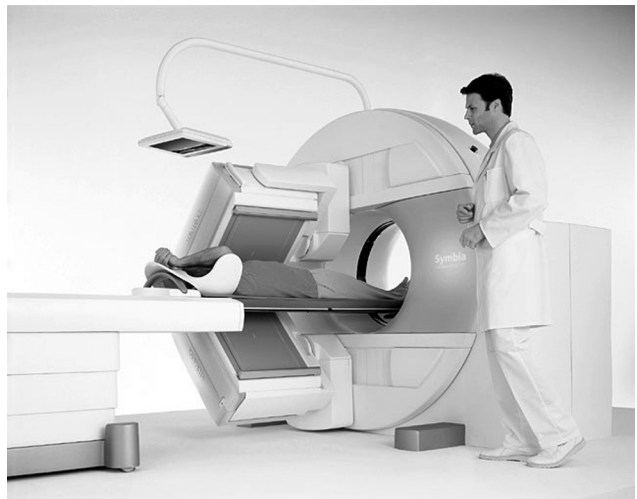

Figure 13 *A scanner used for combined SPECT and CT imaging. The two rectangular units above and below the subject are γ–cameras used for SPECT imaging and the circular structure at the subject's feet is the CT scanner (photo courtesy of Siemens Medical Solutions)*

scanner system is shown in Figure 13. This allows anatomical images from the X-ray CT scanner section to be combined with functional images from the SPECT scanner offering a very powerful diagnostic imaging tool.

The fourth type of radiation, β^+ (positron or positively charged electron), is of diagnostic interest since positron–electron annihilation processes occur close to the β^+ source and produce two 511 keV γ–rays oriented at 180° to one another. Simultaneous detection of these two γ–rays defines a line through the subject in which the decayed nucleus lay (Figure 12b). The observation of multiple decay events allows a detailed image of the distribution of the β^+ emitter to be computed by the technique of Positron Emission Tomography, (PET). Historically radionuclides such as ^{18}F have been incorporated into radiopharmaceuticals for this purpose. However, the short half-life (110 min) of ^{18}F and the chemical procedures required for its incorporation into the radiopharmaceutical are limiting factors on its utility. The metallic β^+ emitter ^{68}Ga is also finding use in diagnostic procedures and, despite a short half-life of 68 min, complex formation offers a rapid and convenient means of incorporating $^{68}Ga^{3+}$ into a radiopharmaceutical formulation. It is in the use of metallic radionuclides such as ^{99m}Tc and ^{68}Ga that coordination chemistry is finding its greatest level of application in providing new radiopharmaceutical agents for non-invasive diagnostic imaging based on γ–ray emission.

3.3.2.2 Radionuclide Production

In order for a radionuclide to be useful in the context of nuclear medicine it must be readily available in a sufficiently pure form, have a suitable half-life,

emit radiation of usable energy and have a chemistry which allows the facile synthesis of the active radiopharmaceutical under clinical conditions. The availability of a particular radionuclide is an important factor in determining its general clinical utility. After a radionuclide is produced it must be transported from the production site to the nuclear medicine facility for use. This can be problematic if the radionuclide has a short half-life and must be transported a considerable distance. Fortunately some radionuclides (*e.g.* ^{99m}Tc and ^{68}Ga) can be conveniently obtained from the radioactive decay of a longer lived and more conveniently transported precursor. This makes it possible to produce the medically useful radionuclide at the nuclear medicine facility itself through the decay of the precursor in what is known as a radionuclide generator. These are convenient to use and readily transported to clinical laboratories remote from the precursor radionuclide production site. This can make an important contribution to the acceptance of a particular radionuclide for clinical use. There are two main sources of radionuclides, nuclear reactors and particle accelerators (cyclotrons).

