

Radio-nuclide imaging in surgery: Part 2

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From extracting natural radioactive substances from crude pitch blende ore to creating artificial radioactivity in betatrons is a long leap indeed. In this treatise the authors tell us about the clinical applications of one of the most versatile radioisotope, namely technetium.

With the discovery of radium from pitch blende, Mme Curie unlocked the secret of the atom. After a lifetime of work with radioactivity her body got ravaged by its effects, but the value of knowledge she left behind is incalculable in terms of benefits to mankind. Having dealt with the harmful and therapeutic effects of radioactivity (and ionising radiation) in the December '98 issue of SURGERY, this issue focuses on the diagnostic applications of radioactivity.

Nuclear physics

The nucleus of a radioactive atom (radio-nuclide), consisting of protons and neutron(s) is in an unstable, high-energy state which tends to revert back to a stable (basal) state (a phenomenon known as ‘decaying’) by releasing the excess energy in the form of electromagnetic and/or corpuscular emission(s). This is the essence of radioactivity. All elements with atomic number (AN) > 83 have this property and the same may be induced in all other known elements. Thus radioactivity may be natural (viz. ^{235}U , ^{40}K) or artificial (viz. ^{60}Co , $^{99\text{m}}\text{Tc}$).

Emissions

These may be electromagnetic and/or corpuscular and all are ionising radiation. They may be produced by machines also, as described in the previous issue. They may be; (a) heterogeneous (particles of various energies or of different types, or photons of different frequencies and wavelengths); (b) homogeneous (mono-energetic particles of a single type, or photons of extremely narrow frequency and wavelength); or (c) mono-energetic (all particles or photons originate with and have the same energy).

Decay of heavy elements ($^{226}\text{Radium}$, $^{222}\text{Radon}$) releases α particles (He^{2+}), short-lived radio-arsenic emits positrons (e^+), ^{32}P emits pure β particles (e^-), $^{99\text{m}}\text{Tc}$ and ^{125}I emit only γ rays, ^{131}I and ^{198}Au (gold) give off mixed β particles and γ rays (table 1). Rearrangement of electrons in the inner shells of atoms, by the capture of an orbital electron by the nucleus during decay, produces x-rays. In mixed emissions one may predominate (^{198}Au gives 0.411 Me V γ rays (6-10 % of total dose) and 0.96 Me V β particles).

Radioisotopes

Isotopes are elements with same AN (number of protons or electrons) but different mass numbers (atomic weight; AW) (number of protons and neutrons in the nucleus). The former is constant for an element and confers its chemical characteristics. The variability of the latter (due to variations in the number of neutrons) gives rise to various isotopes. The decimal in the AW indicates a mixture of isotopes (e.g. AW of K is 39.102, indicating a mixture of ^{39}K and ^{40}K). The pre-superscript is the AW. One isotope may be stable and the other(s) radioactive (radioisotope). Of the 9 isotopes of iodine (123, 125, 127, 130, 131, 132, etc) only ^{127}I is stable. Again, the radioisotopes may be natural or artificial (^{40}K is natural, ^{42}K is artificial). $^{99\text{m}}\text{Tc}$ (technetium) is an artificial radioisotope (it has no stable or natural isotope). After decaying, a radioisotope may get converted to its stable form or to another element, which may be stable or radioactive (e.g. $^{226}\text{Radium}$ decays to $^{222}\text{Radon}$ which is also radioactive). Conversely a stable isotope may get converted into a radioisotope (infra).

Artificial (induced) radioactivity

This is produced by bombarding a stable element with high velocity particles (viz. α , β or neutrons) in a cyclotron or a nuclear reactor. The stable nucleus acquires the excess energy and becomes radioactive. The mechanisms of artificial radioactivity are many. The bombarded atom may disintegrate (e.g. disintegration of nitrogen atom when struck by an α particle) and give radio-nuclides. Radio-actinium is formed by disintegration of actinium. Bombarding boron with α particles gives radio-nitrogen. ^{198}Au is produced by exposing a colloidal suspension of metallic gold to neutrons. Alternatively, the bombarded nucleus may absorb the bombarding particle (as when a hydrogen or nitrogen nucleus captures a slow (thermal) neutron). The transmuted nucleus then becomes radioactive.

Most of the radioactive materials in clinical use are artificial ($^{226}\text{Radium}$ is a notable exception), so that a material with the desired emission (preferably homogeneous and mono-energetic), and a suitable half-life may be used. In most cases $^{99\text{m}}\text{Tc}$ fits the bill.

Half-life($T_{1/2}$): This is the time taken for a given radioactive material to lose half its radioactivity. Generally speaking naturally radioactive substances have very long $T_{1/2}$ (e.g. ^{235}U and ^{40}K have $T_{1/2}$ of hundreds of years) and artificial radioisotopes have $T_{1/2}$ of hours/days, and occasionally months (tables 1a,b). Thus unnecessary radiation to the body is minimised.

Units: The units commonly used to quantify the radiation burden in a sample of radioactive substance are Curie (Ci) and Becquerel (Bq). Both are named after nuclear scientists. One micro-curie ($\mu\text{ Ci}$) and milli-curie (m Ci) are equal to 10^{-6} and 10^{-3} Ci, respectively. [One m Ci = 37 MBq (Milli-Bq)].

Radio-nuclide imaging

Radio-nuclide imaging (RI) requires systemic administration of a radioisotope (tracer) following which it is; (a) selectively concentrated in different parts of the body; and (b) differentially accumulated in diseased and normal tissues in the same organ. It is simple to perform and relatively non-invasive. It is an innocuous approach to evaluating organ structure and function and is suitable for initial screening examination of specific organ-systems. Radioactive tracers reflect (but do not alter) organ function; assessment of physiological alterations represents the most promising use of this diagnostic modality. However, demonstration of organ anatomy is better achieved by USG, CT, spiral CT and MRI scans.

