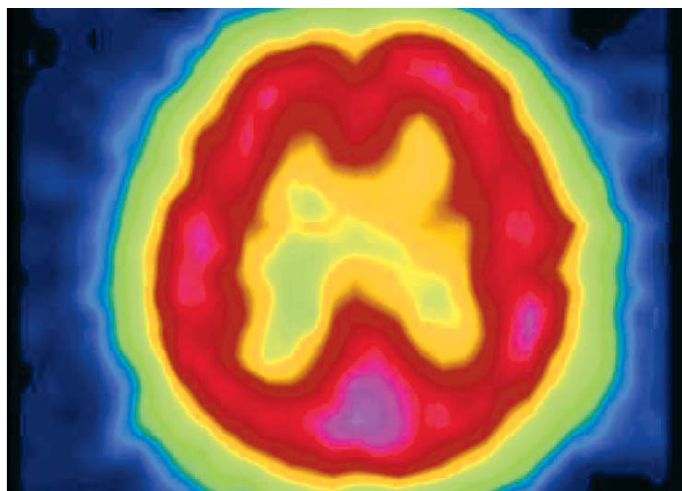


# Radiopharmacy

## — clinical use of the products

By Maggie Cooper, PhD, MRPharmS

Radiopharmaceuticals are compounds which consist of a drug and a radioisotope and can be used in both the diagnosis and the treatment of disease. The first article in this month's special feature discusses some of the more frequently used radiopharmaceuticals and explains their place in practice



Coloured single photon emission computed tomography scan of a normal human brain. The red areas show the most active regions, which have taken up more of the radioactive technetium-99m

**R**adiopharmaceuticals are primarily used in the diagnosis of diseases or disorders of function that occur in various organs of the body. These diagnostic radiopharmaceuticals are designed to demonstrate the normal or disordered function of the organ, tissue or system for which they are designed.<sup>1</sup> Radiopharmaceuticals can also be used to treat disease, most commonly malignancies.

Diagnostic studies can generally be split into imaging and non-imaging procedures. In the imaging studies, a small amount of a chemical agent labelled with a radioactive isotope, usually technetium-99m (<sup>99m</sup>Tc), is injected into the patient. The imaging system, a gamma camera, is placed over the relevant part of the body to obtain images of the distribution of the injected radiopharmaceutical. The images obtained are often linked to an analysis program from which physiologically relevant information can be obtained, eg, measurements of relative function. The advantage of these nuclear medicine studies is that they give functional as well as structural information and this can offer an advantage over other imaging methods.

In non-imaging studies (Panel 1, p298), the radiopharmaceutical is usually injected or swallowed (in the form of a radioactive

capsule) and blood samples are taken at time intervals after administration. In the case of the carbon-14 urea breath test, samples of the patient's breath are taken and this is used to detect the colonisation of the stomach by *Helicobacter pylori*. The amount of radioactivity in the samples can be measured and these measurements give an indication of the function of the organ of interest. For example, the amount of chromium-51 (<sup>51</sup>Cr) remaining in the blood following injection of <sup>51</sup>Cr ethylenediamine tetraacetic acid (EDTA) gives a measure of how well the glomeruli are able to filter EDTA through the kidneys.

### — Radiopharmaceutical design

A radiopharmaceutical is made up of two parts: the vector, ie, the drug, which localises in the target area, and the radioisotope, eg, <sup>99m</sup>Tc, indium-111 (<sup>111</sup>In), iodine-131 (<sup>131</sup>I), etc. The radioisotope allows for the localisation to be tracked. Localisation of the vector may be by a number of mechanisms:

- **Physical** Macroalbumin aggregates (<sup>99m</sup>Tc-MAA) get trapped in the lung capillaries where there is a pulmonary embolism
- **Chemical** Renal scanning agents such as diethylenetriamine pentaacetic acid are hydrophilic and hence localise in the kidney

- **Biological** Receptor imaging agents (eg, <sup>111</sup>In-octreotide) or antibodies (eg, yttrium-90 [<sup>90</sup>Y]-ibritumomab tiuxetan) bind to receptors or tumour-associated antigens

The choice of radioisotope is also important. For diagnosis, a gamma-emitting radioisotope with a short half-life will give the clearest images and the lowest radiation dose to the patient. For this reason, <sup>99m</sup>Tc is an ideal candidate since its six-hour half-life allows adequate time for imaging and the gamma emissions give clear images on conventional cameras. <sup>99m</sup>Tc also has other advantages, in that it is cheap, readily available, the isotope can be eluted daily in-house from a molybdenum-99/<sup>99m</sup>Tc generator, and its interesting chemistry (<sup>99m</sup>Tc can exist in oxidation states from -1 to +7) makes it ideal for complexation to a variety of ligands. <sup>99m</sup>Tc is used in about 90 per cent of all nuclear medicine scans but other gamma emitters including <sup>111</sup>In, gallium-67, thallium-201 and iodine-123 (<sup>123</sup>I) are also useful.

