Reviews in Medicine

Nuclear medicine

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Introduction

This review will embrace the current status of nuclear medicine instrumentation, its main radionuclides and radiopharmaceuticals, its present role in diagnosis and treatment and its current trends and areas of growth.

The World Health Organisation has defined nuclear medicine as 'taken to embrace all applications of radioactive materials in diagnosis or treatment or in medical research, with the exception of the use of sealed radiation sources in radiotherapy'.¹ From the Council of Europe, a European Directive of the 30 October 1989, confers to nuclear medicine the status of an independent speciality. In the UK, the Department of Health has recognized it also as a separate speciality.

By 1990, worldwide, there were approximately 10,000 gamma cameras installed for the medical use of ionizing radiation. Annual sales of this main imaging detector in nuclear medicine are 750 for the USA, 100 for Japan, 85 for the FRG and 35 for France and the UK, respectively. In the European Community, in terms of gamma cameras per million inhabitants, Belgium leads with 22, the FRG follows closely with 21, Italy with 10 and the UK with only 5 instruments per million population. There is a wide variation in nuclear medicine diagnostic procedures carried out per bed/annum. In the USA the figure is of the order of 5.6 and in the UK the figure is well down by at least a factor of 10!

Main radionuclides

Nuclides are atoms characterized by mass number (number of protons plus neutrons in the nucleus), atomic number (number of protons and number of orbital electrons) and nuclear energy state. When the latter is unstable the nuclide emits radiation (a radionuclide) in order to seek a lower and more

stable energetic state. Nuclides with the same atomic number but different mass number are called isotopes.

Most radionuclides used for medical imaging purposes fall into two broad categories: single photon emitters, radionuclides with gamma rays with energies usually varying between 80 and 360 keV; and positron emitters, radionuclides that emit positrons which essentially behave like positive electrons. After colliding with neighbouring electrons, thereby losing kinetic energy, the positron (now at rest or almost at rest) unites with an electron in a process called positron-electron annihilation. This results in the emission of two gamma rays of 511 keV energy, travelling in almost opposite directions. Whether with single photon emitters or with positron emitters, the imaging process in nuclear medicine relies on the detection of emitted gamma rays. Gamma rays stem from the nucleus of the atom, hence the word nuclear medicine. X-rays which are rather similar, stem from the extranuclear electron shell which surrounds the atomic nucleus. Radionuclides are further characterized by the energy spectrum which they emit and a physical half life and decay pattern. In Table I the main radionuclides used in nuclear medicine are given.

Instrumentation

In nuclear medicine there is an almost universally used radiation detector. This was developed by Hal Anger in 1958 and has been known since as the Anger gamma camera.² It basically consists of a collimator, a sodium iodide NaI(Tl) scintillation crystal, an array of photomultiplier tubes, and associated electronics. When radionuclides are given to patients, the emitted gamma rays are detected by the gamma camera, leading to image formation (Figure 1).

The collimator of the gamma camera is a large plate of lead (usually) with literally thousands of small holes placed in front of the crystal between

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Table I The main radionuclides used in nuclear medicine

Radionuclide	Energy (keV)	Half life
Main single photon emitters		
^{99m} Tc	140	6.0 h
¹²³ I	159	13.2 h
¹¹¹ In	171,245	67.3 h
²⁰² Tl	68–82	73.1 h
¹³³ Xe	81	126.0 h
Main positron emitters		
⁸² Rb	511	1.25 min
¹⁵ O	511	2.0 min
¹³ N	511	10.0 min
¹¹ C	511	20.0 min
⁶⁸ Ga	511	68.0 min
¹⁸ F	511	111.0 min

Figure 1 Top, the typical configuration of a multi-detector system with a gantry, a couch, a power supply unit and an operator console. Bottom, a typical single head Anger gamma camera, mounted on a ring which allows the detector to move 360° around the couch/patient.

the gamma camera crystal and the patient. Only gamma rays travelling through the collimator holes may contribute to image formation. Regrettably, most of the gamma rays emitted during the data acquisition time do not travel in the direction(s)

allowed by the collimator(s) and therefore do not contribute to image formation. It is in this sense that radionuclide imaging is a photon limited process. For single photon imaging, typically only 1 in approximately 100,000 emitted gamma rays is actually detected by the gamma camera. The scintillation crystal of the gamma camera acts as a transducer and transforms the incoming gamma rays into photons of light. These are then collected by the photomultiplier tubes, which then by multiplication, generate a measurable electric current. The associated electronic circuitry processes the pulses from the photomultiplier tubes, computes the energy and location (point) of detection of each gamma ray and feeds the information to a computer for image display, processing and storage.

Planar and tomographic imaging

Most imaging studies in nuclear medicine are obtained by conventional Anger gamma cameras which format the images into planar two-dimensional maps of information. There is however an increasing use made of single or multiple Anger gamma cameras which are made to rotate 360 degrees around the patient. With dedicated computer processing, tomographic maps of information can now be recorded; the methodology which is routinely in use today is referred to as single photon emission tomography (SPET). When positron emitting radionuclides are used in the imaging process, special radiation detectors are used (positron cameras). When tomographic imaging is performed, one speaks of positron emission tomography (PET).

Nature of information obtained

With SPET and with PET the imaging method reflects the interaction of the given radiopharmaceutical and the organ or tissue which interacts with this tracer. Since the information recorded is tomographic, it is possible to conceptualize the information obtained as akin to *in vivo* autoradiography. Continuous progress is being made to quantify this information in an accurate manner. SPET and PET have been developed in order to offer different information from the other main tomographic imaging methods used in medicine (X-ray, computed tomography (CT) or nuclear magnetic resonance imaging (MRI)). While SPET and PET primarily depict functional, biochemical and/or metabolic information, X-ray, CT and MRI are primarily used as exquisite tools for the anatomical delineation of normal and abnormal anatomy.

SPET is versatile, clinically effective and widely

available. PET is still a research tool, with unique potential in view of its short-lived tracers labelled with carbon, oxygen, nitrogen or fluoride.

Main radionuclides and radiopharmaceuticals

The greater majority of clinical tests in nuclear medicine are carried out with radiopharmaceuticals labelled with ^{99m}Tc . This radionuclide is produced from a generator which is supplied weekly and can be used on demand throughout the week. The generator contains molybdenum-99 as sodium molybdate adsorbed onto an aluminium oxide column. ^{99m}Tc (technetium-99m) is continuously formed by the decay of ^{99}Mo . Elution of the column with isotonic saline yields a solution of sodium pertechnetate ($\text{Na}^{99m}\text{TcO}_4^-$) which is chemically stable. Modern generators have been developed such that the eluate is sterile and pyrogen free and almost molybdenum and aluminium free. Since 37 MBq (1 mCi) of ^{99m}Tc represents only 1.88×10^{-7} mg ^{99m}Tc , no pharmacological effect is noted when used in man.

^{99m}Tc can either be given to a patient as sodium pertechnetate or it may be used to label a large variety of radiopharmaceuticals. Most radiopharmaceuticals labelled with ^{99m}Tc are conveniently prepared as sterile, pyrogen free, freeze dried powders in multi-dose or single dose vials, i.e. kits. Many of these kits can be prepared instantly with a one-step procedure by aseptically adding the generator eluate in the form of sodium pertechnetate.

^{123}I is the other most important radionuclide in use for radiopharmaceutical labelling. It enables proteins, peptides and antibodies (and its fragments) to be labelled in a relatively simple manner and it is in use in many of more advanced and recent nuclear medicine investigations. Both ^{99m}Tc and ^{123}I are radionuclides with almost optimal properties for detection and imaging studies in man. Table II gives an indication of the wide range of radiopharmaceuticals available for the practice of clinical nuclear medicine. It can be seen that many other radionuclides are also in clinical use.

Nuclear medicine in neurology and psychiatry

The blood-brain barrier

In the 1960s and up to the mid-1970s technetium-99m as pertechnetate was used extensively for blood-brain barrier (BBB) scintigraphy. Since space occupying disease leads to a breakdown in the BBB, technetium-99m as pertechnetate given intravenously will be retained in the extracellular

space within the area of the BBB abnormality. Hence primary and secondary neoplasia, cerebral vascular pathology and infection and inflammatory pathology can be demonstrated by scanning with ^{99m}Tc -pertechnetate.

Blood-brain barrier scanning was in significant demand. It was simple to perform, economic and widely available. Most neoplasia in adults, metastasis and also stroke could be demonstrated on a scan. A negative study carried a high predictive value. Chronic subdural haematoma were almost always and readily recognized and diagnosed.