Safety considerations

Considering the potential harmful effects of ionising radiation on tissues as detailed in the previous issue, the following points are noteworthy. (1) *Emission:* The isotope used in RI should emit, as far as possible, only γ rays. These have low density of ionisation and low linear energy transfer (LET). (2) $T_{1/2}$: This should be few hours/days. ^{125}I ($T_{1/2} = 2$ months), used to diagnose deep vein thrombosis, is a notable exception. RI mostly utilises artificial radioisotopes because they generally conform to these two criteria. Naturally occurring radioisotopes generally have long $T_{1/2}$, and in any case their $T_{1/2}$ and emission cannot be controlled. (3) *Dose:* This should be the minimum possible in order to reduce the radiation burden and not to alter organ function. The dose is determined, not by the pharmacological properties but by the radiation load. (4) *Pharmacology:* It should be rapidly excreted following completion of investigation, should not interfere with the physiology or biochemistry of the organ-system and should not have any undesirable effect on the organism as a whole. Most RI studies impose only about 0.1 to 0.5 rad of total body radiation, which is well within the safety limits.

Radio-nuclides

Although well over 1000 radio-nuclides (RN) have been described, only a handful are in clinical use (tables 2a,b). The therapeutic radioisotopes have been summarised in table 5 of the previous issue of this series.

Iodine (I)

Assessment of thyroid function with radio-iodine represents one of the first applications of isotopes in medicine. Since the thyroid gland metabolises ^{131}I in an identical manner to ^{127}I (stable isotope), this is the one most frequently used. Secondly, iodine has the maximum number of isotopes in clinical use, each with its own clinical significance (table 1b). Finally, radio-iodine can be attached as a radioactive label relatively easily to virtually any substance. This makes it suitable for a wide variety of clinical uses. It is described more comprehensively in the next issue.

Technetium ($^{99\text{m}}\text{Tc}$)

It is a metallic element (AW = 99) and an artificial radioisotope ($T_{1/2} = 6.03$ hours). There are no stable isotopes or natural radioisotopes. The 'm' in the superscript refers to a metastable state. It decays by isomeric transition, emitting 140 keV (kilo electron volts) γ rays. It is the most commonly used RN in nuclear medicine, with the most versatile application and the maximum number of radio-pharmaceutical preparations to its credit. Its *advantages* are; (a) convenient $T_{1/2}$; (b) 140 keV photon emission is ideal for gamma camera performance (better image quality, shorter imaging time); (c) pure γ emission makes it safe because of its low LET (see previous issue); and (d) absence of any particulate emission, which if present, would markedly increase the radiation dose.

Radio-pharmaceuticals

Radio-pharmaceutical preparations (RP) containing $^{99\text{m}}\text{Tc}$ are the maximum in number compared to all other radioisotopes and about 35 of them have been used clinically (tables 3a,b,c). The RP may be; (a) in ionic form ($^{99\text{m}}\text{TcO}_4^-$) for brain imaging; (b) colloidal (sulphur) form for liver and spleen imaging; or (c) particulate form (albumin aggregated particles) for lung perfusion scanning. The $^{99\text{m}}\text{Tc}$ may exist in the form of; (1) discrete compound [sodium pertechnetate ($\text{Na}^{99\text{m}}\text{TcO}_4$)]; (2) radioactive label ($^{99\text{m}}\text{Tc}$ -labelled RBC); (3) stannous (lead) chelate ($^{99\text{m}}\text{Tc}$ stannous pyrophosphate); (4) lipophilic neutral complex ($^{99\text{m}}\text{Tc}$ teboroxime); or (5) lipophilic cation complex ($^{99\text{m}}\text{Tc}$ sestamibi).

$^{99\text{m}}\text{Tc}$ pertechnetate: It binds loosely to plasma proteins and moves rapidly into the extra-vascular space after IV injection. The pertechnetate (TcO_4^-) anion attains a distribution similar to that of Cl^- ions and concentrates in salivary glands, gastric mucosa, choroid plexus and thyroid gland. Cl^- and I^- are halides which share some common properties. This explains why $^{99\text{m}}\text{TcO}_4^-$ is taken up by the thyroid in exactly the same way as ^{131}I , but the former is

not organified in the gland like the latter. Therefore the ^{99m}Tc scan information may not be identical to ^{131}I scan. Because of its wide distribution in body fluids and localisation in many organs, $^{99m}\text{TcO}_4^-$ is the most commonly used RP in clinical practice. It is also used to prepare other radio-pharmaceuticals.

In the normal brain the blood brain barrier (BBB) prevents entrance of $^{99m}\text{TcO}_4^-$ from the circulation. However, disruption of the BBB by any intra-cranial lesion, coupled with the vascularity of the lesion, allows high lesion-to-brain distribution ratio of the isotope; the lesion then appears as an area of increased uptake (positive scan). This contrast is possible because in normal areas of the brain where the BBB is intact, the uptake of $^{99m}\text{TcO}_4^-$ is low (negative scan).

^{99m}Tc sulphur colloid: Sulphur in colloidal form is labelled with ^{99m}Tc and injected IV. The reticuloendothelial cells anywhere in the body (Kupffer cells in the liver, splenic red pulp, mononuclear-phagocytic cells in the marrow) treat this preparation as foreign bodies and scavenge them, thus enabling visualisation of these organs.

