

Nuclear medicine

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Abstract

This article describes the use of nuclear medicine techniques in diagnosis and therapy. The process of generating radiopharmaceuticals is introduced and relevant interactions of radiation with matter are discussed. Instrumentation in diagnostic nuclear medicine is described and future trends in nuclear medicine imaging technology are predicted.

What is nuclear medicine?

Nuclear medicine is a branch of medicine in which patients are given radioactive substances (to be taken internally) either to diagnose or to treat a disease. This differs from traditional radiology and radiotherapy techniques, where radiation is normally applied from an external source. Nuclear medicine has become quite widespread since its inception in the 1950s, and nuclear medicine departments can be found in most medium and large hospitals.

Therapy

A common use of nuclear medicine therapy is in the treatment of thyroid cancer. We know that iodine collects in the thyroid gland, and it turns out that most thyroid cancer cells also accumulate iodine. Therefore, if we give a dose of radioactive iodine (e.g. ^{131}I) to a patient with thyroid cancer, the radioactivity will accumulate within the thyroid cancer cells. If sufficient radioactive iodine is given, the cancer cells will be killed by the radiation, thus (hopefully) curing the patient. Care must be taken to avoid damage to healthy parts of the body when nuclear medicine therapy is given. Luckily, in this case, iodine does not accumulate to any significant extent in other parts of the body, so the radiation dose outside of the tumour is low. Most of the radiation dose in nuclear medicine therapy arises from absorption of beta particles, which have a very

short range in human tissue (a few millimetres or less). The process of calculating the radiation doses to various parts of the body during a nuclear medicine procedure is known as *dosimetry*, and is an important sub-topic within nuclear medicine physics.

Diagnosis

Nuclear medicine is more frequently used in the diagnosis of disease. In this case, a radioactive substance is given to the patient and then its distribution in the body imaged with some form of detector. The distribution might be imaged over time to see how it changes (dynamic imaging), or it might be imaged just once (static imaging). The essential idea is that the radioactive substance should act as a *tracer* for a particular physiological process. To understand the tracer principle, consider a simple tracer used in engineering—the smoke in a wind tunnel. In a wind tunnel, a small amount of smoke is injected into the air stream, where it is carried past the object we are interested in, for example a car or an aircraft wing. When we watch where the smoke goes, we learn something about the airflow around the object of interest—does the air flow smoothly or is there turbulence? In order for the smoke to be a good tracer for the airflow, it should behave in the same way as the air (at least with respect to the phenomena we are examining), and it should not disrupt the airflow. So the smoke particles should be sufficiently small

that the effects of gravity are negligible compared with the effects of the viscosity of the air, and the volume of smoke injected per second should be small compared with the volume of air flowing in the wind tunnel per second. This illustrates a general point about tracers—they should be present in sufficiently small concentrations that they do not disrupt the system they are intended to monitor.

In nuclear medicine, we can perform procedures similar to wind tunnel tests to measure lung function. If we ask a patient to inhale a radioactive aerosol, and subsequently obtain an image of the radioactivity distribution, we can see if there are any regions in the lung which are poorly ventilated (as they might be if the lung has collapsed or there is fluid in it). We can also inject radioactive pharmaceuticals into the blood stream to examine other disease processes. The trick is to identify a compound (not necessarily naturally occurring) which is absorbed by tissue in proportion to some physiological process. We then modify the compound by adding an atom of a radioisotope (a process known as ‘radiolabelling’), but hopefully in such a way that its physiological properties are not significantly changed. For example, we can track bone formation by using methylene diphosphonate labelled with radioactive technetium-99 (^{99m}Tc). The diphosphonate behaves in a similar way to natural phosphates in the body and it is incorporated into bone, bringing the ^{99m}Tc with it. Abnormalities in bone deposition rate can then be identified (see figure 1). Designing nuclear medicine tracers is a highly multidisciplinary process—radiochemists are required to manufacture the tracer, physiologists are needed to understand its behaviour in the body, and physicists are required to work out dosimetry and imaging issues.

