RADIOPHARMACEUTICALS

After reviewing this tutorial, participants should be able to

- discuss the methods of production of isotopes for medical and general commercial use
- define the term "radiopharmaceutical" and to list the properties of the ideal diagnostic and ideal therapeutic radiopharmaceutical
- distinguish between the terms "radiopharmaceutical" and "radiochemical"
- discuss the properties common to all injectable drugs
- state the regulation covering legal limits for calibrated doses compared to prescribed doses
- list several examples of dynamic and static studies as well as in vivo non-imaging studies
- identify the imaging procedures/target organs associated with every radiopharmaceutical used in the United States
- give the typical administered dose for each of these drugs and the route of administration
- describe the kinetics of most of these drugs, including routes of excretion of the more commonly used radiopharmaceuticals
- describe the stannous reduction method
- describe a hexa-coordinated Tc complex and draw its octahedral structure; and should be able to identify special patient preparations and restrictions used for several commonly used radiopharmaceuticals
- list and give examples of the 6 classical mechanisms of localization of radiopharmaceuticals as well as some of the mechanisms associated with the newer radiopharmaceuticals
- understand uptake ratios and excretion rates, e.g., the percentage of each of the 5 renal imaging agents cleared by filtration and secretion as well as the amount bound to the tubules
- describe an antigen-antibody reaction and the part it plays in the uptake of radiolabeled monoclonal antibodies by specific types of malignant tumors
- Should be able to state legal particle size requirements for those preparations containing labeled particles.

Topics to be covered

- Definition of a Radiopharmaceutical
- Properties of the ideal diagnostic radiopharmaceutical
- Properties of the ideal therapeutic radiopharmaceutical
- Properties of all injectable pharmaceuticals
- Categories of Radionuclides
- Categories of Radiopharmaceuticals
- Generators
- Clinical utility
- Mechanisms of Localization of Radiopharmaceuticals
- Basic Chemistry of Radiopharmaceuticals
- Radiopharmaceuticals
- Regulatory Issues Related to Radiation Safety and Usage

DEFINITION OF A RADIOPHARMACEUTICAL

- Radiopharmaceuticals have been defined as radioactive drugs that, when used for the purpose of diagnosis or therapy, typically elicit no physiological response from the patient. This definition is strongly supported by the Nuclear Medicine community's collective experience in administering radiopharmaceuticals: most practitioners, in their entire careers, have not observed a physiological response or an adverse reaction following administration of a radiopharmaceutical.
- The design of these compounds is based solely upon physiological function of the target organ. Unlike radiographic procedures, which depend almost entirely upon tissue density differences, external imaging of radiopharmaceuticals is essentially independent of the density of the target organ. The mechanism of localization of a radiopharmaceutical in a particular target organ can be as simple as the physical trapping of particles or as sophisticated as an antigen-antibody reaction or chemisorption of an inorganic phosphate on the hydroxyapatite crystals deposited in an acute myocardial infarction.
- There is a significant difference between a radioisotope (a radionuclide whose chemical form is unknown) and a radiopharmaceutical whose chemical form is usually precisely known. For example, I-123 is a radioisotope with a characteristic physical half-life. Reference to a biological half-life or an

effective half-life for I-123 is meaningless since we don't know the chemical form. On the other hand, I-123 NaI is a compound with known biodistribution and clearance rates and is associated with both biological and effective half-lives.

- The correct answer to the question, "What is the radiation dose delivered by I-131?" Is, "It is impossible to determine the radiation dose of a radioisotope. What is the chemical form of the I-131 compound?" Dosimetry can be calculated only if biodistribution and clearance rates are known.

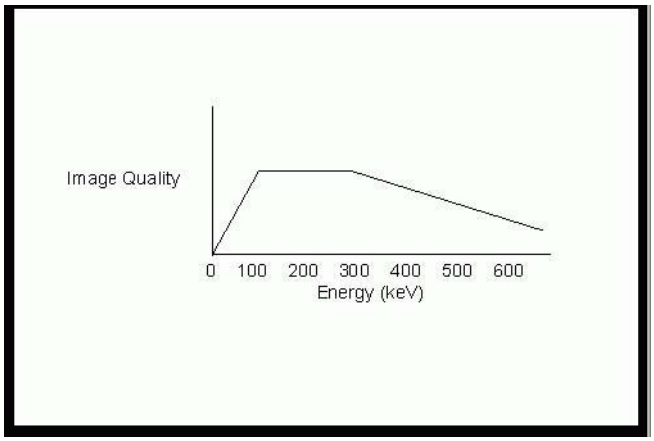
PROPERTIES OF AN IDEAL DIAGNOSTIC RADIOPHARMACEUTICAL

Pure gamma emitter

- When a radiochemist designs a radiopharmaceutical, there are many important factors to be considered. Optimal performance of a radiopharmaceutical requires that it possess certain characteristics. The first of these is that the radioisotope should be a pure gamma ray emitter, decaying by either electron capture or isomeric transition.
- Other non-penetrating kinds of radiation, e.g., alpha and beta particles, are undesirable for two reasons: due to their high linear energy transfer (LET), the fraction of energy deposited per cm of travel is very high. This results in almost quantitative absorption in the body. The few particles that manage to escape the patient's body can't penetrate the crystal to interact. Consequently, alphas and betas are not imageable. In addition, because of their high LET, they confer a very significant radiation dose to the patient.

100 < gamma energy < 250 keV.

- From an imaging standpoint, the ideal imaging energy range is 100-250 keV. Our imaging equipment has been tailored to function best in this range. Image quality is suboptimal above or below it, as illustrated in the figure below.
- Despite this limitation, there are certain radioisotopes that are commonly used clinically whose gamma ray energies are below 100 keV or above 250 keV. For example, on the low end, Tl201 and Xe133 emit photons with energies of about 70-80 keV, while on the high end, Ga67 and I131 emit photons of 300 and 364.5 keV, respectively. Use of these higher energies compromises image quality since greater collimation is required, decreasing both sensitivity and resolution. Commonly used radioisotopes considered ideal from an energy standpoint include Tc-99m, In111, and I123.



<u>Effective half-life</u> ***= 1.5 X test duration.***

- Ideally, a radiopharmaceutical's effective half-life equals approximately 1.5 times the duration of the diagnostic procedure. This provides a good compromise between our desire to minimize radiation dose to the patient and to maximize the dose to be injected so counting statistics are good and image quality is optimal.
- With the sole exception of Xe133 or another noble gas used for a ventilation study, there is no other procedure in which images are acquired and the radiopharmaceutical is expelled from the body almost quantitatively within a few minutes of completing the study. Most compounds exhibit exponential clearance patterns so their effective half-life is moderately long (measured in hours or days as opposed to seconds or minutes).
- The relationship between effective half-life, biological half-life, and physical half-life is shown in the equation below:

$$1 / t_{eff} = 1 / t_{biol} + 1 / t_{phys}$$

- In the special case where the biological half-life of a particular compound is very long compared to the physical half-life (e.g., Tc-99m sulfur colloid in the liver), $1 / t_{biol}$ is a very small number, approximating 0, and the effective half-life therefore equals the physical half-life. Similarly, where the physical half-life is very long compared to the biological half-life (e.
- g., Xe133 gas in the lungs), $1 / t_{phys}$ is a very small number, approximating 0, and the effective half-life equals the biological half-life.

- The classical example of an ideal effective half-life is that of Tc-99m MDP, which has an effective half-life = 6 hr; since bone imaging is a 4 hr procedure, the ratio of effective half-life to duration of the test is 1.5:1, considered ideal. On the other hand, Tc-99m sulfur colloid has a effective half-life of 6 hr in the liver, but the procedure takes only 1 hr. This 6:1 ratio doesn't mean that a liver scan is a bad procedure to perform, but rather that the compound has a residence time in the liver that is longer than desirable, resulting in an increase in the radiation dose to the target organ. In this particular case, simply switching from Tc-99m sulfur colloid to Tc-99m microaggregated albumin decreases the t_{eff} from 6 hr to approximately 3 hr, lowering the ratio of effective half-life to procedure length to 3:1 and decreasing the radiation dose by 50%.

<u>High target:nontarget ratio.</u>

- A high target:nontarget ratio is critical. If this ratio is not high enough (5:1 minimum for planar imaging, about 2:1 for SPECT imaging), a nondiagnostic scan can result, making it difficult or impossible to distinguish pathology from background. For example, when performing a thyroid scan, ideally, all the radioactivity will be in the thyroid and nowhere else in the neck region. While liver uptake of the radioiodide would be undesirable dosimetrically, it would have no impact on the actual imaging process since it is not in the field of view.
- For some procedures, e.g., bone imaging, there are two target:nontarget ratios that must be considered. It is important to see bones against soft tissue, so the bone:soft tissue ratio must be acceptably high. It is also important to be able to identify a metastatic lesion on bone tissue, so the ratio of tumor:bone must also be high. These ratios are multiplicative; if the tumor:bone ratio is 5:1 and the bone:soft tissue ratio is also 5:1, then the tumor:soft tissue is 25:1.
- The result of a very low target:nontarget ratio may be a non-diagnostic scan, resulting in an unnecessary radiation dose, a delay in the diagnosis and the necessity of repeating the procedure. These failures may be related to product quality problems that went unidentified because quality control was not performed; often, however, the patient himself is the source of a poor scan, due perhaps to poor renal function or to interfering medications.