Recently, there has been a major advance in the area of positron emission tomography (PET). A number of useful PET isotopes exist, including oxygen-15, nitrogen-13 and carbon-11, which can be incorporated into biologically relevant molecules to act as tracers for biological pathways. The most frequently used PET radioisotope is fluorine-18 (<sup>18</sup>F), which can be used in labelling

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## Panel 1: Radiopharmaceuticals used in non-imaging nuclear medicine studies

### Non-imaging study

- Vitamin B<sub>12</sub> malabsorption (Shilling test)
- <sup>14</sup>C-carbon-urea breath test for *Helicobacter* infection
- Bile absorption test
- Bile acid breath test
- Red cell mass
- Glomerular filtration rate

### Radiopharmaceutical

- <sup>57</sup>Cobalt-cyanocobalamin
- <sup>14</sup>C-carbon-urea
- <sup>75</sup>Selenium-tauro-23-selena-25 homocholic acid
- <sup>14</sup>C-carbon-glycocholic acid
- <sup>51</sup>Chromium-labelled red blood cells
- <sup>51</sup>Chromium-ethylendiamine tetracetic acid

reactions because it resembles the hydrogen atom in terms of its stereochemistry (eg, 2-<sup>18</sup>F-2-deoxy-D-glucose [FDG]).

In therapeutic radiopharmacy, ideal radioisotopes are those with an abundance of non-penetrating radiations (ie, beta or alpha particle emitters or Auger electron emitters [Auger emitters are nuclides some of whose decays occur via atomic inner shell vacancies following electron capture, internal conversion or isomeric conversion]) and a lack of penetrating radiations (ie, gamma or X-rays) (see Panel 2, p301). This is because when the radiopharmaceutical reaches its target, the energy from the radioisotope should be deposited at that site (ie, the disease site) and not irradiate normal tissue. The energy of particles from different radioisotopes and their range in tissue will vary, as will their half-life, and the most appropriate radioisotope will be different depending on the application, the disease and the accessibility of the diseased tissue. The most frequently used therapeutic radioisotope is <sup>131</sup>I, which can be used at a low dose for thyrotoxicosis and at a high dose for treating cancer of the thyroid. It can also be incorporated into other biological molecules such as antibodies.

### — Diagnostic applications

Diagnostic radiopharmaceuticals, usually labelled with <sup>99m</sup>Tc, can be used in the diagnosis of disorders of a variety of organs as indicated in Panel 3 (p302). Although the list is not exhaustive, it gives a good indication of the range of studies carried out in a typical nuclear medicine department. The dose of radioactivity that can be administered to patients is strictly controlled by legislation and guidance is given by the Administration of Radioactive Substances Advisory Committee.

**Respiratory system** Lung perfusion imaging is performed by intravenously injecting <sup>99m</sup>Tc-MAA (which is formed from macroaggregates of albumin, typically 30–50µm in size, labelled with <sup>99m</sup>Tc). Images of the chest are taken immediately afterwards. The particles lodge in the terminal

arteriolo-capillary bed in proportion to the regional blood supply. Images will show areas of reduced uptake, which could be caused by pulmonary embolism (other explanations include chronic obstructive pulmonary disease, inflammation, neoplasm or pleural effusion).

A lung ventilation study is normally carried out in conjunction with the perfusion scan. Radioactive gases such as krypton-81m or xenon-133 may be inhaled. A more readily available inhaled radiopharmaceutical is <sup>99m</sup>Tc-Technegas, which is produced by evaporating <sup>99m</sup>Tc-sodium pertechnetate. The particulate vapour that is formed is inhaled by the patient.

The result of the ventilation scan is compared with the perfusion scan. A mismatch of perfusion and ventilation is indicative of pulmonary embolism.