Generation of radiotracers

A list of the more common radionuclides used in diagnostic imaging is given in table 1. The half-lives of these radionuclides are quite short, which helps to reduce the radioactive exposure to the patients. However, it is also clear that these substances cannot be stored, but must be produced on demand, either by a nuclear reactor, a cyclotron or a generator. A generator is a device containing a quantity of relatively long-lived



Figure 1. A planar whole-body bone scan showing disease in the left shoulder, spine and right pelvis. The bladder activity is normal. Left: front view. Right: rear view. Note the differences between the two views—this is due to the attenuating effects of human tissue.

Table 1. Some radionuclides commonly used in diagnostic nuclear medicine.

Radionuclide	Photon energies (keV)	Half-life
^{99m}Tc	140	6.0 hours
^{111m}In	172 and 247	2.8 days
^{67}Ga	93, 185 and 300	3.26 days
^{201}Tl	135 and 167, with characteristic x-rays at ~ 80 keV	3.04 days
^{123}I	159 and 529	13.3 hours

‘parent’ radionuclide, which decays into a shorter-lived ‘daughter’ radionuclide that is to be used for imaging purposes. The generator is configured so that daughter radionuclides can be periodically ‘milked’ off by chemical means, before being incorporated into the desired radiotracer.

The most commonly used generator in nuclear medicine is that used for production of ^{99m}Tc . The parent radionuclide is molybdenum (^{99}Mo), which decays to radioactive ^{99m}Tc (87%) and stable ^{99}Tc (13%) with a half-life of 66 hours. The molybdenum, in the form of molybdate ions

