# Production of Radionuclides

# 5

> *Dr. Livingston has asked me to advise you that he has obtained 1,100,000 volt protons. He also suggested that I add "Whoopie"!*
>
> Telegram to Lawrence, 3 August 1931

## 5.1 Nuclear Transformation

When two nuclei come close together, a *nuclear reaction* can occur that results in a *nuclear transformation*, which is the conversion of one element to another. In 1919, Rutherford observed the first nuclear transformation following bombardment of natural nitrogen atoms ($^{14}N$) with α particles (He nuclei) from a radium–carbon source (Segrè 1980). More specifically, he observed that a nitrogen nucleus was converted into an isotope of oxygen, $^{17}O$ with the emission of a proton. The process that Rutherford discovered was the disintegration of the stable nucleus and the formation of a stable oxygen isotope. In 1925, using the cloud chamber, Blackett confirmed Rutherford's observation.

$$ {}^{14}_{7}N + {}^{4}_{2}He \rightarrow {}^{17}_{8}O + {}^{1}_{1}H \qquad (5.1) $$

In 1932, when Chadwick bombarded a stable beryllium atom with α particles, the element beryllium was converted into a stable carbon isotope with the emission of a neutron (Segrè 1980).

$$ {}^{9}_{4}Be + {}^{4}_{2}He \rightarrow {}^{12}_{6}C + {}^{1}_{0}n \qquad (5.2) $$

In the two nuclear reactions described above, the nuclear transformation involved conversion of a stable isotope of one element into a stable isotope of another element. In 1934, Irene Curie and her husband Frederic Joliot were the first to produce an unstable radioisotope that decayed by positron emission and the first to discover the artificial production of radioisotopes (Joliot and Curie 1934).

$$ {}^{27}_{13}Al + {}^{4}_{2}He \rightarrow {}^{30}_{15}P \rightarrow {}^{1}_{0}n \qquad (5.3) $$

$$ {}^{30}_{15}P \rightarrow {}^{30}_{14}Si + \beta^{+} \qquad (5.4) $$

As shown above, the stable Al atom absorbs the helium nucleus and is converted into an unstable $^{30}P$ radionuclide ($T_{½}$ = 3 min), which in turn is converted into a stable $^{30}Si$ atom following positron emission. Soon after the discovery of artificial radioactivity, physicists realized that charged protons with higher energies would be better projectiles for nuclear transformation reactions. During 1930s, charged-particle *accelerators* were developed to generate very high energy subatomic particles, such as protons, deuterons, and α particles.

For almost two decades following Rutherford's pioneering work, α particles from natural radioisotopes such as $^{238}U$ and $^{234}Th$ were used as projectiles to induce nuclear reactions. Following the discovery of neutrons by Chadwick in 1932, Fermi realized that a neutron beam could be used as a projectile to induce a nuclear reaction, because neutrons are neutral and not repelled by the stable target nucleus. He also realized that neutron rich atoms decay by beta emission and the daughter nuclide with an extra proton is normally an element with an atomic number, Z + 1. In 1934, Fermi bombarded $^{238}U$ with neutrons and reported the discovery

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of element 93 (transuranic element not found in nature) (Segrè 1980), however, this turned out to be a false claim. In 1937, a colleague of Fermi, Emilio Segre bombarded the stable $^{98}$Mo with neutrons (a reaction known as *neutron activation*) and produced the element 43, which he called technetium (meaning artificial).

$$^{98}_{42}\text{Mo} + {}^{1}_{0}n \rightarrow {}^{99}_{42}\text{Mo} \xrightarrow{\beta^-} {}^{99m}_{43}\text{Tc} \xrightarrow{IT} {}^{99}_{43}\text{Tc} \qquad (5.5)$$

Otto Han and Lise Meitner continued the experimental strategy to produce transuranics by bombarding uranium with neutrons. However, in 1938 Han discovered that the nucleus of uranium isotope, $^{235}$U undergoes fission, when struck by a neutron (Segrè 1980). More specifically, the $^{235}$U nucleus absorbs the neutron to form a very highly unstable $^{236}$U nucleus, which at once explodes to form two fission fragments (radionuclides) that are neutron rich and decay by beta emission.

Most of the naturally occurring radionuclides are either very long-lived isotopes of heavy elements. With the availability of neutrons and high energy charged particles, hundreds of nuclear reactions have been developed over the years to produce artificial radioisotopes that are either neutron rich or neutron deficient (proton rich). As discussed in the previous chapter, neutron rich radionuclides decay by $\beta^-$ or $\beta^-$, $\gamma$ emission, while neutron deficient radionuclides decay by $\beta^+$ or electron capture. Both these decay modes may also involve emission of gamma photons. In addition, positron annihilation will also lead to the emission of high energy annihilation photons. Some of the early applications of radioisotopes in medicine involved naturally occurring radionuclides. It is the production of artificial radioisotopes, however, that eventually facilitated the development of nuclear medicine and molecular imaging technology.

### *5.1.1 Nuclear Reactions*

In a nuclear reaction, when the atoms of a stable element (target) are bombarded by a subatomic particle (projectile), the nucleus of the stable atom absorbs the subatomic particle. The resultant *compound nucleus* is very unstable and excited. The compound nuclei have life times on the order of approximately $10^{-16}$ s. The compound nucleus may decay in one or more ways, depending on its neutron/proton ratio and excitation energy. It may quickly decompose by emitting some radiation (subatomic particle and/or gamma radiation) to form an unstable product radionuclide.

The general equation for a nuclear reaction can be written as follows:

$$T(P, R)Y \qquad (5.6)$$

where *T* represents the target nuclide, *P* is the projectile, the incident or bombarding particle, *R* represents the radiation (subatomic particle or $\gamma$ photons) emitted by the compound nucleus, and *Y* represents the unstable product radionuclide. The *P* and *R* in parenthesis, written as (*P, R*), represent the nuclear reaction. Reactions such as $(p, n)$, $(p, \alpha)$, $(d, \alpha)$, $(n, p)$, and $(n, \gamma)$ are some of the common nuclear reactions used to produce artificial radioisotopes.

#### 5.1.1.1 Excitation Energy and Q Value

The total amount of *excitation energy* (*U*) of the compound nucleus is given by the following equation (Finn and Schlyer 2002):

$$U = \frac{M_\text{T}}{M_\text{T} + M_\text{P}} T_\text{P} + S_\text{P} \qquad (5.7)$$

where,

$M_\text{T}$ = mass of the target nucleus
$M_\text{P}$ = mass of the incident particle or the projectile
$T_\text{P}$ = kinetic energy of the incident particle
$S_\text{P}$ = binding energy of the incident particle in the compound nucleus

In any nuclear reaction, the total kinetic energy of the products (radiation *R* and product nucleus *Y*) may be either greater or less than the total kinetic energy of the reactants (target *T* and projectile *P*). The *Q value* is the difference between the energy levels of the reactants and products. *Q* value can be calculated on the basis of the relationship $E = mc^2$ and by knowing the rest energies of all the particles involved.

$$Q = (M_\text{T}+M_\text{P}-M_\text{R}-M_\text{Y})(c^2) \qquad (5.8)$$

If *Q* is a positive quantity, energy is given off in a nuclear reaction (*exoergic*). If *Q* is a negative quantity (*endoergic*), kinetic energy (KE) must be supplied to the reacting particles, so that the KE + $Q \geq 0$.