<u>Minimal radiation dose to patient and Nuclear Medicine personnel</u>

- Radiation dosimetry to both the patient and the Nuclear Medicine Technologist requires special attention, especially if one is to maintain compliance with the ALARA guidelines. The smallest dose possible should be injected, consistent with good image quality. In addition, for pediatric patients, the dose should be scaled down based on the patient's body mass. Of necessity, SPECT imaging

may require a larger injected dose than does planar imaging since acquisition time at each orbital stop is so short.

- Radiation dosimetry to both the patient and the Nuclear Medicine Technologist requires special attention, especially if one is to maintain compliance with the ALARA guidelines. The ALARA Concept, which is based upon maintaining the radiation dose As Low As Reasonably Achievable, was implemented in the late 1970's and has contributed to a significant overall reduction in dose to radiation workers. The smallest dose possible should be injected, consistent with good image quality.
- MPD for Radiation Workers = 5 Rem per year
- MPD for our families and other non-radiation workers, the MPD is 2% of our MPD, or 0.1 Rem per year. For radiation workers, the extremities are permitted 10 times the whole body dose, or 50 Rem. This is an acceptable level for the hands since there is essentially no bone marrow to be irradiated. Lifetime cumulative records are maintained and transferred from one institution to another when job changes are made.

Nuclear Medicine Procedures: Dosimetry (Estimated) Reference: RSNA Website, November, 2016

Examination*	Effective Dose (mSv)	Administered Activity (MBq)†	Effective Dose (mSv/MBq)‡
Brain (^{99m}Tc-HMPAO–exametazime)	6.9	740	0.0093
Brain (^{99m}Tc-ECD–Neurolite)	5.7	740	0.0077
Brain (^{18}F-FDG)	14.1	740	0.019
Thyroid scan (sodium iodine 123)	1.9	25	0.075 (15% uptake)
Thyroid scan (^{99m}Tc-pertechnetate)	4.8	370	0.013
Parathyroid scan (^{99m}Tc-sestamibi)	6.7	740	0.009
Cardiac stress-rest test (thallium 201 chloride)	40.7	185	0.22
Cardiac rest-stress test (^{99m}Tc-sestamibi 1-day protocol)	9.4	1100	0.0085 (0.0079 stress, 0.0090 rest)
Cardiac rest-stress test (^{99m}Tc-sestamibi 2-day protocol)	12.8	1500	0.0085 (0.0079 stress, 0.0090 rest)
Cardiac rest-stress test (Tc-tetrofosmin)	11.4	1500	0.0076
Cardiac ventriculography (^{99m}Tc-labeled red blood cells)	7.8	1110	0.007
Cardiac (^{18}F-FDG)	14.1	740	0.019
Lung perfusion (^{99m}Tc-MAA)	2.0	185	0.011
Lung ventilation (xenon 133)	0.5	740	0.00074
Lung ventilation (^{99m}Tc-DTPA)	0.2	1300 (40 actually inhaled)	0.0049
Liver-spleen (^{99m}Tc–sulfur colloid)	2.1	222	0.0094
Biliary tract (^{99m}Tc-disofenin)	3.1	185	0.017
Gastrointestinal bleeding (^{99m}Tc-labeled red blood cells)	7.8	1110	0.007
Gastrointestinal emptying (^{99m}Tc-labeled solids)	0.4	14.8	0.024
Renal (^{99m}Tc-DTPA)	1.8	370	0.0049
Renal (^{99m}Tc-MAG3)	2.6	370	0.007
Renal (^{99m}Tc-DMSA)	3.3	370	0.0088
Renal (^{99m}Tc-glucoheptonate)	2.0	370	0.0054
Bone (^{99m}Tc-MDP)	6.3	1110	0.0057
Gallium 67 citrate	15	150	0.100
Pentreotide (^{111}In)	12	222	0.054
White blood cells (^{99m}Tc)	8.1	740	0.011
White blood cells (^{111}In)	6.7	18.5	0.360
Tumor (^{18}F-FDG)	14.1	740	0.019

Patient Safety

Patient safety is also critical. Ideally, the radiopharmaceutical should exhibit no toxicity to the patient. While most commonly used compounds are inherently safe and provide wide margins of safety, we routinely inject drugs that are potentially toxic.

QUIZ:

Thallous ion (Tl1+), for example, is known to be a potent cardiotoxin and yet we routinely inject Tl-201 thallous chloride intravenously into our patients. Why are we not concerned?

ANSWER:

This is acceptable practice since the specific activity (activity per unit mass) of carrier-free Tl-201 is very high and the amount of Tl-201 contained in the typical 3 mCi dose (only 42 ng) is very small and significantly below the level required for a physiological response from the patient.

Chemical Reactivity

One of the features that makes Tc-99m such an ideal radioisotope for diagnostic imaging is its ability to readily bind to a wide variety of compounds under physiological conditions. The literature continues to document Tc-99m's versatility in forming compounds, from simple molecules like pyrophosphate to sugar analogues like glucoheptonate; from peptides to antibodies; from insoluble colloids and macroaggregates to antibiotics and other complex molecules.

In addition, special consideration must be given to the availability of substrates for radiolabeling reactions. Not every compound can be labeled with every isotope and, in fact, labeling is often quite selective. Compounds which demonstrate acceptable biodistribution often become useless when a radiometal is added or the molecule is iodinated. Even minimal changes in the molecular structure are often enough to completely change the biodistribution. Extensive research is required to determine the optimal molecular structure for a particular molecule to be labeled with a specific isotope.

Inexpensive, readily available radiopharmaceutical.

Radiopharmaceuticals must be stable both pre- and post-reconstitution. If a particular compound performs well for a particular procedure, but is only available at 1 hospital nationwide, its use will be extremely limited. In addition, in the current economic climate, use of radiopharmaceuticals costing hundreds of dollars is limited, especially if less expensive alternates are available.

Simple preparation and quality control if manufactured in house.

Preparation of the drug should be simple and require relatively little manipulation on the part of the preparer. Procedures with more than 3 steps generally do not meet this requirement. In addition, no complicated equipment or time consuming steps should be involved.

If radiopharmaceuticals are manufactured in-house, it is essential that quality control be performed on every batch of drug prepared to insure that each individual preparation that will produce a high-quality image while minimizing the radiation dose to the patient. Altered biodistribution caused by an improperly prepared drug can destroy image quality and have a significant impact on the internal radiation dose conferred to the patient.

Criterion: One must be able to answer "YES" to the question, "Would I inject this into my mother?" Without performing quality control testing, it's impossible to know how well the product will perform.

PROPERTIES OF THE IDEAL THERAPEUTIC RADIOPHARMACEUTICAL

1. Pure beta minus emitter.

In contrast to diagnostic radiopharmaceuticals, therapeutic products are designed to destroy cells. The preferred mode of decay for radioisotopes used to perform radionuclide therapy is pure alpha decay or pure beta minus emission. Due to their high LET, alpha and beta particle emitters are quite capable of destroying tissue. Beta particles are far more controllable than alpha emitting radionuclides from the standpoint of distribution in tissue since an almost perfect distribution is required for effective therapy with alpha emitters, whereas a less-than-perfect tissue distribution is not critical to effective therapy with beta- emitters. This is due to the difference in range in tissue of these 2 particles (several micrometers for alpha emitters compared to several mm to cm for betas). In addition, beta emitters are easier to detect if spilled. Gamma-rays and X-rays are also acceptable, although they contribute significantly less to tissue damage than beta emitters.

QUESTION

The decay scheme for I-131 indicates emission of six beta-minus particles of varying energies and emission of 14 gamma rays of different energies. The total types of emissions is 20. Therefore, True/False: 6/20ths of the total tissue damage caused by I-131 is due to presence of beta-minus emission.

ANSWER:

FALSE. It has been estimated that 90% of the tissue damage from I-131 is caused by beta particles, even though there are far more gamma rays emitted during the decay process. The deciding factor is that the LET, the Linear Energy Transfer rate for beta-

minus particles, is much higher than for gamma rays. In addition, the question gives no information about % abundance for each of these modes of emission, a critical factor in determining the radiation dose.

2. Medium/high energy (>1 meV).

Since the goal of radionuclide therapy is to destroy cells, high energy particles are preferred. While there is no exact minimum energy required, beta emitters with E_{max} >1 meV are preferred. The LET of these high energy particles is sufficient to cause adequate but regulated tissue damage. Some therapeutic isotopes, e.g., I-131, are imageable and add to the information obtained during therapeutic treatment.