Problems, however, remain. Brain scanning with this method carries a definite false negative rate in adult neoplasia (up to 5–15% depending on the tumour size, location and histology), which is even larger in childhood neoplasia. The technique was not helpful in acute trauma, in the crucial differential diagnosis of cerebral haemorrhage from cerebral infarction and in the demonstration of cerebral atrophy and the sizing of cerebral ventricles. Acute stroke became positive only late in the event up to 4 to 5 days after the initial acute period. In all these circumstances, BBB scanning has now been superseded by X-ray computed tomography scanning and nuclear magnetic resonance scanning. In most departments of nuclear medicine, BBB scintigraphy has therefore diminished in frequency, unless the alternative methodologies for imaging are either unavailable or there is limited access for scanning.

Blood-brain barrier imaging remains of interest in the context of clinical research, since it provides for a simple demonstration of the integrity or disruption of the blood-brain barrier. Occasionally BBB scanning is still performed to document the presence of diffuse inflammation, cerebral abscesses and the monitoring of the extent of the process of disruption of the blood-brain barrier. In patients with neurological manifestations of human immunodeficiency virus (HIV) infection, BBB scintigraphy can demonstrate extensive abnormalities in the presence of more localized pathology on CT or MRI of the brain. Chronic subdural haematoma can be easily detected by BBB scintigraphy.

Other radionuclides may have a clinical role in the future. Thallium-201 chloride scintigraphy of the brain and gallium-67 citrate scanning have been recently advocated. Thallium-201 for the study of low-grade malignant tumours and gallium-67 for the study of toxoplasmosis versus lymphoma in patients with AIDS. In oncology, radionuclide brain scanning is emerging with a new role. Two areas appear of interest. The distinction of viable or recurring tumour from necrotic and non-viable malignancy and the general area of tumour grading. In both cases, progress has been achieved with conventional radiotracers and with the more

Table II Radiopharmaceuticals in use in the clinic

Nuclide	Chemical form	Indication
¹²³ I	Sodium iodide	Thyroid function
	Metaiodobenzylguanidine	Neurocrest tumour Localization (phaeochromocytoma, apudoma, paraganglioma) Adrenergic studies (heart)
	Ocreotide	Detection of insulinoma, gastrinoma Somastotatin (+) receptor tumour imaging
	IBZM	D-2 receptor studies
^{99m} Tc	Isopropylamphetamine	CBF studies
	Sodium pertechnetate	Thyroid uptake and scintigraphy BBB scintigraphy Salivary and lacrymal gland scintigraphy Meckel's localization
	Colloids	Liver and spleen scintigraphy Bone marrow scintigraphy Lymphoscintigraphy
	Iminoacid derivatives	Hepatobiliary scintigraphy
	DTPA	Renal scintigraphy and GFR studies
	DMSA	Renal mass imaging (scar detection)
	Diphosphonates	Skeletal scintigraphy
	Particles	Lung perfusion studies
	Aerosols	Lung ventilation and clearance studies
	Red blood cells	Blood pool scintigraphy
	White blood cells	Leucoscintigraphy
	MoAbs	Radioimmunoscintigraphy
	HMPAO	CBF studies
	MIBI, TEBO and others	Myocardial perfusion scintigraphy
²⁰¹ Tl	Chloride	Myocardial perfusion and tumour scintigraphy
⁶⁷ Ga	Citrate	Soft tissue scintigraphy Infection/inflammation Sarcoidosis
¹¹¹ In	Oxine-WBCs	Infection and inflammation and inflammatory bowel disease
⁵¹ Cr	Sodium chromate	Red cell survival and red cell volume studies
^{81m} Kr	Krypton gas	Lung ventilation
¹³³ Xe	Xenon gas	Lung ventilation
		CBF studies
¹²⁵ I	Human serum albumin	Plasma volume studies
⁵⁷ Co	Cobalt	Vitamin B ₁₂ absorption
⁵⁸ Co	Cobalt	Vitamin B ₁₂ absorption
¹³¹ I	Sodium iodide	Thyrotoxicosis – diagnosis and treatment
		Thyroid cancer – diagnosis and treatment
		Thyroid metastases – diagnosis and treatment
⁸⁹ Sr	Chloride	Terminal bone pain treatment
³² P	Orthophosphate	Polycythaemia rubra vera therapy
¹³¹ I	mIBG	Neuroblastoma therapy
		Phaeochromocytoma therapy

complex technology of PET. A tomographic approach to imaging has been of particular value here.

Whilst labelled glucose is taken up poorly by many intracranial tumours, giving poor image contrast between normal and tumour tissue, amino acids such as methionine enhance tumour uptake and contrast. Scanning with labelled methionine has therefore been used, complementing CT and MRI, in order to delineate more accurately the extent of the tumour prior to therapy. SPET when carried out with thallium-201 can be used as a rather simple index of tracer uptake which correlates well with the degree of tumour malignancy.

Blood volume, flow and metabolic studies

The radioactive tracer method is ideal if specific functional information is required. Established but also new radiopharmaceuticals and methodologies permit the investigation of individual aspects of brain function or metabolism.

It is feasible to investigate cerebral blood volume (CBV), cerebral blood flow (CBF) or CBF/CBV (cerebral transit time). Xenon-133 gas has been used for 20 years in a quantitative manner, with measurements of CBF in millilitres per minute per gram of tissue. Most of this technology has been performed with the aid of non-imaging probes which surround the head. Whilst the earlier studies started with 2, then 4 and then 12 probes, modern technology can surround the whole of the head with up to 256 thin probes each measuring the removal of xenon-133 from the brain (following its intravenous administration) and which is assumed to take place according to blood flow. Imaging devices such as gamma cameras have also been used to obtain planar maps of CBF and cerebral transit and applied successfully to the investigation of cerebral vascular disease.

Combined studies of CBF/CBV have been shown to correlate well with the oxygen extraction ratio of the brain. With these methodologies the investigation of the normal brain and its response to a variety of activation protocols (motor, sensory, pharmacological, etc) has been successfully carried out.

Both PET and SPET have been used to obtain tomographic maps of CBF and CBF/CBV. Amongst other areas of current interest, these have been applied to the investigation of acute trauma and acute stroke, focal epilepsy, movement disorders, the dementias and the differential diagnosis with depression. The monitoring of individual drug therapy, protocols or such interventions has been shown to benefit from the applications of these methodologies (Figures 2–6).^{3,4}

Figure 2 A ^{99m}Tc -HMPAO cerebral blood flow SPET study. Tomographic flow maps are compared with the corresponding X-ray CT scan. Note the extent of the flow abnormality, which is less visible on the CT study. Note the presence of cross-cerebellar diaschisis with impaired flow to the cerebellum which is not seen on the X-ray CT study.

Figure 3 An ^{123}I -HIPDM cerebral blood flow study. High parietal tomograms of cerebral blood flow are shown in a patient with an ictal focus precipitated by speech. The ictal focus is shown as an area of circumscribed blood flow.

Figure 4 A ^{99m}Tc -HMPAO cerebral blood flow study in a patient with Alzheimer's disease and typical bi-parietal and temporal parietal blood flow abnormalities. Impaired blood flow to both frontal lobes is also demonstrated.

Figure 5 An ^{123}I -IBZM tomographic study. The tracer is concentrated in the striatum as expected from a dopamine D_2 analogue.

Figure 6 An ^{123}I -benzodiazepine receptor SPET study of the brain in a normal patient.

Acute stroke

With PET it has been shown that blood flow and metabolism are no longer coupled in the early hours of the onset of the event. Areas of increased supply of flow may co-exist within areas of significantly impaired metabolism, suggesting the inappropriateness of intervening with vasodilatory therapy in such circumstances. Such information has permitted the definition and time sequence of phenomena such as luxury perfusion, misery perfusion, cross cerebellar diaschisis and so on.

Tomographic blood flow maps have consistently demonstrated the ability to detect functional change even in the presence of normal CT and MRI imaging of the brain. Blood flow studies often demonstrate areas of disturbed flow distant from small focal abnormalities detected on CT or MRI. This is seen in stroke (of the lacunar type or not), neoplasia, cerebral involvement with HIV. Tomographic studies of blood flow have been used in conjunction with CT, to determine and refine prognosis.

Acute trauma

Tomographic blood flow maps can help to determine outcome in acute cerebral trauma. This has been applied to the investigation of deep sea divers, boxers and other groups at risk.

Focal epilepsy

In the majority of circumstances, metabolism and flow are coupled. Glucose PET studies with ^{18}F FDG (labelled deoxyglucose) have shown that during an ictus there is coupled increased flow and metabolism whilst during the interictal period, glucose and cerebral blood flow remain locally depressed. SPET studies of flow with $^{99\text{m}}\text{Tc}$ -HMPAO have conclusively shown that similar information can be obtained with this more available methodology. CBF studies are therefore useful in the lateralization and the localization of the focus of epilepsy. For example, in temporal lobe epilepsy but also in partial extratemporal seizures. With both PET and SPET techniques localization can be achieved in about 80–85% of all cases.

