Overview of Part III, Quantitative Evaluation in Nuclear Medicine Studies

11

The previous section, Part II, Mathematics of the Biodistribution of Radiopharmaceuticals, reviewed the mathematics that describes the biologic processes that determine the biodistribution of a radiopharmaceutical once it has been administered to a patient. Now in Part III, Quantitative Evaluation in Nuclear Medicine Studies, we will examine how an understanding of the mathematics of the biodistribution of radiopharmaceuticals facilitates (1) the design of optimal study protocols, (2) image interpretation, and (3) quantitation of important functional parameters. Each commonly performed nuclear medicine study is examined with an emphasis on how useful biologic information can be extracted and quantitated. Included for each nuclear medicine study is a brief discussion of the essential aspects of the radiopharmaceutical and relevant biology that are fundamental to the extraction mechanism.

This section proceeds systematically through the diagnostic nuclear medicine studies that are listed in the Nuclear Medicine Procedure Manual 2012–2014 except for several studies that are infrequently performed (see Appendix A: Diagnostic Nuclear Medicine Studies Covered in this Book and Table 11.1) [1]. None of the excluded studies include any unique mathematical technique.

Each organ system plus infection and tumor has its own chapter, and the chapters are presented in alphabetical order. The nuclear medicine studies included within each chapter are also arranged in alphabetical order. Many nuclear medicine studies are included that do not involve quantification of a functional parameter, but they are included for comparison and completeness and because the biodistribution of the radiopharmaceutical in these studies nevertheless follows the mathematics discussed in Part II, Mathematics of the Biodistribution of Radiopharmaceuticals. Eighteen of the 39 nuclear medicine studies that are discussed include some form of explicit quantification and the other 21 do not.

The discussion of each nuclear medicine study is divided into a set of subsections: Overview; Radiopharmaceutical Characteristics; Extraction Mechanism; Extraction Efficiency; Extraction Mechanism, Saturable or Non-saturable;

W.C. Klingensmith III, *The Mathematics and Biology of the Biodistribution of Radiopharmaceuticals-A Clinical Perspective*,
DOI 10.1007/978-3-319-26704-3_11

Table 11.1 Nuclear medicine studies not included in Part III

Study	Category	Reason
Thyroid Imaging Study (Tc-99m-pertechnetate)	Endocrine system	Infrequently performed; replaced by Thyroid Imaging Study (I-123)
Gastroesophageal Reflux Study (Tc-99m-sulfur colloid)	Gastrointestinal system	Infrequently performed
Helicobacter pylori Breath Test (C-14-urea)	Gastrointestinal system	Often not performed in a nuclear medicine lab
LeVeen Shunt Study (Tc-99m-sulfur colloid)	Gastrointestinal system	Infrequently performed
Bone Marrow Study (Tc-99m-sulfur colloid)	Hematologic system	Infrequently performed
Gallium Study (Ga-67-citrate)	Infection imaging	Infrequently performed; inaccurate
Pulmonary Aspiration Study (Tc-99m-sulfur colloid)	Pulmonary system	Infrequently performed
B-Cell Lymphoma Imaging Study (I-131-tositumomab)	Tumor imaging	Infrequently performed; inconvenient
Prostate Cancer Study (In-111-capromab)	Tumor imaging	Infrequently performed; inaccurate

Interventions; Imaging; Protocol Design; Protocol Summary Diagram; and Quantitative Measurement(s).

The "Overview" subsection very briefly describes the biologic process(es) that the study images. The "Radiopharmaceutical Characteristics" subsection describes the basic characteristics of each radiopharmaceutical such as its chemical structure and molecular weight. An optimal radiopharmaceutical is critically important to achieving the goal of a high target to background activity ratio.

> With a good radiopharmaceutical, you can see the lesion with a poor imaging system.
> With a poor radiopharmaceutical, you won't see the lesion even with a good imaging system.
>
> Manny Subramanian, 1976
> Upstate Medical Center, Syracuse, NY

Of course, ideally all components of a study should be optimized: the radiopharmaceutical, the imaging equipment, the protocol, patient preparation, quantitative analysis, and the overall interpretation. Appendix B: Radiopharmaceuticals and their Use in Clinical Studies lists all of the radiopharmaceuticals that are discussed in this book and all of the nuclear medicine studies that are performed with each individual radiopharmaceutical.