**Cardiovascular system** The National Institute for Health and Clinical Excellence (NICE) published guidelines in 2003 on the use of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.<sup>2</sup> In these guidelines, NICE stated that myocardial perfusion scintigraphy using single photon emission computed tomography (SPECT) is recommended for use in the diagnosis and management of coronary artery disease. SPECT before coronary angiography is recommended as the preferred initial diagnostic tool in people with a low likelihood of coronary artery disease and a low risk of future cardiac events. SPECT is also recommended as the preferred initial diagnostic tool in people for whom stress electrocardiography poses particular problems of poor sensitivity or difficulties in interpretation. In addition, SPECT is recommended following stress electrocardiography in the assessment of prognosis following myocardial infarction.

Patients usually undergo myocardial perfusion studies in two parts. In the first part, the heart is stressed either by exercise or pharmacologically using adenosine or dobutamine, or both methods at the same time. Either <sup>99m</sup>Tc-tetrofosmin or <sup>99m</sup>Tc-sestamibi

are injected intravenously at the time of maximum stress. Imaging takes place approximately 40 minutes after injection of the radiopharmaceutical. The patient returns for a subsequent study where he or she is injected at rest with the radiopharmaceutical and rescanned. Comparisons are made between the stress study and the rest study in order to provide a diagnosis.

<sup>18</sup>F-DG-PET is now gaining increasing importance in the assessment of coronary artery disease and its use in nuclear cardiology is sure to increase over the coming years.

Multiple gated acquisition cardiac studies using <sup>99m</sup>Tc-sodium pertechnetate provide data which give a measure of phase and amplitude of left ventricular contraction and regional and global ejection fractions. This study is particularly useful in assessing cardiotoxicity from anthracyclines.

**Musculoskeletal system** The most common application for a bone scan is to assess bone metastases, usually secondary to breast or prostate cancer. <sup>99m</sup>Tc-medronate or <sup>99m</sup>Tc-oxidronate is injected and the patient is scanned approximately three hours after the injection. It is thought that these phosphate and phosphonate complexes of <sup>99m</sup>Tc are taken up into the bone by adsorption onto the surface of hydroxyapatite crystals. Uptake is enhanced in active areas of bone growth such as those typically seen in metastases. Abnormal uptake can be seen as hot spots in the skeleton.

A bone scan can also be used for the diagnosis of osteomyelitis, Paget's disease and stress fractures.

**Central nervous system** Nuclear medicine studies are increasingly important in the diagnosis of neurological disorders, particularly in the assessment of patients with symptoms indicating Alzheimer's disease or Parkinsonian syndrome. It is essential that such radiopharmaceuticals are able to cross the blood-brain barrier and, for this reason, the radiopharmaceuticals tend to be lipophilic.

The first radiopharmaceutical made commercially available for brain imaging was <sup>99m</sup>Tc-hexamethyl propyleneamine oxime (HMPAO) (Ceretek) and it soon became the gold standard for cerebral blood flow imaging. <sup>99m</sup>Tc-HMPAO may be useful as an adjunct in detection of altered regional cerebral perfusion in stroke. In addition, it is useful for ruling out Alzheimer's disease (AD) in patients presenting with AD-like symptoms.<sup>3</sup>

<sup>99m</sup>Tc-bicisate (Neurolite) is indicated as an adjunct to conventional computed tomography or magnetic resonance imaging in identifying the location of stroke in patients in whom stroke has already been diagnosed.

A more recent addition to the field is <sup>123</sup>I-ioflupane (DaTSCAN). DaTSCAN can be





## Panel 2: Therapeutic isotopes used in nuclear medicine

Radioisotope	Emission	Half-life	Maximum range in tissue	Radiopharmaceutical example
■ Iodine-131 ( <sup>131</sup> I)	Beta and gamma	8.04 days	2.4mm	<sup>131</sup> I (sodium iodide), <sup>131</sup> I-metaiodobenzylguanidine and <sup>131</sup> I-tositumomab (Bexxar) for various cancers
■ Yttrium-90 ( <sup>90</sup> Y)	Beta	2.67 days	12.0mm	<sup>90</sup> Y (yttrium ibritumomab tiuxetan [Zevalin]) for non-Hodgkin's lymphoma
■ Phosphorus-32 ( <sup>32</sup> P)	Beta	14.3 days	8.7mm	<sup>32</sup> P (sodium phosphate injection) for treatment of haemoproliferative disease
■ Strontium-89 ( <sup>89</sup> Sr)	Beta	50.5 days	8.0mm	<sup>89</sup> Sr (strontium chloride injection [Metastron]) for palliation of bone pain
■ Samarium-153 ( <sup>153</sup> Sm)	Beta	1.95 days	3.0mm	<sup>153</sup> Sm (samarium lexidronam [Quadramet]) for palliation of bone pain
■ Lutetium-177 ( <sup>177</sup> Lu)	Beta	6.7 days	1.8mm	Research only, used to radiolabel peptides and antibodies
■ Rhenium-188 ( <sup>188</sup> Re)	Beta	17.0hours	10.8mm	Research only, chemically similar to technetium
■ Astatine-211 ( <sup>211</sup> At)	Alpha	7.2hours	65.0mm	Research only, used to label antibodies
■ Indium-111 ( <sup>111</sup> In)	Internal conversion electrons	2.83 days	0.6mm	Labelled somatostatin analogues used in high doses to treat neuroendocrine tumours