The dementias

PET and SPET blood flow tomograms have been able to characterize a number of dementias. Regional blood flow abnormalities correlate with expectations from psychometry but do not correlate with the extent of cerebral atrophy. Impairment of blood flow is often more extensive than the severity of atrophy judged on CT or MRI.

Senile dementia of the Alzheimer type is characterized by a pattern of predominant posterior temporal and parietal impairment of CBF. This is often but not always bilateral. In more advanced disease, it may extent into the frontal lobe. Multi-infarct dementia is characterized by multiple perfusion deficits, widely distributed through the cerebral cortex. Crosscerebellar diaschisis may co-exist. The frontal dementias (Pick's disease)

involve the anterior aspects of the cerebral cortex. In Huntington's chorea there is marked and bilateral impairment of CBF in the head of the caudate nucleus. In contrast, in depression, CBF impairment is seen involving the frontal lobes, but the basal ganglia remain spared. In schizophrenia, no typical patterns of flow abnormalities have emerged but often there is also frontal hypoperfusion.

Progress is continuously being made in the functional characterization of psychiatric disease. In autism there is global and regional impairment of flow, in obsessive compulsive disorder (OCD) increased activity has been demonstrated in the orbital gyri and basal ganglia. We have found in patients with OCD with concurrent Gilles de la Tourette syndrome decreased frontal activity and increased flow in the basal ganglia when compared with subjects with simple Gilles de la Tourette syndrome. In Parkinson's disease flow patterns consistent with hypofrontality and decreased activity in the basal ganglia have been demonstrated.

Neuroreceptor studies

Receptors represent large proteins or glycoproteins which, at the surface of the cell, can identify and bind specific compounds often referred to as ligands. They have the ability to pass on information within the cell or the surrounding milieu. They can also act as messengers.

Neuroimaging with PET and SPET is progressing through a number of neuroreceptor ligands which have become available for clinical studies. The M1 and M2 muscarinic receptors can be studied with ^{123}I labelled with quinuclidinyl-iodo-benzilate or dextetimide, the dopamine D2 receptors are amenable for SPET studies with ^{123}I -labelled IBZM, the benzodiazepine receptor has been investigated with ^{123}I -labelled flumazenil and the serotonin S2 receptor has been investigated with ^{123}I -labelled ketanserin. The opiate receptor system has been studied with ^{123}I -labelled diprenorphine.

Nuclear medicine in benign bone disease

Instrumentation

Anger gamma cameras, operating in single shot or whole body scanning mode are the apparatus of choice. Data is often computer processed, regularly for improvement of image contrast but also occasionally for quantitative studies. In the latter case, profiles, histograms, regions of interest and the odd parametric image (for example, an accre-

tion image), are the tools for such quantitative investigations. Dynamic bone acquisition studies and time versus activity curve data has all been used in this context.

Often, SPET is also carried out. There is no longer any doubt that this approach improves lesion detection and also aids in lesion localization. This is particularly relevant in areas where imaging is difficult (vertebrae, hips, shoulders, knees, etc).

Most recently, multi-detector (gamma camera) technology has also been used. When operating in SPET mode, these instruments permit different imaging options to be implemented: improved counting statistics for a given dose, reduction of a given dose for similar counting statistics for serial studies, improvement in throughput or a combination of these.

Radiopharmaceuticals

Progress has been made since the initial introduction of diphosphonates labelled with $^{99\text{m}}\text{Tc}$. Beyond the simplistic 3-phase imaging approach, a variety of non-specific but also specific radiopharmaceuticals are now available. These include gallium-67 as gallium citrate, $^{99\text{m}}\text{Tc}$ as nanocolloid, $^{99\text{m}}\text{Tc}$ as human serum albumin or as polyclonal human immunoglobulin (HIG) or as an antigranulocyte monoclonal antibody, whilst labelled leukocytes are gaining favour (labelled with ^{111}In or $^{99\text{m}}\text{Tc}$).

It is apparent that not all these tracers can be applied to the same individual for the clarification of any specific pathology. Different combinations of tracer studies can now be used, tuning the tracer or a combination of these to the patient's condition.

If infection is suspected and a 3-phase bone scan is unhelpful, for instance, in chronic osteomyelitis, arthritis, etc, a specific white cell study can and should be carried out if the diagnosis of infection is suspected. If there are difficulties in the *in vitro* labelling of leukocytes, or the patient carries a high risk of infection (HIV, hepatitis), then a monoclonal antibody as an *in vivo* label of leukocytes is the safer approach. If monoclonal antibodies are not available, simple alternative techniques can be used. These include $^{99\text{m}}\text{Tc}$ -labelled nanocolloid or human immunoglobulin or even gallium-67.

Indications

There are a number of clinical indications for skeletal scintigraphy in the study of benign bone disease. These will vary from centre to centre. We offer an outline of the most common causes for referral to our own institution for these conditions (Figures 7–10).⁵

Figure 7 A ^{99m}Tc -MDP whole body bone scan with typical features of Paget's disease in the sternum and femur.

Figure 8 A ^{99m}Tc -MDP bone scan showing multiple pseudo fractures in a patient with osteomalacia.

Benign bone scintigraphy:

1. Extent and diagnosis of (occult) Paget's disease of bone.
2. Diagnosis of stress fractures and shin splints.
3. Diagnosis of osteoid osteoma.
4. Diagnosis and extent of fibrous dysplasia.
5. Diagnosis (quantification) of whole skeletal involvement (metabolic bone disease).
6. Diagnosis of prosthetic implant loosening versus infection.
7. Work up of patient with bone pain of unknown cause.

Figure 9 ^{99m}Tc -MDP bone scan and skull radiograph of a patient with osteoporosis circumscripta.

Figure 10 A ^{99m}Tc -MDP whole body scan in a child, with non-accidental injury. There was a known fracture of the humerus but a diagnosis was made by the presence of other traumatic lesions, in particular, to the posterior rib cage and the right anterior rib cage.

8. Diagnosis of bony infection.
9. Diagnosis of Caisson's disease and its extent.
10. Diagnosis of Legg-Perthes-Calve's disease and its extent.
11. Diagnosis of sympathetic reflex dystrophy.
12. Diagnosis of pseudoarthrosis in implants (Harrington rod).
13. Diagnosis of malunion in long-standing fracture.
14. Work up of patient back pain (SPET in the detection of spondylosis and spondylosisthesis, facet joint arthrosis).
15. Diagnosis of rhabdomyolysis.
16. SPET studies of shoulder, hip or knee (demonstration of avascular necrosis, etc).
17. Estimation of age of fraction.
18. Investigation of suspected trauma (non-accidental injury in children).

Paget's disease

Paget's disease is more often than suspected (by clinical or radiographic criteria) a polystotic condition. Several bones may be affected. Bone scanning will clearly identify the abnormal sites. The pattern of increased tumour definition is often characteris-

tic, if not diagnostic. Often long bones are involved, there is intense tracer uptake, which spares the joint space, with widening and curving of the long bones. Vertebrae may appear characteristically expanded. The skull, scapula, and pelvis are often involved.

Diagnosis of an occult fracture

Because of its ability to identify early sites of bone metabolism, bone scanning is ideally suited for the diagnosis or exclusion of occult fracture. In athletes, runners, joggers, dancers, sports professionals, shin splints or even stress fractures appear relatively common, and may be the cause of intense pain and disability requiring confirmation and treatment. Many of these splints and stress fractures are silent by conventional radiography. The indication for a bone scan (imaging with several projections, tomography when required) is often helpful and diagnostic. In trauma, bone scanning will confirm the site of abnormality or will exclude, with confidence, any injury to the skeleton. In the first 48 h post trauma, some fractures are nevertheless metabolically neutral and escape detection by bone scintigraphy. These abnormalities will become positive on the bone scan in subsequent days. Shin splints and stress fractures appear most commonly in the long bones. Other occult fractures (scaphoid, ribs, femoral neck) may be demonstrated on the bone scan at the time when the X-ray radiograph is negative.

The post-traumatic syndrome of algodystrophy or Sudeck's dystrophy or sympathetic reflex dystrophy gives a pattern of intense tracer uptake in the affected skeleton, which is typically recognized by bone scanning. Intense abnormal uptake is seen, is fairly typical in the feet, but is often less recognized in the hands.

The fracture age can be estimated from a bone scan. When 3-phase bone scanning is carried out, phase one usually returns to normal within 1 month post fracture, phase two returns to normal between 8–12 weeks post fracture, but phase three may remain positive up to 2 years after the acute fracture. In 90% of cases, a fracture will heal on the bone scan up to this interval of 2 years. In weight-bearing areas, where remodelling tends to occur indefinitely, the bone scan may remain positive for many years.