#### 5.1.1.2 Activation Cross-Section

For any specific nuclear reaction, the probability that a bombarding particle will interact with, or activate the target nucleus employs the idea of *cross-section* (σ), which is expressed as an effective area (Beiser 1995). It is assumed that each target nucleus presents a certain area, called its cross section, to the incident particle. Therefore, the greater the cross section, the greater the likelihood of reaction. However, the activation cross section depends on the energy of the bombarding particle and the nature of the specific nuclear reaction. It is the effective "target area" presented by the target nucleus; the SI unit for nuclear cross section is $m^2$. The customary unit, however, is *barn*, where

$$1 \text{ barn} = 1\text{b} = 10^{-24}\,\text{cm}^2 \text{ or } 10^{-28}\,\text{m}^2 = 100\,\text{fm}^2 \tag{5.9}$$

$$1 \text{ millibarn (mb)} = 10^{-3}\,\text{b or } 10^{-27}\,\text{cm}^2 \text{ or } 10^{-31}\,\text{m}^2 \tag{5.10}$$

The cross sections for most nuclear reactions depend on the energy of the incident particle. The nuclear cross sections for thermal neutrons (0.025 eV) with no charge are higher than those for charged particles. The positively charged bombarding particle must have kinetic energy sufficient to overcome the coulomb barrier and the negative *Q* value (kinetic energy of the products is less than that of the reactants). The higher the atomic number (Z) of the target atom, the higher the kinetic energy (*E*) of the charged particle needed for a higher nuclear cross section (Schlyer 2003). A graphical relationship between σ and *E* for a specific nuclear reaction is known as *excitation function*. The excitation function for $^{18}$F production is shown in Fig. 5.1 (Hess et al 2001), as an example.

#### 5.1.1.3 Activity

The amount of radioactivity (dps) produced by irradiation of a target material with a charged particle beam can be described by the following equation (Finn and Schlyer 2002):

$$A(dps) = Inx\sigma(1-e^{-\lambda t}) \tag{5.11}$$

In the above equation,

*I* is the beam current or the number of bombarding particles $cm^{-2}\,s^{-1}$
*n* is the number of target nuclei $cm^{-3}$
*x* is the thickness of a target in cm
σ is the nuclear cross section, expressed in $cm^2$ per nucleus
λ is the decay constant of the product radionuclide and
*t* is the time of irradiation in seconds

##### *Saturation Yield*

The amount of radioactivity (mCi) produced in a nuclear reaction is generally decay corrected to the end of bombardment (EOB). The saturation yield (mCi/μA)

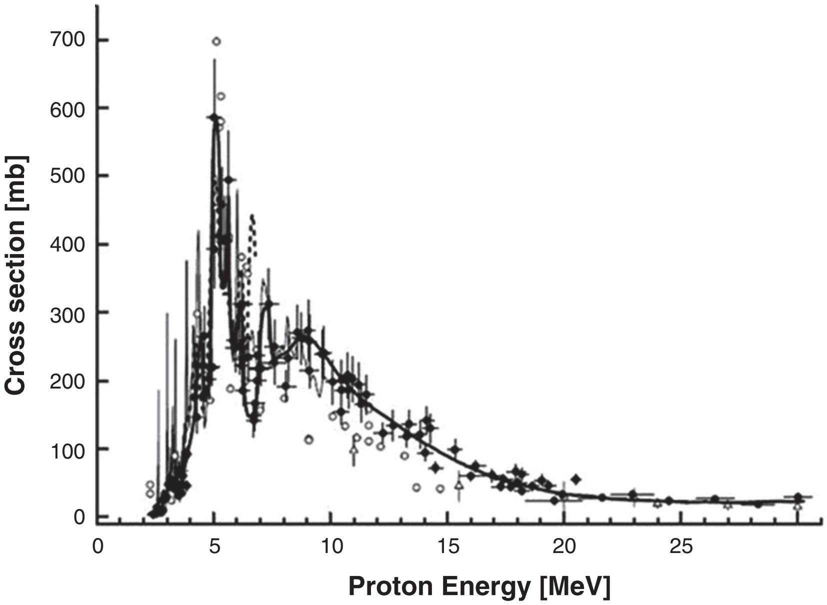

**Fig. 5.1** Excitation function of the $^{18}O(p,n)^{18}F$ reaction. Results from several investigators were plotted with the *solid line* representing the data from the Julich group (Hess et al 2001)

is the theoretical maximum rate of production of a radioisotope for given beam energy conditions and can be calculated using the following equation:

$$\text{Saturation yield (mCi / }\mu A) = \frac{A_0}{I\,(1 - e^{\lambda t})} \qquad (5.12)$$

where, $A_0$ is the activity (mCi) at EOB, $I$ is the beam current, and $1\text{-}e^{-\lambda t}$ is the saturation factor for the radioisotope.

The equation (5.11) is valid only for thin targets where the target beam is not attenuated. With thick targets (in which the energy of bombarding particle is completely absorbed), the particle beam is attenuated and the target nuclei are bombarded with particles of varying energies. Yields with thick targets, therefore, depend on the energy and stopping power (or specific energy loss) in MeV cm$^2$ g$^{-1}$ of the bombarding particle.

### *Specific Activity (SA)*

SA is generally, defined as the amount of radioactivity per unit mass of an element, molecule, or compound, which implies that the mass represents the combined mass of radioactive species and the nonradioactive (stable or cold) counterpart. The unit of SA can be expressed as mCi /mg$^{-1}$, Ci /mmol$^{-1}$, or GBq µmol$^{-1}$. When dealing with chemical or molecular reactions, the standard way to express SA is mCi µmol$^{-1}$. Because 1 mole represents $6.02 \times 10^{23}$ atoms or molecules (Avogadro's number), one µmol consists of $6.02 \times 10^{17}$ atoms or molecules.

For example, when $^{11}$C radionuclide is produced in a cyclotron as [$^{11}$C]CO$_2$ gas, $^{11}$C carbon atoms are always contaminated with natural carbon ($^{12}$C) and it is very difficult to obtain pure [$^{11}$C]CO$_2$ only. Therefore, if the SA of [$^{11}$C]CO$_2$ produced in a cyclotron target is 1.0 Ci µmol$^{-1}$, it implies that 1.0 Ci of radioactivity is present in a total mass of 1 µmole of carbon dioxide gas or a total of $6.02 \times 10^{17}$ molecules ($3.4 \times 10^{14}$ molecules are present as [$^{11}$C]CO$_2$). That means, for every molecule of [$^{11}$C]CO$_2$, there are about 1,700 molecules of cold, nonradioactive CO$_2$. The theoretical maximum SA (Table 4.3) is never really achieved in routine production of positron-emitting radionuclides. However, the SA concept is very important in dealing with PET radiopharmaceuticals, especially in the preparation of radiolabeled receptor binding radiopharmaceuticals.

### *Carrier-Free*

Carrier-free means that the radioactive species is not contaminated with nonradioactive counterpart, known as *carrier*. In the production of radionuclides in a cyclotron, the target element is converted into a different element (with a higher atomic number). As a result, cyclotron produced radionuclides are supposed to be *carrier-free* (CF). In reality, however, it is very difficult to eliminate the contamination of natural carbon, fluorine, or trace metals during the synthesis procedure. A more appropriate concept is *no carrier added* (NCA), because the carrier, a stable, nonradioactive species, is not intentionally added. To facilitate chemical and biochemical reactions, a carrier may be added intentionally during radioisotope production. Such preparations should specifically be reported as *carrier added* (CA).