used to differentiate essential tremor from Parkinsonian syndromes for those patients in whom the diagnosis is clinically uncertain. DaTSCAN passes through the blood-brain barrier and becomes attached to the dopamine transporters in the nigrostriatal dopaminergic system. Reduced uptake of the radiopharmaceutical in the substantia nigra is an indication of Parkinsonian syndrome.

PET has now become increasingly important for brain imaging, particularly in evaluating degenerative brain diseases, and is useful in determining treatment therapies following stroke.

**Gastrointestinal system** Salivary activity and secretion can be monitored using <sup>99m</sup>Tc-sodium pertechnetate. For other gastrointestinal studies the radiopharmaceutical (commonly <sup>99m</sup>Tc-colloid) is normally mixed with food or drink and the preparation swallowed, eg, in gastric emptying studies a radioactive pancake can be made. For assessing oesophageal transit times, the radiopharmaceutical may be mixed with a puree (for example, baby food) and the transit of the preparation can be studied by imaging regions of interest. Irregular passage and back flow is seen in a number of oesophageal disorders, including reflux oesophagitis.

Gastrointestinal bleeding can be assessed using <sup>99m</sup>Tc-labelled red blood cells. One method is to make the cells radioactive *ex vivo* using a pyrophosphate kit and then reinject them. The site of bleeding can be identified.

**Hepatic system** Nuclear medicine studies for investigating the liver have declined as other scanning methods, particularly ultrasound and computed tomography,

have become more prominent in recent times.

<sup>99m</sup>Tc-hepatobiliary iminodiacetic acid is used for imaging the biliary system and evaluating its function. In a normal system, there is an initial pooling of the radioisotope in the heart, followed by rapid uptake and uniform distribution in the liver. The radioisotope appears in the bile after a few minutes. Filling of the gall bladder and appearance of activity in the small intestine and then the large intestine follows. This procedure identifies abnormal transit which occurs in biliary atresia, acute cholecystitis and obstructive jaundice.

**Renal system** There are three types of renal examination that are undertaken in nuclear medicine departments. The study of glomerular filtration rate using <sup>51</sup>Cr-EDTA has already been mentioned. Renal excretion (using <sup>99m</sup>Tc-meritide [MAG3] or <sup>99m</sup>Tc-diethylenetriamine penta-acetic acid) and renal parenchymal function (using <sup>99m</sup>Tc-dimercaptosuccinic acid) can also be assessed. With the addition of furosemide or captopril, these studies are used for a wide range of purposes to evaluate renal function, in particular to identify renal vascular hypertension and renal obstruction, and to assess renal function before nephrectomy and renal transplants.

**Endocrine system** The practice of nuclear medicine started with thyroid imaging, but its use has declined with the advent of ultrasound. However, it still has a place in the diagnosis of disorders of the thyroid.

The thyroid can be imaged using either <sup>123</sup>I-sodium iodide or <sup>99m</sup>Tc-sodium pertechnetate. If a parathyroid scan is required, an image of the parathyroid together with the thyroid can be obtained by injecting a

radiopharmaceutical bearing a different isotope, eg, <sup>99m</sup>Tc-sestamibi or <sup>201</sup>Tl-chloride and the thyroid image subtracted from this image to display the parathyroid alone. In these studies a parathyroid adenoma can be distinguished from a thyroid adenoma. <sup>99m</sup>Tc-sestamibi can also be taken up by medullary carcinoma of the thyroid, by thyroid carcinoma and by metastases from thyroid carcinoma.

<sup>123</sup>I-meta-iodobenzylguanidine is chemically similar to noradrenaline and hence can be used in the diagnosis of disorders of the sympathetic system and in tumours of the neural crest, such as pheochromocytomas.

