generate the charged particles. All these components are contained in a vacuum tank at ~10^{-3} Pa(~10^{-8} atm).

During operation, particles are generated in bursts by the ion source, and a high-frequency alternating current (AC) voltage generated by a high-frequency oscillator (typically 30 kV, 25-30 MHz) is applied across the dees. The particles are injected into the gap and immediately are accelerated toward one of the dees by the electrical field generated by the applied AC voltage. Inside the dee there is no electrical field, but because the particles are in a magnetic field, they follow a curved, circular path around to the opposite side of the dee. The AC voltage frequency is such that the particles arrive at the gap just as the voltage across the dees reaches its maximum

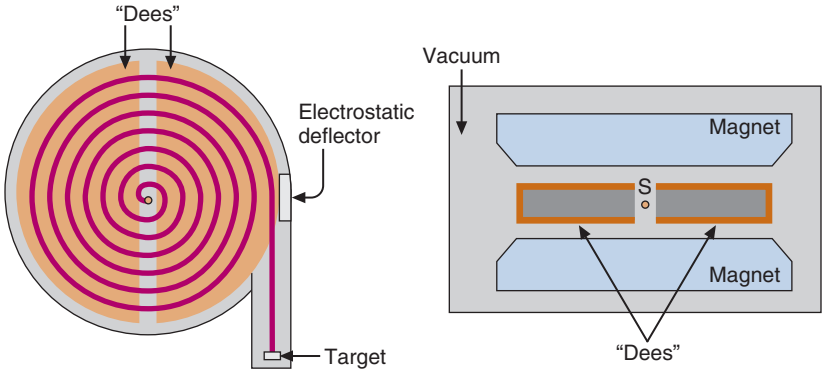

FIGURE 5-3 Schematic representation of a positive ion cyclotron: top (*left*) and side (*right*) views. The accelerating voltage is applied by a high-frequency oscillator to the two "dees." S is a source of positive ions.

value (30 kV) in the opposite direction. The particles are accelerated across the gap, gaining about 30 keV of energy in the process, and then continue on a circular path within the opposite dee.

Each time the particles cross the gap they gain energy, so the orbital radius continuously increases and the particles follow an outwardly spiraling path. The increasing speed of the particles exactly compensates for the increasing distance traveled per half orbit, and they continue to arrive back at the gap exactly in phase with the AC voltage. This condition applies so long as the charge-to-mass ratio of the accelerated particles remains constant. Because of their large relativistic mass increase, even at relatively low energies (~100 keV), it is not practical to accelerate electrons in a cyclotron. Protons can be accelerated to 20-30 MeV, and heavier particles can be accelerated to even higher energies (in proportion to their rest mass), before relativistic mass changes become limiting.*

Higher particle energies can be achieved in a variation of the cyclotron called the *synchrocyclotron* or *synchrotron,* in which the AC voltage frequency changes as the particles spiral outward and gain energy. These machines are used in high-energy nuclear physics research.

The energy of particles accelerated in a cyclotron is given by

$$E\ (\text{MeV}) \approx 4.8 \times 10^{-3}\ (H \times R \times \text{Z})^2/\text{A} \quad (5\text{-}12)$$

in which H is the magnetic field strength in tesla, R is the radius of the particle orbit in centimeters, and Z and A are the atomic number (charge) and mass number of the accelerated particles, respectively. The energies that can be achieved are limited by the magnetic field strength and the dee size. In a typical biomedical cyclotron with magnetic field strength of 1.5 tesla and a dee diameter of 76 cm, protons (Z = 1, A = 1) and α particles (Z = 2, A = 4) can be accelerated to approximately 15 MeV and deuterons (Z = 1, A = 2) to approximately 8 MeV.

When the particles reach the maximum orbital radius allowed within the cyclotron dees, they may be directed onto a target placed directly in the orbiting beam path (internal beam irradiation). More commonly, the beam is extracted from the cyclotron and directed onto an external target (external-beam radiation). Typical beam currents at the target are in the range of 50-100 μA. For cyclotrons using positively charged particles (positive ion cyclotron), the beam is electrostatically deflected by a negatively charged plate and directed to the target (Fig. 5-3). Unfortunately electrostatic deflectors are relatively inefficient, as much as 30% of the beam current being lost during extraction. This "lost" beam activates the internal parts of the cyclotron, thus making servicing and maintenance of the cyclotron difficult.

In a negative-ion cyclotron, negatively charged ions (e.g. H^-, a proton plus two electrons) are generated and then accelerated in the same manner as the positive ions in a positive-ion cyclotron (but in the opposite direction because of the different polarity). When the negatively charged ions reach the outermost orbit within the dee electrodes,

*Even at low energies, protons, deuterons, and α particles gain some mass when accelerated in a cyclotron. Magnetic "field shaping" is used in the cyclotron to compensate for this effect.

they are passed through a thin (5-25 μm) carbon foil, which strips off the electrons and converts the charge on the particle from negative to positive. The interaction of the magnetic beam with this positive ion bends its direction of motion outward and onto the target (Fig. 5-4). The negative-ion cyclotron has a beam extraction efficiency close to 100% and can therefore be described as a "cold" machine that requires minimal levels of shielding. Furthermore, two beams can be extracted simultaneously by positioning a carbon-stripping foil part way into the path of the beam, such that only a portion of the beam is extracted to a target. The remainder of the beam is allowed to continue to orbit and then is extracted with a second stripping foil onto a different target (Fig. 5-4). This allows two different radionuclides to be prepared simultaneously. One disadvantage of negative-ion cyclotrons is the requirement for a much higher vacuum (typically 10^{-5} Pa compared with 10^{-3} Pa for positive ion machines) because of the unstable nature of the H^- ion, the most commonly used particle in negative ion cyclotrons.

3. Cyclotron-Produced Radionuclides

Cyclotrons are used to produce a variety of radionuclides for nuclear medicine, some of which are listed in Table 5-2. General characteristics of cyclotron-produced radionuclides include the following:

1. Positive charge is added to the nucleus in most activation processes. Therefore, the products lie below the line of stability (see Fig. 2-9) and tend to decay by EC or β^+ emission.
2. Addition of positive charge to the nucleus changes its atomic number. Therefore cyclotron-activation products usually are carrier free.
3. Cyclotrons generally produce smaller quantities of radioactivity than are obtained from nuclear reactors. In part this results from generally smaller activation cross-sections for charged particles as compared with neutron irradiation (see Section D) and in part from lower beam intensities obtained in cyclotrons as compared with nuclear reactors.

Cyclotron products are attractive for nuclear medicine imaging studies because of the high photon/particle emission ratios that are obtained in β^+ and EC decay. Of special interest are the short-lived positron emitters ^{11}C ($T_{1/2}$ = 20.4 min), ^{13}N ($T_{1/2}$ = 9.97 min), and ^{15}O ($T_{1/2}$ = 2.03 min). These radionuclides represent elements that are important constituents of all biologic substances, and they can be used to label a wide variety of biologically relevant tracers. Because of their very short lifetimes, these positron-emitting radionuclides must be prepared on site with a dedicated biomedical cyclotron. The high cost of owning and operating such machines has impeded their widespread use. Nevertheless, because of the importance of several positron emitter–labeled radiopharmaceuticals, there are now many hundreds of cyclotrons worldwide producing short-lived positron-emitting isotopes for nuclear medicine imaging studies. A typical biomedical cyclotron is shown in Figure 5-5.

