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Mechanisms of Radiopharmaceutical Localization

Continuing Education for Nuclear Pharmacists
And
Nuclear Medicine Professionals

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MECHANISMS OF RADIOPHARMACEUTICAL LOCALIZATION

STATEMENT OF LEARNING OBJECTIVES:

Upon successful completion of this lesson, the reader should be able to:

1. Describe common mechanisms of biologic localization.
2. Describe, for common radiopharmaceuticals, its mechanism of localization and expected biodistribution.
3. Describe examples of altered radiopharmaceutical biodistribution related to improper product preparation.

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INTRODUCTION

Nuclear pharmacists must understand how radiopharmaceuticals work; i.e., their mechanism of action (or more appropriately, their mechanism of localization). Such knowledge is necessary to understand the performance of clinical nuclear medicine procedures, many drug-radiopharmaceutical interactions, and other causes of altered biodistribution.

The following descriptions and examples are of the author's own categorization; they are similar to, but not the same as, those found in textbooks and review articles¹⁻⁴. These mechanisms are not unique for radiopharmaceuticals, but may be applicable for the description of localization mechanisms for other substances including conventional drugs.

It should be emphasized that the localization of most radiopharmaceuticals is not limited to one simple mechanism, but also involves other processes such as delivery to the tissue and retention in the cells. Moreover, the localization of some radiopharmaceuticals may involve the combination of more than one mechanism.

In each of the following sections, the mechanism is described, its characteristics are detailed, and examples are presented. Although the majority of radiopharmaceuticals are mentioned, not all radiopharmaceuticals or all uses of certain radiopharmaceuticals are included. Rather, the intent is to provide a foundation and framework for understanding mechanisms of localization of existing and most future radiopharmaceuticals.

COMPARTMENTALIZED

Compartmentalized, or compartment localization, refers to the situation where the molecules of interest are distributed in an enclosed volume. The space in which the volume is enclosed is the compartment. Examples of common biologic compartments are listed in Table 1.

Table 1

Examples of common biologic compartments
blood pool (vasculature)
lung airways
cerebrospinal fluid (CSF) space
peritoneal cavity
Gastrointestinal tract
urinary tract
lymphatic channels

Uniform Dispersion Within a Compartment

The classic example of uniform dispersion within a compartment involves the blood pool. The quantitative determination of blood volume can be performed by employing the tracer dilution method. I-125 radioiodinated serum albumin (I-125 RISA), a radiopharmaceutical which disperses in the plasma, is used to determine plasma volume. Cr-51 labeled red blood cells, a radiopharmaceutical that disperses within the cellular content of blood, is used to determine red cell volume (sometimes referred to as red cell mass).

Tc-99m red blood cells (RBCs) are dispersed in the blood and used in gated blood pool imaging of left ventricular wall motion and determination of left ventricular ejection fraction. Figure 1 shows Tc-99m RBCs in the left ventricular blood pool at end-diastole (when the heart relaxed and the chamber is full of blood) and at end-systole (when the heart has contracted and only residual blood remains in the chamber), along with a graphical representation of activity vs. time from which ejection fraction is calculated.

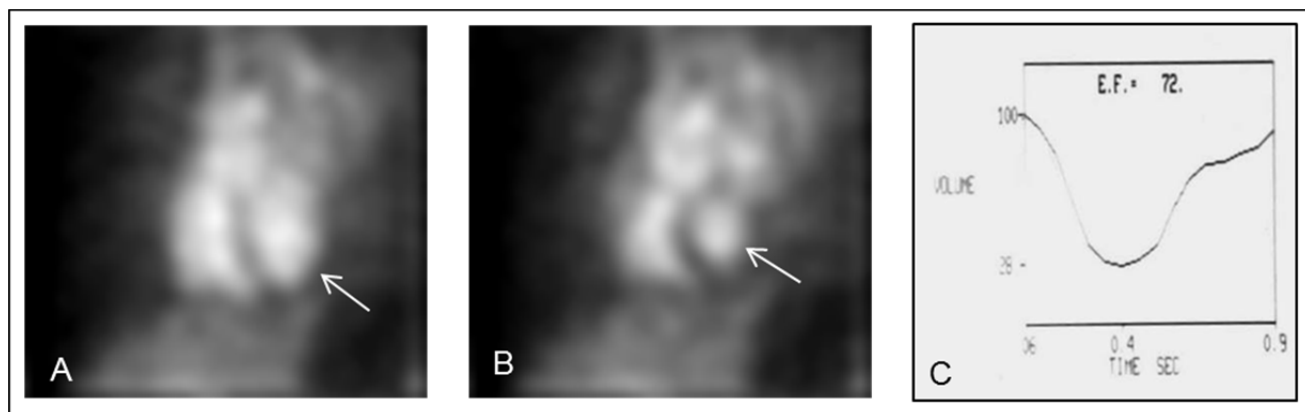


Figure 1. Tc-99m RBCs showing left ventricular blood pool (arrows) at end-diastole (A) and at end-systole (B). Also shown is activity/time graph from which ejection fraction (EF) is calculated (C).

Non-Uniformities Within the Compartment

In some situations, radiopharmaceuticals may demonstrate non-uniformities within the compartment thus reflecting pathophysiology. Areas of increased radiopharmaceutical concentration may reflect pathologic changes in the tissue or organ. For example, a localized area of increased Tc-99m RBCs activity can be caused by increased blood volume in a hemangioma (see Figure 2).

Another example involves cases of hydronephrosis, which causes dilatation of the collecting system in the urinary tract. In this situation, there will be increased urine volume, and thus increased radioactivity concentration of Tc-99m pentetate (DTPA) or Tc-99m mertiatide (MAG3). Such localized increased radioactivity in the collecting system or ureter could also be caused by an ureteral obstruction. Non-obstructive hydronephrosis can be differentiated from ureteral obstruction by its washout in response to furosemide (see Figure 3).

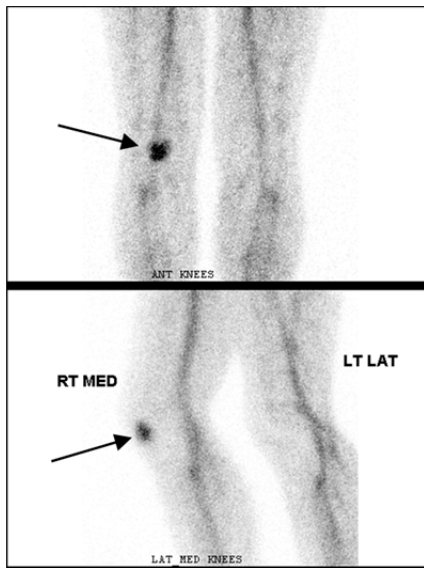


Figure 2. Increased concentration of Tc-99m RBCs in a hemangioma near the right knee (arrows).

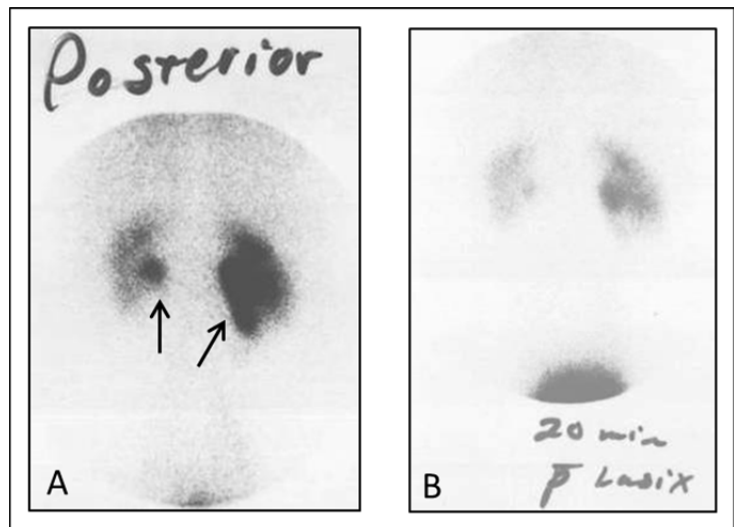


Figure 3. (A) Increased concentration of Tc-99m DTPA in the right renal pelvis and left proximal ureter (arrows). (B) Washout of activity down to the bladder in response to furosemide confirms non-obstructive hydronephrosis.

In other situations, pathophysiology may be demonstrated as areas of decreased radiopharmaceutical concentration. Such areas of decreased radiopharmaceutical concentration are most commonly the result of an obstruction in a compartmental space. One example is obstructions in the lung airways demonstrated by Xe-133 ventilation lung imaging. If complete obstruction, there will be absence of Xe-133 in the area beyond the site of airway obstruction. If partial obstruction (eg, frequently seen in chronic obstructive pulmonary disease [COPD]), there will be absence of Xe-133 in the affected area upon initial inhalation and breath-hold, but Xe-133 gas will pass through the site(s) of partial obstruction over time during equilibrium rebreathing (see Figure 4).

Obstructions can also occur in the CSF space. Following intrathecal injection, In-111 pentetate (DTPA) flows up the spine and throughout the brain. In the case of obstructive hydrocephalus, the obstruction prevents migration of In-111 DTPA to the upper part of the brain (see Figure 5).

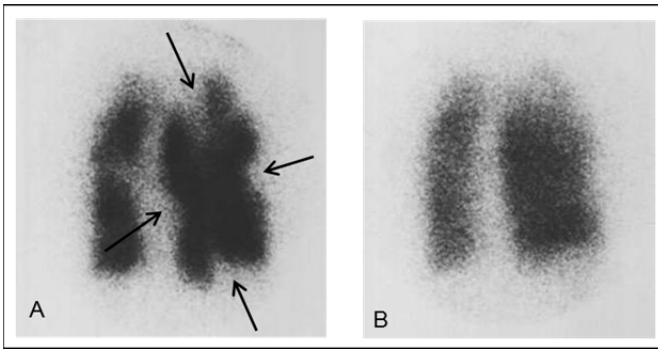


Figure 4. Xe-133 ventilation lung imaging shows areas of airway obstruction during inhalation breath-hold (arrows) (A) which normalize during equilibrium rebreathing (B), thus indicating that these are sites of partial obstruction.