### Infection and inflammation imaging

White blood cells can be radiolabelled with <sup>99m</sup>Tc or <sup>111</sup>In. The white cells are separated from the red cells by sedimentation and then the white cells are made radioactive. Following reinjection, the radioactive white blood cells behave normally migrating to sites of infection and inflammation. These studies are particularly useful for the diagnosis of infection of unknown origin but are also used in the assessment of Crohn's disease and ulcerative colitis.

There has recently been an advance in the area of infection imaging with the emergence of <sup>99m</sup>Tc-labelled antibodies and antibody fragments such as <sup>99m</sup>Tc-sulesomab (Leukoscan)<sup>4</sup> and <sup>99m</sup>Tc-fanolesomab (NeutroSpect).<sup>5</sup> These antibodies bind to markers such as NCA90 and CD15 on the surface of neutrophils which are present at the site of infection.

**Imaging in oncology** Thyroid cancer can be identified as a solitary "cold" node on a <sup>99m</sup>Tc-sodium pertechnetate scan. The diagnosis can be confirmed by ultrasound with fine needle biopsy. Medullary cancer can be

## Panel 3 : Commonly used diagnostic radiopharmaceuticals for nuclear medicine imaging studies<sup>12</sup>

Radiopharmaceutical	Clinical application
■ <sup>67</sup> Gallium citrate	Diagnosis of inflammation and infection Tumour visualisation
■ <sup>111</sup> Indium pentetreotide (Octreotide)	Diagnostic agent for detection of primary sites and metastases of gastro-entero-pancreatic endocrine tumours
■ <sup>123</sup> Iodine ioflupane	Diagnosis of Parkinsonian syndromes
■ <sup>81m</sup> Krypton gas	Lung ventilation studies
■ <sup>99m</sup> Technetium sodium pertechnetate	Lung ventilation studies (Technegas) Multiple gated acquisition (MUGA) studies to find the ejection fraction from the heart Gastrointestinal bleed studies Thyroid imaging studies
■ <sup>99m</sup> Technetium albumin colloid (nanosized)	Bone marrow imaging and lymphoscintigraphic agent
■ <sup>99m</sup> Technetium bicisate	Cerebral blood flow imaging agent
■ <sup>99m</sup> Technetium depreotide trifluoroacetate	Diagnosis of suspected malignant tumours in the lung
■ <sup>99m</sup> Technetium exametazime (HMPAO)	Cerebral blood flow imaging agent and white cell labelling agent
■ <sup>99m</sup> Technetium fanolesomab	Diagnosis of appendicitis
■ <sup>99m</sup> Technetium macrosalb (MAA [albumin aggregated])	Lung perfusion studies
■ <sup>99m</sup> Technetium mebrofenin (trimethyl-bromo-HIDA)	Hepatobiliary imaging agent
■ <sup>99m</sup> Technetium medronate (MDP)	Bone imaging agent
■ <sup>99m</sup> Technetium mertiatide (MAG3)	Diagnostic renal imaging agent
■ <sup>99m</sup> Technetium oxidronate (HDP)	Bone imaging agent
■ <sup>99m</sup> Technetium pentetate (DTPA)	Renal imaging agent Brain imaging agent
■ <sup>99m</sup> Technetium sulesomab	Detection and diagnosis of osteomyelitis and diabetic foot ulcers
■ <sup>99m</sup> Technetium tetrofosmin	Myocardial perfusion imaging agent
■ <sup>99m</sup> Technetium tin pyrophosphate and pyrophosphate	Myocardial and bone imaging agent
■ <sup>99m</sup> Technetium sestamibi	Myocardial perfusion imaging agent Parathyroid imaging agent
■ <sup>99m</sup> Technetium succimer (DMSA)	Renal imaging agent
■ <sup>99m</sup> Technetium sulphur colloid	Liver imaging agent
■ <sup>99m</sup> Technetium tin colloid	Liver imaging agent
■ <sup>123</sup> Iodine iobenguane (MIBG)	Diagnosis of neuroendocrine tumours
■ <sup>123</sup> I (sodium iodide)	Thyroid visualisation and function tests
■ <sup>131</sup> Iodine norcholesterol	Adrenal cortex imaging agent
■ <sup>133</sup> Xenon Gas	Lung ventilation studies
■ <sup>201</sup> Thallous chloride	Myocardial visualisation

identified using <sup>99m</sup>Tc-dimercaptosuccinic acid or <sup>111</sup>In-octreotide.