Fluorine-18 ($T_{1/2}$ = 110 min) is another important positron-emitting radionuclide.

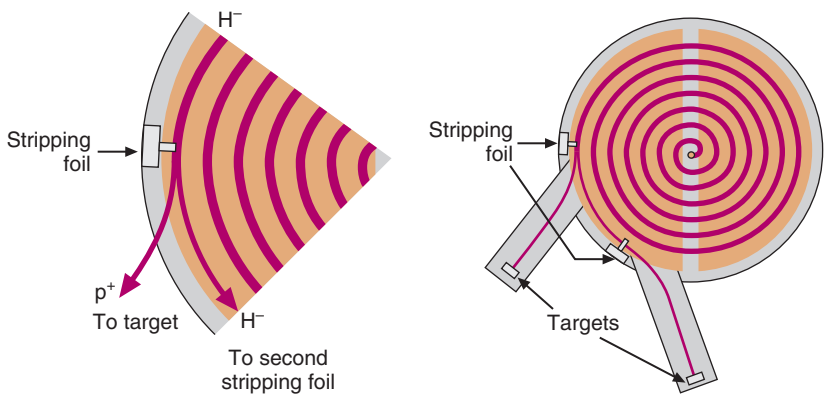

FIGURE 5-4 *Left,* Schematic representation of a negative-ion cyclotron. The carbon stripping foils remove two electrons from negative hydrogen (H^-) ions, converting them into protons (p^+) that bend in the opposite direction in the applied magnetic field. *Right,* The first stripping foil intersects only part of the beam, allowing two beams to be extracted simultaneously.

TABLE 5-2
SOME CYCLOTRON-PRODUCED RADIONUCLIDES USED IN NUCLEAR MEDICINE

Product	Decay Mode	Common Production Reaction	Natural Abundance of Target Isotope* (%)	Energy Threshold (MeV)†
^{11}C	β^+, EC	$^{14}N(p,\alpha)^{11}C$	99.6	3.1
		$^{10}B(d,n)^{11}C$	19.9	0
^{13}N	β^+	$^{16}O(p,\alpha)^{13}N$	99.8	5.5
		$^{12}C(d,n)^{13}N$	98.9	0.35
^{15}O	β^+	$^{14}N(d,n)^{15}O$	99.6	0
		$^{15}N(p,n)^{15}O$	0.37	—
^{18}F	β^+, EC	$^{18}O(p,n)^{18}F$	0.20	2.57
		$^{20}Ne(d,\alpha)^{18}F$	90.5	0
^{67}Ga	(EC,γ)	$^{68}Zn(p,2n)^{67}Ga$	18.8	5.96
^{111}In	(EC,γ)	$^{109}Ag(\alpha,2n)^{111}In$	48.2	—
		$^{111}Cd(p,n)^{111}In$	12.8	—
^{123}I	(EC,γ)	$^{122}Te(d,n)^{123}I$	2.6	—
		$^{124}Te(p,3n)^{123}I$	4.8	—
^{201}Tl	(EC,γ)	$^{201}Hg(d,2n)^{201}Tl$	13.2	—

*Values from Browne E, Firestone RB: *Table of Radioactive Isotopes*. New York, 1986, John Wiley.[1]
†Values from Helus F, Colombetti LG: *Radionuclides Production*, Vols I, II. Boca Raton, 1983, CRC Press.[4]
EC, electron capture.

FIGURE 5-5 Photograph of a negative-ion biomedical cyclotron. *Left,* Cyclotron within concrete shield. *Right,* The cyclotron itself. (*Courtesy Siemens Molecular Imaging Inc., Knoxville, TN.*)

One of its main applications is in the labeling of a glucose analog, ^{18}F-fluorodeoxyglucose (FDG), which provides a measure of the metabolic rate for glucose in the cells of the body. The longer half-life of the ^{18}F label allows FDG to be produced in regional distribution centers and shipped to hospitals tens or even hundreds of miles away. FDG is the most widely used positron-emitting radiopharmaceutical with a wide range of clinical applications in the heart, and brain and especially in cancer imaging. (See Chapter 18, Section F.)

C. RADIONUCLIDE GENERATORS

A radionuclide generator consists of a parent-daughter radionuclide pair contained in an apparatus that permits separation and extraction of the daughter from the parent. The daughter product activity is replenished continuously by decay of the parent and may be extracted repeatedly.

Table 5-3 lists some radionuclide generators of interest to nuclear medicine. They are an important source of metastable

TABLE 5-3
SOME RADIONUCLIDE GENERATORS USED IN NUCLEAR MEDICINE

Daughter*	Decay Mode	$T_{1/2}$	Parent	$T_{1/2}$
^{62}Cu	β^+,EC	9.7 min	^{62}Zn	9.3 hr
^{68}Ga	β^+,EC	68 min	^{68}Ge	271 d
^{82}Rb	β^+,EC	1.3 min	^{82}Sr	25 d
^{87m}Sr	IT	2.8 hr	^{87}Y	80 hr
^{99m}Tc	IT	6 hr	^{99}Mo	66 hr
^{113m}In	IT	100 min	^{113}Sn	120 d

*Generator product.
EC, electron capture; IT, isomeric transition.

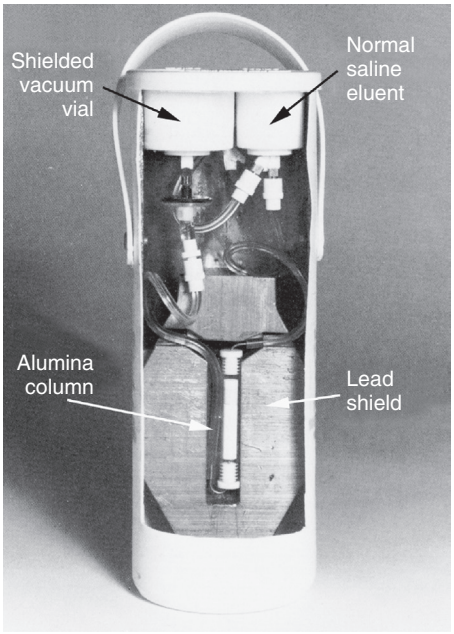

FIGURE 5-6 Cut-away view of a ^{99}Mo-^{99m}Tc generator. (*Adapted from* A Guide to Radiopharmaceutical Quality Control. *Billerica, MA, 1985, Du Pont Company.*)

radionuclides. The most important generator is the ^{99}Mo-^{99m}Tc system, because of the widespread use of ^{99m}Tc for radionuclide imaging. Technetium-99m emits γ rays (140 keV) that are very favorable for use with a gamma camera (Chapter 13). It has a reasonable half-life (6 hours), delivers a relatively low radiation dose per emitted γ ray (Chapter 22), and can be used to label a wide variety of imaging agents. More than 1850 TBq (50,000 Ci) of ^{99}Mo per week are required to meet the worldwide requirements for nuclear medicine procedures.