The "Extraction Mechanism" subsection is of great importance and attempts to summarize the current knowledge of the biologic mechanism that extracts each radiopharmaceutical from the flowing blood. Table 11.2 lists a single example of each of the various extraction mechanisms in approximate order of decreasing extraction efficiency. The table demonstrates a rough inverse correlation between extraction efficiency and time from administration of the radiopharmaceutical to

Table 11.2 Extraction mechanisms for clearing radiopharmaceuticals from blood

Example study	Radiopharmaceutical	Specific mechanism	Extraction efficiency	Saturable	Time to start clearance image
Pulmonary Perfusion Study	Tc-99m-macroaggregated albumin	Microembolization	100 %	No	15 s
Renal Tubular Secretion Study	Tc-99m-MAG3	Anion excretion pathway	65 %	No	1 min
Renal Glomerular Filtration Study	Tc-99m-DTPA	Passive filtration based on size	20 %	No	1 min
Myocardial perfusion	N-13-ammonia	Lipophilicity	High	No	3 min
Liver-Spleen Study	Tc-99m-sulfur colloid	Phagocytosis by sinusoidal macrophages	High	No	5 min
Hepatobiliary Study	Tc-99m-trimethylbromo-IDA	Organic ion transport system	Moderate-high	Yes	5 min
Tumor Glucose Metabolism Study	F-18-fluorodeoxyglucose	GLUT glucose transporters	Moderate	Essentially	60 min
Bone Mineral Study	F-18 as sodium fluoride	Exchange of F^- for OH^- in hydroxyapatite	Moderate	No	60 min
Bone Mineral Study	Tc-99m-MDP/HMDP	Adherence of PO_4 tracers to surface of bone	Low-moderate	No	2 h
White Blood Cell Migration Study	Tc-99m-white blood cells	Migration secondary to chemotaxis	Low	No	2 h
Somatostatin Receptor Study	In-111-pentetriotide	Cell membrane signal receptor	Low	Yes	4 h
Thyroid Imaging Study	I-123 as sodium iodide	Na^+ / I^- symporter (NIS) protein	Low	Yes	6 h
B-cell Lymphoma Imaging Study	In-111-ibritumomab tiuxetan [Zevalin]	Cell membrane CD20 epitope	Very low	Yes	2–24 h

acquisition of clearance images. Other factors that are not listed are also important in determining the optimal time for imaging clearance, e.g., blood flow and excretion of the radiopharmaceutical from the structure in question. In the normal situation, blood flow times extraction efficiency equals clearance rate. Appendix C: Tables of Clearance Mechanisms contains a set of tables that lists the nuclear medicine studies that utilize each of the various clearance mechanisms. And Appendix D: Distribution of Cardiac Output in the Body at Rest lists the percent of cardiac output, blood flow per organ, and blood flow per 100 g of organ for the major organs of the body.

A few nuclear medicine studies involve extraction of the radiopharmaceutical from a flowing substance other than blood, e.g., lymph in the case of the Lymphoscintigraphy Study with filtered Tc-99-sulfur colloid; and in several nuclear medicine studies, there is no extraction of the radiopharmaceutical from the compartment into which the radiopharmaceutical is introduced, e.g., Cardiac Gated Blood Pool Study with Tc-99m-red blood cells. A significant amount of nuclear medicine research is devoted to identifying extraction mechanisms that, once imaged with an optimal radiopharmaceutical, will provide important clinical information. Initial insights often come from advances in molecular biology.

Many of the simplest extraction mechanisms have already been utilized as the basis of current standard nuclear medicine studies, e.g., microembolization, glomerular filtration, and phagocytosis (Table 11.2). There are probably very few similar, mainly physiologic, mechanisms yet to be exploited. On the other hand, it is likely that only a small percentage of potentially useful extraction mechanisms related to the cell membrane have been identified or explored. Proteins imbedded in cell membranes that could possibly serve as an extraction mechanism fall into at least three categories: (1) membrane transport proteins, (2) receptors for signal molecules, and (3) epitopes that are antigenic.

The need for transport proteins within cell membranes arises from the fact that the lipid bilayer of the cell membrane is relatively impermeable to all but small lipophilic molecules (Fig. 11.1) [2]. Transmembrane transport proteins fall into three general categories: (1) channel proteins, (2) passive transporters (or facilitated diffusion), and (3) active transporters (Fig. 11.2) [3].

Channels passively transport inorganic ions down a concentration gradient. Different channels exist for ions of varying size and charge. The interaction of a molecule with a channel is relatively weak. Passive transporters bind a specific molecule or class of molecules. The binding process causes a conformational change in the transporter that moves the molecule across the cell membrane, again down a concentration gradient.

