Medical Science Series

THE PHYSICS OF MEDICAL IMAGING

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6.4 RADIONUCLIDES FOR IMAGING

One of the primary advantages associated with the use of radionuclides in medicine is the large signal (in this case the emitted radiation) obtained from the relatively small mass of radionuclide employed for a given study. Nuclear medicine takes advantage of this physical characteristic by using various radioisotope-tagged compounds (radiopharmaceuticals) in order to 'trace' various functions of the body (McAfee and Thakur 1977). The minute mass of radiolabelled material allows for non-invasive observation without disturbance of the system under study through pharmacological or toxicological effect. For most nuclear medicine studies, the mass of tracer used is in the range of nanograms (see table 6.4), and no other physical technique could be employed to measure mass at these levels. Therefore, the sensitive measurement of biochemical and physiological processes through the use of radioactivity and its detection comprise the fundamental basis of nuclear medicine and is the key to its future growth.

Table 6.4 Approximate mass (g) of 37 GBq (1 Ci) of radionuclide for a given half-life and atomic weight.

$T_{1/2}$	Atomic weight of atom (amu)		
	18	99	201
15 s	2.4×10^{-11}	1.3×10^{-10}	2.7×10^{-10}
15 min	1.4×10^{-9}	7.7×10^{-9}	1.6×10^{-8}
6 h	3.5×10^{-8}	1.9×10^{-7}	3.8×10^{-7}
8 d	1.1×10^{-6}	6.3×10^{-6}	1.2×10^{-5}
15 a	7.7×10^{-4}	4.2×10^{-3}	8.3×10^{-3}

6.4.1 Radioactive decay

The radioactivity Q of a number (N) of nuclei is given by

$$Q = -\lambda N = \mathrm{d}N/\mathrm{d}t \tag{6.13}$$

where λ is defined as the decay constant for the radioisotope. We can see that the rate of decay of nuclei depends only upon λ and the number of nuclei, N. The solution to equation (6.13) is

$$N = N_0 \exp(-\lambda t) \tag{6.14}$$

where N_0 is the number of nuclei at some reference time $t = 0$. If $T_{1/2}$ is the time for half the nuclei to decay, the so-called 'half-life', then

$$T_{1/2} = (\ln 2)/\lambda. \tag{6.15}$$

An alternative form of equation (6.14) is

$$N = N_0(\tfrac{1}{2})^m \tag{6.16}$$

where m is the number of half-lives since the reference time $t = 0$.

Using these simple equations, it is possible to calculate the radioactivity of any mass of nuclei at any time subsequent to a measurement at a reference-zero time.

6.4.2 The production of radionuclides

The fundamental property of all radioactive elements is the imbalance of the proton-to-neutron ratio of the nucleus. A proper balance of protons and neutrons is essential for maintaining a stable atomic nucleus. The balance must be maintained to overcome electrostatic repulsion of the charged protons, and figure 6.48 shows how the neutron-to-proton (n/p) ratio changes with increasing mass. There are four ways by which radionuclides are produced:

(*a*) neutron capture (also known as neutron activation);
(*b*) nuclear fission;
(*c*) charged-particle bombardment; and
(*d*) radionuclide generator.

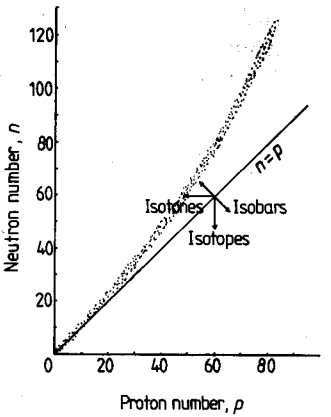

Figure 6.48 Graph of neutron number n versus proton number p, showing the increase in the n/p ratio with atomic number.

Each method affords useful isotopes for nuclear medicine imaging. A description of the methods and examples of some of the useful radioisotopes produced will now be presented.