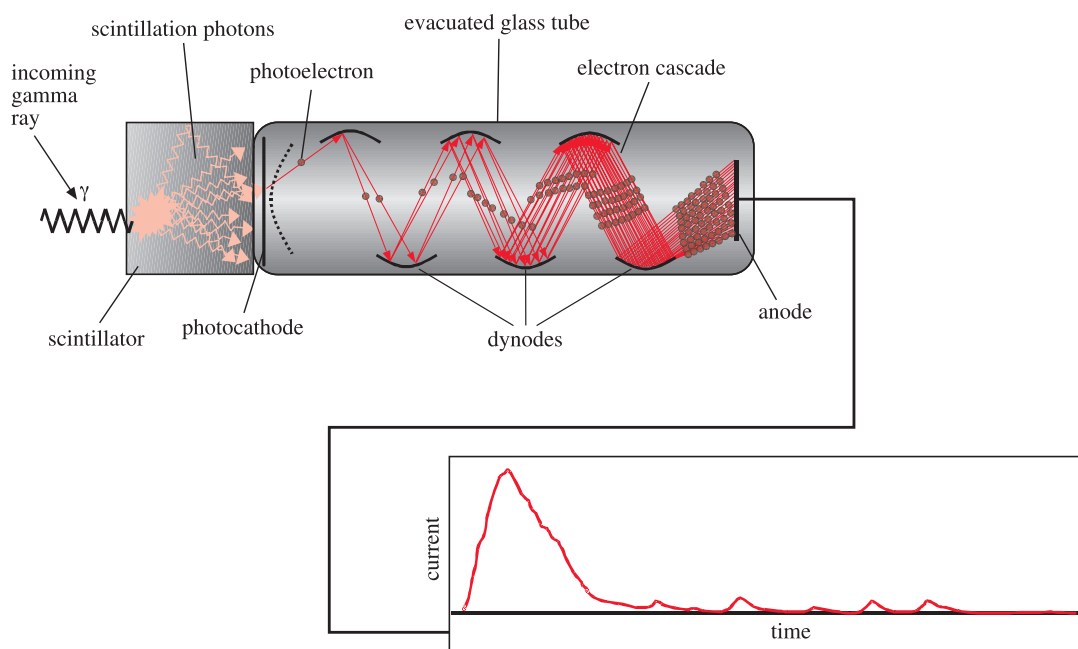


Figure 2. A scintillation detector. The incoming gamma ray interacts with the scintillator to produce a scintillation flash. Photons from the scintillation flash dislodge photoelectrons from the photocathode in the photomultiplier tube. These are accelerated to the nearest dynode, where they dislodge further electrons. This process continues down the tube, resulting in a cascade of electrons. There are usually about ten dynodes, and a multiplication factor of about 6 at each dynode. The efficiency of the photocathode is such that about 3–5 photoelectrons are released for every ten incident scintillation photons. The intensity rise time and decay time of the scintillation flash are determined by the scintillator—the total charge collected from the back of the photomultiplier tube is a measure of the energy deposited by the gamma ray.

(MoO_4^{2-}), is adsorbed onto an alumina column, which resides in a shielded container. As the ^{99}Mo decays, the concentration of $^{99\text{m}}\text{Tc}$ in the column increases, and it reaches a maximum after about 24 hours. The column is then flushed with aqueous sodium chloride, yielding a solution containing sodium pertechnetate, NaTcO_4 , which can then be used to produce the required radiotracer. After flushing, the concentration of $^{99\text{m}}\text{Tc}$ starts to increase again, and a single generator can be used daily for about a week.

Relevant interactions of radiation with matter

Only photon emissions are useful for diagnostic imaging because for the most part alpha and beta radiation has too short a path in human tissue and is absorbed before it can be detected. The energy of the photons used lies in the range of roughly 100 to 400 keV and, at these energies, the photons have two principal interactions with

matter—Compton scattering and photoelectric absorption. In a Compton scattering event, the photon interacts with an electron, giving it some of its energy. The electron recoils, and in order to conserve momentum, the scattered photon (now with less energy) progresses in a different direction. Compton interactions within the body can cause problems in nuclear medicine imaging, because when we detect the scattered photons they appear to come from somewhere other than the point from which they were originally emitted. This causes erroneous signals in the images.

In a photoelectric event, the photon transfers all of its energy to the electron and completely disappears. The relative probability of a Compton interaction or a photoelectric interaction depends on the energy of the photon and on the electron density of the scattering material (and thus on the density and the effective atomic number). In human tissue, Compton interactions dominate for photons in the 100–400 keV range. In materials such as lead, photoelectric interactions dominate.

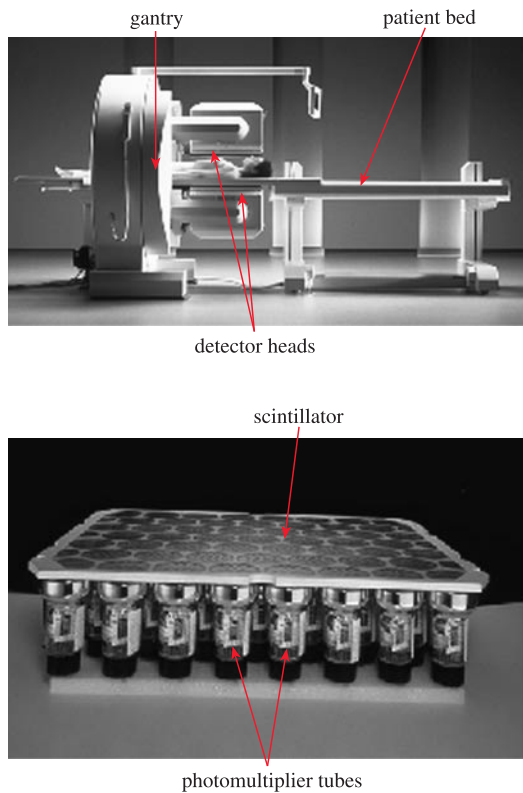


Figure 3. A dual-headed gamma camera (top) and a gamma camera detector (bottom). Each head on the gamma camera consists of a detector with supporting electronics and a collimator (not shown). The detector consists of a crystal of thallium-doped sodium iodide of area approximately 50×60 cm and about 1–2 cm thick. This crystal is viewed by about 50 PMTs. Since sodium iodide is hygroscopic, the crystal must be enclosed in an airtight seal. Photographs courtesy of Siemens Medical Systems.