## 5.2 Production of Radionuclides

### 5.2.1 *Linear Accelerator*

In 1928, two physicists, John Cockcroft and Ernest Walton, working at the Cavendish laboratory in Cambridge, developed an electrostatic *linear accelerator*, based on a voltage multiplying circuit, to accelerate protons along a linear path in order to achieve higher energies (Beiser 1995). The device (Fig. 5.2) consists of a series of tubes connected to a high voltage power supply, which can provide alternating polarities to the tubes. At first, the odd-numbered tubes in the accelerator (1, 3, 5,..) are negatively charged and the even-numbered tubes are positively charged to attract the protons from the H$^+$ ion source. As the protons enter and pass through tube 1, the polarities of the tubes are reversed. As tube 1 is now positive and tube 2 is negative, protons are attracted to tube 2. This process continues through many tubes, until the velocity and energy of the protons increase. The first disintegration of lithium into α particles by artificially accelerated protons was achieved by Cockcroft and Walton in 1932, using a proton beam with 0.77 MeV of energy (Segrè 1980). Following absorption of the proton, the element Li was converted into $^8$Be nucleus, which quickly split into two He nuclei.

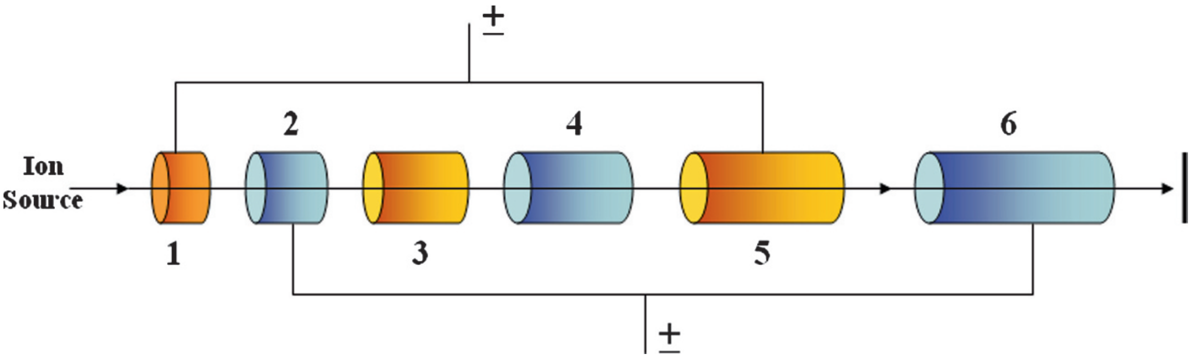

**Fig. 5.2** An electrostatic linear accelerator based on a voltage multiplying circuit designed to accelerate protons along a linear path to achieve higher energies

$$^{7}_{3}\mathrm{Li} + ^{1}_{1}\mathrm{H} \rightarrow ^{8}_{4}\mathrm{Be} \rightarrow 2\,^{4}_{2}\mathrm{He} \quad (5.13)$$

It soon became apparent that protons with higher energies were needed to penetrate the repulsive coulomb forces of the nucleus for the production of nuclear transformations involving higher Z elements. More specifically, based on the principle of linear acceleration, very high voltage (millions of volts) is necessary to increase the kinetic energy of charged particles.

### 5.2.2 Cyclotron

Ernest O. Lawrence, an American physicist and inventor, conceived the idea of a cyclic accelerator or *cyclotron*, in 1929. In the presence of a magnetic field, an ion of specific charge, when introduced at the center of a cyclotron, will accelerate in an expanding spiral path by use of an alternating electric field (Lawrence and Livingston 1931). The first cyclotron built by Lawrence had a diameter of a few inches and the glass vacuum chamber in which ions were supposed to circulate, could be held in one hand (Fig. 5.3). By 1932, the production of several radioisotopes using a 27-in.-diameter cyclotron was reported by Lawrence and his colleagues.

The most widely used particle accelerator is the *medical cyclotron,* which is capable of accelerating protons to low and medium energy levels (10–20 MeV) needed for the production of PET radionuclides (Ruth 2003). Certain cyclotrons have a deuteron beam capability also. The commercial cyclotrons with higher energy proton beams (>30 MeV) are needed to produce proton rich radionuclides that decay by electron capture.

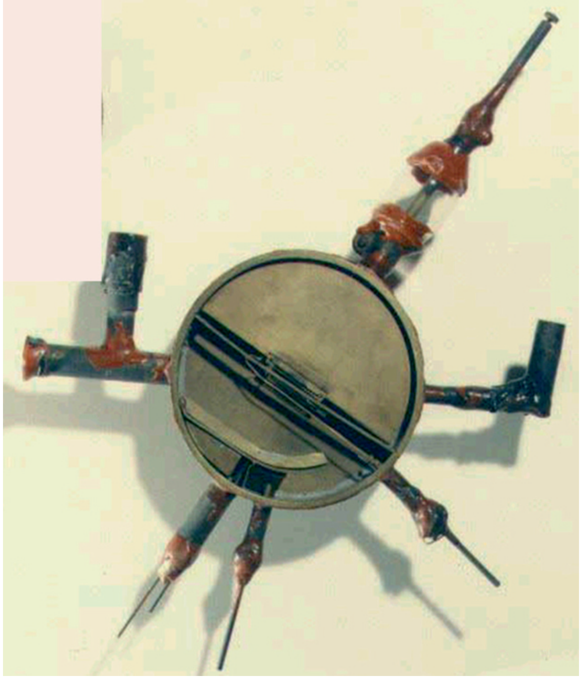

**Fig. 5.3** The first working model of a 4.5 in. cyclotron, which accelerated protons to 80 KeV energy (Lawrence and Livingston 1931)

The technical features of several medical cyclotrons are summarized in Table 5.1.

#### 5.2.2.1 Negative Ion cyclotron

Traditionally, cyclotrons were designed to accelerate positive ions ($H^+$ and $^{2}H^+$). The first cyclotron designed to accelerate negative ions, or hydrogen, or deuterium

**Table 5.1** Cyclotrons for the production of positron-emitting radionuclides

| | | Particle beam | | | Number of targets |
|---|---|---|---|---|---|
| | | Type | Energy MeV | Current µA | |
| CTI[a] | RDS-111 | $H^+$ | 11 | 50 | 4 |
| CTI[a] | RDS-112 | $H^+$ | 11 | 50 | 2 × 8[b] |
| IBA | Cyclone 10/5 | $H^+/{}^2H^+$ | 10/5 | 60/35 | 8 |
| IBA | Cyclone 18/9 | $H^+/{}^2H^+$ | 18/9 | 80/35 | 8 |
| GE[a] | MINItrace | $H^+$ | 9.6 | 50 | 4 |
| GE | PETtrace | $H^+/{}^2H^+$ | 16.5/8.5 | 75/60 | 6 |
| EBCO | TR 13/19 | $H^+/{}^2H^+$ | 13, 19/9 | 150 | 2 × 4[c] |

[a] Self shielding for cyclotrons is standard
[b] Two beam ports, each with a eight target carousel
[c] Two beam ports, each with a four target carousel

atoms with two electrons in the *K*-shell ($H^-$ and ${}^2H^-$), was built in 1966. Since the 1980s, all the commercial and medical cyclotrons are basically negative ion cyclotrons. One of most important advantages of the negative ion cyclotron is the elimination of a complex *beam extraction system*. As a result, negative ion cyclotrons provide the opportunity to extract beams with different energies thereby allowing for the simultaneous bombardment of two different targets (Satyamurthy 1999).