A ^{99}Mo-^{99m}Tc generator is shown in Figure 5-6. The parent ^{99}Mo activity in the form of molybdate ion, MoO_4^{2-} is bound to an alumina (Al_2O_3) column. The daughter ^{99m}Tc activity, produced in the form of $^{99m}TcO_4^-$ (pertechnetate), is not as strongly bound to alumina and is eluted from the column with 5 to 25 mL of normal saline. Technetium-99m activity builds up again after an elution and maximum activity is available about 24 hours later (Equation 4-28); however, usable quantities are available 3 to 6 hours later. Commercially prepared generators are sterilized, well shielded, and largely automated in operation. Typically they are used for approximately 1 week and then discarded because of natural decay of the ^{99}Mo parent.

Decay of the ^{99}Mo-^{99m}Tc parent-daughter pair is an example of transient equilibrium (see Chapter 4, Section G.3). Equation 4-25 and Figure 4-8 describe the buildup and decay of activity for such a pair. Under idealized conditions, and a branching ratio of 0.876, the ratio of ^{99m}Tc/^{99}Mo activity in a generator in a state of transient equilibrium (see Equation 4-27) would be approximately 0.96, and the time to maximum activity following an elution (Equation 4-28) would be approximately 23 hours.

However, these equations do not accurately predict the amount of ^{99m}Tc actually obtained in individual elutions, because most generators do not yield 100% of the available activity. Typical generator elution efficiencies are 80% to 90%, depending on the size and type of generator, volume of eluant, and so on. Furthermore, the efficiency can vary from one elution to the next. In practice, efficiency variations of ±10% or more can occur in successive elutions of the same generator.[5] These may be caused by chemical changes in the column, including some that are caused by the intense radiation levels. Failure to keep a "dry" column in a dry state also can substantially degrade elution efficiency. These issues, as well as other complexities of ^{99}Mo-^{99m}Tc generators, are discussed in detail in references 5 and 6.

If 90% of the ^{99m}Tc activity in a generator is removed during an elution, the activity obtained would be 10% less than predicted from Equation 4-25 and Figure 4-8. Furthermore, the 10% residual ^{99m}Tc activity left in the generator becomes "$A_d(0)$" in Equation 4-25 for the next elution interval. This activity provides a "jump start" for regrowth of ^{99m}Tc in the generator, thereby shortening the time to maximum activity after an elution from that predicted by Equation 4-28.

Figure 5-7A, shows the available ^{99m}Tc activity, relative to parent ^{99}Mo activity, for a generator that is eluted with 90% efficiency at 24-hour intervals, starting at t = 0 hours. Under these conditions, the activity obtained is approximately 77% of the parent ^{99}Mo activity in the generator at the time of elution, and the time to maximum activity after an elution is shortened to approximately 21 hours.

If a generator is eluted at irregular intervals, the situation becomes more complicated, because the residual ^{99m}Tc activity left in the generator varies from one elution to the next. In this situation, the ^{99m}Tc activity in generator can be predicted using Equation 4-25, using the ideal versus actual yield to estimate the amount of residual ^{99m}Tc for $A_d(0)$ for the next elution interval. Figure 5-7B, shows the results of such a calculation for elutions at 0, 24, 30, 48, and 96 hours, each done with 90% elution efficiency.

In a practical environment, it is useful to keep records comparing generator yields to those predicted from the idealized equations. This can be helpful for identifying "low-yield" generators, as well as possible problems that may develop in an individual generator. A simplified equation that can be used to predict yields for elutions performed at regular 24-hour or other similarly "long" intervals is

$$Y_2 = \frac{Y_1 \times \left(e^{-\lambda_p \Delta t_2} - e^{-\lambda_d \Delta t_2}\right)}{\left[1 - e^{-(\lambda_d - \lambda_p)\Delta t_1}\right]} \qquad (5\text{-}13)$$

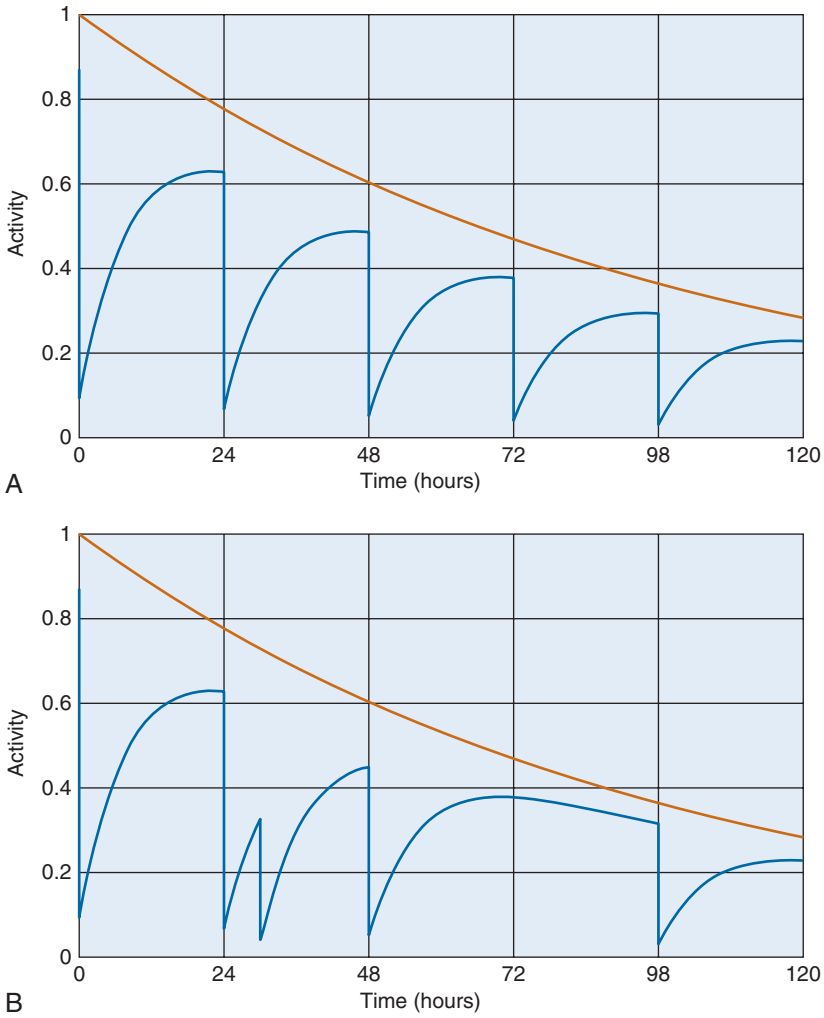

FIGURE 5-7 Orange lines: ^{99}Mo activity in a generator, normalized to 1.0 at t = 0. Blue lines: ^{99m}Tc activity available for elution, assuming 90% elution efficiency. *A*, Generator eluted at regular 24-hour intervals. *B,* Generator eluted at irregular intervals. ^{99m}Tc activities also are expressed relative to the ^{99}Mo activity in the generator, and assume consistent 90% elution efficiency from one elution to the next.

Here, Y_2 is the predicted yield of an elution (in units of activity), Y_1 is the actual yield of the immediately preceding elution, Δt_2 is the time since that elution, Δt_1 is the elution interval between that elution and the one immediately preceding it (i.e., prior to the elution yielding Y_1), and λ_p and λ_d are the decay constants of ^{99}Mo (~0.0105 hr^{-1}) and ^{99m}Tc (~0.115 hr^{-1}), respectively. This equation assumes that the elution efficiency is constant from one elution to the next and that there is insignificant carryover of residual ^{99m}Tc activity in the column at the time of the next elution. The latter condition is reasonably satisfied for 24-hr or similarly long elution intervals that allow for virtually complete decay of any ^{99m}Tc left over from previous elutions.