Neutron capture is the absorption of a neutron by an atomic nucleus, and the production of a new radionuclide via reactions such as

$$n + {}^{98}Mo \rightarrow {}^{99}Mo + \gamma \tag{6.17}$$

$$n + {}^{32}S \rightarrow {}^{32}P + p. \tag{6.18}$$

To produce radioactive elements through neutron capture, neutrons must have a mean energy of 0.03–100 eV. These 'thermal' neutrons are best-suited for interaction with and absorption into the atomic nucleus. The most efficient means of producing radioisotopes by this method is through the use of a nuclear reactor. To produce a radioactive species, a sample of a target element is placed in a field of thermal neutrons. The reaction yield depends on the flux density of incident particles, ϕ ($cm^{-2}s^{-1}$), the number of accessible target nuclei (n_t) and the likelihood or cross section of the reaction, σ (barn). The yield (N_y) is given by

$$N_y = \frac{n_t \phi \sigma}{\lambda}[1 - \exp(-\lambda t)]. \tag{6.19}$$

The radionuclide produced via the (n,γ) reaction is an isotope of the target material, i.e. the two nuclei have the same number of protons. This means that radionuclides produced via the (n,γ) reaction are not carrier-free (compare with nuclear fission), and thus the ratio of radioactive atoms to stable atoms and the specific activity are relatively low. Separation of the radionuclide from other target radionuclides is possible by physical and chemical techniques. Useful tracers produced by neutron absorption are shown in table 6.5.

Nuclear fission is the process whereby heavy nuclei (^{235}U, ^{239}Pu, ^{237}U,

^{232}Th) irradiated with thermal neutrons are rendered unstable due to absorption of these neutrons. Consequently, these unstable nuclei undergo 'fission', the breaking up of the heavy nuclei into two lighter nuclei of approximately similar atomic weight, for example

$$^{235}_{92}\text{U} + {}^{1}_{0}\text{n} \rightarrow {}^{236}_{92}\text{U} \rightarrow {}^{99}_{42}\text{Mo} + {}^{133}_{50}\text{Sn} + 4{}^{1}_{0}\text{n}. \qquad (6.20)$$

As seen from equation (6.20), this reaction produces four more neutrons, which may be absorbed by other heavy nuclei, and the fission process can continue until the nuclear fuel is exhausted. Interaction such as that in equation (6.20) must, of course, conserve Z and A.

Table 6.5 Radionuclides produced by neutron absorption.

Isotope	Gamma-ray energy (keV)	Half-life	Absorption cross section (barn)
^{51}Cr	320	27.7 d	17[a]
^{59}Fe	1099	44.5 d	1.1[a]
^{99}Mo	740	66.02 h	0.13
^{131}I[b]	364	8.05 d	0.2

[a] From BRH (1970).
[b] ^{130}Te(n,γ)^{131}Te $\rightarrow$ ^{131}I.

Nuclides produced by fission of heavy nuclei must undergo extensive purification in order to harvest one particular radionuclide from the mixture of fission products. The fission process affords high specific activity due to the absence of carrier material (non-radioactive isotope of the same element). However, fission products are usually rich in neutrons and therefore decay principally via β^- emission, a physical characteristic that is undesirable for medical imaging, but of interest in therapy. Useful nuclides produced by nuclear fission are shown in table 6.6.

Table 6.6 Radionuclides produced by nuclear fission.

Isotope	Gamma-ray energy (keV)	Half-life	Fission yield[a] (%)
^{99}Mo	740	66.02 h	6.1
^{131}I	364	8.05 d	2.9
^{133}Xe	81	5.27 d	6.5
^{137}Cs	662	30 a	5.9

[a] From BRH (1970).

Charged-particle bombardment is the process of production of radionuclides through the interaction of charged particles ($H^{\pm}$, D^{+}, $^{3}He^{2+}$, $^{4}He^{2+}$) with the nuclei of stable atoms. The particles must have enough kinetic energy to overcome the electrostatic repulsion of the positively charged nucleus. Two basic types of accelerator are used for this purpose, the linear accelerator and the cyclotron. In both systems, charged particles are accelerated over a finite distance by the application of alternating electromagnetic potentials (figure 6.49). In both types of machine, particles can usually be accelerated to various energies. Examples of typical reactions in a target are