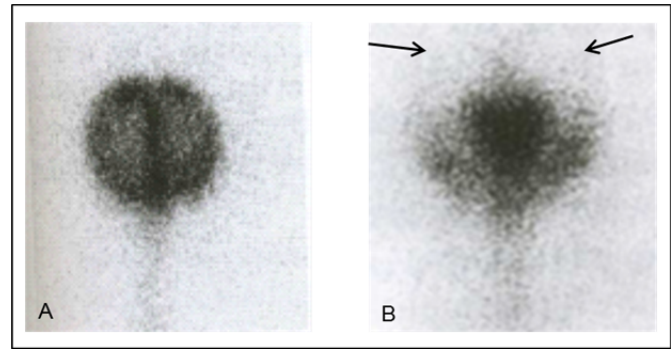


Figure 5. (A) Normal migration of In-111 DTPA throughout the CSF space in the brain. (B) Absent migration of In-111 DTPA in the upper part of the brain (arrows) in a patient with obstructive hydrocephalus.

The biliary tract is another compartment in which an obstruction may be present. Tc-99m hepatobiliary radiopharmaceuticals, disofenin (DISIDA) and mebrofenin (BRIDA), are excreted from the liver into the bile and flow through the biliary tract with normal flow into the gallbladder and into the intestine. If the cystic duct is obstructed, there will be lack of radiopharmaceutical in the gallbladder, and if the common bile duct is obstructed, there will be lack of radiopharmaceutical in the small intestine (see Figure 6).

One final example of an obstruction in a compartment is that of the urinary tract. An obstruction of a ureter will prevent transit of urine to the bladder. Such ureteral obstructions can be seen with renally-eliminated radiopharmaceuticals (see Figure 7). In addition to the obvious radiopharmaceuticals excreted in the urine, Tc-99m DTPA and MAG3, several others also exhibit substantial elimination in the urine including Tc-99m bone agents (medronate [MDP]) and oxidronate [HDP]) and F-18 fludeoxyglucose (FDG).

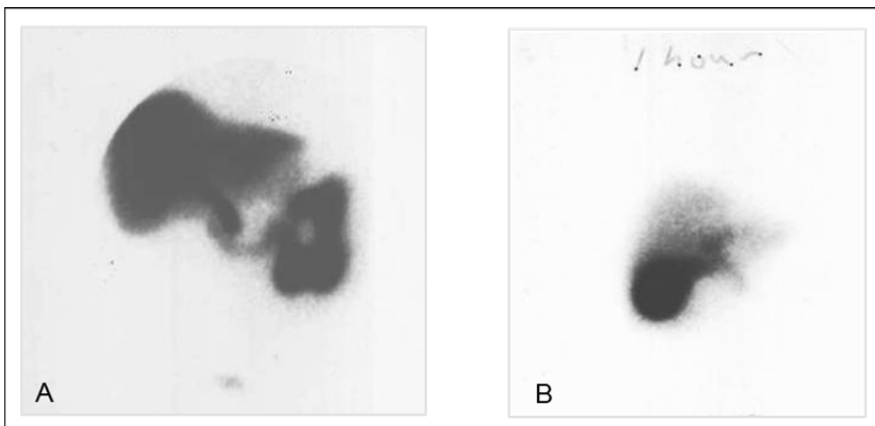


Figure 6. (A) Nonvisualization of gallbladder (arrow) because of cystic duct obstruction. (B) Nonvisualization of activity in the small intestine because of common bile duct obstruction (arrow).



Figure 7. Tc-99m MDP bone scan showing previously unsuspected ureteral obstruction (arrow).

Leakage From the Compartment

In some pathologic conditions there is abnormal leakage of contents from the compartment. Radiopharmaceuticals offer a good method to detect and identify the location of such leakage. For example, in cases of gastrointestinal hemorrhage (GI bleeding), blood extravasates from the vasculature and accumulates in the GI tract. Tc-99m RBCs can be used to visualize the site(s) of the GI bleed (see Figure 8).

Another example of leakage from a compartment in pathologic conditions is cerebrospinal fluid (CSF). Imaging of In-111 DTPA following intrathecal injection may demonstrate CSF leakage (see Figure 9).

One potential complication of a cholecystectomy or other abdominal surgery is an iatrogenic bile leak. Tc-99m disofenin or mebrofenin can be used to visualize whether the bile remains in the biliary tract or if leaks out into the abdominal cavity (see Figure 10).

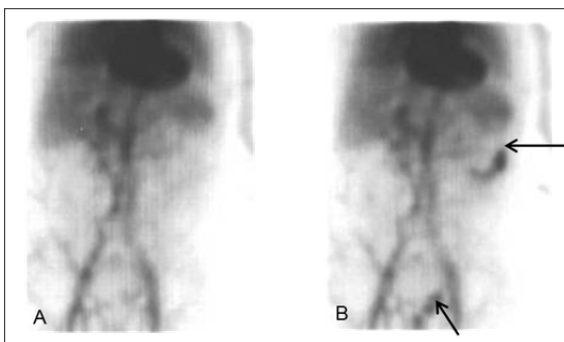


Figure 8. (A) Normal distribution of Tc-99m RBCs in the blood pool. (B) Accumulation of Tc-99m RBCs at two sites of GI bleeding (arrows).

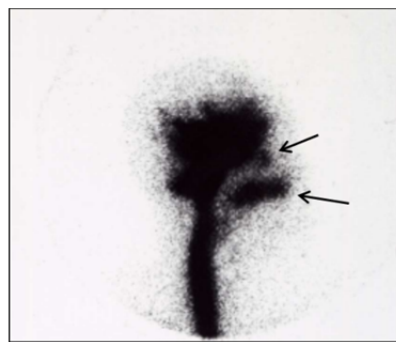


Figure 9. Leakage of In-111 DTPA into nasal pharynx with accumulation in oropharynx/mouth (arrows).

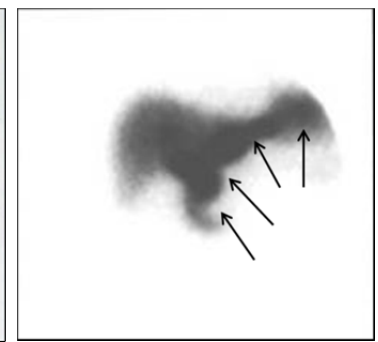


Figure 10. Hepatobiliary imaging shows bile leak into the abdomen (arrows) following cholecystectomy.

Similarly, a urine leak into the abdomen can result from a surgical complication, especially related to surgeries involving the kidneys and urinary tract. Such urine leaks may be visualized with Tc-99m DTPA or MAG3, although MAG3 is preferred because it has much higher concentration in the urine (see Figure 11).

As one more example of leakage from a compartment, peritoneal fluid may leak through a communication across the diaphragm and accumulate in the pleural cavity causing hydrothorax. Such peritoneal-plural communication can be demonstrated by imaging Tc-99m sulfur colloid following intraperitoneal injection (see Figure 12).

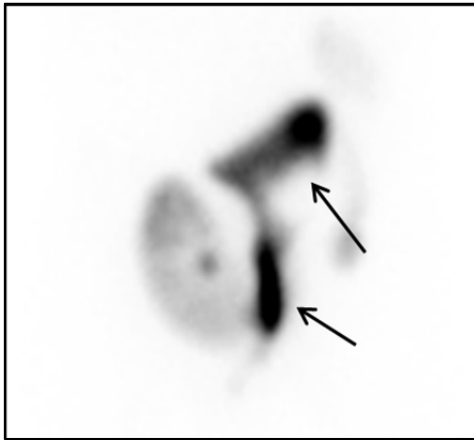


Figure 11. Tc-99m MAG3 SPECT coronal slice of kidney shows leakage of radioactive urine MAG into the abdominal cavity (arrows).

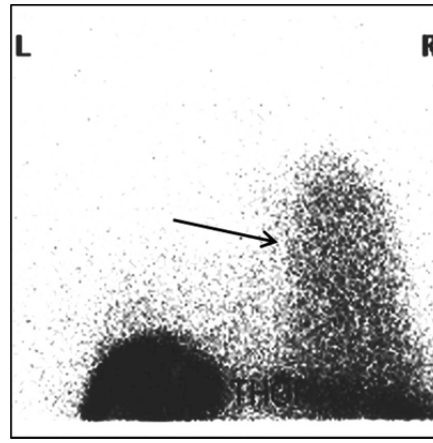


Figure 12. Following intraperitoneal injection of Tc-99m sulfur colloid, activity is seen in the right pleural cavity (arrow).

Movement (Flow) Within a Compartment

In some situations, pathologic conditions may be evaluated by assessing alterations in the direction, rate, and extent of flow within a compartment. For example the rate of emptying of gastric contents into the intestine can be determined by imaging radiopharmaceuticals in the stomach. Tc-99m sulfur colloid is the preferred radiopharmaceutical because it is non-absorbable from the GI tract. Tc-99m sulfur colloid bound in scrambled eggs can be used to evaluate gastric emptying of food solids while Tc-99m sulfur colloid mixed in water (or other liquid such as juice or baby formula) can be used to evaluate gastric emptying of liquids (see Figure 13 and Figure 14). Individual patient gastric emptying is compared to normal values, which are typically taken to be ± 2 standard deviations of the mean of normal controls.

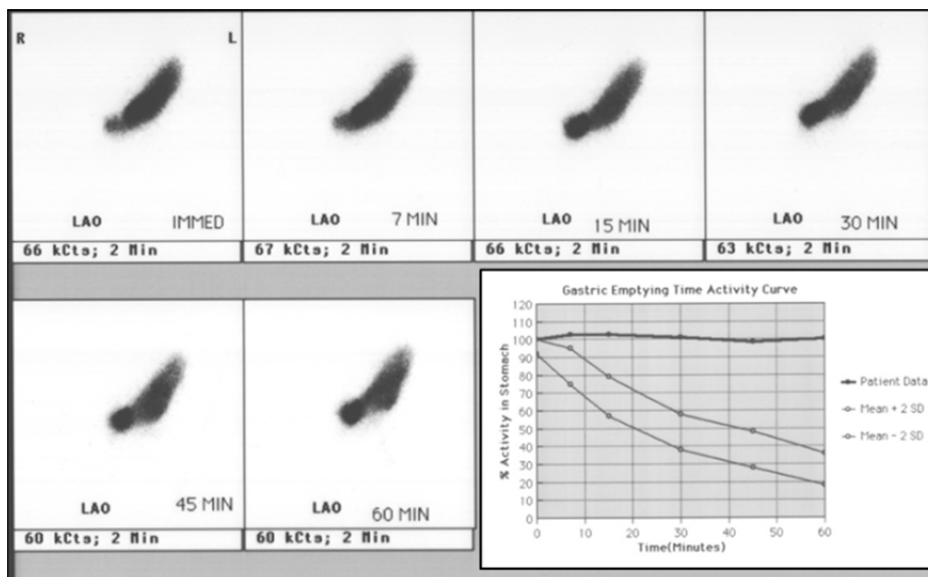


Figure 13. Tc-99m sulfur colloid administered orally in water shows marked abnormally slow rate of gastric emptying (almost no emptying during 1 hour).