Molybdenum-99 activity is obtained by separation from fission fragments produced in a target containing uranium or by (n,γ) activation of stable molybdenum (23.8% ^{98}Mo). The former, sometimes called *fission moly,* has significantly higher specific activity and is the production method of choice for large quantities. The reaction by which it is produced sometimes is called an (n,f) reaction, indicating neutron irradiation causing fission. The production of ^{99}Mo is described in detail in reference 7.

Fission moly is produced by inserting a target (typically shaped as a pin, cylinder, or plate) containing natural uranium, enriched with ^{235}U, via an access port into the reactor core. The target is encapsulated in aluminum or stainless steel. Fission neutrons from the reactor core induce fission reactions in the target, as shown in Equation 5-1. Molybdenum-99 is one of the more abundant fission products (6.1% of fission products), but a wide variety of others are produced as well (see Fig. 5-2B).

After a suitable period of irradiation (typically 5-7 days), the uranium target is removed, allowed to cool, and dissolved either using an acid or alkaline dissolution process. The ^{99}Mo is then extracted by chemical means. Special care is required to assure that the many other radioactive fission products do not contaminate the desired ^{99}Mo product. As well, a large fraction of the original ^{235}U remains in the solution and must be stored as long-term radioactive waste.

The amount of stable molybdenum produced by the (n,f) reaction is small, as compared with its concentration in a target used for neutron activation of ^{98}Mo. Therefore the specific activity of ^{99}Mo in "fission moly" is much higher, and can be loaded into generators containing much smaller quantities of the alumina column.

The volume of alumina required in a ^{99}Mo-^{99m}Tc generator is determined essentially by the amount of stable ^{99}Mo carrier that is present. Therefore "fission moly" generators require much smaller volumes of alumina per unit of ^{99}Mo activity. They can be eluted with very small volumes of normal saline (~5 mL), which is useful in some dynamic imaging studies requiring bolus injections of very small volumes of high activity (740 MBq, 20 mCi) of ^{99m}Tc.

One problem with ^{99m}Tc generators is ^{99}Mo "breakthrough," that is, partial elution of the ^{99}Mo parent along with ^{99m}Tc from the generator. From the standpoint of patient radiation safety, the amount of ^{99}Mo should be kept to a minimum. Maximum amounts, according to Nuclear Regulatory Commission regulations, are 0.15 Bq ^{99}Mo per kBq ^{99m}Tc (0.15 μCi ^{99}Mo per mCi ^{99m}Tc). It is possible to assay ^{99}Mo activity in the presence of much larger ^{99m}Tc activity using NaI(Tl) counting systems by surrounding the sample with approximately 3 mm of lead, which is an efficient absorber of the 140 keV γ rays of ^{99m}Tc but relatively transparent to the 740-780-keV γ rays of ^{99}Mo. Thus small quantities of ^{99}Mo can be detected in the presence of much larger amounts of ^{99m}Tc. Some dose calibrators are provided with a lead-lined container called a "moly shield" specifically for this purpose. Other radioactive contaminants also are occasionally found in ^{99}Mo-^{99m}Tc generator eluate.

A second major concern is breakthrough of aluminum ion, which interferes with labeling processes and also can cause clumping of red blood cells and possible microemboli. Maximum permissible levels are 10 μg aluminum per mL of ^{99m}Tc solution. Chemical test kits are available from generator manufacturers to test for the presence of aluminum ion.

D. EQUATIONS FOR RADIONUCLIDE PRODUCTION

1. Activation Cross-Sections

The amount of activity produced when a sample is irradiated in a particle beam depends on the intensity of the particle beam, the number of target nuclei in the sample, and the probability that a bombarding

particle will interact with a target nucleus. The probability of interaction is determined by the *activation cross-section*. The activation cross-section is the effective "target area" presented by a target nucleus to a bombarding particle. It has dimensions of area and is symbolized by σ. The Systeme International units for σ are m^2. The traditional and more commonly used unit is the *barn* (1 b = 10^{-28} m^2) or *millibarn* (1 mb = 10^{-3} b = 10^{-31} m^2).

Activation cross-sections for a particular nucleus depend on the type of bombarding particle, the particular reaction involved, and the energy of the bombarding particles. Figure 5-8 shows the activation cross-section for the production of ^{18}F from the $^{18}O(p,n)^{18}F$ reaction. Note that the cross-section is a strong function of the energy of the bombarding proton beam, and that for the reaction shown there is a threshold energy of 2.57 MeV below which production of ^{18}F is not possible. The threshold energies for several other cyclotron-produced radionuclides are given in Table 5-2.

Because of their importance in radionuclide production by nuclear reactors, activation cross-sections for thermal neutrons have been measured in some detail. These are called *neutron-capture cross-sections*, symbolized by σ_c. Some values of σ_c of interest for radionuclide production in nuclear medicine are listed in Table 5-1.

2. Activation Rates

Suppose a sample containing n target nuclei per cm^3, each having an activation cross-section σ, is irradiated in a beam having a *flux density* ϕ (particles/cm^2 sec) (Fig. 5-9). It is assumed that the sample thickness Δx (cm) is sufficiently thin that ϕ does not change much as the beam passes through it. The total number of targets, per cm^2 of beam area, is $n\,\Delta x$. They present a total area $n\,\phi\,\Delta x$ per cm^2 of beam area. The reduction of beam flux in passing through the target thickness Δx is therefore

$$\Delta\phi/\phi = n\,\sigma\,\Delta x \qquad (5\text{-}14)$$

The number of particles removed from the beam (i.e., the number of nuclei activated) per cm^2 of beam area per second is

$$\Delta\phi = n\,\sigma\,\phi\,\Delta x \qquad (5\text{-}15)$$

Each atom of target material has mass AW/(6.023×10^{23}) g, in which AW is its atomic weight and 6.023×10^{23} is Avogadro's number. The total mass m of target material per cm^2 in the beam is therefore