$$p + {}^{68}Zn \rightarrow {}^{67}Ga + 2n \tag{6.21}$$

$$\alpha + {}^{16}O \rightarrow {}^{18}F + p + n. \tag{6.22}$$

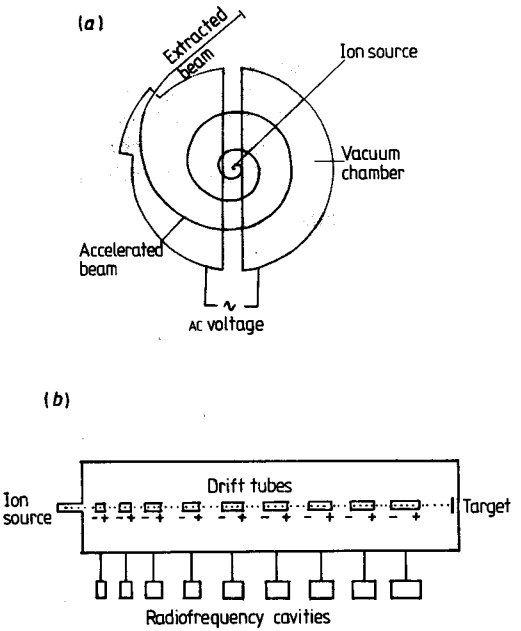

Figure 6.49 Schematic diagrams of (*a*) a cyclotron and (*b*) a linear accelerator for radionuclide production.

For the production of medically useful radionuclides, particle energies per nucleon in the range 1–100 MeV are commonly used. One major advantage of producing isotopes through charged-particle bombardment is that the desired isotope is almost always of different atomic number to the target material. This theoretically allows for the production of radionuclides with very high specific activity and minimal radionuclide

impurity. However, the actual activity and purity obtained is related to the isotopic and nuclidic purity of the target material, the cross section of the desired reaction and the cross section of any secondary reaction.

Charged-particle reactions yield radionuclides that are predominantly neutron-deficient and therefore decay by β^+ emission or electron capture. The latter radioisotopes are particularly useful for clinical imaging due to the lack of particulate emission. Examples of accelerator-produced radionuclides routinely used in nuclear medicine are shown in table 6.7.

Table 6.7 Radionuclides produced by charged-particle bombardment.

Isotope	Principal gamma-ray energy (keV)	Half-life	Reaction
^{11}C	511 (β^+)	20.4 min	$^{14}N(p,\alpha)^{11}C$
^{13}N	511 (β^+)	9.96 min	$^{13}C(p,n)^{13}N$
^{15}O	511 (β^+)	2.07 min	$^{15}N(p,n)^{15}O$
^{18}F	511 (β^+)	109.7 min	$^{18}O(p,n)^{18}F$
^{67}Ga	93	78.3 h	$^{68}Zn(p,2n)^{67}Ga$
	184		
	300		
^{111}In	171	67.9 h	$^{112}Cd(p,2n)^{111}In$
	245		
^{123}I	159	13 h	$^{124}Te(p,2n)^{123}I$
			$^{127}I(p,5n)^{123}Xe \rightarrow {}^{123}I$
^{201}Tl	68–80.3	73 h	$^{203}Tl(p,3n)^{201}Pb \rightarrow {}^{201}Tl$

Radioactive decay can lead to the generation of either a stable or a radioactive nuclide. In either case, the new nuclide may have the same or different atomic number depending on the type of decay (see next section). Radioactive decay leading to the production of a radioactive daughter with a different Z allows for the possibility of simple chemical separation of the parent–daughter combination. If the daughter radionuclide has good physical characteristics compatible with medical imaging and the parent has a sufficiently long half-life to allow for production, processing and shipment, then remote parent–daughter separation means a potentially convenient source of a medically useful short-lived radionuclide. This type of radionuclide production system is known as a *radionuclide generator*.

A radionuclide generator is a means of having 'on tap' a short-lived radionuclide. It is technically achieved by the chemical separation of the daughter radionuclide from the parent. This can be accomplished through the use of chromatographic techniques, distillation or phase partitioning. However, chromatographic techniques have been the most

widely explored and are the current state-of-the-art technology (Yano 1975) for the majority of generator systems in use today (figure 6.50).