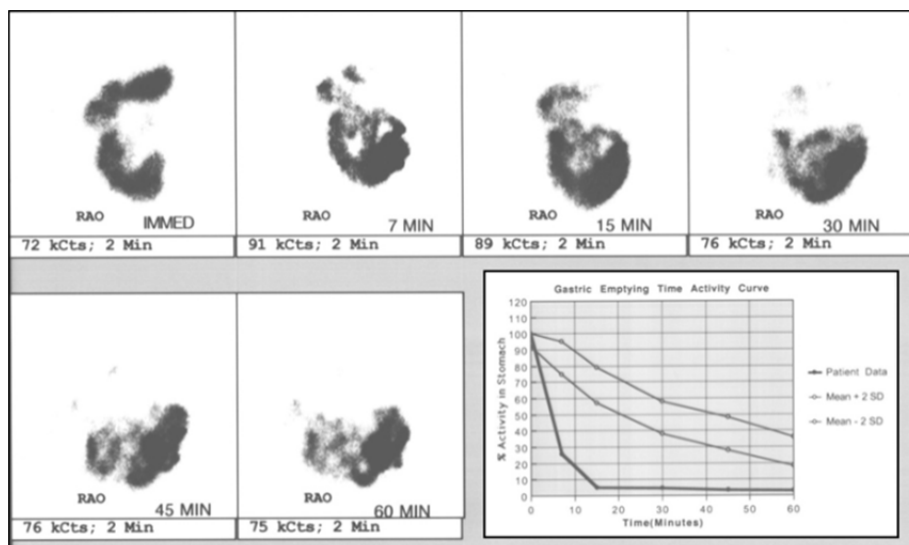


Figure 14. Tc-99m sulfur colloid administered orally in water shows marked abnormally fast rate of gastric emptying (essentially complete emptying within 15 minutes).

The contractile function of the gallbladder may be impaired in conditions such as chronic cholecystitis. Following injection of a hepatobiliary radiopharmaceutical and its accumulation in the gallbladder, the contractile function of the gallbladder can be assessed by its response to sincalide infusion. Sincalide, the synthetic octapeptide of cholecystokinin, stimulates gallbladder contraction and emptying. The extent of emptying, typically in terms of the emptying fraction (EF), can be determined by inspection of a radioactivity vs. time curve (see Figure 15).

Many malignant tumors tend to spread through lymphatic channels to regional lymph nodes. Hence, delineation of lymphatic drainage patterns may be important for selecting biopsy sites. Small particulate radiopharmaceuticals are suitable for visualizing lymphatic drainage from tumor sites. Because lymphatic channels are about 200 microns in size, Tc-99m sulfur colloid filtrate from passage through a 0.1 micron or a 0.2 micron filter is widely used. Following intradermal, subcutaneous, or interstitial injections of filtered Tc-99m sulfur colloid around or near the tumor site, lymphatic drainage channels to regional lymph node beds can be observed (see Figure 16).

Ureteral reflux refers to the abnormal condition of urinary bladder contents refluxing back up the ureter(s) to the kidney(s). Such reflux may contribute to recurrent kidney infections by offering transport to bacteria harbored in the bladder. The presence and extent of reflux can be evaluated by using a radiopharmaceutical instilled via a urinary catheter into the bladder (see Figure 17). Some centers use Tc-99m sodium pertechnetate while others prefer Tc-99m sulfur colloid.

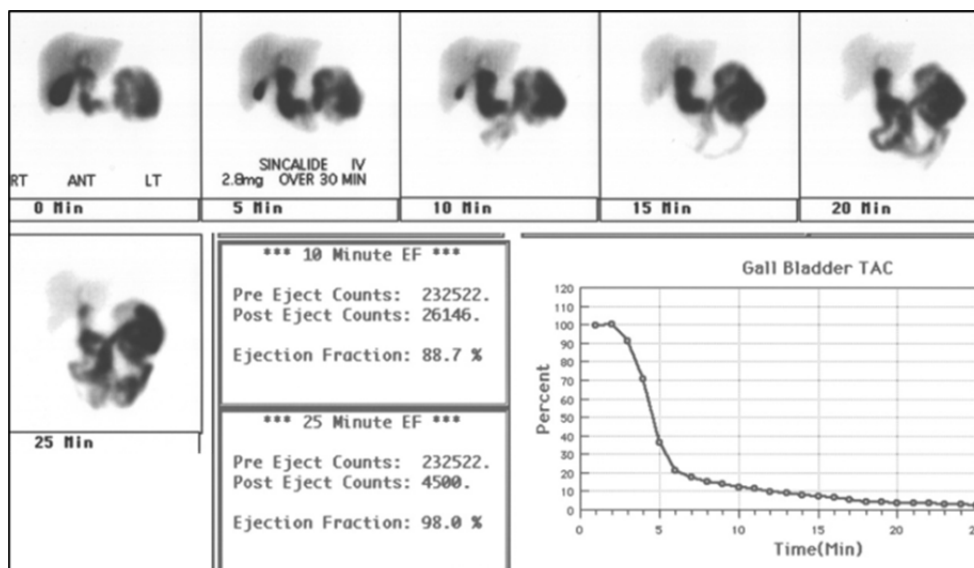


Figure 15. Imaging of Tc-99m mebrofenin in this normal individual shows essentially complete gallbladder emptying in response to sincalide.

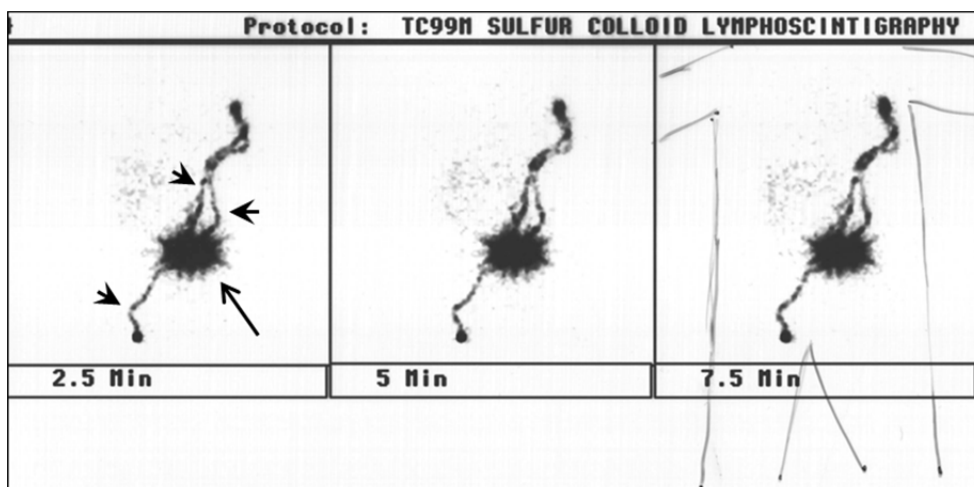


Figure 16. Following injection of 0.1-micron filtered Tc-99m sulfur colloid around an abdominal melanoma (arrow), flow is seen in one lymphatic drainage channel going to the right groin and in two lymphatic drainage channels both going to the left axilla (arrow heads).

The eyes are coated by tears secreted by the lacrimal glands. Excess tears drain from the eye through the nasolacrimal drainage duct to the nasopharynx. Obstruction of the drainage duct can produce epiphora (tears running out of the eyes and down the cheeks). Epiphora can also result from excess tear production (eg, crying). To differentiate, a drop of radiopharmaceutical can be placed on the eye and images obtained to see whether or not the drainage duct is patent (see Figure 18). Some centers use Tc-99m pertechnetate while others prefer Tc-99m sulfur colloid.

Evaluation of the patency of artificial shunts is one more example of assessing flow within a compartment. One treatment for ascites (abnormal fluid accumulation in the peritoneal cavity) is the placement of a catheter (shunt) from the peritoneal cavity to the subclavian vein. Excess ascitic fluid can then drain through the peritoneal-venous shunt into the blood where it can be eliminated in the urine. Evaluation of these shunts can be performed following intraperitoneal injection of Tc-99m macroaggregated albumin (MAA). If the shunt is patent, MAA will flow through it into the venous system, through the right side of the heart, and into the lungs where it lodges (see Figure 19).

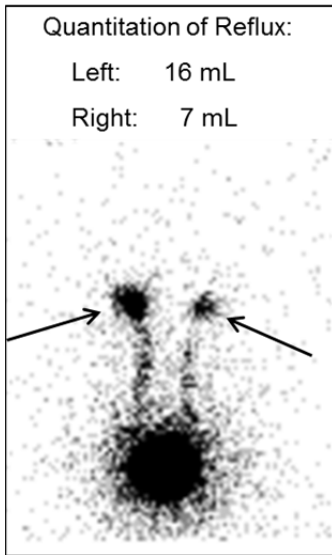


Figure 17. Following installation of Tc-99m sulfur colloid into the bladder, reflux is seen in both ureters ascending to the renal pelvis on both sides (arrows).

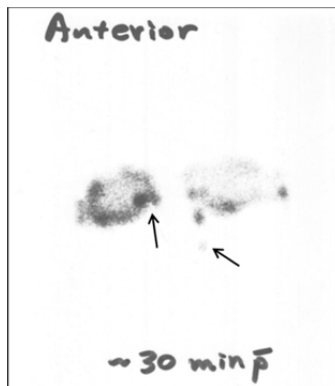


Figure 18. Following a drop of Tc-99m sulfur colloid placed onto the surface of each eye, images show transit of radioactivity through the drainage duct of the left eye but absence of drainage from the right eye due to obstruction of the right drainage duct (arrows)

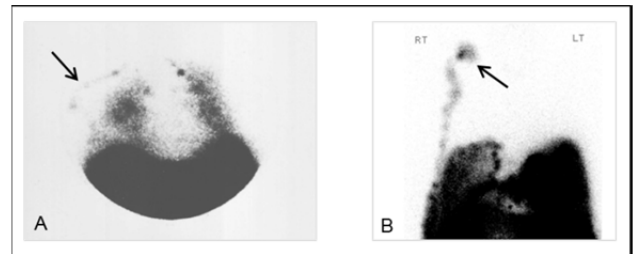


Figure 19. (A) Following intraperitoneal injection of Tc-99m MAA, activity is seen in the shunt tubing (arrow) and in the lungs, which indicates normal patency. (B) Following intraperitoneal injection of Tc-99m MAA, activity is seen in the shunt tubing until a site of obstruction (arrow) but no further.

