Kirk-Othmer Encyclopedia of Chemical Technology.

RADIOPHARMACEUTICALS

Radiopharmaceuticals form the chemical basis of the medical specialty of nuclear medicine, a group of techniques used primarily for diagnosis, but also to a lesser degree in the treatment of disease. *In vivo* diagnostic information is obtained by intravenous injection of compounds tagged with rapidly decaying radioactive isotopes. The biological distribution of these compounds is then determined using a gamma-camera. This distribution usually takes a form that is organ- and lesion-specific, although this is not always the case. From the distribution of radioactivity and its behavior over time, it is possible to obtain information about the presence, progression, and state of disease. Localized changes in the shape or concentration of radioactivity in a given organ or structure reflect alterations in either organ anatomy or local function (see Radioactive elements; Radioisotopes).

Unlike other medical imaging modalities such as x-rays and x-ray computed tomography (see X-ray technology), ultrasound, or magnetic resonance imaging (mri) (see Magnetic spin resonance), nuclear medicine studies provide information about the functional state of tissues rather than primarily anatomy or shape of regions of differing fixed properties (see Medical imaging technology). X-rays and computed tomography yield images that are largely reflective of tissue density, a property that tends to change significantly only with injury, deformity, or advanced disease. Ultrasound imaging, based on reflections arising from the density gradients present in the body, tends to reveal the borders of regions of differing density. Mri tends to measure a gross parameter, water content of tissues, and thus also tends to be reflective of the anatomy of the tissue rather than its function. Although these modalities can yield enhanced information by the use of injected contrast agents, these agents serve primarily to visualize anatomic structures that could not be detected without them. They are not generally used to obtain functional information. This limitation results primarily from the relative insensitivity of these modalities to the small concentrations of contrast, and the even smaller variation in that concentration, that are needed to reveal functional information.

One of the great advantages of techniques using radiopharmaceuticals is extreme sensitivity. Compared to other *in vivo* diagnostic methodologies, nuclear medicine techniques can provide critical information upon introduction of many orders of magnitude less compound into the body. This is possible because the external measurement of radioactivity is accomplished by detection of individual photons, each of which represents the disintegration of a single atom. In order to obtain a sufficient signal to noise ratio, mri imaging must excite approximately one nucleus in 10^6. Thus for each atom producing a readable signal, approximately one million others must be present that produce no signal. Total injected quantities of contrast for mri and computed tomography are in the milligram to tens of grams range.

It is possible to achieve an excellent measure of the quantity of radioactivity upon disintegration of several hundred thousand atoms, ie, 10^{-18} moles. In practice, many effects, including limited sensitivity when imaging, a decay time that is longer than the measurement intervals, and absorption and scatter of photons in transit, result in the need for higher concentrations. Nonetheless, total injected quantities of tracer in the picomole, ie, nanogram range for many compounds, are common.

Nuclear medicine has found applications in measurements of cardiac mechanical function and localized tissue perfusion; in renal, hepatobiliary, and pulmonary function; and in investigations of localized perfusion

in the brain and peripheral vasculature. Nuclear medicine has seen considerable use in finding and following solid tumors and their metastases, particularly those that localize in bone, as well as in identifying regions of abnormal bone metabolism. Therapy using radiopharmaceuticals can reduce pain in bony metastases, ablate hyperactive thyroid tissue in Grave's disease, and cure thyroid cancer. Newer agents have provided the capability to identify a broader range of tumors, and agents on the horizon promise increasing access to this information. Agents under development promise to aid in the discovery and localization of intravascular thrombosis, both arterial and venous, and in localization of the sites of focal infection and of tissues that are hypoxic but remain viable.

A number of excellent general texts are available that describe nuclear medicine and radiopharmaceuticals and the various technologies that underlie both (1–6).

1. Efficacy

In common with other pharmaceuticals, the two primary requirements for success are safety and efficacy. Safety is determined both by chemical toxicity and radiation dose delivered to the patient.

It is truly possible to imagine the characteristics of an ideal radiopharmaceutical only in the context of a specific disease and organ system to which it might be applied. Apart from the physical factors related to the radioisotope used, the only general characteristic that is important in defining the efficacy of these materials is the macroscopic distribution in the body, or biodistribution. This time-dependent distribution at the organ level is a function of many parameters which may be divided into four categories: factors related to delivery of the radiopharmaceutical to a particular tissue; factors related to the extraction of the compound from circulation; factors related to retention of the compound by that tissue; and factors determined by clearance. The factors in the last set are rarely independent of the others.

Delivery factors include tissue perfusion and competing extraction by nontarget tissues, including unwanted binding to blood components. Factors related to extraction are highly dependent on the method of extraction; although in general, greater lipophilicity is related to more efficient tissue extraction from circulation. Some compounds simply diffuse across cell membranes, either passively or as in the case of ^{99m}Tc-sestamibi [109581-73-9], a moderately lipophilic monovalent cation, driven by transmembrane potentials. Others, such as the thallous ion, a potassium analogue, are actively incorporated, usually through a pathway intended for a chemically similar substrate. Still others are not extracted to any significant degree except by excretion pathways, when the target is an accessible intravascular one.

Retention, too, is highly tissue-specific. Sometimes, the extraction mechanism is also the retention mechanism, as for ^{99m}Tc-sestamibi, which is retained in mitochondria as long as transmembrane potentials remain intact. Others are separate. ^{18}F-2-Fluorodeoxyglucose enters the cell by the same pathway as glucose, but is trapped because it is not a substrate for hexokinase, preventing further intracellular metabolism.

Excretion factors are often related to lipophilicity. More lipophilic compounds tend to be excreted by the liver into the bile, resulting in elimination ultimately in the feces. As this is a relatively slow process, much of the radioactivity having a shorter half-life decays before being eliminated. Polar compounds are more likely to be excreted by the kidneys.

The biodistribution of the ideal radiopharmaceutical would show extremely rapid distribution via the circulatory system to the organs of interest and little distribution to others. It would be rapidly extracted by the organ or tissue of interest differentially in a way that reflects the disease process of interest. Ideally, abnormalities should be defined by substantial increases in the concentration of the agent because lesions defined by a decrease from surrounding concentrations, ie, cold-spot imaging, are more difficult to image.

The compound should be rapidly cleared from the circulation, but not so quickly as to preclude complete extraction in the tissue of interest, to keep background radioactivity to a minimum. The excretion pathway should be preferentially via the renal system unless this obscures structures of interest. Renal excretion is

faster and elimination of excreted radioactivity from the body by frequent voiding can reduce the overall body burden more quickly than can fecal excretion via the biliary tree and gut.

Kinetics of the biodistribution must be compatible with the practical aspects of hospital routine and imaging capability. In the case of a diagnostic agent, maximal lesion contrast, maximal radioactivity concentrations in tissue of interest, and minimal background radioactivity during the time imaging takes place are desired. This is primarily limited by practical considerations from several hours to as much as a day following administration, for the beginning of imaging, and about 40 minutes imaging time. One-hour imaging studies can be done, but such procedures tend to be stressful for the patient. Imaging times greater than an hour are generally not practical as few people can remain still for that long, even when healthy.

For therapeutic compounds, the considerations are similar, although timing requirements are quantitatively different. A diagnostic agent must retain the optimal or at least acceptable biodistribution only during the imaging time. For a therapeutic, the agent must exhibit a high target-to-nontarget ratio during the entire time following administration until the radioactive decay of the radioisotope reduces the radiation delivery rate to negligible values.

2. Nuclear Medicine Studies

Nuclear medicine studies may reveal information that is primarily anatomic in nature, or indicate the function of an organ on a regional basis (Table 1). These studies may be intended to identify new disease, confirm or deny suspected disease, or follow the progress of treatment or the course of disease. The diseases may be relatively benign or extremely serious and can range from widespread medical problems such as ischemic heart disease to rarities such as Legge-Perthe's disease and malignant pheochromocytoma (7).

2.1. Nuclear Medicine Images

Two commonly performed nuclear medicine studies are indicative of the way in which radioactive diagnostic agents may be used to elucidate the cause of a specific complaint. In Figure 1, a bone scan is used to identify the cause of acute lower back pain. Plain radiographs showed demineralization of the bones, but no specific abnormalities could be identified to account for the pain. The increased uptake in the sacral bone is in the pattern of the letter H, corresponding to the shape of this bone. This pattern, called the H sign, is typical of sacral insufficiency fracture, a fracture which is the result of severe bone loss. In Figure 2, a lung or V/Q scan is used to rule out or verify the suspicion of pulmonary embolism. The lung scan uses ^{99m}Tc macroaggregated albumin for the perfusion phase and either ^{133}Xe gas, ^{81}Rb gas, or ^{99m}Tc aerosol for the ventilation stage. This ventilation/perfusion mismatch is a result of a pulmonary embolism, ie, blood clots typically from the veins in the legs traveling through the body and lodging in the lungs.

3. Isotopes for Nuclear Medicine

Radioactive isotopes are characterized by a number of parameters in addition to those attributable to chemistry. These are radioactive half-life, mode of decay, and type and quantity of radioactive emissions. The half-life, defined as the time required for one-half of a given quantity of radioactivity to decay, can range from milliseconds to billions of years. Except for the most extreme conditions under very unusual circumstances, half-life is independent of temperature, pressure, and chemical environment.

Table 1. Medicine Diagnostic Studies and Associated Radiopharmaceuticals

Study	Disease target(s)	Organ	Radiopharmaceutical
myocardial perfusion	coronary artery disease, myocardial infarction	heart	^{201}Tl–Cl ^{82}Rb–Cl ^{99m}Tc-sestamibi ^{99m}Tc-teboroxime ^{99m}Tc-tetrafosmin
bone	bone metastases, osteomyelitis, stress fractures	skeleton	^{99m}Tc-medronate ^{99m}Tc-oxidronate
gallium study	primary tumors and metastases, infection, inflammmation	any	^{67}Ga-citrate
white cell study	infection, inflammation	any	^{111}In-WBC[a] ^{99m}Tc-WBC[b]
renal study	impaired renal function	kidney	^{111}In-DTPA ^{131}I-iodohippurate ^{99m}Tc-DTPA ^{99m}Tc-gluceptate ^{99m}Tc-mertiatide
brain perfusion	stroke, other perfusion abnormalities	brain	^{123}I-iofetamine ^{99m}Tc-exametazime ^{99m}Tc-bicisate
hepatobiliary study	acute cholecystitis	gall bladder	^{99m}Tc-disofenin ^{99m}Tc-mebrofenin
lung perfusion–ventilation (V/Q)	pulmonary embolism	lung	^{99m}Tc-albumin aggregated (perfusion) and ^{133}Xe (ventilation)
tumor localization	certain neuroendocrine tumors	any	^{111}In-pentetreotide
tumor localization	nonliver metastases of colorectal or ovarian cancer	any	^{111}In-satumomab pendetide
liver–spleen	metastatic disease of the liver	liver, spleen	^{99m}Tc-albumin colloid
tumor localization	pheochromocytoma neuroblastoma	any	^{131}I-iobenguane sulfate
thyroid study	thyroid carcinoma, hyperthyroidism	thyroid	^{131}I–NaI, ^{123}I–NaI
cardiac ejection fraction/wall motion	coronary artery disease, myocardial infarction, cardiomyopathy, other diseases affecting muscle function	heart	^{99m}Tc-red blood cells[c] ^{99m}Tc-sestamibi

[a] ^{111}In-Oxine.
[b] ^{99m}Tc-Exametazime.
[c] Using $^{99m}\mathrm{Tc} - \mathrm{TcO}_4^-$ and stannous pyrophosphate.