Active transporters move molecules across the cell membrane against a gradient and, therefore, require the input of energy. The energy may come from ATP hydrolysis or an ion gradient (Figs. 11.2 and 11.3) [3, 4]. In the case of active transport driven by ATP hydrolysis, the conformational change of the transporter protein is driven by energy from the release of a phosphate group from ATP. In the case of active transport driven by an ion gradient, the other solute may move in the same

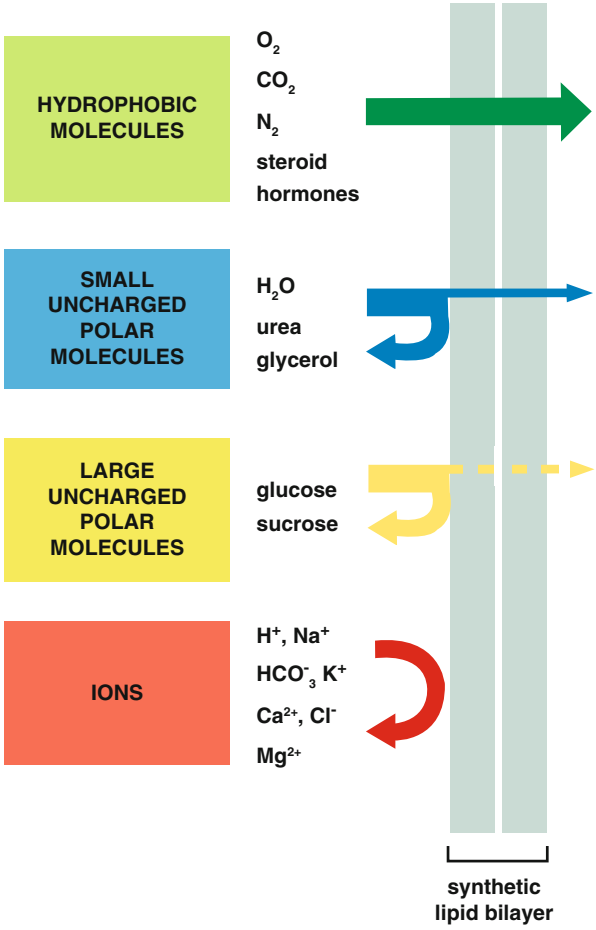

Fig. 11.1 Relative permeability of a cell-like lipid bilayer. The smaller the molecule and, more importantly, the less strongly it associates with water, the more rapidly the molecule diffuses across the lipid bilayer (© Garland Science 2008)

direction as the primary solute, a symporter, or in the opposite direction, an antiporter (Fig. 11.3). The extraction mechanism of thyroid epithelial cells for I-123 in the Thyroid Imaging Study is an example of a symporter; I-123 and Na^+ move across the cell membrane together.

Receptors on cell surfaces for signaling molecules provide another type of extraction mechanism. The signaling molecule binds to receptors on the cell surface with high specificity. The signaling molecule remains on the cell surface but changes the conformation of the receptor protein on the inside of the cell, which triggers a cascade of molecular events that culminates in various changes in the cell's metabolism. The signaling molecule can be converted into a radiopharmaceutical that will localize to cells in proportion to the degree of expression of the signaling receptors in question. The radioisotope label must be attached to the signaling molecule some distance from the binding domain on the signaling molecule. An example of this extraction mechanism in a nuclear medicine study is the Somatostatin Receptor Study with In-111-Octreotide.