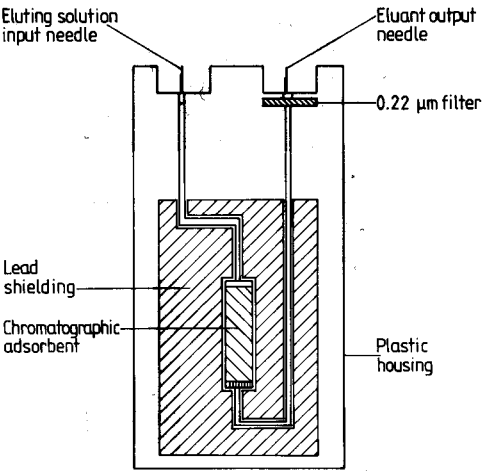

Figure 6.50 Schematic of a radioisotope generator.

The equations governing generator systems stem from the formula

$$A_2 = \frac{\lambda_2}{\lambda_2 - \lambda_1} A_1^0[\exp(-\lambda_1 t) - \exp(-\lambda_2 t)] \tag{6.23}$$

where A_1^0 is the parent activity at time $t = 0$, t is the time since the last elution of the generator, A_2 is the activity of the daughter product ($A_2^0 = 0$), and λ_1 and λ_2 are the decay constants of parent and daughter radioisotopes, respectively.

For the special case of secular equilibrium, defined by $\lambda_2 \gg \lambda_1$, we have

$$A_2 = A_1^0[\exp(-\lambda_1 t) - \exp(-\lambda_2 t)]. \tag{6.24}$$

If t is much less than the half-life of the parent, $\ln(2)/\lambda_1$, and greater than approximately seven times the daughter half-life, $\ln(2)/\lambda_2$, then

$$A_2 \simeq A_1^0. \tag{6.25}$$

This is the equilibrium condition. The growth of the daughter here is given by

$$A_2 = A_1^0[1 - \exp(-\lambda_2 t)]. \tag{6.26}$$

For transient equilibrium, defined by $\lambda_2 > \lambda_1$ but λ_2 not *very* much greater than λ_1, we have

$$A_2 = \lambda_2 A_1^0/(\lambda_2 - \lambda_1). \tag{6.27}$$

Figure 6.51 shows the growth of $^{99}Tc^m$ activity in a $^{99}Mo \rightarrow {}^{99}Tc^m$ generator.

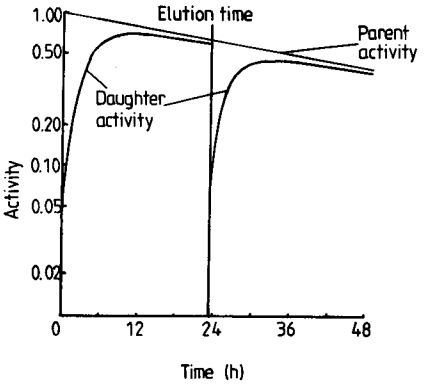

Figure 6.51 The build-up of activity of the daughter product with time for a typical ($^{99}Mo/^{99}Tc^{m}$) radioisotope generator.

The most widely used generator-produced radionuclide in nuclear medicine is $^{99}Tc^{m}$. The parent, ^{99}Mo, has a half-life of about 66 h, can be produced through neutron activation or fission, can be chemically adsorbed onto an Al_2O_3 (alumina) column and decays to $^{99}Tc^{m}$ (85%) and ^{99}Tc (15%). $^{99}Tc^{m}$ has a half-life of 6.02 h, decays to ^{99}Tc by isomeric transition and emits a 140 keV γ-ray (98%) with no associated particulate radiations:

$$^{99}Mo \xrightarrow[\beta^-]{} {}^{99}Tc^{m} \xrightarrow[IT]{} {}^{99}Tc + \gamma. \tag{6.28}$$

In the early days of their development (see Chapter 1), technetium generators were sometimes referred to as 'radioactive cows'. The $^{99}Tc^{m}$ is 'milked' from the chromatographic column of alumina by passing a solution of isotonic saline through the column (0.9% NaCl). This saline solution and the solid phase of Al_2O_3 allow for efficient separation of $^{99}Tc^{m}$ from the ^{99}Mo with only minute amounts of ^{99}Mo breakthrough (less than 0.1%). The eluted $^{99}Tc^{m}$ can be chemically manipulated so that it binds to a variety of compounds, which will then determine its fate *in vivo* (see §6.9). Other generator systems exist producing radionuclides useful for gamma-camera imaging as well as for PET and examples of these are given in table 6.8.