Radioactivity is equal to the rate of decay of a given radioisotope. This quantity is proportional to the number of radioactive atoms present, so that for a single isotope,

$$A = N \cdot \lambda$$

where A is the radioactivity in Becquerels and one Becquerel (1 Bq) is equal to one disintegration per second (the Curie is equal to 3.7×10^{10} Bq); N is the number of radioactive atoms; and λ is the probability of decay

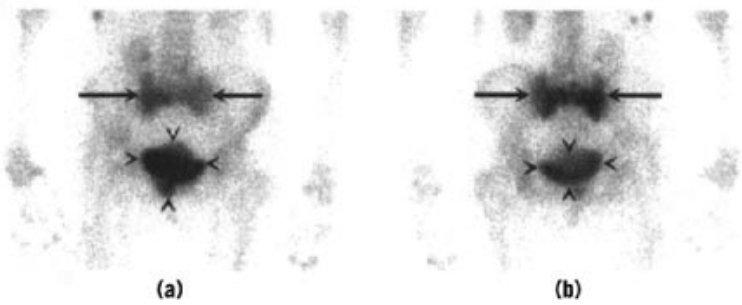


Fig. 1. Bone scan of a 75-year-old woman presented with acute onset of low back pain employing either ^{99m}Tc-medronate [25681-89-4] or ^{99m}Tc-oxidronate [14255-61-9]. The bone scan of (**a**) the anterior and (**b**) the posterior pelvis shows increased uptake in the region of the sacral bone (arrows). The bladder (arrowheads) is a normal route of tracer excretion and is also prominently identified in the image.

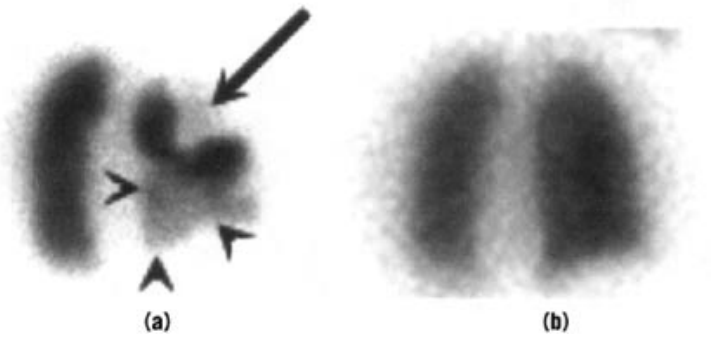


Fig. 2. Right posterior oblique lung or V/Q scan of a 65-year-old man presented with acute onset of shortness of breath and pleuritic chest pain (pain with breathing). (**a**) The perfusion lung scan showing defects in both the right upper lobe (arrow) and in the right lower lobe (arrowheads). (**b**) The ventilation scan in the same projection showing normal ventilation.

per second. The probability of decay is constant, thus

$$\frac{dN}{N} = \lambda\, dt$$

and integrating with respect to time,

$$N = N_0 e^{-\lambda t}$$

where N_0 is the initial number of radioactive atoms present at the beginning of the time interval, t. When N/N_0 is 0.5, the resulting value of t is the half-life, $t_{1/2}$, the time during which a radioactive material decays to one-half its original amount. Radioactive materials are often listed by half-life rather than by decay constant.

Substituting the following result,

$$N = N_0 e - \left((t \cdot \ln 2)\,/\,t_{1/2}\right)$$

from which it may be observed that both radioactivity and the quantity of radioactive atoms present decrease exponentially and are proportional to one another.

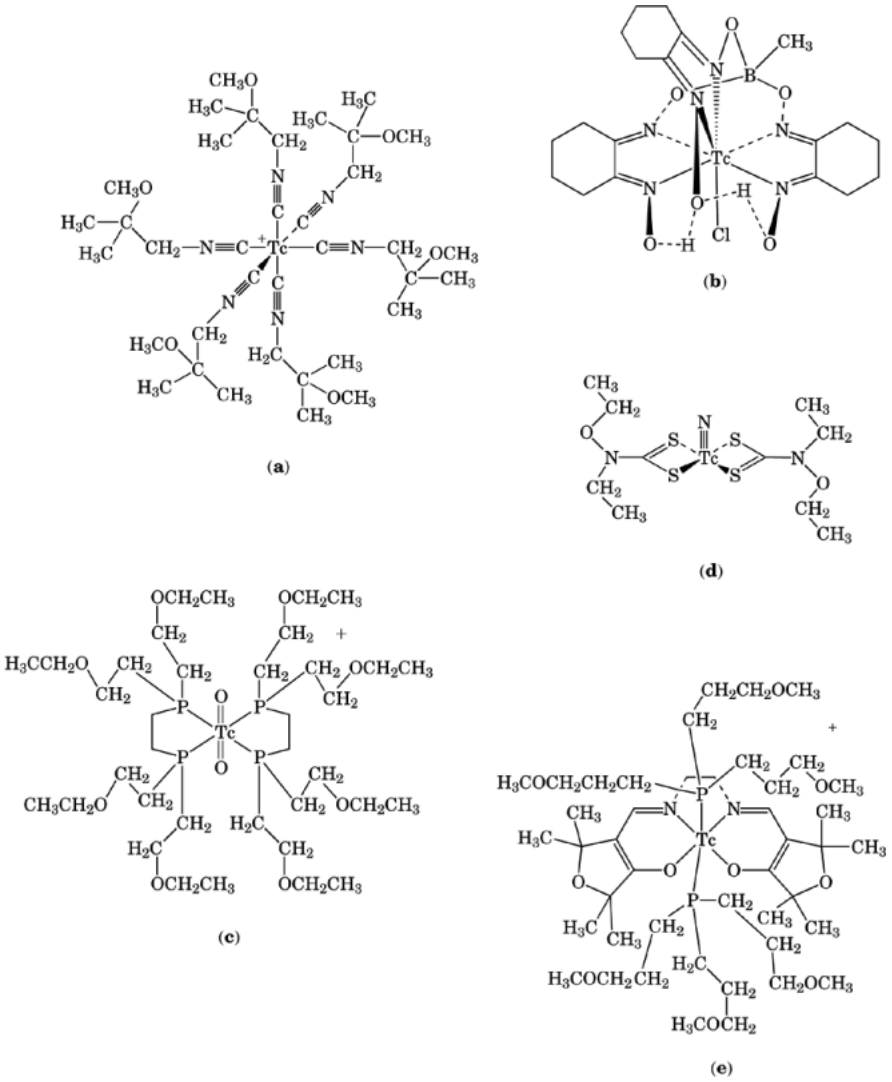


Fig. 3. Structures of ^{99m}Tc myocardial perfusion agents: (**a**) Tc(I)$(MIBI)_6^+$ (^{99m}Tc-sestamibi), where MIBI=2−methoxyisobutylisonitrile; (**b**) Tc(III)Cl(CDO)$(CDOH)_2$BMe (^{99m}Tc-teboroxime [10471-22-5]), where CDO=1,2−cyclohexanedione dioxime and BMe=methylboronic acid adduct; (**c**) Tc(V)O_2(1,2−bis(bis(2−ethoxyethyl)phosphino)ethane)$_2^+$ (^{99m}Tc-tetrofosmin [127455-27-0]); (**d**) Tc(V)N(EtO(Et)dtc)$_2$, where EtO(Et)dtc=*N*,*N*−ethoxyethyldithiocarbamate; and (**e**) Tc(III)(1,2−bis((dihydro−2,2,5,5−tetramethyl3(2*H*)−furanonato)methylene)amino)ethane)$(TMPP)_2^+$ (^{99m}Tc-furifosmin), where TMPP=tris(3−methoxypropyl)phosphine.

3.1. Diagnostic Radioisotopes

In order to be useful as an *in vivo* diagnostic agent, a radioisotope needs to possess a number of characteristics. (*1*) It must be practical to produce in sufficient quantities so that the cost of a patient dose is within acceptable limits. (*2*) It must be available at a concentration, ie, specific activity, sufficient to allow labeling reactions to proceed and to permit practical volumes of injectate for the required amount of radioactivity. (*3*) Its half-life must be sufficiently short so that the patient receives a radiation dose that is within acceptable limits. The half-life

Table 2. Diagnostic Radioisotopes by Means of Production

Radioisotope	Principal decay modes[a]	Half-life
	Accelerator	
commercially available		
^{201}Tl	EC	72 h
^{111}In	EC	67 h
^{133}Xe	EC	5.27 d
^{67}Ga	EC	77.9 h
on-site production		
^{11}C	β^+	20.4 min
^{13}N	β^+	10.05 min
^{15}O	β^+	124 s
^{18}F	β^+	112 min
	Generator	
commercially available		
^{99m}Tc	IT	6.02 h
^{81m}Kr	IT	13 s
^{68}Ga	β^+	68 min
^{82}Rb	β^+	1.25 min
not commercially available		
^{191m}Ir	IT	5 s
^{178}Ta	EC	9.35 min
^{77m}Se	IT	17.5 s
^{113m}In	IT	104 min
	Reactor	
commercially available		
^{133}Xe	EC	5.27 d
^{125}I	EC	60 d
^{131}I	β^-	8.08 d
not commercially available		
^{135m}Ba	IT	28.7 h
^{195m}Pt	IT	3.5 d
	β^+	112 min

[a] IT = isomeric transition, EC = electron capture, β^+ = positron emission, and β^- = beta decay.

must be long enough, however, so that there is not unacceptable loss of isotope from decay during transportation between the site of production and the patient. It must also be long enough that, for a given chemical form and biological system of interest, there is time for the radioactivity to reach the required distribution in the organs of interest. (*4*) It must yield an acceptable radiation dose in patients for the injected chemical form and amount needed for a particular patient procedure. *In vivo* studies always require consideration of radiation dose. Although most *in vivo* studies involve creating images of the radioactivity distribution in the patient using a gamma camera, there are some, such as the Shilling test for circulating levels of cyanocobalamin, that do not. (*5*) It must be possible to manufacture the radioisotope in a form that is compatible with labeling methodologies and be of sufficient radiophysical, ie, isotopic, and radiochemical purity. (*6*) It must emit radiation that can be detected readily in a way that the required information can be extracted.

3.1.1. Types of Diagnostic Isotopes

Isotopes used in nuclear medicine may be characterized by the source used to produce the radioactive isotope, by whether the isotopes are produced at a central location and shipped or at the clinic, or by the type of emission and thus the equipment used to detect them. The first of these, the sources, are summarized in Table 2. Some isotopes may be produced by more than one method.

Isotopes arising from reactors are produced by the addition of neutrons. These lie below the line of stability, thus relatively few diagnostically useful isotopes are produced by reactor methods. These isotopes tend to decay by β^--emission, a mode that results in a generally higher radiation dose per disintegration than other modes. Accelerator-produced radionuclides are formed by the addition of protons. These tend to lie above the line of stability, resulting in a preference for decay by positron, β^+, emission and electron capture. The remainder are produced by generators. The parent isotopes of those produced by generator are often reactor products.

3.1.1.1. Accelerator-Produced Isotopes. Particle accelerators cause nuclear reactions by bombarding target materials, which are often enriched in a particular stable isotope, with rapidly moving protons, deuterons, tritons, or electrons. Proton reactions are most commonly used for production purposes.