^{99m}Tc -MAA: This is a sterile, aqueous suspension of macro-aggregated albumin (MAA) labelled with ^{99m}Tc , and is used in lung perfusion scanning. This was found by Wagner et al in 1964 to give better results than perfusion scanning with xenon gas dissolved in saline. MAA is produced by denaturing normal human serum albumin, to give micro-spheres of controlled particle size (10-50 μ , 10-75 μ , 50-100 μ etc). Following IV injection of the labelled MAA, they are distributed in the lungs in proportion to their regional blood flow and remain trapped in the pre-capillary arterioles/capillaries for a sufficient time for their γ emission to be detected. The size disparity between the MAA particles and the pulmonary capillaries permit easy entrapment of the former, while their $T_{1/2}$ of 6 hours (same as ^{99m}Tc) allow sufficient time for gamma camera visualisation. Only about 0.1 % of the number of pulmonary capillaries are occluded during the study, following which the particles fragment and disappear from the circulation, thus making the procedure safe and free from adverse effects. This test can be performed even in severely dyspnoeic patients.

^{99m}Tc -DTPA: Following IV injection of a sterile solution of labelled diethylenetriaminopenta acetic acid (DTPA), it is concentrated through the functional renal tissue; non-functional areas such as cysts or tumours fail to concentrate the isotope. This is the basis of *renal scintiscanning* and the information provided thus is similar to that obtained by a nephrotomogram. [^{197}Hg chlormerodrin or neohydrin may also be used for the same purpose].

A pair of gamma cameras placed over the renal areas can graphically record the individual renal functions in a triphasic form (vascular, secretory and excretory phases) in the technique of *radioisotope renography*. [^{131}I or ^{125}I may also be used for the same purpose].

Infusion of the same preparation may be used for *renal function tests* (viz. glomerular filtration rate, concentrating ability, renal plasma flow etc). Unlike with creatinine, inulin or para-aminohippurate, the isotope technique does not require total urine collection to evaluate the total renal function accurately. [Labelled chelate of EDTA may also be used for the same purpose].

^{99m}Tc -etidronate, -MDP, -PYP: All are stannous chelates of ^{99m}Tc and the corresponding phosphorus-bearing compound, and are used in bone imaging. Etidronate and MDP (methylene diphosphonate) are both diphosphonate compounds that act as phosphate analogues and localise in bone. The former is not hydrolysed by enzymes, unlike polyphosphates. PYP (pyrophosphate) is a linear polyphosphate that binds calcium and thus constitutes a highly specific bone-seeking compound that accumulates in bone with kinetics similar to PO_4^- . Any process that increases bone metabolism (inflammatory or neoplastic) results in increased tracer uptake. The PYP complex is also used in acute myocardial infarction imaging because it is infarct-avid. The greatest affinity for the tracer occurs from 1 to 7 days after infarction and corresponds to the time of maximum Ca^{++} influx into the mitochondria of injured myocardial cells.

^{99m}Tc -sestamibi, -teboroxime: Both are lipophilic complexes (cation complex of isonitrile and neutral complex of boronic acid-quinolone, respectively) and are used in cardiac studies because of good myocardial uptake. The former has minimum redistribution over several hours (suitable for cardiac imaging); the rapid myocardial clearance of the latter makes it ideal for perfusion studies. ^{99m}Tc sestamibi has also been used to localise solitary parathyroid adenoma.

^{99m}Tc -albumin: This is used in MUGA (multiple updated gated acquisition; gated blood pool) scan of the heart, to record ventricular wall motion and ejection fraction (which constitutes ventricular performance). Following IV injection the blood pool tracer equilibrates in the vasculature. Utilising a computer, multiple images are recorded over a 10-minute period @ 20-30 frames per cardiac cycle, throughout many cardiac cycles. The term MUGA refers to the fact that multiple 'gates' or time-windows at various times after the QRS complex are used to gather data.

^{99m}Tc -RBC: This is used in subtraction scintigraphy to improve the accuracy of a scan image, by producing image enhancement. In the detection of gastrointestinal (GI) bleeding the labelled RBC are injected IV, from where they get distributed in the body and are 'bled' out from the site of GI bleeding. The site is detected as an area of increased radioactivity. But in very minute / slow bleeding, this may be masked by the general background radioactivity. If 5-minute interval images are taken and each is digitally subtracted from the one immediately after it, the background radioactivity can largely be eliminated, allowing the bleeding site to be highlighted. This is the principle of sequential subtraction scintigraphy. It can detect bleeding rates as low as 0.05 ml min^{-1} and the minimum detectable activity volume is 0.5 ml at 10 minutes (as opposed to 3 ml by conventional non-subtraction scintigraphy)¹.

Subtraction is also used to enhance a tumour image in the technique of radioimmunolocalization of tumours (immunoscintigraphy). When ^{131}I -labelled monoclonal antibody (MAB) is injected IV, it localises on the tumour and

also on the thyroid, liver, spleen and urinary bladder. The blood pool is separately labelled with ^{99m}Tc -RBC and the general blood pool image is digitally subtracted from the ^{131}I -MAB image. This enhances the tumour image².

^{99m}Tc -PG, -IDA: The N-substitution of the imino group in iminodiacetic acid (IDA) gives various derivatives; viz. DISIDA, PIPIDA, DIDA (diethyl IDA), HIDA (dimethyl acetanilide IDA). These or pyridoxilidine glutamate (PG) are labelled with ^{99m}Tc to give the corresponding radio-pharmaceutical. After IV injection they are promptly taken up by the hepatocytes, excreted into the bile and thence into the gallbladder and intestine. Normally the entire biliary tree is visualised and the presence of activity in the intestine indicates a patent biliary tract. Visualisation of the cystic duct and gallbladder rules out acute cholecystitis. Interest in cholescintigraphy has been revived by the development of these agents to replace the age-old ^{131}I -Rose Bengal and the technique has been refined by computer data analysis and liver subtraction (see under 'Cholescintiscan' for more details).

