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Altered Biodistribution of Radiopharmaceuticals: Role of Radiochemical/Pharmaceutical Purity, Physiological, and Pharmacologic Factors

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One of the most common problems associated with radiopharmaceuticals is an unanticipated or altered biodistribution, which can have a significant clinical impact on safety, scan interpretation, and diagnostic imaging accuracy. In their most extreme manifestations, unanticipated imaging results may even compromise the utility and or accuracy of nuclear medicine studies. We present here an overall summary of altered biodistribution of radiopharmaceuticals with a special emphasis on the molecular mechanisms involved. Important factors affecting the biodistribution of radiopharmaceuticals can be described in 5 major categories and include (1) radiopharmaceutical preparation and formulation problems; (2) problems caused by radiopharmaceutical administration techniques and procedures; (3) by changes in biochemical and pathophysiology; (4) previous medical procedures, such as surgery, radiation therapy and dialysis; and finally (5) by drug interactions. The altered biodistribution of ^{99m}Tc radiopharmaceuticals are generally associated with increased amounts of ^{99m}Tc radiochemical impurities, such as free $^{99m}TcO_4^-$ and particulate impurities, such as ^{99m}Tc colloids or ^{99m}Tc-reduced hydrolyzed species. Faulty injection, such as dose infiltration or contamination with antiseptics and aluminum during dose administration, may cause significant artifacts. The patient's own medical problems, such as abnormalities in the regulation of hormone levels; failure in the function of excretory organs and systems, such as hepatobiliary and genitourinary systems; and even simple conditions, such as excessive talking may contribute to altered biodistribution of radiopharmaceuticals. Previous medical procedures (chemotherapy, radiation therapy, dialysis) and drug interaction are the some of the nontechnical factors responsible for unanticipated biodistribution of radiotracers. This review provides a comprehensive summary of various factors and specific examples to illustrate the significance of altered biodistribution of radiopharmaceuticals.

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Nuclear scintigraphy determined on the basis of radiopharmaceuticals has been practiced for more than 50 years. In recent years, designer radiopharmaceuticals or molecular imaging probes have been developed to image in vivo biochemical, physiological, and pathologic processes by the use of positron emission tomography/computed tomography (PET/CT) and single-photo emission computed tomography/computed tomography (SPECT/CT) scanners. There are, however, several problems associated with the clinical use of traditional and molecular imaging radiopharmaceuticals. The etiology of most of these problems can be classified into 4 major categories[1] as shown in Table 1. One common result creates an unanticipated or unusual imaging finding. Other common results go undetected, particularly if they mimic pathology or mask underlying disease. Not surprisingly, these cases can have a significant clinical impact in safety, scan interpretation, and diagnostic imaging accuracy. In their most extreme manifestations, unanticipated imaging results may even compromise the utility and or accuracy of nuclear medicine studies. There are many factors both extraneous and in vivo that can alter the normal biodistribution of radiopharmaceuticals. It is important to recognize these factors and to understand the specific mechanisms involved in the altered biodistribution to avoid both false-positive and false-negative interpretation of scans. Over the years, several au-

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Table 1 Classification of Problems Associated With Clinical Use of Radiopharmaceuticals[1]

Unanticipated/unusual imaging results	Altered Biodistribution	Radiopharmaceutical formulation problems
		Pathophysiologic interference
		Concomitant drug therapy
		Latrogenic trauma
		Radiation therapy
		Blood transfusion
		Renal/peritoneal dialysis
		Inappropriate route of dose administration
	Imaging artifacts	Sequencing artifacts
		Operator error
		Instrumentation failure
		Patient-induced error
		Other imaging artifacts
	Normal anatomic variants	
Considerations for special patient populations	Considerations	Radiation safety
		Dosimetry
		Patient preparation
	Special populations	Pregnancy
		Breastfeeding
		Pediatric
		Geriatric
		Dialysis
		Incontinent/catheterized
		Miscellaneous
Adverse reaction/untoward effects		
Patient care, quality assurance failures	Medication errors	
	Misadministration/recordable events	
	Blood handling/reinfusion errors	
	Improper preparation or execution of diagnostic and therapeutic procedures	
	Other problems resulting in inferior patient outcomes	

thors[2-9] have reviewed extensively the various factors contributing to the altered biodistribution of radiopharmaceuticals.

We present here an overall summary of altered biodistribution of radiopharmaceuticals with a special emphasis on the molecular mechanisms involved. Several other articles in the current and previous issues of the journal address the factors involved in the altered biodistribution of [^{18}F]fluorodeoxyglucose (FDG), radioiodide, and ^{99m}Tc radiopharmaceuticals.[10-15] To understand the various factors contributing to the altered biodistribution of radiopharmaceuticals, it is first important to understand the "tracer principle," the specific mechanism(s) involved in the "normal" biodistribution of a radiopharmaceutical.

The "Tracer Principle"

In the 1920s George de Hevesy coined the term *radioindicator* or *radiotracer*, which introduced the *tracer principle* in biomedical sciences.[16] One of the most important characteristics of a tracer is the ability to study the components of a homeostatic system without disturbing their function. The term *homeostasis* is used by physiologists to mean maintenance of static, or constant, conditions in the internal environment by means of positive and negative feedback of information.

A radiotracer can be defined as a specific radiolabeled molecule (or probe) that resembles or traces the in vivo behavior of a natural molecule and can be used to provide information about a specific biological process.[16] The degree of similarity between radiotracer and the natural substance, however, may vary depending on the particular radiotracer. For example, [^{11}C]glucose and [^{14}C]glucose are "true" tracers of glucose because they are chemically identical to natural glucose, whereas [^{18}F]FDG is an analog of glucose that does not behave identically as it is chemically a different molecule. One of the most important characteristics of a true radiotracer, however, is the ability to study the components of a homeostatic system without disturbing their function. Occasionally, the term *radioligand* is also used in the context of imaging studies. Radioligand can be defined as any radiolabeled molecule that can bind with another molecule or substance (binder) in a predictable way under controlled conditions. For example, [^{11}C]raclopride is a radioligand that binds specifically to dopamine D_2 receptors, whereas fluorine-18-L-dihydroxyphenylalanine ([^{18}F]FDOPA) is a radiotracer to image dopamine metabolism.

Radiopharmaceutical

The terms, radiotracer, radioligand, and radiolabeled molecular imaging probe each have specific meaning depending on their clinical context. From a regulatory point of view, the term radiopharmaceutical represents any radiolabeled molecule intended for human use. All radiolabeled compounds or substances used for diagnosis or therapy have been defined as *radioactive drugs* or *radiopharmaceuticals* by the US Food and Drug Administration (FDA). From a regulatory point of view, however, a radiopharmaceutical must also be sterile, pyrogen free, safe for human use, and efficacious for a specific indication. In contrast, radiochemical is not an FDA-approved agent for routine human use. It is important to remember that diagnostic radiopharmaceuticals, however, are administered in trace amounts ($<100\ \mu g$), and typically, do not induce any physiological response or pharmacologic effect in patients.

Factors Affecting the Biodistribution of Radiopharmaceuticals

Although several problems are associated with the clinical use of radiopharmaceuticals (Table 1), important factors affecting the biodistribution of radiopharmaceuticals can be described in the following 5 major categories:

- factors associated with radiopharmaceutical preparation and formulation;
- factors caused by radiopharmaceutical administration techniques and procedures;
- factors caused by pathophysiological and biochemical changes;
- factors caused by medical procedures; and
- factors associated with drug therapy or drug interaction

The physicochemical factors and molecular mechanisms involved in the altered biodistribution of radiopharmaceuticals caused by the aforementioned factors will be described here briefly with specific examples. To understand the basis and mechanisms involved in the altered biodistribution, it is first important to appreciate the quality control criteria and mechanism(s) of radiopharmaceutical localization.

Radiopharmaceuticals: Quality Control Criteria

Although alterations in the biodistribution of radiopharmaceuticals may be related to several factors unrelated to the quality of radiopharmaceutical preparation, the purity and quality of a radiopharmaceutical preparation has a pronounced effect on the in vivo behavior of radiopharmaceutical, the subsequent scan interpretation, and the diagnostic accuracy of the imaging procedure.[3,4]

Before the administration of a radiopharmaceutical into a human subject, several quality control tests need to be performed. These tests generally fall into 2 different categories; the physicochemical tests are essential to determine the, chemistry, purity, and the integrity of a formulation, whereas the biological tests establish the sterility and apyrogenicity of the radiopharmaceutical. Because the defects in radiopharmaceutical formulation are usually observed in the patient as an altered biodistribution, following quality control tests need to be performed:

Radionuclidic Purity (RP)

It is defined as the fraction of total radioactivity present in the form of desired radiopharmaceutical. RP depends on the quantities of desired radionuclide and other radionuclide contaminants, the relative half-lives of all the radionuclides, and changes in the quantities of radionuclides with time. The most common examples are ^{99}Mo contaminant in ^{99m}Tc radiopharmaceuticals and ^{125}I or ^{124}I contaminants in ^{123}I labeled radiopharmaceuticals.

Radiochemical Purity

It is the fraction of the total radioactivity in the desired chemical form of a radiopharmaceutical. Several radiochemical impurities in a radiopharmaceutical formulation may form during radiolabeling process (Table 2) or may arise because

Table 2 Expected Biodistribution of Radiochemical Impurities in Radiopharmaceuticals

Radiopharmaceutical	Factors	Impurity	Biodistribution
^{99m}Tc agents	Radiochemical (RC) impurities	Free $^{99m}TcO_4^-$	Uptake in stomach, gastrointestinal tract, thyroid, salivary glands
		^{99m}Tc-RH colloid, ^{99m}Tc-Sn(OH)$_n$ colloid	Phagocytized by the cells of RES located in liver, spleen and bone marrow
		^{99m}Tc particles ($>10\ \mu$)	Physically lodged in pulmonary capillaries
		Hydrophilic impurities	Uptake in kidney and bladder
		Lipophilic impurities	Uptake in liver and GI tract
	Chemical impurity (Al^{3+} ion)	^{99m}Tc colloids and particles	Uptake in the lung and RES
^{111}In agents	RC impurities	Free ^{111}In (^{111}In-DTPA)	Urinary excretion, bladder activity
		Free ^{111}In (as ^{111}In-transferrin or ^{111}In-RBCs	Increased blood pool and background activity
^{123}I/^{131}I agents	RC impurities	Free iodide (I^-)	Uptake in stomach, gastrointestinal tract, thyroid, salivary glands

of decomposition as the result of unwanted chemical reactions or even because of radiolysis. Unacceptable amounts of radiochemical impurities in a radiopharmaceutical preparation would result in altered biodistribution and poor image quality. The presence of free ^{99m}Tc pertechnetate (>5%-10%) in ^{99m}Tc radiopharmaceuticals and free radio iodide (>5%) in radioiodinated radiopharmaceuticals are the most common examples of radiochemical impurities.

pH and Ionic Strength

The pH of a radiopharmaceutical intended for intravenous administration ideally should be very close to the pH of blood (~7.4). Significant change in pH, ionic strength, and osmolality of a radiopharmaceutical formulation may degrade the in vitro stability and alter the subsequent in vivo behavior or biodistribution.

Particle Size

Certain radiopharmaceutical preparations may consist of radiolabeled particles in the form of particulate suspension. Radiolabeled colloidal or macroaggregate particles should have a proper size range for a specific organ uptake or biodistribution. For example, ^{99m}Tc-MAA particles (10-100 μ) block the capillaries in lungs, whereas ^{99m}Tc-sulfur colloid (SC) particles (0.1-1.0 μ) are taken up by Kupfer cells in reticuloendothelial system (RES) of liver, spleen, and bone marrow.

Specific Activity

It is defined as the amount of radioactivity per unit mass of a radionuclide or radiolabeled molecule. Specific activity is generally expressed as mCi/mg or mCi/μmol. Carrier is defined as the nonradioactive isotope of an element or a molecule. For example, with ^{99m}Tc radiopharmaceuticals, the presence of ^{99}Tc (2.111×10^5 year) can be considered as a carrier, while in the case of ^{111}In-pentetrotide (Octreoscan), the free diethylene triamine pentaacetic acid (DTPA)-octreotide precursor or the drug octreotide (Sandostatin) is regarded as the carrier.

Mechanisms of Radiopharmaceutical Localization

Radiopharmaceuticals can generally be classified on the basis of their unique mechanism of localization in a specific organ/tissue of interest or based on their ability to image a specific physiological and/or biochemical process. For example, ^{99m}Tc-MAA uptake in lungs is due to the blockade of capillaries in lungs by MAA particles > 10 μ. However, the lung scan obtained after intravenous administration of ^{99m}Tc-MAA can be used to assess pulmonary perfusion indirectly. In contrast, FDG is a specific substrate for the enzyme hexokinase necessary for glucose metabolism in vivo. The transport of FDG into cells is dependent on the number of glucose transporters (GLUT) and their subtypes on the cell membrane. The FDG-PET scan reflects altered glucose metabolism in different cell types and may, however, provide useful diagnostic information to detect malignant tissue or simply even cell viability.

Various mechanisms involved in the localization of clinically useful and FDA-approved radiopharmaceuticals are summarized in Table 3. The localization of a radiopharmaceutical in a specific target organ or tissue of interest may, however, depend on 3 important phenomena:

- Plasma protein binding, metabolism in blood, blood clearance, and transport of radiopharmaceutical to the target organ or tissue of interest;
- Transport of radiopharmaceutical from capillaries into the extracellular fluid and subsequent transport into the cells through cell membrane (transport processes, such as simple diffusion, facilitated diffusion, active transport and receptor mediated endocytosis, do all play very important role in the localization of the radiotracer at the target site); and
- Localization at the target site and intracellular trapping, which may be caused by any one of these following biochemical processes:
  - specific binding to receptors or on the cell membrane or within the cell;
  - specific binding to extracellular or intracellular antigens;
  - specific interaction with intracellular enzymes involved in the intracellular metabolism; of radiopharmaceuticals and the subsequent trapping of metabolites; or
  - incorporation into the biochemical synthesis of intracellular proteins or DNA.

Knowledge of transport and intracellular localization mechanisms of a given radiopharmaceutical is essential to understand various factors responsible for the altered biodistribution of a radiopharmaceutical.

Factors Associated With Radiopharmaceutical Preparation and Formulation

On the basis of chemistry, various radiopharmaceuticals used in nuclear medicine/molecular imaging can be grouped into 4 major categories.