For accelerator-produced isotopes, the cost of the isotope is directly related to the time and total energy necessary to produce a unit of radioactivity. A portion of the capital cost of building the cyclotron is also added. Owing to the cost and siting difficulties inherent in a large production-scale cyclotron, there are relatively few cyclotrons. The need to ship the resulting products long distances tends to dictate that these products have relatively long half-lives. The most commonly used accelerator-produced isotopes are ^{201}Tl [15064-65-0] as thallous chloride for myocardial perfusion, ^{133}Xe [14932-42-5] for pulmonary ventilation studies, ^{67}Ga as gallium citrate for imaging of inflammation and certain tumors, and ^{111}In for white cell labeling, studies using antibodies, and other receptor antagonists. In addition, ^{123}I is used in a form bound to an amphetamine derivative, ^{123}I-iofetamine [75917-92-9], for imaging localized brain perfusion.

Alternatively, smaller on-site cyclotrons can provide immediate access to substantial quantities of short half-life positron-emitting isotopes such as ^{11}C, ^{13}N, ^{15}O, and ^{18}F. Less expensive than large, centralized machines, these smaller cyclotrons remain in the neighborhood of $1,500,000. In addition, the annihilation radiation produced indirectly by these isotopes is best imaged using a positron camera. This device has both advantages and disadvantages. Although single-photon emission computed tomography (SPECT) imaging of positron emitters is widely available commercially, this method suffers from poor sensitivity and resolution. Better resolution has been achieved using coincidence methods and dual-headed conventional cameras, although sensitivity remains low and injected activity is restricted owing to count rate limitations.

These cyclotron-produced positron-emitting isotopes of biologically common elements can be used to create direct analogues of molecules of biological interest, obviating the need for complex labeling chemistry involving large nonphysiological moieties. Although this approach is attractive, direct substitution into physiological molecules often results in a tracer that is rapidly metabolized. This creates an unstable biological distribution that can be difficult to image, thus derivatives are often used. The most prominent of these is ^{18}F-2-fluorodeoxyglucose which serves as a marker of glycolytic activity and can create images of viable but stunned myocardial tissue and a variety of tumors.

The combination of a PET camera and small cyclotron facility provides ready access to the ability to image the *in vivo* distribution of an enormous variety of molecules. The importance of this technique to research is substantial.

3.1.1.2. Generator-Produced Isotopes. Although the isotopes from which these are made are derived by one of the other methods described, generators may be considered separately as a production method. Such systems can produce large amounts of radioactivity at high concentrations inexpensively. To create a generator system, a parent–daughter pair of isotopes must be identified in which the daughter has the desirable properties of a diagnostic radiopharmaceutical and the parent has a similar or longer half-life and is sufficiently different chemically that separation is simple. The most commonly used radionuclide, ^{99m}Tc, is produced in a generator system from the parent ^{99}Mo. When configured as a generator, the ^{99}Mo, half-life 66 h, is immobilized and the ^{99m}Tc, half-life 6.02 h, eluted periodically. The long half-life, 200,000 yr, of the daughter ^{99}Tc ensures that only minute amounts of radioactivity remain following injections of ^{99m}Tc-labeled compounds.

$$^{99}\text{Mo} \xrightarrow{^{99m}} \text{Tc} \xrightarrow{^{99}} \text{Tc}$$

A chromatographic generator is a shielded column loaded with a parent radionuclide. The column material is chosen so that the daughter radionuclide can be eluted while the parent remains on the column. The most prevalent example is the ^{99}Mo/^{99m}Tc generator, in which the parent ^{99}Mo-molybdate is adsorbed on an alumina column and the column periodically eluted with saline. The daughter ^{99m}Tc-pertechnetate is selectively eluted resulting in a stock solution of ^{99m}Tc-pertechnetate in saline. Such generators are made to produce radioactivity levels as high as 100 GBq or more (>3 Curies) in 5 mL. The generator delivers the isotope as TcO^-_4 in saline at neutral pH. Although there are clinical applications of ^{99m}Tc as TcO^-_4, it is primarily used in combination with kits for the preparation of complexes for specific functions.

The 140 KeV photons emitted by ^{99m}Tc are accompanied by few conversion and Auger electrons and no beta-particles which increase the radiation dose without adding to the imaged information, and no gamma- or x-rays of other energies. These other gamma- or x-rays, if substantially lower in energy, also add to the radiation dose while being too heavily absorbed to contribute significantly to the image. If significantly higher in energy, they interact poorly with the detector and force compromises in collimator design that reduce detector resolution and efficiency.

^{99m}Tc has a number of other properties that make it the most nearly ideal isotope for diagnostic imaging. The energy is high enough that a substantial fraction of emitted photons escapes the patient without interaction, but low enough that the detector material can absorb virtually all that strike it with little scatter. The half-life is long enough for most preparation procedures that might be considered in a clinical setting and also long enough for convenient storage throughout the day and for equilibration under virtually any physiological process. ^{99m}Tc is easily produced and inexpensive and its variety of oxidation states provide ample opportunity for labeling technologies for many different types of ligands. It has few drawbacks, but among them is the fact that it is large and the even larger chelate complexes necessary to bind it to molecules with biological activity can make difficult the task of doing so without compromising their function. This means that it is rarely if ever possible to create a simple technetium analogue of a molecule of known function.

Other generator systems are possible and many have been constructed, but none thus far has yielded the combination of low cost, high utility, concentration, and activity of the ^{99}Mo–^{99m}Tc system.

3.1.1.3. Reactor-Produced Isotopes. Relatively few radioisotopes for clinical use are produced as the direct result of reactor-based nuclear processes, although ^{99}Mo, the parent of ^{99m}Tc is produced by this method. These processes are either irradiation of source material using thermal, epithermal, or fast neutrons, or chemical separation of isotopes of interest from spent fuel. The former process results in nuclear reactions in which the target atom absorbs a neutron and emits either a gamma-ray, one or more protons, or another neutron and is then transmuted into a new element or a metastable excited form of the original. In the second, the desired material may be the result of neutron irradiation of the fuel or a fission product produced as a result of the fission of the ^{235}U or ^{237}Pu (see Nuclear reactors).

The isotopes produced by reactors are not common as biological markers. The absorption of neutrons generally results in radioisotopes (qv) that lie below the line of stability on the chart of the nuclides. These tend to decay by β^--emission, an undesirable mode for a diagnostic.

The only commonly used radioisotope in this class is ^{131}I, used in small ($\sim$18.5 MBq (500 μCi) injected dose) quantities as a diagnostic for the evaluation of thyroid function. The compound is administered as NaI and these procedures are only possible owing to the favorable biological distribution of iodide. Up to 25% of the entire injected dose of iodide is accumulated in the thyroid with a very slow washout; the rest is rapidly excreted in the urine. No other compound exhibits so high a ratio of concentration in a target tissue to that of other tissues.

3.2. Therapeutic Radioisotopes

Isotopes used for therapy must possess many of the same characteristics as those used for diagnosis (Table 3). Because the purpose is to deliver radiation dose to a tissue, radiation dosimetry considerations are different

Table 3. Isotopes Used for Internal Therapy

Isotope	CAS Registry Number	Therapeutic application
^{131}I	[10043-66-0]	thyroid carcinoma, hyperthyroidism, antibody therapies
^{32}P	[14596-37-3]	polycythemia vera
^{89}Sr	[14158-27-1]	pain palliation in metastatic carcinoma
^{186}Re	[14998-63-1]	pain palliation in metastatic carcinoma
^{153}Sm	[15766-00-4]	pain palliation in metastatic carcinoma
^{165}Dy	[13967-64-1]	synovectomy

from those of the diagnostic isotope. However, the criteria given for diagnostic radioisotopes remain true with the exception of number six and with a redefinition of acceptable dose. Acceptable dose for a therapeutic radioisotope means a radiation dose sufficient to cause the required level of tissue damage in the tissue of interest and as little damage as possible in all others. It is not necessary to be able to detect the distribution *in vivo,* although this can be used, when available, to confirm the concentration and thereby the dose administered to the lesion. Some therapeutic isotopes, notably ^{89}Sr, emit only beta-particles yielding little externally detected radiation. Conversely, externally detectable radiation makes the patient a potential hazard to others until the radioactivity level has decreased significantly. This may require hospitalization, increasing costs.

4. Labeling Chemistry of Radiopharmaceuticals

There are three general types of radiopharmaceuticals: elemental radionuclides or simple compounds, radionuclide complexes, and radiolabeled biologically active molecules. Among the first type are radionuclides in their elemental form such as ^{81m}Kr and ^{127}Xe or ^{133}Xe, and simple aqueous radionuclide solutions such as ^{125}I or ^{131}I-iodide, ^{201}Tl-thallous chloride, ^{82}Rb-rubidium(I) chloride [14391-63-0], ^{89}Sr-strontium(II) chloride, and ^{99m}Tc-pertechnetate. These radiopharmaceuticals are either used as obtained from the manufacturer in a unit dose, ie, one dose for one patient, or dispensed at the hospital from a stock solution that is obtained as needed from a chromatographic generator provided by the manufacturer.

The second type of radiopharmaceuticals are radionuclide complexes. These are almost exclusively metal radionuclides complexed to a ligand or ligand system. The use of a ligand or ligand system allows the physical and chemical properties of the radionuclide to be modified. These properties include the stability, charge, oxidation state, and lipophilicity. Many of the uncomplexed metal radionuclides are not stable in biological media, forming a variety of species with differing biological properties, which confounds the ability to target the radiopharmaceutical to a particular organ or disease state. Metal complexes can be made that remain a single discreet species *in vivo* or that undergo a specific chemical transformation that is central to their utility. A variety of ligands have been used to form radionuclide complexes, ranging from monodentate to octadentate, and both homoleptic and binary ligand systems have been used. Examples of the resulting radionuclide complexes include cationic, neutral, and anionic complexes and cover the range from very hydrophilic to very lipophilic. The vast majority of these examples are coordination complexes of ^{99m}Tc. A variety of ligand systems, ligand denticities, and technetium oxidation states are employed. Some are shown in Figure 3. Those complexes shown in Figure 3**a–c** have been approved for routine clinical use in humans (see Table 1). The complexes in Figure 3**d** and 3**e** are under active clinical development as of this writing (ca 1996).