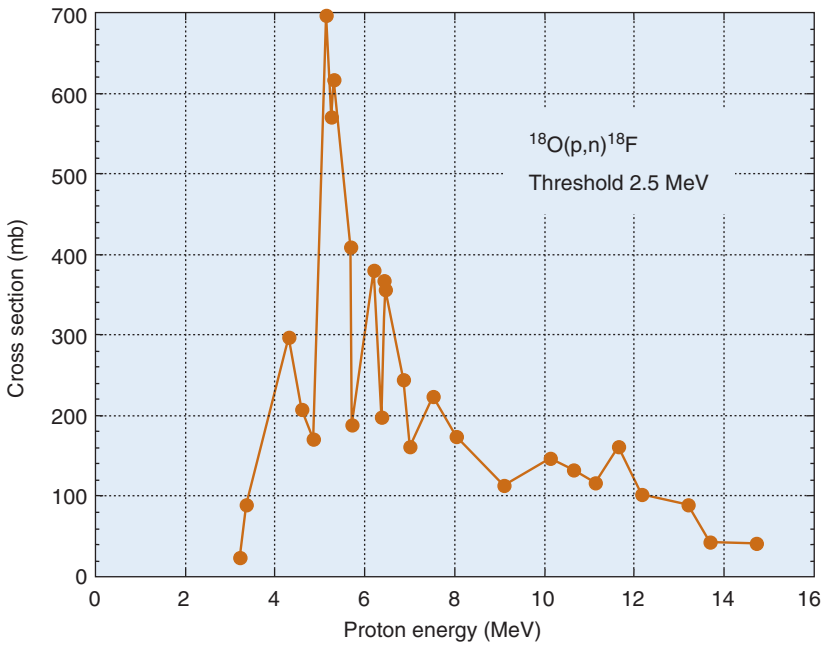

FIGURE 5-8 Activation cross-section versus particle energy for the reaction $^{18}O(p,n)^{18}F$. The energy threshold for this reaction is ~2.5 MeV. [*From Ruth TJ, Wolf AP: Absolute cross sections for the production of ^{18}F via the $^{18}O(p,n)^{18}F$ reaction.* Radiochim Acta *26:21-24, 1979.*]

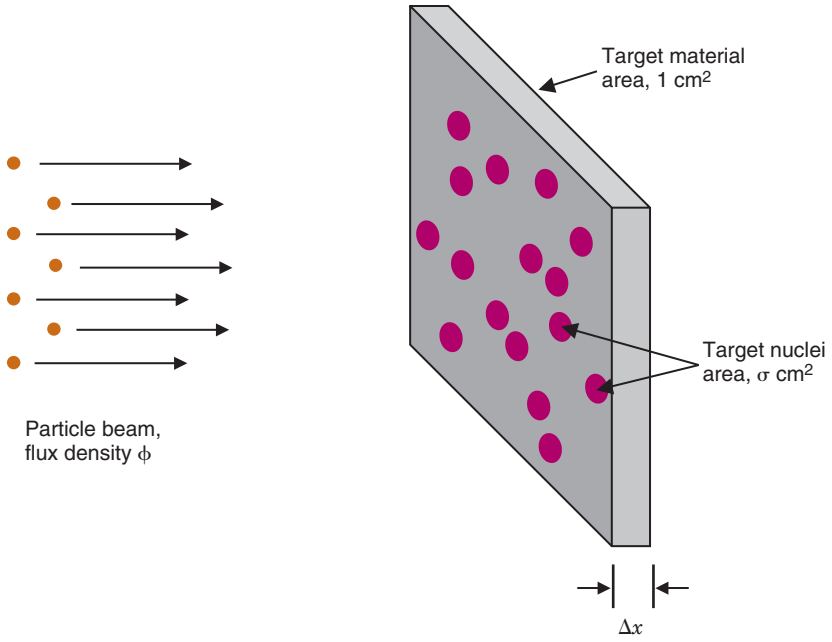

FIGURE 5-9 Activation targets in a particle beam.

$$m \approx n \times \Delta x \times \mathrm{AW}/(6.023 \times 10^{23}) \quad (5\text{-}16)$$

and the activation rate R per unit mass of target material is thus

$$R \approx \Delta\phi/m \quad (5\text{-}17)$$

$$R \approx \frac{(6.023 \times 10^{22}) \times \sigma \times \phi}{\mathrm{AW}} \ (\mathrm{activations/g \cdot sec}) \quad (5\text{-}18)$$

Equation 5-18 can be used to calculate the rate at which target nuclei are activated in a particle beam per gram of target material in the beam.

EXAMPLE 5-1

What is the activation rate per gram of sodium for the reaction $^{23}\mathrm{Na(n,\gamma)}^{24}\mathrm{Na}$ in a reactor thermal neutron flux density of 10^{13} neutrons/cm^2 • sec?

Answer

From Table 5-1, the thermal neutron capture cross-section for ^{23}Na is $\sigma_c = 0.53$ b. The atomic weight of sodium is approximately 23. Therefore (Equation 5-18)

$$R \approx (6.023 \times 10^{23}) \times (0.53 \times 10^{-24}) \times 10^{13}/23$$
$$\approx 1.38 \times 10^{11} \ \mathrm{activations/g \cdot sec}$$

Equation 5-18 and Example 5-1 describe situations in which the isotope represented by the target nucleus is 100% abundant in the irradiated sample (e.g., naturally occurring sodium is 100% ^{23}Na). When the target is not 100% abundant, then the activation rate *per gram of irradiated element* is decreased by the percentage abundance of the isotope of interest in the irradiated material.

EXAMPLE 5-2

Potassium 42 is produced by the reaction $^{41}\mathrm{K(n,\gamma)}^{42}\mathrm{K}$. Naturally occurring potassium contains 6.8% ^{41}K and 93.2% ^{39}K. What is the activation rate of ^{42}K per gram of K in a reactor with thermal neutron flux density 10^{13} neutrons/cm^2 • sec?

Answer

From Table 5-1, the neutron capture cross-section of ^{41}K is 1.2 b. The atomic weight of ^{41}K is approximately 41. Thus (Equation 5-18)

$$R \approx (6.023 \times 10^{23}) \times (1.2 \times 10^{-24}) \times 10^{13}/41$$
$$\approx 1.76 \times 10^{11} \ \mathrm{activations/g(^{41}K) \cdot sec}$$

The activation rate per gram of potassium is 6.8% of this, that is,

$$R \approx 0.068 \times (1.76 \times 10^{11})$$
$$\approx 1.20 \times 10^{10} \ \mathrm{activations/g(K) \cdot sec}$$

Activation rates are less than predicted by Equation 5-18 when the target thickness is

such that there is significant attenuation of particle beam intensity as it passes through the target (i.e., some parts of the target are irradiated by a weaker flux density). Also, when "thick" targets are irradiated by charged-particle beams, the particles lose energy and activation cross-sections change as the beam penetrates the target. The equations for these conditions are beyond the scope of this book and are discussed in reference 8.

3. Buildup and Decay of Activity

When a sample is irradiated in a particle beam, the buildup and decay of product radioactivity is exactly analogous to a special case of parent-daughter radioactive decay discussed in Chapter 4, Section G.2. The irradiating beam acts as an inexhaustible, long-lived "parent," generating "daughter" nuclei at a constant rate. Thus, as shown in Figure 4-7, the product activity starts from zero and increases with irradiation time, gradually approaching a saturation level at which its disintegration rate equals its production rate. The saturation level can be determined from Equation 5-18. The saturation *disintegration rate* per gram is just equal to R, the *activation rate* per gram, so the saturation specific activity A_s is

$$A_s\ (\text{Bq/g}) = R \qquad (5\text{-}19)$$

which, when combined with Equation 5-18, yields

$$A_s\ (\text{Bq/g}) \approx 0.6023 \times \sigma \times \phi/\text{AW} \qquad (5\text{-}20)$$

where σ is the activation cross-section in barns, ϕ is the flux in units of particles per $\text{cm}^2 \cdot \text{sec}$, and AW is the atomic weight of the target material. The final equation for specific activity, A, versus irradiation time is

$$A(t)\ (\text{Bq/g}) = A_s\ (1 - e^{-\lambda t}) \qquad (5\text{-}21)$$

where λ is the decay constant of the product (compare with Equation 4-26). The specific activity of the target reaches 50% of the saturation level after irradiating for one daughter product half-life, 75% after two half-lives, and so on (see Fig. 4-7). No matter how long the irradiation, the sample-specific activity cannot exceed the saturation level. Therefore it is unproductive to irradiate a target for longer than approximately three or four times the product half-life.

