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The Production of Radionuclides for Radiotracers in Nuclear Medicine

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Medical applications represent the vast majority of the uses for radiotracers. This review addresses how accelerators are employed for the production of high purity radionuclides that are used in basic biomedical research, as well as for clinical medicine both for diagnosing disease and for treatment.

Keywords: Radioisotopes; irradiation; nuclear medicine; specific activity; accelerators; cyclotron; imaging; therapy.

1. Introduction

The building of the cyclotron in the 1930s made possible the routine production of radionuclides that would find use in a variety of applications, including medicine, industry, agriculture, and basic physical and biological research. With the high power of the charged particles (energy and flux or beam current) available in the cyclotron, it is possible to produce abundant quantities of a wide variety of radionuclides.

Immediately after World War II, almost all radionuclides and radioisotopes in use were made in a reactor. The production of radionuclides in cyclotrons for medical applications revived in the 1950s, due in large part to the discovery that ^{201}Tl could be used as an analog of potassium ions and thus is an ideal tracer for detecting myocardial perfusion. Thallous chloride labeled with ^{201}Tl remains the standard for measuring cardiac blood flow despite the availability of ^{99m}Tc myocardial perfusion agents. The preparation of ^{18}FDG in the mid-1970s and its use for studying glucose metabolism was a major breakthrough, leading to the development of the now-widely-used imaging modality called positron emission tomography (PET). ^{18}F-FDG when used along with the PET camera yields excellent quality images of the brain (for studying both normal function and functional abnormalities), the heart (for studying viability function), and tumors (for detecting metastasis). A large number of other ^{18}F- and ^{11}C-labeled radiopharmaceuticals were developed subsequently, and the quest for newer and more effective ones continues today.

In addition to the use of PET and single proton emission tomography (SPECT) radionuclides for diagnostic imaging studies, cyclotron-produced radionuclides are finding extensive therapeutic applications. An example is the use of dedicated cyclotrons with large beam currents for the production of ^{103}Pd for brachytherapy applications. Another example of cyclotron-produced radionuclides being used for treatment is the production of alpha-particle-emitting isotopes, notably ^{211}At and ^{213}Bi, for targeted therapy of cancer.

The applications of cyclotron-produced isotopes have been expanding at a much faster pace in the last 15 years, as seen by the large number of new machines being installed for isotope production. Some cyclotrons are dedicated to the production of a single isotope such as ^{18}F or, as indicated above, ^{103}Pd. The International Atomic Energy Agency (IAEA) has published a directory on cyclotrons used for isotope production in 1998, and a revised version of it was published in 2006 (IAEA-DCR/CD) that documents the cyclotrons available in the member states.

This article will describe the fundamental operation of the cyclotron as it is used for producing radionuclides for medical purposes. Some background information on the imaging technologies is provided for completeness.

2. Radioisotope/Radionuclide Production

Radionuclide production is indeed true alchemy that is converting the atoms of one element into those of

another. This conversion involves altering the number of protons and/or neutrons in the nucleus (target). If a neutron is added without the emission of particles, then the resulting nuclide will have the same chemical properties as the target nuclide and thus is an isotope of that element. If, however, the target nucleus is bombarded by a charged particle, such as a proton, the resulting nucleus will usually be that of a different element. The exact type of nuclear reactions a target undergoes depends on a number of parameters, including the type and energy of the bombarding particle. A more complete description of the process of radionuclide production is given below.

The binding energy of nucleons in the nucleus is, on average, of the order of 8 MeV. Therefore, if the incoming projectile has more than this amount of energy, the resulting reaction will cause other particles to be ejected from the target nucleus. By carefully selecting the target nucleus, the bombarding particle and its energy, it is possible to produce a specific radionuclide.

2.1. *Specific activity* [1, 2]

Specific activity (SA) is a measure of the number of radioactive atoms or molecules as compared to the total number of those atoms or molecules present in the sample. It is usually expressed in terms of radiation units per mass unit. The traditional units have been Ci/mole (or Ci/g) or a fraction thereof (now expressed as GBq/mole). If the only atoms present in the sample are those of the radionuclide, then the sample is referred to as carrier-free. For example, a compound labeled with ^{211}At will be carrier-free since there are no stable isotopes of astatine.

However, in most cases there are small quantities of nonradioactive atoms which serve as a carrier or molecules that have a similar chemical behavior and can act as a *pseudocarrier*. The SA of an isotope or radiopharmaceutical is important in determining the chemical/biological effect which the substance may have on the system under investigation.

The number of radioactive atoms in a sample can be calculated from the relationship of radioactivity to quantity expressed as

$$\frac{dN}{dt} = -\lambda N, \tag{1}$$

where dN/dt is the disintegration rate in seconds and λ is the decay constant in reciprocal seconds [$\lambda = \ln(2)/t_{1/2}$, where $t_{1/2}$ is the half-life].

As an example of SA, assume that glucose has been labeled with 10 mCi of ^{11}C with a half-life of 20.3 min. The carrier-free SA can be calculated from the number of atoms contained in the 10 mCi. The number of atoms will be

$$^{11}C = N = \frac{dN/dt}{\lambda} = \frac{(10\,\text{mCi})(3.7 \times 10^7\,\text{dps/mCi})}{\dfrac{\ln(2)}{(20.3\,\text{min})(60\,\text{s/min})}}$$

$$= 6.5 \times 10^{11}\,\text{atoms}$$

Using Avogadro's number, the number of moles is then 1.08×10^{-12} and SA $= 9.3 \times 10^9$ Ci/mol or 9.3×10^3 Ci/μmol.

If the radionuclide had been ^{14}C with its 5715-year half-life and following the same process but using the decay constant ($\lambda = 3.82 \times 10^{-12}\,\text{s}^{-1}$) for ^{14}C, then the SA would be 62 Ci/mol. Therefore, it is easy to see that the short-lived radioisotopes potentially have a much higher SA. If, however, the radiolabeled glucose had been prepared in a plant, the naturally occurring glucose would have lowered the SA due to the nonradioactive glucose molecules.

3. Accelerators

The transformation of one element into another was first demonstrated by Ernest Rutherford in 1919 [3], when he directed the α particles emanating from a sample of polonium onto nitrogen gas and detected the protons being emitted (having produced O-17). The future of accelerator production of radioisotopes reached a turning point with the construction of the cyclotron by Ernest Lawrence in 1931 [4, 5]. With the cyclotron, it became possible to produce radioactive isotopes of a wide variety for the first time. Researchers from all over the world came to Berkeley to use the artificially produced radiotracers such as radioactive sodium and iodine in the late 1930s. Cyclotron-produced radionuclides for biomedical research were used in the late 1930s for some clinical research and for basic research in biochemistry. In 1936 the University of California officially established the Radiation Laboratory as an independent entity within the Physics Department. The reorganized laboratory was dedicated to nuclear science rather than, as in its first incarnation, to accelerator physics. A center for nuclear medicine already existed at the University of California Hospital in San Francisco, where J. G. Hamilton and

Robert Stone were using radioactive sodium clinically in 1937. The use of these artificially produced radiotracers continued with Hamilton and Stone. In 1938 S. Hertz, A. Roberts and R. D. Evans used radioactive iodine in the study of thyroid physiology, followed in 1939 by J. H. Lawrence, K. G. Scott and L. W. Tuttle studying leukemia with radioactive phosphorus. By 1940 Hamilton and M. H. Soley were performing studies on iodine metabolism by the thyroid gland *in situ* by using radioiodine in normal subjects and in patients with various types of goiters [2].