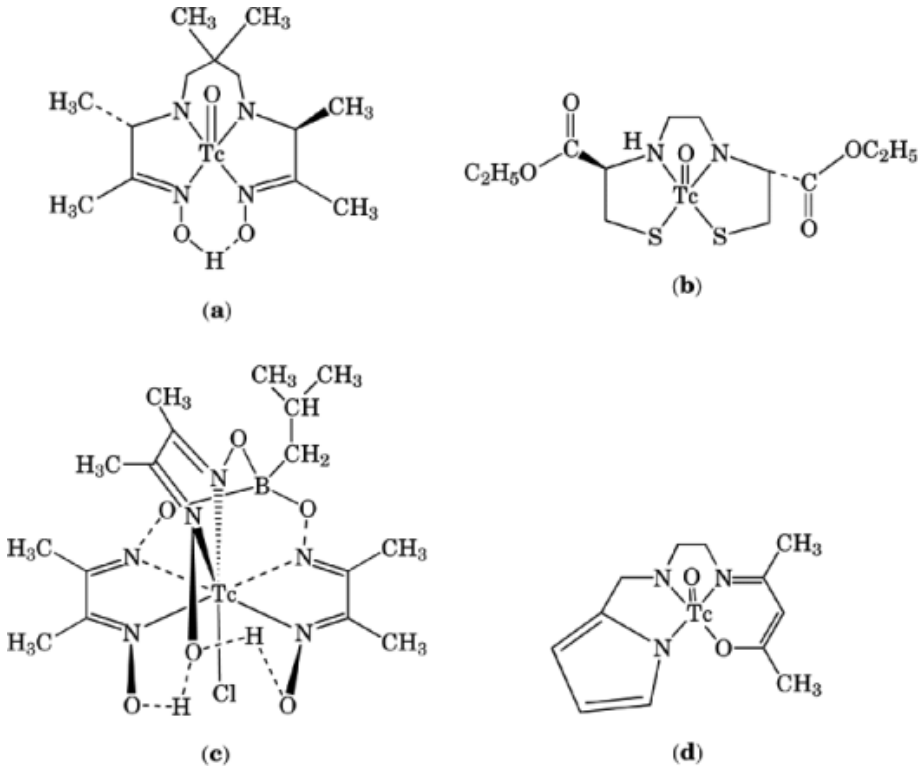


Fig. 4. Structures of ^{99m}Tc cerebral perfusion agents: (**a**) Tc(V)O(HMPAO) (^{99m}Tc-exametazine [105613-48-7]), where HMPAO=3,6,6,9−tetramethyl−4,8−diazaundecane−2,10−dione dioxime; (**b**) Tc(V)O(ECD) (^{99m}Tc-bicisate [121281-41-2]), where ECD=*N*,*N*′−1,2−ethylenediylbis(L−cysteine) diethylester; (**c**) Tc(III)Cl(DMG)(DMGH)$_2$BiBu, where DMG=dimethylglyoxime and BiBu=isobutylboronic acid adduct; and (**d**) Tc(V)O(*N*-(2(1*H*-pyrolylmethyl))*N*′-(4-pentene-3-one-2)ethane-1,2-diamine).

Certain neutral technetium complexes can be used to image cerebral perfusion (Fig. 4). Those in Figure 4**a** and 4**b** have been approved for clinical use. Two other complexes (Fig. 4**c** and 4**d**) were tested in early clinical trials, but were not developed further. An effective cerebral perfusion agent must first cross the blood brain barrier and then be retained for the period necessary for image acquisition. ^{99m}Tc-bicisate is retained owing to a stereospecific hydrolysis in brain tissue of one of the ester groups to form the anionic complex TcO(ECD)$^-$, which does not cross the barrier. This mechanism of retention is termed metabolic trapping.

Several hydrophilic, anionic technetium complexes can be used to perform imaging studies of the kidneys. ^{99m}Tc-Mertiatide (Fig. 5**a**) is rapidly excreted by active tubular secretion, the rate of which is a measure of kidney function. ^{99m}Tc-succimer (Fig. 5**b**), on the other hand, accumulates in kidney tissue thus providing an image of kidney morphology.

A number of other technetium-99m complexes are utilized in nuclear medicine procedures for which the structures of the complexes have not been unambiguously established. Structural determination requires synthesis and characterization of the chemically identical complexes using ^{99}Tc, a long-lived β-particle emitting isotope available in gram quantities. However, it is difficult logistically to maintain the reaction stoichiometries used in the synthesis of the technetium-99m complexes, frequently molar ligand excess of 1000–10,000 (*vide infra*), when performing the syntheses using macroscopic quantities of ^{99}Tc. This can lead to differences in the chemistry observed in the different concentration regimes. Without the characterization of the ^{99}Tc analogues, the structures of the ^{99m}Tc complexes can only be inferred. Examples of such complexes having

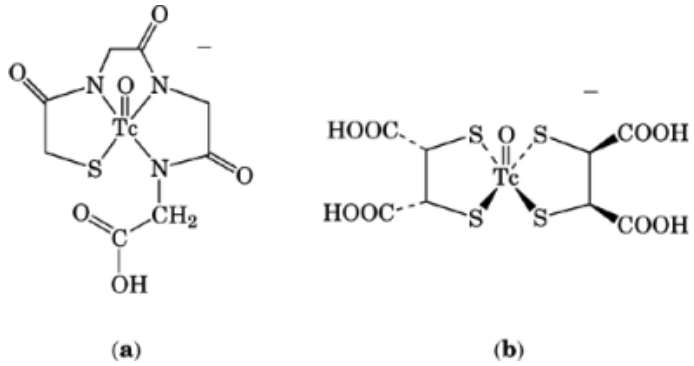


Fig. 5. Structures of ^{99m}Tc renal imaging agents: (**a**) $Tc(V)O(MAG_3)^-$ (^{99m}Tc-mertiatide [66516-09-4]), where MAG_3=*N*−2−mercaptoacetyltriglycine; and (**b**) one isomer of $Tc(O)(dmsa)_2^-$ (^{99m}Tc-succimer), where dmsa=dimercaptosuccinic acid.

inferred structures include the Tc-iminodiacetic acid complexes (^{99m}Tc-mebrofenin [78266-06-5], ^{99m}Tc-disofenin [65717-97-7], and ^{99m}Tc-lidofenin). These are hepatobiliary imaging agents having different substituents on the iminodiacetic acid ligands. The Tc-diphosphonate complexes (^{99m}Tc-medronate, ^{99m}Tc-oxidronate), bone imaging agents having different substituents on the diphosphonate ligands, Tc-DTPA (^{99m}Tc-penetate [12775-34-7], DTPA = diethylenetriaminepentaacetic acid), Tc-glucoheptonate (^{99m}Tc-gluceptate [87-74-1]), and ^{99m}Tc-pyrophosphate, also fall into this category.

Several complexes of other radionuclides are also widely used in nuclear medicine. $In(III)(oxine)_3$ (^{111}In-oxyquinoline) is used to label white blood cells for imaging sites of infection or inflammation, $In(III)(DTPA)^{2-}$ (^{111}In-penetate) is used for radiographic cisternography, and a Ga(III)-citrate complex is used for imaging tumors. The structures of the two indium complexes have been determined by synthesis and characterization of the nonradioactive indium analogues. The structure of the Ga complex is not known. Two complexes of high energy β-particle emitting radionuclides are in clinical trials, ^{186}Re-HEDP (HEDP = hydroxyethylidinediphosphonate) and ^{153}Sm-(EDTMP) (EDTMP = ethylenediamine-*N,N,N′,N′*-tetrakis(methylenephosphonic acid)) for use in bone pain palliation. Neither structure has been unambiguously determined.

The procedures used to synthesize metal radionuclide complexes vary depending on the chemical reactivity of the radionuclide in its available form. Some radionuclides are available as metal halide solutions and can be formed by reaction with the ligand(s) directly. An example of the direct complexation approach is the synthesis of $In(III)(oxine)_3$. In(III)-chloride and 8-hydroxyquinoline react by adjusting the pH to 7. Owing to the dilute concentration of the In–chloride solution, the hydroxyquinoline is added in large excess to achieve a reasonable reaction rate. In contrast, pertechnetate must be reduced to form complexes. Typically this is achieved by addition of the ligand(s) and a reducing agent, such as tin(II) chloride. Both the ligand and the reducing agent are added in large molar excess. If the rate of pertechnetate reduction is significantly more rapid than the rate of complexation, reduced technetium species accumulate in the solution. These reduced species are not stable in aqueous solution, undergoing hydrolysis and disproportionation to form pertechnetate and TcO_2 (Tc-colloid), insoluble, colloidal, Tc(IV)-oxide. The formation of this by-product can be prevented by including in the reaction mixture another ligand that forms complexes more rapidly. The reduced technetium species are then complexed by the additional ligand, termed a transfer ligand (preventing hydrolysis and disproportionation), and subsequently converted to the final ligand complex. For example,

$$^{99m}\text{Tc} - \text{pertechnetate} + \text{tartrte} \xrightarrow{\text{Sn(II)}} {}^{99m}\text{Tc} - \text{tartrate} \xrightarrow{\text{MAG}_3} {}^{99m}\text{TcO}(\text{MAG}_3)^-$$

where MAG_3 is *N*-2-mercaptoacetyltriglycene.

Complexes of radionuclides of high specific activity are synthesized in very dilute aqueous solution. For example, solutions of technetium complexes typically range from 10^{-7} to 10^{-6} M. Most techniques, such as nmr, ir, etc, do not have the necessary sensitivity to analyze for such dilute species. Therefore, radionuclide complexes are analyzed almost exclusively by chromatography (qv), using the radioactive emission as the detectable label. High performance liquid chromatography (hplc) and thin-layer chromatography (tlc) are used extensively. Hplc chromatograms are obtained by monitoring the column effluent with a radioactivity detector, such as a sodium iodide or Geiger-Mueller probe. For tlc, the plate is either scanned using a probe or divided into sections such that the amount of radioactivity in each section can be counted in an ionization chamber. The limit of detection for ^{99m}Tc by these methods is generally $\sim$37 kBq (1 μCi) or $\sim 10^{-15}$ mol.

The third type of radiopharmaceuticals are radiolabeled biologically active molecules. Proteins, antibodies, peptides, and enzyme substrates are modified using a gamma-emitting radionuclide to image biological function. The method of labeling is chosen to have the least impact on the biological activity. Typical radionuclides include ^{11}C, ^{13}N, ^{15}O; the radiohalogens, such as ^{18}F, ^{123}I, ^{125}I, and ^{131}I; and the metal radionuclides, ^{99m}Tc and ^{111}In.

Biologically active molecules may be labeled either directly or indirectly. For direct labeling, that is, incorporating the radiolabel directly into the compounds, the labeling may be isotopic or nonisotopic. For isotopic labeling, one group already present in the molecule is substituted with or exchanged for the radioisotope. For nonisotopic labeling, that is, incorporating the radiolabel into the compounds through a chelator or other functional group which has been incorporated into the compounds, the radioisotope is added to the molecules without substituting with or exchanging for an already existing group.

Generally, labeled compounds are prepared by procedures which introduce the radionuclide at a late stage of the synthesis. This allows for maximum radiochemical yields, and reduces the handling time of radioactive material. When dealing with short half-life isotopes, a primary consideration is the time required to conduct synthetic procedures and purification methods.

Various procedures may be employed in preparing the radiolabeled compounds where the radiolabel is a halogen. Some common synthetic methodologies for isotopic halogen labeling of aromatic compounds or aromatic groups in peptides or proteins are iododediazonization, iododeboration, iododestannylation, iododesilation, iododethallation, and halogen-exchange reactions. The most common synthetic methodology for nonisotopic halogen labeling of aromatic compounds is iododeprotonation or electrophilic aromatic substitution reaction. These methods and additional procedures are described in the literature (8, 9).

Alternatively, radiohalogen-labeled compounds may be prepared by way of isotopic labeling from the unlabeled bromo or iodo derivatives by various two-step reaction sequences. Examples include the use of trialkylsilyl synthons as described in References (10–13), and the use of boronic acid synthons as described in References 14 and 15.