In a nuclear reactor the neutron flux may be used to irradiate a target in which neutron capture converts part of the target material to the required radionuclide, or a precursor which decays to it. Chemical treatment can be used to obtain a solution containing the required radionuclide or its precursor. As an example irradiation of molybdenum oxide isotopically enriched in ^{98}Mo converts some of the ^{98}Mo to ^{99}Mo. If the irradiated target material is dissolved in alkali, a solution of $(NH_4)_2[MoO_4]$ is produced containing a mixture of ^{98}Mo and ^{99}Mo. A major disadvantage of this neutron capture approach to ^{99}Mo production is that the active $[^{99}MoO_4]^{2-}$ is diluted by inactive $[^{98}MoO_4]^{2-}$ so that it is said to be 'not carrier free'. This means that the desired ^{99}Mo only constitutes a part of the Mo present so that larger amounts of material are required to obtain the effect of a given amount of ^{99}Mo. Fortunately, in this case the problem can be avoided by using nuclear fission in the reactor, rather than neutron capture, to produce ^{99}Mo. The fission of ^{235}U produces a mixture of fission products including ^{99}Mo. Since the other fission products are chemically different from Mo, a chemical separation can be carried out using ion exchange chromatography to obtain 'carrier free' $[^{99}MoO_4]^{2-}$ which is free of other Mo isotopes. This can be adsorbed onto an activated alumina column where the ^{99}Mo decays, with a half-life of 66 h, to ^{99m}Tc which in turn decays with a 6 h half-life to ^{99}Tc. Elution of the column with saline solution displaces the $[TcO_4]^-$ daughters by exchange with chloride, but leaves the more highly charged, undecayed $[^{99}MoO_4]^{2-}$ absorbed on the column. This system provides the basis for a '^{99m}Tc generator' from which a solution containing $[^{99m}TcO_4]^-$ can be eluted as long as sufficient undecayed $[^{99}MoO_4]^{2-}$ remains (Figure 14).

Although ^{99m}Tc is being continually produced from ^{99}Mo, once formed it is continually decaying to ^{99}Tc, thus the eluted $[^{99m}TcO_4]^-$ is not completely carrier free. Depending on the time since the column was last eluted, some ^{99}Tc will also be present. Consequently when the radiopharmaceutical is prepared a part will contain the ^{99}Tc label, which is no use for imaging. Fortunately this

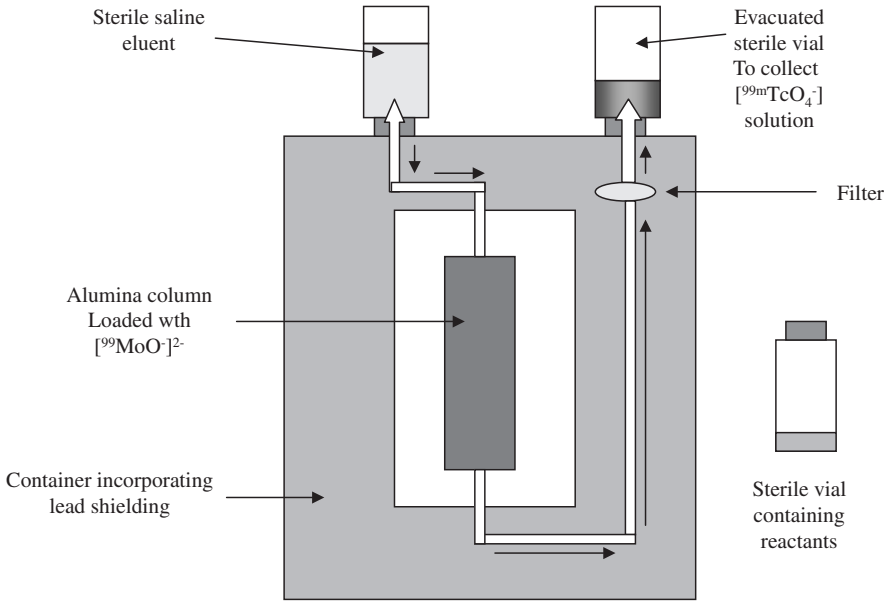

Figure 14 *A schematic representation of a ^{99m}Tc generator producing a saline solution of $[^{99m}TcO_4]^-$*

problem is easily managed and the optimum time between elutions is about 24 h to obtain the maximum ^{99m}Tc activity with minimal ^{99}Tc formation. This can be particularly important when bifunctional agents are involved since the ^{99}Tc-labelled agent will compete with the ^{99m}Tc-labelled agent for receptor sites and reduce the efficacy of the procedure. Once the ^{99}Mo is largely decayed the generator can be returned to the production site and recharged with $[^{99}MoO_4]^{2-}$ for reuse and recycle. Typically a nuclear medicine facility might obtain a new ^{99m}Tc generator on a weekly basis.