A further use of the cardiac scanning agent <sup>99m</sup>Tc-sestamibi is in the diagnosis of breast tumours. This is particularly useful where mammography is difficult to interpret, eg, due to dense breasts. Sentinel node imaging has also become increasingly useful to the breast surgeon. The injection of a small amount of <sup>99m</sup>Tc-nanocolloid into the breast leads to localisation in the sentinel lymph node. A probe can be used to identify the sentinel node and biopsy undertaken to assess if cancer has spread to the lymphatic system. This is useful in

preventing the unnecessary use of lymphadectomy.

<sup>99m</sup>Tc-Depreotide (NeoSpect) can be used in the diagnosis of both non-small cell and small cell lung cancer. The radiolabelled peptide binds to somatostatin receptors, which are overexpressed in lung cancer. <sup>99m</sup>Tc-Depreotide has a negative predictive value of up to 98 per cent in combination with computed tomography or chest X-ray for solitary pulmonary nodules, and so is effective in ruling out malignancy in patients with suspected lung tumours.<sup>6</sup> However, its use has been largely overtaken by the use of <sup>18</sup>FDG. In 2005, NICE published new

guidelines on the diagnosis and treatment of cancer. It stated that every cancer network must have a system of rapid access to <sup>18</sup>FDG-PET scanning. An <sup>18</sup>FDG-PET scan should be performed to investigate solitary pulmonary nodules in cases where biopsy is not possible or has failed, depending on nodule size, position and computed tomography characterisation.<sup>7</sup>

An <sup>18</sup>FDG-PET scan is also useful in the diagnosis of a number of other malignancies, most notably in recurrent brain tumours and tumours of the colon, breast, lymph nodes, skin and other organs.

Much research interest has centred on diagnosis of angiogenesis using the alpha-V-beta-3 receptor as a target.<sup>8</sup> This receptor is present in developing but not developed vasculature. Several promising radioactive peptides that bind to this receptor have been identified. Another target is the gastrin releasing peptide receptor which is expressed on many tumours, including prostate cancer. Analogues of bombesin have been radiolabelled and can be used to identify these tumours.<sup>9</sup>

### — Therapeutic applications

The majority of therapeutic applications in nuclear medicine are in the treatment of malignancy. However, the use of <sup>131</sup>I-sodium iodide in the treatment of thyrotoxicosis and the use of <sup>90</sup>Y-colloids in synovectomy are still important.

Palliation of bone pain from metastases can be achieved using <sup>89</sup>Sr-strontium chloride or Samarium-153-lexidronam. These agents deliver radiotherapy direct to the site where it is required and can be given as an outpatient treatment. They offer cost advantage over the use of conventional drug or radiotherapy treatment for the palliation of bone pain.<sup>10</sup>

The most widely used therapeutic agent in nuclear medicine is <sup>131</sup>I-sodium iodide in its application for the treatment of thyroid carcinoma. <sup>131</sup>I-meta-iodobenzylguanidine or high dose <sup>111</sup>In-octreotide (and more recently <sup>90</sup>Y-somatostatin analogues) are useful in the management of neuroendocrine tumours.

An exciting development in the treatment of non-Hodgkin's lymphoma has been the emergence of radiolabelled antibodies such as <sup>90</sup>Y-ibritumomab tiuxetan (Zevalin) and <sup>131</sup>I-tositumomab (Bexxar) which, alone or in combination with conventional chemotherapy, have given encouraging results.<sup>11</sup> It is expected that the licensed indications for these radiolabelled antibodies will be extended to cover other types of lymphoma.

### — Conclusion

The application of radiopharmaceuticals for the diagnosis and treatment of disease is



extensive and still developing. The advent of PET has led to new possibilities in diagnosis and the development of radiolabelled peptides and antibodies offers increased treatment opportunities for the haematologist and oncologist. Radiopharmacy is an area that few pharmacists are familiar with but perhaps, having read this article, when looking through a patient's notes, there may be recognition of some of the nuclear medicine studies that have been performed and a clearer understanding of their relevance.

### UK Radiopharmacy Group

The UK Radiopharmacy Group was formed in 1995. It exists to promote the further development of radiopharmacy by advancing current practices, setting standards, and supplying timely advice and information. The group also co-ordinates educational programmes and the provision of an expert collective view on all matters pertinent to the science and practice of radiopharmacy. A quarterly newsletter is published, and this and other information about the group is available from [www.ukrg.org.uk/](http://www.ukrg.org.uk/). The website also contains the group's radiopharmacy handbook.

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