Metal radionuclide labeling of biologically active molecules can be performed either directly or indirectly. For example, for proteins or antibodies that contain disulfide linkages, the addition of a reducing agent such as stannous ion, 2-mercaptoethanol, or dithiotheitol generates free thiol groups on the molecules. These free thiol groups can be directly labeled with ^{99m}Tc by reaction with pertechnetate and an additional reducing agent or with a ^{99m}Tc transfer ligand complex. The advantage of direct labeling is that it is easy to carry out. There are two main potential disadvantages. Reduction of the native disulfide linkages to form the free thiols that bind the technetium may adversely affect the biological properties of protein, antibody, or polypeptide. Also, particularly for larger molecules, a number of free thiol-containing sites may be formed that when reacted with the technetium result in binding with a varying degree of stability. Whether these disadvantages become manifest depends on the biologically active molecule chosen to be labeled.

There are two approaches for indirect labeling of biologically active molecules with metal radionuclides. Both approaches require that the molecules be chemically modified to attach the chelator without significantly affecting their biological activity. The first involves attaching a metal chelator to the molecule and then reacting

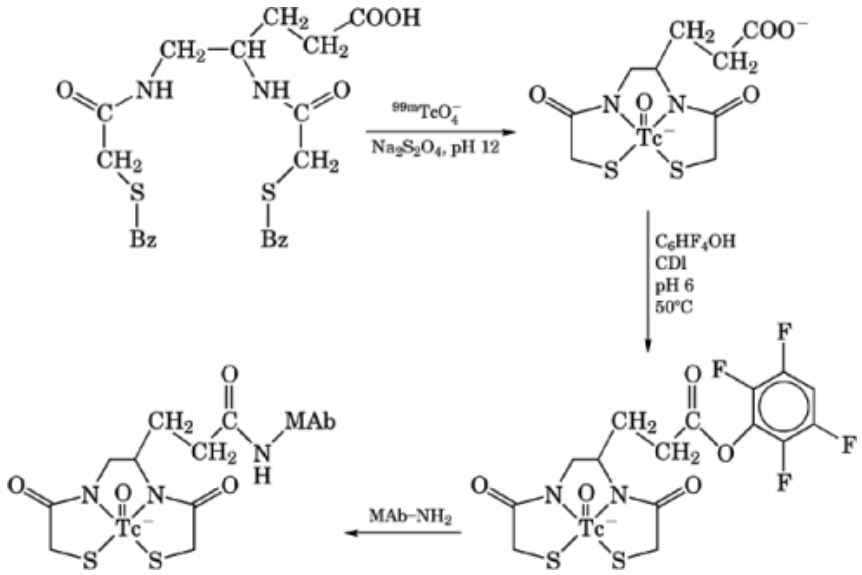
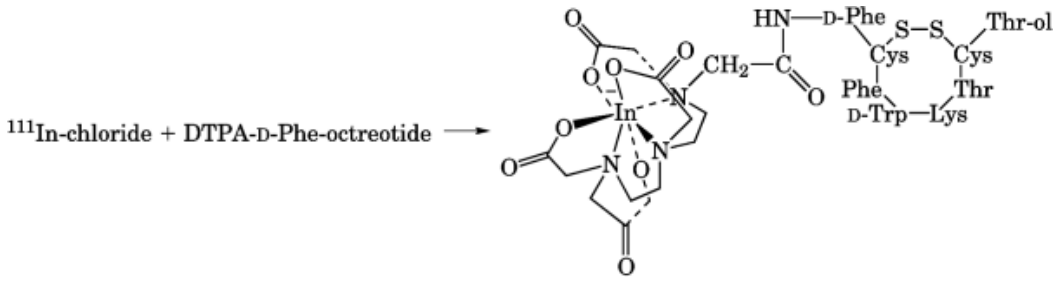


Fig. 6. General reaction scheme for the preformed chelate approach where Bz=benzoyl and MAb=monoclonal antibody.

the resulting conjugate with the radionuclide. The procedures for the reactions are similar to those used to synthesize the corresponding metal chelate complexes. An example of this approach is the synthesis of ^{111}In-labeled octreotide (^{111}In-pentetreotide [13906-04-1]) for imaging neuroendrocrine tumors.



The second indirect approach involves forming a metal radionuclide complex, chemically modifying the complex to generate a reactive site on the complex, and then reaction of the modified complex with the biologically active molecule. This approach is termed the preformed chelate approach or retrolabeling. It requires several more steps than the other approaches, but the molecule is not present during the synthesis of the metal radionuclide complex, which is an advantage if the molecule cannot survive the reaction conditions used for forming the complex (Fig. 6).

Radiolabeled biologically active molecules are analyzed by chromatographic techniques similar to those used for metal radionuclide complexes. Hplc and tlc methods for large molecules generally utilize different chromatographic media to minimize adsorption of the analyte. Common hplc methods include size-exclusion chromatography, gel-permeation chromatography, ion-exchange chromatography, and affinity chromatography.

An important consideration for all radiopharmaceuticals and especially radiolabeled biologically active molecules is specific activity. There are two types of specific activity: radionuclidic and biological. Radionuclidic specific activity refers to the ratio of the number of atoms of a particular radioisotope to the total number of

atoms of the element. For ^{99m}Tc, the radionuclidic specific activity is the number of ^{99m}Tc atoms to the total number of ^{99m}Tc and ^{99}Tc atoms. Because all isotopes of an element are chemically identical, a low specific activity may lead to a low yield in the synthesis of a radiopharmaceutical if a significant proportion of the reagents is consumed by the undesired isotopes.

Biological specific activity refers to the ratio of the number of radiolabeled biologically active molecules to the total number of biologically active molecules. If the biological activity is dependent on the interaction of the molecule with a receptor or binding site, the excess unlabeled molecules may compete with the labeled molecules, limiting the number of detectable molecules that can be localized at the receptor or binding site. Also, the excess unlabeled molecules may cause an undesired biological response, limiting the number of molecules that can be present in the radiopharmaceutical. Therefore, both a high radionuclidic and biological specific activity is preferred.

5. Instrumentation for Imaging and Counting

Detection of the emissions from radiopharmaceuticals is dependent on the type of emission. In practice, only those isotopes emitting either γ-ray or x-ray photons, either directly from the decay reaction or indirectly from annihilation of an emitted positron, are useful for *in vivo* imaging, although β-emissions may be of use for *in vitro* purposes. These high energy photons are ionizing radiation and interact with matter via only two mechanisms. For those photons emitted by commonly available radionuclides, the predominant mechanisms are the photoelectric effect and Compton scattering. The photoelectric effect is an interaction between the photon and inner shell electrons in which the original photon is completely absorbed leaving the atom in an excited state, followed by deexcitation by emission of low energy electrons or fluorescence photons. Compton scattering is an interaction with loosely bound valance electrons resulting in acceleration of the electron and in general a deflection and energy loss for the photon. The direction of the scattered photon is related to that of the electron and to the energies of both, but is nearly isotropic at low energies, with respect to the trajectory of the original photon.

5.1. Measurement of Injected Patient Dose

The patient's injected dose, as distinguished from the radiation dose, must be within 10% of the prescribed dose for a given procedure by law in the United States. This is measured using a large ionization chamber of cylindrical geometry. An ionization chamber is a space filled with air or other gas in which a constant electric field is present. Gamma-rays or other ionizing particles passing through the gas produce electron–ion pairs. The electric field is of sufficient magnitude that these cannot recombine but rather migrate through the gas until they are collected by the electrodes producing the field. Thus, the more electron–ion pairs produced in the gas, the more current flows in the external circuit. This current is a measure of the ionization and therefore of the radioactivity present. If the chamber is arranged so that the ionization produced is relatively independent of the position and shape of the source (thus the cylindrical well) the device can be calibrated for each isotope.

The modern ionization chamber, called a dose calibrator in this application, is capable of linear measurements of radioactivity having a precision in the range of several percent coefficient of variation over a range of 370 kBq (10 μCi) to at least 370 GBq (10 Ci). This extraordinary range is the chief advantage of this instrument. It may only be used when the sample is known to have only a single isotope. It has no capacity to distinguish radiation from different isotopes.

5.2. Counting Systems

Counting of small samples of γ-emitting radioisotopes is commonly accomplished in biology and medicine using a scintillation detector. This is a block of crystalline sodium iodide with a small proportion of thallium, generally cylindrical, and either 5 cm in diameter and 5 cm high (2×2 in.) or 7.6 cm in diameter and 7.6 cm high (3×3 in.). It is hermetically sealed in an aluminum enclosure having one glass wall on a cylinder end. Often the other end has a well or a blind hole centered on the face and a depth of about two-thirds the thickness of the crystal and a diameter that is convenient for a sample tube, usually 10 mm. The glass panel of the crystal enclosure is coupled to a photomultiplier tube that records the bursts of light produced each time a γ-ray interacts to produce ionization in the crystal.

Samples in tubes are placed in the well of the crystal and the number of light bursts observed over a given time recorded. This value is proportional to the number of disintegrations that occurred during that time and therefore to the amount of radioactivity in the sample. Mixtures of isotopes emitting γ-rays of different energies can be assayed in the same tube. This is made possible by the proportionality between the intensity of each light burst with the energy deposited by the photon that created it. If the photon was completely absorbed in the detector, either in a single event or several successive ones, then the recorded light burst yields information about the γ-ray energy and thereby the isotope that produced it.

This type of device is commonly limited to a maximum radioactivity of approximately $3.7 - 7.4 \times 10^4$ Bq (1–2 μCi). Its lower limit is primarily determined by the background count rate and the patience of the investigator. It can be used to separate the contributions of as many as five to six isotopes in a single sample. These counting systems are normally highly automated, incorporating mechanical sample changers with a capacity of several hundred sample tubes and computers controlling the process and recording the result.

5.3. Single-Photon Imaging Systems

There are many materials and schemes for detecting photons, but for nuclear medicine one instrument, the γ-camera, is used almost exclusively. This device consists of a disk or rectangle of crystalline sodium iodide with a small proportion of thallium, generally 10-mm thick and in rectangles of up to 40×60 cm, hermetically sealed in an aluminum enclosure with one glass wall on a large surface. γ-Rays absorbed in the crystal result in the emission of a burst of light photons over a period of several hundred nanoseconds. These are detected by an array of photomultiplier tubes and the centroid of the light distribution, an estimate of the γ-ray interaction point, may be determined by hardware interpolation among this array. For each γ-ray detected, a point on an image plane is incremented in intensity.

In order to produce an image, photons must escape the patient without interaction. Because scattering yields a nearly isotropic distribution of scattered photon directions, any photon undergoing scatter within the patient no longer carries information about its point of origin and must be rejected by an imaging apparatus. Because the light intensity produced for each γ-ray is proportional to its energy, that energy may be determined for each event. This permits the system to reject γ-rays having energy lower than expected, an indication of scatter prior to detection.

γ-Rays cannot be refracted, only scattered or absorbed, thus it is not possible to create a lens in the conventional sense. The collimator, a tall lead honeycomb between the crystal and the patient but very close to the crystal, serves this purpose. Rather than refracting the light to form an image on a focal plane, as does a light camera, the collimator simply discards all rays having a direction not perpendicular to (close to) the crystal surface. This results in a photon flux at each point on the crystal that is proportional to the integral of the radioactivity concentration along a line perpendicular to the crystal surface, with appropriate modification for attenuation in the body.

Collimators for image formation are extremely inefficient compared to conventional lenses. This is a natural result of the physics of the interactions between γ-ray photons and matter, in this case lead or tungsten.

Whereas a lens for image formation using light can refract the light and concentrate it, a γ-ray collimator can only discard those photons not traveling approximately perpendicular to the crystal surface. As a result, the vast majority of photons are excluded from the imaging process.