3. Effective half-life = moderately long, e.g., days.

Therapeutic effects are generally desired relatively quickly following radionuclide therapy; therefore, the effective half-life should ideally be measured in hours or days as opposed to longer time units. Good examples of therapeutic radiopharmaceuticals with an ideal t_{eff} include I-131 sodium iodide for treatment of hyperthyroidism (t_{eff} is 6 days) and Ho-166 FHMA for intraarticular radiation synovectomy (t_{eff} is 1.2 days).

4. High target:nontarget ratio.

Target:non-target ratio is critical in therapeutic procedures. A low target:non-target ratio may result in inadequate treatment of the primary disease and delivery of a potentially lethal radiation dose to bone marrow or other radiosensitive tissues. It is especially important therefore to assure the radiochemical purity of these drugs.

5. Minimal radiation dose to patient and Nuclear Medicine personnel

As was the case with diagnostic radiopharmaceuticals, the goal is a minimal radiation dose absorbed by both the patient, who is probably having a one-time therapeutic procedure, and the Physician or Nuclear Medicine Technologist, who is routinely exposed to radioactive patients on a daily basis. The usual rules of the TDS concept apply: one should minimize TIME, maximize DISTANCE, and use the appropriate amount of SHIELDING. There are specific rules governing the release of patients from the hospital after administration of a therapeutic radiopharmaceutical; in routine clinical practice not involving IND's, they apply most often to I-131. The release criteria are set by the NRC and state that the patient may be released when his radiation burden becomes <30 mCi or when a reading taken 1 meter from the patient's chest is <5 mR/hr, whichever level is reached first. These actions minimize the risk to family members and to the general public.

6. Patient Safety

Patient safety is also critical. Ideally, the therapeutic radiopharmaceutical should exhibit no toxicity to the patient. While most commonly used compounds are inherently safe and provide wide margins of safety, we routinely inject drugs that are potentially toxic. One of the concerns regarding treating a patient with I-131 NaI therapy solution is whether the patient is allergic to iodine. A calculation will show that 10 mCi of carrier-free I-131 contains only 80 ng of elemental iodine, far too small an amount to have a physiological effect on the patient.

7. Inexpensive, readily available radiopharmaceutical.

Inexpensive and readily available therapeutic radiopharmaceuticals are a necessity. Many valuable procedures are being performed infrequently or not at all because of the general unavailability of the isotope or its great expense.

8. Simple preparation and quality control if manufactured in house.

Preparation of the drug should be simple and require relatively little manipulation on the part of the preparer. Procedures with more than 3 steps generally do not meet this requirement. In addition, no complicated equipment or time consuming steps should be involved.

PROPERTIES OF ALL PHARMACEUTICAL INJECTABLES

1. Must be sterile and pyrogen-free.

Additional safety issues related to radiopharmaceutical use in general include sterility and apyrogenicity of the drug product. Every product designed for parenteral use must be sterile and pyrogen-free. Sterility refers to absence of living things, including spores and related substances, which could develop into something living. Assessment of sterility is most commonly performed by culturing samples with special growth media.

Pyrogens are soluble compounds, typically bacterial endotoxins, which induce fevers in humans and other animals. They are not destroyed by autoclaving, are not filterable, and, when injected intrathecally, are estimated to be 1000 times as potent as when injected intravenously. While it is possible to depyrogenate solutions using sophisticated techniques, absence of pyrogens in reagents used to manufacture drug products is preferable.

Testing for pyrogens involves use of either the rabbit test or the Limulus Amoebacyte Lysate test (LAL). The rabbit test involves injection of the drug into three rabbits on a mg/kg basis so the animal dose approximates the human dose. Rectal temperatures are then taken at prescribed points in time post injection and the data recorded. Elevation

of temperature indicates presence of pyrogenic material. This test is moderately sensitive for pyrogens.

The Limulus Amoebacyte Lysate test involves incubation of the sample to be tested with the lysate of amoebacytes of the horseshoe crab, limulus polyphemus. Formation of an opaque gel following 60 min incubation at 37oC indicates presence of pyrogens. This test is simple, rapid, relatively inexpensive, and very sensitive and can detect pyrogens on the ng/ml level.

2. Should be isotonic and have physiological pH

The isotonicity of injectable drug products should be equal to that of a 0.9% NaCl solution, and the pH should approximate that of blood (pH 7.5). While intravenous injection of hypertonic or hypotonic solutions, or those with very low or very high pH, is not recommended, it is possible to inject compounds with these characteristics if done slowly.

3. If radioactive, dose must be calibrated

Finally, there is the NRC and State requirement that every dose of every radiopharmaceutical must be calibrated before administration to the patient and that the dose be within ±20% of the prescribed dose. This calibration is an additional assurance that the patient's radiation dose will be as low as possible, consistent with producing high-quality images. Prescribed doses can only be changed by a physician and the change must be noted on the requisition form. Administration of a diagnostic dose not within 20% of the prescribed dose, or of the incorrect radiopharmaceutical or to the wrong patient, or by an unprescribed route, is no longer classified as a reportable misadministration unless the whole-body dose exceeds 5 R or a single organ dose exceeds 50 R.

CATEGORIES OF RADIONUCLIDES IN NUCLEAR MEDICINE

Methods of Production of Radioisotopes

Radionuclides used in Nuclear Medicine are all synthetic and fall into 4 general categories:

- Generator-produced

RADIOISOTOPE GENERATORS

A generator is a self-contained device housing a parent/daughter mixture in equilibrium, which is designed to yield the daughter for some purpose usually separate from the parent. The principal utility is to produce certain radioisotopes on-site which,

because of their short half-lives, cannot be shipped by commercial sources. To be useful, the parent's half-life must be long compared to the travel time required to transport the generator to the recipient.

The first group includes Ga-68, Kr-81m, Rb-82, Tc-99m, and In-113m, all of which are generator-produced radionuclides. Of particular note is Tc-99m. Due to its ideal imaging energy and physical half-life as well as the ability to bind to so many compounds, approximately 85% of all imaging procedures in the United States are performed following administration of Tc-99m.

IDEAL GENERATOR SYSTEMS

1. If intended for clinical use, the output of the generator must be sterile and pyrogen-free.

2. The chemical properties of the daughter must be different than those of the parent to permit separation of daughter from parent. Most often, separations are performed chromatographically.

3. Generator should ideally be eluted with 0.9% saline solution and should involve no violent chemical reactions. Human intervention should be minimal to minimize radiation dose.

4. Daughter isotope should be short-lived gamma-emitting nuclide (physical half-life = hrs-days)

5. Physical half-life of parent should be short enough so daughter regrowth after elution is rapid, but long enough for practicality.

6. Daughter chemistry should be suitable for preparation of a wide variety of compounds, especially those in kit form.

7. Very long-lived or stable granddaughter so no radiation dose is conferred to patient by decay of subsequent generations.

8. Inexpensive, effective shielding of generator, minimizing radiation dose to users.

9. Easily recharged (we do NOT recharge Mo/Tc generators, but store them in decay areas after their useful life is over).

Thermal Neutron Reactor-produced

- Radioisotopes used in Nuclear Medicine are all synthetic. For thermal neutron reactor-produced radioisotopes, reactor is source of thermal neutrons. An (n,γ) reaction occurs. Net effect: increase of A number by 1 and no change in Z number. Same element is therefore present. Example: ^{98}Mo (n,γ) ^{99}Mo

- The product of an (n,γ) reaction or other reaction may be described in terms of specific activity, i.e., radioactivity per unit mass of the element present. Examples: uCi/mg, dpm/mM, Ci/uM, kci/mole. Various separation techniques are available to separate product from target. Requirement: chemical forms of element in target and product must be different to effect separation.

Cyclotron-produced

The third group includes

- the positron-emitting isotopes C-11, N-13, O-15, and F-18, all of which are cyclotron produced. The very short half-lives of the first three limit their use to a facility at or near the cyclotron site. While it is possible to transport F-18 compounds, great dedication must be made to the transportation arrangements.
- the gamma emitters Co-57, Ga-67, In-111, I-123, and Tl-201. Also cyclotron-produced, they all have reasonably long half-lives and are easily transported across the country.
- Of particular interest in this group is Tl-201. The majority of photons collected by the camera for image formation are the low energy Hg-201 X-rays since the % abundance of the 135 and 167 keV gamma rays is so low. Co-57 is used for flood field, dose calibrator standards, spot markers, and other sealed sources.
- A cyclotron is a source of hi-energy protons, deuterons, and other particles. Various reactions takes place, e.g., (d,n), (p,pn), (p,5n), (p,a). Net effect: change in A number and/or Z number. A different element is usually formed.
    - Example: ^{14}N (d,n) ^{15}O

Fission reactor-produced.