The cyclotron (Fig. 5.4) consists of three major components: an electromagnet with a field strength of 1.5–2.0 tesla, a pair of semicircular hollow copper electrodes, called *dees* located between the poles of the magnet, and an ion source (Penning ion gauge)

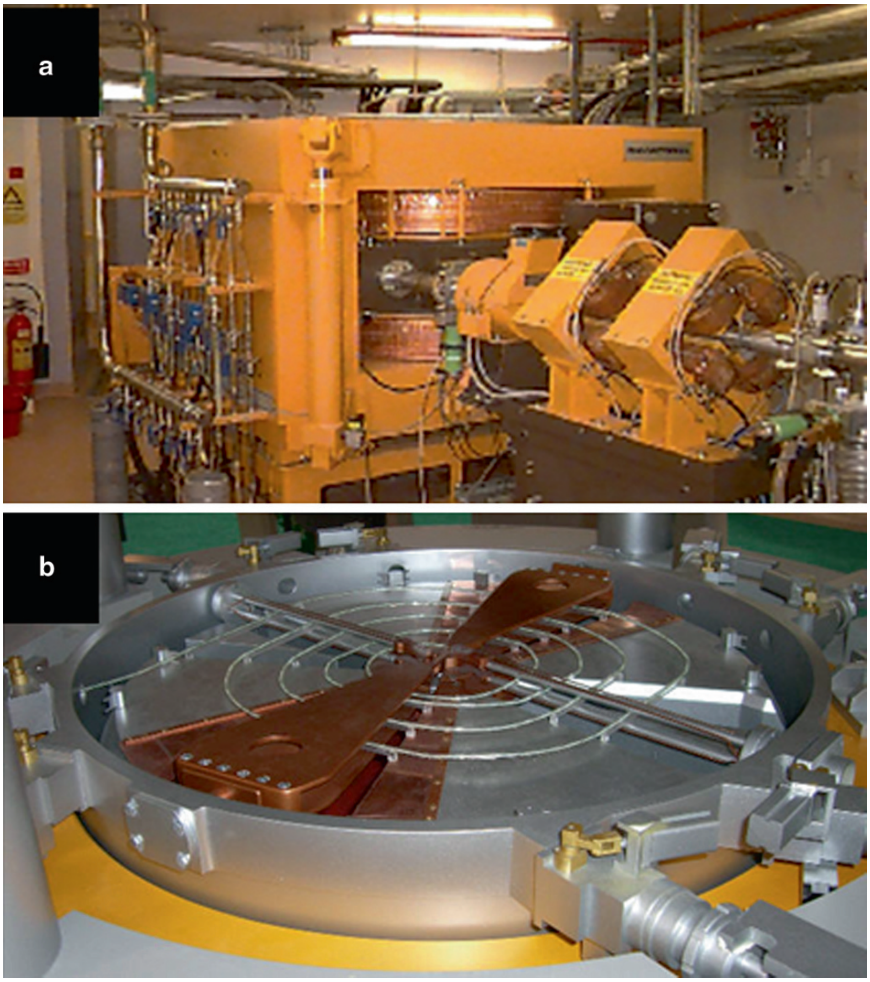

**Fig. 5.4** A negative ion cyclotron (EBCO-TR19) with an external beam line (**a**). A model of the vacuum chamber (CTI systems) showing the copper electrodes (dees) in which a negatively charged proton beam making circular orbits (**b**)

capable of generating high intensity negative ions. The entire structure of the cyclotron is kept under high vacuum (up to $10^{-7}$ torr). Following ionization of the hydrogen gas in an ion source, the ions (protons or deuterons) are injected into the center of the gap between the dees. When a 20–30 MHz radiofrequency alternating potential of 30–100 kV, generated with an oscillator, is applied to the dees, the negative ions will accelerate towards a dee that is at a positive potential. Because the magnetic field is perpendicular to the plane of the dees and particle motion, the negative ions will trace a circular path. Further, because the electrical potential on the dees is alternatively positive and negative, the ions will gain energy at each crossing of the gap between the dees, as they move outward in a spiral path from the center. Lawrence (Lawrence and Livingston 1931) described the basic operational equations as follows:

The magnetic force operating on the ion is a centripetal force ($Bev$), which is exactly balanced by the centrifugal effect ($mv^2/r$).

$$Bev = \frac{mv^2}{r} \text{ and } r = \frac{mv}{Be} \tag{5.14}$$

In the above equations, $B$ is the magnetic field strength while $m$, $e$, and $v$ represent the mass, charge and velocity of the ion, respectively. Finally, $r$ represents the radius of the ion's orbit. For a given cyclotron, the maximum kinetic energy that an ion can attain can be estimated if $B$ and $r$ are kept constant.

$$E = \frac{B^2\, r^2}{2}\left(\frac{e^2}{m}\right) \tag{5.15}$$

### *Beam Extraction*

Once the desired kinetic energy of the accelerating particles is achieved, the positively charges ions ($H^+$ and $2H^+$) are extracted from the cyclotron by passing the negative ion beam through an ultra thin foil of carbon (graphite), which strips the electrons. The positively charged beam will rotate in an opposite direction, which can then be directed to bombard an appropriate target for the production of a positron-emitting radioisotope. The typical intensities (beam currents) and the energies of proton and deuteron beams generated in commercial cyclotrons are shown in Table 6. The beam current is generally expressed in units of microampere (μA). For example, a 1 μA proton beam current is equal to $6.25 \times 10^{12}$ protons or deuterons/s.

## *5.2.3 Production of Positron-Emitters*

The most important nuclear reactions used in the production of positron emitting radionuclides are summarized in Table 5.2 The target designed for the production of a positron-emitter consists of a target body suitable for the bombardment of a specific target material (gas, liquid, or solid) that undergoes nuclear transformation. Typical gas targets are made up of aluminum, while the liquid targets are made up of aluminum, silver, and titanium. A generic cyclotron target (Fig. 5.5) consists of a sealed metal tube with a window of thin metal foil at one end to allow the particle beam to pass through and irradiate the target material. In order to dissipate the excess heat generated during irradiation, the target