Other difficult fractures, often silent on X-rays, can be diagnosed on the bone scan. These include the avulsion fractures and the insufficiency fractures. It is worthwhile to remember that bone scintigraphy can be done effectively through a cast!

Osteoid osteoma

A bone scan is often requested for the investigation of a patient with bone pain of unknown cause.

Conditions leading to this include osteoid osteoma, arthritis, discitis and the already described shin splints and stress fractures. The most common condition which is being referred for bone scanning is, however, the osteoid osteoma.

This is often a difficult entity to diagnose and patients may undergo frequent and non-contributory diagnostic investigations and suffer from considerable discomfort. Bone scanning is often diagnostic demonstrating an area of intense but rather focal bone uptake. Specifically designed radiation probes are available guiding the surgeon to the localization of the abnormality during surgery for removal of the abnormal pathology. A normal bone scan permits exclusion of an osteoid osteoma with confidence.

Fibrous dysplasia

This is a condition of unknown aetiology, probably developmental, characterized by proliferation of fibrous tissue containing variable islands of bones. The disease is mainly monostotic and often affects cranio-facial bone tissue. It can, however, be polystotic. Prior to bone scintigraphy, diagnosis is usually late with deformity of skeletal structure as the foremost complaint. With bone scanning, asymptomatic disease is more often detected.

Lesions are usually seen in the early phase with the extent of bony abnormality better demonstrated on the bone scan than on conventional radiography. The pattern of intense tracer uptake is again seen but is less pronounced and less uniform than that observed with Paget's disease. Widening and curving of bone is absent.

Osteomyelitis and prosthesis assessment (infection/loosening)

A 3-phase bone scan (images taken during the intravenous injection of the tracer at 5 min post injection and at 3 h post injection) is often diagnostic in the assessment of acute osteomyelitis. In all 3 phases of the bone scan, a positive uptake pattern of the tracer can be demonstrated on the scan. In chronic osteomyelitis the bone scan is less helpful – the late bone scan will always demonstrate abnormal bone turnover (remodelling).

Septic arthritis is still best diagnosed with a needle. A specific and alternative tracer method in the investigation of osteomyelitis is by white cell scintigraphy. A sample of the patient's own white cells can be labelled and when reinjected these will localize in areas of active infection.

In the investigation of prostheses and joints in the detection of loosening, the 3-phase bone scan will show a focus of increased tracer deposition at the site of bone remodelling whilst the first 2 phases of the bone scan remain normal.

In prosthetic implants of the femur, distal component loosening is easier to diagnose than proximal (acetabular) loosening. After femoral prosthesis, the bone scan will remain positive up to 1 year after implant if the prosthesis is of the cemented type. 10% of asymptomatic patients have a positive bone scan and serial uptake measurements may help to investigate whether the prosthetic component is worsening.

If the prosthesis is of a porous nature (coated with cobalt or chrome), no uptake of tracer is seen in the porous portion. At the non-coated tip of the prosthesis, uptake may be seen up to 2 years after surgery. In children, some cases of acute osteomyelitis are silent on the bone scan in the first 24–48 h of the acute event. Bone scanning in paediatrics is often also used in the differential diagnosis of osteomyelitis and cellulitis and occasionally in an investigation of a battered child.

Osteonecrosis

The bone scan is often used in the diagnostic context in a patient suspected of having osteonecrosis. Avascular hip necrosis is most often investigated but MRI imaging is now the method of choice for this purpose (in particular in the investigation of Perthe's disease).

In Caisson's disease or diver's disease, whole body scanning is still the method of choice for the demonstration of skeletal abnormality. Typical features have been described, mostly involving the proximal and distal components of the long bones.

Low back pain

Functional information from both planar scintigraphy and SPET can provide information that is complimentary to the anatomical data obtained from plan radiographs of the spine, X-ray CT and MRI. Planar imaging will provide good localization of pathology such as facet joint arthrosis, osteophytes and linear uptake in the vertebral body secondary to osteoporotic collapse. There is growing evidence that increased sensitivity is seen with SPET when compared to planar imaging. This excellent localization is possible within the individual vertebrae and SPET will offer the orthopaedic surgeon or rheumatologist unique information on the functional component in low back pain.

Arthritis

The value of bone scanning is limited here. From a strict clinical point of view, few patients will require such an investigation to be carried out. Occasionally, bone scanning is used to demonstrate suspected multiple joint involvement, an increase or decrease in metabolic activity or the confirmation of

pathology in an X-ray negative but symptomatic positive patient.

The findings *per se*, remain non-specific. There is increased uptake in the joints, associated with regional hyperaemia and bone remodelling. For rheumatoid arthritis particularly and in osteoarthritis, the bone scan may be abnormal before the radiograph confirms such findings. This may help in the objective confirmation of the disease. A negative bone scan strongly suggests the absence of any significant local abnormality.

Pseudoarthrosis

A bone scan is often referred for the investigation of a pseudoarthrosis (Harrington's rod). A negative bone scan goes a long way to help to exclude the diagnosis. A positive bone scan has only 50% accuracy in the confirmation of the existence of a pseudoarthrosis.

Acute trauma

In acute trauma, bone scanning has a complementary role. A negative scan will give solid evidence for absence of significant injury to the skeleton. Where joints are affected, the bone scan may offer additional useful data. When injury to the knee and meniscii is suspected, a negative bone scan may help to elucidate difficult decisions on MRI scans. Typical images of crescent-like tracer uptake are seen in meniscal tears.

Nuclear medicine in endocrine disease

In endocrine disease, nuclear medicine utilizes specific radiopharmaceuticals which have the ability to concentrate and be handled by specific organ systems. Functional imaging is therefore added to the information available from methods which excel in the recording of anatomical information (such as ultrasound, CT or MRI).

The thyroid

The thyroid was the first organ to be scanned (imaged) with a radioactive tracer. The early availability of radioactive ^{131}I and its uptake by the thyroid trap marked the beginning of scanning in nuclear medicine. At the Middlesex Hospital, first uptake recordings of the thyroid were obtained as early as in 1948.

Today, a variety of other imaging modalities can be used for thyroid imaging, including diagnostic ultrasound and magnetic resonance imaging. To assess the functional status of the thyroid gland, the radioactive tracer methodology remains, however, without equal.

For scanning the thyroid gland, ^{99m}Tc as sodium pertechnetate, ^{123}I as sodium iodide, ^{131}I as sodium iodide and thallium-201 as chloride are the radionuclides most often used. In the specific investigation of infection of the gland, gallium-67 as citrate or ^{99m}Tc or ^{111}I -labelled white cells can also be used. The first 3 of the tracers mentioned are routinely used and provide for thyroid uptake measurements and imaging. Thallium-201 chloride is most often used in the investigation of non-differentiated thyroid carcinoma. ^{99m}Tc pentavalent DMSA (dimercapto succinate acid) and ^{123}I -MIBG (metaiodobenzylguanidine) have been shown to be of use in the detection and evaluation of patients with medullary carcinoma of the thyroid.

The main clinical indications for thyroid scanning have remained essentially unchanged over the last 10 years.^{6,7}

Indications for thyroid scintigraphy:

1. Scanning for location, size and volume of the gland (functional volume is uniquely assessed by single photon emission tomography).
2. Scanning for the detection of an unusual location: sublingual or retrosternal thyroid and malformations (congenital abnormalities such as single lobe, etc).
3. Scanning for the evaluation of the function of a thyroid mass.
4. Scanning for the functional evaluation of a single nodule (ultrasound or MRI imaging are deficient in this context) or the investigation of an evolving multi-nodular goitre.
5. Scanning for the diagnostic differentiation between Graves' disease and Plummer's disease.
6. Scanning for the assessment of residual thyroid activity post surgery or ablative therapy.
7. Scanning for the detection of residual or recurring thyroid carcinoma.
8. Scanning for the investigation of neonatal hypothyroidism.
9. Scanning for the confirmation of successful or resistant therapy (autonomous functioning adenoma).
10. Scanning for the investigation of thyroiditis.
11. Scanning prior to therapy with ^{131}I for confirmation of a non-suppressed thyroid trap and estimation of optimal therapy with ^{131}I .
12. Scanning for the demonstration of a suppressed thyroid trap (factitious hyperthyroidism, iatrogenic disease, iodine-induced Jod-Basedow).

The parathyroids

There is renewed interest in the imaging of the parathyroid glands. Whilst the most specific diagnostic investigation is direct hormone assay from

parathyroid venous sampling, this methodology remains rather invasive and not widely available. The radionuclides most used for this purpose are: thallium-201 chloride, ^{99m}Tc as sodium pertechnetate and ^{99m}Tc as MIBI (methoxyisobutylisonitrite).