- The final group of interest includes Xe-133, Mo-99, and I-131, all of which are byproducts of the fission of U-235. These and other radionuclides are produced in great quantity in nuclear reactors. Once they have been purified adequately, however, they are perfectly suitable for human use.
- The process involves the fission of U-235 by bombardment with of neutrons. The result is formation of an unstable "compound nucleus" that fragments into two parts with molecular weights of approximately 100 and 135. As indicated by their atomic masses, Xe-133, Mo-99, and I-131 have molecular weights of 133, 99, and 131, respectively. Many other isotopes are produced which have commercial value.
- The reaction may be represented by the following equation. Note that 2.3 neutrons are released for each one participating in the reaction. The reaction

becomes self propagating and requires special care to prevent it from quickly running out of control.

$$U^{235} + n \longrightarrow {}^{**}U^{236} \longrightarrow 2.3\ n + \text{I-131, Mo-99, Xe-133, and Others}$$

- There are many choices of radioisotopes for performing studies in humans. Table 1 below lists these isotopes and gives half-life and photopeak energy values as well as % abundance of each different photon.

Nuclide	Half-Life	Decay Mode	Gamma Energy	# of Photons/100 Disintegrations
C-11	20.4 min	β+ emitter	511 keV	200%
C-14	5730 yr	β- emitter	--	--
Co-57	270.9 d	EC	122 keV	200%
Cr-51	28 d	EC	320 keV	9
Cs-137	30 yr	β-	662 keV	85
F-18	1.83 hr	β+	511 keV	200
Fe-82	8.3 hr	β+ (56%) EC (44%)	165 keV 511 keV	100 112
Fe-59	45 d	β-	1,099 1,292	56 43
Ga- 67	79.2 h	EC	94 keV 184 keV 296 keV	40 24 22
Ge-68	68 min	β+	511 keV	178
H-3	12.3 yr	β-	---	---
I-123	13.3 hr	β+	159 keV	83
I-125	60 d	EC	35 keV 27-32 (xrays)	7 140
I-131	8.08 d	β-	364.5 keV	82
In-111	67 h	EC	173 keV 247 keV	89 94
In-113m	1.67 h	IT	393 keV	64
Mo-99	67 hr	IT	181 keV 740 keV 780 keV	6 12 4
O-15	2.05 min	β+	511 keV	190
P-32	14.3 d	β-	---	---
Rb-82	75 sec	β+	511 keV	190

Re-186	3.8 d	β- (92%) EC (8 %)	137 keV	190
Sm-153	1.9 d	β-	70 keV 103 keV	5 28
Sr-89	52 d	β-	---	---
Tc-99m	6.02 hr	IT	140.5 keV	90
Tl-201	73 hr	EC	135 keV 167 keV	2 8 71 Hg X-rays
Xe-133	5.3 d	β-	81 keV	37

CATEGORIES OF RADIOPHARMACEUTICALS IN NUCLEAR MEDICINE

- Radiopharmaceuticals fall into several different categories:
  - Ready-to-use radiopharmaceuticals
  - Instant kits for room-temperature preparation of Tc-99m products
  - Kits requiring heating
  - Products requiring significant manipulation.

- Distinction between radiopharmaceutical and radiochemical is important to recognize since there are certain legal implications.

There are many similarities between radiochemicals and radiopharmaceuticals.

- From the standpoint of both chemistry and radionuclide purity, there is usually minimal or no difference. The Tl-201 chloride sold as a radiochemical most likely came from the same cyclotron run as the radiopharmaceutical grade Tl-201 chloride used for diagnostic imaging.
- Radiopharmaceuticals, however, have undergone a very lengthy and expensive regulatory process as well as extensive chemical and physical testing (pH, isotonicity, and chemical parameters) to insure that the final product is sterile, pyrogen-free, safe for human use, and is efficacious. This includes both animal and human studies prior to release of the product for sale.
- Radiochemicals typically don't undergo this rigorous testing and neither their sterility nor apyrogenicity is guaranteed. Radiochemical usage is usually limited to chemical and biological research; in addition, the tracers used in RIA procedures are usually radiochemical grade.
- Radiopharmaceuticals are designed for diagnostic imaging and therapy procedures, but may also serve as tracers in research projects.

- Radiopharmaceuticals fall into several different categories : ready-to-use, instant kits for preparation of Tc-99m products, kits requiring heating, and products requiring significant manipulation.

Examples of each of these categories are listed in the following chart.

Prepared Products: Examples of each category are provided in tabular form. Some are of historical interest only.

- I-123 capsules
- I-131 hippuran
- Ga-67 citrate
- Tl-201 chloride
- Xe-133 gas
- Tc-99m pertechnetate
- Instant Tc-99m kits
- Disofenin
- DTPA
- GH
- HDP
- MDP
- mebrofenin
- MIAA
- MAA
- PYP
- Tc-99m Kits requiring heating
- MAG3
- sestamibi
- sulfur colloid
- teboroxime

Products requiring significant manipulation

- Cr-RBC's
- Tc-99m RBC's
- Tc-99m WBC's
- In-111 WBC's,
- In-111 Platelets
- Xe-133 in saline
- I-123 mIBG
- certain IND's

CLINICAL UTILITY: Radiopharmaceuticals have been used clinically for a wide variety of studies which generally fall into three categories.

1. **Static studies (Those studies in which the image doesn't change as a function of time)**

STUDY TYPE	TRACER	REGION	PATHOLOGY
BONE SCAN	Tc-MDP, Tc-HDP	Whole Body	Bone Tumors, Fractures, Paget's Disease
LIVER SPLEEN SCAN	Tc-SC, Tc-MIAA	Abdomen	Tumors, Cysts, Hepatocellular Disease
BRAIN SCAN	Tc-HMPAO	Brain	Tumors, Trauma, Dementia
TUMOR SCAN	Ga-67 Citrate	Whole Body	Malignant Tumors, Metastatic Disease

2. **Dynamic studies (Those studies in which the image changes as a function of time)**

STUDY TYPE	TRACER	REGION	PATHOLOGY
CARDIOANGIOGRAPHY	Tc-RBC, Tc-HSA	Chest	Aneurysms, Congenital Heart Defects, Myocardia Dyskinesia, Cardiomegaly
CEREBRAL BLOOD FLOW	TcO4	Head,Neck	Cerebral Death, AVM
CHOLECYSTOGRAPHY	Tc-DISIDA	Abdomen	Obstructive Disease
CISTERNOGRAM	In-111 DTPA	Head, Neck	Blockage, Slowed CSF Flow
DYNAMIC KIDNEY	Tc-DTPA	Back	Obstructive Disease
GASTRIC EMPTYING	Tc-Ovalbumin, Tc-SC	Abdomen	Abnormal GE Rates
PULMONARY VENTILATION	Xe-133 gas	Upper Back	Obstructed Airways

RENOGRAM	I-131, TcMag3	Back	Renal Dysfunction
VENOGRAM	Tc-MAA	Legs	Thrombosis
VOIDING CYSTOGRAM	Tc-SC	Abdomen	Urine Reflux, Incomplete Bladder Emptying

3. In vivo non-imaging studies

STUDY TYPE	TRACER	REGION	PATHOLOGY
CO_2 BREATH TEST	C-14 CO_2	Breath	Glucose Intolerance
IRON TURNOVER	Fe-59	Whole Body	Abnormal Ferrokinetics
OCULAR P-32 UPTAKE	P-32 Na_3PO_4	Eyes	Ocular Melanoma
PLATELET SURVIVAL	In-111 Platelets	Blood	Abnormal Platelet Loss
RADIOACTIVE IODINE	I-NaI	Thyroid	Abnormal Uptake, Hyperthyroidism
RBC SURVIVAL	Cr-51 RBC	Blood	Hemolytic Anemias
SCHILLING TEST	Co-57 B12	Urine	Pernicious Anemia, Vit B12 Malabsorption Syndromes
SPLENIC SEQUESTRATION	Cr-51 RBC	Spleen	Hypersplenism

This Table includes a list of positron-emitting radiopharmaceuticals used for imaging, mostly in research applications.

NUCLIDE COMPOUND	T_{PHYS}	RADIATION	PRODUCTION	COMPOUNDS
CARBON-11	20.4 min	β+	$^{10}B(d,n)^{11}C$	CO, CO_2, fatty acids, glucose, cyanide
NITROGEN-13	9.96 min	β+	$^{12}C(d,n)^{13}N$	NH3, cyanide, glutamic acid

OXYGEN-15	2.05 min	β+	$^{14}N(d,n)^{15}O$ $^{16}O(p,pn)^{15}O$ $^{12}C(a,n)^{15}O$	CO, O_2, H_2O
FLUORINE-18	110 min	β+		

This list covers all radiopharmaceuticals used in the US, the typical procedure for which it is used, and the typical dose administered to an adult patient. The list has been arranged in alphabetical order by procedure name. Doses for pediatric studies must be scaled to the patient's body mass.