EXAMPLE 5-3

What is the saturation specific activity for the ^{42}K production problem described in Example 5-2? Compare this with the carrier-free specific activity (CFSA) of ^{42}K (the half-life of ^{42}K is 12.4 hours).

Answer

Applying Equation 5-20 with σ = 1.2 b, $\phi = 10^{13}$, and AW ≈ 41,

$$A_s = 0.6023 \times 1.2 \times 10^{13}/41$$
$$= 1.76 \times 10^{11}\ (\text{Bq } ^{42}\text{K/g } ^{41}\text{K})$$

If natural potassium is used, only 6.8% is ^{41}K. Therefore the saturation specific activity is

$$A_s = (1.76 \times 10^{11}) \times 0.068$$
$$= 1.20 \times 10^{10}\ \text{Bq } ^{42}\text{K/g K}$$

The CFSA of ^{42}K ($T_{1/2}$ ~ 0.5 days) is (Equation 4-21)

$$\text{CFSA} \approx (4.8 \times 10^{18})/(41 \times 0.5)$$
$$\approx (2.3 \times 10^{17})\ \text{Bq } ^{42}\text{K/g } ^{42}\text{K}$$

Example 5-3 illustrates the relatively low specific activity that typically is obtained by (n,γ) activation procedures in a nuclear reactor.

A parameter that is related directly to the saturation activity in an activation problem is the *production rate, A′*. This is the rate at which radioactivity is produced during an irradiation, disregarding the simultaneous decay of radioactivity that occurs during the irradiation. It is the slope of the production curve at time t = 0 (before any of the generated activity has had opportunity to decay). The production rate can be shown by methods of differential calculus to be equal to

$$A'\ (\text{Bq/g} \cdot \text{hr}) = \ln 2 \times A_s\ (\text{Bq/g})/T_{1/2}(\text{hr}) \qquad (5\text{-}22)$$

where $T_{1/2}$ is the half-life of the product.

Reactor production capabilities may be defined in terms of either saturation levels or production rates. If the irradiation time t is "short" in comparison with the product half-life, one can approximate the activity produced from the production rate according to

$$A\ (\text{Bq/g}) \approx A' \times t \qquad (5\text{-}23)$$

$$\approx \ln 2 \times A_s \times t/T_{1/2} \qquad (5\text{-}24)$$

where t and $T_{1/2}$ must be in the same units.

EXAMPLE 5-4

What is the production rate of ^{42}K for the problem described in Example 5-2, and what specific activity would be available after an irradiation period of 3 hours? (The half-life of ^{42}K is 12.4 hours.)

Answer

From Example 5-3, $A_s = 1.20 \times 10^{10}$ Bq ^{42}K/g K. Therefore (Equation 5-22)

$$A' = 0.693 \times (1.20 \times 10^{10})/12.4$$
$$\approx 6.7 \times 10^{8} \text{ Bq } ^{42}\text{K/g K} \cdot \text{hr}$$

After 3 hours, which is "short" in comparison with the half-life of ^{42}K, the specific activity of the target is (Equation 5-23)

$$A(\text{Bq/g}) \approx (6.7 \times 10^{8}) \times 3$$
$$\approx 2.0 \times 10^{9} \text{ Bq } ^{42}\text{K/g K}$$

E. RADIONUCLIDES FOR NUCLEAR MEDICINE

1. General Considerations

In elemental form, radionuclides themselves generally have a relatively small range of biologically interesting properties. For example, ^{131}I as an iodide ion (I^-) is useful for studying the uptake of elemental iodine in the thyroid or in metastatic thyroid cancer or for delivering a concentrated radiation dose to thyroid tissues for therapeutic purposes; however, elemental iodine has no other generally interesting properties for medical usage. For this reason, most studies in nuclear medicine employ *radiopharmaceuticals,* in which the radionuclide is attached as a label to a compound that has useful biomedical properties.

For most applications, the radiopharmaceutical is injected into the patient, and the emissions are detected using external imaging or counting systems. Certain practical requirements must be met for a radionuclide to be a useful label. A portion of the Chart of Nuclides was shown in Figure 3-11. A complete chart contains hundreds of radionuclides that could conceivably be used for some biomedical application, either in elemental form or as a radiopharmaceutical label. However, the number of radionuclides actually used is much smaller because of various practical considerations, as discussed in the following section. A listing of some of the more commonly used radionuclides for nuclear medicine procedures is presented in Table 5-4.

2. Specific Considerations

The *type and energy of emissions* from the radionuclide determine the availability of useful photons or γ rays for counting or imaging. For external detection of a radionuclide inside the body, photons or γ rays in the 50-600 keV energy range are suitable. Very-low-energy photons and γ rays (<50 keV), or particulate radiation, have a high likelihood of interacting in the body and will not in general escape for external detection. The presence of such low energy or particulate emissions increases the radiation dose to the patient. An example of this is ^{131}I, which decays by (β^-,γ) emitting a β^- particle, followed by γ rays at 364 (82%), 637 (6.5%), 284 (5.8%), or 80 keV (2.6%). The γ rays are in an appropriate range for external detection; however, the β^- particle contributes additional dose as compared with radionuclides that decay by (EC,γ).

The *physical half-life* of the radionuclide should be within the range of seconds to days (preferably minutes to hours) for clinical applications. If the half-life is too short, there is insufficient time for preparation of the radiopharmaceutical and injection into the patient. An example of this is the positron emitter ^{15}O ($T_{1/2}$ = 122 sec). This limits ^{15}O-labeled radiopharmaceuticals to simple compounds such as $H_2{}^{15}O$ and $C^{15}O$. If the half-life were longer, a much wider range of compounds could be labeled with ^{15}O. Other radionuclides have half-lives that are too long for practical purposes. Most of the radiation is emitted outside of the examination time, which can result in a high radiation dose to the patient in relation to the number of decays detected during the study. Long-lived radionuclides also can cause problems in terms of storage and disposal. An example of a very long-lived radionuclide that is not used in human studies because of half-life considerations is ^{22}Na ($T_{1/2}$ = 2.6 yr).