They were joined by Lawrence's brother John, who had been interested in the biological effects of neutrons during a visit to Berkeley in the summer of 1935. Funding for the machine promised to Lawrence in 1936 was raised on the grounds of its utility in medicine [6, 7].

Even with this background, in the early years, cyclotrons were mainly used in physics research. Radionuclides for medical applications were a sidelight. The first cyclotron dedicated to medical applications was installed at Washington University, St. Louis in 1941, where radioactive isotopes of phosphorus, iron, arsenic and sulfur were produced. During World War II, a cyclotron at Cambridge, Massachusetts also provided a steady supply of radionuclides for medical purposes. In the mid-1950s a group at Hammersmith Hospital in the United Kingdom put into operation a cyclotron wholly dedicated to radionuclide production. The major change occurred in the early and mid-1960s, when the work in hot atom chemistry (such as the *in situ* chemistry of nucleogenic atoms occurring in a target being bombarded) laid the foundation for the synthesis of organic compounds labeled with positron emitters. A 1966 article by Ter-Pogossian and Wagner focused on the use of carbon-11 [8]. As the field of nuclear medicine has progressed, the number of available types of particle accelerators with varying characteristics dedicated to radionuclide production for nuclear medicine has also expanded. The major classes of accelerators are the positive and negative ion cyclotrons. More recent innovations include superconducting magnet cyclotrons, small low energy linacs, tandem cascade accelerators and helium-particle-only linacs. These types of accelerators have not gained wide acceptance.

Wolf and colleagues [9–11] have reviewed the application of cyclotrons for the production of radionuclides and suggested that the accelerators can be classified into four levels reflecting the particle type and energy of these particles. These are listed in Table 1 (adapted from Refs. 10 and 11).

Table 1. Classification of accelerators.

Classification	Characteristics	Proton energy	Comments
Level I	Single particle, p or d (some dual particle)	10 MeV	
Level II	Single or multiple particle, p, d	20 MeV	^{3}He, ^{4}He — not usually available
Level III	Single or multiple particle, p, d	50 MeV	^{3}He, ^{4}He — may be available
Level IV	Usually p only	70–500 MeV	

The principle advantage of accelerator-produced radioisotopes is the high SAs that can be obtained through the (p, xn) and (p, α) and other reactions involving charged particles that result in the product being a different element than the target. Another significant advantage is that a smaller amount of radioactive waste is generated from charged particle reactions.

Cyclotrons designed for producing medical radioisotopes were initially capable of accelerating protons, deuterons, $^3He^{+2}$ and α particles (the nucleus of ^{4}He). However, the principal radioisotopes currently used in medical applications can all be produced by protons. The simplicity of design for proton-only cyclotrons has resulted in cyclotrons which are capable of generating two or more simultaneous beams of varying energies and intensities. The modern cyclotron is completely controlled by a computer and can be in continuous operation for many days with minimal attention.

3.1. *Development of the linac*

The concept of the linac arose because there is a practical limit to the energy which can be supplied to a particle between two single electrodes. No matter how well the electrodes are insulated, there will be a discharge of the potential to ground. To overcome this limitation, R. Wideroe devised a system in Germany in the 1930s which would allow the particles to be accelerated in many small steps adding up to a much greater potential than one giant push [1].

3.1.1. *Principles of operation*

The principle of acceleration used in all accelerators is the fact that a charged particle has its energy changed when it is acted on by an electric field. In the linac, this change in energy is applied by an alternating potential which must be applied in exactly the proper sequence to keep accelerating the particle. In practice, this is achieved with the use of hollow electrodes called drift tubes, which allow the particle to drift at constant velocity within the tube and then be accelerated between the tubes. The particle is accelerated into the tube by an electric field which is opposite in sign to the charge on the particle. As the particle passes through the hollow tube, the phase of the electric field is changed and, at the exit of the tube, the particle is accelerated with a push from the field, which now has the same sign as the particle.

One fact which helps to maintain the timing of the acceleration is what is referred to as phase stability. The potential at each stage of the accelerator can be set so that the maximum potential is applied just after the particles have passed a point. If the particle arrives too early, the potential applied will be slightly less than optimal and the particle will traverse the next section more slowly and will be in phase for the next accelerating potential. This allows for some margin of error in the timing. If the particle is moving too slowly and arrives a little late, the phase of the accelerator can give it a little extra push and again the particle will move to be in phase at the next section of the accelerator.

This effect will result in the particles emerging from the end of the linac to be in bunches. The magnitude of this effect can sometimes be a problem in the design of targetry for the linac, since the instantaneous power delivered to a target can be quite high.

3.1.2. *Radio frequency acceleration*

The radio frequency (RF) power for the current designs of medical linacs is supplied at high frequency (200–500 MHz) which allows the overall length of the linac to be much shorter. The power for the RF system is usually supplied with a bank of power tubes contained within a coaxial cavity. The use of very high frequencies allows the use of shorter sections for the drift tubes, and also allows the linac to be shorter. This is an extremely important factor, since the particles must traverse the length of one drift tube in one cycle of the RF. This implies that the length of the drift tube must be

$$l = \beta\lambda, \tag{2}$$

where l is the length of the tube, β is the fraction of the speed of light for the particle and λ is the free space wavelength of the RF.

In order to build a linac with reasonable energies and of reasonable size, a high frequency is essential. Power supplies which can provide high power at high frequency have only recently become available.

3.1.3. *Current linacs*

In the late 1980s the United States Department of Defense supported research and development of new accelerators based on the "Star Wars" technology. There were three funded projects, all of which were of a linear design [12]. The aim was to make use of the technology that could produce a very high density of particle beams of low energy. These new accelerators were to compensate for the low production cross-sections at low energy (< 10 MeV) with increased beam current (100–1000 μA).

While the accelerator technology had advanced to achieve these beam currents, the target technology had not been tried under these severe conditions. Science Applications International Corporation, San Diego, California built an 8 MeV $^{3}He^{++}$ RFQ accelerator. Its unique features included simplicity in design and operation with a low neutron field from the accelerator [no inherent neutrons from the accelerating particle or the nuclear reactions to be utilized — (^{3}He, ^{4}He) and (^{3}He, p)]. The machine had particle energy of 10 MeV. AccSys Technology Incorporated, Pleasanton, California proposed a linac, also powered by RFQ, but accelerating protons. A variety of energies could be achieved by varying the length of the accelerator (adding on accelerating cavities). Science Research Laboratory Inc., Somerville, Massachusetts proposed a 3–4 MeV tandem cascade accelerator (TCA) that would accelerate deuterons for ^{15}O and ^{13}N production and protons for ^{18}F production.

The TCA is an electrostatic accelerator that starts with negative ions that pass through a charge stripper to convert to positive ions, which doubles the energy for the same potential difference. At the same time Ion Beam Applications,

Louvain-la-Neuve, Belgium built a 3 MeV deuteron$^+$ cyclotron dedicated to the production of ^{15}O. Several of these small cyclotrons have been situated in Europe. Of the "Star Wars" machines, only the TCA was built, installed and operated on a routine basis to produce radioisotopes for PET.

3.2. *Development of the cyclotron*

Cyclotrons are the most commonly used devices for the acceleration of particles to energies sufficient for bringing about the required nuclear reactions. It was the remarkable idea of Lawrence to bend the path of the particles in a linear accelerator into a circle and therefore use the same electrode system over and over again to accelerate the particles. This idea is the basis of all modern cyclotrons and has made the cyclotron the most widely used type of particle accelerator. The first model was built in 1930, with proof of particle acceleration being provided by M. S. Livingston in 1931.