Organ System	*Radiopharmaceutical*	*Admin Dose (mCi)*
ABSCESS AND INFLAMMATORY SITES	In-111 leukocytes Tc-99m leukocytes Ga-67 citrate	0.5 10-20 5-10
ADRENAL MEDULLA	I-131 m-iodobenzylguanidine I-123 m-iodobenzylguanidine ** In-111 Octreoscan	0.5 5-10 3-6
BONE IMAGING	Tc-99m methylenediphosphonate (MDP) Tc-99m hydroxymethylenediphosphonate (HDP) Tc-99m pyrophosphate (PYP)	15-25 15-25 15-25
BONE PAIN (PALLIATION)	Sr-89 chloride P-32 sodium phosphate Sm-153** EDTMP Ra-223 chloride	4 4 1 mCi/kg 1.49 μCi/kg
BONE MARROW	Tc-99m sulfur colloid	8-10
BRAIN LESIONS	Tc-99m glucoheptonate Tc-99m pertechnetate Tc-99m DTPA	15-25 15-25 15-25
BRAIN PERFUSION	Tc-99m HMPAO Tc-99m ECD I-123 HIPDM ** I-123 IMP	10-20 10-20 5 3-5
CARDIOVASCULAR (BLOOD POOL)	Tc-99m RBC's Cr-51 RBC's Tc-99m human serum albumin (HSA)	15-25 0.05-0.08 15-25

CARDIOVASCULAR (MYOCARDIUM)	Tl-201 chloride Tc-99m sestamibi Tc-99m tetrofosmine Rb-82 chloride	2-3 15-25 15-25 40-60
CISTERNOGRAM	In-111 DTPA	0.5
CYSTOGRAM	Tc-99m sulfur colloid Tc-99m pertechnetate	1-2 1-2
GASTRIC EMPTYING	Tc-99m ovalbumin (solid phase) Tc-99m resin beads in food (solid phase) Tc-99m oatmeal (solid phase) In-111 DTPA (liquid phase)	0.3-0.5 0.3-0.5 0.3-0.5 0.5
GE REFLUX	Tc-99m sulfur colloid	0.3-0.5
HEMANGIOMA	Tc-99m RBC's	15-25
HEPATOBILIARY	Tc-99m disofenin (DISIDA) Tc-99m mebrofenin (CHOLETEC) Tc-99m HIDA	3-8 3-8 3-8
INFARCT- MYOCARDIAL	Tc-99m PYP	15-25
KIDNEYS	Tc-99m dimercaptosuccinic acid (DMSA) Tc-99m DTPA Tc-99m glucoheptonate I-131 o-iodohippurate (HIPPURAN) Tc-99m mercaptoacetyltriglycine (MAG3)	5 10-15 5-10 0.2-0.4 5
LIVER	Tc-99m microaggregated albumin (MIAA) Tc-99m sulfur colloid	5-10 5-10
LUNG PERFUSION	Tc-99m macroaggregated albumin (MAA)	2-4
LUNG VENTILATION	Tc-99m DTPA aerosol Xe-133 gas Xe-127 gas Kr-81m gas	5 15-25 5 ---
LYMPHO-SCINTIGRAPHY	Tc-99m sulfur colloid (ultrafiltered)	0.5-2.0
MECKEL'S DIVERTICULUM	Tc-99m pertechnetate	10
PANCREAS (ISLET CELL CA)	In-111 Octreoscan	5
PARATHYROIDS	Tl-201 chloride/Tc-99m pertechnetate Tc-99 sestamibi	2/1 5
PAROTIDS	Tc-99m pertechnetate	10

SPLEEN	Tc-99m MIAA Tc-99m sulfur colloid Tc-99m damaged RBC's	5-10 5-10 5
TESTICLES	Tc-99m pertechnetate (Torsion) Tc-99m red cells (Varicocele)	15 25
THROMBUS	Tc-99m Acutect In-111 platelets	15-20 0.5
THYROID SCAN	Tc-99m pertechnetate I-123 sodium iodide I-131 sodium iodide (substernal thyroid) I-131 sodium iodide (whole body mets survey)	10 0.4 0.04-0.1 10
THYROID THERAPY	I-131 sodium iodide (Graves) I-131 sodium iodide (hot nodule) I-131 sodium iodide (carcinoma)	5-10 25-29.9 100-225
THYROID UPTAKE	I-123 sodium iodide I-131 sodium iodide	0.2 0.005
TUMOR	F-18 FDG Ga-67 citrate In-111 Oncoscint I-131 sodium iodide I-131 monoclonal antibodies** In-111 monoclonal antibodies**	5 5-12 5 5-10 varies 5
VENOGRAM	Tc-99m MAA	5-10

MECHANISMS OF LOCALIZATION

The design of radiopharmaceuticals is based solely upon physiological function of the target organ. The mechanism of localization of a radiopharmaceutical in a particular target organ depends upon processes as varied as antigen-antibody reactions, physical trapping of particles, receptor site binding, removal of intentionally damaged cells from circulation, and transport of a chemical species across a cell membrane and into the cell by a normally operative metabolic process. Radiochemistry plays a significant part in the development of these compounds and methods of performing quality control to insure radiochemical purity.

Active Transport:

- involves use of a normally operative metabolic pathway in the body for moving a radiopharmaceutical across a cell membrane and into the cell. Example: I- 131 NaI for thyroid imaging. Active Transport involves use of a normally operative energy-dependent metabolic pathway in the body to move a radiopharmaceutical across a cell membrane and into the cell. For example, thyroid uptake of radioiodide is by active transport. The first step involves trapping of the iodide; it then undergoes intermediate syntheses involving a thyroglobulin intermediate and is ultimately converted into T3 and T4 by the process of organification. Initial localization following IV injection is in the thyroid, stomach, parotids, and choroid plexus; ultimately, the iodide is stored in the thyroid as thyroxines with a tbiol of approximately 3 weeks or cleared through the kidneys.
- Myocardial perfusion imaging is routinely performed with Tl-201 in the form of thallous ion (Tl1+). This involves utilization of the normally operative metabolic pathway for handling potassium since Tl1+ is a potassium analog and is therefore handled efficiently by the well-documented ATPase-driven Na/K pump mechanism. Initial localization of Tl1+ following IV injection is in the heart, liver, and muscle; ultimately it is recycled so very little is cleared through the kidneys.The whole body tbiol is approximately 10 days. This use of Tl1+ is also an excellent example of active transport.
- Renal imaging with I-131 o-iodohippurate or Tc-99m MAG3 for tubular secretion studies is also an example of active transport. These compounds are processed predominantly by tubular secretory function. Approximately 80+% of both hippuran and MAG3 is removed from the blood stream by tubular secretion; the remainder is by GFR. Imaging is typically begun immediately post injection and acquisition is divided into frames, permitting generation of renogram curves.
- Uptake by brain localizing radiopharmaceuticals such as Tc-99m HMPAO, Tc-99m ECD, I-123 IMP or I-123 HIPDM, probably also falls under the category of Active Transport. While the mechanism of cerebral uptake has not been completely elucidated, it appears to be related to "pH Shift"; that is, intracerebrocellular pH is lower than blood pH and these agents, which have the unique ability to penetrate an intact blood-brain barrier, are immobilized in brain cells due to this small change in pH of the compound. Their uptake may also be receptor-related. These agents basically take a "snapshot" of cerebral blood flow at the time of injection since brain uptake is very rapid and irreversible. Initial localization in the brain is in the range of 4-9%; often there is significant localization in the lungs, requiring shielding for performance of SPECT studies. Brain uptake remains essentially constant for the duration of the study.
- Imaging tumors of neuroendocrine origin also probably falls under the category of active transport although metabolic incorporation is perhaps a better name for the mechanism. The I-123 or I-131 m-iodobenzylguanidine (mIBG) injected is so similar structurally to guanethidine, the precursor of epinephrine, that these tumors, which

include pheochromocytomas, neuroblastomas, paragangliomas, carcinoid type tumors, and medullary hyperplasia, attempt to use it as a substrate for synthesis of hormones. Because of this attempt at chemistry by the tumors, this material accumulates within them. Since conversion of the mIBG to epinephrine doesn't take place, however, the accumulated tracer activity simply increases in the tumor as a function of time. By 24-48 hr, several % of the injected dose localizes in the tumors; a small amount accumulates in the liver; and parotids and normal adrenals are usually visualized. The remainder is excreted by the kidneys. Depending upon the radioisotope used, initial imaging is typically performed 24-48 hr post injection. In selected patients, imaging may be performed at 72 hr with the I-131 compound.

