3 • THE ROLE OF THE RADIOPHARMACEUTICAL IN NUCLEAR DIAGNOSIS

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Nuclear medicines, alias radiopharmaceuticals, radioindicators, nuclear pharmaceuticals, radioactive tracers, or simply tracers, are the central component of the nuclear diagnostic system. Quality in nuclear medicine thus requires quality nuclear medicines as the starting point in the diagnostic process.

The quality of nuclear medicines must be controlled in two ways. First, from a pharmacist's standpoint, we want to control the formulations, their purity, sterility, stability, and so on. This requires a broad spectrum of test procedures to which one whole section of this book is devoted. Second, from a systems engineer's standpoint, we want to control that component of the system that provides the signals required to arrive at a nuclear medical diagnosis.

This chapter addresses the problem of selection and control of the signal generation characteristics of the system. We reduce radiopharmaceuticals to chemical symbols in order to understand their design characteristics and to help control their pharmaceutical properties. Likewise, we can also reduce radiopharmaceuticals to mathematical symbols in order to understand their signal design characteristics and to help control their signal producing properties. This mathematical transformation is accomplished using simple matrix notation. Thus, the symbol $|D|$ in matrix notation is a substitute for the familiar word *biodistribution*. The reason for using the symbol rather than the word is that it becomes easier to manipulate and express such things as the relationship between biodistributions. Furthermore, definitions of terms like sensitivity and specificity are more easily expressed when the matrix notation is utilized. An understanding of radiopharmaceuticals from this point of view leads to an understanding of how the signal-producing component of the system interrelates with other system components. This is particularly useful when a digital computer is used for data processing and analysis.

The radiopharmaceutical as signal generator

When we administer a radiopharmaceutical to a patient, we create a signal generator—a distribution of molecules containing signal-producing atoms. This signal generator is a matrix of counting rates. The matrix has the dimensions of the three spatial coordinates (x, y, and z) and of time (t). This is designated as: $|D| = f(x, y, z, t)$, where $|D|$ is the biodistribution. Each cell in the matrix represents an individual volume element of the body at a specific time (Fig. 3-1). Each cell of the matrix contains a unit of information characterized by its signal strength, which has the units of concentration of radioactivity per unit volume, that is, disintegrations per second per cell.

When we image a patient or otherwise

make measurements of the radioactivity in the patient, we are sampling this information matrix. Usually our imaging system can record this information in only one spatial plane (x, y) and at one time (t_i). To get three-dimensional information, we have to take images from different points of view. To obtain temporal information, we have to take a series of images at different times.

The images we obtain in nuclear medicine are also matrices and can be described using this same notation:

$$|I| = g(x, y, t_1)$$

$$\vdots$$

$$|I|_n = g(x, y, t_n)$$

This allows us to mathematically relate the images—our samples of the biodistribution—to the total data base, which is the biodistribution.

The task of radiopharmaceutical selection is to pick a tracer in which the biodistribution in the presence of disease is so altered from normal biodistribution that manageable samples of the available information are sufficient to reveal this difference, in spite of variable thicknesses of overlying tissues and other uncontrollable variables that effect sampling. This is simply denoted as follows:

$$|D|_h \equiv |D|_{health} \neq |D|_{disease} \equiv |D|_d$$

and

$$|I|_h \equiv |I|_{health} \neq |I|_{disease} \equiv |I|_h$$

Sensitivity, in this frame of reference, is increased as $|I|_d$ diverges from $|I|_h$. Since $|I|_d$ is derived from $|D|_d$, the tracer that provides the greatest difference between $|D|_d$ and $|D|_h$ is the most sensitive for detecting a given disease provided the images or samples reflect the difference.