Unfortunately, the literature on cyclotrons for medical purposes is somewhat sparse. The book by Livingood published in 1961 [13] and a more recent review by Scharf [14] are general texts on cyclotrons and other particle accelerators. Detailed information on advances in cyclotrons and other accelerators is available as a series of symposium papers [15]. Cyclotrons for biomedical radionuclide production have been reviewed by Wolf and Jones in 1983 [11].

3.2.1. *Principles of cyclotron operation*

The principle of the cyclotron is based on the application of small accelerating voltages repeatedly. See Fig. 1 for a schematic of the cyclotron's principal components. Hollow cavities called dees (because of their shape) serve as the electrodes for the acceleration. An RF oscillator is connected to the dees such that the electrical potential on the dees is alternatively positive and negative with respect to each other. By placing the dees between the poles of a strong magnet so that the magnetic field is perpendicular to the plane of the charged particle undergoing acceleration will move in a circular path. As the particle gains energy it moves in a spiral outward from the center. With the source of negative ions at a point in the center of the cyclotron the positive dee will accelerate the ions toward that dee with a magnetic field, forcing them to move in a curved path. Once inside the cavity the particles no longer experience an electric force. Continuing in the circular path, the particles will exit the dee and enter the gap between the dees where the second dee has changed its potential to be an attracting force, accelerating the particles to that dee.

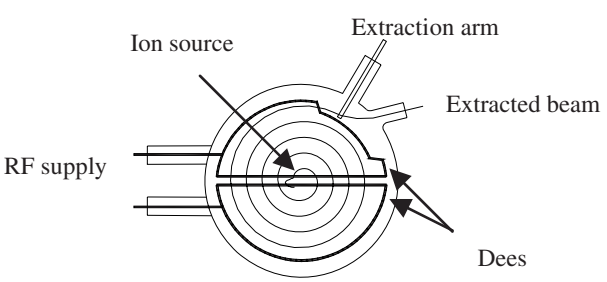

Fig. 1. Schematic of a cyclotron, showing the key components. See text for discussion.

The dees reverse their potential when the particles are inside them, so that at each crossing of the gap the particles receive an increase in energy of the order of 20–50 keV. Lawrence discovered the equations defining this principle of operation in 1929 and built the first cyclotron in 1931.

$$Bev = \frac{mv^2}{r}, \tag{3}$$

where

$$r = \frac{mv}{Be}.$$

Since angular velocity,

$$\begin{aligned} \omega &= \frac{v}{r} \\ \omega &= \frac{Be}{m}, \end{aligned} \tag{4}$$

where m is the mass of the ion, e is its charge and v its velocity with B equaling the magnetic field, and r is the radius of the ion's orbit. Thus the orbit of the particle is directly proportional to the particle momentum, and the particle orbit frequency is constant and independent of energy. This principle breaks down under relativistic effects where the mass is not constant.

While the basic components of modern cyclotrons are essentially the same as the original designs (RF cavities, vacuum tank, magnet, ion source, extraction system), there have been some innovations in the last few decades that have had a major impact on the design of the modern cyclotron. The two most significant changes have occurred in getting

the ions into the cyclotron (ion source) and out of the cyclotron (extraction system).

Nearly all modern cyclotrons now use a negative ion source. Ions are generated by passing the source gas through an electric field that generates negative and positive ions (for example, in the case of H_2, the resulting ions will be H^+ or protons and H^- ions, a proton with two electrons). The advantage of negative ions resides in the ability to easily have a variable energy cyclotron, to have nearly 100% extraction (see below), and to extract multiple beams, simultaneously. The design of the ion source has also changed, in that the ion source can reside inside of the cyclotron, where the ions are generated at the center of the cyclotron (center region) or from outside of the cyclotron (external ion source) and subsequently injected into the center region for acceleration. There are obviously advantages and disadvantages to each approach. With an external ion source the vacuum can be operated at very low pressures with very little beam loss due to stripping of the negative ion by the residual gas. However, the vacuum system must be of a very clean nature to maintain this high vacuum. With an external ion source, maintenance can be performed without opening the cyclotron or breaking the vacuum. In addition, the center region is not disturbed as in the case of the internal ion source that is part of the center region.

The simplicity of the design for proton-only cyclotrons resulted in cyclotrons which accelerate H^- ions capable of two or more simultaneous beams of varying energies and intensities. The modern cyclotron is completely controlled by a computer and is capable of running for many days with minimal attention. The major drawback of these proton cyclotrons lies in the fact that in some cases an enriched target material must be used for sufficient products to be generated.

3.2.2. *Energies and particles*

The energy of the accelerator needed again depends on the demands of the program. However, this increase in the number of radionuclides which may be produced comes with a price both in the equipment expenses and in the infrastructure. In addition, the number of side channel reactions rises as the energy increases and unwanted radionuclides can be produced. This is especially true at energies greater than 30 MeV.

The production of the traditional radioisotopes used in nuclear medicine (^{201}Tl, ^{67}Ga, ^{123}I and ^{111}In) has been via proton reactions for more than 25 years. However, many of the most useful radionuclides can be produced with proton energies below 30–40 MeV. Higher energy cyclotrons (greater than 40 MeV) are usually installed only at large laboratories, government facilities or large commercial facilities where radionuclides are produced for sale. The particular choice of particle(s) and energy will depend on the envisioned program. The selection of a cyclotron will also depend on which radionuclides are needed to prepare the radiopharmaceuticals used in the clinical and research programs, and whether these radioisotopes will be distributed to other locations.

3.3. *Choice of an accelerator*

The question we are left with is: Which type of accelerator is best for my situation? There are some practical considerations when one is making that decision. The main factors are the initial cost, the reliability, the radiological hazards, the operating costs, the installation costs and the available support from the manufacturer. Some of these aspects are outlined in the next sections.

3.3.1. *Comparison between cyclotrons and other accelerators* [1]

There are several aspects to consider when one is choosing an accelerator. Some of the characteristics that may be considered are given in Table 2.

The first consideration with any accelerator is whether or not it is capable of producing sufficient quantities of radionuclides for particular needs of the facility. Regardless of what type of accelerator is installed, it must be kept in mind that the accelerator delivers protons, deuterons or, less commonly, helium-3 and helium-4 ions. Cross-sections of nuclear reactions for production of most radioisotopes are well characterized, and the practical yields as a function of the particle energy are also well known.

The selection of an accelerator is determined in practice by the energy of the particle beam required for the desired nuclear reaction. For example, for a facility wishing to produce only the conventional PET isotopes (^{11}C, ^{13}N, ^{15}O and ^{18}F), the level

Table 2. Comparisons of accelerators for radionuclide production.

Accelerator type	Advantages	Disadvantages
Positive ion cyclotron	Proven record Versatility Ease of maintenance	High cost High activation
Negative ion cyclotron	Extraction efficiency Low activation Beam uniformity	High cost High vacuum requirements Maintenance of stripper foil
Superconducting cyclotron	Compact size Low power	Liquid helium Maintenance
Linac	Stable operation Low power	Targetry Size
Tandem cascade	Low power Low cost	Targetry
Helium-3 linac	Low power Stable operation	Low specific activity Targetry

I cyclotron, which delivers a 10 MeV proton beam, may be sufficient.

On the other hand, a center wishing to manufacture the SPECT isotopes (Tl, ^{67}Ga, ^{123}I, ^{111}In, etc.) must consider a cyclotron capable of delivering a higher energy particle beam (level II or level III).