- ^{99m}Tc radiopharmaceuticals;
- Radiopharmaceuticals based on group III metals;
- Radioiodinated radiopharmaceuticals; and
- PET radiopharmaceuticals

A brief description of chemistry, radiolabeling methods, and the purity of radiopharmaceutical preparations are described in the section to follow with special emphasis on the factors contributing to the altered biodistribution.

^{99m}Tc Radiopharmaceuticals

The altered biodistribution of ^{99m}Tc radiopharmaceuticals are generally associated with increased amounts of ^{99m}Tc radiochemical impurities (Table 3), such as free $^{99m}TcO_4^-$ and particulate impurities, such as ^{99m}Tc colloids or ^{99m}Tc-reduced hydrolyzed species (^{99m}Tc-RH).[9,17] In addition, to

Table 3 Mechanism(s) of Localization of Radiopharmaceuticals

Mechanism	Radiopharmaceutical
Isotope dilution	^{99m}Tc-red blood cells (RBC)
Capillary blockade	^{99m}Tc-macroaggregated albumin (MAA)
Phagocytosis	^{99m}Tc-SC
Cell migration	^{111}In-oxine-white blood cells (WBC), ^{99m}Tc-HMPAO-WBCs
Cell sequestration	^{99m}Tc-RBCs (heat damaged)
Simple diffusion	^{133}Xe gas, ^{99m}Tc-pertechnegas [^{15}O]water
Diffusion and mitochondrial binding	^{99m}Tc-sestamibi (Cardiolite®)
	^{99m}Tc-tetrofosmin (Myoview®)
Diffusion and intracellular binding	^{99m}Tc-exametazine (HMPAO) (Ceretec®)
	^{99m}Tc-bicisate (ECD) (Neurolite®)
	^{99m}Tc-(DMSA)
Diffusion and increased capillary permeability	^{67}Ga-citrate
Facilitated diffusion	[^{18}F]fluorodeoxyglucose (FDG)
Active transport	
Na^+/I^- sodium iodide symporter (NIS)	^{123}I and ^{131}I sodium iodide (I^-)
Na^+/K^+ ATPase pump	^{201}Tl-thallous chloride (Tl^+)
	^{82}Rb-chloride (RB^+)
	[^{13}N]ammonia as ammonium ion (NH_4^+)
Ion exchange with hydroxyapatite	
Exchange with OH^- ion	[^{18}F]fluoride (F^-)
Exchange with Ca^{2+} or calcium phosphate	^{99m}Tc-medronate (MDP)
	^{99m}Tc-oxidronate (HDP)
Glomerular filtration	^{99m}Tc-pentetate (DTPA)
Tubular secretion	^{99m}Tc-merteatide (MAG3)
Metabolic trapping	
Glucose metabolism	[^{18}F]fluorodeoxyglucose (FDG)
Tissue hypoxia and acidic pH	^{67}Ga-citrate
Specific receptor binding	
Hepatocyte anionic receptor	^{99m}Tc-disofenin, DISIDA (Hepatolite®)
	^{99m}Tc-mebrofenin (Choletec®)
Somatostatin (SSTR2) receptor	^{111}In-pentetreotide (octreotide) (OctreoScan®)
Dopamine transporter	^{123}I-ioflupane (DaTSCAN)
Norepinephrine and serotonin transporters and energy-dependent type I amine uptake mechanism	^{123}I and ^{131}I-meta-iodobenzylguanidine (mIBG)
Antigen-antibody binding	
Carcino embryonic antigen	^{99m}Tc-arcitumomab (CEA-SCAN®)
PSMA	^{111}In-capromab pendetide (ProstaScint®)
CD20 antigen on B lymphocytes	^{111}In-ibritumomab tiuxetan (^{111}In-Zevalin®)
	^{90}Y-ibritumomab tiuxetan (^{90}Y-Zevalin®)
CD20 antigen on B lymphocytes	^{131}I-tositumomab (Bexxar®)

these common ^{99m}Tc impurities, certain radiopharmaceutical preparations, such as ^{99m}Tc-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) and ^{99m}Tc-MAG3 may also contain hydrophilic or lipophilic impurities of the active ingredient, resulting in altered biodistribution.

Factors Associated With ^{99m}Tc Generators

Carrier ^{99}Tc. The decay of ^{99m}Tc results in rapid buildup of carrier ^{99}Tc and decrease in specific activity of ^{99m}Tc pertechnetate (TcO_4^-) eluted from the generator. The amount of ^{99}Tc present in ^{99m}Tc pertechnetate eluate from a generator, therefore, depends on the time elapsed from the previous elution (Fig. 1). The ^{99m}Tc content in the eluate is generally expressed as a mole fraction (f) of ^{99m}Tc.[9] For example, a generator eluted only 3 hours after previous elution will contain mostly ^{99m}Tc atoms (73%). In contrast, a Monday morning elution (after 48 hours) will contain only a small fraction (13%) of ^{99m}Tc atoms. Because ^{99}Tc competes with ^{99m}Tc in labeling reactions, the total amount of ^{99}Tc atoms affects the labeling efficiency of ^{99m}Tc radiopharma-ceuticals, such as ^{99m}Tc-labeled red blood cells (^{99m}Tc-RBCs), ^{99m}Tc-HMPAO, ^{99m}Tc-DTPA, ^{99m}Tc-sulfur colloid (SC), ^{99m}Tc-MAG3, and ^{99m}Tc-sestamibi. As a result, unacceptable levels of ^{99m}Tc pertechnetate impurity may be present in the final injected dose.

Factors Associated With ^{99m}Tc Labeling When Using Cold Kits

The $^{99m}TcO4^-$ ion with an oxidation state of 7+ is chemically stable, unreactive, and does not label any molecule directly. In most ^{99m}Tc kits, previous reduction of ^{99m}Tc from 7+ oxidation state to lower a lower oxidation state (such as 5+ or 1+) is achieved by the use of stannous (Sn^{2+}) chloride as a reducing agent. The reduced ^{99m}Tc species are chemically very reactive and form complexes with a wide variety of che-

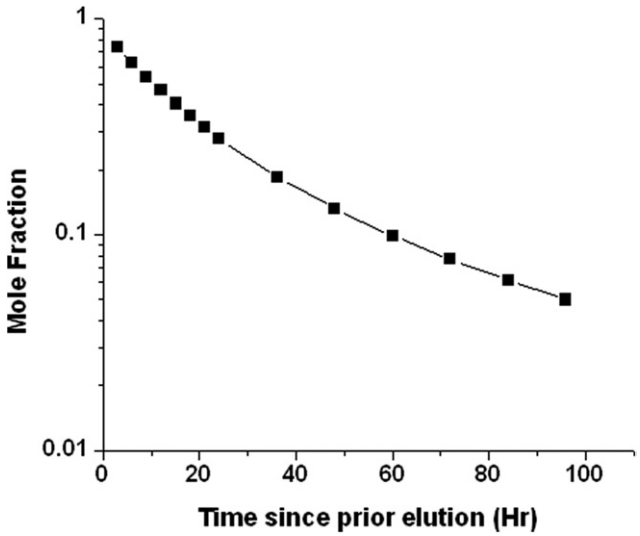

Figure 1 Mole fraction of ^{99m}Tc in ^{99m}Tc generator eluant at different times after elution.

lating agents, such as methylene diphosphate (MDP), DTPA, MAG3, and sestamibi.

Because the amount of ^{99m}Tc mass is very small ($\sim 10^{-9}$ M), only a small amount of Sn^{2+} ion (<1.0 μg) are needed. However, most ^{99m}Tc reagent kits contain large excess of stannous chloride. The reducing capacity of Sn^{2+}, however, is drastically reduced by a variety of factors, such as oxidation during storage and kit preparation. Therefore, optimal Sn^{2+} levels in the reagent kits are essential to minimize ^{99m}Tc impurities. Hydrolysis of excess stannous ion may result in the formation of ^{99m}Tc-stannous colloids, which subsequently are taken up by the RES.

Reagent Concentration. Most ^{99m}Tc kits are prepared by the use of 1 to 8 mL of ^{99m}Tc-pertechnetate solution. At greater volumes, the reagent concentration decreases, and as a result, the labeling efficiency may decrease resulting in higher levels of radiochemical impurities. It has been documented that in the preparation of ^{99m}Tc-DMSA, ^{99m}Tc-iminodiacetic acid (IDA) derivatives, and ^{99m}Tc-MAA, radiochemical impurities increase with decreased reagent concentration.

Factors Associated With Preparation Procedures

Mixing and Mixing Order. Optimal radiolabeling yields are achieved when the different components of the reaction mixture in the vial are adequately mixed; sometimes even the order in which different components are added or mixed may have a significant effect on the quality of the final formulation. In general, the chelating agent and the reducing agent (stannous chloride) must be mixed before ^{99m}Tc-pertechnetate is added to the reagent vial. If ^{99m}Tc interacts with Sn^{2+} in the absence of a chelating agent very high levels of ^{99m}Tc-stannous colloid impurity will be formed. The radiopharmaceutical preparations most affected by the mixing order are ^{99m}Tc-sulfur colloid and ^{99m}Tc-RBCs (using Ultra Tag RBC kit). Therefore, the procedure for the preparation of these agents must be carefully followed as described in the package insert.

Incubation. Although most ^{99m}Tc-chelates, such as ^{99m}Tc-MDP and ^{99m}Tc-DTPA, are formed very rapidly, some complexation reactions, such as ^{99m}Tc-MAG3 and ^{99m}Tc-sestamibi, require a substantial incubation time. Incubation times of approximately 10 to 30 minutes may be required to achieve maximal labeling. Also, excessive incubation times or excessive time delays between preparation steps can produce undesirable effects. For example, inferior labeling of ^{99m}Tc-MAG3 occurs if there is an excessive time delay (>5 min) before air is added or if there is an excessive time delay (>3 min) between the addition of air and boiling.[18]

Heating. Many ^{99m}Tc radiopharmaceutical preparations do require heating to accelerate the kinetics of chemical reaction. Insufficient or over heating may lead to poor radiolabeling or formation of radiochemical impurities. Several factors, such as temperature and duration of heating mixture, may affect the quality of the final product. In addition, heating of small volumes is more uniform and efficient than heating of large volumes. The preparation of ^{99m}Tc-SC, ^{99m}Tc-MAG3, and ^{99m}Tc-sestamibi, heating under optimal conditions as described in the package insert are essential to avoid formation of radiochemical impurities. For example, in the preparation of ^{99m}Tc-SC, the reaction of HCl with sodium thiosulfate ($Na_2S_2O_3$) is optimal at 95 to 100°C for 5 minutes. If the mixture is heated for an insufficient period, poor liver and splenic uptake can result; if it is heated for an extended period, lung uptake of large "colloidal" particles may result.[19] The chemical form and/or nature of a radiopharmaceutical may change during the incubation period, with resultant alteration in biodistribution. For example, bone-to-soft tissue ratios for ^{99m}Tc-MDP are reportedly greater after a 30- to 60-minute incubation period than after shorter incubation times, although the percentage labeling efficiency remains unchanged.[20] Similarly, when ^{99m}Tc-DTPA is used to determine glomerular filtration rate (GFR), it is recommended that the preparation is used within 1 hour of preparation; however, it has been observed that protein binding of ^{99m}Tc-DTPA to human serum albumin actually decreases over time, suggesting a radiochemical impurity that is minimized after 60 to 90 minutes of incubation.[21]

Factors Associated With In Vitro Stability

^{99m}Tc radiopharmaceuticals are generally stable for several hours (up to 8 h). Following radiolabeling, the stability of ^{99m}Tc radiopharmaceutical, may be affected by several factors.[22,23] For example, even large volume of ^{99m}Tc-DTPA and ^{99m}Tc bone agents may deteriorate due to generation of free ^{99m}Tc pertechnetate.

Oxidation/Reduction Reactions and Radiolysis. Also, oxidation caused by soluble oxygen, hydrogen peroxide (H_2O_2), or hydroperoxy free radicals ($\times$ HO_2) and even radiolytic decomposition, may all lead to increased levels of ^{99m}Tc-pertechnetate and/or ^{99m}Tc-colloid impurities. The radiolytic production of oxidizing agents in ^{99m}Tc-pertechnetate solutions is a contributing factor in the poor labeling efficiency and stability of ^{99m}Tc-HMPAO prepared with aged eluates.[24] In contrast, purposeful addition of oxidizing agents may be

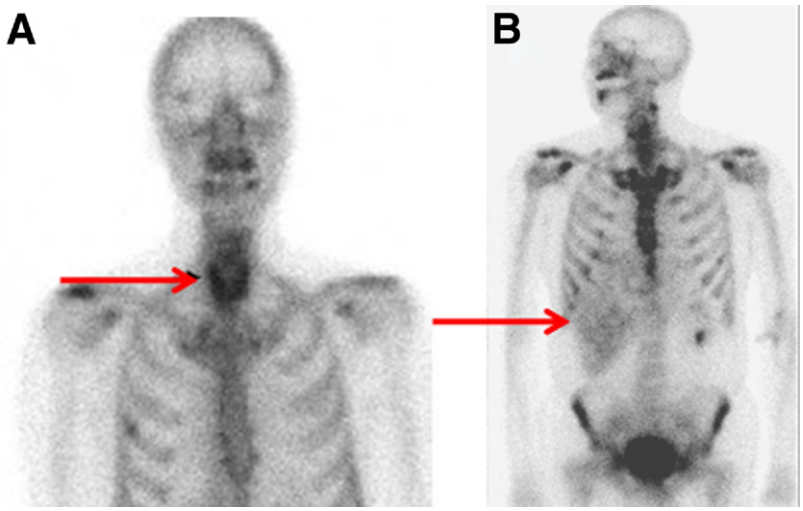

Figure 2 Altered biodistribution of ^{99m}Tc-MDP bone scan caused by radiochemical impurities. (A) Thyroid uptake caused by free ^{99m}Tc pertechnetate. (B) Diffuse liver uptake caused by ^{99m}Tc colloids. (Color version of figure is available online.)