Imaging techniques

The γ rays emitted by ^{99m}Tc are detected by a *scintillation counter* (activated sodium iodide (NaI) crystal). When γ rays strike this crystal, light is produced. When this light hits the photo-cathode of a *photo-multiplier tube* electrons are released which are amplified to give an electrical pulse. This pulse is further amplified and analysed by an *electrical processing unit* and a recording is then made. The radiation from the isotope taken up by organs in the body can be recorded by the following methods.

Rectilinear scanner: In this machine the crystal detector mechanism is moved backwards and forwards in a grid-like pattern over the area being scanned. The result is usually recorded photographically as a printout of dots which vary in number with the intensity of radiation at different sites.

Anger gamma camera: The detecting surface of this instrument consists of a large NaI scintillation crystal, 25 to 50 cm in diameter, coupled to an array of photo-multiplier tubes arranged as a circular detector with a large field of view, which electronically positions the gamma interactions detected by the crystal. The large field of view afforded by the array of tubes allows large areas (viz. both lungs or liver and spleen) to be examined without having to move either the patient or the detector. The gamma camera is much more sensitive than the rectilinear scanner and takes much less time to build up a picture. Therefore it is most commonly used to image the distribution of radioactivity.

Imaging: The data from the gamma camera may be digitised for computer processing or viewed as an analogue image. This may be seen on a cathode ray tube (CRT) or on a television screen or stored on videotape, radiographic film or special photographic film. On a CRT and a developed photographic film, areas of increased photon emission appear as areas of increased brightness and blackness, respectively.

Emission vs. camera function: The gamma camera functions optimally at particular levels of energy emission. The 140 keV of photon emission of ^{99m}Tc is ideal for detection by the standard gamma cameras. The high energy of emission by ^{131}I (γ and β) is associated with a relatively low efficiency of detection by the gamma camera. This limits the resolution of the image and may give false-negative results. The relatively low energy of γ emission by ^{123}I is more efficiently detected by the gamma camera. The γ emission of ^{111}In is also in the suitable range.²

Tomoscintigraphy

This is also known as emission tomography and gives an opportunity to visualise the distribution of the isotope and obtain a 3-dimensional image. ^{111}In is more suitable for this than ^{131}I . Comparison of tomoscintigraphy with conventional rectilinear immunoscintigraphy has shown that the former detects smaller tumour sites (10 cm³ vs. 50 cm³) and has a higher detection rate (94% vs. 43%)². Positron emission tomography (PET) uses short-lived, on-the-spot cyclotron-produced positron-emitting radio-nuclides to obtain axial images of the brain, depicting its functional status.

Cholescintiscan

Though ^{131}I -Rose Bengal has been in use traditionally, ^{99m}Tc -HIDA, -DIDA, -PIPIDA, -DISIDA, -PG are better. They are all excreted by the hepatocytes into the bile and thence into the intestine.

Obstructive conditions

Visualisation of radioactivity in the intestine (or otherwise) is used as the criterion to diagnose; (a) congenital biliary atresia; (b) biliary-enteric anastomotic patency; and (c) complete biliary obstruction in jaundiced patients. In the last situation, since the isotope is not excreted through the biliary system but through the kidneys, the scan image is less satisfactory than PTC, ERCP or USG in diagnosing the obstructive condition. Definition of isotope scanned image is not as good as conventional radiology. However, its role in acute cholecystitis appears promising.

Acute cholecystitis

Evidence of patent cystic duct and visualisation of the gallbladder excludes the diagnosis of acute cholecystitis (AC) in the vast majority of patients. Conversely, non-visualisation of the cystic duct and gallbladder (due to obstruction of the cystic duct) but visualisation of the CBD is diagnostic of AC in a high percentage of patients.

Delayed imaging: Since certain conditions may affect gallbladder contraction, delayed imaging may highlight the same along with the cystic duct in many cases which were negative in the early films. However some recent studies suggest that non-visualisation even on delayed images of cholescintigraphy is a non-specific finding (i.e. it does not confirm AC).

Sincolide pre-treatment: Cholecystokinin (CCK; sincolide: stimulant of gallbladder contraction) is administered IV over 3-5 minutes @ 0.02 $\mu\text{g kg}^{-1}$, followed by 185-481 MBq (5-13 m Ci) of ^{99m}Tc -mebrofenin (adjusted to patients' bilirubin levels), and sequential imaging is performed until gallbladder activity is identified or till 90 minutes post-

injection of ^{99m}Tc . Sincalide pre-treatment, when administered at the physiological rate, is helpful when functional resistance to tracer flow into the gallbladder is present. CCK pre-treatment does not obviate the need for delayed imaging when the morphine augmentation technique (infra) is not used.

Morphine augmentation: Morphine produces spasm of sphincter of Oddi and improves visualisation, with or without sincalide pre-treatment. It has a reasonably good, though imperfect, specificity and positive predictive value, which are significantly better than for delayed imaging, apart from its logistical advantage (shorter imaging time). This technique is therefore recommended for routine clinical use in patients with non-visualisation of the gallbladder at 1 hour. After sincalide pre-treatment if there is no visualisation till 90 minutes, a second dose of tracer is injected, followed by morphine sulphate (@ 0.04 mg kg^{-1}) and imaging is done for 30 minutes or till gallbladder visualisation. This significantly increases the frequency of gallbladder visualisation (from 72% to 84%, in one study) and improves the efficacy of the test^{3,4}.