Of all the various accelerators, cyclotrons are by far the most extensively used for the production of PET and SPECT radioisotopes. It is therefore to be expected that there is a great deal more information concerning the application and reliability of the cyclotron in comparison with the other types of accelerators. In general, cyclotrons have proven to be reliable accelerators and to provide optimum conditions for consistent isotope production. The linacs and Van de Graaff accelerators have also been used for production of isotopes, but not commonly.

Although linacs are also stable machines, they have been used in centers where there are accelerator physicists to address any problems and do not have a history of radioisotope production facilities. As these accelerators are placed, however, a better idea can be obtained as to how reliable they will be.

The tandem cascade accelerator and the He-3 linac RFQ are accelerators which were built and tested, but proved to have very limited application in radionuclide production.

4. Medical Applications

Diagnostic nuclear medicine makes use of the fact that certain radioisotopes emit gamma rays with sufficient energy that the gamma rays can be detected outside of the body.

If these radioisotopes are attached to biologically active molecules, the resulting compounds are called radiopharmaceuticals. They can either localize in certain body tissues or follow a particular biochemical pathway. The following discussion will concentrate on the uses of radioactive substances for the diagnosis or therapeutic treatment of human pathology.

4.1. *Historical background* [2]

Nuclear medicine has its origins in the pioneering work of the Hungarian physician George de Hevesy, who, in 1924, used radioactive isotopes of lead as tracers in bone studies. Shortly thereafter, R. H. Stevens made intravenous injections of radium chloride to study malignant lymphomas.

As indicated above, the first medical cyclotron was installed in 1941 at Washington University, St. Louis, where radioactive isotopes of phosphorus, iron, arsenic and sulfur were produced. With the development of the fission process during the Second World War, most radioisotopes of medical interest began to be produced in nuclear reactors. After the War the wide use of radioactive materials in medicine established the new field of what was then called atomic medicine, which later became known as nuclear medicine. Radioactive carbon, tritium, iodine, iron, and chromium began to be used more widely in the study of disease processes.

Ben Cassen, in 1951, developed the concept of the rectilinear scanner, which opened the way to obtaining in a short amount of time the distribution of radioactivity in a subject. This was followed by production of the first gamma camera by Hal Anger in 1958. The original design was modified in the late 1950s to what is now known as the anger scintillation camera, thus heralding the modern era of gamma cameras, whose principles are still in use today.

Powell Richards developed the ^{99}Mo/^{99m}Tc generator system at Brookhaven National Laboratory in 1957. Technetium-99m produced via this

generator system has become the most widely used radionuclide in nuclear medicine today, accounting for as many as 85% of all diagnostic procedures.

The modern era of nuclear medicine has become known as molecular medicine, since it is now possible to translate advances in molecular biology and biochemistry into an understanding of human physiology, and from there into clinical treatment, and the diagnosis of pathology and anatomical abnormalities. The advent of clinical PET for cancer diagnosis makes use of sophisticated tracers to unravel cancer biology.

4.2. *Radionuclides for imaging*

Nuclear medicine imaging differs from other types of radiological imaging, in that the radiotracers used in nuclear medicine map out the function of an organ system or metabolic pathway and, thus, imaging the concentration of these agents in the body can reveal the integrity of these systems or pathways. This is the basis for the unique information that a nuclear medicine scan (described in Table 3) provides with various scanning procedures for the various organ/functional systems of the body.

Table 4 provides the various low energy production routes along with the half-lives of the radioisotopes. Technetium-99m is included, since this isotope alone accounts for nearly 85% of all nuclear medicine imaging studies. There have been a number of proposals suggesting that ^{99m}Tc could be produced at an accelerator. The economics of producing ^{99m}Tc at an accelerator can never compete with the extremely low costs of producing it at a reactor. While there is concern about the ability to build new reactors and thus jeopardize the availability of this important isotope, and the recent leakage problems with the primary reactors producing Mo-99, there is growing concern about alternatives. Consequently, the prospect for producing Mo-99 or Tc-99m directly via charged particle reactions or from photons needs to be revisited.

Iodine-123 has been of interest for nearly three decades. Its unique chemistry that makes it possible to attach this isotope to a wide variety of molecules and the γ-ray energy (159 keV), which is well matched to SPECT cameras. The ability to produce this isotope in high purity from enriched ^{124}Xe targets made it possible to ship ^{123}I over long distances and still have high SA ^{123}I available for labeling. However, the production costs are still very high

Table 3. Typical radioisotopes and their uses for imaging.

Radioisotope	Half-life	Uses
Technetium-99m	6 h derived from ^{99}Mo parent 66 h	Used to image the skeleton and heart muscle, in particular; but also for the brain, thyroid, lungs (perfusion and ventilation), liver, spleen, kidneys (structure and filtration rate), gall bladder, bone marrow, salivary and lachrymal glands, heart blood pool, infection and numerous specialist medical studies.
Cobalt-57	272 d	Used as a marker to estimate organ size and for *in vitro* diagnostic kits.
Gallium-67	78 h	Used for tumor imaging and localization of inflammatory lesions (infections).
Indium-111	67 h	Used for specialist diagnostic studies, e.g. brain, infection, and colon transit studies.
Iodine-123	13 h	Increasingly used for diagnosis of thyroid function, it is a gamma emitter without the beta radiation of ^{131}I.
Krypton-81m	13 s from ^{81}Rb 4.6 h	^{81m}Kr gas can yield functional images of pulmonary ventilation, e.g. in asthmatic patients, and for the early diagnosis of lung diseases and function.
Rubidium-82	65 h	Convenient PET agent for myocardial perfusion imaging.
Strontium-92	25 d	Used as the "parent" in a generator to produce ^{82}Rb.
Thallium-201	73 h	Used for diagnosis of coronary artery disease and other heart conditions, such as heart muscle death and for location of low-grade lymphomas.
Carbon-11 Nitrogen-13 Oxygen-15 Fluorine-18	20.4 m 9.97 m 2 m 110 m	These are positron emitters used in PET for studying brain physiology and pathology, particularly for localizing the epileptic focus, and in dementia, psychiatry and neuropharmacology studies. They also have a significant role in cardiology. ^{18}Fin FDG has become very important in the detection of cancers and the monitoring of progress in their treatment, using PET.

Table 4. Routes to production for imaging radionuclides.

Radionuclide	$t^{1/2}$	Reaction	Energy (MeV)
^{99m}Tc	6.0 h	^{100}Mo$(p,2n)$	30
^{123}I	13.1 h	^{124}Xe$(p,2n)^{123}$Cs	27
		^{124}Xe$(p,pn)^{123}$Xe	
		^{124}Xe$(p,2pn)^{123}$I	
		^{123}Te$(p,n)^{123}$I	15
		^{124}Te$(p,2n)^{123}$I	25
^{201}Tl	73.1 h	^{203}Tl$(p,3n)^{201}$Pb$\rightarrow{}^{201}$Tl	29
^{11}C	20.3 m	^{14}N(p,α)	11–19
		^{11}B(p,n)	10
^{18}F	110 m	^{18}O(p,n)	15
		^{20}Ne(d,α)	14
		$^{\text{nat}}$Ne(p,X)	40
^{64}Cu	12.7 h	^{64}Ni(p,n)	15
		^{68}Zn$(p,\alpha n)$	30
		$^{\text{nat}}$Zn$(d,\alpha xn)$	19
		$^{\text{nat}}$Zn$(d,2pxn)$	19
^{124}I	4.14 d	^{124}Te(p,n)	13
		^{125}Te$(p,2n)$	25

in comparison with other radioisotopes, which will limit its use for the foreseeable future. While ^{123}I can be produced for local use via the ^{123}Te(p,n) or ^{124}Te$(p,2n)$ reactions, the coproduction of ^{124,125}I limits the product's shelf-life.