PASSIVE DIFFUSION

Passive diffusion can be described as the random movement of molecules with the net effect toward achieving uniform concentration. A well-known example of passive diffusion is the movement of tea from a tea bag into and throughout a container of water.

In the context of biological systems, passive diffusion typically involves passage across a membrane. Several factors are involved in the ability of molecules to cross membranes. First is lipid solubility. Because membranes are composed primarily of phospholipids, molecules that are highly lipid soluble can usually ‘dissolve’ through and across membranes whereas hydrophilic polar molecules cannot. A second factor is pH/ionization. Many molecules may exist in either a neutral state or in a charged ionic state, depending on pH. For example, an amine can be neutral at a higher pH, but becomes protonated

at a lower pH. Hence, depending on the pH of the immediate environment, a molecule may be able to diffuse across a membrane in its unionized, lipophilic form but cannot diffuse across the same membrane in its ionized, hydrophilic form. A third factor is molecular size. Many membranes have small pores, or holes, that allow certain small molecules to pass through. However, this is generally limited to molecules having a molecular weight of less than 80 daltons.

Passive diffusion can be further described in terms of several characteristics. First, passive diffusion requires a concentration gradient; that is, the net flow of molecules is from an area of high concentration to an area of low concentration. In biological systems, membranes typically separate these areas of high concentration vs. low concentration, so diffusion occurs across the membrane. Second, the rate of diffusion is a function of the concentration gradient; that is, the rate is faster at higher concentration gradients and is slower at lower concentration gradients. Third, it is a passive process involving only molecular motion and does not require the input of other external energy. Fourth, no transporters, carriers, or other receptors are involved so passive diffusion is non-selective, is not competitively inhibited by similar molecules, and is not subject to saturation.

A classic example of passive diffusion in nuclear medicine is Tc-99m DTPA brain imaging. Tc-99m DTPA cannot normally penetrate the blood-brain barrier (BBB), so it normally remains in the blood pool until cleared by the kidneys. In conditions that result in disruption of the BBB, such as tumor, stroke, and infection, the Tc-99m DTPA can diffuse across the disrupted BBB and accumulate in that affected area of the brain (see Figure 20).

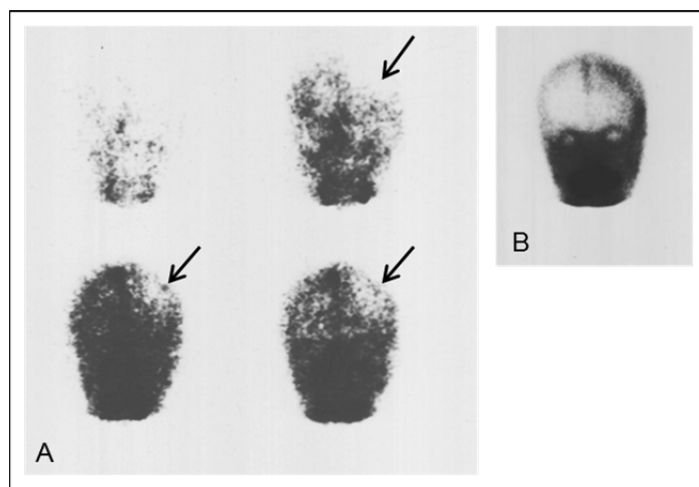


Figure 20. (A) Following IV injection of Tc-99m DTPA, dynamic imaging shows poor cerebral blood flow to an area of stroke (arrows). (B) Delayed imaging at 3 hours after injection shows increased accumulation of Tc-99m DTPA in the same area of stroke (arrow) because of diffusion across a disrupted BBB.

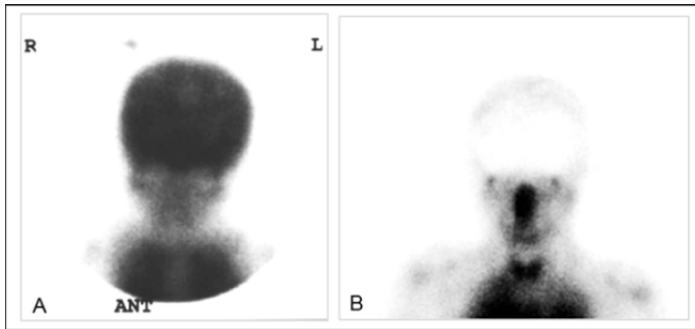


Figure 21. (A) Normal uptake of Tc-99m HMPAO in the brain of a living person. (B) Absence of Tc-99m HMPAO uptake in the brain is consistent with brain death. Also seen is normal uptake in lacrimal glands, nasopharynx, thyroid, and lungs.

In many cases, passive diffusion necessarily requires delivery of the molecule to the location of interest. Moreover, because diffusion is not a unidirectional process, accumulation typically involves some method of retention. Hence, passive diffusion is often inter-related with delivery (eg, blood flow to

the area) and retention of the material in the tissue of interest. For example, localization of the cerebral perfusion radiopharmaceuticals Tc-99m exametazime (HMPAO) and Tc-99m bicisate (ECD) involves delivery via cerebral arterial blood flow, diffusion into the brain, and retention in the brain due to conversion to a hydrophilic species and enzymatic metabolism, respectively. Whole brain cerebral perfusion can be assessed for evaluation of brain death (see Figure 21), as well as evaluation of altered cerebral perfusion to discrete areas within the brain (see Figure 22).

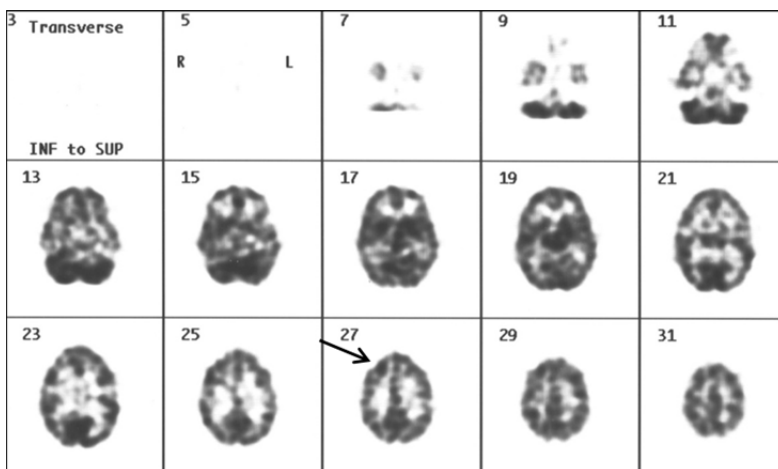


Figure 22. SPECT imaging following ictal injection of Tc-99m ECD shows increased uptake in the seizure focus (arrow).

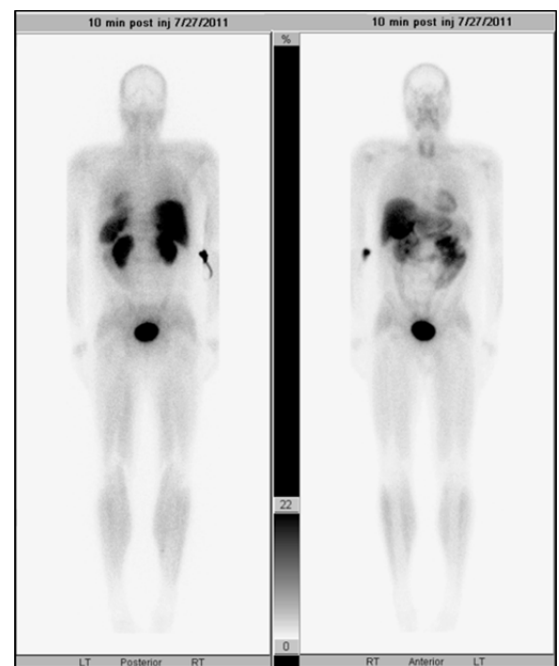


Figure 23. Following injection of Tc-99m sestamibi, activity is seen in the heart, salivary glands, thyroid, skeletal muscle (note lack of uptake in bone), excretion by the kidneys into the urine with collection in the bladder, excretion by the liver into the bile with collection in the gallbladder and intestines, and infiltration at the injection site

Tc-99m myocardial perfusion agents are another group of radiopharmaceuticals that depend on delivery (ie, blood flow through the coronary arteries), diffusion into myocardial cells, and retention in those cells. Both Tc-99m sestamibi and Tc-99m tetrofosmin cross the cell membranes by lipophilic diffusion and then are retained by electrostatic binding to negative electrical charges on the mitochondrial membranes. Because only about 5% of cardiac output goes into the coronary arteries, the majority of these radiopharmaceuticals goes elsewhere in the body (see Figure 23).

FILTRATION

Filtration refers to a special case of diffusion involving transit of molecules through pores, or channels, driven by a hydrostatic or osmotic pressure gradient. This prime example of this is glomerular filtration by the kidney. There are two primary factors involved in filtration. The first is molecular size vs. pore size. For glomerular filtration, only small hydrophilic molecules (i.e., molecular weight of <5000) are typically able to pass through the glomerular pores. The second factor is availability. For glomerular filtration, only those molecules that are free in plasma (i.e., not protein bound) are available to be filtered.

Filtration can be further described in terms of several characteristics. First, filtration requires some sort of force or pressure gradient. For glomerular filtration, this is blood pressure. However, it does not require the local input of other external energy. Third, no transporters, carriers, or other receptors are involved so filtration is non-selective, is not competitively inhibited by similar molecules, and is not subject to saturation.

Although many radiopharmaceuticals are excreted, at least in part, by glomerular filtration, the radiopharmaceutical used for glomerular function renal imaging is Tc-99m DTPA (see Figure 24).

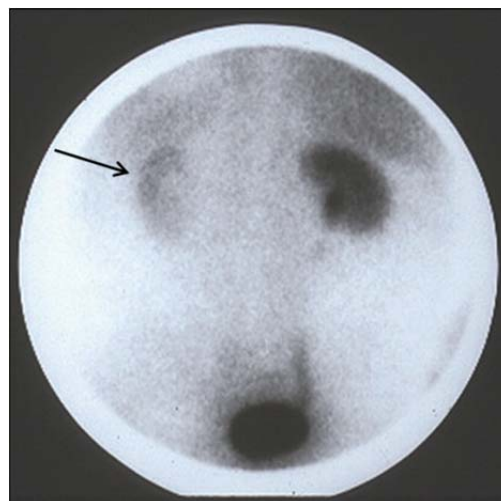


Figure 24. Following pre-treatment with captopril, decreased glomerular filtration of Tc-99m DTPA is seen in the left kidney (arrow). As an ACE inhibitor, captopril blocked the compensatory mechanism activated by left renal artery stenosis, resulting in decreased glomerular pressure in the left kidney.