2. <u>Phagocytosis:</u>

- physical entrapment of colloidal particles by Kupffer cells in the RE System. Example: Tc-99m sulfur colloid for liver/spleen imaging.Phagocytosis involves the physical entrapment of colloidal particles by Kupffer cells in the reticulothelial system following an intravenous injection. Colloidal suspensions contain particles in the range of approximately 0.05 to 4 μm and may include things as diverse as Tc-SC and cigarette smoke in air. The most commonly used phagocytic agents, Tc-sulfur colloid and Tc-microaggregated albumin, typically have particle sizes ranging from approximately 0.1-2.0 μm. The smaller the particles, the greater the bone marrow uptake; larger particles tend to localize in the liver and spleen. Due to the small size of the colloid compared to the diameter of the average capillary, which is 7 μm, capillary blockade does not occur. Distribution in the RES is typically 85% in the liver, 10% in the spleen, and 5% in marrow. In severely diseased livers, the ratio may change significantly with increased uptake in the spleen. The t_{biol} of Tc-sulfur colloid in the liver is infinitely long; by comparison, t_{biol} of microaggregated albumin is 6-12 hr. The $t_{1/2}$ of clearance from the blood for these agents is approximately 2.5 min, so in 10 min only approximately 6% remains in the blood stream. Imaging may therefore begin as early as 5-10 min post injection.

3. <u>Capillary blockade</u>:

- intentional microembolization of a capillary bed with particles. Example: Tc-99m MAA for pulmonary perfusion imaging.Capillary blockade involves the intentional microembolization of a capillary bed with particles, permitting external visualization of the perfusion of this capillary bed. This is achieved by the IV injection of a radiolabeled, precipitated, biodegradable macroaggregate of human serum albumin commonly known as Tc-99m MAA 34. Compared to the 7 μm diameter of the average capillary, at least 90% of the MAA particles

are between 10-90 μm in size; none are >150 μm in their longest aspect.These are the legal particle size requirements as listed in the manufacturers' package inserts and in the current USP.

- For an adult without known pulmonary hypertension, the ideal number of particles to be injected is 350,000 with a suggested range of 200,000-700,000. Even though these appear to be very large numbers, there is a very large margin of safety since fewer than 1/1,000 capillaries are blocked by the typical injection. For a patient with known pulmonary hypertension, the number of particles should be limited to 150,000. The t_{biol} of Tc-MAA is 5-12 hr, depending upon the manufacturer.

4. <u>Cell Sequestration:</u>

- Injection of damaged RBC's to produce a spleen scan with no visualization of the liver. Example: heat damaged autologous Tc-99m RBC's.Cell Sequestration involves radiolabeling and then heat damaging a small volume of the patient's red cells (usually 10 ml) to take advantage of the spleen's normal function, i.e., removal of damaged red cells. If the cells are radiolabeled properly, this procedure permits visualization of the spleen with minimal visualization of the liver. Rarely performed, it nevertheless is considered one of the classical mechanisms of localization of radiopharmaceuticals. The labeled damaged red cells have a moderately long tbiol, probably in the range of 10-20 hr.

5. <u>Simple/exchange diffusion</u>:

- a mechanism whereby a radiotracer diffuses across cell membranes and then binds/attaches to a cell component. Example: F-18 NaF for bone imaging.

  Exchange diffusion involves the diffusion of a radiotracer into a cell where a chemical exchange takes place. For example, one of the earliest bone imaging agents, the F-18 fluoride ion (F-), was capable of exchanging with the hydroxide ion (OH-) on the hydroxyapatite structure of bone tissue to form F-18 fluorapatite, a very stable molecule. This permitted external visualization by collecting the 511 keV annihilation photons produced during the decay by positron emission of this isotope.
- Simple diffusion describes a mechanism whereby a radiotracer diffuses across cell membranes and then redistributes itself elsewhere in the body. The perfect example is the ability of Xe-133 gas to diffuse across membranes in the lungs and to circulate in the blood stream.

6. Compartmental Localization:

- placement of a radiotracer in a fluid space and imaging of that fluid space. Example: Tc-99m HSA for MUGA's, In-111 DTPA for cisternograms, Xe-133 gas for pulmonary ventilation. Compartmental localization is defined as the placement of a radiopharmaceutical in a fluid space and maintaining it there long enough to image that fluid space. Since a fluid is defined as a liquid or a gas, the airways of the lungs qualify as a fluid space. The use of Xe-133 gas, Xe-127 gas, or Kr-81m gas as a ventilation agent is therefore a good example of this mechanism. Immediate distribution is to the lungs; since Xe-133 is lipophilic and can cross cell membranes, the gas passively diffuses into pulmonary capillaries and the activity is circulated through the blood stream, permitting cerebral blood flow studies. The tbiol of all these gases in the lungs is <0.5 min in most patients. Ultimately the activity is cleared from the body through the lungs.
- Another example of compartmental localization is blood pool imaging using autologous Tc-99m labeled red cells or Tc-99m Human Serum Albumin within the blood pool. The immediate distribution is within the blood pool; ultimately the Tc-99m dissociates from these compounds and is cleared through the kidneys. The tbiol of Tc-99m HSA in the blood pool is approximately 1-2 hr; for Tc-99m RBC's, The tbiol is approximately 20 hr.
- One can perform a cisternogram following injection of In-111 DTPA directly into the cerebrospinal fluid (CSF). This use of compartmental localization involves early and delayed views, permitting tracing of the kinetics of CSF. Immediate distribution is entirely within CSF; ultimately the activity bathes the brain and brain stem and indicates the presence of CSF leakage into the nasopharynx. The tbiol of In-DTPA is approximately 20 hr; radioactivity is eventually cleared through the kidneys.
- Even an "artificial" localization such as the infusion of a dilute solution of Tc-99m pertechnetate or a suspension of Tc-99m sulfur colloid into the urinary bladder in a voiding cystogram qualifies as compartmental localization. The immediate localization is in the bladder; the activity is rapidly emptied via catheter with a t_{biol} measured in minutes. This study provides significant clinical information while conferring a minimal radiation dose to the patient due to the short retention time of the radiopharmaceutical in the bladder.

7. Chemisorption:

- surface binding of radiopharmaceutical to a solid structure, e.g., In- 111 platelets bound to surface of an active thrombus. Another important mechanism

is known as physicochemical adsorption or chemisorption. The phosphate or phosphonate groups on currently used bone agents bind instantaneously, avidly, and essentially irreversibly to the hydroxyapatite structure of bone tissue. In addition, by the same mechanism, they localize in lesions metastatic to bone. Tc-99m MDP, Tc-99m HDP, and Tc-99m PYP all bind to bone tissue by this mechanism. Typically, 40-50% of the injected dose localizes in bone; the remainder is excreted through the kidneys. Since bone uptake is relatively slow, especially in adults, it is common practice to begin imaging 3 hr post injection.

- A closely related example is the imaging of acute myocardial infarctions with Tc-99m PYP 3. When myocardial cells become necrotic following an acute myocardial infarction, there is an influx of calcium ions into the cells. The Ca2+ ions react with circulating phosphate ions to form Ca3(PO4)2 crystals, known as hydroxyapatite. Tc-99m pyrophosphate binds avidly and irreversibly to these crystals at the periphery of the infarct where some perfusion is maintained (none localizes in the central region of the infarct). Images are routinely taken approximately 2 hr post injection. Optimal imaging time post-infarct is 1-3 days; after 6 days an infarct is considered "old" and the rate of false negative studies increases significantly.

8. Antigen/antibody reaction:

- One of the newer mechanisms to consider is the antigen/antibody reaction.. Uptake at tumor site is due to specific binding of radiolabeled antibody to surface antigens on tumors. Example: In-111 ProstaScint for localization of recurrent prostate cancer.
- In this case, highly purified radiolabeled monoclonal antibodies with high specificity for a particular antigen are injected intravenously and imaged at a later point in time, often 1-3 days post injection. For example, In-111 ProstaScint, a monoclonal antibody specific for PSMA (Prostate Specific Membrane Antigen), has been very useful in evaluating recurrence of prostate cancer.
- A variety of these radiolabeled antibodies is in clinical trials for imaging a wide variety of diseases such as lung carcinoma, prostate and breast cancer. In addition, a commercially available radiopharmaceutical, Y-90 Zevalin, is designed for therapy of non-Hodgkin's Lymphoma. It is a radiolabeled antibody targeted to the CD-20 receptors on B-cell lymphoma.

9. Receptor-binding:

- binding of radiopharmaceutical to high-affinity receptor sites. Example: In-111 octreotide for localization of neuroendocrine and other tumors based on binding of a somatostatin analog to receptor sites in tumors.
- An increasingly important mechanism to consider is use of receptor binding radiopharmaceuticals designed specifically to trace receptor sites; for example, I-123 IQNB localizes at the site of muscarinic receptors, I-123 iomazenil localizes in benzodiazepine receptors, and I-123 mIBG permits visualization of adrenergic receptors in the myocardium. Critical features of drug development in this case include special attention to the specific activity and radiochemical purity of the starting material; otherwise, the specific activity of the final product may be unsuitable for localizing receptor sites due to saturation with cold, nonradioactive material.