Thallium-201 was developed at Brookhaven National Laboratory, where it was shown that ^{201}Tl could be used as a tracer for detecting myocardial perfusion. Thallous chloride labeled with ^{201}Tl has been used extensively for more than 30 years and remains the gold standard for measuring blood flow. Over this period there have been numerous reports of its demise due to the availability of ^{99m}Tc-labeled alternatives, yet the growth in demand for this isotope is still upward, especially during shortages of Tc-99m.

The remaining isotopes listed are used in PET imaging. Carbon-11 is extremely attractive because, in principle, one can replace an existing carbon atom in the molecule of interest with the radioactive isotope without altering the biochemistry of the molecule. However, because of the short half-life, its availability will be limited to those sites possessing an accelerator or which are in the vicinity of one.

The demand for ^{18}F exceeds its availability. To overcome this shortage, a number of central distribution centers have been placed in large metropolitan areas in North America, Europe and Asia. Although several nuclear reactions are possible, the (p,n) reaction is the choice for producing large quantities of ^{18}F. If the availability of ^{18}F continues to grow, ^{18}F-labeled compounds may begin to compete with SPECT agents such as ^{123}I.

The two other isotopes (^{64}Cu and ^{124}I) are candidates for both PET imaging and possible use in therapy (see below). The interest in these two is primarily related to the relatively long half-lives. Such properties would enable studies to be performed where the kinetics are slow and exceed the ability to image with ^{18}F. The disadvantages include the low production rate (^{124}I) and the need for expensive enriched target material (^{64}Ni, ^{124}Te). Results from Washington University in St. Louis have shown that even with the high energy β^+ particles associated with ^{124}I decay and other photons in coincidence with the β^+ decay, they can still be imaged at high resolution (^{64}Cu) [16, 17].

While there is a wide range of radionuclides that are used in imaging, a relatively small number make up the vast majority of all studies in SPECT and PET imaging.

Table 4 lists the most widely used radionuclides for imaging, along with a couple of potentially useful radionuclides.

PET imaging has been in use for several decades for human brain and whole body imaging, first only as a research tool, now gaining acceptance as a diagnostic imaging modality in selected applications such as oncology and, very recently, as an aid in the diagnosis of Alzheimer's disease. All of these advances have been made possible through the improvement in resolution and sensitivity of the scanners but, more importantly, through the development of more specific tracers.

4.3. *Radionuclides for therapy*

The idea of a radioisotope used in therapy is based on the desire to link a radionuclide which has a high linear energy transfer (LET) associated with its decay products, such as Auger electrons, β particles or α particles, to a biologically active molecule that can be directed to a tumor site. Since the β^--emitting radionuclides are neutron-rich, they have, in general, been produced in reactors. Table 5 lists some of the radionuclides that have been proposed as possible radiotoxic agents and their routes of production via charged particle reactions.

Table 5. Charged particle production routes and decay modes for selected therapy isotopes.

Radionuclide	$t^{1/2}$	Decay mode	Reaction	Energy (MeV)
^{77}Br	2.4 d	Auger electrons	^{75}As$(a, 2n)$	27
			^{77}Se(p, n)	13
			^{78}Se$(p, 2n)$	24
			^{79,81}Br$(p, xn)^{77}$Kr	45
			^{nat}Mo$(p,$ spall.)	>200
^{103}Pd	17.5 d	Auger electrons	^{103}Rh(p, n)	19
			^{nat}Ag(p, xn)	>70
^{186}Re	90.6 h	β^-	^{186}W(p, n)	18
			^{186}W$(d, 2n)$	20
			^{197}Au$(p,$ spall.)	>200
			^{nat}Au$(p,$ spall.)	>200
			^{nat}Ir$(p,$ spall.)	>200
^{211}At	7.2h	α	^{209}Bi(a,2n)	28
			^{209}Bi(7Li,5n)^{211}Rn	60
			^{232}Th$(p,$ spall.)^{211}Rn	>200

The attractive feature of ^{77}Br is its chemical versatility in addition to its half-life. Production rates are relatively low and purity may be an issue since ^{76}Br is often coproduced. The demand for ^{103}Pd, which is used in treating prostate cancer, is continuing to grow. A large number of low energy (19 MeV) cyclotrons are dedicated solely to the production of this isotope.

Rhenium-186 is attractive for a number of reasons. Besides the decay characteristics, rhenium is in the same chemical family as technetium, and thus much of the extensive chemistry developed for technetium can be applied to rhenium.

The production rates from all of the reactions for this radioisotope listed in Table 6 are very low. Thus, the only practical route to this potentially important isotope is via neutron capture in a reactor. This route results in a very low SA product, which severely limits its utility.

And, finally, the α-emitting isotopes have been of interest for use in therapy because of the high LET associated with the α decay.

Astatine is of interest because it possesses many properties of halogens and each decay of ^{211}At has an α particle associated with it. Because of its short half-life, multiple production sites would be required for practical applications. Thus, the interest in producing its parent radionuclide (^{211}Rn, $t_{1/2} = 14.6$ h) has been suggested as a way of producing and shipping ^{211}At to remote sites.

Table 6. Examples of generator systems available today.

Generator	Parent $t_{1/2}$	Daughter $t_{1/2}$	Uses
^{99}Mo/^{99m}Tc	66 h	6 h	Tc-99m is the most widely used radionuclide in nuclear medicine, single photon emitter.
^{68}Ge/^{68}Ga	270 d	68 m	In equilibrium as a long-lived positron source; Ga metal chemistry
^{82}Sr/^{82}Rb	25.5 d	76.4 s	Cardiac blood flow
^{81}Rb/^{81m}Kr	4.58 h	13 s	Lung ventilation studies
^{225}Ac/^{213}Bi	10.0 d	45.6 m	Radionuclide therapy (α particles)
^{62}Zn/^{62}Cu	9.26 h	9.7 m	Blood flow, hypoxia

4.4. *Radioisotope production rates and yield considerations*

The rate of radionuclide production is dependent on a number of factors, including the magnitude of the reaction cross-section as a function of energy, the incident particle energy, the thickness of the target in nuclei per cm^2 which will determine the exit particle energy, and the flux (related to the beam current) of incoming particles. The rate of production is given by

$$-\frac{dn}{dt} = R = nI(1 - e^{-\lambda t}) \int_{E_s}^{E_0} \frac{\sigma(E)}{dE/dx} dE, \qquad (5)$$

where:

- R is the number of nuclei formed per second;
- n is the target thickness in nuclei per cm^2;
- I is the incident particle flux per second and is related to the beam current;
- λ is the decay constant and is equal to $\ln 2/t_{1/2}$;
- t is the irradiation time in seconds;
- σ is the reaction cross-section, or the probability of interaction, expressed in cm^2, and is a function of energy;
- E is the energy of the incident particles;
- x is the distance traveled by the particle in the target;
- $\int_{E_s}^{E_0}$ is the integral from the initial to the final energy of the incident particle along its path.