Most imaging methods rely on digital data acquired by a gamma camera computer system which is enhanced and subtracted. Two radiopharmaceuticals are given, one which is taken up by the parathyroid and the thyroid glands and another which is trapped mainly by the thyroid. Subtraction imaging will then locate the site of the affected parathyroid, since parathyroid adenomas will exhibit increased metabolism which is avid for the radiopharmaceutical given.⁸⁻¹²

Preoperative imaging There is debate as to the value of this technique as a routine scanning procedure for all patients but there is agreement that only biochemically confirmed disease should be investigated by scanning. The reported sensitivities of detection vary significantly (between as low as 42% and as high as 85–90%). Glands weighing over 500 mg will be more frequently detected than glands weighing less than 300 mg, although exceptions to this rule have also been reported. Those centres which have confirmed success with the methodology find preoperative scanning of value in helping the surgeon to reduce the time and magnitude of the operation.

Postoperative imaging Parathyroid scanning as a method and second look approach is more universally accepted. Particularly post surgery, other imaging modalities, such as CT or diagnostic ultrasound appear to fare considerably worse, in view of the disturbed anatomy. In these more difficult patients, parathyroid scanning with the radiopharmaceuticals described above appear to be most useful in the location of abnormal glands.

Secondary hyperparathyroidism This methodology is less satisfactory in this circumstance and results are often disappointing.

Secondary sites Parathyroid scanning is successful and the method of choice in the detection of pathology at sites remote from the thyroid bed (seedlings).

The adrenals

Adrenal cortical scanning Two tracers are in current use for the scanning of the adrenal cortex. These are ^{131}I -6-beta-iodomethyl-19-norcholesterol (NP-59) and ^{75}Se -6-beta-selenomethyl-19-norcholesterol (SMC). Both radiopharmaceuticals exhibit similar distribution *in vivo* in man. Normal

uptake in both adrenals ranges from 0.07–0.3% of the given dose to humans, with a mean dose of 0.16–0.19%. SMC is the tracer of choice for imaging. ACTH increases the uptake of these tracers (equivalent to a stimulation test) whilst dexamethasone (a suppression test) reduces the uptake of these tracers by the cortex of the adrenal gland. CT and MRI imaging has significantly increased the ability to locate abnormalities of the adrenal gland but the functional assessment of such masses is still aided by the radioactive tracer methodology.¹³

In ACTH-independent Cushing's syndrome, adrenal scanning helps in distinguishing unilateral adenoma from bilateral hyperplasia. Scanning can also be recommended if the cause of Cushing's disease is not known. In the diagnosis of primary aldosteronism (Conn's syndrome), unilateral adenomas can be separated from bilateral adrenal hyperplasia by scanning and the procedure is therefore recommended. Scanning is also helpful for functional assessment of an incidentally localized adrenal mass.

Adrenal medulla scanning ¹²³I- or ¹³¹I-labelled metaiodobenzylguanidine (mIBG) are the radiopharmaceuticals in current use. mIBG scanning has been shown to be highly effective in the detection of a variety of neural crest tumours. In phaeochromocytoma and its metastasis, reported sensitivity is of the order of 90%, with similar results obtained in the workup of patients with neuroblastoma (see Table III).^{14,15}

Receptor imaging

A recent development in nuclear medicine relates to the progress with radiolabelled receptor ligands for functional imaging. Whilst greater effort has been placed in the development of neuroreceptor ligands, others emerged, with specific interest in the area of endocrine studies.¹⁶ ¹²³I-labelled octreotide, an octapeptide somatostatin analogue, has been recently reported as a promising agent for the localization of endocrine tumours.¹⁷ Tables IV and V show initial data and the detection rates in a variety of pathologies which express the somatostatin receptor.

Nuclear medicine in oncology

Bone scanning in metastatic disease

Radionuclide bone scanning is a well established technique for the investigation of a patient suspected of metastatic disease to bone. Most commonly, primary cancers of breast, prostate and lung tend to metastasize to the skeleton. In all of

Table III mIBG scintigraphy in neural crest tumours: cumulative sensitivity per indication

Diagnosis	Patients	Cumulative sensitivity
Phaeochromocytoma	> 1,000	88.2%
Neuroblastoma	841	91.0%
Carcinoid	237	69.8%
Medullary thyroid carcinoma	178	34.5%
Other neural crest tumours	144	57/144
Total reported cases	> 2,400	

Table IV Endocrine malignancies

Type	Incidence
Carcinoid tumours	3.2/million/year
Insulinomas	0.9/million/year
Gastrinoma	0.4/million/year
Islet cell tumour	0.2/million/year

Table V Results of ¹²³I-octreotide scanning

Pathology	n	Detection rate (%)
Carcinoid tumours	75	90
Insulinomas	14	50
Gastrinomas	10	100
MTC	15	60
Neuroblastoma	10	90
Phaeochromocytoma	8	80
Carcinoma of breast	50	75
Sarcoidosis	6	100
Sjogren	3	33

these, bone scanning is very sensitive in the detection of bony deposits in the skeleton. Conventional X-rays may remain silent for several months, with lesions all clearly visible on the bone scan. For the detection of bony metastases, a whole body scan, accompanied by local radiology only when necessary, is the recommended sequence of imaging tests. Despite the now known sensitivity of magnetic resonance imaging for the detection of bone marrow involvement, bone scanning continues to be the methodology of choice in view of its simplicity, low cost and ability to screen the whole body. Tumour markers such as prostate-specific antigen have a new role to play in the investigation of metastasis arising from prostate carcinoma. Whilst bone seeking radionuclide tracers have, on the whole, remained unchanged from a diagnostic point of view, new bone-seeking tracers have been developed for the treatment of unremitting pain in

patients with multiple secondaries to the skeleton. This new area appears particularly promising and will widen the scope of the radionuclide tracer method as a therapeutic modality.^{18,19}

Bone scanning and magnetic resonance imaging

With the arrival of MRI and fast scanning sequences, it will be possible to scan areas of the body in reasonable scanning time. This will permit the scanning of bone and bone marrow with the advantage of high spatial resolution. The localized detection of abnormal spread to bone marrow can be uniquely achieved by magnetic resonance imaging.²⁰

Since whole body scanning is still best carried out by skeletal scintigraphy, the work up of patients suspected of metastatic disease to bone will increasingly make use of a whole body nuclear medicine scan, followed by, in areas of uncertainty on the bone scan, localized MRI imaging. This combined approach is logical, will improve lesion detection and accuracy, reduce diagnostic uncertainty and improve the staging in cancer.

Bone scan and cancer of the breast

Breast cancer is still the most frequent referral for nuclear medicine bone scans. In a recent report, Glynn Jones *et al.*²¹ have confirmed the value of bone scanning in patients with carcinoma of the breast, particularly in Stage II and Stage III. A total of 398 patients clinically staged I to III (UICC criteria) were studied retrospectively over a 10 year period. Skeletal scintigraphy alone identifies 78% of those patients with detectable metastatic disease at 3 months, whilst skeletal scintigraphy and liver ultrasound will identify 95% of such patients. Chest X-ray added little to the yield of positive results (2.9%), and serum alkaline phosphatase was also deemed unhelpful.

Bone scan and cancer of the prostate

Bone scans should be used in the initial work up of newly diagnosed cancer of the prostate, for patients in clinical trials every 3 to 6 months if the prognostic grouping is poor, or every 12 months if patients belong to a group with better prognosis. Bone scanning should also be carried out if there is a significant rise in serum markers.

A most important study is that of Chybowski *et al.*²² Retrospectively, 521 randomly chosen patients with newly diagnosed and non-treated prostate cancer were investigated. Clinical staging was carried out, tumour grading and the measurement of serum acid phosphatase, serum prostatic acid phosphatase and serum prostatic specific antigen were looked at and correlated with the findings

from bone scanning. Prostatic specific antigen (PSA) has a negative predicted value of 99.7% for a value of PSA of 20 ng/mg or less. The authors suggest that a staging bone scan in previously untreated prostate cancer patients is no longer required.

The level of PSA, whilst helpful, is of course not an indicator for the extent and localization of bony deposits. Bone scintigraphy would still be the method of choice for such purposes. PSA has been shown to be more sensitive than serum osteocalcin measurements in patients with prostate carcinoma.

Bone scan and cancer of the lung

Tornyos *et al.*²³ advocate the use of bone scanning before thoracotomy for patients referred to surgery for potentially resectable non-small cell lung cancer. A total of 50 patients were investigated. In 17% of these, the bone scan changed the patient's management towards medical therapy (the scan demonstrating the presence of bony metastasis). In a further 36% of patients, evidence of bone spread confirmed the need for conservative treatment. Clinical findings, chest X-ray or thoracic CT were not sensitive to the demonstration of peripheral spread to the skeleton.