required to produce a high labeling yield. For example, at least 2 mL of air must be added during the preparation of ^{99m}Tc-MAG3 to prevent the progressive formation of radiochemical impurities.[18] Similarly, oxygen bubbling will convert ^{99m}Tc-DMSA (trivalent complex), the traditional renal cortex agent, into ^{99m}Tc-DMSA (pentavalent) complex, a tumor-imaging agent.[25] Some radiopharmaceuticals are also vulnerable to chemical decomposition; for instance, hydrolysis of ^{99m}Tc-ECD after radiolabeling can lead to formation of its monoacid monoester product, which does not cross the blood–brain barrier.[26]

pH

Hydrogen ion concentrations have a dramatic impact on ionic equilibria, solubility, and oxidation/reduction reactions. Therefore, it is not surprising that pH affects the stability and purity of many radiopharmaceuticals. Significant alterations in pH of the labeling media can have marked effects on the radiochemical purity and/or stability of many ^{99m}Tc-labeled radiopharmaceuticals. Sn^{2+} solutions become insoluble and form colloidal precipitates at neutral and alkaline pH. With ^{99m}Tc bone agents, acidic pH formulations are ideal, but at neutral and alkaline formulations, poor bone affinity and kidney localization have been observed. Different radiolabeled complexes with significant differences in biodistribution have also been reported with ^{99m}Tc-DMSA and ^{99m}Tc-IDA formulations.[3] The stability of some radiopharmaceuticals is affected by pH. For example, ^{99m}Tc-sulfur colloid, ^{99m}Tc-HMPAO and ^{99m}Tc-MAG3 may decompose at pH values > 7.0 and form radiochemical impurities.[3]

Role of Aluminum Ion (Al^{3+}) Contamination

The interaction of Al^{3+} with several ^{99m}Tc radiopharmaceuticals is known to alter their biodistribution. The source of Al^{3+} is either breakthrough from the alumina column used in the ^{99m}Tc generator or because of leaching from aluminum-hub needles. The Al^{3+} from the generators may not be a problem with the current generators, but the leakage from syringe needles depends on pH and other factors. Even at very low concentrations (1.0 μg/mL), Al^{3+} reacts with phosphate buffer and forms insoluble aluminum phosphate.[27] ^{99m}Tc-SC coprecipitates with aluminum phosphate and the flocculated particles are trapped in the lung capillaries.[3] At higher concentrations ($>$10 μg/mL), Al^{3+} may react with ^{99m}Tc-MDP forming insoluble particles, which are taken up by the cells of RES in liver (Fig. 2) and spleen.[28] Altered biodistribution in the presence of excess Al^{3+} was also observed with ^{99m}Tc pertechnetate and ^{99m}Tc-DTPA.[3]

Radiopharmaceuticals Determined on the Basis of Group IIIa Metals

The 3 important metals (M) in group IIIa (or group 13) are gallium (Ga), indium (In), and thallium (Tl). These 3 metals are posttransition metals and have 3 electrons in the outer most shell. In contrast, yttrium (y), a transition metal has an incomplete *d* shell with 1 electron and 2 electrons in the outermost shell.

The aqueous chemistry of these metals is dominated by their ability to form strong complexes (both soluble and insoluble) with the hydroxyl ion. At neutral pH, Tl predominantly exists as a mono cation, $Tl(OH)_2^+$, and as a result, ^{201}Tl (as thallous chloride) is considered to behave similarly to potassium with respect to biochemistry and physiology.

In contrast, with Ga, in and Y, the fully hydrated M^{3+} ions are only stable under acidic conditions. Their coordination chemistry is somewhat similar and the most important oxidation state is M^{III}. As the pH is raised above 3, these metals form insoluble hydroxides ($M(OH)_3$) and the total solubility at physiological pH is very limited. Very high SA of radiometals is needed to keep them soluble in water. However, it is a common practice to add weak chelating agents (such as citrate, acetate or tartrate ion) to complex the metal and prevent precipitation at neutral pH. For example, ^{67}Ga is used in the clinic as ^{67}Ga-citrate. These 3 metals also share chemical

characteristics with the ferric ion (Fe^{3+}). This similarity with ferric ion is important in the development of radiopharmaceuticals because iron is an essential element in the human body and many iron binding proteins, such as transferrin in blood, do exist to transport and store iron in vivo. As a result, the atoms of iron always compete with these radiometals in vivo for specific binding with proteins, such as transferrin, lactoferrin, and ferritin.[29] For example, following intravenous administration of ^{67}Ga-citrate, ^{67}Ga, binds to transferrin in plasma and transported to tumor and infectious foci as "Ga-transferrin complex."[30] Several important radiopharmaceutical, preparation/formulation pitfalls, and artifacts associated with radiometals do generate radiochemical impurities responsible for the altered biodistribution.

Factors Associated With the Radionuclide

Specific Activity and Carrier. For the cyclotron produced radiometals (^{67}Ga,^{111} In, ^{201} Tl), the SA is very high and generally available as no-carrier-added (n.c.a) form, which means that the radiometal is produced without any addition of stable isotopes of the same element (specific carrier) in the system. The presence of excessive carrier in the ^{67}Ga citrate leads to a dramatic change in biodistribution, and ^{67}Ga becomes a bone-seeking agent.[31,32]

In labeling reactions, the presence of carrier decreases the incorporation rate of the radionuclide and therefore the SA of the radiopharmaceutical. The same effect arises by the presence of unspecific carriers, namely other metallic cations in the system. They can be either stable decay products of the radionuclide or external chemical impurities. Thus, di- and trivalent metals, such as Cu, Zn, Fe, and Ln, even at microgram levels were found to be strong competitors in the radiolabeling reactions.[33]

Commercial Source. There may be significant differences in the purity and formulation of radiometals supplied as radiopharmaceuticals or as radiochemicals for labeling reactions. In 1970s, different sources of ^{67}Ga-citrate were implicated in different localization characteristics in cerebral infarcts. The $^{111}InC1_3$ supplied with the octreotide kit and the $^{111}InC1_3$ specified for antibody labeling are not interchangeable. They differ in many ways, including buffer, pH, and trace metal ion concentrations, all of which can affect labeling yields and radiochemical purity.

Factors Associated With Preparation Procedures

Mixing Order and Incubation. In the preparation radiolabeled peptides and antibodies with ^{111}In and ^{90}Y, the order of mixing is very important. As described previously, ^{111}In chloride and ^{90}Y chloride hydrolyze at neutral pH and therefore are supplied in dilute hydrochloric acid. In the absence of a solubilizing ligand, such as citrate, the metal hydroxide will precipitate. The kits for the preparation of Octreoscan, ProstaScint, and Zevalin® include 3 components: $^{111}InCl_3$, acetate buffer, and the peptide or antibody. It is imperative that the directed amount of buffer be mixed with the $^{111}InCl_3$ before it is mixed with the peptide or antibody. Failure to follow this order of mixing and use the correct volume of buffer results in inadequate yields and radiochemical impurities, such as colloids (Table 2).

Most reactions involving chelating agents require an optimal incubation time (20-60 min) and temperature (25-45°C). For example, labeling of WBCs with ^{111}In or ^{99m}Tc requires an incubation time of at least 20 to 30 minutes. However, prolonged incubation and/or delay in reinjection (>3 hours) leads to significantly decreased viability of leukocytes.

Ingredients of the Incubating Medium. The presence of plasma transferrin reduces labeling yields for WBCs because it complexes ^{111}In much more avidly than does oxine.[34] With ^{111}In, the presence of transferrin or increased RBC contamination in the incubation mixture will cause binding to transferrin and RBCs and shows very high blood pool activity and increased uptake in spleen. It has been documented that if saline is used to rinse out the ^{111}In vial when DTPA-octreotide is labeled, radiochemical purity decreases due to trace metal ions in the saline. For ^{111}In-oxine-labeled WBCs, ACD solution is preferred as an anticoagulant because it decreases the adherence of neutrophils to the walls of the vessel and pipettes.[35]

Stability. Radiolytic generation of free radicals is a major factor responsible for degradation of radiolabeled preparation. Radiolytic decomposition, especially of disulfide bonds in the peptide molecule, decreases the stability and purity of Octreoscan. Similarly, the stability of ^{111}In and, especially ^{90}Y-labeled antibodies decreases with time and with increasing temperature. One of the potential problems with monoclonal antibody preparations is the precipitation of denatured protein particles, which will localize in the lung, liver, and/or spleen depending on their size. Similarly clumping and/or cellular damage of radiolabeled WBCs results in lung, liver, and/or spleen uptake. Radiolabeled proteins must be kept frozen to minimize the radiolysis effects. With ^{111}In-WBCs, if the handling and storage are done in saline instead of plasma, viability of labeled leukocytes decreases. A lower sensitivity for abscess detection was reported when the labeled cells were stored in saline for more than 1 hour.[3]

Aluminum Ions. Al^{3+} ions from aluminum hub needles may also have a significant effect on ^{111}In labeling reactions. For example, decreased labeling yields and purity with ^{111}In-pentetreotide (Octreotide®) have been observed. That is why a stainless-steel needle is supplied with the kit. ^{111}In-oxine may from a cloudy precipitate by reaction with Al^{3+} ion leached from the glass vials and tubes of some suppliers' vials. As a result, ^{111}In-WBC preparation may have unacceptable levels of radiochemical impurities, such as colloids and cell precipitates.

pH. As discussed earlier, pH has a dramatic impact on ionic equilibria and solubility of radiometals. The oxidation state of ^{201}Tl ions is strongly influenced by pH. An alkaline pH favors the formation of the desired thallous ions ($Tl(OH)_2^+$), whereas a low acidic pH favors the formation of thallic ions (Tl^{3+}), which may form complex ions that give thyroid and

RBCs uptake and/or hydrated colloids that are phagocytized by the RES.[36] In the preparation of OctreoScan® and ProstaScint®, the reagent kits contain citrate and acetate buffers, respectively, which help raise and maintain the pH at the optimum levels (pH 5-6) for improved labeling and stability of the carrier molecule, but also prevent hydrolysis of ^{111}In ions.

Specific Activity. SA is an important quality control parameter for target specific radiopharmaceuticals and the effects of decreased SA on biodistribution are most pronounced when the mechanism for localization of the agent shows saturation pharmacokinetics. Whenever a limited number of receptor sites, carriers, enzymes, or antigens are responsible for the localization, the carrier (the unlabeled molecule) will compete with the specific radiopharmaceutical for these limited sites; if saturation occurs, target-to-background radioactivity ratios will decrease.

Radioiodinated Radiopharmaceuticals

Iodine belongs to Group 7-A elements (halogens) and is characterized by the presence of 2 *s* electrons and 5 *p* electrons in the outer most valence shell ($5s^2\ 5p^5$). Among the radioisotopes of iodine, ^{123}I, ^{124}I, and ^{131}I have suitable physical characteristics for developing radiopharmaceuticals. Besides ^{131}I as sodium iodide, 2 other important radiopharmaceuticals used for therapy are ^{131}I-Bexxar® and ^{131}I-mIBG. ^{123}I as sodium iodide and several ^{123}I labeled investigational radiopharmaceuticals are used for imaging studies.

A total of 15 to 20 mg of iodine is concentrated in thyroid tissue and hormones, but 70% of the body's iodine is distributed in other tissues, including mammary glands, eyes, gastric mucosa, the cervix, and salivary glands. In the cells of these tissues, iodide enters directly by Na^+/I^- symporter.[37] The thyroid gland needs no more than 70 μg/d to synthesize the requisite daily amounts of T4 and T3, but the average daily dose is 150 to 300 μg. The US Food and Nutrition Board and Institute of Medicine recommended daily allowance of iodine ranges from 150 μg/d for adult humans to 290 μg/d for lactating mothers.

The free molecular iodine (I_2) has the structure of I^+-I^- in aqueous solution. However, the electrophilic species (I^+) does not exist as a free species but forms complexes with nucleophilic entities, such as water or pyridine. The hydrated iodonium ion, H_2OI^+ and the hypoiodous acid, HOI, are believed to be the highly reactive electrophilic species. In an iodination reaction, iodination occurs by (1) electrophilic substitution of hydrogen ion by an iodonium ion in a molecule of interest or (2) nucleophilic substitution (isotope exchange) where a radioactive iodine atom is exchanges with a stable iodine atom that is already present in the molecule.[9]

Several important factors that affect the altered biodistribution of radio iodide and radioiodinated radiopharmaceuticals are briefly discussed here. Anatomic and physiological variants in radioiodine studies are discussed in greater detail in this issue.[14]

Carrier. The dietary iodide, ^{127}I (carrier), and iodine-containing drugs alter the normal biodistribution and depress the uptake, especially by the thyroid gland. As little as 1.0 mg of stable iodide decreases the 24-hour uptake, and >10 mg virtually blocks the thyroid uptake of radio iodide.[38] The volatility of ^{131}I from therapeutic sodium iodide solutions increases at higher total iodide (radioactive + stable iodide) concentrations.[39]

Radionuclidic Impurities. The contamination of other radioisopes of iodine in ^{123}I sodium iodide capsules or liquis formulation depends on the nuclear reaction used for the production of ^{123}I in a cyclotron. ^{124}I (β+ emitter, $T_{½}$ = 100.8 hours) and ^{125}I ($T_{½}$ = 60 days) are the major radionuclidic impurities. Significant image degradation may be caused by Compton scatter and septal penetration from high-energy photons emitted by ^{124}I.

Commercial Source. Differences have been reported for the dissolution and bioavailability of radioiodine capsules.[40] ^{131}I-sodium iodide capsules from different sources have shown differences in thyroid uptake when compared with uptake measurements performed with liquid ^{131}I preparation.[41]

Radiolysis and Stability. Radiolytic generation of free radicals is a problem with ^{131}I because it emits high-linear energy transfer radiation. High specific concentrations and the high linear energy transfer of the particulate radiations result in a high level of free radical production and radiolysis. In radiopharmaceutical formulations of ^{131}I-mIBG and ^{131}I-Bexxar®, radiolysis generates radiochemical impurities, such as free ^{131}I iodide.[42] In case of ^{131}I-Bexaar®, radiolysis may decrease the immunoreactivity of labeled monoclonal antibodies. To prevent the effects of radiolysis, ^{131}I-Bexxar® is supplied frozen and is safe for use when it is kept frozen (at −20°C) for several days.

Volatility. The production of volatile airborne iodine occurs as the result of the oxidation of iodide by dissolved oxygen in slightly acidic solution. The use of buffers to increase the pH to alkaline levels or addition of reducing agents (sodium bisulfite or thiosulfate) will significantly lower the rate of volatility. Inhalation of gaseous iodine is a potential radiation safety problem and there may be significant radiation exposures to the thyroid glands of occupational workers.

Radiopharmaceuticals for PET

The 4 radiopharmaceuticals approved by FDA for routine clinical studies[43] are FDG, [^{18}F]fluoride, [^{13}N]Ammonia (NH_4^+ ion), and ^{82}Rb-chloride (RB^+). Because FDG is the only PET radiopharmaceutical widely used, some of the important factors responsible for the altered biodistribution are discussed in the sections to follow.