6.4.3 Types of radioactive decay

All radionuclides used in nuclear medicine are produced via one of the four ways described above. Each of these radionuclides has a unique process by which it decays. The *decay scheme* describes the type of decay, the energy associated with it and the probability for each type of decay. These decay schemes can be very complex since many of the radionuclides decay via multiple nuclear processes (figure 6.52).

Table 6.8 Generator-produced radionuclides.

Parent P	Parent half-life	Mode of decay P→D	Daughter D	Mode of decay of D	Daughter half-life	Gamma-ray energy from daughter (keV)
^{99}Mo	2.7 d	β^-	^{99}Tc^m	IT	6 h	140
^{82}Sr	25 d	EC	^{82}Rb	EC	1.3 min	777
				β^+		511
^{68}Ge	280 d	EC	^{68}Ga	EC	68 min	511
				β^+		
^{52}Fe	8.2 h	EC	^{52}Mn^m	EC	21 min	511
		β^+		β^+		
				IT		
^{81}Rb	4.7 h	EC	^{81}Kr^m	IT	13 s	190
^{62}Zn	9.1 h	EC	^{62}Cu	EC	9.8 min	511
		β^+		β^+		
^{178}W	21.5 d	EC	^{178}Ta	EC	9.5 min	93

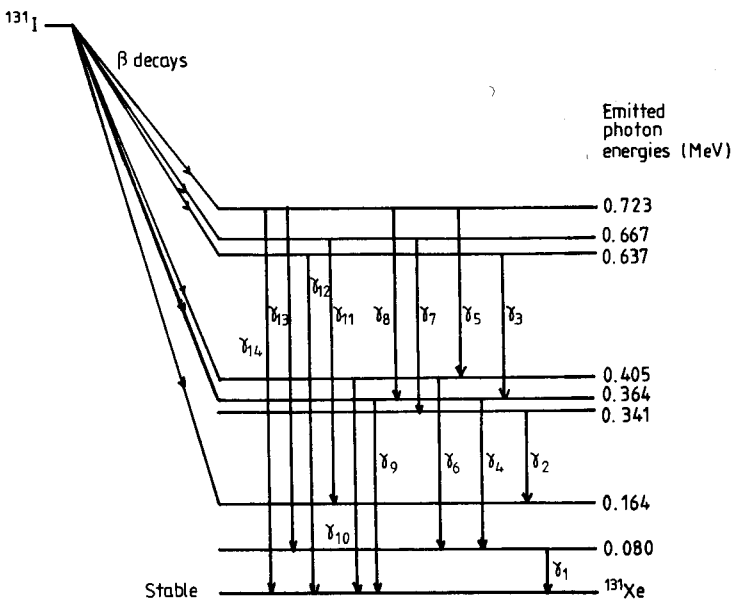

Figure 6.52 The nuclear decay process for ^{131}I.

Alpha decay is the process of spontaneous emission of an α-particle (a helium nucleus) in the decay of heavy radioisotopes, with a discrete energy in the range 4–8 MeV. If α decay leaves the nucleus in an

excited state, the de-excitation will be via the emission of γ-radiation. Most of the energy released in the transition is distributed between a daughter nucleus (as recoil energy) and the α-particle (as kinetic energy). In the α-decay process, the parent nucleus loses four units of mass and two units of charge. As an example we show

$$^{226}_{88}\mathrm{Ra} \rightarrow {}^{222}_{86}\mathrm{Rn} + \alpha. \tag{6.29}$$

Although α-emitting nuclides have no use in medical imaging (since the α-particles travel virtually no distance in tissue), there has been a renewed interest in their use for targeted (i.e. highly localised) therapy.