CHEMISTRY OF RADIOPHARMACEUTICALS IN NUCLEAR MEDICINE

Stannous Reduction Method

- The majority of Tc-99m compounds employ the stannous reduction method, which makes use of the fact that stannous chloride is one of the most powerful reducing agents available to chemists. Tc-99m obtained from the Mo/Tc generator is in the chemical form of TcO4, or pertechnetate. While the anion has an overall negative charge of -1, the oxidation number of the Tc is 7+.
- The chelating agents commonly used to prepare Tc-99m products are also anions with an overall negative charge due to the presence of N, O, and P atoms, each of which has 1 or more extra pairs of electrons. These negative charges repel each other so pertechnetate will not form chelates. A reducing agent is therefore required to convert the Tc-99m into an electropositive cationic form capable of binding to chelating agents.
- Tc-99m sulfur colloid does not use the stannous reduction method.
- The following reduction/oxidation reactions (REDOX) indicate that the pertechnetate is typically reduced to Tc^{4+} while the stannous ion (Sn^{2+}) is converted to stannic ion (Sn^{4+}). In the overall reaction, the stannous ion is the reducing agent, and therefore the substance oxidized, while pertechnetate is the oxidizing agent and therefore the substance reduced.

  $3\ Sn^{2+} - 6e \rightarrow 3Sn^{4+}$

  $2TcO_4^- + 16H^+ + 6\ e \rightarrow 2Tc^{4+} + 8H_2O$

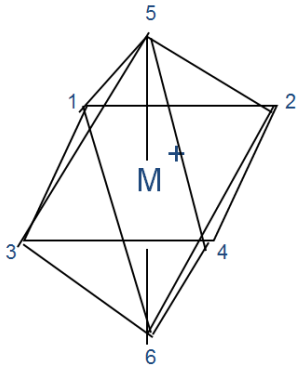
  Overall, $3Sn^{2+} + 2TcO_4^- + 16H+ \rightarrow 3Sn^{4+} + 2Tc^{4+} + 8H_2O$

The Tc4+ is now in the appropriate chemical form to react with an anion like PYP, MDP, or DTPA. The complex formed is known as a chelate; the generic equation is shown below.

Tc^{4+} + chelating agent n- ---> Tc-chelate

For example, Tc^{4+} + pyrophosphate4- ---> Tc-pyrophosphate

Hexa-coordinated Compound
Octahedral Structure



Most soluble Tc-99m compounds, excluding those containing a protein, have octahedral structures and are said to be hexa-coördinated since there are typically 6 binding sites available consisting of N, O, or P atoms. An octahedral structure is shown in Figure 3. In the diagram, Mn+ represents a radiometal ion with a net positive charge due to the loss of n electrons. Certain compounds, e.g., the porphyrins, have a square planar array of N atoms in their center and are tetra-coördinated. Iron atoms bound to the heme portion of the hemoglobin molecule are located within the square planar array of nitrogen atoms (see Figure 4). In most kits, the desired molecule is already present and it is a simple matter of binding the reduced Tc- 99m to the molecule. In the case of MAG3 and teboroxime, however, the desired molecule is actually formed during the first part of a 10 min heating cycle and this molecule then binds to the reduced Tc to form the Tc-chelate. This reaction requires the presence of the correct precursors in the reaction vial at the right concentration to produce the desired product.

TcO_4^{1-} ----> Tc^{4+} (reduction; gain = 3e)

Sn^{2+} ----> Sn^{4+} (oxidation; loss = 2e)

- Pertechnetate is the oxidizing agent; stannous ion is the reducing agent. In the presence of a chelating agent (a compound with electronegative character that is capable of binding radiometal cations), the metal ion is tightly bound in the center of the octahedral structure.
- In the presence of a chelating agent (a compound with electronegative character that is capable of binding radiometal cations), the metal ion is tightly bound in the center of an octahedral structure. It is said to be hexa-coordinated since there are typically 6 binding sites available consisting of O- N-, or P-atoms. The bound complex is called a chelate, e.g., Tc-MDP, In-DTPA. The diagram below

represents an octahedral structure for a hexa-coordinated complex. Other methods are useful in formation of Tc-99m compounds. In addition, special procedures are available for preparation of Tc-99m RBC's.

PRODUCTION METHODS

- Iodination techniques, e.g., chloramine T, Bolton and Hunter
- Tritiation and C-14 reactions
- Tc-99m reactions by the Stannous Reduction Method result in chelate formation. Most Tc- 99m complexes have octahedral structures and are hexa-coordinated.

  OVERALL, _ 2Tc7+O4 + 16H+ + 3Sn2+ 2Tc4+ +3Sn4+ +8H2O

- Tc-99m reactions by the Thiol Reduction Method result in complex formation. In this reaction, two thiol groups (-SH) lose their H-atoms and link together to form a disulfide bridge, comparable to the cystine/cysteine reactions.
- Biological synthesis, e.g., Co^*Cl_2 in presence of streptomyces griseus produces Co* vitamin B_{12}; yeast growing in a medium high in Se-75 and low in sulfur produces Se-75 selenomethionine.

Preparation of Radiopharmaceuticals

- Pertechnetate: used "as is" after elution from the Mo/Tc Generator

- Tc-99m sulfur colloid
  - To 0.5 ml of 1 N HCl is added Tc-99m pertechnetate and sodium thiosulfate.
  - The mixture is shaken then boiled for 5 min.
  - Acetate buffer is then added and mixture cooled.
  - Ready for quality control and then injection

- Tc-99m sestamibi and Tc-99m teboroxime
  - Tc-99m pertechnetate is added to a vial of the Sn2+ compound
  - The solution is gently mixed and then boiled for 10 min.
  - Vial is permitted to cool for 10 min
  - Product is ready for quality control and then injection

- Other Tc-99m radiopharmaceuticals
  - To vial of freeze-dried cold kit is added a controlled volume of Tc-99m pertechnetate diluted, if necessary, in 0.9% saline solution
  - Solution is shaken gently then permitted to stand for 5 min.. Solution is ready for quality control and then injection

- Cr-51 RBC
    - 30 ml of patient's blood added to 10 ml ACD solution.
    - 50-100 μCi of Cr-51 sodium chromate is added to the anticoagulated blood and mixture is incubated for 15 min with occasional gentle agitation.
    - Ascorbic acid is added to terminate the reaction and prevent labeling from continuing in vivo.
    - Labeled cells are ready for reinjection. NOTE: successful labeling of these cells without damaging them requires a 20 ga or larger bore needle.

V. Ready-to-use radiopharmaceuticals

- Includes all non-technetium products, e.g., Tl chloride, Ga citrate, Xe-133 gas, all iodinated products not prepared on-site; and others.

METHODS OF RBC LABELING

I. *In vivo/in vivo* method:

A. Procedure

1. Sn^{2+} pyrophoshate, given intravenously, ideally 200 ng/ml whole blood

2. 20 min waiting period to permit mixing of the Sn-PYP (often referred to as "cold PYP") in body and diffusion of Sn2+ into RBC.

3. Injection of Tc-99m pertechnetate (usually 2 mCi/m2 of body surface area).

4. 10 min waiting period to permit diffusion of the pertechnetate into RBC's where the radiolabeling takes place.

5. Expected labeling efficiency: 80-85%

B. Advantages/disadvantages

1. Advantages: quick, simple, inexpensive method.

2. Disadvantage: lowest labeling efficiency of all commonly used procedures, but perfectly acceptable for routine work, e.g., MUGAs.

II. *In vivo/in vitro* method (*in vivtro* method)

A. Procedure

1. Sn^{2+} pyrophoshate, given intravenously, ideally 200 ng/ml whole blood

2. 20 min waiting period to permit mixing of the Sn-PYP in body and diffusion of Sn^{2+} into RBC.

3. Withdrawal of 6-10 ml of blood anticoagulated with heparin or ACD solution into a syringe containing Tc-99m pertechnetate (usually 2 mCi/m^2 of body surface area).

4. 10 min waiting period to permit diffusion of the pertechnetate into RBC's and to permit labeling to reach equilibrium.

5. Reinjection of labeled cells into patient.

6. Expected labeling efficiency: 92%

B. Advantages/disadvantages

1. Advantages: quick, simple, inexpensive method; achieves higher labeling efficiency than in vivo/in vivo technique since incubation with RBC is extracorporeal. More suitable for GI Bleeding Studies than previously described technique.

2. Disadvantage: takes extra tech time; potential for breaking sterility; images taken at 24 hr post injection not as good as with packed cell techniques.

III. Modified In vivo/in vitro method (packed cell technique)

A. Procedure

1. Sn2+, usually as pyrophosphate, given intravenously, ideally 200 ng/ml whole blood

2. 20 min waiting period to permit mixing of the Sn-PYP in body and diffusion of Sn2+into RBC.

3. Withdrawal of 6-10 ml of blood anticoagulated with heparin or ACD solution into a vacutainer

4. Centrifugation of the vacutainer in inverted position for 5 min at 3000 rpm.

5. Removal of 1-2 ml of packed cells through a 20 ga or larger needle.

6. Aseptic addition of these tinned, packed cells to a sterile vial containing 35 mCi of Tc-99m pertechnetate.

7. 10 min incubation to permit labeling reaction to go to completion. Expected labeling efficiency: 98-100%

8. Reinjection of Tc-RBC

B. Advantages/disadvantages

1. Advantages: simple, inexpensive method; achieves highest labeling efficiency of all procedures since reaction of Tc with plasma proteins has been eliminated. Ideally suited for GI Bleeding Studies- produces best delayed images.