The other means of preparing radionuclides involves irradiating a suitable target with ions accelerated in a cyclotron. As an example proton irradiation of ^{69}Ga produces ^{68}Ge in a (p, 2n) reaction whereby a proton is absorbed by the ^{69}Ga nucleus and two neutrons are subsequently lost forming ^{68}Ge. The target material can be dissolved in HCl to give a solution containing $^{68}Ge^{2+}$ which can be absorbed on an alumina column which has been pre-treated with ethylenediaminetetra acetic acid (edtaH_4, **4**). The ^{68}Ge decays with a 280 day half-life to the positron emitter ^{68}Ga. This ^{68}Ga daughter may then be eluted from the system providing the basis of a $^{68}Ga^{3+}$ generator. Cyclotron production of radionuclides is expensive compared with reactor irradiations, but higher specific activities are possible than with the neutron capture process. Some radionuclides, which cannot be obtained from a reactor, may be prepared by cyclotron irradiation. Examples of the more important radionuclides used in diagnostic imaging are presented in Table 6.

Table 6 *Some radionuclides used in diagnostic nuclear medicine*

Radionuclide	$T_{1/2}$[a]	*γ energy (keV)*	*Source or Generator*[b] *($T_{1/2}$)*	*Applications*
^{51}Cr	27.8 d	322	Reactor ^{50}Cr (n, γ)	Red blood cell labeling
^{57}Co	267 d	120	Cyclotron ^{60}Ni (p, α)	Pernicious anaemia studies
^{62}Cu (PET)	10 min	511	Generator ^{62}Zn (9 h)	Pre-clinical studies for myocardial and cerebral perfusion, hypoxia
^{67}Ga	78 h	300, 180	Cyclotron ^{65}Cu (α, 2n)	Abcesses and neoplasms
^{68}Ga (PET)	1.13 h	511	Generator ^{98}Ge (288 d)	Tumor imaging
^{99m}Tc	6 h	140	Generator ^{99}Mo (6 d)	Many and varied
^{111}In	2.8 d	250, 170	Cyclotron ^{109}Ag (α, 2n)	White and red blood cells, antibody and peptide labelling for cancer diagnostics
^{201}Tl	74 h	0	Cyclotron ^{203}Tl (p, 3n)^{201}Pb(EC)	Myocardial perfusion, parathyroid and tumor

[a] Half life, d = days, h = hours, min = minutes
[b] EC = electron capture, n = neutron, p = proton

3.3.3 Radiopharmaceuticals

In order for a radiopharmaceutical to be effective in diagnostic imaging it must meet a number of criteria

(i) It must have low radioactive and chemical toxicity.
(ii) In a clinical environment it must be easily prepared from the radionuclide supplied in adequate purity and yield using simple procedures. The preparative timescale must be acceptable in comparison with the half-life of the radionuclide involved.
(iii) It must be sufficiently stable to reach the target tissue intact.
(iv) It must show sufficiently selective uptake in the target tissue and be cleared rapidly enough from non-target tissue to give a sufficiently high target to non-target concentration ratio that useful imaging data can be obtained.
(v) It must remain in the target tissue long enough for the imaging procedure to be completed and not redistribute significantly during this time.

(vi) The radionuclide biodistribution must accurately reflect the status of the disease.

(vii) The decay products and excretion pathways of the radiopharmaceutical and its degradation products must not pose a health hazard to the patient.

The chemical and radiotoxicity issue is not usually a significant problem in radiopharmaceutical formulations. The short half-lives of radionuclides used in diagnostic imaging result in their rapid decay to more stable nuclides with little or no radiotoxicity. As examples ^{67}Ga, ^{68}Ga, ^{111}In and ^{201}Tl all decay to stable nuclides while ^{99m}Tc decays, with a 6 h half-life, to ^{99}Tc. ^{99}Tc is a low energy (0.292 MeV) β^--emitter with a half-life of 214,000 years which, in turn, decays to stable ^{99}Ru and so has low radiotoxicity. Furthermore the quantity of radioactive material required for imaging applications is extremely small so that the chemical toxicities of the proligand, complex or other reactants are usually the main limiting factor. As an example the concentration of Tc in the eluate from a ^{99m}Tc generator is a few micrograms per litre (10^{-7}–10^{-8} mol l^{-1}). Even though the complexing agent will be present in excess of this figure it would need to be very toxic to present problems.