It is of historical interest to note that the unit for the cross-section is the barn, which is equivalent to 10^{-24} cm^2. The word barn comes from the fact

that the probability for a neutron to interact with a target is proportional to the area of the nucleus, which, compared to the size of the neutron, appeared *as big as a barn.*

For routine production of radioisotopes, the practical yield can be quite different from the saturation yield of a radionuclide usually found in the literature. The rate of production is, of course, affected by the fact that the resulting nuclide is radioactive and thus undergoes radioactive decay. For short-lived nuclides the competing reaction rates, production and decay will achieve equilibrium at sufficiently long bombardment times since the rate of decay is proportional to the number of radionuclei present. The point where equilibrium is reached is called saturation. This means that there is no benefit to longer irradiations, as the production rate equals the rate of decay, and therefore no additional product will be formed. At shorter irradiation times the fraction of the product that is yielded is related to the saturation factor given by $(1 - e^{-\lambda t})$, where λ is the decay constant of the decaying nuclide and t is the bombardment time. It is evident that an irradiation equivalent to one half-life would result in a saturation factor of 50%. For practical reasons, an irradiation rarely exceeds three half-lives (90% saturation) except for the shortest-lived radionuclides.

For long-lived species, the quantity produced is usually expressed in terms of the integrated dose or total beam flux (μA-h). For example, with a long-lived radionuclide such as ^{82}Sr ($t_{1/2} = 25\,$d) the amount produced will be essentially the same whether it is produced from $100\,\mu$A in 1 h or $50\,\mu$A in 2 h (both represent $100\,\mu$A-h of the beam).

The chemical form of the radionuclide is also of major interest in considering the attributes of any machine. The target material must withstand the intensely ionizing particle beam, and must also be able to withstand the intense radiation field accompanying the particle bombardment. The question of the chemical form of the radioisotope coming from the target, which target material to use and the specific bombardment conditions have been a matter of research since the early 1950s. Target conditions can be manipulated to some extent to provide the desired precursors for syntheses of labeled compounds directly from the target.

Another aspect relating to chemistry is the choice between proton-only machines and two-particle (proton, deuteron) machines. If a proton-only machine is chosen, enriched isotopes are needed to produce some of the four PET radionuclides. If a dual particle machine is chosen, the production of ^{15}O and ^{13}N can be done with natural abundance target materials. Other radioisotopes may require enriched isotope targets with either protons or deuterons.

Cyclotrons employed for producing medical radionuclides were initially designed for physics experiments and used only part-time for medical applications. These cyclotrons were capable of accelerating protons, deuterons, ^{3}He^{+2} and α particles (the nucleus of ^{4}He). As can be seen from Table 4, however, the PET radionuclides are produced from either proton or deuteron reactions. In the early 1980s, small compact proton-only cyclotrons became available and cyclotrons specifically designed for producing PET radionuclides were installed in many hospitals.

One of the major drawbacks to the widespread availability of PET is the high capital cost associated with the cyclotrons and scanners. However, the success of the small low energy cyclotron encouraged research into the design of even lower energy accelerators, i.e. linear accelerators and cyclotrons of a-few-MeV extracted energy. To date, there are very few of these machines in routine use.

4.5. *Generators*

Finally, the other source of radionuclides used in medicine is the generator. A radioactive generator takes advantage of the cases where one longer-lived (parent) radionuclide decays, usually by β^- emission, to a shorter-lived (daughter) radionuclide. The chemical differences in the two elements are exploited to separate the daughter product from the parent. The parent radionuclide is produced by one of the methods described above and then attached to an inert substance, from which the desired product can be eluted or washed off the support. The product can be used directly, as in the case of ^{82}Rb^{+} from the Sr/Rb generator, or after undergoing a chemical reaction, as in the case of ^{99m}Tc from the Mo/Tc generator (see Table 6).

The equilibrium equations that reflect the relative radioactivity of parent and daughter are given

by the general equation

$$A_d(t) = A_p(0)\left[\frac{(\lambda_d)(e^{-\lambda_p t} - e^{-\lambda_d t})}{\lambda_d - \lambda_p}\right] + A_d(0)e^{-\lambda_d t}, \tag{6}$$

where A is the radioactivity of the daughter (d) and parent (p) respectively. A_d is equal to the product of the decay constant, λ_d, and the number of radioactive nuclei, N, present ($\lambda_d N$). The first term accounts for the growth of the daughter as a function of the decay of the parent as well as the disappearance of the daughter due to its own decay. The last term accounts for the presence of daughter nuclei at zero time.

All generator systems used routinely in nuclear medicine form an equilibrium between parent and daughter radionuclei. In the case of the ^{99}Mo/^{99m}Tc generator, the parent (^{99}Mo) decays at a rate sufficiently similar to that of the daughter (^{99m}Tc). With a half-life of 66 h for ^{99}Mo vs. 6 h for ^{99m}Tc, there is an appreciable decay of the parent before the daughter reaches the steady state. This steady state condition is referred to as transient equilibrium. With transient equilibrium, the daughter radioactivity grows in and surpasses that of the parent before equilibrium is reached. The ratio of the daughter radioactivity to that of the parent is given by the equation

$$\frac{A_d}{A_p} = \frac{T_p}{T_p - T_d}, \tag{7}$$

where T is the half-life for each species, respectively.

For the situation where the parent has a half-life much longer than the daughter, e.g. ^{68}Ge/^{68}Ga and ^{82}Sr/^{82}Rb, the change in the amount of the parent during the time for the steady state to be reached will be negligible; the steady state condition is referred to as secular equilibrium. The quantity of daughter activity at any time is then expressed by the equation

$$A_d(t) = A_d(0)(1 - e^{-\lambda_d t}). \tag{8}$$

Thus, in secular equilibrium, when $e^{-\lambda t} \approx 0$, the daughter and parent radioactivity are approximately equal.

From Table 6, it is easy to see that generators have a wide variety of uses and half-lives of both parent and daughter nuclides.

Obviously, from an end user perspective, the long-lived parent makes it possible to have a single generator in use for an extended period of time.

The utility of the generator is actually based primarily on the daughter's half-life and the chemistry required to provide the radionuclide in a useful species. The simplest systems make use of the daughter nuclide directly; ^{82}Rb$^+$ and ^{81m}Kr are used directly as a K$^+$ ion analog and as an inert gas ventilation tracer, respectively.

The parent radionuclides are or can be all produced in accelerators. Ac-225 is extracted from the decay chain of Th-232 but efforts are underway to produce this radionuclide by irradiation of a radium target.

Of course, the most widely used generator system is the ^{99}Mo/^{99m}Tc pair, where over 80% of all nuclear medicine procedures performed worldwide use Tc-99m as the imaging radionuclide. There are numerous Tc-99m kits for producing tracers to examine the brain, kidney, heart, bone, liver, lung, red blood cells and TcO_4^- for the thyroid. Based on the successful use of Tc-99m in radiopharmaceuticals for diagnostic purposes, similar tracers are being developed based on the ^{68}Ge/^{68}Ga generator system, where the parent Ge-68 is produced in a cyclotron.

5. Imaging

While a detailed discussion on imaging is beyond the scope of this review, it is worth pointing out a few of the specifics in order to place the choice of radionuclide into context.

5.1. *Planar imaging*

By far the most common imaging device in nuclear medicine is the planar camera or the Anger camera. The basic components of the camera include a thin crystal of NaI scintillator coupled to a cluster of photomultiplier tubes (PMTs), an X, Y positioning circuit and a readout device that may be an oscilloscope or a photographic film. The NaI scintillator design minimizes multiple interactions with the incident γ-rays so that the position of interaction can be determined with great accuracy. Typical scintillation cameras have detectors 25–45 cm in diameter and 0.64–1.27 cm in thickness. The thickness is determined to match the photopeak for low energy photons emanating from Tc-99m.