**Table 5.2** Nuclear reactions for the production of positron emitting radionuclides

| Radio isotope | Nuclear reaction | Target | | | Yield | Product chemical |
|---|---|---|---|---|---|---|
| | | Body | Material | mL | mCi/μA | |
| $^{18}F$ | $^{18}O\,(p,n)\,^{18}F$ | Ag, Ti | $[^{18}O]H_2O$ | 0.3–3.0 | 110 | $^{18}F^-$ |
| $^{18}F$ | $^{20}Ne\,(d,\alpha)^{18}F$ | Al, Ni | Ne gas + 0.1–0.2% $F_2$ gas | | 51 | $^{18}F_2$ |
| $^{11}C$ | $^{14}N\,(p,\alpha)\,^{11}C$ | Al | $N_2$ gas + <1% $O_2$ gas | | 40 | $^{11}CO_2$ |
| $^{13}N$ | $^{16}O\,(p,\alpha)\,^{13}N$ | Al | $H_2O$ | | 7 | $^{13}NH_4^+$ |
| $^{15}O$ | $^{14}N\,(d,n)^{15}O$ | Al | $N_2$ gas | | 50 | |
| $^{15}O$ | $^{15}N\,(p,n)^{15}O$ | Al | $N_2$ gas | | 47 | |
| $^{64}Cu$ | $^{64}Ni\,(p,n)^{64}Cu$ | | Ni metal | | 73 | |
| $^{124}I$ | $^{124}Te(d,2n)^{124}I$ | | AL oxide and Te oxide solid solution matrix | | 73 | $^{124}I$ as iodide |

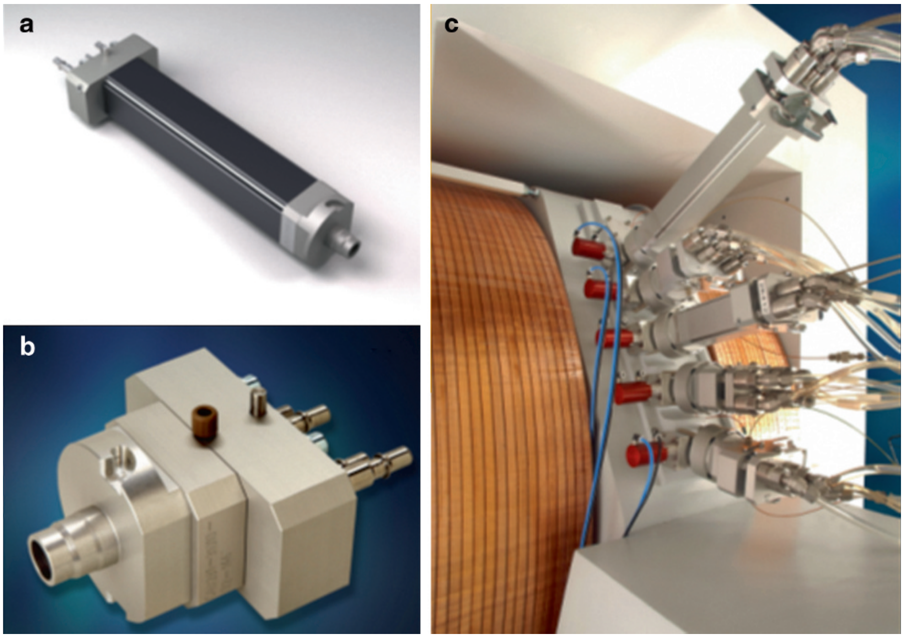

**Fig. 5.5** $^{14}N$ gas target chamber (**a**) for the production of $^{11}C$ as carbon dioxide and an $^{18}O$ water target chamber (**b**) for the production of $^{18}F$ as fluoride. Placement of these targets in the PETtrace (GE) cyclotron (**c**)

body is generally surrounded by a cooling water jacket, while helium gas is circulated through the foils separating the target material and the vacuum isolation foil through which the beam enters the target.

#### 5.2.3.1 Positron-Emitting Halogens

Among halogens, $^{18}F$ is the most important radionuclide for PET. The other halogens, $^{75}Br$ and $^{124}I$ may have potential clinical utility and can also be made using medical cyclotrons.

##### *Production of $^{18}F$*

Basically, there are two kinds of targets used to produce two different chemical forms of fluorine. A liquid target for the production of $^{18}F$ as nucleophilic fluoride ion ($^{18}F^-$) and a gas target for the production of $^{18}F$ as electrophilic fluorine as $[^{18}F]F_2$ gas (Ruth and Wolf 1979; Casella et al 1980)

The most common nuclear reaction used to produce $^{18}F$ as fluoride ion is on the basis of proton bombardment of $^{18}O$ atoms using highly enriched $[^{18}O]$ water as the target material (Ruth and Wolf 1979; Schlyer 2003). A typical target body is made of aluminum to hold 0.3–3.0 mL of target water. Several curies of $^{18}F$ can easily be made in 1–2 h using 10–19 MeV protons with 20–35 μA beam current. While the theoretical SA of $^{18}F$ is 1,700 Ci/μmol$^{-1}$, the NCA $^{18}F$ is generally produced with a SA of <10 Ci/μmol$^{-1}$.

The most common nuclear reaction to produce $[^{18}F]$ fluorine gas is on the basis of deuteron bombardment of $^{20}Ne$ atoms using natural neon gas (Schlyer 2003). A passivated nickel target (NiF) is loaded with neon gas containing 0.1% of natural fluorine gas. Following bombardment for 1–2 h with 8–9 MeV deuterons, <1.0 Ci of $[^{18}F]F_2$ is generated with a very low SA of (10–20 mCi/μmol$^{-1}$). A "double shoot" method was developed to produce $[^{18}F]$fluorine gas on the basis of proton bombardment of $^{18}O$ atoms using $[^{18}O]$oxygen gas loaded into a gas target (Nickels et al 1983). After irradiation, $^{18}F$ species stick to the walls of the target. The $^{18}O$ target gas is removed from the target, which is then loaded with argon gas mixed with 1% of cold fluorine gas. A second short irradiation for <10 min will generate $[^{18}F]F_2$ gas. This method is very useful to make electrophilic $^{18}F$, using cyclotrons generating proton beams only. Since $[^{18}F]F_2$ is always diluted with carrier (cold) fluorine gas, the SA of electrophilic [$^{18}$F] fluorine is very low and not optimal for synthesizing high SA $^{18}$F labeled radiopharmaceuticals.

#### *Production of $^{75}$Br and $^{76}$Br*

Both these radionuclides are generally made by proton (17 MeV) bombardment of $^{76}$Se atoms using [$^{76}$Se]selenium enriched (96%) $Cu_2Se$ as the target material (Schlyer 2003). Subsequently, $^{76}$Br is separated from the solid target by thermal diffusion. The longer half-life (16.2 h) of $^{76}$Br is favorable for the synthesis of radiopharmaceuticals, and commercialization. However, $^{76}$Br has a complex decay scheme and high energy positrons which may provide an unfavorable radiation dose to the patient.

$^{75}$Br with a shorter half-life (97 min) may be more optimal for developing PET radiopharmaceuticals. One of the common nuclear reactions is $^{76}\mathrm{Se}(p,2n)^{75}\mathrm{Br}$, but the energy of proton needed for this reaction is between 18–28 MeV. $^{75}$Br is separated from a solid target by dry distillation method and trapped using platinum wool.

#### *Production of $^{124}$I*

A method using the proton bombardment of enriched $^{124}$Te atoms using low energy protons (15 MeV), has been recently developed (Scholten et al 1995; Sheh et al 2000). The solid target material consists of a solid solution matrix containing aluminum oxide and enriched $^{124}$Te oxide. [$^{124}$I]iodide is recovered from the target using dry distillation. The volatile radioiodine is trapped on a thin pyrex glass tube that is coated with a small amount of sodium hydroxide.