FACILITATED DIFFUSION

Facilitated diffusion is a type of carrier-mediated transport across membranes. It can be thought of as a revolving door. There are several characteristics that help define facilitated diffusion. Importantly, a carrier in the membrane is used to carry the molecule across the membrane. Because a carrier is used, it is selective (i.e., only certain molecules fit into the carrier). Accordingly, it can be competitively inhibited by the presence of similar molecules that also fit into the carrier. Because there are a limited number of carriers, it is possible to achieve saturation (i.e., the maximum response when all carriers are engaged). Facilitated diffusion uses carriers that are passive (i.e., like an un-motorized revolving door), so it requires a concentration gradient to operate. However, it does not use external energy.

The prime example of facilitated diffusion is glucose. Glucose enters cells via transmembrane protein transporters [GLUT]. The radiolabeled analog of glucose, F-18 fludeoxyglucose (FDG), similarly enters cells via the glucose transporters [GLUT]. Once inside cells, both glucose and FDG are phosphorylated by hexokinase. Glucose-6-phosphate then enters the glycolytic pathway. Further metabolism of FDG-6-phosphate is blocked, however, so it is retained in the cells. Hence, cellular uptake reflects glucose metabolism (see Figure 25). It is important to remember that glucose and FDG are competing for the same GLUT transporters, so elevated blood levels of glucose will decrease cellular uptake of FDG.

ACTIVE TRANSPORT

Active transport is another type of carrier-mediated transport across membranes. Unlike facilitated diffusion, however, it requires energy, usually from ATP, for the transporters to function. Hence, it can be thought of as a motorized revolving door or as a pump. Using energy-dependent carriers allows the transport of molecules against a concentration gradient (i.e., from an area of low concentration to an area of high concentration). Other characteristics of active transport, however, are similar to facilitated diffusion. Because a carrier is used, it is selective (i.e., only certain molecules fit into the



Figure 25. Following injection of F-18 FDG in a normal patient, there is high uptake in brain, variable uptake in heart (high uptake in this patient), and moderate uptake in liver, GI tract, and marrow. F-18 FDG filtered by the kidneys is not reabsorbed by the distal tubules so it remains in the urine, demonstrating activity in the renal collecting system, ureters, and bladder.

carrier). Accordingly, it can be competitively inhibited by the presence of similar molecules that also fit into the carrier. Because there are a limited number of carriers, it is possible to achieve saturation (i.e., the maximum response when all carriers are engaged).

A well-known example of active transport is the concentration of iodide in the thyroid gland. Iodide ions are transported into thyroid cells via the Na^+/I^- symporter. Hence, radioisotopes of iodine such as I-123 and I-131 are useful radiopharmaceuticals to evaluate thyroid function. Additionally, Tc-99m pertechnetate (TcO_4^-) is of similar ionic radius and a negative charge so it is also transported like iodide (see Figure 26). It should be emphasized that high concentrations of iodide in the blood, such as from injection of iodinated x-ray contrast media, will competitively inhibit thyroid uptake of these radiopharmaceuticals (see Figure 26).

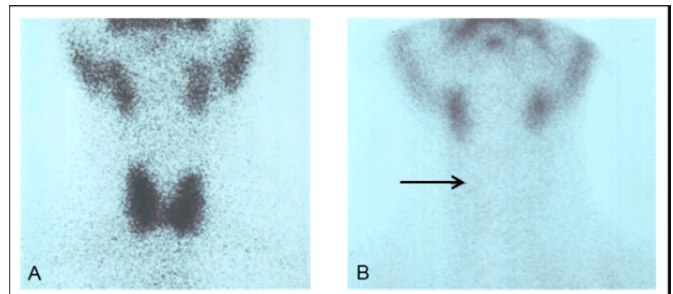


Figure 26. (A) Normal uptake of Tc-99m pertechnetate in thyroid (and salivary glands). (B) Absent thyroid uptake (arrow) of Tc-99m pertechnetate in a patient who was administered iodinated x-ray contrast media a few days before.

A second example of active transport is glucose absorption from the GI tract into the blood and reabsorption of glomerular-filtered glucose back into the blood by the distal renal tubules. This is accomplished using the sodium-dependent glucose cotransporter (SGLT). Although F-18 FDG is a ligand for facilitated diffusion via GLUT transporters, it is not readily transported by SGLTs. Therefore, glomerular filtered F-18 FDG remains in the urinary tract and flows to the bladder rather than being reabsorbed into the blood as is glucose (see Figure 25).

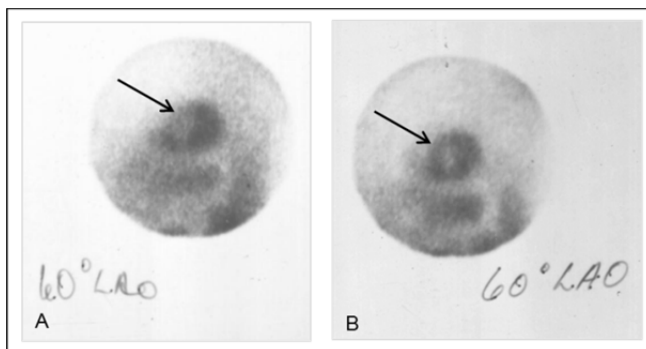


Figure 27. (A) Reduced uptake of Tl-201 in an area of heart muscle (arrow) due to stress-induced ischemia in a patient with coronary artery disease. (B) Normalization of uptake following redistribution in the same patient.

Another well-known example of active transport is the Na^+/K^+ pump, especially of importance in the heart muscle. Thallous chloride Tl-201 has been widely used for myocardial perfusion scans. Thallium is not a chemical analog of potassium, but rather is a transition metal. However, thallous ion (Tl^+) happens to have an ionic radius similar to K^+ and fits in the Na^+/K^+ pump. Uptake in heart muscle demonstrates viability. Also important is delivery to the myocardial cells via blood flow

through the coronary arteries. Hence, uptake in heart muscle also reflects coronary perfusion (see Figure 27). A second radiopharmaceutical is rubidium chloride Rb-82, which is used for PET myocardial perfusion scans. Rubidium is a chemical analog of potassium, falling immediately below it on the periodic table of the elements, and Rb^+ also fits in the Na^+/K^+ pump.

A fourth example of active transport is the norepinephrine transporter in adrenergic nerve terminals. This transmembrane carrier transports monoamine neurotransmitters into neurons where they are accumulated in storage vesicles. I-123metaiodobenzylguanidine (MIBG) is structurally related to norepinephrine and fits in this transporter. Over-expression of this transporter occurs in certain neoplasms such as neuroblastoma and pheochromocytoma (see Figure 28).

A final example of active transport involves the tubular cells in the renal cortex. Tc-99m succimer (DMSA) is taken up by, and retained in, these cells (see Figure 29).

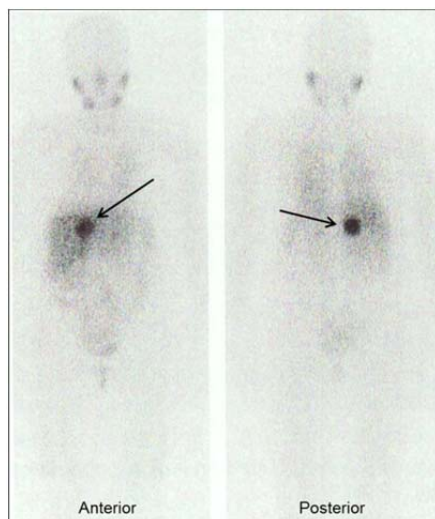


Figure 28. I-123 MIBG demonstrates increased uptake in a pheochromocytoma in the right adrenal gland (arrow). Normal uptake is also seen in salivary glands, liver, heart, and bowel.



Figure 29. Tc-99m DMSA renal scans shows normal uptake throughout the renal cortex. Areas of decreased uptake in both the upper and lower poles of the right kidney (arrows) are scar formation subsequent to recurrent kidney infections.

SECRETION

Secretion refers to the special case of active transport out of glands and other tissues. Three common examples are secretion of hydrochloric acid by the stomach, secretion of certain substances by the kidney tubular cells into the urine, and secretion of certain substances by the liver in the bile.

Meckel's Diverticulum is a patch of ectopic stomach tissue, usually in the intestine. Being stomach tissue, it secretes hydrochloric acid which, being in the intestine, erodes the intestinal wall to the point of bleeding. Tc-99m pertechnetate (TcO_4^-) is of similar size and like charge to chloride (Cl^-) so it is secreted as pertechnic acid ($\text{H}^+ \text{TcO}_4^-$) by both normal stomach tissue and Meckel's Diverticuli (see Figure 30).

The tubular cells in the kidneys secrete certain substances, such as some waste products, into the urinary collecting system. Tc-99m mertiatide (MAG3) is cleared from the blood by this mechanism, resulting in much higher urinary concentrations and better contrast compared to radiopharmaceuticals eliminated by glomerular filtration (see Figure 31).

The hepatocytes in the liver extract certain substances from the blood and secrete them into the bile. Tc-99m IDA agents (disofenin, mebrofenin) are excreted using the same organic ion transport system as is used by bilirubin (see Figure 32).

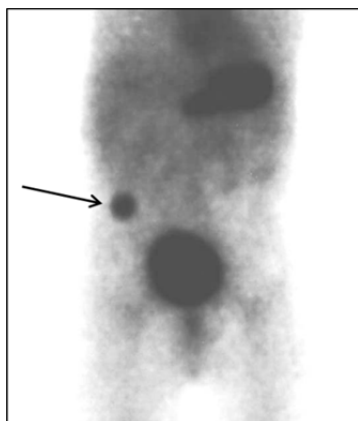


Figure 30. Tc-99m sodium pertechnetate scan in child with GI bleeding shows marked uptake in a Meckel's Diverticulum (arrow). Also seen is normal retention in blood pool, uptake in stomach, and excretion in urine (bladder).

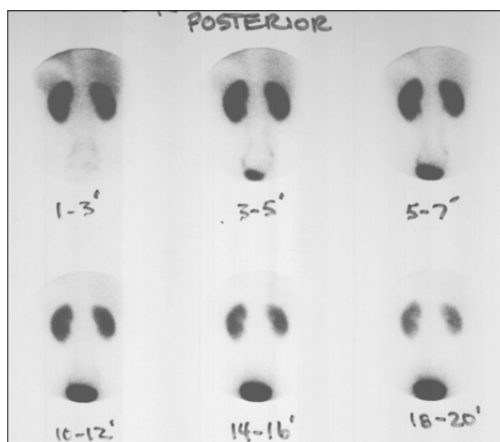


Figure 31. Normal Tc-99m MAG3 renal scan showing prompt extraction from the blood and secretion into the urine.