Although performance varies with the isotopes for which they are intended, and with the balance in the design between resolution and efficiency, the overall sensitivity of a γ-camera collimator is on the order of 5000counts/(MBq·min) (several hundred counts/(μCi·min)). In terms of photons detected per photon emitted, this is equivalent to about 2×10^{-4}. In other words, about two photons out of 10,000 emitted arrives at the crystal. This necessitates exposure times that range from several minutes to the better part of an hour. Fortunately, the large number of photons available from a modest injected radioactive dose more than offsets the poor detector sensitivity. The camera's ability to resolve small objects, however, is ultimately limited by the collimator inefficiency.

The resolution of the γ-camera is determined by both the collimator and the crystal/photomultiplier tube combination. In general, the resolution is significantly poorer than that of other modalities such as magnetic resonance imaging (mri) and x-ray computerized tomography (ct). For single-photon imaging, a system resolution of the order of 6–7 mm full-width at half-maximum (FWHM), the width of the spot that results in an image from a very small point of radioactivity, at the surface of the collimator and approximately 1 cm FWHM, 10 cm away is common when a higher resolution collimator is used.

The image is created either on film by allowing each detected photon to brighten a corresponding point on an oscilloscope screen viewed by high speed film, either conventional medical transparency or rapid development film, or by computer. The computer method is becoming nearly universal and consists of incrementing an appropriate location in a two-dimensional array in memory upon detection of each photon. This is then available for display, processing, calculation, and printing. The resulting digital image is created by transferring the contents of this array to an array of picture elements (pixels) on the computer display, in which increasing values are translated to colors of increasing shades of gray.

Several types of studies may be performed using modern equipment. Static studies are simply views of the body from various perspectives, arranged so as to yield the maximum isolation of a given structure of interest. Dynamic studies are composed of a series of images of a single organ or structure, repeated over time so that replay of them in sequence yields a motion picture-like change. Gated studies are similar to dynamic studies, except that they are used for the imaging of structures, primarily the heart, that have a rhythmic movement. Data are acquired into a series of images for a single period, then data for subsequent periods are added to these images in a synchronized fashion.

Single-photon emission computed tomography (SPECT) studies are acquired by rotating the γ-camera around the patient's long axis. These data are then used to reconstruct the radioactivity distribution in three dimensions. This may be displayed as slices of radioactivity concentration or rendered so as to present the appearance of a solid volume.

As a modality, SPECT imaging represents a growing segment of nuclear medicine studies. Although it does not require a specific agent, many agents yield significantly better information when SPECT acquisitions are used. SPECT eliminates the uncertainty that occurs in planar images when organs at different depths cannot be distinguished. Because overlapping organs no longer pose a problem, contrast and visualization are both improved. Although it is not yet possible to obtain truly quantitative estimates of radioactivity concentration using SPECT because of scatter and attenuation, compensation methods are improving and the modality should compete with positron imaging in the area.

Several specialized devices exist, among both commercialized systems and those used for research, that yield improved SPECT images for specific organs. For many of these, the brain is the target and systems using rings of scintillating detectors or arrays of individually collimated scanning scintillation detectors can create images with significantly better resolution or, in some cases, dynamic SPECT images.

5.4. Positron Imaging

Creating images of distributions of positron emitters requires a somewhat different type of apparatus. Positron cameras use many of the same technologies as do cameras for other isotopes, but there is a broader array of methods and physical arrangements. All of these systems take advantage of the physical characteristics of positrons.

Positrons are emitted having energies that can range from several tens of keV to several MeV. As for all charged particles, they travel a distance that is proportional to their starting energy, leaving a trail of ionization as they slow down. This distance can range from less than one micrometer to several millimeters in tissue. As the positron energy decreases, its probability of undergoing an annihilation reaction with an electron increases. This reaction results in the emission of two 511 keV γ-rays traveling essentially in opposite directions, yielding conservation of both momentum and energy. The rest energies of the electron and the positron are both 511 keV.

Detectors are arranged on opposite sides of the patient and circuitry detects coincidence events in which photons are detected simultaneously within the time resolution of the system. These events mark annihilations that have occurred somewhere along the line connecting the detectors. If there are many detectors at different angles, this data may then be used, as is SPECT, to reconstruct the three-dimensional distribution of the radioisotope. Because virtually all positron imaging is tomographic, that is, a three-dimensional reconstruction or literally slice writing, positron imaging is normally called positron emission tomography (PET).

The camera actually images the annihilation events, not the radioactive decay events directly. Thus imaging of high energy positron emitters can have a limiting resolution owing to the range of the positron.

Although energy resolution is rarely employed in positron camera systems, scatter is not normally a problem. This is because of the very short time window within which two photons must arrive in order to be counted. At low decay rates, the incidence of accidental events is very low, rising only slightly for those that occur as the result of scatter. Some systems employ time-of-flight measurements of the time difference between the arrival of the two photons to obtain additional information about the location of an annihilation along the line. This has been used to improve resolution and statistical accuracy. Resolution is in the range of 3–4 mm and is less dependent on position than is SPECT (16).

Because few scatter events are recorded, attenuation compensation is relatively easier for PET using an external positron emitting source. As a result, the technology for quantitative determinations of radioactivity distributions is significantly more advanced in PET imaging. Technology development for SPECT, however, is improving this parameter.

PET imaging systems are somewhat more complex, and therefore more expensive than are SPECT systems, and the price factor is generally between two and three. The primary cost premium associated with these systems, however, is the need for a cyclotron and its attendant staff combined with the relative complexity of radiopharmaceutical preparation for short half-life isotopes. As of 1996, there are considerable hurdles blocking widespread regulatory approval and full reimbursement of PET studies.

5.5. Other Instrumentation

5.5.1. Health Physics Instruments

Minimization of radiological hazards to personnel and patients in a nuclear medicine environment requires appropriate instrumentation. It is in many ways easier to protect people from nuclear agents than chemical ones because the great sensitivity of measuring apparatus permits the identification and localization of extremely small quantities quite readily. The general armamentarium of radiation monitoring includes a survey meter, generally employing a gas-media detector, such as a Geiger-Müller tube, or a small scintillation detector if additional sensitivity is required. Also needed is a system for assay of wipe tests. This consists of wiping a defined area of the bench, floor, and countertop and assaying the wipes using a survey meter or specialized

system for the detection of removable radioactive contamination. An air-ionization chamber survey meter, called a cutie pie from qT-π for charge, time, and four-pi geometry, is necessary if high radiation fields are likely to be present. A thyroid counter is necessary if radioiodine is used in the facility. Finally, area monitors of appropriate type are necessary wherever radioactivity is used. These must include the capability for detecting all radionuclides used in the facility, including heavy gases such as ^{133}Xe.

5.5.2. Thyroid Uptake Systems

Studies involving absolute thyroid uptake can be performed without imaging using small amounts of ^{131}I or ^{123}I and a simple scintillation probe. This is calibrated using a phantom, ie, a model of a portion of the human body, loaded with the isotope being used. This instrument is also useful for assaying thyroid exposure to radioiodine among personnel.

6. Safety

For virtually all radiopharmaceuticals, the primary safety consideration is that of radiation dosimetry. Chemical toxicity, although it must be considered, generally is a function of the nonradioactive components of the injectate. These are often unreacted precursors of the intended radioactive product, present in excess to facilitate the final labeling reaction, or intended product labeled with the daughter of the original radioactive label.

6.1. Radiation Dosimetry

Radioactive materials cause damage to tissue by the deposition of energy via their radioactive emissions. Thus, when they are internally deposited, all emissions are important. When external, only those emissions that are capable of penetrating the outer layer of skin pose an exposure threat. The biological effects of radiation exposure and dose are generally credited to the formation of free radicals in tissue as a result of the ionization produced (17).

By definition (18), radiation dose represents the energy deposited per mass of tissue and has the units of Gray, where 1 Gy = 10 μJ/g (1 rad = 0.01 Gy). Exposure is a material-independent measure of the radiation incident on a volume as defined by the electrical charge it produces in air. Exposure is measured in charge per mass, ie, C/kg (one Röentgen (1 R = esu/g dry air at STP) = 2.58×10^{-4} C/kg)). Effective dose is a measure of radiation effect that includes biological factors, weighted on an organ-by-organ basis, and factors related to the microscopic distribution of the energy deposition and the effects of dose rate. Its unit is the Sievert (same dimensions as the Gray) or the rem (same dimensions as the rad).

Radiation dose for radiopharmaceuticals in a given patient can only be estimated. There are significant variations in dose from internally deposited radionuclides arising from the shape and location of organs and of the circulation within them. Thus, over the years, computer modeling methods have been developed to obtain estimates of dose, primarily under the auspices of the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine. These methods employ models of human beings of various sizes and both sexes, data on the biological distribution of a particular radioactive compound, physical data on the radionuclide, and the results of Monte Carlo modeling of different types of emissions from each organ of interest. Monte Carlo codes for calculating the transport and absorption of radiation from radioactivity were developed primarily for weapons and nuclear reactor design; however, they have proven to be readily adaptable to medical applications. These codes are extremely well validated and most have undergone many years of testing. In addition, studies have been conducted to validate the results generated specifically for the human models as well.

Nonetheless, these methods only estimate organ-averaged radiation dose. Any process which results in high concentrations of radioactivity in organs outside the MIRD tables or in very small volumes within an organ

can result in significant error. In addition, the kinetic behavior of materials in the body can have a dramatic effect on radiation dose and models of material transport are constantly refined. Thus radiation dosimetry remains an area of significant research activity.

The actual hazard from radiation exposure experienced by the patient in a nuclear medicine study is relatively small. The dose for a commonly performed study, the bone scan (see Fig. 1), ranges with tissue from approximately 650 μGy (65 mrad) for breast to 46 mGy (4.6 rad) for the bone surfaces. The International Committee on Radiation Protection has compiled standard values for radiation dose, making these available in book form (19, 20). Calculations of effective dose have been derived (21). These yield a single number that is weighted by organ radiosensitivity and radiation type. Although disputed as absolute measures for nuclear medicine risk because the weights are based on long-term occupational exposure, effective dose provides a convenient way of comparing risk among different types of nuclear medicine studies.

6.2. Chemical Toxicity

Radiopharmaceuticals are subject to the same requirements for safety as are other pharmaceuticals, and are tested for chemical toxicity in much the same manner. It is generally understood, however, that patients are likely to receive relatively few doses of any given radiopharmaceutical so that the effects of long-term chronic exposure to the compound rarely need be assessed. Safety margins, that is, the ratio of the administered dose to the lowest dose that produces an observable effect, are usually on the order of 100 or more.

7. Formulation and Packaging

The diversity of radionuclide half-life and chemical nature of commonly used radiopharmaceuticals demands a variety of formulation matrices, packaging containers, and storage conditions. The containers, ingredients, and processes used in these products must meet the stringent requirements for parenteral pharmaceuticals, as well as provide safe conditions for storage, handling, and disposal of the radioactive material.

Route of administration is a primary factor in formulation design. Orally administered compounds are commonly given in either solution or gel capsules. ^{99m}Tc sulfur colloid bound to egg albumin is given as a solid meal. Parenteral products are given in solution with either water or a dilute alcohol as the solvent. The solution is ideally sterile, isotonic, and nonpyrogenic. For multidose preparations, it must also include a bactericidal additive. Alternatively, the injection can be given as colloidal suspensions (^{99m}Tc sulfur colloid or ^{99m}Tc albumin colloid) or as microaggregates (^{99m}Tc albumin) or microspheres. Pulmonary function is tested using radioactive gases such as ^{95}Kr and ^{133}Xe which are supplied in glass vials, metal cylinders, or aerosols (qv).