The *specific activity* of the radionuclide largely determines the mass of a compound that is introduced for a given radiation dose. Because nuclear medicine relies on the use of subpharmacologic tracer doses that do not perturb the biologic system under study, the mass should be low and the specific activity high. At low specific activities, only a small fraction of the molecules in the sample are radioactive and therefore signal producing, whereas the rest of the molecules add to the

TABLE 5-4
PHYSICAL PROPERTIES OF RADIONUCLIDES USED IN NUCLEAR MEDICINE STUDIES

Radionuclide	Decay Mode	Principal Photon Emissions	Half-Life	Primary Use
^{11}C	β^+	511 keV	20.4 min	Imaging
^{13}N	β^+	511 keV	9.97 min	Imaging
^{15}O	β^+	511 keV	2.03 min	Imaging
^{18}F	β^+	511 keV	110 min	Imaging
^{32}P	β^-	—	14.3 d	Therapy
^{67}Ga	EC	93, 185, 300 keV	3.26 d	Imaging
^{82}Rb	β^+	511 keV	1.25 min	Imaging
^{89}Sr	β^-	—	50.5 d	Therapy
^{99m}Tc	IT	140 keV	6.02 hr	Imaging
^{111}In	EC	172, 247 keV	2.83 d	Imaging
^{123}I	EC	159 keV	13.2 hr	Imaging
^{125}I	EC	27-30 keV x rays	60.1 d	In vitro assays
^{131}I	β^-	364 keV	8.04 d	Therapy/ imaging
^{153}Sm	β^-	41, 103 keV	46.7 hr	Therapy
^{186}Re	β^-	137 keV	3.8 d	Therapy
^{201}Tl	EC	68-80 keV x rays	3.04 d	Imaging

EC, electron capture; IT, isomeric transition.

mass of the compound being introduced, without producing signal. Theoretically, the attainable specific activity of a radionuclide is inversely proportional to its half-life, although in practice, many other factors (e.g., the abundance of stable isotopes in air and glassware) can determine the actual specific activity of the injected labeled compound, as described in Section F.1.

The *radionuclidic purity* is defined as the fraction of the total radioactivity in a sample that is in the form of the desired radionuclide. Radionuclidic contaminants arise in the production of radionuclides and can be significant in some situations. The effect of these contaminants is to increase the radiation dose to the patient. They may also increase detector dead time, and if the energy of the emissions falls within the acceptance window of the detector system, contaminants may result in incorrect counting rate or pixel intensities in images. Of concern in radionuclide generator systems is contamination with the long-lived parent radionuclide. In the case of the ^{99}Mo-^{99m}Tc generator, the radionuclidic purity of the ^{99m}Tc must be higher than 99.985%, as discussed in Section C.

The *chemical properties* of the radionuclide also are an important factor. Radionuclides of elements that can easily produce useful *precursors* (chemical forms that react readily to form a wide range of labeled products) and that can undergo a wide range of chemical syntheses are preferred (e.g., ^{123}I, ^{18}F, and ^{11}C). Radionuclides of elements that are easily incorporated into biomolecules, without significantly changing their biochemical properties, also are attractive. Examples are ^{11}C, ^{13}N, ^{15}O, elements that are found naturally in many biomolecules. Metals such as ^{99m}Tc and ^{67}Ga also are widely used as labels in nuclear medicine, because of the desirable imaging properties of the radionuclide. To incorporate such elements into biologically relevant molecules is challenging but can be achieved by *chelation* and other techniques that seek to "hide" or shield the metal atom from the biologically active sites of the molecule.

Finally, the *cost and complexity* of preparing a radionuclide must be considered. Sufficient quantities of radionuclide for radiopharmaceutical labeling and subsequent patient injection must be produced at a cost

(both materials and labor) consistent with today's health care market.

F. RADIOPHARMACEUTICALS FOR CLINICAL APPLICATIONS

As noted earlier, radionuclides almost always are attached as labels to compounds of biomedical interest for nuclear medicine applications. Because of the practical considerations discussed in the preceding section, the number of different radionuclides routinely used in nuclear medicine is relatively small, perhaps fewer than a dozen even in large hospitals. On the other hand, the number of labeled compounds is much larger and continuously growing, owing to very active research in radiochemistry and radiopharmaceutical preparation. The following sections summarize the properties of some radiopharmaceuticals that enjoy widespread usage at this time. More detailed discussions are found in the articles and texts listed in the Bibliography.

1. General Considerations

The final *specific activity* of a radiopharmaceutical (as opposed to the radionuclide) is determined by losses in specific activity that occur during the chemical synthesis of the radiopharmaceutical. This is particularly an issue for isotopes of elements that have high natural abundances. For example, the theoretical maximum specific activity for ^{11}C is 3.5×10^8 MBq/μmol (CFSA from Equation 4-22), whereas the specific activity of ^{11}C-labeled radiopharmaceuticals actually obtained in practice is approximately 10^5 MBq/μmol. This is largely because of the presence of stable carbon in the air (as CO_2) and in the materials of the reaction vessels and tubing used in the chemical synthesis procedure.

Radiochemical purity is the fraction of the radioactivity in the sample that is present in the desired chemical form. Radiochemical impurities usually stem from competing chemical reactions in the radiolabeling process or from decomposition (chemical or radiation induced) of the sample. Radiochemical impurities are problematic in that their distribution in the body is generally different, thus adding a background to the image of the desired compound. The typical radiochemical purity for radiopharmaceuticals is higher than 95%. *Chemical purity* (the fraction of the sample that is present in the desired chemical form) is also important, with desirable values of greater than 99%.

The dynamic time course of the radiopharmaceutical in the body must be considered. Some radiopharmaceuticals have rapid uptake and clearance, whereas others circulate in blood with only slow uptake into tissues of interest. The rate of clearance of the radiopharmaceutical from the body is called the *biologic half-life*. Together with the physical half-life of the radionuclide, this determines the number of radioactive decays that will be observed from a particular region of tissue as a function of time. These two factors also are important factors in determining the radiation dose to the subject (see Chapter 22, Section B). It is important that radiopharmaceuticals be labeled with radionuclides with half-lives that are long enough to encompass the temporal characteristics of the biologic process being studied. For example, labeled antibodies generally require hours to days before significant uptake in a target tissue is reached and blood levels have dropped sufficiently for the target to be visualized. Short-lived radionuclides with half-lives of minutes or less would not be useful in this situation.

The radiopharmaceutical must not be toxic at the mass levels administered. This requirement usually is straightforward in nuclear medicine studies because of the relatively high specific activity of most radiopharmaceuticals, resulting in typical injections of microgram to nanogram quantities of material. Generally, milligram levels of materials are required for pharmacologic effects. Safety concerns also require that all radiopharmaceuticals be sterile and pyrogen-free prior to injection. Organisms can be removed by filtration through a sterile filter with a pore size of 0.22 μm or better. Use of pharmaceutical-grade chemicals, sterile water, and sterilized equipment can minimize the risk of pyrogens. Finally, the pH of the injected solution should be appropriate.

2. Labeling Strategies

There are two distinct strategies for labeling of *small molecules* with radionuclides. In *direct substitution,* a stable atom in the molecule is replaced with a radioactive atom of the same element. The compound has exactly the same biologic properties as the unlabeled compound. This allows many compounds of biologic relevance to be labeled and studied in vivo using radioactive isotopes of elements that are widely found in nature (e.g., hydrogen, carbon, nitrogen, and oxygen). An

example is replacing a ^{12}C atom in glucose with a ^{11}C atom to create ^{11}C-glucose. This radiopharmaceutical will undergo the same distribution and metabolism in the body as unlabeled glucose.

The second approach is to *create analogs*. This involves modifying the original compound. Analogs allow the use of radioactive isotopes of elements that are not so widely found in nature but that otherwise have beneficial imaging properties (e.g., fluorine and iodine). Analogs also allow chemists to beneficially change the biologic properties of the molecule by changing the rates of uptake, clearance, or metabolism. For example, replacing the hydroxyl (OH) group on the second carbon in glucose with ^{18}F results in FDG, an analog of glucose. This has the advantage of putting a longer-lived radioactive tag onto glucose compared with ^{11}C; and even more important, FDG undergoes only the first step in the metabolic pathway for glucose, thus making data analysis much more straightforward (see Chapter 21, Section E.5). FDG is now a widely used radiopharmaceutical for measuring metabolic rates for glucose. The downside to analogs are that they behave differently from the native compound, and these differences need to be carefully understood if the analog is used to provide a measure of the biologic function related to the native molecule.