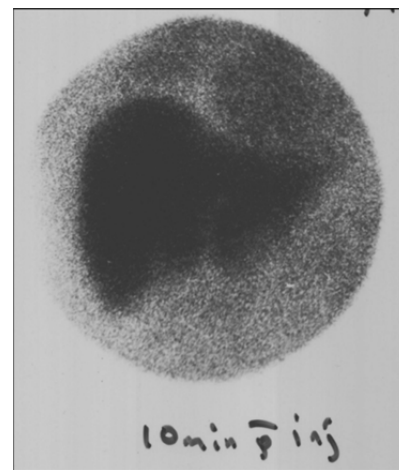


Figure 32. Hepatic uptake of Tc-99m mebrofenin in a transplanted liver indicates organ viability (because active transport/secretion requires energy, the tissue is alive).

PHAGOCYTOSIS

The term phagocytosis comes from Greek words that translate as 'cell eating.' It is the process whereby the cell engulfs a particle and internalizes it. A prime example involves reticuloendothelial system (RES) cells, such as Kupffer cells in the liver, phagocytizing colloid particles. Although this mechanism is potentially saturable, it is unlikely for the small doses of particles used in

radiopharmaceuticals. Tc-99m sulfur colloid, the traditional radiopharmaceutical used for liver scans, is localized by this mechanism. Focal areas lacking Kupffer cells, such as a tumor, cyst, abscess, or hemangioma, will be demonstrated as areas of lack of uptake (see Figure 33). If the entire liver is poorly functioning, such as with hepatitis or cirrhosis, there is typically a ‘colloid shift’ – i.e., a shift in normal uptake away from the liver with increased uptake in the spleen and bone marrow (see Figure 34).

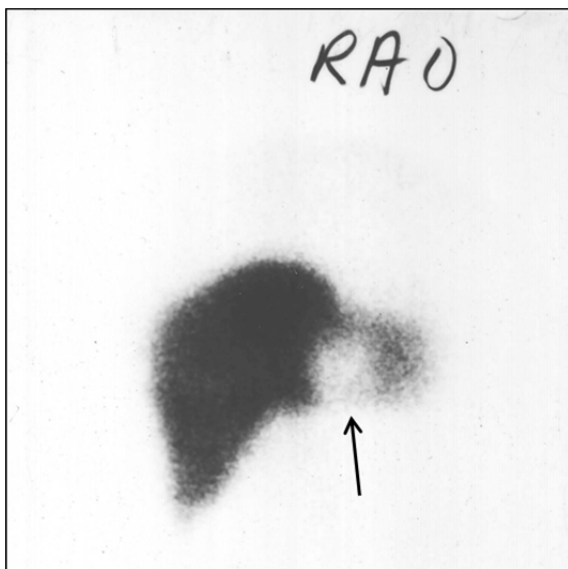


Figure 33. Tc-99m sulfur colloid scan shows normal uptake in liver but lack of uptake in a cavernous hemangioma.



Figure 34. Tc-99m sulfur colloid scan in a patient with severe alcoholic cirrhosis demonstrating colloid shift away from the liver (arrow) to the spleen and marrow.

CELL SEQUESTRATION

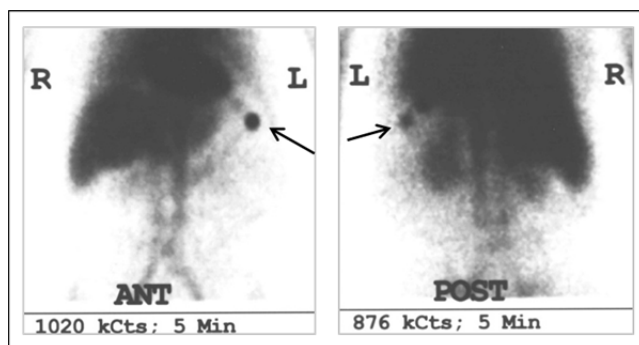


Figure 35. Imaging with heat-damaged Tc-99m RBCs in a post-splenectomy patient shows uptake in an accessory spleen (arrows). Also seen is normal retention in blood pool (heart, liver, and major blood vessels).

Cell sequestration refers to the process whereby old or damaged red blood cells are removed from the circulation. This process is generally associated specifically with the spleen. Although this mechanism is potentially saturable, it is unlikely for the relatively small numbers of cells used for imaging. The radiopharmaceutical is generally prepared by labeling RBCs in vitro with Tc-99m (using the modified Brookhaven labeling method facilitated with use of commercial product

UltraTag™ and then damaging them by heating at 49°C for 15 minutes. This imaging procedure is especially useful for localizing and/or identifying ectopic accessory spleens (see Figure 35).

CAPILLARY BLOCKADE

Capillary blockade refers to the microembolization (i.e., physical trapping) of particles in capillaries and pre-capillary arterioles. Because the diameter of capillaries and pre-capillary arterioles are about 10 microns and 20-30 microns, respectively, such particles should be slightly larger in size, for example 10-50 microns. Obviously, delivery to the capillary bed via blood flow is also a necessary component of this localization.

When such sized particles are injected intravenously, the first capillary beds encountered are the lungs. Hence, radiolabeled aggregates (e.g., Tc-99m macroaggregated albumin [MAA]) have long been used for perfusion lung imaging (see Figure 36).

Because this mechanism necessarily involves delivery to the capillary beds via blood flow, localization of Tc-99m MAA in each of the two lungs is a surrogate for relative blood flow to each of the two lungs. Hence, Tc-99m MAA perfusion lung imaging can also be used to assess blood flow through the pulmonary arteries (see Figure 37).

A similar procedure can be used to evaluate blood flow within the liver. When Tc-99m MAA is injected through a catheter positioned in the hepatic artery, it is delivered via hepatic blood flow to the capillaries in the liver (see Figure 38).

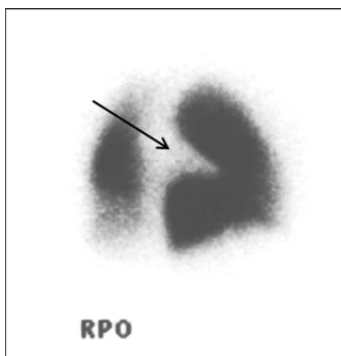


Figure 36. Tc-99m MAA perfusion lung scan showing a classic wedge-shaped defect (arrow) in a patient with pulmonary embolism.

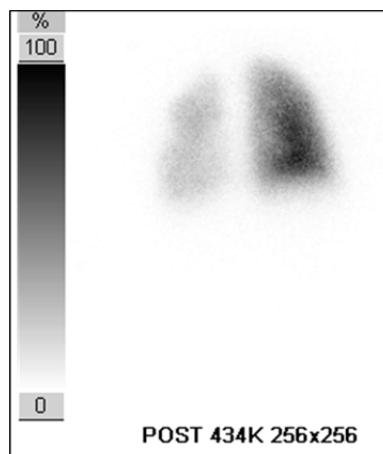


Figure 37. Tc-99m MAA perfusion lung imaging in a child with congenital heart disease including left pulmonary artery stenosis shows differential perfusion to be 23% left lung and 77% right lung.

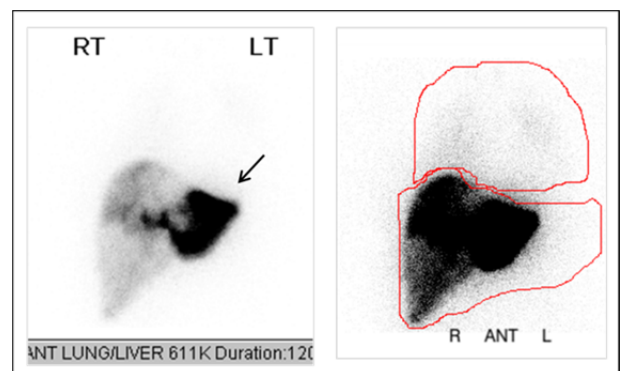


Figure 38. Imaging of Tc-99m MAA injected into hepatic artery shows the majority of uptake in the left lobe of the liver (arrow), the area of known metastases, with no significant shunting to the lungs or GI tract. Because of this favorable biodistribution, this patient was treated with Y-90 microspheres.

ION EXCHANGE

Ion exchange refers to the exchange of ionic chemical analogs, especially in a crystalline matrix. Classic examples include exchange of Sr^{+2} for Ca^{+2} and F^- for OH^- in hydroxyapatite. Although potentially saturable, it is unlikely for the small doses used in radiopharmaceuticals.

Current radiopharmaceuticals that localize in bone by this mechanism are Sr-89 strontium chloride, a beta-emitter used to treat painful bone metastases, and F-18 sodium fluoride, a PET agent used for bone scans.

CHEMISORPTION

Chemisorption refers to the binding of phosphate-type compounds onto the surface of bone. The strength of this binding is intermediate between chemical covalent bonding and hydrogen bonding (adsorption), hence the coined term chemi•sorption. Examples of such compounds are diphosphonates such as Tc-99m medronate (MDP) and oxidronate (HDP) for bone imaging and Sm-153 leixidronam (EDTMP) for treatment of painful bone metastases. Because localization is on the surface, uptake reflects surface area. Hence, there is increased uptake in areas of greater surface area associated with increased bone metabolism (e.g., fracture, infection, tumor) (see Figure 39). Although potentially saturable, it is unlikely for the small doses used in radiopharmaceuticals.

In addition to chemisorption on the surface of bone, there can also be chemisorption onto calcium phosphate crystals that precipitate in certain tissues as a consequence of severe hyperparathyroidism and hypercalcemia (see Figure 40).