Detector systems for nuclear medicine

The photons encountered in nuclear medicine most often have substantially higher energies than those used in x-ray imaging. Film-based imaging systems such as those found in dentistry clinics don't work at these high energies, because the high-energy photons just pass straight through the film. The detector of choice for nuclear medicine is the scintillation detector. This consists of a crystal attached to a photomultiplier tube (see figure 2). The crystal is a scintillator: when a gamma ray interacts with it, a flash of visible light is produced. Optically coupled to the scintillator is a photomultiplier tube (PMT), which turns incoming light into an electrical pulse. Ideally, the gamma ray should undergo a photoelectric

interaction with the crystal, because then all of its energy is turned into scintillation light.

A scintillation detector on its own is not an imaging device. We can use it to detect the presence of a high-energy photon. We can use it to measure its energy as well, within certain limits. However, to obtain an image, we need the position of the interaction of the photon with the detector, and we need the direction of the photon's flight. These last two pieces of information can be obtained using a gamma camera (also known as an Anger Camera, after its inventor, Hal Anger). A gamma camera consists of a large scintillating crystal (usually made of thallium-doped sodium iodide) with about 50 photomultiplier tubes on the back (figure 3). In front of the detector is a lead collimator. The collimator ensures that only those photons with paths parallel to the collimator holes strike the detector (figure 4). In this way we can be sure of the direction of the photons we detect. Positional information is obtained by examining the flash of scintillation light generated by the incoming photon when it interacts with the crystal. This light propagates through the crystal and is picked up by the PMTs. The most intense signal is obtained from the PMT nearest the event, and progressively weaker signals are found as the distance increases. By examining the relative strength of the signals from all of the PMTs, the location of the interaction point can be determined to within a few millimetres.

Planar imaging

The simplest way to use an Anger camera is analogous to a plain x-ray film. The camera is placed adjacent to the patient and both patient and camera are kept still while the signal accumulates. This results in a single planar view of the patient. The advantage of this method is that it is fast and computationally simple, but the disadvantage is that structures that overlay each other along the line of sight to the camera are difficult to distinguish. In addition, gamma rays arising from tracer concentrations on the far side of the patient tend to be scattered and absorbed ('attenuated') by the patient's body, rendering them difficult to see. It may therefore be necessary to acquire more than one view of the patient (from different angles) to obtain the necessary information (see figure 1).