An alternative approach to labeling materials that is possible only for *larger biomolecules* is to keep the radioactive label away from the biologically active site of the molecule. Thus large molecules (e.g., antibodies, peptides, and proteins) may be labeled with many different radionuclides, with minimal effect on their biologic properties.

3. Technetium-99m-Labeled Radiopharmaceuticals

The ^{99}Mo-^{99m}Tc generator produces technetium in the form of $^{99m}TcO_4^-$. A number of "cold kits" are available that allow different ^{99m}Tc complexes to be produced by simply mixing the $^{99m}TcO_4^-$ and the contents of the cold kit together. The cold kit generally contains a reducing agent, usually stannous chloride, which reduces the ^{99m}Tc to lower oxidation states, allowing it to bind to a complexing agent (also known as the *ligand*) to form the radiopharmaceutical. Using these kits, a range of ^{99m}Tc-labeled radiopharmaceuticals that are targeted to different organ systems and different biologic processes can be prepared quickly and conveniently in the hospital setting. Table 5-5 lists a few examples of ^{99m}Tc radiopharmaceuticals that are prepared from kits.

4. Radiopharmaceuticals Labeled with Positron Emitters

Positron emitters such as ^{11}C, ^{13}N, and ^{15}O can be substituted for stable atoms of the same elements in compounds of biologic importance. This results in radiolabeled compounds with exactly the same biochemical properties as the original compound. Alternatively, ^{18}F, another positron-emitting radionuclide, can be substituted for hydrogen to produce labeled analogs. Several hundreds of compounds have been synthesized with ^{11}C, ^{13}N, ^{15}O, or ^{18}F labels for imaging with positron emission tomography. The short half-life of ^{11}C, ^{13}N, and ^{15}O requires in-house radionuclide production in a biomedical cyclotron and rapid synthesis techniques to incorporate them into radiopharmaceuticals. On the other hand, the

TABLE 5-5
SOME ^{99m}Tc-LABELED RADIOPHARMACEUTICALS PREPARED FROM KITS

Compound	Abbreviation Stands for	Applications
^{99m}Tc-MDP	Methylene diphosphonate	Bone scans
^{99m}Tc-DMSA	2,3-Dimercaptosuccinic acid	Renal imaging
^{99m}Tc-DTPA	Diethylenetriaminepenta acetic acid	Renal function
^{99m}Tc-sestamibi	2-Methoxy-2-methylpropyl isonitrile	Myocardial perfusion, breast cancer
^{99m}Tc-HMPAO	Hexamethylpropylene-amine oxime	Cerebral perfusion
^{99m}Tc-HIDA	*N*-(2,6-dimethylphenol-carbamoylmethyl)-iminodiacetic acid	Hepatic function
^{99m}Tc-ECD	N,N'-1,2-ethylenediyl-*bis*-L-cysteine diethylester	Cerebral perfusion

relatively longer half-life of ^{18}F permits its distribution within a radius of a few hundred miles from the site of production, thus obviating the need of a cyclotron in the nuclear medicine imaging facility.

The most widely used positron-labeled radiopharmaceutical is the glucose analog FDG. Glucose is used by cells to produce adenosine triphosphate, the energy "currency" of the body, and accumulation of FDG in cells is proportional to the metabolic rate for glucose. Because the energy demands of cells are altered in many disease states, FDG has been shown to be a sensitive marker for a range of clinically important conditions, including neurodegenerative diseases, epilepsy, coronary artery disease, and most cancers and their metastases.

5. Radiopharmaceuticals for Therapy Applications

Other radiopharmaceuticals are designed for therapy applications. These are normally labeled with a β^- emitter, and the radiopharmaceutical is targeted against abnormal cells, commonly cancer cells. The β^- emitter deposits radiation only within a small radius (typically 0.1 to 1 mm) and selectively kills cells in this region through radiation damage. If the radiopharmaceutical is more readily accumulated by cancer cells than normal cells, a therapeutic effect can be obtained.

6. Radiopharmaceuticals in Clinical Nuclear Medicine

Many different radiopharmaceuticals have been approved for use in clinical nuclear medicine studies. Each of these radiopharmaceuticals is targeted to measuring a specific biologic process, and therefore what is measured depends directly on which radiopharmaceutical is administered to the patient. Some of the more common radiopharmaceuticals are listed in Table 1-1 and Table 5-5.

Most radiopharmaceuticals are used in conjunction with imaging systems that can determine the location of the radiopharmaceutical within the body. Often, the rate of change of radiopharmaceutical localization within a specific tissue (the rate of uptake or clearance) is also important and is measured by acquiring multiple images as a function of time. The imaging systems used in nuclear medicine studies are discussed in Chapters 13, 14, and 17-19.

REFERENCES

1. Browne E, Firestone RB: *Table of Radioactive Isotopes*, New York, 1986, John Wiley.
2. Wang Y: *Handbook of Radioactive Nuclides*, Cleveland, 1969, Chemical Rubber Company.
3. Schwartz SW, Gaeble GG, Welch MJ: Accelerators and positron emission tomography radiopharmaceuticals. In Sandler MP, Coleman RE, Patton JA, et al, editors: *Diagnostic Nuclear Medicine*, ed 4, Philadelphia, 2003, Lippincott, Williams & Wilkins, pp 117-132.
4. Helus F, Colombetti LG: *Radionuclides Production*, Vols I, II, Boca Raton, 1983, CRC Press.
5. Holland ME, Deutsch E, Heineman WR: Studies on commercially available $^{99}Mo/^{99m}Tc$ radionuclide generators—II. Operating characteristics and behavior of $^{99}Mo/^{99m}Tc$ generators. *Appl Radiat Isot* 37:173-180, 1986.
6. Boyd RE: Molybdenum-99: Technetium-99m generator. *Radiochim Acta* 30:123-145, 1982.
7. *Medical Isotope Production Without Highly Enriched Uranium*. Washington, D.C., 2009, National Academies Press.
8. Murray RL: *Nuclear Energy*, ed 5, Boston, 2001, Butterworth Heinemann.

BIBLIOGRAPHY

Further information on radionuclide production and radiopharmaceutical preparation can be found in the following:

Knapp FF, Mirzadeh S: The continuing role of radionuclide generator systems for nuclear medicine. *Eur J Nucl Med* 21:1151-1165, 1994.

Lieser KH: *Nuclear and Radiochemistry*, ed 2, Weinheim, Germany, 2001, Wiley VCH.

Sampson CB: *Textbook of Radiopharmacy: Theory and Practice*, ed 2, New York, 1994, Gordon & Breach.

Tewson TJ, Krohn KA: PET radiopharmaceuticals: State-of-the-art and future prospects. *Semin Nucl Med* 28:221-234, 1998.

Welch MJ, Redvanly CS: *Handbook of Radiopharmaceuticals: Radiochemistry and Applications.* Chichester, England, 2003, John Wiley & Sons.