As discussed previously, many radionuclides are unstable due to the neutron/proton imbalance within the nucleus. The decay of neutron-rich radionuclides involves the ejection of a β^--particle (e^-), resulting in the conversion of a neutron into a proton. Decay via β^- *emission* results in the atomic number of the atom changing but the atomic weight remaining the same. The energy of the emitted β^--particles is not discrete but a continuum (i.e. varies from zero to a maximum, E_m) and, since the total energy lost by the nucleus during disintegration must be discrete, an additional process must be responsible. Energy conservation of β decay is maintained by the emission of a third particle—the neutrino (ν). The neutrino has no measurable mass nor charge, and interacts weakly with matter. An example of β^- decay is

$$^{99}\mathrm{Mo} \rightarrow {}^{99}\mathrm{Tc}^{m} + e^- + \nu. \tag{6.30}$$

Beta decay may be accompanied by γ-ray emission if the daughter nuclide is produced in an excited state. After β^- decay, the atomic number of the daughter nuclide is one more than the parent nuclide, but the atomic mass remains the same.

Nuclei that are rich in protons or are neutron-deficient may decay by *positron emission* from the nucleus. This decay is also accompanied by the emission of an uncharged particle, the antineutrino ($\bar{\nu}$). After positron decay, the daughter nuclide has an atomic number that is one less than that of the parent, but again the atomic weight is the same. The range of a positron (e^+) is short (of the order of 1 mm in tissue) and, when the particle comes to rest, it combines with an atomic electron from a nearby atom, and is annihilated. Annihilation (the transformation of these two particles into pure energy) gives rise to two photons both of energy 511 keV emitted approximately antiparallel to each other. These photons are referred to as annihilation radiation. Positron emission only takes place when the energy difference between the parent and daughter nuclides is larger than 1.02 MeV. An example of positron decay is

$$^{68}\mathrm{Ga} \rightarrow {}^{68}\mathrm{Zn} + e^+ + \bar{\nu}. \tag{6.31}$$

An alternative to positron emission for nuclides with a proton-rich nucleus is *electron capture*. Electron capture involves the absorption within the nucleus of an atomic electron, transforming a proton into a

neutron. For this process to occur, the energy difference between the parent and the daughter nuclides can be small, unlike positron emission. Usually the K-shell electrons are captured because of their closeness to the nucleus. The vacancy created in the inner electron orbitals is filled by electrons from the outer orbitals. The difference in energy between these electron shells appears as an x-ray that is characteristic of the daughter radionuclide. The probability of electron capture increases with increasing atomic number because electron shells in these nuclei are closer to the nucleus. An example of electron capture is

$$^{123}\mathrm{I} \rightarrow {}^{123}\mathrm{Te} + \gamma. \tag{6.32}$$

A nucleus produced in a radioactive decay can remain in an excited state for some time. Such states are referred to as *isomeric states*, and decay to the ground state can take from fractions of a second to many years. A transition from the isomeric or excited state to the ground state is accompanied by γ *emission*. When the isomeric state is long-lived, this state is often referred to as a metastable state. $^{99}\mathrm{Tc}^{\mathrm{m}}$ is the most common example of a metastable isotope encountered in nuclear medicine (see equation (6.28)).

Internal conversion is the process that can occur during γ-ray emission when a photon emitted from a nucleus may knock out one of the atomic electrons from the atom. This particularly affects K-shell electrons, as they are the nearest to the nucleus. The ejected electron is referred to as the *conversion electron* and will have a kinetic energy equal to the energy of the γ-ray minus the electron binding energy. The probability of internal conversion is highest for low-energy photon emission. Again, vacancies in the inner orbitals are filled by electrons from the outer shells, leading to the emission of *characteristic x-rays*. Furthermore, characteristic x-rays produced during internal conversion may themselves knock out other outer orbital electrons provided the x-rays have an energy greater than the binding energy of the electron with which they interact. This emitted electron is then referred to as an *Auger electron*. Again, vacancies in the electron shells due to Auger emission are filled by other electrons in outer orbitals leading to further x-ray emission.

6.4.4 Choice of radioisotope for imaging

The physical characteristics of radionuclides that are desirable for nuclear medicine imaging include:

(*a*) a suitable physical half-life;
(*b*) decay via photon emission;
(*c*) associated photon energy high enough to penetrate the body tissue with minimal tissue attenuation; but
(*d*) low enough for minimal thickness of collimator septa; and
(*e*) absence of particulate emission.