Tracer vs. IVC: The findings described above (excluding or confirming AC) are similar to intravenous cholangiography (IVC), but the accuracy is more with isotope scanning, there is no risk of hypersensitivity reactions (as with IVC) and it can be done on patients with serum bilirubin levels as high as 8 mg % (as against 4 mg % with IVC). Radioisotope scanning is rapid, simple and safe for diagnosing AC in emergency admissions.

Parathyroid scan

Accurate pre-operative localisation of the parathyroid gland is difficult because of many reasons (table 4). A solitary adenoma is the most common finding (multiple in 6% of cases only). For the surgeon, inability to identify such an adenoma in a normal anatomical location constitutes his Waterloo, and that is the primary reason of failure at the initial neck exploration. Table 4 lists a few localisation techniques.

Radio-immunoassay (RIA): This was developed by Berson and Yallow in 1963. The several immunologically and biologically distinct species of parathormone (PTH) in plasma necessitate a non-homologous assay system (labelled bovine PTH and bovine PTH antiserum) to measure human PTH in blood. RIA is applied to *selective venous samples* (obtained by percutaneous catheterisation) from veins of the neck and thorax, in order to localise the parathyroid pre-operatively. But selective venous sampling allows only lateralisation (not localisation) of single adenoma (denoted by marked unilateral gradient in PTH concentration in small thyroid veins), and is also unhelpful in 4-gland hyperplasia (denoted by gradients in PTH concentration on both sides of thyroid plexus). Thus, *selective thyroid arteriography*, guided by venous sampling results, is often more helpful in localisation. These invasive methods are used for cases with persistent / recurrent hyperparathyroidism following neck operation.

^{75}Se -methionine scan: The labelled amino acid is taken up by the gland for PTH production. Scanning is; (a) non-invasive; (b) often helpful in identifying large parathyroid neoplasms; and (c) rarely helpful in localising the more common smaller ones. The same points apply to *thermography* (recording the infrared rays emitted by the gland).

^{99m}Tc sestamibi scan: This has been recently introduced for parathyroid localisation⁵. It has; (a) a success rate of 85% in pre-operative adenoma localisation; (b) improves the success rate of resection at first neck exploration; (c) gives 27% reduction in bilateral neck exploration time; and (d) is a likely predictor of multigland disease also. The scan uses a double-phase, delayed imaging technique. The adenoma concentrates the isotope and appears as a focal spot of delayed tracer washout in the late image (positive scan). Thyroid nodules also show the same characteristics, thus accounting for 15% of false-positive scan with respect to parathyroid adenoma. Absence of focal delayed washout of tracer constitutes a 'negative scan' for solitary adenoma, but is a highly accurate (nearly 100%) pre-operative predictor of multigland disease. Thus a 'negative scan' allows for preparation for cryopreservation for subsequent autotransplantation⁵.

Adrenal scan

Beierwaltes et al introduced the technique in 1971. Normal adrenal glands are easily identified by their uptake of ^{131}I -labelled cholesterol, a precursor in the synthesis of corticosteroids.

Preparations: $19\text{-}(^{131}\text{I})\text{iiodocholesterol}$ and $6\text{B}\text{-}(^{131}\text{I})\text{iiodomethyl-19-norcholesterol}$ are taken up by the adrenal cortex in the usual way following injection. A major disadvantage with the former preparation is the necessity to perform repeat scans 4 to 19 days later to identify the cortical pathology. This is obviated by the latter preparation.

Cortical pathology: Adrenocortical tumours may be visualised by these techniques. The second preparation has been used in primary aldosteronism (Conn's syndrome) where there is excessive mineralocorticoid (aldosterone) production due to adrenocortical adenoma, hyperplasia or carcinoma. However, carcinomas frequently fail to be visualised because they do not concentrate the tracer efficiently, unlike the normal cortex.

Medullary tumours: Adrenal medulla is the largest paraganglion (collection of neural crest cells adjacent to the ganglia of the autonomic nervous system). All functional (i.e. catecholamine-secreting) paragangliomas, whether chromaffin or non-chromaffin (i.e. staining positive or negative with chromic salts), are nowadays termed *pheochromocytoma*. These may be in the adrenal medulla or extra-adrenal. Locating the latter presents a formidable problem because they may be situated anywhere from the thorax to pelvis (wherever there are cells of the sympathetic nervous system or other chromaffin cells whose embryological origin is in common with that of the autonomic nervous system). Even adrenal pheochromocytomas are very difficult to discern by isotope scanning techniques because; (a) the tracers are not concentrated by the adrenal medulla because their secretions do not utilise

cholesterol as a precursor; and (b) the medullary tumours may markedly displace or attenuate the surrounding cortex. However, large tumours may occasionally be demonstrated by adrenal scans.

Adrenal scans in general are of extremely limited value in detecting adrenal lesions. CT scan (resolution < 2 cm; smallest lesion identified so far has been 1 cm) is the preferred choice in this regard.

Renal scan: There may be downward displacement or extrinsic compression of the kidney by a large adrenal mass. Less than 50% of adrenal lesions are detected by this technique. Valuable ancillary information and functional integrity of the kidneys can be documented by renal scans (infra).

'Incidentaloma': This is an adrenal mass (clinically asymptomatic) *incidentally* discovered by imaging. The incidence of discovery of incidentalomas has increased with the advent and application of sensitive non-invasive imaging techniques. When an incidentaloma has been discovered, adrenal (cortical and medullary) functions should be tested and it should be removed if it is; (a) hormonally active; (b) suspected to be malignant; and (c) > 6 cm. Others should be followed by CT scan at 3, 9 and 18 months after the initial diagnosis ⁶.