Bone scan in primary bone cancer

Tumour detection and preliminary diagnosis will be carried out by radiography, definition of extent by MRI/CT and tumour spread by bone scanning (skeletal) and CT (lungs). The utility of bone scanning in the early detection of soft tissue spread to lungs in primary osteosarcoma is well documented in the literature. Approximately 20% of osteosarcomas develop skeletal metastasis prior to soft tissue metastasis.^{24,25}

New tracers

An interesting new development with the radioactive tracer method relies on the radiolabelling of specific monoclonal antibodies, to image active bone marrow.

These can now be easily labelled with ^{99m}Tc, ¹¹¹In or ¹²³I. ^{99m}Tc-labelled antigranulocyte monoclonal antibody (BW250/183) was used by Duncker *et al.*²⁶ for the imaging of bone marrow in patients with suspected bony metastasis from primary bone cancer. The advantage of the scintigraphic method is underlined again, the methodology being ideal for screening and rapid whole body assessment. In 32 patients, bone marrow scans with this antibody were followed by a conventional bone scan within one month: 78% of patients showed evidence of bone marrow invasion, whilst the bone scan was only positive in 53% of cases.

It is clear that bone marrow scanning with monoclonal antibodies will further extend the sensitivity of the radioactive tracer methodology in the early detection of tumour spreading to bone marrow and subsequently to bone.

Bone-seeking radiopharmaceuticals are increasingly used for the treatment of painful skeletal metastasis. A number of new radiopharmaceuticals have emerged with significant clinical potential in the therapy of terminal and unremitting bone pain. Maxon *et al.*²⁷ have used ¹⁸⁶Re-Sn-hydroxy ethylene diphosphonate in the treatment of painful osseous metastases. In 20 patients, significant pain relief was observed in 80% of all cases. A number of other radiopharmaceuticals have or are being introduced for this purpose. ⁸⁹Sr is the most widely tested so far, within clearly designed therapy trials. Similar success rates have been reported.²⁸

Sequential studies and response evaluation

Serial bone scanning has been advocated as a simple means to monitor the progression/regression of documented metastatic disease. Nevertheless, it has not been easy to document utility for bone scanning in this context. The known flare up phenomenon (worsening appearance of bone scan) in a patient undergoing bony repair and a surge in osteoblastic activity has not helped to use serial bone scanning in the sequential follow-up of therapy. It is also known that in very advanced disease when the immunological response is already compromised, serial bone scanning will fail to detect rapid clinical deterioration.

Monoclonal antibodies and radioimmunoscintigraphy

Granowska and Britton²⁹ have recently reviewed the clinical role of radioimmunoscintigraphy in urology. From this review, which evaluates the diagnostic use of a number of labelled monoclonal antibodies, some clinical applications can be highlighted. Other authors have also recently reviewed this subject.³⁰

Ovarian cancer – clinical applications:

1. Evaluation of chemotherapy before second-look surgery.
2. Reduction of the need for second-look surgery.
3. Evaluation of pelvic masses after therapy as to the presence of viable tumour or not.
4. Evaluation of raised serum markers.
5. Evaluation of ultrasound screened pelvic lesions in well women.
6. Prelude to radioimmunotherapy.

Colorectal cancer – clinical applications:

1. The demonstration of subclinical and sub-radiological disease.
2. The demonstration of recurrences before the elevation of serum markers.

3. The localization of the site of recurrence when serum markers are elevated.
4. The demonstration that a mass seen on ultrasound or X-ray CT is viable tumour not post-surgical fibrosis.
5. The demonstration of the extent of recurrence for radiotherapy planning.

Nuclear medicine in the study of the lungs

Ventilation and perfusion lung scanning

Ventilation (V) and perfusion (Q) lung scanning is a well recognized technique in nuclear medicine. Labelled particles, aerosols (liquid or solid) and gases are available for ventilation scintigraphy and labelled albumin microspheres or aggregates are most often used for perfusion scintigraphy of the lungs. Radioactive gases include ¹³³Xe and ¹²⁷Xe. Single (posterior) projection imaging is carried out and wash-in, equilibrium and washout studies can be performed. With ^{81m}Kr gas, and aerosols, multiple projection imaging is possible. Between 5×10^4 to 5×10^5 small albumin particles are given i.v. for the perfusion study.

Emboic lung disease

It is in the investigation of a patient suspected of having embolic lung disease that V/Q lung scanning is most helpful. In life, the diagnosis of embolic lung disease is made in only 30–50% of cases. In the absence of treatment, mortality can be as high as 40%. Treatment itself (anticoagulation) has a complication rate of 10% and a mortality of the order of 0.5–1.5%. Traditionally a normal ventilation study, when accompanied by typical perfusion abnormality, is diagnostic of embolic lung disease (V/Q mismatch). Typical perfusion abnormalities include the criteria of multiplicity, segmental distribution and wedged-shaped defects. In the presence of ventilation abnormalities, the deficits in perfusion tend to be larger than the co-existent regional ventilation abnormalities but the single most important criteria continues to be that of perfusion and ventilation mismatch.

Recently, the value of ventilation and perfusion scintigraphy has come under scrutiny in a study commonly known in the literature as the PIOPEd trial. V/Q lung scans were classified into high probability, intermediate, low, very low probability and normal studies, according to defined criteria for perfusion abnormalities. V/Q lung scanning was confirmed as having a rather high sensitivity for the detection of embolic lung disease (98%). Interestingly, 12% of patients had embolic lung disease even when classified as belonging to a low probability category. Combined clinical

opinion and V/Q lung scan interpretation was found to be most valuable. A high probability study has a positive predictive value of 87%. A normal study has a negative predictive value of 96%.

A past history of embolic lung disease reduces the accuracy of V/Q scan interpretation. In the PIOPED trial, an intermediate probability assessment of a V/Q scan was unhelpful in the diagnosis of embolic lung disease. A total of 14% of patients had a normal V/Q lung scan and 13% of patients had high probability scans.

Other studies

Clinical referral for V/Q lung scanning other than for the investigation and diagnosis of embolic lung disease is infrequent. Occasionally, V/Q scanning is carried out in order to offer baseline data on ventilation and perfusion in patients with carcinoma of the lung, particularly in the pre-operative assessment of these patients.

Ventilation studies in respiratory disease

Inhaled ^{99m}Tc -DTPA aerosol can be used to measure alveolar clearance of this tracer. An increase in the time clearance is compatible with parenchymal lung disease, smoking and pneumonitis. In HIV patients, aerosol clearance is increased in the presence of pneumocystic carinii and is a useful method in the early study of this condition.

^{67}Ga scanning is also used in the detection of inflammation of the lungs, sarcoidosis and HIV-positive patients. The sensitivity of a positive ^{67}Ga scan in the detection of active sarcoid is very high (in the 90% range). Similar high values for sensitivity are seen in HIV-positive patients with pneumocystic carinii. In some centres these techniques are used to reduce the number of bronchoscopic examinations, thus diminishing the risk to staff.

Nuclear medicine in cardiology

There is now an established role for the radioactive tracer method within the clinical practice of cardiology. In broad terms, nuclear medicine successfully covers:

- (a) the investigation of ventricular function
 - (b) the documentation of myocardial perfusion.
- Whilst other tracer techniques have been developed to study more specific issues such as myocardial infarction, atherosclerosis, cardiac shunting, cardiac rejection with labelled antibodies or cardiac adrenergic status with mIBG, this review will not address these specific methodologies. The review

will also not discuss in detail the general methods available for these studies (first pass studies, equilibrium blood pool studies, SPET and PET) but rather concentrate on main areas of clinical interest.³¹

Ventricular function

Nuclear medicine is ideally placed to study right and left ventricular function by non-invasive means, with simple and cost-effective methodology. The techniques can be easily applied to the study of the heart at rest, during dynamic exercise, at different levels of workload, or during pharmacologically induced stress (dipyridamole, dobutamine, adenosine). Global or regional parameters of right and left ventricular function can be obtained. The most commonly used parameters in clinical practice are the assessment of global ventricular ejection fraction, the assessment of regional wall motion and the measurement of left/right stroke volume ratio (Figures 11 and 12).³²⁻³⁵

Ejection fraction

Left ventricular ejection fraction (LVEF) is the most commonly measured parameter. Its normal value (65%) and range varies from laboratory to laboratory, and local control values must be established. Typical is the response of LVEF with dynamic exercise. A rise or no change is consistent with normality, whilst a fall of 5 or more ejection fraction points is compatible with myocardial ischaemia. Significantly, depressed values of LVEF at rest correlate with poor outcome. Useful is the pre-operative assessment of patients undergoing major surgery. Those with LVEF below 30% are at a significant high risk of poor outcome, compared with the other groups. Moreover, clinical criteria alone correlate poorly with outcome when one compares such correlation with the simple and single measurement of resting left ventricular ejection fraction. Resting LVEF values are often obtained prior to chemotherapy, particularly in the context of known cardiotoxic drug administration.