The effective half-life T_{E} of a radiopharmaceutical is a combination of

the physical half-life T_P and the biological half-life T_B, i.e.

$$\frac{1}{T_E} = \frac{1}{T_B} + \frac{1}{T_P}. \tag{6.33}$$

Close matching of the effective half-life with the duration of the study is an important dosimetric as well as practical consideration in terms of availability and radiopharmaceutical synthesis.

The photon energy is critical, for various reasons. The photon must be able to escape from the body efficiently and it is desirable that the photopeak should be easily separated from any scattered radiation. These two characteristics favour high-energy photons. However, at very high energies, detection efficiency using a conventional gamma camera is poor (see figure 6.5) and the increased septal thickness required for collimators decreases the sensitivity further. In addition, high-energy photons are difficult to shield and present practical problems for staff handling the isotope.

The radionuclide that fulfils most of the above criteria is technetium-99m ($^{99}Tc^m$), which is used in more than 90 % of all nuclear medicine studies. It has a physical half-life of 6.02 h, is produced via decay of a long-lived ($T_{1/2}$ = 66 h) parent ^{99}Mo, and decays via isomeric transition to ^{99}Tc emitting a 140 keV γ-ray. The short half-life and absence of $\beta^{\pm}$ emission results in a low radiation dose to the patient. The 140 keV γ emission allows for 50% penetration of tissue at a thickness of 4.6 cm but is easily collimated by lead. Most importantly, the radioisotope can be produced from a generator lasting the best part of a week, supplying imaging agents 'on tap'.

Other radioisotopes in common use in nuclear medicine include ^{123}I, ^{111}In, ^{67}Ga, ^{201}Tl and $^{81}Kr^m$. ^{123}I has proved a valuable replacement for ^{131}I as it decays via electron capture emitting a γ-ray of energy 159 keV and has a 13 h half-life. It is easily bonded to proteins and pharmaceuticals that can be iodinated. However, like most of the other radioisotopes in this list, it is cyclotron-produced (table 6.7) and presently still very expensive in a form free of other iodine isotopes.

The radionuclides ^{111}In and ^{67}Ga are very similar chemically and both decay via electron capture (table 6.9). Most recently, there has been an increased interest in their use as antibody labels via bifunctional chelates. ^{111}In is the superior imaging isotope, emitting acceptable photon energies for gamma-camera studies, but again it is expensive as it is produced by charged-particle bombardment (table 6.7). ^{67}Ga has long been used as a tumour localising agent in the form of gallium citrate and has also proved useful in the same form in the detection of abcesses. ^{201}Tl is utilised by the cardiac muscle in a similar fashion to potassium and is in widespread use for imaging myocardial perfusion. However, the photon emissions used in myocardial imaging are the 80 keV x-rays, which are close in energy to lead x-rays produced by the collimator, and this, together with the long half-life (73 h), makes the isotope a poor imaging agent. Hence there is continued search for a $^{99}Tc^m$-labelled myocardial perfusion agent.

Table 6.9 Main gamma emissions of ^{67}Ga and ^{111}In.

Radionuclide	Gamma-ray emission	Gamma-ray energy (keV)	Mean number per disintegration
^{67}Ga	γ_2	93	0.38
	γ_3	185	0.24
	γ_5	300	0.16
	γ_6	394	0.043
^{111}In	γ_1	171	0.90
	γ_2	245	0.94

Radioisotopes emitting positrons (table 6.7) have been used extensively for physiological research, in the main, rather than clinical nuclear medicine because of the need for an on-site or nearby cyclotron to produce them in view of their relatively short half-lives. The radionuclides ^{15}O, ^{13}N, ^{11}C and ^{18}F have many applications in the field of functional imaging but have had little impact, as yet, in routine nuclear medicine because of lack of availability. ^{68}Ga and ^{82}Rb, however, are two generator-produced positron-emitting nuclides that could provide invaluable radiopharmaceuticals for clinical PET. In particular, ^{68}Ga can be used to label many agents in a manner similar to $^{99}Tc^m$, and ^{82}Rb is a greatly superior myocardial perfusion agent to ^{201}Tl. These radioisotopes, coupled with the development of low-cost PET cameras (§6.3.7), may bring the much-needed advantages of high sensitivity and spatial resolution to clinical nuclear medicine.