2. Disadvantage: takes extra tech time; requires clinical centrifuge; potential for breaking sterility.

IV. In vitro/in vitro method (Ultratag)

A. Procedure

1. Withdrawal of 10 ml of blood anticoagulated with heparin into a special vacutainer containing several ~ 50 μg of a stannous compound.

2. 10 min waiting period to permit diffusion of Sn^{2+} into RBC.

3. Centrifugation of the vacutainer in inverted position for 5 min at 3000 rpm.

4. Removal of 1-2 ml of packed cells through a 20 ga or larger needle.

5. Aseptic addition of these tinned, packed cells to a sterile vial containing 35 mCi of Tc-99m pertechnetate.

6. 10 min incubation to permit labeling reaction to go to completion.

7. Expected labeling efficiency: 98-100%

8. Reinjection of Tc-RBC

B. Advantages/disadvantages

1. Advantages: simple, inexpensive method; like the packed cell technique described above, achieves highest labeling efficiency of all procedures since reaction of Tc with plasma proteins has been eliminated. Ideally suited for GI Bleeding Studies- produces best delayed images. Requires no injection of Sn2+ ion into patient.

2. Disadvantage: takes extra tech time; requires clinical centrifuge; potential for breaking sterility.

RADIOPHARMACEUTICALS

a. Precautions

- There are many precautions one must take during the preparation and use of radiopharmaceuticals, in general, and Tc-99m radiopharmaceuticals, in particular. Since most radiopharmaceuticals are intended to be administered intravenously, it is imperative to use aseptic technique in order to maintain sterility of the product. The vial septum must be wiped with 70% isopropanol prior to puncturing the septum with a needle. This is really a cleansing step rather than a true sterilizing

step since the alcohol doesn't remain on the septum long enough to kill all pathogens that might be present.

- Air must NEVER be injected into any radiopharmaceutical vial, especially one containing a Tc-99m product. The oxygen contained in only 0.1 ml of air is enough to completely destroy the stannous ion used in many commercially available cold kits as a reducing agent. In addition, room air is not sterile so it is possible to introduce pathogens into the vial by using a preliminary injection of air to increase internal pressure in the vial and ease the removal of the contents.
- Prior to reconstituting a cold kit with Tc-99m pertechnetate, oxidant-free pertechnetate must be diluted to the required final volume with 0.9% NaCl solution. Ideally, oxidant-free saline (Low Dissolved Oxygen Saline) should be used for the dilution step. Reconstitution of a cold kit with a small volume of pertechnetate followed a few minutes later by dilution with saline solution can cause dissociation of certain weak chelates, resulting in the formation of significant amounts of Free Tc. This is not a problem with sulfur colloid or other insoluble Tc-99m compounds.

b. Tc-99m radiopharmaceuticals

Sodium pertechnetate may be used "as is" after elution from the Mo/Tc Generator and is the only Tc-99m compound that requires no manipulation on the part of Nuclear Medicine personnel. It may be injected intravenously, used to label blood cells or other molecules for intravenous injection, or bound to molecules suitable for oral administration.

The majority of Tc-99m compounds employ the stannous reduction method, which makes use of the fact that stannous chloride is one of the most powerful reducing agents available to chemists. Tc-99m obtained from the Mo/Tc generator is in the chemical form of TcO_4^-, or pertechnetate. While the anion has an overall negative charge of -1, the oxidation number of the Tc is 7+. The chelating agents commonly used to prepare Tc-99m products are also anions with an overall negative charge due to the presence of N, O, and P atoms, each of which has 1 or more extra pairs of electrons. These negative charges repel each other so pertechnetate will not form chelates. A reducing agent is therefore required to convert the Tc-99m into an electropositive cationic form capable of binding to chelating agents. Tc-99m sulfur colloid is the only 2 commercially available Tc-99m compound that does not use the stannous reduction method.

The following reduction/oxidation reactions (REDOX) indicate that the pertechnetate is typically reduced to Tc^{4+} while the stannous ion (Sn^{2+}) is converted to stannic ion (Sn^{4+}). In the overall reaction, the stannous ion is the reducing agent, and therefore the

substance oxidized, while pertechnetate is the oxidizing agent and therefore the substance reduced.

$3\ Sn^{2+} - 6e^- \text{---> } 3Sn^{4+}$

$2TcO4^- + 16H^+ + 6\ e^- \text{---> } 2Tc4+ + 8H2O$

Overall, $3Sn^{2+} + 2TcO4^- + 16H+ \text{---> } 3Sn^{4+} + 2Tc^{4+} + 8H2O$

The Tc^{4+} is now in the appropriate chemical form to react with an anion like PYP, MDP, or DTPA. The complex formed is known as a chelate; the generic equation is shown below. Tc^{4+} + chelating agent n -----> Tc-chelate.

For example, Tc^{4+} + pyrophosphate 4- ----> Tc-pyrophosphate

Most soluble Tc-99m compounds, excluding those containing a protein, have octahedral structures and are said to be hexa-coördinated since there are typically 6 binding sites available consisting of N, O, or P atoms. An octahedral structure is shown in Figure 3. In the diagram, M+ represents a radiometal ion with a net positive charge due to the loss of n electrons. Certain compounds, e.g., the porphyrins, have a square planar array of N atoms in their center and are tetra-coördinated. Iron atoms bound to the heme portion of the hemoglobin molecule are located within the square planar array of nitrogen atoms (see Figure). In most kits, the desired molecule is already present and it is a simple matter of binding the reduced Tc-99m to the molecule. In the case of MAG3 and teboroxime, however, the desired molecule is actually formed during the first part of a 10 min heating cycle and this molecule then binds to the reduced Tc to form the Tc-chelate. This reaction requires the presence of the correct precursors in the reaction vial at the right concentration to produce the desired product.

Tc-99m reactions by the Thiol Reduction Method also result in complex formation. In this reaction, two thiol groups (-SH) lose their H-atoms and link together to form a disulfide bridge, comparable to the cystine/cysteine reactions. This is the reduction method used in the formation of Tc-99m DMSA, shown in the following reaction. The Tc-99m is trapped within the 4-member ring structure or between the S—S bonds in two molecules of Tc-DMSA.

Tc-99m sulfur colloid is formed by the acid-catalyzed conversion of soluble thiosulfate ion to an insoluble Tc-99m heptasulfide, which coprecipitates with colloidal sulfur. Sodium thiosulfate solution is mixed with a small volume of 1 N hydrochloric acid and pertechnetate is then added to the mixture, which is shaken to insure homogeneity. The mixture is then heated at 100OC for 5-10 min depending upon manufacturer. Alternatively, it may be heated in a microwave oven for 12-25 sec depending upon the particular oven and the power level selected. At the end of the heating cycle, a small

volume of a sodium acetate buffer is added to the reaction mixture to raise the pH to approximately 5.5. The Tc-SC is then cooled prior to quality control testing and injection.

c. Other radiopharmaceuticals

Preparation of Cr-51 RBC's is achieved by incubation of 20-30 ml of anticoagulated whole blood with 50-100 μCi of sodium chromate Na251CrO4. The blood is typically anticoagulated with heparin or ACD solution. After 15 min incubation at room temperature, the reaction is terminated by the addition of a small amount of ascorbic acid, which converts unreacted (CrO4)

2-to Cr3+ (chromous ion). This prevents the continuation of cell labeling after the material is injected into the patient. The Cr-51 binds avidly and irreversibly to the b-globin chains on the hemoglobin molecule, forming labeled cells with excellent in vivo stability. The labeling of RBC's with Tc-99m also involves the binding of the radioisotope to the b-globin chains on the hemoglobin molecule. Cells may be labeled in vivo or in vitro by a variety of different procedures, described in detail in the chapter on Cell Labeling.

I-123 mIBG and I-131 mIBG can be easily prepared by heating a mixture containing 0.5-2.0 mg of mIBG hemisulfate, 12 mg of ammonium sulfate, and the appropriate radioiodide. After two 45-60 min heating cycles in the dry state, radioiodinated mIBG is formed in high yield and with an average radiochemical purity in excess of 97%. The I-131 compound is currently commercially available; the I-123 compound must be manufactured on-site under a Physician sponsored Investigational New Drug Exemption.

Radiopharmaceuticals may also be produced by biological synthesis. Before the chemical synthesis of Vitamin B_{12} was elucidated, ^{57}Co labeled vitamin B_{12} was made by placing $^{57}CoCl_2$ in a broth containing streptomyces griseus. This resulted in the biological production of ^{57}Co labeled vitamin B12. By a similar process, yeast growing in a medium high in ^{75}Se and low in sulfur produced ^{75}Se selenomethionine, a radiopharmaceutical formerly used for pancreatic imaging.