The outcome of patients with acute myocardial infarction is again best assessed with the measurement of a resting LVEF value. This measurement is the most important predictor of outcome and most useful in the stratification of patients into high, medium or low-risk categories.

The development of regional wall motion abnormality with exercise in conjunction with a fall of LVEF with exercise is highly correlated with the presence of myocardial ischaemia. Regional wall motion abnormalities can be localized to the conventional 5 segments of the ventricle (anterior, inferior, lateral, septal and apical) and classified as

Figure 11 Ventricular function study. A typical rest and stress protocol with images at end-diastole, amplitude and phase for both ventricles, and values for left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF). Bicycle ergometer stress is carried out with 25 W increments of 2 min duration. There is a normal response to exercise without the development of regional wall motion abnormality during stress.

Figure 12 A resting ventricular function study showing images of end diastole amplitude and phase image. The phase image shows the normal timing of both ventricles coloured in green with an area in red and yellow indicating left ventricular wall motion hypokinesia (yellow) and dyskinesia (red), which is typical of an LV aneurysm. The resting total left ventricular ejection fraction was measured at 20% and if the contractile segment of the left ventricle only was measured, the ejection fraction is measured at 32%, indicating an expected improvement from aneurysmectomy.

localized areas of hypokinesia or dyskinesia. Dyskinetic segments correlate highly with localized ventricular aneurysms. The detection of aneurysms is hence fairly straightforward and efficient by ventricular function studies. The effect of surgery on aneurysms can be monitored and a pre-operative estimate of LVEF recovery post-aneurysmectomy can be made. Computer processing of images facilitates this approach. Similarly, the effect of coronary artery bypass grafting can be judged in terms of the overall pump performance of the left ventricle, by comparing pre- and post-operative data.

Myocardial perfusion

Nuclear medicine offers the only modality for the direct study of myocardial perfusion. There is therefore a major role for myocardial perfusion scintigraphy in the investigation of coronary artery disease (CAD). It is now well documented that exercise electrocardiography has approximately 20% poorer sensitivity than thallium-201 perfusion scintigraphy in the detection of CAD. Neither angina (pain) nor abnormalities of the electrocardiogram (ECG) correlate well with the severity of

CAD. Significant ST segment abnormalities of the ECG can be seen in patients with normal myocardial perfusion and apparent mild ST segment changes on the ECG can co-exist with major CAD. Pain is a poor indicator of severity of disease, the site, extent and the severity of myocardial ischaemia can be best judged by the thallium-201 myocardial perfusion scan. The extent and severity of reversible thallium defects constitute an independent predictor of cardiac events at one year.³⁶⁻³⁹

Myocardial perfusion scintigraphy:

(a) Diagnosis of coronary artery disease:

1. When ECG is uninterpretable (left bundle branch block, pre-excitation, left ventricular drug effects).
2. When ECG is equivocal.
3. When ECG is normal and clinical suspicion persists.
4. In the establishment of the functional significance of a known coronary artery lesion (stenosis).
5. In the baseline investigation of patients before treatment.
6. To establish the site and degree of reversible ischaemia versus viable myocardium.

7. To monitor the efficacy of medical or interventional treatment (angioplasty, bypass surgery, thrombolysis).
8. To monitor recurrence of coronary artery stenosis post-intervention.

(b) Prognosis in coronary artery disease:

1. To stratify patients in categories of high, medium, or low risk of further cardiac events.
2. To aid in the management and follow-up of patients with known coronary artery disease.
3. To identify the extent of reversible ischaemia.

A recent debate concerns itself with the diagnosis of viable myocardium. Conventional thallium-201 myocardial perfusion imaging has been shown to overreport the extent of non-viable myocardium. New imaging protocols, taking advantage of late imaging, re-injection of a second dose of thallium-201 or a ^{99m}Tc -labelled perfusion tracer with or without single photon computed emission tomography, have considerably reduced the magnitude of this problem. A small defined patient population will persist where thallium-201 myocardial perfusion imaging, as described, may incorrectly interpret the degree of non-viable myocardium. While there is still debate on the clinical relevance of this finding, myocardial imaging with positron tomography (and tracers for metabolism such as glucose and perfusion such as oxygen, rubidium or nitrogen) are a further nuclear medicine tool available for the study of this sub-type of patients. It is claimed that PET can identify CAD in asymptomatic patients with mild coronary artery disease. Again, the implication of this finding needs further assessment. What is clear is that coronary angiography is no longer the ultimate and only gold standard with which to judge the extent, or indeed the severity, of coronary artery disease.

In addition, it has been shown that there is a poor correlation between functional narrowing of a coronary artery and degree of reversible ischaemia. It is however, reversible ischaemia which determines management (Figures 13–15).^{40–45}

Other tracers are emerging in nuclear cardiology, such as ^{123}I -mIBG (Figure 16).

Nuclear medicine in gastroenterology

Radionuclide tracer techniques are uniquely suited to the measurement of transit times. In gastroenterology, these have been used to detect or measure oesophageal transit, oesophageal reflux, gastric emptying and intestinal transit. Labelled liquid, mixed or solid meals can be used to investigate organ transit and relate it to the effect of treatment (for example, vagotomy) or disease (for

Figure 14 A normal rest and stress ^{99m}Tc -MIBI myocardial perfusion tomographic study.

Figure 15 A thallium-201 myocardial perfusion study which demonstrates during stress a typical inferior wall perfusion abnormality which (fills in) at rest, confirming the presence of myocardial ischaemia in viable myocardium of the inferior wall.

example, dumping). Such measurements are expressed in a numerical manner, are sensitive to small changes and remain reproducible. The action of drugs affecting the motility of the gastrointestinal (GI) tract can be assessed. By labelling therapeutic pellets directly, the site and timing of the release of the active substance of these compounds in the GI tract can also be monitored.⁴⁶

Liver scanning

Conventional liver scanning for the detection of space occupying disease has been superseded by diagnostic ultrasound and/or CT/MRI. Whilst the methodology is simple, economic and fairly sensitive in the protection of secondary spread to the liver, both ultrasound and CT offer within the same examination, complementary anatomical information relevant to the surrounding structures, which liver scanning with radionuclide tracers is unable to deliver.

Hepatobiliary scanning is, however, a unique tracer methodology and tool with clear areas of clinical interest. A labelled tracer which is excreted by the biliary system, can offer a number of important functional data.

Indications for hepatobiliary scintigraphy:

1. Information on patency of cystic duct (diagnosis of acute cholecystitis).

Figure 16 A normal study of the distribution of ¹²³I-labelled mIBG in the myocardium.

2. Information on cholestasis and indication on bile transit. Diagnosis of sclerosing cholangitis.
3. Diagnosis of biliary reflux and/or leakage (investigation of the post-operative patient, shunt patency, biliary anastomosis, etc).
4. Investigation of the syndrome of biliary dyskinesia.
5. Diagnosis of biliary atresia.

Vitamin B₁₂ absorption

Vitamin B₁₂ deficiency caused by lack of intrinsic factor can be easily diagnosed with a tracer technique which uses ⁵⁷Co- and ⁵⁸Co-labelled B₁₂ (Schilling test).

Bile acid malabsorption

This can be studied with a taurine conjugate of a synthetic-like acid labelled with ⁷⁵Se (the SeHCAT test). Usually 15% of SeHCAT is retained over 7 days in normal patients, less than 8% retention is diagnostic of bile acid malabsorption.

Inflammatory bowel disease

Labelling the patient's own white cells (leucoscintigraphy) can now be readily achieved by several methods and radionuclides. Whatever the chosen method, the clinical indications for white cell scintigraphy are now established.

Indications for white cell scintigraphy:

1. The investigation of site and extent of inflammatory bowel disease (IBD).
2. The localization of abscess.

3. The monitoring of persistent or flare-up of known IBB.

Crohn's disease and ulcerative colitis can be usefully assessed with leucoscintigraphy. The extent of involved colon is more accurately assessed by this method than by any other imaging modality. Disease activity is better reflected on the white cell scan than by other parameters of disease monitoring. Abscesses can be detected, as well as unusual sites of drainage (Figure 17).

Gastrointestinal tract bleeding

With labelled red cells, sites of acute occult haemorrhage can be diagnosed and often localized. This is particularly helpful in lesions of the small bowel and colon (Figure 14). This method is sensitive to the detection of loss of small volumes of blood but haemorrhage can only be detected in the acute phase. Intermittent bleeding is difficult to diagnose, since bleeding can only be localized with a tracer technique when it occurs.