FDG and Fluoride

Among the halogens, fluoride ion (F^-) is more stable than iodide because fluorine is the most electronegative element and has only 1 oxidation state (−1). When a water ($H_2{}^{18}O$)

target is used, ^{18}F is generally produced in a cyclotron as [^{18}F]fluoride ion with a very high SA (>1 Ci/μmol). For bone imaging studies, [^{18}F]fluoride (n.c.a) injection is provided in physiological saline or phosphate-buffered saline with a very high radiochemical purity (>99%). The synthesis of [^{18}F]FDG is based on a nucleophilic fluorination reaction, using [^{18}F]fluoride and mannose triflate (precursor). The radiochemical purity must be >90%. The only major radiochemical impurity is [^{18}F]fluoride (<10%).

Factors Cause by Radiopharmaceutical Administration

Techniques and Procedures

Faulty Injection Technique

Infiltrated Injection. Most defects related to radiopharmaceutical administration are the result of extravascular or infiltrated activity at the injection site (Fig. 3).[3] When significant subcutaneous extravasation occurs in the antecubital region, regional lymph nodes can be visualized as the infiltrated radiopharmaceutical is partially cleared through the lymph vessels.[5] These defects, however, should not be mistaken for loci of abnormal uptake. For example, infiltration of ^{99m}Tc-MDP showed focal axillary uptake ipsilateral to the injection site.[44]

A potential harmful effect of extravascular injection is the radiation "burn" caused by the significant amount of local absorbed radiation dose from the infiltrated radionuclide,[3] especially if decays by pure β^- emission (eg, ^{131}I or ^{90}Y) or electron capture (eg, ^{201}Tl, ^{111}In or ^{67}Ga). Maximum radiation dose to the tissue, however, depends on the nuclide, activity and volume of infiltrated dose.[45] For example, infiltration of 74 MBq of ^{201}Tl may deliver up to 200 Gy (20,000 rads) radiation dose to the local tissue.[46] Specific corrective actions (such as local heat, massage, and steroid application) for infiltrated radiopharmaceuticals are recommended.[3]

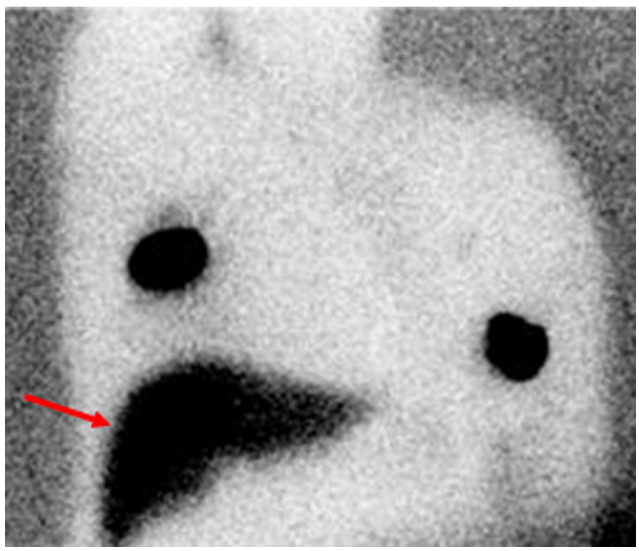

Figure 3 Bilateral lymphoscintigrapy with ^{99m}Tc-SC: One of the injections infiltrated the venous system causing reticuloendothelial uptake generally seen in a liver-spleen scan. (Color version of figure is available online.)

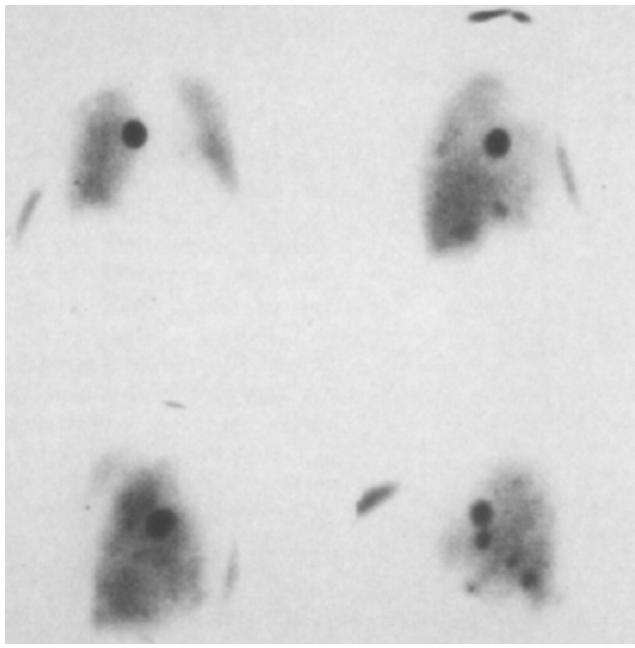

Figure 4 Lung scan showing blood clots. During intravenous administration of ^{99m}Tc-MAA, blood was first withdrawn into the syringe and labeled clots were subsequently reinjected.

Formation of Blood Clots in the Syringe. While radiopharmaceuticals are being injected intravenously, during back withdrawal of unanticoagulated blood into the syringe, blood clots may form.[3] The radiopharmaceutical could then bind to clots and localize in the lung.[47] Such focal "hot spots" in lungs (Fig. 4) have been observed following administration of ^{99m}Tc-MAA and ^{99m}Tc-albumin colloid.

Hang Up of Activity in Administration Lines. If the patient has difficult veins to access, central line or porta catheter injection of radiopharmaceuticals usually is required. Following administration of the radiopharmaceutical, if the line is not entirely flushed with physiological saline to remove any residual activity in the line, imaging artifacts may show up as focal or tubular activity because of the hang-up of activity at the tip or in the tubing. The administration of ^{99m}Tc radiopharmaceuticals via heparinized catheters may also produce artifacts. ^{99m}Tc may bind to heparin and the ^{99m}Tc-heparin complex may localize avidly in the kidneys.[3]

Patient Position During Radiopharmaceutical Administration. Decreased activity in the upper lobes of the lung perfusion scan (Fig. 5) with the use of either ^{99m}Tc-MAA or ^{99m}Tc-DTPA radioaerosol has been observed when the patient was sitting at the time of dose administration.[48]

Contamination of RP With Swab Antiseptic or Components of a Syringe. If an antiseptic used to swab the vial is not allowed to dry completely on the septum, the antiseptic may enter the vial when the syringe needle punctures the septum.

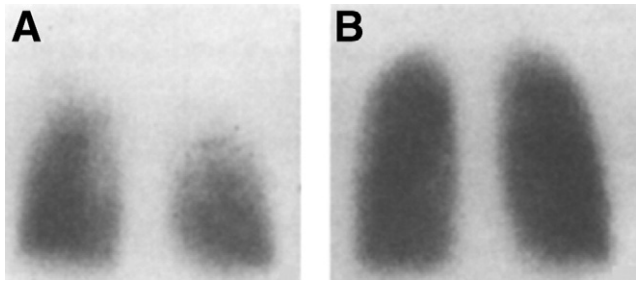

Figure 5 Lung perfusion scan with ^{99m}Tc-MAA. (A) Hypoperfusion of upper lobes when the patient was sitting at the time of injection. (B) Repeat scan on the next day shows normal perfusion while the patient was supine during the injection.

The antiseptic may interact with the radiopharmaceutical and produce radiochemical impurities (Fig. 6). The antiseptic proviodine has been reported to inhibit the ^{99m}Tc-SC labeling reaction and cause increase of free pertechnetate formation.[49] Chlohexidine was reported to have produced ^{99m}Tc colloid complex during ^{99m}Tc-DMSA preparation, and may also have caused aggregates in ^{99m}Tc-SC preparation.[3] Also, isopropyl alcohol was known to cause the breakdown of ^{99m}Tc-hydroxymethylene diphosphonate (HDP) into free ^{99m}Tc pertechnetate.[50]

Factors Caused by Pathophysiological and Biochemical Changes

Altered biodistribution of a radiopharmaceutical may sometimes be the result of unanticipated or atypical pathophysiologic and biochemical mechanisms often beyond those for which the study was originally indicated. A patient's own medical problems, such as abnormalities in the regulation of hormone levels; failure in the function of excretory organs and systems, such as hepatobiliary and genitourinary systems; and even simple conditions, such as excessive talking, exercise, and restlessness, may all contribute to the unexpected alterations in the biodistribution of radiopharmaceuticals. As discussed previously, an understanding of the normal pharmacokinetics, biodistribution, and mechanisms of radiopharmaceutical localization is very important to determine the pathophysiological basis for the altered biodistribution. Some of these factors as they are pertinent to specific radiopharmaceuticals are discussed in the sections to follow.

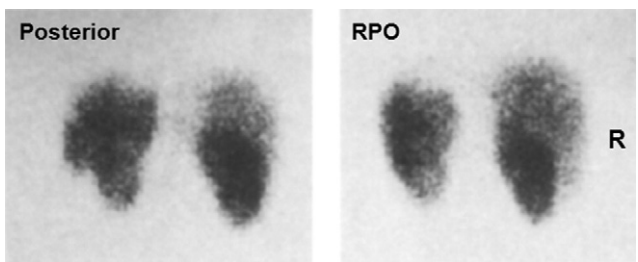

Figure 6 Kidney scan with ^{99m}Tc-DMSA contaminated with a bactericide. The images show abnormal uptake in liver and spleen.

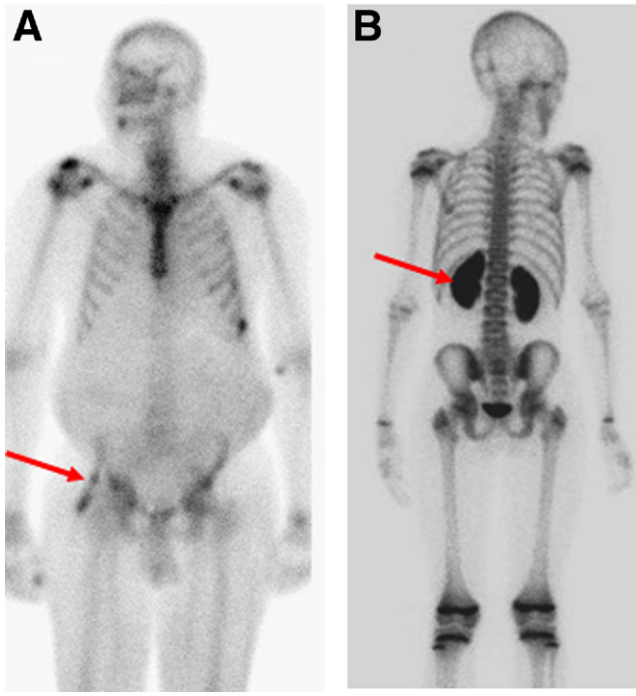

Figure 7 Altered biodistribution in ^{99m}Tc-MDP bone scans. (A) As the result of chronic renal failure, a peritoneal dialysis catheter and poor bony localization is seen. (B) As the result of acute renal insufficiency from chemotherapy-induced acute tubular necrosis, intense renal uptake is seen. (Color version of figure is available online.)

Bone Scan

The main mechanism of bone uptake of ^{99m}Tc agents and [^{18}F]fluoride is by ion exchange or chemisorption onto bone surface. The bone crystal, hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, has a surface composed of many different ions, including monovalent, divalent, and trivalent species of both positive and negative charge. ^{99m}Tc agents (MDP and HDP) appear to localize by cationic substitution for calcium ions. In contrast, [^{18}F]fluoride ions localize by anionic substitution for the hydroxyl ions (OH^-) forming fluoroapatite. The favorable properties of bone agents include their rapid clearance from plasma and high urinary excretion, which contribute to the high contrast between bone and soft tissue. Plasma protein binding may be significant (25%-55%) with ^{99m}Tc agents, whereas plasma protein binding of fluoride is negligibly small, and fluoride ions are freely filtered by the glomerulus. In general, uptake of [^{18}F] fluoride and ^{99m}Tc agents in bone, depend on local blood flow, osteoblastic activity and extraction efficiency. The bone uptake of fluoride was reported in both sclerotic and lytic lesions, while the uptake of ^{99m}Tc-MDP in lytic lesions is relatively insignificant.

Extraosseous uptake of ^{99m}Tc agents has been observed in several soft tissues, such as breasts, lungs, muscle, liver, calcified arteries and kidney.[11,51-53] In general the mechanisms of uptake in soft tissue are reported to be similar to those for bones.[11,51] Urinary contamination is a common problem,

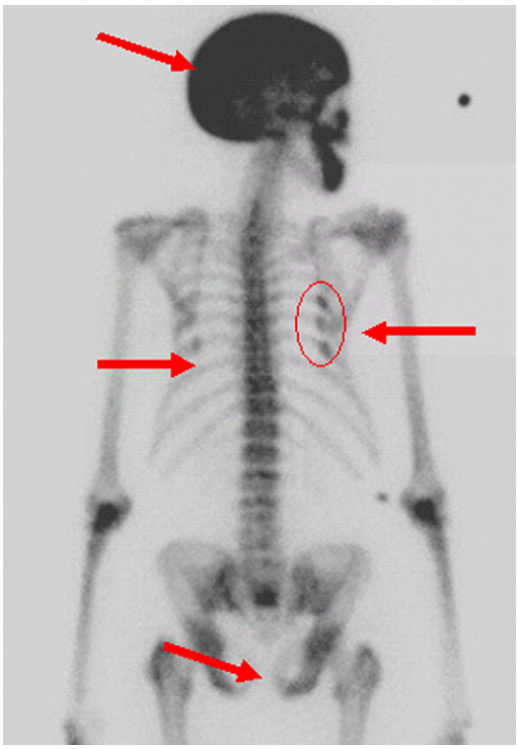

Figure 8 ^{99m}Tc-MDP "superscan" caused by hypercalcemia. Intense skull uptake with a paucity of excretory activity, posterior rib fractures and subperiostial resorbtion at the symphesis pubis are all clues. (Color version of figure is available online.)

which may simulate focal lesions, especially if close to or overlying the bone. Increased muscle uptake and poor contrast as the result of renal failure (Fig. 7) may degrade image quality significantly. "Super scan" appearance on bone scan (Fig. 8) as the result of hypercalcemia shows intense skull uptake with a paucity of excretory activity, posterior rib fractures and subperiostial resorbtion at the synphesis pubis, all indicating altered biodistribution.