Pancreatic scan

Apudomas

These are tumours arising from the *apud* (Amine Precursor Uptake Decarboxylation) cells, which are argyrophilic (have affinity for silver salts) and are distributed throughout a diffuse neuroendocrine system (predominantly in the gut mucosa, medullary (C) cells of the thyroid and pancreatic islets of Langerhan). Based their secretion they are termed; (a) gastrinoma; (b) insulinoma; (c) glucagonoma; (d) somatostatinoma; (e) pancreatic peptidoma (PPoma); (f) VIPoma; and (g) residioblastoma.

Isotope scan: Most techniques have attempted to localise pancreatic apudomas, with variable success. The small size and multiplicity of these tumours make detection difficult or impossible.

RIA-(peptides): The principle is the same as for parathyroid adenoma localisation. Trans-hepatic selective portal venous catheterisation and RIA of the venous sample may show a sudden step-up in the peptide hormone concentration. By combining this with selective pancreatic arteriography and employing a subtraction technique a high proportion of apudomas can be identified. Predominant secretion by hepatic metastases may also be detected by simultaneous hepatic vein sampling ⁷.

RIA-(NSE): Neuron-specific enolase (NSE), a neural form of the glycolytic enzyme, enolase, is produced in large quantities by all types of apudomas (but not by non-endocrine tumours), and its elevated levels in the plasma of such patients can be detected by RIA. NSE is thus a tumour marker. NSE assay may be important in the diagnosis of apudomas and for monitoring the response to therapy ⁷.

Immunoscintigraphy: ¹³¹I-anti-insulin antibody in polyclonal antiserum has been used to radioimmunolocalise pancreatic insulinoma ² (see under 'Radioimmunolocalisation' in the next issue).

⁷⁵Se-methionine: This is only of historical interest today. Radio-labelling methionine by replacing its sulphur with ⁷⁵Selenium does not change its metabolic properties. It is taken up by the pancreas and concentrated sufficiently to be imaged by gamma camera. However, simultaneous liver uptake often obscures the pancreatic image. Because of this and the better definition obtained by other modalities of imaging the pancreas, ⁷⁵Se-methionine scan is no longer used for the pancreas.

Renal scan

Renal function tests: Evaluation of the total renal function (glomerular filtration rate, renal plasma flow etc) is achieved by measuring the degree of retention in the blood, and excretion of, IV infused radioactive substances (table 5). These do not require total urine collection, unlike urea, creatinine (endogenous substances) or inulin, para-aminohippurate, PSP (exogenous substances), which depend on total urine collection, and give inaccurate results when there is significant residual urine.

Radioisotope renogram: This indicates the individual renal function in a qualitative fashion. Following IV injection of a radioisotope, gamma cameras over each renal area measure the; (a) rate of renal blood flow and uptake; the vascular spike (an initial steep rise of ½ minute); (b) rate of renal concentration, by accumulation of radioactivity, dependent on renal function (4-6 minutes); and (c) rate of clearance of the substance, by a decrease in radioactivity to blood levels, dependent on excretion. This is the triphasic graphic representation of the normal kidneys. Abnormal findings are given in table 6. If urine, blood and an inactive of the body are simultaneously monitored, additional information can be obtained. The 'blood graph' matches all the 3 phases of the renogram except that all the phases occur faster and the peak is higher. A simultaneously obtained dynamic renal scintiscan (infra) adds anatomical information, and computerised analysis permits quantitative interpretation of individual renal function.

Scintiscan: The isotopes (table 5) are concentrated throughout the functioning renal tissue and provide excellent definition and functional assessment. Areas of non-functioning tissue (cysts, tumours, abscesses etc) do not concentrate the isotope, and show as filling defects in the static scan.

The subsequent issues will contain scanning techniques of all the other organ-systems of the body.

References

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Table-1A			
Radioisotopes: Half-lives and characteristics			
Element	Isotope(s)	Half-life	Comments
Calcium	^{45}Ca	180 days	Study of calcium metabolism
Gold	^{195}Au , ^{198}Au , ^{199}Au	2.5 days (^{198}Au)	Procured fresh from atomic pile for bladder cancer therapy (^{198}Au), used for scintiscan and cancer therapy (all isotopes)
Potassium	^{40}K	Years (hundreds)	Natural isotope
	^{42}K	12.4 hours	Study of potassium interchange in the body
Sodium	^{22}Na , ^{23}Na , ^{24}Na		Study of blood flow, water balance, peripheral vascular disease, renal function tests (see text)
Strontium	^{85}Sr	65 days	
	^{87m}Sr	2.8 hours	Bone scan for metastases
	^{89}Sr	51 days	Importance in clinical scintiscan and nuclear fallout lies in their affinity for bone
	^{90}Sr	28 years	
Indium	^{111}In	2.8 days	Needs chelating agent to form radio-ligand
	^{113m}In		Platelet life span, splenic scan
Tantalum	^{192}Ta	4 months	Can be stored in hospital for bladder cancer therapy
Radium	^{226}Ra	1622 years	Cancer therapy; produces α particles and ^{222}Rn
Radium A		3 minutes	Ra A, B, C are decay products of ^{222}Rn
Radium B		26.7 minutes	Ra B, C give β and γ radiation and are used in clinical therapy
Radium C		19.5 minutes	
Radon	^{222}Rn	3.85 days	Acronym for <i>radium emanation</i> ; gas and solid form; emits α particles; seeds used in cancer therapy
Cobalt	^{60}Co	5.27 years	Cancer therapy