Meckel's diverticulae and Barrett's oesophagus are classical entities diagnosed by nuclear medicine techniques with simple ^{99m}Tc as pertechnetate. Nevertheless, only 50% of Meckel's diverticulae have a mucosa lining capable of concentrating pertechnetate. Whilst the positive scan is diagnostic, a negative study does not carry the same predictive value. For the reasons explained earlier, the same is true for the detection of gastrointestinal tract bleeding (Figure 18).

Nuclear medicine and nephro-urology

Radiopharmaceuticals

^{99m}Tc -DTPA is exclusively excreted by glomerular filtration. It is therefore used to measure glomerular filtration rate (GFR). Its extraction efficiency is less than that of labelled orthoiodohippurate (OIH). When renal function is poor, organ imaging is therefore difficult. Nevertheless, ^{99m}Tc -DTPA is available daily from a simple kit and a ^{99m}Tc generator.

^{123}I -OIH is tubular secreted and is an excellent although expensive tracer for gamma camera renography. Its availability is however restricted and daily supply is not available.

^{99m}Tc -MAG 3, is a relatively new radiopharmaceutical. Labelled with ^{99m}Tc , mercapto glycine glycine, glycine combines some of the advantages of OIH with the advantage of ^{99m}Tc . It is mainly tubular secreted with a smaller volume of distribution than OIH. It is now widely available and can be made daily with a kit and the eluate of a ^{99m}Tc generator.

^{99m}Tc -DMSA is labelled dimercaptosuccinate

Figure 17 Top, ^{111}In -labelled white cells. Bottom, ^{99m}Tc -HMPAO-labelled white cells. A typical positive study in ulcerative colitis.

acid, a compound designed for static imaging of the kidneys. It is almost completely retained by the proximal tubules of the kidneys. Its main use is for the individual assessment of renal cortical mass,

Figure 18 ^{99m}Tc -labelled red cells demonstrate an area of active bleeding.

demonstration of renal scarring, horseshoe kidney and other abnormality of anatomy.

*Main clinical indications in renography*⁴⁷

Renovascular disease Renography is often used to investigate a patient with hypertension and suspected renovascular disease. Typical is a demonstration of a small kidney with reduced tracer uptake and delayed transit time of tracer. Recently the Captopril test has been introduced for the demonstration of renal artery stenosis. ^{99m}Tc -DTPA or ^{123}I -OIH renogram is performed before and after the intravenous administration of Captopril. An asymmetric fall of GFR and a shift and a delay of a renogram activity peak of the affected kidney is strong evidence for unilateral renal artery disease. ^{99m}Tc -DMSA is also used to confirm the presence of a small kidney for the detection of renal cortical scarring.

Renal outflow disorder (obstruction) Frusemide renography is well established for the investigation of the patient with a suspected obstructed kidney. A ^{99m}Tc -DTPA or ^{99m}Tc -MAG 3 renogram is carried out before the i.v. administration of Frusemide. Recently some centres recommend the administration of Frusemide before the beginning of the renogram test. An obstructive uropathy is diagnosed if following the administration of

Frusemide, little or no response to an increase in the rate of excretion of the tracer from the kidneys is demonstrated (Figures 15 and 16). The measurement of parenchymal transit times of tracer have also been advocated as a further refinement in the sensitive diagnosis of obstructive uropathy.^{48–53}

Renal transplant The renogram is used widely in a number of contexts: To investigate the normalcy of the function of the kidney of the donor; to confirm baseline function in the first 24–48 h post-renal transplant, to diagnose acute tubular necrosis (ATN); to diagnose the presence of an urinary leak and to monitor functional recovery of a transplanted kidney at risk (also to detect ATN and/or rejection). With ^{99m}Tc -DTPA ATN is diagnosed when a kidney which remains well perfused fails to concentrate tracer and little or no excretion is seen in the collecting systems. Rejection is monitored with serial renograms and the measurement and follow-up of the perfusion index of a kidney. A repeated rise of this index strongly raises the suspicion of on-going rejection.

Split renal function A renogram is often used to investigate split renal function. A variety of methods have gained clinical acceptance. The aim is to give a quantitative assessment of individual kidney function which can be used repeatedly and reproducibly with a non-invasive methodology. Since computer-aided analysis is used, it is fairly simple to investigate not only individual kidney function but its regional distribution within the kidney. It is therefore straightforward to obtain quantitative indices of upper or lower pole function, parenchymal function versus pelvic function, regional horseshoe kidney assessment, etc.^{54–56}

Vesico-ureteric reflux Reflux nephropathy appears to be presiding as often as diabetes mellitus over the development of end-stage renal disease. It is therefore important to diagnose early and monitor the development of this condition. Radioactive tracer techniques are called upon in the investigation of this condition. Renal scarring is often associated with reflux nephropathy – it can be detected by ^{99m}Tc -DMSA scintigraphy. Vesico-ureteric reflux can be diagnosed on the radio-nuclide micturating renogram. During micturition, radioactive DTPA tracer is seen refluxing into the ureter and the PUJ junction of the kidney. In the indirect method, the patient is simply asked to empty a full bladder during a renogram procedure. A direct method where the tracer is introduced directly into the bladder is available for infants or non-cooperative patients.⁵⁷

Renal bone disease In patients with renal bone disease, the bone scan is often used to confirm the

presence of skeletal or soft tissue abnormality. Chronic renal failure can lead to skeletal fractures or pseudofractures, Brown's tumour, crystal deposition, tumour calcinosis, osteonecrosis (exacerbated by steroid use). All these conditions can be shown by skeletal scintigraphy. In patients on long-term haemodialysis aluminium-related bone disease needs to be considered. Low skeletal uptake of bone-seeking tracer and raised soft tissue activity of this tracer is a feature of this condition of the bone scan. Another condition which may occur in these patients is amyloidosis due to the deposition of beta-2 microglobulin. New tracers, such as ^{123}I serum amyloid P-protein⁵⁸ or ^{131}I -beta 2 microglobulin may contribute in the investigations of these patients.

GFR measurements There are a number of methods (and tracers) available to measure GFR. GFR as measured by radionuclide tracers is accurate, reproducible and preferred to creatinine clearance.

Nuclear medicine in paediatrics

Nuclear medicine has been applied to paediatrics since the early 1970s. It is now widely accepted as a non-invasive and safe methodology, useful in a significant number of clinical problems. Maturation can be investigated and interesting observations have been made in the brain, the lung and the kidney. From a clinical point of view, nuclear medicine paediatrics is most often used for the investigation of urinary tract infection, vesico-ureteric reflux or renal scarring, in the functional assessment of a transplanted kidney, in the investigation of the lung (infections in patients with bronchiectasia, gastric oesophageal reflux), in the study of malignant and benign bone tumours, in the early detection of osteomyelitis, in the investigation of the abused child and the study of neonatal hypothyroidism (thyroid ectopia, agenesis). An excellent review on paediatric nuclear medicine has recently been published,⁵⁹ but useful data in the literature span several decades.^{60,61}

Radionuclide therapy

An excellent and updated review on radionuclide therapy has been written by Hoefnagel.⁶²

Iodine-131

Radionuclide therapy is most often used in the treatment of benign thyroid disease and in the treatment of iodine avid thyroid carcinoma and its metastases. There is a huge body of literature on this subject, documenting the experience gained over 40 years. Details of protocols in this significant area of nuclear medicine practice falls outside the scope of this review. The literature shows ample evidence for the efficacy, efficiency and safety of this therapeutic modality.

^{131}I -mIBG-labelled metaiodobenzilguanidine is now in use in the treatment of documented metastatic phaeochromocytoma and neuroblastoma. Worldwide, over 300 patients have by now been treated with this tracer for phaeochromocytoma indication, neuroblastoma, paraganglioma, carcinoid and medullary thyroid carcinoma.

^{32}P -orthophosphate

As an alternative to chlorambucil or busulphan this tracer is still on offer for the treatment of polycythaemia rubra vera or essential thrombocythaemia.

^{89}Sr chloride

Approximately 1,000 patients have now been treated worldwide with this tracer. The main indication is the treatment of terminal bone pain in patients with metastatic skeletal spread, mainly from carcinomas of the prostate and breast. Response rates of the order of 80% have been achieved. Similar studies are in progress with ^{186}Re (Sn) HEDP and ^{153}Sm EDTMP.

^{131}I -lipiodol

This tracer has been advocated for intra-arterial administration and therapy of hepatoma.

Intra-cavitary treatment

Progress has been made particularly with the administration of therapeutic quantities of labelled monoclonal antibodies.

Radionuclide sinovectomy

Progress is expected with new radionuclide tracers administered into the joint space of the larger joints namely the knees.

An excellent and updated review on radionuclide therapy has been written by Hoefnagel.⁶²

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