Glucose Metabolism

The transport of glucose into cells is mainly through *facilitated diffusion*, also called *carrier-mediated diffusion*, because the carrier facilitates the transport of glucose into the cell. Insulin can increase the rate of facilitated diffusion 10- to 20-fold. Six isoforms of GLUT have been identified, which differ in kinetic properties, tissue location, etc. It has been shown that the overexpression of GLUT-1, GLUT-3, and GLUT-5 play a major role in increased transport of glucose by tumor cells. Glucose may also be transported into the cell by active transport, which mostly occurs in renal tubules and gastrointestinal membrane. As a glucose analogue, [^{18}F]FDG enters the cell membrane by using the same transporters as glucose. It is then phosphorylated into [^{18}F]FDG-6-phosphate. This metabolite is not a substrate for further enzymes and thus is trapped and accumulates inside the cell in proportion to the metabolism of glucose.[16] Although many tissues and cells accumulate FDG to a predictable extent, for example, the brain typically shows intense uptake of FDG, whereas myocardial uptake is intense in patients who have not fasted but highly variable in patients who have fasted, adipose tissue typically shows minimal FDG uptake. However, certain adipose deposits (so-called "brown fat") can be dramatically activated in a cold or nervous patient.[12]

Although many tissues and cells accumulate FDG to a predictable extent, for example, the brain typically shows intense uptake of FDG, whereas myocardial uptake is intense in patients who have not fasted but highly variable in patients who have fasted, the glycolytic activity of a given tumor is generally assumed to be characteristic of its state of differentiation. The extent of FDG uptake in tumors, especially untreated tumors, appears to relate directly to the number of viable cells. Inflammatory cells, especially macrophages, can sometimes accumulate FDG to a considerable extent, so inflammatory or infectious sites are sometimes visualized on PET. Adipose tissue typically shows minimal FDG uptake, but certain adipose deposits (so-called "brown fat") can be dramatically activated in a cold or nervous patient.[54]

One of the important factors making FDG-PET scan difficult to interpret is variable physiological uptake of FDG by normal tissues.[13,54-58] Altered biodistribution of FDG related is mainly because of hyperglycemia or hyperinsulinemia and bone marrow activation commonly encountered in cancer patients. Unlike glucose, FDG is not well reabsorbed by the proximal tubules of the kidney. Thus, it can be predicted that intense activity will be seen in the kidneys and bladder. How-

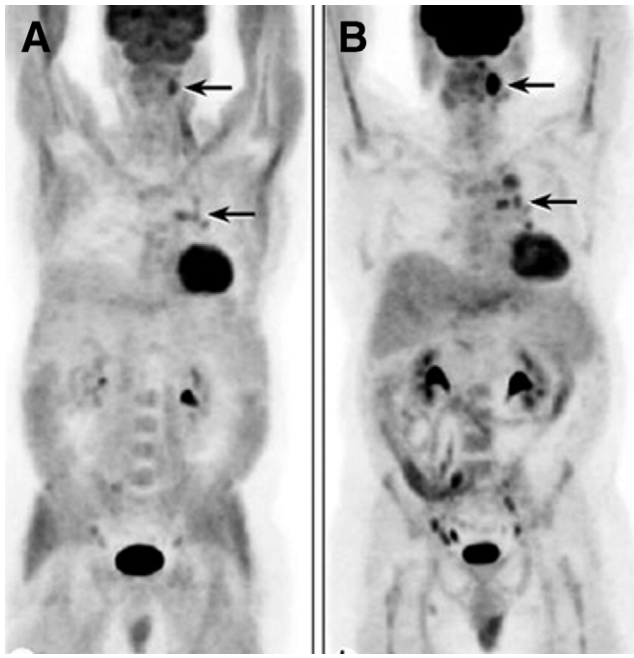

Figure 9 Effect of sudden increase in insulin levels on FDG-PET. In a patient undergoing staging of lymphoma, the FDG-PET scan (A) was performed after the patient had eaten a candy bar 30 minutes before FDG injection. Note the extensive myocardial and muscle uptake caused by high insulin levels. Diminished activity is seen in the brain and in tumor sites in the neck and chest (arrows). A repeat study (B) after the patient complied with routine fasting shows more normal biodistribution of tracer and better visualization of tumor foci (arrows).

ever, focal pooling of excreted activity in a ureter could be confused with a hypermetabolic iliac lymph node metastasis. Hyperglycemia and hyperinsulinemia are very important considerations when preparing a patient for a PET study with FDG. Acute hyperglycemia is a well-documented factor that reduces FDG uptake by the tumor tissue and augments muscular uptake but this effect has mostly been demonstrated with glucose-loading studies.[59] High levels of insulin will push FDG, along with glucose, into skeletal muscle and myocardium, increasing the image background and decreasing the availability of the tracer for uptake by the tumor.[60] Fasting is essential for the quality of the FDG-PET scan: altered tracer biodistribution caused by ingestion of even a small meal (Fig. 9) shortly before a FDG injection can impair the visualization of malignant lesions. In premenopausal women, increased ovarian or endometrial FDG uptake can be functional or malignant. Benign functional uptake of ovaries or uterus is related to the menstrual cycle.[61]

Myocardial Perfusion Imaging

Several SPECT and PET radiopharmaceuticals are available for imaging the relative myocardial perfusion or blood flow. The ideal flow tracer accumulates in or clears from myocardium proportionally linear to myocardial blood flow (MBF). The relationship between uptake and clearance of the radiotracer and MBF should be constant and independent of MBF, of physiological and pathologic changes of myocardial tissue state, and myocardial metabolism. Most radiotracers used for imaging myocardial perfusion/blood flow, however, do not fully meet these requirements.[62]

The PET tracers, [^{13}N]Ammonia (NH_3) and $^{82}Rb^+$ (as a K^+ analog) are actively transported into myocardial cells via Na^+/K^+ pump. The lipid soluble ammonia may also be transported into the myocardial cells by passive diffusion. Inside the cell, ammonia is quickly converted to ammonium ion which is rapidly converted and trapped as glutamine by the enzyme glutamine synthase.[62]

^{201}Tl (thallous chloride) at pH 4-7 predominantly exists as a mono cation, $Tl(OH)_2^+$, and like K^+ ion, it relies on cell membrane integrity and active metabolic transport using Na^+/K^+ pump for its uptake into myocardial cells. After initial localization, however, there is rapid redistribution of ^{201}Tl activity in the myocardium. In contrast, the ^{99m}Tc agent (cardiolite® or Myoview®) as a cationic complex, is transported into the myocardium by passive diffusion.[63,64] The subsequent myocardial retention is mainly due to mitochondial binding. Because tumor cells have a greater mitochondrial density than the surrounding epithelial cells, ^{99m}Tc-sestamibi also accumulates more avidly in tumor cells.[64]

The uptake and clearance kinetics of myocardial perfusion radiotracers, especially from liver and kidney, establish the tracer levels in the circulating blood, which in turn affects the myocardial tracer kinetics. Tracer activity in lungs and liver complicates imaging of the heart. The biodistribution of these tracers may also be affected by the level of exercise or the type of pharmacologic stress.[63]

Radio Iodide Scan

Sodium iodide (^{123}I and ^{131}I) is readily absorbed from the gastrointestinal tract. After absorption, the iodide is distributed primarily within the extracellular fluid of the body. It is concentrated and organified by the thyroid and trapped but not organified by the stomach and salivary glands. It is also promptly excreted by the kidneys. Stimulation of radioiodide uptake by the thyroid may be achieved by the administration of thyrotropin. Radioiodide will not be taken up by giant cell and spindle cell carcinoma of the thyroid nor by the amyloid solid carcinomas. The uptake of radio iodide will be affected by recent intake of stable iodine in any form, or by the use of thyroid, antithyroid, and certain other drugs. Accordingly, the patient should be questioned carefully regarding previous medication and procedures involving radiographic contrast media. A phenomenon known as thyroid stunning has been described in which a diagnostic dose (2-10 mCi) of ^{131}I sodium iodide decreases uptake of a subsequent therapeutic dose by remnant thyroid tissue or functioning metastases. Whether stunning is a temporary phenomenon whereby stunned tissue eventually rejuvenates, or whether observed stunning actually constitutes "partial ablation," is yet to be delineated.[65] Radioiodine is excreted in human milk during lactation.

Several potentially misleading artifacts can arise from contamination by physiological or pathologic secretions derived from those organs that are capable of uptake and excretion of radioiodine (Table 3). These include urine, saliva, nasal secretions, other respiratory tract secretions, sweat, vomit, and breast milk (Fig. 10). False-positive radioiodine scans in thyroid cancer attributable to anatomic and physiological variants, such as (1) contamination by physiological secretions, (2) abnormalities of gastrointestinal uptake, (3) urinary tract abnormalities, (4) mammary uptake, (5) uptake in serous cavities and cysts (pleural, peritoneal, and pericardial effusions), (6) sites of infection/inflammation, and (7) nonthyroidal neoplasms have been extensively reviewed previously.[66,67]

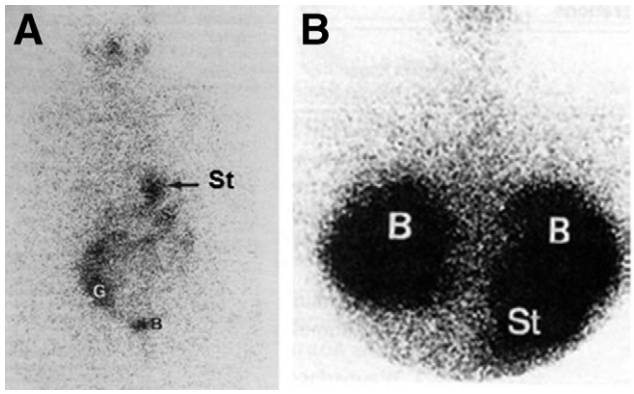

Figure 10 Diagnostic scan with of ^{131}I sodium iodide, 37 MBq, in patients after thyroidectomy. (A) normal biodistribution showing stomach and GI activity. (B) Abnormal breast uptake in a patient 1 week after weaning after 18 months of lactation.

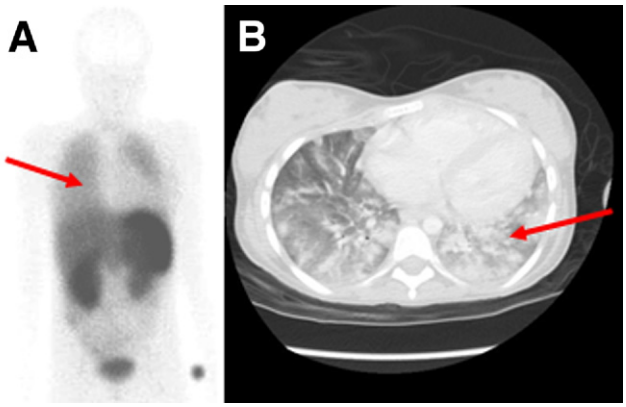

Figure 11 ^{111}In-Octreoscan (A) and axial CT lung window images (B). Unusual lung uptake of ^{111}In activity due to diffuse inflammatory processes (pulmonary interstitial fibrosis). (Color version of figure is available online.)

Infection/Inflammation

Inflammation is a complex tissue reaction to injury, specifically caused by or involves living microbes. Acute inflammation is the early or an immediate response to injury and is associated with many regional and systemic changes, such as vasodilation and increased vascular permeability. Several inflammatory cells, particularly polymorphonuclear leukocytes accumulate and aggregate at the site of inflammation. When the inflammation progresses to a chronic stage, the inflammatory cells are predominantly lymphocytes, plasma cells and fibroblasts. The two important radiopharmaceuticals routinely used for imaging infection/inflammation are leukocytes (WBCs) labeled with ^{111}In-xine or ^{99m}Tc-HMPAO (Ceretec®) and ^{67}Ga-citrate.[68] The radiolabeled cell preparations are the only target specific radiopharmaceutical localizing at the site of acute inflammation caused by cellular migration.

^{67}Ga-citrate is a nonspecific agent and the localization at the sites of inflammation is mostly due to the leakage of ^{67}Ga-transferrin complex from blood into the extracellular fluid space of the inflamed tissue. The acidic pH at the site of infection, favors dissociation of 67 Ga from transferrin with subsequent ^{67}Ga binding to other iron-binding proteins, such as lactoferrin in the extracellular fluid or within the inflammatory cells. Because tracer amounts of ^{67}Ga administered dose (<50 ng) is bound to transferrin, any physiological and pathologic conditions decreasing the iron binding capacity of transferrin (such as iron-overload), would significantly alter the biodistribution of ^{67}Ga-citrate.

Receptor Imaging

The term receptor is generally used to denote a specific cellular binding site for a small ligand, such as peptide hormones and neurotransmitters. Because the mechanism of localization of receptor binding radiopharmaceuticals is specific and depends on receptor expression on target cells, multiple factors representing many characteristics of the radiopharmaceutical will influence the uptake of radiotracer in the target tissue, image quality, and ultimately the clinical utility of these agents. The major factors include (1) blood clearance, (2) specific activity, (3) affinity of the tracer, (4) in vivo stability, (5) nonspecific binding, and (6) blood flow and perfusion of tissue or organ of interest. The pathophysiological mechanisms involved with some of the receptor binding radiopharmaceuticals are discussed below:

Hepatobiliary System

^{99m}Tc-labeled IDA derivatives (disofenin [Hepatolite®] and mebrofenin [Choletec®]) are negatively charged lipophilic complexes, extracted by liver via the anionic receptors on hepatocytes, and excreted into the bile duct, the gall bladder, and ultimately into the intestine. In fasting individuals, the maxim microliter amount of liver uptake occurs approximately by 10 minutes and peak gall bladder activity by 30 to 60 minutes after injection. The mechanism for the clearance of ^{99m}Tc-hepatobiliary agents involves hepatic extraction, hepatocyte binding, storage, and excretion into biliary canaliculi by an active transport process.[9] Because bilirubin competes more avidly with the anionic receptor sites on the hepatocytes, the liver uptake of ^{99m}Tc disofenin and mebrofenin is compromised at high bilirubin levels. In acute cholecystitis, prolonged fasting, acute pancreatitis, and severe liver disease can lead to nonvisualization of gall bladder. Cholecystokinin (CCK), synthetic CCK (Kinevac), and even fatty meal will cause the gall bladder to contract and the sphincter of Oddi to relax, and increases the secretion of bile.

Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms originating from endocrine cells, which are characterized by the presence of secretory granules as well as the ability to produce biogenic amines and polypeptide hormones, such as somatostatin (SST). The diverse biological effects of SST are mediated through a family of G protein coupled receptors of which 5 subtypes (SSTR1-5) have been identified by molecular cloning.[47] Because most NETs express SSTR-2 subtype, they can be successfully targeted with high SA, ^{111}In-DTPA-pentetreotide or OctreoScan®.[69] Nor-

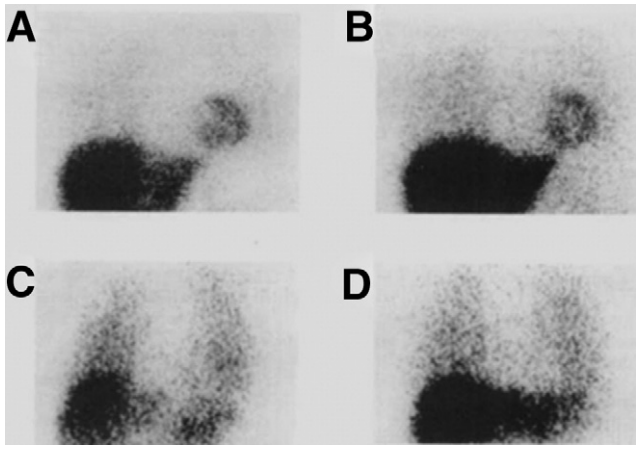

Figure 12 ^{131}I-MIBG scan: Planar cardiac early (A) and delayed (B) images in a normal subject. In contrast, the early (C) and delayed (D) images in a patient with Parkinson's disease show minimal or absent myocardial uptake of MIBG.

mal scintigraphic pattern includes visualization of organs, which express SST receptors, including the thyroid, spleen, liver, kidneys and, in some patients, the pituitary. Other organs are depicted at different times because of tracer excretion, including the renal collecting system and urinary bladder, gallbladder, and bowel. Any uptake in nonphysiological areas reflects the presence of lesions with increased density of SST receptors, which can be related to malignant but sometimes also to benign lesions. Altered distribution of Octreoscan images (Fig. 11) show aberrant lung uptake in a patient with diffuse inflammatory processes, such as pulmonary interstitial fibrosis.

Adrenergic Presynaptic Receptors and Storage

Tumors arising from the neural crest share the characteristic of amine precursor uptake and decraboxylation and contain large amounts of adrenaline, dopamine and serotonin within the secretary granules in cytoplasm. Tumors of the adrenergic system include pheochromocytoma (arise in adrenal medulla) or paragangliomas (extraadrenal tissue) and neuroblastomas. ^{131}I or ^{123}I labeled meta-iodobenzylguanidine (MIBG) is used specifically to depict and localize catecholamine-secreting tumors.[42] MIBG structurally resembles norepinephrine and, to some extent, shares its biological behavior in that it is taken up by an active, sodium- and energy-dependent amine uptake mechanism (uptake 1) in the cell membrane of sympathomedullary tissues and is stored into the intracellular catecholamine storing granules by another specific, active uptake mechanism.[69] The normal distribution usually shows uptake in the salivary glands, spleen, liver, and urinary bladder. Heart, lungs, colon, and kidneys were less frequently visualized. Thyroid and stomach uptake are primarily due to free radio iodide species due to in vivo dehalogenation.[42] Bilateral symmetric activity is sometimes evident in the neck and shoulders of children, and it seems to be related to uptake in brown adipose tissue. MIBG imaging is characterized by high specificity with very few (1%-5%) false-positive findings, ie, because of retention of radioactivity in the urinary tract, or the presence of adrenal hyperplasia following contralateral adrenalectomy or very rarely to non-NET or benign lesions.[69]

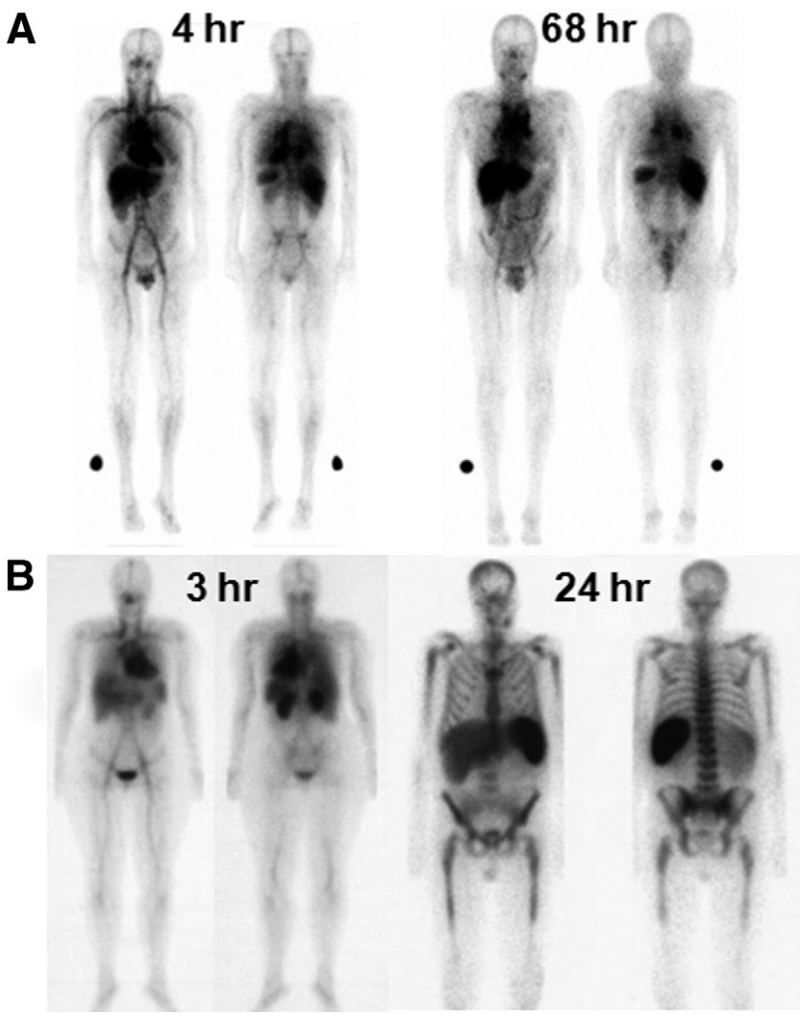

Figure 13 Biodistribution of ^{111}In-Zevalin®: (A) Normal distribution at 4 and 86 hours and patient eligible for therapy with ^{90}Y-Zevalin®. (B) Abnormal biodistribution at 3 and 24 hours showing increased bone marrow uptake. Patients is not eligible for therapy.

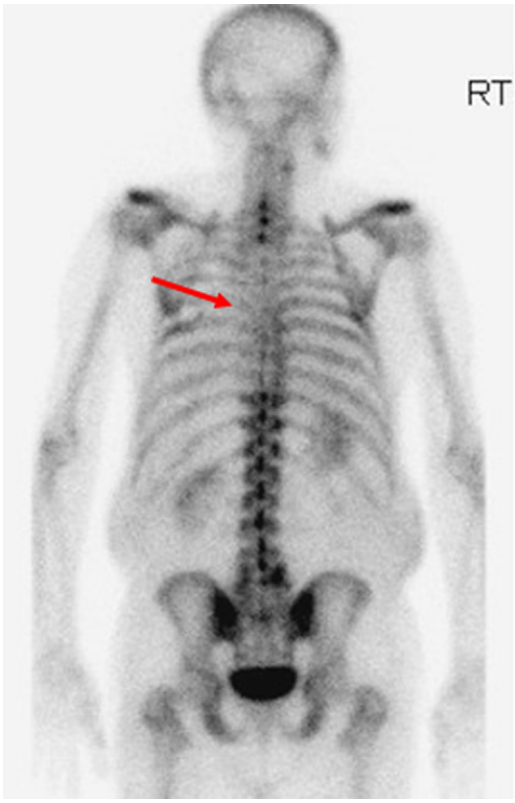

Figure 14 ^{99m}Tc-MDP bone scan demonstrating decreased thoracic spine uptake due to prior radiation therapy.

Because MIBG uptake is dependent on the expression of NET on the presynaptic adrenergic neurons of the heart, MIBG imaging has a diagnostic role in the assessment of patients with cardiomyopathy and heart failure.[70] MIBG cardiac uptake was shown to be significantly decreased (Fig. 12) in patients with dementia and movement disorders, such as Parkinson's disease.[71,72]

Antibody Imaging

Most cancer cells and synthesize many proteins or glycoproteins that are antigenic in nature. These antigens may be intracellular, or expressed on the cell surface or shed or secreted from the cell into extracellular fluid or circulation. Tumor-associated antigens and receptors present on the tumor cell surface include prostate-specific membrane antigen (PSMA) and CD20 antigen on lymphoma cells. The 3 important FDA approved radiolabeled monoclonal antibodies (mAbs) are ProstaScint® for diagnostic imaging and Zevalin® and Bexxar® for radioimmunotherapy.[73-76] Imaging studies with ^{111}In-Zevalin are essential to determine eligibility for radioimmunotherapy with ^{90}Y-Zevalin. In contrast, patients receiving ^{131}I-Bexxar therapeutic regimen involves obtaining 3 whole-body scans during the week after a small dose (185 MBq) of ^{131}I-Bexxar administered only for purposes of determining the residence time, which is necessary to determine the therapeutic dose. Imaging studies, however, are not performed to determine targeting or to assess biodistribution.

ProstaScint

PSMA is more highly expressed in malignant prostate cells compared with nonmalignant cells. A murine IgG_1 mAb (mAb 7E11-C5.3) Conjugated to the ^{111}In chelator GYK-DTPA to form the immunoconjugate, ^{111}In capromab pendetide (ProstaScint). There is a high degree of tumor binding to all prostate cancers tested in vitro and a very high degree of specificity. ProstaScint uptake by tumor cells in vivo is dependent on the degree of PSMA expression. PMSA may be expressed by a small number of nonprostatic malignant tumors (renal cell carcinoma and small cell carcinoma of the lung), and these can result in false-positive examinations.

ProstaScint imaging has been advocated in patients with newly diagnosed prostate cancer, who are at risk for advanced disease, and for patients treated with definitive local therapy (prostatectomy or radiation therapy) who present with increasing prostate-specific antigen levels.[73] The interpretation of ProstaScint SPECT images is challenging because of the low spatial resolution of SPECT, and the nonspecific antibody localizations in normal blood pool. Some nonantigen-dependent localization occurs, probably secondary to catabolism, in normal liver, spleen, and bone marrow. In

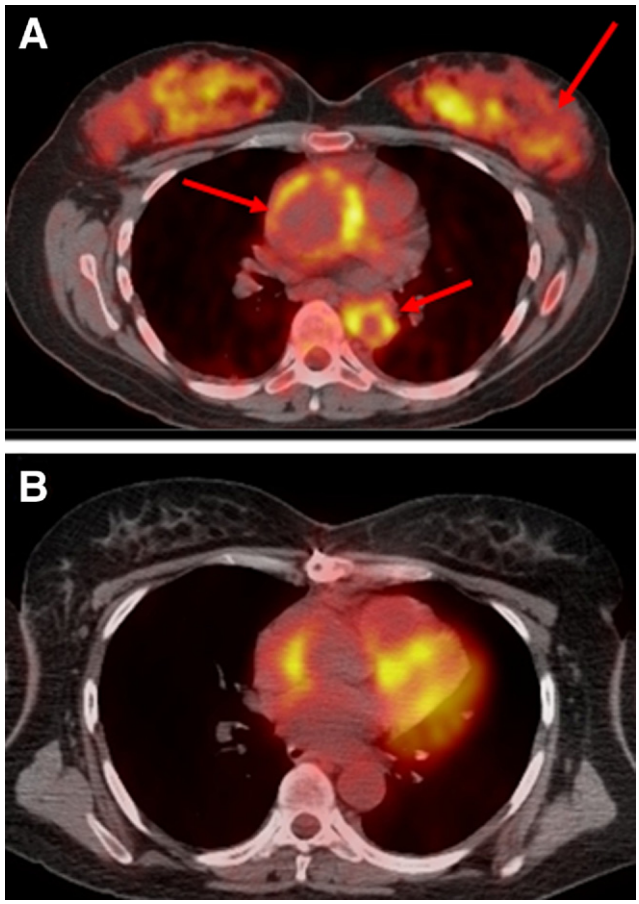

Figure 15 Axial FDG-PET/CT images at the level of the aortic root in a patient with Takayasu's arteritis. (A) A postpartum disease flair demonstrates transmural uptake at the aortic root and descending thoracic aorta. Bilateral breast activity is seen secondary to breastfeeding. (B) After methotrexate therapy and cessation of lactation, both abnormalities recede.

certain subjects uptake in bowel, kidneys, and genitalia has been observed. Human antimurine antibody caused by previous exposure to murine-antibody products may alter the clearance and biodistribution of ProstaScint. Also, other medical problems or conditions, such as aneurysms, abdominal or bowel adhesions, postoperative and colostomy or Inflammatory lesions may show unexpected uptake of radioactivity.