Specificity is increased as $|I|_{d_1}$ diverges from $|I|_{d_2}$. (The inferior notation, "d1,"
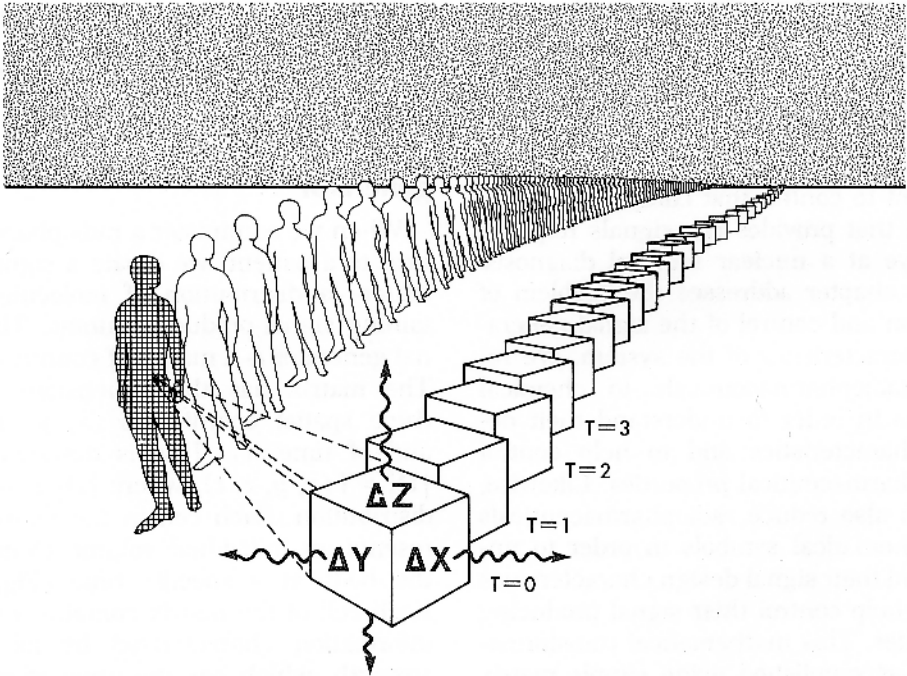

Fig. 3-1. A radioactive tracer administered to a patient creates an information matrix that can be used to diagnose disease. Each unit in the matrix is an emission rate defined at coordinates (x, y, z, t).

is a given disease; "d2" is a different given disease.) Since $|I|_{d_1}$ is derived from $|D|_{d_1}$, the tracer that provides the greatest difference between $|D|_{d_1}$ and $|D|_{d_2}$ is the most sensitive for discriminating between diseases—provided, of course, that the images or samples reflect this difference. The best radiopharmaceutical depends on which disease we are trying to diagnose, what the alternative disease possibilities are, and our ability to obtain manageable samples that discriminate between $|D|_{d_1}$ and $|D|_{d_2}$ or $|D|_h$. Our choice of a tracer therefore depends on the available nuclear detection equipment, and data handling, and processing hardware and software. Note that sensitivity and specificity are dependent on the tracer we choose and on our ability to obtain appropriate samples of the tracer's biodistribution.

Standardizing the biodistribution

The biodistribution or the information matrix, $|D|$, is subject to much inherent variability. Some of the factors are controllable; others are not. The primary uncontrollable variable is the normal biologic variation in physiology and metabolism. Size and anatomic variations will also change $|I|$ even if $|D|$ remains constant. The controllable variables of $|D|$ include total administered radioactivity, specific activity, volume and method of tracer administration, and use of ancillary drugs or physiologic maneuvers. For example, if a dose of a lung scanning radiopharmaceutical is administered as a rapid bolus, $|D|$ depends on the distribution of pulmonary blood flow over a very short interval of time; if the tracer is administered slowly over several respiratory cycles then $|D|$ depends more on the average distribution of pulmonary blood flow. Since pulmonary blood flow is changed depending on whether one is standing or supine, the position of the patient during the injection also becomes a controllable variable requiring standardization. Chapter 4 deals more extensively with controlling and standardizing the input function.