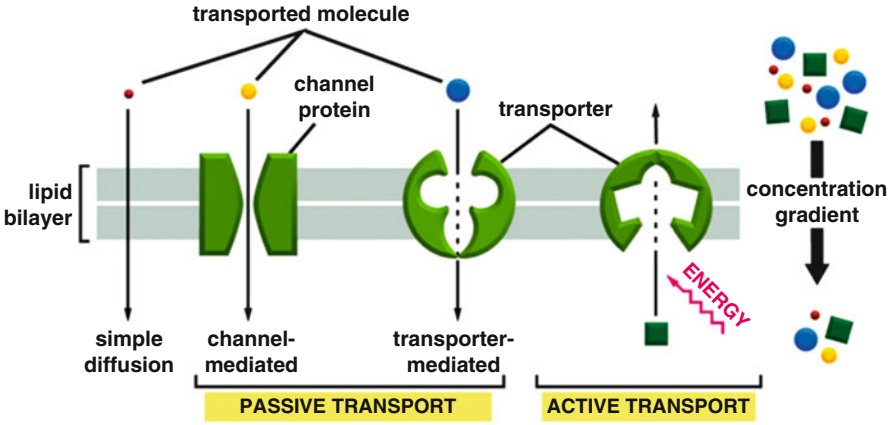

Fig. 11.2 Comparison of active and passive transport. Passive transport down an electrochemical gradient occurs spontaneously, either by simple diffusion through the lipid bilayer or by facilitated diffusion through channels and passive transporters. By contrast, active transport requires input of metabolic energy (© Garland Science 2008)

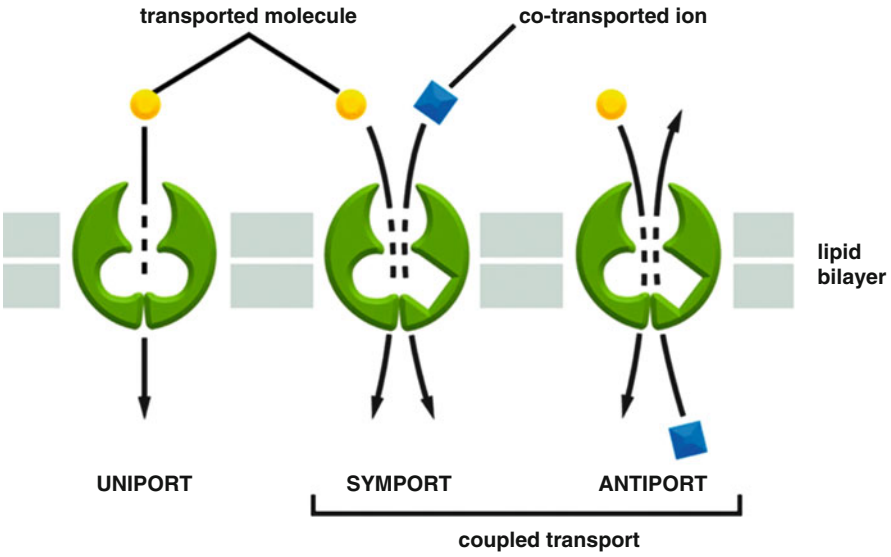

Fig. 11.3 Three types of active transporter-mediated movement. This diagram shows transporters functioning as uniporters, symporters, and antiporters. In each type of transport, the energy is supplied by an electrochemical gradient (© Garland Science 2008)

The extraction mechanism with the highest specificity is the binding of an antibody to an antigen or epitope. An antibody can distinguish between two proteins that differ by only one amino acid or between optical isomers of the same molecule [5]. Cells express many proteins on their surface which can serve as relatively

characteristic markers for cells of interest such as prostate cancer or B-cell lymphoma. However, because of their large size, antibodies are slow to leave the vascular space and enter the interstitium, and foreign antibodies can induce patient antibodies that inactivate the administered antibodies. Some progress has been made in reducing antibody size without affecting binding specificity and humanizing antibodies to eliminate the induction of patient antibodies, but the problems are still significant. Primarily for these reasons, there are no successful antibodies for imaging and only one successful antibody for therapy. In-111-ibritumomab tiuxetan [Zevalin] is effective therapy for B-cell lymphoma even though it does not always achieve a high target to background ratio because lymphomas are very radiosensitive [6].

An interesting extraction mechanism is the labeling of white blood cells that then follow cytokine and chemokine gradients to areas of infection by the process of diapedesis. However, the localization or clearance process is slow, which increases the radiation dose to the patient and delays obtaining diagnostic information. In addition, the patient's blood has to be sent to a laboratory for cell labeling and then the labeled cells are reinjected, which runs the risk of laboratory error. Tc-99m-HMPAO-white blood cells are still occasionally used for imaging infection but have been largely replaced by F-18-fluorodeoxyglucose.

The "Extraction Efficiency" subsection indicates the percent of potentially available radiopharmaceutical that is normally cleared. Sometimes this percent is well known, e.g., 20 % for glomerular filtration, but often it can only be estimated from the length of time following injection that it takes to achieve a target to background ratio that is sufficient for imaging. For example, the extraction efficiency must be high in the Liver-Spleen Study with Tc-99m-sulfur colloid because imaging can begin within 5 min, and it must be low in the Prostate Cancer Study with In-111-capromab [ProstaScint®] because imaging must be delayed until approximately 3 days after injection of the radiopharmaceutical. These estimates ignore the role of blood flow.