Zevalin®

The mAb moiety of Zevalin is ibritumomab, a murine IgG_1 kappa monoclonal antibody directed against the CD20 antigen on lymphocytes (B cells). Radioimmunotherapy with ^{90}Y-Zevalin is indicated for the treatment of relapsed or refractory, low-grade follicular or B-cell non-Hodgkin's lymphoma, including patients with rituximab-refractory follicular non-Hodgkin's lymphoma.[74,75] The therapeutic regimen consists of an imaging study first with ^{111}In-Zevalin (and rituximab 250 mg m^{-2}) on the day of injection, and again on days 2 to 3 to confirm appropriate biodistribution. Tumor uptake may be visualized; however, tumor visualization on the ^{111}In-Zevalin scan is not required for ^{90}Y-Zevalin therapy. The expected normal biodistribution includes (1) blood pool activity in heart, abdomen, neck, and extremities, (2) moderately high to high uptake in normal liver and spleen, and (3) moderately low or very low uptake in normal kidneys, urinary bladder, and normal (uninvolved) bowel. The criteria for altered biodistribution (Fig. 13) are (1) an intense uptake of the radiotracer in RES (liver and spleen and bone marrow), (2) diffuse uptake in normal lung more intense than the liver,

Table 4 Pharmacologic and Toxic Effects of Drugs

Group of Drugs	Drugs	Pharmacologic and Toxic Effect
Narcotic analgesics	Morphine, codeine, oxycodone, Percodan, Roxicodone, Demerol, methadone	Opioids constrict the Sphinctor of Oddi, which may cause nonvisualization of the intestine in hepatobiliary imaging
Xanthine (theophilline and caffeine) containing medications	Aerolate, Slo-Phyllin, Theolair, Anacin, Excedrin, Midol, Cafegot, coffee, Tea, and soft drinks	Block the vasodilatory effects of adenosine
Beta blockers	Acebutalol, atenolol, pindolol, propranolol, Tenerotec, Inderide	Prevent patients from reaching their target heart rate during treadmill stress test
ACE inhibitors	Losartan, valsartan, Ailskiren	Reduce GFR by blocking angiotensin II receptors or directly inhibiting the action of renin
MIBG interactions	Adrenergic neuron and NET blockers	Prevent MIBG uptake by inhibition of reuptake of norepinephrine or deplete storage vesicle contents
Calcium channel blockers	Verapamil, nifedipine, diltiazem, Lotrel, Lexxel	Interfere with stress testing and MIBG imaging studies
Cytotoxic drugs	Cyclophosphamide, vincristine, bleomycin,cis-platin, Nitrosoureas	Decrease membrane transport and intracellular retention of major ogans (liver, kidney)
Drugs altering hormonal status	Stilboestrol, gonadotrophins, oral contraceptives	Increase the production of estrogen. induce gynecomastia and hyperprolactinemia
Inhibitors of Na^+/I^- symporter (NIS)	Lugol's iodine, iodides, perchlorate, antithyroid drugs, contrast media (Hypaque, Dionosil, Diodrast)	Competitive inhibition of NIS by anions and prevent trapping of iodide by thyroid
Drugs that can cause iatrogenic disease	Paracetamol, aspirin, tetracycline	Cause liver toxicity and cause necrosis of liver cells
	Long-term use of contraceptive pill	Cause the formation of hepatic tumors
	Aminoglycoside antibiotics, penicillins, sulfonamides, frusemide, cyclosporin	Cause renal failure and decrease glomerular filtration rate
	Bleomycin, aminodarone, busulphan, nitrofurantoin	Causes lung disease and pulmonary interstitial fibrosis
	Doxorubicin	Cardiotoxic and impairs left ventricular function
	Adriamycin	Cariotoxic and induces changes in cell membrane permeability
Drugs interfering with labeling cells	Hydralazine, methyldopa	Oxidation of stannous ion in the kt prevents labeling RBCs with Tc^{99m}
	Digoxin	Inhibits Na^+/K^+-ATPase pump and affects membrane transport of RBCs
	Antibiotics, corticosteroids	Reduce chemotaxis of labeled leukocyes

Table 5 Altered Biodistribution of Radiopharmaceuticals Attributable to Drug Interactions

Radiopharmaceutical	Drugs	Effects on the Imaging Study
^{99m}Tc-MDP and ^{99m}Tc-HDP	Aluminum containing drugs	Reduced uptake in bone, increased hepatic and renal uptake
	Iron salts	High blood pool and renal activity diffuse liver uptake
	Amphotericin, cyclophosphamide, gentamicin, vincristine, doxorubicin	Increased renal retention due to nephrotoxicity
	Drugs causing gynecomastia, eg, stilboestrol, spironolactone, phenothiazines, cimetidine, oral contraceptives	Increased uptake in breast
	Methotrexate	Diffuse uptake in liver due to nephrotoxicity
	Nifedipine	Reduced bone uptake
	Diphosphonates (etidronate, pamidronate) vitamin D supplements	Reduce bone uptake
^{99m}Tc-DISIDA (Hepatolite®)	Narcotic analgesics (morphine, methadone)	Delay in hepatic clearance
^{99m}Tc-Bida (Choletec®)	Barbiturates, cholecystokinin and analogs	Enhanced biliary excretion
	Nicotinic acid (chronic high doses)	Abnormal or absence of tracer in gallbladder
	Total parental nutrition	Reduced uptake into gallbladder
	Erythromycin	Increased liver uptake due to hepatotoxicity
^{99m}Tc-sulfur colloid	Aluminum compounds, magnesium salts	Flocculation of colloids, deposition in lung
	Anesthetic agents (halothane)	Shift of activity from liver to spleen
	Estrogens and androgens	Abnormal uptake due to drug toxicity
	Methotrexate, cytosine arabinoside and nitrosoureas	Irregular liver uptake, shift of activity to bone marrow and spleen
^{99m}Tc-DTPA	Al containing drugs	Abnormal GFR
	Nephrotoxic drugs (sulfonamides, cyclosporine)	Reduced GFR
	Angiotensin-converting enzyme inhibitors, diuretics, such as furosemide	Reduced GFR
	Dipyridamole infusion	Reduced GFR
^{99m}Tc-DMSA	Ammonium chloride, sodium bicarbonate	Reduced renal uptake, increased liver uptake
	Angiotensin-converting enzyme inhibitors	Reduced renal uptake in renal artery stenosis
^{99m}Tc-RBC (in vivo labeling)	Heparin, dextran, penicillin, hydralazine, doxorubicin, iodinated contrast media	Poor labeling, increased uptake in thyroid, and stomach
^{123}I/^{131}I sodium iodide	Iodine-containing compounds (SSKI, Lugol's solution)	Reduced uptake in thyroid
^{99m}Tc pertechnetate	Antithyroid drugs (propylthiouracil, Topazol)	Reduced uptake in thyroid
	Thyroid supplements (Cytomel, Synthroid)	Reduced uptake in thyroid
	Meprobamate, phenylbutazone, sulfonamides, corticosteroids, ACTH, sulfonylureas, perchlorate, antihistamines	Reduced uptake in thyroid
^{131}I-mIBG	Antihypertensives (Lebatolol, reserpine, adrenergic neuron blockers)	Inhibition of tumor and myocardial uptake
	Sympathomimetics (phenylpropanolamine, imipramine)	Decrease in cardiac uptake
	Nifedipine	Increased tumor uptake and delay in washout
	Antidepressants (tricyclics, maprotiline, trazodone)	Reduced tumor uptake
	Antipsychotics (phenothiazens, thioxanthines)	Educed tumor uptake
^{67}Ga citrate	Cytotoxic drugs (cisplatin, methotrexate, cyclophosphamide, vincristine)	Reduced tumor/abscess and hepatic uptake increased blood pool, skeletal and renal activity
	Bleomycin, busulphan, amiodarone, nitrofurantoin, methotrexate, cyclophosmamide	Abnormal uptake in lung (drug-induced pulmonary interstitial pneumonitis and/or fibrosis)

Table 5 Continued

Radiopharmaceutical	Drugs	Effects on the Imaging Study
	Corticosteroids	Absence or reduced tumor size
	Drugs causing hyperprolactinemia (phenothiazines, stilboestrol, methyldopa, metoclopramide, cimetidine, gonadotropins)	Increased uptake in breast
	Frusemide, phenylbutazone, ibuprofen, sulfonamides, penicillins, cephalosporins	Delayed and increased renal uptake due to drug-induced interstitial nephritis
^{111}In-pentetreotide (Ocreoscan®)	Somatostatin analogues (octreotide or Sandostatin)	Reduced tumor, splenic, hepatic and renal uptake enhanced detection of hepatic metastases
^{111}In and ^{99m}Tc-leukocytes (WBCs)	Antibiotics and steroids	May cause reduced uptake of leukocytes
^{201}Tl-thallous chloride	β-blockers and nitrate	Decreased Number and size of exercise-induced perfusion defects
	Vasopressin	Perfusion defects in the absence of CAD
	Doxorubicin	Reduced myocardial uptake caused by cardiotoxicity
	Inhibitors of Na–K ATPase pump (ouabain, furosemide)	Decrease the uptake of tumor and myocardial cells
[^{18}F]FDG	Insulin in patients with hyperglycemia	Increased uptake in tumor and skeletal muscle
	Benzodiazepines	Decrease paraspinal and posterior cervical muscle uptake in tense patients
	Growth factors (hepatocyte growth factor, granulocyte/macrophage colony stimulating factor) and erythropoietin	Increased diffuse intense uptake in bone marrow, and spleen

and (3) kidney uptake is greater than the liver on the posterior view.[76]

Factors Caused by Medical Procedures

The biodistribution of radiopharmaceuticals may also be altered significantly because of medical procedures, such as radiation therapy surgery, and hemodialysis.[2,77] The effects of radiotherapy on the biodistribution of several radiopharmaceuticals have been well documented, and depending upon the radiation dose level, the effects may be transient or permanent in nature.[77] In the early phase of radiation therapy, an inflammatory response may be predominant with increased vascular permeability and leukocyte migration. In bone scans, ^{99m}Tc-MDP activity in soft-tissue areas within a radiation field may increase.[78] The long-term effect of radiation therapy is reduced blood flow as the result of fibrosis, and as a result, the bone uptake of ^{99m}Tc-MDP may be significantly reduced (Fig. 14). The local effects of radiation-causing osteoblastic suppression and hepatitis with defective uptake, respectively, of bone-seeking radiotracers and colloids are widely recognized. Also, following radiation therapy, iron-overload may lead to decrease in iron-binding capacity of iron.[32] As a result, the biodistribution of ^{67}Ga-citrate is significantly altered showing increased bone uptake and decreased soft tissue uptake in the irradiated areas.[77] Flare phenomenon in FDG-PET (Fig. 15) showing an increase in standard uptake values in the tumor or soft-tissue disease, has been reported during post therapy (chemotherapy and/or radiation therapy) follow-up period.[56,79,80] The increased FDG uptake may confound estimation of treatment response or may also indicate recurrent disease.

Recent surgery commonly results in the accumulation of radiopharmaceuticals in scars and tissues around the operation site probably due to local edema. ^{67}Ga citrate and ^{99m}Tc-MDP show increased localization in operative sites and tissue adjacent to prostheses. Also, FDG and radiolabeled cells may also show uptake at surgical sites. Defibrillation has been found to result in increased uptake of ^{99m}Tc-MDP in the chest wall tissues.

Chronic renal failure and dialysis (both hemo- and peritoneal dialysis) are fairly well known causes of altered clearance and biodistribution of several radiopharmaceuticals. Elimination of most radiopharmaceuticals is disrupted in patients with compromised renal function, resulting in prolonged blood pool activity, and possibly increased clearance through the liver. In hemodialysis, small solute molecules, such as ^{99m}Tc-chelating agents and radioiodide, move from the area of high concentration in blood to the area of lower concentration in the dialyzate. Renal dialysis substitutes for kidney elimination. Often, dialysis will not adversely affect the imaging results as long as the administered radiopharmaceutical has been given time to localize in its organ of interest before beginning dialysis. However, the components of the dialyzate fluid that enter the patient's bloodstream may cause very noticeable alterations in how a radiopharmaceutical is handled by the patient's body. In contrast, peritoneal dialysis

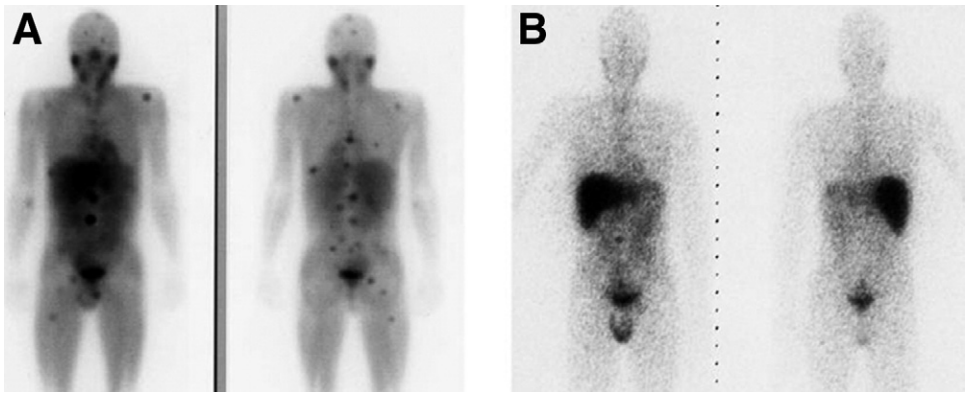

Figure 16 Drug interference with MIBG uptake in a patient with metastatic paraganglioma. (A) ^{131}I-MIBG scan following therapeutic dose shows uptake in the metastatic lesions. (B) Post MIBG therapy, the scan failed to detect the vast majority of metastatic lesions identified by FDG-PET. The most likely cause of this "false scan" is probably attributable to recreational drugs (such as cocaine, ephedrine) taken just before the recent MIBG therapy.[81]

removes metabolic waste from blood by use of the patient's own semipermiable membrane—the peritoneal membrane. Dialyzate is placed into the patient's peritoneal cavity where it accumulates radioactivity that passes through the peritoneal membrane along concentration and osmotic pressure gradients.

Factors Cause by Pharmacologic Factors and Drug Interactions

There is considerable evidence that the biodistribution or pharmacokinetics of radiopharmaceuticals may be altered by patient medication.[2,5-7,77] Many reports on drug/radiopharmaceutical interactions are anecdotal, and in some instances a direct cause and effect relationship has not been unequivocally established. The drug and radiopharmaceutical interactions may arise because of the pharmacologic action of the drug or due to physicochemical interactions between the drug and radiophamaceutical. Even contamination with antiseptics during dispensing or administration can also lead to alterations in the biodistribution of the tracer. Many drugs in everyday use may cause or aggravate disease, and that the iatrogenic (drug induced) disease itself may then produce an unexpected biodistribution of the radiopharmaceutical. Drug/radiopharmaceutical effects may be classified by organ of interest, radiopharmaceutical used, chemical class of the drug, or the type of drug interaction.