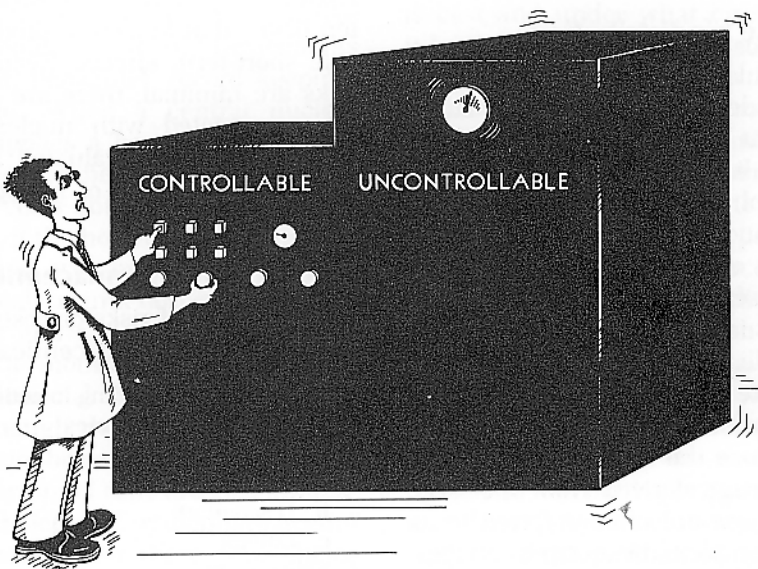A powerful diagnostic technique is to introduce into the procedure conditions that

Fig. 3-2. The use of a radiopharmaceutical as a signal generator is subject to controllable and uncontrollable variables. The controllable variables include amount of administered radiopharmaceutical, the injection procedure, use of ancillary drugs, patient preparation, and physiologic maneuvers. The uncontrollable variables include patient size, individual biochemical and physiologic variations, diet, age, and extent of disease.

enhance the differences between $|D|_{health}$ and $|D|_{disease}$. A classical example of this is found in the biodistribution of radioactive potassium. When this tracer is injected into supine, resting, normal subjects and into patients with ischemic heart disease, the biodistribution is often not different. However, if the subject exercises to the point of experiencing angina pectoris and the tracer is injected while he is in an upright position, the ischemic region of the myocardium gets relatively less radiopotassium than surrounding areas do.

In the selection or comparison of radiopharmaceuticals the effects of the controllable variables must be kept in mind (Fig. 3-2). Under a given set of conditions one tracer may give a greater difference in the biodistribution between normal subjects and those with disease, but under a different set of conditions another tracer may provide greater differences. Hence, an in-depth understanding of the physiology of the subject and pharmacology of the tracers is necessary when tracers are being intercompared.

Sampling the biodistribution

When should the images or measurements be made? What regions should be imaged? What samples should be taken? The answers lie first in the knowledge of the normal physiology and biochemistry and its alteration by the disease process. The objective of the sampling is to obtain maximum discrimination with minimum sampling. Usually this requires only two or three simple images.

An alternate technique is to obtain a large data base and use computer techniques to reduce the data so the final $|I|$ is a single image derived from the large data base. These are often referred to as functional, complex, or derived images. The functional image can be denoted as, $|I|_2$ obtained from $|I|_1$, that is:

$$|I|_1 = f(x, y, t)$$
$$\downarrow \text{ computer reduction of data}$$
$$|I|_2 = g(x, y)$$

The compound image is $|I|_3$, that is:

$$|I|_1 = f(x, y, t)$$
$$|I|_2 = g(x, y, t)$$
$$\begin{array}{l} \text{computer reduction and} \\ \text{integration of data from} \\ \text{both matrices} \end{array}$$
$$|I|_3 = h(x, y, c)$$

The third dimension, c, in the complex image is color. For example, a color scale can be used to show the ratio of two physiologic functions such as Natarajan and Wagner[8] used when they displayed the distribution of pulmonary ventilation in one color and the distribution of pulmonary perfusion in a second color. They used double exposure color photography to blend the two functional images and thereby created a single compound image from a computer memory stuffed with data.