Because, radioiodination of proteins and peptides is relatively easy, $^{124}$I has significant potential for the development of radiopharmaceuticals for PET. However, the longer half-life and complicated decay schemes with a number of high energy positrons may make this radionuclide suboptimal, as the radiation dose to the patient can be relatively high.

### 5.2.3.2 Organic Positron-Emitters

The greatest advantage of PET is the potential to image and study biochemical processes in vivo, without altering or affecting the homeostasis in any way. Low atomic number elements such as carbon, nitrogen, oxygen, and phosphorous are naturally stable. The development of cyclotrons in the 1930s created an opportunity to produce positron emitting radioisotopes of carbon ($^{11}$C), nitrogen ($^{13}$N), and oxygen ($^{15}$O). Since the 1950s, radioisotopes of organic interest have played a significant role in the development of biochemistry and pharmacology. Because, the half-lives of these radionuclides are relatively short, they have not been exploited to their full potential to develop radiopharmaceuticals for routine clinical PET imaging studies. However, with the availability of several hundred commercial medical cyclotrons, PET radiopharmaceuticals for routine clinical use have been developed by incorporating the organic positron-emitters.

#### *Production of $^{11}$C*

The most common nuclear reaction used to produce $^{11}$C is the proton bombardment of $^{14}$N atoms by using natural nitrogen as the target gas (Casella et al 1978; Bida et al 1980; Schlyer 2003). Because nitrogen gas is relatively inert, it does not interfere with the carbon chemistry and can be easily eliminated. By mixing trace amounts (<1%) of oxygen or hydrogen with the target nitrogen gas, the chemical forms of $^{11}$C produced in the target can be either [$^{11}$C]$CO_2$ or [$^{11}$C]$CH_4$ (methane). The gas target body is basically made up of an aluminum cylinder (or cone shape) that should be able to handle gas (10–100 cc) at pressures of 300–800 psi. Beam currents of 20–40 $\mu$A are typically used. It is very important to prepare or polish the inside of the aluminum target in order to significantly reduce the contamination of natural carbon. As the natural nitrogen gas is also contaminated with $CO_2$ gas, it is essential to use extremely high purity (99.99999%) target gases. [$^{11}$C]$CO_2$ can be produced in most cyclotron targets with a SA of 5–20 Ci/$\mu$mol$^{-1}$ at EOB. Even higher SA can be achieved by producing [$^{11}$C]$CH_4$ directly in the target.

#### *Production of $^{13}$N*

The first production of $^{13}$N was based on bombarding boron atoms with $\alpha$ particles (Joliot and Curie 1934). The most common nuclear reaction for the production of $^{13}$N is the proton (10–15 MeV) bombardment of natural, stable $^{16}$O atoms, using oxygen gas target or liquid (water) target (Tilbury and Dahl 1979; Berridge and Landmeier 1993; Schlyer 2003). When $^{13}$N is produced in the target, it reacts with water forming nitrate and nitrite ions. The addition of a reducing agent, such as titanium chloride, to the target water will generate [$^{13}$N]$NH_3$. With a pressurized target, aqueous ethanol can be used in the target since ethanol acts as a hydroxyl free radical scavenger to improve the production of [$^{11}$N]$NH_3$.

Because the half-life of $^{13}$N is very short (9.98 min), it is very difficult to synthesize $^{13}$N labeled radiotracers for routine clinical PET studies. In the 1970s, [$^{13}$N] Ammonia ($NH_3$ or $NH_4^+$ ion) has been shown to be clinically useful as a myocardial perfusion imaging agent. Therefore, the production of $^{13}$N involves the generation of [$^{13}$N]$NH_3$ gas directly in the target itself.

#### *Production of $^{15}$O*

$^{15}$O was one of the first artificial radioisotopes produced by low-energy deuterons using a cyclotron (Livingston and McMillian 1934). In order to use low energy protons (10–11 MeV), the target must be highly enriched $^{15}$N gas (Vera-Ruiz and Wolf 1977; Schlyer 2003). However, the most common nuclear reaction used for the production of $^{15}$O as [$^{15}$O]$O_2$ gas is deuteron bombardment of $^{14}$N atoms using natural nitrogen containing 0.2–0.5% oxygen as the target gas. The target body is generally made of aluminum. To produce $^{15}$O as [$^{15}$O]$CO_2$, the target nitrogen gas is mixed with 2–2.5% carbon dioxide. To produce [$^{15}$O]water, outside the target, a stream of nitrogen gas continuously flows through the target to a hot cell containing a water synthesis module, in which $^{15}$O combines with $H_2$ gas in the presence of palladium–aluminum catalyst at high temperatures (300–400°C) to produce water.

### 5.2.3.3 Positron-Emitting Metals ($^{66}$Ga, $^{86}$Y and $^{64}$Cu)

A number of positron emitting radionuclides, belonging to the Group III elements (Ga, In and Y), can be made in many of the medical cyclotrons. In addition, several radionuclide generator systems are available, yielding positron-emitting daughter radiometals of significant clinical interest.

For example, $^{66}$Ga which is a medium half-life radionuclide, emitting very high energy (4.1 MeV) positrons and it can be produced via the $^{66}$Zn($p$,$n$)$^{66}$Ga nuclear reaction (Schlyer 2003). Subsequently, $^{66}$Ga can be easily separated from zinc by cation exchange or solvent extraction techniques.

$^{86}$Y is also a medium half-life radionuclide emitting high energy (3.15 MeV) positrons. It can be produced via the $^{86}$Sr($p$,$n$)$^{86}$Y nuclear reaction using isotopically enriched $^{86}$Sr foil or strontium carbonate pellet. Subsequently, $^{86}$Y can be separated by dissolving the target in an acidic solution, followed by precipitation and purification by ion exchange chromatography.

Copper has several positron emitting radioisotopes, such as $^{61}$Cu, $^{62}$Cu, and $^{64}$Cu. Because of its longer half-life of 12.7 h and low energy positrons, $^{64}$Cu is more appropriate for developing commercial PET radiopharmaceuticals. It can be produced via the $^{64}$Ni($p$,$n$)$^{64}$Cu nuclear reaction using enriched nickel solid target foils (Schlyer 2003). Subsequently, $^{64}$Cu is separated by dissolving the target in an acidic solution, followed by ion exchange chromatography. Using similar techniques, $^{61}$Cu can also be produced via the $^{61}$Ni($p$,$n$)$^{61}$Cu nuclear reaction, using enriched nickel solid target foils.

### 5.2.3.4 SPECT Radionuclides ($^{67}$Ga, $^{111}$In and $^{123}$I)

$^{67}$Ga can be produced by several nuclear reactions using commercial cyclotrons. The most common reactions are $^{68}$Zn($p$,2$n$)$^{67}$Ga and $^{66}$Zn($d$,$n$)$^{67}$Ga. Following irradiation, the zinc target is dissolved in concentrated HCl (7 N) and $^{67}$Ga is extracted into an organic phase using isopropyl ether. Following evaporation of the organic phase, $^{67}$Ga is formulated as chloride using dilute HCl (0.1 N). The typical SA of $^{67}$Ga is around 1,000 mCi $mg^{-1}$ (67 mCi $\mu mol^{-1}$) and radionuclidic purity is about 99.4%.