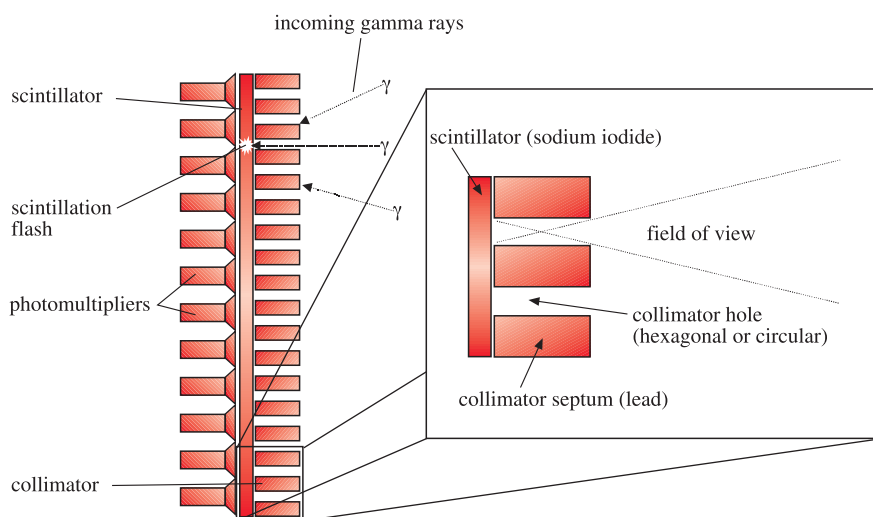


Figure 4. A gamma camera collimator. The collimator prevents photons which are not approximately perpendicular to the collimator holes from interacting with the detector. The field of view for the detector element behind each collimator hole is divergent, so that in a gamma camera spatial resolution degrades as the distance to the object is increased. The collimators are usually made of lead. For medium energy photon imaging, the holes are typically about 3 mm across, with the sides (the ‘septa’) being about 1 mm thick and the collimator depth about 40–50 mm. Not all collimators use parallel holes—there are converging or diverging slant-hole collimators, and pin-hole collimators which can be used for very high resolution imaging.

Single-photon emission computed tomography (SPECT)

If many views are taken from different angles around the patient, it is possible to mathematically reconstruct slices through the patient from the views. This process uses very similar methods to those used to obtain the slices in x-ray computed tomography (so-called ‘CAT’ or CT scanning) or magnetic resonance imaging (MRI) and is known as single-photon emission computed tomography (SPECT). The advantage of the SPECT technique is that the full three-dimensional nature of the tracer distribution in the patient can be appreciated, but the disadvantage is that it takes longer and requires more signal to reduce noise in the cross-sectional images. In practice, both SPECT and planar imaging methods are frequently used in concert. Attenuation of signal is still a problem in SPECT, but since views are taken from all around the patient, it is the centre of the tracer distribution that is affected most. Attenuation correction schemes for SPECT are becoming more widely available, and very substantial efforts have been made in recent years to optimize the treatment of the noisy data during the image reconstruction process.

Positron emission tomography (PET)

An exciting and developing area of nuclear medicine is the field of positron emission tomography or PET. In PET, the radionuclide used for labelling is a positron emitter rather than a gamma emitter. The positrons are emitted with an energy of the order of 1 MeV, and being beta particles, they have a very short range in human tissue ($\sim 1\text{--}2$ mm). When an emitted positron has given up most of its kinetic energy through collisions with ambient particles (i.e., it has reached thermal energy) it combines with an electron to form a short-lived entity called *positronium* (see figure 5). This rapidly undergoes an *annihilation reaction*, in which the all the energy of the electron and positron pair is converted into radiation. The most likely course of this reaction is the production of two photons, each of energy very close to 511 keV (equivalent to the rest mass of the electron). In order to conserve momentum, the two photons are emitted in exactly opposite directions in the frame of the positronium. Since the positronium has some momentum in the observer’s frame, the observer detects a small uncertainty in the direction of travel of the photons, amounting to about 0.5° about a mean of 180° .

It is possible to image positron-emitting

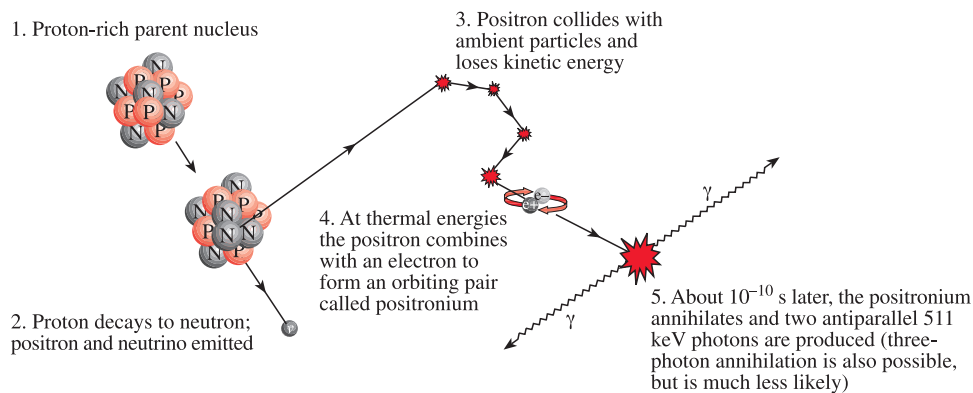


Figure 5. Positron emission and annihilation.