Drugs that alter the functional status of an organ will have significant effect on the biodistribution of radiopharmaceuticals. Some of the important groups of drugs and their pharmacologic effect are summarized in Table 4. Drug interactions with radiopharmaceuticals and the corresponding effects on imaging studies are summarized in Table 5. Drug interference with mIBG uptake in a patient with metastatic paraganglioma is shown in Fig. 16. During earlier therapies, ^{131}I-mIBG uptake in the metastatic lesions was very high. A posttherapeutic whole-body scan after recent mIBG therapy failed to detect the vast majority of metastatic lesions. FDG-PET, however, showed metastases with a similar distribution to the initial mIBG scan. The most likely cause of this "false scan" is the rapid interference of recreational drugs (such as cocaine, ephedrine) with the mIBG uptake, which probably were taken just before the recent mIBG therapy.[81]

References

1. Hladik WB, Norenberg JP: Problems associated with the clinical use of radiopharma-ceuticals: A proposed classification system and trouble shooting guide. Eur J Nucl Med 23:997-1002, 1996
2. Lentle BC, Scott JR, Noujaim AA, et al: Iatrogenic alterations in radionuclide biodistributions. Semin Nucl Med 9:131-143, 1979
3. Hung JC, Pronto JA, Hammers RJ: Radiopharmaceutical-related pitfalls and artifacts. Semi. Nucl Med 26:208-255, 1996
4. Hojelse C, Kristensen K, Sampson CB: Factors which affect the integrity of radiopharmaceuticals, in Sampson CB (ed): Textbook of Radiopharmacy, Theory and Practice (ed 2). Amsterdam, Gordon and Breach Science Publishers, 1994, pp 145-152
5. Hladik WB, Nigg NK, Rhodes BA: Drug induced changes in the biologic distribution of radiopharmaceuticals. Semin Nucl Med 12:184-218, 1982
6. Hesselewood S, Leung E: Drug interactions with radiopharmaceuticals. Eur J Nucl Med 21:348-356, 1994
7. Sampson CB: Adverse reactions and drug interactions with radiopharmaceuticals. Drug Saf 8:280-294, 1993
8. Leung E, Hesslewood S: Use of non-radioactive drugs in nuclear medicine. Pharm J 249:HS32-HS36, 1992
9. Saha GB: Adverse reactions to and altered biodistribution of radiopharmaceuticals, in Saha GB (ed): Fundamentals of Nuclear Pharmacy (ed 4). New York, Springer, 2004, pp 351-353
10. Chamarthy M, Travin MI: Altered biodistribution and incidental findings on myocardial perfusion imaging. Semin Nucl Med 40:257-270, 2010
11. Zuckier LS, Freeman LM: Nonosseous, nonurologic uptake on bone scintigraphy: atlas and analysis. Semin Nucl Med 40:242-256, 2010
12. Cohade C: Altered biodistribution on FDG-PET with emphasis on brown fat and insulin effect. Semin Nucl Med 40:283-293, 2010
13. Liu Y, Ghesani NV, Zuckier LS: Physiology and pathophysiology of incidental findings detected on FDG-PET scintigraphy. Semin Nucl Med 40:294-315, 2010
14. Shapiro B, Rufini V, Janwan A, et al: Artifacts, anatomic and physiological variants, and unrelated diseases that might cause false-positive whole-body 131-I Scans in patients with thyroid cancer. Semin Nucl Med 30:115-132, 2000
15. Love C, Palestro CJ: Altered biodistribution and incidental findings on

gallium and labeled leukocyte/bone marrow scans. Semin Nucl Med 40:271-282, 2010
16. Vallabhajosula S: Molecular Imaging: Radiopharmaceuticals for PET and SPECT (ed 1). Berlin, Springer, 2009
17. Deutsch E, Libson K, Jurisson S, et al: Technetium chemistry and technetium radiopharmaceuticals. Prog Inorg Chem 30:75-139, 1983
18. Nosco DL, Wolfangel RG, Bushman MJ, et al: Technetium-99m MAG3: Labeling conditions and quality control. J Nucl Med Technol 121:69-74, 1993
19. Morrissey GJ, Powe JE: Microwave preparation of technetium-99m sulfur colloid. J Nucl Med Technol 20:159-162, 1992
20. Henkin RE, Woodruff A, Chang W, et al: The effect of radiopharmaceutical incubation time on bone scan quality. Radiology 135:463-466, 1980
21. Russell CD, Rowell K, Scott JW: Quality control of technetium-99m DTPA: Correlation of analytic tests with *in vivo* protein binding in man. J Nucl Med 27:560-562, 1986
22. McBride MHD, Shaw SM, Kessler WV: Deterioration of stannous 1on in radiopharmaceutical kits during storage. Am J Hosp Pharm 36:1370-1372, 1979
23. Owunwanne A, Church LB, Blau M: Effect of oxygen on the reduction of pertechnetate by stannous ion. J Nucl Med 18:822-826, 1977
24. Bavne VJ, Forster AM, Tyrrell DA: Use of sodium iodide to overcome the eluate age restriction for Ceretec® reconstitution. Nucl Med Commun 10:29-33, 1989
25. Kobayashi H, Suzuki KH, Sakahara H, et al: Oxygen bubbling can improve the labeling of pentavalent technetium-99m dimercaptosuccinic acid. Eur J Nucl Med 22:559-562, 1995
26. Green JM, Donohoe ME, Foster ME, et al: Thin layer chromatographic procedures for the characterization of technetium-99m bicisate. J Nucl Med Technol 22:21-26, 1994
27. Study KT, Hladik WB, Saha GB: Effects of Al^{+3} ion on ^{99m}Tc sulfur colloid preparations with different buffers. J Nucl Med Technol 12:16-18, 1984
28. Jovanovi V, Jovanovic MS, Maksin T: Effect of aluminum on the radiochemical purity and ^{99m}Tc-MDP biodistribution. J Radioanal Nucl Chem Artic 122:57-63, 1988
29. Wener RE, Thakur ML: Chemistry of gallium and indium radiopharmaceuticals, in Welch MJ and Redvanly CS (eds): Handbook of Radiopharmaceuticals John Wiley & Sons, West Sussex, England, 2003
30. Vallabhajosula S, Harwig JF, Siemsen JK, et al: Radiogallium localization in tumors: Blood binding and transport and the role of transferrin. J Nucl Med 21:650-656, 1980
31. Hoffer P: Gallium: Mechanisms. J Nucl Med 21:282-285, 1980
32. Weiner RE: The mechanism of ^{67}Ga localization in malignant disease. Nucl Med Biol 23:745-751, 1996
33. Breeman WAP, Marion J, Visser TJ, et al: Optimising conditions for radiolabelling of DOTA-peptides with ^{90}Y, ^{111}In and ^{177}Lu at high specific activities. Eur J Nucl Med Mol Imaging 33:917-920, 2003
34. Steffel FG, Rao S: Rapid and simple methods for labeling white blood cells and platelets with indium-111 oxine. J Nucl Med Technol 15:61-65, 1987
35. McAfee JG, Gagne GM, Subramanian G, et al: Distribution of leukocytes labeled with In-llloxine in dogs with acute inflammatory lesions. J Nucl Med 21:1059-1068, 1980
36. Hunter VW, Kulkarni MV, Price R: Thallous vs thallic TI-201: Factors influencing biodistribution and myocardial turnover. J Nucl Med 22: 82, 1981 (abstr)
37. Dadachova E, Carrasco N: The Na^+/I^- symporter (NIS): Imaging and therapeutic applications. Semin Nucl Med 34:23-31, 2004
38. Sternthal E, Lipworth L, Stanley B, et al: Suppression of thyroid radioiodine uptake by various doses of stable iodine. N Engl J Med 303: 1083-1088, 1980
39. Oswald WM, Hung JC, Gross GP: A study to measure the volatility of liquid 1-131 for clinical applications. J Nucl Med Technol 122:123, 1994
40. Yu M-D, Huang W-S, Cherng C-C, et al: The effect of formulation on reduced radioiodide thyroid uptake. J Nucl Med 43:56-60, 2002
41. Rini JN, Vallabhajosula S, Zanzonico P, et al: Thyroid uptake of liquid versus capsule ^{131}I tracers in hyperthyroid patients treated with liquid ^{131}I. Thyroidology 9:347-352, 1999
42. Wafelman AR, Hoefnagel CA, Beijnen JH: Radiochemical stability during infusion of ^{131}I-labeled metaiodobenzylguanidine for therapeutic use. Nucl Med Commun 14:819-822, 1993
43. Vallabhajosula S: ^{18}F-labeled positron emission tomographic radiopharmaceuticals in oncology: An overview of radiochemistry and mechanisms of tumor localization. Semin Nucl Med 37:400-419, 2007
44. Ongseng F, Goldfarb CR, Finestone H: Axillary lymph node uptake of technetium-99m-MDP. J Nucl Med 36:1797-1799, 1995
45. Hoop B: The infiltrated radiopharmaceutical injection: Risk considerations. J Nucl Med 32:890-891, 1991
46. Piers DA, Beekhuis H: Local radiation dose from extravascular T1-201. J Nucl Med 28:684, 1987 (abstr)
47. Goldberg E, Lieberman C: "Hot spots" in lung scans. J Nucl Med 18: 499, 1977
48. Gentili A, Miron SD, Adler LP: Review of some common artifacts in nuclear medicine. Clin Nucl Med 19:138-143, 1994
49. Fisher SM, Brown RG, Greyson ND: Unbinding of ^{99m}Tc by iodinated antiseptics. J Nucl Med 18:1139-1140, 1977 (letter)
50. Peterson EM, Ryan JW, Martin WB: Gastric activity on Tc-99m oxidronate bone scans can be caused by isopropyl alcohol. J Nucl Med 27:1090, 1986 (abstr)
51. Gnanasegaran G, Cook G, Adamson K, et al: Patterns, variants, artifacts, and pitfalls in conventional radionuclide bone imaging and SPECT/CT. Semin Nucl Med 39:380-395, 2009
52. Ergün EL, Kiratli PÖ, Günay EC, et al: A report on the incidence of intestinal ^{99m}Tc-methylene diphosphonate uptake of bone scans and a review of the literature. Nucl Med Commun 27:877-885, 2006
53. Loutfi I, Collier BD, Mohammed AM: Nonosseous abnormalities on bone scans. J Nucl Med Technol 31:149-153, 2003
54. Griffeth LK: Use of PET/CT scanning in cancer patients: Technical and practical considerations. Proc (Bayl Univ Med Cent) 18:321-330, 2005
55. Cook GJR, Fogelman I, Maisey MN: Normal physiological and benign pathological variants of 18-fluoro-2-deoxyglucose positron-emission tomography scanning: Potential for error in interpretation. Semin Nucl Med 26:308-314, 1996
56. Tu D-G, Yao W-J, Chang T-W, et al: Flare phenomenon in positron emission tomography in a case of breast cancer-a pitfall of positron emission tomography imaging interpretation. Clin Imaging 33:468-470, 2009
57. Abouzied MM, Crawford ES, Nabi HA: ^{18}F-FDG imaging: Pitfalls and artifacts. J Nucl Med Technol 33:145-155, 2005
58. Kostakoglu L, Hardoff R, Mirtcheva R, et al: PET-CT fusion imaging in differentiating physiologic from pathologic FDG uptake. Radiographics 24: 1411-1431, 2004
59. Lindholm P, Minn H, Leskinen-Kallio S: Influence of the blood glucose concentration on FDG uptake in cancer: A PET study. J Nucl Med 34:1-6, 1993
60. Roy FN, Beaulieu S, Boucher L, et al: Impact of intravenous insulin on ^{18}F-FDG PET in diabetic cancer patients. J Nucl Med 50:178-183, 2009
61. Liu Y: Benign ovarian and endometrial uptake on FDG-PET/CT. Ann Nucl Med 23:107-112, 2009
62. Schelbert HR: Positron emission tomography of the heart: Methodology, findings in the normal and disease heart, and clinical applications, in Phelps ME (ed): PET: Molecular Imaging and Its Clinical Applications. New York, Springer, 2004
63. Kailasnath P, Sinusas AJ: Comparison of Tl-201, with Tc-99m labeled myocardial perfusion agents: Technical physiologic and clinical issues. J Nucl Cardiol 8:482-498
64. Fukumoto M: Single-photon agents for tumor imaging: ^{201}Tl, ^{99m}Tc-MIBI, and ^{99m}Tc-tetroformin. Ann Nucl Med 18:79-95, 2004
65. Morris LF, Waman AD, Braunstein GD: Thyroid stunning. Thyroidology 13:333-340, 2003
66. Shapiro B, Rufini V, Jarvan A, et al: Artifacts, anatomical, and physiological variants, and unrelated diseases that might cause false-positive whole-body ^{131}I scans in patients with thyroid cancer. Semin Nucl Med 30:115-132, 2000

67. Smith JR, Oates E: Radionuclide imaging of the thyroid gland: Patterns, pearls and pitfalls. Clin Nucl Med 29:181-193, 2004
68. Goldsmith SJ, Vallabhajosula S: Clinically proven radiopharmaceuticals for infection imaging: Mechanisms and applications. Semin Nucl Med 39:2-10, 2009
69. Rufini V, Calcagni ML, Baum RP: Imaging of neuroendocrine tumors. Semin Nucl Med 36:228-247, 2006
70. Agostini D, Verberne HJ, Hamon A, et al: Cardiac 123I-mIBG scintigraphy in heart failure. Q J Nucl Med Mol Imaging 52:369-377, 2008
71. Nakajima K, Yoshita M, Matsuo S, et al: Iodine-123 mIBG sympathetic imaging in Lewy body diseases and related movement disorders. Q J Nucl Med Mol Imaging 52:378-387, 2008
72. Iwasa K, Nakajima K, Yoshikawa H, et al: Decreased myocardial ^{123}I-mIBG uptake in Parkinson's disease. Acta Neurol Scand 97:303-306, 1998
73. Taneja SS: ProstaScint scan: Contemporary use in clinical practice. Rev Urol 6:S19-S28, 2004 (suppl 10)
74. Fink-Bennett DM, Thomas K: ^{90}Y-ibritumomab tiuxetan in the treatment of relapsed or refractory B-cell non-Hodgkin's lymphoma. J Nucl Med Technol 31:61-68, 2003
75. Goldsmith SJ: Radioimmunotherapy of lymphoma: Bexxar and Zevalin. Semin Nucl Med 40:122-135, 2010
76. Conti PS, White C, Pieslor P, et al: The role of imaging with 111In-ibritumomab tiuxetan in the ibritumomab tiuxetan (Zevalin) regimen: Results from a Zevalin Imaging Registry. J Nucl Med 46:1812-1818, 2005
77. Sampson CB, Cox PH: Effect of patient medication and other factors on the biodistribution of radiopharmaceuticals, in Sampson CB (ed): Textbook of Radiopharmacy, Theory and Practice (ed 2). Amsterdam, Gordon and Breach Science Publishers, 1994, pp 215-227
78. Morrison RT, Steuart RD: Delayed massive soft tissue uptake of Tc-99m MDP after radiation therapy for cancer of the breast. Clin Nucl Med 20:770-771, 1995
79. Mankoff DA, Dunnwald LK, Gralow JR, et al: Changes in blood flow and metabolism in locally advanced breast cancer treated with neoadjuvant chemotherapy. J Nucl Med 44:1806-1814, 2003
80. Dehadashi F, Flanagan FL, Mortimer JE, et al: Positron emission tomography assessment of "metabolic flare" to predict response of metastatic breast cancer to antiestrogen therapy. Eur J Nucl Med 26:51-56, 1999
81. Zaplatnikov K, Menzel C, Dobert N, et al: Drug interference with mIBG uptake in a patient with metastatic paraganglioma. Br J Radiol 77:525-527, 2004