Table-1B		
Radioisotopes and half lives		
Elements	Isotope(s)	Half-life
Carbon	^{14}C	> 5000 years
Iodine	^{123}I	13 hours
	^{125}I	60 days (pure β emission)
	^{127}I	Stable
	^{131}I	8.04 days (γ and β emission)
	^{132}I	2.3 hours
Iron	^{55}Fe	4 years
	^{59}Fe	47 days
Phosphorus	^{32}P	14.3 days (pure β emission)
	^{33}P	
Technetium	^{99m}Tc	6.03 hours (pure γ emission)
Thallium	^{201}Tl	3 days

Table-2A		
Light radio-nuclides (AW < 80) and their diagnostic applications		
Radioisotopes	Salt/preparation/radio-pharmaceutical/ radioligand	Uses / applications
³ H {Tritium; heavy hydrogen, (1 proton, 2 neutrons)}; stable H has 1proton and no neutrons	Tritium incorporated in thymidine of DNA (tritiated thymidine-labelled cells)	Cellular proliferation, turnover and DNA synthesis studies
^{13,14} Carbon ©	Radiocarbon urea {CO(NH ₂) ₂ }, giving radiocarbon dioxide (CO ₂)	Urea breath test for gastric H. pylori; exhaled radioCO ₂ measured
¹⁸ Fluorine (F)		Bone scan for breast cancer metastases (few studies; see text)
²³ Sodium (Na)	²³ Na iodohippurate (Hippuran)	Renal function studies
³² Phosphorus(P); (AN=15, AW=30.974)	Diisopropylfluoro(³² P)phosphate; colloidal chromic(³² P)phosphate	RBC life span, splenic scan, polycythaemia vera treatment; liver blood flow studies
⁵¹ Chromium (Cr)	Sodium(⁵¹ Cr)chromate (Na ₂ CrO ₄)-tagged RBC	RBC, platelet life span; splenic scan
^{57, 58} Cobalt (Co); (AN=27, AW=58.9332)	(Radio-cobalt) cyanocobalamin (vitamin B ₁₂)	Schilling test, renal function tests, experimental biology and medicine
^{55, 59} Iron (Fe)		Erythropoiesis studies
⁶⁷ Gallium (Ga)	Gallium(⁶⁷ Ga) citrate	Soft tissue inflammation and cancer scan (liver, lung, mediastinal nodes, seminoma metastases, Hodgkin's, malignant lymphoma)
⁷⁵ Selenium (Se)	Selenomethionine (sulphur in methionine substituted with ⁷⁵ Se)	Thyroid, pancreas scan (obsolete)

Table-2B		
Heavy radio-nuclides (AW > 80) and their diagnostic applications		
Radioisotopes	Salt / preparation	Uses / clinical applications
⁸⁵ Krypton (Kr); (AN=36, AW=83.8)	⁸⁵ Kr gas dissolved in saline	Cardiac shunt studies
^{87m} Strontium (Sr)	Metastable preparation	Bone scan for breast cancer metastases
⁹⁹ Molybdenum (Mo)	Ammonium(⁹⁹ Mo)molybdate	Liver scan
^{111, 113m} Indium (In)	¹¹¹ In-labelled WBC	Liver scan (pyogenic abscess)
	^{111, 113m} In-labelled platelets	Platelet life span, splenic scan
	¹¹¹ In-labelled monoclonal antibodies (MAB)	Tomo-/immunoscintigraphy (tumour radioimmunolocalisation)
^{127, 133} Xenon (Xe)	^{127, 133} Xe gas (inhalation), dissolved in saline (IV injection)	Lung ventilation scan, thermal inhalation injury scan, ventilation-perfusion scintiphography, brain perfusion scan
^{197, 203} Mercury (Hg)	(^{197, 203} Hg) chlormerodrin, neohydrin	Radioisotope renogram, renal scintiscan, brain scan
¹⁹⁸ Gold(Au); (AN=79, AW=196.967)	Colloidal(¹⁹⁸ Au) gold	Liver scan, liver blood flow studies
²⁰¹ Thallium (Tl)		Cardiac scan for ischaemia (after stress and dipyridamole)
²⁴¹ Americium (Am)		Fluorescence scan of thyroid

**Radioactive arsenic (brain scan) and radioactive bromine (bone metastases scan) have also been used. Radioactive thorium (thorotrast) was once used for cerebral ventriculography and arteriography. However it remains trapped in the splenic red pulp till 20 years and produces radiation fibrosis and hyposplenism. Hence its use has been discontinued.*

Table-3A		
Clinical applications of ^{99m}Tc radio-pharmaceuticals		
	^{99m}Tc radio-pharmaceuticals	Clinical applications
1	^{99m} Tc pertechnetate; ionic pertechnetate (TcO ₄ ⁻) as sodium salt (Na ^{99m} TcO ₄)	Scan of brain, thyroid, salivary gland, stomach, heart, joints, Meckel's diverticulum; preparation of other ^{99m} Tc radio-pharmaceuticals
2	^{99m} Tc sulphur colloid; a.k.a. colloidal technetium sulphide	Liver blood flow studies, liver and spleen scan
3	^{99m} Tc-MAA; (macro-aggregated albumin); a.k.a. technetated aggregated albumin (human);	Lung perfusion scan, venous thrombosis scan
4	^{99m} Tc-DTPA; (diethylenetriaminopenta acetic acid); a.k.a. ^{99m} Tc pentetate (^{99m} Tc complexed with pentetic acid in NaCl solution)	Kidney, brain, lung scan; renal function tests, radioisotope renogram
5	^{99m} Tc MDP; (methylene diphosphonate); stannous chelate of ^{99m} Tc and MDP	Skeletal imaging (diphosphonate localises in bone)
6	^{99m} Tc etidronate; stannous chelate of ^{99m} Tc and etidronate, a diphosphonate compound	Bone scan (this diphosphonate not hydrolysed by enzymes)