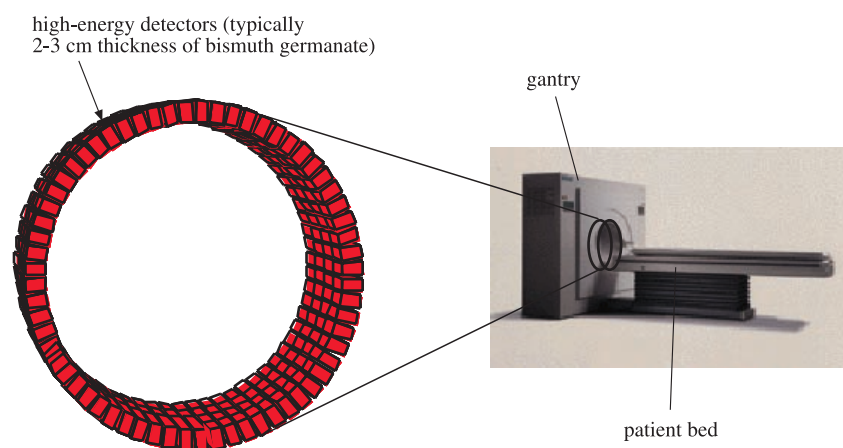


Figure 6. A dedicated PET system (photograph courtesy of CTI, Inc.).

tracers by detecting the annihilation radiation using a conventional Anger camera as described above, but problems arise because of the high energy of the photons. They tend to penetrate the collimators, leading to loss of image contrast, and are not easily stopped by the thin scintillation crystals, resulting in a loss of sensitivity. PET imaging is best performed using a dedicated system with specialized high-energy detectors and operating on the principle of *coincidence detection*. Coincidence detection takes advantage of the fact that each annihilation event gives rise to two photons travelling in opposite directions to obtain information about the direction of flight of the photons *without the use of a collimator*. This avoids the problems of collimator penetration and at the same time leads to a substantial increase in sensitivity. Dedicated PET systems usually consist of a series of rings of detector units sharing

common electronics (see figure 6).

In coincidence detection, the time of arrival of each detected photon interaction is checked to see if it is contemporaneous with a photon seen at any other detector. If so, the two photons are deemed to be in coincidence, and are assumed to have come from the same annihilation event. This event can then be assigned to a *line of response* joining the two detectors (figure 7). During a PET scan, the lines of response are populated with data according to the number of coincidence events recorded. The data in the lines of response can then be reordered into views and reconstructed into three-dimensional images in the same way as SPECT data.

A factor that has significantly contributed to the recent growth in the clinical use of PET is the nature of the tracers that can be created using positron emitters. The more commonly

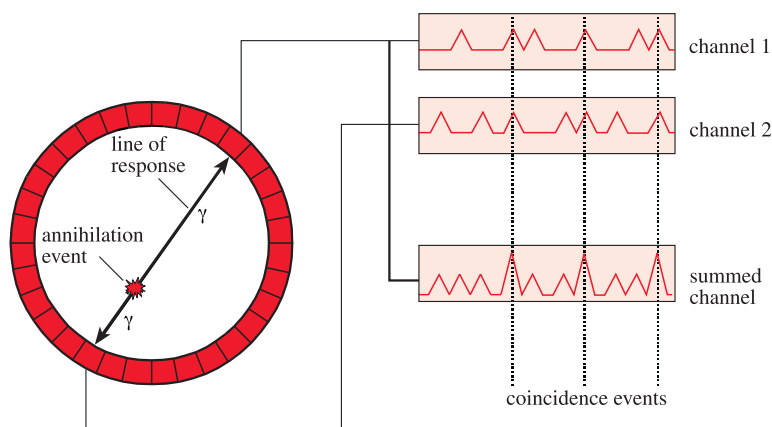


Figure 7. The concept of coincidence detection. If pulses from separate detector elements overlap in time, it is assumed that the detectors registered photons arising from the same annihilation event. In practice, events are assigned digital time stamps, which are compared to find coincidences.