$^{111}$In can be produced by proton bombardment of cadmium using either $^{111}$Cd($p$,$n$)$^{111}$In reaction or $^{112}$Cd($p$, 2$n$)$^{111}$In reaction. Following irradiation, the cadmium target is dissolved in mineral acid and the acidity is kept at 1 N using HCl.

$^{111}$In is separated from the target using anion exchange resin and HCl (1 N). The high SA, no-carrier added $^{111}$In has a radionuclidic purity of ≥99.9%.

$^{123}$I can be produced directly in a cyclotron using $^{124}$Te($p$,2$n$) reaction. The most common methods, however use indirect methods based on the following nuclear reactions:

$$^{127}\mathrm{I}(p,5n)^{123}\mathrm{Xe}\rightarrow^{123}\mathrm{I}$$

$$^{124}\mathrm{Xe}(p,2n)^{123}\mathrm{Cs}\rightarrow^{123}\mathrm{Xe}\rightarrow^{123}\mathrm{I}$$

$$^{124}\mathrm{Xe}(p,pn)^{123}\mathrm{Xe}\rightarrow^{123}\mathrm{I}$$

The high SA, NCA $^{123}$I is supplied as sodium iodide in a 0.1 N NaOH solution with a radionuclidic purity >99.8%.

#### 5.2.3.5 Nuclear Reactor

Shortly after the discovery of nuclear fission, scientists realized that, because fission leads to the release of additional neutrons, in a given mass of uranium fuel, known as the critical mass, a self-sustaining sequence of additional fissions can lead to a *chain reaction*, induced by at least one fission neutron. Such a reaction, in which the *multiplication factor* (MF) is ≥1, is called a *critical* reaction. However, if too few neutrons cause fissions, the reaction is *subcritical* (MF <1) and will stop. If the frequency of fissions increases at a faster rate (MF >1), the "runaway" reaction can be *supercritical* and may lead to a nuclear explosion. In 1942, Fermi was able to demonstrate that by carefully controlling the availability of neutrons, a sustained chain reaction (MF = 1) can be maintained. The *nuclear reactor* operates on the basis of this principle of controlled chain reaction.

Compared to $^{238}$U, the cross section for induced fission reaction with slow or *thermal neutrons* (0.25 eV) is much higher for $^{235}$U. Because the natural uranium contains only 0.7% of $^{235}$U isotope, *enriched uranium* containing >3% of $^{235}$U, is typically used as the fuel in a reactor core. In a nuclear reactor, the fuel cells containing enriched uranium (as $UF_6$ or $UO_2$) pellets are surrounded by a *moderator*, graphite or heavy water, to slow down the energetic fission neutrons. *Control rods* (cadmium and boron) capable of absorbing neutrons, but not undergoing any nuclear reaction, are used to sustain the chain reaction. In addition to $^{235}$U, several other nuclides such as $^{232}$Th, $^{233}$U, $^{237}$Np, and $^{239}$Pu can all be used as fuel for nuclear reactors. Following the absorption of a neutron, the natural $^{238}$U decays by emitting a beta particle to become $^{239}$Np, which in turn emits a beta particle to become $^{239}$Pu. These reactions are the basis of a *breeder reactor*, in which uranium produces more fuel in the form of $^{239}$Pu.

#### 5.2.3.6 Reactor Produced Radionuclides

When the reactor is in operation, the nuclear reaction *(n, f)* produces a number of neutron rich fission fragments (Z = 28–65), which decay by $\beta^-$ or $\beta^-$, $\gamma$ emission. Radionuclides, such as $^{99}$Mo, $^{131}$I, and $^{137}$Cs, accumulate in the fuel rods to produce enormous activity (thousands of GBq). All the fission fragments can be chemically separated and purified to yield no carrier added, high SA radionuclides.

##### *Neutron Activation*

A nuclear reaction in which a neutron is captured or absorbed by the nucleus of a stable atom, leading to a nuclear transformation, is called *neutron activation*. The most common nuclear reactions are $(n, \gamma)$ $(n, p)$, $(n, 2n)$, and $(n, \alpha)$, in which the atomic mass or atomic number of the target nucleus may change.

The neutrons released during the fission reaction have a wide range of energies, from a few KeV to 10 MeV. The average energy is approximately 2 MeV, which decreases substantially as a result of collisions with other atoms in the core and the moderator. The average energy of thermal neutrons at room temperature is about 0.038 eV. Neutrons between 0.01 and 0.1 MeV are known as slow or resonance neutrons, while neutrons with >0.1 MeV are known as fast neutrons. In general, the cross section ($\sigma$) for thermal neutrons in neutron activation reactions is very high, compared to that of higher energy neutrons.

In a $(n,\gamma)$ reaction, the target nucleus with a mass number A captures a neutron to become an unstable, excited radioisotope of the target nucleus, with a mass number A + 1. The excited nucleus immediately emits a gamma photon and the product radionuclide will eventually decay by beta emission to reach a ground state. Because the product nuclide is an isotope of the target element, the product can not be separated and purified to avoid the contamination of the carrier. As a result, radioisotopes produced using $(n, \gamma)$ reaction are generally very low in SA.

$$^{98}_{42}\mathrm{Mo}\,(n,\gamma)\,^{99}_{42}\mathrm{Mo}$$

It is possible to produce carrier-free, high SA nuclides in a reactor. Certain $(n, \gamma)$ reactions produce a short-lived radioisotope of the target element, which decays by beta emission to another unstable radioactive nuclide with longer half-life compared to that of the intermediate. $^{131}$I can be produced by neutron activation of enriched $^{130}$Te isotope.

$$^{130}_{52}\mathrm{Te}\ (n,\gamma)\ ^{131}_{52}\mathrm{Te}\ \left(T_{1/2}=25\,\mathrm{min}\right)\xrightarrow{\beta^-}\ ^{131}_{53}I\ \ \left(T_{1/2}=8.04\ \mathrm{days}\right)$$

In a (*n, p*) reaction, the target and the product are two different elements. As a result, it is very easy to separate the product from the target, chemically.

$$^{67}_{30}\mathrm{Zn}\ (n,\,p)\ ^{67}_{29}\mathrm{Cu}$$

There are several examples of the reactor production of neutron deficient radionuclides that decay by $\beta^+$ emission or EC. However, these methods are not necessarily practical for routine production for clinical utility.

## 5.3 Radionuclide Generators

As discussed in Chap. 4, a parent–daughter radionuclide pair may exist either in a transient or in a secular equilibrium, when the parent is a longer lived radionuclide than the daughter. The parent radionuclide can be made in a reactor or in a cyclotron. If the parent and daughter nuclides are two different elements, they can be separated chemically, and the radioactivity of the daughter can be of high SA. Such a parent–daughter (mother–daughter) radionuclide pair is ideal to build a generator system to produce the daughter radionuclide, when needed (Qaim 1987; Welch and McCarthy 2000). The *radionuclide generator* is a device used to separate the daughter radionuclide from the parent radionuclide. Various types of physicochemical separation methods, such as distillation or liquid/liquid extraction may be used. A chromatographic method based on an inorganic or resin adsorbent material, however, is the most practical method for routine clinical utility. Four important generator systems (Table 5.3) are available to produce radionuclides of clinical interest.