The administration of a radiopharmaceutical to convert a patient into a signalling device can be accomplished with relative safety using current radiopharmaceuticals. The amount of the tracer is usually orders of magnitude below that which is pharmacologically active, and the amount of radiation exposure is also several factors of ten below that known to produce measurable short-term effects. Even though the risks are minimal, there are always some risks associated with nuclear diagnosis. These should be evaluated and used in the intercomparison of radiopharmaceuticals.

Risks of radiopharmaceutical use

Three types of risks or costs result from the use of radiopharmaceuticals:

1. Misinformation leading to actions that result in undesirable outcomes
2. Costs
   a. Time
   b. Discomfort
   c. Dollars
3. Side effects
   a. Reactions to the trauma of the test
   b. Reactions to the administration of the tracer or ancillary drugs
   c. Long-term effects of radiation exposure and cumulative or latent toxicity

Thus, a major objective in radiopharmaceutical selection is to minimize these factors:

Misinformation risks are a function of the differences between $|D|_h$ and $|D|_d$, of the statistical variability of populations of $|D|_h$ and $|D|_d$, and the ease with which $|I|_h$ and $|I|_d$ can be reliably obtained from the basic signal matrices.

Another risk parameter is related to tracer reliability. There is likely to be an optimum point during the diagnostic work-up when the tracer study is most useful. Thus, the system should be functional at this time. The tracer study is most useful prior to the occurrence of structural manifestations of disease. The radiopharmaceutical that is a central component of the system must be available; if it is not, the system fails to respond to the demands of the medical care system, and its usefulness is lost.

Costs of radiopharmaceuticals

The direct dollar costs per dose administered is a major consideration in radiopharmaceutical selection. There are also other significant but less obvious costs like floor space requirements and investments in equipment, personnel, record keeping, and overhead. When a central nuclear pharmacy supplies a hospital with its radiopharmaceutical needs, many of these less obvious costs enter into the decision. For example, if the hospital gains a needed room in a vital area by buying its radiopharmaceuticals as unit doses from an outside supplier and this room can be converted into a money earning scanning room, the financial benefits are significant, even though the actual value of the change may not be easy to calculate.

Costs of personnel time are also influential in the choice of a radiopharmaceutical, particularly when there is a choice between an extemporaneous preparation (low material costs, high personnel costs) or kit preparations (high material cost, low personnel costs).

Regulatory agencies may at times have a negative influence on the quality of health care. Quality is lost when the costs of developing, licensing, and marketing needed radiopharmaceuticals are so high that it becomes too financially risky for commercial enterprise. It has taken years and millions of investment dollars to get ^{125}I-fibrinogen into the American market. How does one calculate the cost of all these patient years in which Americans have had to do without this radiopharmaceutical, whose value in the management of thromboembolic disease was well established and widely used outside the United States. It is a mistake for regulatory agencies to ignore any of the cost factors when approving a new radiopharmaceutical. The purpose of regulations is to assure quality; if some of the parameters like availability, costs, and so on are ignored, the primary objectives for having the regulations may not be achieved.

Measures to compare and evaluate radiopharmaceuticals

Are you using the best tracer? How do you know that a particular tracer really is best and under what circumstances is it best? If you change to a so-called better tracer, does your diagnosis improve as a result? Does diagnosis improve in spite of the fact that you are familiar with the idiosyncrasies of the biodistribution of the old tracer and in spite of the fact that you really do not know all the peculiarities of the new tracer? Tracer selection has been discussed off and on in the literature since about 1961, usually through comparisons of one radiopharmaceutical to another. Little, however, has been said about the problem of matching the tracer to the other components of the nuclear diagnostic system and particularly about matching it to the experience of its user. The earlier analysis of the problem of tracer selection has fairly well established three general criteria for choosing among alternative tracers. These criteria are high uptake in the target organ, the ratio of the radioactivity in the target organ to that of the

surrounding tissue, and minimization of the radiation exposure. In brief, the objective has been to maximize the number of detectable or useful photons per unit of radiation exposure dose.