The X, Y positioning circuit relies on the light output from the many (19–91) PMTs mounted on the back of the scintillator. The PMT located nearest

to the γ-ray interaction will receive the maximum amount of light, and the other PMTs will receive light in proportion to the solid angle subtended by the tube at the point of interaction. The positioning circuit sums the output of the PMTs and produces X and Y pulses proportional to X and Y coordinates of the γ-ray interaction.

In between the radioactive source and the detector is a collimator constructed of dense metal such as lead or tungsten. The collimator has one or more holes drilled through it to allow the passage of γ-rays. Since γ-rays cannot be bent or focused, the collimator's function is to absorb those γ-rays that do not pass through the openings.

In its simplest form the collimator has a single pin hole and acts like a camera lens. Other collimators are constructed with the holes converging, diverging or parallel to the imaginary line connecting the object to be imaged and the camera face. The converging collimator has the effect of magnifying the imaged object, while the diverging collimator minifies the object. The parallel collimator is used for high resolution. Regardless of which collimator is used they all absorb a large fraction of the photons emitted by the radiotracer in the patient.

5.2. *Single photon emission computed tomography*

Single photon emission computed tomography (SPECT) acquires views of the emitted photons from many different angles and reprojects these views to reconstruct the image or distribution of radioactivity in the object or patient. In SPECT, the radiopharmaceuticals used contain radionuclides such as Tc-99m that emit single photons (ones that are not in timed coincidence with one another). Directional information is achieved by collimating the photons incident on the detector of the Anger camera. The collimator thus reduces the sensitivity of the camera because all of the photons not parallel to the holes in the collimator are prevented from reaching the detector surface.

Since the reconstructed image contains the three-dimensional information on the distribution of radioactivity, SPECT also has the potential for quantification. The factors in this capability are similar to those in PET, e.g. system sensitivity, dead time, spatial resolution, sampling interval, reconstruction filters and the size of the object being imaged. Also, as in PET, the photons emerging from the subject are attenuated by the amount of matter between their origin and the detector, and, of course, they have a definite probability of being scattered along their path.

Because of the inherently lower energies (100–150 keV) of the photons emitted by radionuclides used in SPECT, the effect of attenuation can be quite dramatic, with reductions as great as a factor of 5 or more. Thus, with single photon emitters, it is difficult to determine whether data reflect a weak source near the surface or a stronger source located at a greater depth. In addition, the amount of scatter is strongly dependent on the energy of the photons, with the photons from ^{201}Tl having a scatter fraction of as much as 40–50%, depending on the depth of the source. It is for these reasons that attenuation and scatter are the most significant and difficult nonlinear effects to correct for.

Whereas scintillation camera images show the distribution of the radiopharmaceutical in defined regions in the planar view, they suffer from the superimposition of organs and background contributions to the areas of interest. It is because of these shortcomings in planar imaging that SPECT has a major role to play in diagnostic imaging regardless of whether SPECT can achieve the difficult task of providing quantitative information. The ability to view the distribution in three dimensions greatly affects the interpretation of the images.

5.3. *Positron emission tomography*

PET imaging makes use of the self-collimating nature of positron decay, as two nearly collinear photons are utilized to define the location of an annihilation event. PET cameras are typically made up of a ring of detectors that are in timed coincidence (resolving time of a few nanoseconds), allowing a line of response to define the cord along which the positron was annihilated (the location of the emission is not known because of the short distance the positron travels before annihilation). By mathematically back-projecting the lines of response, a density map can be generated that reflects the distribution of the positron emitter.

There are several physical limitations inherent in PET technology. Firstly, as the emitted positron has kinetic energy, varying from a few hundred keV to several MeV, depending upon the radionuclide,

it will travel a few millimeters to centimeters before annihilating with an atomic electron. As such, the site of annihilation is not the site of emission, thus resulting in a limitation when one is defining the origin of the decay. Another limitation is the fact that the positron–electron pair are not at rest when the annihilation occurs, and thus by conservation of momentum the two photons are not exactly collinear. Although the lack of colinearity becomes increasingly important with greater detector separation, this effect is ignored, for the most part, in existing tomographs because the detector ring diameter is less than a meter, at which distance the deviation from 180° is a fraction of a millimeter.

One of the major strengths that PET has over SPECT is the ability to measure, directly, the attenuation effect of the object being viewed. This is the result of requiring that both photons be detected. Thus, if one photon of the pair is not observed then there is no line of response. Along the path to the detectors, one or both photons (511 keV each, the rest mass of the electron) can undergo absorption by the photoelectric effect or Compton scattering when interacting with surrounding material. Thus, in order to be detected as an event, both photons must be detected in temporal coincidence. By using an external source of the positron emitter, the attenuating (absorbing) extent of the object to be measured can be determined. However, that advantage has been eliminated, since all commercial PET (and many SPECT) cameras are now built with a CT scanner (x-ray tomography) so that a merged image of structure and function can be obtained. In addition, as the CT image is a measure of electron density, it is used to calculate the necessary coefficients for attenuation correction. However, the calculated attenuation coefficients are difficult to perform in the thorax. Nevertheless, the use of the CT image is standard for attenuation corrections now, although its primary function is to provide a detailed view of the section of the body under investigation. Figure illustrates the power of this approach.

Once the attenuation of the object is measured and the radiotracer is injected, the temporal and spatial distribution of the tracer may be determined. However, to make a quantitative estimate of the distribution, other corrections are required. First of all, for true quantitative extraction of information the detector system must be normalized to account for the nonuniform response of the detector system. This is achieved by placing a cylindrical flood phantom of known tracer concentration in the field of view and measuring the responses of all detector pairs.

Other corrections needed are to account for scattered photons, which for modern systems can be anywhere from 30 to 50% of the events. The amount of scatter can be reduced by selecting a narrow energy window of acceptance so as to eliminate large angle scatter (large angle scatter results in lower energy of the scattered photon). This will, however, reduce the efficiency. The remaining scatter profile is removed by analytical techniques, discussion of which is beyond this article.

Finally, there are random coincidences that must be subtracted. Because of the finite timing window for defining the coincidences, there is the possibility of unrelated events arriving within the timing window. The amount of random events is related to the size of the timing window and the number of events in any one detector. Random events can be reduced by using fast detectors and electronics which enable a short timing window to be employed. Randoms are usually estimated by monitoring the single event rate and subtracting globally from the image.

6. Functional Imaging

Functional imaging using PET started as a research tool in neuroscience in the late 1970s and still remains a major research tool for the current day neurosciences. However, its major impact recently has been in the diagnosis of cancer. While simple tracer molecules such as water, carbon monoxide and carbon dioxide had been used for many years, the first complex molecule to be used extensively was the glucose analog, ^{18}F-fluorodeoxyglucose (FDG), developed at Brookhaven National Laboratory in collaboration with researchers at the National Institutes of Health in the US and the University of Pennsylvania around 1975. Since the human brain uses glucose as its primary energy source, the availability of the tracer led to groundbreaking work for studying the human brain in health and disease. This effort was driven by the success at using C-14-labeled deoxyglucose developed at the NIH by Louis Sokolov in the 1960s. Since C-14 is not imageable *in vivo*, the effort went into developing a labeled analog that could be shipped from a cyclotron facility (BNL

in this case) to the PET camera (the University of Pennsylvania) [2].