Table-3B		
^{99m}Tc radio-pharmaceuticals (continued)		
	^{99m}Tc radio-pharmaceuticals	Clinical applications
7	^{99m} Tc-PYP; (pyrophosphate); complex of tin (stannous) and PYP labelled with ^{99m} Tc	Skeletal imaging (affinity for Ca ⁺⁺ , distribution like PO ₄ ³⁻); MI scintigraphy (affinity for Ca ⁺⁺);
8	^{99m} Tc sestamibi; (hexakis 2-methoxyisobutyl nitrile); lipophilic monovalent cation complex of isocyanide (isonitrile) family containing ^{99m} Tc	Cardiac imaging (good myocardial uptake, minimal redistribution over several hours); solitary parathyroid adenoma localisation
9	^{99m} Tc teboroxime; lipophilic neutral complex of boronic acid, ^{99m} Tc and 8-hydroxyquinoline (BATO)	Myocardial perfusion studies (good myocardial uptake but rapid clearance)
10	^{99m} Tc albumin; normal human serum albumin labelled with ^{99m} Tc	Dynamic radio-nuclide angiocardiology (MUGA scan) for ventricular performance
11	^{99m} Tc-RBC; red blood cells labelled with ^{99m} Tc	Sequential subtraction scintigraphy for GI bleeding; contrast enhancement in tumour immunoscintigraphy
12	^{99m} Tc-IDA; (iminodiacetic acid); HIDA(dimethyl acetanilide IDA), DIDA(diethyl IDA), DISIDA and PIPIDA labelled with ^{99m} Tc	Cholescintigraphy (acute cholecystitis, atresia, biliary-enteric anastomotic patency, biliary obstruction)
13	^{99m} Tc-PG; (pyridoxilidine glutamate)	Same indications as ^{99m} Tc-IDA

Note: (A) Soft tissue organ scan (#1 to 4); (B) bone scan (#5 to 7); (C) cardiac scan (# 7 to 10); (D) contrast enhancement (# 11); (E) biliary scan (# 12 and 13)

Table-3C		
^{99m}Tc radio-pharmaceuticals which are of limited use		
^{99m} Tc albumin colloid	^{99m} Tc gluceptate	^{99m} Tc oxidronate
^{99m} Tc albumin microaggregated	^{99m} Tc isonitrile (isocyanide)	^{99m} Tc pentetate calcium
^{99m} Tc antimony trisulphide colloid	^{99m} Tc lidofenin	^{99m} Tc pyrophosphate
^{99m} Tc bicisate	^{99m} Tc mebrotfenin*	^{99m} Tc metaphosphate
^{99m} Tc dicarboxypropane-diphosphate	^{99m} Tc hexamethyl propylenamineoxime	^{99m} Tc N-piperidinyl ethyl-DADT
^{99m} Tc disofenin	^{99m} Tc medronate	^{99m} Tc siboroxime
^{99m} Tc exametazime	^{99m} Tc medronate sodium	^{99m} Tc succimer
^{99m} Tc ferpentetate	^{99m} Tc mertiatide	^{99m} Tc tiatide

*See text under "Cholescintigraphy".

Table-4		
Methods of parathyroid localisation		
<i>Non-invasive (pre-operative)</i>		<i>Invasive (after failed operation)</i>
<i>Isotopic</i>	<i>Non -isotopic</i>	
⁷⁵ Se-methionine	Barium swallow cine-oesophagography	Selective venous sampling (+ RIA)
^{99m} Tc sestamibi	Parathyroid thermography	Selective arteriography
Thyroid scan		
Causes of difficulty in localisation		
1. Small (0.5-1cm) even when hyperplastic		
2. Variable position: From pharyngeal mucosa (upper extreme limit, rare) to thymus in upper anterior mediastinum {lower extreme limit, more common (5%)}		
3. Variable number: 2-7 (Alveryd's series – 1968)		
4. May be intra-thyroidal: Superior parathyroids and lateral thyroid complex are from 4 th pharyngeal pouch		
5. May be intra-thymic: Inferior parathyroids and thymus are from 3 rd pharyngeal pouch		
<i>Dual problem: difficult pre-operative localisation; difficult intra-operative identification</i>		

Table 5	
Isotopes used for renal studies	
Total renal function	¹²⁵ I-, ¹³¹ I-diatrizoate (Hypaque)
	⁵⁷ Co-, ⁵⁸ Co-cyanocobalamin (vitamin B ₁₂)
	^{99m} Tc-EDTA (ethylenediaminetetra acetic acid)
	^{99m} Tc-DTPA (diethylenetriaminopenta acetic acid)
Radioisotope renogram	^{99m} Tc-DTPA
	²⁰³ Hg (Chlormerodrin 1.25 μ Ci kg ⁻¹)
	²³ Na-iodohippurate (Hippuran)
	¹²⁵ I-, ¹³¹ I-diatrizoate (Hypaque)
Scintiscan	¹⁹⁷ Hg, ²⁰³ Hg (Chlormerodrin, Neohydrin)
	^{99m} Tc-DTPA

Table 6	
Radioisotope renogram findings	
Renal impairment	Slow first phase
	Low peak
	Shallow (slow) third phase, plateau midway between peak and base
Acute obstruction	Slow first phase
	No third phase, high plateau
Renal artery stenosis	First phase even slower
	Very low peak
	Quick fall to basal levels