### 5.3.1 $^{99m}$Tc generator

The $^{99m}$Tc generator was first developed in 1960s at the Brookhaven National Laboratories in New York (Richards 1965). As discussed earlier, $^{99}$Mo is one of the fission products of $^{235}$U fission and is known as "fission moly", and is produced in very high SA compared to $^{99}$Mo which is produced by neutron activation. Most commercial generators are made with fission produced $^{99}$Mo. The generator is made on the basis of a solid column method, in which 5–10 g of preheated alumina ($Al_2O_3$) is loaded in a plastic or glass column. The $^{99}$Mo activity (2–32 Ci) in the form of molybdate ion $MoO^2_H$ is adsorbed on the column. The column is thoroughly washed to remove undesirable contaminants. The amount of $^{99}$Mo activity on the column along with the date and time of calibration, for each generator, is provided. Commercial generators are sterilized and well shielded with lead or depleted uranium.

After the generator has been washed and calibrated, at time $T_0$, there is no $^{99m}$Tc activity on the column. As $^{99}$Mo($T_{½}$ = 66 h) decays, $^{99m}$Tc activity ($T_{½}$ = 6 h) is produced and builds up in the column as a function of time, as shown in Fig. 5.6. Unlike molybdenum, technetium does not bind to alumina, but is immediately converted into $^{99m}$Tc-pertechnetate ion ($^{99m}$TcO4$^-$), which is the most stable chemical form of technetium with an oxidation state of +7. Typically, >75% of $^{99m}$Tc-activity can be eluted with 3–10 mL of physiological saline solution. The equations to estimate the amount of $^{99m}$Tc activity in a generator have been previously shown (equations (4.21) and (4.23)).

Small amounts of $^{99}$Mo activity may occasionally *breakthrough* (leakage or partial elution) the column into the $^{99m}$Tc-pertechnetate solution. The maximum $^{99}$Mo contamination allowed is 0.15 μCi/mCi$^{-1}$ or 0.15 KBq MBq$^{-1}$ of $^{99m}$Tc-pertechnetate solution at the time of elution. Each $^{99m}$Tc dose to a patient, however, should not contain >5 μCi of $^{99}$Mo activity. As a chemical impurity, Al ion concentration should be <10–20 μg mL$^{-1}$ of eluant.

**Table 5.3** Radionuclide generators

| Parent | | | | Daughter | | | Generator | |
|---|---|---|---|---|---|---|---|---|
| Nuclide | $T_{½}$ | Decay | NR | Nuclide | $T_{½}$ | Decay | Column | Eluent |
| $^{99}$Mo | 66 h | $\beta^-$ | $^{235}$U fission | $^{99m}$Tc | 6 h | IT | $A_{12}O_3$ | 0.9% Saline |
| $^{82}$Sr | 2.5 days | EC | $^{85}$Rb(*p*, 4*n*)$^{82}$Sr | $^{82}$Rb | 75 s | $\beta^+$ | $SnO_2$ | 0.9% Saline |
| $^{68}$Ge | 271 days | EC | $^{69}$Ga(*p*, 2*n*)$^{68}$Ge | $^{68}$Ga | 68 min | $\beta^+$ | $TiO_2$ | 1N HCl |
| $^{62}$Zn | 9.3 h | EC, $\beta^+$ | $^{63}$Cu(*p*, 2*n*)$^{62}$Zn | $^{62}$Cu | 9.7 min | $\beta^+$ | Dowex | 2N HCl |

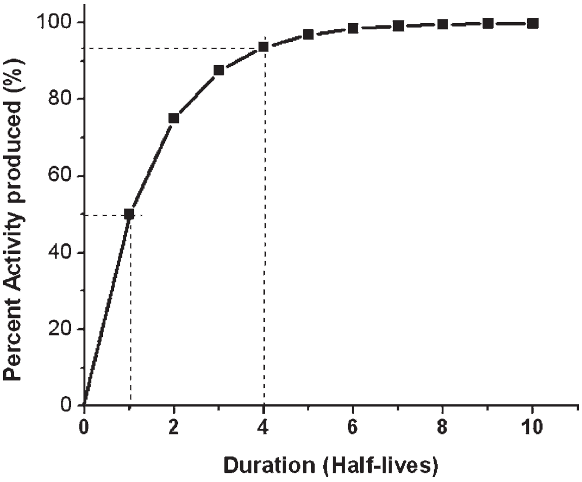

**Fig. 5.6** The build-up of $^{99m}$Tc activity in a generator as a function of time (half-life): 50% of the expected maximum yield can be produced following irradiation of the target for a minimum of one half-life of the radionuclide

Both, $^{99}$Mo (13%) and $^{99m}$Tc decay producing the long lived $^{99}$Tc, which in turn decays slowly by beta emission, to the stable $^{99}$Ru. Since $^{99m}$Tc and $^{99}$Tc are isomers and chemically the same element, $^{99}$Tc may act as a carrier in the preparation of $^{99m}$Tc radiotracers. If the generator is eluted once a day (every 24 h), the number of $^{99m}$Tc atoms is 27% of the total Tc atoms. If the generator is eluted after 4 days, for example, the number of $^{99m}$Tc atoms is only 5% of the total Tc atoms.

### 5.3.2 $^{82}$Rb Generator (Cardiogen®)

$^{82}$Rb chloride was the first PET radiopharmaceutical approved by the FDA in 1989 for assessment of regional myocardial perfusion. Cardiogen® is manufactured and supplied by Bracco Diagnostics. The parent $^{82}$Sr ($T_{½}$ = 25.6 days) is a neutron deficient radionuclide that decays by electron capture and is produced using a high energy cyclotron (Thomas 1987). $^{82}$Sr (90–150 mCi) is loaded on a stannic oxide column and the daughter $^{82}$Rb ($T_{½}$ = 75 s) is eluted from the column with a sterile saline solution using an infusion pump calibrated to administer a specific unit dose to a patient.

### 5.3.3 $^{62}$Cu Generator

Several $^{62}$Cu radiotracers are under development and clinical evaluation for assessing perfusion and hypoxia. $^{62}$Zn ($T_{½}$ = 9.13 h) is a neutron deficient radionuclide produced by the proton irradiation of a copper disc or copper electroplated alloy on the basis of the nuclear reaction $^{63}$Cu($p$,2$n$)$^{62}$Zn using 26-21 MeV protons (Finn and Schlyer 2002). $^{62}$Zn is separated from the target copper using an anion-exchange column. Subsequently, an acidic solution of $^{62}$Zn can be loaded onto an anion-exchange column and the daughter $^{62}$Cu ($T_{½}$ = 9.76 min) can be eluted from the generator for the preparation of radiotracers (Robinson 1980; Haynes et al 2000; Fukumura 2006).

### 5.3.4 $^{68}$Ga Generator

In many PET facilities, $^{68}$Ga is routinely used for transmission scans (for attenuation correction of PET data) using a $^{68}$Ge rod source (5–10 mCi). The parent, $^{68}$Ge is a long lived ($T_{½}$ = 278 days) neutron deficient radionuclide, generally produced by a high energy cyclotron based on spallation reaction (Finn and Schlyer 2002). The $^{68}$Ga generator was developed, in 1960s for brain imaging studies (Yano and Anger 1964) and, subsequently, improved (Schuhmacher et al 1981). Recent modifications involve loading $^{68}$Ge onto a tin oxide column and the daughter, $^{68}$Ga is eluted as chloride using dilute hydrochloric acid solution (Zhernosekov et al 2007).

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