Today, many more tracers are used to investigate the various neuronal systems probing both the presynaptic and postsynaptic pathways. Several hundred tracers have been prepared and tested for the utility in investigating various enzymatic and receptor systems, while only a handful are routinely used. There are tracers specifically designed to monitor cell proliferation, the hypoxic nature of cells, and cell apoptosis.

Because diagnostic imaging is driven by a digital approach (present/absent, yes/no), the desire to have uncluttered images resulting from PET is strong. Nevertheless, the true power of PET is its ability to track the distribution of a tracer over time, and extract detailed kinetic data as in a physical chemistry experiment where rate constants are determined. So the conflict between using the technology for clinical diagnosis and using PET as an *in vivo* biochemistry tool will not be easily resolved, nor should it be.

With the advances in the technology enabling increasingly better resolution, it has become possible to build PET scanners capable of imaging small animals. The pharmaceutical industry has recognized the power of using such small animal PET scanners as a screening tool for their preclinical research. PET can be used as a surrogate to monitor changes in metabolism or receptor occupation or by labeling the drug directly and determining the distribution and time course of the compound, *in vivo*. One of the strengths of PET in this regard is that animals can be used many times so that they can serve as their own controls and changes due to interventions monitored. Such an approach increases the statistical power of the study.

Pharmaceutical companies also recognize that human PET scanning can be used as surrogates for monitoring the therapeutic efficacy of drugs in phases II and III drug trials. By performing base line scans and scans at intervals following intervention, the PET data can often reveal biochemical changes much sooner than the clinical signs — thus shortening the assessment time. Most often, surrogate markers are used to monitor a particular functional change.

As the physical limit of detection are approached, the remaining avenue is to increase signal-to-noise by utilizing tracers that are uniquely suited to imaging the function in question, and otherwise clears rapidly from surrounding tissue. To this end, the development of more specific tracers is believed to be the most critical component of PET.

7. Radiotracer and Chemistry Development

Tracer development is an extremely important component of PET and SPECT imaging. The scanner measures only radioactive decays and cannot by itself identify a biological process of interest. This is accomplished by careful radiotracer design and development to make it as specific as possible for the relevant biological sites and processes, while minimizing its binding to other tissue types [18, 19]. As the imaging instrumentation becomes more powerful, there is an increasing demand for new tracers as more sites and processes become potentially observable *in vivo*. In addition to undergoing *in vitro* validation, however, the new tracers must undergo a rigorous validation of their behavior *in vivo* and, where necessary, new imaging protocols and analysis methods must be developed. Presently there are a number of small molecules that have been used in human scanning for years.

7.1. *Radiopharmaceuticals*

The term "radiopharmaceutical" is derived from the fact that a radionuclide has been attached to a biologically active compound as opposed to using radiotracers that are elements, or their analogs, found in the body and suitable for human use. Radiopharmaceuticals differ in one major aspect from regular pharmaceuticals: they are given in such small concentrations that they do not elicit any pharmacological response. Because of this there have been a number of attempts to change the name used to describe these substances, such as "radiotracers." Present day radiopharmaceuticals are used for diagnostic purposes in about 95% of the cases, and the remainder are used in therapy. However, the use of radiopharmaceuticals in therapy is seen as the next major area of growth in the use of radionuclides.

In order for a radiotracer (radiopharmaceutical) to be used in humans safely, it must meet the quality standards, which include chemical and radiochemical purity, that it be sterile and free from pyrogenic material.

The ideal diagnostic radiopharmaceutical for imaging should:

(1) Be readily available at a low cost.
(2) Be a pure gamma emitter, i.e. no particle emission such as α and β. These particles contribute a radiation dose to the patient while not providing any diagnostic information (see the section on dosimetry). This is, of course, not followed with PET.
(3) Have a short effective half-life, so that it is eliminated from the body as quickly as possible.
(4) Have a high target-to-nontarget ratio, so that the resulting image has a high contrast, i.e. the background does not blur the image.
(5) Possess the proper metabolic activity, in that it follows or is trapped in the metabolic process of interest.

The ability to measure regional biochemical function requires a careful design process with these principles in mind. However, in reality it is not possible to meet all of these criteria. For example, all decay processes involve the emission of particles, as in the case of the pure γ-emitters which have Auger electrons emitted during some fraction of the decays. Thus, it is necessary to address the following steps [20] in the development of a biochemical probe:

(1) Develop a radiotracer that binds preferentially to a specific site;
(2) Determine the sensitivity of the radiotracer to a change in biochemistry;
(3) Find a biochemical change as a function of a specific disease that matches that sensitivity.

A large number of radiotracers have been synthesized to probe metabolic turnover such as oxygen consumption, glucose utilization and amino acid synthesis. Enzymatic activity, neurotransmission, receptor density and occupancy have all been measured via appropriately designed radiotracers. It should be pointed out that the development of radiotracers for PET fundamentally violates rule No. 2 for the ideal tracer because PET radionuclides, by nature, emit β^+ particles. However, the resulting coincident γ-rays from the β^+ annihilation form the basis for the technique.

In addition to consideration of the above principles, the synthetic chemist must plan how to insert the radionuclide into the molecule at a point in the synthetic process where there is minimal handling, yet late enough in the synthesis to minimize loss due to chemical yield and radioactive decay. For these reasons the preparation of radiopharmaceuticals requires planning and techniques not encountered by traditional synthetic chemistry.

The development and use of PET tracers can be viewed as covering two major areas: (1) tracers that can be used as surrogate markers for biological processes and (2) tracers that are specific to a particular process, whether it is intended to measure enzyme activity or receptor concentration or the expression protein synthesis. A major hindrance to tracer development is the complex nature of the synthesis process itself. While major strides have been made to simplify the synthesis steps, there are still areas in need of improvement, such as miniaturization of the synthesis instrumentation. Miniaturization provides the opportunity to use small amounts of starting materials and radioactivity that would make the purification simpler and easier. Simple solid phase columns could be used instead of cumbersome high performance liquid chromatography. In addition, if the miniaturization can be realized it is conceivable that multiple compounds could be prepared in parallel for testing with a single supply of radionuclides. This can be viewed as the radiochemist's attempt at screening compounds.

8. Future Directions

In order for PET to develop, the availability of F-18 and other positron-emitting radionuclides must be secured. Several commercial networks have been established throughout North America and Europe and parts of Asia. They have concentrated on supplying F-18, although some suppliers have made I-124 and Cu-64 available in small quantities.

The need for C-11 will probably remain of interest primarily to the research community and drug developers. The short half-life of C-11 makes it almost impossible to transport it over long distances; thus, if C-11 is to have an impact on clinical care, a small inexpensive accelerator will be required, as will modules for the rapid synthesis of C-11-labeled agents. As indicated above, such machines are being explored.

With superconducting technology reaching maturation, a number of areas in accelerator development will become possible, including building very

small cyclotrons and using electron linear accelerators for radionuclide production.

The challenges of building new reactors for radionuclide production will force alternative routes to be explored using accelerators, especially with respect to Mo-99 and Tc-99m. Recent papers indicate that local production and distribution of Tc-99m may be possible on a limited basis [21, 22]. The availability of powerful e-linacs may indeed be a solution through the photofission of U-238 if the ability to handle megawatt power in the converter and targets can be addressed. The interesting aspect of the photofission approach is that the distribution of radionuclides is almost identical to the thermal neutron fission of U-235. The challenge is that the yields are several orders of magnitude lower for photons than for neutrons.

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