The ease of preparation of the radiopharmaceutical benefits from a coordination chemistry approach since complexation reactions are typically fast and simple to perform. The use of generator systems can allow a very simple 'shake and shoot' approach. The eluate from the generator is collected in a sterile vial. An aliquot is then transferred to a vial containing a complexing agent and any other reagents needed for the 'kit'. The contents of the vial are mixed, allowed to react and then injected into the patient. Sometimes, especially with some ^{99m}Tc agents, it may be necessary to form a precursor complex then transfer the solution to a further vial containing the ultimate complexing agent in which ligand exchange occurs. In some cases this approach may improve the purity of the final radiopharmaceutical and the efficiency of the preparation procedure.

Radiopharmaceutical purity is a more challenging issue. It is difficult, and sometimes impossible, to apply conventional chemical characterisation methods at the very low concentrations involved in radiopharmaceutical synthesis. Often more than one radiolabelled product is formed and there can be uncertainty about the exact chemical nature of the active radiopharmaceutical species. Work on a macroscopic scale with stable nuclides, or with ^{99}Tc, can provide very useful chemical information about the likely nature of the radiopharmaceutical but does not necessarily produce definitive results. At the clinical application level this may not seem too important provided the agent works and is safe, but a more detailed understanding may be needed to meet all the necessary regulatory requirements. In subsequent sections radiopharmaceuticals are described as if they were single well-characterised compounds. It is important to bear in mind that this is not always the case and that the chemical information is often based more on macroscopic studies than a detailed knowledge of what is present *in vivo*.

The stability of the radiopharmaceutical *in vivo* depends not only on the stability of the ligand system towards processes such as oxidation, hydrolysis or

enzymatic attack, but also on the inert binding of the metal ion. Kinetically inert metal complexes are needed and some *d*-block metal ions exhibit such behaviour. However, other metal ions, such as Ga^{3+} and In^{3+}, do not exhibit inert behaviour. In these cases very high thermodynamic stability is required to resist transmetallation reactions with *in vivo* binding agents such as albumin and transferrin. Conventional stability constants of themselves may not provide an adequate measure of the stability of a complex towards *in vivo* transmetallation reactions. To allow for this a *pM* value, or conditional stability constant, has been proposed. This is determined at pH 7.4 and takes account of ligand basicity (Lewis base character), ligand protonation, hydrolysis reactions, metal ligand stoichiometry and dilution effects. These *pM* values allow a more meaningful *in vivo* comparison between metal complexes with potential radiopharmaceutical applications. The issue of metal complex stability is addressed through the design of the ligand system, although in the case of Tc selection of oxidation states showing more inert behaviour is also possible. Careful ligand design and experimental studies are necessary to address the remaining issues relating to the biodistribution and pharmokinetics of the radiopharmaceutical and its degradation products.

Despite the extremely demanding requirements placed on them, a wide variety of radiopharmaceuticals have been developed to allow a range of non-invasive diagnostic imaging applications. In particular the availability of ^{99m}Tc from a generator system, its favourable nuclear properties and its rich and varied chemistry combine to explain why it has become pre-eminent in diagnostic nuclear medicine applications.

3.3.4 Aspects of Technetium Chemistry

The chemistry of the p-block metal ions most commonly used in diagnostic imagining applications, *i.e.* Ga^{3+}, In^{3+} and Tl^{+}, is comparatively simple. They act as filled electron shell systems and form labile complexes so that complex stability *in vivo* depends on thermodynamic stability constants, and the ability of the ligand set to occupy space around the metal ion so as to block the approach of competitor ligands. In aqueous solution these elements do not normally exhibit multiple oxidation states. Oxidation state (+2) is unimportant for this group, Ga^{+} is not stable and both In^{+} and Tl^{3+} are unstable in water. The chemical properties of the ions in solution are largely determined by their charges and radii. Thus Ga^{3+} (62 pm, CN6) with a similar radius to high spin Fe^{3+} (65 pm, CN6) tends to be incorporated in Fe^{3+} binding sites, for example in transferrin. The behaviour of In^{3+} is similar but its larger ionic radius (80 pm, CN6) is a poorer match for Fe^{3+} leading to slightly different behaviour. Both Ga^{3+} and In^{3+} are hard metal ions and prone to hydrolysis in aqueous media forming hydroxides. This reaction can be suppressed by complex formation, for example with citrate or polyamine carboxylates such as ethylenediamine tetraacetate ($edta^{4-}$). It is often said that Tl^{+} (159 pm, CN8) behaves like K^{+} (150 pm, CN8) as an explanation for its myocardial uptake and there is certainly a close similarity in charge/radius ratio for these two ions. The chemistry of technetium is quite different.