The strategy for formulation may require, in addition to the optimal concentration of radionuclide and/or active ingredient, a selection of appropriate ionic strength, buffer, stabilizers, reactants, reductants, and bulking agents. The following parameters of the final product are then assayed: total radioactivity, specific radioactivity, carrier concentration, pH, quality control for final and intermediate components, and radionuclidic purity. The solution is dispensed into containers, sealed, packaged, and stored under appropriate conditions. The liquid contents of the nonradioactive kits are either frozen or lyophilized to achieve greater stability, and an inert gas is often added. The final contents must be sterile, nonpyrogenic, isotonic, and aqueous for parenteral use.

The container size is selected for either unit or multiple dose use. The type and extent of the shielding of the radionuclide container depends on the path length and energy of the emitted particles, as well as the amount of the individual product. The β-emitters are typically stored in thick-walled glass containers; γ-emitters require an additional layer or layers of lead shielding. These external layers are designed to provide protection for shipping and storage as well as convenient access to the container during use.

The labeling on the containers and packages for use and storage are regulated by the Nuclear Regulatory Commission. The Federal Department of Transportation regulates the conditions of shipment, and requires a

Transportation Index on the label that gives a rapid indication of the rheological hazard of the package. There are additional regulations at state and local levels, as well as those by the Federal Drug Administration and the U.S. Public Health Service. The container labeling includes the name of the preparation, the amount of radioactivity, the half-life, expiration date, calibration date, and the statement "Caution—Radioactive Material", as well as a statement that correction must be made for radioactive decay.

7.1. Direct

Some radionuclides are packaged in solution for direct sampling (qv) via a septum and injection into the patient. Gallium-67 is a marker of inflammation, infection, and various tumor types. Its half-life is 78.3 h and it is supplied as the gallium citrate salt. Indium-111 chloride is supplied for the labeling of white blood cells. The ^{111}In chloride is mixed with oxine (9-hydroxyquinoline) to form a lipophilic, cationic ^{111}In oxine complex, which enters the white blood cell. The complex dissociates within the cell, and the cationic In^{3+} ion is trapped within the cell, owing to its charge.

Technetium-99m pertechnetate is produced from a ^{99}Mo/^{99m}Tc TcO_4 generator. The product, ^{99m}Na TcO_4, may be supplied directly or by elution from an on-site generator. Upon iv administration, it accumulates in the stomach, small and large bowel, salivary glands, thyroid gland, choroid plexus, sweat glands, and kidney. This distribution is used to assess a variety of conditions including thyroid transport, bowel function, and blood brain barrier integrity. An additional important use of ^{99m}Tc pertechnetate is in the radiolabeling of a variety of substances to form ^{99m}Tc radiopharmaceuticals.

Thallium-201 is a potassium analogue as the thallous ion. This radionuclide is used for the diagnosis and localization of myocardial perfusion and parathyroid function. It is supplied as the thallous chloride salt in an aqueous injectable solution and has a half-life of 73.1 h. Sodium iodide I-131, used for the treatment of hyperthyroidism and selected cases of thyroid cancer, is supplied in capsules for oral administration containing 37–1850 MBq (1–50 mCi) of I-131. I-131 MIBG (iobenguane sulfate [77679-27-7]) is used for localization of primary or metastatic pheochromocytomas and neuroblastomas. It is supplied in a sterile, nonpyrogenic solution. I-123 iofetamine is a brain imaging agent and is useful for evaluating nonlacunar stroke within 96 h of focal neurological deficit. It is supplied as a single vial injectable solution, and is stored at 5–30°C. I-131 iodohippurate is used as a diagnostic aid in determining renal function, renal blood flow, and urinary obstruction. The appearance, concentration, and excretion of the tracer in the kidney can be followed, and an index of renal vascular competence and renal evacuation may also be estimated.

Strontium-89 chloride is a calcium analogue that rapidly clears from the blood and is taken up into bone mineral, particularly in areas of active osteogenesis, as well as primary bone tumors and metastases. It is used for relief of bone pain in patients having painful skeleton bone metastases. It is supplied in an injectable solution.

7.2. Kits

Kits for the preparation of radiopharmaceuticals are a convenient solution to synthesis of products containing short-lived radionuclides (eg, ^{111}In, ^{123}I, ^{99m}Tc) bound to a nonradioactive moiety. The labeling step is performed either at a commercial radiopharmacy, or within the institutional nuclear medicine laboratory. The kits are usually stored as a frozen solution or lyophilized product. The material of interest is then metered out into kit dosages. The kit vials are thawed or reconstituted and mixed with the appropriate radionuclide.

Many kits contain the indicated biologically active ingredient in a lyophilized form with stannous chloride. A ^{99m}Tc-labeled radiopharmaceutical, which can be used for six hours, is formed when mixed with ^{99m}Tc pertechnetate. Preparation of the agent is at room temperature, unless otherwise stated.

7.2.1. Technetium-99m

Available ^{99m}Tc kits are listed below.

Technetium-99m sestamibi is used in myocardial perfusion imaging for the evaluation of ischemic heart disease. It is prepared from a lyophilized kit containing tetrakis(2-methoxy isobutyl isonitrile) copper(I) tetrafluoroborate stored under nitrogen. Upon reconstitution with up to 5.6 GBq (150 mCi) of ^{99m}Tc pertechnetate, the product is formed by boiling for 10 minutes.

Technetium-99m oxidronate is a bone imaging agent used to demonstrate areas of altered osteogenesis. It is rapidly cleared from the blood and taken up in areas of bone that are undergoing osteogenesis. The kit is a vial containing a lyophilized powder where sodium oxidronate is the active ingredient.

Technetium-99m teboroxime is a myocardial imaging agent and is excreted primarily by the hepatobiliary system. It is rapidly taken up by the myocardium and mostly washes out within 30 minutes. Imaging protocols are performed immediately after injection. The product is a lyophilized mixture of boronic acid, dioxine, and other excipients, and the agent is formed with a heating step.

Technetium-99m pentetate (*N,N*-bis[2-[bis(carboxymethyl)amino]ethyl]-glycinato(5-)) distributes into the extracellular space and is excreted by glomerular filtration through the kidney. It is indicated for kidney imaging, brain imaging, assessment of renal perfusion, and estimation of glomerular filtration rate. The active ingredient is pentetate calcium trisodium and the kit contents are stored under nitrogen. The product is formed by addition of up to 7.4 GBq (200 mCi) of ^{99m}Tc pertechnetate.

Technetium-99m gluceptate is used in brain and kidney imaging. Sodium gluceptate is the active ingredient. The product is formed by the addition of up to 7.4 GBq (200 mCi) of ^{99m}Tc pertechnetate.

Technetium-99m disofenin is used for hepatobiliary imaging. Disofenin (2,6-diisopropylphenylcarbamoylmethyliminodiacetic acid) is the active ingredient. Product formation is accomplished by addition of up to 3.7 GBq (100 mCi) of ^{99m}Tc pertechnetate.

Technetium-99m albumin colloid is cleared by the reticuloendothelial (RE) cells and is used for visualization of the RE system of the liver, spleen, and bone marrow. The product is formed by the addition of up to 2.8 GBq (75 mCi) of ^{99m}Tc pertechnetate.

Technetium-99m medronate (^{99m}Tc methylene diphosphonate) is used as a bone imaging agent to delineate areas of altered osteogenesis. The product is formed by the addition of up to 7.4 GBq (200 mCi) of ^{99m}Tc pertechnetate.

Technetium-99m albumin aggregated (^{99m}Tc-macroaggregated albumin) is trapped in the pulmonary alveolar bed and is used as a lung imaging agent. The aggregated particles (10–90 μm dia) are formed by denaturation of human albumin in a heating and aggregation process. The ^{99m}Tc complex is formed by the addition of up to 1850 MBq (50 mCi) of ^{99m}Tc pertechnetate.

Technetium-99m pyrophosphate is used for bone imaging. The compound appears to have an affinity for the hydroxyapatite crystals within bone, and is formed by addition of up to 7.4 GBq (200 mCi) pertechnetate.

Technetium-99m mertiatide (*N*-[*N*-[*N*-[(benzoylthio)acetyl]glycyl]glycine) is a renal imaging agent. It is excreted by the kidneys via active tubular secretion and glomerular filtration. The kit vial is reconstituted by using 740–3700 MBq (20–100 mCi) of ^{99m}Tc pertechnetate and boiling for 10 minutes.

Technetium-99m mebrofenin is an iminodiacetic acid derivative used as a hepatobiliary agent. The kit is supplied as a single vial containing lyophilized mebrofenin. The reconstituted kit has 18-hour usage, owing to the preservative, propylparaben.

Technetium-99m exametazime [(*RR,SS*)-4,8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime] is used as an adjunct in the detection of altered regional cerebral perfusion in stroke. The kit for the preparation of the radiopharmaceutical is supplied as a single dose vial.

Technetium-99m tetrafosmin (^{99m}Tc-(V)O_2 (1,2-bis(bis(2-ethoxyethyl)phosphino)ethane) (see Fig. 3**d**)) is a myocardial perfusion agent. It is used as an adjunct in the diagnosis and localization of myocardial ischemia and/or infarction.

Technetium-99m bicisate is a brain imaging agent that is used for localization of stroke. The lyophilized kit contains ethyl cysteine dimer as the active ingredient.

7.2.2. Indium-111

Kits for labeling using other radionuclides include two indium-111 compounds. Indium-111 pentetreotide is used for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors. For octreotide DTPA, the active agent is supplied in a lyophilized kit with gentisic acid, citrate buffer, and inositol.

Indium-111 satumomab pendetide [148805-91-8] is used for determining location and extent of extrahepatic malignant disease in patients having known colorectal or ovarian cancer. The compound is a conjugate produced from the murine monocolonal antibody, CYT-099 (MAb B72.3), an antibody directed to a high molecular weight tumor-associated glycoprotein (TAG 72). This is a two-vial kit, stored as refrigerated solutions. The active ingredient is in one vial and sodium acetate in the other.

7.3. On-Site

Positron-emitting radionuclides are short-lived (see Table 2) and are produced either by a generator (^{82}Rb, ^{62}Cu, ^{68}Ga) or within a cyclotron at a given institution for immediate formulation and use (^{15}O, ^{13}N, ^{11}C, ^{18}F). Because carbon, nitrogen, and oxygen can all be produced as positron emitters, the technique is amenable to following biochemical processes directly. Commonly used positron-emitting radiopharmaceuticals include the following:

Radiopharmaceutical	Application
[^{15}O]–O_2	cerebral O_2 extraction and metabolism
[^{15}O]–CO	cerebral and myocardial blood volume
[^{15}O]–H_2O	cerebral and myocardial blood flow
[^{13}N]–NH_3	myocardial blood flow
[^{11}C]–butanol	cerebral blood flow
[^{18}F]–2-fluorodeoxyglucose	cerebral and myocardial metabolism; tumor localization
[^{82}Rb]–Rb^+	myocardial blood flow
[^{68}Ga]–gallium citrate	plasma volume transferrin

8. Future Directions

8.1. Radiopharmaceuticals

Research in radiopharmaceuticals is ongoing. Progress in radiopharmaceuticals is derived not only from the identification of new compounds but, also in new uses for existing, approved agents. An example of the latter is the use of ^{99m}Tc-exametazime for the labeling of white blood cells in the investigation of localized inflammatory disease and occult focal infection. The initial use for which this compound was approved was the investigation of perfusion abnormalities in the brain. For some time, more than half of the sales of ^{99m}Tc-exametazime was for use in white cell labeling at a time when this compound had not been approved for this purpose. Physicians, however, have the latitude to use any approved product as they see fit, consistent with training and ethical obligations. Thus, although ^{99m}Tc-exametazime for labeling white blood cells is an indication that was only approved by the U.S. Food and Drug Administration in 1995, its use for this purpose has been widespread in the United States for some years.