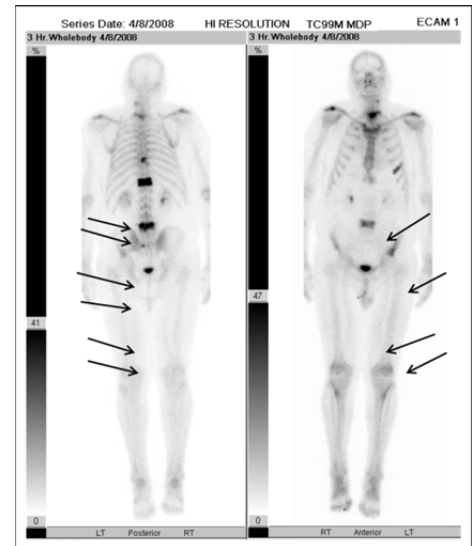


Figure 39. Tc-99m MDP bone scan shows increased uptake in reactive bone around metastatic tumors (arrows). Note: there is lack of primary uptake in the tumors themselves. Also seen is normal excretion into the urine (kidneys,

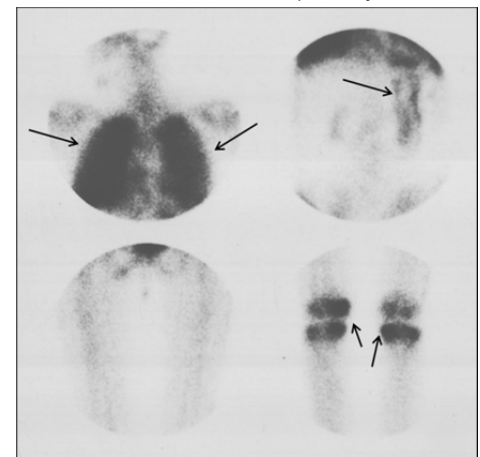


Figure 40. Tc-99m MDP scan in a patient with hyperparathyroidism and hypercalcemia shows uptake in sites of metastatic calcification (i.e., calcium phosphate precipitation), specifically the lungs, stomach, and knee joints (arrows).

CELLULAR MIGRATION



Figure 41. In-111 leukocyte scan in a patient with Crohn's disease shows uptake in a right abdominal abscess and in a superficial infection at the colostomy site on the left side (arrows). Also seen is normal uptake in spleen, liver, and bone marrow.

Cellular migration refers to the directed migration of cells, especially in response to stimuli. The prime example is the chemotaxis of white blood cells to sites of infection. Hence, autologous leukocytes radiolabeled with In-111 oxine or Tc-99m exametazime (HMPAO) can be used to localize sites of infection (see Figure 41).

RECEPTOR BINDING

Receptor binding refers to the “lock-and-key” binding of a molecule to a specific receptor site. A classic example is the binding interaction of an antibody (or antibody fragment) to an antigen. Other examples of ligands that bind to particular receptor sites include peptides/hormones and neurotransmitter analogs. General characteristics of receptor binding include selectivity, competitive inhibition by similar molecules, and the possibility of being saturated.

Although much research has been conducted with radiolabeled antibodies, few are currently marketed. In-111 capromab pentetide, a monoclonal murine IgG antibody directed to prostate specific membrane antigen (PSMA), is used for staging and follow-up of prostate cancer (see Figure 42). I-131 tositumomab and In-111/Y-90 ibritumomab tiuxetan, monoclonal murine IgG antibodies directed to CD20 receptors on B-cells and non-Hodgkin's lymphoma tumor cells, are used for treatment of non-Hodgkin's lymphoma (see Figure 43).

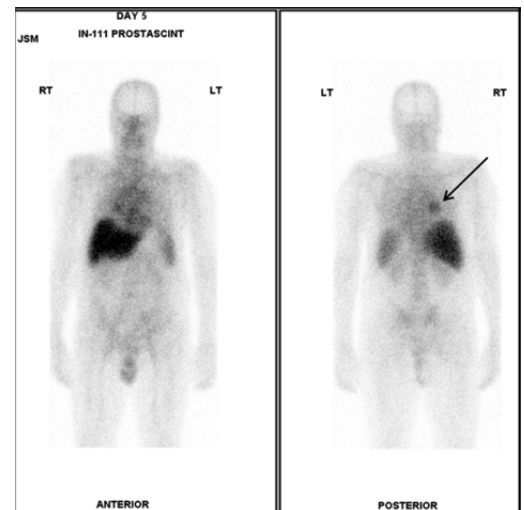


Figure 42. In-111 capromab pentetide image shows uptake in a prostate cancer metastasis in the right lung (arrow). Also seen is normal retention in blood pool and normal uptake in liver, spleen, and marrow.

Many neuroendocrine tumors exhibit enhanced expression of somatostatin receptors. In-111 pentetreotide, a radiolabeled form of octreotide (the synthetic octapeptide derivative of the active portion of somatostatin), is used to detect, localize, and evaluate such somatostatin-expressing tumors by binding to these receptors (see Figure 44).

I-123 ioflupane is a chemical derivative of cocaine. It binds to pre-synaptic dopamine transporters, which are primarily located in the striatum (i.e., caudate nuclei and putamen). Loss of dopamine transporter density, as occurs in Parkinson's Disease, results in reduced uptake of the radiopharmaceutical compared to normal (see Figure 45).

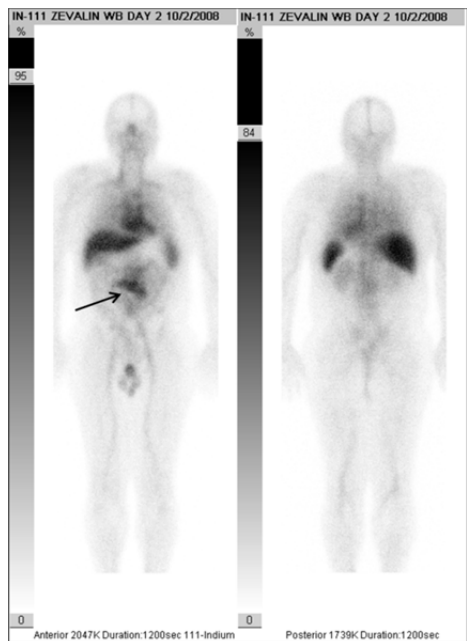


Figure 43. Pre-therapy In-111 ibritumomab tiuxetan image shows uptake in an abdominal lymphoma (arrow). Also seen is normal retention in blood pool, normal high uptake in liver and spleen, and normal low uptake in bone marrow and kidneys. This patient was subsequently treated with Y-90 ibritumomab tiuxetan. Note: Prior to radiopharmaceutical administration, the patient is pre-treated with rituximab to saturate CD20 receptors on normal B cells.

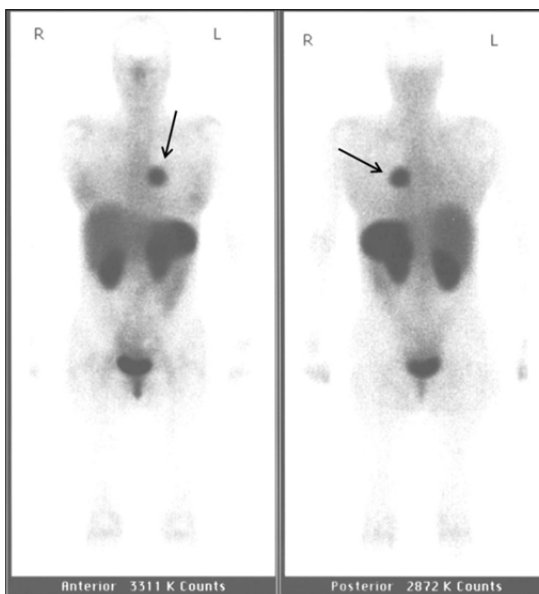


Figure 44. In-111 pentetreotide image shows increased uptake in a somatostatin-expressing carcinoid tumor in the left lung (arrow). Also seen is normal uptake in liver and spleen, and normal excretion by the kidneys into the urine (bladder).

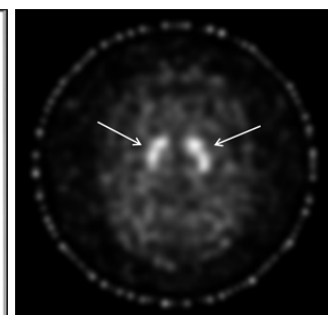


Figure 45. I-123 ioflupane image shows normal uptake in the caudate nucleus and putamen, which appears as a crescent (or comma) shape, on both sides (arrows).

A number of investigational radiopharmaceuticals currently in clinical trials are localized by receptor binding. For example, several agents have been developed that bind to beta amyloid deposits in the brain, which is the hallmark of Alzheimer's Disease (see Table 2).

Table 2

Selected radiopharmaceuticals that bind to beta amyloid.
C-11 PiB (Pittsburgh compound B)
F-18 flutemetamol (fluoro-PiB)
F-18 florbetapir (AV-45)
F-18 florbetaben (BAY 94-9172)

ALTERED BIODISTRIBUTION RELATED TO IMPROPER PREPARATION

Improper preparation or other problems that might occur during preparation can result in abnormally high levels of radiochemical impurities. Radiochemical impurities have different biodistributions from the intended product, and abnormally high levels of these impurities can potentially interfere with the imaging procedure. Hence it is important for nuclear pharmacists to recognize common radiochemical impurities and their localizations.

The predominant radiochemical impurity in Tc-99m labeled radiopharmaceuticals is Tc-99m pertechnetate. Free pertechnetate is localized in salivary glands, thyroid, stomach, GI tract, and urine/bladder (see Figure 46).

In some cases, small particles or precipitates may be formed. These small particles are then phagocytosed by the liver (see Figure 47).

In other cases, particulate impurities may be much larger in size (e.g., flocculation). Particles larger than 10 microns will lodge in the first capillary bed that they encounter (i.e., lungs following intravenous injection) (see Figure 48).

In some situations there may be radiochemical impurities that are excreted in the urine by glomerular filtration. Such impurities are typically hydrophilic, ionized, non-protein bound, and have a MW of <5000. One example of these impurities is the group of radiopharmaceuticals that employ transfer ligands as intermediate chelating agents subsequent to complexation with the final product (see Table 3). If the final complexation reaction is of substandard yield, residual radiolabeled transfer ligand will be excreted in the urine.



Figure 46. Very old, poor-quality bone scan shows Tc-99m pertechnetate impurity localization in salivary glands, thyroid, stomach, GI tract, and urine/bladder



Figure 47. Very old, poor quality bone scan shows colloid impurities taken up by the liver (arrow).

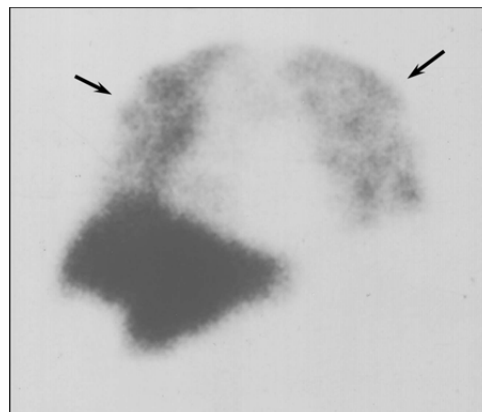


Figure 48. Tc-99m sulfur colloid liver scan shows uptake of large particle impurities in the lungs (arrows).