Rads per usable photon: the classic selection criteria

Most of the classic radiotracer selection criteria were derived at a time when the objective of many nuclear diagnostic procedures was to obtain images of organs that were difficult to image by regular x-ray techniques. Thus, measurements indicative of photon output from the target organ and image contrast were developed. Photon output depended on how much of a tracer could be administered without giving an amount of radiation exposure to the whole body or target organ sufficient to cause medical complication and on the percentage of tracer uptake in the target organ. Image contrast depended on amounts of tracer in the target organ relative to amounts in the surrounding tissues. Table 3-1 summarizes measures for comparing the signal to noise that have been used as indicators of inherent contrast. The following is a summary of the factors of a radiopharmaceutical that contribute to the number of detectable photons per rad:

1. Factors contributing to number of detectable photons
   a. Gamma ray energy
   b. Gamma ray abundance
   c. Collimator-detector efficiency
   d. Concentration in target at imaging time
2. Factors contributing to number of rads
   a. All particulate and nonparticulate radiation, their energies and abundance
   b. Half-life
   c. Pharmacodynamics

This calculation depends also on the detector that is used to obtain the image and thus begins in a primitive sort of way to be a system evaluation technique.

New selection criteria

With current usage of ^{99m}Tc and other short-lived tracers, individual patient expo-

Table 3-1. Measures of signal-to-noise ratios[10]

T/NT	Target to nontarget ratios
T – NT	Difference between target and nontarget
$\dfrac{T - NT}{\sqrt{T + NT}}$	Difference between target and nontarget divided by standard deviation of the difference
$\sqrt{T} - \sqrt{NT}$	Difference between target and nontarget in terms of their standard deviations

sure levels are much less critical than they once were. Also, with most of the current imaging systems, we have all the photons that we can count and sort. What happens is that the ratios, such as the number of detectable photons per rad, are currently approaching a constant. For example, if criteria listed in Table 3-1 were used to try to sort out which of the various technetium-labeled bone scanning agents would be best, probably the differences would not be significant. Reliability and costs became the more important criteria in the selection of a radiopharmaceutical for bone scanning.

The obsolescence of the classical criteria is becoming apparent as the aim of nuclear imaging changes. Formerly we concentrated our efforts on trying to visualize organs not seen by other radiographic techniques. Currently, we more often aim to map and quantify physiologic or pathophysiologic functions.

Thus, in choosing from among several possible radiopharmaceuticals, it is important to consider which would maximize (1) sensitivity, (2) specificity, (3) simplicity of sampling, and minimize (1) risks, (2) costs, (3) interferences with other tests, and (4) supply problems.

Summary

The radiopharmaceutical is that component in the nuclear diagnostic system that is used to provide a signal generating matrix or biodistribution. The tracer that pro-

vides a simpler and more error-free sampling of unique biodistribution is favored, particularly if it is more reliable and less costly than other tracers. It is important to evaluate the tracer as a component of the system and to consider how well it matches other components of the system in providing critical diagnostic data with minimum risk to the patient. The trend in nuclear diagnosis is to map and quantify physiologic functions rather than to merely visualize the anatomy of the soft tissue organs; criteria based on image contrast considerations are less applicable now than they were in earlier periods of nuclear medicine. (See David Preston's Aphorisms on Nuclear Medicine.)

David Preston's aphorisms on nuclear medicine

1. Nuclear medicine is to physiology what diagnostic roentgenography is to anatomy.
2. Physiologic and biochemical changes always occur (except in trauma) prior to anatomic change.
3. Nuclear medicine has the potential to detect disease nondestructively prior to anatomic change. Thus, it becomes possible to detect disease when it is reversible.
4. During the introductory phase of a nuclear medicine procedure, false positives may really be unrecognized sensitivity.

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