Another example is the use of ^{99m}Tc-sestamibi, approved for use in the evaluation of coronary artery disease and myocardial infarction, in patients with breast cancer. Use in breast cancer is under investigation by a number of physicians. The data are not yet sufficient to determine the efficacy of this agent in this setting. Its safety, of course, has already been demonstrated as part of its initial evaluation for heart disease.

A number of promising new approaches to *in vivo* diagnosis have appeared. Intravascular thrombosis in the femoral veins of the leg, resulting in detached emboli traveling to the heart and ultimately the lungs, can result in pulmonary embolism (PE). Blockage of the circulation in the lungs results in symptoms ranging from coughing and pain to sudden death. Diagnosis of the underlying deep vein thrombosis (DVT) in the legs is often difficult. Even when the patient presents at the hospital with symptoms suggestive of PE, the procedure for making a definitive diagnosis can be complex. A ventilation/perfusion study, involving two separate acquisitions with two separate isotopic agents, is usually required, then possibly a pulmonary angiogram, and then an ultrasound procedure to confirm the presence of clotting in the leg veins. A single agent that identifies thrombosis directly by binding to it would provide a better answer, fewer steps, and thus result in lower costs and more rapid initiation of appropriate therapy.

A number of promising approaches have emerged in the early to mid-1980s that may ultimately provide an agent. In general these approaches have focused on compounds that bind to the platelet glycoprotein (GP) IIb/IIIa receptor. This receptor on the platelet surface is responsible for its binding to fibrin. It is expressed in large numbers in activated platelets but is present only in small numbers on circulating platelets. Some of these compounds are derived from several of a series of small peptides known to block this receptor by binding to it. The peptides incorporate the recognition sequence of amino acid residues, arginine–glycine–aspartic acid, in either a linear or cyclic configuration. Initial work in this area was presented by two companies in 1994 (22, 23). Another approach uses the snake venom-derived compound bitistatin, a member of the integrin family of polypeptides.

Another type of agent that is undergoing investigation is one that localizes in regions of tissue hypoxia. This is anticipated to find use in the evaluation of tissues that are chronically ischemic but potentially viable should blood flow be restored completely. This occurs in coronary artery disease, and in particular after reperfusion with tissue plasminogen activator (tPA) or streptokinase following myocardial infarction. It also may have applications in the brain during the period following a stroke, and in localizing tumors with hypoxic regions.

General trends in radiopharmaceutical research emphasize the use of small peptides. These molecules, of which the agents mentioned for thrombosis localization are an example, exhibit rapid and specific binding, and rapid blood clearance, two important parameters for a successful radiopharmaceutical. Peptides are readily labeled with ^{99m}Tc and lend themselves to formulation as lyophilized kits that can be rapidly and reliably reconstituted. Possible targets for these molecules are quite varied, ranging from atherosclerotic plaque to β-amyloid (for Alzheimer's disease), to a variety of somatic receptors the populations of which are increased or decreased in disease.

Much research has been directed toward the development of targeted antibodies. The results have been less fruitful than was hoped. Radiopharmaceutical imaging requires not only a sufficiently high concentration of agent in the lesion or abnormalities, but also a sufficiently low concentration in the surrounding normal tissues to permit a contrast that proves discernible in the final image. Naturally, for imaging in which the abnormality reveals itself as a decrease in radioactivity, the reverse must be true. Thus the excretion pathways, through which the vast majority of the radioactivity passes, are as influential in the final result as the behavior in the lesion. In the case of antibodies, imaging is impeded by slow clearance of the antibody from the circulation, despite rapid binding to the target. As a result, the contrast is rarely sufficient on the first day after administration to obtain an image. One solution to this has been to use ^{111}In as the radiolabel. This isotope has a 67-h physical half-life, a time better matched to the clearance of the drug. The slow clearance of the antibody requires the patient to be injected one day and return a day or two later for imaging. This is considerably less

than ideal from a practical standpoint. The half-life and physical emissions of the isotope results in a generally higher radiation dose per MBq injected than is usually the case for shorter half-life isotopes such as ^{99m}Tc. This restricts injected doses to between 37 and 110 MBq (1–3 mCi). The higher energy of the γ-rays from ^{111}In combined with the lower photon emission rate resulting from the lower injected radioactivity (owing to the longer half-life) yields a poorer image than is possible with ^{99m}Tc.

8.2. Instrumentation

The future of radiopharmaceuticals is highly dependent on imaging instrumentation. Instrumental methods can evolve rapidly. Performance and characteristics of these instruments are important in the choice of disease target, lesion size, location, and contrast.

As of 1995, single-photon imaging instrumentation could produce excellent three-dimensional, ie, SPECT, images having a resolution between 7 and 15 mm, depending on location and methodology, using an injected dose of roughly 740 MBq (20 mCi) of ^{99m}Tc. Straying from these parameters results in poorer performance. It is possible to decrease injected doses to the neighborhood of 37–110 MBq (1–3 mCi) and photon energies to approximately 80 KeV, but at the cost of poorer resolution and a more photon deficient, ie, statistically more grainy image. Higher energies also yield poorer resolution when energies are above $\sim$200 KeV. Higher injected doses are not feasible owing to the increase in radiation dose.

One active area of instrumentation research is the absolute quantification of radioactivity, which principally involves identifying methods for correcting properly for attenuation and scatter. This should permit more accurate estimates of radiation dose for therapeutic radioisotopes. Another important area related to instrumentation is the trend toward the fusion of images from a variety of imaging modalities, such as magnetic resonance imaging or x-ray computed tomography, with PET and SPECT data. Registration and simultaneous display of images permits a more accurate definition of the location of a given lesion, particularly in a complex geometry such as that of the brain. It has the potential to increase a physician's confidence in the information provided by the nuclear medicine data and allow more accurate localization of lesions for surgical treatment.

A number of devices suggest the possibility of improvement in the basic limitations of resolution and sensitivity for single-photon instrumentation. One device (24) employs an array of pinholes in a hemispherical shield that lies inside a hemispherical solid-state detector array. Simulations and initial experience using early models have suggested that the device could achieve a resolution in the brain of less than 3 or 4 mm and possibly as low as 1 mm.

Another entirely different class of devices may extend the range of radioisotopic imaging in a different way. These rely on the scatter of primary photons in the detector to extract information about the trajectory of each incoming γ-ray. Back-projection of these trajectories into the conic surface representing all possible paths can yield a reconstruction of the linear integrals of the radioactivity along each path. Regrouping and conventional reconstruction can then yield three-dimensional concentration information. These devices, known as double-Compton imaging systems or Compton scatter imaging devices were, as of early 1996, in an extremely early stage of development. A wide variety of detector types and geometries were under investigation. In addition, the mathematical problem of accurate reconstruction had not yet been solved. If successful, these devices promise the ability to image isotopes having γ-ray energies greater than 1 MeV without a collimator, suggesting considerable sensitivity as well.

9. Economic Aspects

Radiopharmaceutical manufacture in the United States was dominated as of the mid-1990s by three primary suppliers: Du Pont Pharma, Mallinckrodt, and Amersham International. The last was through its Medi-Physics subsidiary. Bracco Diagnostics is also a supplier, as is CIS-US. Cytogen has a product in this group as well.

In addition, Golden Pharmaceuticals supplies Indium-131 for clinical use. These companies plus a number of smaller firms are engaged in research and development activities involving radiopharmaceutical products. In Europe, the suppliers include the same companies as operate in the United States with the addition of Medgenix in an alliance with Du Pont Pharma. Here, CIS, based in France, plays a larger role as do a number of smaller companies, many of them nationally based. Nordion, a Canadian firm, is a supplier of the ^{99}Mo used in generators and other raw materials as well as some clinical products both in the United States and Europe. In Japan, the primary suppliers are Nihon-Medi-Physics and Daiichi. Many of these companies also supply products to other parts of the world. The degree varies considerably from one country to another.

Table 4 is a breakdown of radiopharmaceutical studies by imaging areas from the late 1980s through the early 1990s. The cost of a given radiopharmaceutical, and therefore its relative contribution to the total market size, varies considerably. Newer agents, such as those for tumor localization, ^{99m}Tc myocardial perfusion, and regional brain indications, involve newer and more expensive agents.

Table 4. Nuclear Medicine Studies Performed in the United States, 1988–1993[a]

	Total U.S. studies $\times 10^3$						
Organ system	1988	1989	1990	1991	1992	1993	1994[b]
bone	2,397	2,611	3,794	3,794	3,844	3,939	3,624
brain	73	101	130	109	104	121	136
cardiovascular	2,233	2,529	2,878	3,109	3,720	3,874	4,106
liver	466	440	514	457	381	306	275
renal/hepatobiliary	687	782	850	827	882	853	853
respiratory	1,233	1,184	1,105	1,052	1,015	976	996
tumor localization	0	0	0	0	21	88	264
other	1,089	1,190	667	752	802	710	710
Total	8,179	8,838	9,938	10,100	10,769	10,867	10,964

[a] Courtesy of TMG Marketing.
[b] Values are estimated.

Radiopharmaceuticals may be sold either directly or through nuclear pharmacies. These entities, some of which are owned by manufacturers, provide radiopharmaceuticals in unit dose form. In the United States, both Mallinckrodt and Amersham own nuclear pharmacies in many cities. In addition the market is also served by Syncor, an independent nuclear pharmacy that has a nonexclusive strategic alliance with Du Pont Pharma.

For radiopharmaceuticals, such as ^{201}Tl–Cl, the role of the nuclear pharmacy is simply to draw a dose in an appropriate syringe, providing quality control and primary injected dose readings. For other products the service involves preparing radiopharmaceuticals from kits, maintaining ^{99}Mo/^{99m}Tc generators, and associated quality control. When radiopharmaceuticals and kits are sold directly, the hospital department, typically the nuclear medicine department, is responsible for all quality control. In either case, the hospital and the attending physician are responsible for verifying that the dose is correct and is administered to the patient for whom it is intended.

The total U.S. market for radiopharmaceuticals in 1993 was $406 million. Radiopharmaceuticals sold directly to U.S. hospital nuclear medicine departments accounted for approximately 25% of the total sales, or about $98 million. Another $308 million were sold via nuclear pharmacies. Of direct sales among the primary U.S. manufacturers, one had approximately 49% of the market, another approximately 34%, and the third about 9%.

The total U.S. market grew from about $332 million in 1991 to $372 million in 1992 to $406 million in 1993. Uncertainties in health care financing and restructuring in 1994 may have led to stabilization or a slight decline.

The unique information available from nuclear medicine studies suggests continued steady growth in sales. However, products introduced since the late 1980s account for only 8% of total nuclear medicine studies

(25), suggesting that work in product development must be more targeted toward providing information that is critical in patient management and/or must concentrate on situations affecting a large percentage of the populace.

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