Table 3

Selected transfer ligands	
Transfer ligand	Radiopharmaceutical
acetate	In-111 capromab pendetide, In-111/Y-90 ibritumomab tiuxetan
citrate	Tc-99m sestamibi, In-111 pentetretotide
edetate	Tc-99m bismate (ECD)
gluconate	Tc-99m tetrofosmin
tartrate	Tc-99m mertiatide (MAG3)

In some other situations there may be radiochemical impurities that are excreted by the liver into the biliary system. Such impurities are typically lipophilic, possess both polar and non-polar groups, and have a MW of 300-1000. One example of this type of impurity is a radiochemical impurity in MAG3 that undergoes hepatobiliary excretion.

In yet other situations there may be radiochemical impurities that remain in the blood pool. These situations generally involve impurities that label to red blood cells or are highly protein bound.

Improper preparation of In-111 labeled radiopharmaceuticals may result in several radiochemical impurities. In^{+3} is soluble in acid, but precipitates at $\text{pH} > 3$; these precipitate particles are phagocytized by liver and spleen. Excess free In^{+3} in the blood binds avidly to plasma transferrin, and hence exhibits prolonged blood pool retention. In some cases, there may be In-111 labeled peptides as impurities, which are excreted by the kidneys into the urine. In other cases, there may be In-111 labeled large particles (e.g., antibody aggregates) which localize in the liver and/or embolize in the lungs.

Improper preparation of I-123 or I-131 labeled radiopharmaceuticals may result in radiochemical impurities. The predominant impurity of concern is free I^- . Free iodide localizes in the thyroid, so administration of radioiodinated radiopharmaceuticals typically require pre-treatment or concurrent administration of SSKI to block thyroidal uptake.

Improper preparation of F-18 labeled radiopharmaceuticals may result in radiochemical impurities. The predominant impurity of concern is free F^- . Free fluoride localizes in the bone and is excreted in the urine.

INTERESTING CASE

Tc-99m sestamibi is widely used for parathyroid imaging. Tc-99m sestamibi is taken up in both parathyroid adenomas and normal thyroid. However, it tends to be retained in parathyroid adenomas whereas it slowly washes out of normal thyroid. Hence, delayed imaging is typically performed in order to better identify parathyroid adenomas. Many physicians like to also perform a thyroid only scan, using Tc-99m pertechnetate, as an adjunct in these procedures.⁵

A patient seen in our clinic underwent a parathyroid/thyroid imaging procedure using Tc-99m sestamibi and Tc-99m pertechnetate (see Figure 49).

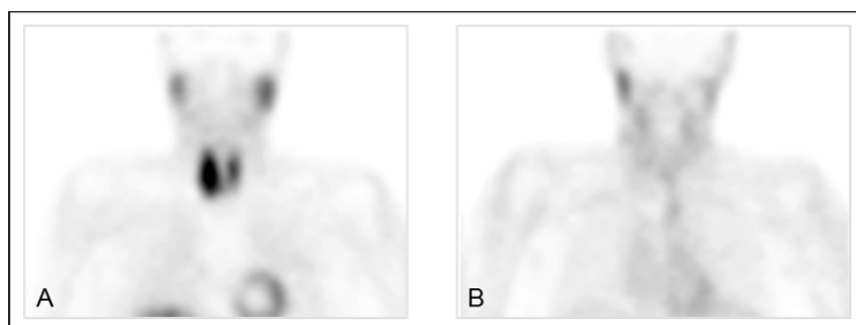


Figure 49. (A) Tc-99m sestamibi parathyroid SPECT image shows uptake in parathyroid/thyroid, salivary glands, heart, and liver. (B) Tc-99m pertechnetate thyroid SPECT image performed 4.5 hours later shows negligible uptake in the thyroid.

A technologist asked me: Why is there a discrepancy in thyroid uptake between the two scans?

The immediate, albeit only partial, answer is that the two radiopharmaceuticals have different mechanisms of uptake. Tc-99m sestamibi localizes by passive diffusion (with

intracellular retention) whereas Tc-99m pertechnetate is taken up by active transport via the Na^+/I^- symporter. A key piece of information in this particular case is that the patient was being treated with levothyroxine. Levothyroxine inhibits pituitary release of TSH, so there was lack of TSH stimulation of the thyroid to take up iodide (or pertechnetate). However, TSH has no effect on passive diffusion uptake. This difference in uptake mechanism explains why Tc-99m pertechnetate was not taken up in this patient's thyroid whereas Tc-99m sestamibi had normal uptake in the same thyroid.

SUMMARY

A variety of mechanisms are involved in the localization of radiopharmaceuticals. It is important to recognize that uptake often involves other processes as well (e.g., delivery to the tissue, retention in cells). Radiopharmaceutical preparation problems can yield radiochemical impurities that demonstrate altered biodistribution.

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ASSESSMENT QUESTIONS

1. All of the following are examples of common biologic compartments, EXCEPT:
 - a. lung airways.
 - b. lymphatic channels.
 - c. peritoneal cavity.
 - d. Meckel's diverticulum.

2. Use of which of the following radiopharmaceuticals is based on a classic example of uniform dispersion within a compartment?
 - a. I-123 sodium iodide
 - b. I-125 RISA
 - c. I-131 tositumomab
 - d. Tc-99m exametazime

3. All of the following are examples of diseases/conditions that present non-uniformities within a compartment, EXCEPT:
 - a. pulmonary embolism.
 - b. acute cholecystitis.
 - c. COPD.
 - d. hydronephrosis.

4. Which of the following mechanisms is the basis for visualization of a site of GI bleeding?
 - a. cell sequestration
 - b. cellular migration
 - c. facilitated diffusion
 - d. leakage from compartment

5. Movement (flow) within a compartment is the mechanism of localization for each of the following procedures, EXCEPT:
 - a. gastric emptying.
 - b. lacrimal drainage.
 - c. ureteral reflux.
 - d. myocardial perfusion.

6. Regarding passive diffusion, which of the following is true?
 - a. In some biological systems, net movement can be from an area of low concentration to an area of higher concentration.
 - b. Its rate is a function of the concentration gradient.
 - c. Input of external energy is needed for diffusion across biologic membranes.
 - d. It may be competitively inhibited by similar molecules.

7. Localization of Tc-99m tetrofosmin in the myocardial muscle is dependent on all of the following, EXCEPT:
- glucose blood levels.
 - coronary blood flow (delivery to the tissue).
 - passive diffusion in the cells.
 - retention in the cells.
8. Regarding glomerular filtration, which of the following situations would NOT be a problem?
- cardiovascular shock (abnormally low blood pressure)
 - highly and tightly protein-bound
 - high concentration of similar molecules in the blood
 - MW > 5000
9. Characteristics of facilitated diffusion include all of the following, EXCEPT:
- It can be saturated.
 - It requires a concentration gradient.
 - Its rate is solely a function of the concentration gradient.
 - It uses a carrier (membrane transporter).
10. Characteristics of active transport include all of the following, EXCEPT:
- It can be competitively inhibited by similar molecules.
 - It can transport molecules against a concentration gradient.
 - It requires the input of external energy.
 - Saturation is theoretically possible but unlikely in biological systems.
11. Examples of active transport systems include all of the following, EXCEPT:
- GLUT.
 - Na⁺/I⁻ symporter.
 - Na⁺/K⁺ pump.
 - norepinephrine transporter.
12. Localization of Tc-99m pertechnetate in a Meckel's diverticulum is by the mechanism of:
- ion exchange.
 - secretion.
 - passive diffusion.
 - receptor binding.
13. "Colloid shift" refers to a shift in the biodistribution of Tc-99m sulfur colloid in patients with diffuse liver disease, resulting in decreased uptake in liver with increased uptake in:
- spleen and bone marrow.
 - kidneys/urine.
 - lungs.
 - lymphatic system/lymph nodes.

14. Which of the following is an example of cell sequestration?
- localization of In-111 leukocytes in a site of infection
 - localization of Tc-99m RBCs in cardiac blood pool
 - localization of Tc-99m RBCs in a site of GI bleeding
 - localization of heat-damaged Tc-99m RBCs in the spleen
15. An appropriate particle size for capillary blockade is _____ microns.
- 10-50
 - 0.1-0.5
 - 1-5
 - 100-500
16. Treatment of liver tumors with Y-90 microspheres relies on which of the following mechanisms of localization?
- compartmentalization
 - passive diffusion
 - phagocytosis
 - capillary blockade
17. Localization of Sr-89 strontium chloride in skeletal hydroxyapatite is by the mechanism of:
- active transport.
 - ion exchange.
 - chemisorption.
 - receptor binding.
18. Localization of Sm-153 lexidronam (EDTMP) at sites of bone metastases is by the mechanism of:
- active transport.
 - chemisorption.
 - ion exchange.
 - receptor binding.
19. Which of the following is localized by cellular migration?
- leukocytes
 - metastatic tumor cells
 - platelets
 - red blood cells
20. Which of the following antibodies does NOT bind to CD20 receptors?
- ibritumomab
 - rituximab
 - tositumomab
 - capromab pendetide

21. Which of the following radiopharmaceuticals binds to somatostatin receptors?
- C-11 PiB
 - I-123 iobenguane
 - I-123 ioflupane
 - In-111 pentetreotide
22. If faulty preparation of a Tc-99m labeled radiopharmaceutical results in a large fraction of free pertechnetate impurity, localization would be expected in all of the following organs, EXCEPT:
- salivary glands.
 - stomach.
 - liver.
 - thyroid.
23. For radiopharmaceuticals that are prepared using a transfer ligand, excessive radiolabeled transfer ligand impurity will be:
- excreted in the bile.
 - phagocytized by the liver.
 - excreted in the urine.
 - remain in the blood pool (bound to plasma proteins).
24. If the pH of an InCl_3 solution is raised to 7.0, the impurity likely formed will be:
- excreted in the bile.
 - excreted in the urine.
 - phagocytized by liver and spleen.
 - remain in the blood pool (bound to plasma transferrin).
25. Regarding parathyroid/thyroid scintigraphy, which of the following statements is true?
- Tc-99m pertechnetate and Tc-99m sestamibi are localized by the same mechanism.
 - Thyroid uptake of Tc-99m sestamibi is NOT affected by TSH.
 - Tc-99m sestamibi is localized in parathyroid adenomas by passive diffusion whereas it is localized in thyroid by active transport.
 - Tc-99m sestamibi washes out of parathyroid adenomas whereas it tends to be retained in normal thyroid tissue.