Table 2. Some positron-emitting radionuclides using in PET imaging.

Radionuclide	Half-life (min)	Maximum positron energy (MeV)
^{11}C	20.3	0.96
^{13}N	9.97	1.19
^{15}O	2.03	1.70
^{18}F	109.8	0.64
^{82}Rb	1.26	3.15

used positron-emitting radionuclides are listed in table 2, and it can be seen that many of them are either directly biogenic or can be easily incorporated into naturally occurring biological substances. To date, the most widely used PET tracer has been ^{18}F -fluoro-deoxyglucose (FDG). This substance is taken up into cells using the same mechanism as normal glucose, but once in the cell, it cannot be further metabolized and remains trapped there. Consequently, it preferentially accumulates in cells with a high glucose metabolic rate. Since most tumours have an elevated glucose metabolic rate, it acts as an excellent tumour marker (figure 8), and it has also been very successfully used in cardiology and neurology.

A disadvantage of PET (at least in the clinical sphere) is the short half-life of the positron emitters. They must be created on the day of use and indeed, for all radionuclides except ^{18}F , actually at the site of use. Only ^{82}Rb can be produced in a generator (from ^{82}Sr)—the others are all produced in cyclotrons. Since most

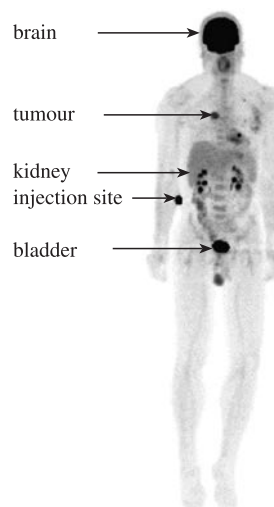


Figure 8. A whole-body ^{18}F -FDG image.

hospitals cannot afford the expense of an on-site cyclotron and radiopharmaceutical production facility, this is a serious limitation. Luckily the two-hour half-life of ^{18}F is sufficiently long that tracers can be labelled with it and shipped to several hospitals from a central location, and ^{18}F is likely to remain the workhorse clinical PET radionuclide for the near future.

The future: multi-modal imaging

Diagnostic nuclear medicine is essentially a *functional imaging* process—we are trying to obtain information on physiological processes.

This contrasts with conventional radiology, where the aim is predominantly to obtain *anatomical* images reflecting form and structure. To illustrate this difference, consider a CT scan of the brain of a man who has just died of a heart attack. The brain may well appear perfectly normal. However, an FDG PET scan will be completely blank—there will be no glucose metabolism at all. Functional and anatomical images are highly complementary—for example, a nuclear medicine image using a good tumour marker will show tumours but will not show very much normal tissue. As a result, determining the position of the tumours can be difficult. If a CT or MRI scan is obtained simultaneously, the tumours revealed by the nuclear medicine scan can be correlated with the anatomy shown by the CT or MRI, and the location of the tumours can be established much more precisely. New scanning devices combining CT with PET, and CT with SPECT, are already

on the market. Combining MRI with PET or SPECT is much harder, but small-scale systems for animals have been built and we may see human-sized systems within the decade.

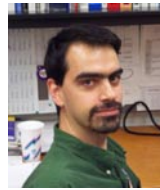
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Further reading

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Ramsey D Badawi entered the field of nuclear medicine in 1992, and obtained a PhD in biophysics from the University of London in 1998. He is currently responsible for positron emission tomography physics at the Dana-Farber Cancer Institute in Boston, Massachusetts, and is an Assistant Professor at Harvard Medical School.