The "Extraction Mechanism, Saturable or Non-saturable" subsection simply indicates whether the extraction mechanism can be saturated or not. The microembolization extraction mechanism in the Pulmonary Perfusion Study with Tc-99m-MAA cannot be saturated, but the sodium/iodide symporter extraction mechanism in the Thyroid Imaging Study with I-123 can be saturated, e.g., free iodide associated with CT iodinated contrast material.

The "Interventions" subsection indicates whether any interventions, e.g., medications or exercise, are used in a study. An example is pharmacologic or exercise stress in the various myocardial perfusion studies. The "Imaging" subsection indicates what imaging equipment is used, e.g., simple scintillation probe, gamma camera, or PET-CT machine. The "Protocol Design" subsection briefly describes the rationale of the study protocol and the "Protocol Summary Diagram" depicts the timing of radiopharmaceutical administration, image acquisition, and any interventions. It also includes labels that indicate what physiologic or molecular biologic process is reflected in the images. The definitions of the symbols used in the "Protocol Summary Diagrams" are listed in Fig. 11.4.

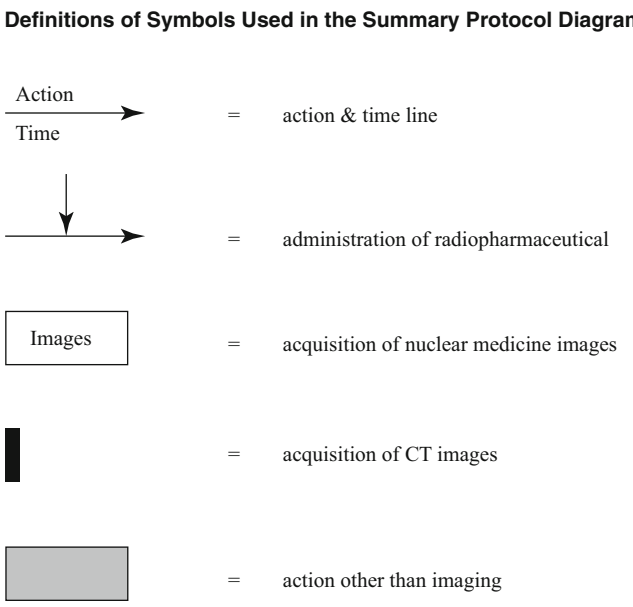

Fig. 11.4 Definitions of symbols used in the protocol summary diagrams

The "Quantitative Measurement" subsection examines in detail any quantitative measurement that is a routine part of the study. This includes the type of measurement as discussed in Part II, Mathematics of the Biodistribution of Radiopharmaceuticals, the normal range, the pathologic meaning of the measurement, and selected clinical examples.

There are many variables involved in any nuclear medicine study and, therefore, many different, but satisfactory, ways to perform, interpret, and quantify nuclear medicine studies. The approach presented here is felt to be representative.

The nuclear medicine therapeutic procedures are not included because essentially every therapeutic procedure has a corresponding diagnostic study with an identical radiopharmaceutical biodistribution.

References

1. Klingensmith WC, Eshima D, Goddard J. Nuclear medicine procedure manual 2012–14. 10th ed. Englewood: Wick Publishing; 2012.
2. Membrane transport of small molecules and the electrical properties of the cell. In: Albert B, Johnson A, Lewis J, Raff M, Roberts K, Walter P, editors. Molecular biology of the cell. 5th ed. New York: Garland Science; 2008. p. 652.
3. Membrane transport of small molecules and the electrical properties of the cell. In: Albert B, Johnson A, Lewis J, Raff M, Roberts K, Walter P, editors. Molecular biology of the cell. 5th ed. New York: Garland Science; 2008. p. 654.

4. Membrane transport of small molecules and the electrical properties of the cell. In: Albert B, Johnson A, Lewis J, Raff M, Roberts K, Walter P, editors. Molecular biology of the cell. 5th ed. New York: Garland Science; 2008. p. 656.
5. The adaptive immune system. In: Albert B, Johnson A, Lewis J, Raff M, Roberts K, Walter P, editors. Molecular biology of the cell. 5th ed. New York: Garland Science; 2008. p. 1540.
6. Goldsmith SJ. Radioimmunotherapy of lymphoma: Bexxar and Zevalin. Semin Nucl Med. 2010;40:122–35.